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Predictors of echocardiographic response to cardiac resynchronization therapy: A systematic review with Meta-Analysis

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ABSTRACT

Background: At least 30% of the patients do not respond to cardiac resynchronization therapy (CRT). We performed a systematic review and *meta*-analysis of real-world studies trying to identify predictors of response to CRT.

Methods: PubMed, Embase and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for observational prospective studies, referring the evaluation of response to CRT, defined as a decrease in left ventricle end-systolic volume (LVESV) $\geq$ 15% at 6-month follow-up, via two-dimensional echocardiography.

Results: A total of 24 studies were included. The *meta*-analysis showed that female gender ($p = 0.018$), non-ischemic cardiomyopathy (NICM) ($p < 0.001$), left bundle branch morphology (LBBB) ($p = 0.001$), longer QRS ($p < 0.001$) and New York Heart Association (NYHA) class II ($p = 0.014$) appear to favor response to CRT. After ROC analysis and logistic regression procedures, female gender (kappa = 0.450; $p < 0.001$), NICM (kappa = 0.636; $p < 0.001$), LBBB (kappa = 0.935; $p < 0.001$), and NYHA class II (kappa = 0.647; $p < 0.001$) were identified as independent predictors of response to CRT, being LBBB the most reliable one (sensitivity = 97.24%; specificity = 98.86%).

Conclusions: Female gender, NICM, LBBB and NYHA class II are baseline variables with an apparent capability to independently predict response to CRT, being LBBB the most reliable one.

1. Introduction

Cardiac resynchronization therapy (CRT) is a proven therapeutic option in properly selected patients with heart failure with reduced ejection fraction (HFrEF), that improves functional status and LV systolic function, and reduces morbidity and mortality. [1,2] CRT entails a modality in which both ventricles are submitted to electrical stimulation, correcting the existent mechanical desynchrony. [3] Even though CRT is recognized as an effective treatment in this context, at least 30% of patients do not benefit from it, and some of them even worsen their health status. [4] Therefore, it is crucial to improve patients' selection for CRT, in order to achieve better outcomes from it in these patients.

Over the last decade, observational studies and several randomized clinical trials, including a *meta*-analysis of clinical trials, [5] reported some patients' characteristics that increase the chance of response to CRT and that are present on current guidelines. [6] However, to our knowledge, it still does not exist a systematic review with *meta*-analysis of real-world evidence assessing specifically predictors of response to CRT.

This paper aims to synthesize the large quantity of real-world data regarding predictors of echocardiographic response to CRT, by conducting a *meta*-analysis of the available prospective CRT studies. Real-world evidence *meta*-analysis on this issue could provide valuable insights to confirm predictors of CRT response in routine clinical practice.

2. Methods

2.1. Protocol and registration

The design of this study respected all the standards present on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. At inception, a registration in the PROSPERO database (CRD42020211520) was completed (Appendix I).

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2.2. Eligibility criteria

The following eligibility criteria were considered: (1) observational prospective studies, referring a study design that involved the evaluation of response to CRT, defined here as a decrease in LVESV $\geq$ 15%; (2) a responder had to be defined, at no other time period than 6 months of follow-up, and with no other method than a two-dimensional echocardiography, as a patient that achieved a decrease in LVESV $\geq$ 15% (otherwise defined as non-responder); (3) patients older than 18 years old, with a wide QRS duration $\geq$ 120 ms and submitted, for the first time in their lives, to a conventional CRT; and (4) baseline data, comparing responders and non-responders, had to be present and explicit, presenting, at least: age, gender, etiology of cardiomyopathy, QRS duration, left ventricle ejection fraction (LVEF) and LVESV. Studies that included patients with a previous cardiac device (such as pacemaker), only one cardiomyopathy subtype (ischemic or non-ischemic) and sarcoidosis were excluded. Articles that considered non-responders, besides not reaching the response definition at 6 months of follow-up, as the patients that died before the considered follow-up period, were also excluded.

