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Postoperative Outcomes Following Liver Transplantation for Wilson's Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Liver transplant is indicated in patients with Wilson's disease for acute hepatic failure, advanced cirrhosis, and disease refractory to chelation therapy. This study aims to systematically review data about overall morbidity, hepatic, neuropsychiatric, and survival outcomes following liver transplantation for Wilson disease.

Methods: MEDLINE, Embase, and Central were searched from inception until July 2023. Peer-reviewed articles and published abstracts evaluating patients diagnosed with Wilson's disease and undergoing any type of liver transplant as a result of the disease were eligible for inclusion. A restricted maximum likelihood random effects model was used to generate the pooled proportion of each outcome. The risk of bias for each included observational study was assessed using the Methodological Index for Non-Randomized Studies tool.

Results: A total of 39 studies met all inclusion criteria. All studies were observational. Specific indications for liver transplant were most commonly acute liver failure (36.73%), chronic liver failure (45.02%), and acute-on-chronic liver failure (8.35%). The pooled proportions of mortality at 30 days, 1, and 5 years were 0.10 (95% CI 0.08, 0.13; $I^2 = 16\%$), 0.11 (95% CI 0.09, 0.14; $I^2 = 37\%$), and 0.15 (95% CI 0.11, 0.20; $I^2 = 81\%$), respectively. The postoperative complication with the greatest prevalence was biopsy-proven acute rejection with a pooled proportion of 0.20 (95% CI 0.12, 0.31; $I^2 = 84\%$). The mean MINORS score for risk of bias for all studies was 8.19.

Conclusion: Overall, reporting quality and consistency of outcomes included in the studies was poor as assessed using the MINORS score. Pooled proportions for 30-day, 1- and 5-year mortality are similar, suggesting most postoperative deaths are acute in nature. Future research should incorporate objective measures and the reporting of standardized parameters to allow more robust comparisons between studies.

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1 | Introduction

Wilson's disease or hepatolenticular degeneration follows an autosomal recessive pattern of inheritance and is caused by one of several mutations in the ATP7B gene on the long arm of chromosome 13 [1]. This codes for the copper-transporting ATP7B protein, which is responsible for biliary copper excretion in the liver [1]. A qualitative or quantitative defect in this protein prevents the transportation of copper from the cytosol to the trans-Golgi network, resulting in the accumulation of copper in lysosomes. Lysosomes burst upon reaching their storage capacity, causing the release of copper into the cytosol, which induces hepatocyte damage and necrosis. The process of hepatocyte damage causes a rapid release of copper into the circulation, where it can damage other organs [2].

Approximately 30% of patients with Wilson's disease are diagnosed through family screening and remain in the pre-destructive phase of copper accumulation [3]. Half of the remaining patients present with both hepatic and neurologic manifestations, while the other half present with either simple liver disease or neurologic symptoms [3]. Medical treatment of Wilson's disease typically involves chelation therapy with D-penicillamine, zinc salts, or trientine [4]. The European Association for the Study of the Liver (EASL) Clinical Practice Guidelines 2012 include acute liver failure with a revised King's score of 11 or higher and decompensated cirrhosis unresponsive to chelation treatment as indications for transplantation [5]. However, a systematic review by Khanna et al. identified other common indications for liver transplantation that included acute hepatic failure associated with hemolysis and hypercupremia, advanced cirrhosis, hepatic insufficiency unresponsive to chelation therapy, and refractory extrahepatic manifestations, including neurological symptoms, in the absence of hepatic diseases [6–8].

Previous observational studies have evaluated postoperative survival, hepatic, and neurological outcomes independently in patients undergoing liver transplantation for this indication. A systematic review by Turgut et al. synthesized survival and neurological outcomes. They demonstrated a 1-year survival rate of 84%, with a 4% mortality rate for the following 1–10 years and a 74.2% decrease in neurological symptoms [9]. However, postoperative hepatic and overall morbidity outcomes have not yet been synthesized in patients with Wilson's disease undergoing liver transplantation. Additionally, there have been recent large observational studies since the most recent data synthesis study. As such, we aim to perform the first systematic review and meta-analysis collating data pertaining to overall morbidity, hepatic, neuropsychiatric, and survival outcomes following liver transplantation for Wilson's disease.

2 | Methods

This systematic review and meta-analysis are reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [10]. The study protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) a priori (CRD42023437967). This study did not require local ethics review board approval.

2.1 | Eligibility Criteria

Articles were eligible for inclusion if they were randomized controlled trials (RCTs), cohort studies, case-control studies, or case series examining any type of liver transplantation for any indication in patients diagnosed with Wilson's disease. Conference abstracts and unpublished data were eligible for inclusion. The exclusion criteria were as follows: (1) studies evaluating liver transplantation for conditions other than Wilson's Disease; (2) non-human studies; (3) systematic reviews, meta-analyses, letters to the editor, editorials, and any other study that did not report primary data. Studies were not excluded on the basis of language alone.

2.2 | Search Strategy

A comprehensive search strategy covering the period from database inception through July 2023 was conducted. Searched databases included MEDLINE, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL). The search strategy was developed in consultation with a research librarian and modified for each database accordingly. Medical Subject Headings were used when available, and search terms included "Wilson's Disease," "hepatolenticular degeneration," "Wilsonian hepatitis," "liver transplantation," and more (Table S1). The references of included studies were also searched to ensure all relevant articles were included.

2.3 | Study Selection

Two reviewers independently screened the titles and abstracts through a standardized pre-piloted form. Discrepancies that occurred at the title and abstract screening phase were resolved by inclusion of the study. Cohen's Kappa at this stage was 0.35. All included studies were then screened based on full-text review for final inclusion in the present study. At the full-text screening stage, discrepancies were resolved by consensus between the two reviewers. If disagreement persisted, a third independent reviewer was consulted. Cohen's Kappa at this stage was 0.39.

2.4 | Data Extraction

Four reviewers independently extracted data into a Microsoft Excel extraction form, which was designed a priori. Extracted data included: (1) study characteristics (e.g., author, year of publication, location, study design, inclusion/exclusion criteria); (2) patient characteristics (e.g., age, sex, body mass index [BMI]); (3) treatment characteristics (e.g., specific indication for transplant, medical management prior to transplant, surgical technique); (4) postoperative outcomes (e.g., postoperative 30-day morbidity, infection, hepatic artery thrombosis, change in neurological, and psychiatric symptoms). If a study investigated liver transplantation for a variety of conditions, including Wilson's disease, only the data pertaining to patients with Wilson's disease were included.

2.5 | Outcomes

The primary outcomes were postoperative mortality at 30 days, 1, and 5 years. This was defined as a recorded postoperative

death within the given time frame across included studies. If studies reported overall survival (OS), these data were also included. Postoperative morbidity, including biopsy-proven acute rejection, biliary strictures, primary non-function, hepatic artery thrombosis, intra-abdominal bleeding, postoperative sepsis, and changes to neurological or psychiatric symptoms were recorded as secondary outcomes. The American Association for the Study of Liver Diseases (AASLD) Practice Guidance on Wilson's Disease defines neurological clinical patterns of disease as including dysarthria, movement disorders, pseudobulbar palsy, drooling/transfer dysphagia, rigid dystonia, dysautonomia, seizures, sleep disorders, and insomnia [11]. The EASL further classifies neurological abnormalities into four categories, including akinetic-rigid syndrome, pseudosclerosis dominated by tremor, ataxia, and dystonic syndrome. Dystonia can be focal, segmental, or generalized [5]. The AASLD defines psychiatric clinical patterns of disease to include depression, bipolar disorder/bipolar spectrum, neurotic behaviors, personality changes, and psychosis [11]. The EASL definition also includes declining school performance, impulsivity, labile mood, sexual exhibitionism, and inappropriate behavior [5]. Lastly, treatment characteristics, including medical management, transplant approach, and indication for transplantation were reported as outcomes.

2.6 | Risk of Bias Analysis

The risk of bias for each included observational study was assessed using the Methodological Index for Non-Randomized Studies (MINORS) tool [12]. Two reviewers assessed the quality of each study independently. Discrepancies were discussed amongst reviewers until consensus was reached.

2.7 | Statistical Analysis

All statistical analyses will be performed on STATA version 18 (StataCorp, College, TX). Meta-analyses were performed with the "meta" package in STATA 18. The threshold for statistical significance was set a priori at a p of < 0.05 . Descriptive statistics were used to characterize the included studies. Baseline study characteristics were assessed to ensure adequate homogeneity between studies in terms of demographics, interventions, and outcomes prior to performing a meta-analysis. A logit-transformed proportion was estimated as the effect size. A restricted maximum likelihood random effects model was used to generate the pooled proportion, or weighted average of all study-level proportions, of each outcome along with their respective 95% confidence intervals (CI). Following the completion of each meta-analysis, an assessment of heterogeneity was completed by visual inspection of the forest plot as well as the inconsistency (I^2) statistic. An I^2 greater than 40% was considered to represent considerable heterogeneity [13]. A systematic narrative review was provided for each outcome.

3 | Results

3.1 | Results of the Search

The process to identify studies for inclusion is summarized in the PRISMA flow diagram in Figure 1. The bibliographic search

of MEDLINE, Embase, and Central identified 1015 publications. Of 810 studies screened, 108 were eligible for full-text screening. A total of 49 studies met all inclusion criteria; however, only 39 studies were included as the other 10 were abstracts for which a full text was already included (Table S2) [7, 8, 14–50].

3.2 | Study Characteristics

The included studies were published between 1993 and 2023. Thirty-six of the included studies were single-armed analyses, while Tang et al. compared 18 patients undergoing piggyback method hepatic transplantation with 20 patients medically managed with penicillamine [7]. Upon pooling all included studies, 3086 patients undergoing liver transplantation for Wilson's Disease were included. The majority of studies were conducted in Asia ($n = 15$) and Europe ($n = 15$), with the remainder being conducted in North America ($n = 6$), South America ($n = 1$), and both North America and Europe ($n = 1$). Detailed study characteristics are provided in Table 1.

