

Prognostic Significance of Elevated Troponin in Adult Heart Transplant Recipients: A Systematic Review and Meta-Analysis

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Abstract

Objectives: Cardiac troponin is a highly specific biomarker of myocardial injury that is of prognostic significance in a range of cardiovascular diseases. However, the prognostic value of elevated troponin in cardiac transplant recipients is uncertain. We aimed to evaluate the prognostic value of elevated cardiac troponin in predicting adverse recipient outcomes following heart transplant.

Materials and Methods: We searched MEDLINE (Ovid), Embase (Ovid), and the Cochrane Library from inception until December 2020 and included studies reporting associations between elevated recipient troponin and outcomes after cardiac transplant. We generated summary odds ratios for associations with short- and long-term adverse events and used descriptive analyses where meta-analyses were inappropriate.

Results: We included 15 studies involving 1830 patients undergoing cardiac transplant. The risk of primary graft failure was greater in recipients with elevated troponin than in those without (odds ratio = 3.09; 95% CI, 1.08-8.87). Considerable interstudy heterogeneity (I² statistic 98%) was partially explained by variations in study design, troponin subtype, and overall risk of bias. Descriptive analyses suggested associations between elevated recipient troponin and long-term adverse cardiac events, coronary artery disease, and mortality. **Conclusions:** Elevated cardiac troponin in cardiac transplant recipients may be prognostic for primary

graft failure, adverse cardiac events, coronary artery disease, and mortality. Further high-quality, prospective, and multicenter research is needed to demonstrate the clinical applicability of these findings.

Key words: Biomarker, Graft failure, Myocardial injury

Introduction

Although numerous risk stratification tools exist to predict patient outcomes after cardiac transplant, their clinical utility is limited by poor discriminative ability.¹ A recent systematic review identified 16 models for predicting adverse outcomes after cardiac transplant; however, no single model was sufficiently prognostic to merit recommendation over others.¹ In particular, few prognostic models have incorporated recipient serum biomarkers beyond bilirubin and renal function, despite their routine measurement after cardiac transplant.¹

In an attempt to enrich existing clinical risk prediction models, an emerging field of research has aimed to evaluate the prognostic value of additional blood-based indices,²⁻⁹ including cardiac troponin. Cardiac troponin is a highly specific marker of myocardial injury that is of broad predictive significance across a range of cardiovascular conditions.¹⁰⁻¹³ A recent systematic review investigating the utility of serum troponin in diagnosing acute cellular rejection after heart transplant found that high-sensitivity troponin assays may have sufficient sensitivity and negative predictive value to exclude acute cellular rejection and limit the need for surveillance endomyocardial biopsies¹⁴; however, the prognostic value of troponin is unclear.

We therefore conducted this systematic review and meta-analysis of the prognostic value of elevated cardiac troponin in predicting adverse recipient outcomes after cardiac transplant.

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Materials and Methods

Study design and registration

This systematic review and meta-analysis of prognostic observational studies was designed in accordance with the latest methodological guidance^{15,16} and was reported in compliance with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines.¹⁷ Protocol details were prospectively registered on PROSPERO (CRD42021227861); there were no major protocol deviations. This study design did not require review board approval; in addition, this study analyzed data at the study level, so individual patient consent was not required.

Eligibility criteria

We included original research studies that reported the prognostic association between recipient troponin and primary graft failure, acute cellular rejection, acute kidney injury, adverse cardiac events, coronary artery disease, and mortality after cardiac transplant. We excluded abstracts and conference presentations, case reports, case series, editorials, expert opinions, publications with incompletely reported data, and nonhuman studies.

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 heart transplantation.¹⁸ We placed no restrictions on language or publication period. Our MEDLINE search strategy was as follows: ((exp Troponin/ OR troponin.mp.) AND (exp Heart Transplantation/ OR ((heart* adj3 transplant*) OR (cardiac adj3 transplant*).mp.)). This strategy was adapted for Embase and the Cochrane Library.

