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The impact of liver transplantation on the phenotype of primary biliary cirrhosis patients in the UK-PBC cohort

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Abstract

Background & Aims—Liver transplantation improves survival in end-stage primary biliary cirrhosis (PBC), but the benefit for systemic symptoms including fatigue is less clear. The aim of this study was to utilise the comprehensive UK-PBC Research Cohort, including 380 post-transplant patients and 2300 non-transplanted patients, to answer key questions regarding transplantation for PBC.

Methods—Cross-sectional study of post-transplant PBC patients and case-matched non-transplanted patients. Detailed clinical information was collected, together with patient systemic symptom impact data using validated assessment tools.

Results—Over 25% of patients in the transplant cohort were grafted within 2 years of PBC diagnosis suggesting advanced disease at presentation. Transplanted patients were significantly younger at presentation than non-transplanted (mean 7 years) and >35% of all patients in the UK-

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Conflict of interest

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PBC cohort who presented under 50 years had already undergone liver transplantation at the study censor point (>50% were treatment failures (post-transplant or unresponsive to UDCA)). Systemic symptom severity (fatigue and cognitive symptoms) was identical in female post-transplant patients and matched non-transplanted controls and unrelated to disease recurrence or immunosuppression type. In males, symptoms were worse in transplanted than in non-transplanted patients.

Conclusions—Age at presentation is a major risk factor for progression to transplant (as well as UDCA non-response) in PBC. Although both confirmatory longitudinal studies, and studies utilising objective as well as subjective measures of function, are needed if we are to address the question definitively, we found no evidence of improved systemic symptoms after liver transplantation in PBC and patients should be advised accordingly. Consideration needs to be given to enhancing rehabilitation approaches to improve function and life quality after liver transplant for PBC.

Keywords

Primary biliary cirrhosis; Transplantation; Quality of life; Fatigue

Introduction

Liver transplantation (LT) is a highly effective treatment for end-stage primary biliary cirrhosis (PBC), and most programmes report excellent long-term survival when compared to predicted survival without transplantation [1–3], while survival rates for PBC exceed those for almost all other conditions. Despite the advent of effective primary therapy with ursodeoxycholic acid (UDCA), PBC is the underlying liver disease in up to 10% of the patients listed for LT in the UK. The PBC patient population listed for LT for end-stage disease consists of both late-presenting patients, who first come to clinical attention with advanced disease, and patients who progress despite UDCA therapy and who may represent UDCA unresponsive patients. Despite the recurrence of PBC following LT [4], the intervention remains well-tolerated, successful and cost-effective [5,6].

Whereas LT for patients with high-risk, advanced PBC with complications is well-established, there has been a more recent move towards considering transplantation in those without end-stage disease, but with prominent symptoms of PBC, including cholestatic pruritus and controversially, systemic fatigue [7]. Symptoms may also influence the decision to accept an offer of LT in patients who meet listing criteria in the belief that marked symptoms will also improve. Recent data suggest, however, that whereas LT for PBC may be highly effective at treating the specific clinical features of end-stage liver disease, such as overt encephalopathy and ascites, and may be beneficial for pruritus [8], the impact on systemic symptoms such as fatigue and cognitive impairment may be more limited [8,9]. The outcome following LT for PBC may be more complex than originally thought, since ongoing fatigue and physical or functional limitation are common [10–12]. Significant residual symptoms after LT for PBC need to be balanced against the significant survival gains, but realistic expectations are essential to prepare for the recovery phase and the return to ‘normal’ life.

The aim of this study was to utilise the UK-PBC patient cohort to identify a fully representative and comprehensive population of UK patients who have undergone LT for PBC and to explore the functional and systemic symptomatic associations in these patients in comparison to matched non-transplanted patients. The findings provide important information regarding expectations after LT for PBC, which will inform future management in the development of novel strategies.

Patients and methods

Study design and subjects

This was a cross-sectional cohort study of post-transplant PBC patients recruited to the UK-PBC Research Cohort [13]. This is a sizeable cohort of PBC patients that was initially established to support high-throughput genetic studies of PBC and its sub-phenotypes. Clinical characteristics of the cohort are described in detail elsewhere ([14] and Supplementary Material). In the current study, we report the characteristics of patients in the cohort who have undergone LT for PBC, compared to those who have not.

