






# Two decades of research on autoimmune liver disease in Turkey

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## ABSTRACT

**Background/Aims:** Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) are the 3 main autoimmune liver diseases (AILDs). The epidemiology of AILD in Turkey is not known. To determine the scientific status, we performed a scientometric analysis of AILD-related original articles that originated from Turkey.

**Materials and Methods:** We searched the Web of Science database, the Science Citation Index Expanded (SCI-E), and the Social Sciences Citation Index (SSCI) by using the keywords "autoimmune hepatitis," "primary biliary cholangitis/primary biliary cirrhosis," and "primary sclerosing cholangitis" in conjunction with "Turkey." A scientometric analysis was done on the search results.

**Results:** We identified 117 AILD-related papers that were published in Turkey from 1997 to 2019. Among these, 70 case reports, letters, and reviews and 2 original articles that were not cited in SCI-E/SSCI were excluded. The remaining 45 original articles were further analyzed. These studies were related to AIH (n=22), PBC (n=7), PSC (n=9), PBC-AIH overlap (n=5), and others (n=2). Four of the publications originated in pediatric settings; 9 of 45 papers were published from 1997 to 2008 and 36 papers were published from 2009 to 2019. Most papers (75%) were reported from 5 centers; 9 papers (20%) were published in journals with an impact factor of 3 or higher.

**Conclusion:** The overall number and quality of AILD-related papers in Turkey are unexpectedly low, although a number of papers have received considerable international recognition. More epidemiologic, prospective, and multicenter research projects are warranted to advance AILD knowledge and to produce high-quality research from Turkey.

**Keywords:** Autoimmunity, liver failure, liver transplantation

## INTRODUCTION

Autoimmune hepatitis (AIH), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC) are the 3 main autoimmune liver diseases (AILDs) (1). AIH usually presents with elevated aminotransferase levels and hepatocellular injury on liver histology, whereas PBC and PSC are characterized by laboratory, radiological, and histologic features of cholestasis (2-4). The global prevalence rates of PBC are 19.1 to 402 cases per million inhabitants and incidence rates of 0.33 to 5.8 cases per million inhabitants per year (2). The reported incidence and prevalence rates for PSC are 0-1.3 to 0-16.2 per 100,000 inhabitants, respectively (3). For AIH, the mean incidence is 1 to 2 per 100,000 persons/year and the prevalence is approximately 11 to 17 per 100,000 persons/year (4). Several recent studies have reported that the incidence of AILD is increasing worldwide (5, 6). The exact incidence and prevalence rates in Turkey are not well known.

During 1999-2009, 12% of liver transplantations were done for AILD in Europe (7). Several standard and non-standard therapies have been developed for AIH and PBC (2, 4). These therapies prolong survival in most treated patients, but there is still no therapeutic option that prevents disease progression in PSC (3). Therefore, liver transplantation for PBC and AIH tends to decrease over time, whereas transplantations increase for PSC (7).

Viral hepatitis B and C are the most common causes of chronic liver disease in Turkey, and many studies from Turkey have addressed this form of chronic hepatitis (8-10). The global burden of viral hepatitis B and C will be alleviated because of modern, highly effective therapies and vaccination for hepatitis B. Nonalcoholic fatty liver disease (NAFLD) and AILD seem to be increasing and remain important causes of chronic liver disease worldwide and also in Turkey. To understand where we stand scien-

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tifically on AILD in Turkey, we performed a scientometric analysis of AILD-related papers that have been published from Turkey. We think that our work will be illustrative and useful for designing future research projects on AILD in Turkey.

**MATERIALS AND METHODS**

**Study Protocol**

A scientometric analysis was performed based on PubMed and MEDLINE. We searched “autoimmune hepatitis,” “primary biliary cirrhosis/primary biliary cholangitis,” and “primary sclerosing cholangitis” in the title, abstract, or keywords. In addition, “Turkey” was used as a keyword. Only articles from the Social Sciences Citation Index and the Science Citation Index Expanded were included. We used Web of Science (WOS), which is an important database for detecting scientific indices of articles and current impact factors.

