



openheart Comparison of troponin and natriuretic peptides in Takotsubo syndrome and acute coronary syndrome: a meta-analysis

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ABSTRACT

Objective Takotsubo syndrome (TTS) is an acute heart failure syndrome which resembles acute coronary syndrome (ACS) at presentation. Differentiation requires coronary angiography, but where this does not occur immediately, cardiac biomarkers may provide additional utility. We performed a meta-analysis to compare troponin and natriuretic peptides (NPs) in TTS and ACS to determine if differences in biomarker profile can aid diagnosis.

Methods We searched five literature databases for studies reporting NPs (Brain NP (BNP)/NT-pro-BNP) or troponin I/T in TTS and ACS, identifying 28 studies for troponin/NPs (5618 and 1145 patients, respectively).

Results Troponin was significantly lower in TTS than ACS (standardised mean difference (SMD) -0.86 ; 95% CI, -1.08 to -0.64 ; $p < 0.00001$), with an absolute difference of 75 times the upper limit of normal (\times ULN) higher in ACS than TTS. Conversely, NPs were significantly higher in TTS (SMD 0.62 ; 95% CI, 0.44 to 0.80 ; $p < 0.00001$) and $5.8 \times$ ULN greater absolutely. Area under the curve (AUC) for troponin in ACS versus TTS was 0.82 (95% CI, 0.70 to 0.93), and 0.92 (95% CI, 0.80 to 1.00) for ST-segment elevation myocardial infarction versus TTS. For NPs, AUC was 0.69 (95% CI, 0.48 to 0.89). Combination of troponin and NPs with logistic regression did not improve AUC. Recursive Partitioning and Regression Tree analysis calculated a troponin threshold $\geq 26 \times$ ULN that identified 95% cases as ACS where and specificity for ACS were 85.71% and 53.57%, respectively, with 94.32% positive predictive value and 29.40% negative predictive value.

Conclusions Troponin is lower and NPs higher in TTS versus ACS. Troponin had greater power than NPs at discriminating TTS and ACS, and with troponin $\geq 26 \times$ ULN patients are far more likely to have ACS.

INTRODUCTION

Takotsubo syndrome (TTS) is a stress-induced acute heart failure syndrome¹ which typically presents with cardiac chest pain and dyspnoea. ECG abnormalities are common, most frequently manifesting as ST-segment elevation, but may also present as ST-segment depression, widespread T-wave inversion and

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The literature suggests troponin is higher in acute coronary syndrome (ACS) than Takotsubo syndrome (TTS), whereas natriuretic peptides are higher in TTS. Prospective data is lacking and retrospective studies are often small. Meta-analysis in this context summarises the differences in biomarker release profiles and enables analysis of any diagnostic utility.

WHAT THIS STUDY ADDS

⇒ This study including 6763 total patients confirms troponin is lower and natriuretic peptides higher in TTS than ACS, and troponin alone was found to enable better discrimination than either natriuretic peptides, or troponin and natriuretic peptides in combination. Further, in patients presenting with acute cardiac chest pain, a troponin threshold of greater than 26 times the upper limit of normal identifies over 95% cases as ACS.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ While no substitute for immediate coronary angiography, cardiac biomarkers represent a useful clinical tool and in cases of diagnostic uncertainty, significantly elevated troponin levels make ACS far more likely.

QTc prolongation.² While this classically is not localised to a coronary territory, differentiating from acute coronary syndrome (ACS) based on clinical features alone in the emergency department is often not possible, and diagnosis depends on invasive or non-invasive coronary angiography, where exclusion of culprit coronary artery stenosis or occlusion is required. Subsequent ventriculography shows typical regional wall motion abnormalities, with a pattern of circumferential apical hypokinesia and basal hypercontractility being the most common anatomical variant.

Early studies suggested 1–2% of patients with suspected ACS are eventually diagnosed with TTS,^{3,4} although with increasing awareness and more widespread access to early coronary angiography, more recent estimates suggest TTS may constitute up to 5–6% of female patients presenting with suspected ST-segment elevation myocardial infarction (STEMI).⁵

Where patients do not undergo coronary angiography immediately, patients must be treated as ACS. Cardiac biomarkers represent a possible tool in understanding the differences between these two conditions which present similarly. TTS patients exhibit increases in creatine kinase-MB, cardiac troponin (cTn) and natriuretic peptides (NPs),² although the release profile appears different from ACS. The literature suggests smaller rises in troponin and creatine kinase, and higher brain NP in TTS compared with ACS.⁶ This likely reflects the modest acute myocyte damage in contrast to the extreme ventricular dilatation and wall stress which occurs in TTS. Indeed, brain NP (BNP) or NT-pro-BNP levels may be extremely high, and elevated NP levels have been included in the updated diagnostic criteria for TTS from the European Society of Cardiology.¹ Admission NT-pro-BNP levels are an independent predictor of 30-day major adverse clinical events and long-term mortality.⁷ Consequently, the ratio of NP to troponin has been proposed to differentiate TTS from STEMI.⁸ Alternative biomarkers for TTS exist, such as microRNAs and those linked with inflammation and vascular dysfunction and these have recently been reviewed but are not routinely available for clinical practice.^{9–11}

There is a paucity of prospective data in TTS and retrospective studies reporting the levels of established cardiac biomarkers in TTS are often small. To enhance clinical understanding of the differences in biomarker release between ACS and TTS, we performed a meta-analysis of all available literature to compare cTn and NPs (BNP or NT-pro-BNP) profiles in TTS versus ACS and demonstrate a troponin ‘threshold’ above which cases are extremely likely to be ACS.

