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The predictive role of autonomic neuropathy in pre- and post-liver transplantation outcomes: a systematic review and meta-analysis

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Abstract

Background Autonomic neuropathy (AN) in cirrhotic patients has been linked to a higher risk of cirrhosis-related complications and worse outcomes before, during or after liver transplantation (LT). However, only a few studies exist with inconsistent results.

Methods We searched for all articles published until September 2023 that described a diagnosis of AN based on cardiovascular autonomic reflex tests (CARTs), assessment of the rate-corrected QT interval (QTc), heart rate variability (HRV), and baroreflex sensitivity (BRS) tests, in order to evaluate the predictive role of AN in cirrhosis and/or peri-/post-LT prognosis.

Results Twenty-five studies were included: 5, 12, 9, and 1 study, respectively, assessed the predictive role of CARTs, prolonged QTc, HRV indices, and BRS in cirrhosis or peri-/post-LT prognosis. In CARTs-based analysis, the pre-LT pooled mortality rate was significantly higher in cirrhotics with AN compared to those without AN (20% vs. 6%; P=0.01). However, no difference was found between patients with and without pre-LT prolonged QTc in the pre-LT pooled mortality rates (41% vs. 18%; P=0.08), pooled peri-transplant risk of major complications (29% vs. 17%; P=0.08) or post-LT pooled mortality rates (15% vs. 12%; P=0.36). In HRV-based analysis, the standard deviation of normal-to-normal intervals was significantly lower in non-survivors, compared to survivors with cirrhosis: standardized mean difference -2.59, 95% confidence interval -4.75 to -0.43; P=0.04.

Conclusions The presence of CARTs- and HRV-based AN was a good predictor of mortality in the pre-LT setting. Preoperative prolonged QTc did not seem to be associated with the outcome before or after LT.

Keywords Cirrhosis, liver transplantation, cardiovascular autonomic neuropathy, autonomic neuropathy, mortality

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Introduction

Autonomic neuropathy (AN), a disorder of the autonomic nervous system [1], was first studied through the assessment of cardiac AN (CAN) [2]. The latter, a condition of impaired autonomic control of the cardiovascular system, can be evaluated by measuring changes in blood pressure, heart rate and the heart's electrophysiological activity [3,4]. Cardiovascular autonomic reflex tests (CARTs), assessment of the rate-corrected QT interval (QTc), heart rate variability (HRV), and baroreflex sensitivity (BRS) tests, all represent useful tools in the evaluation of CAN [2,5-8]. CAN is a well-established complication in patients with type 2 diabetes mellitus (T2DM) [9,10], while it has been associated with an increased risk of cardiovascular events and mortality [10,11]. According to a recent meta-analysis of patients with T2DM, in those with CAN, compared to those without CAN, the pooled relative risks for future cardiovascular events and for all-cause mortality were 3.16 (95% confidence interval [CI]

2.42-4.13; P<0.001), and 3.17 (95%CI 2.11-4.78; P<0.001), respectively [12].

AN has also been reported in patients with cirrhosis, and is considered to be the consequence of metabolic, inflammatory, toxic, and immunological changes occurring alongside the establishment of hyperdynamic circulation and portal hypertension [3,13]. Regenerative fibrotic nodules release substances that induce endothelial dysfunction and vasoconstriction [14], while increased portal vein pressure stimulates the synthesis of vasodilators. The subsequent activation of the sympathetic nervous system (SNS) and the renin–angiotensin–aldosterone system (RAAS) contributes to hemodynamic and neurohumoral alterations, potentially leading to autonomic dysfunction [3]. The presence of ascites and decompensated liver disease accentuates the progression of these mechanisms, ultimately contributing to the development of AN in cirrhosis [13].

The prevalence of AN in cirrhosis ranges from 30-67% [15,16]. It is estimated that at least 1 of the CARTs is abnormal in 36-77% of cirrhotics, while a prolonged QTc is observed in 37-84% of cirrhotics [13]. In cirrhosis, AN has also been linked to increased death rates and negative outcomes following liver transplantation (LT) [15-20]. A recent meta-analysis [17] showed a significantly higher survival hazard ratio (HR) in cirrhotic patients with QTc <440 msec, compared to those with QTc >440 msec (HR 2.228, 95%CI: 1.640-2.815; P<0.001). Additionally, a systematic review [19] concluded that low values of HRV indices can predict mortality independently of the severity of cirrhosis. However, the prognostic utility of CART- and BRS-based AN in cirrhosis, as well as the impact of AN before LT on post-LT outcomes, have only been evaluated in a few individual studies, with inconsistent results.

The aim of this systematic review and meta-analysis was to compile and summarize all the relevant studies that provide insight into the predictive role of AN in cirrhosis, as well as the impact of pre-LT AN on the prognosis after LT.

Materials and methods

CAN evaluation

CARTs

CARTs are 5 noninvasive diagnostic tests, including the deep breathing test, the supine-to-stand test, the Valsalva maneuver, the orthostatic hypotension test and the sustained handgrip test [2]. They indirectly assess ANS function by measuring the variability of heart rate and blood pressure. Based on CARTs, CAN is defined on the basis of 1 (possible/early CAN) or ≥2 (definite CAN) positive tests [1].

QTc

The QT interval represents the time from the onset of ventricular depolarization to the end of repolarization [21]. It is measured from the beginning of the QRS complex to the end of the T wave on a standard 12-lead electrocardiogram (ECG) [22]. To account for heart rate variability, the QT interval should be adjusted based on the heart rate.

HRV

HRV analysis provides measures of heart rate variations in an ECG over a short monitoring period, reflecting the balance between the SNS and the parasympathetic nervous system (PNS) [23].

Time domain HRV analysis assesses both the short- and long-term variability of the heart [23-25]. The standard deviation of normal-to-normal (NN) intervals (SDNN) measures the total variability of the time intervals between successive NN heartbeats on an ECG. The root mean square of differences of successive RR intervals (RMSSD) and pNN50 (a time domain HRV parameter that quantifies the percentage of NN intervals that differ from each other by more than 50 msec) provide information about short time intervals and reflect the influence of the PNS on HRV [26-28].

