SYSTEMATIC REVIEW AND META-ANALYSIS
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Elevated Cardiac Troponin to Detect Acute Cellular Rejection After Cardiac Transplantation: A Systematic Review and Meta-Analysis

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Cardiac troponin is well known as a highly specific marker of cardiomyocyte damage, and has significant diagnostic accuracy in many cardiac conditions. However, the value of elevated recipient troponin in diagnosing adverse outcomes in heart transplant recipients is uncertain. We searched MEDLINE (Ovid), Embase (Ovid), and the Cochrane Library from inception until December 2020. We generated summary sensitivity, specificity, and Bayesian areas under the curve (BAUC) using bivariate Bayesian modelling, and standardised mean differences (SMDs) to quantify the diagnostic relationship of recipient troponin and adverse outcomes following cardiac transplant. We included 27 studies with 1,684 cardiac transplant recipients. Patients with acute rejection had a statistically significant late elevation in standardised troponin measurements taken at least 1 month postoperatively (SMD 0.98, 95% CI 0.33–1.64). However, pooled diagnostic accuracy was poor (sensitivity 0.414, 95% CrI 0.174–0.696; specificity 0.785, 95% CrI 0.567–0.912; BAUC 0.607, 95% CrI 0.469–0.723). In summary, late troponin elevation in heart transplant recipients is associated with acute cellular rejection in adults, but its stand-alone diagnostic accuracy is poor. Further research is needed to assess its performance in predictive modelling of adverse outcomes following cardiac transplant.

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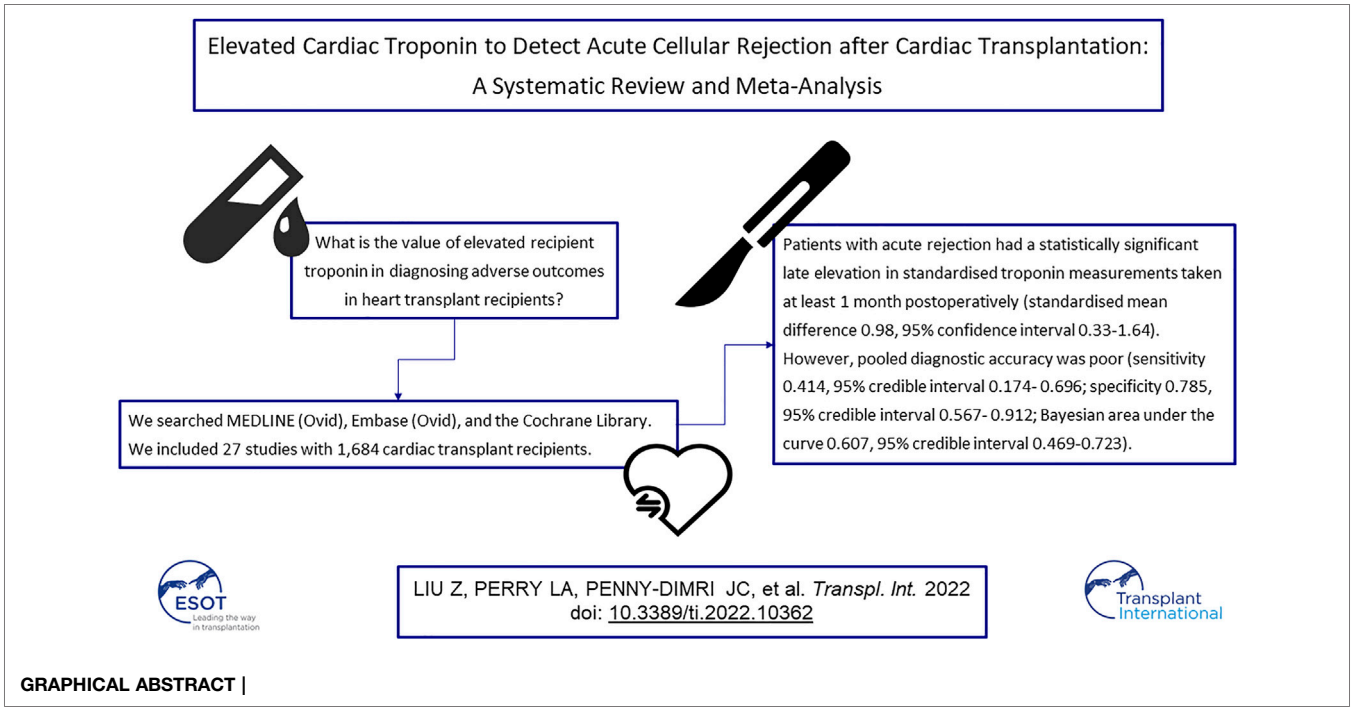
Keywords: heart transplantation, meta-analysis, systematic review, cardiac troponin, acute cellular rejection

Abbreviations: ANOVA, analysis of variance; AUC, area under the ROC curve; BAUC, Bayesian AUC; BSROC, Bayesian summary ROC; CI, confidence interval; CrI, credible interval; EMB, endomyocardial biopsy; ISHLT, International Society for Heart and Lung Transplantation; MOOSE, meta-analysis of observational studies in epidemiology; QUADAS-2, quality assessment of diagnostic accuracy studies 2; ROC, receiver operating characteristic; SMD, standardised mean difference.



GRAPHICAL ABSTRACT |

INTRODUCTION

The endomyocardial biopsy (EMB) has remained the gold standard for detecting acute allograft rejection after cardiac transplant since its introduction in the early 1970s (1). However, this diagnostic test is invasive, can be poorly concordant amongst grading pathologists (2), and repeat procedures are associated with small but significant risks of complications including tricuspid regurgitation, cardiac tamponade, arrhythmias, and haemorrhage (3–5).

In light of these challenges, various biomarkers have been explored as diagnostic alternatives to EMB, contributing to an emerging sphere of multidisciplinary interest in the predictive (both diagnostic and prognostic) ability of routine serum biomarkers for adverse outcomes in a variety of conditions (6–13). In particular, cardiac troponin, a sensitive and specific marker of myocardial injury, is of broad prognostic significance across a range of cardiovascular diseases (14, 15). Although most classically elevated in the context of acute coronary syndromes, elevated troponin levels are also associated with a range of other cardiac and non-cardiac conditions including atrial fibrillation, congestive cardiac failure, myocarditis, myocardial contusion, pulmonary embolism, sepsis, renal failure, and hypovolaemia (16). Both donor and recipient troponin have been associated with adverse outcomes following cardiac transplant (17, 18). We have previously found that troponin elevations in cardiac transplant recipients may be prognostic for primary graft failure, adverse cardiac events, coronary artery disease, and long-term mortality, but its prognostic value in the context of acute rejection up to 1 year after transplant was uncertain (19). Donor troponin elevations though, were not associated with increased 30-day, 1-year, or long-term mortality post cardiac transplant despite increasing the risk of graft rejection at 1 year (but not at 30 days) (20).

