Supplementary material

Box S1 – Description of the administrative healthcare data source

Fondazione ReS is a non-profit foundation working on Italian healthcare real-world data with the aim of planning and monitoring healthcare policy issues, for different stakeholders and in various clinical fields since its establishment in 2018 [1-3]. Through the collaboration with Cineca (Interuniversity Consortium [4]), which guarantees quality and security of the data management (international standard certifications), the ReS database, after further quality and accuracy data checks, collects and integrates the administrative healthcare data that Italian Local and Regional Healthcare Authorities (HAs) annually convey to the Italian Ministry of Health. Some HAs, owners of the data, have made available to Fondazione ReS under specific agreements the administrative data to be analysed in aggregated form, after being anonymized. Demographics (age, sex, local HA of residency and disease waiver claim for co-payment) of each patient are completely anonymized at the source according to European privacy rules [5]. The pharmaceuticals' database contains drugs reimbursed by the SSN and supplied from local and hospital pharmacies (Italian marketing code, ATC code – Anatomical Therapeutic Chemical classification, dose, number of packages and dispensing date). The hospitalizations' database contains in-hospital diagnoses and procedures, according to the Italian version of the 2007 ICD-9-CM (International Classification of Diseases- 9th version – Clinical modification [6]), accessible through the hospital discharge forms of overnight and daily in-hospital stay. The outpatient specialist care database (visits, diagnostic and invasive/non-invasive procedures charged to the SSN) is analysed based on the current national classification system, 2017 version [7]. Healthcare administrative databases contain the actual amounts reimbursed by the Italian National Health System (Servizio Sanitario Nazionale – SSN) for each healthcare resource, i.e. each reimbursed drug, each hospital admission, and each specialist outpatient service. These values are routinely recorded within administrative flows and were directly extracted from the corresponding cost fields, without any retrospective recalculation by the investigators. Reimbursement amounts are defined according to the applicable national fee schedules (e.g. diagnosis-related group (DRG) tariffs for hospital admissions and the "Nomenclatore tariffario" for specialist services) and may reflect any applicable price adjustments or discounts arising from regional procurement and tendering processes. As regards the cost of

drugs, administrative data enables us to determine the net amount, which is the sum actually borne by the SSN after deducting any contributions such as the regional co-payment, the difference paid by the patient for drugs that are more expensive than the reference price (in the case of equivalent medicines), or discounts and rebates already applied at an earlier stage.

For the cost analysis, we used the expenditure variables available in the administrative database that represent the actual amounts paid by the SSN for each healthcare encounter.

REFERENCES

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5. European Parliament and Council of the European Union: Regulation (EU) 2016/679 of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). 2016.
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Table S1 – Criteria for the identification of patients with primary biliary cholangitis referred to as "prevalent cohort"

Administrative data flow	Codes and descriptions
At least one of the following	
Pharmaceuticals	At least one free filled dispensation of the following drug (ATC code), from 1st August 2017 to 31st December 2021: A05AA04 - Obeticholic acid
Hospitalizations	At least one hospital discharge form with the following primary/secondary diagnosis (ICD-9-CM code), from 1st January 2014 to 31st December 2021: 571.6 - Biliary cirrhosis
Disease waiver claim	Active disease waiver claim code for co-payment of services in 2021 related to: 008.571.6 - Biliary cirrhosis
Exclusion criteria from 1st January 2014 to 31st December 2022	
Disease waiver claim	Active disease waiver claim code for co-payment of services related to: RI0050 - primary sclerosing cholangitis 016 - Chronic hepatitis

Figure S1 – Study design for identifying patients with primary biliary cholangitis in 2021 (prevalent cohort) and describing the healthcare resource utilisation and cost over a 1-year follow-up

