Development of the Natural History Component of an Economic Model for Primary Sclerosing Cholangitis (PSC)

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Introduction

- Primary sclerosing cholangitis (PSC) is a rare, chronic cholestatic disease of unknown cause characterized by liver inflammation, fibrosis and destruction of intrahepatic and extrahepatic bile ducts[1]
- There is variability in the published natural history of PSC reflecting the variation of both stage at initial diagnosis and patient phenotype over time[2]
- In the USA, the age- and sex-adjusted incidence of PSC is 1.47 per 100,000 person-years[2]
- The lack of an effective non-transplant therapy, the high rate of recurrence, and the nearly inevitable development of costly comorbidities and complications result in a substantial clinical and economic burden for patients with PSC[3]
- Several drugs for PSC are under investigation, but there is a paucity of economic models to compare the cost-effectiveness and value of new treatments

Objective

- The objective of this study was to develop an early economic model framework for PSC and to validate the natural history component through discussions with clinical and health economic experts

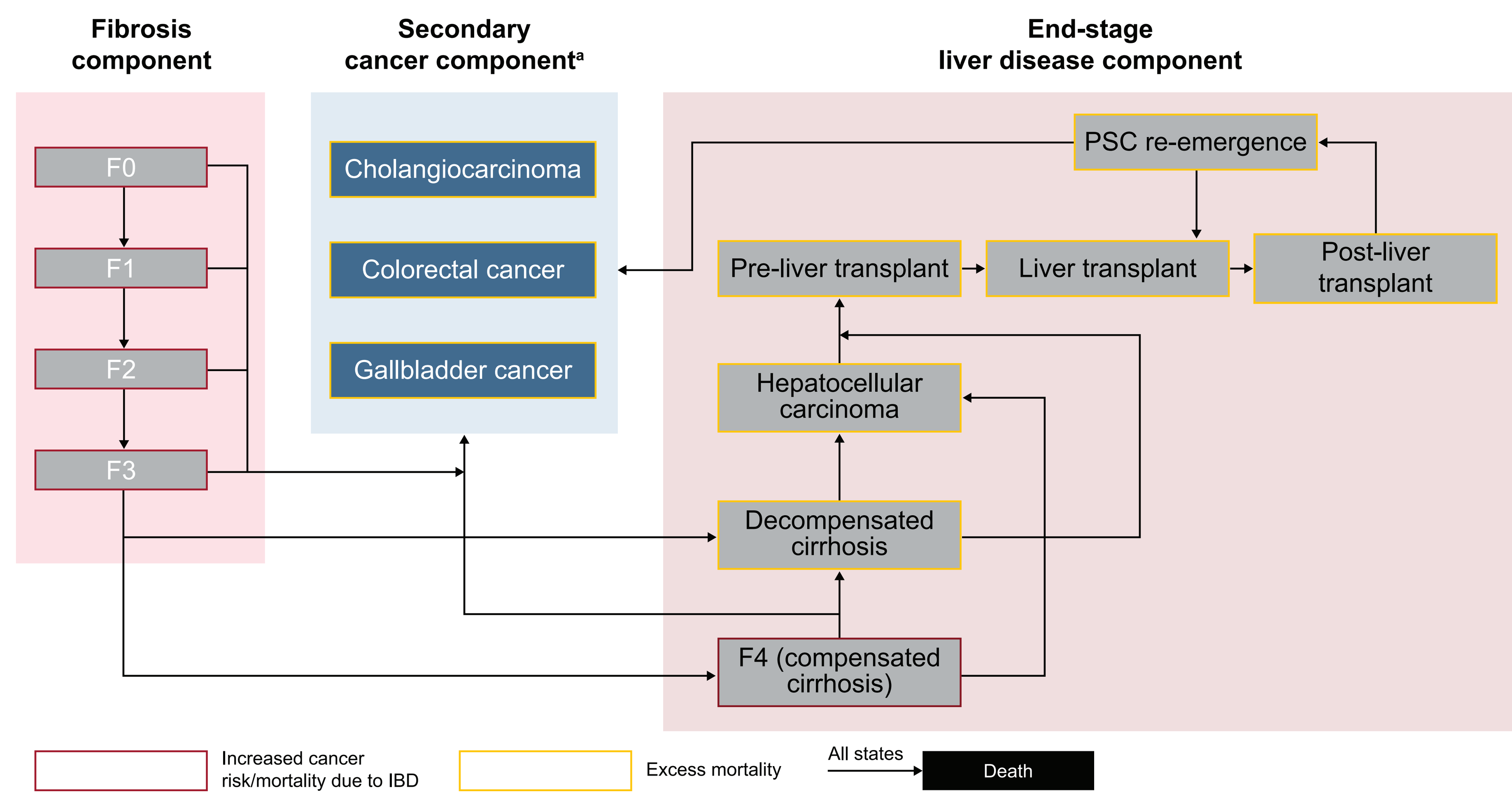
Methods

- A lifetime-horizon Markov-cohort model was developed to track the progression of disease in adults with PSC with or without inflammatory bowel disease (IBD)
- Given the limited number of published natural history models in PSC and owing to similar clinical characteristics between PSC and primary biliary cholangitis (PBC),[4] the model structure was based upon a similar model used in health technology assessment submissions for PBC[5]
- Model structure and inputs were validated via interviews with three US clinical experts and three health economic experts. Model inputs were derived from published literature