METHODS

Search strategy and selection criteria

We identified studies of interest through systematic search of existing literature into TTS and cardiac biomarkers. Five literature databases were searched up to 10 July 2023, including PubMed, Ovid MEDLINE, EMBASE Ovid, Scopus and Cochrane Central Register of Controlled Trials (CENTRAL) without language, publication year or publication status restrictions. Search terms were adjusted as per individual database requirements but consisted of a stem of ‘(Takotsubo cardiomyopathy OR Takotsubo syndrome OR stress induced cardiomyopathy) AND (biomarker OR troponin OR BNP) AND (acute coronary syndrome OR STEMI OR NSTEMI)’. Collated papers were imported into Mendeley Desktop (V.1.19.8), and duplicates were automatically identified

and manually removed. This list was incorporated into Excel, where further duplicates were removed, and papers methodically screened for inclusion.

Two review authors (LSC or BA) independently assessed whether the titles and abstracts were eligible for further reading. Articles were read to assess eligibility for inclusion. Any disagreements about study inclusion were resolved through discussion with a third review author (TEK or MM).

Studies that compared TTS to ACS (STEMI, non-STEMI (NSTEMI or pooled ACS) for troponin I, troponin T, BNP or NT-pro-BNP were identified for this analysis. Studies must have used either Mayo clinic¹² or European Society of Cardiology criteria¹ for the diagnosis of TTS, or these were retrospectively applied. For inclusion, data must have been displayed as mean and SD or median and lower/upper quartile. Abstracts, case reports and case series with fewer than 10 patients were excluded from the analysis.

Data extraction and statistical analysis

Where available, included studies had data extracted for patient number, troponin and/or NP, biomarker assay, diagnostic criteria and reference ranges used. In cases where the biomarker assay was not reported, authors were contacted. Where they did not respond, an averaged value per assay for each isoform was formulated using published upper limits of normal (ULN) for troponin I/T (TnI/TnT)¹³ or for NT-pro-BNP/BNP for rule-out of heart failure as per the International Federation of Clinical Chemistry.¹⁴ Peak troponin and BNP/NT-pro-BNP values were used for analysis where specified.

Median and lower/upper quartile was converted to an estimated mean±SD to facilitate inclusion of the data within the meta-analysis using established methodology produced by Wan *et al.*¹⁵ Data extracted was normalised to the ULN (×ULN) to enable standardised comparison of various biomarker isoforms and assays. Where studies reported NSTEMI and STEMI groups separately against a single TTS control group, NSTEMI and STEMI values were pooled into a single ‘ACS’ group. Analysis of study data was performed by an inverse-variance method with random effects using RevMan V.5.¹⁶ Despite standardisation, data in forest plots are displayed as standardised mean difference (SMD) with 95% CI due to high study heterogeneity. The presence of heterogeneity among studies was assessed with χ^2 or Higgins and Thompsons’ I^2 index. Risk of bias analysis was performed using the National Heart, Lung and Blood Institute (NHLBI) National Institute of Health (NIH) Quality Assessment of Case–Control Studies tool¹⁷ by JAH. A planned sensitivity analysis and investigation of heterogeneity based on the study design, sex distribution, timing of blood biomarkers and overall risk of bias was performed. Statistical significance was determined using a Z-test, with p value displayed. Recursive Partitioning and Regression Tree analysis was performed for systematic identification

