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ORIGINAL ARTICLE

Right ventricular dysfunction and tricuspid regurgitation in functional mitral regurgitation

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Abstract

Aim The objective of this study was to investigate the prognostic importance of right ventricular dysfunction (RVD) and tricuspid regurgitation (TR) in patients with moderate–severe functional mitral regurgitation (FMR) receiving MitraClip procedure. RVD and TR grade are associated with cardiovascular mortality in the general population and other cardiovascular diseases. However, there are limited data from observational studies on the prognostic significance of RVD and TR in FMR receiving MitraClip procedure.

Methods and results A systemic review and meta-analysis were performed using MEDLINE, Scopus, and Embase to assess the prognostic value of RVD and TR grade for mortality in patients with functional mitral regurgitation (FMR) receiving MitraClip procedure. Hazard ratios were extracted from multivariate models reporting on the association of RVD and TR with mortality and described as pooled estimates with 95% confidence intervals. A total of eight non-randomized studies met the inclusion criteria with seven studies having at least 12 months follow-up with a mean follow-up of 20.9 months. Among the aforementioned studies, a total of 1112 patients (71.5% being male) were eligible for being included in our meta-analysis with an overall mortality rate of 28.4% (n = 316). Of the enrolled patients, RVD was present in 46.1% and moderate–severe TR in 29.2%. RVD was significantly associated with mortality compared to normal RV function (HR, 1.79, 95% CI, 1.39–2.31, $P < 0.001$, $I^2 = 0$). Patients with moderate–severe TR showed increased risk of mortality compared with those in the none-mild TR group (HR, 1.61. 95% CI, 1.11–2.33, $P = 0.01$, $I^2 = 14$).

Conclusions This meta-analysis demonstrates the prognostic importance of RVD and TR grade in predicting all-cause mortality in patients with significant FMR. RV function and TR parameters may therefore be useful in the risk stratification of patients with significant FMR undergoing MitraClip procedure.

Keywords Right ventricular dysfunction; Tricuspid regurgitation; Functional mitral regurgitation; MitraClip procedure; Mortality; Meta-analysis

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Introduction

Functional mitral regurgitation (FMR) is a common clinical entity in patients with primary left ventricular (LV) dysfunction with normal mitral valve anatomy. FMR has been associated with adverse prognosis independent of both LV ejection fraction (LVEF) and other clinical markers of heart failure.[1–3] Percutaneous mitral valve repair using the MitraClip device has been proposed to correct FMR. The COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial confers a survival benefit compared with

optimal medical therapy.[4] On the contrary, the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) trial did not demonstrate a survival benefit.[5] The difference in the results of two landmark randomized trials have underscored the importance of correct patient selection for this intervention. Noticeably, compared with patients in the MITRA-FR trial, those enrolled in the COAPT trial had less advanced stage of the LV disease with smaller LV end-diastolic volume index (COAPT: 101 ± 34 mL/m^2 vs. MITRA-FR: 135 ± 35 mL/m^2) and greater LVEF (COAPT: 20–50% vs. MITRA-FR 15–40%).

In light of the available evidence, identifying patients who will benefit from the intervention and searching for prognostic predictors are of utmost importance. Right ventricular dysfunction (RVD) and tricuspid regurgitation (TR) grade have been demonstrated to be associated with increased cardiovascular mortality in the general population,[6] primary MR,[7,8] and other cardiovascular and respiratory diseases.[9–13] Recently, Naksuk *et al*. showed that RVD is a significant predictor of sudden cardiac death (SCD) irrespective of left ventricular ejection fraction.[14] However, there are limited data from observational studies on the prognostic significance of RVD and TR in FMR. Importantly, the two landmark randomized trials did not account the importance of RVD into their protocols. The ongoing clinical trial 'A Clinical Evaluation of the Safety and Effectiveness of the MitraClip System in the Treatment of Clinically Significant Functional Mitral Regurgitation' (Reshape-HF2) has not mentioned RV function in their inclusion and exclusion criteria.[15]

The objective of this study was to investigate the prognostic importance of RVD, and TR in patients with moderate–severe FMR undergoing MitraClip procedure by performing a systematic review of the literature and meta-analysis.

