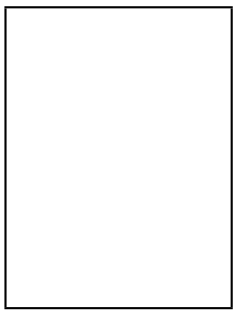
Journal Pre-proof



Predição da resposta à terapêutica de ressincronização cardíaca utilizando critérios eletrocardiográficos: revisão sistemática

Paulo Dias Costa João Pedro Bessa Mariana Canelas Pais Daniela Ferreira-Santos Fernando Montenegro Sá Matilde Monteiro-Soares António Hipólito-Reis Mário Martins Oliveira Pedro Pereira Rodrigues

PII: S0870-2551(25)00221-5

DOI: https://doi.org/doi:10.1016/j.repc.2025.02.011

Reference: REPC 2463

To appear in: *Revista Portuguesa de Cardiologia*

Received Date: 25 October 2024

Accepted Date: 14 February 2025

Please cite this article as: Costa PD, Bessa JP, Pais MC, Ferreira-Santos D, Fernando Montenegro S, Monteiro-Soares M, Hipólito-Reis A, Oliveira MM, Rodrigues PP, Predição da resposta à terapêutica de ressincronização cardíaca utilizando critérios eletrocardiográficos: revisão sistemática, *Revista Portuguesa de Cardiologia* (2025), doi: https://doi.org/10.1016/j.repc.2025.02.011

Predição da resposta à terapêutica de ressincronização cardíaca utilizando critérios eletrocardiográficos: revisão sistemática

Prediction of response to cardiac resynchronization therapy using electrocardiographic criteria: systematic review

Authors

Paulo Dias Costa[1,2] [0000-0003-0827-6055], João Pedro Bessa[3], Mariana Canelas Pais[2,4] [0000-0002-6487-313X], Daniela Ferreira-Santos[2,5] [0000-0002-0390-9944], Fernando Montenegro Sá[6] [0000-0003-3175-3673], Matilde Monteiro-Soares[1,2,7,8] [0000-0002-4586-2910], António Hipólito-Reis[9] [0000-0002-0820-226X], Mário Martins Oliveira[10,11] [0000-0002-8371-8354] Pedro Pereira Rodrigues[1,2] [0000-0001-7867-6682]

1. Center for Health Technology and Services Research, Porto, Portugal
2. Department of Community Medicine, Information and Decision Sciences; Faculty of Medicine, University of Porto, Porto, Portugal
3. Hospital da Luz, Grupo Luz Saúde, Aveiro, Portugal
4. MTG Research and Development Lab, Porto, Portugal
5. Institute for Systems and Computer Engineering, Technology and Science, Porto, Portugal
6. Matosinhos Local Health Unit, Pedro Hispano Hospital, Matosinhos, Portugal
7. Portuguese Red Cross Health School Lisbon, Lisboa, Portugal
8. Cross I&D, Lisboa, Portugal
9. Santo António Local Health Unit, Porto, Portugal
10. São José Local Health Unit, Lisboa, Portugal
11. Faculty of Medicine of Lisbon, Lisboa, Portugal

Corresponding author

Paulo Dias Costa

Department of Community Medicine, Information and Decision Sciences

Faculty of Medicine, University of Porto

Rua Dr Plácido da Costa, s/n

Porto, 4200-450

Portugal

Email: paulo.diascosta@outlook.com

Resumo

***Contexto**: A terapêutica de ressincronização cardíaca (TRC) é uma opção terapêutica consolidada para a insuficiência cardíaca; no entanto, apesar da seleção criteriosa, cerca de 30% dos pacientes não respondem a esta terapêutica. O eletrocardiograma (ECG) padrão é uma ferramenta prática e económica para avaliar potenciais respondedores à TRC, mas existem evidências contraditórias sobre o valor de diferentes parâmetros do ECG. Assim, realizámos uma revisão sistemática de estudos em contexto clínico real para avaliar o valor dos parâmetros de ECG padrão antes da implantação na predição de resposta à TRC.* ***Métodos**: Realizámos uma pesquisa nas bases de dados PubMed, Scopus e Web of Knowledge para identificar estudos analíticos e sintetizámos os resultados em tabelas de evidências.* ***Resultados**: Foram incluídos 62 artigos elegíveis nesta revisão. Os preditores tradicionais de resposta foram a duração do QRS ≥ 150ms e a presença de bloqueio do ramo esquerdo (BRE) com morfologia típica. Parâmetros de ECG contemporâneos, como a presença de entalhes ou fragmentação do QRS, a análise da onda S, o tempo de deflexão intrinsicóide (ID) nas derivações laterais e uma razão na derivação DI (LOR) ≥ 12, mostraram também grande potencial na avaliação da resposta à TRC.* ***Conclusões**: Esta revisão destaca a capacidade promissora do ECG padrão em prever a resposta à TRC, particularmente ao utilizar preditores mais contemporâneos, sublinhando a necessidade de mais investigação para validar o valor prognóstico destes preditores.*