However, the diagnostic utility of elevated cardiac troponin is controversial, and this biomarker has yet to be routinely integrated into the diagnostic pathway for acute allograft rejection or recommended by international guidelines (21, 22). Hence, we conducted this systematic review and meta-analysis of elevated cardiac troponin in diagnosing acute allograft rejection in heart transplant recipients.

METHODS

Study Design and Registration

This systematic review and meta-analysis evaluated study level data, and was reported in compliance with the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines (23). Protocol details were prospectively registered on PROSPERO (CRD42021227861) and there were no major protocol deviations.

Eligibility Criteria

We included all original research studies which reported the diagnostic accuracy of elevated recipient troponin to detect adverse outcomes in heart transplant recipients. We excluded non-human studies, abstracts and conference presentations, case reports and series, editorials and expert opinions, review articles, and studies with incompletely reported data.

Search Strategy

We searched MEDLINE (Ovid), Embase (Ovid), and the Cochrane Library from inception to December 2020. Our search strategy included a comprehensive set of search terms for troponin and cardiac transplantation (**Supplementary Material**) (24). We placed no restrictions on language or publication period.

Study Selection

Two authors (ZL and MH) independently screened titles and abstracts of each search result for potentially relevant studies. The same two authors assessed full texts of shortlisted studies against eligibility criteria, with a third author (LAP) adjudicating any disagreements. We reviewed the reference and citation lists of included studies for further potentially relevant studies.

Data Extraction and Management

Two authors (ZL and LAP) independently extracted data from included studies using standardised spreadsheets. We recorded the following, where reported and applicable: study design, population baseline characteristics including comorbidities, operative details, troponin type and measurement details, troponin threshold, definitional threshold of significant rejection by the International Society for Heart and Lung Transplantation (ISHLT) acute cellular rejection grade (25), outcomes, and diagnostic performance measures. Where studies reported dichotomous measures of diagnostic performance, we standardised reported data in confusion matrices and calculated sensitivity and specificity values; where studies reported continuous measures of effect, we standardised data reported as mean and standard deviation and calculated standardised mean differences (SMDs) (26).

Assessment of Methodological Quality and Risk of Bias

Two authors (ZL and LAP) independently assessed the methodological quality of included studies using a modified version of the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool (27), with discrepancies resolved through discussion with a third author (MH). For this study, we expanded the grading of overall risk of bias to three categories (low, unclear, and high risk) from 2 categories (low risk and at risk), for greater consistency with the domain level risk of bias reporting (also low, unclear, and high risk) (28).

Statistical Analysis and Data Synthesis

A detailed description of the statistical analysis is provided in the **Supplementary Material**. Anticipating significant between study variation in included studies, we pre-specified the use of random-effects models in all meta-analyses performed. Where studies reported continuous effect measures, we tabulated SMDs and associated confidence intervals (CIs) of recipient troponin measurements between acute cellular rejection and non-rejection groups, and used random effects inverse variance modelling to generate pooled SMDs. Where studies reported dichotomous effect measures and used receiver operating characteristic (ROC) analysis we noted optimised cut-off values, areas under the ROC curve (AUCs), sensitivities, specificities, and associated 95% CIs. From these, we calculated true positive, false positive, false negative, and true negative rates, and generated Bayesian Summary ROC (BSROC) curves and summary sensitivity, specificity, and Bayesian AUC (BAUC) statistics with 95% credible intervals (CrI) using a bivariate Bayesian modelling approach (29).

We estimated statistical heterogeneity using the I^2 statistic for each meta-analysis. Where reporting of pre-specified covariates was sufficient across included studies, we used meta-regressions to explore possible sources of heterogeneity.

Where there were more than 10 included studies, we formally assessed publication bias with visual inspection of funnel plot skew and a regression test for funnel plot asymmetry (30). All analyses and figures were generated using Review Manager (RevMan) 5.4 (31) and the R statistical packages "metafor" (32) and "bamdit" (33).

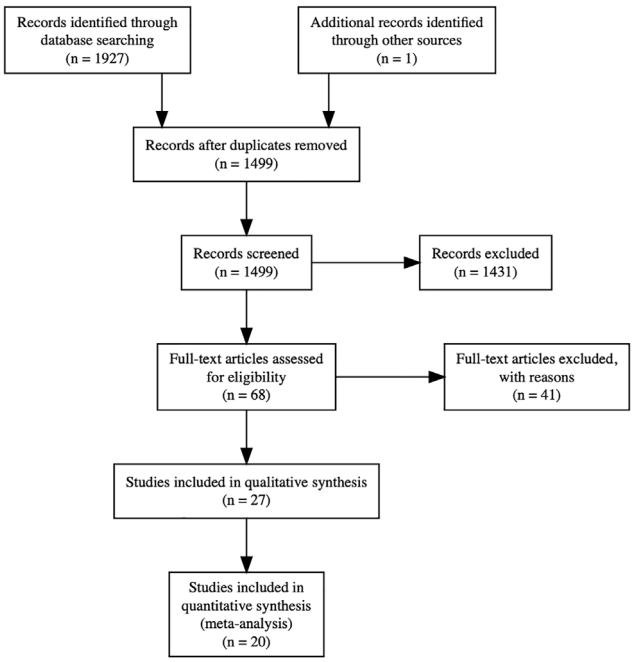


FIGURE 1 | Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. Full text articles were excluded for the following reasons: 19 due to incorrect exposure measurement (donor troponin rather than recipient troponin), 15 due to incorrect study design (prognostic rather than diagnostic), 4 due to lack of troponin reporting, and 3 due to incorrect outcome measurement. Twenty studies were included in quantitative syntheses: for acute cellular rejection in adults with no exclusion of measurements from the early postoperative period, 8 studies were included in the meta-analysis of dichotomous effect measures and 11 studies were included in the meta-analysis of continuous effect measures; for acute cellular rejection in adults with exclusion of measurements from the early postoperative period, 8 studies were included in the meta-analysis of dichotomous effect measures and 5 studies were included in the meta-analysis of continuous effect measures.

