**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| Method of handling abstracts and  unpublished studies | Yes | 11 |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 volume reduction or re-distribution, irregular margins, coarse texture or nodular liver, any of the 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 vein  obstruction (EHPVO) | ultrasound of the abdomen with portal and hepatic  vein 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 for  CD 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 and  steatosis]) 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 typeⅠ  Viral 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-Sm  antibody, Anti-LKM-1 antibody, AMA, P-ANCA, serum Alpha-1 anti-tripsin level (not phenotyping since  it was not available), HBS Ag, HBC antibody, HCV antibody, TG, cholesterol, LDL, HDL, and liver  ultrasonography | 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 was  diagnosed on the basis of clinical, biochemical, and imaging features. Portal hypertension was defined as the presence of gastroesophageal varices (GEV) and/or high  gradient ascites. For etiology of portal hypertension, patients were screened for history of alcohol intake, HBsAg,  anti-HCV antibody, ultrasound abdomen with Doppler  of portal vein and hepatic veins, multiphase contrastenhanced computed tomography abdomen, IgA-tTG, autoantibodies (AMA, ASMA, LKM, ANA, IgG), and serum  ceruloplasmin as per clinical evaluation. Patients of CD  with portal hypertension (PHT) were also subjected to  ultrasound-guided percutaneous liver biopsy in absence  of absolute contraindications. Patients of cirrhosis with  PHT and negative evaluation for cause of liver disease  were defined as cCLD. NCPF was defined as the presence  of PHT, patient hepatic and portal veins on Doppler, no  identifiable etiology for liver disease, and absence of  cirrhosis.14 EHPVO was diagnosed in the presence of  PHT with obstruction of the extrahepatic portal vein  with or without involvement of intrahepatic portal vein  radicles or splenic or superior mesenteric veins with the  presence of portal cavernoma and absence of cirrhosis.15,16  Autoimmune hepatitis (AIH) was diagnosed by a simplified scoring system: probable AIH when pretreatment  aggregate score $6, and definite AIH | ultrasound of the abdomen with portal and hepatic  vein 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 for  CD 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 and  steatosis]) 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 hepatic  venous outflow tract, HBsAg, HCV antibody, autoantibodies  (AMA, SLA, LKM, ANA), serum ceruloplasmin, and  iron studies. Patients with cirrhosis with portal hypertension, with negative noninvasive evaluation for cause  of liver disease, were labelled as cryptogenic chronic liver  disease. | 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 other  toxic 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 volume reduction or re-distribution, irregular margins, coarse texture or nodular liver, any of the 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 was  diagnosed on the basis of clinical, biochemical, and imaging features. Portal hypertension was defined as the presence of gastroesophageal varices (GEV) and/or high  gradient ascites. For etiology of portal hypertension, patients were screened for history of alcohol intake, HBsAg,  anti-HCV antibody, ultrasound abdomen with Doppler  of portal vein and hepatic veins, multiphase contrastenhanced computed tomography abdomen, IgA-tTG, autoantibodies (AMA, ASMA, LKM, ANA, IgG), and serum  ceruloplasmin as per clinical evaluation. Patients of CD  with portal hypertension (PHT) were also subjected to  ultrasound-guided percutaneous liver biopsy in absence  of absolute contraindications. Patients of cirrhosis with  PHT and negative evaluation for cause of liver disease  were defined as cCLD. NCPF was defined as the presence  of PHT, patient hepatic and portal veins on Doppler, no  identifiable etiology for liver disease, and absence of  cirrhosis.14 EHPVO was diagnosed in the presence of  PHT with obstruction of the extrahepatic portal vein  with or without involvement of intrahepatic portal vein  radicles or splenic or superior mesenteric veins with the  presence of portal cavernoma and absence of cirrhosis.15,16  Autoimmune hepatitis (AIH) was diagnosed by a simplified scoring system: probable AIH when pretreatment  aggregate 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 typeⅠ  Viral 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 disorders  such as mitochondrial disease, benign cholestasis of pregnancy, dysfunction of  the sphincter of Oddi, 1-antithrypsin deficiency, drug-induced hepatitis, Gilbert  syndrome, and secondary hemochromatosis | HBV, HCV, alcohol, sclerosing cholangitis | 94/98 patienst were positive for hepatitis markers |
| Methodology for evaluation of liver diseases | Cirrhosis was  diagnosed on the basis of clinical, biochemical, and imaging features. Portal hypertension was defined as the presence of gastroesophageal varices (GEV) and/or high  gradient ascites. For etiology of portal hypertension, patients were screened for history of alcohol intake, HBsAg,  anti-HCV antibody, ultrasound abdomen with Doppler  of portal vein and hepatic veins, multiphase contrastenhanced computed tomography abdomen, IgA-tTG, autoantibodies (AMA, ASMA, LKM, ANA, IgG), and serum  ceruloplasmin as per clinical evaluation. Patients of CD  with portal hypertension (PHT) were also subjected to  ultrasound-guided percutaneous liver biopsy in absence  of absolute contraindications. Patients of cirrhosis with  PHT and negative evaluation for cause of liver disease  were defined as cCLD. NCPF was defined as the presence  of PHT, patient hepatic and portal veins on Doppler, no  identifiable etiology for liver disease, and absence of  cirrhosis.14 EHPVO was diagnosed in the presence of  PHT with obstruction of the extrahepatic portal vein  with or without involvement of intrahepatic portal vein  radicles or splenic or superior mesenteric veins with the  presence of portal cavernoma and absence of cirrhosis.15,16  Autoimmune hepatitis (AIH) was diagnosed by a simplified scoring system: probable AIH when pretreatment  aggregate score $6, and definite AIH with score 7 | In patients with chronic liver disease different etiologies of liver disease were detad  as 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 histological  lesions suggestive of PBC (35). The diagnosis of primary sclerosing cholangitis  (PSC) was based on biochemical and/or clinical signs of cholestasis, compatible  liver 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 for  the diagnosis of either PBC or PSC (2, 35). The diagnosis of nonalcoholic fatty  liver disease was based on the presence of metabolic syndrome and exclusion of  other causes of chronic liver disease, including alcohol abuse, and compatible  liver histology (32), while alcoholic liver disease was diagnosed on the grounds of  a history of increased alcohol consumption; viral markers | Not given | Alcohol intake, use of drugs,  and exposure to potential hepatic toxins were  investigated. Laboratory investigations included routine liver and kidney function tests.  