Abstract

Background: Cardiac resynchronization therapy (CRT) is an established therapeutic option for heart failure, but despite careful selection around 30% of the patients still do not respond to this therapy. The standard electrocardiogram (ECG) is a practical and inexpensive tool to assess potential responders to CRT but with conflicting evidence regarding the value of different ECG parameters. As such, we conducted a systematic review of real-world studies to assess the value of pre-implantation standard ECG parameters in predicting response to CRT. **Methods**: We searched on PubMed, Scopus, and Web of Knowledge online databases to identify analytic studies and synthesized results through evidence tables. **Results**: 62 eligible articles were included in this review. Traditional predictors of response were QRS duration ≥ 150ms and the presence of left bundle branch block (LBBB) morphology. Contemporary ECG parameters, such as the presence of QRS notching or fragmentation, the S wave assessment, the time to intrinsicoid deflection (ID) in lateral leads, and a lead one ratio (LOR) ≥ 12 also showed great potential in assessing response to CRT. **Conclusions:** This review highlights the promising capability of the standard ECG in predicting response to CRT, particularly when using more contemporary predictors, while emphasizing the necessity for further research to validate the prognostic value of these predictors.

Palavras-Chave

Terapêutica de ressincronização cardíaca; insuficiência cardíaca; seleção de pacientes; revisão sistemática.

Keywords

Cardiac resynchronization therapy; heart failure; patient selection; systematic review.

Introduction

Heart failure (HF) is a major public health problem, with an incidence in Europe of about 5/1000 person-years(1, 2) and a prevalence of 1–2% in adults(3), although there is evidence that these figures might be underestimated(4). The increasing prevalence of chronic HF, compounded by improved patient survival and higher elderly patient proportion, puts additional economic strain on healthcare systems(5). Cardiac resynchronization therapy (CRT) is currently an established therapeutic option for patients with symptomatic HF and electromechanical dyssynchrony(6), improving cardiac function and functional capacity while reducing morbidity, mortality, and hospitalizations(7). Nevertheless, and despite careful patient selection, improvement in implantation techniques and optimal device programming, the response to CRT is variable and up to 30% of patients demonstrate sub-optimal response(8) notwithstanding the use of several approaches to improve CRT response(9). Standard electrocardiogram (ECG) is recommended in all patients with suspected chronic HF not only for diagnosis but also for CRT candidate selection, and remains an accessible and practical tool to identify patients with a higher potential for CRT response, at a significantly lower cost than other methods(10). Parameters such as QRS duration (QRSd) and morphology have been traditionally used but with conflicting results in predicting CRT response, particularly in patients with borderline QRSd and atypical left bundle branch block (LBBB) pattern(10). Recently, other ECG parameters have shown promising results in predicting response to CRT, but the evidence is limited, dispersed and in need of additional validation(11). As such, we aim to assess the ability of standard ECG to predict response to CRT by systematically reviewing the available literature. Specifically, our objective was to identify pre-implantation ECG parameters/criteria that independently predict outcomes after CRT.

Methods

Search strategy

A preliminary search was conducted on Medical Literature Analysis and Retrieval System Online (MEDLINE) using the MEDLINE (PubMed)[i] and the International Prospective Register of Systematic Reviews (PROSPERO)[ii]. No current or underway similar systematic review or meta-analysis protocols were identified. This study was carried out according to a protocol, registered in PROSPERO (CRD42022374879), and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)(12, 13).

We systematically searched all available literature on PubMed, Scopus[iii], and Web of Knowledge[iv] databases using search queries adapted for each database (described in detail in Supplemental Methods SM1. The search was restricted to articles published from 1 January 1995 (the date of the first CRT publication) through 10 November 2022. No other restrictions were applied. Manual scanning of the reference list of all selected articles was performed to identify additional pertinent articles. Specialists in the field were contacted to confirm if all pertinent information had been retrieved.

Eligibility criteria

Studies that met all the following criteria were considered for inclusion: a.) included patients with HF and implanted CRT devices; b.) evaluated response to CRT (symptomatic and/or volumetric); c.) defined response and stated the criteria used; d.) predicted response based (isolated or in association) in at least one independently assessable electrocardiographic parameter; e.) had an analytic study design; f.) reported objective effect measures (association and/or accuracy tests). Studies that did not meet all the criteria defined above or had any of the following criteria were

[i] https://pubmed.ncbi.nlm.nih.gov
[ii] https://www.crd.york.ac.uk/prospero
[iii] https://www.scopus.com
[iv] https://www.webofknowledge.com

excluded: a.) non-medical related research area; b.) ECG parameter determined only post-implant (i.e. predictor not assessable pre-CRT implantation at baseline conditions; c.) involving non-standard ECG methods/techniques (e.g. ECG mapping or ECG imaging techniques); d.) involving animals; e.) including humans below 18 years of age; f.) full-text information not available, even after contacting the corresponding author; f.) articles in languages not fully understood by the review team.

Selection process

After duplicate removal, each study was screened for inclusion by two out of five reviewers (PDC, DFS, MCP, FMS and JPB). The screening was made blindly and independently, initially by reading the title/abstract and later by reviewing the full text, using Rayyan (Rayyan web application [Computer program]. Rayyan Systems Inc., 2022)(14). Results were blinded to reviewers, and any discrepancies were resolved by an independent reviewer (PPR). The level of agreement between the reviewers was measured using overall agreement proportions.