3.3 | Treatment Characteristics

Detailed treatment characteristics are reported in Table 2. Nineteen studies reported the type of medical management used by participants. Reported chelation drugs include D-penicillamine (n studies = 14), tetrathiomolybdate (n studies = 1), zinc (in sulfate, acetate, and elemental forms) (n studies = 6), trientine (n studies = 5), or a combination of these (n studies = 6). Chelation therapy in combination with albumin dialysis was reported by Markiewicz-Kijewska et al. [14]. Specific indications for liver transplant were most commonly acute liver failure, chronic liver failure, and acute-on-chronic liver failure. Thirty-six patients across six studies were transplanted for neurological symptoms only, while one patient reported by Sutcliffe et al. was transplanted for neurological symptoms in combination with chronic liver failure and one patient was transplanted by Schilsky et al. for a GI bleed [7, 8, 27–29, 38, 41, 46]. Transplant organs were sourced from both deceased and living donors, with one study specifying the degree of relatedness between the organ donor and recipient [30]. All studies reporting surgical technique reported an orthotopic transplant technique. Surgical technique was reported according to vena cava reconstruction by Tang et al. and Yagci et al. which used the piggyback technique, while the technique was reported according to biliary reconstruction by Dal et al. which used the duct-to-duct and Roux-en-Y reconstruction techniques [7, 25, 40]. Both patients receiving full and split transplants were included in studies in this review; however, few studies specified the number of whole and partial liver transplants, and no studies analyzed the outcomes of transplantation according to this parameter.

3.4 | Postoperative Mortality

Detailed postoperative mortality and morbidity data are reported in Table 3. Twenty-one studies reported 30-day mortality. The pooled proportion of 30-day mortality was 0.10 (95% CI 0.08, 0.13, $I^2 = 15.56\%$) (Figure 2). Twenty-five studies reported 1-year mortality. A pooled proportion of 1-year mortality was 0.11 (95% CI

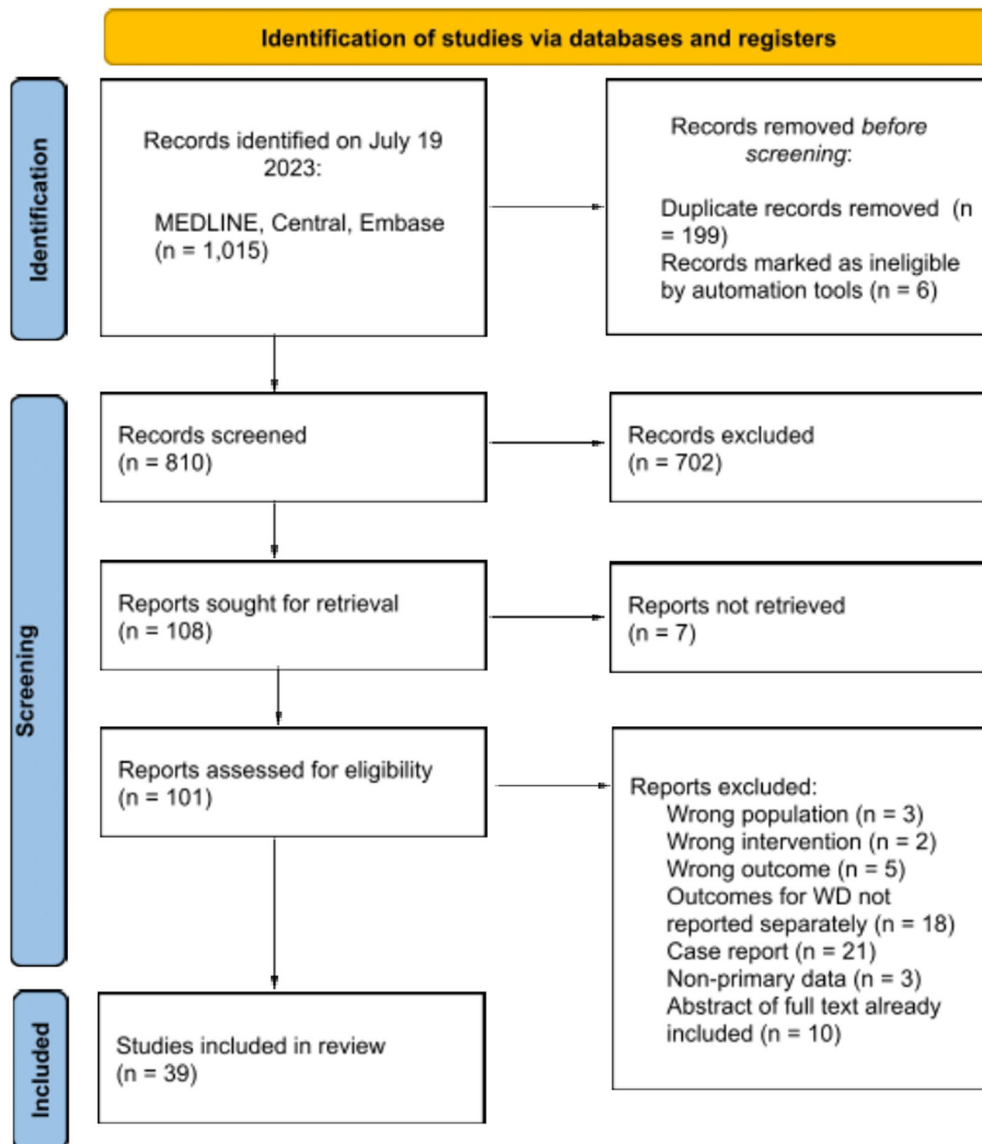


FIGURE 1 | PRISMA diagram—Transparent reporting of systematic reviews and meta-analysis flow diagram outlining the search strategy results from initial search to included studies.

0.09, 0.14, $I^2 = 37.41\%$) (Figure 3). Twenty-one studies reported on 5-year mortality. A pooled proportion of 5-year mortality was 0.15 (95% CI 0.11, 0.20, $I^2 = 81.46\%$) (Figure 4). Medici et al. reported the highest proportion of postoperative mortality at 5 years at 0.43 (95% CI 0.28, 0.59) [31]. This study followed 37 adult patients who underwent orthotopic liver transplantation for Wilson's disease. The authors concluded that patients with neuropsychiatric symptoms have significantly shorter survival even though liver transplantation had a positive impact on neurological symptoms. The mean OS of patients with neuropsychiatric symptoms was 79 months, compared with 135 months in patients with hepatic symptoms only in their study. The only comparative study that was conducted by Tang et al. found a range in length of survival between 11 months to 6.5 years, with three acute deaths due to postoperative infection in the transplant group. The nonoperative group was managed with penicillamine and supportive treatment for 1–5 years, resulting in four deaths throughout the entire length of follow-up [7].

3.5 | Postoperative Morbidity

The most frequently reported postoperative complications by number of studies were postoperative sepsis ($n = 25/39$), hepatic artery thrombosis ($n = 17/39$), biliary strictures ($n = 14/39$), biopsy-proven acute rejection ($n = 13/39$), primary nonfunction ($n = 12/39$), and intra-abdominal bleeding ($n = 7/39$). The pooled proportion of biopsy-proven acute rejection was 0.20 (95% CI 0.12, 0.31, $I^2 = 83.70\%$) (Figure 5). The largest included ($n = 121$) study reporting biopsy-prove acute rejection by Guillaud et al. found a particularly high proportion of 0.42 (95% CI 0.35, 0.51) [38]. All patients experiencing biopsy-proven acute rejection were treated successfully by increasing the basal immunosuppressive regimen or administering corticosteroid boluses [38]. The pooled proportion of biliary strictures was 0.09 (95% CI 0.07, 0.13, $I^2 = 0\%$), primary non-function was 0.06 (95% CI 0.04, 0.09, $I^2 = 0\%$), hepatic artery thrombosis was 0.06 (95% CI 0.04, 0.08, $I^2 = 0\%$), postoperative intra-abdominal bleeding was 0.09 (95% CI 0.05,

TABLE 1 | Demographic data of included studies.

	Country	Setting	Study design	Study period	Patients with WD (n)	Age (mean years [SD])	Male n (%)	BMI (mean kg/m ² [SD])
Aksoy 2022	Turkey	—	Retrospective observational	2007–2020	24	34	45.8%	—
Al-Hilou 2012	United Kingdom	—	Retrospective observational	1987–2011	21	NA	NA	—
Arnon 2011	United States + Canada	—	Retrospective observational	1987–2008	572	Children: 14.38 +/- 3.29 Adults: 31.72 +/- 10.69	42.7%	Children FHF: 22.16 (4.51) Children CLF 20.62 (3.78) Adults FHF 26.94 (5.60) Adults CLF 26.50 (4.51)
Cheng 2009	China	Tertiary care	Retrospective observational	2001–2007	36	NA	22.2%	21.84
Choudhary 2018	India	Tertiary care	Retrospective observational	—	18	32.44 (10.84)	83.3%	—
Couchonnal 2021	France	Secondary and tertiary care	Mixed retrospective + prospective observational	1995–2019	182	10.7 (4.2)	50%	—
Dal 2021	Turkey	Tertiary care	Prospective observational	2006–2020	27	20.8 (11.1)	59.3%	20.50 (3.2)
Eghtesad 1999	USA	Tertiary care	Retrospective analysis	1971–1993	45	22.3 (9.4)	42.2%	—
Emre 2001	USA	Tertiary care	Retrospective observational	1998–2000	17	28 (14.8)	53%	—
Ferrarese 2020	Italy	Tertiary care	Retrospective observational	2006–2016	27	—	33.3%	—
Guillaud 2014	France	Tertiary care	Retrospective observational	1985–2009	121	—	41%	—
Ismail 2020	United States + Canada	—	Retrospective observational	1987–2016	671	—	45.9%	Adult: 26.0 (range 15.5–52.9) Pediatric: 20.9 (range 13.4–33.2)
Jozwik 2019	Poland	Tertiary care	Retrospective observational	2000–2018	25	—	—	—
Kasahara 2014	Japan	—	Retrospective observational	1989–2010	59	—	—	—
Lai 2013	USA	Tertiary care	Retrospective review	1988–2007	22	23.7 (15.6)	—	—
Lankarani 2016	Iran	Tertiary care	Retrospective observational	2000–2014	107	—	59.8%	—
Mainardi 2019	Uruguay	Tertiary care	Retrospective, descriptive	2009–2017	6	18	0%	—
Markiewicz-Kijewska 2008	Poland	Tertiary care	Retrospective observational	1999–2007	13	15.5	8.3%	—
Martin 2008	Germany	Tertiary care	Retrospective observational	1993–2006	11	29.7	54.5%	—