Immunoglobulin levels were  underwent serological screening for viral  hepatitis B and C (HCV); anti-HCV immune reactivity  Sera were also tested for  hepatitis B surface antigen using a commercial  ELISA.  ANA antimitochondrial (AMA),  antismooth muscle (ASMA), microsomal (anti-LKM) antibodies was  also 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-Sm  antibody, Anti-LKM-1 antibody, AMA, P-ANCA, serum Alpha-1 anti-tripsin level (not phenotyping since  it was not available), HBS Ag, HBC antibody, HCV antibody, TG, cholesterol, LDL, HDL, and liver  ultrasonography | 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 most  frequent etiologies of chronic liver disease:  viral: HBsAg and HBV-DNA negative; anti-HCV and  HCV-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 past  chronic drug use, no professional exposure to hepatotoxins.  All patients underwent liver biopsy by Menghini type (1.6  mm) 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 histological  lesions suggestive of PBC (35). The diagnosis of primary sclerosing cholangitis  (PSC) was based on biochemical and/or clinical signs of cholestasis, compatible  liver 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 for  the diagnosis of either PBC or PSC (2, 35). The diagnosis of nonalcoholic fatty  liver disease was based on the presence of metabolic syndrome and exclusion of  other causes of chronic liver disease, including alcohol abuse, and compatible  liver histology (32), while alcoholic liver disease was diagnosed on the grounds of  a history of increased alcohol consumption; viral markers | All were negative for hepatitis B (hepatitis B surface  antigen), hepatitis C (antibody and RNA) and hepatitis  G. Antinuclear, anti-mitochondria, anti-smooth-muscle,  anti-liver–kidney and anti-neutrophil cytoplasmic autoantibodies were all negative. Metabolic hepatic disease  was 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 any  other cause that could explain hypertransaminasaemia were ruled out | Ingestion of ethanol > 60 g/daily in male patients  and 30 g/daily in females (16); b) use of potentially hepa -  totoxic drugs and toxins; c) positive testing in assays for  hepatitis B surface antigen, antibody to hepatitis C virus  or 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) uncompensated  liver 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 the  main 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 screening  for viral hepatitis B and C. The presence of anti-HCV antibodies was  determined 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 were  also 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, ethanol  abuse, and professional exposure to hepatotoxins that could account  for the hypertransaminasemia.  3) Negativity of the following tests to exclude viral infection:  hepatitis B surface antigen (HBsAg; radioimmunoassay, Abbott  Laboratories, North Chicago, IL), antibody to hepatitis C virus  (HCV; recombinant immunoblot assay; RIBA II; Ortho Diagnostic  System, 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 DIG  Labelling Mix, Boehringer Mannheim, Mannheim, Germany) and  anticytomegalovirus (standard immunoenzymatic method).  4) Negativity of the assays for antinuclear, antimitochondria,  antismooth muscle, antiliver–kidney microsomes, antineutrophil  cytoplasmic autoantibodies (indirect immunofluorescence).  5) No evidence of hemochromatosis on the basis of serum iron  and total iron binding capacity, transferrin saturation percent, and  serum ferritin levelsNormal plasma levels of a1-antitrypsin and caeruloplasmin  levels. |
| Diseases ruled out prior to classifying as cryptogenic liver disease | viral hepatitis  or 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 other  toxic liver insults (such as alcoholic liver injury) were included: cases included aih, nash, pbc, psc, viral hepatitis, Wilson’s | lcoholic liver cirrhosis,  Autoimmune hepatitis typeⅠ  Viral 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 with  transaminasemiadue to hyperthyroidism, and 7 with miscellaneous disorders  such as mitochondrial disease, benign cholestasis of pregnancy, dysfunction of  the sphincter of Oddi, 1-antithrypsin deficiency, drug-induced hepatitis, Gilbert  syndrome, and secondary hemochromatosis | All were negative for hepatitis B (hepatitis B surface  antigen), hepatitis C (antibody and RNA) and hepatitis  G. Antinuclear, anti-mitochondria, anti-smooth-muscle,  anti-liver–kidney and anti-neutrophil cytoplasmic autoantibodies were all negative. Metabolic hepatic disease  was 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 patients  and 30 g/daily in females (16); b) use of potentially hepa -  totoxic drugs and toxins; c) positive testing in assays for  hepatitis B surface antigen, antibody to hepatitis C virus  or 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) uncompensated  liver 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 the  main 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 screening  for viral hepatitis B and C. The presence of anti-HCV antibodies was  determined 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 were  also 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, ethanol  abuse, and professional exposure to hepatotoxins that could account  for the hypertransaminasemia.  3) Negativity of the following tests to exclude viral infection:  hepatitis B surface antigen (HBsAg; radioimmunoassay, Abbott  Laboratories, North Chicago, IL), antibody to hepatitis C virus  (HCV; recombinant immunoblot assay; RIBA II; Ortho Diagnostic  System, 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 DIG  Labelling Mix, Boehringer Mannheim, Mannheim, Germany) and  anticytomegalovirus (standard immunoenzymatic method).  4) Negativity of the assays for antinuclear, antimitochondria,  antismooth muscle, antiliver–kidney microsomes, antineutrophil  cytoplasmic autoantibodies (indirect immunofluorescence).  5) No evidence of hemochromatosis on the basis of serum iron  and total iron binding capacity, transferrin saturation percent, and  serum ferritin levelsNormal plasma levels of a1-antitrypsin and caeruloplasmin  levels. |
| Reference | 13 | 7 | 6 | 14 | 15 | 10 | 16 | 17 | 18 | 19 | 20 |

