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Pruritus in primary biliary cholangitis is under-recorded in patient medical records

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ABSTRACT

Objective Cholestatic pruritus in primary biliary cholangitis (PBC) reduces patients' health-related quality of life (HRQoL). Despite this, existing research suggests that pruritus is under-recorded in patients' health records. This study assessed the extent to which pruritus was recorded in medical records of patients with PBC as compared with patient-reported pruritus, and whether patients reporting mild itch were less likely to have pruritus recorded. We also evaluated clinico-demographic characteristics and HRQoL of patients with medical record-documented and patient-reported pruritus.

Design This cross-sectional study used clinical information abstracted from medical records, together with patient-reported (PBC-40) data from patients with PBC in the USA enrolled in the PicnicHealth cohort. Medical record-documented pruritus was classified as 'recent' (at, or within 12 months prior to, enrolment) or 'ever' (at, or any point prior to, enrolment). Patient-reported pruritus (4-week recall) was assessed using the first PBC-40 questionnaire completed on/after enrolment; pruritus severity was classified by itch domain score (any severity: ≥1; clinically significant itch: ≥7). Patient clinico-demographic characteristics and PBC-40 domain scores were described in patients with medical record-documented and patient-reported pruritus; overlap between groups was evaluated. Descriptive statistics were reported.

Results Pruritus of any severity was self-reported by 200/225 (88.9%) patients enrolled; however, only 88/225 (39.1%) had recent medical record-documented pruritus. Clinically significant pruritus was self-reported by 120/225 (53.3%) patients; of these, 64/120 (53.3%) had recent medical record-documented pruritus. Patients reporting clinically significant pruritus appeared to have higher mean scores across PBC-40 domains (indicating reduced HRQoL), versus patients with no/mild patient-reported pruritus or medical-record documented pruritus.

Conclusion Compared with patient-reported measures, pruritus in PBC is under-recorded in medical records and is associated with lower HRQoL. Research based only on medical records underestimates the true burden of pruritus, meaning physicians may be unaware of the extent and impact of pruritus, leading to potential undertreatment.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Cholestatic pruritus in primary biliary cholangitis (PBC) is common and debilitating but prior studies suggest it is under-recorded in patient medical records.

WHAT THIS STUDY ADDS

⇒ This study, which quantified the extent of under-recording of pruritus in patients with PBC by contrasting the frequency of pruritus recorded in medical records compared with patient-reported PBC-40 responses, found that pruritus of any severity was self-reported by almost 90% of patients; however, less than 40% had recent pruritus documented in their medical records.

⇒ Quality of life was most impaired in patients with clinically significant self-reported pruritus.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Pruritus is not documented in the medical records of around half of patients with clinically significant pruritus.

⇒ Improved recording of pruritus could increase physician awareness and appreciation of the burden of this debilitating condition, ultimately resulting in more widespread treatment and improvement in the quality of life of patients with PBC.

INTRODUCTION

Primary biliary cholangitis (PBC) is a rare, chronic, progressive, autoimmune condition that has a strong female preponderance, affecting women up to nine times more frequently than men.[1–3] The prevalence estimates vary by region but have been found to be as high as 39.2 per 100 000 people in the USA.[1] If left untreated, PBC can lead to end-stage liver disease, requiring liver transplantation[4]; however, when well managed, patients have a close to normal life expectancy and the main impact of the disease is from the symptoms associated with PBC.[5] Cholestatic pruritus is common, occurring in approximately 55%–81% of patients with PBC,[6–10] and significantly impacts patients' health-related quality of life (HRQoL), including

social and emotional well-being.[6 11] Furthermore, sleep disturbance is commonly reported in those with pruritus, which worsens fatigue—a frequent symptom in patients with PBC.[10 12–14] Severe pruritus can be debilitating and, in extreme cases, require liver transplant or lead to suicidal ideation.[14]

Routine medical records are not only key for ensuring patients consistently receive high-quality care, they are also widely used in research to provide insights into comorbidity burden and treatment use in real-world settings.[15 16] Despite extensive evidence in the literature showing that a large proportion of patients with PBC are affected by pruritus, previous research suggests that itch is under-recorded in medical records and insurance claims databases.[13 15] In addition, these data sources do not allow assessment of the severity of pruritus or its impact.[15] It is unclear whether physicians fail to evaluate pruritus, or if diagnosis and treatment are not being documented.[13 15] However, one study showed that 44% (280/633) of patients with PBC did not remember being asked about itch at their most recent clinic visit.[17] As pruritus is either underevaluated or under-recorded, the impact of itch on HRQoL, and thus the need to treat pruritus, might be underestimated in clinical practice.

This study used medical record and self-reported outcomes data from patients with PBC recruited into the PicnicHealth PBC cohort. The objectives of the study were to quantify the extent of reporting of pruritus by contrasting the prevalence of patient-reported pruritus in the cohort, with the prevalence of medical record-documented pruritus; to evaluate the overlap between individuals with patient-reported and medical record-documented pruritus in relation to pruritus severity and to understand if there are specific characteristics that are common to the patients with medical record-documented pruritus; describe the clinico-demographic profile of these patients, including recent use of PBC and pruritus treatments, by pruritus severity at or following enrolment; and explore the HRQoL of patients with patient-reported and medical record-documented pruritus.

METHODS

Study design

This cross-sectional, non-interventional study was conducted among patients who received care for PBC in the USA. Patients were invited to participate in the study by enrolling in the PicnicHealth PBC cohort from January 2021 to May 2022 through PBC patient advocacy groups, affiliate partners and social media campaigns. Patients were unaware that the purpose of the study was to evaluate pruritus, and pruritus presence and severity were not known prior to enrolment. Patients who opted to participate entered the study with the date of enrolment into the PicnicHealth cohort defined as baseline. Data from patient medical records were abstracted at and prior to baseline and contrasted with patient-reported pruritus from the first PBC-40 questionnaire that a patient completed at or following baseline (see figure 1 for further details).

