

SUPPLEMENTAL MATERIAL

Supplementary Methods

Mathematical approach for indirect standardisation

Indirect standardisation generates the expected rate/proportion in a study population if it was subject to the stratum-specific rates/proportions of the standard population. The number of observed events versus the number of expected events can be expressed as a ratio – the standardised rate (or proportion) ratio.

In the context of this study, the study population is defined as all eligible patients meeting the case definition of PBC, while the standard population is defined as all eligible patients who did not meet the case definition of PBC. Strata are defined as groupings based on the age and sex of individuals.

For a study population, the number of expected events (d_e) can be calculated as follows:

$$d_e = \sum_{(k, i=1)} n_i R_i$$

d_e = the number of expected events; n_i = the number of individuals in the i^{th} stratum of the study population; R_i = stratum-specific rate or proportion in the i^{th} stratum of the standard population; k = the number of strata.

The indirect standardised ratio (ISR) is the ratio of the number of observed events (d_o) to the number of expected events (d_e) in the study population:

$$ISR = d_o/d_e = d_o/\sum_{(k, i=1)} n_i R_i$$

d_o = the number of observed events; d_e = the number of expected events; n_i = the number of individuals in the i^{th} stratum of the study population; R_i = stratum-specific rate or proportion in the i^{th} stratum of the standard population; k = the number of strata.

Confidence intervals for the ISR are calculated per Owen's exact Poisson method.²⁵

$$ISR_l = \chi^2_{1-\alpha/2, 2d_o} / 2d_e$$

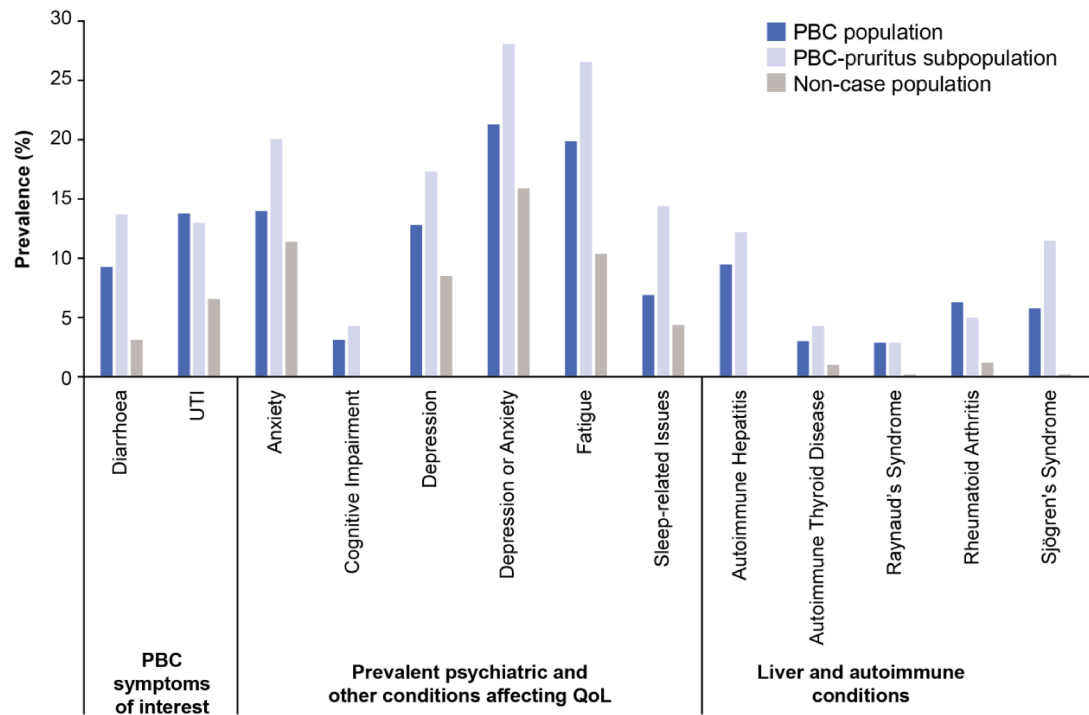
$$ISR_u = \chi^2_{1-\alpha/2, 2(d_o+1)} / 2d_e$$

ISR_l = the lower bound of the confidence interval; ISR_u = the upper bound of the confidence interval;

d_o = the number of observed events; d_e = the number of expected events.