Data extraction

Data from the selected studies was extracted to an Excel spreadsheet (Microsoft 365 Apps for Enterprise [Computer program]. Version 2210, Microsoft Corporation, 2022) by two reviewers (PDC and JPB) using standardized forms. Data extraction forms (Supplemental Methods SM2) included: a.) study information: such as first author, date and country of publication, number of centers involved, device type(s), study design and period; b.) population: sample size, age, gender, indication, selection method, and participants lost to follow-up; c.) exposure: statistical method(s) used, and predictor(s) assessed; and d.) outcomes: response cut-off, assessment timing, responder proportion, co-variables used, and effect measures.

If appropriate, authors were contacted to request unpublished, missing, or additional data. Any missing study information will be reported as ‘Not reported’ (NR) and any information that is not clear or is ill-defined, leading to uncertainty in interpretation, will be reported as ‘Unclear’ (U); if an item is not applicable in context, it will be labeled as ‘Not applicable’ (NA).

Any disagreements between the reviewers were resolved through discussion.

Risk of bias assessment

To assess the risk of bias (RoB), data from the selected studies was extracted to an Excel spreadsheet (Microsoft 365 Apps for Enterprise [Computer program]. Version 2210, Microsoft Corporation, 2022) using a customized form (Supplemental Methods SM3) of the Quality in Prognostic Studies (QUIPS) tool(15). Three of the authors (PDC, DFS and MCP) independently classified all studies for the rating of reporting ('Yes' if all relevant signaling items were present, 'No' if none of the key items was present, 'Partial' if some key items to assess were present, 'Unsure' if some key items were ill-defined, unclear, or ambiguous, and 'Not applicable' if the key item did not apply to the study), and assigned a rating for RoB ('High', 'Moderate' and 'Low') to each of the six domains assessed (study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis and reporting). The overall RoB was categorized into low (if all domains were classified as having low RoB, or up to one moderate RoB), high (if one or more domains were classified as having high RoB, or more than three moderate RoB), or moderate RoB (all other situations)(16). The level of agreement (agreement proportions) between the reviewers was measured by overall agreement and determined for each domain/overall RoB. RoB plots were created using the Risk-of-bias VISualization (robvis) tool.(17)

Synthesis Methods

To analyze and compare findings, categorical data were represented as proportions. Continuous variables were presented as mean (standard deviation) or median [along with interquartile range] when appropriate. Dichotomous data was analyzed by odds ratios (OR) or hazard ratios (HR) and presented as the respective test result [95% confidence interval]; receiver operating characteristic and diagnostic accuracy measures (DAM) – which included sensitivity, specificity, positive predictive value, and negative predictive value – are presented as accuracy or percentages. Data was synthesized and presented through evidence tables and included a descriptive report of eligible studies' general characteristics, methods, and summarized results (refer to Supplemental Tables ST1 to ST4). Since there were not two or more eligible studies assessing the same ECG predictor using similar methods, meta-analysis was not possible.

