**Supplementary tables and figures**

**Supplementary Digital Content 1: MOOSE Statement - Reporting Checklist for Authors, Editors, and Reviewers of Meta-analyses of Observational Studies**

|  |  |  |
| --- | --- | --- |
| **Reporting Criteria** | **Reported (Yes/No)** | **Reported on Page** |
| **Reporting of Background** |  |  |
|  Problem definition | Yes | 6,7 |
|  Hypothesis statement | Yes | 7 |
|  Description of Study Outcome(s) | Yes | 7,9-10 |
|  Type of exposure or intervention used | Yes | 8 |
|  Type of study design used | Yes | 8 |
|  Study population | Yes | 7,9-10 |
| **Reporting of Search Strategy** |  |  |
|  Qualifications of searchers (eg, librarians and investigators) | Yes | 9 |
|  Search strategy, including time period included in the synthesis and keywords | Yes | 8 |
|  Effort to include all available studies,  including contact with authors | Yes | 8,11 |
|  Databases and registries searched | Yes | 8 |
|  Search software used, name and  version, including special features used  (eg, explosion) | Yes | 8 |
|  Use of hand searching (eg, reference  lists of obtained articles) | Yes | 9,Figure 1 |
|  List of citations located and those  excluded, including justification | Yes | 25, Supplementary Digital Content 3-7 |
|  Method for addressing articles  published in languages other than  English | Yes | 8 |
|  Method of handling abstracts and  unpublished studies | Yes | 11 |
|  Description of any contact with authors | Yes | 11 |
| **Reporting of Methods** |  |  |
|  Description of relevance or  appropriateness of studies assembled for  assessing the hypothesis to be tested | Yes | 9-12 |
|  Rationale for the selection and coding of  data (eg, sound clinical principles or  convenience) | Yes | 11-12 |
|  Documentation of how data were  classified and coded (eg, multiple raters,  blinding, and interrater reliability) | Yes | 11-12 |
|  Assessment of confounding (eg,  comparability of cases and controls in  studies where appropriate | Yes | NA |
|  Assessment of study quality, including  blinding of quality assessors;  stratification or regression on possible  predictors of study results YES 5 | Yes | 12 |
|  Assessment of heterogeneity | Yes | 13, Supplementary digital content 9 |
|  Description of statistical methods (eg,  complete description of fixed or random  effects models, justification of whether  the chosen models account for predictors  of study results, dose-response models,  or cumulative meta-analysis) in sufficient  detail to be replicated | Yes | 13 |
|  Provision of appropriate tables and  Graphics | Yes | Figures1-4 and Tables1-2; Supplementary Digital Content 1-8  |
| **Reporting of Results** |  |  |
|  Table giving descriptive information for  each study included | Yes | Supplementary Digital Content 3-6 |
|  Results of sensitivity testing (eg,  subgroup analysis) | Yes | 15-18, Table 1 |
|  Indication of statistical uncertainty of  Findings | Yes | 15-18 |
| **Reporting of Discussion** |  |  |
|  Quantitative assessment of bias (eg,  publication bias) | Yes | Table 2, Supplementary Digital Content 8 |
|  Justification for exclusion (eg, exclusion  of non–English-language citations) | Yes | Supplementary Digital Content 7 |
|  Assessment of quality of included studies | Yes | Table 2 |
| **Reporting of Conclusions** |  |  |
|  Consideration of alternative explanations  for observed results | Yes | 25 |
|  Generalization of the conclusions (ie,  appropriate for the data presented and  within the domain of the literature review) | Yes | 25 |
|  Guidelines for future research | Yes | 25 |
|  Disclosure of funding source | Yes | 2 |

**Supplementary Digital Content 2a: Search strategy for PubMeD**

|  |  |  |  |
| --- | --- | --- | --- |
| Search number | Query | Filters | Results |
| 10 | #5 AND #9 | from 1990/1/1 - 3000/12/12 | 1,470 |
| 9 | #6 OR #7 OR #8 | from 1990/1/1 - 3000/12/12 | 861,582 |
| 8 | ((cirrhosis[MeSH Terms] OR cirrhosis[Title/Abstract]) OR (liver failure[MeSH Terms])) OR (end stage liver disease[MeSH Terms]) | from 1990/1/1 - 3000/12/12 | 199,299 |
| 7 | (liver[MeSH Terms] OR liver[Title/Abstract]) | from 1990/1/1 - 3000/12/12 | 731,082 |
| 6 | ((((((((alanine transaminase[MeSH Terms]) OR (aspartate transaminase[MeSH Terms])) OR (alanine aminotransferase[MeSH Terms])) OR (aspartate aminotransferase[MeSH Terms])) OR (hypertransaminasemia[Title/Abstract])) OR (transaminitis[Title/Abstract])) OR (cytolysis[Title/Abstract]) ) OR (transaminase[Title/Abstract])) OR (aminotransferase[Title/Abstract]) | from 1990/1/1 - 3000/12/12 | 74,979 |
| 5 | #1 OR #2 OR #3 OR #4 | from 1990/1/1 - 3000/12/12 | 31,058 |
| 4 | ((transglutaminases[MeSH Terms]) OR (transglutaminase[Title/Abstract])) OR (antigliadin[Title/Abstract] OR antiendomysium[Title/Abstract] OR antiendomysial[Title/Abstract] OR "deamidated gliadin peptide"[Title/Abstract]) | from 1990/1/1 - 3000/12/12 | 10,794 |
| 3 | (diet, gluten free[MeSH Terms]) OR (enteropathies, gluten sensitive[MeSH Terms]) | from 1990/1/1 - 3000/12/12 | 14,746 |
| 2 | ((glutens[MeSH Terms]) OR (gluten[Title/Abstract]) OR (gliadin[MeSH Terms]) OR (gliadin[Title/Abstract]))  | from 1990/1/1 - 3000/12/12 | 14,733 |
| 1 | ((celiac disease[MeSH Terms]) OR ("celiac disease"[Title/Abstract])) OR ("coeliac disease"[Title/Abstract]) | from 1990/1/1 - 3000/12/12 | 18,489 |

