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Munster, K.N. van; Mol, B.; Goet, J.C.; Munster, S.N. van; Weersma, R.K.; Vries, A.C. de; ... ; EpiPSC2 Study Grp

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ORIGINAL ARTICLE

Disease burden in primary sclerosing cholangitis in the Netherlands: A long-term follow-up study

Kim N. van Munster[1] | Bregje Mol[1] | Jorn C. Goet[2] | Sanne N. van Munster[1] | Rinse K. Weersma[3] | Annemarie C. de Vries[2] | Adriaan J. van der Meer[2] | Akin Inderson[4] | Joost P. Drenth[5] | Karel J. van Erpecum[6] | Kirsten Boonstra[7] | Ulrich Beuers[1] | Marcel G. W. Dijkgraaf[8] | Cyriel Y. Ponsioen[1] | on behalf of the EpiPSC2 Study Group

[1]Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, location AMC, Amsterdam Gastroenterology, Endocrinology & Metabolism, Amsterdam, The Netherlands

[2]Department of Gastroenterology and Hepatology, Erasmus MC, University Medical Center, Rotterdam, The Netherlands

[3]Department of Gastroenterology and Hepatology, University of Groningen and University Medical Center Groningen, Groningen, The Netherlands

[4]Department of Gastroenterology and Hepatology, Leiden University Medical Center, Leiden, The Netherlands

[5]Department of Gastroenterology and Hepatology, Radboud University Medical Center, Nijmegen, The Netherlands

[6]Department of Gastroenterology and Hepatology, University Medical Center Utrecht, Utrecht, The Netherlands

[7]Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, location VUmc, Amsterdam Gastroenterology & Metabolism, Amsterdam, The Netherlands

[8]Department of Epidemiology and Data Science, Amsterdam University Medical Center, location University of Amsterdam, Amsterdam Public Health, Amsterdam, The Netherlands

Abstract

Background & Aims: Primary sclerosing cholangitis (PSC) is a progressive, cholestatic liver disease which greatly impacts the lives of individuals. Burden of disease due to shortened life expectancy and impaired quality of life is ill-described. The aim of this study was to assess long-term disease burden in a large population-based registry with regard to survival, clinical course, quality adjusted life years (QALYs), medical consumption and work productivity loss.

Methods: All PSC patients living in a geographically defined area covering ~50% of the Netherlands were included, together with patients from the three liver transplant centres. Survival was estimated by competing risk analysis. Proportional shortfall of QALYs during disease course was measured relative to a matched reference cohort using validated questionnaires. Work productivity loss and medical consumption were evaluated over time.

Results: A total of 1208 patients were included with a median follow-up of 11.2 year. Median liver transplant-free survival was 21.0 years. Proportional shortfall of QALYs increased to 48% >25 years after diagnosis. Patients had on average 12.4 hospital contact days among which 3.17 admission days per year, annual medical costs were €12 169 and mean work productivity loss was 25%.

Conclusions: Our data quantify for the first time disease burden in terms of QALYs lost, clinical events, medical consumption, costs as well as work productivity loss, and show that all these are substantial and increase over time.

Abbreviations: AIH, autoimmune hepatitis; CIC, cumulative incidence curve; CRC, colorectal cancer; EQ-5D, EuroQol-5D; GBC, gall bladder cancer; HCC, hepatocellular carcinoma; IBD, inflammatory bowel disease; iMCQ, iMTA Medical Consumption Questionnaire; iMTA, Institute for Medical Technology Assessment; IPCQ, iMTA productivity Cost Questionnaire; IQR, interquartile range; LT, liver transplantation; PSC, primary sclerosing cholangitis; PRO, patient-reported outcome; QALY, quality adjusted life years; QoL, quality of life.

Kim van Munster and Bregje Mol contributed equally to this manuscript.

Correspondence
Cyriel Y. Ponsioen, Department of Gastroenterology and Hepatology, Amsterdam University Medical Center, location AMC, Amsterdam Gastroenterology, Endocrinology & Metabolism, Amsterdam, The Netherlands.
Email: c.y.ponsioen@amsterdamumc.nl

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1 | INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease characterized by multifocal biliary lesions. Inflammatory bowel disease (IBD), mainly ulcerative colitis (UC), coexists in 70% of PSC patients.[1] At diagnosis, 44% of patients had symptoms in a large Swedish cohort.[2] Pruritus, fatigue and right upper quadrant abdominal pain were most frequently reported. With disease progression, recurrent cholangitis and complications of cirrhosis can occur.[1] To date there is no curative therapy other than liver transplantation (LT), although patients might develop recurrent PSC.[1] PSC is associated with an increased risk of malignancies, mainly hepatobiliary malignancies such as cholangiocarcinoma and gallbladder cancer (GBC).[3,4] Risk of colorectal cancer (CRC) is fivefold higher in PSC-IBD patients compared to IBD only patients.[4] PSC is a severe disease with a dismal prognosis. The reported median time between diagnosis and LT or death varies from 14.5 years for tertiary centre cohorts to 21 years for population-based cohorts.[4,5]

Studies regarding the natural history and disease management have provided some insight in the clinical events which PSC patients may encounter. However, benchmark studies containing quantitative data regarding quality of life (QoL), medical consumption and work productivity loss are lacking. Such data are essential for assessing the burden that these patients experience throughout their disease course and for development of new therapies in terms of healthcare evaluation studies. Accurate data on medical consumption are also indispensable for healthcare policy makers to allocate sufficient resources to the care of patients. Burden of disease is driven by shortened life expectancy and loss of QoL when alive. Hence, assessment of disease burden starts with accurate description of long-term survival.

The aim of this study was to assess long-term disease course with an emphasis on disease burden that patients experience during their extended patient journey in terms of survival, clinical events, QoL, medical consumption and work productivity loss.

Key points

Primary sclerosing cholangitis (PSC) is a rare and severe liver disease which is thought to cause substantial disease burden, although a comprehensive assessment is lacking so far. Disease burden is partly driven by shortened life expectancy. Median transplant-free survival is reported to be 14.5–21 years. Quality adjusted life years (QALY) assessment, medical consumption and work productivity loss have previously not been described in PSC. Disease burden in PSC is predominantly driven by shortened life expectancy. Around 21 years after diagnosis, half of the patients has died from PSC or underwent liver transplantation. Ultimately, years lived with optimal quality of life relative to a Dutch reference cohort is reduced by 50%. Moreover, patients spend on average 12 days per year in a hospital, generate €12.000 medical costs per year and have a work productivity loss of 25%. It is estimated that PSC is responsible for >1 billion € of medical expenditure and economic loss annually in the European area. Our data demonstrate the severe disease burden in terms of QALY loss, medical consumption and work productivity loss caused by PSC. These data emphasize the urgent need for effective therapies and may aid in providing benchmark data for cost-effectiveness analyses of new therapies.