**Time Frame**

Based on results from the initial PubMed analysis, the study time span was limited to between January 1997 and September 2019. Our last search was done on September 2019. Only papers published in English were included in the analysis.

**Statistical Analysis**

Using the WOS tools, all gathered data were analyzed on the basis of the following parameters: year, institution, journal, and impact factor. To determine the effects of international collaborations, we included articles with affiliations from more than 1 country. Other analyses, including the preparation of graphs, were performed using Microsoft Excel 2016.

**RESULTS**

We identified 117 AILD-related papers that were published from Turkey during the years 1997 to 2019. A total of 70 case reports, letters, reviews, and 2 original articles that were not cited in reference indices were excluded (Figure 1). The remaining 45 original articles

**Autoimmune liver disease-related papers from Turkey**

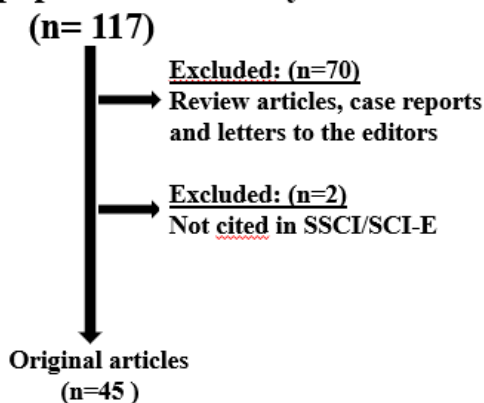


Figure 1. Flowchart of searching and selecting the original articles.

were further analyzed for the study. The general characteristics of these studies are presented in Supplemental Table 1.

The number of published papers in the field of AILD according to the disease types and institutions in Turkey is presented in Table 1. The Hacettepe University was the leading institution with 13 published papers, followed by Ankara Yuksek Ihtisas Education and Research Hospital (n=9), Ankara Numune Research and Education Hospital (n=6), Ankara University (n=4), and Ege University (n=2). Other centers had 1 published AILD-related paper each; 9 of 45 papers (20%) were published from 1997 to 2008, whereas 36 papers (80%) were published from 2009 to 2019. The number of articles published in this area has increased since 2009 (Figure 2).

Only papers from Hacettepe University, Ankara Yuksek Ihtisas Education and Research Hospital, and Ankara Numune Research and Education Hospital were done in international collaborations. The number of papers from the top 5 institutions, with and without international collaborations, is presented in Figure 3.

The *European Journal of Gastroenterology and Hepatology*, *The Turkish Journal of Gastroenterology*, *Digestive Diseases and Sciences*, and *Hepato-Gastroenterology* were the journals with the most published AILD-related papers from Turkey. The names and current impact factors of the journals that published AILD-related papers from Turkey are presented in Table 2.

**MAIN POINTS**

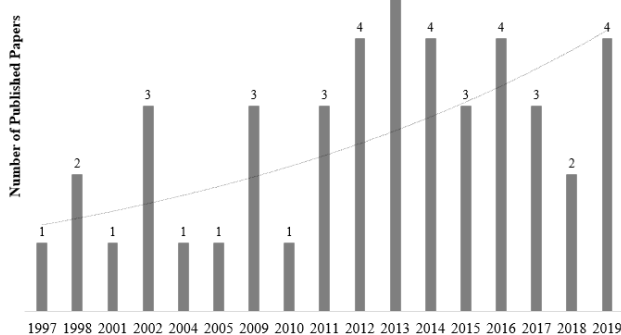
- Autoimmune liver diseases are rare liver diseases.
- We showed that number of scientific papers from Turkey on this topic is not enough.
- Our findings suggest that multicenter and prospective study projects are needed to produce high-quality papers from Turkey.