**Supplementary Digital Content 2b: Search strategy for Embase**

|  |  |  |
| --- | --- | --- |
| #7 | (#1 OR #2 OR #3 OR #4) AND (#5 OR #6) | 5400 |
| #6 | ('liver function test'/exp OR 'liver function test' OR 'aspartate aminotransferase'/exp OR 'alanine aminotransferase'/exp OR 'transaminase' OR 'aminotransferase' OR 'hypertransaminasemia' OR 'transaminitis' OR 'cytolysis') AND [1990-2022]/py | 280048 |
| #5 | ('liver disease'/exp OR 'liver disease' OR 'liver cirrhosis'/exp OR 'liver cirrhosis' OR 'cirrhosis'/exp OR 'cirrhosis' OR 'cirrhotic\*' OR 'end stage liver disease'/exp OR 'chronic liver disease' OR 'liver failure' OR 'chronic liver failure' OR 'liver'/exp OR 'liver':ti,ab,kw) AND [1990-2022]/py | 1543236 |
| #4 | ('gluten free diet'/exp OR 'gluten free diet':ti,ab,kw OR 'gluten-free diet') AND [1990-2022]/py | 11126 |
| #3 | ('gliadin antibody'/exp OR 'gliadin antibody':ti,ab,kw OR 'deamidated gliadin peptide antibody'/exp OR 'deamidated gliadin peptide antibody':ti,ab,kw OR 'antigliadin':ti,ab,kw OR 'anti-gliadin':ti,ab,kw OR 'transglutaminase':ti,ab,kw OR 'endomysium':ti,ab,kw OR 'endomysial':ti,ab,kw OR 'antiendomysium':ti,ab,kw OR 'antiendomysial':ti,ab,kw OR 'anti-endomysium':ti,ab,kw OR 'anti-endomysial':ti,ab,kw OR 'gliadin antibody' OR 'deamidated gliadin peptide antibody' OR 'transglutaminase'/exp) AND [1990-2022]/py | 16899 |
| #2 | ('gluten'/exp OR 'gliadin'/exp OR 'gluten' OR 'gliadin' OR 'gluten':ti,ab,kw OR 'gliadin':ti,ab,kw) AND [1990-2022]/py | 23312 |
| #1 | ('celiac disease'/exp OR 'celiac disease':ti,ab,kw OR 'celiak\*':ti,ab,kw OR 'coeliac disease\*':ti,ab,kw OR 'coeliak\*':ti,ab,kw OR 'non-tropical sprue':ti,ab,kw OR 'nontropical sprue':ti,ab,kw OR 'sprue':ti,ab,kw OR 'gluten sensitive enteropathy':ti,ab,kw OR 'gluten induced enteropathy':ti,ab,kw OR 'celiac disease' OR 'celiak\*' OR 'coeliac disease' OR 'coeliak\*' OR 'non-tropical sprue' OR 'nontropical sprue' OR 'sprue' OR 'gluten sensitive enteropathy' OR 'gluten induced enteropathy') AND [1990-2022]/py | 33590 |