(Continues)

TABLE 1 | (Continued)

	Country	Setting	Study design	Study period	Patients with WD (n)	Age (mean years [SD])	Male n (%)	BMI (mean kg/m ² [SD])
Martinez-Camacho 2009	USA	Tertiary care	Retrospective observational	1995–2007	315	—	—	—
Medici 2005	Italy	Tertiary care	Retrospective observational	1985–2000	37	27.5 (9.8)	54.1%	—
Ocal 2020	Turkey	Tertiary care	Retrospective observational	—	15	35.2	80%	—
Ocal 2018	Turkey	Tertiary care	Retrospective observational	2005–2017	19	26	73.7%	—
Pabon 2008	France	Tertiary care	Retrospective observational	1987–2006	13	20	38.5%	—
Poujois 2020	France	—	Retrospective observational	1994–2016	18	—	55.6%	—
Pratschke 1998	Germany	—	Retrospective observational	1988–1997	14	—	—	—
Rela 1993	United Kingdom	—	Retrospective observational	1988–1992	12	—	33.3%	—
Sarici 2023	Turkey	Tertiary care	Retrospective observational	2002–2018	23	13	52.2%	—
Schilsky 1994	United States + Europe	Tertiary care	Retrospective observational	—	55	23.1 (10.1)	41.8%	—
Sevmis 2008	Turkey	—	Retrospective observational	2001–2007	24	15.6 (9.9)	70.8%	—
Soy 2018	Turkey	Tertiary care	Retrospective observational	1988–2017	53	—	—	—
Stankiewicz 2021	Poland	Tertiary care	Prospective observational	2001–2017	20	—	15%	—
Sutcliffe 2003	United Kingdom	Tertiary care	Prospective observational	1988–2000	24	—	25%	—
Tamura 2005	Japan	Tertiary care	Retrospective observational	1996–2004	5	—	60%	—
Tang 2002	Wuhan	Tertiary care	Cohort study	—	18 (LT) 20 (Control)	—	72.2% (LT) 30% (Control)	—
Weiss 2013	Germany	Tertiary care	Prospective observational	1987–2010	19	29.3 (14.1)	31.6%	—
Yagci 2015	Turkey	Tertiary care	Retrospective observational	2002–2014	9	—	77.8%	19.8 (range 15.1–30.8)
Yoshitoshi 2009	Japan	Tertiary care	Retrospective observational	1992–2006	32	16 (3.9)	46.9%	—
Yu 2013	China	Tertiary care	Retrospective analysis	2005–2010	9	24.5	44.4%	—

TABLE 2 | Pre-operative data of patients included in individual included studies.

	Primary presentation (<i>n</i>)				MELD/PELD score	Child-Pugh score	Specific indications (n ALF, CLF, neurological)	ALT (IU/L)	AST (IU/L)	Total bilirubin (μmol/L)	INR
	Medical management (n [%])	Neurological, Mixed [%]	Hepatic, [%]								
Aksoy 2022	Chelators, Zinc salts	Mixed (24/24 [100%])			24.9 (range 15–41)	—	CLF: 24/24	—	90.5 (range 26–341; ± 77.5)	171 (range 10.26–607.05, ± 184.68)	11 (range 1–6.8, ± 10.8)
Al-Hilou 2012	—	Hepatic (11/21 [52.38%]) Mixed (10/21 [47.61%])			—	—	ALF: 11/21 CLF: 9/21	—	—	—	—
Arnon 2011	—	—		Adult: 24 Pediatric: 22	—	—	—	Children ALF 108.69 ± 87.36 Children CLF 138.38 ± 70.91 Adult ALF 168.05 ± 185.14 Adult CLF 90.72 ± 103.97	—	Children ALF 21.27 ± 17.40 Children CLF 5.55 ± 5.23 Adult ALF 32.20 ± 19.99 Adult CLF 11.36 ± 12.23	Children ALF 2.99 ± 1.68 Children CLF 2.32 ± 1.19 Adult ALF 3.27 ± 1.63 Adult CLF 2.26 ± 1.21
Cheng 2009	—	Hepatic (21/36 [58.44%]) Mixed (15/36 [41.67%])		</= 10 (<i>n</i> = 4) 11–20 (<i>n</i> = 15) 21–30 (<i>n</i> = 13) > / = 30 (<i>n</i> = 2)	—	A: 2/36 B: 14/36 C: 18/36	ALF: 2/36 CLF: 34/36	—	—	—	—
Choudhary 2018	Zinc and D-penicillamine (17/18 [94.4%])	Hepatic (15/18 [83.33%]) Mixed (3/18 [16.67%])		18 ± 6	—	10 ± 2	ALF: 1/18 A on CLF: 1/18 ^b CLF: 16/18	—	—	51.3 (range 35.91–124.83)	1.56 (range 1.36–2.07)
Couchonnal 2021	D-penicillamine (131/132 [99.2%]) Zinc (24/132 [18.2%]) Trientine (17/132 [12.9%])	Neurological (19/182 [23.17%]) Hepatic (154/182 [84.62%]) Asymptomatic (9/182 [4.95%])		—	—	—	ALF: 26/182 CLF: 7/182 Neurological: 6/182	147.16	144.51	—	—
Dal 2021	—	Hepatic (23/27 [85.19%]) Mixed (4/27 [14.81%])		Adult: 16.5 +/- 6.3 Peds: 19.6 +/- 17.2	—	—	ALF: 5/27 CLF: 22/27	—	—	—	—

(Continues)

TABLE 2 | (Continued)

	Medical management (n [%])	Primary presentation (n Hepatic, Neurological, Mixed [%])	MELD/PELD score	Child-Pugh score	Specific indications (n ALF, CLF, neurological)	ALT (IU/L)	AST (IU/L)	Total bilirubin (μmol/L)	INR
Eghtesad 1999	D-penicillamine (27/45 [60%]) Data not available (5/45 [11.1%])	Hepatic (28/45 [62.22%]) Mixed (17/45 [37.78%])	—	—	ALF: 30/45 CLF: 15/45	—	—	—	—
Emre 2001	D-penicillamine (3/17 [17.6%])	Hepatic (17/17 [100%])	—	—	ALF: 11/17 CLF: 6/17	110.2 (15–397)	257.6 (26–871)	32.5 (6.1–70)	2.5 (1.27–7.37) ^c
Ferrarese 2020	D-penicillamine (13/27 [52%]) Zinc sulfate (5/27 [20%]) No medical mgmt (5/27 [20%])	Hepatic (17/27 [63%]) Neurological (2/27 [7%]) Mixed (8/27 [29.63%])	27 (range 6–49)	11 (range 5–15)	ALF: 17/27 CLF with neurological symptoms: 8/27 Neurological: 2/27	49 (10–358)	84 (22–337)	153 (10–932)	2.4 (0.8–7.1)
Guillaud 2014	No chelation therapy (28/114 [24.6%]) D-penicillamine only (10/114 [1]) D-penicillamine and zinc sulfate (11/114 [1]) Trientine monotherapy (9/114 [1]) 1/59: Trientine and zinc sulfate (5/114 [1])	Hepatic (114/121 [94.2%]) Neurological (7/121 [5.8%])	29 (range 6–40)	12 (range 5–15)	ALF: 64/121 CLF: 50/121 Neurological: 7/121	45 (3–1343)	101 (10–1774)	144 (4–1469)	3.4 (1–12.7)
Ismail 2020	—	Hepatic (671/671 [100%])	</ = 14: 29 >/ = 15: 372 Unreported: 270	—	ALF: 267/671 CLF: 404/671	—	—	—	—
Jozwik 2019	—	—	—	—	—	—	—	—	—
Kasahara 2014	D-penicillamine, trientine, Zinc sulfate, Ammonium tetrathiomolybdate	Hepatic (59/59 [100%])	—	—	ALF: 17/59 CLF: 42/59	—	—	—	—

(Continues)

TABLE 2 | (Continued)