Data collection and extraction from medical records

PicnicHealth curates datasets including clinical data from both structured and unstructured portions of medical records. Following informed consent and Health Insurance Portability and Accountability Act

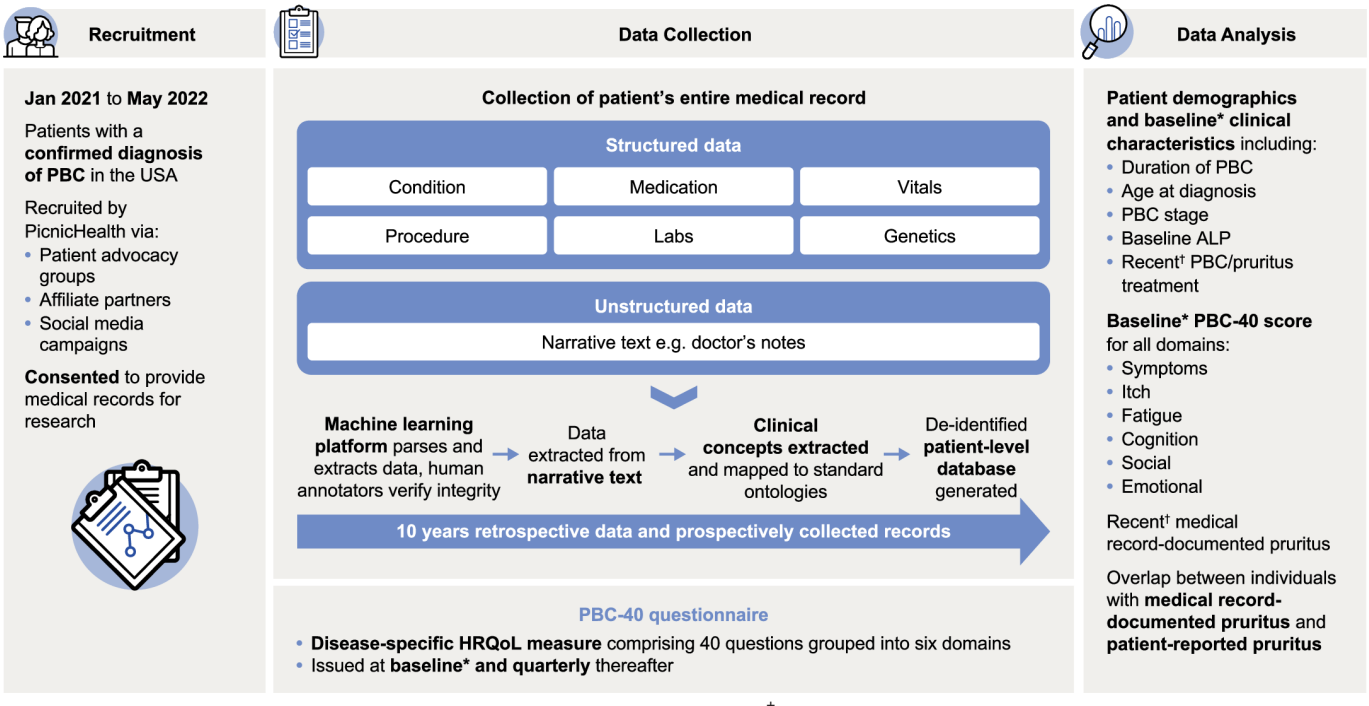

Figure 1 Study overview. *Baseline was defined as cohort enrolment. †On or within 12 months prior to baseline. ALP, alkaline phosphatase; HRQoL, health-related quality of life; PBC, primary biliary cholangitis.

authorisation, PicnicHealth contacted providers or facilities listed by the patient to collate all medical records on the patient's behalf. Medical records were received in any format used by the transmitting facility or provider, and natural language processing (NLP) and human-reviewed machine learning (ML) algorithms were used to abstract clinical data. All abstractions resulting from the NLP and ML models, as well as the surrounding context in the clinical notes, were reviewed by experienced human abstractors to ensure data relevancy and quality.[18 19] Records were mapped into a common data format, with clinical concepts mapped to standard medical ontologies (ie, common terminologies, vocabularies and coding schemes to facilitate data analysis). The abstracted data from the medical record included both structured data such as International Classification of Diseases (ICD)-9 or ICD-10 coded lists, medication lists and laboratory results, as well as unstructured narrative text, which was mapped to disease-specific variables and outcomes of interest (further details in online supplemental methods). An example of data that was only available through narrative data extraction included PBC Stage.[20] To facilitate the acquisition of all available patient medical records, obtained records were also examined for indications of additional visits or providers, and claims data were used to identify additional missing providers. Patients were provided access to their compiled medical reports.

Patient population

Individuals included in the study agreed to enrol in the PicnicHealth PBC cohort, were receiving medical care in the USA and had evidence of a physician-confirmed PBC diagnosis that was documented in their medical records. Individuals who never completed the itch domain of the PBC-40 were excluded from the analysis cohort.

Outcome measures

Patient demographics, PBC-related clinical measures, details of PBC diagnosis and treatment, and evidence of pruritus diagnosis and treatment were abstracted from medical records (further details in online supplemental methods). Medical record-defined pruritus was identified based on documentation of pruritus in either structured or unstructured data in medical records and was further defined as 'ever' (on, or at any point prior to, baseline) or 'recent' (on, or within 12 months prior to, baseline).

Patient-reported pruritus was derived from the itch domain of the PBC-40 instrument based on the first PBC-40 completed on or after baseline. The PBC-40 is a validated disease-specific HRQoL measure for PBC[21] which evaluates patients' experience with PBC over the previous 4 weeks.[22] The instrument comprises 40 questions, each scored on a scale of 0 or 1–5 (0: least impact and 5: greatest impact) and grouped into six domains (symptoms, itch, fatigue, cognition, social and emotional). Patient-reported pruritus was subclassified by severity according to patients' score in the itch domain (no itch: 0; any severity: ≥1; mild itch: 1–6 and clinically significant itch: ≥7).[6] Thresholds for clinical significance (and the minimum and maximum possible score) for each of the domains were as follows: itch: 7 (3–15), fatigue: 33 (11–55), cognitive: 18 (6–30), symptoms: 18 (6–35), social: 32 (8–50) and emotional: 12 (3–15).[11 22] In this study, the PBC-40 was issued to patients at baseline and quarterly thereafter. Completion was optional.