**Supplementary Digital Content 3: Characteristics of studies included in the systematic review for cryptogenic cirrhosis**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Tanwar | Joshi  | Balkan  | Sood | Maiwall | Wakim-Fleming | Drastich | Emami | Kaukinen |
| Published | 2019 | 2019 | 2017 | 2017 | 2014 | 2014 | 2012 | 2011 | 2002 |
| Design | Prospective | Prospective | Retrospective | Prospective | Prospective | Prospective | Retrospective | Prospective | Retrospective and prospective screening |
| Period | June 2017 - December 2018 | January 2015 - December 2017 | January 2010 - December 2015, | 2012 - 2014 | January 2009-December 2010 | May 2008 - May 2010 | Sera from 1994-2010 used, 2009-2010 | 2003-2008 | 2002 |
| Geographical region  | India, Asia | India, Asia | Turkey, Europe | India, Asia | India, Asia | USA, North America | Czech Republic, Europe | Iran, Asia | Finland, Europe |
| Setting  | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care |
| Overall Population | 382 Consecutive patients with portal hypertension with chronic liver disease (CLD) of defined etiology (ethanol, hepatitis B or C, Budd–Chiari syndrome [BCS], autoimmune-related cirrhosis, and cCLD) | 84 Children of less than 18 years old attending Pediatric and Gastroenterology clinic with a diagnosis of CLD | 161 patients diagnosed with HBV and HCV-associated liver cirrhosis and cryptogenic liver cirrhosis in the hepatology clinic | 595 consecutive patients with chronic liver disease [defined as presence of volumereduction or re-distribution, irregular margins, coarse texture or nodular liver, any ofthe preceding changes noted in the liver on imaging (ultrasound, CT or MRI scan) | 61 patients with cirrhosis and portal hypertension  | 204 consecutive cirrhotics scheduled for ugie | 523 end stage liver disease lt recipients during 1994-2010 (not mentioned as pretransplant sera) | 224 patients, presenting within the first-level screening steps with abnormal LFT  | 185 patients who underwent transplantation for end-stage liver disease |
| Age of overall population  | 26-68years | <18 years | 57.7 ± 13 years | 51.4 ± 11.1 years | 7–67 years | 55.4± 11.4 years | 18-66 years | 39.6±1.2years for males, 38.5± 1.4years for females | 17-72years |
| Sample size of liver disease of interest | 147 | 84 | 83 | 52 | 47 | 17 | 28 | 19 | 20 |
| Females | Not given | 24 | Not given | Not given | Not given | Not given | 12 | Not given | Not given  |
| Children | None | 84 | None | None | None | None | None | None | None |
| First level seroassay(s) | Human TTG-IgA | IgA anti-tTG | Human TTG-IgA, EMA-IgA | Human TTG-IgA | Human TTG-IgA | Human TTG-IgA, EMA-IgA | Human TTG-IgA | Human TTG-IgA | TTG-IgA, EMA-IgA |
| Second level seroassay(s) | No | No | No | EMA-IgA on whom biopsy could not be done after TTG-IgA positive | No | No | EMA-IgA and DGP-IgA | No | No |
| Whether IgA level done | No | No | Yes- with TTG-IgG | No | No | Yes | Yes | Yes | Yes |
| No. of seropositive | 13 | 16 | 15 | 7 | 34 | 1 | 0 | 2 | 2 |
| No. of TTGpositive in whole sample  | 13 | 16 | 15 | 7 | 34 | 1 | 0 | 2 | 2 |
| No. of AEA positive in whole sample | Not applicable | Not applicable | 3 | Not applicable | Not applicable | 1 | Not applicable | Not applicable | 0 |
| Small bowel-biopsied | 13 | 16 | 15 | 7 | 34 | 1 | 0 | 2 | 2 |
| Biopsy positive  | 13 | 9 | 3 | 3 | 2 | 1 | 0 | 2 | 0 |
| Response to a GFD checked | Not done | 6months- improved albumin, PT, CPS, but none in varices | Not done | Not done | 2 patients remained stable CTP-wise | MELD and aminotransferases decreased- 2years | Not applicable | Aminotransferase decreased | 3 of 8 liver tx patients had a gfd before liver tx (2-9 months of a strict gfd), while 1 congenital fribrosispt of 8 had 11 years of a strict gfd and still underwent liver tx, the rest had no strict GFD |
| Whether invasive workup used for etiological evaluation for liver disease | Yes | No | No | No | No | No | Yes | No | No  |
| Diseases ruled out prior to claasifying as cryptogenic liver disease |  ethanol, hepatitis B or C, Budd–Chiari syndrome [BCS],autoimmune-related cirrhosis, NCPH, which included noncirrhotic portal fibrosis (NCPF) and extrahepatic portal veinobstruction (EHPVO)  | ultrasound of the abdomen with portal and hepaticvein doppler study, serum hepatitis B surface antigen(HBsAg), anti-hepatitis C (HCV) antibody, auto-antibodies(antinucelar antibody [ANA], anti-smooth muscle antibody[ASMA], anti-liver kidney microsomal [LKM] antibody), serum ceruloplasmin, iron studies, and α1-antitrypsin levels.After excluding all the known causes of liver disease, a diagnosis of cryptogenic CLD was made and further evaluation forCD undertaken. | Cryptogenic liver cirrhosis was diagnosed when tests performed on cirrhosis aetiology (preprandial blood glucose,cholesterol, triglyceride, HBsAg, Anti-HCV, ANA, ASMA, AMA, immunoglobulins, iron, iron binding capacity, ferritin,ceruloplasmin, 24 h urine copper test) and monitoring methods (portal doppler USG [in terms of vascular pathologies andsteatosis]) were negative and chronic use of alcohol was absent | In patients with chronic liver disease different etiologies of liver disease were defined as follows: (a) alcohol : history of significant alcohol consumption (>30 g/day for >10 yr)(9); (b)viral : Hepatitis B : HBsAg and Hepatitis B DNA positive; Hepatitis C : anti HCV and HCV-RNA positive; (c) Wilson’s disease (≥2 criteria of the following criteria satisfied): low serum ceruloplasmin, elevated 24 hour urinary copper and presence of Kayser Fleischer ring on slit lamp examination of eye(10);(d) autoimmune hepatitis : using simplified criteria for autoimmune hepatitis (≥7 points)(11);(e) Non-alcoholic fatty liver disease(NAFLD): evidence of hepatic steatosis on imaging and no other cause of secondary hepatic fat accumulation like alcohol, drugs or hereditary disorders(12); (f) Cryptogenic: no etiology of chronic liver disease evident after non-invasive evaluation | Alcoholic, autoimmune, metabolic liver disease, Wilsons, hemochromatosis, buddchiari, viral  | HCC PBC NASH HCV Cryptogenic PSC HBV AIH Alcoholic liver disease | Alcoholic liver cirrhosis, Autoimmune hepatitis typeⅠViral hepatitis B Viral hepatitis C Wilson’s disease Primary biliary cirrhosis Primary sclerosing cholangitis Cryptogenic liver cirrhosis Budd-Chiari syndrome Polycystic liver | serum Cu, ceruloplasmin, Fe, TIBC, ANA, Anti-Smantibody, Anti-LKM-1 antibody, AMA, P-ANCA, serum Alpha-1 anti-tripsin level (not phenotyping sinceit was not available), HBS Ag, HBC antibody, HCV antibody, TG, cholesterol, LDL, HDL, and liverultrasonography | Primary biliary cirrhosis Acute liver failure Primary sclerosing cholangitis Cirrhosis of unknown origin Alcohol cirrhosis Budd-Chiari syndrome Hepatic malignancies Autoimmune hepatitis Hepatitis C Toxic damage Miscellaneous  |
| Method for evaluation of liver diseasea | Cirrhosis wasdiagnosed on the basis of clinical, biochemical, and imaging features. Portal hypertension was defined as the presence of gastroesophageal varices (GEV) and/or highgradient ascites. For etiology of portal hypertension, patients were screened for history of alcohol intake, HBsAg,anti-HCV antibody, ultrasound abdomen with Dopplerof portal vein and hepatic veins, multiphase contrastenhanced computed tomography abdomen, IgA-tTG, autoantibodies (AMA, ASMA, LKM, ANA, IgG), and serumceruloplasmin as per clinical evaluation. Patients of CDwith portal hypertension (PHT) were also subjected toultrasound-guided percutaneous liver biopsy in absenceof absolute contraindications. Patients of cirrhosis withPHT and negative evaluation for cause of liver diseasewere defined as cCLD. NCPF was defined as the presenceof PHT, patient hepatic and portal veins on Doppler, noidentifiable etiology for liver disease, and absence ofcirrhosis.14 EHPVO was diagnosed in the presence ofPHT with obstruction of the extrahepatic portal veinwith or without involvement of intrahepatic portal veinradicles or splenic or superior mesenteric veins with thepresence of portal cavernoma and absence of cirrhosis.15,16Autoimmune hepatitis (AIH) was diagnosed by a simplified scoring system: probable AIH when pretreatmentaggregate score $6, and definite AIH | ultrasound of the abdomen with portal and hepaticvein doppler study, serum hepatitis B surface antigen(HBsAg), anti-hepatitis C (HCV) antibody, auto-antibodies(antinucelar antibody [ANA], anti-smooth muscle antibody[ASMA], anti-liver kidney microsomal [LKM] antibody), serum ceruloplasmin, iron studies, and α1-antitrypsin levels.After excluding all the known causes of liver disease, a diagnosis of cryptogenic CLD was made and further evaluation forCD undertaken. | Cryptogenic liver cirrhosis was diagnosed when tests performed on cirrhosis aetiology (preprandial blood glucose,cholesterol, triglyceride, HBsAg, Anti-HCV, ANA, ASMA, AMA, immunoglobulins, iron, iron binding capacity, ferritin,ceruloplasmin, 24 h urine copper test) and monitoring methods (portal doppler USG [in terms of vascular pathologies andsteatosis]) were negative and chronic use of alcohol was absent | In patients with chronic liver disease different etiologies of liver disease were defined as follows: (a) alcohol : history of significant alcohol consumption (>30 g/day for >10 yr)(9); (b)viral : Hepatitis B : HBsAg and Hepatitis B DNA positive; Hepatitis C : anti HCV and HCV-RNA positive; (c) Wilson’s disease (≥2 criteria of the following criteria satisfied): low serum ceruloplasmin, elevated 24 hour urinary copper and presence of Kayser Fleischer ring on slit lamp examination of eye(10);(d) autoimmune hepatitis : using simplified criteria for autoimmune hepatitis (≥7 points)(11);(e) Non-alcoholic fatty liver disease(NAFLD): evidence of hepatic steatosis on imaging and no other cause of secondary hepatic fat accumulation like alcohol, drugs or hereditary disorders(12); (f) Cryptogenic: no etiology of chronic liver disease evident after non-invasive evaluation | alcohol intake, features of metabolic syndrome (body mass index, blood sugars, lipid profile), ultrasound abdomen with Doppler of portal vein and hepaticvenous outflow tract, HBsAg, HCV antibody, autoantibodies(AMA, SLA, LKM, ANA), serum ceruloplasmin, andiron studies. Patients with cirrhosis with portal hypertension, with negative noninvasive evaluation for causeof liver disease, were labelled as cryptogenic chronic liverdisease. | Not given  | diagnostic criteria for primary biliary cirrhosis included clinical symptoms, clinical chemistry, exclusion of infection with hepatitis viruses and evidence of antimitochondrial antibodies type M2. The diagnosis of autoimmune hepatitis was based on the scoring system devised by the International Autoimmune Hepatitis Group and International Association for the Study of the Liver[16]. The main diagnostic criteria for alcoholic liver cirrhosis were the patient’s medical history, liver histology, and exclusion of other causes of liver cirrhosis. Diagnosis of Wilson’s disease was based on the recommendation of Kodama et al[17], and Budd-Chiari syndrome in accordance with the concept of Fox et al | abnormal LFT not known to be related to acute drug toxicity, ischemic attack, or othertoxic liver insults (such as alcoholic liver injury) were included: cases included aih, nash, pbc, psc, viral hepatitis, Wilson’s | Not given  |
| Reference |   | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |

**Supplementary Digital Content 4: Characteristics of the studies included in the systematic review for all-cause cirrhosis**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Tanwar | Sood | Wakim-Fleming | Drastich | Germenis | Vecchi | Caroccio |
| Published | 2019 | 2017 | 2014 | 2012 | 2005 | 2003 | 2001 |
| Design | Prospective | Prospective | Prospective | Retrospective | Prospective | Prospective | Prospective |
| Period | June 2017 - December 2018 | 2012 – 2014 | May 2008 - May 2010 | Sera from 1994-2010 used, 2009-2010 | 2000-2005 | Not given | September 1998 - May 1999 |
| Geographical region  | India, Asia | India, Asia | USA, North America | Czech Republic, Europe | Greece, Europe | Italy, Europe | Italy, Europe |
| Setting  | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care |
| Overall Population | 382 Consecutive patients with portal hypertension with chronic liver disease (CLD) of defined etiology (ethanol, hepatitis B or C, Budd–Chiari syndrome ], autoimmune-related cirrhosis, and cCLD) | 595 consecutive patients with chronic liver disease [defined as presence of volumereduction or re-distribution, irregular margins, coarse texture or nodular liver, any ofthe preceding changes noted in the liver on imaging (ultrasound, CT or MRI scan) | 204 consecutive cirrhotics scheduled for upper gastrointestinal endoscopy | 523 end stage liver disease liver transplant recipients during 1994-2010  | 738 patients with chronic liver diseases (including hepatitis, steatosis, cirrhosis) | 19 patients with cirrhosis | 98 patients with chronic hypertransaminasaemia, evaluated for the first time in a hepatology clinic |
| ­Age of overall population  | 26-68years | 51.4 ± 11.1 years | 55.4± 11.4 years | 18-66 years | 6-85years | 51.8 ± 9.5 years | 18–64 years |
| Sample size of liver disease of interest | 382 | 595 | 204 | 528 | 146 | 19 | 7 |
| Females | 133 | 107 | 94 | 199 | Not given  | 4 | Not given |
| Children | None | None | None | None | None | None | None |
| First level seroassay(s) | Human TTG-IgA | Human TTG-IgA | Human TTG-IgA, AEA-IgA | Human TTG-IgA | Human TTG-IgA | Human and TTG-IgA and Guinea Pig TTG-IgA and AEA-IgA | Human and TTG-IgA and Guinea Pig TTG-IgA and AEA-IgA |
| Second level seroassay(s) | No | AEA-IgA on whom biopsy could not be done after TTG-IgA positive | No | EMA-IgA and DGP-IgA | No | No |  |
| Whether IgA level done | No | No | Yes | Yes | Yes | No | Yes |
| No. of seropositive | 29 | 150 | 16 | 10 | 23 | 11 | 7 |
| No. of TTG positive in whole sample  | 29 | 150 | 15 | 10 | 23 | 11 | 1 |
| No. of AEA positive in whole sample | Not applicable | Not applicable | 5 | 5 | Not applicable | 0 | 0 |
| Small bowel-biopsied | 29 | 85 | 16 | 5 | 23 | Not done | 1 |
| Biopsy positive  | 17 | 14 | 5 | 5 | 0 | Not applicable | 0 |
| Response to a GFD checked | Not done | 6months- improved albumin, PT, CPS, but none in varices | MELD and aminotransferases decreased- 2years | Not done | Not applicable | Not applicable | Not applicable |
| Whether invasive workup used for etiological evaluation for liver disease | Yes | No | No | Yes | Yes | Yes | Yes |
| Liver diseases included in all-cause cirrhosis group | Cirrhosis wasdiagnosed on the basis of clinical, biochemical, and imaging features. Portal hypertension was defined as the presence of gastroesophageal varices (GEV) and/or highgradient ascites. For etiology of portal hypertension, patients were screened for history of alcohol intake, HBsAg,anti-HCV antibody, ultrasound abdomen with Dopplerof portal vein and hepatic veins, multiphase contrastenhanced computed tomography abdomen, IgA-tTG, autoantibodies (AMA, ASMA, LKM, ANA, IgG), and serumceruloplasmin as per clinical evaluation. Patients of CDwith portal hypertension (PHT) were also subjected toultrasound-guided percutaneous liver biopsy in absenceof absolute contraindications. Patients of cirrhosis withPHT and negative evaluation for cause of liver diseasewere defined as cCLD. NCPF was defined as the presenceof PHT, patient hepatic and portal veins on Doppler, noidentifiable etiology for liver disease, and absence ofcirrhosis.14 EHPVO was diagnosed in the presence ofPHT with obstruction of the extrahepatic portal veinwith or without involvement of intrahepatic portal veinradicles or splenic or superior mesenteric veins with thepresence of portal cavernoma and absence of cirrhosis.15,16Autoimmune hepatitis (AIH) was diagnosed by a simplified scoring system: probable AIH when pretreatmentaggregate score $6, and definite AIH with score $7 | In patients with chronic liver disease different etiologies of liver disease were defined as follows: (a) alcohol : history of significant alcohol consumption (>30 g/day for >10 yr)(9); (b)viral : Hepatitis B : HBsAg and Hepatitis B DNA positive; Hepatitis C : anti HCV and HCV-RNA positive; (c) Wilson’s disease (≥2 criteria of the following criteria satisfied): low serum ceruloplasmin, elevated 24 hour urinary copper and presence of Kayser Fleischer ring on slit lamp examination of eye(10);(d) autoimmune hepatitis : using simplified criteria for autoimmune hepatitis (≥7 points)(11);(e) Non-alcoholic fatty liver disease(NAFLD): evidence of hepatic steatosis on imaging and no other cause of secondary hepatic fat accumulation like alcohol, drugs or hereditary disorders(12); (f) Cryptogenic: no etiology of chronic liver disease evident after non-invasive evaluation | HCC PBC NASH HCV Cryptogenic PSC HBV AIH Alcoholic liver disease | Alcoholic liver cirrhosis, Autoimmune hepatitis typeⅠViral hepatitis B Viral hepatitis C Wilson’s disease Primary biliary cirrhosis Primary sclerosing cholangitis Cryptogenic liver cirrhosis Budd-Chiari syndrome Polycystic liver | Viral , autoimmune, nafld, alcoholic, wilson’s disease, transaminasemia due to hyperthyroidism, and miscellaneous disorderssuch as mitochondrial disease, benign cholestasis of pregnancy, dysfunction ofthe sphincter of Oddi, 1-antithrypsin deficiency, drug-induced hepatitis, Gilbertsyndrome, and secondary hemochromatosis | HBV, HCV, alcohol, sclerosing cholangitis | 94/98 patienst were positive for hepatitis markers |
| Methodology for evaluation of liver diseases | Cirrhosis wasdiagnosed on the basis of clinical, biochemical, and imaging features. Portal hypertension was defined as the presence of gastroesophageal varices (GEV) and/or highgradient ascites. For etiology of portal hypertension, patients were screened for history of alcohol intake, HBsAg,anti-HCV antibody, ultrasound abdomen with Dopplerof portal vein and hepatic veins, multiphase contrastenhanced computed tomography abdomen, IgA-tTG, autoantibodies (AMA, ASMA, LKM, ANA, IgG), and serumceruloplasmin as per clinical evaluation. Patients of CDwith portal hypertension (PHT) were also subjected toultrasound-guided percutaneous liver biopsy in absenceof absolute contraindications. Patients of cirrhosis withPHT and negative evaluation for cause of liver diseasewere defined as cCLD. NCPF was defined as the presenceof PHT, patient hepatic and portal veins on Doppler, noidentifiable etiology for liver disease, and absence ofcirrhosis.14 EHPVO was diagnosed in the presence ofPHT with obstruction of the extrahepatic portal veinwith or without involvement of intrahepatic portal veinradicles or splenic or superior mesenteric veins with thepresence of portal cavernoma and absence of cirrhosis.15,16Autoimmune hepatitis (AIH) was diagnosed by a simplified scoring system: probable AIH when pretreatmentaggregate score $6, and definite AIH with score 7 | In patients with chronic liver disease different etiologies of liver disease were detadas follows: (a) alcohol : history of significant alcohol consumption (>30 g/day for >10 yr)(9); (b)viral : Hepatitis B : HBsAgand Hepatitis B DNA positive; Hepatitis C : anti HCV and HCV-RNA positive; (c) Wilson’s disease (≥2 criteria of the following criteria satisfied): low serum ceruloplasmin, elevated 24 hour urinary copper and presence of Kayser Fleischer ring on slit lamp examination of eye(10);(d) autoimmune hepatitis : using simplified criteria for autoimmune hepatitis (≥7 points)(11);(e) Non-alcoholic fatty liver disease(NAFLD): evidence of hepatic steatosis on imaging and no other cause of secondary hepatic fat accumulation like alcohol, drugs or hereditary disorders(12); (f) Cryptogenic: no etiology of chronic liver disease evident after non-invasive evaluation | Not given  | diagnostic criteria for primary biliary cirrhosis included clinical symptoms, clinical chemistry, exclusion of infection with hepatitis viruses and evidence of antimitochondrial antibodies type M2. The diagnosis of autoimmune hepatitis was based on the scoring system devised by the International Autoimmune Hepatitis Group and International Association for the Study of the Liver[16]. The main diagnostic criteria for alcoholic liver cirrhosis were the patient’s medical history, liver histology, and exclusion of other causes of liver cirrhosis. Diagnosis of Wilson’s disease was based on the recommendation of Kodama et al[17], and Budd-Chiari syndrome in accordance with the concept of Fox et al | (PBC) met the following criteria: positivity for anti-mitochondrial antibodies(AMA) detected at titers of , elevated cholestatic enzymes, and histologicallesions suggestive of PBC (35). The diagnosis of primary sclerosing cholangitis(PSC) was based on biochemical and/or clinical signs of cholestasis, compatibleliver histology, and typical findings on endoscopic retrograde cholangio-pancreatography or magnetic resonance cholangiography (35). Patients with overlapping syndromes fulfilled the criteria for the diagnosis of AIH, as well as those forthe diagnosis of either PBC or PSC (2, 35). The diagnosis of nonalcoholic fattyliver disease was based on the presence of metabolic syndrome and exclusion ofother causes of chronic liver disease, including alcohol abuse, and compatibleliver histology (32), while alcoholic liver disease was diagnosed on the grounds ofa history of increased alcohol consumption; viral markers | Not given  | Alcohol intake, use of drugs,and exposure to potential hepatic toxins wereinvestigated. Laboratory investigations included routine liver and kidney function tests.Immunoglobulin levels were underwent serological screening for viralhepatitis B and C (HCV); anti-HCV immune reactivity Sera were also tested forhepatitis B surface antigen using a commercialELISA. ANA antimitochondrial (AMA),antismooth muscle (ASMA), microsomal (anti-LKM) antibodies wasalso evaluated by indirect immunofluorescence |
| Reference | 9 | 3 | 5 | 6 | 10 | 11 | 12 |

