# PBC-10: A short quality of life measure for clinical screening in primary biliary cholangitis.

**Short title: PBC-10**

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**Abbreviations:**

HRQL, health related quality of life; PBC, Primary Biliary cholangitis; EQ5D, European Quality of Life Five Dimensions; VAS, Visual Analogue Scale; CVI, content validity index; MIC, minimal important change; SRM, standardised response mean; SEM, standard error of measurement ; SDC, smallest detectable change; ICC, intra-class correlation coefficient;

**Abstract**

Background: Current guidelines in Primary Biliary Cholangitis ( PBC) recommend routine screening for symptoms in PBC. However, at present there are no validated practical tools suitable for screening use in practice.

Aim: The purpose of this study was to develop a short quality of life questionnaire for in PBC.

Methods: The short PBC HRQL questionnaire was derived and validated by analysing the PBC-40 questionnaires from the UK-PBC Research Cohort. Construct validity was assessed using European Quality of Life Five Dimensions (EQ5D) questionnaire. Test-retest analysis was done by asking a subgroup of patients to complete the questionnaire twice within 2-4 weeks.

Results: A total of 2219 patients completed PBC-40 questionnaire in 2013. Stepwise regression identified 10 questions that contributed to more than 95% of the PBC-40 score variance and covered the main domains of PBC. The short HRQL questionnaire, PBC-10, had good internal consistency (Cronbach's α 0.905) and item-total correlations. PBC-10 demonstrated no ceiling effects but a floor effect was noted. Further validation on 2502 patients who completed the PBC questionnaire in 2017 confirmed the psychometric properties of PBC-10. Further analysis on 186 patients showed that PBC-10 demonstrated good internal consistency (Cronbach's α = 0.936), had good reproducibility (intraclass correlation coefficient = 0.945), good correlation with the EQ5D (r = 0.736), and was responsive to change. A change of 4 points in the PBC-10 score would be considered clinically important.

Conclusion: PBC-10 is a short and valid questionnaire for assessing the HRQL in patients with PBC in clinical practice.

**Key words:** Health related quality of life; Primary Biliary Cholangitis; Patient reported outcome measures; quality of life

**Introduction:**

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease. An often asymptomatic early phase is typically followed by the progressive development of disease-related symptoms which can have a significant impact on life quality [1, 2]. Typical PBC-related symptoms include fatigue, pruritus, dry eyes and mouth, and occasional abdominal and bone pain [3, 4]. Fatigue can be profound and persistent, and is typically unrelated to histological stage or activity of the disease [5-7].

Recent years have seen significant evolution in the treatment of PBC. Furthermore, the importance of health-related quality of life (HRQoL) [8] is widely appreciated, and approaches to the management of the symptoms contributing to HRQoL, most notably pruritus, continues to improve. HRQoL provides insights into how patients perceive their own disease processes, which understandably may be different from the way they are perceived by clinicians. Considering the importance of symptoms and their impact on the quality of life of patients all current guidelines, including those from the British Society of Gastroenterology [1] and the European Association for the Study of the Liver [9], recommend routine screening for the presence of symptoms in PBC. None of these guidelines, however, suggest how such screening should be achieved in practice, and at present there are no validated tools suitable for screening use in practice.

In contrast to the low level of routine assessment in clinical practice, research assessment of symptoms and HRQoL in PBC has been extensive. Much of this research has been undertaken using the PBC-40 [3], a patient derived disease specific HRQoL measure validated for self-completion by PBC patients. Although PBC-40 is a valuable research tool (including as a patient reported outcome measure in trials of new therapies) it is too lengthy and time consuming to use in normal clinical practice. Given the importance of symptoms and HRQoL in PBC, the emergence of new treatments which can target these symptoms[10-12], and the guideline recommendation that clinicians screen for PBC symptoms on an annual basis there is a pressing need for a valid, short and practical symptom screening tool that is suitable for routine use in patients with PBC at the point of care.

The purpose of this study was to use rigorous statistical methods to develop and validate a short version of the PBC-40 quality of life questionnaire for clinical use. The short version would address the clinical need for a rigorously developed, valid, simple and short measure, that can be easily completed by patients in routine clinical practice.