2 | METHODS

2.1 | Study design and population

Patients in this observational dynamic registry were included from 2008 until 2020. Data were collected retrospectively from the date of diagnosis until 2008, and prospectively from that date onwards. The study cohort consisted of the population-based EpiPSCPBC registry[4]—with all PSC patients of all 44 hospitals in a geographically defined area covering 50% of the Netherlands—supplemented with newly diagnosed patients after 2011 and patients from all three Dutch LT centres. This registry evolved into the population-based EpiPSC2 registry, which is an open and dynamic registry, with continuous influx of new patients, resulting in variable patient-reported outcome (PRO) follow-up periods. All eligible patients (patients alive and approachable) with regard to General Data Protection Regulation (GDPR) were invited to fill in digital, validated PRO questionnaires. Questionnaires were sent 3-monthly between May 2017 and May 2020. Inclusion criteria were an established PSC diagnosis according to the EASL Clinical Practice guidelines[6] and age >18 years. Details regarding case finding and ascertainment have

been described previously, however, elevated alkaline phosphatase levels were not required for PSC diagnosis after 2013.[4] A diagnosis of autoimmune hepatitis (AIH)-PSC overlap was based on patients also fulfilling the simplified criteria for AIH.[7] Diagnosis of IBD was based on the Lennard–Jones criteria.[8] The study was approved by the institutional review board of the UMC Utrecht (reference: NL14614.041.06/METC 06-267/E).

2.2 | Patient involvement

Patients were involved in the development of both design and content of the study. Important study topics, frequency and extent of questionnaires and practical implementation were consulted with the patient organization. After every questionnaire, feedback of patients was evaluated and incorporated where possible. Progress of the study and interim results were biannually presented in digital news flashes and on patient conferences.

2.3 | Data collection

Data were collected retrospectively from the date of PSC diagnosis onwards (baseline), followed by annual medical chart review and/or medical letters from treating physicians. At baseline, demographics and clinical data regarding PSC diagnosis and coexisting IBD were collected. Alkaline phosphatase (ALP) >1.3 times the upper limit of normal (ULN) at diagnosis was recorded as an indicator of poorer prognosis.[9] Patients were stratified based on PSC subtype. During follow-up, PSC-related clinical events and interventions were monitored. Complete follow-up was defined as follow-up until death or last clinical follow-up <1 year before the end of the study period.

Periodic surveys contained validated questionnaires regarding health-related QoL (EQ-5D-5L), medical consumption (iMCQ) and work productivity loss (iPCQ, iMTA productivity Cost Questionnaire). These surveys were sent four times per year in February, May, August and November. Data were collected via CastorEDC, a cloud-based research data platform, fully compliant with Good Clinical Practice 21CFR, part 11, EU annex 11 and the European data protection directive.

2.4 | Data handling and statistics

2.4.1 | Clinical events

Incidence rates per 1000 patient years at risk were presented with 95%CI calculated using the Rothman/Greenland formula.[10] In case of zero events, the upper bound of the 95%CI was calculated using the Bayr's method. Incidence rates were calculated for large duct PSC, small duct PSC and patients with features of AIH (either large or small duct) separately. 95%CI of the difference between subgroups was calculated using the Bayr's approximation method and tested with the mid-P method using WinPEPI en OpenEpi software.[11,12]

2.4.2 | Survival

The endpoint LT-free survival is a combined endpoint consisting of LT- or PSC-related mortality (death from end-stage liver disease, hepatobiliary malignancy or CRC). Cumulative incidence function (CIF) was calculated in R using the cmprsk package.[13] CIF was calculated for four endpoints: (a) LT- or PSC-related mortality (LT-free survival); (b) LT or death from liver failure; (c) biliary malignancy and (d) CRC occurrence. Competing risks were taken into account to avoid overestimation of occurrence of events in patients who prematurely died or underwent LT when using Kaplan–Meier estimates. With regard to the endpoint LT-free survival, unrelated mortality was considered a competing risk. For LT or death from liver failure-unrelated mortality and death by biliary malignancy was considered a competing risk. For biliary malignancy, all-cause mortality and LT were considered competing risks.

2.4.3 | Quality adjusted life years loss

Quality adjusted life years (QALYs) of PSC patients in the 30 years after diagnosis were compared to an age- and sex-matched reference cohort, by combining survival data and QoL data in various disease stages. The composition of the PSC population changes over time with the major impact being LT and death. In other words, the proportion follow-up days of the entire cohort per 5 years spent for example as severely ill, e.g. 1 year before LT, or deceased changes over time. To obtain insight in how disease burden progressed over time not only until death or LT, but also beyond the latter, we delineated five different disease stages with putative different QoL values: >1 year pre-LT; <1 year pre-LT; <1 year post-LT; >1 year post-LT; and death. This delineation was designed based on the following notions: (i) the waiting time for LT is approximately 1 year after listing in the Netherlands, and the criteria for listing usually imply severe disease; (ii) the first year after LT is accompanied by substantial morbidity. The distribution of these various disease stages was assessed for each patient per 5 years after diagnosis and was derived from the entire registry. Health-related QoL in these distinct disease stages was assessed with the EQ-5D-5L health status questionnaire. Scoring profiles are assigned health utility weights based on an available Dutch health scoring algorithm[14] and range from −0.446 for extreme problems on all dimensions to 1.0 for no problems at all. By definition, death is assigned zero health utility. One year in full health equals one QALY. Given that the repeating EQ-5D-5L measures were equidistant in time, the mean QALYs per 5 years after diagnosis could be derived by taking the average health utility during the distinct disease stages, weighted for the mean lengths of time spent in each disease stage for each window of 5 years. For example, if a

patient gets a liver transplant exactly 6 years after diagnosis and dies exactly 2 years later, his time period 'between 5 and 10 years after diagnosis' is divided as follows; 20% (365.25 days) '<1 year pre-LT', 20% (365.25 days) 'one year after LT', 20% (365.25 days) 'more than one year after LT' and the other 40% of time (730.5 days) deceased. Time spent in every disease state is multiplied by the corresponding average weighted health utility index. Survival and health utility was extracted from Centraal Bureau voor de Statistiek (CBS, a Dutch government agency responsible for collecting statistical information) and Dutch EQ-5D-5L reference data, age and gender distribution of the cohort was taken into account.[14,15] Proportional shortfall (loss of QALYs relative to QALYs in the reference cohort) was calculated per 5 years after diagnosis.