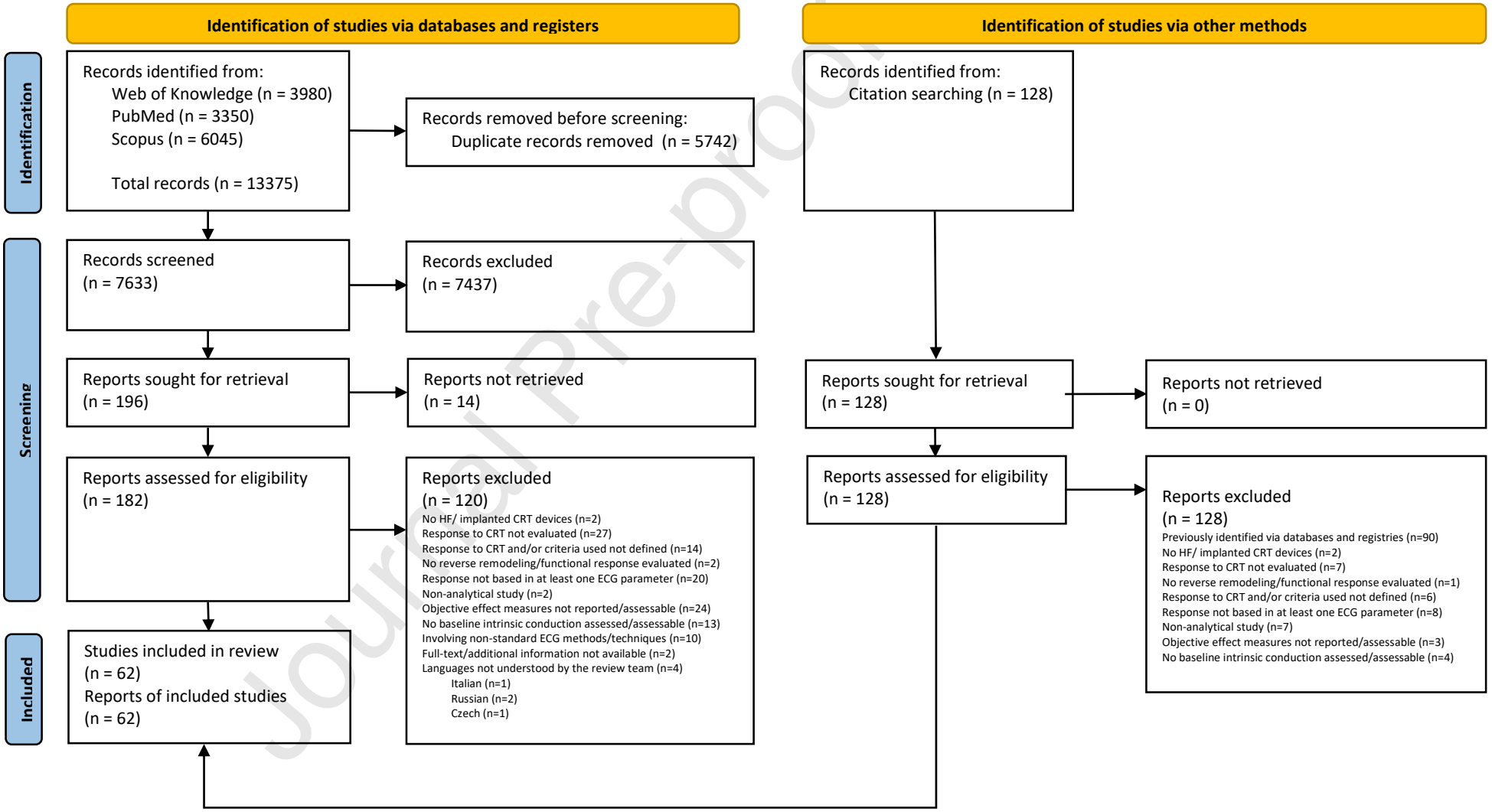


Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses study selection flowchart. Adapted from Page et al.[12].

Results

Study selection

A total of 13 503 records (13 375 from databases plus 128 from citation cross-referencing) were identified and uploaded into the Rayyan platform. After duplicate removal (5742), 7633 records were screened using the title and abstract, and, of those, 182 were assessed for eligibility through full-text review. Following full-text examination for compliance, 120 articles were excluded, resulting in 62 eligible articles included in this review (18-79). Figure 1 illustrates in detail the study selection process. The overall agreement between reviewers in the screening and eligibility stages was 98% and 86%, respectively.

Study characteristics

The most frequent inclusion criteria comprised patients in New York Heart Association (NYHA) class II-IV, with left ventricular ejection fraction (LVEF) ≤35% and QRSd ≥120ms, analyzing a total of 11774 patients (median of 100 patients, ranging from 30(79) to 1718(40)), of which 8535 (71%) were male. All studies were observational, comprising mostly cohort studies (57; 92%) from single centers (42; 68%). Studies were published between 2007 and 2022, 22 of which (35%) within the last five years. Most studies were set in European (27; 44%) and Asian countries (24; 39. Left ventricle (LV) lead delivery was described to be via the coronary sinus in 49 (79%) studies; the remaining 13 studies (21%) did not report where the LV lead was positioned.

These results are summarized in Table I. A detailed description of the general characteristics of all included studies is available in Supplemental Table ST1.

Table I: Summary of the general characteristics of all included studies.