Study selection

Two authors (ZL and MH) independently screened titles and abstracts of each search result for potentially relevant studies. The full texts of these shortlisted studies were extracted and assessed against eligibility criteria independently. A third author (LAP) adjudicated any disagreements. We also reviewed the reference and citation lists of

included studies for additional potentially relevant studies.

Data extraction and management

Two authors (ZL and LAP) independently used standardized spreadsheets to extract data from included studies. Where reported, the following were recorded: study design, population baseline characteristics, operative details, follow-up time, preoperative history of comorbidities, association between troponin values and adverse recipient outcomes (maximally adjusted odds ratios [ORs], hazard ratios [HRs], or mean differences [MDs]), troponin subtype and means of measurement, and threshold for determining troponin elevation if applicable. We evaluated associations between elevated troponin and the following outcomes: primary graft failure, acute rejection, acute kidney injury, adverse cardiac events, coronary artery disease, and mortality.

For studies that compared troponin levels between groups with and without the outcomes of interest, we standardized the reported data into means and standard deviations¹⁹ and calculated the log OR from the standardized mean difference.²⁰ For studies that reported data in graphical display only, we extracted numerical data using validated online software.^{21,22}

Assessment of methodological quality

Two authors (ZL and LAP) independently assessed the methodological quality of included studies using the Quality in Prognosis Studies (QUIPS) tool,²³ with discrepancies resolved through discussion with a third author (MH). The Cochrane Prognosis Methods Group recommends the use of the QUIPS tool when assessing risk of bias in prognostic factor studies, which evaluates methodological quality over 6 domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting.

Statistical analyses and data synthesis

We tabulated the maximally adjusted ORs with associated 95% CIs from each study and generated summary estimates using random-effects inverse-variance modeling.

We estimated statistical heterogeneity using the I^2 statistic for each outcome. We were unable to

perform meta-regression due to insufficient (<10) study numbers in each analysis.²⁴ However, we explored potential sources of between-study heterogeneity with a series of subgroup analyses, investigating the impact of troponin subtype (troponin I, troponin T, and high sensitivity variants), study risk of bias, and study design, where relevant, on pooled effect sizes. For outcomes where meta-analysis could not be performed because of variable reporting or significant interstudy heterogeneity, we performed qualitative descriptive analyses.

When there were fewer than 10 included studies, publication bias could not be formally assessed.²⁵ All analyses and figures were generated using Review Manager (RevMan) 5.4.²⁶

Results

Search results

The search returned 1927 results. One additional citation was identified from reference lists. After duplicates were removed, 1499 studies underwent title and abstract screening. Sixty-eight potentially relevant studies underwent full-text review, from which 15 studies were included in this study. Of these, 4 studies were included in a quantitative meta-analysis (Figure 1).

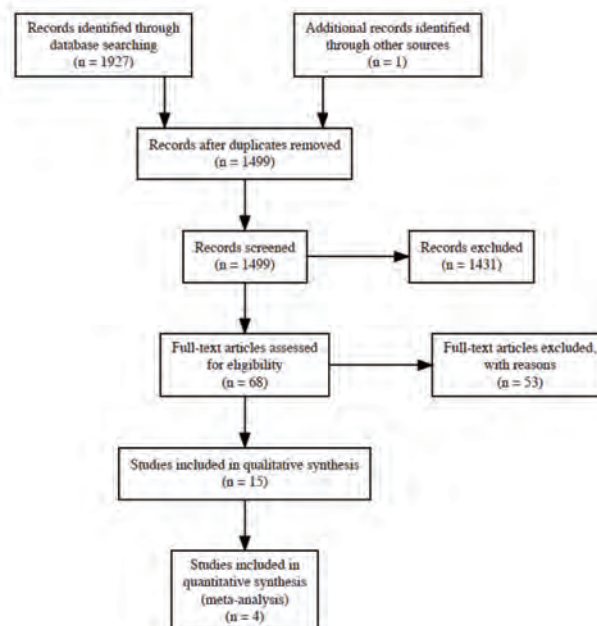
Description of included studies

Fifteen studies²⁷⁻⁴¹ involving 1830 patients undergoing cardiac transplant were included. All patients were adults. Detailed characteristics of included studies are shown in Table 1.