**Table 1.** Number of published AILD-papers according to disease types and institutions in Turkey (1997-2019).

Institution	AIH	PSC	PBC	Overlap	All*	Total
Hacettepe University	11	1		1		13
Ankara Yuksek Ihtisas Training and Research Hospital	3	5				8
Ankara Numune Training and Research Hospital	2		1	3	1	7
Ankara University Hospital		2	2			4
Ege University Hospital	1			1		2
Ankara Ataturk Training and Research Hospital			1			1
Istanbul University, Capa Medicine School	1					1
Istanbul Sisli Etfal Training and Research Hospital	1					1
Gazi University Hospital	1					1
Ankara Ulucanlar Eye Training and Research Hospital					1	1
Gaziantep Children’s Hospital	1					1
Diyarbakır Gazi Yaşargil Training and Research Hospital			1			1
Sisli Florence Nightingale Hospital		1				1
Dokuz Eylul University School of Medicine		1				1
Eskisehir Osmangazi University School of Medicine	1					1
Tepecik Training and Research Hospital	1					1
<b>Total</b>	<b>23</b>	<b>10</b>	<b>5</b>	<b>5</b>	<b>2</b>	<b>45</b>

\*Related to all types of AILD.

AIH: autoimmune hepatitis; AILD: autoimmune liver disease; PBC: primary biliary cirrhosis; PSC: primary sclerosing cholangitis.



**Figure 2.** Number of autoimmune liver diseases-related papers in Turkey (1997-2019).

The numbers of papers from the top 5 institutions, based on the types of AILD including AIH, PBC, PSC, and overlap syndromes, are shown in Figure 4.

## DISCUSSION

We identified 45 AILD-related original articles that originated from Turkey during the last 2 decades (1997-2019). The prevalence of viral hepatitis and NAFLD has been well studied in the Turkish population—all AILD-related studies are descriptive, and none provide information about the estimated prevalence of AILD in Turkey (10, 11). Turkish papers comprise a small minority of all papers on AILD and few have been published in high-ranking journals. However, study provides good news: between 2009 and 2019, the number of AILD-related papers from Turkey has nearly quadrupled and some papers have been published in high-quality journals.

The best AILD-related paper from Turkey was published by Kaymakoglu et al. (12) in 1998. In this pioneer study, the authors showed that biochemical and genetic characteristics of some patients who previously had been considered to have cryptogenic hepatitis actually had AIH. This study highlighted that AIH may present with-

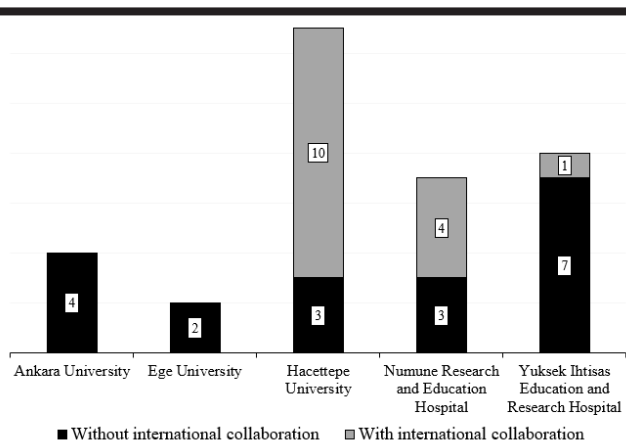


Figure 3. Number of papers on autoimmune liver diseases from the top 5 institutions in Turkey (1997–2019), with and without international collaboration.

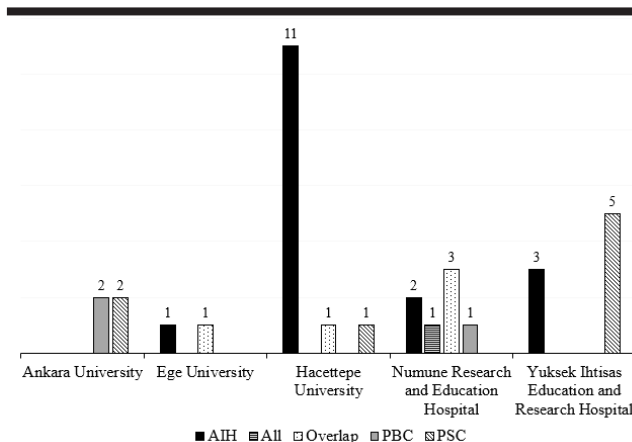


Figure 4. Number of papers from the top 5 institutions in Turkey regarding the type of autoimmune liver diseases (1997–2019).