This specific criterium of response was chosen based on the fact that is considered one of the most reliable parameters to assess cardiac reverse remodeling after CRT. [7]

2.3. Information sources and search strategy

A systematic search was conducted in PubMed®, Embase® and Cochrane Central Register of Controlled Trials (CENTRAL), for articles written in English and published from October 31st of 2010 to October 31st of 2020. MeSH terms were used to improve the search, as well as specific filters of each database, when appropriate.

The following search equation was applied in PubMed®: ("Cardiac Resynchronization Therapy"[Mesh] OR "Cardiac Resynchronization Therapy Devices"[Mesh] OR "cardiac resynchronization therapy"[Title/Abstract] OR "biventricular pacing"[Title/Abstract] OR "biventricular pacemaker"[Title/Abstract] OR CRT[Title/Abstract]) AND ("Echocardiography"[Mesh] OR echocardiography[Title/Abstract]) AND ("response"[Title/Abstract] OR "responders"[Title/Abstract] OR "reverse remodelling"[Title/Abstract] OR "clinical improvement"[Title/Abstract]), considering the filters; articles written in English, published in the last 10 years. This search strategy was applied for the other considered databases, adapting it to the specifications of each one.

2.4. Data collection and management

Regarding study selection, two authors screened, independently and systematically, titles and abstracts of obtained publications from the previous search strategy. Subsequently, the full text assessment of the eligible articles was carried out by the same two reviewers, independently. Disagreements between individual judgements were solved by consensus, including a third author. Data regarding the following baseline variables were collected, concerning responders and non-responders: age, gender, cardiomyopathy subtype, bundle branch block morphology, rhythm status, QRS duration, ejection fraction, LVESV, NYHA functional classes, diabetes, hypertension, dyslipidemia, and chronic renal insufficiency. All the variables were considered for *meta*-analyses, except dyslipidemia and chronic renal insufficiency, due to the small number of occurrences. Some articles only reported data relative to LVEF and LVESV via other methods than 2D echography (3D echography [8] and MRI [9,10]), while another had data regarding only LVESV index, instead of LVESV. [9,11] Therefore, correspondent variable data from these articles were not used in the *meta*-analyses.

2.5. Risk of bias assessment

Only prospective observational studies were included on this manuscript. The Newcastle-Ottawa Scale (NOS) for non-randomized studies was used, independently, by two reviewers, to appraise the risk of bias of the included articles. Using this tool, three domains were assessed, based on a 'star system': selection of the study groups (it implies four items; each one can value one star, depending on the study's characteristics); comparability of them (it can value a total of two stars); and the evaluation of the outcome (it implies three items; each one can value one star). The NOS summary (Table 1– E component 1) presents the quality appraisal for each study.

2.6. Statistical analysis – Synthesis of results and additional analyses

A random-effects model *meta*-analysis was performed using as effect size the standardized mean difference of each one of the variables in analysis (z-scores). Heterogeneity of the results was evaluated through the I^2 measure and plotted the overall summary measures in a summary forest plot with a lateral table, where confidence intervals and p-values are described (adjusted p-values using Benjamini-Hochberg correction assuming a false discovery rate = 20%). With this analysis, performed in R, version 4.0.3 through the *metaphor* package, it was possible to identify which variables presented statistical differences between response and non-response to CRT.

Afterwards, a ROC analysis was applied to each variable identified in the previous *meta*-analyses as presenting statistically significant differences (considering $p < 0.05$ and adj-$p < 0.10$), in order to identify eventual thresholds for the variables identified before as possible discriminator of response. For each variable considered as discriminating response with ROC analysis, the variable was dichotomized according to the threshold defined by the highest Youden index and the sensitivity, specificity, positive and negative predictive values were obtained. Predictive values may be used to determine the probability having a response when the characteristic that is in analysis is present or absent. Also, the Cohen's kappa was calculated to accomplish concordance between predictions and observed classification for response. These former analyses were performed in IBM SPSS®, version 26, using study precision as weights for analysis, defined as the inverse of the sampling variance, and weights were determined as the percentage of sample variance of each study relative to the total variance. For binary variables, expressed as percentages, and using the Bernoulli distribution, it was assumed that the sampling variance is given by p(1-p), where p is the percentage of cases satisfying that condition.