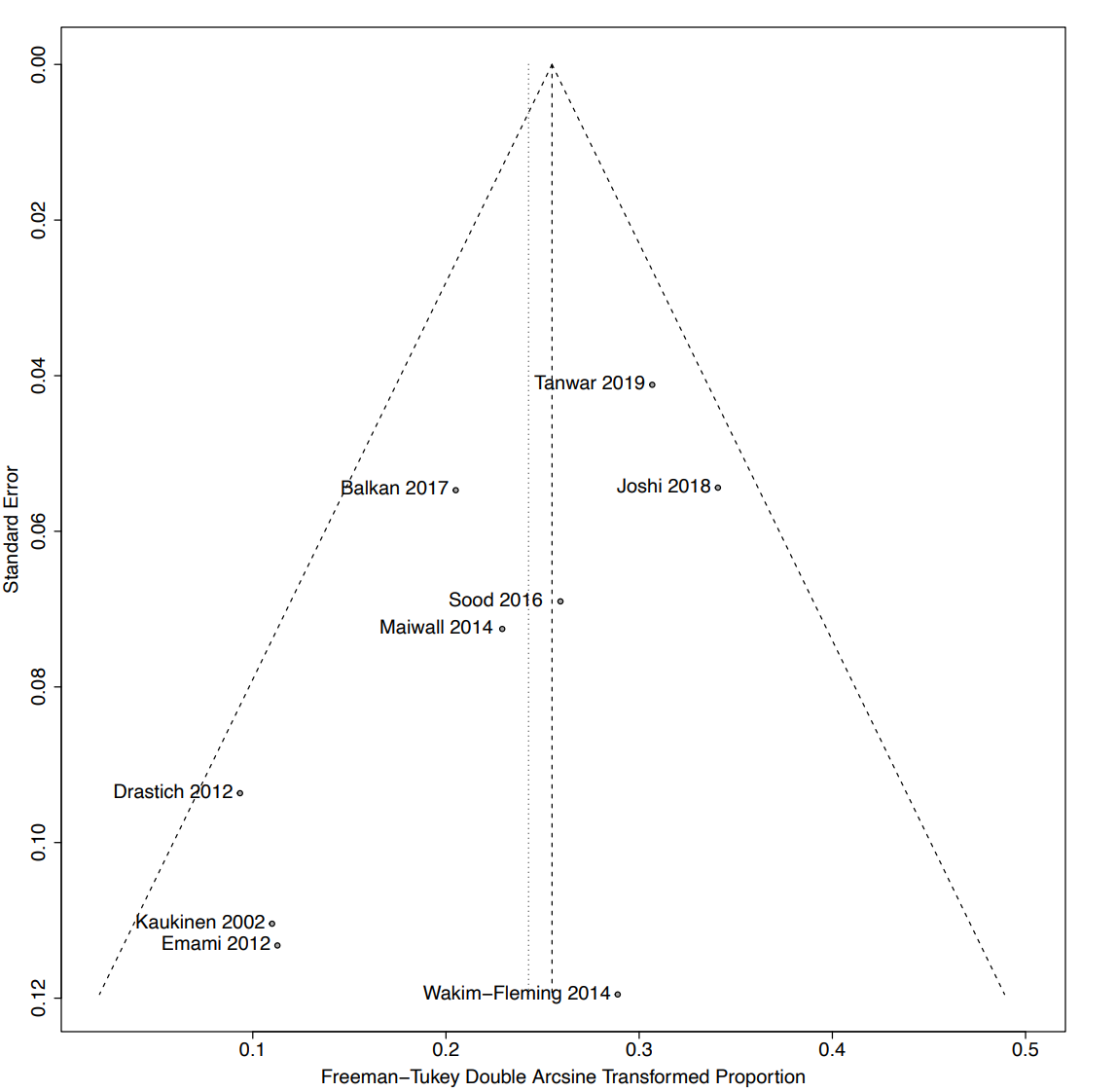
**Supplementary Digital Content 6: Characteristics of the studies included in the systematic review for all-cause hypertransaminasemia**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| 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 patients  presenting with abnormal LFT not known to be related to acute drug toxicity, ischemic attack, or other  toxic 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-Sm  antibody, Anti-LKM-1 antibody, AMA, P-ANCA, serum Alpha-1 anti-tripsin level (not phenotyping since  it was not available), HBS Ag, HBC antibody, HCV antibody, TG, cholesterol, LDL, HDL, and liver  ultrasonography | Alcohol intake, use of drugs,  and exposure to potential hepatic toxins were  investigated. Laboratory investigations included routine liver and kidney function tests.  Immunoglobulin levels were  underwent serological screening for viral  hepatitis B and C (HCV); anti-HCV immune reactivity  Sera were also tested for  hepatitis B surface antigen using a commercial  ELISA.  ANA antimitochondrial (AMA),  antismooth muscle (ASMA), microsomal (anti-LKM) antibodies was  also evaluated by indirect immunofluorescence | Not applicable |
| References | 21 | 7 | 12 | 22 |