**Methodology:**

***Study Design:***

***Phase 1: Shortening the PBC-40:***

This phase was completed by analysing the PBC-40 questionnaire data from the UK PBC registry obtained in 2013. PBC-40 questionnaire reduction was done using stepwise regression analysis of the total scores on the individual items [13,14, 15]. We selected the items that represented most of the variation in the PBC-40 scores that covered the main domains in PBC related quality of life [3]. To explore the underlying domains/themes, we used Principal Components analysis (PCA) on the PBC-40 questions, using the approach of varimax rotation to simplify the analysis of the principal factors [16,17].

Internal consistency (as assessed using Cronbach α) of the short questionnaire was determined acceptable if it was between 0.7 and 0.9. In addition to the main PBC-40 questions, patients were asked to rate their general health on a 5-point scale from poor to excellent to assess the construct validity of the short PBC QoL measure.

We assessed the correlation of each item with the total score as a measure of internal reliability. It has been proposed that the accepted range is between 0.2 to 0.8 [20]. Maximum response rate should be between 20-80%. Items with lower or higher values were considered as candidates for exclusion because they added little value to the health outcome measure [20, 21].

We examined the distribution of the patients' scores for flooring and ceiling effect looking at the central tendency of the values, using mean, median as well as standard deviation and range. If there were no ceiling or floor effects, the data distribution should be in a normal or bell shape pattern. Skewness of the data was also examined. We took a skewness value of -1 to +1 as acceptable [22]. If more than 15% of patients score the lowest or highest possible score, respectively, we would consider that the short version of PBC QoL would have floor or ceiling effects respectively [22].

We assessed the face and content validity of the proposed short version of PBC QoL. We consulted eight experts in the field to judge face and content validity. We used the content validity index proposed by Lynn in 1986 [23]. It includes a two-step method for determining content validity by calculating a content validity index (CVI). When there are six or more panellists, the CVI is advisable to be higher than 0.78. We also computed the CVI of the items and the CVI of the overall scale [24]. The CVI of the overall measure is the proportion of items on an instrument that achieved a rating of 3 or 4. A CVI of 0.70 represents average agreement; 0.80, adequate agreement; and 0.90, good agreement [16].

***Phase 2: Validation of the short version of PBC QoL:***

In order to confirm the validity of the short version of PBC-QoL, we analysed the psychometric properties of the short version of PBC questionnaire using the data collected from the PBC database of patients who returned the PBC-40 questionnaire in 2017. We confirmed the psychometric properties of the short version of the PBC-QoL; item-total correlation, items response rate, ceiling and flooring effect, and Cronbach α reliability.

***Phase 3: Further evaluation of the short version of PBC QoL***

To check the psychometric characteristics of the short version of PBC questionnaire, a convenience group of patients with PBC were asked to complete the PBC-10 questionnaire on two occasions, 2-4 weeks apart by post. Participants were first identified from the previously completed PBC-40 questionnaires. The participants were selected randomly. In addition to the quality of life questions, patients were asked to report information of treatments.

The retest questionnaire , which was sent 2-4 weeks after the first set, included a 5-point transition question asking participants whether their general health had improved slightly, much improved, got worse slightly, got much worse, or remained the same since completing the first questionnaire. The principal aim of the validation phase of the study was to evaluate the final psychometric properties of the measure against established criteria. We examined the following psychometric properties of the short PBC QoL [20, 25]:

1. We assessed construct validity by calculating Pearson's correlation coefficient (r) against the EQ5D generic QoL. An appropriate correlation coefficient for construct validity should be somewhere between 0.4 and 0.8.
2. We assessed the test-retest reliability including those patients who reported no change in their condition. An intra-class correlation (ICC) between the first and second completion of the PBC should exceed 0.75 for good reproducibility.
3. We assessed the responsiveness statistics of the short PBC QoL in those patients who reported a change in their health status (got worse or improved) at the time of the 1-month follow up questionnaire. We calculated three responsiveness statistics, which were: effect size, standardised response mean (SRM) and the responsiveness ratio. The acceptable value for responsiveness ratio is 0.5 or 50%. The effect size and SRM cut-offs were defined as: 0.2–<0.5, small; 0.5–<0.8, medium; ≥0.8, large [20,26].
4. We calculated the minimal important change (MIC), which is the minimum change in the PBC-10 score that is perceived significant by patients, to aid interpretation of the

short PBC QoL [27]. It is recommended that the patient's perspective is used to measure the MIC [28]. MIC is defined as the mean change of the scores of patients who had improved or got worse “slightly” on the retest questionnaire.

