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Short Review Article

Primary Sclerosing Cholangitis and Psychological Wellbeing: A Scoping Review

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ABSTRACT

Primary Sclerosing Cholangitis (PSC) is a chronic liver disease resulting from the inflammation and scarring of an individual's hepatic bile ducts. With no curative treatment available and a risk of potentially severe complications and death, it is likely that those diagnosed with the illness may experience impairments in their psychological wellbeing. The aim of this scoping review is to locate, chart and summarize all the available literature on how PSC affects mental health and psychological wellbeing, as well as the factors that may or may not impact on the psychological wellbeing of those who have this diagnosis. This exercise identified five key themes within the literature: prevalence and characteristics of mental health problems; quality of life; unmet needs; medical treatment; and, biomarkers. Three key recommendations for clinical practice emerge from this review.

Keywords

primary sclerosing cholangitis

mental health

psychological wellbeing

scoping review

Primary Sclerosing Cholangitis (PSC) is a cholestatic liver disease characterized by a continuous and worsening inflammation and scarring of the liver's bile ducts which progresses unpredictably to end stage liver disease with a risk of cancer.¹ Diagnosis of PSC often occurs upon examining the cause of abnormal Liver Function Tests (LFT).² Although the illness can be asymptomatic at first, abdominal pain, pruritus, jaundice and fatigue feature for many sufferers.¹ Recent estimates suggest that PSC is prevalent in 0-16.2 cases per every 100,000 persons.³ This rate appears to be increasing, however, it is unclear as to whether this reflects diagnostic improvements, greater awareness of the illness or a true increase in illness prevalence.¹

At present, there is no known cause for PSC, though both genetic and environmental factors are believed to contribute to its incidence and progression.⁴ Furthermore, there is no curative medical treatment for the illness, with sufferers of end-stage liver disease requiring a liver transplant to survive.⁵ Complications such as portal hypertension, vitamin deficiencies, metabolic bone diseases, and bile duct and colon cancers can arise from the illness.^{6,7} In light of such physical difficulties, it is likely that those with a long-term physical illness such as PSC may experience some psychological difficulties. Numerous publications have linked chronic medical illnesses to higher instances of psychological problems.⁸ Mental health problems such as depression, are up to three times more prevalent in those with chronic medical illness compared to a general cohort of individuals accessing primary care.⁸ In a recent survey undertaken by PSC Support, a national UK charity that supports all those affected by PSC, symptoms of depression were reported by a third of their cohort.⁹ This is important as depression's frequent comorbidity with chronic medical illness is believed to worsen health outcomes for these individuals.⁸

Although there is ample information on how a long-term physical health condition impacts the psychological health of its sufferers, there is much less information of how living with PSC affects the mental health of those with this diagnosis. With this in mind, the aim of this review is to examine how PSC affects mental health and psychological wellbeing, and summarize the factors that may or may not impact on the psychological wellbeing of those who have this diagnosis.

METHOD

Scoping review

The aim of this scoping review was to map out the available literature on the topic of Primary Sclerosing Cholangitis (PSC) and its relationship to mental health or psychological wellbeing, in order to identify and highlight knowledge gaps to address in future research. Our primary research questions were the following: 1) What is known, in the literature, about the mental health and wellbeing of individuals with PSC? 2) How does PSC impact the lives of those with PSC? 3) What factors influence the mental health and wellbeing of those with PSC?

We chose to conduct a scoping review, rather than a systematic review, for its ability to synthesize and link broad areas within the PSC literature. It is designed as a rapid mapping of the available literature, and more fitted to a large topic where it is not possible to specify a research question, especially in areas which have not received much attention. Furthermore, this method allowed us to review and summarize a broad spectrum of studies with varying research methodologies, ranging from editorials to systematic reviews, inclusive of both qualitative and quantitative research designs, without restricting ourselves to a predetermined research design.

Arksey & O'Malley's¹⁰ framework for conducting scoping reviews was adopted as a skeleton for this scoping review. This framework begins with identifying a clear research question that enables the researcher to search and select relevant studies from the literature. Selected studies are then charted, summarized and reported as findings. Although the importance of incorporating a quality assessment of included studies in scoping reviews is debated by some authors, this scoping review does not contain one as there is no method of uniformly assessing a range of types of articles. Nevertheless, in agreement with these later articles, extensive screening, reviewing and discussion regarding both the included and excluded articles was carried out between members of the research team to ensure that only relevant articles were included in the review. All titles, abstracts and full-text articles were screened by two members of the research team (VR and KM) separately to ensure that these adhered to our inclusion criteria. Duplicates were identified at title screening and eliminated from the review.

Search strategy

This scoping review included all relevant English-language articles published until March 2018. The following search engines were included for their ability to source a vast range of journals across health and social sciences: PubMed, Scopus, PsychINFO and JStor. Google Scholar was later included to our list of search engines in order to check for additional articles and grey literature. Our search term was: (PSC OR primary sclerosing cholangitis) AND (psychological distress OR psychol* OR distress OR depression OR depress* OR anxiety OR anx* OR mental* OR mental health OR wellbeing OR experiences OR emotion OR emotion* OR quality of life).

We included all English-language articles that either referred to PSC and mental health or psychological wellbeing, or examined mental health or psychological wellbeing in a sample

that included individuals with a diagnosis of PSC. Such studies could include the effects of a form of treatment used to help alleviate symptoms that impacted on the mental health or psychological wellbeing of PSC sufferers, or the impact of a condition, specifically linked to PSC, on the mental health or psychological wellbeing of the PSC sufferer. We included articles employing a range of research methodologies and commentaries, editorials or opinion pieces. We excluded publications if the study did not include individuals with a diagnosis of PSC, or if it did not examine mental health or psychological wellbeing in this cohort.

Data extraction

All included articles were charted onto an Excel spreadsheet. These details included article authors, country in which the research was carried out, year of publication, journal, article type (ie. editorial or research), sample population, study design, and key findings. Overarching topics based on the similarities or differences found across the literature were grouped into themes. Each theme was categorized by one researcher (VR) and reviewed by all authors. A narrative summary of each theme is described below.

RESULTS

Our database search produced 1,218 potentially relevant articles to screen. Articles were screened in a four-step process (see figure 1). 1) Articles were first screened for duplicates. 137 articles were found to be duplicates and, therefore, excluded from further screening. 2) The remaining 1,081 articles were screened according to whether their titles pertained to PSC. Titles that solely featured an illness other than PSC or whose subject matter was irrelevant to PSC were excluded. 900 articles were deemed ineligible for abstract screening based on their titles and were excluded. 3) Abstracts for the remaining 181 articles were then screened to assess whether the abstracts discussed PSC, and wellbeing or a mental-health related aspect. Abstracts

that solely featured an illness other than PSC, or did not pertain to wellbeing or mental health were excluded. Abstracts that included wellbeing or a mental-health related aspect, and a yet unspecified cholestatic disease were included in the next stage of screening. 105 articles met the exclusion criteria and were excluded from full-text screening. 4) Finally, 76 full-text articles were screened for their relevance to PSC, and wellbeing or a mental-health related aspect. 23 articles were excluded as they did not fit the inclusion criteria. A total of 53 articles were included in the final review.