AUTHORS	STUDY TYPE	CENTERS INVOLVED	YEAR	COUNTRY	SAMPLE SIZE	AGE (years)	SEX (male)
Adelstein et al.(18)	Unclear	Single	2009	USA	636	67.2±11.8	464 (73%)
António et al.(19)	Cohort	Single	2010	Portugal	87	62±11	55 (63%)
Assadian Rad et al.(20)	Cross-sectional	Single	2015	Turkey	65	62±12	38 (58.5%)
Atwater et al.(21)	Cohort	Multiple	2015	USA	76	65 [56–72]	54 (71%)
Bani et al.(22)	Cohort	Multiple	2015	Italy	172	70±10	116 (67%)
Bertaglia et al.(23)	Cohort	Multiple	2017	Italy	335	Unclear	241 (71.9%)
Bonakdar et al.(24)	Cohort	Single	2009	Iran	82	56±15	61 (74.4%)
Bouwmeester et al.(25)	Cohort	Single	2022	Netherlands	99	70 [65–76]	63 (64%)
Brunet-Bernard et al.(26)	Cohort	Multiple	2014	France	207	66±10 65±10 (D) 68±12 (V)	144 (70%)
Caputo et al.(27)	Cohort	Multiple	2018	Multiple	316	71 [62–77]	230 (73%)
Celikyurt et al.(28)	Unclear	Single	2019	Turkey	38	63±12	18 (47.4%)
Celikyurt et al.(29)	Unclear	Single	2013	Turkey	105	63±12	65 (62%)
Celikyurt et al.(30)	Unclear	Single	2012	Turkey	53	61±12	34 (64.2%)
Chen et al.(31)	Cohort	Single	2017	China	61	74.0±10.7	25 (41%)
Chen et al.(32)	Cohort	Single	2018	China	72	62.9±13.1	40 (56%)
Cvijic et al.(33)	Cohort	Single	2015	Slovenia	101	63.2±10.9	66 (65.2%)
De Pooter et al.(34)	Cohort	Single	2016	Belgium	52	66±12	34 (65%)
Del-Carpio Munoz et al.(35)	Cohort	Single	2013	USA	135	72 [64–77]	98 (73%)
Domenichini et al.(36)	Cohort	Multiple	2012	Multiple	56	66±11	42 (75%)
Fabiszak et al.(37)	Cohort	Single	2020	Poland	42	66.4±8.3	23 (54%)
Feeny et al.(38)	Cohort	Multiple	2019	USA	925	65.6±12.6	605 (65%)
Garcia-Seara et al.(39)	Cohort	Single	2008	Spain	80	70±7	57 (73%)
Gasparini et al.(40)	Cohort	Multiple	2022	Italy	1718	66±10	1352 (78.7%)
Ghani et al.(41)	Cohort	Single	2017	Netherlands	347	67±9	243 (70%)
Gunduz et al.(42)	Cohort	Single	2021	Turkey	77	63.35±8.9	49 (63.6%)
Guo et al.(43)	Cohort	Single	2020	China	101	61.22±9.54	70 (69.3%)
Hsu et al.(44)	Cohort	Multiple	2012	Multiple	752	64.39±10.8	567 (75.4%)
Jiang et al.(45)	Cohort	Multiple	2020	China	181	61.2±11.7	124 (68.5%)
Kang et al.(46)	Cohort	Multiple	2015	China	106	60.8±12.7	66 (70.97%)
Karaca et al.(47)	Cohort	Single	2016	Turkey	125	63.5±11.7	80 (64%)
Kataoka et al.(48)	Cohort	Single	2021	Japan	69	71 [62–78]	28 (60%)
Kuznetsov et al.(49)	Cohort	NR	2020	Russia	93	56.6±9.3	76 (81.7%)
Lin et al.(50)	Cohort	Single	2014	China	193	64±12	133 (69%)
Lipoldova et al.(51)	Cohort	Single	2010	Czech Republic	194	62.1±9.4	146 (75%)
Liu et al.(52)	Cohort	Single	2020	China	387	58.66±10.9	250 (64.6%)
Loutfi et al.(53)	Cohort	Multiple	2016	Multiple	170	68.8±9.7	121 (77.1%)
Mollema et al.(54)	Cohort	Single	2007	Netherlands	242	67±10	197 (81.4%)
Mollo et al.(55)	Cohort	Single	2013	Italy	51	67.3±9.5	36 (71%)
Mugnai et al.(56)	Cohort	Multiple	2022	Italy	236	69.7±9.9	183 (77.5%)
Nakai et al.(57)	Cohort	Single	2020	Japan	199	65.6±13	158 (79.4%)
Nesti et al.(58)	Cohort	Multiple	2020	Italy	178	70±10	120 (67.4%)
Pan et al.(59)	Cohort	Single	2013	China	82	62.6±11.8	65 (79%)
Park et al.(60)	Cohort	Single	2012	USA	125	68±12	94 (75%)
Pastore et al.(61)	Cohort	Multiple	2018	Italy	66	70.64±10.37	60 (90.9%)
Raj et al.(62)	Cohort	Single	2022	India	93	61.19±7.89	61 (65.6%)
Rickard et al.(63)	Cohort	Single	2011	USA	99	64.1±11.3	85 (86%)
Rickard et al.(64)	Cohort	Single	2010	USA	233	65.0 [57.3–73.3]	171 (73.4%)
Sabbag et al.(65)	Cohort	Single	2020	Israel	239	67±10	201 (84%)
Sassone et al.(66)	Cohort	Multiple	2015	Italy	243	69±7	180 (74%)
Sebag et al.(67)	Cohort	Multiple	2012	France	85	64.8±10.5	61 (71.8%)
Serdoz et al.(68)	Cohort	Multiple	2011	Italy	75	64±8.6	65 (87%)
Shen et al.(69)	Cohort	Single	2011	USA	100	70±10	73 (73%)
Storkas et al.(70)	Cohort	Multiple	2020	Multiple	68	69±8	55 (81%)
Tian et al.(71)	Cohort	Single	2013	China	58	59.7±11.7	50 (86.2%)
Toniolo et al.(72)	Cohort	Single	2013	Italy	197	68±8	169 (86%)
Van't Sant et al.(73)	Cohort	Single	2015	Netherlands	227	65.4±10.5	153 (67%)
Yang et al.(74)	Cohort	Single	2019	USA	114	67.6±11.2	83 (72.8%)
Yeim et al.(75)	Cohort	Single	2007	France	100	66±11	74 (77%)
Yin et al.(76)	Cohort	Single	2019	United Kingdom	54	46±13	40 (74%)
Yu et al.(77)	Cohort	Single	2017	China	227	60.4±12.3	163 (71.8%)
Zhang et al.(78)	Cohort	Single	2014	China	45	62.9±9.3	38 (84.4%)
Zhang et al.(79)	Cohort	Single	2015	China	30	57.10±12.58	22 (73.3%)

Synthesis results

Electrocardiographic Predictors

The most frequent ECG parameters used for outcome prediction were QRS duration (43 studies), morphology (39), and amplitude (two studies). QRS axis was used in seven studies, PR interval in four studies, QT interval in three studies and heart rhythm in two studies.