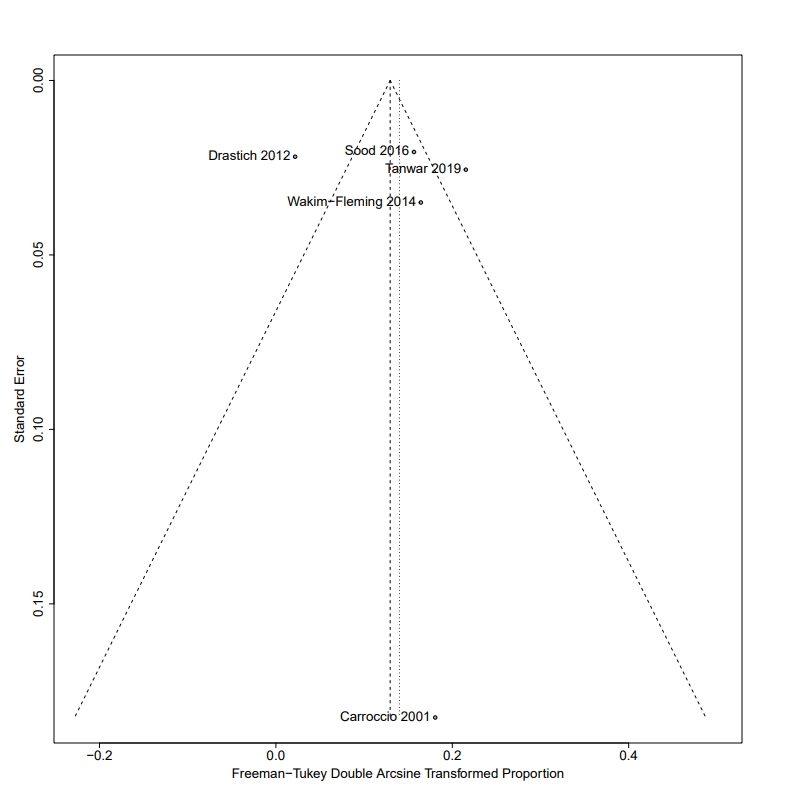
Supplementary table 7: Reasons for exclusion among studies considered for full text review