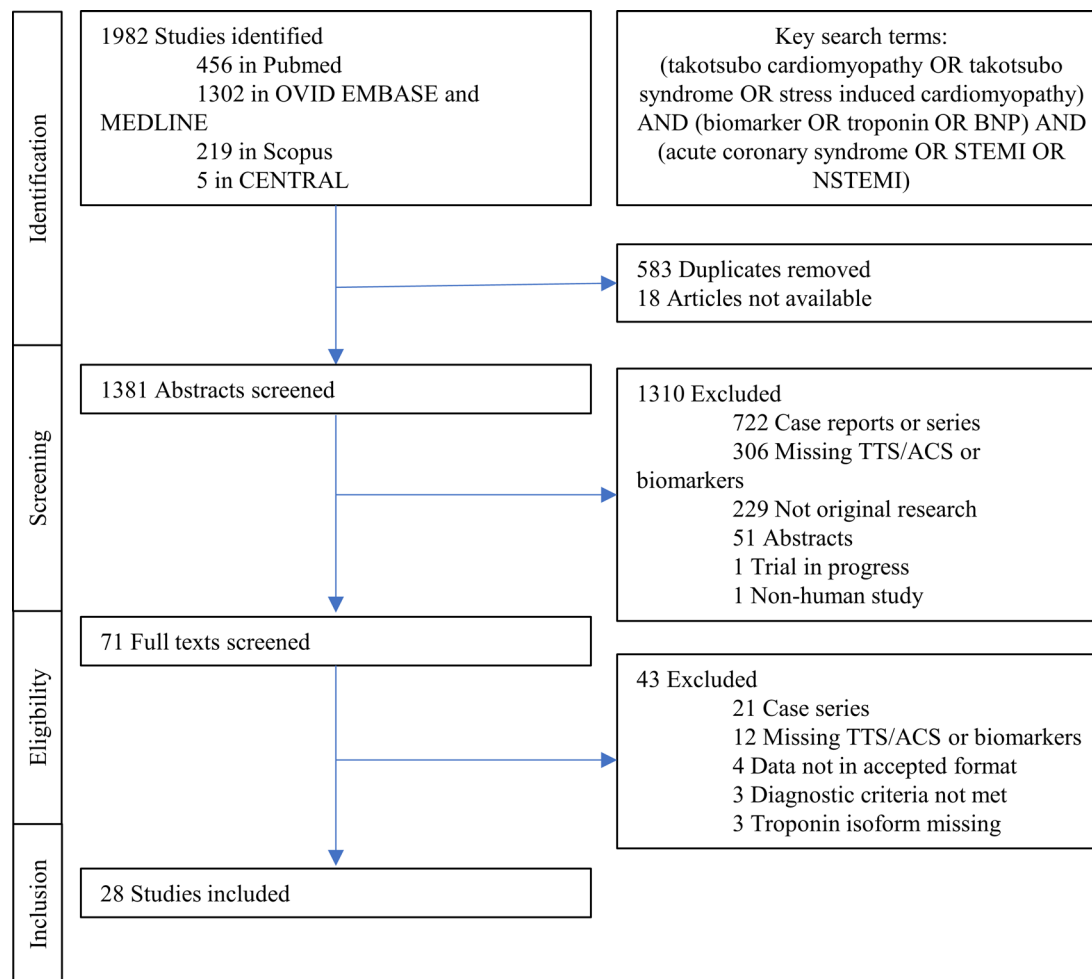


Figure 1 Schematic representation of the workflow for identifying studies. Shown is the process involved in performing the meta-analysis, where studies were identified, screened and then ultimately included or excluded. ACS, acute coronary syndrome; NSTEMI, non-STEMI; STEMI, ST-segment elevation myocardial infarction; TTS, Takotsubo syndrome.

of cut-off thresholds using the `rpart` module in RStudio based on established methodology from Breiman *et al.*¹⁸

RESULTS

Literature selection

During the initial literature search, 1982 studies were identified using the search strategy outlined above. After removal of duplicates, 1381 unique articles were screened, 28 studies ultimately met criteria for inclusion in this meta-analysis (figure 1). This enabled comparison of total 5618 patients for troponin and 1145 patients for NPs.^{2 6 8 10 19–42}

Troponin in TTS versus ACS

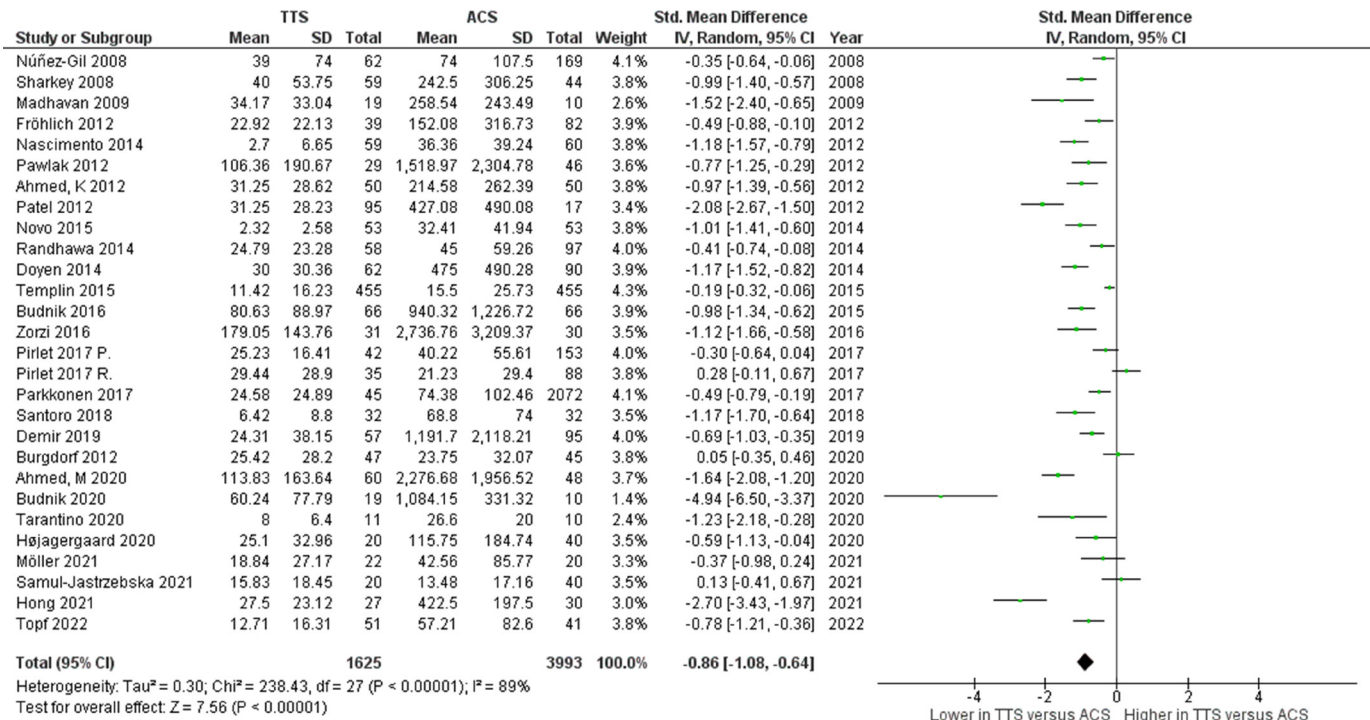
Twenty-seven studies compared troponin measurements in TTS and ACS resulting in a total of 1625 patients included for TTS and 3933 for ACS. When normalised to the ULN, troponin was significantly lower in TTS than in ACS (figure 2A), with an SMD of $-0.86 \times \text{ULN}$ (95% CI, -1.08 to -0.64 ; $p < 0.00001$). Absolutely, troponin was 75.35 times the ULN (95% CI, 57.94 to 92.77) higher in ACS than TTS ($p < 0.00001$; online supplemental figure 1A).