	Primary presentation (n)		MELD/PELD score	Child-Pugh score	Specific indications (n ALF, CLF, neurological)	ALT (IU/L)	AST (IU/L)	Total bilirubin (μmol/L)	INR
	Medical management (n [%])	Hepatic, Neurological, Mixed [%]							
Lai 2013	—	—	—	—	—	—	—	—	—
Lankarani 2016	D- penicillamine, tetrathiomolybdate, trientine and zinc salts	Hepatic (107/107 [100%])	Acute: 20.5 (IQR 12.5–40) Chronic: 20 (IQR 17.7–24)	—	ALF: 21/107 CLF: 86/107	Acute: 7 (IQR 47–237) Chronic: 63.5 (IQR 32–135)	Acute: 145 (IQR 89–240) Chronic: 77.5 (IQR 2.4–9.6)	Acute: 119.7 (IQR 4.3–10) Chronic: 4.9 (IQR 1.6–3.07)	Acute: 5.7 (IQR 2.7–6.5) Chronic: 1.9 (IQR 1.6–3.07)
Mainardi 2019	D-penicillamine	—	36 (range 20–49)	—	ALF: 6/6	51 (range 15–119)	156 (range 83–250)	460.25	4.2 (range 2–7)
Markiewicz-Kijewska 2008	Chelation therapy and albumin dialysis (1/13 [7.7%])	Hepatic (13/13 [100%])	38 (range 21–58)	—	—	190.2 (range 59–503)	268.5 (range 66–763)	42.24 (range 4.5–71.6) mg/dl	5.4 (range 2.9–10.0)
Martin 2008	D-penicillamine and zinc (11/11 [100%])	Mixed (11/11 [100%])	—	A: 1/11 B: 4/11 C: 3/11 Unspecified: 3/11	—	—	—	—	—
Martinez-Camacho 2009	—	Hepatic (315/315 [100%])	—	—	ALF: 3/11 CLF: 6/11 Acute on chronic: 2/11	—	—	—	—
Medici 2005	—	Hepatic (27/37 [72.97%]) Mixed (6/37 [16.22%]) Data not available (4/37 [10.81%])	—	B: 13/37 C: 18/37 Unspecified: 6/37	ALF: 8/37 CLF: 29/37	ALF: 356.6 ± 637 CLF: 57.2 ± 46	ALF: 433.6 ± 773.5 CLF: 67.6 ± 39.7	ALF: 307.8 ± 241.11 CLF: 104.31 ± 123.12	—
Ocal 2020	—	—	—	—	—	—	—	—	—
Ocal 2018	—	Hepatic (19/19 [100%])	—	—	—	—	—	—	—
Pabon 2008	D-penicillamine (7/13 [53.8%]) Trientine (1/13 [7.7%]) No medical treatment (5/13 [38.5%])	Hepatic (12/13 [92.3%]) Mixed (1/13 [7.7%])	—	—	ALF: 4/13 CLF: 9/13	352	596	253	—

(Continues)

TABLE 2 | (Continued)

	Medical management (n [%])	Primary presentation (n [%])		MELD/PELD score	Child-Pugh score	Specific indications (n ALF, CLF, neurological)	ALT (IU/L)	AST (IU/L)	Total bilirubin (μmol/L)	INR
		Hepatic, Neurological, Mixed	Hepatic, Neurological, Mixed							
Poujois 2020	Trientine (12/18 [66.7%]) D-penicillamine (15/18 [83.3%]) Zinc acetate (8/18 [44.4%])	Neurological (13/18 [72.22%]) Hepatic ^a (5/18 [27.78%])	Neurological (4/14 [28.57%]) Hepatic (10/14 [71.43%])	8.5 (range 7–10.8)	A: 17/18 B: 1/18 C: 7/14 not specified: 7/14	Neurological: 18/18 ALF: 3/14 CLF: 7/14 Neurological: 4/14	—	—	—	—
Pratschke 1998	—	Neurological (4/14 [28.57%]) Hepatic (10/14 [71.43%])	Neurological (4/14 [28.57%]) Hepatic (10/14 [71.43%])	—	—	—	—	—	—	—
Rela 1993	D-penicillamine (8/12 [66.7%])	Hepatic (11/12 [91.67%]) Mixed (1/12 [8.33%])	Hepatic (11/12 [91.67%]) Mixed (1/12 [8.33%])	—	—	ALF: 10/12 CLF: 2/12	—	140	257	3.00
Sarici 2023	Zinc plus either Trientine or D-penicillamine (23/23 [100%])	Hepatic (13/23 [56.6%]) Mixed (10/23 [43.4%])	Hepatic (13/23 [56.6%]) Mixed (10/23 [43.4%])	19 (range 8–34)	A: 2/23 B: 9/23 C: 12/23	ALF: 3/23 CLF: 20/23	—	740 (range 92–3710)	3.9 (range 0.3–34.7)	1.9 (range 0.3–34.7)
Schilsky 1994	—	—	—	—	—	ALF: 21/55 CLF: 32/55 Neurological: 1/55 GI bleed: 1/55	—	—	35 mg/dl	—
Sevmis 2008	D-penicillamine (17/18 [94.4%])	—	—	—	B: 7/18 C: 11/18	ALF: 6/55 CLF: 18/24	—	—	36.2 ± 12.7	4.17 ± 0.79 ^c
Soy 2018	—	Neurological (5/53 [9.43%]) Hepatic (48/53 [90.57%])	Neurological (5/53 [9.43%]) Hepatic (48/53 [90.57%])	—	—	—	—	—	—	—
Stankiewicz 2021	—	Hepatic (20/20 [100%])	Hepatic (20/20 [100%])	36.1 +/- 8.4	—	ALF: 20/20	134 ± 300	240 ± 210	35.31 ± 14.25	4.12 ± 2.16

(Continues)

TABLE 2 | (Continued)

	Medical management (n [%])	Primary presentation (n Hepatic, Neurological, Mixed [%])	MELD/PELD score	Child-Pugh score	Specific indications (n ALF, CLF, neurological)	ALT (IU/L)	AST (IU/L)	Total bilirubin (μmol/L)	INR
Sutcliffe 2003	—	Hepatic (23/24 [95.84%]) Mixed (1/24 [4.17%])	—	—	ALF: 15/24 Subacute LF: 3/24 CLF: 6/24 CLF/Neurological: 1	—	—	—	—
Tamura 2005	—	Hepatic (4/5 [80%]) Mixed (1/5 [20%])	—	B: 2/5 C: 1/5 Unspecified: 2/5	ALF: 1/5 CLF/Neurological: 1/5 CLF: 3/5	—	—	—	—
Tang 2002	D-penicillamine (20/38 [52.6%])	Neurological (38/38 [100%])	—	—	Neurological: 38/38	—	—	—	—
Weiss 2013	D-penicillamine (7/19 [64%]) Zinc (3/19 [27%]) Trientine (1/19 [9%])	Hepatic (15/19 [78.94%]) Mixed (4/19 [21.05%])	26.4 +/- 9.1	A: 4/19 B: 7/19 C: 8/19	ALF: 8/19 CLF: 11/19	HFH: 97.7 ± 87.8 CLF: 125.6 ± 117.3	HFH: 209.0 ± 94.6 CLF: 269.0 ± 371.8	HFH: 24.1 ± 15.6 CLF: 18.5 ± 20.1	HFH: 2.32 ± 1.16 CLF: 2.05 ± 1.09
Yagci 2015	—	Mixed (9/9 [100%])	18.3 (range 15–26)	8.9 (range 6–12)	—	—	—	—	—
Yoshitoshi 2009	D-penicillamine, trientine or zinc (29/32 [90.6%])	Hepatic (32/32 [100%])	31.3 +/- 9.2	—	ALF: 21/32 CLF: 11/32	—	—	—	—
Yu 2013	—	—	—	A: 5/9 B: 2/9 C: 2/9	—	134.00 ± 137.97	189.38 ± 208.33	55.96 ± 33.57	—

Abbreviations: ALF, acute liver failure; ALT, alanine transaminase; AST, aspartate transaminase; CLF, chronic liver failure; INR, international normalized ratio; MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease.

^aProgressed to mixed after discontinuation of treatment.

^bAcute on chronic presentation due to anti-tubercular therapy.

^cStudy provided PT, INR calculated using 12.5 s as normal PT.

TABLE 3 | Post-operative mortality and morbidity proportions in individual included studies.

	Mortality at 30 days	Mortality at 1 year ^a	Mortality at longest ^a	Early graft failure	Biopsy-proven acute rejection	Biliary strictures	Primary nonfunction	Hepatic artery thrombosis	Intra abdominal bleeding	Sepsis/infection
Aksoy 2022	1/24 (4.17%)	—	—	—	—	3/24 (12.5%)	—	1/24 (4.2%)	1/24 (4.2%)	COVID-19:2/24 (8.3%)
Al-Hilou 2012	0/21 (0.00%)	1/21 (4.76%)	>10 years: 4/21 (19.05%)	10% at 1 year, 19% at 5 years	—	2/21 (9.5%)	—	2/21 (9.5%)	4/21 (19.0%)	—
Arnon 2011	Children ALF 10% Children CLF 0% Adult ALF 9.7% Adult CLF 3.6%	Children ALF 10% Children CLF 0% Adult ALF 9.7% Adult CLF 5.3%	5 years: Children ALF 12.5% Children CLF 0% Adult ALF 10.3% Adult CLF 9.9%	Children ALF 21 (12.5%) Children CLF 0 (0%) Adult ALF 50 (12.1%) Adult CLF 22 (5.5%)	—	—	—	—	—	Sepsis: 2/572 (0.3%)
Cheng 2009	—	9.30%	5 years: 25%	—	1/36 (2.8%)	2/36 (5.6%)	2/36 (5.6%)	—	—	Intra-abdominal abscess: 1/36 (2.8%) Bacterial pneumonia: 1/36 (2.8%) CMV: 1/36 (2.8%) Fungal infection: 1/36 (2.8%) Pulmonary tuberculosis: 1/36 (2.8%)
Choudhary 2018	—	—	—	—	2/18 (11.1%)	2/18 (11.1%)	—	1/18 (5.6%)	—	Culture-positive infection: 4/18 (22.2%) Sepsis: 2/18 (11.1%)
Couchonnal 2021	—	—	2/39 (5.13%)	—	—	—	—	—	—	—
Dal 2021	3/27 (11.11%)	11.60%	15.80%	1/27 (3.7%)	—	—	1/27 (3.7%)	1/27 (3.7%)	2/27 (7.4%)	Sepsis: 1/27 (3.7%)

(Continues)

TABLE 3 | (Continued)