Frequency domain HRV analysis decomposes HRV into specific frequency bands. The high frequency (HF) band is associated with PNS function, while the low frequency (LF) band is associated with both SNS and PNS function. Their ratio LF: HF assesses the balance between SNS and PNS. Poincaré plot analysis uses standard deviation (SD)1 and SD2 values to graphically represent the relationship between 2 consecutive data points in a time series. SD1 and SD2 reflect both the short- and long-term influence of the autonomic nervous system on the heart rate [27,28].

Detrended fluctuation analysis is a complex technique that evaluates long-range correlations or fractal-like patterns within a time series. The slope of the plot, known as the α scaling exponent, gives insight into those long-range correlations in the time series. The A2 scaling exponent is associated with long-term correlations [29].

BRS test

The BRS test reflects the functionality of arterial baroreceptors, expressing the degree of heart rate variation per unit change in arterial pressure [30]. In recent years, BRS evaluation has been based on noninvasive, computer-assisted analysis of spontaneous fluctuations of cardiovascular variables [31,32].

Data sources and searches

PubMed/Medline was searched from 1992 to September 2023, in accordance with the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) guidelines [33], in order to carry out a systematic review and meta-analysis of observational studies. We aimed to identify all relevant medical literature included under the following search text terms: "Liver cirrhosis", "Cardiovascular autonomic

neuropathy", "Heart rate variability", "QT prolongation" and "Baroreflex sensitivity". In addition, we performed a full manual search of all relevant review articles and original studies. All studies identified from the search were uploaded to Rayyan software, duplicates were removed and 2 independent reviewers (AN, VL) performed title and abstract screening.

Study selection

All studies published in English as full papers were included if they fulfilled all of the following criteria: 1) they were observational studies; 2) they included adults with cirrhosis; 3) they evaluated CAN through CARTs, the HRV test, the BRS test and/or the assessment of QTc; and 4) they compared indices—CARTs, HRV indices, BRS, prolonged QTc (defined as QTc >440/450 msec for men, >470 msec for women—between survivors and non-survivors, or between patients with and without major adverse events post-LT. Exclusion criteria were: 1) review articles, case reports, and letters; 2) duplicated or overlapping studies; and 3) studies published only as abstracts. The process was performed independently by 2 authors (AN, VL).

Data extraction and quality assessment

Data extraction from selected papers was carried out based on a predefined form, in accordance with the PRISMA guidelines (Supplementary Table 1) [33]. The Newcastle–-Ottawa scale [34], which allocates a maximum score of 5 for selection, 2 for comparability, and 2 for outcome, was used to assess the quality of the included studies. Data extracted from selected studies included: country and center(s) of origin, date of publication, first author, type of study, sex, etiology of cirrhosis, Child–-Pugh (CP) and model for end-stage liver disease (MELD) scores, aim of the study, follow-up data, sample and group sizes (sample, survivors/non-survivors, with/without cirrhosis-related complications), CAN/HRV/BRS indices calculated, QTc prolongation definition, hazard/odds ratios, cutoff values for area under receiver operating characteristic curve, LT status, mean CAN/QTc/HRV/BRS values of survivors and non-survivors, or patients with and without major adverse events of cirrhosis, cirrhosis-related complications and peri- or post-LT adverse events.

Data synthesis and statistical analysis

The generalized linear mixed model was used to conduct the meta-analysis [35]. CIs for individual study proportions were determined using the Clopper and Pearson method [36]. Estimation of the between-study variance component ($\tau 2$) was achieved through maximum likelihood estimation, utilizing marginal distribution [37]. Heterogeneity was assessed using the I^2 statistic, with values of 25%, 50% and 75% indicating low, moderate and high degrees of heterogeneity, respectively [38]. Pooled proportions, along with 95%CI and prediction intervals (PI), were computed [39]. The analysis was carried out using R version 4.3.1, utilizing meta-packages and metaprop functions [40]. In addition, standardized mean differences (SMD) were calculated for each study, using the formula $SMD = X_1 - X_2/SD_p$, where X_1 and X_2 represent the means of the experimental and control groups, respectively, and SDp is the pooled standard deviation [41]. We fitted a random-effects meta-analysis model to the calculated effect sizes using the "metafor" package in R. This model allowed for heterogeneity between studies and provided estimates of the overall effect size, along with its confidence interval [38].

Results

A total of 35 articles were initially identified from the literature review that discussed the predictive role of AN in cirrhosis or after LT. However, 10 articles [42-51] were excluded after the full text review; thus, a total of 25 were finally included (Supplementary Fig. 1). Among these, 5 [15,16,52-54], 12 [18,52,55-64], 9 [4,20,65-71], and 1 [20] articles assessed the predictive role of CARTs, prolonged QTc, HRV indices and BRS, respectively. The main characteristics of the included studies are provided in Tables 1, 2 and 3, respectively.

CARTs

A total of 5 articles discussed the predictive role of CARTs [15,16,52-54]. One retrospective and 4 prospective cohort studies were included, with follow-up durations ranging from 10-50 months.

A total of 336 patients—138 (41%) women, 147 (44%) CP class A, 121 (36%) CP class B, and 68 (20%) CP class C—were evaluated (Table 1).

CARTs and pre-LT mortality

Three studies examined the association between CARTs-based AN and pre-LT mortality in 223 patients [15,16,52]. The pooled mortality rate was significantly higher in patients with CARTs-based AN compared to those without AN: 20% (95%CI 27-14%; heterogeneity I^2=0%; P=0.37) vs. 6% (95%CI 2-14%; heterogeneity I^2= 0%; P=0.98), P=0.01 (Fig. 1A). Two of the aforementioned studies further examined the association between severity of CARTs-based AN (namely definite vs. possible/early vs. absent CAN) and pre-LT mortality in 163 patients. The pooled mortality was 21% (95%CI 13-32%; heterogeneity I^2=0%) vs. 14% (95%CI 7-26%; heterogeneity I^2=0%; P=0.55) vs. 5% (95%CI 1-19%; heterogeneity I^2=0%; P>0.99), respectively, but the difference was only significant