2.4.4 | Medical consumption and costs

Medical consumption was measured with the iMTA Medical Consumption Questionnaire (IMCQ)[16] and was calculated over all completed questionnaires between May 2017 and May 2020. The questionnaire enabled patients to report on in-hospital stay (including day-care treatment, emergency help), major diagnostic and therapeutic procedures, use of maintenance medication (both IBD and PSC related), out-patient clinic visits and others (consultations by general physicians or paramedics, other institutional care like nursing homes, formal home care and own reimbursements) in the previous 3 months. All hospitalization days, diagnostic and therapeutic procedures, and out-patient clinic visits were expressed as mean per patient-year follow-up. Also, a general index for burden of in-hospital medical care was calculated as the number of hospital contact days (HCD) with 1 day of admission counting as one hospital contact day and out-patient clinic visits and diagnostic and therapeutic procedures counting as 0.5 or 1 depending on the time typically spent in-hospital for receiving such care. All unscheduled care was considered acute and all scheduled care (i.e. outpatient visits and colonoscopies) was considered planned.

Unit costing of used healthcare resources was based the most recent Dutch guideline for costing in healthcare provided by the Institute for Medical Technology Assessment (iMTA) on behalf of the Dutch National Health Care Institute.[17] In addition, unit costs of in-hospital resources including personnel costs and all-in costs for a liver transplant procedure not provided in the guideline were extracted from the hospital ledger of one of the largest including centres. The reference year for costing was 2017. Unit costs from different base years were price-indexed, using general consumer price indices from Statistics Netherlands.[18] The distribution of mean costs per patient-year across the different components of hospital care are reported for all PSC patients as well as for two subgroups: patients without LT and patients more than 1 year after LT. A general healthcare expenditure for age- and sex-matched Dutch citizens was calculated based on 2017 data of Statistics Netherlands.[19]

2.4.5 | Work productivity loss

Disease-related work productivity loss was measured repetitively with the IPCQ in the working population and pertained to the week prior to the data of the questionnaire.[20] The working population was defined as all patients who stopped working because of progressive PSC and/or IBD—the fully disabled—and patients at work, some of whom may be temporarily on sick leave due to PSC and/or IBD complaints. Fully disabled patients were considered to have 100% productivity loss. Productivity loss while having a paid job was expressed as the percentage of normal working hours spent on sick leave. Data on work productivity loss are presented per 5 years after diagnosis before LT and <1 and >1 year after LT as mean percentage productivity loss of the working population and patients with paid work.

2.4.6 | Statistical analysis (other)

Pearson's chi-squared test was used for categorical data. Independent *t*-test, one-way ANOVA, Mann–Whitney U test or Kruskal–Wallis was used for continuous data, depending on the number of groups, the distribution of data and the variance (based on Levene's test). Normality was assessed by normality tests and visual inspection of histograms and Q–Q plots. In case of median values of 0, because of highly skewed data, the median with interquartile range was not informative to report. Therefore, data were presented as mean (SD), but non-parametric tests were used for the analyses. A p-value of <0.05 was considered statistically significant. IBM SPSS version 26.0 and R Studio were used for the statistical analyses.[21,22]

2.5 | Role of the funding source

The study was funded by ZonMW (grant number: 836041010). The funder had no role in study design, data collection, data analysis and interpretation, writing of the manuscript or decision to submit for publication. None of the authors was paid to write this article by a pharmaceutical company or other agency.

3 | RESULTS

3.1 | Patients and response

A total of 1208 patients were included with a median follow-up of 11.2(5.9–17.6) years. Baseline characteristics of the entire cohort and the 359 patients participating in the PRO substudy are presented in Table 1. Baseline characteristics according to PSC phenotype are shown in Table S1. A sensitivity analysis comparing patients who participated in the PRO questionnaires versus those alive at the issuing of the first questionnaire but not participating is presented in Table S2. There was a small but significant decrease in the amount

of patients with a coexisting IBD diagnosis, mostly UC, transplanted and an elevated ALP >1.3× ULN at diagnosis in the patients in the PRO substudy compared to the non-responders alive at the first questionnaire. Survival, clinical events and QALY loss were based on the entire cohort, medical consumption and costs, as well as work productivity loss was evaluated in patients returning PRO questionnaires. For various reasons, not all patients could be approached to receive PRO questionnaires (Figure S1). Out of 511 invited patients, 359 (70%) agreed to receive questionnaires. Of those, 316 patients (91%) completed at least one questionnaire. During 3 years, 3525 questionnaires were sent and 67% were completed. To check for potential bias on reporting by phenotype, we determined whether completing more questionnaires was associated with certain factors. Spearman correlation showed no significant bias, see Table S3.

3.2 | Clinical events

Incidence rate per 1000 patient years of decompensated cirrhosis was 16.9 in large duct as opposed to 3.4 in small duct PSC patients ($p = 0.004$) (Table 2). Incidence rate of LT was 21.2 in large duct and 3.8 in small duct PSC. The occurrence of biliary malignancy was more than twice as common in large duct PSC compared to PSC/AIH (8.0 vs. 3.2, $p = 0.095$) or SD-PSC (8.0 vs 2.5, $p = 0.065$); however, contrast did not reach a statistically significant difference. No GBC, hepatocellular carcinoma (HCC) or pancreatic cancer occurred in PSC-AIH or small duct PSC. We found no significant differences in clinical events in PSC-only and PSC-IBD patients, except for HCC, CRC and colectomy (Table S4). During the prospective FU phase 2/76 (3%), small duct patients were documented to have progressed to large duct disease.