Type of literature

Included articles were mostly led by European (n=25) or North American (n=19) authors. A further six articles were Asian and the remaining three articles were Australian. The majority of included articles reported empirical research (79%, n=42), and were solely quantitative in nature (n=40). Nine reviews (17%) were included in this scoping review, of which two were systematic. The remaining articles consisted of either editorials or commentaries. Publication dates spanned from 1988 until March 2018 and papers were identified from 35 journals. Further information regarding the type of articles included in this review can be found in table 1. Articles were initially divided into one of two groups according to whether results pertained to those with a specific diagnosis of PSC, or whether scores of individuals with PSC were grouped into a general score for all individuals with a chronic liver disease. As both groups reported similar findings overall, a single set of key themes is displayed in this review. For a list of all included articles divided into these two groups, please see Table (supplementary). The measures used in each study are also available in Table 3 (supplementary). Five themes emerged on identifying and synthesizing commonalities and contrasts found within the literature, as presented below.

Theme 1: Prevalence and characteristics of mental health problems

There is a dearth of literature chronicling mental health problems in those with a diagnosis of PSC. The available literature on the topic focuses predominantly on depression and, to a lesser extent, anxiety. Throughout the literature, there are differing opinions regarding the prevalence of depression in those with a diagnosis of PSC in comparison to the general population.¹¹⁻¹³ The studies included in this scoping review cited prevalence figures for depression between 3.1 to 14% of those diagnosed with PSC.^{14,15} Given these figures, it appears that the prevalence of depression does not appear greater in this group of individuals compared to the general population. Though prevalence may not differ from the expected in the background population, those who have a diagnosis of PSC tend to reveal a greater number of depressive symptoms and a lower level of wellbeing, with suicide attempts also occurring.^{16,17} The presence of such symptoms has been linked to the stage of liver disease experienced by the individual.¹⁴ Severe depression was particularly prevalent in those who have a comorbid diagnosis of inflammatory bowel disease (IBD).¹⁸ However, such distress is also found in those who are clinically asymptomatic.¹⁹

There are varying opinions as to whether the presence of depressive symptoms leads to fatigue.^{11,12,15,20} Much less is written with regard to other types of mental health problems. Current available literature on the topic indicates that anxiety in those with PSC is a common experience. Fear of malignancies associated with PSC (colorectal cancers, cholangiocarcinomas and other hepatobiliary malignancies) and possible mortality as a consequence is frequently reported.^{16,21} Lower feelings of self-control regarding the illness and the future appeared in the narratives of those with PSC and comorbid anxiety.¹¹ This may, in part, be due to fears regarding liver transplantation including whether they will be able to

receive a suitable donor organ, fear and anguish of causing the donor harm and fear regarding financial costs.²²

Theme 2: Quality of life

Quality of life featured prominently in the articles identified in this scoping review. With the exception of one mixed-methods study, exclusively quantitative assessments of quality of life were found in the PSC literature.²³ These revealed that those diagnosed with PSC had similar quality of life scores compared to other chronic illnesses^{21,24,25}, but significantly inferior quality of life scores in comparison with the general population.^{12,21,26-28} Such inferior quality of life was linked to increased work disability and sexual function impairment in those with PSC.^{16,21,29} Links with social isolation and anxiety, as well as greater levels of psychological burden, distress and depression were also identified,²¹

Six key factors were highlighted as predictors of lower quality of life: gender; age; severity of symptoms; the type of symptoms; comorbidity; and disease type.^{12,16,18,27,30-39} Women and older adults with PSC showed significantly lower levels of quality of life compared to males and younger counterparts.^{16,27,30-32,36} An increase in symptom severity, the presence of systemic symptoms, having comorbid IBD and large-duct, rather than small-duct, disease all predicted worsened quality of life.^{12,18,32-36} In addition to these predictors, one further article emphasized the likelihood that acquisition of care in itself (ie. undergoing a medical intervention, and the transport and time needed to undergo an intervention) may negatively impact on quality of life.¹⁶

Theme 3: Unmet needs

Individuals with a diagnosis of PSC spoke of a range of unmet needs that affected their psychological wellbeing.²¹ These unmet needs emerged from a need for greater emotional and

mental health support due to the rarity and severity of the disorder.^{21,40} Feeling unheard by medical professionals who often lacked empathy and knowledge regarding the disease was a major source of psychological distress, often because professionals themselves lacked any experience with PSC and so were learning ‘on the job’.²¹ Being unable to access information regarding their illness, lack of awareness of treatment options or becoming aware of limited treatment options was also attributed to greater distress.^{21,40} Further compounding this distress in a quarter of those living with PSC, was a perception of social isolation from their family.^{16,21} In light of such isolation from social support networks, individuals from these studies spoke of a need for hope for the future.

Theme 4: Medical treatment

Some medical treatments have been linked to ameliorations in mental health and wellbeing, though not all. Liver transplantation was the most frequently published medical treatment in this scoping review. Multiple studies have reported a marked improvement in quality of life and mental health post-liver transplantation, sometimes long-term.⁴¹⁻⁴⁴ Such improvements have been associated with a return to activities of daily living, a reduction in distressing symptoms and an increased level of general wellbeing, including social and sexual functioning (particularly in women).^{31,45,46} Higher scores of quality of life also predicted lower instances of mortality in those awaiting a transplant.⁴⁷ Nevertheless, these studies also chronicled continued limitations in activities of daily living and difficulties with mood swings in a minority of cases. Those who experienced ongoing mood difficulties post-transplant, reported a lower quality of life, feelings of unhappiness, nervousness and sadness, and manifested physical symptoms such as sleep disruption and difficulties maintaining concentration.⁴⁸⁻⁵¹ A continued poor or worsening level of mental health accompanied by a lack of social support post-transplant, was linked to post-traumatic stress disorder in some.⁵²

In addition to liver transplantation, one further medical treatment, ursodeoxycholic acid, was found to significantly improve the mental health of some PSC patients in the limited available studies.⁵³ This improvement was not replicated with regard to quality of life.⁵⁴ Fluvoxamine, a selective serotonin re-uptake inhibitor often used to treat depressive and anxiety disorders, showed no impact on quality of life or fatigue in those with PSC.⁵⁵ Unfortunately, the remaining trials testing the effectiveness of Rifaximin therapy, restorative proctocolectomy, and potent bile acid sequestrant colesevelam also failed to reveal a reduction in mental health symptoms or increased mental health-related quality of life scores post-testing.⁵⁶⁻⁵⁹

Themes 5: Bio-markers

Research into the biomarkers of PSC have revealed some notable results in relation to mental health. However, these studies are also few in number. Although some of these studies identified that certain biomarkers were linked to poorer outcomes, it is important to emphasize that there are no indications of direct causation. From the studies we identified, a raised serum alkaline phosphatase was linked to worsened mental health.¹² The presence of Apa-I polymorphism of vitamin D receptors was found to be associated with poorer quality of life, mental- and emotional-health related scores⁶⁰ Finally, the other two existing studies found that neither serum autotaxin nor plasma tyrosine concentrations affected mental health or quality of life.^{61,62}

DISCUSSION

This purpose of this scoping review was to map out and summarize what is known about mental health and wellbeing in those living with PSC. This exercise identified five key areas of research within the literature: prevalence and characteristics of mental health problems; quality

of life; unmet needs; medical treatment and biomarkers. The included studies revealed similar prevalence figures for depression as seen in the general population, however such symptoms tended to be more severe and, in some cases, led to suicide attempts. Anxiety, though less studied, centered upon fears regarding disease progression or the development of PSC related malignancy (such as the incidence of colorectal cancers, cholangiocarcinomas and other hepatobiliary malignancies), low self-control, receipt of liver donation, and mortality.