|  |  |  |
| --- | --- | --- |
| 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 |

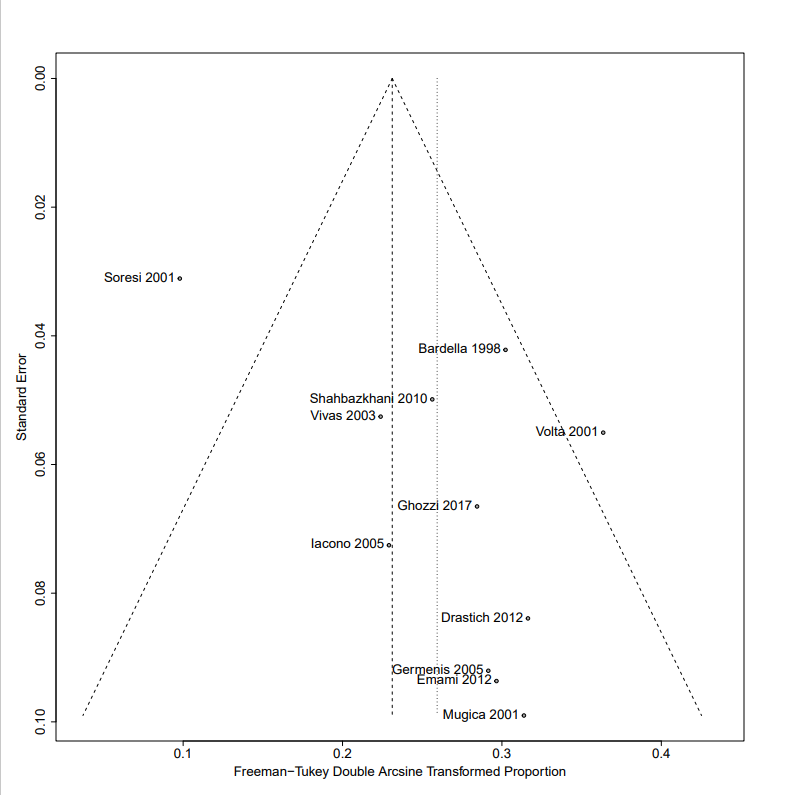
**Supplementary Digital Content 8a: Funnel plot for publication bias in the meta-analysis of studies on prevalence of biopsy-confirmed celiac disease in cryptogenic cirrhosis**



**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**



**REFERENCES**

1. Joshi, A., Falodia, S. & Kumar, N. Prevalence of celiac disease among pediatric patients with cryptogenic cirrhosis and effect of gluten-free-diet. (2018).

2. Balkan, A. *et al.* Prevalence of celiac disease in patients with hepatitis B and C virus related cirrhosis and cryptogenic liver cirrhosis. *Biomedical Research* **28**, (2017).

3. Sood, A. *et al.* Prevalence and clinical significance of IgA anti-tissue transglutaminase antibodies in patients with chronic liver disease. *Journal of Gastroenterology and Hepatology* **32**, 446–450 (2017).

4. Maiwall, R. *et al.* Investigation into celiac disease in Indian patients with portal hypertension. *Indian J Gastroenterol* **33**, 517–523 (2014).

5. Wakim-Fleming, J. *et al.* Prevalence of celiac disease in cirrhosis and outcome of cirrhosis on a gluten free diet: a prospective study. *J.Hepatol.* **61**, 558–563 (2014).

6. Drastich, P. Celiac disease markers in patients with liver diseases: A single center large scale screening study. *World Journal of Gastroenterology* **18**, 6255 (2012).

7. Emami, M. H., Hashemi, M., Kouhestani, S., Taheri, H. & Karimi, S. Should We Look for Celiac Disease among all Patients with Liver Function Test Abnormalities? *International Journal of Preventive Medicine* **3**, 167–172 (2012).

8. kaukinen 2002, Red, F., Blood, C. & Service, T. Celiac Disease in Patients With Severe Liver Disease : Gluten-Free Diet May Reverse Hepatic Failure. 881–888 (2002) doi:10.1053/gast.2002.32416.

9. Tanwar, A. *et al.* Celiac Disease and Portal Hypertension: A Causal Association or Just a Coincidence? *J Clin Exp Hepatol* **10**, 290–295 (2020).

10. Germenis, A. E. *et al.* Prevalence and clinical significance of immunoglobulin A antibodies against tissue transglutaminase in patients with diverse chronic liver diseases. *Clinical and Diagnostic Laboratory Immunology* **12**, 941–948 (2005).

11. Vecchi, M. *et al.* High rate of positive anti-tissue transglutaminase antibodies in chronic liver disease. Role of liver decompensation and of the antigen source. *Scand. J. Gastroenterol.* **38**, 50–54 (2003).

12. Carroccio, A. *et al.* Guinea pig transglutaminase immunolinked assay does not predict coeliac disease in patients with chronic liver disease. *Gut* **49**, 506–511 (2001).