**Results:**

***Phase 1: Shortening the PBC-40:***

We analysed the dataset of 2219 patients who completed PBC-40 in 2013 to derive the short PBC-QoL (Table 1). Regressing the total PBC-40 questions on the total score identified 10 questions (Appendix 1) that contributed more than 95% of the variance and covered the main domains of PBC-40. These questions were therefore chosen for the short form of PBC-QoL measure (henceforth referred to as PBC-10) (Table 2).

Items in the PBC-10 had good internal consistency (Cronbach's α 0.905) and item-total correlations between 0.2-0.8. PBC-10 demonstrated a good correlation with the general health question (Pearson correlation co-efficient 0.558) and, unsurprisingly, with PBC-40 ($r$=0.978).

Using the 15% recommended value for the percentage of patients who score the highest or the lowest [22], the PBC-10 demonstrated no ceiling effects, apart from questions 8 which had a small ceiling effect of 16.6% (Table 3). Skewness values of all 10 items were acceptable and ranged between 0-1. However, a floor effect was noted in all 10 questions (Table 3). The content validity index (CVI) of the PBC-10 of the whole index was 1.00, which is good. Individual CVI ranged between 0.5 -1.0.

**Principal component analysis (PCA):**

The Kaiser-Meyer-Olkin measure of sampling adequacy (KMO=0.0.908) and Bartlett’s test of sphericity ($p<0.001$) confirmed that the sample was good enough for PCA. Attribution of the 10 items of PBC-10 to their factors showed that the items covered all 6 quality of life domains identified in the PBC-40 previously which provided good representation of all different QoL aspects of patients with PBC (Table 4).

Scoring of PBC-10: Responses were scores on a Likert scale from 1-5 . The resulting PBC-10 score sums up all the 10 questions scores to yield the total score; the range of scores can be from 10 to 50; the higher the score the worse the quality of life.

***Phase 2: Validation of the short version of PBC QoL:***

We carried out further validation of the PBC-10 on the second cohort of 2502 patients with PBC who completed the PBC-40 in 2017 (2251 (90%) females , 251 (10%) males). Mean age was 66 years (SD10)). Results showed that PBC-10 had good internal consistency (Cronbach's α was 0.915). Psychometric analysis showed good item-total correlations and maximum response rate within the recommended range (Table 5). There were no ceiling effects but a floor effect was obvious, as discussed above. Skewness value remained within the acceptable range of -1 to +1 [22].

***Phase 3: Further evaluation of the short version of PBC QoL***

A total of 186 patients completed the PBC-10 questionnaires (169 (91%) females,17 (9.1%) males). Mean age was 71 years (SD10.86)). Medications use was reported in 169 patients; 165 patients were taking Ursodeoxycholic acid, one patient was taking Ursodeoxycholic acid and obeticholic acid and 2 patients were taking Ursodeoxycholic acid and fibrate and one patient reported taking only fibrate. For the test-retest study, 172 (93%) returned the re-test questionnaires within 2-4 weeks. A total of 118 (69%) patients reported no change and their data were used to examine the test-retest reliability. A total of 54 (31%) patients reported a change and were included in the responsiveness analysis.

The results showed that PBC-10 correlated well with the EQ5D ($r = 0.736$ $p < 0.005$). Internal consistency was excellent with Cronbach α of 0.936. Intra-class correlation of the test-retest questionnaires was excellent (ICC = 0.945 $p < 0.005$). Responsiveness statistics showed responsiveness ratio of 0.38, effect size of 0.39 and standardised response mean of 1.25.

With regards to the interpretability of PBC-10, the minimal important change was 3.539 which, when rounded up, means that a change of 4 points in the PBC-10 score would be considered clinically important.

## DISCUSSION

In this study we developed and validated a brief quality of life measure for patients with PBC, the PBC-10, suitable for use as a screening and monitoring tool in routine clinical practice.

