Risk for Appendicitis, Cholecystitis, or Diverticulitis in Patients With Psoriasis

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PRACTICE **POINTS**

- Patients with psoriasis may have elevated risk of diverticulitis compared to healthy patients. However, psoriasis patients do not appear to have increased risk of appendicitis or cholecystitis.
- Clinicians treating psoriasis patients should consider assessing for other risk factors of diverticulitis at regular intervals.

Numerous comorbidities have been associated with psoriasis; however, no studies have considered the relationship between psoriasis and appendicitis, cholecystitis, or diverticulitis. To determine the incidence rate and hazard risk (HR) ratio of appendicitis, cholecystitis, or diverticulitis in patients with psoriasis, we compared psoriasis patients with healthy controls from the Kaiser Permanente Southern California (KPSC) health network. The Cox proportional hazards regression model was used to examine the risk for appendicitis, cholecystitis, or diverticulitis. Patients with psoriasis had a 1.16 times greater risk for developing diverticulitis compared to controls ($P<.01$). There was no significant difference in risk for developing appendicitis or cholecystitis. Patients with psoriasis may have an elevated risk for diverticulitis compared to the general population and therefore might require additional monitoring by clinicians.

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Psoriasis is a chronic skin condition affecting approximately 2% to 3% of the population.[1,2] Beyond cutaneous manifestations, psoriasis is a systemic inflammatory state that is associated with an increased risk for cardiovascular disease, including obesity,[3,4] type 2 diabetes mellitus,[5,6] hypertension,[5] dyslipidemia,[3,7] metabolic syndrome,[7] atherosclerosis,[8] peripheral vascular disease,[9] coronary artery calcification,[10] myocardial infarction,[11-13] stroke,[9,14] and cardiac death.[15,16]

Psoriasis also has been associated with inflammatory bowel disease (IBD), possibly because of similar autoimmune mechanisms in the pathogenesis of both diseases.[17,18] However, there is no literature regarding the risk for acute gastrointestinal pathologies such as appendicitis, cholecystitis, or diverticulitis in patients with psoriasis.

The primary objective of this study was to examine if patients with psoriasis are at increased risk for appendicitis, cholecystitis, or diverticulitis compared to the general population. The secondary objective was to determine if patients with severe psoriasis (ie, patients treated with phototherapy or systemic therapy) are at a higher risk for these conditions compared to patients with mild psoriasis.

Methods

Patients and Tools—A descriptive, population-based cohort study design with controls from a matched cohort

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The eTable is available in the Appendix online at www.mdedge.com/dermatology.

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was used to ascertain the effect of psoriasis status on patients' risk for appendicitis, cholecystitis, or diverticulitis. Our cohort was selected using administrative data from Kaiser Permanente Southern California (KPSC) during the study period (January 1, 2004, through December 31, 2016).

Kaiser Permanente Southern California is a large integrated health maintenance organization that includes approximately 4 million patients as of December 31, 2016, and includes roughly 20% of the region's population. The geographic area served extends from Bakersfield in the lower California Central Valley to San Diego on the border with Mexico. Membership demographics, socioeconomic status, and ethnicity composition are representative of California.

Patients were included if they had a diagnosis of psoriasis (*International Classification of Diseases, Ninth Revision, Clinical Modification* [*ICD-9-CM*] code 696.1; *International Classification of Diseases, Tenth Revision, Clinical Modification* [*ICD-10-CM*] codes L40.0, L40.4, L40.8, or L40.9) for at least 3 visits between January 1, 2004, and December 31, 2016. Patients were not excluded if they also had a diagnosis of psoriatic arthritis (*ICD-9-CM* code 696.0; *ICD-10-CM* code L40.5x). Patients also must have been continuously enrolled for at least 1 year before and 1 year after the index date, which was defined as the date of the third psoriasis diagnosis.