Table 2. Journals publishing AILD-related studies from Turkey (1997–2019).

Journal name	Number of published papers	Impact factor*
<i>European Journal of Gastroenterology &amp; Hepatology</i>	7	2.1
<i>Turkish Journal of Gastroenterology</i>	4	1.1
<i>Digestive Diseases and Sciences</i>	4	2.9
<i>Hepato-Gastroenterology</i>	4	0.7
<i>Scandinavian Journal of Gastroenterology</i>	3	2.5
<i>European Journal of Radiology</i>	2	2.9
<i>Clinics and Research in Hepatology and Gastroenterology</i>	2	2.8
<i>Clinical Gastroenterology and Hepatology</i>	2	7.9
<i>Journal of Clinical Gastroenterology</i>	2	2.7
<i>American Journal of Gastroenterology</i>	1	10.2
<i>Journal of Gastroenterology and Hepatology</i>	1	3.6
<i>Ocular Immunology and Inflammation</i>	1	2.2
<i>European Journal of Internal Medicine</i>	1	3.6
<i>Acta Gastro-Enterologica Belgica</i>	1	0.5
<i>Hepatobiliary &amp; Pancreatic Diseases International</i>	1	1.5
<i>Hepatology Research</i>	1	3.4
<i>Rheumatology International</i>	1	2.2
<i>Diagnostic and Interventional Radiology</i>	1	1.4
<i>World Journal of Gastroenterology</i>	1	3.4
<i>Journal of Hepatology</i>	1	18.9
<i>Liver International</i>	1	5.5
<i>Transplantation Proceedings</i>	1	0.9
<i>Experimental And Clinical Transplantation</i>	1	0.7
<i>Croatian Medical Journal</i>	1	1.6

\*2019 Journal impact factors.

out classical autoimmune serology. Antibodies to soluble liver antigen (anti-SLA) are a specific serologic marker of AIH. Efe et al. (13) reported a 15% prevalence of anti-SLA in Turkish patients with AIH, and the specificity of these antibodies was 99.5%.

Purnak et al. (14) retrospectively evaluated treatment response and outcome of 71 Turkish patients with AIH. Only 5.6% of the patients (4/71) had liver-related death or needed a liver transplantation after a median of 60-month follow-up. Another study evaluated a large cohort of patients with AIH and showed that mycophenolate mofetil and tacrolimus are effective and safe alternative therapies in patients who failed or developed side effects to standard therapy (15).

AIH may develop after, possibly as a consequence of, drug-induced liver injury (DILI). Kuzu et al. (16) evaluated the data of 82 patients with DILI, and 3 of them were diagnosed as having AIH during follow-up. Another study from Turkey reported 8 patients who were diagnosed as having AIH after DILI, and importantly, ornidazole was the cause in all cases (17).

A recent study from Turkey, which was also performed in an international collaborative effort, evaluated the performance of risk scoring systems in PBC (18). This study showed that current risk scores are accurate enough to predict PBC outcome. Several other studies from Turkey have evaluated treatments and outcomes of PBC-AIH overlap or variant syndrome of PBC (19-22). In the first study, Gunsar et al. (19) evaluated data on 23 Turkish patients with PBC-AIH overlap syndrome. After this report, Ozaslan et al. (22) performed an international study on 88 patients with PBC with features of AIH. This study indicated that ursodeoxycholic acid alone was sufficient in patients with moderate interface hepatitis, but that additional immunosuppression was required for controlling disease activity in patients with PBC who had severe interface hepatitis.