- The natural history component of the model includes inputs for disease progression, mortality and adverse events (AEs), with optional inputs for PSC complications (including secondary cancer)
- Patients enter the model at an average age of 39 years and 70% of the cohort had concomitant IBD as observed in a PSC population-based cohort study[6]
- All patients were assumed to be initially pre-cirrhotic (F0–F3) and were distributed across individual stages as reported in previously published PSC clinical trial data.[7] A transition through progressive fibrosis stages was assumed, as depicted in **Figure 1**
- Progression to hepatocellular carcinoma (HCC) was assumed to be achievable only after developing compensated cirrhosis or decompensated cirrhosis (DCC), and no disease regression was also assumed
- Liver transplantation (LT) was assumed to be performed in 4% and 6% of patients with HCC or DCC per year, respectively.[5] Recurrence of PSC (rPSC) for patients surviving LT was assumed at a rate of 2.8% per year.[8] The annual rate of LT after rPSC was assumed to be 43.8%[9]
- AEs included pruritus, depression, fatigue, IBD flares and ascending cholangitis. IBD flares only occurred in patients with IBD. All patients were assumed to be at risk of ascending cholangitis but no excess mortality was attributed to the infection
- Secondary cancers included cholangiocarcinoma, gallbladder cancer and colorectal cancer (the latter of which was assumed in the model to be possible among patients with concomitant IBD only)
- Model outcomes included: overall survival and transplant-free survival reported as life-years (LYs), the proportion of patients undergoing LT and second LT after rPSC, and the proportion of patients developing rPSC after LT. All model outcomes were reported over a lifetime horizon basis