Each patient with psoriasis was assigned to 1 of 2 cohorts: (1) severe psoriasis: patients who received UVB phototherapy, psoralen plus UVA phototherapy, methotrexate, acitretin, cyclosporine, apremilast, etanercept, adalimumab, infliximab, ustekinumab, efalizumab, alefacept, secukinumab, or ixekizumab during the study period; and (2) mild psoriasis: patients who had a diagnosis of psoriasis who did not receive one of these therapies during the study period.

Patients were excluded if they had a history of appendicitis, cholecystitis, or diverticulitis at any time before the index date. Only patients older than 18 years were included.

Patients with psoriasis were frequency matched (1:5) with healthy patients, also from the KPSC network. Individuals were matched by age, sex, and ethnicity.

Statistical Analysis—Baseline characteristics were described with means and SD for continuous variables as well as percentages for categorical variables. Chi-square tests for categorical variables and the Mann-Whitney *U* Test for continuous variables were used to compare the patients' characteristics by psoriasis status. Cox proportional hazards regression models were used to examine the risk for appendicitis, cholecystitis, or diverticulitis among patients with and without psoriasis and among patients with mild and severe psoriasis. Proportionality assumption was validated using Pearson product moment correlation between the scaled Schoenfeld residuals and log transformed time for each covariate.

Results were presented as crude (unadjusted) hazard ratios (HRs) and adjusted HRs, where confounding factors (ie, age, sex, ethnicity, body mass index [BMI], alcohol use, smoking status, income, education, and membership length) were adjusted. All tests were performed with SAS EG 5.1 and R software. $P<.05$ was considered statistically significant. Results are reported with the 95% confidence interval (CI), when appropriate.

Results

A total of 1,690,214 KPSC patients were eligible for the study; 10,307 (0.6%) met diagnostic and inclusion criteria for the psoriasis cohort. Patients with psoriasis had a significantly higher mean BMI (29.9 vs 28.7; $P<.0001$) as well as higher mean rates of alcohol use (56% vs 53%; $P<.0001$) and smoking (47% vs 38%; $P<.01$) compared to controls. Psoriasis patients had a shorter average duration of membership within the Kaiser network ($P=.0001$) compared to controls.

A total of 7416 patients met criteria for mild psoriasis and 2891 patients met criteria for severe psoriasis (eTable). Patients with severe psoriasis were significantly younger and had significantly higher mean BMI compared to patients with mild psoriasis ($P<.0001$ and $P=.0001$, respectively). No significant difference in rates of alcohol or tobacco use was detected among patients with mild and severe psoriasis.

Appendicitis—The prevalence of appendicitis was not significantly different between patients with and without psoriasis or between patients with mild and severe psoriasis, though the incidence rate was slightly higher among patients with psoriasis (0.80 per 1000 patient-years compared to 0.62 per 1000 patient-years among patients without psoriasis)(Table 1). However, there was not a significant difference in risk for appendicitis between healthy patients, patients with severe psoriasis, and patients with mild psoriasis after adjusting for potential confounding factors (Table 2). Interestingly, patients with severe psoriasis who had a diagnosis of appendicitis had a significantly shorter time to diagnosis of appendicitis compared to patients with mild psoriasis (7.4 years vs 8.1 years; $P<.0001$).

Cholecystitis—Psoriasis patients also did not have an increased prevalence of cholecystitis compared to healthy patients. However, patients with severe psoriasis had a significantly higher prevalence of cholecystitis compared to patients with mild psoriasis ($P=.0038$). Overall, patients with psoriasis had a slightly higher incidence rate (1.72 per 1000 patient-years) compared to healthy patients (1.46 per 1000 patient-years). Moreover, the time to diagnosis of cholecystitis was significantly shorter for patients with severe psoriasis than for patients with mild psoriasis (7.4 years vs 8.1 years; $P<.0001$). Mild psoriasis was associated with a significantly increased risk (HR, 1.33; 95% CI, 1.09-1.63; $P<.01$) for cholecystitis compared to individuals without psoriasis in both the crude and adjusted

models (Table 2). There was no difference between mild psoriasis patients and severe psoriasis patients in risk for cholecystitis.