**Supplementary Digital Content 5: Characteristics of the studies included in the systematic review for cryptogenic hypertransaminasemia**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author | Ghozzi | Emami | Drastich | Shahbazkhani | Iacono | Germenis | Vivas | Mugica | Volta | Soresi | Bardella |
| Published | 2017 | 2011 | 2012 | 2010 | 2005 | 2005 | 2003 | 2001 | 2001 | 2001 | 1999 |
| Design | Retrospective | Prospective | Prospective | Prospective | Prospective | Prospective | Prospective | Prospective | Prospective | Prospective | Prospective |
| Period | Not given | 2003-2008 | 2009-2010 | Not given | January 1997 - December 2003 | 2000-2005 | June 2000 - September 2001 | May 1998 - December 2000. | September 1995 - Dec 1999 | Not given | January 1996 - March 1997 |
| Geographical region  | Tunisia, Africa | Iran, Asia | Czech Republic, Europe | Iran, Asia | Italy, Europe | Greece, Europe | Spain, Europe | Spain, Europe | Italy, Europe | Italy, Europe | Italy, Europe |
| Setting  | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Tertiary Care | Primary Care | Tertiary Care |
| Overall Population |  56 patients with raised aminotransferases unrelated to viral/autoimmune/other liver insults (drug, alcoholic) | 224 patients, presenting within the first-level screening steps with abnormal LFT  | 523 end stage liver disease lt recipients during 1994-2010 (not mentioned as pretransplant sera) | 100 patients with liver enzymes with unknown cause for more than 6 months, after excluding viral hepatitis, autoimmune, hemochromatosis, Wilson, Fatty liver, Alcoholic liver and drug causes | 168 consecutive patients of NAFLD or cryptogenic chronic hepatitis | 738 patients with chronic liver diseases (including hepatitis, steatosis, cirrhosis) | 90 patients with chronic unexplained transaminasemia |  147 consecutive patients with chronic hypertransaminasemia (alcoholic, drugs, viral, autoimmune, hemochromatosis, alfal-antitrypsin deficiency, Wilson’s disease, congestive liver excluded). | 110 patients consecutively classified as cryptogenic hypertransaminasaemia | 258 subjects with cryptogenic hypertransaminasemia | 140 consecutive patients with chronic unexplained hypertransaminasemia |
| Age of overall population  | 16-80 years | 39.6±1.2years for males, 38.5±1.4years for females | 18-66 years | 39.79±16.77 years | 40.7 ± 12.6 years | 6-85years | 14–66years | 18-78years | 16-56years  | 34.4 ± 12.0 years | 21-62 years |
| Sample size of liver disease of interest | 56 | 28 | 35 | 100 | 47 | 29 | 90 | 125 | 82 | 258 | 140 |
| Females | 33 | Not given  | Not given  | 45 | Not given  | Not given | 21 | 21 | Not given | 94 | 47 |
| Children | None | None | None | None | None | None | None | None | None | None | None |
| First level seroassay(s) | Human TTG-IgA and AEA TTG-IgA and AEA-IgA | Human TTG-IgA | Human TTG-IgA | Human TTG-IgA | Human TTG-IgA | Human TTG-IgA | Human TTG-IgA, AEA-IgA | AEA-IgA | Guinea pig TTG-IgA, AEA-IgA | Guinea pig TTG-IgA, AEA-IgA | AEA-IgA |
| Second level seroassay(s) | No | No | AEA-IgA and DGP-IgA | No | No | No | No | No | No | No  | No |
| Whether IgA level done | No | Yes | Yes | No | No | Yes | Yes | Yes | Yes | Yes | Yes |
| No. of seropositive | 5 | 3 | 7 | 6 | 6 | 2 | 4 | 1 | 10 | 4 | 13 |
| No. of TTG positive in whole sample  | 5 | 3 | 7 | 6 | 6 | 2 | 4 | Not applicable | 10 | 4 | 12 |
| No. of AEA positive in whole sample | 5 | Not applicable | Not applicable | Not applicable | Not applicable | Not applicable | 3 | 1 | 10 | 3 | 12 |
| Small bowel-biopsied | 5 | 3 | 3 | 6 | 6 | 2 | 4 | 1 | 10 | 4 | 13 |
| Biopsy positive  | 4 | 2 | 3 | 6 | 2 | 2 | 4 | 1 | 10 | 2 | 13 |
| Response to a GFD checked | 2 of 3 patients on a strict GFD- aminotransferases decreased | Aminotransferases decreased | Not done  | Not done | Not done | Not done | Aminotransferases decreased | Aminotransferases decreased | Aminotransferases decreased in 9 of 10 patients on a GFD  | Aminotransferases decreased with 3 months of a GFD | Aminotransferases decreased with 12 months of a GFD in 12/13 patients |
| Whether invasive workup used for etiological evaluation of liver disease | No | No | Yes | No | Yes | Yes | No | Yes | Yes | Yes | Yes |
| Methodology for evaluation of liver diseases | Not explained  | serum Cu, ceruloplasmin, Fe, TIBC, ANA, Anti-Smantibody, Anti-LKM-1 antibody, AMA, P-ANCA, serum Alpha-1 anti-tripsin level (not phenotyping sinceit was not available), HBS Ag, HBC antibody, HCV antibody, TG, cholesterol, LDL, HDL, and liverultrasonography | diagnostic criteria for primary biliary cirrhosis included clinical symptoms, clinical chemistry, exclusion of infection with hepatitis viruses and evidence of antimitochondrial antibodies type M2. The diagnosis of autoimmune hepatitis was based on the scoring system devised by the International Autoimmune Hepatitis Group and International Association for the Study of the Liver[16]. The main diagnostic criteria for alcoholic liver cirrhosis were the patient’s medical history, liver histology, and exclusion of other causes of liver cirrhosis. Diagnosis of Wilson’s disease was based on the recommendation of Kodama et al[17], and Budd-Chiari syndrome in accordance with the concept of Fox et al | Not explained | following criteria were applied to exclude the mostfrequent etiologies of chronic liver disease: viral: HBsAg and HBV-DNA negative; anti-HCV andHCV-RNA negative; HIV negative (by commercial tests) autoimmune: ANA, AMA, SMA, LKM assay negative (indirect immunofluorescence); metabolic: BMI < 30 kg/m2; normal serum levels of ceruloplasmin andα1-antitripsin; transferrin saturation<45%; toxic: alcohol intake < 20 g per day, no current or pastchronic drug use, no professional exposure to hepatotoxins.All patients underwent liver biopsy by Menghini type (1.6mm) to evaluate histological damage (inflammation, fibrosis,and steatosis). Histological findings (grading and staging)and steatosis were classified | (PBC) met the following criteria: positivity for anti-mitochondrial antibodies(AMA) detected at titers of 1/40, elevated cholestatic enzymes, and histologicallesions suggestive of PBC (35). The diagnosis of primary sclerosing cholangitis(PSC) was based on biochemical and/or clinical signs of cholestasis, compatibleliver histology, and typical findings on endoscopic retrograde cholangio-pancreatography or magnetic resonance cholangiography (35). Patients with overlapping syndromes fulfilled the criteria for the diagnosis of AIH, as well as those forthe diagnosis of either PBC or PSC (2, 35). The diagnosis of nonalcoholic fattyliver disease was based on the presence of metabolic syndrome and exclusion ofother causes of chronic liver disease, including alcohol abuse, and compatibleliver histology (32), while alcoholic liver disease was diagnosed on the grounds ofa history of increased alcohol consumption; viral markers | All were negative for hepatitis B (hepatitis B surfaceantigen), hepatitis C (antibody and RNA) and hepatitisG. Antinuclear, anti-mitochondria, anti-smooth-muscle,anti-liver–kidney and anti-neutrophil cytoplasmic autoantibodies were all negative. Metabolic hepatic diseasewas excluded by testing for serum iron, total ironbinding capacity, transferrin saturation, ferritin, ceruloplasmin and alpha-1-anti-trypsin. drug use, ethanol or toxins abuse, or anyother cause that could explain hypertransaminasaemia were ruled out | Ingestion of ethanol > 60 g/daily in male patientsand 30 g/daily in females (16); b) use of potentially hepa -totoxic drugs and toxins; c) positive testing in assays forhepatitis B surface antigen, antibody to hepatitis C virusor serum HCV-RNA; d) positive testing in assays for anti -mitochondria, antinuclear, anti-smooth muscle or anti-li -ver-kidney microsome auto-antibodies at readings of >1/40 on more than one occasion; e) hemochromatosis,Wilson’s disease or alpha1-antitripsin deficiency; f)echography showing lesions of the biliary tract or hepa -tic veins, or with space-occupying lesions; g) AST or ALT> 500 UI/l; h) congestive heart failure; i) uncompensatedliver disease. | viral aetiology was ruled out by tests for hepatitis B surface antigen (some were tested and found negative for anti-HBc), antibodies to hepatitis C virus (HCV), HCV-RNA, and hepatitis G virus-RNA by nested reverse transcription (RT) polymerase chain reaction (PCR). Autoimmune liver disease - namely type-l and type-2 autoimmune hepatitis, as well as primary biliary cirrhosis - was excluded by negativity for non-organ specific autoantibodies (antibodies to nuclei, smooth muscle, liver-kidney microsomes, liver cytosol, and mitochondria), detected at 1:40 dilution by indirect immunofluorescence (IFL) on rodent tissues. A condition of enzyme deficiency was ruled out by normal values of caeruloplasmin and al-antitrypsin. Toxic and over-load-related causes (alcohol, drugs, iron) were also excluded, as well as normal thyroid function observed in all cases. Assessment of liver and absorption tests including ALT, AST, AP, y-GT, serum albumin and gamma globulins, prothrombin time, iron, transfer& ferritin, calcium, vitamin B~z, and folic acid, was performed in all cases with hypertransaminasaemia of unknown origin. Liver ultrasonography was also carried out.  | Laboratory investigations included hemogram and tests of themain parameters of liver and kidney functions. Immunoglobulin levels were evaluated to exclude IgA deficiency. The presence of hemochromatosis was determined on the basis of serum and total ironbinding capacity, transferrin saturation percentage, and serum ferritin levels. Furthermore, all subjects underwent serological screeningfor viral hepatitis B and C. The presence of anti-HCV antibodies wasdetermined by a third-generation enzyme immunoassay (EIA 3,Ortho HCV 3rd generation; Ortho Diagnostic Systems, Raritan,N.J.) in accordance with the manufacturer’s instructions. Sera werealso tested for HBsAg by a commercial enzyme-linked immunosorbent assay (Abbott Diagnostics, North Chicago, Ill., USA). In all subjects, the presence of antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies, and anti-liver-kidney-microsomal antibodies was also evaluated by indirect immunofluorescence, using commercial kits. | No current or past medical treatment, illicit drug use, ethanolabuse, and professional exposure to hepatotoxins that could accountfor the hypertransaminasemia.3) Negativity of the following tests to exclude viral infection:hepatitis B surface antigen (HBsAg; radioimmunoassay, AbbottLaboratories, North Chicago, IL), antibody to hepatitis C virus(HCV; recombinant immunoblot assay; RIBA II; Ortho DiagnosticSystem, Milan, Italy), serum HCV-RNA (reverse-transcriptase polymerase chain reaction; Amplicat HCV test, Hoffman-La Roche,Basel, Switzerland), hepatitis G virus RNA (HGV-RNA; PCR DIGLabelling Mix, Boehringer Mannheim, Mannheim, Germany) andanticytomegalovirus (standard immunoenzymatic method).4) Negativity of the assays for antinuclear, antimitochondria,antismooth muscle, antiliver–kidney microsomes, antineutrophilcytoplasmic autoantibodies (indirect immunofluorescence).5) No evidence of hemochromatosis on the basis of serum ironand total iron binding capacity, transferrin saturation percent, andserum ferritin levelsNormal plasma levels of a1-antitrypsin and caeruloplasminlevels. |
| Diseases ruled out prior to classifying as cryptogenic liver disease | viral hepatitisor autoimmune hepatitis or other liver insults (drug toxicity,alcoholic liver injury) | abnormal LFT not known to be related to acute drug toxicity, ischemic attack, or othertoxic liver insults (such as alcoholic liver injury) were included: cases included aih, nash, pbc, psc, viral hepatitis, Wilson’s | lcoholic liver cirrhosis, Autoimmune hepatitis typeⅠViral hepatitis B Viral hepatitis C Wilson’s disease Primary biliary cirrhosis Primary sclerosing cholangitis Cryptogenic liver cirrhosis Budd-Chiari syndrome Polycystic liver  | viral hepatitis, autoimmune, hemochromatosis, Wilson, Fatty liver, Alcoholic liver and drug causes | Viral, metabolic, autoimmune, toxic causes  | Viral , autoimmune, nafld, alcoholic, wilson’s disease, 2 withtransaminasemiadue to hyperthyroidism, and 7 with miscellaneous disorderssuch as mitochondrial disease, benign cholestasis of pregnancy, dysfunction ofthe sphincter of Oddi, 1-antithrypsin deficiency, drug-induced hepatitis, Gilbertsyndrome, and secondary hemochromatosis | All were negative for hepatitis B (hepatitis B surfaceantigen), hepatitis C (antibody and RNA) and hepatitisG. Antinuclear, anti-mitochondria, anti-smooth-muscle,anti-liver–kidney and anti-neutrophil cytoplasmic autoantibodies were all negative. Metabolic hepatic diseasewas excluded by testing for serum iron, total ironbinding capacity, transferrin saturation, ferritin, ceruloplasmin and alpha-1-anti-trypsin. | Ingestion of ethanol > 60 g/daily in male patientsand 30 g/daily in females (16); b) use of potentially hepa -totoxic drugs and toxins; c) positive testing in assays forhepatitis B surface antigen, antibody to hepatitis C virusor serum HCV-RNA; d) positive testing in assays for anti -mitochondria, antinuclear, anti-smooth muscle or anti-li -ver-kidney microsome auto-antibodies at readings of >1/40 on more than one occasion; e) hemochromatosis,Wilson’s disease or alpha1-antitripsin deficiency; f)echography showing lesions of the biliary tract or hepa -tic veins, or with space-occupying lesions; g) AST or ALT> 500 UI/l; h) congestive heart failure; i) uncompensatedliver disease. | viral aetiology was ruled out by tests for hepatitis B surface antigen (some were tested and found negative for anti-HBc), antibodies to hepatitis C virus (HCV), HCV-RNA, and hepatitis G virus-RNA by nested reverse transcription (RT) polymerase chain reaction (PCR). Autoimmune liver disease - namely type-l and type-2 autoimmune hepatitis, as well as primary biliary cirrhosis - was excluded by negativity for non-organ specific autoantibodies (antibodies to nuclei, smooth muscle, liver-kidney microsomes, liver cytosol, and mitochondria), detected at 1:40 dilution by indirect immunofluorescence (IFL) on rodent tissues. A condition of enzyme deficiency was ruled out by normal values of caeruloplasmin and al-antitrypsin. Toxic and over-load-related causes (alcohol, drugs, iron) were also excluded, as well as normal thyroid function observed in all cases. Assessment of liver and absorption tests including ALT, AST, AP, y-GT, serum albumin and gamma globulins, prothrombin time, iron, transfer& ferritin, calcium, vitamin B~z, and folic acid, was performed in all cases with hypertransaminasaemia of unknown origin. Liver ultrasonography was also carried out.  | Laboratory investigations included hemogram and tests of themain parameters of liver and kidney functions. Immunoglobulin levels were evaluated to exclude IgA deficiency. The presence of hemochromatosis was determined on the basis of serum and total ironbinding capacity, transferrin saturation percentage, and serum ferritin levels. Furthermore, all subjects underwent serological screeningfor viral hepatitis B and C. The presence of anti-HCV antibodies wasdetermined by a third-generation enzyme immunoassay (EIA 3,Ortho HCV 3rd generation; Ortho Diagnostic Systems, Raritan,N.J.) in accordance with the manufacturer’s instructions. Sera werealso tested for HBsAg by a commercial enzyme-linked immunosorbent assay (Abbott Diagnostics, North Chicago, Ill., USA). In all subjects, the presence of antinuclear antibodies, antimitochondrial antibodies, anti-smooth muscle antibodies, and anti-liver-kidney-microsomal antibodies was also evaluated by indirect immunofluorescence, using commercial kits. | No current or past medical treatment, illicit drug use, ethanolabuse, and professional exposure to hepatotoxins that could accountfor the hypertransaminasemia.3) Negativity of the following tests to exclude viral infection:hepatitis B surface antigen (HBsAg; radioimmunoassay, AbbottLaboratories, North Chicago, IL), antibody to hepatitis C virus(HCV; recombinant immunoblot assay; RIBA II; Ortho DiagnosticSystem, Milan, Italy), serum HCV-RNA (reverse-transcriptase polymerase chain reaction; Amplicat HCV test, Hoffman-La Roche,Basel, Switzerland), hepatitis G virus RNA (HGV-RNA; PCR DIGLabelling Mix, Boehringer Mannheim, Mannheim, Germany) andanticytomegalovirus (standard immunoenzymatic method).4) Negativity of the assays for antinuclear, antimitochondria,antismooth muscle, antiliver–kidney microsomes, antineutrophilcytoplasmic autoantibodies (indirect immunofluorescence).5) No evidence of hemochromatosis on the basis of serum ironand total iron binding capacity, transferrin saturation percent, andserum ferritin levelsNormal plasma levels of a1-antitrypsin and caeruloplasminlevels. |
| Reference | 13 | 7 | 6 | 14 | 15 | 10 | 16 | 17 | 18 | 19 | 20 |