Results

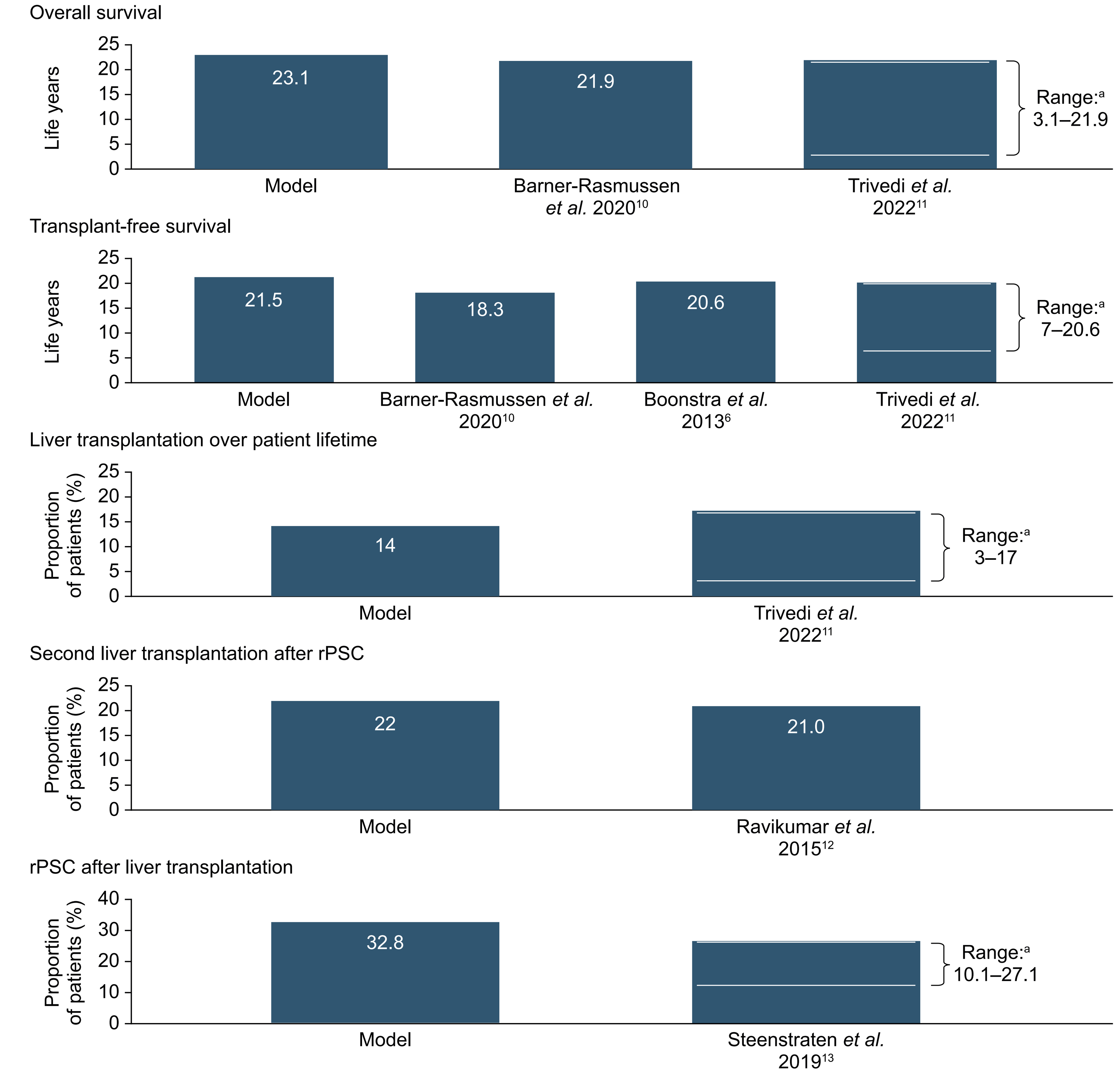
- The overall and transplant-free survival estimates generated by the model (23.1 and 21.5 LYs, respectively) (**Figure 2**) were similar to the findings of a Finnish population-based study (21.9 and 18.3 LYs, respectively).[10] A similar study conducted using data from the Netherlands estimated a similar transplant-free survival estimate of 20.6 LYs[6]
- The estimated proportion of patients in the model undergoing LT during their lifetime was 14% (**Figure 2**). This falls within the range of 3–17% as reported in a systematic literature review of eight studies[11]
- Similarly, the estimated proportion of patients undergoing a second LT after rPSC was 22% (**Figure 2**), which is similar to the rate of 21.0% observed in an observational UK study of rPSC[12]
- The proportion of patients developing rPSC after LT over a lifetime was estimated to be 32.8% (**Figure 2**), slightly higher than the upper bound of the range reported in a systematic literature review (10.1–27.1%). Notably, follow-up periods of included studies are heterogenous and shorter than the time frame of the model (3.5–9 years)[13]

Figure 1. Model structure



[a]The secondary cancer component was not included in the base case analysis.
IBD, inflammatory bowel disease; PSC, primary sclerosing cholangitis.

Figure 2. Estimated outcomes generated by the economic model in comparison with other published studies



[a]Ranges reported in referenced systematic literature reviews.
LY, life-years; rPSC, recurrence of primary sclerosing cholangitis.

Conclusions

- **The natural history component of the early economic model in PSC generated similar survival and LT outcomes to those reported in the published literature**
- **Differences in the rate of rPSC between the results generated by the model and the estimates from published studies may be due to limitations in matching the population analyzed (e.g. age at diagnosis and age at LT) and the duration of follow-up in the studies versus the lifetime time horizon of the model**
- **Although the model was able to simulate the progression of PSC and generate validated estimates of survival and LT, more research is needed to ensure reliable data are available to populate economic models and thus enable evaluation of the benefits of future treatments for PSC**

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