Although prevalence rates for mental health problems, such as depression, appear to be similar to the general population, quality of life was significantly lower in those with PSC. Linked to both depression and anxiety, lower quality of life was associated with increased work disability, sexual dysfunction, and social isolation. Reduced quality of life in those with PSC was predicted by female gender, older age, greater symptom severity, the presence of systemic symptoms, comorbidity with other illnesses, and being diagnosed with large-duct PSC. Six key medical treatments were studied in an effort to help improve quality of life and mental health. However, only two of these were found to be effective overall: ursodeoxycholic acid and liver transplantation. Although the use of ursodeoxycholic acid was less frequently associated with improved psychological wellbeing, liver transplantation was linked to notable improvements in quality of life, mental health, and daily functioning, in part, due to a reduction of distressing symptoms. Finally, in addition to medical treatments, the presence of two biomarkers, alkaline phosphatase and Apa-I polymorphism of vitamin D receptors, were associated with psychological wellbeing.

Within the literature, there is an understandable preponderance of studies searching for an effective treatment for PSC or a biomarker that may help researchers identify its cause or pathophysiology. As a consequence of this, much less is known about how the illness impacts the mental health and psychological wellbeing of those who live with it. This scoping review

is novel in that it is the first to group together and describe the factors that may or may not influence the mental health and psychological wellbeing of those who have a diagnosis of PSC. Its key strength is that it incorporates a wide breadth of literature ranging from editorials/commentaries to studies employing quantitative and qualitative research methods. However, such inclusiveness also results in a limitation. As the review employed a diverse type of articles with various methodologies ranging from editorials to mixed-methods research, there was no consistent method of conducting an assessment of the quality of the studies included. Basic information regarding sample sizes, types of samples and settings can be found in Table 2 (supplementary). Furthermore, although many of the findings included pertained to those with a specific diagnosis of PSC, some studies grouped the scores of individuals with PSC into a general score for all individuals with a chronic liver disease. To help in distinguishing which studies presented a general group score in comparison to separate scores for samples of individuals with PSC only, this information is provided in Table 2 (supplementary).

Treatment options for PSC are limited, and rely on surgical interventions in patients with advanced disease. As evidenced by this review, PSC is accompanied by significant reductions in psychological health and quality of life. This data, therefore, suggests a need to consider integrating psychological perspectives and therapeutic approaches in the treatment of PSC. This may potentially help reduce the depression, anxiety and reduced functioning experienced by those with the illness. Furthermore, as many experience social isolation due to the rarity of the disorder, training primary and secondary care providers to recognize the symptoms, comorbidities and complications that can arise from PSC could help address this isolation. In addition to training healthcare providers, the provision of psychoeducation and advice to caregivers could help ensure that both those with PSC and their caregivers feel less socially

isolated and more supported by health services. In response to such isolation, charities such as PSC Support, based in the UK, have emerged to provide clear information and support to all those who need it.

This review identified three major gaps within the literature. As highlighted above, there is a dearth of data examining how PSC affects mental health and psychological wellbeing. Substantive data on the lived experiences of those with a diagnosis of PSC are missing, as are the experiences of those who provide care to those with PSC, both professionally and at home. Another important gap in the literature pertained to the research method employed by the included studies. In the absence of a universal and PSC-specific tool to measure quality of life and psychological wellbeing in those with PSC, measurements differed between studies rendering their results more difficult to compare. Furthermore, such assessments were heavily skewed towards quantitative methodologies. Although this is a useful method for quantifying the prevalence of mental health problems and the extent to which individuals either feel distressed or report a poor quality of life, it does not provide detail regarding the factors that may be precipitating or perpetuating such experiences. Future studies must, therefore, address this shortcoming by illustrating these constructs using qualitative data. Although this review acts as a first step in summarizing and highlighting both the available evidence and what is missing, following this review, we propose conducting a study employing qualitative methods to further understand the lived experiences of those with PSC and those who provide care to them.

Key Concepts & Learning Points

- The aim of this scoping review was to map out what is published on how PSC affects the mental health and wellbeing of those diagnosed with the condition.

- This exercise identified five key areas of research within the literature: prevalence and characteristics of mental health problems; quality of life; unmet needs; medical treatment and biomarkers.
- PSC is accompanied by significant reductions in psychological health and quality of life. This review suggests a need to consider integrating psychological perspectives and therapeutic approaches in the treatment of PSC.

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Figure 1 PRISMA Diagram of screening process.

Table 1 Types of publications reviewed (N=53)

Types of publications	No. of publications reviewed	Examples
Editorials/Commentaries	2	Arndtz & Hirschfield (2018) Ypinazar (2015)
Empirical	42	Gross et al. (1998) Haapamaki et al. (2015) Van Os et al. (2007) Wunsch et al. (2014)
Reviews	9	Martins & Chapman (2000) Serigado et al. (2018) Yang et al. (2014)

Table (Supplementary) Authorship and publication details of all articles included in the scoping review (extra online material)

N	Authors	Year	Title	Country	Journal	Design	Sample	Key Findings
	<i>Studies specific to PSC</i>							
1	Aberg, Hockerstedt, Roine, Sintonen, Isoniemi	2012	The Influence Of Liver-Disease Etiology On Long-Term Quality Of Life And Employment After Liver Transplantation.	Finland	Clinical Transplantation	Empirical : quantitative research	Miscellaneous	Similar Health-Related Quality of Life (HRQOL) (15D) scores across several liver diseases.
2	Ananthkrishnan, Beaulieu, Ulitsky, Zadvornova,	2010	Does Primary Sclerosing Cholangitis Impact Quality Of Life	USA	Inflammatory Bowel Disorders	Empirical : quantitative research	Individuals with IBD who have PSC	PSC does not seem to influence disease-specific HRQOL in our patients

	Skaros, Johnson, Naik, Perera, Mazen Issa, Binion, and Saeian		In Patients With Inflammatory Bowel Disease?					with IBD but is associated with a higher rate of work disability.
3	Arndtz, and Hirschfield	2018	Quality Of Life And Primary Sclerosing Cholangitis: The Business Of Defining What Counts	UK	Hepatology	Editorial	Individuals with PSC	There is a need for better measurements of quality of life outcomes, beyond quantitative assessments.
4	Benito De Valle, Rahman, Lindkvist, Björnsson,Chapm	2012	Factors That Reduce Health-Related Quality Of Life In Patients With Primary Sclerosing Cholangitis	UK	Clinical Gastroenterolo gy and Hepatology	Empirical : quantitative research	Individuals with PSC vs general population	Patients with PSC had significantly lower quality of life scores compared to the general population. Age and systemic symptoms

	an, and Kalaitzakis							were linked to lower quality of life scores.
5	Björnsson, Simren, Olsson & Chapman	2004	Fatigue In Patients With Primary Sclerosing Cholangitis	Sweden	Scandinavian Journal of Gastroenterology	Empirical : quantitative research	Individuals with PSC, some with IBD	Depression predicted fatigue scores in those with PSC. There were no significant differences between PSC patients, and others on depression.
6	Cheung, Patel, Meza-Cardona, Cino, Sockalingam, and Hirschfield	2016	Factors That Influence Health-Related Quality Of Life In Patients With Primary Sclerosing Cholangitis	Canada	Digestive Diseases & Sciences	Empirical : mixed- methods research	Individuals with PSC or PBC or non- autoimmune cholestatic liver disease or IBD	Individuals with PSC have significantly lower HRQOL than healthy controls, but similar quality of life to those with other cholestatic liver diseases.