	Mortality at 30 days	Mortality at 1 year ^a	Mortality at longest ^a	Early graft failure	Biopsy-proven acute rejection	Biliary strictures	Primary nonfunction	Hepatic artery thrombosis	Intra abdominal bleeding	Sepsis/ infection
Eghtesad 1999	10/14 (71.4%)	12/14 (85.7%)	9 years: 14/14 (100%)	1/14 (7.1%)	0/14 (0.00%)	0/14 (0.00%)	6/14 (42.9%) ALF: 4/14 CLF: 2/14	1/14 (7.1%)	2/14 (14.3%)	Intraabdominal abscess: 1/14 (7.1%) Sepsis: 7/14 (50%) Pneumonia: 2/14 (14.3%)
Emre 2001	—	12.5%	—	—	2/17 (11.8%)	—	2/17 (11.8%)	—	—	Bacterial and fungal infections: 4/17 (23.5%) Sepsis: 1/17 (5.9%) Tuberculosis: 1/17 (5.9%)
Ferrarese 2020	—	12%	5 years: 17%	—	4/27 (14.8%)	3/27 (11.1%)	1/27 (3.7%)	1/27 (3.7%)	—	10/27 (37.0%)
Guillaud 2014	12/121 (9.92%)	14/121 (11.57%)	15/121 (12.40%)	—	51/121 (42.1%)	14/121 (11.6%)	3/121 (2.5%)	9/121 (7.4%)	—	Sepsis: 8/121 (6.6%)
Ismail 2020	—	Pediatric: 8.00% Adult: 8.8%	Pediatric, 10 years: 13.50% Adult, 10 years: 19.50%	—	—	—	—	—	—	—
Jozwik 2019	1/25 (4.00%)	8.00%	10 years: 8.00%	—	—	—	—	1/25 (4.0%)	—	1/25 (4.0%)
Kasahara 2014	—	1.60%	15 years: 12.50%	—	7/59 (11.90%)	1/59 (1.7%)	—	1/59 (1.7%)	—	—
Lai 2013	—	9.10%	5 years: 11.10%	—	—	—	—	—	—	—
Lankarani 2016	13/107 (12.14%)	14.00%	5 years: 18.00%	—	32/107 (30%)	—	—	2/107 (1.9%)	—	—
Mainardi 2019	1/6 (16.67%)	1/6 (16.67%)	1/6 (16.67%)	—	—	—	—	—	—	—
Markiewicz-Kijewska 2008	2/13 (15.38%)	—	—	—	—	—	1/13 (7.7%)	—	—	Sepsis: 1/13 (7.7%)

(Continues)

TABLE 3 | (Continued)

	Mortality at 30 days	Mortality at 1 year ^a	Mortality at longest ^a	Early graft failure	Biopsy-proven acute rejection	Biliary strictures	Primary nonfunction	Hepatic artery thrombosis	Intra abdominal bleeding	Sepsis/infection
Martin 2008	—	—	—	—	—	2/11 (18.2%)	—	1/11 (9.1%)	—	—
Martinez-Camacho 2009	—	10.60%	5 years: 14.90%	—	—	—	—	—	—	—
Medici 2005	—	10.90%	10 years: 42.20%	—	17/37 (45.9%)	—	1/37 (2.7%)	—	—	Sepsis: 5/37 (13.5%) Hepatitis C: 1/37 (2.7%)
Ocal 2020	—	—	—	—	—	—	—	—	—	—
Ocal 2018	—	—	—	—	—	—	—	—	—	—
Pabon 2008	0.00%	0.00%	—	—	2/13 (15.4%)	—	—	—	—	—
Poujois 2020	—	11.20%	5 years: 27.8%	—	—	—	—	—	—	Sepsis: 4/13 (30.8%)
Pratschke 1998	0.00%	—	—	0.00%	—	—	—	—	—	—
Rela 1993	—	—	—	—	6/12 (50%)	1/12 (8.3%)	—	1/12 (8.3%)	2/12 (16.6%)	Liver abscess: 1/12 (8.3%) Sepsis leading to death: 2/12 (16.7%) Bacterial sepsis: 3/12 (25%) Fungal sepsis: 2/12 (16.7%) CMV hepatitis: 1/12 (8.3%) Wound infection: 3/12 (25%)
Sarici 2023	—	13.0%	5 years: 46.0%	1/23 (4.3%)	—	7/23 (30.0%)	1/23 (4.3%)	2/23 (8.9%)	1/23 (4.3%)	Sepsis: 1/23 (4.3%) Pneumonia: 2/23 (8.9%)

(Continues)

TABLE 3 | (Continued)

	Mortality at 30 days	Mortality at 1 year ^a	Mortality at longest ^a	Early graft failure	Biopsy-proven acute rejection	Biliary strictures	Primary nonfunction	Hepatic artery thrombosis	Intra abdominal bleeding	Sepsis/infection
Schilsky 1994	—	21.0%	—	—	—	—	—	—	—	Pneumonia: 1/55 (1.8%) Sepsis: 1/55 (1.8%) Sepsis: 2/24 (8.3%)
Sevmis 2008	—	—	—	—	—	—	1/24 (4.20%)	—	—	—
Soy 2018	6/53 (11.32%)	—	—	—	—	—	1/53 (1.90%)	—	—	—
Stankiewicz 2021	3/20 (15.00%)	5/20 (25.00%)	—	—	—	—	1/20 (5.00%)	1/20 (5%)	—	—
Sutcliffe 2003	1/24 (4.17%)	2/24 (8.33%)	—	—	9/24 (37.5%)	3/24 (12.5%)	—	2/24 (8.3%)	2/24 (8.3%)	—
Tamura 2005	0/5 (0.00%)	1/5 (20.00%)	—	1/5 (20%)	—	—	—	1/5 (20%)	—	Abscess: 1/5 (20%) CMV: 1/5 (20%) Cholangitis: 1/5 (20%)
Tang 2002	3/38 (7.89%)	—	—	—	—	—	—	—	—	—
Weiss 2013	3/19 (15.70%)	1/19 (5.30%)	5 years: 1/19 (5.3%)	—	—	—	1/19 (5.3%)	—	—	—
Yagci 2015	—	—	—	1/9 (11.1%)	—	1/9 (11.1%)	—	1/9 (11.1%)	—	—
Yoshitoshi 2009	1/32 (3.13%)	2/32 (6.25%)	2/32 (6.25%)	—	2/32 (6.3%)	1/32 (3.1%)	—	—	1/32 (3.1%)	1/32 (3.1%)
Yu 2013	0/9 (0.00%)	0/9 (0.00%)	0/9 (0.00%)	—	—	—	—	—	—	—

Abbreviations: ALF, acute liver failure; CLF, chronic liver failure.

^aCumulative mortality.

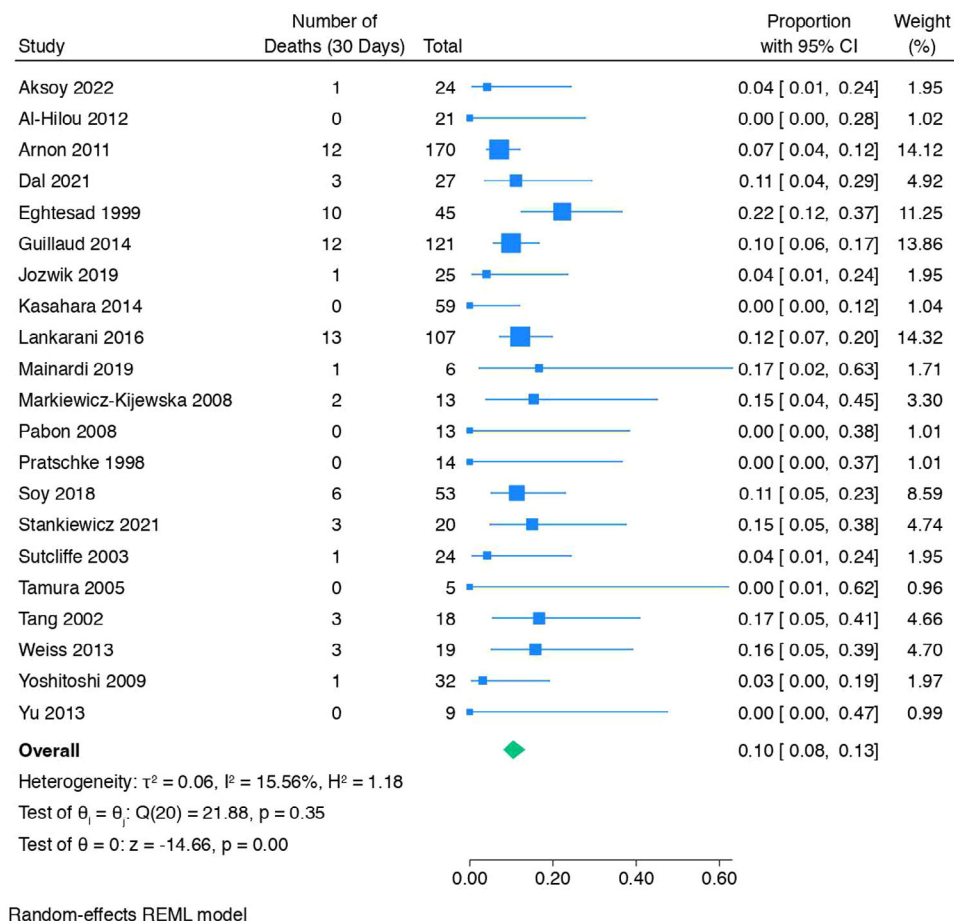


FIGURE 2 | 30-day mortality—Random effects by restricted maximum likelihood meta-analysis of outcome using data from observational studies.

0.15, $I^2 = 14.86\%$), and sepsis was 0.11 (95% CI 0.06, 0.18, $I^2 = 83.97\%$) (Figures S1–S5).

3.6 | Neurological and Psychiatric Outcomes

Twenty-two studies reported on neurological or psychiatric outcomes after hepatic transplant (Table 4). General improvement was assessed using the Mini-Mental status examination (n studies = 1), Unified Wilson's Disease Rating Scale (n studies = 2), a study-specific patient questionnaire (n studies = 3), scoring systems taken from another study (n studies = 1), and general author observation ($n = 15$ studies). Twenty-two studies reported on the number of patients who experienced improvement, with the pooled proportion of improvement being 0.56 (95% CI 0.45, 0.66, $I^2 = 82.28\%$) (Figure 6). Improvement was defined broadly as any degree of improvement in symptoms, not necessitating a return to baseline. The variation in the proportion of improvement between studies varied between 0.20 reported by Ferrarese et al. and Yu et al. and 1.00 reported by Martin et al., Pratschke et al., and Soy et al. [18, 20, 28, 33, 41]. Emre et al. reported on the new onset of seizures due to tacrolimus toxicity, potentially indicating iatrogenic cases of neurological symptoms as a result of hepatic transplantation [44]. The comparative study by Tang et al. reported that 13 out of 15 patients had resolution of neurological symptoms after transplantation, as compared to 3 out of 8 treated medically [7].