All cases in the current study were enrolled in the cohort between 1st January, 2008 and 31st December, 2011. Detailed clinical information was collected at enrolment, including the following data pertinent to this study: date of diagnosis of PBC; LT-status and the date of LT (if applicable); use of UDCA, and measurements of liver biochemistry (LFT) up to the time of enrolment. In non-LT recipients who had been receiving treatment with UDCA for at least two years prior to enrolment, UDCA response status was determined by assessing whether the most-recent LFT fulfilled the Paris I UDCA response criteria [15]. We used the Paris I criteria because in a previous study these criteria were shown to most accurately predict outcome in the UK-PBC Research Cohort [14].

As part of the UK-PBC project, participants in the current study have also been phenotyped with regard to symptoms and quality of life using well-established and validated measures. For the study of symptom impact, transplanted PBC patients were case-matched by age, sex and year of diagnosis of PBC to non-transplanted patients within the UK-PBC Research Cohort. Data relating to symptoms in patients with histologically-confirmed PBC recurrence, and receiving different immuno-suppressive regimes, were available for patients from 3 of the 7 UK LT centres (Supplementary Material) [16].

Symptom assessment measures

PBC-40—The PBC-40 is a patient-derived, disease-specific QOL measure with robust psychometric properties [17]. The measure includes a fatigue domain reported here. The measure is optimised for self-completion.

Epworth Sleepiness Scale (ESS)—Previous small studies have reported increased levels of daytime somnolence in PBC typically not associated with obstructive sleep apnoea. ESS is a self-completion assessment tool, previously used in PBC, consisting of 6 items with a potential score range of 0–24. A score of 10 or over is regarded as indicating a clinically significant level of daytime somnolence warranting intervention [18].

Orthostatic Grading Scale (OGS)—Previous small studies have identified an increased prevalence of vasomotor autonomic symptoms in PBC (at early disease stages in addition to the well-recognised prevalence in cirrhotic disease). OGS is a validated measure of vasomotor autonomic dysfunction previously applied in PBC [19]. The measure has 5 items (potential score range 0–20) and is optimised for patient completion. A score of 4 or greater is regarded as being indicative of the presence of vasomotor autonomic dysfunction.

Hospital Anxiety and Depression Scale (HADS)—Depression and anxiety symptoms are seen in PBC patients and contribute to distress and poor coping capacity [20]. HADS is a validated anxiety and depression measure optimised for use in patients with chronic disease. It has previously been applied in PBC [20]. Individual sub-scales reflecting anxiety and depression consist of 7 items each with a potential score range of 0–21. Clinical cut-offs are variable. For the purposes of this study, ‘caseness’ for depression or anxiety was defined as a score of 11 or greater for the sub-scale.

Statistical analysis

Analysis was performed using the statistical analysis software PRISM 3.0 (Graphpad Prism, CA, USA) and SPSS (SPSS, NY, USA). Where data were normally distributed, they are presented as mean $\pm$ standard deviation and comparisons were made between groups using unpaired *t* tests. Where data were non-normally distributed, they are presented as median and range and comparisons were made by Mann–Whitney *U*-test. Differences in proportions were determined using Chisquare tests. LT-free survival analysis was undertaken using the Kaplan-Meier method and Cox proportional hazards regression, implemented using the “survival” package in R v2.14.2 (<http://www.r-project.org/>). A statistically significant result was considered for $p < 0.05$.

Results

The current study included 380 PBC patients who have undergone LT in the UK (Table 1). Forty percent of the patients who had undergone LT had been grafted within 5 years of clinical presentation and 70% within 10 years (Fig. 1A). The goal of this study was to explore the impact of LT on patients in terms of life quality, and to explore the extent to which altered or improved therapy might alter the requirement for transplant. Therapy to prevent LT requires an early and accurate diagnosis. Just under 30% of patients underwent LT within 2 years of presentation and were likely to have had advanced disease at presentation, which may have been too late for therapy to modify the course of PBC.

Compared to non-transplanted PBC patients in the UK-PBC Research Cohort, patients who had undergone LT were significantly younger at diagnosis of PBC (by a mean 7 years, Fig. 1B). The proportion of patients in the UK-PBC Research Cohort in each age cohort who had undergone LT was strongly linked to age, with younger presenting patients significantly more likely to have undergone LT than older presenting patients (Fig. 1C). We confirmed the impact of age at diagnosis on LT-free survival in formal time-to-event analysis, taking duration of follow-up and eligibility for LT into account (Supplementary Fig. 2A and B; Supplementary Table 1A and B). We have previously demonstrated that age is also an important independent predicting factor in clinical response to UDCA with, again, younger

presenting patients at higher risk [14]. When UDCA non-responding patients were combined with transplanted patients to form a group of primary treatment failure patients it was found that over 50% of patients presenting below the age of 50 met the criteria for primary treatment failure (Fig. 1D). The enhanced risk of primary treatment failure appeared to be sustained throughout the natural history of PBC (Fig. 1E). The implication of this finding is that although there is a group of patients presenting at younger age, who will respond to primary therapy with UDCA, there is significant risk that individuals will not do so and future therapy should be targeted at this high-risk patient group.