13. Ghozzi, M. *et al.* Screening for celiac disease, by endomysial antibodies, in patients with unexplained hypertransaminasaemia. *Scand. J. Clin. Lab. Invest.* **77**, 454–457 (2017).

14. Shahbazkhani B. Celiac disease in cryptogenic hypertransaminasemia. *embase* https://www.embase.com/a/#/search/results?subaction=viewrecord&rid=12&page=1&id=L359954461.

15. Iacono, O. L. *et al.* Anti-Tissue Transglutaminase Antibodies in Patients with Abnormal Liver Tests : Is It Always Coeliac Disease ? 2472–2477 (2005) doi:10.1111/j.1572-0241.2005.00244.x.

16. Vivas, S. *et al.* Human recombinant anti-transglutaminase antibody testing is useful in the diagnosis of silent coeliac disease in a selected group of at-risk patients. *Eur J Gastroenterol Hepatol* **15**, 479–483 (2003).

17. Múgica, F. *et al.* Prevalence of coeliac disease in unexplained chronic hypertransaminasemia. *Rev Esp Enferm Dig* **93**, 707–714 (2001).

18. Volta, U., Granito, A., De Franceschi, L., Petrolini, N. & Bianchi, F. B. Anti tissue transglutaminase antibodies as predictors of silent coeliac disease in patients with hypertransaminasaemia of unknown origin. *Dig Liver Dis* **33**, 420–425 (2001).

19. Soresi, M. *et al.* Screening for autoantibodies to tissue transglutaminase reveals a low prevalence of celiac disease in blood donors with cryptogenic hypertransaminasemia. *Digestion* **64**, 87–91 (2001).

20. Bardella, M. T. *et al.* Chronic unexplained hypertransaminasemia may be caused by occult celiac disease. *Hepatology* **29**, 654–657 (1999).

21. Yuan, J., Gao, J., Yao, Y. & Chen, H. Serologic testing for celiac disease in young people with elevated transaminases. *Turk J Med Sci* **45**, 668–673 (2015).

22. Aggarwal, N. *et al.* Prevalence of elevated alanine aminotransferase levels in adult participants from a community-based study from northern part of India. *Indian J Gastroenterol* **39**, 608–613 (2020).

23. Reiberger, T. *et al.* Non-selective betablocker therapy decreases intestinal permeability and serum levels of LBP and IL-6 in patients with cirrhosis. *J. Hepatol.* **58**, 911–921 (2013).

24. Kochhar, R. *et al.* Celiac disease suspected at endoscopy in patients with chronic liver disease. *Indian J Gastroenterol* **30**, 166–169 (2011).

25. Wakim-Fleming, J. *et al.* Histological abnormalities of the small bowel mucosa in cirrhosis and portal hypertension. *World J. Gastroenterol.* **14**, 6370–6375 (2008).

26. Cvetkovic, L. *et al.* Discordance Between Serology and Histology for Celiac Disease in a Cohort with Coexisting Liver Disorders. *J Can Assoc Gastroenterol* **3**, 185–193 (2020).

27. Iorio, R., Sepe, A., Giannattasio, A., Cirillo, F. & Vegnente, A. Hypertransaminasemia in childhood as a marker of genetic liver disorders. *J. Gastroenterol.* **40**, 820–826 (2005).

28. Khorashad, A. *et al.* Causes of Persistently Elevated Alanine Aminotransferase Levels in Patients who Presented to Two Referral Hospitals in Mashhad, Iran during 2011. *Middle East J Dig Dis* **6**, 18–22 (2014).

29. Villalta, D. *et al.* False positive reactions for IgA and IgG anti-tissue transglutaminase antibodies in liver cirrhosis are common and method-dependent. *Clin. Chim. Acta* **356**, 102–109 (2005).

30. Lindgren, S., Sjöberg, K. & Eriksson, S. Unsuspected coeliac disease in chronic ‘cryptogenic’ liver disease. *Scandinavian Journal of Gastroenterology* **29**, 661–664 (1994).

31. Ferrari, F., Mennini, M. & Cucchiara, S. Portal hypertension and celiac disease: a true association? *Indian J Gastroenterol* **34**, 273–274 (2015).

32. Maggiore, G. & Caprai, S. The liver in celiac disease. *J. Pediatr. Gastroenterol. Nutr.* **37**, 117–119 (2003).

33. Maggiore, G. & Caprai, S. Liver involvement in celiac disease. *Indian J Pediatr* **73**, 809–811 (2006).

34. Narciso-Schiavon, J. L. & Schiavon, L. L. To screen or not to screen? Celiac antibodies in liver diseases. *World J. Gastroenterol.* **23**, 776–791 (2017).