TABLE 1 | Characteristics of included studies.

Study ID	Design	Number of patients, number of samples, and demographic	Age (Mean ± SD, years)	Sex (% male)	Troponin type	Troponin measurement period post transplantation and early measurement exclusions	Troponin measurement method	Troponin threshold (ng/ml) and Selection method	Classification threshold for significant rejection and samples with significant rejection (%)	Outcome(s) and effect measure(s)	Modified QUADAS-2 risk of bias
Ahn (34)	Single Centre Retrospective	47 252 Adult	47.4 ± 15.8	68.1%	TnI, hsTnI Index[a]	2 weeks postoperative onwards Exclusions: none and first 2 months after transplantation	ARCHITECT i2000sr STAT TnI and hsTnI assay (Abbott Diagnostics, Abbott Park, Illinois, USA)	1.17 (hsTnI Index) Receiver operating characteristic analysis	ISHLT 2004, 2R 7%	Acute Cellular Rejection Dichotomous and continuous	high
Alexis (35)	Single Centre Prospective	90 256 Adult	48.0 ± 15.2	74.4%	TnT	1 week to 72 months postoperative Exclusions: none and first 3 months after transplantation	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.1 Manufacturer's recommendation	ISHLT 1990, 3A 5%	Acute Cellular Rejection Dichotomous	high
Balduini (36)	Single Centre Prospective	57 149 Adult	37.5 (SD not reported)	Not reported	TnT	1 month to 12 months Exclusions: first 1 month after transplantation	Elecsys Electrochemiluminescence Immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA)	Not reported Not reported	ISHLT 1990, 1B 23%	Acute Cellular Rejection Continuous	unclear
Cauliez (37)	Single Centre Prospective	56 100 Adult	Not reported	Not reported	TnI	10 to 3,807 days (median 458 days) No exclusions	Stratus Cardiac TnI fluorometric enzyme immunoassay (Dade-Behring, Newark, Delaware, USA)	0.6 Manufacturer's recommendation	ISHLT 1990, 2 9%	Acute Cellular Rejection Continuous	unclear
Chance (38)	Single Centre Prospective	145 704 Adult	Not reported	Not reported	TnT	3 days to 206 months (median 29 months) Exclusions: none and first 1 month after transplantation	Elecsys Electrochemiluminescence Immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA)	0.1 Manufacturer's recommendation	ISHLT 1990, 3A 20%	Acute Cellular Rejection Dichotomous and continuous	unclear
Dengler (39)	Single Centre Retrospective	95 271 Adult	48.2 ± 11.4	82.1%	TnT	3 months–70 months (median 15 months) Exclusions: first 3 months after transplantation	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.015 Lower limit of assay detection	ISHLT 1990, 3A 17%	Acute Cellular Rejection Dichotomous and continuous	unclear
Dyer (40)	Single Centre Prospective	42 53 Paediatric	11.1 (SD not reported)	Not reported	hsTnT	3 months onwards (median 24 months) Exclusions: first 3 months after transplantation	Elecsys Electrochemiluminescence Immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA)	0.014 99th percentile of healthy adult reference population	ISHLT 2004, 2R 13%	Acute Cellular Rejection Dichotomous and continuous	unclear
Faulk (41)	Single Centre Prospective	68 151 Adult	30.3 ± 14.2	60.3%	TnT	6 months onwards Exclusions: first 6 months after transplantation	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.1 Manufacturer's recommendation	ISHLT 1990, 3A 6%	Acute Cellular Rejection Dichotomous	high
Forni (42)	Single Centre Prospective	114 385 Adult	52.0 ± 6.0	86.0%	TnI	15 to 1,740 days (mean 640 ± 95 days) No exclusions	Dimension Rx L clinical chemistry system (Siemens Medical Solutions Diagnostics, Erlangen, Germany)	0.1 Manufacturer's recommendation	ISHLT 1990, 3A 3%	Acute Cellular Rejection Dichotomous and continuous	high

(Continued on following page)

TABLE 1 | (*Continued*) Characteristics of included studies.

Study ID	Design	Number of patients, number of samples, and demographic	Age (Mean ± SD, years)	Sex (% male)	Troponin type	Troponin measurement period post transplantation and early measurement exclusions	Troponin measurement method	Troponin threshold (ng/ml) and Selection method	Classification threshold for significant rejection and samples with significant rejection (%)	Outcome(s) and effect measure(s)	Modified QUADAS-2 risk of bias
Garrido (43)	Single Centre Prospective	21 Not applicable Adult	60.0 ± 10.0	81.0%	TnT	1 year onwards No exclusions	Electrochemiluminescence immunoassays with a Modular Analytics E170 analyzer (Roche Diagnostics GmbH, Mannheim, Germany)	0.026 Receiver operating characteristic analysis	Not applicable	Cardiac allograft vasculopathy Dichotomous and continuous	high
Gleissner (44)	Single Centre Retrospective	132 788 Adult	58.5 ± 9.4	85.6%	TnT	3 months–48 months (mean 13 months) Exclusions: first 3 months after transplantation	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.14 Receiver operating characteristic analysis	ISHLT 1990, 3A 13%	Acute Cellular Rejection Dichotomous and continuous	Low
Halwachs (45)	Single Centre Retrospective	15 183 Adult	49.8 ± 13.6	80.0%	TnT	1 day to 2 years No exclusions	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.2 Manufacturer's recommendation	ISHLT 1990, 3A 1%	Acute Cellular Rejection Continuous	unclear
Hossein-Nia (48)	Single Centre Prospective	15 65 Adult	Not reported	Not reported	TnT	Postoperative onwards No exclusions	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.2 Manufacturer's recommendation	ISHLT 1990, 2 16%	Acute Cellular Rejection Continuous	low
Hossein-Nia (46)	Single Centre Prospective	29 Not reported Adult	48.5 ± 7.8	83.9%	TnT	Postoperative onwards (mean 87 ± 32 weeks) No exclusions	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.2 Manufacturer's recommendation	ISHLT 1990, 2 Not reported	Acute Cellular Rejection Dichotomous	unclear
Hossein-Nia (47)	Single Centre Prospective	17 214 Adult	Not reported	Not reported	TnI	Postoperative onwards (mean 61 ± 16 days) No exclusions	TnI Assay (Sanofi Diagnostic Pasteur Ltd., Guildford, United Kingdom)	Not reported Not reported	ISHLT 1990, 2 4%	Acute Cellular Rejection Continuous	unclear
Hsu (49)	Single Centre Prospective	51 71 Adult	47.8 ± 11.3	80.0%	TnI	1 week to 5 years No exclusions	R&D Systems ELISA (R & D Systems USA, Minneapolis, Minnesota, USA)	Not reported Not reported	ISHLT 1990, 2 23%	Acute Cellular Rejection Continuous	high
Mendez (50)	Multicentre Prospective	73 224 Adult	54.0 ± 14.0	71.2%	hsTnT	Within 3 months of surgery to over 18 months, as needed No exclusions	Elecsys Electrochemiluminescence Immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA)	0.017 Receiver operating characteristic analysis	ISHLT 2004, 2R 7%	Acute Cellular Rejection Dichotomous and continuous	low
Moran (51)	Single Centre Prospective	37 85 Paediatric	Median 12.4, range 1.3–30.0	Not reported	TnI, TnT	2.05 ± 2.43 years (median, 0.9; range, 0.03–9.1) No exclusions	Elecsys Electrochemiluminescence Immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA)	TnI: 0.5 Receiver operating characteristic analysis TnT: Not reported	ISHLT 1990, 3A 15%	Acute Cellular Rejection Dichotomous and continuous	high