All the analyses were evaluated at a 5% significance level and confidence intervals were determined for 95% confidence.

3. Results

3.1. Study selection and search results

A total of 2462 publications were identified through the literature search strategy previously defined (Fig. 1).

After removal of duplicates, 1773 records were screened based on their title and abstract and 1576 of these were excluded. At this stage, 197 papers were considered for full-text assessment and 173 of those were excluded for the following reasons: conference abstracts (42); retrospective studies or included retrospective data collection (19); absence of all the demanded variables to be included on this systematic review (19); absence of the pretended data regarding responders and non-responders (52); considered other definition of response (31); had other definition of non-response, considering death before the 6-month evaluation as non-response (5); evaluated patient's response at different follow-up period (10); included patients with a previous cardiac device (15); considered other pacing modality, including multipoint CRT (2); included patients only with a specific cardiomyopathy subtype (1); had the presence of desynchrony as an inclusion criteria (2); included patients with sarcoidosis (2); included patients with narrow QRS (1); were only available in Russian (2). At this point, 25 studies fulfilled all the

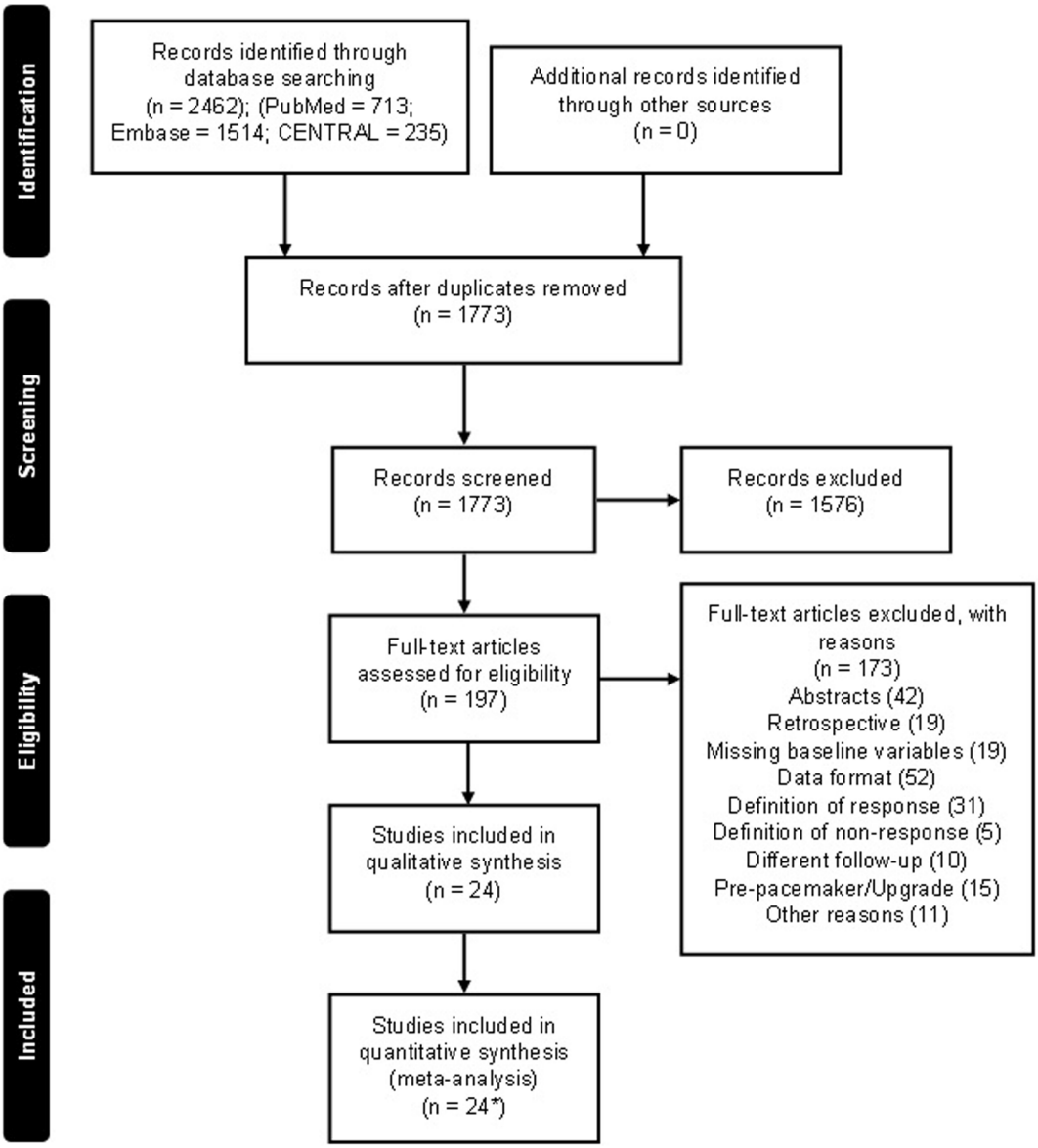

Fig. 1. PRISMA flow diagram of search strategy.

inclusion criteria for the systematic review, being twenty-four observational prospective studies and only one an RCT. Given this fact, the RCT was also excluded to study only "real-world" patients. Therefore, twenty-four studies were included in the qualitative synthesis, and all of them contributed to the quantitative synthesis (with the variables present on each article). A summary of their characteristics is presented on Table 2 (E-component 2).