Statistical analysis

Descriptive statistics were used to characterise the patient population including cohort attrition; clinico-demographics (for the overall sample and stratified by medical record-documented and patient-reported pruritus); pruritus prevalence including the overlap between patient-reported and medical record-documented pruritus; and HRQoL across different pruritus groups.

For the descriptive statistics, continuous measures are presented as mean, SD, median and IQR; categorical data are presented as percentages. 95% CIs are presented for estimates of pruritus prevalence and for PBC-40 domain scores. The overlap of medical record and patient-reported pruritus (overall, mild, clinically significant) was assessed as the number and proportion of patients with medical record-documented pruritus that also self-reported having pruritus, and vice versa. All results are presented descriptively, without formal statistical comparisons.

RESULTS

Patient population

Overall, 250 patients were enrolled in the PicnicHealth PBC cohort, of whom 225 completed the itch domain of the PBC-40 at or following baseline and were included in the analysis cohort. Of the 225 patients included, 192 completed their PBC-40 survey on the date of enrolment, the remaining 33 patients completed the PBC-40 at a later date. For the overall population (n=225), the median (range) number of days between enrolment and PBC-40 completion was 0 (0, 246), and for the 33 patients who completed the PBC-40 after enrolment, it was 6 (1, 246). Patients in the analysis contributed a median (IQR) of 10.1 (6.2–13.9) years of retrospective medical record data prior to enrolment.

Baseline demographics and clinical characteristics are summarised in table 1. The majority of patients were female (97.8%, n=220), and the mean (SD) age at baseline was 55.4 (10.9) years (table 1). Recent ursodeoxycholic acid (UDCA) and obeticholic acid therapy was recorded for 87.1% (n=196) and 16.4% (n=37) of patients, respectively; 97.3% (n=219) of patients had received UDCA and 20.4% (n=46) had received obeticholic acid at any time prior to baseline (table 1). Recent treatment with fibrates was reported by 7.6% (n=17) patients and 8.4% (n=19) had received fibrates at any time prior to baseline (table 1). In total, 53.3% (n=120) of patients had received a recent prescription for medication defined in

Table 1 Clinico-demographic characteristics of the PicnicHealth PBC analysis cohort

Description	PBC (N=225)
Demographics	
Female, n (%)	220 (97.8)
Age at baseline, years, mean (SD)	55.4 (10.9)
Age at PBC diagnosis, years, mean (SD)	50.3 (10.4)
PBC duration at baseline, years, mean (SD)	5.1 (5.5)
Ethnicity	
Not Hispanic or Latino, n (%)	204 (90.7)
Hispanic or Latino, n (%)	16 (7.1)
Prefer not to say, n (%)	5 (2.2)
Disease status	
Cirrhosis, n (%)	66 (29.3)
ALP at baseline, IU/L, mean (SD)*	188.1 (141.0)
PBC Stage, n (%)	
Patients with available data	82 (36.4)
1†	30 (36.6)
2†	25 (30.5)
3†	15 (18.3)
4†	12 (14.6)
PBC treatments	
Recent use of UDCA, n (%)‡	196 (87.1)
Ever use of UDCA, n (%)§	219 (97.3)
Recent use of obeticholic acid, n (%)‡	37 (16.4)
Ever use of obeticholic acid, n (%)§	46 (20.4)
Recent use of fibrates, n (%)‡	17 (7.6)
Ever use of fibrates, n (%)§	19 (8.4)
Pruritus treatments‡¶	
Recent use of, n (%)	
Any antipruritic medication	120 (53.3)
Bile acid sequestrants	29 (12.9)
Sertraline	31 (13.8)
Rifampin	7 (3.1)
Naltrexone/naloxone	13 (5.8)
Antihistamines	96 (42.7)
Other medications potentially used for pruritus**	5 (2.2)

Baseline was defined as cohort enrolment.
*Closest to baseline but within 12 months.
†PBC Stage (1–4) percentages are calculated out of the subset of the cohort with available data (n=82); 143 patients of the total cohort (63.6%) were not included because they had missing data on PBC Stage.
‡On or within 12 months prior to baseline.
§Ever documented in the medical record.
¶Indication for use may or may not have been pruritus.
**Includes ondansetron, metronidazole or propofol. There is evidence that these medications may potentially function as antipruritics; however, they are not guideline-recommended therapies for pruritus as they have limited evidence of efficacy.[38]
ALP, alkaline phosphatase; PBC, primary biliary cholangitis; UDCA, ursodeoxycholic acid.

this study as a potential antipruritic; however, the indication for which the medications were taken was not always documented in medical records (table 1). Antihistamines were the most frequently prescribed antipruritic medication (42.7%, n=96), followed by sertraline (13.8%, n=31) and bile acid sequestrants (12.9%, n=29). PBC staging was available in the records of 82 (36.4%) patients; most of these patients (67.1%, n=55) had Stages 1–2 disease and 14.6% (n=12) had Stage 4 (advanced) disease (table 1).

Table 2 Patient-reported* and medical record-documented pruritus (recent†/ever)

Pruritus definition	No of patients	% (95% CI)
Medical record-documented pruritus		
No pruritus ever in medical record	67	29.8 (24.0 to 36.3)
Pruritus ever in medical record	158	70.2 (63.7 to 76.0)
No recent pruritus in medical record	137	60.9 (54.2 to 67.2)
Recent pruritus in medical record	88	39.1 (32.8 to 45.8)
Patient-reported pruritus		
No patient-reported pruritus	25	11.1 (7.5 to 16.1)
Any patient-reported pruritus	200	88.9 (83.9 to 92.5)
Mild patient-reported pruritus	80	35.6 (29.4 to 42.2)
Clinically significant patient-reported pruritus	120	53.3 (46.6 to 60.0)

Overall N=225.
*No patient-reported pruritus, defined as PBC-40 itch domain score 0; mild, defined as scores 1–6; clinically significant defined as score ≥7.
†Recorded on or within the 12-month period prior to baseline on patient medical record.
PBC, primary biliary cholangitis.