NPs in TTS versus ACS

NP (BNP and NT-pro-BNP) measurements comparing TTS and ACS were performed from 14 studies, yielding 570 patients with TTS and 575 with ACS. NPs were significantly higher in TTS than ACS (SMD $0.62 \times \text{ULN}$; 95% CI, 0.44 to 0.80; $p < 0.00001$; figure 2B) with an absolute difference of 5.88 times the ULN greater in TTS (95% CI, 3.75 to 8.00; $p < 0.00001$; online supplemental figure 1B).

Subgroup analysis was performed based on NP subtype, BNP or NT-pro-BNP (online supplemental figure 2). There was a significant difference between the mean differences in BNP and NT-pro-BNP ($3.58 \times \text{ULN}$; 95% CI, 2.05 to 5.11; vs $13.39 \times \text{ULN}$; 95% CI, 5.97 to 20.81, respectively; $p = 0.01$), and both were significantly higher in TTS than ACS ($p < 0.00001$ and $p = 0.0004$, respectively, online supplemental figure 2A). However, when standardised to variability, the SMD trended to be greater in BNP than NT-pro-BNP ($0.83 \times \text{ULN}$; 95% CI, 0.63 to 1.03; vs $0.48 \times \text{ULN}$; 95% CI, 0.19 to 0.76, respectively; $p = 0.05$, online supplemental figure 2B).

A



B

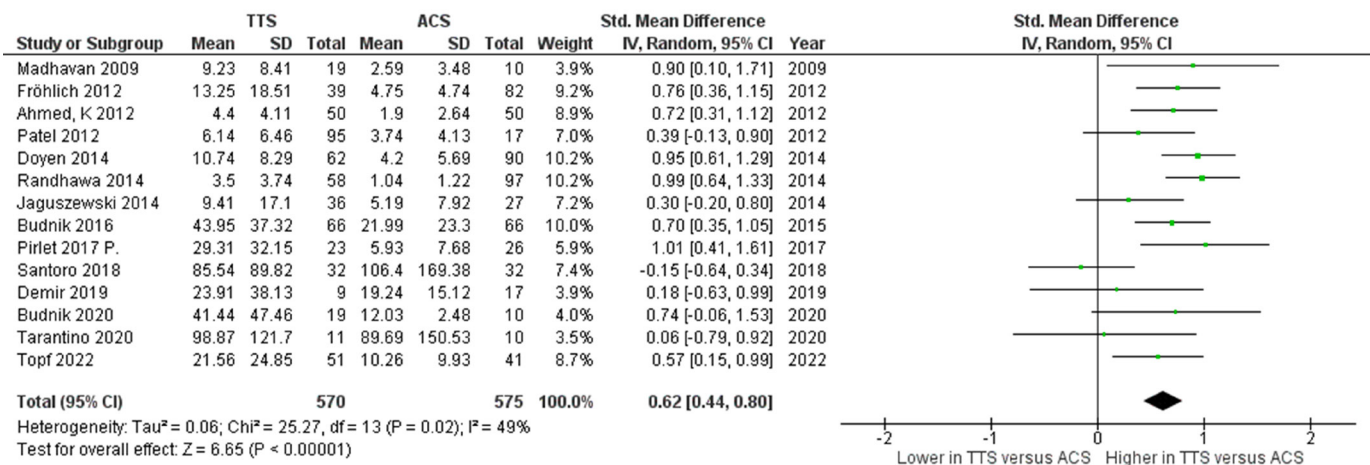


Figure 2 Forest plots for troponin and natriuretic peptide in Takotsubo syndrome versus acute coronary syndrome. Standardised mean difference shown for included studies in TTS versus ACS for (A) troponin and (B) natriuretic peptides. Data displayed as mean±SD to two decimal places. Studies included within this forest plot. ^{2 6 8 10 19-42} ‘Pirlet 2017 P’ and ‘Pirlet 2017 R’ represent the prospective and retrospective cohorts from this study, respectively. ACS, acute coronary syndrome; TTS, Takotsubo syndrome.

