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Donor Cardiac Troponin for Prognosis of Adverse Outcomes in Cardiac Transplantation Recipients: a Systematic Review and Meta-analysis

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Background. Cardiac troponin is a highly specific and widely available marker of myocardial injury, and elevations in cardiac transplant donors may influence donor selection. We aimed to investigate whether elevated donor troponin has a role as a prognostic biomarker in cardiac transplantation. **Methods.** In a systematic review and meta-analysis, we searched MEDLINE, Embase, and the Cochrane Library, without language restriction, from inception to December 2020. We included studies reporting the association of elevated donor troponin with recipient outcome after cardiac transplant. We generated summary odds ratios and hazard ratios for the association of elevated donor troponin with short- and long-term adverse outcomes. Methodological quality was monitored using the Quality In Prognosis Studies tool, and interstudy heterogeneity was assessed using a series of sensitivity and subgroup analyses. **Results.** We included 17 studies involving 15 443 patients undergoing cardiac transplantation. Elevated donor troponin was associated with increased odds of graft rejection at 1 y (odds ratio, 2.54; 95% confidence interval, 1.22-5.28). No significant prognostic relationship was found between donor troponin and primary graft failure, short- to long-term mortality, cardiac allograft vasculopathy, and pediatric graft loss. **Conclusions.** Elevated donor troponin is not associated with an increased short- or long-term mortality postcardiac transplant despite increasing the risk of graft rejection at 1 y. Accordingly, an elevated donor troponin in isolation should not exclude donation.

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Over 25 y ago, it was estimated that over 25 000 patients per year could benefit from cardiac transplantation for the management of end-stage heart disease in the United States alone.[1] Technological advancements in mechanical circulatory support and improvements in patient survival with advanced heart failure have only seen this demand for donor hearts increase.[2] However, this rising demand has remained unmet, with stagnating annual transplantation rates at around 2500–4000 per year in the United States[3] and 4000–6000 per year globally.[4,5] Cardiac transplant waitlist mortality remains substantial at 6% at 6 mo, 8% at 1 y, 14% at 3 y, and 20% at 5 y.[3]

Cardiac troponin is a highly specific marker of myocardial injury, which is of broad predictive significance across a range of cardiovascular conditions.[6-9] Elevations in recipient cardiac troponin have been evaluated for predicting acute

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cellular rejection after cardiac transplantation[10]; however, the prognostic value of donor troponin is unclear. Although guidelines from the International Society for Heart and Lung Transplantation do not support the inclusion of donor troponin in assessment of cardiac allograft suitability,[11,12] elevated donor troponin has, in practice, been associated with donor heart nonuse.[13]

Hence, we performed a systematic review and meta-analysis to assess the prognostic value of donor cardiac troponin in predicting adverse outcomes following cardiac transplantation.

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[14,15] and was reported in compliance with the Meta-analysis Of Observational Studies in Epidemiology guidelines.[16] Protocol details were prospectively registered on International Prospective Register of Systematic Reviews (CRD42021227857); there were no major protocol deviations. This study design did not require ethics review board approval; this study analyzed data at the study level, so individual patient consent was not required.

Eligibility Criteria

We included original research studies that reported a prognostic association between donor troponin and adverse recipient outcomes after cardiac transplantation. 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 cardiac transplantation (SDC, http://links.lww.com/TXD/A389).[17] We placed no restrictions on language or publication period.

Study Selection

Two authors (Z.L. and M.H.) independently screened titles and abstracts for potentially relevant studies. The full texts of shortlisted studies were extracted and assessed against eligibility criteria independently and in duplicate. A third author (L.A.P.) 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 (Z.L. and L.A.P.) 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 value and adverse recipient outcomes (maximally adjusted odds ratios [ORs], hazard ratios [HRs], or mean differences [MDs]), troponin subtype and means of measurement, and threshold elevated troponin if applicable. We evaluated the prognostic impact of elevated donor troponin on the following recipient outcomes: primary graft failure; graft rejection at 30 d and 1 y; mortality at 30 d, 1 y, and long-term; cardiac allograft vasculopathy; and graft loss in pediatric populations.