3.2. Results of individual studies

3.2.1. Baseline variables between groups

A summary of comparisons of baseline variables between responders and non-responders is presented in Table 3 (E-component 3). It is to highlight that NICM was more often present in the responder group, with a reported significant statistically difference in eight studies, [9,10,12,14,17–20] as well as a longer QRS duration. [12,13,15,16,19].

3.2.2. Univariate and Multivariate analyses

LBBB is the most relevant baseline variable that stands out from the analyses reported from the various studies, both in univariate and multivariate analyses (Appendix II)

3.3. Additional analyses – Meta-analysis and classification

A *meta*-analysis was conducted for each variable, if values corresponding to it were present in, at least, two of the twenty-four articles considered for qualitative analysis. However, given the quantity of data available for analysis and subsequent discussion, it was decided to present the results deemed more relevant for this manuscript (all the *meta*-analyses made are present in the Appendix III). Some articles only reported data relative to LVEF and LVESV via other methods than 2D echography (3D echography [8] and MRI [9,10]) – these values were not used in *meta*-analyses. One study [17] reported values of LVEF and LVESV via 3D echography, however it was also used 2D echography on the same study, and the differences of measurement between the two methods were non-significant. Therefore, those values were considered for *meta*-analysis. A forest plot with the summary of the more important *meta*-analyses results obtained for each variable, as a screening of the tendencies reported from all studies, is presented in Fig. 2. All the information regarding the *meta*-analyses conducted is present in the Appendix III.