Diverticulitis—Patients with psoriasis had a significantly greater prevalence of diverticulitis compared to the control cohort (5.1% vs 4.2%; $P<.0001$). There was no difference in prevalence between the severe psoriasis group and the mild psoriasis group ($P=.96$), but the time to diagnosis of diverticulitis was shorter in the severe psoriasis group than in the mild psoriasis group (7.2 years vs 7.9 years; $P<.0001$). Psoriasis patients had an incidence rate of diverticulitis of 6.61 per 1000 patient-years compared to 5.38 per 1000 patient-years in the control group. Psoriasis conferred a higher risk for diverticulitis in both the crude and adjusted models (HR, 1.23; 95% CI, 1.11-1.35 [$P<.001$] and HR, 1.16; 95% CI, 1.05-1.29; [$P<.01$], respectively)(Table 3); however, when stratified by disease severity, only patients with severe psoriasis were found to be at higher risk (HR, 1.26; 95% CI, 1.15-1.61; $P<.001$ for the adjusted model).

TABLE 1. Number of New Events, Follow-up Time, and Incidence Rates

	Patients Without Psoriasis	Patients With Psoriasis
Appendicitis		
No. of events	218	65
Incidence rate per 1000 patient-years	0.62	0.80
95% CI	0.54-0.71	0.62-1.02
Cholecystitis		
No. of events	510	140
Incidence rate per 1000 patient-years	1.46	1.72
95% CI	1.33-1.59	1.45-2.04
Diverticulitis		
No. of events	1857	526
Incidence rate per 1000 patient-years	5.38	6.61
95% CI	5.14-5.63	6.06-7.20

Abbreviation: CI, confidence interval.

TABLE 2. Cox Proportional Hazard Regression Results for Patients With Mild and Severe Psoriasis Compared to Patients Without Psoriasis

		Crude Risk			Adjusted Risk[a]		
	Psoriasis Severity	Hazard Risk	95% CI	*P* Value	Hazard Risk	95% CI	*P* Value
Appendicitis	Mild	1.33	0.98-1.81	.07	1.20	0.87-1.65	.28
	Severe	1.14	0.68-1.93	.62	1.10	0.65-1.86	.73
Cholecystitis	Mild	1.33	1.09-1.63	<.01	1.25	1.02-1.54	.03
	Severe	0.78	0.52-1.17	.23	.78	0.52-1.18	.23
Diverticulitis	Mild	1.25	1.02-1.53	<.01	1.10	0.98-1.23	.09
	Severe	1.35	1.14-1.59	<.001	1.26	1.15-1.61	<.001

Abbreviation: CI, confidence interval.
[a]Adjusted for body mass index, alcohol use, smoking status, income, education, and Kaiser network membership length.

TABLE 3. Cox Proportional Hazard Regression Results for Patients With and Without Psoriasis

	Crude Risk			Adjusted Risk[a]		
	Hazard Risk	95% CI	*P* Value	Hazard Risk	95% CI	*P* Value
Appendicitis	1.28	0.97-1.69	.08	1.17	0.88-1.26	.29
Cholecystitis	1.17	0.98-1.43	.07	1.13	0.94-1.37	.20
Diverticulitis	1.23	1.11-1.35	<.001	1.16	1.05-1.29	<.01

Abbreviation: CI, confidence interval.
[a]Adjusted for body mass index, alcohol use, smoking status, income, education, and Kaiser network membership length.

Comment

The objective of this study was to examine the background risks for specific gastrointestinal pathologies in a large cohort of patients with psoriasis compared to the general population. After adjusting for measured confounders, patients with severe psoriasis had a significantly higher risk of diverticulitis compared to the general population. Although more patients with severe psoriasis developed appendicitis or cholecystitis, the difference was not significant.