7	Gorgun, Remzi, Manilich, Preen, Shen, and Fazio	2005	Surgical Outcome In Patients With Primary Sclerosing Cholangitis Undergoing Ileal Pouch–Analanastomosis: A Case-Control Study	USA	Surgery	Empirical : quantitative research	Individuals with IBD undergoing restorative proctocolectomy, with or without a comorbid diagnosis of PSC	Quality of life did not significantly improve at short- and long-term follow-ups.
8	Gotthardt, Rupp, Bruhin, Schellberg, Weiss, Stefan, Donnerstag, Stremmel, Löwe,	2014	Pruritus Is Associated With Severely Impaired Quality Of Life In Patients With Primary Sclerosing Cholangitis	Germany	European Journal of Gastroenterology & Hepatology	Empirical : quantitative research	Individuals with PSC	Women report more difficulty with physical functioning and emotional problems. Those with comorbid IBD have higher scores of depression.

	Juenger, and Sauer							
9	Gross, Malinchoc, Kim, Evans, Wiesner, Petz, Crippin, Klintmalm, Levy, Ricci, Therneau, and Dickson	1998	Quality Of Life Before And After Liver Transplantation For Cholestatic Liver Disease	USA	Hepatology	Empirical : quantitative research	Individuals with either PSC or PBC	Quality of life did not significantly differ between those diagnosed with PSC and PBC. However, quality of life significantly improved post-transplant.
10	Haapamaki, Tenca, Sintonen, Barner-Rasmussen, and Faarkkila	2015	Health-Related Quality Of Life Among Patients With Primary Sclerosing Cholangitis	Finland/ Italy	Liver International	Empirical : quantitative research	Individuals with PSC, some with IBD vs general population	Quality of life overall did not differ between those with PSC and the general population. However, scores of depression,

								distress and vitality were worse in those with PSC.
1 1	Kalaitzakis, Benito de Valle, Rahman, Lindkvist, Bjornsson, Chapman, and Kontodimopoulos	2016	Mapping Chronic Liver Disease Questionnaire Scores Onto Sf-6d Utility Values In Patients With Primary Sclerosing Cholangitis	Multi- Europea n	Quality of Life Research	Empirical : quantitative research	Individuals with PSC	Poorer quality of life was linked to decompensated liver disease and fatigue, systemic symptoms, and emotional distress.
1 2	Kempinska- Podhorodecka, Milkiewicz, Jabøonski, Milkiewicz, and Wunsch	2017	Apa-I Polymorphism Of Vitamin D Receptor Affects Health-Related Quality Of Life In Patients With Primary Sclerosing Cholangitis	Canada	PLOS One	Empirical : quantitative research	Individuals with PSC vs healthy controls	Apa-I polymorphism of vitamin D receptor affects physical and mental component summary scores.

1 3	Martins, and Chapman	2000	Sclerosing Cholangitis	USA	Current Opinion in Gastroenterology	Review	Individuals with PSC	Orthotopic Liver Transplant significantly improves quality of life in those with end-stage PSC.
1 4	Olsson, Boberg, Schaffalitsky De Muckadell, Lindgren, Hultcrantz, Folvik, Bell, Gangsøy- Kristiansen, Matre, Rydning, Wikman, Danielsson, Sandberg-	2005	High-Dose Ursodeoxycholic Acid In Primary Sclerosing Cholangitis: A 5-Year Multicenter, Randomized, Controlled Study	Sweden/ Norway	Gastroenterology	Empirical : quantitative research	Individuals with PSC	Those who underwent treatment with high-dose ursodeoxycholic acid revealed similar physical and mental health summary scores to the general population.

	Gertzén, Ung, Eriksson, Lööf, Prytz, Marschall, and Broomé							
1 5	Pavlidis, Cleland, Rahman, Christian, Doyle, Gaunt, Travis, Mortensen, and Chapman	2013	Outcomes After Ileal Pouch Anal Anastomosis In Patients With Primary Sclerosing Cholangitis	UK	Journal of Crohn's and Colitis	Empirical : quantitative research	Individuals with PSC and IPAA vs individuals with ulcerative colitis and IPAA	Quality of life did not differ between the two IPAA groups.
1 6	Rahman, Desmond, Mortensen, and Chapman	2011	The Clinical Impact Of Primary Sclerosing Cholangitis In Patients With An Ileal Pouch–	Australia	International Journal of Colorectal Disorders	Review	Individuals with PSC who underwent IPAA	Quality of life does not appear to be worse than in patients without PSC.

			Anal Anastomosis For Ulcerative Colitis					
1 7	Raszeja- Wyszomirska, Kucharski, Zygmunt, Safranow, Miazgowski	2015	The Impact Of Fragility Fractures On Health- Related Quality Of Life In Patients With Primary Sclerosing Cholangitis	Poland	Hepatitis Monthly	Empirical : quantitative research	Individuals with PSC	Mental Component Summary scores were significantly lower in women.
1 8	Raszeja- Wyszomirska, Wunsch, Krawczyk, Rigopoulou, Bogdanos, and Milkiewicz	2015	Prospective Evaluation Of Pbc-Specific Health- Related Quality Of Life Questionnaires In Patients With Primary Sclerosing Cholangitis	Multi- Europea n	Liver International	Empirical : quantitative research	Individuals with PSC vs healthy controls	Quality of life is poorer in those with PSC than controls. Female gender and age were linked to worse Mental Health Component Summary scores.

19	Ruppert, Kuo, Dimartini, and Balan	2010	In A 12-Year Study, Sustainability Of Quality Of Life Benefits After Liver Transplantation Varies With Pretransplantation Diagnosis	USA	Gastroenterology	Empirical : quantitative research	Liver transplant recipients	Sleeplessness, mood swings, nervousness, depression and difficulties with concentration were present one year post-transplant.
20	Serigado, Barboza, Marcus & Sigal	2018	Clinical Impact Of Depression In Cirrhosis	USA	Current Hepatology Reports	Review	Individuals with cirrhosis	The prevalence of depression in individuals with PSC was similar to other chronic liver disorders and is linked to increased severity of cirrhosis.

2 1	Tabibian, Gossard, El- Youssef, Eaton, Petz, Jorgensen, Enders, and Lindor	2017	Prospective Clinical Trial Of Rifaximin Therapy For Patients With Primary Sclerosing Cholangitis	USA	American Journal of Therapeutics	Empirical : quantitative research	Individuals with PSC	Rifaximin therapy did not improve mental health or emotional scores.
2 2	ter Borg, Fekkes, Maarten Vrolijk, and van Buuren	2005	The Relation Between Plasma Tyrosine Concentration And Fatigue In Primary Biliary Cirrhosis And Primary Sclerosing Cholangitis	Netherla nds	BMC Gastroenterolo gy	Empirical : quantitative research	Individuals with either PSC or PBC	Plasma tyrosine concentration was not linked to disease activity or severity, fatigue or quality of life.