In light of single centre pilot reports suggesting ongoing significant functional symptom severity in transplanted PBC patients [9], we explored symptom status in post-transplant patients across the whole UK-PBC cohort. Critically, amongst female PBC patients, fatigue severity was identical in patients who had undergone transplantation compared to non-transplanted patients (case-matched for gender, age at presentation, age at study and disease duration) (Fig. 2A and Table 2). When male patients were studied, worsening fatigue associated with transplant was noted. The post-transplant male patients had a similar level of fatigue to transplanted female patients (Fig. 2A and Table 2) with the reduced level of fatigue reported previously in non-transplanted male PBC patients not being observed in transplanted patients. No difference in fatigue severity was seen between patient receiving cyclosporine A and tacrolimus as primary immunosuppression (Fig. 2B) and between patients with and without histologically-confirmed recurrent disease (Fig. 2C).

The study was cross-sectional rather than linear in design, meaning that we cannot exclude the possibility that transplanted patients experienced even greater levels of fatigue prior to their transplant, with improvement after transplantation to more typical levels of fatigue. The UK-wide data suggest, however, that PBC patients should expect to suffer fatigue after transplantation at levels typical of the average for PBC patient. Post-transplant fatigue in PBC was universal and observed in patients from all seven UK transplant centres, not just those centres with interests in fatigue, a potential source of bias (Fig. 2D).

In order to explore the causes of the apparent increase in fatigue following transplant in male PBC patients, we next explored the systemic symptoms of autonomic dysfunction, daytime somnolence and depression, which have previously been shown to associate with fatigue. No difference was seen between transplanted and non-transplanted female patients with regards to daytime somnolence, autonomic dysfunction, and depression (Fig. 3 and Table 2). In male patients, in contrast, although daytime somnolence and depression levels were similar in transplanted and non-transplanted patients, autonomic dysfunction symptom severity was significantly greater in the transplanted patients mirroring, again, the levels of symptoms seen in transplanted female patients. Furthermore, the relative increase in fatigue severity in male transplant patients compared to non-transplanted patients was directly related to the difference in autonomic symptom severity seen between the patients in the two groups, further emphasising the postulated role for autonomic dysfunction in the pathogenesis of fatigue in PBC (Fig. 4A). Symptoms of cognitive dysfunction mirrored fatigue, with increase in symptom impact in male (but not female) patients post-transplant (Fig. 4B), with the increase seemingly being directly related to the increase in autonomic dysfunction symptoms seen in the transplanted male patients compared to the non-transplanted subjects

(Figs. 3C and 4C). This observation suggests a direct link between autonomic dysfunction and cognitive symptoms as well as fatigue.

More broadly in terms of PBC-associated symptoms, significant lowering of symptom impact with transplantation was only seen in female patients for the PBC-40 symptoms and emotional domains (Table 2). All PBC-40 domains were worse in transplanted male patients than in matched non-transplanted male patients (with all the domains except symptoms reaching significance (Table 2)). No association was seen between severity of any symptom in the post-transplant patients and the length of time following transplantation (Table 3), suggesting that symptoms are neither an early phenomenon associated with the recovery period from surgery nor a degenerative process associated with longevity and time-dependent risk.

Discussion

The size and comprehensive nature of the UK-PBC Research Cohort presents a unique opportunity to explore the clinical characteristics of a large post-LT PBC patient population and to compare them with age, sex and disease duration matched nontransplanted PBC patients from the cohort. The findings of the study provide potentially important insights into the impact of transplantation in PBC. A significant proportion of patients in the UK-PBC Research Cohort who underwent LT did so soon after the initial diagnosis. It is likely that this is a group of patients presenting with already advanced disease. This group is of real importance if we are to improve overall outcomes in PBC because the critical issue is not one of failure to respond to primary therapy, but of failure of diagnosis within a time-frame within which primary therapy might work. If we are to reduce the number of patients requiring transplantation for advanced PBC, we will not only need to develop effective therapies, but also to optimise our approach to diagnosis, to allow therapy to be used in a timely fashion.