The pathogenesis of diverticulosis and diverticulitis has been thought to be related to increased intracolonic pressure and decreased dietary fiber intake, leading to formation of diverticula in the colon.[19] Our study did not correct for differences in diet between the 2 groups, making it a possible confounding variable. Studies evaluating dietary habits of psoriatic patients have found that adult males with psoriasis might consume less fiber compared to healthy patients,[20] and psoriasis patients also might consume less whole-grain fiber.[21] Furthermore, fiber deficiency also might affect gut flora, causing low-grade chronic inflammation,[18] which also has been supported by response to anti-inflammatory medications such as mesalazine.[22] Given the autoimmune association between psoriasis and IBD, it is possible that psoriasis also might create an environment of chronic inflammation in the gut, predisposing patients with psoriasis to diverticulitis. However, further research is needed to better evaluate this possibility.

Our study also does not address any potential effects on outcomes of specific treatments for psoriasis. Brandl et al[23] found that patients on immunosuppressive therapy for autoimmune diseases had longer hospital and intensive care unit stays, higher rates of emergency operations, and higher mortality while hospitalized. Because our results suggest that patients with severe psoriasis, who are therefore more likely to require treatment with an immunomodulator, are at higher risk for diverticulitis, these patients also might be at risk for poorer outcomes.

There is no literature evaluating the relationship between psoriasis and appendicitis. Our study found a slightly lower incidence rate compared to the national trend (9.38 per 10,000 patient-years in the United States in 2008) in both healthy patients and psoriasis patients.[24] Of note, this statistic includes children, whereas our study did not, which might in part account for the lower rate. However, Cheluvappa et al[25] hypothesized a relationship between appendicitis and subsequent appendectomy at a young age and protection against IBD. They also found that the mechanism for protection involves downregulation of the helper T cell (T_H17) pathway,[25] which also has been found to play a role in psoriasis pathogenesis.[26,27] Although our results suggest that the risk for appendicitis is not increased for patients with psoriasis, further research might be able to determine if appendicitis and subsequent appendectomy also can offer protection against development of psoriasis.

We found that patients with severe psoriasis had a higher incidence rate of cholecystitis compared to patients with mild psoriasis. Egeberg et al[28] found an increased risk for cholelithiasis among patients with psoriasis, which may contribute to a higher rate of cholecystitis. Although both acute and chronic cholecystitis were incorporated in this study, a Russian study found that chronic cholecystitis may be a predictor of progression of psoriasis.[29] Moreover, patients with severe psoriasis had a shorter duration to diagnosis of cholecystitis than patients with mild psoriasis. It is possible that patients with severe psoriasis are in a state of greater chronic inflammation than those with mild psoriasis, and therefore, when combined with other risk factors for cholecystitis, may progress to disease more quickly. Alternatively, this finding could be treatment related, as there have been reported cases of cholecystitis related to etanercept use in patients treated for psoriasis and juvenile polyarticular rheumatoid arthritis.[30,31] The relationship is not yet well defined, however, and further research is necessary to evaluate this association.

Study Strengths—Key strengths of this study include the large sample size and diversity of the patient population.

Kaiser Permanente Southern California membership generally is representative of the broader community, making our results fairly generalizable to populations with health insurance. Use of a matched control cohort allows the results to be more specific to the disease of interest, and the population-based design minimizes bias.

Study Limitations—This study has several limitations. Although the cohorts were categorized based on type of treatment received, exact therapies were not specified. As a retrospective study, it is difficult to control for potential confounding variables that are not included in the electronic medical record. The results of this study also demonstrated significantly shorter durations to diagnosis of all 3 conditions, indicating that surveillance bias may be present.

Conclusion

Patients with psoriasis may be at an increased risk for diverticulitis compared to patients without psoriasis, which could be due to the chronic inflammatory state induced by psoriasis. Therefore, it may be beneficial for clinicians to evaluate psoriasis patients for other risk factors for diverticulitis and subsequently provide counseling to these patients to minimize their risk for diverticulitis. Psoriasis patients do not appear to be at an increased risk for appendicitis or cholecystitis compared to controls; however, further research is needed for confirmation.

