

The Majority of Fatigued PBC Patients do not Have Clinically Significant Itch

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Introduction

The two dominant symptoms of primary biliary cholangitis (PBC) are itch and chronic fatigue. There has been significant recent progress with itch treatment, with clear benefits from fibrates, PPAR agonists and iBAT inhibitors. At present, we lack a specific therapy for fatigue. The impact of itch on quality of life (QOL) is broad-based, with sleep disturbance being prominent. Sleep abnormality has, in turn, been strongly linked to fatigue in PBC (Newton et al 2006). This has led to the suggestion that effective itch treatment will also be effective for treating fatigue.

Despite the importance of these symptoms for PBC patients, there is remarkably little data to help us understand the true association between itch, fatigue and PBC and the likelihood that effective fatigue treatment can come through itch therapy.

Aim

To explore the link between itch severity and fatigue severity in a large, unselected PBC patient cohort to determine the extent to which effective itch treatment could be expected to improve fatigue.

Method

Re-analysis of symptom severity data from the previously reported UK-PBC cohort (Dyson et al 2016). Itch and fatigue severity were assessed using a validated, PBC-specific QOL measure (Jacoby et al 2005). Symptom severity for each domain was graded as none/mild/moderate or severe using previously defined cut-off values (Newton et al 2007). Analysis was restricted to patients taking UDCA therapy. Population demographics were as previously described and in keeping with published patterns for UK-PBC patients. Group comparisons were by non-parametric t-test. Linear regression was by Spearman's test.

Results

- The study cohort consisted of 1964 patients, 1320 of whom had no or mild itch and 644 moderate or severe itch. Fatigue severity was significantly higher in the moderate/severe itch group (Figure 1). 81% of the moderate/severe itch group had moderate or severe fatigue.
- 46% (608) of the group conventionally thought to not have clinically significant itch (no or mild group) also had fatigue, as did 36% of the no itch group.
- Overall, 1128 patients (57%) had significant fatigue, but only 520 (46%) of these had significant itch.
- Progressive increase in fatigue severity was seen across the itch severity range (Figure 2). Strikingly, although itch in the mild range is conventionally regarded as not being clinically significant, there was a significantly higher level of fatigue in the mild itch patients than in the no itch patients. Consideration should, therefore, be given to treating itch in this setting.
- There are **itch-independent** and **itch-related** components to PBC fatigue (Figure 3). Itch-independent fatigue makes a significantly greater contribution to overall fatigue in the fatigue with cognitive symptoms (central fatigue) group (Phaw et al 2021). This is the form of fatigue with the greatest QoL impact.