Female gender, NICM and LBBB appears to favor response to CRT, as well as the presence of a longer QRS duration and a NYHA functional

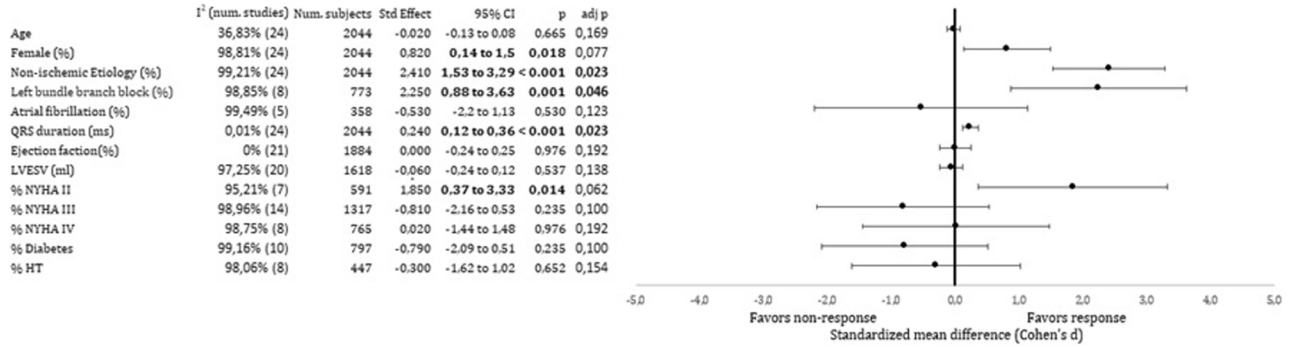

Fig. 2. Forest plot with the summary of all the *meta*-analyses performed.

class II (Fig. 2). Fig. 3 presents the studies that contributed for each *meta*-analysis regarding female gender, NICM, LBBB and NYHA class II.

Thereby, considering the variables that presented relevant tendencies on *meta*-analyses, a ROC analysis was performed using those in an univariate way, so that important studies were not placed out. The weight of each study was considered in order to ascertain which baseline variables were able to discriminate responders from non-responders.

It is possible to infer that study samples that have more than about 40% of subjects with NICM (Table 1), have more than three quarts of subjects with LBBB and have more than about one fifth of women (≥20.66%) and NYHA class II patients (≥22.17%) are more likely to discriminate responders from non-responders to CRT. This means that the presence of those characteristics may, in advance, identify patients who will benefit more in terms of reverse remodeling from CRT.

The classification was carried out for studies in which previous mentioned baseline variables were identified as discriminators of response to CRT, after dichotomization according to the threshold defined in Table 1, considering study weights. Among those, it was found that four of them may be considered as independent predictors of response to CRT. Concordance between observed and predicted response (based on the cut-off points resulted from the ROC analysis), regarding the response to CRT, is higher in the presence of the following characteristics (Table 5 – E component 4): female gender (kappa = 0.450; $p < 0.001$), NICM (kappa = 0.636; $p < 0.001$), LBBB (kappa = 0.935; $p < 0.001$), and NYHA class II (kappa = 0.647; $p < 0.001$). Of note, since these variables were considered in a binary form, it can be said that, within the deemed variables, the presence of LBBB is the most potent predictor of response to CRT by far, with an almost perfect concordance between the CRT response that occurs in fact and what is predicted by the ROC analysis, and with both sensitivity and specificity higher than 95%. From this data, it is suggested that, in a certain sample, with more than about 75% of patients with LBBB, the probability of response to CRT is almost certain if this characteristic is present (99.69%), and clearly drops to 8.65% if LBBB is absent. The same logic can be applied to the other variables with significant both thresholds and kappa, however with less reliability.

4. Discussion

4.1. Summary of evidence

This *meta*-analysis of real-world evidence demonstrates that: (1) female gender, NICM, LBBB morphology and NYHA class II are baseline variables more frequent in responders than in non-responders to CRT, with an apparent capability to independently predict the response to CRT - populations with higher proportion of patients with these