Methods

Search strategy

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines when performing our systematic review and meta-analysis.[16] We searched PubMed, Scopus, and Embase databases using English-language references from inception through April 2020 using the search term ('TAPSE' OR 'Tricuspid annular plane systolic excursion' OR 'right ventricular dysfunction' OR 'right ventricular function' OR 'right ventricle' OR 'right ventricular' OR 'tricuspid regurgitation' OR 'tricuspid valve regurgitation' OR 'pulmonary hypertension') AND ('functional' OR 'secondary') AND ('mitral valve regurgitation' OR 'mitral valve insufficiency' OR 'mitral regurgitation' OR 'mitral insufficiency'). Additional strategies involved reference searches to ensure the identification of all relevant studies pertinent to the topic. The search was limited to human studies published in English. Abstracts without complete published articles, review articles, editorial comments, and letters to the editor were excluded.

Study selection

The PICO (the patient, population or problem, intervention, comparison, outcomes) framework was used as a tool to outline the components of the research questions (*Table 1*).[17] Studies were included if the articles met the following criteria: (i) reporting an association between RVD or tricuspid regurgitation and an outcome, either mortality or heart failure (HF) related hospitalization among patients with FMR; (ii) having at least 6 month follow-up; (iii) controlling for other important covariates in multivariable survival analysis; (iv) having low risk of bias assessed by the Newcastle-Ottawa scale (see Quality assessment section for more details). In the studies that reported an association of RVD or TR with outcomes among those with FMR mixed with primary MR, we contacted the authors of the studies for accessing data related to FMR.[18,19] Paediatric populations were excluded to minimize heterogeneity between studies.

Data extraction

Each eligible article meeting the inclusion criteria was reviewed by two independent reviewers (T. N and V. T. or T. P.). Disagreements were resolved by a consensus with a

Table 1 'PICOS' approach for selecting clinical studies in the systematic search

PICOS	Characteristics of clinical studies included for the qualitative synthesis and meta-analysis
1. Participants	Adult patients with functional mitral regurgitation
2. Intervention	Patients with right ventricular dysfunction defined as a TAPSE ≤16 mm or tissue Doppler-derived tricuspid lateral annular systolic velocity (S′TDI) < 10 cm/s and moderate–severe tricuspid regurgitation
3. Comparison	Patients with normal right ventricular function and none-mild tricuspid regurgitation
4. Outcomes	Mortality and Heart failure related hospitalization (at least 6 month follow-up)

third investigator (K. P. or T. N.). The following data were extracted and entered into an electronic database: (i) study: first and last authors, year of publication; (ii) socio-demographics: number of subjects, age, and gender; (iii) clinical factors: proportion of ischemic cardiomyopathy, NYHA, MitraClip procedure; (iv) echocardiographic parameters: LV end-diastolic diameter (LVEDD), LV end-systolic diameter (LVESD), LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV), LVEDV index, LVESV index, and LV ejection fraction (EF), systolic pulmonary artery pressure (SPAP), TAPSE, TR, and MR. RVD was defined as a TAPSE $\leq$ 16 mm or tissue Doppler-derived tricuspid lateral annular systolic velocity (S′TDI) $<$ 10 cm/s.[20] The severity of tricuspid regurgitation (TR) assessed in line with recommendations and TR was graded as none, mild, moderate, moderate, or severe; and (v) clinical outcomes: follow-up (months), mortality, HF-related hospitalization. In situations in which we believed that multiple articles were published using the same dataset, the study with the largest sample size was included in our meta-analysis.

Analysis of outcomes

Mortality and HF-related hospitalizations were the major outcomes of interest. HF-related hospitalization was defined as new-onset or worsening signs and symptoms of HF that required urgent therapy and resulted in hospitalization. Analysis of an outcome was pooled if at least two studies reported that outcome.

Quality assessment

Quality assessment of the studies was performed using the Newcastle–Ottawa scale, one of the most used tool for evaluating quality in meta-analyses of observational studies.[21] The Newcastle–Ottawa scale, including nine items, appraises methodological quality in three domains: selection, comparability, and outcome with a maximum of 9 points. Based on the quality assessment tool, studies were classified as having high-risk (1–3 points), intermediate-risk (4–5 points), or low-risk of bias (6–9 points). Two reviewers (V. T. and T. P.) independently performed the quality assessment across all potentially eligible studies for this systematic review and meta-analysis. Only studies with low risk of bias (6–9 points) were included in our meta-analysis.