TABLE 1 Baseline characteristics of the entire cohort

Baseline characteristics	Entire cohort (*N* = 1208)	Patients in PRO substudy (*N* = 359)
Male gender, *n* (%)	767 (64)	218 (62)
Age at diagnosis, med (IQR)	39 (28–49)	40 (28–48)
Large duct PSC, *n* (%)	1002 (86)	290 (83)
PSC-AIH, *n* (%)	83 (7)	30 (9)
Small duct PSC, *n* (%)	76 (7)	30 (9)
Coexisting IBD, *n* (%)	820 (70)	224 (64)
Ulcerative colitis, *n* (%)	606 (74)	156 (70)
Crohn's disease, *n* (%)	169 (21)	57 (25)
IBD-U, *n* (%)	45 (5)	11 (5)
Signs of dec. liver cirrhosis during FU, *n* (%)	176 (22)	12 (3)
Liver transplanted, *n* (%)	287 (24)	72 (20)
ALP at diagnosis >1.3× ULN, *n* (%)	367 (74)	89 (66)
Bilirubin times ULN at diagnosis, med (IQR)	0.8 (0.5–1.9)	0.7 (0.5–1.4)
Non-related comorbidities, med (IQR)		1 (0–2)
Cardiovascular disease, *n* (%)		55 (21)
Diabetes type I and II, *n* (%)		22 (8)

3.3 | Survival analysis

Figure 1 presents the CIF of LT- or PSC-related mortality (LT-free survival) (A), LT or death from liver failure (B) and biliary malignancy (C) from diagnosis onwards accounting for competing risks as well as the CIF of the competing risks. Median LT-free survival respecting competing risks was 21.0 (10–37) years after diagnosis (A). Median survival until LT or death from liver failure was 28.3 (13–44) years. Cumulative incidence of biliary malignancy was 19.0% at 44 years (C). Median time from diagnosis until all-cause mortality was 28.1 (25–31).

Total number of deaths was 292, of which 152 PSC related; 54 liver failure, 66 hepatobiliary cancer, 12 CRC, 16 complications pertaining to LT and 4 other PSC-related cause. A total of 287 patients received ≥1 LT. The cumulative incidence function of the occurrence of CRC is shown in Figure S4.

3.4 | Shortfall of QALYs

Health utility calculation for each disease stage was based on the EQ-5D-5L scores from the patients participating in the PRO substudy ($N = 359$). Shortfall of QALY's was calculated based on the survival data and person years contributed to each disease stage of the entire cohort ($N = 1208$). Health utility at the time of PSC diagnosis was 0.89 for both patients and the matched reference population. From diagnosis until 1 year before LT, health utility ranged from 0.822 to 0.866 depending on disease duration. Health utility was 0.797, 0.834 and 0.836 for patients <1 year pre-LT, <1 year post-LT and >1 year post-LT respectively. The distribution of time spent in distinct disease stages per 5 years after diagnosis is presented in Figure 2A. LT was infrequently observed during the first 5 years after diagnosis with 93% of all follow-up time spent in the disease stage >1 year pre-LT, while 26–30 years after diagnosis death already reduced the time alive to 42% with almost half of that time (19%) being alive after LT. In the first 30 years after diagnosis, PSC patients generated a total of 18.2 QALYs on average. This is 5.7 QALYs less than a Dutch age- and sex-matched reference cohort in the same period (Figure 2B). Proportional shortfall of QALYs was 7% in the first 5 years after diagnosis and rose to 48% 26–30 years after diagnosis.

3.5 | Medical consumption and costs

Analyses regarding medical consumption and costs were based on the subset of patients participating in the PRO substudy ($N = 359$). PSC patients spent on average 12.3 (±27.6) days per year in hospital,

TABLE 2 Incidence rates (95% CI) per 1000 patient years at risk for clinical events in all patients and stratified for PSC type

	All patients ($n = 1208$)	Large duct PSC ($n = 1002$)	PSC-AIH ($n = 83$)	Small duct PSC ($n = 76$)	Mid-p value large duct vs PSC-AIH	Mid-p value large duct vs small duct
Signs of dec. cirrhosis	16.4 (14.1; 16.4)	16.9 (14.5; 19.8)	19.7 (12.3; 31.8)	3.4 (0.9; 13.6)	0.534	0.004
Liver transplantation	19.7 (17.5; 19.7)	21.2 (18.8; 23.9)	15.2 (9.0; 25.7)	3.8 (1.2; 11.7)	0.223	<0.001
Biliary malignancy	7.4 (6.2; 7.4)	8.0 (6.6; 9.8)	3.2 (1.1; 10.1)	2.5 (0.6; 10.0)	0.095	0.065
Cholangiocarcinoma	6.4 (5.5; 6.4)	6.8 (5.6; 8.5)	3.3 (1.1; 10.1)	2.5 (0.6; 10.0)	0.189	0.128
Gallbladder cancer	1.0 (0.6; 1.0)	1.2 (0.7; 2.0)	0.0 (0.0; 5.1)	0.0 (0.0; 5.9)	0.351	0.402
Hepatocellular carcinoma	0.8 (0.4; 0.8)	1.5 (1.0; 2.3)	0.0 (0.0; 5.1)	0.0 (0.0; 5.9)	0.265	0.315
Pancreas cancer	0.3 (0.1; 0.3)	0.3 (0.1; 0.8)	0.0 (0.0; 5.1)	0.0 (0.0; 5.9)	0.756	0.784
Colorectal cancer	4.2 (3.3; 4.2)	4.5 (3.5; 5.8)	2.2 (0.5; 8.7)	1.3 (0.2; 8.9)	0.316	0.166
Colectomy	10.8 (9.2; 10.7)	10.6 (9.0; 12.6)	12.0 (6.6; 21.6)	11.3 (5.9; 21.7)	0.679	0.822

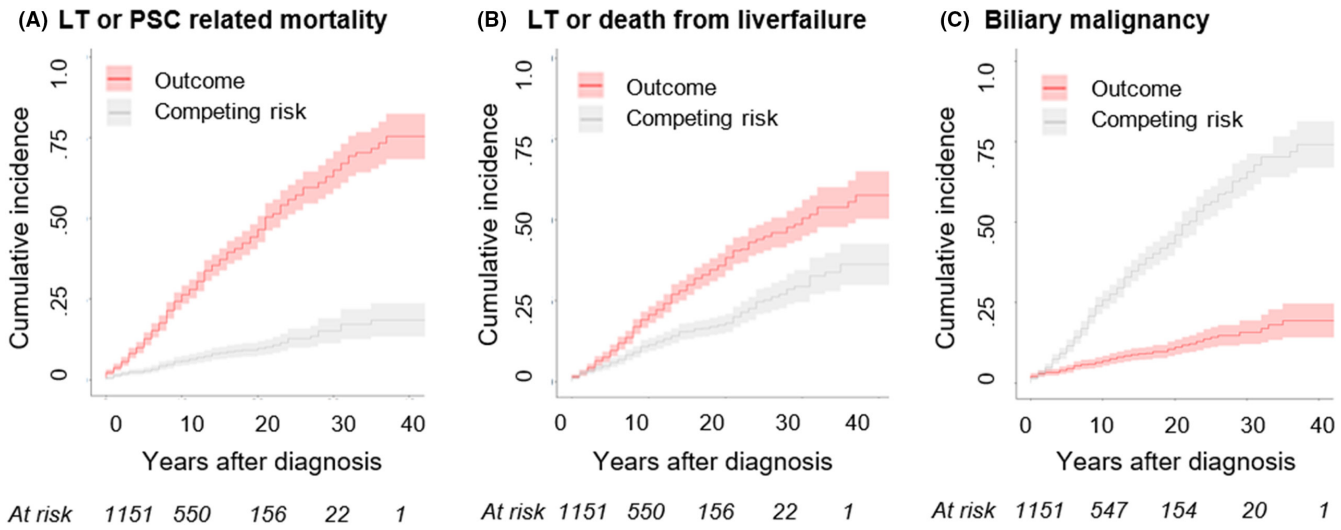

FIGURE 1 Cumulative incidence curves (95% CI intervals) for PSC-related mortality or LT (A), LT or death from liver failure (B) and biliary malignancy (C). The red line represents the cumulative incidence of the outcome respecting competing risks, the grey line represents the cumulative incidence of competing risk for reference.