A single-center experience showed that the prevalence of PSC-associated inflammatory bowel disease in Turkey was similar to that of western countries (23). In another study from the same center, the authors described retraction of the papilla into the duodenal wall during follow-up of patients with PSC (24). The estimated prevalence of PSC in Turkey seems to be lower than in western countries. A retrospective analysis provided 56 patients with PSC diagnosed between 1993

and 2010 in the largest endoscopic retrograde cholangiopancreatography (>2500/per year) and hepatology center in Turkey (25). Two other studies supported this hypothesis on a low PSC prevalence and reported that very few patients undergo a liver transplantation for PSC in Turkey (26, 27).

AIH and PSC also affect children. Although 41 of the papers were published by adult hepatologists, pediatric hepatologists published only 4 papers, of which all were related to AIH (28-31). Geylani et al. (28) examined HLA phenotypes in Turkish type 1 and type 2 AIH. Their study suggested associations between certain HLA antigens and susceptibility to AIH in Turkish children. The genetic susceptibility of Turkish patients with AIH has been shown also in adult type 1 AIH (12). In a single-center study, 5 pediatric patients with AIH (10.6%) progressed into end-stage liver failure during a median 4-year follow-up (29). Authors did not report any prognostic factors that affect disease outcome. Another study showed that IgG4-associated AIH had a quicker therapy response than that of AIH in Turkish children (30).

In conclusion, our study suggests that AILDs need more attention in Turkey. Even if these rare forms of chronic liver disease have low prevalence, their impacts on individual patients are potentially devastating. Neglecting the importance of AILD may lead to overlooking new effective and potentially life-changing therapies for our patients. Considering the large population of Turkey, both the number and quality of AILD-related papers should be improved. We call upon both adult and pediatric gastroenterologists to focus their efforts on future multicenter and prospective study projects in Turkey and to initiate high-quality AILD-related studies.

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**Informed Consent:** N/A.

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**Author Contributions:** Concept – C.E, S.W.; Design – N.D.; Supervision – C.E., S.W.; Resource – N.D., N.E.; Materials – N.D., M.T.; Data Collection and/or Processing – N.D., N.E., M.T.; Analysis and/or Interpretation – M.T.; Literature Search – N.D., N.E., M.T.; Writing – N.D., C.E., X.X.; Critical Reviews – C.E., S.W.

**Conflict of Interest:** The authors have no conflict of interest to declare.

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**Supplement Table 1.** The general characteristics of the studies.