Statistical analysis

All statistical analyses were performed using the Comprehensive Meta-Analysis (version 3.3). For the incidence rate data, we calculated the hazard ratio (HR) with 95% CI as reported in the individual studies. Study-specific data were then combined to create pooled estimates using DerSimonian–Laird random-effects models.[22] Heterogeneity among studies was assessed using Cochrane's *Q* test with *P* value of $<$0.1 considered as statistically significant heterogeneity and the I^2 statistic. I^2 statistic was categorized as low ($<$25%), moderate (25% to 75%), or high ($>$75%) levels of heterogeneity.[23] Publication bias was assessed using visual funnel plot and the Egger's and Begg's tests, with significant bias defined as a *P*-value $<$0.1. The 'trim and fill' method was used to examine whether hypothetical missing studies substantially changed our estimates.[24]

The additional sensitivity analyses were planned: the first including studies using TAPSE to define RVD, the second using the 'leave-one-out-at-a-time' approach, where one study is excluded at a time and the impact of removing each of the studies is on the pooled estimates and the between-study heterogeneity.[25]

Results

Study selection

Figure 1 shows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of our study. The search identified 446 titles on Medline, 1137 on EMBASE, 436 on Scopus. After excluding duplicate and triplicate articles (*n* = 846), there were 1173 articles screened for relevance. We further excluded articles unrelated to the topic (*n* = 416) or abstracts without text (*n* = 528), reviews (*n* = 92), and articles not in humans (*n* = 11). Searching the bibliographies did not reveal any additional results. No ongoing studies were found in the clinical trials registries. One hundred twenty-six full-text studies were assessed for eligibility. After removing further 117 studies due to aforementioned reasons or those with repeated datasets, eight datasets were included in our meta-analysis.[18,19,26–31]

Association of ventricular dysfunction dysfunction and tricuspid regurgitation with mortality in functional mitral regurgitation

The baseline characteristics of study participants and echocardiographic data were shown in *Tables 2 and 3*. Among the eight studies eligible to be included in our meta-analysis, there were a total of 1112 patients (71.5% being male) with an overall mortality rate of 28.4% (*n* = 316). Study-specific follow-up duration was reported in *Table 2* with seven studies having at least 12 months follow-up with a mean follow-up of 20.9 months. There were 85% of patients who presented with NYHA class III–IV. The pooled mean LVEF among all participants was 29.3 ± 8.8%.

Figure 1 Study design. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart demonstrating study selection process.