of which 4.2 (±19.2) days were for acute care (Figure 3). Distribution of HCD was skewed to the right (Figure S2). Total mean HCD (before LT) was lowest in the first 5 years after diagnosis (8.8 ± 16.2) and highest 16–20 years after diagnosis (11.8 ± 19.0). Quantity of planned care remained stable over time, but acute care increased significantly from 2.1 (±12.2) to 3.8 (±12.1) per year ($p = 0.016$). HCD was on average 86.3 (±104.0) the first year after LT. This significantly decreased to 13.8 (±23.5) days >1 year after LT. Patients with large duct PSC reported more HCD (planned and acute) compared with small duct PSC (Figure S3). Planned HCD occurred more frequently in PSC-IBD patients compared to PSC alone (8.1 ± 11.2 vs 6.8 ± 8.2, $p = 0.006$).

Medical costs were based on 576 patient-years of follow-up. On average, patients visited their gastroenterologist/hepatologist with a median number of visits of 4, (IQR: 0–4), other medical specialist 0 (IQR: 0–4); blood sampling was performed four times per year (IQR:0–4). Mean annual medical costs per patient were €12,169 (Figure 4, Table S5) compared to €5436 for age- and sex-matched Dutch citizens. Clinical care accounted for the largest share with €2736, followed by other costs (€2717). Mean yearly costs of all patients before LT was €8856. Within 1 year post-LT, annual costs were €126 295 including costs for the transplantation itself (€45,638). More than 1 year post-LT annual costs were €15 376.

3.6 | Work productivity loss

The analysis regarding work productivity loss was based on the patients participating in the PRO substudy ($N = 359$). IPCQ was completed at least once by 324 patients, of which 68 (21%) had no paid work due to other causes, resulting in a working population of 256 patients. Patients with paid work had on average 34 contract hours per week. In Figure 5, mean productivity loss of the working population was 25%. Before LT, productivity loss increased from 18% to 34% ($p < 0.001$). Productivity loss among patients with paid work (working population without fully disabled patients) was stable over time. The grey area represents the survival curve of the entire cohort. It is important to notice that during follow-up, severely ill patients disappeared from the cohort due to death or LT.

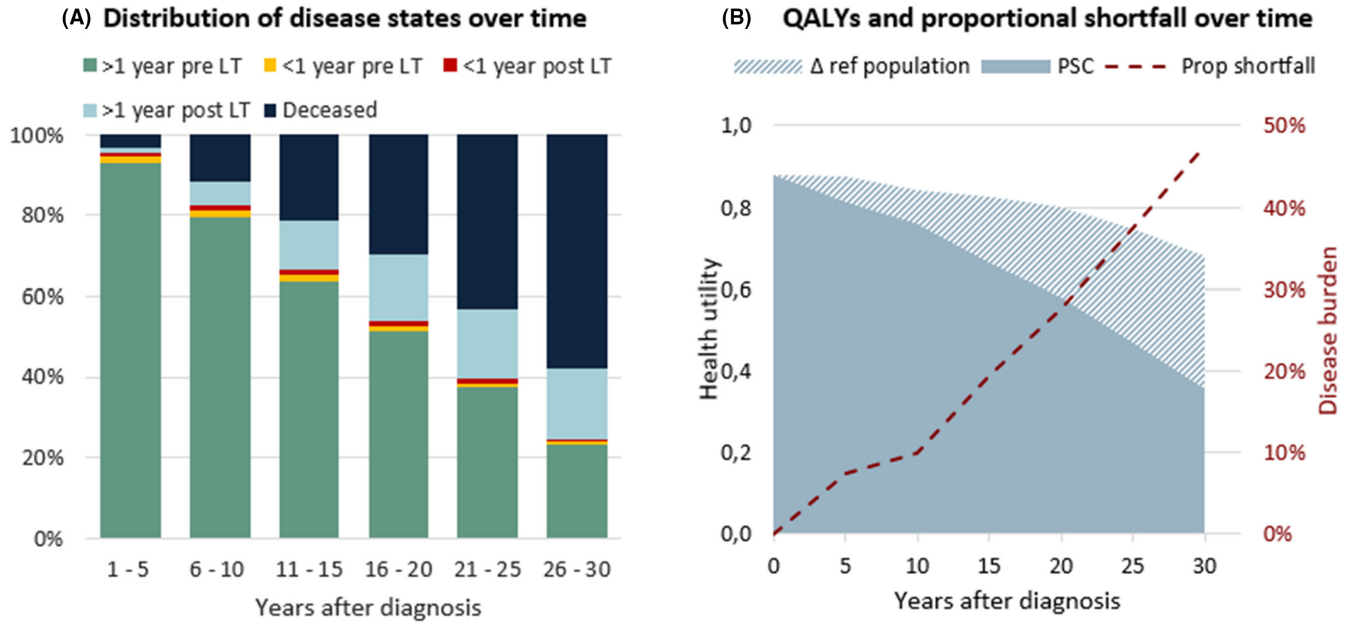

FIGURE 2 Proportional shortfall of QALYs. Distribution of disease states of all patients per 5 years after diagnosis (A) and health utility in the years after diagnosis in PSC versus an age- and sex-matched reference population, the red line represents proportional shortfall of QALYs of PSC patients relative to the reference population (B).