Where studies stratified participants into >2 groups based on troponin level (eg, tertiles or quartiles), we collated data contrasting cumulative upper and lower quantiles separated by a cutoff troponin threshold most comparable with that of other included studies. Where studies did not report HRs and their 95% confidence intervals (CIs) but reported either a combination of *P* values and survival data or presented high resolution Kaplan-Meier curves with the numbers at risk at each time point, we derived the HR based on validated formulae.[18] Where studies compared donor troponin levels between groups with and without the outcome of interest, we standardized reported data into mean and standard deviation[19] and calculated log OR from the standardized MD.[20] Where studies described short- and medium-term outcome data with uniform follow-up using inconsistent effect measures, we standardized reported data as ORs for the meta-analysis.[21,22]

Assessment of Methodological Quality

Two authors (Z.L. and L.A.P.) 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 (M.H.). 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 Analysis and Data Synthesis

We tabulated the maximally adjusted ORs and HRs with associated 95% CIs from each study and generated summary estimates using random-effects inverse-variance modeling. We performed separate meta-analyses for each outcome where reporting was sufficient across studies; otherwise, we performed qualitative analyses.

We estimated statistical heterogeneity using the I^2 statistic for each outcome. We were unable to perform meta-regression because of insufficient (<10) study number in each analysis[24]; however, we explored potential sources of between-study heterogeneity with a series of sensitivity and subgroup analyses, investigating the impact of troponin subtype (troponin I, T, and high-sensitivity variants), end point definition, study risk of bias, and study design, where relevant, on pooled effect sizes.

Where there were fewer than 10 included studies reporting on an outcome, publication bias was unable to be formally assessed.[25] All analyses and figures were generated using Review Manager 5.4.[26]

RESULTS

Search Results

The search returned 1927 results. One additional citation was identified from secondary searching of reference lists. After deduplication, 1499 studies underwent title and abstract screening. Sixty-eight potentially relevant studies underwent full-text review, from which 17 studies were

included in this review. Of these, 9 were included in the quantitative analysis (Figure 1).

Description of Included Studies

Seventeen studies[13,27-42] involving 15 443 participants (14 studies with 14 403 adults and 3 studies with 1040 pediatric patients) undergoing cardiac transplantation were included. Detailed characteristics of included studies are explored in Table 1.

Methodological Quality

Included studies had variable risk of bias as assessed by the QUIPS tool. Two studies[38,39] were deemed to have overall low risk of bias, 13 studies[13,27-37,40] were rated moderate, and 2 studies[41,42] were rated to have high overall risk of bias. All studies performed well in domains of study attrition, prognostic factor measurement, and outcome measurement. Anderson et al[42] was characterized by highly limited general reporting, no evidence of consideration of possible study confounders, minimal description of baseline population characteristics, and hence a high overall risk of bias. Boccheciampe et al[41] demonstrated selective nonreporting of donor troponin details and was judged to be at high overall risk of bias. The complete QUIPS assessment can be found in the SDC, http://links.lww.com/TXD/A389.

RESULTS BY OUTCOME

Rejection

Thirty Days

Freundt et al[38] reported a nonsignificant OR of 1.30 (95% CI, 0.11-14.65) for elevated donor troponin and graft rejection within 30 d.

One Year

From 3 studies[38,41,42] involving 271 patients, we found a moderate and statistically significant association between elevated donor troponin and graft rejection within 1 y (OR, 2.54; 95% CI, 1.22-5.28) (Figure 2). Interstudy statistical heterogeneity was minimal (I^2 statistic 0%).