Table 1 Characteristics of studies with available data on CARTs-based AN

Author (Year) [ref.]	Country	Type of study	S/Female	CP class	Age (years)	Ascites / HE, n	With/ Without AN, n	Early/ Definite AN, n	NS Early/ Definite AN, n	Etiology, n	Index measured	Follow up (months)	Cause of death, n	CAN indices	NOS
Fleckenstein (1996) [15]	USA	P	33/11 33/11	A=7 B=16 C=10	CPA: 52±10.2 CPB: 52.9±6.5 CPC: 44.8±15	22/ 9	22/ 11	10/12	2/2	ALD=11 HCV=9 PBC=5 PSC=2 AIH=2 Other=5	Mortality	10 (1-14)	Sepsis=3 Post-LT sepsis=2 Car accident=1	BP response to standing, HR response to the Valsalva maneuver, HR response to standing (30:15 ratio), HR response to deep breathing	8
Puthumana (2001) [56]	USA	P	130/61	A=42 B=53 C=35	Normal QTc: 51.2±11 Prolonged QTc: 52.9±8.5	77/ 40	103/ 27	47/56	6/12	ALD=25 HCV=41 PBC=14 PSC=14 AIH=8 Cryptogenic=15 Other=13	Mortality	17,3±14,8	NA	HR response to the Valsalva maneuver, HR response to deep breathing, BP response to standing (30:15 ratio), BP response to sustained handgrip	8
Hendrickse (1992) [16]	UK	P	60/27	A=57	56 (32-67)	0/ 0	27/33	16/11	10	ALD=19 PBC=18 AIH=9 VIRAL=10	Mortality	50(42-53)	Sepsis=2 Variceal bleeding=3 SBP=1 hepatoma=1 progressive disease=1 other=2	HR response to the Valsalva maneuver, HR response to deep breathing, BP response to standing (30:15 ratio)	9
Maheswari (2004) [57]	USA	R	72/28	A=35 B=31 C=6	51.1±9.2	NA	55/17	NA	NA	ALD=17 HCV=22 HBV=2 PBC=4 PSC=7 AIH=5 Other=15	New-onset HE	39,5±27,3	NA	HR response to the Valsalva maneuver, HR response to deep breathing, BP response to standing (30:15 ratio), BP response to sustained handgrip	8
Pérez-Peña (2003) [58]	Spain	P	41/11	A=3 B=21 C=17	51 (19-67)	NA	NA	NA	NA	ALD=24 HCV+HBV=11 PBC=4 Other=2	Peri-transplant: PRS, arterial hypotension, need for inotropic support	Peri-transplant risk	NA	HR response to rest, HR response to the Valsalva maneuver, HR response to deep breathing, BP response to standing (30:15 ratio), BP response to sustained handgrip, BP response to cold pressure	7

CARTs, cardiovascular autonomic reflex tests; S, sample; CP, Child–Pugh; HE, hepatic encephalopathy; AN, autonomic neuropathy; NS, non-survivors; CAN, cardiovascular autonomic neuropathy; P, prospective; R, retrospective; ALD, alcoholic liver disease; HCV, hepatitis C virus; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; PRS, post-reperfusion syndrome; BP, blood pressure; HR, heart rate; SBP, spontaneous bacterial peritonitis; QTc, rate-corrected Q-T complex describing time between the start of the Q-wave and T-wave of an ECG recording; NOS, Newcastle–-Ottawa scale; NA, not available

Table 2 Characteristics of studies with available data on prolonged QTc

Author (Year) [ref.]	Country	Type of study	S/Female	Age (years)	Ascites/ HE, n	CP class	MELD	Index measured	QTc prol, n	NS/ MACE QTc prol, n	Etiology, n	Follow up (months)	QTc cutoff (ms)	NOS
Li (2021) [65]	China	P	110/51	63.98±11.44	49/13	A=39 B=53 C=18	11.3±3.3	ESLD Mortality	55	66	HBV/HBC=36 ALD/ NAFLD=29 AIH=16 OTHER=29	36	440	9
Ko (2020) [18]	Australia	R	408/135	57.1±12	186/180	9.5±3	NA	Post-LT prognosis/ Peri-LT risk (OC)	314	35/ 87	HBV/HBC=133 NASH=52 ALD=38 HCC=36 OTHER=149	36	440	9
Flaherty (2018) [63]	USA	R	527/177	58(51-64)	NA	NA	20 (13-32)	Post-LT prognosis/ Peri-LT risk (heart failure)	220	22/ 56	NA	3	450 men, 470 women	8
Glowczynska (2018) [60]	Poland	R	151/56	49±12	41/32	A=50 B=73 C=28, 7.8±2.1	11.8±4.6	Post-LT prognosis	51	7	ALD=27 HBV/ HCV=68 AIH=36 OTHER=20	24	440	8
Lee (2016) [59]	Korea	R	283/70	55 (50-60)	160/NA	NA	16(6-45)	Post-LT prognosis	180	42	NA	31	440	9
Patel (2014) [62]	USA	R	51/16	57.0±8.9		A=17 B=23 C=11	16±5.6	Post-LT prognosis	26	4	HBC=20 ALD=7 HCV+ALD=5 NASH=5 OTHER=14	24	440	7
Josefson (2012) [67]	Sweden	R	234/72	52±10.5	167/53	9 ±2.2	16.5±6.8	Peri-LT risk (heart failure)	58	31	ALD=85 HBV/ HCV=55 PBC/PSC=42 CRYPTOGENIC=20 OTHER=18	63	440	7
Bal (2003) [64]	USA	R	409/180	49.0±14.2	161/66	B=273 C=136/ 8.9±2.1	NA	ESLD Mortality	162	34	ALD=80 HCV=113 HBC=19 PSC=32 AIH=29 CRYPTOGENIC=28 PBC=22 OTHER=86	107.64	440	9
Bernardi (1998) [66]	Italy	R	94/26	53.1±1.4	58/26	8(5-14)	NA	ESLD Mortality	40	19	HBV/HCV=70 ALD=18 PBC=3 CRYPTOGENIC=3	19	440	9
Mohamed (1996) [61]	England	P	52/26	51(16-69)	36/19	NA	NA	Post-LT prognosis	44	7	PBC=21 PSC=11 4 ALD=9 HCV=3 WD=2 BUDD-CHIARI=2 OTHER=5		440	9

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between definite-AN compared to absent-AN (P=0.05) (Fig. 1B).