The PBC-10 was derived from the original PBC-40 questionnaire [3] using the extensive UK-PBC Research Cohort and a stepwise regression analysis technique to select the smallest number of items that represent the majority of the PBC-40 scores. The ten items of the PBC-10 covered all domains of the PBC-40 and explained more than 95% of the variance of the questionnaire scores collected from 2219 patients with PBC. The potential drawback of

shortening any questionnaire is the possibility of compromising its psychometric properties of validity and reliability. However, the PBC-10 demonstrated a high degree of validity and reliability on subsequent analysis of the dataset collected from 2502 patients with PBC. It had a good Cronbach α, well above the threshold of 0.7 recommended in the literature [20].PBC-10 items correlated very well with the total score with item-total correlations ranging between the recommended 0.2-0.8. The content and face validity of PBC-10 was confirmed by consultation with hepatology experts in PBC. Principal Component Analysis showed that PBC-10 items correlated very well with all the six PBC specific quality of life domains (symptoms, itch, fatigue, cognition, social, and emotional) which provides good representation of all different QoL aspects of patients with PBC. Scoring of PBC-10 is very simple to compute. We gave all questions equal weighting, to keep the calculation simple and based on the assumption that each domain of QoL is equally important to the individual responding [29].

In further evaluation, PBC-10 correlated very well with other generic measures of the quality of life (EQ5D and general health questions we used in the study). PBC-10 had good test-re-test reliability with an ICC values 0.945. Responsiveness analysis showed that the PBC-10 had small to moderate responsiveness values. Only 54 (31%) patients reported a change in their general health in 2-4 weeks and were included in the responsiveness analysis. The small proportion of patients who reported change may have impacted on the evaluation of the responsiveness assessment. A change of 4 points or more in the total PBC-10 score would be considered as the minimal important change ( MIC) which is 10% of the possible range of PBC-10 scores ( 10-50). MIC score change was noted in 18 (10%) in the re-test questionnaires. Due to the small proportion of patients who reported a change, the responsiveness and MIC properties of PBC-10 will need further validation in a large cohort of patients.

Although we have not asked the patients about the time needed to complete the PBC-10, we believe it will take less time to complete it is significantly shorter than the PBC-40 and consists of only 10 questions. More importantly, the interpretation by the clinician takes less time and it is therefore much “nimbler” for everyday use. Scoring the PBC-40 can be quite complex unless he clinicians are familiar with it (domains are mixed up and some questions are scored in reverse. For this, as well as the patient reasons, PBC-40 is not currently used in routine clinical practice. Hence the issue. A brief score that is used is always more valuable than a detailed score if that detailed score is complex to use.

When the original PBC-40 questionnaire was developed [3], there were no ceiling effects but there was a noticeable floor effect in the itch domain (36.7%) in PBC-40, which is again because most patients with PBC will have stable disease and are managed in the community.

Another possible reason for the floor effect in PBC quality of life questionnaires is the penetrance of pruritus being incomplete. A recent paper showed that about a third of PBC patients have no itch at all at any point in their disease [30].

There was no evaluation of the responsiveness in the original study that developed PBC-40 questionnaire [3]. Responsiveness can only be properly assessed when there is a significant change in the disease progression. PBC is a chronic illness and the majority of symptoms in PBC do not respond quickly to any current treatment [31,32] and therefore responsiveness is a challenge to assess (the lack of such treatments was a actually a main driver for measurement tools that would help us develop future treatments. Current treatments, except liver transplantation [33,34], will not results in a significant quick change in disease outcome within a short period to allow quantifying the responsiveness of the PBC-10. However, validation is an ongoing process and it is imperative to be able to test and further develop PBC-10 in future studies to establish PBC-10 responsiveness and MIC (Minimal important change).

We propose the use of PBC-10 as a quick screening tool for symptoms as well as assess response to treatment in patients with PBC. We recommend using PBC-10 in routine clinical setting as a quick symptoms screening questionnaire as well as research or clinical trials to screen for symptoms, as recommended by the international societies [1, 9]. The measure was developed using rigorous statistical and methodological approach using currently recommended guidelines [22] in a large patient cohort. In chronic conditions such as PBC, it is important to measure treatment in terms of impact on quality of life not just survival [35]. Having good face and content validity will encourage patients and clinicians' engagement to use the PBC-10 questionnaire. Items that are seen irrelevant may cause respondents to not take them seriously or decline to answer.