Supplementary Results

Supplementary Figure 1. Prevalence of prespecified comorbidities among patients in the PBC population (N=1,963) or the PBC-pruritus subpopulation (N=139) relative to the respective non-case populations*



*N for the non-case population (N=10,245,592), relates to the comparison versus the PBC population not versus the PBC-pruritus population (N=9,984,009)

PBC, primary biliary cholangitis; QoL, quality of life; UTI, urinary tract infection

Supplementary Table 1. The 30 most common comorbidities (ICD-10-CM diagnosis codes) in the PBC population and the PBC-pruritus subpopulation

PBC (N=1,963)	N (%)	PBC-pruritus subpopulation (N=139)	N (%)
Essential (primary) hypertension	896 (45.6)	Essential (primary) hypertension	58 (41.7)
Hyperlipidaemia, unspecified	555 (28.3)	Hypothyroidism, unspecified	41 (29.5)
Gastro-esophageal reflux disease without esophagitis	493 (25.1)	Hyperlipidaemia, unspecified	39 (28.1)
Unspecified cirrhosis of liver	473 (24.1)	Vitamin D deficiency, unspecified	36 (25.9)
Hypothyroidism, unspecified	470 (23.9)	Gastro-oesophageal reflux disease without oesophagitis	33 (23.7)
Biliary cirrhosis, unspecified	433 (22.1)	Biliary cirrhosis, unspecified	32 (23.0)
Vitamin D deficiency, unspecified	407 (20.7)	Cough	27 (19.4)
Cough	335 (17.1)	Anxiety disorder, unspecified	22 (15.8)
Type 2 diabetes mellitus without complications	299 (15.2)	Fatty (change of) liver, not elsewhere classified	22 (15.8)
Low back pain	278 (14.2)	Cholangitis	22 (15.8)
Other fatigue	268 (13.7)	Anaemia, unspecified	22 (15.8)
Mixed hyperlipidaemia	268 (13.7)	Actinic keratosis	20 (14.4)
Shortness of breath	244 (12.4)	Portal hypertension	19 (13.7)
Unspecified abdominal pain	241 (12.3)	Low back pain	19 (13.7)
Age-related osteoporosis*	239 (12.2)	Abnormal levels of other serum enzymes	19 (13.7)
Anaemia, unspecified	234 (11.9)	Abnormal results of liver function studies	18 (12.9)
Other specified abnormal findings of blood chemistry	232 (11.8)	Type 2 diabetes mellitus without complications	18 (12.9)
Abnormal results of liver function studies	226 (11.5)	UTI, site not specified	18 (12.9)
UTI, site not specified	224 (11.4)	Autoimmune hepatitis	17 (12.2)
Abnormal levels of other serum enzymes	222 (11.3)	Acute bronchitis, unspecified	16 (11.5)
Fatty (change of) liver, not elsewhere classified	219 (11.2)	Neoplasm of uncertain or unknown behavior: Skin	16 (11.5)
Other seborrheic keratosis	215 (11.0)	Depressive episode, unspecified	16 (11.5)
Acute upper respiratory infection, unspecified	207 (10.5)	Postmenopausal osteoporosis	16 (11.5)
Chest pain, unspecified	207 (10.5)	Liver disease, unspecified	15 (10.8)
Age-related nuclear cataract, bilateral	202 (10.3)	Mixed hyperlipidaemia	15 (10.8)
Dry eye syndrome of bilateral lacrimal glands	198 (10.1)	Obesity, unspecified	14 (10.1)
Neoplasm of uncertain or unknown behavior: Skin	196 (10.0)	Chronic obstructive pulmonary disease, unspecified	12 (8.6)
Cholangitis	194 (9.9)	Other specified disorders of bone density and structure	12 (8.6)
Autoimmune hepatitis	187 (9.5)	Pure hypercholesterolaemia	12 (8.6)
Cervicalgia	186 (9.5)	Headache	12 (8.6)
		Hypokalaemia	12 (8.6)
		Acute pharyngitis, unspecified	12 (8.6)
		Cervicalgia	12 (8.6)
		Splenomegaly, not elsewhere classified	12 (8.6)