Methodological quality

Overall risk of bias was variable across studies as assessed by the QUIPS tool. Five studies^{28,29,32,35,36} were graded low risk of bias, 6 studies^{27,31,34,38,39,41} were graded moderate, and 4 studies^{30,33,37,40} were graded as having high overall risk of bias. The full QUIPS assessment is shown in Table 2.

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), 22 due to incorrect study design (diagnostic rather than prognostic), 7 due to lack of troponin reporting, 4 due to incorrect outcome measurement, and 1 due to identical cohorts to included studies.

Primary graft failure

From 4 studies^{27,31,39,40} involving 965 patients, we found a positive association between elevated recipient troponin and occurrence of primary graft failure after cardiac transplant (OR = 3.09; 95% CI, 1.08-8.87) (Figure 2).

Interstudy statistical heterogeneity was considerable (I^2 statistic 98%). We analyzed potential sources of heterogeneity with a series of subgroup analyses, grouping studies by troponin subtype, risk of bias, and study design, and investigated whether or not subgroup differences could account for observed between-study heterogeneity. All 3 studies^{27,31,39} measuring troponin I were deemed as having moderate risk of bias, and 1 study⁴⁰ measuring high-sensitivity troponin T had high risk of bias. Between-study heterogeneity was partly

Figure 2. Forest Plot for Elevated Recipient Troponin in Predicting Primary Graft Failure After Cardiac Transplant