Pruritus prevalence in the PicnicHealth PBC cohort

Self-reported pruritus (of any severity) using the PBC-40 instrument was reported by 88.9% (n=200) of patients at baseline (table 2). Mild pruritus was reported by 35.6% (n=80) of patients and clinically significant pruritus was reported by 53.3% (n=120) of patients. Only 39.1% (n=88) of patients had recent pruritus documented in their medical record (table 2), while 70.2% (n=158) of patients had pruritus reported at any time in their medical record (table 2).

Overlap between patient-reported and medical record-documented pruritus

Of the 120 patients with clinically significant patient-reported pruritus, only 53.3% (n=64) had recent pruritus documented in their medical record (online supplemental table 1). Among patients without recent medical record-documented pruritus (n=137), 44.5% (n=61) had mild patient-reported pruritus, and 40.9% (n=56) had clinically significant patient-reported pruritus (figure 2; online supplemental table 2). Among patients with recent medical record-documented pruritus (n=88), 5.7% (n=5) had no patient-reported pruritus, 21.6% (n=19) had mild patient-reported pruritus and 72.7% (n=64) had clinically significant patient-reported pruritus (figure 2; online supplemental table 2).

Clinical characteristics and demographics in patients with patient-reported versus medical record-documented pruritus

In the PicnicHealth analysis cohort, mean (SD) baseline alkaline phosphatase (ALP) was higher for those with recent medical record-documented pruritus (221.9 (175.5) IU/L) and clinically significant patient-reported

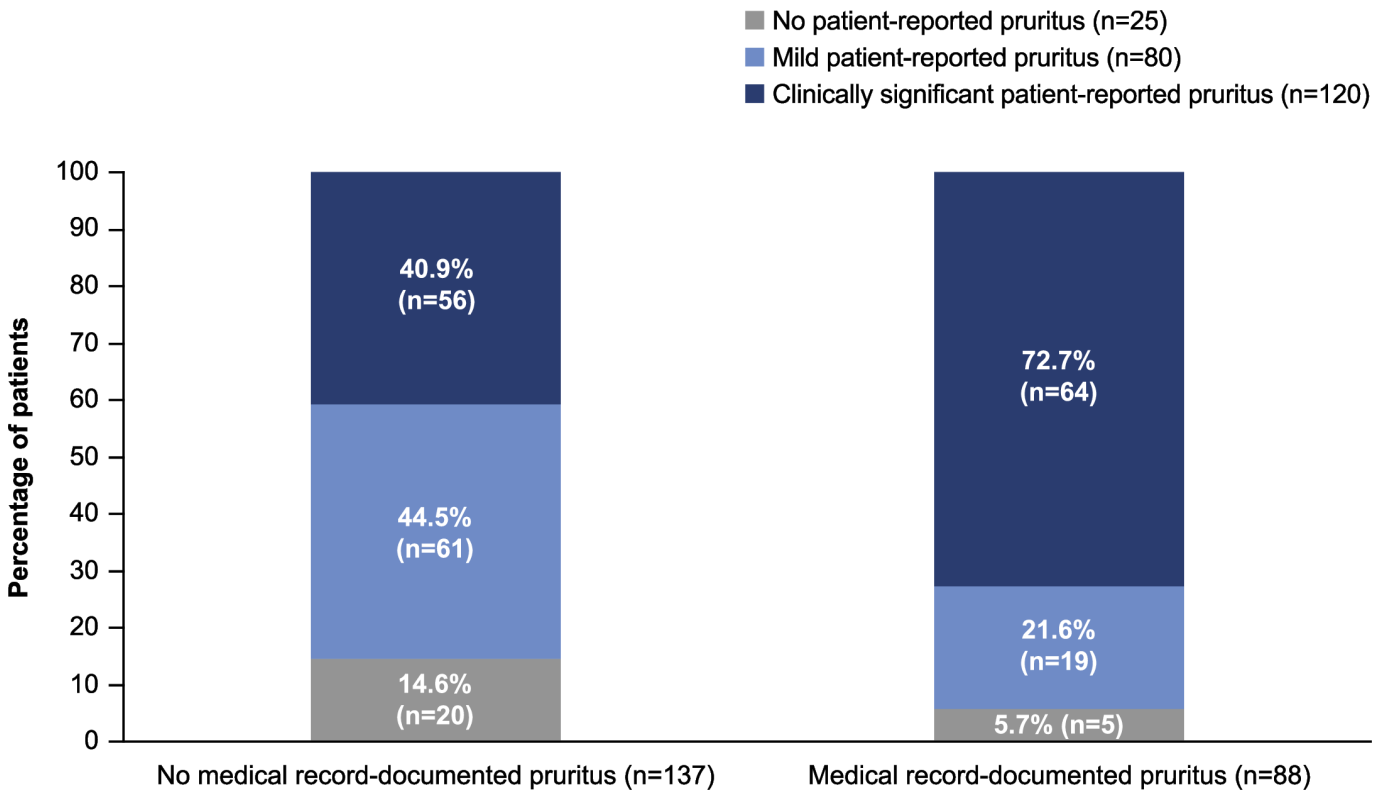

Figure 2 Percentage of patients with no, mild or clinically significant patient-reported itch* according to whether or not they had recent† pruritus documented in their medical record. *No patient-reported pruritus defined as PBC-40 itch domain score 0; mild, defined as score 1–6; clinically significant defined as score ≥7. †Recorded on or within the 12-month period prior to baseline. PBC, primary biliary cholangitis.

pruritus (212.5 (162.1) IU/L) than those with mild (158.6 (93.9) IU/L) or no (157.2 (129.5) IU/L) patient-reported pruritus (online supplemental table 3). Additionally, patients with recent medical record-documented pruritus (mean (SD); age 48.4 (10.5) years) and clinically significant patient-reported pruritus (48.1 (9.5) years) were slightly younger at PBC diagnosis than those with mild (52.2 (10.9) years) or no (54.7 (10.2) years) patient-reported pruritus (online supplemental table 3).