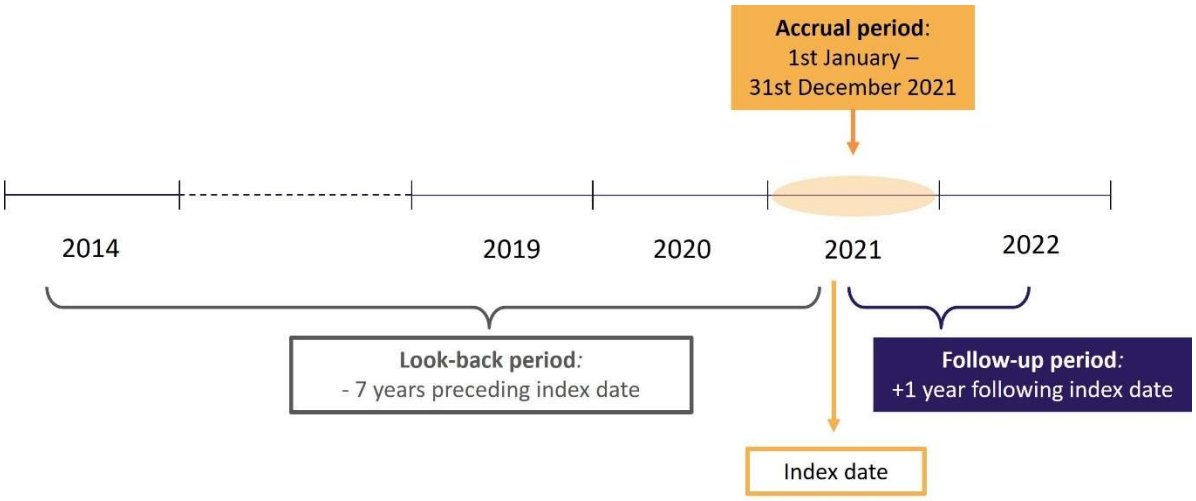

Figure S2 – Study design for identifying patients with primary biliary cholangitis in 2019 (incident cohort) and describing the treatment pattern over a 3-year follow-up

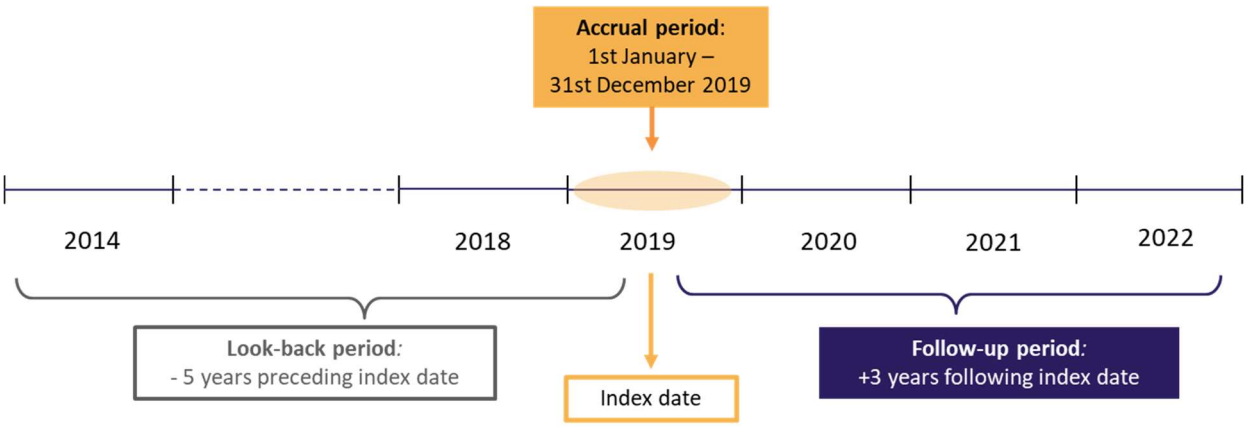

Table S2 – Criteria for the identification of patients with primary biliary cholangitis referred to as "incident cohort"