Study name	Year	Journal name	International collaboration	First author name	Organization
1-A comparison of the prevalence of autoantibodies in individuals with chronic hepatitis C and those with autoimmune hepatitis: the role of interferon in the development of autoimmune diseases.	1997	Hepatogastroenterology.	Yes	Bayraktar Y	Hacettepe University
2-Is severe cryptogenic chronic hepatitis similar to autoimmune hepatitis?	1998	Journal of Hepatology	No	Kaymakoglu S	Istanbul University, Capa
3-What is the association of primary sclerosing cholangitis with sex and inflammatory bowel disease in Turkish patients?	1998	Hepatogastroenterology.	No	Bayraktar Y	Hacettepe University
4-Primary sclerosing cholangitis in patients with inflammatory bowel disease in Turkey	2001	J Clin Gastroenterology	No	Parlak E	Yuksek Ihtisas Education and Research Hospital
5-The prevalence of autoimmune hepatitis in Hashimoto's thyroiditis in a Turkish population.	2002	Acta Gastroenterol Belg.	No	Cindoruk M	Gazi University
6-Clinical and biochemical features and therapy responses in primary biliary cirrhosis and primary biliary cirrhosis-autoimmune hepatitis overlap syndrome.	2002	Hepatogastroenterology.	No	Günsar F	Ege University
7-Type 1 autoimmune hepatitis in Turkish patients: absence of association with HLA B8	2002	J Clin Gastroenterology	Yes	Kosar Y	Yuksek Ihtisas Education and Research Hospital
8-Endoscopic treatment of primary sclerosing cholangitis	2004	Turk J Gastroenterology	No	Parlak E	Yuksek Ihtisas Education and Research Hospital
9-Primary sclerosing cholangitis: MR cholangiopancreatography and T2-weighted MR imaging findings.	2005	Diagn Interv Radiology	No	Düsünceli E	Ankara University
10-Primary biliary cirrhosis: evaluation with T2-weighted MR imaging and MR cholangiopancreatography.	2009	Eur J Radiology	No	Haliloglu N	Ankara University
11-Pancreatic changes in patients with primary sclerosing cholangitis: MR cholangiopancreatography and MRI findings.	2009	Eur J Radiology	No	Ozkavukcu E	Ankara University
12-Primary sclerosing cholangitis in Turkish patients: characteristic features and prognosis.	2009	Hepatobiliary Pancreat Dis Int.	No	Ataseven H	Yuksek Ihtisas Education and Research Hospital
13-Therapy response and outcome of overlap syndromes: autoimmune hepatitis and primary biliary cirrhosis compared to autoimmune hepatitis and autoimmune cholangitis.	2010	Hepatogastroenterology.	No	Ozaslan E	Numune Research and Education Hospital
14-Ornidazole-induced autoimmune hepatitis	2011	Turk J Gastroenterology	No	Ersöz G	Ege University
15-Relations between human leukocyte antigens and autoimmune hepatitis in Turkish children.	2011	Turk J Gastroenterology	No	Geylanı Güleç S	Şişli Etfal Hospital
16-Autoimmune liver disease in patients with systemic lupus erythematosus: a retrospective analysis of 147 cases.	2011	Scand J Gastroenterology	Yes	Efe C	Numune Research and Education Hospital

**Supplement Table 1.** The general characteristics of the studies. (Continue)

Study name	Year	Journal name	International collaboration	First author name	Organization
17-Ocular findings in patients with autoimmune liver disease.	2012	Ocul Immunol Inflammation	No	Citirik M	Ankara Ulucanlar Eye Education and Research Hospital
18-Autoimmune hepatitis in the postpartum period	2012	Clin Res Hepatol Gastroenterology	No	Efe C	Numune Research and Education Hospital
19-Autoimmune hepatitis/primary biliary cirrhosis overlap syndrome and associated extrahepatic autoimmune diseases.	2012	Eur J Gastroenterol Hepatology	Yes	Efe C	Numune Research and Education Hospital
20-Liver biopsy is a superior diagnostic method in some patients showing the typical laboratory features of autoimmune hepatitis.	2012	Clin Res Hepatol Gastroenterology	No	Efe C	Hacettepe University
21-Late autoimmune hepatitis after hepatitis C therapy.	2013	Eur J Gastroenterol Hepatology	Yes	Efe C	Hacettepe University
22-Diagnostic difficulties, therapeutic strategies, and performance of scoring systems in patients with autoimmune hepatitis and concurrent hepatitis B/C.	2013	Scand J Gastroenterology	Yes	Efe C	Hacettepe University
23-Antibodies to soluble liver antigen in patients with various liver diseases: a multicentre study.	2013	Liver International	Yes	Efe C	Numune Research and Education Hospital
24-Features of systemic lupus erythematosus in patients with autoimmune hepatitis.	2013	Rheumatol International	No	Onder FO	Yuksekt Ihtisas Education and Research Hospital
25-Circulating CD4+CD25+ regulatory T cells in the pathobiology of ulcerative colitis and concurrent primary sclerosing cholangitis.	2013	Dig Dis Sci.	No	Kekilli M	Yuksekt Ihtisas Education and Research Hospital
26-Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis.	2014	Dig Dis Sci.	Yes	Efe C	Hacettepe University
27-Sequential presentation of primary biliary cirrhosis and autoimmune hepatitis.	2014	Eur J Gastroenterol Hepatology	Yes	Efe C	Hacettepe University
28-Factors associated with response to therapy and outcome of patients with primary biliary cirrhosis with features of autoimmune hepatitis.	2014	Clin Gastroenterol Hepatology	Yes	Ozaslan E	Numune Research and Education Hospital
29-Manometric assessment of esophageal motor function in patients with primary biliary cirrhosis.	2014	Eur J Intern Medicine	No	Bektas M	Ankara University
30-Angiotensin-converting enzyme for noninvasive assessment of liver fibrosis in autoimmune hepatitis	2015	Eur J Gastroenterol Hepatology.	Yes	Efe C	Hacettepe University
31-Nitric oxide is a potential mediator of hepatic inflammation and fibrogenesis in autoimmune hepatitis.	2015	Scand J Gastroenterology	Yes	Efe C	Hacettepe University
32-Increased mean platelet volume is related to histologic severity of primary biliary cirrhosis.	2015	Eur J Gastroenterol Hepatology	No	Tahtaci M	Ataturk Education and Research Hospital, Ankara