2 3	van Os, van den Broek, Mulder, ter Borg, Bruijn, and van Buuren	2007	Depression In Patients With Primary Biliary Cirrhosis And Primary Sclerosing Cholangitis	Netherlands	Journal of Hepatology	Empirical : quantitative research	Individuals with either PSC or PBC	The prevalence of depression in patients with PSC is similar to the general population.
2 4	Wunsch, Krawczyk, Milkiewicz, Trottier, Barbier, Neurath, Lammert, Kremer, and Milkiewicz	2016	Serum Autotaxin Is A Marker Of The Severity Of Liver Injury And Overall Survival In Patients With Cholestatic Liver Diseases	Poland/ Germany / Canada	Scientific Reports	Empirical : quantitative research	Individuals with either PSC or PBC	Serum autotaxin does not affect mental health components of quality of life in individuals with PSC.
2 5	Wunsch, Trottier, Milkiewicz, Raszeja-	2014	Prospective Evaluation Of Ursodeoxycholic Acid Withdrawal In	Poland/ Canada/ UK	Hepatology	Empirical : quantitative research	Individuals with PSC	Individuals with PSC mostly reported an

	Wyszomirska, Hirschfield, Barbier, and Milkiewicz		Patients With Primary Sclerosing Cholangitis					improvement in their well-being.
2 6	Younossi, Kiwi, Boparai, Price, and Guyatt	2000	Cholestatic Liver Diseases And Health- Related Quality Of Life	USA	The American Journal of Gastroenterolo gy	Empirical : quantitative research	Individuals with either PSC or PBC	Individuals with PSC revealed a higher level of impairment in mental health compared to the healthy population.
2 7	Ypinazar	2015	Supporting Patients With A Rare Disease	Australia	Australian Family Physician	Commentar y	Caregiver viewpoint	Difficulty accessing information, experienced GPs and face-to-face support is a challenge due to the rarity of the illness.

28	Zakharia, Tabibian, Lindor, and Tabibian	2018	Complications, Symptoms, Quality Of Life And Pregnancy In Cholestatic Liver Disease	USA	Liver International	Review	Individuals with either PSC or PBC	Older age, female gender, large duct disease, severity of disease, concomitant IBD and systemic symptoms predict poorer HRQOL in those with PSC.
	<i>Studies not specific to PSC</i>							
29	Belle, Porayko, Hoofnagle, Lake, and Zetterman	1997	Changes In Quality Of Life After Liver Transplantation Among Adults	USA	Liver Transplantation and Surgery	Empirical : quantitative research	Liver transplant recipients	Distress and distressing symptoms decreased post-transplantation. Wellbeing worsened for 15% of those who received a liver transplant.

30	Bryan, Ratcliffe, Neuberger, Burroughs, Gunson, and Buxton	1998	Health-Related Quality Of Life Following Liver Transplantation	UK	Quality of Life Research	Empirical : quantitative research	Liver transplant recipients	Longer disease duration was affiliated with poorer quality of life scores. Mental HRQOL improved significantly post-transplant.
31	Davis, De-Nour, Shouval, and Melmed	1998	Psychological Distress In Patients With Chronic, Nonalcoholic, Uncomplicated Liver Disease	Israel	Journal of Psychosomatic Research	Empirical : quantitative research	Individuals With Chronic, Nonalcoholic, Uncomplicated Liver Disease	This study found a significant incidence of psychological distress, even in those who were clinically asymptomatic.
32	Davydow, Lease, and Reyes	2015	Posttraumatic Stress Disorder In Organ Transplant Recipients: A Systematic Review	USA	General Hospital Psychiatry	Review	Organ transplant recipients	Clinician ascertained PTSD featured in the accounts of some transplant recipients.

3 3	Day, Best, Sweeting, Russell, Webb, Georgiou. and Neuberger	2009	Predictors Of Psychological Morbidity In Liver Transplant Assessment Candidates: Is Alcohol Abuse Or Dependence A Factor?	UK	Transplant International	Empirical : quantitative research	Individuals assessed for liver transplant	Female transplant candidates reported a higher number of distressing symptoms.
3 4	Eraydın, Akarsu, Hakim, Keskinoglu, and Ellidokuz	2014	The Validity And Reliability Of “The Liver Disease Symptom Index 2.0” For Turkish Society	Turkey	Turkish Journal of Gastroenterolo gy	Empirical : quantitative research	Individuals with Chronic Liver Disease	Worry and depression featured in the accounts of those with chronic liver disease.
3 5	Garcia, Garcia, and McMaster	2000	Chronic Rejection Of The Liver. The Role Of Immunosuppression.	UK	Biodrugs	Review	Liver transplant recipients	Most liver transplant recipients experience an increase in quality of life

								and a return to full activities post-transplant.
3 6	Gralnek, Hays, Kilbourne, Rosen, Keeffe, Artinian, Kim, Lazarovici, Jensen, Busuttil, and Martin	2000	Development And Evaluation Of The Liver Disease Quality Of Life Instrument In Persons With Advanced, Chronic Liver Disease—The Ldqol 1.0	USA	The American Journal of Gastroenterology	Empirical : quantitative research	Individuals with advanced Chronic Liver Disease	Poorer HRQOL was linked to poorer prognosis, increased liver disease severity, and a greater number of disability days.
3 7	Gutteling, De Man, Van Der Plas, Schalm, Busschbach, and Darlington	2006	Determinants Of Quality Of Life In Chronic Liver Patients	Netherlands	Alimentary Pharmacology and Therapeutics	Empirical : quantitative research	Individuals with Chronic Liver Disease	HRQOL was linked to disease severity, joint and abdominal pain, depression, decreased appetite and fatigue.

38	Jin and Khan	2016	Quality Of Life Among Patients Suffering From Cholestatic Liver Disease-Induced Pruritus: A Systematic Review	Malaysia	Journal of the Formosan Medical Association	Systematic review	Individuals with cholestatic liver disease-induced pruritus	Pruritus is linked to HRQOL, and affects emotional wellbeing.
39	Kalaitzakis, Simrén, Olsson, Henfridsson, Hugosson, Bengtsson, and Björnsson	2006	Gastrointestinal Symptoms In Patients With Liver Cirrhosis: Associations With Nutritional Status And Health-Related Quality Of Life	Sweden	Scandinavian Journal of Gastroenterology	Empirical : quantitative research	Individuals with cirrhosis	Those with cirrhosis revealed higher gastrointestinal symptom severity and profound reductions in quality of life and mental component summary scores.

40	Kanwal, Gralnek, Hays, Zeringue, Durazo, Han, Saab, Bolus, and Spiegel	2009	Health-Related Quality Of Life Predicts Mortality In Patients With Advanced Chronic Liver Disease	USA/Israel	Clinical Gastroenterology and Hepatology	Empirical : quantitative research	Individuals awaiting liver transplant	Higher scores of HRQOL predict lower mortality in patients with cirrhosis.
41	Kanwal, Spiegel, Hays, Durazo, Han, Saab, Bolus, Kim, and Gralnek	2008	Prospective Validation Of The Short Form Liver Disease Quality Of Life Instrument	USA/Israel	Alimentary Pharmacology and Therapeutics	Empirical : quantitative research	Liver transplant recipients vs non-recipients	HRQOL improved in those who received a liver transplant.
42	Kuiper, van Erpecum, Beuers, Hansen, Thio, de	2010	The Potent Bile Acid Sequestrant Colesevelam Is Not Effective In Cholestatic Pruritus: Results Of A	Netherlands	Hepatology	Empirical : quantitative research	Individuals with cholestatic pruritus	Colesevelam did not impact physical functioning, bodily pain, general health, vitality, social functioning,

	Man, Janssen, and van Buuren		Double-Blind, Randomized, Placebo-Controlled Trial					emotional functioning, or mental health.
4 3	Le Strat, Le Foll, and Dubertret,	2014	Major Depression And Suicide Attempts In Patients With Liver Disease In The United States	France/ Canada	Liver International	Empirical : quantitative research	Individuals with liver disease vs those without liver disease	Incidences of major depression and lifetime rates of suicide attempts were significantly higher in those with liver disease
4 4	Noma, Hayashi, Uehara, Kuwabara, Tanaka, Furuno, Ogawa, and Hayashi	2008	Psychosocial Predictors Of Psychiatric Disorders After Living Donor Liver Transplantation	Japan	International Journal of Psychiatry in Clinical Practice	Empirical : quantitative research	Liver transplant recipients	Anxiety and depression were greater in those who received a transplant compared to healthy persons.