3.7 | Risk of Bias

The mean MINORS score for single-armed studies was 8.33 (SD: 2.14, range: 4–12) (Table 5). Tang et al. was the only comparative study and had a MINORS score of 9 out of 24 [7]. Studies scored highest in Domain 1 - Clearly stated aim (mean 1.8), and lowest in Domain 8 - Prospective calculation of study size (mean 0). Follow-up was deemed inadequate for primary outcome assessment in two of the included studies [23, 42]. Full MINORS score breakdowns for all included studies are shown in Table 5.

4 | Discussion

This was the first systematic review and meta-analysis of the postoperative mortality, morbidity, and neuropsychiatric outcomes of liver transplantation for Wilson's Disease. This study synthesizes the mortality rates at 30 days, 1, and 5 years, indicating that the greatest proportion of postoperative deaths occur within the first 30 days. A previous systematic review about liver transplant for Wilson's Disease in a mixed adult and pediatric population performed by Turgut et al. reports a pooled survival rates for 1 year of 84.7%, and 2-, 3-, 5- and 10-year success rates of 82%, 81%, 81%, and 80%, respectively [9]. This supports the finding that the majority of postoperative mortality occurs in the shortest period of follow-up, with subsequent years of follow-up contributing less to overall mortality rates. The reporting of postoperative

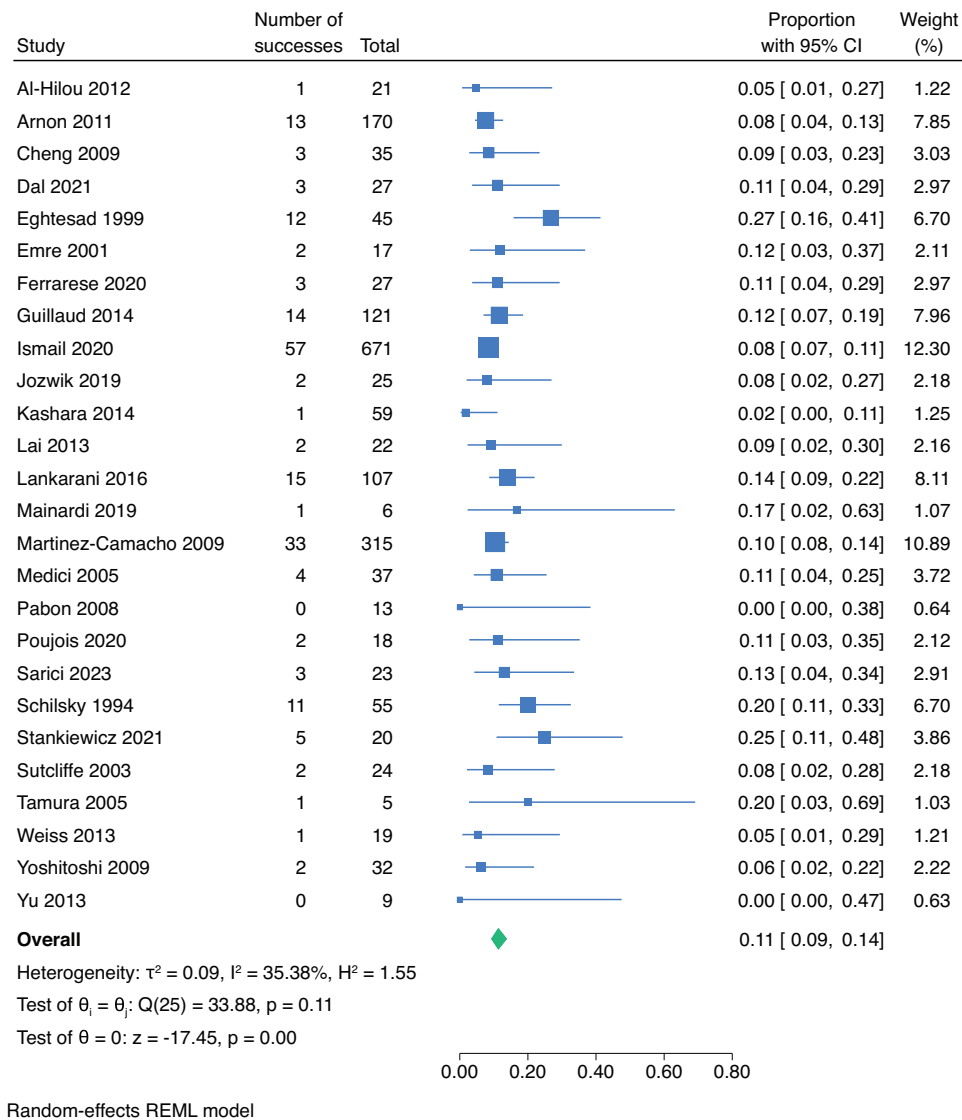


FIGURE 3 | One-year mortality—Random effects by restricted maximum likelihood meta-analysis of outcome using data from observational studies.

morbidity outcomes across studies was heterogeneous, with I^2 values ranging from 0% to 83.97%. Apart from sepsis, which was reported by 64.1% of the included studies, less than half of the included studies reported on each of these outcomes. A small number of included studies in these meta-analyses led to wide 95% CIs for morbidity outcomes of sepsis and primary nonfunction. Thus, despite point estimates suggesting low prevalences of these outcomes, the Type II error risk associated with the wide 95% CIs suggests that significant uncertainty remains. The overall improvement in neurological symptoms in this systematic review was high, with a pooled proportion of 0.56 (95% CIs 0.45, 0.66). The same study by Turgut et al. reported a 74.2% improvement in neurological complications, calculated by percent change in number of patients experiencing symptoms before and after transplantation [9].

A systematic review and meta-analysis investigating liver transplant for acute-on-chronic liver failure and chronic liver failure for various causes including alcohol-related liver disease, hepatitis B, hepatitis C, non-alcoholic fatty liver disease, and hepatocel-

lular carcinoma found a 30 day survival rate of 96.2% in acute on chronic live failure and 98.1% in chronic liver failure. The 1- and 5-year survival rates were 86.0% and 66.9% in acute on chronic liver failure and 91.9% and 80.7% in chronic liver failure, respectively. Compared to the results of the present study, a lower 30-day but a higher 5-year survival rate is seen in patients receiving liver transplants for Wilson's disease. This again supports the trend that the greatest proportion of postoperative deaths in this patient population occurred within the acute period [51].

Several included studies reported an inability to assess neurological and psychiatric symptoms posttransplantation due to patient death from infectious or acute causes. Yoshitoshi et al. reported on one case of a patient with ataxia who could not be reassessed for improvement due to death on post-operative day 14 due to variceal bleeding [35]. As this study reported on neurological outcomes in only four patients, the censoring of data due to patient death could introduce survival bias as patients who are less stable and thus have poorer prognosis are not included in the final analysis of outcomes [52]. Additionally, the same study also reported one

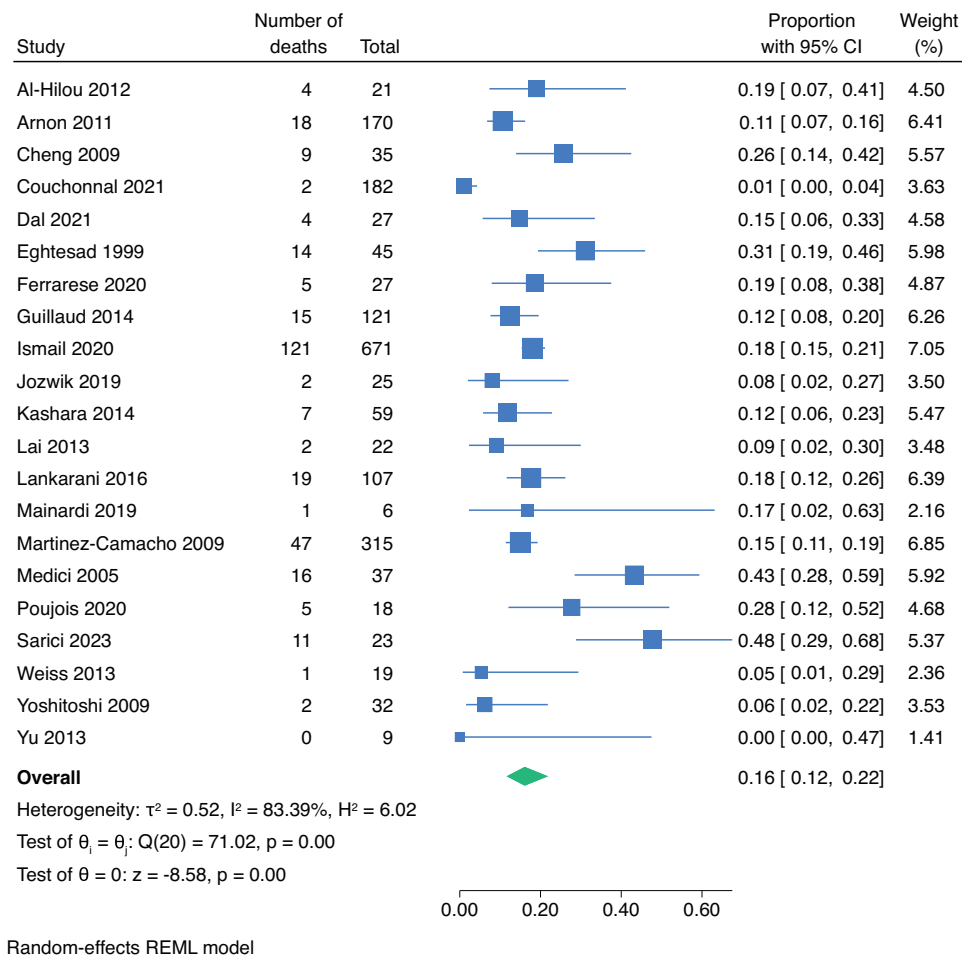


FIGURE 4 | Five-year mortality—Random effects by restricted maximum likelihood meta-analysis of outcome using data from observational studies.