CARTs and complications of cirrhosis

Only 1 study including 72 patients (55 with AN at baseline) assessed the association between CARTs-based AN and the development of major cirrhosis-related complications [53]. During the follow-up period, 30 individuals developed hepatic encephalopathy (HE): patients with AN had a higher incidence of HE, compared to those without (49% vs. 18%), but this difference was not significant (no P-value was provided).

CARTs and peri-transplant risk

One study investigated the association between AN and the perioperative risk of complications in 41 patients [54]. The results showed that patients with AN before LT exhibited higher hemodynamic instability, arterial hypotension, and a greater need for vasopressor therapy during operation for LT, compared to those without AN (Table 1).

QTc

A total of 12 studies (9 retrospective and 3 prospective) investigated the predictive impact of prolonged QTc on cirrhosis, or on peri- and post-LT prognosis [18,52,55-64]. A total of 5020 patients were evaluated (1597 women, 32%). Based on the available data, 1767 (35%) and 801 (16%) patients had ascites and HE, respectively (Table 2).

Prolonged QTc and pre-LT mortality

Four studies assessed the association between prolonged QTc (defined as >440 msec) and mortality in 735 patients with cirrhosis [50,60-62]. One study investigated the 1-year mortality rate in cirrhotics with markedly prolonged QTc (defined as >500 msec) and was therefore excluded from this subgroup analysis [64]. The pooled mortality rate was higher in patients with QTc >440 ms, compared to those with QTc <440 ms—41% (95%CI 19-68%; heterogeneity I^2=95%; P=0.04) vs. 18% (95%CI 10-30%; heterogeneity I^2=87%; P=0.01)—but this difference was not significant (P=0.08) (Fig. 2A).

Pre-operative prolonged QTc and peri-transplant risk

Four studies examined the peri-transplant risk of major complications in 3748 patients, with vs. without prolonged QTc (defined as longer than 440 msec in 2 studies [18,63] and longer than 450/470 msec for men and

Table 2 (*Continued*)

Author (Year) [ref.]	Country	Type of study	S/Female	Age (years)	Ascites/ HE, n	CP class	MELD	Index measured	QTc prol, n	NS/ MACE QTc prol, n	Etiology, n	Follow up (months)	QTc cutoff (ms)	NOS
Puthumana (2001) [56]	USA	P	130 /61	Normal QTc: 51.2±11 Prolonged QTc: 52.9±8.5	77/40	A=42 B=53 C=35	NA	ESLD Mortality	58	12	ALD=25 HCV=41 PBC=14 PSC=14 AIH=8 Cryptogenic=15 Other=13	17.3±14.8	440	8
Kim (2020) [68]	Korea	P	2579/727	53.1±8.8	832/372	NA	13(9-22)	Peri-LT risk (MACE)	1105	147	HBV/HCV=1661 ALD=549 PBC=97 OTHER=69	1	450 men, 470 women	9

S, sample; CP, Child–Pugh; HE, hepatic encephalopathy; MELD, model for end-stage liver disease; NS, non-survivors; MACE, major adverse cardiovascular events P, prospective; R, retrospective; ESLD, end-stage liver disease; LT, liver transplantation; OC, operative complications; ALD, alcoholic liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; PBC, primary biliary cholangitis; PSC, primary sclerosing cholangitis; AIH, autoimmune hepatitis; NASH, nonalcoholic steatohepatitis; HCC, hepatocellular carcinoma; QTc, rate-corrected Q-T complex describing time interval between the start of the Q-wave and T-wave of an ECG recording; NOS, Newcastle–Ottawa scale; NA, not available

Table 3 Characteristics of studies with available data on HRV-based AN

Author (Year) [ref.]	Country	Type of study	S/Female	Age(years)	Etiology, n	CP class, n	NS, n	HRV INDICES NS/S. n	Follow- up (months)	Duration time	NOS
Ates (2006) [4]	Turkey	P	30/11	52±13	HBV=22 HCV=8	A=5 B=11 C=14	13	SDNN 51±13/ 84±15NN 542±127/ 796±143 SDANN 44±7/ 62±13 RMSSD 10±9/ 17±11 pNN50 2.3±0.9/ 5.3±1.2	24	24 h	8
Genovesi (2009) [20]	Italy	P	45/0	52±13	HCV=23 HBV=7 ALD=15	A=26 B=13 C=6	NA	SDNN 77.1±36.3/ 108.3±31.7 SDANN 64.3±33.6/101.6±32.4	24±11	24 h	9
Bottaro (2020) [69]	Italy	P	38/8	64.62±10.4	NA	NA	11	SDNN 67.35±6.46/ 86.79±3.5 cSDNN 236±23.8/ 316.8±22.6 SD1 26.25±4.99/ 16.82±2.79 SD2 90.25±8.62/ 121.01±8.37 VLF 3315±591/6219±852 HF 420±161/ 170±49 a1 0.940±0.075/ 1.107±0.062 a2 0.089±0.032/ 1.142±0.036	12	24 h	8
Bhogal (2019) [70]	Italy	P	74/25	56±10.8	NA	NA	24	SDNN 18.9±2/ 29.1±2.1 cSDNN 68.1±5.4/ 81.9±5 SD1 9.5±1.3/ 15.1±1.4 SD2 24.8±2.5/ 37.7±2.7 VLF 205.8±38/ 483±73 a1 1.01±0.04/ 0.96±0.04 a2 1.03±0.03/ 0.99±0.33	12.3±6.4	10 min	8
Jansen (2019) [71]	London/ Germany	P	111 stable: 62/22 Decomp: 42/15	stable: 59 (19-89) Decomp: 53 (28-77)	ALD stable: 43 Decomp: 35/ viral stable: 12 Decomp:7/ NASH stable: 4 Decomp: 3/ other stable: 3 Decomp: 4	stable: A=52 B=10 C=0 Decomp: A=2 B=24 C=23	12	SDNN 11(10-12)/ 26(17-38)	3	10 min	9
Satti (2019) [72]	Italy	P	74	55±11.8	HBV=6 HCV=17 OTHER=4	B=8 C=14	24	HR:SD2 0.950 (0.918-0.982)	18	8 min	7