*Without current pathological fracture

ICD-10-CM, International Classification of Diseases, 10th Revision, Clinical Modification; PBC, primary biliary cholangitis; UTI, urinary tract infection

Supplementary Table 2. The 30 most commonly prescribed medications by category* in the PBC population and the PBC-pruritus subpopulation

PBC (N=1,963)	N (%)	PBC + coded pruritus (N=139)	N (%)
Gallstone solubilizing agents	1,724 (87.8)	Gallstone solubilizing agents	116 (83.5)
Analgesics	858 (43.7)	Analgesics	70 (50.4)
Dermatological agents [†]	642 (32.7)	Anxiolytics, sedatives, and hypnotics	66 (47.5)
Antihyperlipidemic agents [‡]	621 (31.6)	Dermatological agents [†]	65 (46.8)
Proton pump inhibitors	598 (30.5)	Antihyperlipidemic agents [‡]	53 (38.1)
Adrenal cortical steroids	586 (29.9)	Proton pump inhibitors	51 (36.7)
Antidepressants	575 (29.3)	Antidepressants	49 (35.3)
Thyroid hormones	539 (27.5)	Adrenal cortical steroids	47 (33.8)
Anxiolytics, sedatives, and hypnotics	510 (26.0)	Antihistamines	43 (30.9)
Penicillins	494 (25.2)	Thyroid hormones	42 (30.2)
Beta-adrenergic blocking agents	431 (22.0)	Penicillins	37 (26.6)
Macrolide derivatives	412 (21.0)	Diuretics	34 (24.5)
Diuretics	396 (20.2)	Antiemetic/antivertigo agents	33 (23.7)
Anticonvulsants	380 (19.4)	Anticonvulsants	32 (23.0)
Ophthalmic preparations	358 (18.2)	Macrolide derivatives	31 (22.3)
Quinolones	352 (17.9)	Beta-adrenergic blocking agents	30 (21.6)
Antiemetic/antivertigo agents	339 (17.3)	Immunosuppressive agents	28 (20.1)
Bronchodilators	325 (16.6)	Antimalarial agents	27 (19.4)
Cephalosporins	317 (16.1)	Bronchodilators	26 (18.7)
Antimalarial agents	310 (15.8)	Cephalosporins	24 (17.3)
Calcium channel blocking agents	288 (14.7)	Sex hormones	24 (17.3)
Nasal preparations	272 (13.9)	Immunostimulants	22 (15.8)
Laxatives	268 (13.7)	Laxatives	21 (15.1)
Antidiabetic agents	267 (13.6)	Ophthalmic preparations	21 (15.1)
Antirheumatics	266 (13.6)	Tetracyclines	21 (15.1)
Sex hormones	266 (13.6)	Vitamins	21 (15.1)
Immunostimulants	259 (13.2)	Miscellaneous GI agents	20 (14.4)
Immunosuppressive agents	252 (12.8)	Quinolones	20 (14.4)
ACE inhibitors	247 (12.6)	Antifungals	18 (12.9)
Muscle relaxants	239 (12.2)	Antirheumatics	18 (12.9)
		Antiviral agents	18 (12.9)
		Muscle relaxants	18 (12.9)
		Sulfonamides	18 (12.9)
		Vaginal preparations	18 (12.9)

*Medications are grouped according to NDC Multum Level 2 and listed from most to least frequently prescribed.