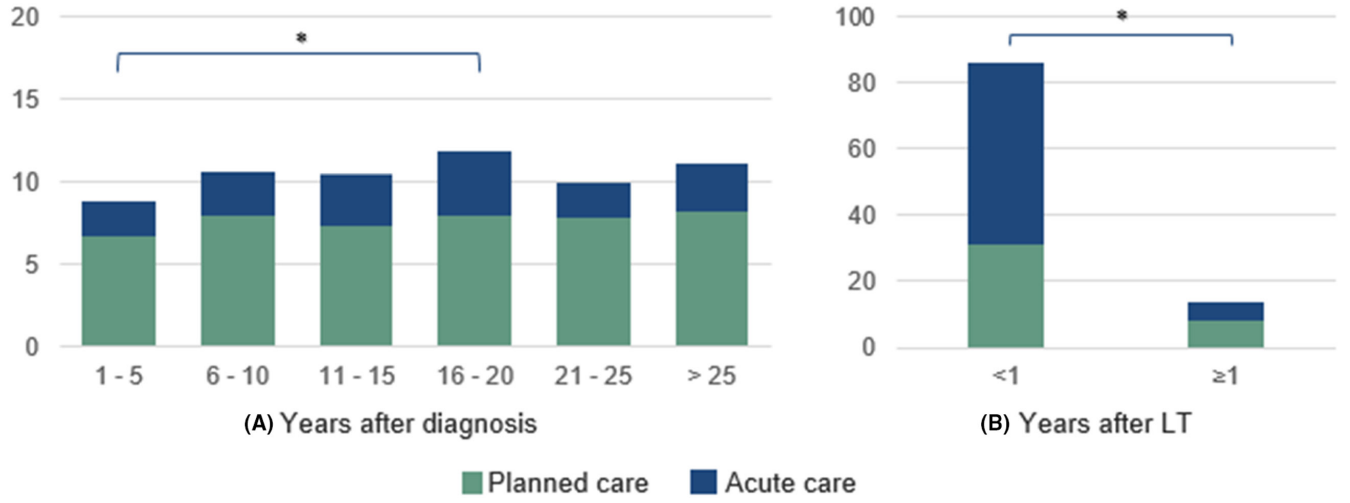

FIGURE 3 Mean hospital contact days. During follow-up in patients before LT stratified by years after diagnosis (A) and after LT stratified by the first year and after the first year after LT (B). Planned care is depicted in green, acute care in blue. A significant difference is indicated with an "*".

Mean productivity loss of the working population in the first year after LT and >1 year after LT was 58% and 38% respectively ($p = 0.085$). Patients after LT with paid work had production loss of 43% in the first year decreasing to 9% >1 year post-LT ($p < 0.001$).

4 | DISCUSSION

We here present the first longitudinal data on disease burden in PSC in the largest population-based registry to date. Disease burden is driven by both morbidity and mortality. LT-free survival in this study, taking into account competing risks, is slightly better than in most other population-based studies.[2,4,5,23] Survival until LT or all-cause mortality without taking competing risks into account was 18.0 years in our cohort, which is ~4 years longer than the same endpoint in the IPSCSG study which consisted mainly of tertiary care patients.[5] This is likely explained by selection bias.[2]

Besides decreased life expectancy, patients experience substantial disease burden during the course of their illness. PSC is a slowly progressive, but ultimately severe disease, which is reflected by relatively low disease burden in the first years after diagnosis (9%) and

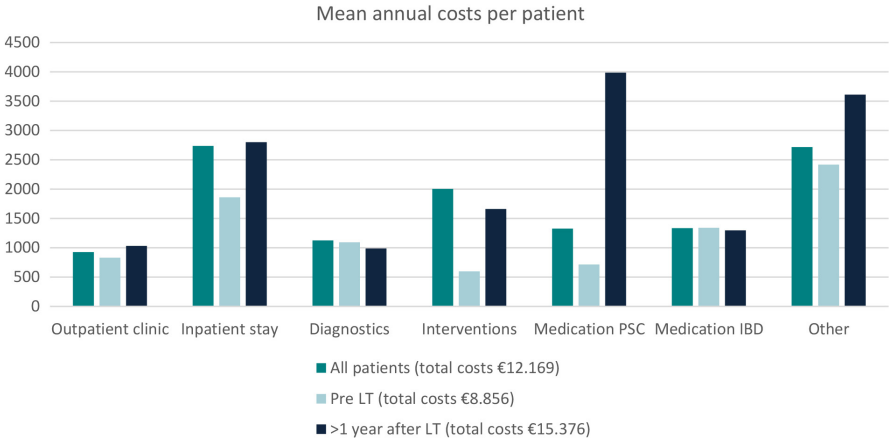

FIGURE 4 Distribution of mean costs per person-year. Costs are stratified by seven categories and presented for all patients, only patients before LT and only patients >1 year after LT. Costs associated with each category are specified in Table S5.

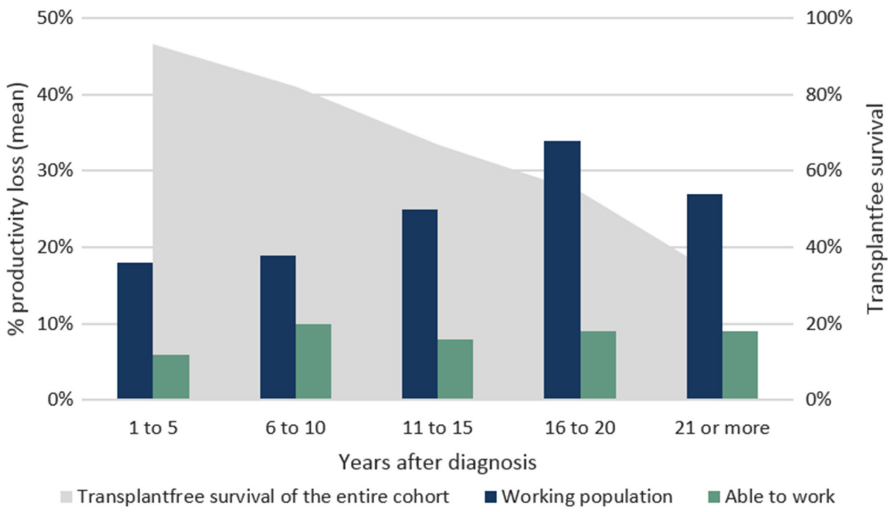

FIGURE 5 Work productivity loss during follow-up. In the working population (blue) and in patients who are able to work (working population without fully disabled patients) (green). The grey area represents the proportion of patient days alive without LT (patients with LT-free survival).

the exponential increase to a sizeable ~48% proportional shortfall after 26 years.