4 5	Parvizi, Sadati, Azarpira, Parvizi, Tabrizi, Heydari, Lankarani	2016	Study Of Quality Of Life Among Liver Transplant Candidates In Shiraz, Southwestern Iran	Iran	Galen Medical Journal	Empirical : quantitative research	Liver transplant candidates	Poorer quality of life of liver transplant candidates was linked to being female and under 30.
4 6	Raszeja-Wyszomirska, Kucharski, Kotarska, Zalewska, and Miazgowski	2015	The Impact Of Osteoporosis On Health-Related Quality Of Life In Patients After Liver Transplantation – A Pilot Study	Poland	Przegląd Gastroenterologiczny	Empirical : quantitative research	Liver transplant recipients with fractures vs without fractures	HRQOL did not differ between those with or without fractures.
4 7	Rogal, Winger, Bielefeldt, and Szigethy	2013	Pain And Opioid Use In Chronic Liver Disease	USA	Digestive Diseases & Sciences	Empirical : quantitative research	Individuals with Chronic Liver Disease	Emotional distress, mood-related symptoms, age, nicotine use, advanced liver disease and etiology of liver

								disease predicted opioid use for pain.
48	Sarkar, Wat, Terrault, Berenguer	2015	Outcomes In Liver Transplantation: Does Sex Matter?	USA/Spain	Journal of Hepatology	Review	Liver transplant recipients	There is conflicting data regarding the effect of sex on quality of life. Newer studies report poorer quality of life and psychosocial adjustment in women.
49	ter Borg, van Os, van den Broek, Hansen, and van Buuren	2004	Fluvoxamine For Fatigue In Primary Biliary Cirrhosis And Primary Sclerosing Cholangitis: A Randomised Controlled Trial	Netherlands	BMC Gastroenterology	Empirical : quantitative research	Individuals with either PSC or PBC	Fluvoxamine did not improve fatigue or quality of life.

50	van Ginneken, van den Berg-Emonsa, van der Windta, Tilanus, Metselaarc, Stama, and Kazemier	2010	Persistent Fatigue In Liver Transplant Recipients: A Two-Year Follow-Up Study	Netherlands	Clinical Transplantation	Empirical : quantitative research	Liver transplant recipients	Fatigue continued post-transplant and predicted daily functioning and some HRQOL domains. Fatigue was linked to sleep quality, anxiety and depression.
51	Watanabe and Inoue	2009	Transformational Experiences In Adult-To-Adult Living-Donor Liver Transplant Recipients	Japan	Journal of Advanced Nursing	Empirical : qualitative research	Individuals with adult-to-adult liver transplant	Donor-related anxieties included fears about the donor and impacting the survival of the donor.
52	Yang, Shan, Saxena, and Morris	2014	Liver Transplantation: A Systematic Review	Australia	Liver International	Systematic review	Liver transplant recipients	Quality of life remains similar to that of the general

			Of Long-Term Quality Of Life					population, up to 20 years post-transplant.
5 3	Younossi, Boparai, Price, Kiwi, McCormick, and Guyatt	2001	Health-Related Quality Of Life In Chronic Liver Disease: The Impact Of Type And Severity Of Disease	USA / Canada	The American Journal of Gastroenterolo gy	Empirical : quantitative research	Individuals with Chronic Liver Disease	No difference in HRQOL between types of chronic liver disease. Older age and disease severity were linked to poorer HRQOL.

Table (supplementary) Measures employed by all articles included in the scoping review (extra online material)

N°	Authors	Year	Title	Country	Journal	Design	Measurement
	<i>Studies specific to PSC</i>						
1	Aberg, Hockerstedt, Roine, Sintonen, Isoniemi	2012	The Influence Of Liver-Disease Etiology On Long-Term Quality Of Life And Employment After Liver Transplantation.	Finland	Clinical Transplantation	Empirical : quantitative research	Health-Related Quality of Life (HRQOL) (15D)
2	Ananthkrishnan, Beaulieu, Ulitsky, Zadvornova, Skaros, Johnson, Naik, Perera, Mazen Issa,	2010	Does Primary Sclerosing Cholangitis Impact Quality Of Life In Patients With Inflammatory Bowel Disease?	USA	Inflammatory Bowel Disorders	Empirical : quantitative research	Health-Related Quality of Life (HRQOL) (15D)

	Binion, and Saeian						
3	Arndtz, and Hirschfield	2018	Quality Of Life And Primary Sclerosing Cholangitis: The Business Of Defining What Counts	UK	Hepatology	Editorial	N/A
4	Benito De Valle, Rahman, Lindkvist, Björnsson, Chapman, and Kalaitzakis	2012	Factors That Reduce Health-Related Quality Of Life In Patients With Primary Sclerosing Cholangitis	UK	Clinical Gastroenterology and Hepatology	Empirical : quantitative research	Medical Outcomes Study Short-Form 36 (SF-36); Fatigue Impact Scale (FIS); Hospital Anxiety and Depression Scale (HADS).
5	Björnsson, Simren, Olsson & Chapman	2004	Fatigue In Patients With Primary Sclerosing Cholangitis	Sweden	Scandinavian Journal of Gastroenterology	Empirical : quantitative research	Fatigue Impact Scale (FIS); the Psychological General Well-Being Index (PGWB);

							the Gastrointestinal Symptom Rating Scale (GSRS); the Beck Depression Inventory (BDI).
6	Cheung, Patel, Meza-Cardona, Cino, Sockalingam, and Hirschfield	2016	Factors That Influence Health-Related Quality Of Life In Patients With Primary Sclerosing Cholangitis	Canada	Digestive Diseases & Sciences	Empirical : mixed-methods research	Medical Outcomes Study Short Form-36 (SF-36); Disease-specific instruments scores [PBC-40, Short IBD questionnaire, Liver Disease Quality of Life Questionnaire (LDQOL)]
7	Gorgun, Remzi, Manilich, Preen, Shen, and Fazio	2005	Surgical Outcome In Patients With Primary Sclerosing Cholangitis Undergoing Ileal	USA	Surgery	Empirical : quantitative research	Cleveland Global Quality of Life score (CGQOL); Medical Outcomes Study Short Form

			Pouch–Analanastomosis: A Case-Control Study				36; Female Sexual Satisfaction Index (FSFI)
8	Gotthardt, Rupp, Bruhin, Schellberg, Weiss, Stefan, Donnerstag, Stremmel, Löwe, Juenger, and Sauer	2014	Pruritus Is Associated With Severely Impaired Quality Of Life In Patients With Primary Sclerosing Cholangitis	Germany	European Journal of Gastroenterology & Hepatology	Empirical : quantitative research	Medical Outcomes Study Short Form 36 (SF-36); Patient Health Questionnaire
9	Gross, Malinchoc, Kim, Evans, Wiesner, Petz, Crippin,	1998	Quality Of Life Before And After Liver Transplantation For Cholestatic Liver Disease	USA	Hepatology	Empirical : quantitative research	National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database –