35. Rubio-Tapia, A. & Murray, J. A. The liver in celiac disease. *Hepatology* **46**, 1650–1658 (2007).

36. Sainsbury, A., Sanders, D. S. & Ford, A. C. Meta-analysis: Coeliac disease and hypertransaminasaemia. *Aliment. Pharmacol. Ther.* **34**, 33–40 (2011).

37. Vajro, P., Paolella, G., Maggiore, G. & Giordano, G. Pediatric Celiac Disease, Cryptogenic Hypertransaminasemia, and Autoimmune Hepatitis: *Journal of Pediatric Gastroenterology and Nutrition* **56**, 663–670 (2013).

38. Volta, U. Liver dysfunction in celiac disease. *Minerva Med.* **99**, 619–629 (2008).

39. Verslype, C. Evaluation of abnormal liver-enzyme results in asymptomatic patients. *Acta Clin Belg* **59**, 285–289 (2004).

40. Al-Busafi, S. A. & Hilzenrat, N. Mild Hypertransaminasemia in Primary Care. *ISRN Hepatol* **2013**, 256426 (2013).

41. Analysis, A. E. *Clinical Utility of Serologic Testing for Celiac Disease in Asymptomatic Patients*. vol. 11 (2011).

42. Alavi Moghaddam, M. *et al.* The effects of gluten-free diet on hypertransaminasemia in patients with celiac disease. *Int J Prev Med* **4**, 700–704 (2013).

43. Villavicencio Kim, J. & Wu, G. Y. Celiac Disease and Elevated Liver Enzymes: A Review. *Journal of Clinical and Translational Hepatology* **0**, 1–9 (2020).

44. Abdo, A., Meddings, J. & Swain, M. Liver abnormalities in celiac disease. *Clinical Gastroenterology and Hepatology* **2**, 107–112 (2004).

45. Burda-Muszynska, B. *et al.* ATYPICAL CELIAC DISEASE IN RISK GROUPS OF POLISH CHILDREN. *Journal of Pediatric Gastroenterology and Nutrition* **42**, E23 (2006).

46. Hill, I. D. *et al.* NASPGHAN Clinical Report on the Diagnosis and Treatment of Gluten-related Disorders. *J. Pediatr. Gastroenterol. Nutr.* **63**, 156–165 (2016).

47. Carroccio, A., Soresi, M., Di Prima, L. & Montalto, G. Screening for celiac disease in patients with chronic liver disease. *Gastroenterology* **125**, 1289 (2003).

48. Nejad, M. R. & Alavian, S. Celiac Disease and Abnormal Liver Function Test. **3**, 745–746 (2012).

49. El Hasbaoui, B., El Mahi, J., Abilkassem, R. & Agadr, A. Coeliac disease hidden by cryptogenic hypertransaminasaemia in children: a case report. *Pan Afr Med J* **41**, 27 (2022).

50. Foroutan, M., Nejad, M. R., Molanaee, S., Hogg-Kollars, S. & Rostami, K. Celiac disease hidden by cryptogenic hypertransaminasemia mistaken for fatty liver. *Bratisl Lek Listy* **114**, 547–548 (2013).

51. Kaya, M., Beştaş, R., Çetın, S. & Büyükbayram, H. Clinical remission after strict gluten-free diet in a patient with celiac disease, advanced cryptogenic cirrhosis and splenic atrophy. *Turk J Gastroenterol* **23**, 619–621 (2012).

52. Ojetti, V. *et al.* Acute cryptogenic liver failure in an untreated coeliac patient: a case report. *Eur J Gastroenterol Hepatol* **17**, 1119–1121 (2005).

53. Vajro, P. *et al.* Elevated serum aminotransferase activity as an early manifestation of gluten-sensitive enteropathy. *J. Pediatr.* **122**, 416–419 (1993).

54. Stevens, F. M. & McLoughlin, R. M. Is coeliac disease a potentially treatable cause of liver failure? *Eur J Gastroenterol Hepatol* **17**, 1015–1017 (2005).

55. Singh, P. *et al.* Celiac disease and chronic liver disease: is there a relationship? *Indian J Gastroenterol* **32**, 404–408 (2013).

56. Somani, V. & Amarapurkar, D. Celiac Disease in Patients with Liver Cirrhosis. *Tropical Gastroenterology* **39**, 101–105 (2019).

57. Sharma, B. C., Bhasin, D. K. & Nada, R. Association of celiac disease with non-cirrhotic portal fibrosis. *J Gastroenterol Hepatol* **21**, 332–334 (2006).

58. Mounajjed, T., Oxentenko, A., Shmidt, E. & Smyrk, T. The Liver in Celiac Disease: Clinical Manifestations, Histologic Features, and Response to Gluten-Free Diet in 30 Patients. *American Journal of Clinical Pathology* **136**, 128–137 (2011).