Interestingly, QALY loss in PSC patients appears to be predominantly driven by shortened life expectancy rather than impaired QoL when alive. Health utility indices were comparable to the limited number of available studies in other chronic liver disease populations.[24,25]

PSC patients spend on average one day per month in a hospital and generate on average ~€12 000 medical costs per year. This is more than double the costs of the Dutch reference population (~€5.700).[19] Inferring this to an estimated 45 000 PSC patients in 50 countries of Europe lead to an estimated relative annual medical expenditure on this rare disease of >€475 million, accommodating for differences in purchasing power parities across Europe.[26] Work productivity loss of all patients that are willing to work (working population) is 25% and increases over time, even though the more severely ill patients drop-out due to LT or death. This adds another estimated €530 million economic loss in the wider European area only, taking into account disparities in wages and labour costs throughout Europe.[27]

Annual medical costs of PSC patients are much higher compared to other studies with IBD patients (~€2600[28]), PBC (~€950[29]) or AIH (~€1000[30]). However, paramedical costs and patients' own reimbursements were not included in these studies as well as costs for co-morbidities. Direct medical costs in an American study with chronic liver disease patients was $19 000.[31] Although we cannot directly compare our study to others, PSC patients appear to generate substantial economic burden.

Work productivity loss is mainly driven by a high rate of fully disabled patients. PSC/IBD-related absenteeism in patients with paid work was on average 7.5%. Recent data on the general Dutch population show that disease-related absenteeism is around 4.4%.[32] Hence, work productivity loss in PSC causes substantial economic burden.

The major strengths of this study lay in its large sample size with more than 1200 patients, its population-based nature, and the long median follow-up period of more than 11 years. With numbers more than doubled and a median FU 1.5 times longer we strengthen and recapitulate results from our earlier study confirming that prognosis is considerably better than that observed in predominantly tertiary care series.[2,4,5,23] Moreover, disease burden was not based on one single measurement, but instead measured longitudinally, which allows a more accurate overall estimation of a variable outcome measure such as the EQ-5D-5L.

Some limitations need to be addressed. Healthcare costs may be difficult to generalize as unit costs and management policies

differ per country. This may also apply to work productivity loss as the definition of work disability and availability of a social security systems vary. Also, clinical course of Dutch PSC patients might not be fully representative of the global situation. However, median transplant-free survival was quite similar to two population-based cohorts from Oxford, UK and the Helsinki and Uusimaa hospital district, Finland.[23,33] Until 2013, elevated alkaline phosphatase was required to make a diagnosis of PSC. This implies that there could be a bias towards underrepresentation of less severe PSC patients in those cases that were accrued before 2013. However, this bias may be mitigated by the fact that PSC is usually a progressive disease, with resultant elevations in alkaline phosphatase and other liver enzymes, with probable surfacing of the diagnosis before 2020. Clinical data were retrospectively accrued from medical charts and due to recently introduced GDPR legislation constraints, follow-up could only be obtained after written informed consent. For the same reason, not all patients could be approached for the PRO part of the study. Moreover, the PRO questionnaires were sampled longitudinally albeit follow-up was at maximum 3 years and not the whole diseased period (in contrast to the clinical follow-up). Hence, patients who filled in PRO questionnaires in the first 5 years after diagnosis are not the same as the ones 20 years after diagnosis. Although we encouraged patients from the whole PSC spectrum (from asymptomatic to severely diseased) to participate, there may be some selection/responder bias. Clinical characteristics of patients receiving PRO questionnaires were mostly similar to those who did not participate in the prospective PRO measurements. The amount of patients with a coexisting IBD diagnosis in general, but not with regard to IBD-phenotype, and an elevated ALP >1.3x ULN at diagnosis were slightly, albeit significantly, less represented among the patients in the PRO substudy. Furthermore, age at diagnosis was slightly higher in those taking part in the PRO study.

The generic EQ-5D-5L health-related QoL instrument was used to derive QALYs and assess the burden of disease of PSC patients from a societal perspective. Although generic, the EQ-5D-5L domain and index scores reflect the impact of symptoms as pain, itching and fatigue[34] which are recognized features of how patients experience having PSC in daily life.[35] The EQ-5D-5L scores undoubtfully would also reflect worries, depressed feelings and limited functioning in work and social activities to a reasonable extent, but for more details what makes PSC patients worry, why they may feel depressed or which activities they are unable to perform in particular, more disease and domain-specific questionnaires should be used for a full account of the relevant QoL issues in PSC.[36]

QALY analysis is in general complicated by a heterogeneous and episodic disease course, which are both the case in PSC.[37] Taking into account these limitations, follow-up was split in different disease stages based on the available data. Recall bias can never be ruled out completely, although we deliberately chose in conjunction with the patient panel for 3-monthly questionnaires in order to limit this potential confounder as much as possible. Several studies have shown that a recall period of 3 months gives reliable data regarding medical consumption.[38,39] In addition, medical charts and annual letters to the GP were scanned for medical consumption items yearly.

In conclusion, these long-term FU data confirm that on population-based level LT-free median survival is more favourable than reported earlier. This study for the first time quantifies the severe burden PSC patients suffer from during their disease course, underscoring the urgent need for an effective therapy, and call for replication in other regions. Our data may serve as benchmark in (cost-)effectiveness analyses of new therapies, as well as may aid healthcare planners in future budget allocation.

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CONFLICT OF INTEREST

All authors disclosed no financial or personal relationship relevant to this publication.

ETHICAL APPROVAL

The study was approved by the institutional review board of the UMC Utrecht (reference: NL14614.041.06/METC 06-267/E).

ORCID

Kim N. van Munster https://orcid.org/0000-0001-7019-5083
Joost P. Drenth https://orcid.org/0000-0001-8027-3073
Ulrich Beuers https://orcid.org/0000-0001-5114-7799
Cyriel Y. Ponsioen https://orcid.org/0000-0001-5203-0453

REFERENCES

1. Dyson JK, Beuers U, Jones DEJ, Lohse AW, Hudson M. Primary sclerosing cholangitis. *Lancet (London, England)*. 2018;391(10139):2547-2559.
2. Broome U, Olsson R, Loof L, et al. Natural history and prognostic factors in 305 Swedish patients with primary sclerosing cholangitis. *Gut*. 1996;38(4):610-615.
3. Steenstraten IC, Sebib Korkmaz K, Trivedi PJ, et al. Systematic review with meta-analysis: risk factors for recurrent primary sclerosing cholangitis after liver transplantation. *Aliment Pharmacol Ther*. 2019;49(6):636-643.
4. Boonstra K, Weersma RK, van Erpecum KJ, et al. Population-based epidemiology, malignancy risk, and outcome of primary sclerosing cholangitis. *Hepatology*. 2013;58(6):2045-2055.
5. Weismuller TJ, Trivedi PJ, Bergquist A, et al. Patient age, sex, and inflammatory bowel disease phenotype associate with course of primary Sclerosing cholangitis. *Gastroenterology*. 2017;152(8):1975-84.e8.
6. European Association for the Study of the L. EASL clinical practice guidelines: management of cholestatic liver diseases. *J Hepatol*. 2009;51(2):237-267.
7. Hennes EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. *Hepatology (Baltimore, Md)*. 2008;48(1):169-176.
8. Lennard-Jones JE. Classification of inflammatory bowel disease. *Scand J Gastroenterol Suppl*. 1989;170:2-6. discussion 16-9.
9. de Vries EM, Wang J, Leeflang MM, et al. Alkaline phosphatase at diagnosis of primary sclerosing cholangitis and 1 year later: evaluation of prognostic value. *Liver International*. 2016;36(12):1867-1875.