†Level 2 group ‘dermatological agents’ contains the following topical agents: anti-infectives, steroids, anaesthetics, miscellaneous agents, anti-infectives with steroids, acne agents, antipsoriatics, emollients, antibiotics, antivirals, antifungals

‡Including statins

ACE, angiotensin-converting enzyme; GI, gastrointestinal; NDC, national drug code; PBC, primary biliary cholangitis

Supplementary Table 3. Age-specific estimates of prespecified comorbidities by PBC status

N (%)	Non-case population*					PBC population				
	Age group (years)					Age group (years)				
	18–34	35–54	55–64	65–74	≥75	18–34	35–54	55–64	65–74	≥75
Source population	2,693,650 (100)	4,071,602 (100)	2,443,349 (100)	568,235 (100)	468,756 (100)	40 (100)	584 (100)	808 (100)	336 (100)	195 (100)
UTI	164,926 (6.1)	227,400 (5.6)	160,607 (6.6)	50,456 (8.9) (15.4)	72,211 (15.4)	3 (7.5)	80 (13.7)	93 (11.5)	58 (17.3)	37 (19.0)
Rheumatoid arthritis	8,078 (0.3)	41,973 (1.0)	42,340 (1.7)	14,012 (2.5)	12,077 (2.6)	0	40 (6.9)	56 (6.9)	18 (5.4)	9 (4.6)
Raynaud's syndrome	3,909 (0.2)	10,068 (0.3)	6,890 (0.3)	2,044 (0.4)	1,422 (0.3)	0	15 (2.6)	28 (3.5)	9 (2.7)	5 (2.6)
Sjögren's syndrome	1,764 (0.1)	9,290 (0.2)	8,804 (0.4)	2,694 (0.5)	1,875 (0.4)	2 (5.0)	42 (7.2)	44 (5.5)	14 (4.2)	12 (6.2)
SLE	4,411 (0.2)	13,880 (0.3)	8,422 (0.3)	2,051 (0.4)	1,132 (0.2)	0	22 (3.8)	17 (2.1)	3 (0.9)	5 (2.6)
Autoimmune thyroid disease	17,888 (0.7)	46,447 (1.1)	26,286 (1.1)	5,496 (1.0)	2,951 (0.6)	2 (5.0)	25 (4.3)	19 (2.4)	12 (3.6)	1 (0.5)
Autoimmune hepatitis	431 (0.02)	1,208 (0.03)	1,217 (0.1)	381 (0.1)	239 (0.1)	10 (25.0)	66 (11.3)	80 (9.9)	22 (6.6)	9 (4.6)
Depression or anxiety	404,669 (15.0)	653,326 (16.1)	379,403 (15.5)	98,712 (17.4)	88,704 (18.9)	8 (20.0)	119 (20.4)	174 (21.5)	85 (25.3)	32 (16.4)
Depression	205,633 (7.6)	337,124 (8.3)	214,302 (8.8)	58,600 (10.3)	54,579 (11.6)	6 (15.0)	62 (10.6)	112 (13.9)	49 (14.6)	22 (11.3)

Anxiety	316,553 (11.8)	475,887 (11.7)	252,219 (10.3)	63,239 (11.1)	54,917 (11.7)	7 (17.5)	82 (14.0)	110 (13.6)	56 (16.7)	20 (10.3)
Sleep-related issues	63,603 (2.4)	187,725 (4.6)	132,263 (5.4)	32,173 (5.7)	29,536 (6.3)	5 (12.5)	40 (6.9)	51 (6.3)	21 (6.3)	19 (9.7)
Pruritus	35,244 (1.3)	57,802 (1.4)	39,861 (1.6)	13,010 (2.3)	12,231 (2.6)	6 (15.0)	48 (8.2)	51 (6.3)	20 (6.0)	8 (4.1)
Diarrhoea	83,613 (3.1)	112,690 (2.8)	73,709 (3.0)	24,168 (4.3)	26,708 (5.7)	4 (10.0)	50 (8.6)	68 (8.4)	41 (12.2)	19 (9.7)
Fatigue	194,643 (7.2)	440,621 (10.8)	266,746 (10.9)	69,335 (12.2)	96,564 (20.6)	10 (25.0)	127 (21.8)	149 (18.4)	62 (18.5)	42 (21.5)

[†]N for the non-case population (N=10,245,592), relates to the comparison versus the PBC population not versus the PBC-pruritus population (N=9,984,009)

Data shown reflects given conditions with ≥ 1 claim(s) during the 2017 calendar year

PBC, primary biliary cholangitis; SLE, systemic lupus erythematosus; UTI, urinary tract infection

Supplementary File 1. ICD-10 codes for prespecified comorbidities.