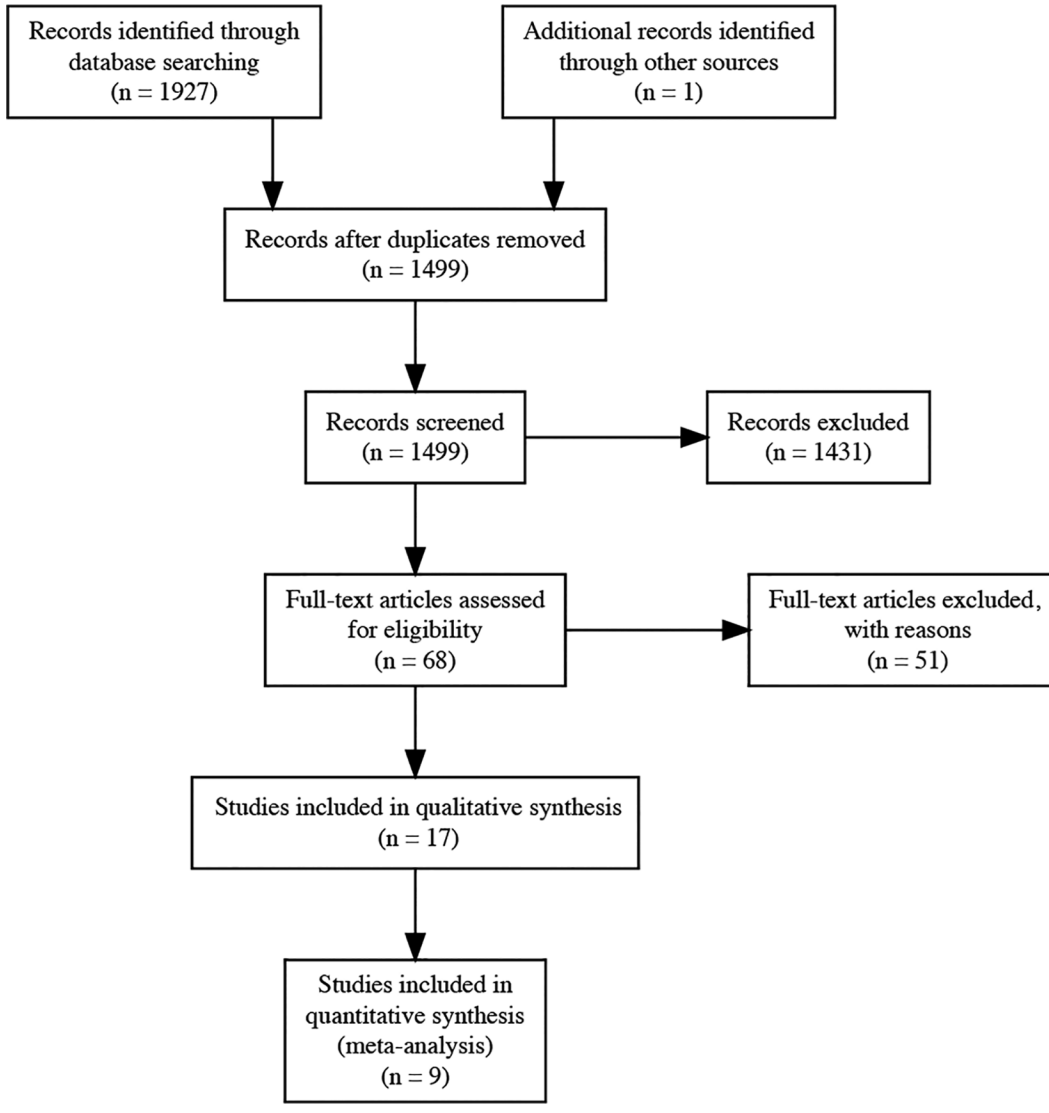

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. Full-text articles were excluded for the following reasons: 38 because of incorrect exposure measurement (recipient troponin rather than donor troponin), 6 because of incomplete troponin reporting, 4 because of incorrect outcome measurement, and 3 because of identical cohorts to included studies.

TABLE 1.