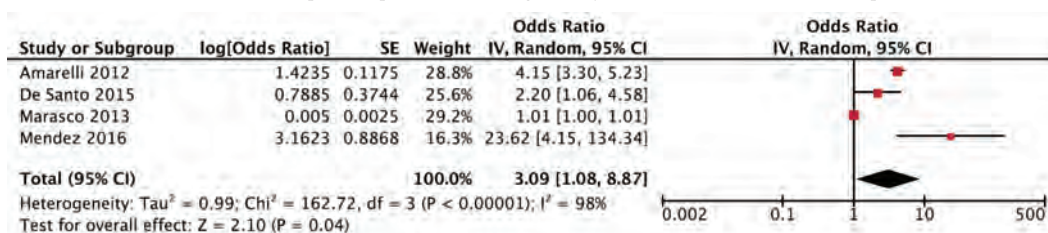


Table 1. Characteristics of Included Studies

Study	Design	Sample Size	Age (mean ± SD), y	Sex, % male	Troponin Type	Troponin Measurement Time & Method	Follow-Up Time (Long Term Outcomes Only)	Troponin Threshold (ng/mL) & Selection Method	Outcomes Measured	QUIPS Risk of Bias
Amarelli ²⁷	Single center, prospective	317	47.2 ± 14.0	79.8%	TnI	Postoperative day 1; method NR	NA	NR; NR	Primary graft failure	Moderate
Ambrosi ²⁸	Single center, prospective	100	55.6 ± 17.6	70.0%	hsTnI	13.0 ± 6.0 (mean ± SD) y post-Tx; ADVIA Centaur ECI (Siemens Medical Solutions Diagnostics)	21.3 ± 4.9 (mean ± SD) mo after troponin measurement	0.006; assay lower detection threshold	Cardiac events (cardiac death, acute coronary syndrome, coronary revascularization, hospitalization for cardiac causes)	Low
Battes ²⁹	Single center, retrospective	77	49.0 ± 9.2	67.5%	TnT	1 wk to 1 y post-Tx; Elecsys ECI (Roche Diagnostics)	NA	0.02; clinical upper reference limit	Acute rejection	Low
Biagioli ³⁰	Single center, prospective	18	54.5 ± 10.5	77.8%	TnI	Days 1 and 7 post-Tx (higher measurement taken); ADVIA Centaur chemiluminescence immunoassay (Bayer Healthcare)	NA	NR; NR	Acute rejection	High
De Santo ³¹	Single center, prospective	362	47.8 ± 13.7	79.8%	TnI	Postoperative day 1; method NR	NA	10; NR	Primary graft failure, AKI	Moderate
Erbel ³²	Single center, retrospective	141	Not reported	71.6%	hsTnT	6 wk post-Tx; Elecsys ECI (Roche Diagnostics)	5 y post-Tx	0.03355; ROC analysis	Mortality (1 year, 5 year)	Low
Esmaili-bandboni ³³	Single center, prospective	9	40.7 ± 11.8	66.7%	TnT	Postoperative days 1 and 3; Elecsys ECI Roche Diagnostics)	NA	NR; NR	Acute rejection resulting in death within 1 mo post-Tx	High
Faulk ³⁴	Single center, prospective	68	30.3 ± 14.2	60.3%	TnT	68.8 ± 11.9 (mean ± SD) mo post-Tx; Enzymun-Test TnT (Boehringer Mannheim)	39.5 ± 12.9 (mean ± SD) mo after troponin measurement	0.1; NR	CAD	Moderate
Franeková ³⁵	Single center, prospective	121	53.9 ± 12.9	84.3%	hsTnT	10 d post-Tx; hsTnT STAT kits Roche Cobas 6000 analyzer (Roche Diagnostics)	NA	0.014; 99th percentile of healthy reference population	Acute rejection, 5-year mortality	Low
Hofmann ³⁶	Single center, prospective	108	55.0 ± 12.0	75.9%	hsTnT	NR; hsTnT quantitative ECI Cobas 411 (Roche Diagnostics)	4.1 ± 4.7 (mean ± SD) y after troponin measurement	0.014; 99th percentile of healthy reference population	Cardiac events (cardiac death, nonfatal myocardial infarction, percutaneous coronary intervention)	Low
Hökl ³⁷	Single center, prospective	17	Not reported	Not reported	TnT	Immediately post-Tx to 3 y; method NR	3 y post-Tx	NR; NR	CAD	High
Labarrere ³⁸	Single center, prospective	110	48.4 ± 10.0	67.3%	TnI	Immediately post-Tx to 1 y; OPUS Immunoassay System/OPUS Plus Analyzer (Dade Behring)	100 mo post-Tx	0.5; assay lower detection threshold	CAD, mortality or retransplant	Moderate
Marasco ³⁹	Single center, retrospective	215	48.5 ± 13.9	77.7%	TnI	Postoperative day 1; method NR	NA	NR; NR	Primary graft failure	Moderate
Mendez ⁴⁰	Single center, prospective	71	54.0 ± 12.0	73.0%	hsTnT	On ICU arrival; Elecsys ECI (Roche Diagnostics)	NA	2; ROC analysis	Primary graft failure	High
Mirabet ⁴¹	Single center, retrospective	96	47.0 ± 16.0	78.0%	hsTnT	9 ± 7 y post-Tx; Elecsys ECI Cobas e601 (Roche-Diagnostics)	45 ± 15 (mean ± SD) mo after troponin measurement	0.021; ROC analysis	Cardiac events (cardiac death, acute myocardial infarction or angina, LVEF <50%, or HF not due to an acute rejection)	Moderate

Abbreviations: AKI, acute kidney injury; CAD, coronary artery disease; ECI, electrochemiluminescence immunoassay; HF, heart failure; hsTnI, high-sensitivity troponin I; hsTnT, high-sensitivity troponin T; ICU, intensive care unit; LVEF, left ventricular ejection fraction; NA, not applicable; NR, not reported; QUIPS, Quality in Prognosis Studies; ROC, receiver operating characteristic; TnI, troponin I; TnT, troponin T; Tx, transplant