In the subset of patients with PBC staging data available (n=82; table 1), PBC Stages 1 and 2 were the most frequently recorded in patients across all the groups regardless of pruritus presence, documentation or severity (online supplemental table 3). Among those with staging data available, patients with clinically significant itch had the highest prevalence of Stage 4 disease contrasted with the other groups (23.9%, n=11/46; online supplemental table 3).

Recent use of UDCA was slightly higher in patients with recent medical record-documented pruritus (94.3% (83/88)) than in patients with patient-reported pruritus of any severity (87.0% (174/200); online supplemental table 3). Recent use of obeticholic acid was slightly higher in patients with recent medical record-documented pruritus (21.6% (19/88)) than in patients with no recent medical record-documented pruritus (13.1% (18/137)). Additionally, recent use of obeticholic acid was lower in patients with mild patient-reported pruritus (8.8% (7/80)) than in patients reporting clinically significant pruritus (22.5% (27/120)) or patients reporting no pruritus (12% (3/25); online supplemental table 3).

Most patients with recent pruritus documented in their medical records also had recent use of any medication that could be considered an antipruritic (77.3% (68/88); online supplemental table 3). For patient-reported pruritus, recent use of any antipruritic medication was documented for 67.5% (81/120) of patients reporting clinically significant pruritus, 40.0% (32/80) of patients reporting mild pruritus, 56.5% (113/200) of patients with any patient-reported pruritus and 28.0% (7/25) of patients reporting no pruritus. Antihistamines were the most commonly used treatment for all groups, though the indication may or may not have been for pruritus (online supplemental table 3).

HRQoL for different pruritus definition groups

Median (IQR) and mean (SD) PBC-40 domain scores from the first PBC-40 questionnaire completed at or following baseline for the analysis cohort are shown in (figure 3 and online supplemental table 4). Patients with clinically significant patient-reported pruritus appeared to have the highest (worst) mean (SD) domain scores versus all other groups (online supplemental table 4), and this trend was similarly reflected in the median (IQR) values (figure 3).

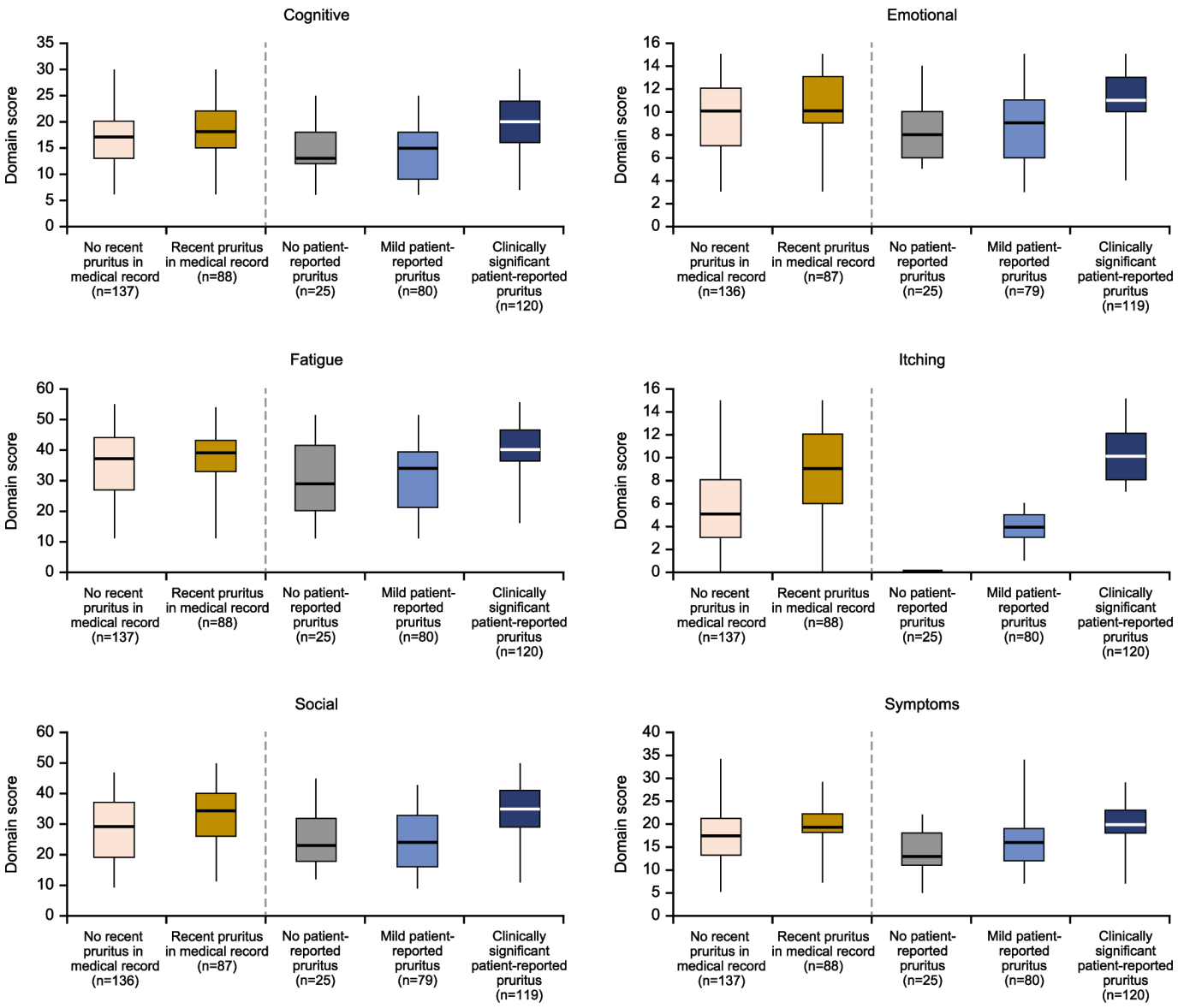

Figure 3 Median (IQR) PBC-40 domain scores on or after baseline* for the analysis cohort. Higher domain scores indicate poorer HRQoL. The black/white horizontal lines indicate the median values. The boxes represent the IQR (Q1–Q3). The error bars represent the recorded ranges for each domain. The minimum and maximum possible scores differ across domains (fatigue: 11–55, cognitive: 6–30, symptoms: 6–35, social: 8–50, itch: 3–15 and emotional: 3–15).[22] Patients were required to complete the itch domain of the PBC-40 for inclusion in the analysis; however, patients may have omitted some or all questions in another domain of the survey. Therefore, patient numbers do not reflect the whole cohort in certain domains. *Baseline was defined as cohort enrolment. HRQoL, health-related quality of life; PBC, primary biliary cholangitis.