Traditional ECG predictors

Six studies (24, 43, 60, 63, 75, 76) have shown that QRS duration significantly predict response to CRT, albeit with modest effect sizes. The study by Chen et al.(32) showed a greater magnitude of effect (adjusted OR: 2.68), although this was a single-center study, with a small sample size and a short follow-up period. The study by Ghani et al.(41) also found QRS duration to be a good predictor when assessing super response. Two other studies also suggest that patients with shorter QRS durations are less likely to respond(36) (adjusted OR: 13.8)(19) although there was a considerable degree of uncertainty in this estimate. For patients with wide QRS, five studies(25, 44, 47, 53, 73) have shown that a QRS duration ≥150ms significantly increases the odds of response, with the studies by Loutfi et al.(53) and Bouwmeester et al.(25) showing the effect to be around four times higher. However, Sassone et al.(66) suggested that the chances of non-response increase significantly in patients with very wide QRS (≥178ms), possibly associated to the absence of mechanical dyssynchrony and therefore not correctable by biventricular pacing.

There is no evidence in four of the analyzed studies that non-LBBB or right ventricular bundle branch block patterns can predict response (40, 50, 61, 74). On the other hand, three studies (18, 36, 78), using the ACC/AHA/HRS criteria(80), showed a high likelihood of response in patients with LBBB morphology (adjusted OR: ~7). Even more, Rickard et. al(64) and Yang et al.(74) found that the presence of LBBB was able to predict super response (adjusted OR: ~5 and ~2, respectively). Caputo et. al(27), using the 2009(81) and 2013(82) ESC criteria found similar results (adjusted OR: ~8). Using the same criteria, Liu et al.(52) showed that it was able to predict super response (adjusted OR: 2.57). LBBB remained a good predictor of response in the study by Bouwmeester et al.(25), using the more recent ESC criteria (2021)(83). The 'strict' LBBB criteria proposed by Strauss(84) was also found to be a good predictor of response in the studies by Brunet-Bernard et al.(26) (adjusted OR: 3.18), Jiang et al.

(adjusted HR: 3.01) and Van't Sant et al.(73) (adjusted OR: 2.45). The study by Tian et al.(71) reported that patients with LBBB were 11 times more likely to be super responders, although with a high degree of associated uncertainty (adjusted OR: 11.680 [1.966-69.390]).

Contemporary electrocardiographic predictors

Fragmented QRS and notched QRS

The presence of fragmented QRS (fQRS) is a sign of myocardial scar and was identified in the study by Assadian Rad et al.(20) has a predictor of non-response to CRT (adjusted OR: 4.55). However, this study did not include an assessment of myocardial scar, and, therefore, it was not possible to determine the relationship between fQRS and scar in that population. Furthermore, the study by Nesti et al.(58) failed to find such an association.

Pan et al.(59) and Bertaglia et al.(23) reported, respectively, that a notched QRS (nQRS) in lateral leads (adjusted OR: 4.04) or a notched QRS in at least one lead (adjusted OR: 2.1) are good predictors of response to CRT. Although novel, due to the presence of selection bias in one study and the limited size of the sample in another study, these results may not be generalizable and need to be interpreted with caution.

S waves

The study by Kataoka et al.(48) aimed at identifying the potential role of QRS amplitude in optimal patient selection by using the S-wave amplitude in right and left precordial leads. The averaged S-wave amplitude in V1-3 emerged as an independent predictor of CRT response (adjusted OR: 2.181). In contrast, the study by Jiang et al.(45) showed that an S wave in V6 was significantly associated with non-response to CRT (adjusted HR: 0.33).

Lead one ratio

Lead one ratio (LOR) is derived by dividing the maximum positive and the maximum negative amplitudes of the QRS complex in lead I. In their study, Raj et al.(62) found that a LOR ≥12 was associated with a better response to CRT (OR: 1.78 – for QRS duration ≥150ms; OR: 2.58 – for LBBB morphology), although this resulted from univariate analysis.

Intrinsicoid deflection

Del-Carpio Munoz et al.(35) identified the difference of the time to intrinsicoid deflection (ID) in leads I and aVL (adjusted OR: ~3) and the difference of the time to ID between lead I-V1 (adjusted OR: 2.41) and lead I-QRS ratio (adjusted OR: 3.10) as a good predictor of response in patients with LBBB or a non-specific IVCD.

Other electrocardiogram predictors

QRS axis showed a marginal ability to predict response to CRT in three of the studies(37, 48, 67), with an OR of around one in univariate analysis. The presence of left axis deviation (LAD) appears to be associated with higher odds of responding to CRT in the study by Garcia-Seara et al.(39) (adjusted OR: 5.04), albeit with a very wide CI. Similarly, Storkas et al.(70) suggested that the presence of LAD is associated with lower odds of non-response to CRT (adjusted OR: 0.21).

PR interval prolongation in the studies by Gasparini et al.(40) and Sabbag et al.(65) showed a decreased likelihood of response, however with several concerns regarding the degree of uncertainty and the true effect size of the estimates. In contrast, according to Gasparini et al.(40), a 'normal' PR interval is associated with a higher likelihood of response (adjusted OR: 2.51).