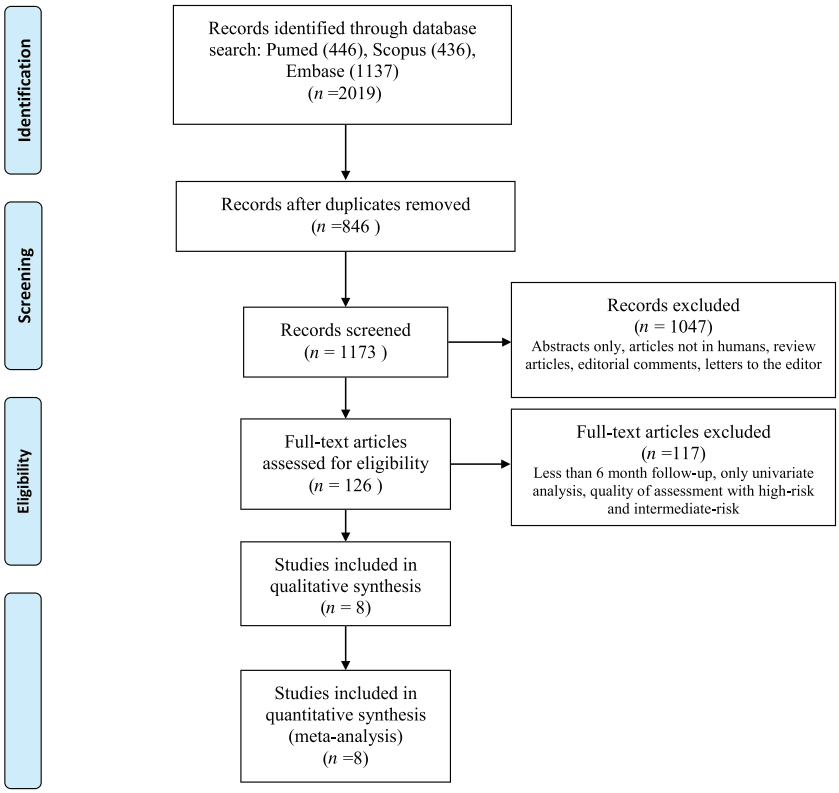


Table 2 Clinical characteristics of included observational studies

Author	Year	*n*	Age	Male (%)	Ischaemic cardiomyopathy	NYHA III–IV	Follow-up (months)	Mortality
Gyoten *et al*.	2020	80	72 ± 8.7	60 (75)	39 (49)	79 (98.75)	24 (IQR, 11–34)	46 (57.4)
Bannehr *et al*.	2019	108	71.9 ± 9.7	84 (77.8)	72 (66.7)	108 (100)	33.3 (IQR, 14.7–46.8)	52 (48.1)
Osteresch *et al*.	2018	130	72.7 ± 10.7	83 (63.8)	77 (59.2)	130 (100)	10.5 ± 4	42 (32)
Godino *et al*.	2016	60	73 ± 8	50 (83.3)	40 (67)	42 (70)	18.6 ± 10.2	18 (32)
Kaneko *et al*.	2016	117	71 ± 9	92 (78.6)	NR	113 (96.6)	23.2 ± 19.4	56 (47.8)
Giannini *et al*.	2016	169	72.1 ± 8.3	132 (78.1)	109 (64)	130 (77)	13.9 (IQR, 5.4–26.9)	53 (31.4)
Ohno *et al*.	2014	146	72 ± 9	93 (63.7)	NR	118 (81)	12	12 (8)
Hahn and Stone *et al*.	2020	302	71.7 ± 11.8	201 (66.6)	184 (60.9)	172 (57)	24.1 (IQR: 11.7 to 35.9)	83 (27.5)

Of the enrolled patients, RVD was present in 46.1% and moderate–severe TR in 29.2%. Our meta-analysis showed that patients with RVD was significantly associated with mortality compared with normal RV function (HR, 1.79, 95% CI, 1.39–2.31, $P < 0.001$) (*Figure 2*) with low heterogeneity between studies ($Q = 3.83$, $P = 0.58$, and $I^2 = 0\%$). Additionally, patients with moderate–severe TR showed increased mortality rate (HR, 1.61. 95% CI, 1.11–2.33, $P = 0.01$) compared with those in the none-mild TR group (*Figure 3*) with low heterogeneity between studies ($Q = 4.66$, $P = 0.32$, and $I^2 = 14\%$).

Sensitivity analysis

The first subgroup analysis was undertaken among the studies that used TAPSE to assess the RV function. Again, RVD that was

Table 3 Echocardiographic characteristics of included observational studies

Author	LVEDD (mm)	LVESD (mm)	LVEDV (ml)	LVESV (ml)	LVSV[c]	LVEF (%)	EROA (cm^2)	SPAP (mmHg)	TAPSE (mm)	RV dysfunction (%)	Moderate–Severe TR (%)	Severe MR (%)
Gyoten *et al.*	73 ± 6.4	66 ± 7.1	242 ± 69	182 ± 64	60 ± 67	22 ± 5.3	NR	54 ± 15	14 ± 4.65	50 (62.5)[a]	44 (55.0)	NR
Bannehr *et al.*[a]	62.9 ± 8.5	52.1 ± 10.4	NR	NR	NR	29.6 ± 11.1	0.29 ± 0.26	40.7 ± 12.4	16.9 ± 4.8	57 (52.8)	51 (47.2)	52 (48.1)
Osteresch *et al.*	60 ± 9	55 ± 9	NR	NR	NR	32 ± 7	0.38 ± 0.2	49 ± 12	18 ± 4	58 (44.6)	15 (11.5)	106 (81.5)
Godino *et al.*	66.8 ± 9.2	56.1 ± 10.2	210 ± 78	147 ± 69	63 ± 74	30 ± 10	NR	50 ± 16	19.3 ± 4.2	22 (36.7)	15 (25.0)	50 (83)
Kaneko *et al.*	67 ± 9.4	58 ± 9.7	NR	NR	NR	24.9 ± 7.35	NR	NR	16.5 ± 2.6	41 (35.0)	25 (21.4)	75 (64.1)
Giannini *et al.*	37 ± 6[b]	31 ± 6[b]	111 (90–136)[b]	79 ± 35[b]	31 ± 34	31 ± 9	NR	50 ± 13	18 ± 4	NR	84 (49.7)	78 (72)
Ohno *et al.*	61.5 ± 10.6	46.6 ± 12.8	173.3 ± 71.9	119.4 ± 65.7	54 ± 69	33.2 ± 11.2	> 0.4	45.6 ± 11.3	18.6 ± 4.1	NR	47 (32.2)	74 (51)
Hahn and Stone *et al.*	60.2 ± 7.0	50.3 ± 9.0	194.4 ± 69.2	135.5 ± 56.1	59 ± 63	31.3 ± 9.1	0.43 ± 0.73	44.0 ± 13.4	NR	NR	44 (15.0)	154 (51.0)