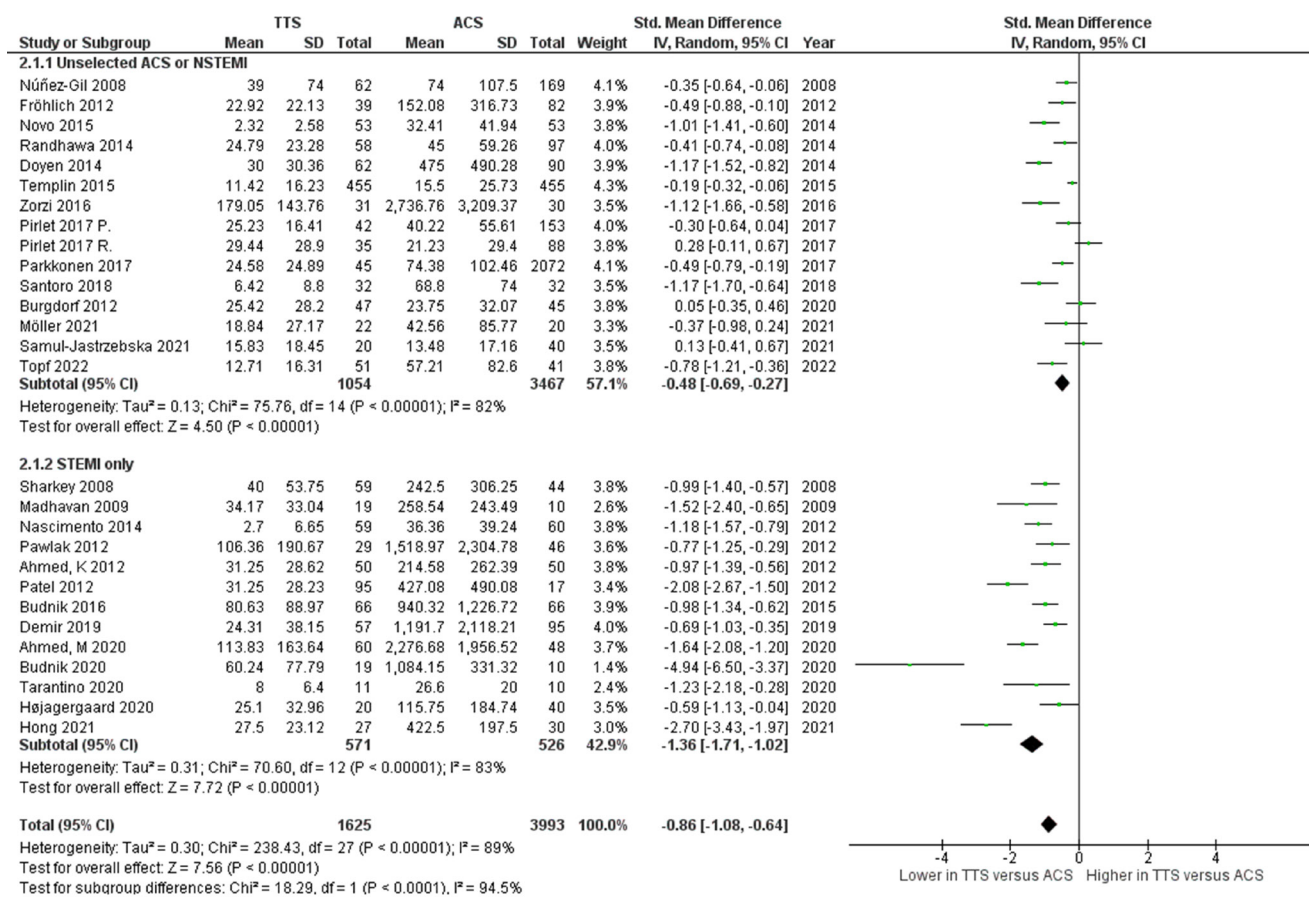
Subgroup analysis based on type of ACS

A subgroup analysis was performed to assess whether the magnitude of difference in troponin or NP varies based on type of acute myocardial infarction (AMI) versus TTS. Troponin measurements (figure 3A) were significantly lower in TTS than both subgroups (SMD for unspecified ACS/NSTEMI -0.48×ULN; 95% CI, -0.69 to -0.27; p<0.00001 and STEMI -1.36×ULN; 95% CI, -1.71 to -1.02; p<0.00001). The magnitude of the difference was

larger in the STEMI subgroup than for unselected ACS/NSTEMI (p<0.0001).

NPs (figure 3B) were significantly higher in TTS than both subgroups (SMD for unspecified ACS/NSTEMI 0.70×ULN; 95% CI, 0.38 to 1.02; p<0.0001; and STEMI 0.56×ULN; 95% CI, 0.37 to 0.75; p<0.00001). However, there was no difference in the SMD between these two subgroups (p=0.46).