DISCUSSION

The results of this study using data from the real-world PicnicHealth PBC cohort, which includes both patient-reported outcome data and medical record data curated through the combined use of NLP and ML with human review, have provided novel insights into the profile of patients with PBC and pruritus. The results show that pruritus is common but under-recorded in medical records compared with patient self-reported pruritus. The high percentage of patients reporting pruritus despite available antipruritic therapies suggests that itch appears to be undertreated or undermanaged as previously documented.[6 10 13] Furthermore, some patients with clinically significant pruritus received no recent treatment for pruritus. This is notable given the impact that itch has on HRQoL as seen in the broader literature[6 23] and as documented in our results, with patients reporting clinically significant pruritus appearing to have worse HRQoL as assessed by the PBC-40 relative to patients with mild or no self-reported itch. Finally, this study enabled characterisation of the clinico-demographics of patients with self-reported and medical record-documented pruritus to contextualise differences in patient populations across medical-recorded and self-reported pruritus definitions.

Our results revealed a discordance between patient-reported and medical record-documented pruritus, with nearly half of patients reporting clinically significant pruritus having no recent itch documented in

their medical record. This suggests that pruritus may be overlooked or under-recorded by physicians, which could be due to several factors. First, physicians may be unfamiliar with available guidelines for recognising and treating pruritus or they may be aware of the lack of clinical evidence supporting the use of the current guideline-recommended therapies,[24] which may mean that the condition is not screened for and/or treated by physicians as frequently as required.[10] Second, it is possible that the management of PBC in clinical practice is recorded in medical records, but associated conditions such as pruritus/itch are not.[15] Consistent with this, 53.3% of patients in this study had documentation of recent treatment with any medication that could be considered an antipruritic when only 39.1% of patients had medical record-documented pruritus in the same period. Finally, patients with severe pruritus may be more likely to interact with physicians and are thus more likely to have itch documented in their medical record.[15] However, 40.9% of patients without medical record-documented pruritus later reported clinically significant itch on the PBC-40, suggesting that itch may be under-recorded and undertreated when a patient is not directly queried about the level and severity of their pruritus.

Prior studies surveying patients with PBC have found that many patients do not recall having their pruritus evaluated or discussing itch with their providers.[13 17] Furthermore, in clinical practice, a physician's assessment of pruritus among patients with PBC often undercaptures the presence and severity versus patient self-report.[25] Although this disconnect can be mitigated through the use of simple and validated questionnaires to objectively evaluate pruritus (eg, numerical rating scale, Visual Analogue Scale, 5-D itch, PBC-40),[26] these measures are not used consistently by physicians, resulting in the undermonitoring and suboptimal treatment of many patients.[13] Conversely, if patient pruritus were to be more routinely measured and documented by providers with objective assessments, both the patient and physician would benefit from the enhanced evaluation of the presence of pruritus, the impact of pruritus on the patient's health and HRQoL, helping to evaluate the efficacy of any treatments that the patient receives.[26 27]

In total, 67.5% of patients with clinically significant patient-reported pruritus had received recent treatment with any antipruritic medication. This is somewhat higher than the proportion of patients (50.8%) with clinically significant pruritus who were currently receiving treatment for itch in the TARGET-PBC population, a longitudinal observational cohort of patients with PBC from the USA.[6] Together, the results from the current study and TARGET-PBC suggest that current antipruritic therapies may not be sufficient to manage pruritus given that many treated patients still had clinically significant itch (versus mild or no itch). Prior research has found that pruritus in PBC is often difficult to treat: patients need to experiment with different treatments to gain respite as no single drug or therapy exists which effectively eliminates itch.[13 28 29] In clinical practice and in clinical trials, it is common to see low numbers of patients responding to the guideline-suggested drugs for pruritus including cholestyramine, rifampicin, naltrexone and sertraline.[24 30] While there is evidence supporting the use of fibrates for PBC and pruritus,[31–33] the European Association for the Study of the Liver (EASL) 2017 guidelines did not recommend their use as data from phase 3 clinical trials were not published at the time of its release.[4] In the 2021 update to the American Association for the Study of Liver Diseases (AASLD) practice guidance, it was indicated that fibrates could be considered as an off-label treatment for patients with PBC; but it did not recommend fibrates for pruritus treatment.[34] However, many patients with PBC and pruritus do not receive any treatment for itch. In the current study, 32.5% of patients with clinically significant itch did not receive any medications for itch in the year preceding cohort enrolment. Similarly, in the TARGET-PBC cohort, 49.2% of patients with clinically significant itch were not receiving current antipruritic medications, and one-third had never received any medications for pruritus.[6] Additionally, although nearly all patients reported recent or ever use of therapies for PBC, currently approved medications are ineffective in relieving pruritus, in some cases can exacerbate itch,[8 14 26 35 36] and have been associated with poor tolerability and adverse events.[14] Here, we noted that recent use of obeticholic acid was higher in patients reporting clinically significant pruritus (22.5%) versus mild pruritus (8.8%) and was higher in patients with recent medical record-documented pruritus (21.6%) than in patients without recent pruritus documented (13.1%). Given that pruritus is the most common side effect linked with obeticholic acid treatment,[7] it is possible that this therapy is exacerbating pruritus in these patients.

In the current study, the PBC-40 mean domain scores appeared highest for patients self-reporting clinically significant pruritus relative to patients with mild or no pruritus. These results align with similar analyses conducted in the TARGET-PBC cohort, which found that clinically significant pruritus was associated with impaired HRQoL across fatigue, social, emotional and cognitive domains compared with patients with mild or no pruritus.[6] Across both cohorts, the association between pruritus severity and HRQoL impact was present despite the receipt of real-world standard-of-care for both PBC and pruritus.