Administrative data flow	Codes and descriptions
At least one of the following criteria from 1st January 2019 to 31st December 2019	
Pharmaceuticals	At least one free filled dispensation of the following drug (ATC code): A05AA04 - Obeticholic acid
Hospitalizations	At least one hospital discharge form with the following primary/secondary diagnosis (ICD-9-CM code): 571.6 - Biliary cirrhosis
Disease waiver claim	Active disease waiver claim code for co-payment of services related to: 008.571.6 - Biliary cirrhosis
Exclusion criteria from 1st January 2014 to 31st December 2018	
Disease waiver claim	Active disease waiver claim code for co-payment of services related to: 008.571.6 - Biliary cirrhosis
Pharmaceuticals	At least one free filled dispensation of the following drug (ATC code): A05AA04 - Obeticholic acid A05AA02 - Ursodeoxycholic acid
Hospitalizations	At least one hospital discharge form with the following primary/secondary diagnosis (ICD-9-CM code): 571.6 - Biliary cirrhosis

Table S3 - Criteria identifying comorbidities in the look-back period (i.e., 7 years preceding the index date) among patients with primary biliary cholangitis in 2021

Diabetes mellitus		
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**
250.x – Diabetes mellitus	013 – Diabetes mellitus	A10 – Drugs used in diabetes
Dyslipidaemia		
At least one hospital discharge form with primary/secondary diagnosis	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**
272.x - Disorders of lipoid metabolism	025 - Type IIa and IIb heterozygous familial hypercholesterolemia – Polygenic hypercholesterolemia – Familial combined hypercholesterolemia – Type III hyperlipoproteinemia	C10A – Lipid modifying agents, plain C10B - Lipid modifying agents, combinations
Arterial hypertension		
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**
401.x – Essential hypertension 402.x – Hypertensive heart disease 403.x – Hypertensive chronic kidney disease 404.x – Hypertensive heart and chronic kidney disease 405.x - Secondary hypertension	031 – Arterial hypertension 0A31 - Arterial hypertension without organ damage	C02 – Antihypertensives C03 – Diuretics C07 – Beta blocking agents C08 – Calcium channel blockers C09 – Agents acting on the renin-angiotensin system
Heart failure		

At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**
402.01 – Malignant hypertensive heart disease with heart failure 402.11 – Benign hypertensive heart disease with heart failure 402.91 – Unspecified hypertensive heart disease with heart failure 404.01 – Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified 404.03 – Hypertensive heart and chronic kidney disease, malignant, with heart failure and with chronic kidney disease stage V or end stage renal disease 404.11 – Hypertensive heart and chronic kidney disease, benign, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified 404.13 – Hypertensive heart and chronic kidney disease, benign, with heart failure and chronic kidney disease stage V or end stage renal disease 404.91 – Hypertensive heart and chronic kidney disease, unspecified, with heart failure and with chronic kidney disease stage I through stage IV, or unspecified 404.93 – Hypertensive heart and chronic kidney disease, unspecified, with heart	021 – Heart failure	C09DX04 – Valsartan and sacubitril

failure and chronic kidney disease stage V or end stage renal disease 428.x - Heart failure		
Inflammatory bowel diseases		
At least one hospital discharge form with primary/secondary diagnosis or procedure (ICD-9-CM code)	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**
555.x - Regional enteritis 556.x - Ulcerative colitis	009 - Ulcerative colitis and Crohn's disease	A07EA - Corticosteroids acting locally A07EC02 - Mesalazine L04AA33 - Vedolizumab
Chronic kidney disease		
At least one hospital discharge form with	**Disease waiver claim**	**At least one local outpatient specialist service (national tariffs)**
Primary/secondary diagnoses (ICD-9-CM code): 250.4 – 582.x – Chronic glomerulonephritis 583.x – Nephritis and nephropathy not specified as acute or chronic 584.x - Acute renal failure 585.x – Chronic kidney disease 586.x – Renal failure unspecified 587.x – Renal sclerosis unspecified 588.x – Disorders resulting from impaired renal function 590.x – Infections of kidney V42.0 – Kidney replaced by transplant	023 – Chronic renal failure 061 – Chronic kidney disease 052.V42.0 – Renal transplantation	39.95 – Haemodialysis 54.98 - Peritoneal dialysis