10. Sullivan KMSM. *Confidence Intervals for a Rate*. Rollins School of Public Health EMORY University; 2006.
11. Abramson JH. WINPEPI (PEPI-for-windows): computer programs for epidemiologists. *Epidemiol Perspect Innov*. 2004;1(1):6.
12. Kevin M. Sullivan AGD. PersonTime2—Comparing Two Person-Time Rates. https://testopenepi.com/PersonTime2/PersonTime2.htm.
13. Gray B. Subdistribution analysis of competing risks. 2022. https://cran.r-project.org/web/packages/cmprsk/cmprsk.pdf.
14. Versteegh MM, Roijen L, Vermeulen KM, et al. Dutch tariff for the five-level version of EQ-5D. *Value Health*. 2016;19(4):343-352.
15. CBS. Statline. https://opendata.cbs.nl/statline/#/CBS/nl/.
16. Bouwmans C, Koopmanschap MA, Krol M, et al. Handleiding iMTA Medical Cost Questionnaire (iMCQ). 2013.
17. Hakkaart-van Roijen LVLN, CAM B, Kanters TA, Tan SS. *Cost Guide. Cost Research Methodology and Reference Prices for Economic Evaluations in Health Care*. Zorginstituut Nederland; 2015 (versie 1.6 23 November 2016).
18. STATLINE C. Consumer prizes; price index 2015=100. https://opendata.cbs.nl/statline/?dl=3F0E#/CBS/nl/dataset/83131NED/table
19. RIVM. [Cost of illness]. 29 oktober 2019 2019. https://statline.rivm.nl/#/RIVM/nl/dataset/50050NED/table?ts=1608275685025
20. Bouwmans C, Krol M, Severens H, Koopmanschap M, Brouwer W, Hakkaart-van RL. The iMTA productivity cost questionnaire: a standardized instrument for measuring and valuing health-related productivity losses. *Value Health*. 2015;18(6):753-758.
21. IBM. SPSS Statistics for Windows, Version 26.0; 2017.
22. Team R. *RStudio: integrated development for R*. RStudio, PBC; 2020.
23. Barner-Rasmussen N, Pukkala E, Jussila A, Farkkila M. Epidemiology, risk of malignancy and patient survival in primary sclerosing cholangitis: a population-based study in Finland. *Scand J Gastroenterol*. 2020;55(1):74-81.
24. Younossi ZM, Boparai N, McCormick M, Price LL, Guyatt G. Assessment of utilities and health-related quality of life in patients with chronic liver disease. *Am J Gastroenterol*. 2001;96(2):579-583.
25. McLernon DJ, Dillon J, Donnan PT. Health-state utilities in liver disease: a systematic review. *Med Decis Making*. 2008;28(4):582-592.
26. OECD. Purchasing power parities (PPP) (indicator). 2020. https://www.oecd-ilibrary.org/finance-and-investment/purchasing-power-parities-ppp/indicator/english_1290ee5a-en.
27. Eurostat. Wages and labour costs. 2020. https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Wages_and_labour_costs
28. Burisch J, Vardi H, Schwartz D, et al. Health-care costs of inflammatory bowel disease in a pan-European, community-based, inception cohort during 5 years of follow-up: a population-based study. *Lancet Gastroenterol Hepatol*. 2020;5(5):454-464.
29. Gerussi ARU, Croce D, Bonfanti M, Invernizzi P, Carbone M. Cost of illness of primary biliary cholangitis – a population-based study. *Digest Liver Dis*. 2020;52:e36.
30. Kim BH, Choi HY, Ki M, Kim KA, Jang ES, Jeong SH. Population-based prevalence, incidence, and disease burden of autoimmune hepatitis in South Korea. *PLoS One*. 2017;12(8):e0182391.
31. Stepanova M, De Avila L, Afendy M, et al. Direct and indirect economic burden of chronic liver disease in the United States. *Clinical Gastroenterol Hepatol*. 2017;15(5):759-66 e5.
32. CBS. Employee sickness absence increased further in 2019. 16-03-2020 2020. https://www.cbs.nl/en-gb/news/2020/12/employee-sickness-absence-increased-further-in-2019
33. Al Mamari S, Djordjevic J, Halliday JS, Chapman RW. Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol*. 2013;58(2):329-334.
34. van Munster KN, Dijkgraaf MGW, van Gennep S, Beuers U, Ponsioen CY. The simple Cholestatic complaints score is a valid and quick patient reported outcome measure in primary sclerosing cholangitis. *Liver Int*. 2020;40:2758-2766.
35. van Munster KN, Dijkgraaf MGW, Oude Elferink RPJ, Beuers U, Ponsioen CY. Symptom patterns in the daily life of PSC patients. *Liver Int*. 2022;42(7):1562-1570.
36. Marcus E, Stone P, Thorburn D, Walmsley M, Vivat B. Quality of life (QoL) for people with primary sclerosing cholangitis (PSC): a pragmatic strategy for identifying relevant QoL issues for rare disease. *J Patient Rep Outcomes*. 2022;6(1):76.
37. Vijgen SVHF, Obradovic M. Disease burden in daily practice. The theory and practice of calculation of disease burden during assessments of the health care package. Diemen; 2018.
38. van den Brink M, van den Hout WB, Stiggelbout AM, Putter H, van de Velde CJ, Kievit J. Self-reports of health-care utilization: diary or questionnaire? *Int J Technol Assess Health Care*. 2005;21(3):298-304.
39. Goossens ME, Rutten-van Molken MP, Vlaeyen JW, van der Linden SM. The cost diary: a method to measure direct and indirect costs in cost-effectiveness research. *J Clin Epidemiol*. 2000;53(7):688-695.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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