Figure 3. Forest Plot for Elevated Recipient Troponin in Predicting Primary Graft Failure After Cardiac Transplant: Subgroup Analysis by Troponin Subtype and Risk of Bias

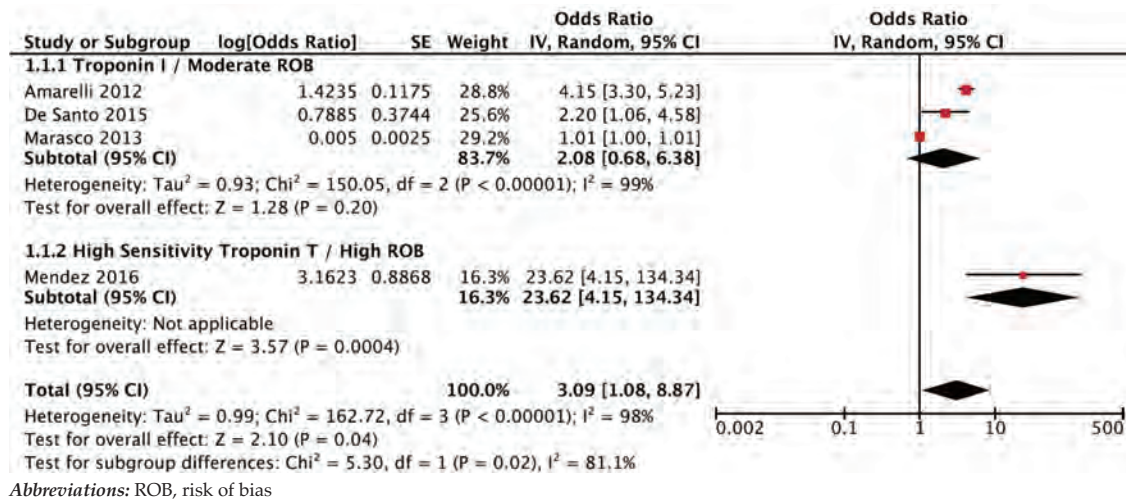
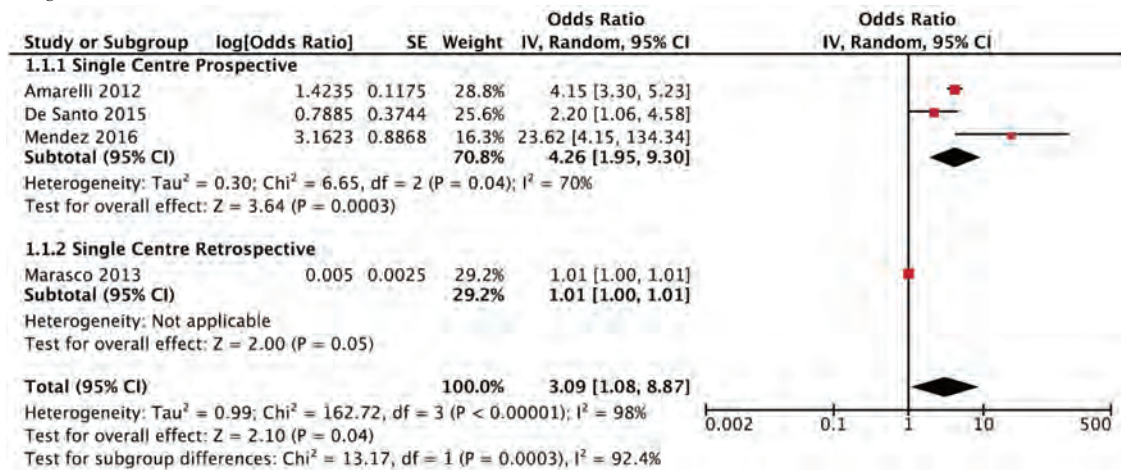


Figure 4. Forest Plot for Elevated Recipient Troponin in Predicting Primary Graft Failure After Cardiac Transplant: Subgroup Analysis by Study Design



between elevated troponin and postoperative acute kidney injury, albeit with a statistically significant difference (OR = 1.031; 95% CI, 1.001-1.064).