**Supplement Table 1.** The general characteristics of the studies. (Continue)

Study name	Year	Journal name	International collaboration	First author name	Organization
33-Autoimmune hepatitis and long-term disease course in children in Turkey, a single-center experience	2016	Eur J Gastroenterol Hepatology	No	Karakoyun M	Gaziantep Children's Hospital
34-Clinical and histological features of idiosyncratic liver injury: Dilemma in diagnosis of autoimmune hepatitis.	2016	Hepatology Research	No	Kuzu UB	Yuksekt Ihtisas Education and Research Hospital
35-The relationship between liver histology and noninvasive markers in primary biliary cirrhosis.	2016	Eur J Gastroenterol Hepatology	No	Olmez S	Numune Research and Education Hospital
36-Comparative assessment of prognostic value for revised-Mayo risk model and Child-Pugh score in patients with primary sclerosing cholangitis.	2016	Turk J Gastroenterology	No	Oztas E	Yuksekt Ihtisas Education and Research Hospital
37-Treatment Response and Outcome with Two Different Prednisolone Regimens in Autoimmune Hepatitis	2017	Dig Dis Sci.	Yes	Purnak T	Hacettepe University
38-Relationship between serum adenosine deaminase levels and liver histology in autoimmune hepatitis	2017	World J Gastroenterology	no	Torgutalp M	Hacettepe University
39-Efficacy and Safety of Mycophenolate Mofetil and Tacrolimus as Second-line Therapy for Patients With Autoimmune Hepatitis	2017	Clin Gastroenterol Hepatology	Yes	Efe C	Hacettepe University
40-Tacrolimus and Mycophenolate Mofetil as Second-Line Therapies for Pediatric Patients with Autoimmune Hepatitis	2018	Dig Dis Sci.	Yes	Efe C	Hacettepe University
41-Clinical and histopathological features of immunoglobulin G4-associated autoimmune hepatitis in children	2018	J Gastroenterology and Hepatology	No	Aydemir Y	Eskisehir Osmangazi University
42-Validation of Risk Scoring Systems in Ursodeoxycholic Acid-Treated Patients With Primary Biliary Cholangitis	2019	Am J Gastroenterology	Yes	Efe C	Diyarbakir Gazi Yaşargil Education and Research Hospital
43-Experience in Liver Transplantation Due to Primary Sclerosing Cholangitis: A Single Center Experience	2019	Transplant Proceedings	No	Emek E	Sisli Florence Nightingale Hospital
44-Liver Transplant in Patients with Primary Sclerosing Cholangitis: Long-Term Experience of a Single Center	2019	Exp Clin Transplant	No	Astarcioğlu I	Dokuz Eylul University
45-The efficacy and adverse effects of budesonide in remission induction treatment of autoimmune hepatitis: a retrospective study	2019	Croat Med Journal	No	Binicier OB	Tepecik Training and Research Hospital