Characteristics of included studies

Study ID	Design	Sample size and demographic	Donor eligibility criteria	Age, mean ± SD, y	Sex (% male)	Troponin type	Troponin measurement	Troponin threshold (ng/mL) and selection method	Outcomes measured	QUIPS risk of bias
Anderson et al,[42] 1999	Single-center prospective	23 adult	Not reported	Donor: not reported Recipient: not reported	Donor: 69.6% Recipient: not reported	TnT	Not reported	Not reported Not reported	Rejection = 1 y	High
Boccheciampe et al,[41] 2009	Single-center retrospective	87 adult	Age <60, no history of cardiac disease, DBD	Donor: 36.7 ± 12.1 Recipient: 51.0 ± 10.0	Donor: 60.0% Recipient: 82.7%	TnI	Flex reagent cartridge CTNI catalog no. RF 421C heterogeneous colorimetric enzyme immunoassay (Dade Behring, Newark, Delaware)	2.29 Upper quartile in all potential donors	Rejection = 1 y Mortality = 1 y	High
D'Alessandro et al,[40] 2011	Single-center retrospective	402 adult	Not reported	Donor: 46.0 ± 13.0 Recipient: 48.0 ± 14.0	Donor: 64.4% Recipient: 77.9%	Not reported	Not reported	3 Not reported	Primary graft failure (within 48 h post-transplantation)	Moderate
Easterwood et al,[39] 2013	Multicenter retrospective	182 pediatric	UNOS criteria	Donor: 9.9 ± 12.7 Recipient: 7.8 ± 9.0	Donor: not reported Recipient: 53.3%	Not reported	Not reported	Not reported Not reported	Graft loss = 10 y	Low
Freundt et al,[38] 2018	Single-center retrospective	161 adult	Not reported	Donor: 43.0 ± 12.5 Recipient: 52.6 ± 10.0	Donor: 64.4% Recipient: 83.2%	TnI	ADVIA Centaur immunoassay system (Siemens Medical Solutions Diagnostics, Erlangen, Germany)	0.3 Not reported	Rejection = 30 d, 1 y Mortality = 30 d, 5 y	Low
Galeone et al,[37] 2017	Single-center retrospective	584 adult	Patients undergoing multiorgan and retransplantation were excluded from the study	Donor: 47.4 ± 12.1 Recipient: 49.0 ± 13.8	Donor: 64.7% Recipient: 77.9%	TnT	Not reported	0.87 Upper quartile of donor values	Mortality = 30 d, 1 y, 10 y	Moderate
Grant et al,[36] 1994	Single-center prospective	19 pediatric	All donor hearts with available TnI measurements were included	Donor: 0.5 ± 0.6 Recipient: not reported	Donor: Not reported Recipient: not reported	TnI	Double monoclonal sandwich enzyme immunoassay	3.1 Upper limit of normal based on nonparametric analysis of hospitalized adults without overt cardiac disease.	Graft loss = 1 y	Moderate
Khush et al,[13] 2013	Multicenter retrospective	808 adult	Age between 14 and 69, DBD	Donor: 31.0 ± 17.1 Recipient: 50.6 ± 15.4	Donor: 71.9% Recipient: 73.0%	TnI	Not reported	1.0 Highest cutoff of included centers	Mortality = 30 d, 1 y	Moderate
Kutschmann et al,[35] 2014	Multicenter retrospective	774 adult	DBD	Donor: 42.7 ± 13.4 Recipient: 53.0 ± 11.1	Donor: 56.6% Recipient: 81.5%	TnI or TnT	Not reported	0.1 Not reported	Mortality = 3 y	Moderate
Lin et al,[34] 2011	Multicenter retrospective	839 pediatric	All donor hearts with available TnI measurements were included	Donor: 11.0 ± 11.3 Recipient: 8.0 ± 7.4	Donor: 59.4% Recipient: 55.9%	TnI	Not reported	1.0 Not reported	Graft loss = 2 y	Moderate

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TABLE 1. (Continued)

Characteristics of included studies

Study ID	Design	Sample size and demographic	Donor eligibility criteria	Age, mean ± SD, y	Sex (% male)	Troponin type	Troponin measurement	Troponin threshold (ng/mL) and selection method	Outcomes measured	QUIPS risk of bias
Madan et al,[33] 2016	Multicenter retrospective	10 943 adult	Exclusion criteria: donor age >55 y, left ventricular ejection fraction <50%, significant donor coronary artery disease ≥50% stenosis, structural abnormalities in the donor heart (left ventricular hypertrophy, wall motion abnormalities, or valvular disease), simultaneous multiorgan transplants, retransplants, pediatric recipients, and unavailable donor troponin I values.	Donor: 30.3 ± 13.4 Recipient: 54.7 ± 11.9	Donor: 71.6% Recipient: 74.5%	TnI	Not reported	1.0 Not reported	Mortality = 30 d, 1 y, 5 y Primary graft failure (within 30-d post-transplantation) Cardiac allograft vasculopathy = 5 y	Moderate
Marasco et al,[32] 2013	Single-center retrospective	215 adult	DBD	Donor: 35.5 ± 13.2 Recipient: 48.5 ± 13.9	Donor: 71.6% Recipient: 77.7%	TnI	Not reported	Not reported Not reported	Primary graft failure (definitional time frame not reported)[b]	Moderate
Miller et al,[31] 2005	Single-center retrospective	171 adult	Not reported	Donor: 30.0 ± 14.1 Recipient: 47.0 ± 15.6	Donor: Not reported Recipient: 70.8%	TnI and TnT	TnI: Stratus CS TnI (Dade Behring, Newark, Delaware) TnT: Enzymun-Test TnT (Boehringer Mannheim GmbH, Mannheim, Germany)	Not reported Not reported	Cardiac allograft vasculopathy = 10 y	Moderate
Potapov et al,[30] 2001[a]	Single-center retrospective	79 adult	Exclusion: serum creatinine >2.0 mg/dL, donors scheduled for acute retransplantation within 30 d	Donor: 45.4 ± 14.7 Recipient: 50.7 ± 13.4	Donor: 57.0% Recipient: 82.3%	TnI and TnT	TnI: AxSYM (Abbott Laboratories, Abbott Park, IL) TnT: Elecsys 2010 (Roche Diagnostics, Mannheim, Germany)	TnI: 1.6, manufacturer's recommendation TnT: 0.1, manufacturer's recommendation	Primary graft failure mortality = 30 d	Moderate
Potapov et al,[29] 2003[a]	Single-center retrospective	92 adult	Exclusion: serum creatinine >2.0 mg/dL, donors scheduled for acute retransplantation within 30 d	Donor: 44.5 ± 14.6 Recipient: not reported	Donor: 58.7% Recipient: not reported	TnT	Elecsys 2010 (Roche Diagnostics, Mannheim, Germany)	0.1 Manufacturer's recommendation	Primary graft failure (within 12 h post-transplantation)	Moderate
Szarszoi et al,[28] 2016	Single-center prospective	64 adult	Not reported	Donor: 40.3 ± 13.7 Recipient: 51.6 ± 13.1	Donor: 60.9% Recipient: 78.1%	hsTnT	T hs STAT, Cobas e411 (Roche Diagnostics GmbH, Mannheim, Germany)	Not reported Not reported	Primary graft failure (within 24 h post-transplantation)	Moderate
Venkateswaran et al,[27] 2009	Single-center not reported	79 adult	Age between 16 and 65, no history of confirmed ischemic heart disease or major thoracic trauma	Donor: 45.2 ± 13.7 Recipient: 47.4 ± 13.4	Donor: 51.9% Recipient: 76.0%	TnI	Not reported	1 Not reported	Mortality = 30 d and 1 y	Moderate