LVEDD, left ventricle end-diastolic diameter; LVEDV, left ventricle end-diastolic volume; LVEF, left ventricle ejection fraction; LVESD, left ventricle end-systolic diameter; LVESV, left ventricle end-systolic volume; NR, not reported; RV, right ventricular; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.
[a]Data availability from author.
[b]Index to BSA.
[c]Standard deviation estimated from Cohen's formula.

defined as TAPSE ≤ 16 mm was significantly associated with increased mortality (HR, 1.72, 95% CI, 1.20–2.48, P = 0.003, I^2 = 0%) (Supporting Information, *Figure S1*). Our sensitivity analysis using the leave-one-out-at-a-time approach showed the same direction of the association between mortality and RVD (HR, ranged between 1.73 and 1.86), and so did the association between mortality and moderate–severe TR (HR, ranged between 1.42 and 1.95).

Quality assessment and publication bias

All included studies were of low risk of bias with scores ≥7 points on the Newcastle–Ottawa scale (Supporting Information, *Table S1*). All studies included in the meta-analysis defined their study objective and outcomes, time to follow-up, potential confounders, as well as outlined main study findings. No evidence of significant publication bias was observed in the funnel plots (*Figures 4* and *5*) and the Egger test (P = 0.15 for RVD, P = 0.48 for moderate–severe TR). Our additional analyses using the 'trim and fill' method suggested that hypothetical 'missing' studies did not substantially change our pooled estimates for both RVD (HR, 1.74, 95% CI, 1.35–2.23) and moderate–severe TR (HR, 1.61. 95% CI, 1.11–2.33).

Discussion

To the best of our knowledge, this is the first meta-analysis investigating the prognostication of RV function and TR by echocardiographic assessment in patients with significant FMR receiving MitraClip procedure. The main findings of this study were that an increased risk of mortality was associated with RVD, defined as TAPSE by echocardiography ≤16 mm or S′TDI < 10 cm/s, and with moderate to severe TR. It has been well established that RVD and TR have a negative impact on prognosis among patients with cardiovascular diseases,[9,10,12,13] but little is known about the prognostic impact of RVD and TR in patients significant FMR receiving MitraClip procedure. Some investigators reported that RVD and TR have been associated with adverse outcomes, but others did not.[27,26,31] Because TAPSE and S′TDI are easily obtainable and reproducible, and these measurements have been shown to correlate with cardiovascular magnetic resonance (CMR)-derived RV ejection fraction,[32–34] we pooled the results of observational studies reporting RV function and TR by echocardiography in this meta-analysis. Our objective was to fully understand the implications of RVD and TR in the setting of significant FMR receiving MitraClip procedure.

Our meta-analysis suggests that those with RVD (abnormal TAPSE was defined as ≤16 mm or abnormal S′TDI < 10 cm/s) and with moderate–severe TR were more likely to have poor survival outcomes in significant FMR receiving MitraClip procedure, confirming the results of the previous studies. Dini

Figure 2 The forest plot displays the hazard ratio and 95% confidence intervals (CIs) for difference between patients with and without right ventricular dysfunction. Square markers indicate hazard ratios; horizontal lines, the 95% CIs, with marker size reflecting the statistical weight of the study using random-effects meta-analysis. The diamond marker represents the overall hazard ratio and 95% CI for the outcome of interest.