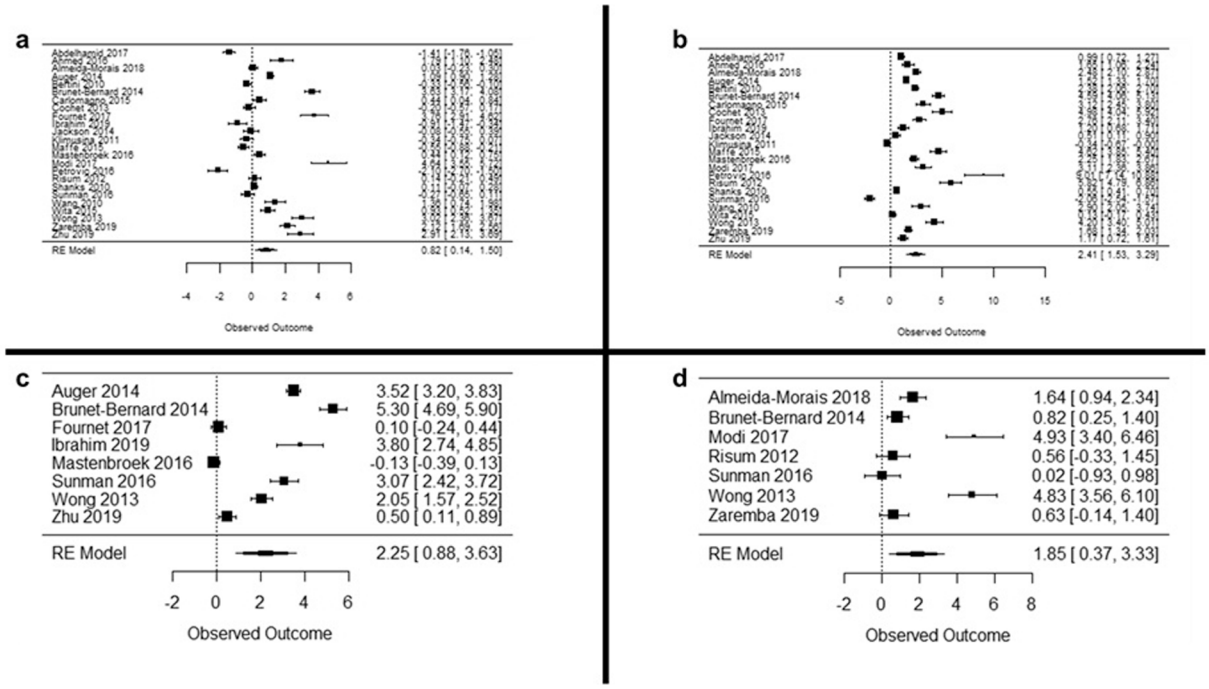

Fig. 3. Forest plots for the most relevant *meta*-analyses, with all the contributing studies and synthetic overall measure considering a random-effects model.

Table 1
Results from ROC analysis.

	AUC (SE)	95 %CI	P	Cut-off	S	E
Female gender (%)	0.721 (0.031)	0.782–0.782	< 0.001	≥ 20,66%	90.50%	51.06%
NICM (%)	0.773 (0.032)	0.710–0.837	< 0.001	≥ 39.65%	99.58%	55.17%
LBBB (%)	0.969 (0.011)	0.947–0.991	< 0.001	≥ 73.96%	97.24%	98.96%
QRS duration (ms)	0.555 (0.038)	0.480–0.630	0.096	–	–	–
NYHA II (%)	0.815 (0.028)	0.759–0.871	< 0.001	≥ 22.17%	75.95%	96.15%

LBBB, left bundle branch block; NICM, non-ischemic cardiomyopathy; NYHA, New York Heart Association.

characteristics are more likely to benefit from CRT; (2) LBBB morphology appears to be the most reliable independent predictor of CRT response.

The tendency of responders to have baseline characteristics that are vastly studied as potential predictors of response to CRT in the current literature is confirmed by this *meta*-analysis. A previous systematic review on this topic showed that NICM, LBBB, longer QRS, and female gender are associated with improvement in various outcomes after CRT. [21] In consonance with previous studies, [22–25] the present *meta*-analysis confirmed, with data from real-world, the importance of these clinical variables to achieve the desired left ventricular reverse remodeling with CRT.