Overall, the clinico-demographic profile of the PicnicHealth PBC cohort appeared broadly consistent with the expected profile of patients with PBC. The prevalence of any patient-reported pruritus appeared to be somewhat higher than other published studies (55%–81%),[6 8–10] with 88.9% of patients in the current study reporting itch of any severity at baseline. Additionally, there was a slightly higher proportion of female participants (97.8%), though prior studies have documented that PBC is up to nine times more common in women.[2] Within the PicnicHealth cohort and across

levels of pruritus severity, patients reporting clinically significant pruritus appeared to have higher baseline ALP levels and a higher percentage of patients with Stage 4 disease than patients reporting mild or no pruritus. These trends also appeared to be present when contrasting patients with recent pruritus documented in the medical record versus patients with no recent medical record diagnosis. Although these findings appear to be consistent with results from the TARGET-PBC cohort and the UK-PBC cohort (a longitudinal study recruiting patients with PBC across the UK) documenting similar trends in higher ALP levels and more advanced disease among patients with clinically significant pruritus versus mild or no pruritus, substantial uncertainty remains.[6 10] Prior studies have not documented a consistent clinico-demographic profile to accurately identify which patients with PBC are most at risk of developing pruritus (eg, based on biochemical liver tests, disease stage, disease duration).[6 13 26 37] The uncertainty about which patients are most at risk highlights the importance of using validated and objective tools to directly ask all patients with PBC about the presence and severity of pruritus.

This study provided a novel opportunity to evaluate the clinico-demographic characteristics, HRQoL and extent to which pruritus may be under-recorded in medical records versus patient self-report in a real-world setting by leveraging patient-reported outcomes data linked to patient medical records data (including a median of 10.1 years of structured and unstructured data available in the baseline period). Nevertheless, there are several limitations to be considered when interpreting the results. Patients who enrolled in PicnicHealth may have more complex or severe disease than other patients with PBC, as well as be more engaged in with research, social media, or be involved in patient advocacy groups. Second, the PBC-40 has a limited recall period (4 weeks) versus the 1-year period prior to enrolment used to assess recent medical record documentation of pruritus in the current study. The different length of the periods to define pruritus could have affected results, though this was likely mitigated by the chronicity and stability of pruritus over time, as documented in prior studies.[10] Third, our list of antipruritic medications did not include fibrates,[32] which were only captured as PBC treatment in the current study but are used by some clinicians to treat itch. However, these medications were not frequently used in this analytic cohort, and clearly distinguishing fibrate use for refractory PBC versus pruritus management was not feasible in this study. Fourth, given that the majority of medications recommended to manage pruritus in the USA are used off-label,[30] it is difficult to reliably conclude that the recent antipruritic treatments documented were used for itch, which could lead to overestimating the number of patients recently receiving antipruritic therapy. Finally, the study population only included patients in the United States, which may limit generalisability of the results to other countries.

In conclusion, this study combining patient-reported outcomes data and medical record data found that nearly 50% of patients who self-reported pruritus did not have itch documented in their medical records. This indicates that pruritus is likely under-recorded in patients' medical records as described in previous studies.[15] Although the majority of patients with medical record-documented pruritus reported clinically significant itch, there were also a substantial number of patients without medical record-documented pruritus with clinically significant itch in the PicnicHealth PBC cohort. As pruritus is common,[6–8 10] not well-recorded in the medical record of patients with PBC,[15] and there is no clear patient profile to identify who is most at risk, this raises awareness about the need for routine screening using validated and objective assessments to measure the severity and impact of pruritus. Additionally, the impact of pruritus severity on multiple aspects of physical and social well-being despite use of standard-of-care therapies highlights the need for new treatment options for this debilitating condition.

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Contributors Study design and data analysis were conducted by GSK. PicnicHealth provided scientific input and consultation services, and were responsible for patient recruitment, data acquisition, extraction and curation for analysis. UG is responsible for the overall manuscript content. UG, HTS, RvM, JL, JF-B and LM were involved in study conception/design, data analysis and data interpretation. DP was involved in data analysis and data interpretation. AM and JNH were involved in data interpretation. CLR and MT were involved in data acquisition. HSF was involved in data acquisition and analysis. All authors took responsibility for the content of the manuscript and for the decision to publish; all authors reviewed and approved the final manuscript.