PBC-10 did not have a significant ceiling effect which means it has good ability to measure QoL in patients with severe symptoms. However, flooring effects were observed with PBC-10. This could have happened because the majority of patient in the study were managed in the outpatient setting with stable and less severe symptoms. Stepwise regression analysis showed that the questions beyond question number 8 had minimal contribution to the total score but significant floor effect. However, as they are clinically very relevant, they were included in PBC-10. Additional studies are needed to further examine the flooring and ceiling effects of PBC-10 in other setting such as following a therapeutic intervention.

There is no published rule defining the number of patients required to validate a QoL measure. However, a ratio of 5 or 10 patients per item has been suggested [16]. Recent studies suggest

that a minimum of 100 patients is sufficient for a proper validation study [22]. Therefore, the sample size used for the current study more than fulfils the guidance for developing and shortening a QoL measure. Further studies will be needed to confirm the psychometric properties of the PBC10 in different samples of patients, including in other cultural groups and settings.

The focus of this study was to develop and psychometrically validate a short tool to measure the quality of life in patients with PBC. Therefore, the questionnaires that were completed by the UK-PBC cohort group in 2013 and again in 2017 did not include specific questions about treatment. As new treatment options are emerging in PBC, more validation studies will be needed to assess the QoL of patients using different treatments.

Fatigue and cognitive symptoms are not specific for PBC but remain an issue that is common in the PBC and important to patients. As a screening tool, PBC-10 can establish the presence of those symptoms. Future studies will help to examine the effect of co-morbidities related symptoms on the QoL in PBC.

There is an unavoidable selection bias when asking patients to fill in questionnaires, as not all of them will be willing to participate. However, the sample was drawn from a large cohort of patients with PBC from different parts of the UK to ensure a good representation of patients and to mirror routine clinical practice.

Our findings support the validity, internal reliability, and reproducibility of the PBC-10, a short QoL tool for patients with PBC. PBC-10 had small to moderate responsiveness and noticeable floor effect. Therefore, further validation is needed in this aspect. PBC-10 is shorter and can be more easily applied in clinical practice than existing QoL measures. We therefore hope that it will be widely used, both in normal clinical practice and in health care evaluation to assess the effect of interventions on QoL. The simplicity, validity and reliability of the PBC-10 make it a strong candidate for PBC clinical registries and databases, and in audits that assess the efficacy of new treatments in PBC.

**Tables:**



**Table 1: Characteristics of the patients who completed the baseline PBC-40 questionnaire ***

| | |
|---|---|
| Total | 2219 |
| Age | 65 (10.85) years |
| Gender | |
| Male | 262 (11.81%) |
| Female | 1957 ( 88.19%) |
| PBC-40 score | 96.25 ( 34.03) |
| Individual domains score: | |
| Symptoms | 18.18 (4.57) |
| Itch | 5.27 (4.49) |
| Fatigue | 29.74 (11.34) |
| Cognition | 13.20 (6.29) |
| Social | 24.23 (9.82) |
| Emotional | 7.69 3.51) |

* Categorical data are presented as numbers(percentages). Continuous data are presented as means ( SD)

**Table 2: PBC-10 questionnaire**

***PBC-10 questions***

Please answer all the questions to the best of your ability. If a particular question does not apply to you, or you do not know the answer to a particular question, simply write this on the questionnaire.