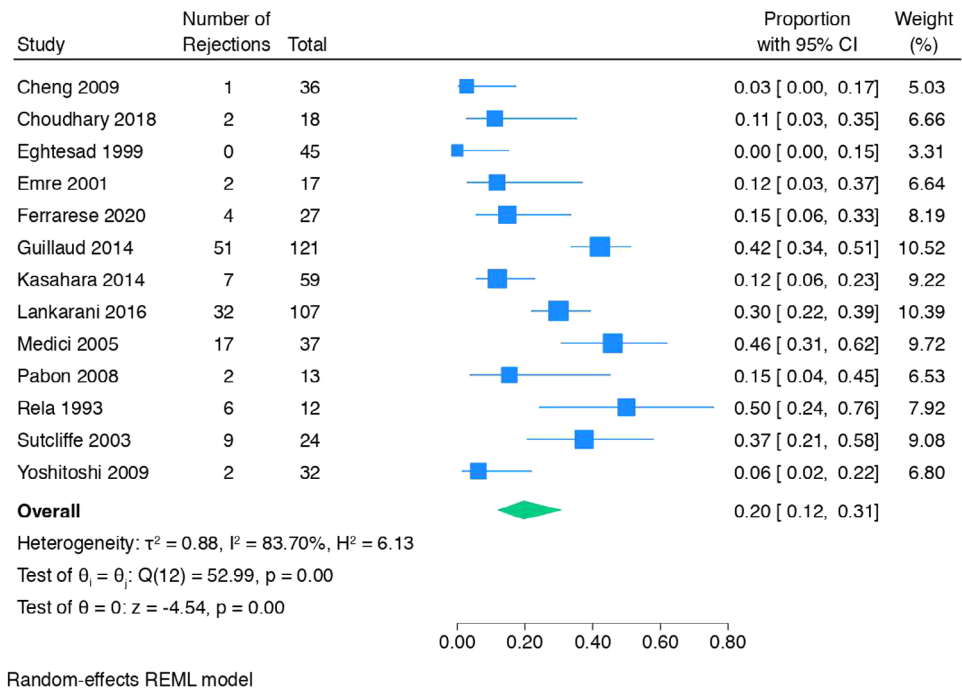


FIGURE 5 | Biopsy-proven acute rejection—Random effects by restricted maximum likelihood meta-analysis of outcome using data from observational studies.

TABLE 4 | Neurological and psychiatric outcomes—Proportion of improvement and narrative synthesis of findings in individual studies.

Study	Neurological and psychiatric outcomes	
	General improvement (%) ^a	Specific changes reported ^b
Aksoy 2022	6 (25)	Improvement in dystonia (<i>n</i> = 4), tremor (<i>n</i> = 1), and bradykinesia (<i>n</i> = 2) No significant change to MMSE
Al-Hilou 2012	4 (40)	Resolution of Parkinsonism (<i>n</i> = 3), anxiety (<i>n</i> = 2), epilepsy, OCD, depression, ataxia, and migraine New onset of seizures (<i>n</i> = 2), psychosis (<i>n</i> = 1), and euphoria (<i>n</i> = 1)
Cheng 2009	8 (53.3)	Improvement in severe impairments (<i>n</i> = 5), improvement in mild/moderate impairments (<i>n</i> = 3)
Choudhary 2018	2 (66.7)	Improvement in dysarthria (<i>n</i> = 2)
Couchonnal 2021	5 (26.3)	Improvement (<i>n</i> = 5), persistent behavioral abnormalities (<i>n</i> = 1)
Dal 2021	—	Perioperative convulsion-epilepsy (<i>n</i> = 6)
Eghtesad 1999	11 (64.7)	Improvements in ataxia (<i>n</i> = 3), tremor (<i>n</i> = 2), muscular weakness (<i>n</i> = 3), dysarthria (<i>n</i> = 3), hypomania (<i>n</i> = 2), dysgraphia (<i>n</i> = 2), and seizures (<i>n</i> = 2)
Emre 2001	—	New acute psychiatric illness, on lithium (<i>n</i> = 1) and seizures (<i>n</i> = 2) ^c
Ferrarese 2020	2 (20)	Improvement in dystonia (<i>n</i> = 1) and tremor (<i>n</i> = 1)
Guillaud 2014	3 (42.9)	Improvement in dystonia (<i>n</i> = 3), and ataxia (<i>n</i> = 1)
Lankarani 2016	40 (66.7)	Improvement in dystonia (<i>n</i> = 1), ataxia (16), tremor (17), fine motor task performance (<i>n</i> = 11), drooling (<i>n</i> = 8), dysarthria (<i>n</i> = 8), rigidity (<i>n</i> = 10), gait disorder (8), poor school performance (<i>n</i> = 1), apraxia (<i>n</i> = 1), seizure (<i>n</i> = 12), anxiety (<i>n</i> = 2), depression (<i>n</i> = 14), compulsion (2), phobia (<i>n</i> = 4), aggression (<i>n</i> = 1), poor memory (<i>n</i> = 6), neurosis (<i>n</i> = 2), and psychosis (<i>n</i> = 2)
Markiewicz-Kijewska 2008	9 (69.2)	Full neurological improvement (<i>n</i> = 9)
Martin 2008	11 (100)	All patients with neurologic symptoms showed improvement (<i>n</i> = 11), dramatic improvement of previously severely disabling symptoms (<i>n</i> = 2)
Medici 2005	6 (66.7)	Improvement in neurological condition (<i>n</i> = 6), deterioration of neurological condition (<i>n</i> = 3)
Ocal 2020	4 (26.7)	Improvement in dystonia (<i>n</i> = 1), tremor (<i>n</i> = 4) New onset tremor (<i>n</i> = 1)
Ocal 2018	—	New onset encephalopathy (<i>n</i> = 1), seizures (<i>n</i> = 2), tremor (<i>n</i> = 3), headache (<i>n</i> = 1)
Poujois 2020	14 (77.8)	Major improvement in UWDRS score (<i>n</i> = 8), moderate improvement (<i>n</i> = 4), mild improvement (<i>n</i> = 2) New complex partial seizures (<i>n</i> = 1)
Pratschke 1998	4 (100)	—
Sarici 2023	2 (33)	Full recovery of speech and gait symptoms (<i>n</i> = 2), partial recovery of speech and gait symptoms (<i>n</i> = 2) New onset seizure (<i>n</i> = 2)
Schilsky 1994	5 (62.5)	Improvement in catatonia (<i>n</i> = 1), dysarthria (<i>n</i> = 1), severe neurological dysfunction (<i>n</i> = 1), hypersexuality (<i>n</i> = 1) and depression (<i>n</i> = 1) New onset seizure (<i>n</i> = 1)
Soy 2018	5 (100)	—
Tamura 2005	—	Worsening of intention tremor with new onset drop foot (<i>n</i> = 1)

(Continues)

TABLE 4 | (Continued)

Study	Neurological and psychiatric outcomes	
	General improvement (%) ^a	Specific changes reported ^b
Tang 2002	15 (83.3)	Resolution of tremor (<i>n</i> = 5), gait difficulty (<i>n</i> = 11), inability to walk (<i>n</i> = 3), dysphagia/drooling/slurred speech (<i>n</i> = 14), cognitive impairment (<i>n</i> = 7), hypomimia (<i>n</i> = 8) and general psychiatric symptoms (<i>n</i> = 3)
Weiss 2013	7 (63.6)	Improvement of neurological symptoms (<i>n</i> = 7), mild worsening (<i>n</i> = 1)
Yagci 2015	7 (77.8)	Improvement of neurological symptoms (<i>n</i> = 7), improvement of psychiatric symptoms (<i>n</i> = 5)
Yoshitoshi 2009	1 (25)	Complete remission of walking difficulty (<i>n</i> = 1) and mild dysarthria (<i>n</i> = 1)
Yu 2013	1 (20)	Improvement of symptoms within 1 month (<i>n</i> = 1)

^aPercent is calculated from *n* improved divided by *n* with neurological or mixed form of Wilson Disease preoperatively.

^bTotal *n* improvement in each symptom; some patients improved in more than 1 symptom.

^cDue to cerebral hematoma and tacrolimus toxicity.