	Klintmalm, Levy, Ricci, Therneau, and Dickson						Quality of Life (NIDDK LTD-QOL Adult Version)
10	Haapamaki, Tenca, Sintonen, Barner- Rasmussen, and Faarkkila	2015	Health-Related Quality Of Life Among Patients With Primary Sclerosing Cholangitis	Finland/ Italy	Liver International	Empirical : quantitative research	Health-Related Quality of Life (HRQOL) (15D)
11	Kalaitzakis, Benito de Valle, Rahman, Lindkvist, Bjornsson, Chapman, and Kontodimopoulos	2016	Mapping Chronic Liver Disease Questionnaire Scores Onto Sf-6d Utility Values In Patients With Primary Sclerosing Cholangitis	Multi- European	Quality of Life Research	Empirical : quantitative research	Medical Outcomes Study Short Form 6D (SF-6D)

12	Kempinska-Podhorodecka, Milkiewicz, Jabøonski, Milkiewicz, and Wunsch	2017	Apa-I Polymorphism Of Vitamin D Receptor Affects Health-Related Quality Of Life In Patients With Primary Sclerosing Cholangitis	Canada	PLOS One	Empirical quantitative research	: Health-Related Quality of Life (HRQOL) (15D)
13	Martins, and Chapman	2000	Sclerosing Cholangitis	USA	Current Opinion in Gastroenterology	Review	N/A
14	Olsson, Boberg, Schaffalitsky De Muckadell, Lindgren, Hulterantz, Folvik, Bell,	2005	High-Dose Ursodeoxycholic Acid In Primary Sclerosing Cholangitis: A 5-Year Multicenter, Randomized, Controlled Study	Sweden/ Norway	Gastroenterology	Empirical quantitative research	: N/A

	Gangsøy– Kristiansen, Matre, Rydning, Wikman, Danielsson, Sandberg– Gertzén, Ung, Eriksson, Lööf, Prytz, Marschall, and Broomé						
15	Pavlidis, Cleland, Rahman, Christian, Doyle, Gaunt, Travis,	2013	Outcomes After Ileal Pouch Anal Anastomosis In Patients With Primary Sclerosing Cholangitis	UK	Journal of Crohn's and Colitis	Empirical quantitative research	: Cleveland Global Quality of Life Questionnaire (CGQOL); Medical Outcomes Study Short Form-36 (SF-36)

	Mortensen, and Chapman						
16	Rahman, Desmond, Mortensen, and Chapman	2011	The Clinical Impact Of Primary Sclerosing Cholangitis In Patients With An Ileal Pouch–Anal Anastomosis For Ulcerative Colitis	Australia	International Journal of Colorectal Disorders	Review	N/A
17	Raszeja-Wyszomirska, Kucharski, Zygmunt, Safranow, Miazgowski	2015	The Impact Of Fragility Fractures On Health-Related Quality Of Life In Patients With Primary Sclerosing Cholangitis	Poland	Hepatitis Monthly	Empirical : quantitative research	Medical Outcomes Study Short Form 36 (SF-36)

18	Raszeja- Wyszomirska, Wunsch, Krawczyk, Rigopoulou, Bogdanos, and Milkiewicz	2015	Prospective Evaluation Of Pbc-Specific Health-Related Quality Of Life Questionnaires In Patients With Primary Sclerosing Cholangitis	Multi-European	Liver International	Empirical : quantitative research	Medical Outcomes Study Short Form 36 (SF-36)
19	Ruppert, Kuo, Dimartini, and Balan	2010	In A 12-Year Study, Sustainability Of Quality Of Life Benefits After Liver Transplantation Varies With Pretransplantation Diagnosis	USA	Gastroenterology	Empirical : quantitative research	National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database – Quality of Life (NIDDK LTD-QOL Adult Version)

20	Serigado, Barboza, Marcus & Sigal	2018	Clinical Impact Of Depression In Cirrhosis	USA	Current Hepatology Reports	Review	N/A
21	Tabibian, Gossard, El- Youssef, Eaton, Petz, Jorgensen, Enders, and Lindor	2017	Prospective Clinical Trial Of Rifaximin Therapy For Patients With Primary Sclerosing Cholangitis	USA	American Journal of Therapeutics	Empirical : quantitative research	Fisk Fatigue Impact Scale (FFIS); Chronic Liver Disease Questionnaire (CLDQ); Medical Outcomes Study Short Form Health Survey (SF-36) scores
22	ter Borg, Fekkes, Maarten Vrolijk, and van Buuren	2005	The Relation Between Plasma Tyrosine Concentration And Fatigue In Primary Biliary Cirrhosis And Primary Sclerosing Cholangitis	Netherlan ds	BMC Gastroenterology	Empirical : quantitative research	Visual Analogue Scale (VAS); the Fisk Fatigue Severity Scale (FFSS)

23	van Os, van den Broek, Mulder, ter Borg, Bruijn, and van Buuren	2007	Depression In Patients With Primary Biliary Cirrhosis And Primary Sclerosing Cholangitis	Netherlands	Journal of Hepatology	Empirical : quantitative research	Beck Depression Inventory (BDI)
24	Wunsch, Krawczyk, Milkiewicz, Trottier, Barbier, Neurath, Lammert, Kremer, and Milkiewicz	2016	Serum Autotaxin Is A Marker Of The Severity Of Liver Injury And Overall Survival In Patients With Cholestatic Liver Diseases	Poland/ Germany/ Canada	Scientific Reports	Empirical : quantitative research	Medical Outcomes Study Short Form-36 (SF-36)
25	Wunsch, Trottier, Milkiewicz, Raszeja-	2014	Prospective Evaluation Of Ursodeoxycholic Acid	Poland/ Canada/ UK	Hepatology	Empirical : quantitative research	Medical Outcomes Study Short Form-36 (SF-36)

	Wyszomirska, Hirschfield, Barbier, and Milkiewicz		Withdrawal In Patients With Primary Sclerosing Cholangitis				
26	Younossi, Kiwi, Boparai, Price, and Guyatt	2000	Cholestatic Liver Diseases And Health-Related Quality Of Life	USA	The American Journal of Gastroenterology	Empirical : quantitative research	Medical Outcomes Study Short Form-36 (SF-36); Chronic Liver Disease Questionnaire
27	Ypinazar	2015	Supporting Patients With A Rare Disease	Australia	Australian Family Physician	Commentary	N/A
28	Zakharia, Tabibian, Lindor, and Tabibian	2018	Complications, Symptoms, Quality Of Life And Pregnancy In Cholestatic Liver Disease	USA	Liver International	Review	N/A

	<i>Studies not specific to PSC</i>						
29	Belle, Porayko, Hoofnagle, Lake, and Zetterman	1997	Changes In Quality Of Life After Liver Transplantation Among Adults	USA	Liver Transplantation and Surgery	Empirical : quantitative research	National Institute of Diabetes and Digestive and Kidney Diseases Liver Transplantation Database – Quality of Life (NIDDK LTD-QOL Adult Version)
30	Bryan, Ratcliffe, Neuberger, Burroughs, Gunson, and Buxton	1998	Health-Related Quality Of Life Following Liver Transplantation	UK	Quality of Life Research	Empirical : quantitative research	Medical Outcomes Study Short Form-36 (SF-36); EuroQol (EQ-5D)