[a]These studies are based on overlapping cohorts. Where outcomes were reported by both studies, the data presented in Potapov et al,[29] 2003, were included in analyses.
[b]However, because peak recipient troponin levels within 24 h posttransplantation was analyzed as a prognostic marker for primary graft failure, it can be inferred that definitional threshold for primary graft failure diagnosis was >24 h.
DBD, donation after brain death; hsTnT, high-sensitivity troponin T; QUIPS, Quality in Prognosis Studies; TnI, troponin I; TnT, troponin T; UNOS, United Network for Organ Sharing.

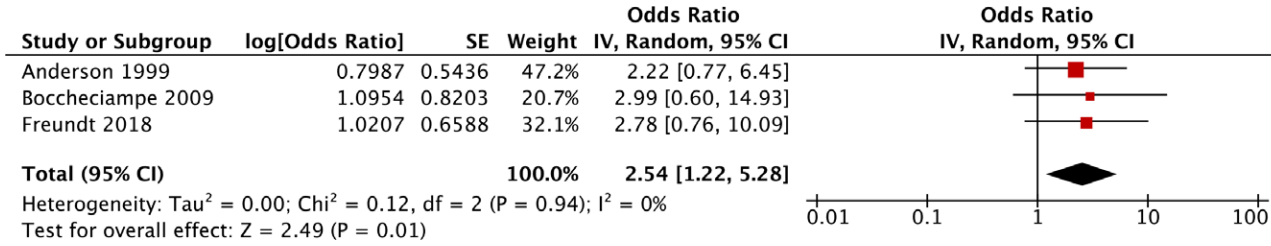


FIGURE 2. Forest plot for elevated donor troponin in predicting 1-y rejection post cardiac transplantation. CI, confidence interval; df, degree of freedom.

Mortality

Thirty Days

Elevated troponin was not associated with an increased risk of 30-d mortality (OR, 1.19; 95% CI, 0.84-1.69; 6 studies; 12 654 participants) (Figure 3A).[13,27,30,33,37,38]