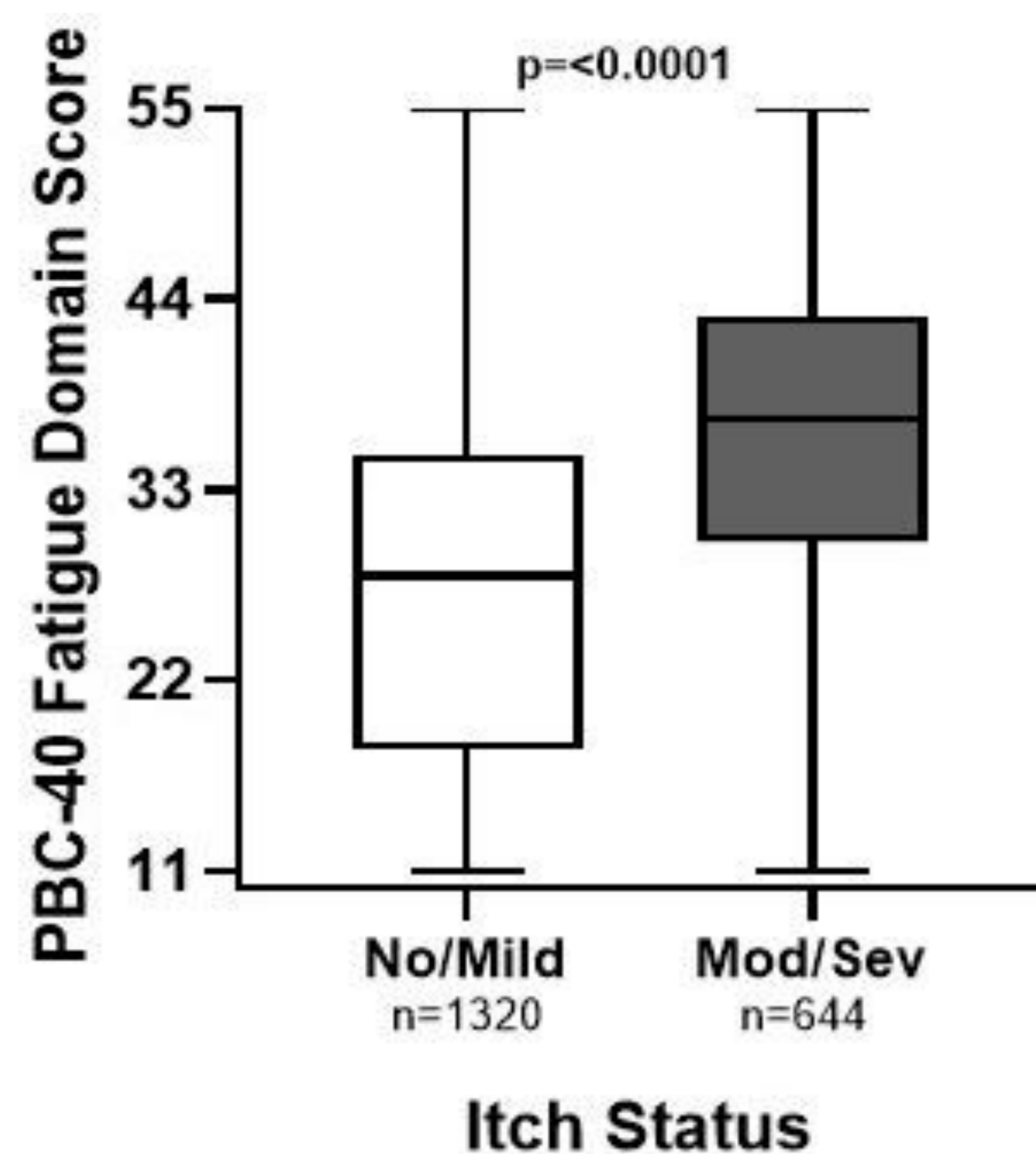


Figure 1: Fatigue severity in patients with low and high levels of itch as determined using published PBC-40 cut offs