V56.x – Encounter for dialysis and dialysis catheter care AND/OR **Primary/secondary procedures (ICD-9-CM code):** 39.95 – Haemodialysis 54.98 – Peritoneal dialysis 55.6x – Renal transplantation		
Cardiac arrythmias		
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**
426.x – Conduction disorders 427.x - Cardiac dysrhythmias	002.426; 0A02.426 – Conduction disorders 002.427; 0A02.427 - Cardiac dysrhythmias	C01B – Antiarrhythmics, Class I and III
Depression		
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**
296.2x - Major depression, single episode 296.3x - Major depression, recurring episode 296.5x – Bipolar disorder type I, most recent (or current) depressive episode 296.82 – Atypical depressive disorder	044.296.2 - Psychosis (major depression, single episode) 044.296.3 - Psychosis (major depression, recurring episode) 044.296.5 - Psychosis (bipolar affective syndrome, depressive episode)	N06A - Antidepressants

298.0x – Depressive psychosis 300.4 - Dysthymic disorder 301.12 - Chronic depressive personality disorder	044.296.8 - Psychosis (manic-depressive disorder) 044.298.0 – Psychosis (depressive psychosis)	
Chronic lung diseases		
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**
490.x - Bronchitis, not specified as acute or chronic 491.x - Chronic bronchitis 492.x - Emphysema 493.x - Asthma 494.x - Bronchiectasis 496.x - Chronic airway obstruction, not elsewhere classified 518.81- 518.84 - Respiratory failure	024 – Chronic respiratory failure 007 – Asthma 057 – Chronic airway obstruction	R03 – Drugs for obstructive airway diseases

Neoplasia (current or history)			
At least one hospital discharge form with	**Disease waiver claim**	**At least one local outpatient specialist service (national tariffs)**	**At least one drug supplies (ATC codes)**
Primary/secondary diagnosis (ICD-9-CM code) 140.x - 208.x - Neoplasms V10.x - Personal history of malignant neoplasm V58.0 - Radiotherapy V58.1x – Chemotherapy AND / OR	048 – Malignant neoplasms and tumors of uncertain behavior	92.2x - Therapeutic radiology and nuclear medicine 99.24.1 - Infusion of hormonal substances 99.25 - Injection or infusion of chemotherapy substances for cancer	L01 - Antineoplastic agents

Primary/secondary intervention or procedure (ICD-9-CM code) 00.10 - Implantation of chemotherapeutic agents 92.2x - Therapeutic radiology and nuclear medicine 92.3x – Stereotactic radiosurgery as antineoplastic agents 99.28 - Injection or infusion of biological response modifying agents (BRM) 99.25 - Injection or infusion of chemotherapy substances for cancer		92.28.6- palliative pain therapy from bone metastases	
Thyroid diseases			
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**	**At least 2 drug supplies within one year before the index date (ATC codes)**	
242.x - Thyrotoxicosis with or without goiter 243 - Congenital hypothyroidism 244.x - Acquired hypothyroidism 245.x - Thyroiditis 246.x - Other disorders of thyroid	056 - Hashimoto thyroiditis 027 - Congenital, severe acquired hypothyroidism 035 - Graves' Disease Basedow, other forms of hyperthyroidism	H03AA01 - Levothyroxine sodium H03BB02 - Thiamazole	