A



B

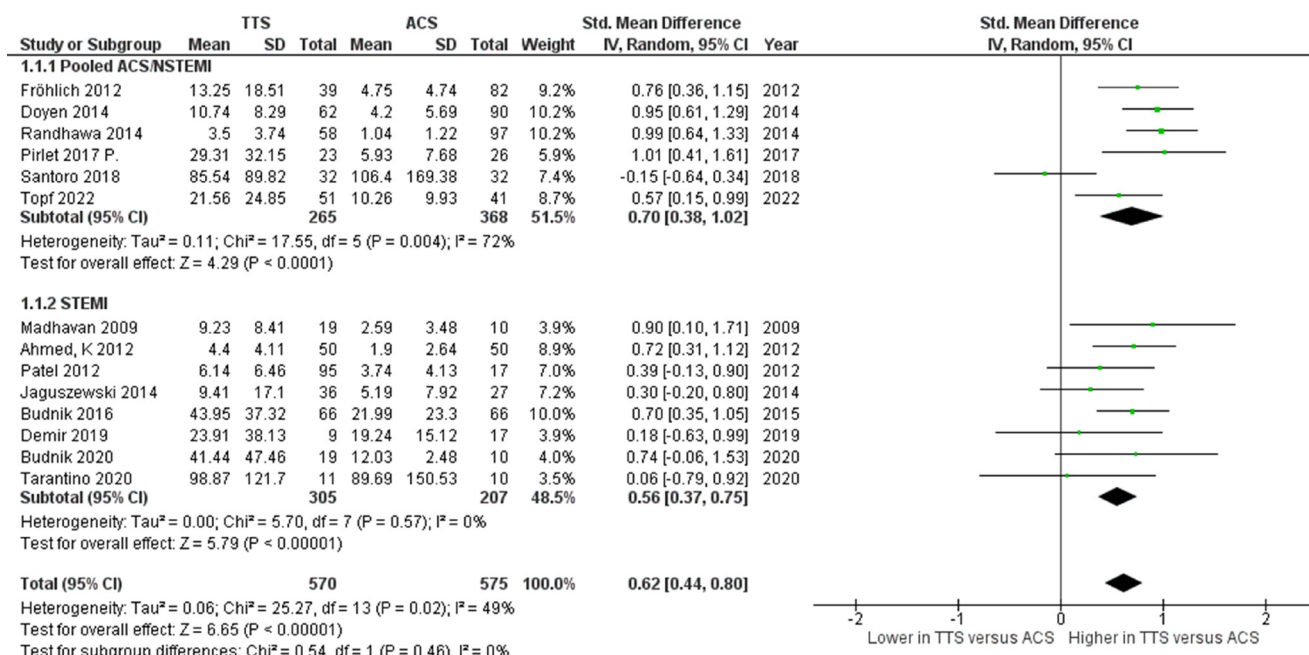


Figure 3 Subgroup analysis comparing the effect of acute myocardial infarction subtype. Standardised mean difference shown stratified by ACS subgroup for (A) troponin and (B) natriuretic peptides. Data displayed as mean±SD to two decimal places. Studies included within this forest plot.^{2 6 8 10 19–42} ‘Pirlet 2017 P’ and ‘Pirlet 2017 R’ represent the prospective and retrospective cohorts from this study, respectively. ACS, acute coronary syndrome; STEMI, ST-segment elevation myocardial infarction; TTS, Takotsubo syndrome.

Receiver operating characteristic curves for troponin and NP for the differentiation of TTS from ACS

Receiver operating characteristic (ROC) curves were constructed based on included studies (online supplemental figure 3). Since troponin is a sensitive biomarker for myocyte injury and the priority would be to not miss any cases of ACS, TTS was selected for use as the control. Based on included studies, area under the curve (AUC) for troponin in ACS versus TTS (online supplemental figure 3A) was 0.82 (95% CI, 0.70 to 0.93), which enabled good discrimination. Sensitivity was 100% at a troponin value of 13.09 times the ULN, although specificity was 21.43%. A troponin value of 40.11 times the ULN provided sensitivity of 75.00% and specificity of 82.14%. Interestingly, performing ROC analysis on the STEMI subgroup improved AUC to 0.92 (95% CI, 0.80 to 1.00, online supplemental figure 3B).

ROC analysis revealed a lower AUC (AUC 0.69; 95% CI, 0.48 to 0.89, online supplemental figure 3C) in the 14 studies including NP measurement. A NP of 3.04 times the ULN provided specificity of 100% and sensitivity of 21.43%, whereas for an NP of 6.03 times the ULN sensitivity was 85.71% and specificity was 57.14%.

The two cardiac biomarkers were combined using a logistic regression model to investigate whether the biomarkers in combination increased the power of discrimination. Here, we only included the 13 studies which recorded both troponin and NPs to enable a paired comparison. In this subanalysis, the AUC for troponin was 0.92 (95% CI, 0.82 to 1.00) and 0.69 (95% CI, 0.47 to 0.90) for NP (online supplemental figure 3D,E, respectively). After combination, AUC did not improve over troponin alone (AUC=0.91; 95% CI, 0.79 to 1.00; online supplemental figure 3F).

Decision tree analysis to identify 'optimal' biomarker threshold

A Recursive Partitioning and Regression Tree analysis was performed to systematically identify biomarker 'threshold' values to differentiate TTS from ACS based on the included studies.¹⁸ Given TTS is potentially under diagnosed, we made the conservative assumption that prior to definitive diagnosis, 90% of cases represent MI and 10% account for TTS. Offering both NP and troponin to the decision tree with all available data and favouring ACS as the diagnosis, a value for troponin of 25.92 times the ULN was produced, which when exceeded, defined 95.12% cases as ACS. At this cut-off value, sensitivity and specificity are 85.71% and 53.57%, respectively (online supplemental figure 3A), with a positive predictive value (PPV) of 94.32% and negative predictive value (NPV) of 29.40%.

Risk of bias, heterogeneity and sensitivity analyses

The risk of bias analysis of included studies was performed using the NHLBI NIH Quality Assessment of Case-Control Studies tool (online supplemental table 1).¹⁷

Overall, 13 studies were found to be of good quality, 12 studies of fair quality and 2 studies of poor quality.

We conducted a sensitivity analysis of the study designs, sex distribution, risk of bias and timing of blood biomarkers (online supplemental tables 2 and 3). Excluding poor quality studies, retrospective study design and in studies where timing of biomarker sampling was not given in the study made no significant difference to the point estimate of either the SMD or mean difference for troponin or NP. The sensitivity analysis demonstrated that in studies of only female patients, the SMD of troponin (-1.49; 95% CI, -1.99 to -0.99) was lower compared with studies not with only female participants (-0.66; 95% CI, -0.88 to -0.45) and lower than the overall cohort. This observation was also seen in the mean difference, with a greater mean difference observed in the women only studies (-1087.48; 95% CI, -1548.48 to -626.48). Excluding studies with unequal sex distribution did not affect the SMD or mean difference of either troponin, or NP.