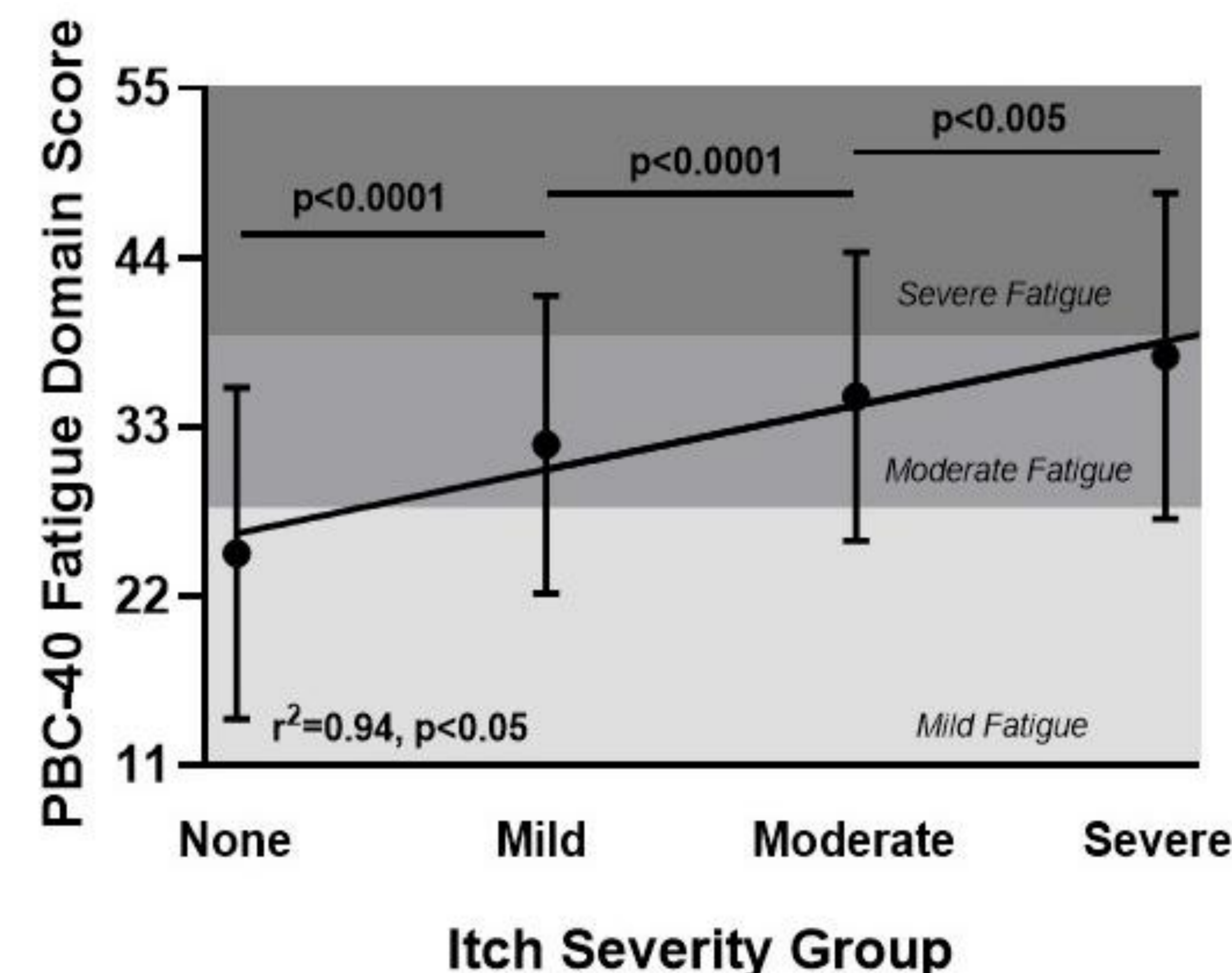


Figure 2: Mean fatigue severity across the range of itch severity. There is a clear and significant progression across the itch severity range. This can be described in the formula $y=4.64x + 26.06$. The implication of this is that there is a component of fatigue severity that is **itch independent** (mean score of 26.06 for the PBC-40 fatigue domain) and a component that is **itch related** (a mean increase of 4.64 in the PBC-40 fatigue domain score per increase in the degree of itch across the range (i.e. none to mild, mild to moderate, moderate to severe)