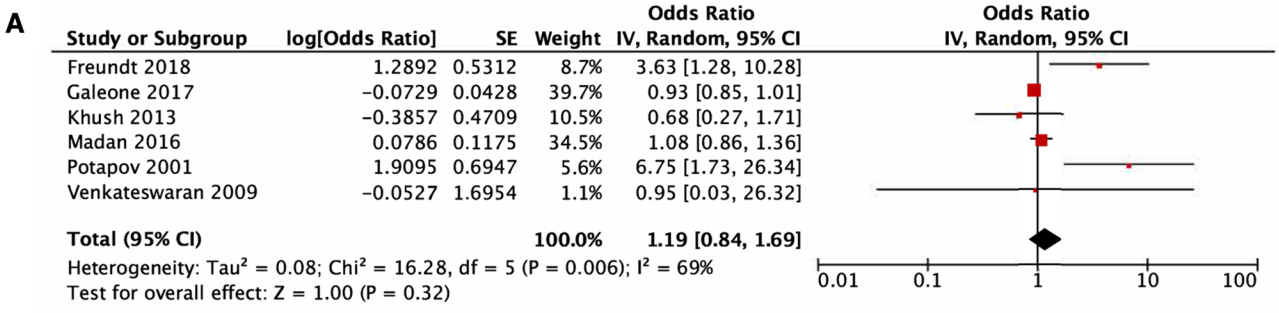
Interstudy statistical heterogeneity was substantial (I^2 statistic 69%). All studies were deemed to have a moderate risk of bias. We explored sources of heterogeneity in a series of subgroup analyses, grouping studies by troponin subtype and study design, and investigated whether or not subgroup differences could account for observed between-study heterogeneity. Troponin subtype and study design accounted for up to 56.4% and 35.2% of interstudy heterogeneity, respectively; however, tests for subgroup differences were not statistically significant (P = 0.13, and P = 0.21, respectively) (Figures S1 and S2, SDC, http://links.lww.com/TXD/A389, respectively, and SDC, http://links.lww.com/TXD/A389). Residual heterogeneity may be attributable to systematic differences in unreported study baseline characteristics and other study and patient-level factors.

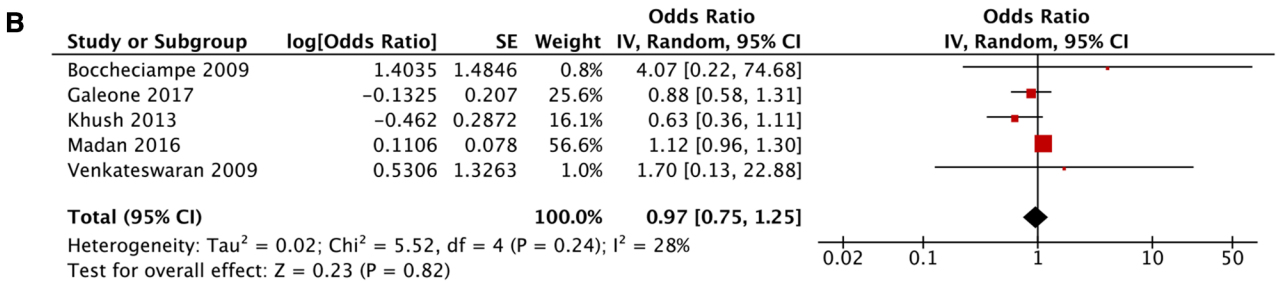
One Year

From 5 studies[13,27,30,33,37,38,41] involving 12 501 patients, we found no association between elevated donor troponin and 1-y mortality; the result was not statistically significant (OR, 0.97; 95% CI, 0.75-1.25) (Figure 3B). There was not significant interstudy statistical heterogeneity (I^2 statistic 28%).

Long-Term

We found no association between elevated troponin and long-term mortality after cardiac transplant (HR, 1.36; 95% CI, 0.89-2.08; 4 studies; 12 462 patients).[33,35,37,38] (Figure 3C).





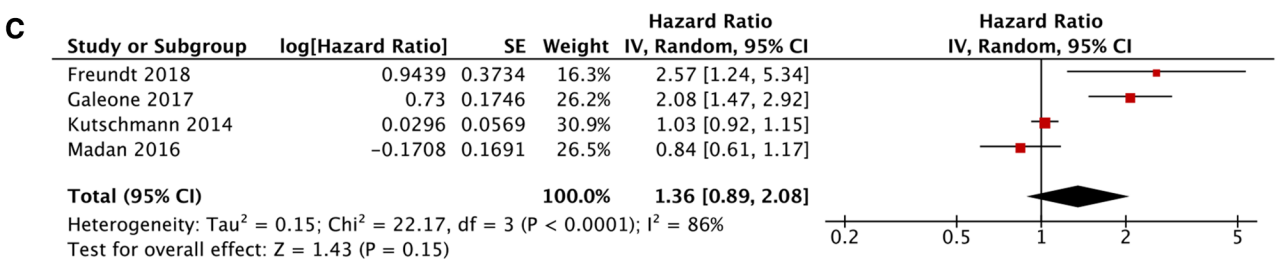


FIGURE 3. Forest plot for elevated donor troponin in predicting mortality post cardiac transplantation. (A) 30 d mortality, (B) 1 y mortality, and (C) long-term mortality. CI, confidence interval; df, degree of freedom.