In our original description of the UK-PBC Research Cohort, we showed that age at presentation with PBC was strongly associated with a poor response to UDCA therapy, an alteration in the nature of failure of response and increased symptoms [14]. The effect of younger age was mirrored in the transplant cohort; patients who went on to transplantation were a mean 7 years younger at presentation than non-transplanted patients. The cumulative effects of non-response to UDCA and requirement for transplantation (both, it could be argued, manifestations of ineffective primary therapy) can be seen in a sustained pattern of high risk throughout the disease time course. Over the whole UK-PBC patient cohort, 60% of patients presenting below the age of 40 years met our criteria for ineffective therapy. This compares with only 10% of patients presenting over the age of 70 years. This finding reinforces the view that PBC carries greater risk in younger patients and that attention should be particularly focused on this group in terms of improved treatment if we are to alleviate the burden of transplantation in PBC.

Transplantation in PBC is an accepted, effective therapy for end-stage disease and pruritus, but our observations regarding systemic symptom severity in post-transplant PBC patients when compared to age, disease duration, and sex-matched non-transplanted control patients

raise concerns that fatigue and cognitive symptoms may persist following transplantation. Confirmation of the degree of ongoing symptom impact following transplantation will require longitudinal studies, ideally incorporating objective as well as subjective measures of symptom impact to limit the impact of patient reporting bias with the former; approaches which the study design and nature precluded us from adopting. Without longitudinal data in particular, we cannot exclude the possibility that the post-transplant patients studied had, prior to transplantation, higher levels of fatigue and cognitive symptoms than their matched non-transplanted controls and thus had some benefit from transplantation. What we can conclude, however, is that, within the limitations of the study, a reasonable expectation for a PBC patient undergoing transplantation in the UK is that following transplant, they will have the same fatigue and cognitive symptom severity as an age- and sex-matched non-transplanted patient would expect. Given the burden of cognitive and fatigue symptoms in untransplanted patients, this suggests a significant degree of ongoing symptom load.

A key question is why, given the manifest biological improvements seen in end-stage PBC patients following transplantation, is little or no apparent improvement in the linked symptoms of fatigue and cognitive abnormality seen. One potential explanation would be that the factors or mechanisms responsible for fatigue in the pre-transplant patient group operate outside the liver and are thus not-directly modified by organ replacement. Potential mechanisms might include ongoing presence of AMA (which is normally still present in patients post-transplant), which has been implicated in bioenergetic abnormality in PBC linked to fatigue [21–23]. The similarity in fatigue severity between posttransplant patients with and without disease recurrence, along with the broad-based nature of fatigue and cognitive symptoms post-transplant (broader than disease recurrence) and the finding in the current study that fatigue and cognitive symptom severity are, in contrast to likelihood of recurrence, unrelated to length of time post-transplant, would argue against a significant role for PBC recurrence in post-transplant systemic symptom impact.

Another potential explanation for post-transplant symptoms would be the occurrence of those symptoms as a direct consequence of extra-hepatic injury occurring prior to transplant which is, again, not reversed by transplantation. Evidence in favour of this model would include ongoing brain neurophysiology abnormality demonstrated in post-transplant PBC patients [24], and the demonstrated association between cognitive symptoms in PBC and white matter brain lesions on MRI [25]. In this model, autonomic dysfunction resulting from injury to areas of the brain regulating the autonomic nervous system plays a key role in fatigue and cognitive symptom expression [26,27]. Our demonstration, in the current study, that the apparent increase in both cognitive and fatigue symptoms in transplanted male patients over their matched non-transplanted controls is directly related to autonomic symptom severity would be fully supportive of this model.