There is weak evidence, due to lack of large randomized trials, regarding the benefit of CRT in patients with permanent AF. The systematic review Rickard J et al. points out that eligible patients with sinus rhythm have better outcomes following CRT. [21] However, regarding reduction in ventricular volume (reverse remodeling) after CRT, the present *meta*-analysis suggests that AF is not so determinant, supporting the recommendation of experts in favor of CRT in permanent AF patients with NYHA class III to IV with the same indications as for patients in sinus rhythm. Accordingly, a recent *meta*-analysis of Mustafa U *et al.* demonstrates that the positive change in LVEF achieved with CRT is comparable in patients with normal sinus rhythm and AF. [26].

One of the most interesting and, to our knowledge, innovative findings of this study is that NYHA II may be an independent predictor of response to CRT. This conclusion corroborates, in some way, the results reported by Sze et al., that described that delaying access to CRT in detrimental of trying medical management first, in an eligible heart failure patient for CRT, has no benefit at all, being, possibly, even harmful for the patient. [27] Bank et al. also reported that LV reverse remodeling tend to improve more in patients with fewer symptoms. [28] Despite that the symptoms of heart failure do not necessarily correlate to its severity, it is expected that a lesser symptomatic patient represents, in principle, less advanced stages of the disease. Consequently, it is expected that this patient presents a more preserved myocardial structure with less scar tissue, which, in turn, makes cardiac reverse remodeling more likely to happen, fact that could explain why NYHA class II may predict CRT response.

Other additional interesting finding of this study is that LBBB morphology, in an eligible patient for CRT, may be the most potent independent predictor of response. Several studies have demonstrated that patients with LBBB morphology are more likely to respond favorably to CRT than their non-LBBB morphology counterparts. Sipahi et al. [29] conducted a *meta*-analysis in which they evaluated the impact of QRS morphology on clinical outcomes after CRT, and it was verified that a baseline LBBB was associated with a 36% risk reduction, and such benefit was not observed in patients with non-LBBB morphologies.

Although it is consensual that patients with larger QRS and LBBB benefit from CRT, it is still unclear which is the key predictor of response, since LBBB frequently coexists with longer QRS. [30] Even though there is evidence showing that QRS morphology do not give important information regarding clinical response (after adjustment for QRS duration), [5] the opposite is also reported. [31] Results of three landmark CRT clinical trials (MADIT-CRT, REVERSE trial and RAFT) indicate that all patients with baseline LBBB morphology benefit from CRT, regardless of QRS duration. [24,32,33] The fact that this *meta*-analysis identifies LBBB as a such important predictor suggests that the major impact of CRT is on the electro-mechanical resynchronization of the LV.

4.2. Limitations

This analysis is based on data from study samples, and not from individual patient data. Therefore, the results should not be extrapolated to individual patients, but rather to populations. Also, it has to be pointed out that data heterogeneity is high, and that variability of two studies was estimated from their range and interquartile range instead of their standard deviations. Finally, it was not possible to conduct a multivariate logistic regression, since a great quantity of data would be excluded and it would be difficult to attribute weights based on different variables.

4.3. Conclusions

This *meta*-analysis filled a gap that persisted on the literature: compiles several important potential predictors of response to CRT, in a systematic way, and conducts a cohesive statistical analysis, giving insights of the importance of each one. Female gender, NICM, LBBB and NYHA class II are baseline variables with an apparent capability to independently predict response to CRT in real-world clinical practice – populations with higher proportion of patients with these characteristics are more likely to benefit from this therapy. From these variables, LBBB is the most reliable to predict cardiac reverse remodeling. Future studies can address the application of CRT in patients in contexts that were not so focused until these days: CRT in earlier heart failure stages and populations with large proportions of AF.

5. Funding Statement

Not applicable.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcha.2022.100979.

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