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Table 3 (*Continued*)

Author (Year) [ref.]	Country	Type of study	S/Female	Age(years)	Etiology, n	CP class, n	NS, n	HRV INDICES NS/S. n	Follow- up (months)	Duration time	NOS
Pimentel (2022) [73]	Brazil	P	103/46	51.2±12.9		A=23 B=68 C=12 / 7.1 ± 1.8	11	SDNN 75±24/ 96.9±31.2 SDANN 64±18.7/ 84.8±28.8	10	24 h	9
Mani (2009) [74]	London	P	80/27	54±10	ALD=6 HBV/ HCV=7 OTHER=8	A=51 B=13 C=16	11	RR:SD2:0.926 (0.059- .0.213)	20.3	5 min	8
Nagasako (2009) [75]	Brazil	P	32/20	CPA=41±16 CPB=49±10	HCV=16 PBC=6 CRYPTOGENIC=6 OTHERS=4	A=13 B=19	4	HF 100/203	19±12	24 h	8

S, sample; CP, Child--Pugh; NS, non-survivors; S, survivors; P, prospective; HCV, hepatitis C virus; HBV, hepatitis B virus; ALD, alcoholic liver disease; NASH, nonalcoholic steatohepatitis; PBC, primary biliary cholangitis; Decomp, decompensated; SDNN, standard deviation of normal-to-normal (NN) intervals; SDANN, standard deviation of the average NN intervals; RMSSD, root mean square of differences of successive NN intervals; pNN50, percentage of NN intervals that differ by more than 50 ms; SD, standard deviation; VLF, very low frequency; HF, high frequency; HR, hazard ratio; RR, relative risk; NOS, Newcastle--Ottawa scale; NA, not available

women, respectively in 2 studies [59,64]). The recorded perioperative complications were major cardiovascular adverse events [59,63,64], and complications including infections, bleeding and thrombosis [18]. The pooled risk for perioperative complications was higher in patients with prolonged QTc compared to those without prolonged QTc—29% (95%CI 17-45%; heterogeneity I^2=97%; P=0.01) vs. 17% (95%CI 13-22%; heterogeneity I^2=84%; P<0.001)—but this difference was not significant (P=0.08) (Fig. 2B).

Preoperative prolonged QTc and post-LT prognosis

Six studies assessed the association between preoperative prolonged QTc and post-LT mortality risk in 1472 patients [18,55-59]. The pooled mortality rate was similar between the patients with and without prolonged QTc, defined as longer than 440 msec in 5 studies [18,55-58] and longer than 450/470 msec for men and women, respectively, in 1 study [59]: 15% (95%CI 11-19%; heterogeneity I^2 = 66%; P=0.01) vs. 12% (95%CI 8-16%; heterogeneity I^2=57%; P=0.04), respectively (P=0.36) (Fig. 2C).

HRV

A total of 9 studies evaluated the predictive role of HRV indices in cirrhosis [4,20,65-71], while no study assessed the impact of pre-LT HRV tests on peri- and post-LT prognosis. All 9 were prospective cohort studies, with a follow-up duration from 3-24 months. A total of 513 patients were included, 174 (34%) women, 172 (34.2%) CP class A, 160 (32%) CP class B, and 170 (33.8%) CP class C (Table 3).

SDNN and pre-LT mortality

A total of 5 studies evaluated the predictive role of SDNN in 356 patients (127 women, 36%), of whom 75 died during the follow- up [4,65-67,69]. A large effect size was observed, with significantly lower SDNN in non-survivors compared to survivors: SMD (95%CI) -2.59 (-4.75 to -0.43); heterogeneity I^2=94%; P=0.04 (Fig. 3).

HRV indices in cirrhosis

The limited number of studies available did not allow a meta-analysis of HRV indices other than SDNN. In our systematic research, we found 9 studies that assessed the predictive role of HRV indices in cirrhosis. All studies found that, compared to survivors, non-survivors had lower HRV indices, including corrected SDNN (cSDNN), SDANN, SD1, SD2, VLF, a2 and HF (Table 3), while in 3 studies, this difference was significant regarding SDANN [4,20,73], with a cutoff value of 100 msec (P=0.001, b=19.25, 95%CI -19.86 to -18.3) [69]. The measures a2,