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TABLE 1 | (*Continued*) Characteristics of included studies.

Study ID	Design	Number of patients, number of samples, and demographic	Age (Mean ± SD, years)	Sex (% male)	Troponin type	Troponin measurement period post transplantation and early measurement exclusions	Troponin measurement method	Troponin threshold (ng/ml) and Selection method	Classification threshold for significant rejection and samples with significant rejection (%)	Outcome(s) and effect measure(s)	Modified QUADAS-2 risk of bias
Mullen (52)	Single Centre Prospective	29 173 Adult	52.0 ± 5.4	79.3%	TnI, TnT[b]	12–564 days (mean 129 ± 9 days) No exclusions	Not reported	Not reported Not reported	ISHLT 1990, 3A 1%	Acute Cellular Rejection Continuous	low
Munoz-Esparza (53)	Single Centre Prospective	72 Not reported Adult	53.0 ± 13.0	75.0%	hsTnT	Within 1 year No exclusions	Elecsys Electrochemiluminescence Immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA)	0.035 Receiver operating characteristic analysis	ISHLT 2004, 2R 43%	Acute Cellular Rejection Dichotomous and continuous	high
Ogawa (54)	Multicentre Prospective	69 683 Adult	50.0 ± 10.0	79.7%	TnT	9–141 weeks (mean 53 ± 26 weeks) No exclusions	Elecsys Electrochemiluminescence Immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA)	Not reported Not reported	ISHLT 1990, 3A 4%	Acute Cellular Rejection Continuous	unclear
Patel (55)	Multicentre Retrospective	98 418 Adult	53.8 ± 12.1	83.0%	hsTnI	1 week—long term (median 1522 (IQR 773–2160) days) No exclusions	ARCHITECT i2000sr STAT high-sensitivity cTnI assay (Abbott Diagnostics, Abbott Park, Illinois, USA)	0.015 Receiver operating characteristic analysis	ISHLT 2004, 2R 5%	Acute Cellular Rejection Dichotomous and continuous	unclear
Siaplaouras (56)	Single Centre Retrospective	25 Not reported Paediatric	Mean 2 months, range 2 weeks–13 years	40.0%	TnI	3 weeks to 4 years No exclusions	Stratus Cardiac TnI fluorometric enzyme immunoassay (Dade-Behring, Newark, Delaware, USA)	0.6 Manufacturer's recommendation	ISHLT 1990, 3A Not reported	Acute Cellular Rejection Dichotomous	high
Vazquez-Rodriguez (57)	Single Centre Prospective	62 259 Adult	Not reported	85.5%	TnT	Postoperative onwards Exclusions: None and first 3 months after transplantation	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.1 Manufacturer's recommendation	ISHLT 1990, 2 25%	Acute Cellular Rejection Dichotomous	low
Wåhlander (58)	Single Centre Prospective	14 78 Paediatric	Not reported	Not reported	TnI	1 month onwards Exclusions: first 1 month after transplantation	Elecsys Electrochemiluminescence Immunoassay (Roche Diagnostics, Indianapolis, Indiana, USA)	0.1 Manufacturer's recommendation	ISHLT 1990, 3A 12%	Acute Cellular Rejection Dichotomous and continuous	unclear
Walpoth (59)	Single Centre Prospective	25 392 Adult	Not reported	Not reported	TnT	Postoperative to 2 years No exclusions	Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	0.2 Manufacturer's recommendation	Texas score, 4 Not reported	Acute Cellular Rejection Continuous	unclear
Wang (60)	Single Centre Prospective	186 358 Adult	Not reported	Not reported	TnI, TnT[b]	Postoperative onwards Exclusions: first 5 weeks after transplantation	TnI: Stratus Cardiac TnI fluorometric enzyme immunoassay (Dade-Behring, Newark, Delaware, USA) TnT: Enzymun-Test TnT enzyme immunometric assay (Boehringer Mannheim Diagnostics GmbH, Mannheim, Germany)	TnI: 1.7 Not reported TnT: 0.07 Not reported	ISHLT 1990, 3A 21%	Acute Cellular Rejection Dichotomous and continuous	high

[a]*Where studies measured both conventional and high sensitivity troponin variants and underwent meta-analysis, high sensitivity troponin was included in quantitative analysis where appropriate.*

[b]*Where studies measured both troponin I and T subtypes and underwent meta-analysis, troponin I measurements was chosen for quantitative synthesis and a sensitivity analysis was performed by including troponin T measurements to determine the impact of this decision. TnT, Troponin T; TnI, Troponin I; hsTnT, High Sensitivity Troponin T; hsTnI, High Sensitivity Troponin I.*

RESULTS

Search Results

We identified 1,927 results through the search, and one additional citation through reference lists. After automatic deduplication, we screened 1,499 titles and abstracts. We reviewed full texts of 68 potentially relevant studies, from which 27 were included in this review, with 20 in quantitative form (**Figure 1**).

Description of Included Studies

Twenty-seven studies (34–60) involving 1,684 cardiac transplant recipients were included. Detailed characteristics of included studies are reported in **Table 1**.