Osteoporosis	
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**At least 2 drug supplies within one year before the index date (ATC codes)**
733.0x - Osteoporosis	H05AA02 – Teriparatide M05BX03 - Strontium ranelate M05BX04 - Denosumab G03XC01 - Raloxifene G03XC02 - Bazedoxifene M05BA04 – Alendronic acid M05BA07 – Risedronic acid M05BA06 – Ibandronic acid M05BB03 – Alendronic acid and colecalciferol
Rheumatoid arthritis	
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**
714.0 - Rheumatoid arthritis 714.1 - Felty's syndrome 714.2 - Other rheumatoid arthritis with visceral or systemic involvement 714.3x - Juvenile chronic polyarthritis	006 - Rheumatoid arthritis
Connective tissue disease	
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**
710.x - Diffuse diseases of connective tissue	RM0010 - Dermatomyositis RM0020 – Polymyositis RM0021 - Anti-synthetase syndrome RM0030 - Mixed connective tissue disease RM0120 - Progressive systemic sclerosis 028 - Systemic lupus erythematosus 030 - Sjögren's disease

	067 - Undifferentiated connective tissue disease (formerly RMG010)
Coronary artery disease	
At least one hospital discharge form with	**Disease waiver claim**
Primary/secondary diagnosis (ICD-9-CM code) 410.x - Acute myocardial infarction 411.x - Other acute and subacute forms of ischemic heart disease 412 - Old myocardial infarction 413.x - Angina pectoris 414.x - Other forms of chronic ischemic heart disease AND / OR **Primary/secondary intervention or procedure (ICD-9-CM code)** 36.x – Operations on vessels of heart 00.66 – Percutaneous Transluminal Coronary Angioplasty (PTCA) or coronary atherectomy	(002.414) 0A02.414 – Diseases of the circulatory system
Cerebrovascular disease	
At least one hospital discharge form with primary/secondary diagnosis (ICD-9-CM code)	**Disease waiver claim**
430 – 438.x - Cerebrovascular Disease	002.433; 0B02.433 - Occlusion and stenosis of precerebral arteries 002.434; 0B02.434 - Occlusion of cerebral arteries 002.437; 0B02.437 - Other and ill-defined cerebrovascular disease

Box S2 - Treatment approach for PBC within 2019 incident patients

Throughout a 3-year follow-up, proportions of patients treated and untreated with drugs authorized for PBC, time intervals between the index date and the therapy initiation, change of treatment, treatment discontinuation and interruptions, and mean length of therapy (months) were given. The dispensation of two different drugs the same date or within 30 days was considered as concomitant therapy.

The change of treatment was defined as:

- the free filled prescription of another drug recommended for PBC after 30 days from the first prescription;
- the free filled prescription of an additional drug recommended for PBC, which could be considered as a concurrent drug when dispensed the same date or within 30 days from the first prescription.

Among patients not changing their treatment and with at least 3 years of follow-up, the proportions of patients and the mean length of therapy (months) were given.

Table S4 – Treatment approach for PBC within the incident cohort that has at least 3 years of follow-up available (N=40)

First PBC-related treatment	Time to therapy initiation (months)	Patients treated (n; n/N%) N=40	No change of treatment						Change of treatment
			Continuous treatment		Interrupted treatment		Discontinuous treatment		2nd treatment: UDCA+OCA
			n; n/N%	Therapy length (months)	n; n/N%	Therapy length (months)	n; n/N%	Therapy length (months)	n; n/N%
UDCA (n_1=38)	[0-3]	33 (82.5)	20 (52.6)	35.2	8 (21.1)	4.9	4 (10.5)	2.3	NI
	[3-12]	NI	NI	29.5	0 (0.0)	-	0 (0.0)	-	0 (0.0)
	[13-24]	NI	NI	16.3	0 (0.0)	-	0 (0.0)	-	0 (0.0)
	Total	38 (95.0)	25 (65.8)		8 (21.1)	4.9	4 (10.5)	2.3	NI
UDCA + bezafibrate (n_2=1)	[0-3] – Total	NI	NI	36.0	0 (0.0)	-	0 (0.0)	-	0 (0.0)
OCA (n_3=1)	[0-3] - Total	NI	0 (0.0)	-	NI		0 (0.0)	-	0 (0.0)

UDCA: ursodeoxycholic acid; OCA: obeticholic acid; NI: not issuable due to privacy reasons, because patients are less than 4.