59. Rudolph, B. *et al.* Yield of diagnostic tests in obese children with an elevated alanine aminotransferase. *Acta Paediatr.* **104**, e557-563 (2015).

60. Hussain, F., Karim, A. S. M. B. & Anwar, S. A. Frequency of Celiac Disease in Children Presented with Liver Disease at a Tertiary Care Center. **40**, 144–148 (2016).

61. Gatselis, N. K. *et al.* IgA antibodies against deamidated gliadin peptides in patients with chronic liver diseases. *Clin. Chim. Acta* **413**, 1683–1688 (2012).

62. Fine, K. D. *et al.* Celiac sprue: another autoimmune syndrome associated with hepatitis C. *Am. J. Gastroenterol.* **96**, 138–145 (2001).

63. Yodoshi, T. *et al.* Alternative Etiologies of Liver Disease in Children With Suspected NAFLD. *Pediatrics* **147**, e2020009829 (2021).

64. Rubio-Tapia, A. *et al.* Celiac disease autoantibodies in severe autoimmune liver disease and the effect of liver transplantation. *Liver Int* **28**, 467–476 (2008).

65. Regev, A. *et al.* Elevated liver enzymes of newly diagnosed pediatric celiac patients-a prospective-observational study. *Eur J Pediatr* **181**, 753–762 (2022).

66. Saadah, O. I. Celiac disease in children and adolescents at a singe center in Saudi Arabia. *Ann Saudi Med* **31**, 51–57 (2011).

67. Kwiatek-Średzińska, K. A. *et al.* Liver pathology in children with newly diagnosed celiac disease. *Clinical and experimental hepatology* **5**, 129–132 (2019).

68. Morillas, M. J. *et al.* [Adult celiac disease and hepatopathy]. *Rev Esp Enferm Dig* **79**, 197–200 (1991).

69. Dickey, W. *et al.* Liver abnormalities associated with celiac sprue. How common are they, what is their significance, and what do we do about them? *J Clin Gastroenterol* **20**, 290–292 (1995).

70. Novacek, G. *et al.* Prevalence and clinical importance of hypertransaminasaemia in coeliac disease. *Eur J Gastroenterol Hepatol* **11**, 283–288 (1999).

71. Castillo, N. E. *et al.* Prevalence of abnormal liver function tests in celiac disease and the effect of a gluten-free diet in the US population. *Am J Gastroenterol* **110**, 1216–1222 (2015).

72. Frequency of elevated ALT in untreated coeliac disease and the impact of compliance with gluten free diet on ALT normalisation-Web of Science Core Collection. https://www.webofscience.com/wos/woscc/full-record/WOS:000270551200311?SID=EUW1ED0ABAOBAAQuLz9uzDLdfsV4O.

73. Elwenspoek, M. M. C. *et al.* The accuracy of diagnostic indicators for coeliac disease: A systematic review and meta-analysis. *PLoS One* **16**, e0258501 (2021).

74. Dutta, R., Das, P., Makharia, G. & Iqbal, A. 42. Analysis of histological features and co-localisation patterns of IGA and IGG anti-tissue transglutaminase antibody in liver biopsies of patients with treatment naïve celiac disease, presenting with liver dysfunctions. *Journal of Clinical and Experimental Hepatology* **8**, S122–S123 (2018).

75. Kalas, M. A., Chavez, L., Leon, M., Taweesedt, P. T. & Surani, S. Abnormal liver enzymes: A review for clinicians. *World J Hepatol* **13**, 1688–1698 (2021).

76. Kochhar, R. *et al.* Prevalence of coeliac disease in healthy blood donors: A study from north India. *Digestive and Liver Disease* **44**, 530–532 (2012).

77. Taylor, P. *et al.* Prevalence and Clinical Significance of Gliadin Antibodies in Healthy Children and Adults Prevalence and Clinical Significance of Gliadin Antibodies in Healthy Children and Adults. (2015) doi:10.3109/00365529409090472.

78. Lachaux, A., Sakly, W., Spiteri, A. & Fabien, N. IgA anti-transglutaminase antibodies as a tool for screening atypical forms of coeliac disease in a French at-risk paediatric population. 235–239.

79. Romiti, A. *et al.* Malabsorption and nutritional abnormalities in patients with liver cirrhosis. *Ital J Gastroenterol* **22**, 118–123 (1990).

80. Vilppula, A. *et al.* Clinical benefit of gluten-free diet in screen-detected older celiac disease patients. *BMC Gastroenterology* **11**, 136 (2011).

81. Floreani, A. *et al.* Prevalence of coeliac disease in primary biliary cirrhosis and of antimitochondrial antibodies in adult coeliac disease patients in Italy. *Dig Liver Dis* **34**, 258–261 (2002).

82. Volta, U. *et al.* Coeliac disease hidden by cryptogenic hypertransaminasaemia. *Lancet* **352**, 26–29 (1998).