Methodological Quality

Methodological quality was variable. Five studies (44, 48, 50, 52, 57) were deemed low risk of bias, 12 studies (36–40, 45–47, 54, 55, 58, 59) unclear risk of bias due to no specific reporting of certain domain characteristics, and 10 studies (34, 35, 41–43, 49, 51, 53, 56, 60) high risk of bias. The full QUADAS-2 assessment can be found in the **Supplementary Material**.

Descriptive Analyses and Meta-Analysis

Acute Cellular Rejection

Adult

No Temporal Exclusion Criteria.

Dichotomous Measure of Diagnostic Accuracy. Eight studies (35, 38, 42, 50, 53, 55, 57, 60) with 840 participants reported sensitivity, specificity, and AUC values regarding the ability of troponin to diagnose acute cellular rejection in heart transplant recipients. We found a pooled sensitivity of 0.479 (95% CrI 0.190–0.783), specificity of 0.702 (95% CrI 0.395–0.910), and BAUC 0.584 (95% CrI 0.377–0.760) (**Figure 2**).

As one included study (60) measured both troponin I and T values, we performed a sensitivity analysis investigating the effects of including troponin T measurements instead of troponin I in quantitative synthesis. The result was not significantly different; pooled sensitivity was 0.498 (95% CrI 0.206–0.788), specificity 0.696 (95% CrI 0.387–0.901), and BAUC 0.591 (95% CrI 0.385–0.758) (**Supplementary Figure S1**).

Hossein-Nia 1995 (46) reported sensitivity of 0.333 but did not report a corresponding specificity.

We investigated potential sources of statistical heterogeneity with a meta-regression, and found that the troponin assay sensitivity and ISHLT rejection criteria, study year, and number of study centres were significant AUC modifiers (**Supplementary Table S1**). In particular, studies which used high sensitivity troponin assays were also those which used the ISHLT 2004 criteria, and this was associated with a 0.210 increased AUC (p = 0.0006) (**Supplementary Figure S2**). A unit increase in study year was associated with an increased AUC of 0.014 (p = 0.0010), and a multicentre study design was associated with an increased AUC of 0.189 (p = 0.0154) compared to a single centre design (**Supplementary Figure S3**). Notably, the following were not significant AUC modifiers: ISHLT cut-off grade for definition of significant rejection (1R vs. 2R in ISHLT 2004; 2 vs. 3A in ISHLT 1990), prevalence of samples with significant rejection per cohort, troponin threshold, and study risk of bias.

Continuous Measure of Diagnostic Accuracy. Eleven studies (34, 37, 42, 45, 47, 49, 50, 52–55) with 641 participants reported troponin mean differences between those with and without acute cellular rejection. We found that the standardised troponin measurements were not significantly different in those with and without acute cellular rejection (SMD 0.49, 95% CI −0.33–1.31) (**Figure 3**).

As one included study (52) measured both troponin I and T values, we performed a sensitivity analysis investigating the effects of including troponin T measurements instead of troponin I in quantitative synthesis. The result was not significantly different (pooled SMD 0.26, 95% CI −0.64–1.16) (**Supplementary Figure S4**).

Wang 1996 (60) reported mean measurements in both troponin I and T between acute cellular rejection vs. non-rejection groups (0.216 vs. 0.707 and 0.134 vs. 0.088 ng/ml respectively); however, neither were statistically significant (p = 0.357 and p = 0.374 respectively). Contrary to this, Walpoth 1998 (59) reported statistically significant elevations (no measure of statistical significance reported) troponin T measurements between acute cellular rejection (0.77 ± 0.80 ng/ml) and non-rejection (0.02 ± 0.05 ng/ml) groups. Hossein-Nia 1993 (48) reported an elevated median troponin T in those with acute cellular rejection compared to without (0.370 vs. 0.300 ng/ml); however, statistical significance was not reported.

Between-study statistical heterogeneity was considerable (I^2 statistic 95%). We investigated potential sources of statistical heterogeneity with a meta-regression, and found that the troponin assay sensitivity and ISHLT rejection criteria (overlapping exactly; all studies using high sensitivity troponin also used ISHLT 2004 criteria), study year, troponin threshold, and standard deviation of age were significant SMD modifiers and accounted for up to 49% of heterogeneity on univariable analysis (**Supplementary Table S2**). Notably, the following were not significant SMD modifiers: ISHLT cut-off grade for definition of significant rejection (1R vs. 2R in ISHLT 2004; 2 vs. 3A in ISHLT 1990), prevalence of samples with significant rejection per cohort, and study risk of bias.

A regression test for funnel plot asymmetry was unable to detect significant publication bias (p = 0.1023) (**Supplementary Figure S5**).

Early Postoperative Exclusion Criteria.

Dichotomous Measure of Diagnostic Accuracy. After exclusion of measurements from the early postoperative period (at least 1 month postoperatively), eight single centre studies (34, 35, 38, 39, 41, 44, 57, 60) with 825 participants reported sensitivity, specificity, and AUC values regarding the ability of troponin to diagnose acute cellular rejection in heart transplant recipients. We found a pooled sensitivity of 0.414 (95% CrI 0.174–0.696), specificity of 0.785 (95% CrI 0.567–0.912), and BAUC 0.607 (95% CrI 0.469–0.723) (**Figure 4**).