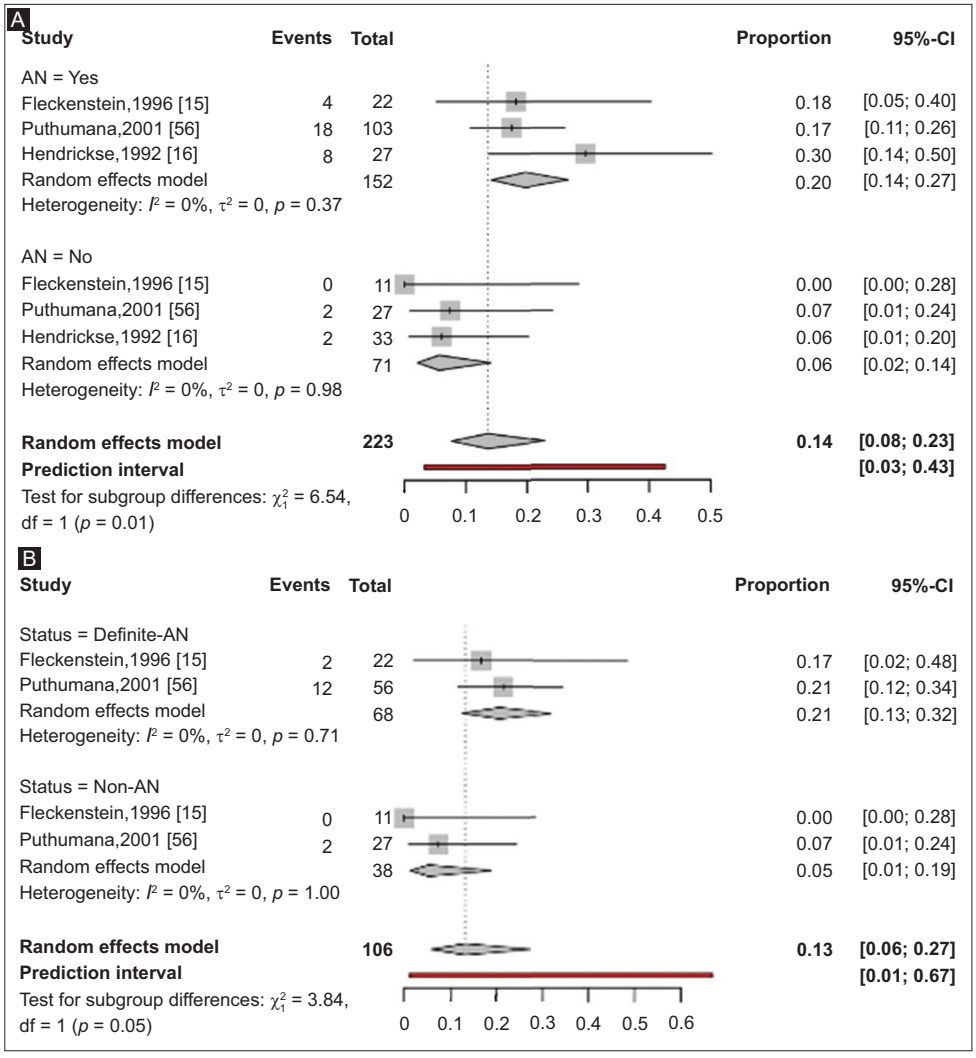

Figure 1 (A) Pooled mortality rate in cirrhotic patients with and without CARTs-based AN. (B) Pooled mortality rate in cirrhotic patients according to the severity of AN
CARTs, cardiovascular autonomic reflex tests; AN, autonomic neuropathy

SD2 and cSDNN were good predictors of mortality in 4 studies [65,66,68,69], independently of MELD and CP scores, with a cutoff value of 1.07 for a2 (log-rank test, chi square=13.08; P<0.001) [58]. Finally, in 2 studies, lower values of HRV indices (SDNN, HF, LF, total power, HF/LF, SD1, SD2) were significantly associated with an increased risk for HE [70,71].

BRS

Only 1 study assessed the relationship between BRS and mortality in 45 patients with cirrhosis (median age 55 years, 24±11 months follow- up) [20]. The results showed that non-survivors had significantly lower mean values of BRS compared to survivors (6.3±2.5 vs. 9.7±3.6 ms/mmHg; P=0.03). No study assessed the impact of pre-LT BRS on post-LT outcomes.

Discussion

In this systematic review and meta-analysis, we synthesized data from 25 studies that used all the main tools for AN assessment, including CARTs, HRV, QTc, and/or BRS, in order to assess the predictive role of AN in cirrhosis and/or post-LT prognosis. In fact, this is the first meta-analysis to evaluate the predictive role of CARTs and HRV indices in the pre-LT setting, as well as the impact of prolonged pre-LT QTc on the post-LT outcome. Our results reveal an association between CARTs- and HRV-based AN and mortality in patients with cirrhosis, particularly in those with more advanced stages of AN. However, prolonged QTc before LT did not appear to be a predictor of pre- or post-LT risk for adverse events and mortality.

In our meta-analysis, CARTs-based AN was significantly associated with mortality, since cirrhotics with AN had a significantly higher pooled mortality rate compared to those