Interstudy statistical heterogeneity was considerable (I^2 statistic 86%). We explored sources of heterogeneity in a series of sensitivity and 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. Kutschmann et al[35] did not report the subtype of donor troponin measured; reassuringly, sensitivity analysis removing this study revealed no significant change to the overall summary estimate's direction or statistical significance (Figure S3, SDC, http://links.lww.com/TXD/A389). Study design accounted for up to 94.8% of observed interstudy heterogeneity. A test for subgroup differences was statistically significant ($P < 0.0001$), with forest plots suggesting subgroup differences between single-center and multicenter study designs (Figure S4, SDC, http://links.lww.com/TXD/A389). Risk of bias accounted for up to 67.4% of interstudy heterogeneity; however, a test for subgroup differences was not statistically significant ($P = 0.08$) (Figure S5, SDC, http://links.lww.com/TXD/A389). Troponin subtype accounted for 0% of observed interstudy heterogeneity, and a test for subgroup differences was not statistically significant ($P = 0.50$) (Figure S3, SDC, http://links.lww.com/TXD/A389). Residual heterogeneity may be attributable to systematic differences in unreported study baseline characteristics and other study and patient-level factors.

Primary Graft Failure

Five included studies[28,29,32,33,40] involving 11 716 patients reported the association between elevated donor troponin and primary graft failure. We elected not to perform meta-analysis in light of significant clinical, methodological, and reporting heterogeneity.

D'Alessandro et al[40] and Potapov et al[29] reported statistically significant ORs for elevated donor troponin and primary graft failure within 48 h (OR, 2.33; 95% CI, 1.09-5.01) and 12 h (OR, 68.4; 95% CI, 11.5-405.4), respectively. No association between donor troponin and primary graft failure was reported by Marasco et al[32] (OR, 0.98; 95% CI, 0.92-1.04), Szarszoi et al[28] (MD, −0.01 ng/mL; 95% CI, −0.03 to 0.01 ng/mL), and Madan et al[33] (HR, 1.20; 95% CI, 0.83-1.73 for troponin elevated between 1 and 10 ng/mL; HR, 0.53; 95% CI, 0.13-2.20 for troponin elevated >10 ng/mL).

Cardiac Allograft Vasculopathy

Two included studies[31,33,38,43] involving 11 114 patients reported the association between donor troponin and long-term development of cardiac allograft vasculopathy. Miller et al[31] reported significantly lower donor troponin I (MD, −0.31 ng/mL; 95% CI, −0.36 to −0.25) and troponin T (MD, −0.03 ng/mL; 95% CI, −0.04 to −0.03) in 83 recipients who developed cardiac allograft vasculopathy compared to 88 who did not at 10-y follow-up. However, in a much larger cohort of 10 943 patients, Madan et al[33] reported no association between donor troponin levels and 5-y development of cardiac allograft vasculopathy (HR, 1.00; 95% CI, 0.88-1.13).

Pediatric Graft Loss

Three studies[34,36,39] involving 1040 pediatric patients measured the association between elevated donor troponin and graft loss. In a single-center observational study, Grant et al[36] prospectively followed 19 pediatric patients. At 1 y, all 5 episodes of graft loss were associated with elevated donor troponin levels, whereas 3 patients with elevated donor troponin did not experience graft loss. Easterwood et al[39] and Lin et al[34] were larger, retrospective, multicenter studies analyzing donor troponin in 182 and 839 pediatric patients, respectively. Both studies found no significant association between donor troponin levels and pediatric graft loss, at 10-y (HR, 0.40; 95% CI, 0.15-1.20) and 2-y (OR, 1.01; 95% CI, 0.55-1.85) follow-up, respectively.

DISCUSSION

To our knowledge, this is the first systematic review and meta-analysis investigating the prognostic value of elevated donor troponin in predicting adverse outcomes after cardiac transplantation. Synthesizing data from over 15 000 patients, we found that the prognostic utility of donor troponin in predicting primary graft failure, acute rejection at 30 d, mortality, cardiac allograft vasculopathy, and pediatric graft loss is limited.

From a small sample size (3 studies of 271 patients), we found a signal that elevated troponin was associated with graft rejection at 1 y. However, the clinical implications of this finding are unclear given the lack of association of donor troponin with both early rejection and mortality. Further research is needed to interrogate the clinical significance of this association and to corroborate the relationship between donor troponin and other late adverse outcomes.