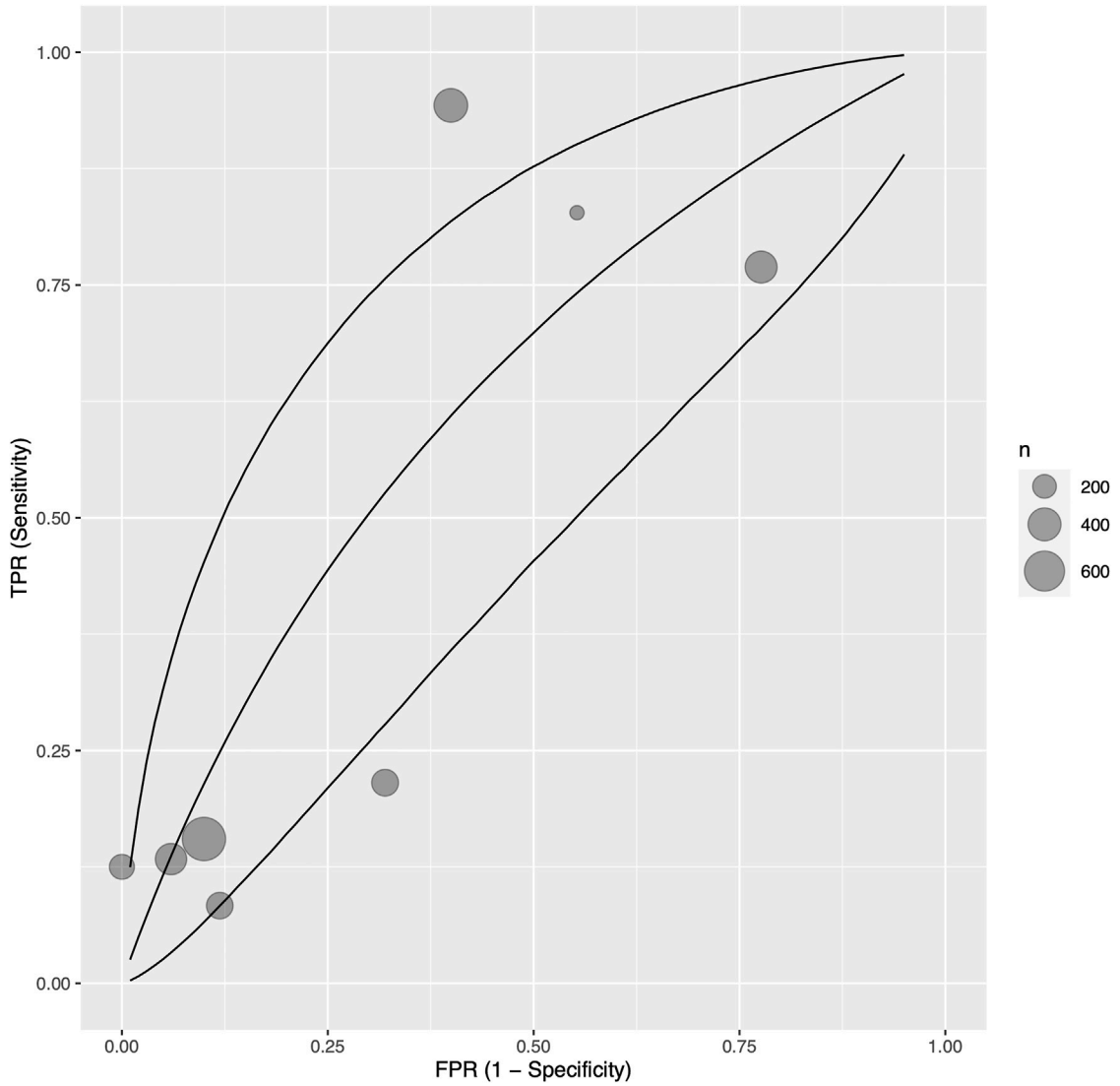

FIGURE 2 | Bayesian summary receiver operating characteristic curve showing summary diagnostic accuracy of recipient troponin in acute rejection with no temporal exclusions, with upper and lower 95% credible bands. Each filled circle represents one included study, the size of which is weighted in proportion to the study's sample size.

We investigated potential sources of statistical heterogeneity with a meta-regression, and found that the troponin assay sensitivity and ISHLT rejection criteria, and troponin type, and study design were significant AUC modifiers (**Supplementary Table S3**). In particular, use of high sensitivity troponin I assays by one study (34) corresponded exactly to use of ISHLT 2004 criteria, and was associated with a 0.257 increase in AUC ($p = 0.0270$) (**Supplementary Figure S6**). Of note, the length of early postoperative exclusion (from 1 month to 6 months) was not associated with significant changes to troponin's diagnostic ability. Additionally, the following were not significant SMD modifiers: ISHLT cut-off grade for definition of significant rejection (1R vs. 2R in ISHLT 2004; 2 vs. 3A in ISHLT 1990), prevalence of samples with significant rejection per cohort, troponin threshold, and study risk of bias.

Continuous Measure of Diagnostic Accuracy. Five studies (34, 36, 38, 39, 44) with 476 participants reported troponin mean differences between those with and without acute cellular rejection. We found that the standardised troponin measurements were higher in those with acute cellular rejection, and that this was a large and statistically significant effect (SMD 0.98, 95% CI 0.33–1.64) (**Figure 5**).

Wang 1996 (60) reported mean measurements in both troponin I and T between acute cellular rejection vs. non-rejection groups (0.059 vs. 0.102 and 0.069 vs. 0.044 ng/ml respectively) after measurements during the first 5 weeks were

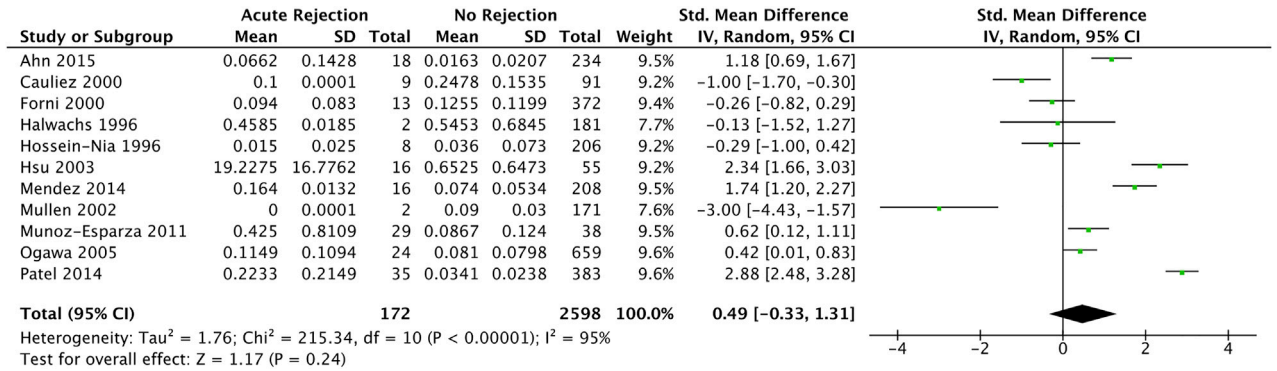

FIGURE 3 | Forest plot of standardised mean differences for elevated recipient troponin in diagnosing acute rejection post cardiac transplantation, with no temporal exclusions.

excluded; however, neither were statistically significant ($p = 0.713$ and $p = 0.382$ respectively).

Statistical heterogeneity was considerable (I^2 statistic 95%); however, meta-regression was not possible due to insufficient study numbers ($n = 5$).