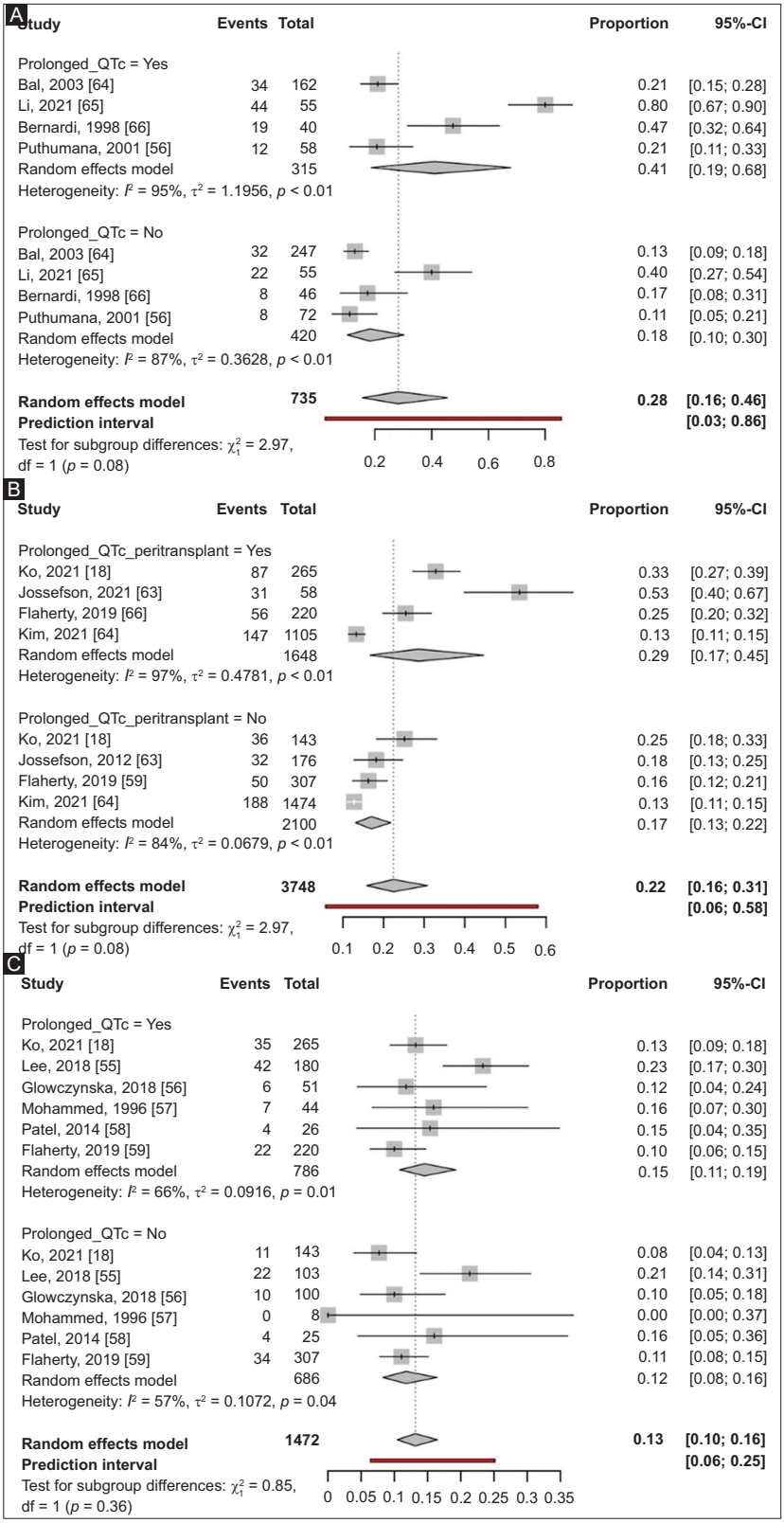

Figure 2 (A) Pooled mortality rate in cirrhotic patients with and without preoperative prolonged QTc in the pre-LT setting. (B) Pooled peri-LT risk of major complications in LT recipients with and without prolonged QTc. (C) Pooled mortality rate in cirrhotic patients with and without preoperative prolonged QTc in the post-LT setting
LT, liver transplantation; CI, confidence interval

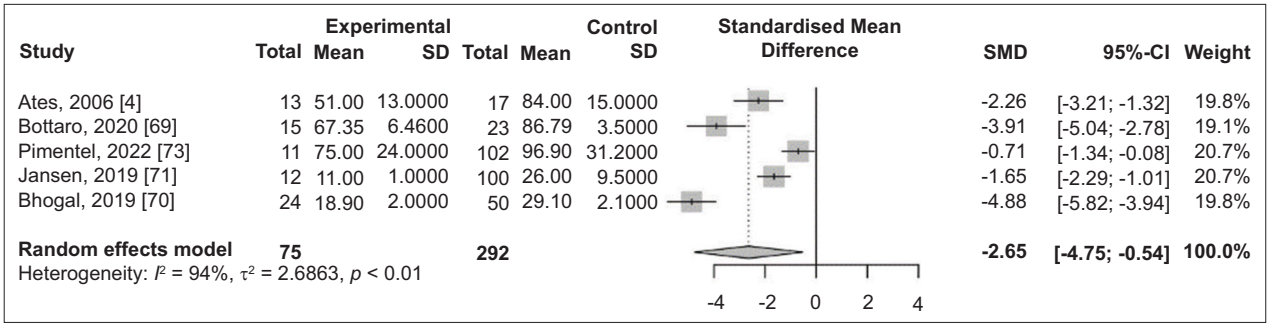

Figure 3 Standardized mean difference of SDNN values between survivors and non-survivors
SDNN, standard deviation of normal-to-normal (NN) intervals on the surface electrocardiogram; SD, standard deviation; CI, confidence interval

without (20% vs. 6%; P=0.01). Interestingly, when patients with cirrhosis were stratified based on the severity of CAN (namely definite vs. possible vs. absent CAN), the only significantly higher risk of mortality was seen in those with definite CAN, compared to those without CAN (21% vs. 5%; P=0.05). This finding aligns with previous studies in patients with T2DM [12,72] and underscores the importance of specific criteria in AN diagnosis.

In addition, regarding HRV-based AN, we found in this meta-analysis that SDNN in cirrhotic patients differed significantly between survivors and non-survivors (SMD 2.59, 95% CI -4.75 to -0.43; P=0.04). In fact, this is the first meta-analysis to investigate the predictive role of HRV indices, especially SDNN, in cirrhosis. In the literature, there is only 1 previous relevant systematic review [19] that showed an association between HRV indices and mortality in the cirrhotic setting, but the authors did not conduct a meta-analysis because of the limited number of studies included.

Concerning the risk for major cirrhosis-related complications, we were not able to perform a meta-analysis. However, based on our systematic review, we found that lower values of specific time and frequency domain HRV indices were associated with a higher risk for HE [70,71]. Moreover, this association was confirmed in patients with CARTs-based AN [53,54]. Interestingly, HRV indices, particularly SDNN, have been correlated with inflammatory biomarkers [60], while a decrease in SDNN has been associated with the progression to acute decompensation and the development of the inflammatory syndrome in acute-on-chronic liver failure [67]. Thus, it could be suggested that the regular assessment of CAN through CARTs or HRV tests might be a valuable tool for stratifying cirrhotics at heightened risk of major complications or death.

QTc prolongation in cirrhosis reflects a delay in ventricular repolarization, mainly observed in the presence of "cirrhotic cardiomyopathy", a term used to describe the long-term impact of cirrhosis on the heart. Although there is a well-established association between QTc prolongation and the presence of CAN in T2DM [6], it is controversial in the setting of cirrhosis [52,57,73,74]. Moreover, it is debatable whether QTc is a good predictor of mortality during the clinical course of cirrhosis [60,61], or of peri- and/or postoperative mortality in the case of LT [18,59,63]. A recent meta-analysis with 3 studies indicated significantly better survival in patients with QTc <440 msec (HR 2.228; 95%CI 1.640-2.815; P<0.001) [17]. In our meta-analysis, based on 4 studies with 735 patients, we found that the pooled mortality rate was lower in patients with QTc <440 msec, compared to those with QTc >440 msec (18% vs. 41%, respectively), but this difference was not significant (P=0.08). This discrepancy may be due to the fact that, in our analysis, we used a different statistical methodology based on the absolute number of deaths and the total population at risk in order to mitigate potential bias. Nevertheless, given the limited number of studies included, the high heterogeneity among them, and the different follow-up periods, more studies are needed to better clarify the impact of QTc prolongation on pre-LT mortality. Interestingly, our study represents the first meta-analysis to investigate the predictive impact of prolonged QTc on peri- and post-LT prognosis. Our findings reveal that the cirrhotics with prolonged QTc, compared with those without, had a higher pooled peri-transplant risk of major complications, although the difference was non-significant (29% vs. 17%; P=0.08). This slightly higher perioperative LT risk may be due to additional perioperative stress and the hemodynamic instability, in the setting of reduced ventricular repolarization and diastolic dysfunction, which characterizes cirrhotic cardiomyopathy. In addition, no difference was found in the post-LT pooled mortality rates between the patients with versus those without pre-LT prolonged QTc (15% vs. 12%; P=0.36). This finding is not surprising, given that QTc tends to improve [17] or may even be fully restored after LT in up to 70% of patients [75]. Nevertheless, more research is necessary before final conclusions can be drawn regarding these issues.