Adverse cardiac events

Three studies,^{28,36,41} which included 304 patients, reported associations between troponin and long-term adverse cardiac events. Adverse cardiac events were variably defined by the study authors (Table 1); however, all included cardiac death and myocardial infarction. Mean follow-up ranged from 1.8 to 4.1 years. In light of significant interstudy heterogeneity, we elected not to perform a meta-analysis.

All results were statistically significant. In their report of 100 patients, Ambrosi and colleagues (2015)²⁸ reported a strong association between elevated high-sensitivity cardiac troponin I and

adverse cardiac events (HR = 7.2; 95% CI, 5.1-9.3). Hofmann and associates (2014)³⁶ (108 patients) and Mirabet and associates (2018)⁴¹ (96 patients) also reported an increased risk of adverse cardiac events in patients with elevated high-sensitivity troponin T; however, the association was weaker with lower 95% CIs, suggesting no clinically meaningful difference (HR = 1.03; 95% CI, 1.00-1.06; and HR = 1.03; 95% CI, 1.015-1.04 respectively).

Coronary artery disease

Two studies,^{34,38} which analyzed a total of 195 patients, reported associations between elevated troponin and long-term coronary artery disease. Labarrere and associates (2000)³⁸ reported a statistically significant association between cardiac troponin I elevated above 0.5 ng/mL and coronary artery disease up to 100

months posttransplant (OR = 4.3; 95% CI, 1.8-10.1). Faulk and colleagues (1998)³⁴ reported similarly statistically significant findings (relative risk of 1.6; 95% CI, 1.2-2.0) for each unit increase of troponin T of 0.10 ng/mL. All patients in this study with troponin T levels over 0.10 ng/mL developed coronary artery disease by 15 months, compared with 25% of those with levels under 0.10 ng/mL.

A third study³⁷ reported increased troponin T levels in those with coronary artery disease (0.09 ± 0.07 ng/mL) compared with those without (0.05 ± 0.04 ng/mL); however, a statistical significance could not be calculated due to nonreporting of numbers in each group.

Mortality

Three studies,^{32,35,38} which included 372 patients, reported associations between elevated troponin and long-term mortality. Labarrere and associates (2000)³⁸ reported a statistically significant positive association between elevated cardiac troponin I and graft failure (defined as mortality or need for retransplant) up to 100 months posttransplant (OR = 3.4; 95% CI, 1.2-9.7). The mortality rate was not reported independently. By 1 year posttransplant, Erbel and colleagues (2013)³² reported a marginally increased rate of dying (HR = 1.11; 95% CI, 1.00-1.23), which had increased substantially by 5 years posttransplant (HR = 6.67; 95% CI, 2.86-16.67). Franeková and colleagues³⁵ also reported an increased mortality rate in patients with an elevated troponin at 5 years, albeit with a markedly lower hazard ratio (HR = 1.03; 95% CI, 1.01-1.04). In light of significant interstudy heterogeneity, we elected not to perform a meta-analysis.

Discussion

This is the first systematic review and meta-analysis investigating the prognostic value of elevated recipient troponin levels in predicting adverse recipient outcomes after cardiac transplant. Incorporating 15 studies with 1830 patients, we found that elevated troponin levels may be prognostic for primary graft failure, adverse cardiac events, coronary artery disease, and mortality. Overall methodological quality was variable as determined by the QUIPS tool.