A further obvious potential contributing factor for functional symptoms following transplantation in PBC, and one which would help explain the apparent worsening of symptoms seen in some post-transplant patient groups (e.g., men), would be an effect of immuno-suppressive medication [28]. Cyclosporine has a direct effect on mitochondrial function, inducing alterations in energy metabolism [29], whilst sirolimus and tacrolimus have been shown to impair attention and working memory [30]. Furthermore, hippocampal

infusion of cyclosporine in rats results in impaired short-term memory, object recognition, reference memory and associative learning through, it has been postulated, binding to, and inactivation of cyclophilin D which is thought to play a physiological role in these key cognitive processes [31]. Improvement in fatigue, vitality, and social functioning has been reported in patients being moved away from cyclosporine-based immunosuppression regimes following renal transplantation [32]. The numbers of comparator patients in the UK-PBC posttransplant cohort receiving non-CNI immunosuppression were insufficient, however, to allow us to address the role played by the class in post-transplant systemic symptom pathogenesis and severity. Our finding of equivalent levels of fatigue in patients receiving cyclosporine A and tacrolimus as primary immunosuppression would argue that if CNI immunosuppression does play a role in post-transplant systemic symptom pathogenesis, the effect is broadly-based. One way to begin to approach this issue would be to explore the levels of systemic symptoms in patients transplanted for other forms of chronic liver disease. This would allow us to distinguish between PBC-specific (e.g., AMA-related) and PBC non-specific (e.g., immunosuppression-related) mechanisms.

Although further work is clearly needed to understand the causes of post-transplant systemic symptoms in PBC, one obvious implication of the demonstration of such a significant symptom burden is a need to develop positive approaches to management, and in particular improved rehabilitation to increase function. One approach to enhanced rehabilitation following liver transplant in PBC might be through increased physical activity or, more specifically, exercise intervention. Increase in physical activity has been shown to result in increased quality of life following liver transplant in general [33], with supervised exercise training having specific benefits in terms of daily function, participation, and fatigue [34]. Exercise-based rehabilitation may be of particular relevance in PBC, given the evidence from both MRI and exercise physiology to suggest impaired bioenergetic function, which associates with fatigue severity [21,23,35] and appears to lessen with exercise training [22]. Good social support structures and increased awareness about the disease with access to information have also been shown to have positive impact on life quality following transplant (mirroring similar contributions in non-transplant patients and are important additional factors in rehabilitation package development [36,37]).

In conclusion, this study has added to our awareness of the apparent risk associated with PBC in younger patients, adding increased risk of needing transplantation to the already demonstrated risk of non-response to UDCA. It has also demonstrated a high systemic symptom burden in post-transplant PBC. Although the study design does not allow us to exclude individual benefit, as a group of post-transplant PBC patients exhibit similar levels of systemic symptoms to non-transplanted patients. Further research is needed to explore whether our findings are specific to PBC or whether similar findings occur in large cohorts of patients requiring transplantation for other chronic liver diseases, and to identify the mechanisms responsible for this symptom burden, and their appropriate treatments, if the full value of transplantation to PBC patients is to be optimised. In the mean-time attention needs to be focused on ways in which we can improve the rehabilitation and return to function of PBC patients approaching LT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

PBC	primary biliary cirrhosis
UDCA	ursodeoxycholic acid
AMA	anti-mitochondrial antibody
ESS	Epworth Sleepiness Scale
OGS	Orthostatic Grading Scale
HADS	Hospital Anxiety and Depression Scale

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Fig. 1. Transplantation parameters in PBC.

(A) Timing of LT in relation to timing of diagnosis with PBC for the post-transplant UK-PBC patient cohort. 50% of patients undergoing transplantation had done so by six years following diagnosis. The kinetics of reaching transplantation suggests that a significant proportion of patients presenting with PBC, and who will require transplantation, have advanced disease at the point of presentation. Improved therapy to reduce the need for transplantation will require improved diagnosis and case finding as well as application of effective therapies. (B) Age of diagnosis of PBC in the transplanted (trans) and non-

transplanted patient groups in the UK-PBC patient cohort. Patients who had undergone transplantation presented at a significantly younger age. The effect of age of presentation in all age groups on (C) likelihood of the patient within the cohort being transplanted and (D) being in treatment failure (defined as either having had a transplant or having serum biochemistry compatible with non-response to UDCA at the study point). (E) The impact of age of presentation (dichotomised around age 45 on the likelihood of patients being in treatment failure) throughout the disease natural history. Younger age at presentation is associated with significantly increased risk of treatment failure at all points through the disease course. n.a., not available.

Fig. 2. Fatigue severity assessed using the PBC-40 fatigue domain.

(A) Transplanted (trans) male and female PBC patients and case-matched nontransplanted patients (matched for age at diagnosis and disease duration). (B) Post-transplant PBC patients treated with cyclosporine A and tacrolimus immunosuppression (data for 3 of the 7 UK transplant centres). (C) Post-transplant PBC patients with and without histologically confirmed recurrent PBC (data for 3 of the 7 UK transplant centres). (D) Post-transplant PBC patients according to the centre in which they were transplanted within the UK. No differences of significance were observed. n.s., not significant.