Paediatric

No Temporal Exclusion Criteria. Two studies (51, 56) with 62 participants investigated the association between troponin and adverse outcomes in cardiac transplantation recipients. Moran 2000 (51) found that troponin I values differed significantly across ISHLT 1990 grades 0, 1, 2, and 3 on analysis of variance (ANOVA) ($p = 0.034$), with a diagnostic sensitivity of 0.500 and specificity of 0.776. However, troponin T values were not significantly different across ISHLT 1990 grades 0, 1, 2, and 3 on ANOVA ($p = 0.16$)—sensitivity was 0.421 and specificity was 0.837. Siaplaouras 2003 (56) found a sensitivity of 0.750, but did not report a corresponding specificity.

Early Postoperative Exclusion Criteria. After exclusion of measurements from the early postoperative period (at least 1 month postoperatively), three studies (40, 56, 58) with 81 participants studied the association between troponin and adverse outcomes in cardiac transplantation recipients. Excluding measurements from the first 3 months after transplantation, Dyer 2012 (40) reported a statistically significant elevation in high sensitivity troponin T values in those with acute cellular rejection (SMD 2.44, 95% CI 1.51–3.37), and a sensitivity of 0.857 and specificity of 0.913. Wa˚hlander 2002 (58) found that conventional troponin T values were also elevated in those with acute cellular rejection (SMD 1.43, 95% CI 0.70–2.17), reporting a sensitivity of 0.556 and specificity of 0.768. Siaplaouras 2003 (56) found a sensitivity of 0.591, but did not report a corresponding specificity.

DISCUSSION

In this systematic review and meta-analysis of 27 diagnostic observational studies involving over 1,600 patients, we provide the most up-to-date evidence of the value of troponin in diagnosing adverse outcomes in heart transplant recipients. We found that late troponin levels (measured at least 1 month postoperatively) were significantly elevated in adult recipients with acute cellular rejection. Diagnostic accuracy of plasma troponin was slightly higher for measurements taken after the early postoperative period compared to those taken across all postoperative periods; however, the diagnostic ability of both were poor.

The poor diagnostic utility of troponin in the immediate to early post-operative period in detecting acute cellular rejection is not surprising given the manifold pathologies that can drive elevated plasma troponin in this setting (61). Our results suggest that this "early" post-operative period is confined to 1 month, with no significant difference in diagnostic accuracy of troponins measured after 1 month compared to 6 months post-transplant. However, risk of rejection is also highest in the first months after transplant (62), coinciding with this period of poorer diagnostic utility. Biomarkers capable of distinguishing between early acute rejection and routine perioperative cardiac injury are needed.

Additionally, our meta-regressions suggest that the utility of troponin may be improving over time, with study year being positive effect modifier in multiple analyses. While this is possibly attributable to the transition to high-sensitivity troponin assays, these findings are also confounded by a perfect overlap with a transition to the ISHLT 2004 criteria for acute cellular rejection.

Our search revealed one other systematic review, without meta-analysis, on a similar topic (63). However, this literature search excluded key databases (Embase and the Cochrane Library) and therefore may have lacked sensitivity, with only 88 abstracts identified and 12 studies included in the final analysis; there was no formal assessment of methodological quality; and there was no quantitative meta-analysis or assessment and management of potential sources of heterogeneity. Hence, we believe our study adds to the existing knowledge base, and provides the most recent and high-quality synthesis regarding the diagnostic value of cardiac troponin in heart transplant recipients.