**Supplementary Digital Content 6: Characteristics of the studies included in the systematic review for all-cause hypertransaminasemia**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Author | Yuan | Emami | Carroccio | Aggarwal  |
| Published | 2015 | 2012 | 2001 | 2019 |
| Design | Prospective | Prospective | Prospective | Retrosepctive |
| Period | September 2010 - October 2010 | 2003-2008 | September 1998 - May 1999 |  |
| Geographical region  | China, Asia | Iran, Asia | Italy, Europe | India |
| Setting  | Community | Tertiary Care | Tertiary Care | Community |
| Overall Population | Subjects with elevated transaminases from students who underwent routine physical examinations at the School Hospital | 224 patients, presenting within the first-level screening steps with abnormal LFT  | 98 patients with chronic hypertransaminasaemia, evaluated for the first time in a hepatology clinic | 1246 patients with elevated ALT among 6209 individuals that consented to provide blood samples for testing for CeD. |
| Age of overall population  | 17-21years | 39.6±1.2years for males, 38.5±1.4years for females | 18–64 years | 18-? Years |
| Sample size of liver disease of interest | 125 | 224 | 98 | 1246 |
| Females | 13 | 93 | 32 | 589 |
| Children | None | None | None | None |
| First level seroassay(s) | Human TTG-IgA | Human TTG-IgA | Human and TTG-IgA and Guinea Pig TTG-IgA and AEA-IgA | Human TTG-IgA-Aeskulisa kit |
| Second level seroassay(s) | No | No | No | Human TTG-IgA by a more specific kit- INOVA |
| Whether IgA level done | Yes | Yes | Yes | No |
| No. of seropositive | 0 | 10 | 15 | 104 |
| No. of TTG positive in whole sample  | 0 | 10 | 15 | 104 |
| No. of AEA positive in whole sample | Not applicable | Not applicable | 2 | Not applicable |
| Small bowel-biopsied | 0 | 10 | 15 | 0 |
| Biopsy positive  | Not applicable | 4 | 2 | Not applicable |
| Response to a GFD checked | Not applicable | Aminotransferases decreased with 8 weeks of a GFD | Aminotransferases decreased with 5 months of a GFD | Not applicable |
| Whether invasive workup used for etiological evaluationfor liver disease | No | No | No | No |
| Liver diseases included in all-cause hypertransaminasemia group | Not applicable | All patientspresenting with abnormal LFT not known to be related to acute drug toxicity, ischemic attack, or othertoxic liver insults (such as alcoholic liver injury) were included: cases included aih, nash, pbc, psc, viral hepatitis, Wilson’s | 94/98 patienst were positive for hepatitis markers | Not applicable |
| Methodology for evaluation of liver diseases  | Not applicable | serum Cu, ceruloplasmin, Fe, TIBC, ANA, Anti-Smantibody, Anti-LKM-1 antibody, AMA, P-ANCA, serum Alpha-1 anti-tripsin level (not phenotyping sinceit was not available), HBS Ag, HBC antibody, HCV antibody, TG, cholesterol, LDL, HDL, and liverultrasonography | Alcohol intake, use of drugs,and exposure to potential hepatic toxins wereinvestigated. Laboratory investigations included routine liver and kidney function tests.Immunoglobulin levels were underwent serological screening for viralhepatitis B and C (HCV); anti-HCV immune reactivity Sera were also tested forhepatitis B surface antigen using a commercialELISA. ANA antimitochondrial (AMA),antismooth muscle (ASMA), microsomal (anti-LKM) antibodies wasalso evaluated by indirect immunofluorescence | Not applicable |
| References | 21 | 7 | 12 | 22 |