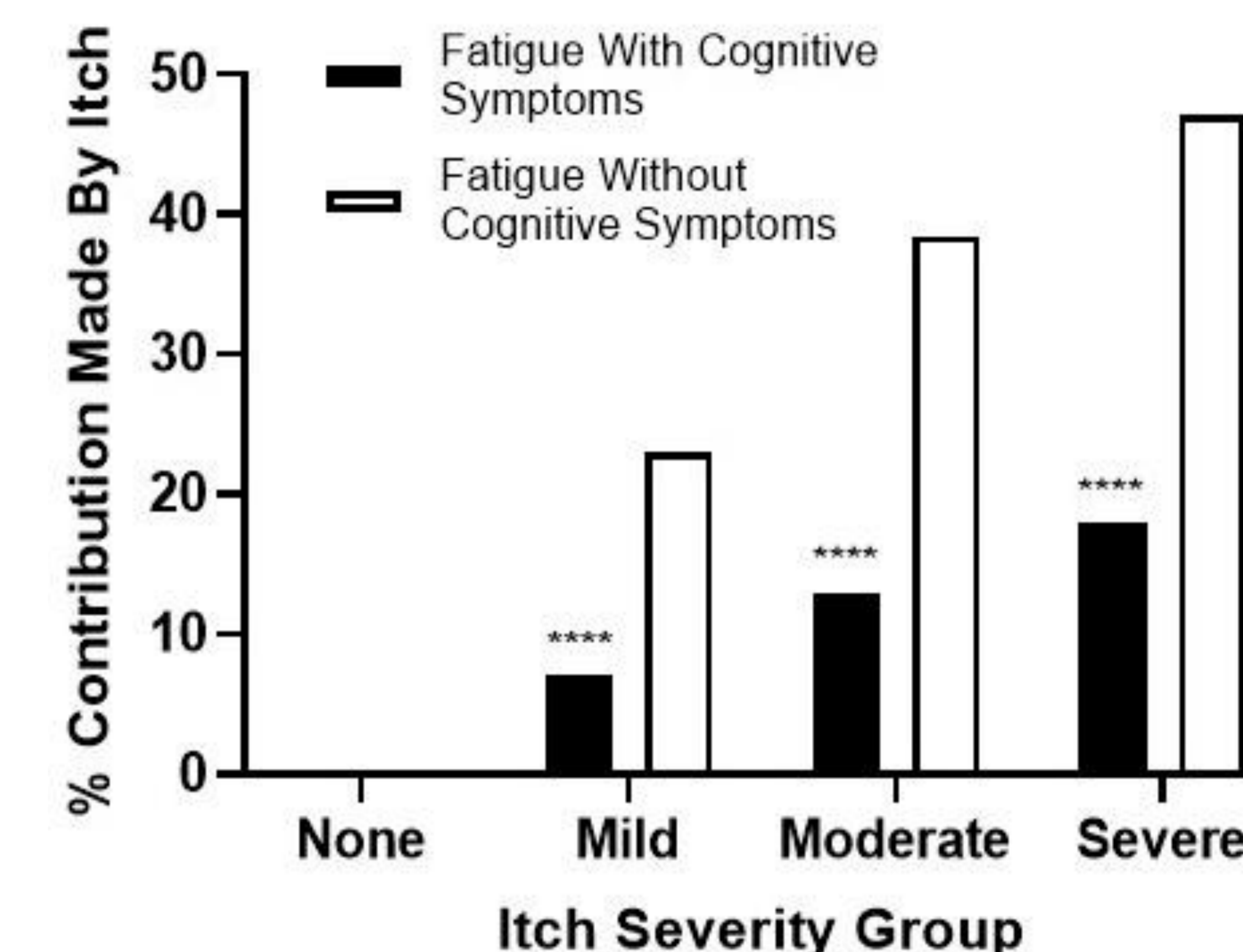


Figure 3: Contribution made by itch-related fatigue to overall fatigue severity for the 4 itch severity groups for patients with fatigue with and without cognitive symptoms. Across the range of itch severity, itch makes a smaller contribution to fatigue with cognitive symptoms (i.e. "central fatigue"). This is the form of fatigue which has the greatest degree of impact on quality of life, and which is more frequent in younger patients (Phaw et al 2021)

Conclusions

- Fatigue levels are significantly higher in PBC patients with itch, with the majority of patients with significant itch also having significant fatigue
- Any degree of itch was associated with some increase in fatigue and it is therefore worth treating itch in patients in whom fatigue is a significant problem
- The majority of PBC patients did not have itch and therefore itch was not the cause of their fatigue**
- Where itch and fatigue are currently present, itch should be the first target of treatment (the low hanging fruit). Where itch is not present or itch independent, fatigue remains a problem and should be treated in its own right
- The contribution of itch to fatigue appears to be lowest in the group with central fatigue; the most pervasive fatigue form in PBC
- Treatment of itch-related fatigue and central fatigue should be recognized as distinct but complementary therapeutic targets

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