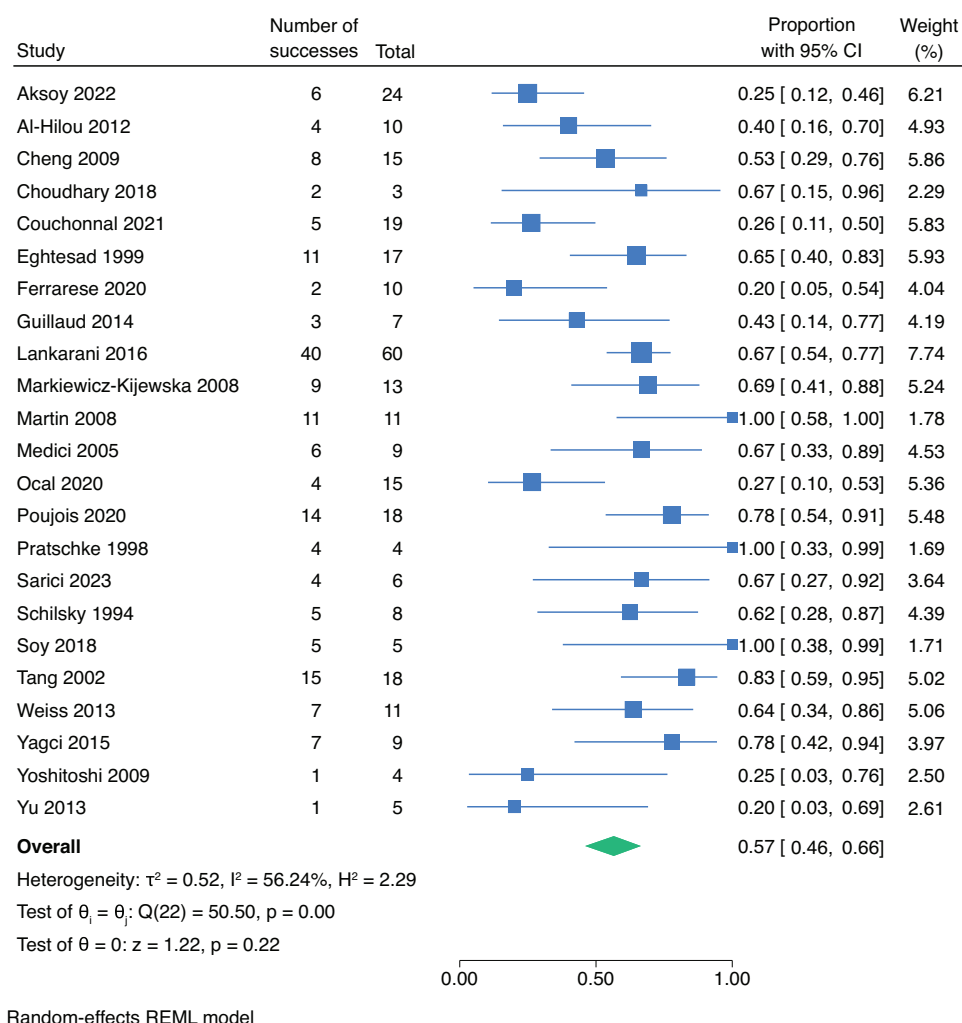


FIGURE 6 | Improvement in neurological and psychiatric symptoms—Random effects by restricted maximum likelihood meta-analysis of outcome using data from observational studies.

TABLE 5 | Methodological index for non-randomized studies (MINORS) for the included full-text studies.

Study	For all studies					For comparative studies							
	Clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to aim of study	Unbiased assessment of study endpoint	Follow up period appropriate	<5% loss to follow up	Prospective calculation of study size	Adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total (/24)
Aksoy 2022	2	1	1	2	0	2	0	0					8
Al-Hilou 2012	2	0	0	0	0	2	0	0					4
Arnon 2009	2	1	0	1	0	1	0	0					5
Arnon 2011	2	1	0	2	0	2	0	0					7
Cheng 2009	1	1	0	1	0	2	0	0					5
Choudhary 2018	1	1	0	2	0	1	2	0					7
Couchonnal 2021	2	1	1	2	0	2	2	0					10
Dal 2021	2	2	1	2	0	2	2	0					11
Eghtesad 1999	2	1	0	1	0	2	2	0					8
Emre 2001	2	2	0	1	0	1	2	0					8
Ferrarese 2020	2	2	0	2	2	2	2	0					12
Guillaud 2014	2	2	0	2	0	2	2	0					10
Ismail 2020	2	2	0	2	1	2	0	0					9
Jozwik 2019	1	1	0	1	0	2	0	0					5
Kasahara 2014	2	2	1	2	1	2	0	0					10
Lai 2013	1	1	0	1	0	1	0	0					4
Lankarani 2016	2	1	0	2	1	2	0	0					8
Mainardi 2019	2	1	0	2	1	2	0	0					8
Markiewicz-Kijewska 2008	2	2	2	2	0	2	2	0					12
Martin 2008	2	2	0	2	0	2	2	0					10
Martinez-Camacho 2009	2	1	0	2	0	2	0	0					7
Medici 2005	2	1	0	2	0	2	1	0					8

(Continues)

TABLE 5 | (Continued)

For all studies										For comparative studies			
Study	Clearly of con- stated aim	Inclusion secutive patients	Prospective collection of data	Endpoints appropri- ate to aim of study	Unbiased assess- ment of study endpoint	Follow up period appropri- ate	<5% loss to follow up	Prospective calcula- tion of study size	Adequate control group	Contem- porary groups	Baseline equiva- lence of groups	Adequate statisti- cal analyses	Total (/24)
Ocal 2020	2	1	0	2	0	0	2	0					7
Ocal 2018	2	2	0	2	0	0	0	0					6
Pabon 2008	2	1	0	2	0	2	2	0					9
Poujois 2020	2	2	2	2	0	2	2	0					12
Pratschke 1998	1	2	0	1	0	2	2	0					8
Rela 1993	1	2	0	1	0	1	2	0					7
Sarici 2023	2	1	0	1	0	2	2	0					8
Schilsky 1994	2	1	0	1	0	2	2	0					8
Sevmis 2008	2	2	0	2	0	2	2	0					10
Soy 2018	1	0	0	2	0	2	2	0					7
Stankiewicz 2021	1	2	2	1	0	1	2	0					9
Sutcliffe 2003	2	2	1	2	0	2	2	0					11
Tamura 2005	2	2	0	2	0	1	2	0					9
Tang 2002	2	0	0	2	0	1	1	0	2	0	1	0	9
Weiss 2013	2	2	1	2	0	1	2	0					10
Yagci 2015	2	2	0	2	0	2	2	0					10
Yoshitoshi 2009	2	2	0	2	0	2	2	0					10
Yu 2013	2	2	0	2	0	2	2	0					10

Note: MINORS tool score for individual studies: Red (0) = not reported, yellow (1) = reported but not adequate, green (2) = reported and adequate.

case of complete remission of symptoms followed by recurrence of dysarthria, dystonia, and gait disability due to decreased compliance to d-penicillamine over the observational period [35]. This indicates the need for long-term follow-up and detailed reporting of recurrence of symptoms to delineate whether the reemergence of symptoms is due to intervention or individual patient-related factors. Aside from the MMSE used by Aksoy et al. and the UWDRS used by Ferrarese et al. and Poujois et al., no other studies used validated rating scales to assess neurologic outcomes [8, 41, 49]. There were a number of non-validated scales that were relied upon. For example, the scale used by Medici et al. consisted of six neurological signs and four neurological functions, which were rated out of three based on the degree of impairment [31]. Although this allows for a more objective rating of symptoms due to clear definitions of outcomes, intra and interrater reliability is still uncertain. As the majority of studies used author-based subjective assessments of improvement, they are more susceptible to observer bias and selective reporting bias. A systematic review by Litwin et al. investigating liver transplant as a treatment for Wilson's disease with neurological presentation supports the limited use of objective rating scales, with only one included study in this review using the UWDRS [53]. Consensus on which tool to use moving forward will allow for higher quality data when studying this rare disease.

The average MINORS score for included studies was 8.33 compared to the global ideal score of 16. This indicates inadequate reporting and inadequate control of sources of bias in studies included in this systematic review [12].

The strengths of the present review include rigorous methodology, a thorough systematic search, and novelty. However, there are several limitations that should be taken into consideration when interpreting these results. Firstly, all studies were observational and, therefore, at risk of selection biases and residual confounding. This study included only one comparative study. In current literature, few comparative studies are available due to the nature of the intervention. Hepatic transplantation is typically only indicated in cases where medical management has failed or is not possible due to resource allocation and surgical risk. Thus, patients undergoing each of these interventions would have differing baselines, making outcome data difficult to compare. The limited resource also makes it difficult to randomize adequate numbers of patients. Secondly, there was significant heterogeneity in the study population, with several studies including patients undergoing transplantation for acute, acute-on-chronic, or chronic liver failure. These patients in different disease stages, and thus with different prognoses, contributed to heterogeneity in the synthesis and comparison of outcomes between studies. Additionally, reporting of pre-operative medical management was low, with 51.3% of included studies not reporting whether or how patients were managed pre-operatively. The reporting of degree of improvement in neurological symptoms was also absent, with included studies not specifying partial or complete improvement. There was also heterogeneity and lack of reporting of the type of transplant (full vs. partial) and lack of reporting in several morbidity outcomes. The relatively small proportions of reported outcomes introduce significant uncertainty into our meta-analyses, hence the high corresponding 95% CIs. This must be considered when interpreting the findings. This also highlights the need for more standardized reporting.

Finally, re-transplantation was reported in several studies due to primary nonfunction, hepatic artery thrombosis, and acute or delayed rejection. Yet, morbidity and mortality following re-transplantation were not included in most studies. Thus, bias toward lower postoperative mortality is likely as the patients requiring re-transplantation were presumably at greater risk of postoperative morbidity and mortality.

5 | Conclusion

The pooled mortality and secondary outcome proportions indicate that liver transplantation for Wilson's disease has curative efficacy in cases of acute liver failure and acute-on-chronic liver failure, albeit with moderate proportions of mortality and postoperative morbidity. However, the reporting of outcomes remains poor, with reporting of post-operative morbidity outcomes being particularly limited. The heterogeneity of the patient population and the variability of timing of transplant, timing, and method of treatment for Wilson's disease limit the ability to interpret the results. The wide 95% CIs association with most meta-analyzed outcomes and large I^2 values suggest that significant uncertainty remains with regard to most clinically significant outcomes. Further research should follow a standardized system of reporting these outcomes to allow for a more robust assessment of risk following this procedure.

Author Contributions

Austine Wang, Noor Bakir, Clarissa Ngo, Justin Kang, Felipe Rodriguez, Tyler McKechnie, Cagla Eskicioglu, Maja Segedi, Pablo E. Serrano: All authors: conception and design of the study, analysis and interpretation of data, drafting and revision of the manuscript, approval of the final version of the protocol, and agreement to be accountable for all aspects of the work. Austine Wang, Noor Bakir, Justin Kang, Tyler McKechnie, Felipe Rodriguez: Acquisition of data.

Acknowledgments

The authors have nothing to report.

Ethics Statement

Local ethics review board approval was not required.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Derived data supporting the findings of this study are available from the corresponding author upon request.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.