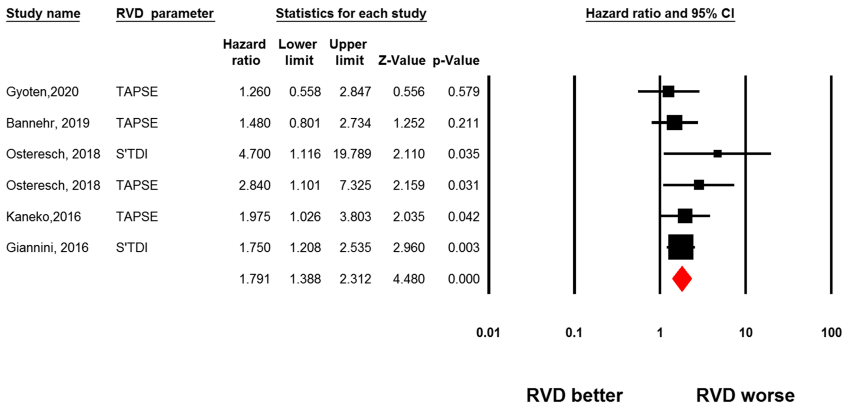


Figure 3 The forest plot displays the hazard ratio and 95% confidence intervals (CIs) for difference between patients with and without moderate–severe tricuspid regurgitation. Square markers indicate hazard ratios; horizontal lines, the 95% CIs, with marker size reflecting the statistical weight of the study using random-effects meta-analysis. The diamond marker represents the overall hazard ratio and 95% CI for the outcome of interest.

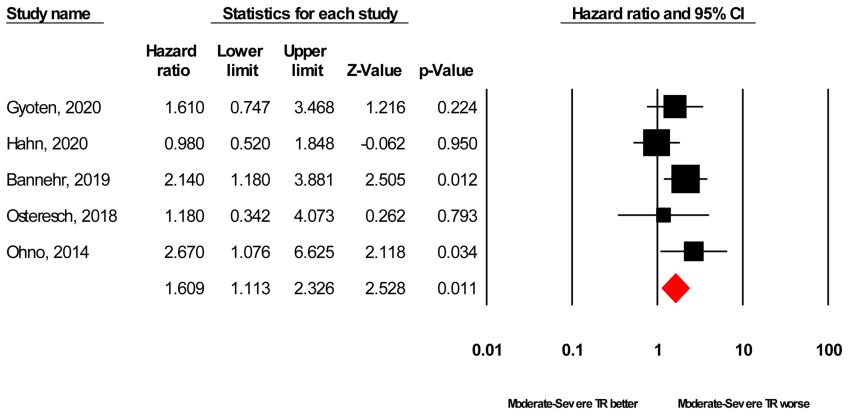
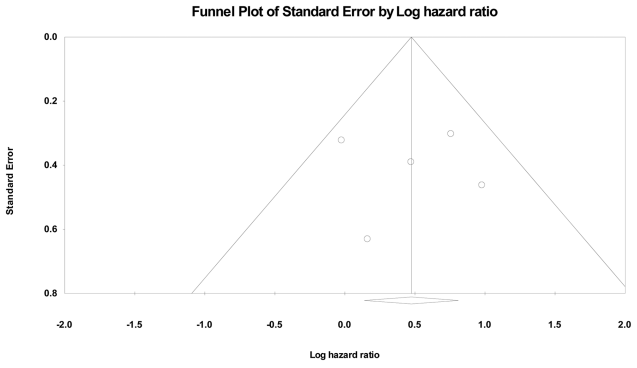


Figure 4 Funnel plot of publications included in the meta-analysis for right ventricular dysfunction.