There was a high degree of heterogeneity in the overall analysis, with I^2 values for SMD of 89% for troponin and 49% for NP (online supplemental table 2). There was no change in the heterogeneity of the included cohorts based on risk of bias, study design or timing of biomarker. For NP, less heterogeneity was seen in the four studies of women only studies ($I^2=0%$; online supplemental tables 2 and 3), although there was no meaningful difference in either the SMD or mean difference as described above. In the former analysis of NP subtype (online supplemental figure 2), heterogeneity was reduced when SMD for BNP and NT-pro-BNP were analysed separately, with I^2 values of 9% and 52%, respectively.

DISCUSSION

TTS remains a diagnostic challenge and cardiac biomarkers represent a tool that could aid clinicians when coronary angiography is not performed (or not accessible) acutely. Here we perform a meta-analysis of all available literature in TTS to demonstrate that: (1) troponin is significantly higher in ACS than TTS; (2) NPs are significantly higher in TTS than ACS; (3) on subgroup analysis, expectedly the mean difference in troponin is greater for STEMI than unspecified ACS/NSTEMI versus TTS; (4) troponin alone and not in combination with NPs enabled good discrimination of TTS from ACS; (5) an 'optimal' troponin value of ≥ 25.92 times the ULN identifies ACS with high clinical probability.

Troponin and BNP as biomarkers in TTS

Patients presenting with acute cardiac chest pain and ECG changes should undergo rapid assessment for ACS with consideration of urgent diagnostic coronary angiography. However, utility of cardiac biomarkers remains in cases of diagnostic uncertainty, or as a parallel line of investigation. Chest pain represents one of the most frequent presentations to emergency services and therefore ACS

represents a common and important differential diagnosis.⁴³ The fourth Universal Definition of Myocardial Infarction classifies TTS as a form of myocardial injury, with high catecholamine surges known to trigger troponin release from cardiomyocytes and coronary microvascular dysfunction, high myocardial strain hypercontractility and high ventricular afterload each being present in TTS which may contribute to an element of myocardial ischaemia.⁴⁴ Owing to the high sensitivity and diagnostic accuracy of newer troponin assays,⁴⁵ where primary percutaneous coronary intervention is not indicated, rapid 'rule-in' and 'rule-out' algorithms are used to reduce delays in diagnosis and discharge/treatment for ACS. However, European Society of Cardiology guidelines for ACS⁴⁶ or acute heart failure⁴⁷ do not give advice to assist in the diagnosis of TTS (or its differentiation from ACS), and it remains a diagnosis of exclusion. The higher troponin concentrations measured in ACS, when compared with TTS (figure 2A) reflects the extent of myocyte damage present in each condition, with an even larger difference present on subgroup analysis for STEMI (figure 3A). This more modest increase in troponin concentration is present in TTS despite grossly, although mostly temporary abnormal left ventricular (LV) contractile function.

Elevation of serum cardiac NPs (BNP or NT-proBNP) is frequent in the acute phase of TTS, consequent to increased ventricular myocardial strain, regional wall motion abnormality and direct catecholamine-induced NP release.¹ The finding that BNP is significantly higher in TTS than ACS (570 patients vs 575, respectively, figure 2B) is therefore unsurprising. The lack of change on subgroup analysis by ACS type (figure 3B) likely reflects the equivocal magnitude of myocardial dysfunction in NSTEMI compared with STEMI. Interestingly, the absolute magnitude of change in NT-pro-BNP was significantly greater than BNP ($p=0.01$, online supplemental figure 2A), however this difference was reversed on standardisation with the difference in BNP trending to be higher than NT-pro-BNP ($p=0.05$, online supplemental figure 2B). NT-pro-BNP has previously been suggested to increase in greater increment with New York Heart Association (NYHA) score in heart failure and have higher power to detect modest reductions in LV ejection fraction (LVEF) when compared with BNP.⁴⁸ These differences between biomarker isoforms likely result from differences in the kinetics of BNP/NT-pro-BNP generation, release and clearance.

Selection of optimal biomarker values

The ratio of NP to troponin has previously been proposed to differentiate TTS from STEMI.⁸ Doyen *et al* present BNP to TnI ratios of 642.0 pg/ μ g (331.8–1226.5 pg/ μ g) in TTS compared with 184.5 pg/ μ g (50.5–372.3 pg/ μ g) for NSTEMI and 7.5 pg/ μ g (2.0–29.6 pg/ μ g) for STEMI ($p<0.001$ for both).²⁵ Budnik *et al* similarly present a ratio of NT-pro-BNP to TnI ratio of 2235.2 (1086.2–9480.8) for TTS versus 81.6 (47.9–383.3) for STEMI ($p<0.001$).²¹

Finally, Randhawa *et al* provide a ratio of BNP to TnT of 1292.1 (443.4–2657.9) for TTS and 226.9 (69.91–426.32) for AMI ($p<0.001$).³⁶ Unfortunately, it is not possible to create a standardised ratio on this information alone due to the differences in biomarker isoform and assays used, and lacking of patient level data.