Two studies addressed the value of the QT interval, either by assessing super response(33) or non-response(77). The work by Yu et al.(77) highlights the value of the ratio between the T wave from peak to end interval (TpTe) and QTc (TpTe/QTc) in predicting CRT non-response (adjusted OR=5.2). These results need to be interpreted with caution as this study had a small size sample from a single center and, since TpTe was not statistically significant, TpTe/QTc could have been largely determined by QTc. Moreover, it showed moderate discriminatory power for TpTe/QTc in predicting non-response to CRT (AUC: 0.616; Se: 57.3%; Sp: 63.8%).

A summary of all relevant ECG predictors is presented in Table II.

Table II: Standard electrocardiogram predictors of response and non-response to cardiac resynchronization therapy.

	RESPONSE	NON-RESPONSE
QRS AXIS	▪ LAD (> -30°)(39, 70)	
PR INTERVAL	▪ PRi [150-170]ms(40)	

QRS INTERVAL	**duration**	▪ Increasing QRSd(32, 43, 60, 63, 75, 76) ▪ QRSd ≥ 150ms(25, 44, 53, 73) ▪ TID (LBBB/NSIVCD patients)(35) I: 110ms; aVL: 130ms; I-V1: 90ms; I-QRS ratio: 0.69 ▪ QRSi ≥ 5.5 ms.m2/kg(47) ▪ RS in V1≥45 ms(55) ▪ QRSd >140 ms [males] or >130 ms [females](56)	▪ QRSd < 120ms(19) ▪ QRSd ≥ 178ms(66) ▪ Q-f interval <32.5ms(28)
	morphology	▪ Absence of fQRS(52) ▪ Absence of f-wQRS(30) ▪ Presence of LBBB morphology AHA/ACCF/HRS(18, 36, 49, 64, 74, 78) ESC 2009(27) ESC 2013(27, 49, 52, 56) ESC 2021(25) Strauss(26, 45, 49, 71, 73) ▪ nQRS (lateral leads)(59) ▪ Mid nQRS (at least one lead)(23)	▪ Presence of fQRS(20) ▪ Presence of S wave in V6(45)
	amplitude	▪ Average S wave amplitude in V1-3 ≥ 1.44mV(48) ▪ LOR ≥ 12(62)	
ST-T SEGMENT		▪ SS ≤ 5(21)	▪ Increasing mSS & sSS(22) ▪ SS ≥7(58)
QT INTERVAL			▪ TpTe/QTc >0.203(77)

Caption:
AHA/ACCF/HRS: American Heart Association/American College of Cardiology Foundation/Heart Rhythm Society; BMI: Body Mass Index; ESC: European Society of Cardiology; f-wQRS: fragmented wide QRS; LAD: Left Axis Deviation; LBBB: Left Bundle Branch Block; LOR: Lead One Ratio; mSS: modified Selvester Score; nQRS: notched QRS; NSIVCD: Non-Specific Intraventricular Conduction Delay; PRi: PR interval: Q-f interval: time interval from Q wave to the onset of QRS fragmentation; QRSd: QRS duration; QRSi: QRS index; QTc: corrected QT interval; RS: R wave peak to S wave peak time; sSS: simplified Selvester Score; SS: Selvester Score; TID: Time to intrinsicoid deflection; TpTe: T wave from peak to end interval.

Results of association and diagnostic accuracy measures are available, respectively, in the Supplemental Tables ST2 and ST3.

Other Predictors

To understand the interplay between electrocardiographic parameters and other factors regarding CRT response prediction, we identified other co-variates used in the reviewed studies. Consequently, 25 echocardiographic variables were identified in 49 studies while 17 clinical variables were used in 40 studies.

The most frequent variables used were gender (26 studies) and etiology of HF (20 studies). A complete description of all adjusted variables identified is available in Supplemental Table ST4.

Response Outcomes

The CRT response was assessed by using a single criterium - either symptomatic (2; 3%), volumetric (42; 68%) or compounded (9; 15%) - or by assessing differential response separately using symptomatic, volumetric, and/or compounded criteria independently (9; 15%). In addition, eight studies assessed super response, either

comparing it with response or using it as a single criterium of response(33, 41, 44, 52, 64, 68, 71, 74). Response thresholds varied, with the most frequent cut-off criteria for symptomatic and volumetric responses being a decrease of at least one point in the NYHA class and a decrease of at least 15% of the LV end-systolic volume, respectively. When using compounded thresholds, the most frequent cut-off was a decrease of at least one point in NYHA class and an increase of 5% in LVEF. Response assessment timing was mostly performed at 6 (37; 60%) and 12 months (11; 18%), with only three studies assessing a follow-up longer than 12 months. The median response proportion in studies using symptomatic criteria was 69%, ranging from 38% to 88%. For volumetric criteria, the median response rate was 58% varying from 42% to 75%. In studies using compounded criteria, the median responder proportion was 69%, with a minimum of 65% and a maximum of 90%. Super-response rates varied from 14% to 32%, with a median response rate of around 17%.

Error! Reference source not found. Table III summarizes the method, cut-offs and responder proportions of each study. A detailed description of the outcomes of all included studies is available in Supplemental Table ST1.