Figure 5 Funnel plot of publications included in the meta-analysis for tricuspid regurgitation.



et al. demonstrated that overall survival was greater with TAPSE ≥ 16 mm (82%) when compared with TAPSE <16 mm (42%) at follow up of 36 months ($P < 0.001$).[35] Importantly, RVD was a significant predictor of all-cause mortality even after adjusting for important confounding factors or covariates (HR, 2.64; 95% CI, 1.28–5.47, $P = 0.009$). Similarly, Giannini and colleagues revealed that RVD assessed by S′TDI was an independent predictor of cardiovascular mortality in significant FMR.[29] In addition to the association between RVD and mortality, moderate–severe TR has been demonstrated to be associated with adverse prognosis in significant FMR.[30] Calafiore *et al*. demonstrated, in a propensity score analysis of functional TR that was graded as moderate-or-severe, when left untreated, both midterm survival and functional status were impaired.[36] In our meta-analysis, RVD and moderate–severe TR at baseline posed an increased risk of poor prognosis among patients undergoing MitraClip procedure. RVD is a result of pressure overload or volume overload, or a combination of both, and serves as a common final pathway in the progression of congestive heart failure. Additionally, RVD and the severity of TR associated with maladaptive RV remodelling with cardiac myocyte loss and myocardial fibrosis, reducing the possibility of RV functional recovery after intervention of FMR and impacting survival.[37] Therefore, consideration of RV function and the severity of TR could identify FMR patients who may benefit from early intervention before decompensated RV function presents. As also discussed in Introduction section, differences in the results between the COAPT and MITRA-FR studies may lead to underscoring the importance of appropriate patient selection prior to intervention. RV function plays an incremental role in determining survival outcomes of patients with FMR, and this factor is important for candidate selection for patients undergoing MitraClip procedure. RVD confers worse outcomes in significant FMR may be explained by (i) RVD with pressure overload, in the setting of ventricular interdependence, may compromise left ventricular function; (ii) RVD may be unable to maintain the forward output required to maintain adequate left ventricular preload[38]; (iii) the presence of RVD in patients with a history of preexisting cardiac disease is a significant predictor of SCD irrespective of left ventricular ejection fraction.[14] In light of the differing outcomes from MITRA-FR and COAPT trials, an additive value of RVD indices for risk stratification in this population deserves further investigation. Early recognition of RVD by using the index of RV longitudinal contraction (TAPSE) may also be invaluable in planning and timing of intervention for prevention or delay of irreversible RVD. Thus, a deeper investigation into the prognostication of RVD in patients with moderate-to-severe FMR may have both clinical significance and therapeutic implications. Importantly, FMR patients with RVD and/or moderate and severe TR seemed to benefit less frequently from MitraClip procedure, and randomized controlled trials are necessary to provide further insight into these parameters and their roles in identifying patients that are most likely to benefit.

Study limitations

First, all of the eligible studies in this meta-analysis were observational with variations in the inclusion criteria, so that heterogeneity is more likely to be present. However, we tried to minimize the bias by carefully selecting studies with low risk of bias, reflected by high scores on the Newcastle–Ottawa scale. The heterogeneity assessed using Cochrane's Q test and the I^2 statistic among included studies was not significant, suggesting the limitation did not greatly impact our conclusion. Second, to minimize the risk of false positives in association of RVD and TR with outcomes, we only included studies that adjusted for confounders in multivariable survival analysis. Third, atrial FMR has been under-recognized until recently as a cause of functional MR. Nevertheless, given that included studies are not differentiated between atrial and ventricular FMR in this analysis, we are not able to assess the difference in prognostic impact of right ventricular function and tricuspid regurgitation in these two entities of FMR. Further studies need to be conducted to assess the difference between these two entities. Additionally, haemodynamics of the right ventricle and pulmonary circulation are very crucial components in FMR and should be studied to assess its importance on the clinical outcome. Finally, although our data demonstrated the prognostication of RVD and moderate–severe TR in FMR patients undergoing mitral clip procedure, future studies are still needed to elucidate its role in patient selection

Conclusions

This meta-analysis demonstrates the prognostic importance of RVD and TR grade in predicting all-cause mortality in patients with significant FMR. RV function and TR parameters may therefore be useful in the risk stratification of patients with significant FMR undergoing MitraClip procedure.

Conflict of interest

The authors have no conflicts of interest to declare.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Figure S1. The forest plot displays the hazard ratio and 95% confidence intervals (CIs) for difference between patients with and without right ventricular dysfunction using TAPSE. Square markers indicate hazard ratios; horizontal lines, the 95% CIs, with marker size reflecting the statistical weight of the study using random-effects meta-analysis. The diamond marker represents the overall hazard ratio and 95% CI for the outcome of interest.

Table S1. Newcastle-Ottawa scale for assessment of quality of included cohort studies. Each asterisk represents fulfilment of the acceptable criteria within each subsection.

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