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REFERENCES

1 Lu M, Zhou Y, Haller IV, *et al*. Increasing prevalence of primary biliary cholangitis and reduced mortality with treatment. *Clin Gastroenterol Hepatol* 2018;16:1342–50.
2 Smyk DS, Rigopoulou EI, Pares A, *et al*. Sex differences associated with primary biliary cirrhosis. *Clin Dev Immunol* 2012;2012:610504.
3 Lv T, Chen S, Li M, *et al*. Regional variation and temporal trend of primary biliary cholangitis epidemiology: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2021;36:1423–34.
4 Hirschfield GM, Beuers U, Corpechot C, *et al*. European Association for the study of the liver. EASL clinical practice guidelines: the diagnosis and management of patients with primary biliary cholangitis. *J Hepatol* 2017;67:145–72.
5 Engel B, Taubert R, Jaeckel E, *et al*. The future of autoimmune liver diseases - understanding pathogenesis and improving morbidity and mortality. *Liver Int* 2020:149–53.
6 Mayo MJ, Carey E, Smith HT, *et al*. Impact of pruritus on quality of life and current treatment patterns in patients with primary biliary cholangitis. *Dig Dis Sci* 2023;68:995–1005.
7 Pate J, Gutierrez JA, Frenette CT, *et al*. Practical strategies for pruritus management in the obeticholic acid-treated patient with PBC: proceedings from the 2018 expert panel. *BMJ Open Gastroenterol* 2019;6:e000256.
8 Talwalkar JA, Souto E, Jorgensen RA, *et al*. Natural history of pruritus in primary biliary cirrhosis. *Clin Gastroenterol Hepatol* 2003;1:297–302.
9 de Veer RC, van Hooff MC, da Silva G, *et al*. Quality of life in Dutch patients with primary biliary cholangitis: discrepancies between patients' perspectives and objective disease parameters. *Hepatol Res* 2023;53:401–8.
10 Hegade VS, Mells GF, Fisher H, *et al*. Pruritus is common and undertreated in patients with primary biliary cholangitis in the United Kingdom. *Clin Gastroenterol Hepatol* 2019;17:1379–87.
11 Mells GF, Pells G, Newton JL, *et al*. Impact of primary biliary cirrhosis on perceived quality of life: the UK-PBC national study. *Hepatology* 2013;58:273–83.
12 Montagnese S, Nsemi LM, Cazzagon N, *et al*. Sleep-wake profiles in patients with primary biliary cirrhosis. *Liver Int* 2013;33:203–9.
13 Rishe E, Azarm A, Bergasa NV. Itch in primary biliary cirrhosis: a patients' perspective. *Acta Derm Venereol* 2008;88:34–7.
14 Tajiri K, Shimizu Y. Recent advances in the management of pruritus in chronic liver diseases. *World J Gastroenterol* 2017;23:3418–26.
15 Gungabissoon U, Gibbons DC, Requena G, *et al*. Disease burden of primary biliary cholangitis and associated pruritus based on a cross-sectional US claims analysis. *BMJ Open Gastroenterol* 2022;9:e000857.
16 Schneeweiss S, Avorn J. A review of uses of health care utilization databases for epidemiologic research on therapeutics. *J Clin Epidemiol* 2005;58:323–37.
17 Leighton J, Thain C, Mitchell-Thain R, *et al*. Patient ownership of primary biliary cholangitis long-term management. *Frontline Gastroenterol* 2021;12:370–3.
18 Hanson G, Chitnis T, Williams MJ, *et al*. Generating real-world data from health records: design of a patient-centric study in multiple sclerosis using a commercial health records platform. *JAMIA Open* 2022;5:ooab110.
19 PicnicHealth. How Picnichealth generates real-world data from medical records [white paper]. 2021. Available: https://assets-global.website-files.com/6074d822c3c38b07ef63efe56074d822c3c38b07ef63efe56074d822c3c38b07ef63efe56074d822c3c38b07ef63efe5/609d684878e516dd99c3a4ae609d684878e516dd99c3a4ae609d684878e516dd99c3a4ae609d684878e516dd99c3a4ae_How%20PH%20Generates%20RWD%20from%20Medical%20Records-compressed.pdf
20 Onofrio FQ, Hirschfield GM, Gulamhusein AF. A practical review of primary biliary cholangitis for the gastroenterologist. *Gastroenterol Hepatol (N Y)* 2019;15:145–54.
21 Jacoby A, Rannard A, Buck D, *et al*. Development, validation, and evaluation of the PBC-40, a disease specific health related quality of life measure for primary biliary cirrhosis. *Gut* 2005;54:1622–9.
22 UK-PBC. Coded PBC-40, Available: https://www.uk-pbc.com/wp-content/uploads/2015/12/coded-PBC-40.pdf [Accessed 23 Jun 2023].
23 Jin XY, Khan TM. Quality of life among patients suffering from cholestatic liver disease-induced pruritus: A systematic review. *J Formos Med Assoc* 2016;115:689–702.
24 Levy C. Management of pruritus in patients with cholestatic liver disease. *Gastroenterol Hepatol (N Y)* 2011;7:615–7.
25 Carey EJL, Mayo MJ, Bowlus CL. Patient-reported indicators of health and symptoms in US patients with primary biliary cholangitis (PBC). *AASLD* 2018.
26 Hegade VS, Bolier R, Oude Elferink RP, *et al*. A systematic approach to the management of cholestatic pruritus in primary biliary cirrhosis. *Frontline Gastroenterol* 2016;7:158–66.
27 Hirschfield GM, Dyson JK, Alexander GJM, *et al*. The British Society of Gastroenterology/UK-PBC primary biliary cholangitis treatment and management guidelines. *Gut* 2018;67:1568–94.
28 Lindor KD, Bowlus CL, Boyer J, *et al*. Primary biliary cholangitis: 2018 practice guidance from the American Association for the Study of Liver Diseases. *Hepatology* 2019;69:394–419.
29 You H, Ma X, Efe C, *et al*. APASL clinical practice guidance: the diagnosis and management of patients with primary biliary cholangitis. *Hepatol Int* 2022;16:1–23.
30 Smith HT, de Souza AR, Thompson AH, *et al*. Cholestatic pruritus treatments in primary biliary cholangitis and primary sclerosing cholangitis: a systematic literature review. *Dig Dis Sci* 2023;68:2710–30.
31 Corpechot C, Chazouillères O, Rousseau A, *et al*. A placebo-controlled trial of bezafibrate in primary biliary cholangitis. *N Engl J Med* 2018;378:2171–81.
32 de Vries E, Bolier R, Goet J, *et al*. Fibrates for itch (FITCH) in Fibrosing Cholangiopathies: A double-blind, randomized, placebo-controlled trial. *Gastroenterology* 2021;160:734–43.
33 Dyson JK, Jeffreys Jones DE. Bezafibrate for the treatment of cholestatic pruritus: time for a change in management. *Gastroenterology* 2021;160:649–51.
34 Lindor KD, Bowlus CL, Boyer J, *et al*. Primary biliary cholangitis: 2021 practice guidance update from the American Association for the Study of Liver Diseases. *Hepatology* 2022;75:1012–3.
35 Trivedi HD, Lizaola B, Tapper EB, *et al*. Management of pruritus in primary biliary cholangitis: a narrative review. *Am J Med* 2017;130:744.
36 Nevens F, Andreone P, Mazzella G, *et al*. A placebo-controlled trial of obeticholic acid in primary biliary cholangitis. *N Engl J Med* 2016;375:631–43.
37 Düll MM, Kremer AE. Evaluation and management of pruritus in primary biliary cholangitis. *Clin Liver Dis* 2022;26:727–45.
38 Bergasa NV. Pruritus of cholestasis. In: Carstens E, Akiyama T, eds. *Itch: Mechanisms and Treatment. Boca Raton (FL): CRC Press/Taylor & Francis*. 2014.