While these studies suggest clear benefit to the clinical use of NP to troponin ratio, based on the 13 studies that reported paired values for troponin and NPs, ROC curve analysis demonstrated there was no additional value of combining NP with cTn over cTn alone, as baseline discriminatory power from cTn is higher (online supplemental figure 3). This also suggested that optimal biomarker thresholds could not be selective based on ROC curves alone. The Youden Index is often used to determine an 'optimal' point, however, it is not useful in this context as cannot appreciate the different 'weight' one might ascribe to prioritising a certain clinical diagnosis, or where differences in prevalence are present. In this case, sensitivity of diagnosing ACS should be valued higher than any 'optimal' cut-off, and initiation of therapy for ACS should not be delayed over a possible TTS diagnosis. The Youden Index would attribute equal weights to sensitivity and specificity and therefore accept missing a STEMI over misclassifying a TTS.

An alternative approach that incorporates both pretest likelihood and predefined performance goals was using Recursive Partitioning and Regression Tree analysis.¹⁸ This enables for a 'prior' probability distribution to account for the increased prevalence of ACS when compared with TTS. Given early estimates suggested 1–2% of patients with suspected ACS are eventually diagnosed with TTS^{3,4} and more recent estimates report TTS constitute up 6% of female patients presenting with suspected STEMI,⁵ we used a conservative prior assumption that 90% of cases would ultimately be diagnosed as ACS, to reflect that TTS is still ultimately an overlooked condition.

When the decision tree considered all available data for both NPs and cTn, a threshold value for cTn alone of ≥ 25.92 times the ULN made ACS far more likely—with a probability exceeding 95%. This provided a systematic and unbiased method of identifying the 'optimal' value for the differentiation of the two conditions; and demonstrates that troponin alone is the superior biomarker for diagnostic discrimination in this context.

Translating this to 'real-world' assay concentrations, this represents values of 492.5 ng/L for Abbott Architect high sensitivity (hs)-TnI assay and 414.7 ng/L for Roche Cobas hs-TnT. Overall, this threshold yielded sensitivity and specificity values for troponin of 85.71% and 53.57%, respectively, with a PPV of 94.32% and NPV of 29.40%. This seems adequately powered to discern ACS and TTS above these troponin concentrations; below, however, NPV is too low for troponin to provide a meaningful clinical differentiation.

Novel biomarkers for TTS

This study further highlights the lack of specific biomarkers for TTS and illustrates the need for novel biomarkers. In brief, non-coding RNA (ncRNA) represent novel disease biomarkers as ncRNA expression profiles change specifically in various disease states.⁴⁹ microRNAs (miR) -1, miR-16, miR-26a and miR-133a are all significantly raised in TTS versus healthy control,¹⁰ and the pattern of change was significantly different to STEMI. miR-1 and miR-133a were higher in STEMI, whereas miR-16 and miR-26a were raised only in TTS.¹⁰ Interestingly, miR-16 and miR-26a have recently been identified to be involved in the pathophysiology of TTS.¹¹

Given the pathophysiological involvement of inflammation and microvascular dysfunction in TTS,^{50–52} markers of inflammation and vascular stress response have been investigated for use as diagnostic tools in TTS. Interleukin (IL)-2, IL-4, IL-10, interferon- γ and tumor necrosis factor alpha (TNF- α) were observed to be higher in patients with acute TTS versus AMI, and IL-6 higher in AMI.³⁸ The two vasoconstricting peptides co-peptin and endothelin are differentially changed in TTS versus AMI. Co-peptin levels are normal or marginally elevated in TTS compared with more substantial elevations in patients with AMI,^{22 23 27} whereas endothelin levels are increased to a similar degree in TTS and STEMI.¹⁰ Glycocalyx levels also seem significantly elevated in Takotsubo compared with healthy controls.⁵³ The mechanisms underlying these changes has recently been reviewed elsewhere.⁹ Taken together, this highlights the need for further work within this field to identify more specific biomarkers than enables the rapid triage of patients with ACS and TTS.

Limitations

There are several limitations present of our study. First, research in TTS is largely retrospective, and therefore the trials included within this analysis may have been subject to sampling bias. Due to the paucity of randomised control trials in TTS, data was standardised to a factor of the ULN and pooled for total NPs and total troponin. Large repositories such as interTAK² were used to strengthen the data. However, inclusion of a wide variety of study designs lead to increased study heterogeneity, which is seen throughout the data presented and was largely unaffected on sensitivity analysis by exclusion of studies based on study design, timing of biomarker or presence of bias. Further, approximately only half of the included studies included the paired comparison of troponin and NPs. This limited the ability to create a standardised NP to troponin ratio that could undergo ROC curve analysis. Finally, studies frequently did not clarify the biomarker assay used and corresponding authors often did not respond to requests for clarification. We substituted averaged assay values from standard populations^{13 14} to attempt to compensate for this, however, we would have preferred to use local assay specific thresholds.

CONCLUSION

While no substitute for coronary angiography, cardiac biomarkers represent a useful tool in routine clinical diagnosis. Troponin is significantly lower, and NPs are significantly higher in TTS compared with ACS. Troponin had greater power than NPs at discriminating TTS and ACS, and a threshold value of ≥ 26 times the ULN for troponin was found to identify patients as extremely likely to have ACS.

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Contributors LSC and TEK are joint guarantors and were involved in the contextualisation, methodology, data analysis and writing of this manuscript. BA and LSC performed data extraction. MM and TEK were primary supervisors for this project. GLDM, KC, APB, ARL and MM were involved in refinement of project rationale, and review/revision of draft manuscripts. JWG, JAH and RK performed data collection and analysis. JWG and RK additionally assisted with methodology.

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Ethics approval Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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