31	Davis, De-Nour, Shouval, and Melmed	1998	Psychological Distress In Patients With Chronic, Nonalcoholic, Uncomplicated Liver Disease	Israel	Journal of Psychosomatic Research	Empirical : quantitative research	Brief Symptom Inventory (BSI); the Impact of Event Scale (IES)
32	Davydow, Lease, and Reyes	2015	Posttraumatic Stress Disorder In Organ Transplant Recipients: A Systematic Review	USA	General Hospital Psychiatry	Review	N/A
33	Day, Best, Sweeting, Russell, Webb, Georgiou. and Neuberger	2009	Predictors Of Psychological Morbidity In Liver Transplant Assessment Candidates: Is Alcohol Abuse Or Dependence A Factor?	UK	Transplant International	Empirical : quantitative research	Symptom Checklist-90-Revised instrument
34	Eraydın, Akarsu, Hakim,	2014	The Validity And Reliability Of “The Liver Disease Symptom Index 2.0” For Turkish Society	Turkey	Turkish Journal of Gastroenterology	Empirical : quantitative research	Liver Symptom Index 2.0 (LDSI 2.0); Medical

	Keskinoglu, and Ellidokuz						Outcomes Study Short Form-36 (SF-36)
35	Garcia, Garcia, and McMaster	2000	Chronic Rejection Of The Liver. The Role Of Immunosuppression.	UK	Biodrugs	Review	N/A
36	Gralnek, Hays, Kilbourne, Rosen, Keeffe, Artinian, Kim, Lazarovici, Jensen, Busuttil, and Martin	2000	Development And Evaluation Of The Liver Disease Quality Of Life Instrument In Persons With Advanced, Chronic Liver Disease—The Ldqol 1.0	USA	The American Journal of Gastroenterology	Empirical : quantitative research	The Liver Disease Quality of Life instrument, LDQOL 1.0
37	Gutteling, De Man, Van Der Plas, Schalm,	2006	Determinants Of Quality Of Life In Chronic Liver Patients	Netherlands	Alimentary Pharmacology and Therapeutics	Empirical : quantitative research	Liver Disease Symptom Index 2.0;

	Busschbach, and Darlington						
38	Jin and Khan	2016	Quality Of Life Among Patients Suffering From Cholestatic Liver Disease-Induced Pruritus: A Systematic Review	Malaysia	Journal of the Formosan Medical Association	Systematic review	N/A
39	Kalaitzakis, Simrén, Olsson, Henfridsson, Hugosson, Bengtsson, and Björnsson	2006	Gastrointestinal Symptoms In Patients With Liver Cirrhosis: Associations With Nutritional Status And Health-Related Quality Of Life	Sweden	Scandinavian Journal of Gastroenterology	Empirical : quantitative research	Gastrointestinal symptom rating scale (GSRS); Medical Outcomes Study Short Form (SF-36)
40	Kanwal, Gralnek, Hays, Zeringue,	2009	Health-Related Quality Of Life Predicts Mortality In Patients	USA/Israe l	Clinical Gastroenterology and Hepatology	Empirical : quantitative research	Short Form Liver Disease Quality of Life (SF-LDQOL)

	Durazo, Han, Saab, Bolus, and Spiegel		With Advanced Chronic Liver Disease				
41	Kanwal, Spiegel, Hays, Durazo, Han, Saab, Bolus, Kim, and Gralnek	2008	Prospective Validation Of The Short Form Liver Disease Quality Of Life Instrument	USA/Israe l	Alimentary Pharmacology and Therapeutics	Empirical : quantitative research	Short Form Liver Disease Quality of Life (SF-LDQOL)
42	Kuiper, van Erpecum, Beuers, Hansen, Thio, de Man, Janssen, and van Buuren	2010	The Potent Bile Acid Sequestrant Colesevelam Is Not Effective In Cholestatic Pruritus: Results Of A Double-Blind, Randomized, Placebo-Controlled Trial	Netherlan ds	Hepatology	Empirical : quantitative research	Visual analogue scale (VAS); Medical Outcomes Study Short Form 36 (SF-36); Liver Disease Symptom Index 2.0

43	Le Strat, Le Foll, and Dubertret,	2014	Major Depression And Suicide Attempts In Patients With Liver Disease In The United States	France/ Canada	Liver International	Empirical : quantitative research	National Epidemiologic Survey on Alcohol and Related Conditions (NESARC)
44	Noma, Hayashi, Uehara, Kuwabara, Tanaka, Furuno, Ogawa, and Hayashi	2008	Psychosocial Predictors Of Psychiatric Disorders After Living Donor Liver Transplantation	Japan	International Journal of Psychiatry in Clinical Practice	Empirical : quantitative research	Beck Depression Inventory (BDI); State-Trait Anxiety Inventory; World Health Organization Quality-of-Life Assessment-26; Psychosocial Assessment of Candidates for Transplantation (PACT)
45	Parvizi, Sadati, Azarpira, Parvizi, Tabrizi,	2016	Study Of Quality Of Life Among Liver Transplant Candidates In Shiraz, Southwestern Iran	Iran	Galen Medical Journal	Empirical : quantitative research	Chronic Liver Disease Questionnaire (CLDQ)

	Heydari, Lankarani						
46	Raszeja- Wyszomirska, Kucharski, Kotarska, Zalewska, and Miazgowski	2015	The Impact Of Osteoporosis On Health-Related Quality Of Life In Patients After Liver Transplantation – A Pilot Study	Poland	Przegląd Gastroenterologiczny	Empirical : quantitative research	Medical Outcomes Study Short Form-36 (SF-36); PBC-40 instruments
47	Rogal, Winger, Bielefeldt, and Szigethy	2013	Pain And Opioid Use In Chronic Liver Disease	USA	Digestive Diseases & Sciences	Empirical : quantitative research	Patient self-reports
48	Sarkar, Wat, Terrault, Berenguer	2015	Outcomes In Liver Transplantation: Does Sex Matter?	USA/Spain	Journal of Hepatology	Review	N/A

49	ter Borg, van Os, van den Broek, Hansen, and van Buuren	2004	Fluvoxamine For Fatigue In Primary Biliary Cirrhosis And Primary Sclerosing Cholangitis: A Randomised Controlled Trial	Netherlan ds	BMC Gastroenterology	Empirical : quantitative research	Visual analogue scale (VAS); Fisk Fatigue Severity Scale (FFSS); the Multidimensional Fatigue Inventory; Short Form-36 (SF-36)
50	van Ginneken, van den Berg- Emonsa, van der Windta, Tilanusb, Metselaarc, Stama, and Kazemier	2010	Persistent Fatigue In Liver Transplant Recipients: A Two- Year Follow-Up Study	Netherlan ds	Clinical Transplantation	Empirical : quantitative research	Fatigue Severity Scale (FSS); Visual Analog Scales (VAS); Sickness Impact Profile-68 (SIP-68); Medical Outcomes Study Short Form-36 (SF-36); the RAND-36 Health Survey (RAND-36); Hospital Anxiety and Depression Scale (HADS); Pittsburgh Sleep Quality Index (PSQI)

51	Watanabe and Inoue	2009	Transformational Experiences In Adult-To-Adult Living-Donor Liver Transplant Recipients	Japan	Journal of Advanced Nursing	Empirical : qualitative research	N/A
52	Yang, Shan, Saxena, and Morris	2014	Liver Transplantation: A Systematic Review Of Long-Term Quality Of Life	Australia	Liver International	Systematic review	N/A
53	Younossi, Boparai, Price, Kiwi, McCormick, and Guyatt	2001	Health-Related Quality Of Life In Chronic Liver Disease: The Impact Of Type And Severity Of Disease	USA / Canada	The American Journal of Gastroenterology	Empirical : quantitative research	Medical Outcomes Study Short Form-36 (SF-36); Chronic Liver Disease Questionnaire