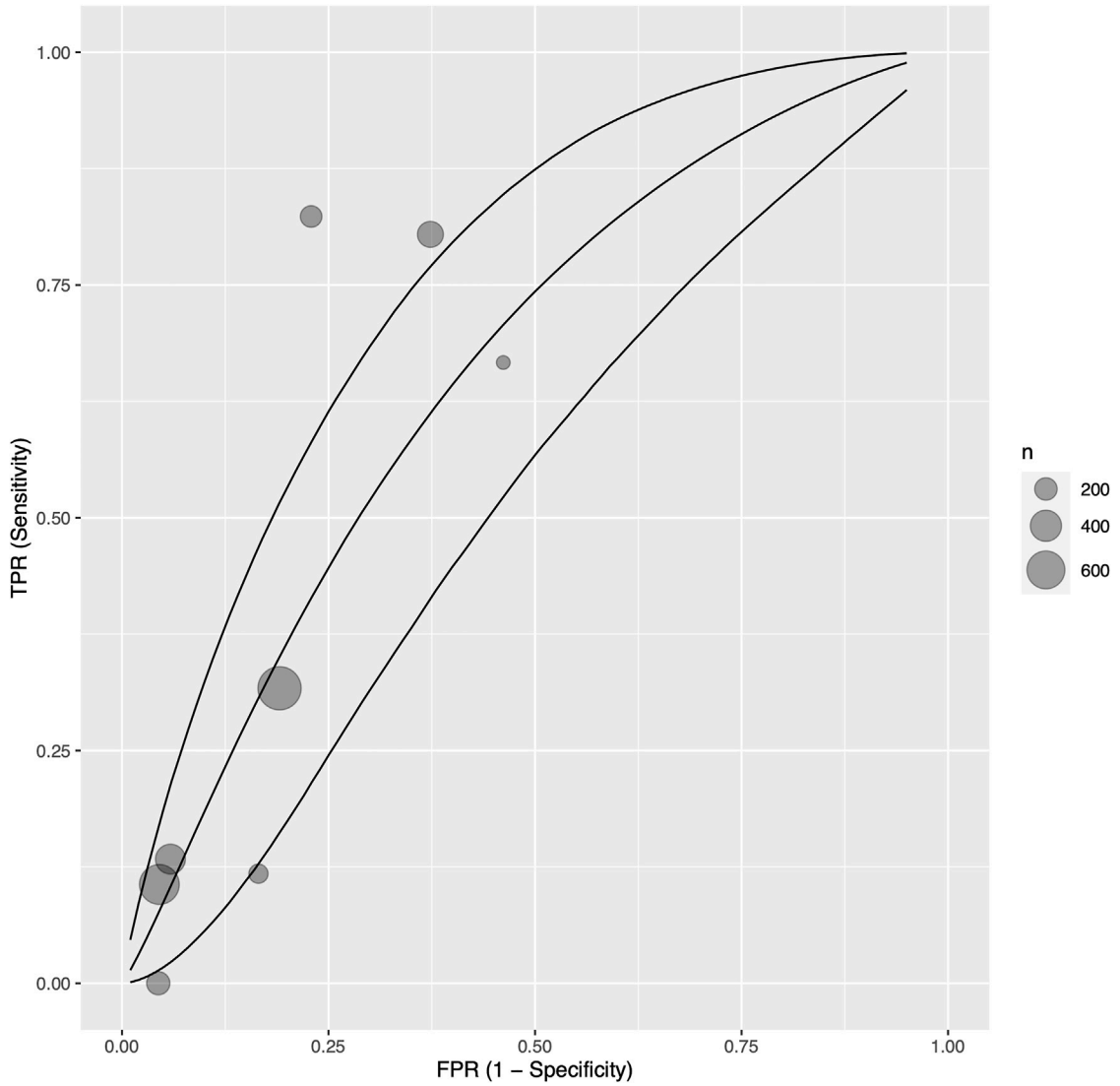

FIGURE 4 | Bayesian summary receiver operating characteristic curve showing summary diagnostic accuracy of recipient troponin in acute rejection with early postoperative measurements (at least 1 month postoperative) excluded, with upper and lower 95% credible bands. Each filled circle represents one included study, the size of which is weighted in proportion to the study's sample size.

	Acute Rejection			No Rejection				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Ahn 2015	0.0593	0.1281	17	0.0096	0.0096	166	18.8%	1.26 [0.75, 1.78]
Balduini 2003	0.1063	0.0958	34	0.06	0.0445	115	19.8%	0.77 [0.38, 1.16]
Chance 2001	0.1061	0.0525	39	0.0578	0.022	624	20.2%	1.95 [1.61, 2.29]
Dengler 1998	0.0601	0.0576	46	0.0276	0.0384	369	20.3%	0.79 [0.48, 1.10]
Gleissner 2003	0.133	0.1566	101	0.1051	0.1406	687	20.9%	0.20 [−0.01, 0.40]
Total (95% CI)			**237**			**1961**	**100.0%**	**0.98 [0.33, 1.64]**

Heterogeneity: Tau² = 0.52; Chi² = 78.42, df = 4 (P < 0.00001); I² = 95%
Test for overall effect: Z = 2.96 (P = 0.003)

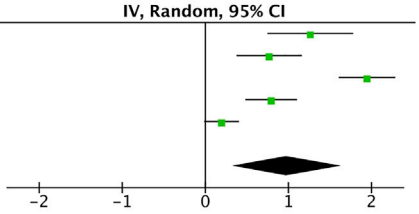

FIGURE 5 | Forest plot of standardised mean differences for elevated recipient troponin in diagnosing acute rejection post cardiac transplantation, with early postoperative measurements (at least 1 month postoperative) excluded.

Our review should be interpreted with the following limitations. While five studies were identified to be at low risk of bias, the 22 remaining studies were at unclear or high risk of bias; reassuringly though, study risk of bias was not found to be a significant effect modifier in all meta-regressions where this was possible. Studies did not report timing of troponin sample

procurement—before vs. after EMB—despite this being a possible confounder as procedure related injury can occur. The majority of studies were single centre, raising potential concerns for external validity. Finally, despite our efforts in determining significant sources of statistical heterogeneity, we were not able to account for all observed statistical heterogeneity. Although our prespecified use of a random-effects model is a strength of our study design, our findings are nonetheless tempered by unaccounted heterogeneity—an inherent part of meta-analysis methodology—which may be attributable to systematic differences in unreported study baseline characteristics as well as other study and patient-level factors. Large, high quality, randomised studies would be needed to control for these unmeasured factors in particular.

In accordance with international guidelines (21, 22), our results do not support the routine use of troponin for surveillance or diagnosis of acute cellular rejection. However, our work identifies many opportunities for future research. The current gold standard diagnostic test for acute cellular rejection involves an invasive EMB which exposes patients to small but significant risks (3–5) and can be associated with poor pathological concordance (2); safer and more effective diagnostic tests are urgently needed. While numerous imaging parameters and biomarkers have been investigated for this purpose, donor-derived cell-free DNA has recently emerged as a promising, non-invasive marker of acute rejection detection (64). Not only is donor-derived cell-free DNA able to detect episodes of rejection with remarkable sensitivity and specificity, but it may also be able to distinguish between acute cellular rejection and antibody mediated rejection, at time points earlier than possible with EMBs (65). As accurate as any one diagnostic marker may be however, experience from multiple disciplines has supported the implementation of well-selected multi-biomarker diagnostic panels over any singular biomarker (66–68). Accordingly, opportunity exists to assess elevated high-sensitivity cardiac troponin—a sensitive and specific marker of the cardiomyocyte death which occurs during acute rejection—in conjunction with emerging biomarkers representing different pathophysiological aspects of acute cellular rejection to optimise the "liquid biopsy" approach and reduce uncertainty and clinical risk of the current EMB approach. While the diagnostic ability of troponin (in the early postoperative month in particular) as a single parameter is insufficient to warrant implementation, whether or not its diagnostic utility can be enriched by integration into sophisticated multivariable diagnostic models with other non-invasive haematological and clinical markers is a field with significant potential. High-sensitivity troponin in particular may possess sufficiently high negative predictive value aid in ruling out acute cellular rejection (55, 63). Additionally, in order to optimise methodological quality and minimise risk of study bias, future researchers should design and report diagnostic test accuracy studies in accordance with QUADAS-2, among other design and reporting guidelines.

CONCLUSION

In this systematic review and meta-analysis, we found a positive association between late troponin elevation and acute cellular rejection in adults, however diagnostic performance was insufficient to support its routine use in the diagnostic pathway. Further research is warranted to assess whether the addition of troponin to emerging biomarkers of acute cellular rejection, such as circulating cell-free DNA, could lead to an enhanced "liquid biopsy" capable of superseding invasive testing.

AUTHOR CONTRIBUTIONS

ZL—Data acquisition, analysis, and interpretation, drafting and critical revisions of manuscript. LP—Study conception, data interpretation, critical revisions of manuscript. JP-D—Study conception, data analysis, critical revisions of manuscript. MH—Data acquisition, analysis, and critical revisions of manuscript. IO—Data acquisition and critical revisions of manuscript. MP—Data interpretation and critical revisions of manuscript. RS—Data interpretation and critical revisions of manuscript. JS—Data interpretation and critical revisions of manuscript. All authors approve the version to be published.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontierspartnerships.org/articles/10.3389/ti.2022.10362/full#supplementary-material

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