Supplementary table 7: Reasons for exclusion among studies considered for full text review

|  |  |  |
| --- | --- | --- |
| No. | Reason for exclusion | Studies  |
| 1 | Excludedceliac disease prior to recruiting sample | 23 |
| 2 | Reported only serology but did not perform biopsies hence only included for seroprevalence and not biopsy-confirmed prevalence | 11,22 |
| 3 | Only small bowel biopsy done without CeD serology | 24,25 |
| 4 | No commitment to uniform screening of all consecutive subjects for celiac disease | 26–2824,26,29–31 |
| 5 | Percentage of seropositive subjects that underwent biopsy not given hence included for seroprevalence and not biopsy-confirmed prevalence | 10 |
| 6 | Review  | 28,32–44 |
| 7 | Abstract only  | 45,46 |
| 8 | Letter to editor only | 47,48 |
| 9 | Case report or series | 49–57 |
| 10 | Study population was not relevant/did not fit diagnostic criteria | 58–64 |
| 11 | Studies on prevalence of liver involvement in celiac disease | 65,6665,67–73 |
| 12 | Irrelevant topic | 74–80 |
| 13 | Use of Antigliadin antibodies only for first line serological testing | 81 |
| 14 | Study population is a subset of another study’s population  | 82 |

**Supplementary Digital Content 8a: Funnel plot for publication bias in the meta-analysis of studies on prevalence of biopsy-confirmed celiac disease in cryptogenic cirrhosis**



**Supplementary Digital Content 8b: Funnel plot for publication bias in the meta-analysis of studies on prevalence of biopsy-confirmed celiac disease in all-cause cirrhosis**



**Supplementary Digital Content 8c: Funnel plot for publication bias in the meta-analysis of studies on prevalence of biopsy-confirmed celiac disease in cryptogenic hypertransaminasemia**



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