Finally, to our knowledge, only 1 study [20] has focused on the predictive role of impaired BRS in cirrhosis. In that study, Genovesi *et al* [20], concluded that a more severe impairment of BRS was associated with more severe liver dysfunction, worse survival and lower HRV indices.

This meta-analysis represents the first attempt to evaluate the predictive role of all main diagnostic tools for CAN assessment in patients with cirrhosis. Additionally, it is the first study that sought to assess the prognostic ability of preoperative CAN in the peri- and post-LT settings. However, certain limitations should be acknowledged. These include the limited number of studies included in certain subgroup analyses, the variability in the follow-up data, and the absence

of several variables, such as data on the etiology of death or the influence of comorbidities. Furthermore, when investigating the impact of QTc prolongation on the peri-transplant risk of major complications, not all studies provided specific details regarding the nature of these complications.

In conclusion, based on our systematic review/meta-analysis, both CARTs- and HRV-based AN were linked to a higher risk of mortality in cirrhotics, as well as the development of adverse events in the pre-LT setting. Preoperative prolonged QTc, on the other hand, did not seem to be associated with pre-, peri- or post-LT adverse events or mortality. Regular assessment of AN, based on CARTs or HRV indices, might be suggested as a useful prognostic tool in cirrhosis. Future research on determining cutoff values for HRV indices in AN diagnosis could aid clinical implementation.

Summary Box

What is already known:

- Autonomic neuropathy (AN) is a well-established complication in patients with cirrhosis, with a considerably high prevalence
- AN can be evaluated indirectly through cardiovascular autonomic reflex tests (CARTs), rate-corrected QT (QTc) measurement, heart rate variability (HRV), and baroreflex sensitivity tests
- In cirrhosis, AN is considered the result of metabolic, inflammatory, toxic and immunological changes that occur alongside the development of hyperdynamic circulation and portal hypertension

What the new findings are:

- CARTs- and HRV- based AN was associated with mortality in cirrhosis
- CARTs- and HRV-based AN appears to be associated with an increased risk of cirrhosis-related complications
- QTc prolongation does not appear to be a predictor of pre- or post-liver transplantation risk for complications or mortality

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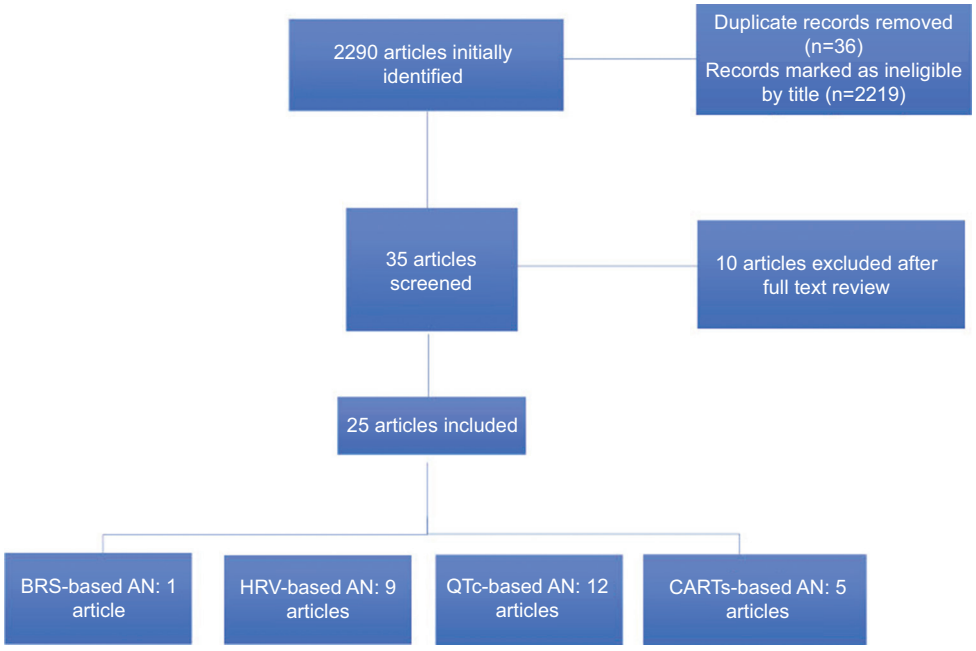
Supplementary material



Supplementary Figure 1 Flowchart

BRS, baroreflex sensitivity; HRV, heart rate variability; QTc, rate-corrected Q-T complex describing time interval between the start of the Q-wave and T-wave of an ECG recording; CARTs, cardiovascular autonomic reflex tests

Supplementary Table 1 Prisma Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
		TITLE	
Title	1	Identify the report as a systematic review.	Page 1
		ABSTRACT	
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	Page 1
		INTRODUCTION	
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Page 1-2
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Page 2
		METHODS	
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Page 3
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Page 2-3
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Page 2-3
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Page 2-3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Page 2-3
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Page 3
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Page 3
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Page 3
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Page 3
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis).	Page 3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Page 3
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Page 3
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Page 3
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Page 3
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Page 3

(Contd...)

Supplementary Table 1 *(Continued)*

Section and Topic	Item #	Checklist item	Location where item is reported
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Page 3
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Page 3
		RESULTS	
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Page 3 and Supplementary Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Page 3
Study characteristics	17	Cite each included study and present its characteristics.	Page 3, Tables 1,2,3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table 1,2,3
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Figure 1,2,3, Pages 3-9
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Tables 1,2,3, Pages 3-9
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Figure 1,2,3, Pages 3-9
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Page 3,6, Figure 1a
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Page 3,6, Figure 1a
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Page 3-9, Figures 1,2,3
		DISCUSSION	
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Page 9-11
	23b	Discuss any limitations of the evidence included in the review.	Page 11-12
	23c	Discuss any limitations of the review processes used.	Page 11-12
	23d	Discuss implications of the results for practice, policy, and future research.	Page 12