Beyond diagnosis of acute myocardial infarction, cardiac troponin has been investigated as a prognostic marker in numerous other cardiovascular and

transplant contexts. Elevated cardiac troponin has been associated with increased risk of cardiovascular death in patients with coronary artery disease.⁴² Furthermore, troponin elevation has also been related to adverse outcomes in patients with chronic kidney disease, patients on hemodialysis, and patients with pulmonary embolism, independently of acute coronary syndrome.^{12,43-46} Attention has been given to cardiac troponin in bone marrow transplant, liver transplant, and renal transplant.⁴⁷⁻⁴⁹ In heart transplant, donor troponin levels have been evaluated for prognostic utility but have not been shown to be associated with increased risk of graft rejection or mortality.^{50,51}

Our systematic review provides novel insights into the prognostic utility of recipient troponin levels after cardiac transplant. In particular, pooled data from 4 studies with 965 patients found that elevated troponin tripled the risk of primary graft failure. Three studies with 304 patients found an increased risk of adverse cardiac events in transplant recipients with elevated troponin; although the strengths of these associations ranged from mild to strong, all were statistically significant. Similar conclusions could be drawn for coronary artery disease and mortality: although variations in outcome definition, choice of effect measure, and timing of serum sample collection meant that meta-analyses could not be performed, consistent, unidirectional, and statistically significant results allowed qualitative characterization of the association between elevated recipient troponin and these outcomes. Further research is needed to clarify the magnitude of these associations, whether at-risk recipients could be better identified and stratified postoperatively based on troponin levels to optimize subsequent surveillance regimens and rehabilitation, and whether preventative interventions could be implanted to minimize modifiable risk factors for high-risk patients. In addition, our subgroup analysis suggested a greater prognostic value of high-sensitivity cardiac troponin compared with conventional cardiac troponin. Although this was confounded by study risks of bias, this finding mirrors those in the existing literature.¹⁴ Accordingly, the utility of troponin as a prognostic marker may increase as conventional troponin assays are phased out in favor of high-sensitivity assays in routine clinical practice.

There were however limitations. This systematic review was characterized by significant interstudy heterogeneity. Only 4 of 15 studies were deemed to

have high risk of bias; however, only 5 studies were of low risk of bias. Furthermore, all studies were single center, and the lack of large multicenter studies in this area raises concerns for general applicability. All studies were of adult patients, and whether recipient troponin could be prognostic for adverse outcomes in pediatric recipients is unclear. Because of insufficient numbers (<10) of included studies in each analysis, we were unable to formally assess for publication bias, which we presume to be present,²⁵ and we were not able to assess statistical heterogeneity using meta-regression with potential confounding covariates as continuous variables.²⁴ Included studies used variable approaches for threshold determination for elevated recipient troponin; for troponin to have utility in risk stratification, high-quality, multicenter trials are needed to generate universally acceptable cut-off thresholds. Lastly, although the majority of statistical heterogeneity in the meta-analysis for primary graft failure was attributable to factors identified on subgroup analysis, residual heterogeneity remains.

Many opportunities for future research are highlighted by our results. Future research in this area will benefit from following the Cochrane Prognosis Methods Group and the QUIPS tool to optimize assessable methodological quality and minimize risk of bias. In particular, studies should report potential confounders to allow for adjustment in multivariable statistical modeling and to ensure detailed reporting of baseline characteristics and results. Whether the prognostic value of troponin can be enhanced in combination with other hematological and clinical indices or by incorporation into existing multivariable prognostic models deserves attention. Finally, whether a heightened risk of adverse outcomes after heart transplant may be mitigated with clinical screening or intervention and whether such actions actually translate to improved postoperative outcomes will require further scrutiny, with a view toward implementation into health care policy and delivery.⁵²

Conclusions

This systematic review and meta-analysis found that elevated recipient troponin was associated with an increased risk of primary graft failure, adverse cardiac events, coronary artery disease, and mortality following cardiac transplant. Further high-quality, prospective, and multicenter research is needed to demonstrate the clinical applicability of these findings.

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