Interstudy heterogeneity was particularly significant in the meta-analysis of long-term mortality. However, through a series of subgroup analyses, we found that differences in study design offered a convincing explanation, contributed up to 94.8% of observed interstudy heterogeneity. Specifically, heterogeneity arises from smaller studies with single-center designs reporting higher and statistically significant effect estimates, whereas larger, multicenter studies reported more conservative HRs, which were not statistically significant. Given the need for external validity and generalizability across centers and populations for troponin-based predictions to be viable, the findings of the multicenter studies are especially important, and their consistency with our pooled finding of no effect strengthens our pooled finding despite statistical heterogeneity. It is also worth noting that the subtype of troponin measured (I versus T) was not a significant modifier of outcome effect in any subgroup analysis, allowing generalization of results to cardiac troponin in general rather than any specific measured subtype.

We identified a paucity of studies utilizing high-sensitivity troponin assays compared to conventional troponin assays. Of the 17 studies included in this systematic review, only one study used high-sensitivity troponin assays. The greater predictive power of high-sensitivity troponin is well appreciated in cardiovascular disease[44,45]; in cardiac transplantation, a recent systematic review of troponin in diagnosing acute cellular rejection found that high-sensitivity troponin assays were superior to conventional troponin assays in ruling out acute cellular rejection.[10] Whether or not this increased predictive value may extend into the prognostic realm remains to be clarified. Future prospective observational studies may provide more sophisticated insights in risk determination.

Limitations exist in our study. Troponin levels appear influenced by the time at which they are measured during donor management, with higher levels soon after brain death and

lower levels subsequently as cardiac function improves.[2] However, since this information was conspicuously absent from the reporting of most included studies, it is difficult to know whether or to what extent timing of donor troponin measurement influenced our findings or contributed to interstudy heterogeneity. In addition, the methodologies of included studies were such that only donor troponin levels of hearts selected for transplantation are analyzed. Given that elevated donor troponin has, in practice, been associated with donor heart nonuse,[13] our results may be influenced by selection bias if hearts with lower troponin levels were more likely to be transplanted in the first place, leading to an artificially narrowed range of lower donor troponin levels in our sample, or vice versa. Although randomization of donor hearts to recipients could eliminate this bias, such practice would be ethically questionable. Furthermore, although only a few studies were identified to have high risk of bias, studies at low risk of bias were also rare. Additionally, the majority of included studies were retrospective and single centered, and we were also unable to formally assess the presence and effect of publication bias because of the low study numbers per analysis, which we presume is present.[25] There was marked heterogeneity in definitions of elevated troponin and cutoff values ranging from 0.1 to 3.1, and we were unable to account for this difference in a meta-regression because of insufficient (<10) studies in our analyses. Finally, although subgroup analyses revealed substantial contributors to heterogeneity, residual heterogeneity remains.

This review highlights opportunities for future research. The unmet need for additional donor hearts has seen the implementation of expanded criteria for donor organ selection and increasing utilization of marginal hearts—including hearts with left ventricular dysfunction or hypertrophy, from donors with multiple medical comorbidities, or after cardiopulmonary resuscitation—in patients who would not otherwise have qualified for transplantation.[2] This highlights the importance of comprehensive, multimodal risk stratification including clinical, echocardiographic, and blood-based biomarker data in donor selection to maximize donation potential. Whether or not existing clinical risk stratification models may be enhanced by the inclusion of blood-based parameters is a sphere of growing interest.[46-53] Sixteen risk prediction models exist for predicting adverse outcomes post cardiac transplantation; however, all have poor to moderate discriminative power, and few incorporate donor hematological biomarkers.[54] Although this systematic review and meta-analysis suggests that donor troponin is unlikely to predict adverse outcomes following cardiac transplantation, the addition of other potentially prognostic donor serum parameters such as B-type natriuretic peptide and, more recently, donor-derived cell-free DNA into multibiomarker prognostic models could enrich clinical evaluation and prognostication.[2,55-59] Donor-derived cell-free DNA, in particular, has shown remarkable promise in the detection of allograft rejection in both cardiac and renal transplantation[57,60]; whether or not early measurements could be prognostic for future adverse outcomes remains to be investigated in prognostic marker studies.[61] Future high-quality studies with comprehensive, nonselective study reporting of baseline characteristics and results and consideration of important confounders through multivariable analyses are needed in the identification of potentially prognostic factors in cardiac transplantation and validate their inclusion in sophisticated prognostic modeling.[61,62]

Reassuringly, an elevated donor troponin does not necessarily portend a poor prognosis, and the available evidence does not support the routine exclusion of donor hearts on the basis of an elevated troponin level. Otherwise eligible donor hearts with isolated elevated troponin should be considered for transplantation.

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