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APPENDIX

eTABLE. Characteristics and Incidence of Appendicitis, Cholecystitis, and Diverticulitis Among Patients With Mild and Severe Psoriasis and a Matched Cohort

		Patients With Psoriasis			
	Patients Without Psoriasis	Mild	Severe	Total	*P* Value[a]
No. of patients	44,589	7416	2891	54,896	
Mean age (SD), y	55.2 (14.1)	55.7 (14.2)	52.6 (13.8)	55.1 (14.1)	<.0001
Gender, n (%)					.02
Female	22,997 (51.6)	3789 (51.1)	1557 (53.9)	28,343 (51.6)	
Male	21,592 (48.4)	3627 (48.9)	1334 (46.1)	26,553 (48.4)	
Race or ethnicity, n (%)					.0001
Asian	5044 (11.4)	796 (10.7)	381 (13.2)	6221 (11.3)	
Black	2432 (5.5)	377 (5.1)	175 (6.1)	2984 (5.4)	
Hispanic	10,969 (24.6)	1863 (25.1)	745 (25.8)	13,577 (24.7)	
White	24,988 (56.0)	4212 (56.8)	1515 (52.4)	30,715 (56.0)	
Other	1156 (2.6)	168 (2.3)	75 (2.6)	1399 (2.5)	
Mean BMI (SD)	28.7 (5.9)	29.8 (6.6)	30.2 (6.4)	28.9 (6.1)	.0001
Mean years of Kaiser membership (SD)	26.5 (10.9)	26.5 (11.2)	25.5 (10.6)	26.4 (10.9)	.0001
Smoking status, n (%)					.03
Yes	16,493 (37.0)	3347 (45.1)	1381 (47.8)	21,221 (38.7)	
No	27,283 (61.2)	3935 (53.1)	1478 (51.1)	32,696 (59.6)	
Unknown	813 (1.8)	134 (1.8)	32 (1.1)	979 (1.8)	
Alcohol use, n (%)					.25
Yes	23,549 (52.8)	4125 (55.6)	1627 (56.3)	29,301 (53.4)	
No	18,817 (42.2)	3031 (40.9)	1135 (39.3)	22,983 (41.8)	
Unknown	2223 (5.0)	260 (3.5)	129 (4.5)	2612 (4.8)	
High school graduate or higher, n (%)					.28
0%–50%	1556 (3.5)	226 (3.0)	98 (3.4)	1880 (3.4)	
51%–75%	9925 (22.3)	1627 (21.9)	667 (23.1)	12,219 (22.3)	
76%–100%	33,020 (74.1)	5552 (74.9)	2124 (73.5)	40,696 (74.1)	
Unknown	88 (0.2)	11 (0.1)	2 (<0.1)	101 (0.2)	

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eTABLE. (CONTINUED)

		Patients With Psoriasis			
	Patients Without Psoriasis	Mild	Severe	Total	*P* Value[a]
Median household income, n (%)					.34
≤$45,000	9102 (20.4)	1571 (21.2)	636 (22.0)	11,309 (20.6)	
$45,001–$80,000	22,071 (49.5)	3637 (49.0)	1373 (47.5)	27,081 (49.3)	
>$80,000	13,332 (30.0)	2197 (29.6)	880 (30.4)	16,409 (29.9)	
Unknown	84 (0.2)	11 (0.1)	2 (<0.1)	97 (0.2)	
Appendicitis, n (%)	218 (0.5)	50 (0.7)	15 (0.5)	283 (0.5)	.37
Years to diagnosis (SD)	7.9 (3.4)	8.1 (3.3)	7.4 (3.5)	7.9 (3.3)	<.0001
Cholecystitis, n (%)	510 (1.1)	116 (1.6)	24 (0.8)	650 (1.2)	<.01
Years to diagnosis (SD)	7.9 (3.4)	8.1 (3.3)	7.4 (3.5)	7.9 (3.3)	<.0001
Diverticulitis, n (%)	1857 (4.2)	378 (5.1)	148 (5.1)	2383 (4.3)	.96
Years to diagnosis (SD)	7.7 (3.4)	7.9 (3.3)	7.2 (3.6)	7.7 (3.4)	<.0001

Abbreviation: BMI, body mass index.
[a]Comparing patients with mild and severe psoriasis.