Fig. 3. Comparison between non-transplanted and transplanted female and male patients for the PBC fatigue-associated symptoms.

(A) Daytime somnolence as assessed using ESS, (B) depression as assessed using HADS-D, and (C) autonomic dysfunction as assessed using OGS.

Fig. 4. Differences between transplanted and case-matched non-transplanted PBC patients that would directly implicate autonomic dysfunction in the pathogenesis of cognition abnormality and, as previously suggested, fatigue in PBC.

(A) Differences in OGS score between transplanted and case-matched non-transplanted male PBC patients and PBC-40 fatigue domain score. (B) Cognitive symptoms assessed using the PBC-40 cognitive domain in transplanted (trans) and case-matched non-transplanted male and female PBC patients. (C) Association between the differences in OGS score between transplanted and case-matched non-transplanted male PBC patients and PBC-40 cognitive domain score. In male PBC patients, the difference in severity of autonomic symptoms seen between case-matched transplanted and non-transplanted patients is directly proportional to the difference in cognitive and fatigue symptoms. n.s., not significant.

Table 1
Clinical characteristics of the study groups.

No significant differences were seen between the transplanted and matched non-transplanted comparator patients for any parameter indicating effective matching. No significant differences were seen for any parameter between male and female transplanted patients.

Parameter	Female		Male	
	Transplanted (n = 351)	Non-transplanted control (n = 351)	Transplanted (n = 29)	Non-transplanted control (n = 29)
Age at PBC diagnosis	47.7 ± 9.7	49.1 ± 9.5	50.5 ± 8.3	52.2 ± 6.6
Total follow-up (yr)	18.6 ± 6.9	17.1 ± 6.2	16.7 ± 6.7	15.3 ± 5.7
Age at study (yr)	66.2 ± 9.2	66.2 ± 9.2	67.2 ± 7.1	67.5 ± 6.9
Age at transplantation (yr)	54.6 ± 9.4	n.a.	57.1 ± 8.5	n.a.
Diagnosis to transplanted disease duration (yr)	7.7 ± 6.7	n.a.	6.6 ± 6.4	n.a.
Post-transplantation follow-up (yr)	11.7 ± 6.5	n.a.	10.1 ± 4.9	n.a.

n.a., not applicable.

Table 2
Symptom impact in the study groups.

Values are for median and range. Differences between male and female post-transplant patients were non-significant for all symptom domains.

Parameter	Female		<i>p</i> value	Male		<i>p</i> value
	Transplanted (n = 351)	Non-transplanted control (n = 351)		Transplanted (n = 29)	Non-transplanted control (n = 29)	
PBC-40 fatigue	30 [11-55]	33 [11-55]	n.s.	29 [11-55]	23 [11-52]	<0.05
PBC-40 cognitive	13 [6-30]	13 [6-30]	n.s.	14 [6-24]	8 [6-29]	<0.005
PBC-40 social	22 [10-50]	24 [9-49]	n.s.	24 [10-42]	19 [10-45]	<0.05
PBC-40 emotional	6 [3-15]	7 [3-15]	0.01	7 [3-15]	5 [3-14]	<0.05
PBC-40 symptoms	16 [7-30]	18 [6-30]	<0.0001	14 [7-22]	12 [6-23]	n.s.
Daytime somnolence (ESS)	6 [3-24]	7 [0-24]	n.s.	7 [0-19]	7 [0-20]	n.s.
Autonomic dysfunction (OGS)	3 [0-18]	3 [0-15]	n.s.	2 [0-15]	0 [0-9]	0.01
Depression (HADS-D)	4 [0-21]	4 [0-17]	n.s.	6 [0-16]	4 [0-10]	n.s.
Anxiety (HADS-A)	6 [0-21]	5 [0-14]	n.s.	6 [0-14]	5 [0-14]	n.s.

n.s., not significant.

Table 3
Relationship between post-transplant follow-up duration and symptom severity score in the UK-PBC post-transplant cohort.

Symptom domain	r ²	p value
PBC-40 fatigue	0.000	0.9
PBC-40 symptoms	0.000	0.9
PBC-40 cognitive	0.009	0.1
PBC-40 emotional	0.009	0.1
PBC-40 social	0.000	0.6
ESS	0.001	0.6
OGS	0.001	0.5
HADS-A	0.010	0.07
HADS-D	0.000	0.8