***IN THE LAST FOUR WEEKS*, how often did you experience any of the following?**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 1. | I have felt embarrassed because of the itching | Never | Rarely | Occasionally | Frequently | Always | Does not apply |
| 2. | If I eat or drink a small amount and still felt bloated | Never | Rarely | Occasionally | Frequently | Always | Does not apply |
| 3. | My mouth was very dry | Never | Rarely | Occasionally | Frequently | Always | Does not apply |
| 4. | Fatigue interfered with my daily routine | Never | Rarely | Occasionally | Frequently | Always | Does not apply |
| 5. | I had to force myself to do the things I needed to do | Never | Rarely | Occasionally | Frequently | Always | Does not apply |
| 6. | If I was busy one day I needed at least another day to recover | Never | Rarely | Occasionally | Frequently | Always | Does not apply |
| 7. | Because of PBC, I found it difficult to concentrate on anything | Never | Rarely | Occasionally | Frequently | Always | Does not apply |

**Now some more general statements about how PBC may be affecting you as a person. How much do the following statements apply to you?**

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8. | I feel guilty that I can't do what I used to do because of having PBC | Not at all | A little | Somewhat | Quite a bit | Very much | Not applicable |

**These statements relate to the possible effects of PBC on your social life and your life overall. Thinking of your own situation, how much do you agree or disagree with them?**

| | | | | | | |
|---|---|---|---|---|---|---|
| 9. | My social life has almost stopped | Strongly agree | Agree | Neither agree nor disagree | Disagree | Strongly disagree |
| 10. | PBC has reduced the quality of my life | Strongly agree | Agree | Neither agree nor disagree | Disagree | Strongly disagree |

**Table 3 Flooring and ceiling effect of PBC-10**

| | Ceiling effect (percentage of patients who scored the maximum response =5) | Floor effect (percentage of patients who scored the minimum response =1) |
|---|---|---|
| 1. I have felt embarrassed because of the itching | 5.1 | 28.7 |
| 2. I ate or drank only a small amount and still felt bloated | 4.5 | **34.5** |
| 3. My mouth was very dry | 13.8 | 23.6 |
| 4. Fatigue interfered with my daily routine | 8.4 | 24.2 |
| 5. I had to force myself to do the things I needed to do | 7.4 | 19.2 |
| 6. If I was busy one day I needed at least another day to recover | 13.4 | **24.3** |
| 7. Because of PBC, I found it difficult to concentrate on anything | 4.6 | 36.1 |
| 8. I feel guilty that I can't do what I used to do because of having PBC | 16.6 | 41.4 |
| 9. My social life has almost stopped | 6.9 | **32.7** |
| 10. PBC has reduced the quality of my life | 8.9 | 24.5 |

**Table 4: Correlation of the PBC-10 items with the 6 subdomains of the PBC QoL .**

| | Sub-domains | | | | | |
|---|---|---|---|---|---|---|
| | Symptoms | Itch | Fatigue | Cognition | Social | Emotional |
| 1. I have felt embarrassed because of the itching | | 0.921 | | | | |
| 2. I ate or drank only a small amount and still felt bloated | 0.602 | | | | | |
| 3. My mouth was very dry | 0.745 | | | | | |
| 4. Fatigue interfered with my daily routine | 0.898 | | | | | 0.601 |
| 5. I had to force myself to do the things I needed to do | 0.905 | | | | | 0.613 |
| 6. If I was busy one day I needed at least another day to recover | | | 0.875 | | | 0.566 |
| 7. Because of PBC, I found it difficult to concentrate on anything | | | | 0.930 | | 0.567 |
| 8. I feel guilty that I can't do what I used to do because of having PBC | | | | | 0.830 | 0.738 |
| 9. My social life has almost stopped | | | | | 0.834 | 0.596 |
| 10. PBC has reduced the quality of my life | | | | | 0.846 | 0.671 |

**Table 5: Further validation and psychometric properties of PBC-10**

| | PBC QoL questions | Item total correlations | Max response rate |
|---|---|---|---|
| 1 | Fatigue interfered with my daily routine | .857 | 35% |
| 2 | Because of PBC, I found it difficult to concentrate on anything | .779 | 41% |
| 3 | PBC has reduced the quality of my life | .824 | 25% |
| 4 | I have felt embarrassed because of the itching | .565 | 41% |
| 5 | I feel guilty that I can't do what I used to do because of having PBC | .818 | 44% |
| 6 | I had to force myself to do the things I needed to do | .857 | 37% |
| 7 | My mouth was very dry | .617 | 32% |
| 8 | My social life has almost stopped | .789 | 35% |
| 9 | I ate or drank only a small amount and still felt bloated | .630 | 33% |
| 10 | If I was busy one day I needed at least another day to recover | .850 | 26% |

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