Table III: Outcome assessment of all included studies.

AUTHORS	METHODS	CUT-OFF	RESPONDER PROPORTION
Adelstein et al.(18)	Symptomatic Volumetric	↓ ≥0.5 NYHA Mean and median changes in ejection volumes	130/249 (52.2%) NR/324
António et al.(19)	Symptomatic Volumetric	↓ ≥1 NYHA ↓ ≥15% LVESV	63/87 (72%) 47/87 (54%)
Assadian Rad et al.(20)	Volumetric	↓ ≥15% LVESV	46/65 (70.8%)
Atwater et al.(21)	Volumetric	↓ ≥15% LVEDV	33/76 (43%)
Bani et al.(22)	Volumetric	↑ ≥10% LVEF or ↓ ≥15% LVESV	103/172 (60%)
Bertaglia et al.(23)	Volumetric	↓ ≥15% LVESV	205/335 (61%)
Bonakdar et al.(24)	Volumetric	↓ ≥15% LVESV	56/82 (68%)
Bouwmeester et al.(25)	Volumetric	↓ ≥15% LVESV	63/99 (63.6%)
Brunet-Bernard et al.(26)	Volumetric	↓ ≥15% LVESV	98/162 (60.5%) – D 32/45 (71.1%) - V
Caputo et al.(27)	Volumetric	↓ ≥15% LVESV	176/316 (55.7%)
Celikyurt et al.(28)	Volumetric	↓ ≥15% LVESV	24/38 (63%)
Celikyurt et al.(29)	Volumetric	↓ ≥15% LVESV	74/105 (71%)
Celikyurt et al.(30)	Volumetric	↓ ≥15% LVESV	38/53 (72%)
Chen et al.(31)	Volumetric	↓ ≥15% LVESV	35/61 (57.4%)
Chen et al.(32)	Volumetric	↓ ≥15% LVESV	34/72 (47.2%)
Cvijic et al.(33)	Volumetric	↓ ≥15% LVESV (R) ↓ ≥30% LVESV (SR)	15/101 (14.9%) - R 32/101 (31.7%) - SR 47/101 (46.5%) - CR*
De Pooter et al.(34)	Compounded	↑ ≥7.5% LVEF and ↓ ≥1 NYHA	40/52 (77%)
Del-Carpio Munoz et al.(35)	Volumetric	↓ ≥15% LVESV	NR/108 (NR)
Domenichini et al.(36)	Volumetric	↑ ≥5% LVEF	23/48 (48%)
Fabiszak et al.(37)	Symptomatic Volumetric	↓ ≥1 NYHA ↑ ≥10% LVEF	16/42 (38%) 19/42 (45%)
Feeny et al.(38)	Volumetric	↑ ≥10% LVEF	385/925 (42%)
Garcia-Seara et al.(39)	Compounded	↑ ≥5% LVEF and ↓ ≥1 NYHA	52/78 (66.7%)

Gasparini et al.(40)	Volumetric	↓ >15% LVESV (relative)	969/1718 (56.4%)
Ghani et al.(41)	Volumetric	LVEF [30%-50%] (R) LVEF >50% (SR)	153/347 (44%) - R 56/347 (16%) - SR 209/347 (60.2%) - CR*
Gunduz et al.(42)	Volumetric	↑ ≥10% LVEF	43/77 (55.8%)
Guo et al.(43)	Compounded	↓ ≥1 NYHA and ↑ ≥5% LVEF	68/101 (67.3%)
Hsu et al.(44)	Volumetric	LVEF variation [7.9%–14.4%] (R) LVEF variation ≥14.5% (SR)	371/752 (49.3%) - R 191/752 (25.4%) - SR 562/752 (74.7%) - CR*
Jiang et al.(45)	Volumetric	↓ ≥15% LVESV	104/181 (57.5%)
Kang et al.(46)	Volumetric	↓ ≥15% LVEDV	54/93 (58%)
Karaca et al.(47)	Compounded	↓ ≥1 NYHA and ↓ ≥15% LVESV	81/125 (65%)
Kataoka et al.(48)	Volumetric	↓ >15% LVESV	25/47 (53.2%)
Kuznetsov et al.(49)	Volumetric	↓ ≥15% LVESV	66/93 (71%)
Lin et al.(50)	Volumetric	↑ ≥5% LVEF	132/193 (68.4%)
Lipoldova et al.(51)	Symptomatic	↓ ≥1 NYHA	119/194 (61%)
Liu et al.(52)	Volumetric	↑ >15% LVEF	109/387 (28.2%) - SR
Loutfi et al.(53)	Compounded	↓ ≥1 NYHA and ↑ >10% 6MWT and ↓ >15% LVESD and/or ↑ >10% LVEF	114/170 (67.1%)
Mollema et al.(54)	Symptomatic Volumetric	↓ ≥1 NYHA ↓ ≥10% LVESV	164/242 (68%) 145/242 (60%)
Mollo et al.(55)	Compounded	↑ ≥5% LVEF and ↓ ≥1 NYHA	36/51 (71%)
Mugnai et al.(56)	Volumetric	↓ >15% LVESV or ↑ ≥5% LVEF	130/236 (55.1%)
Nakai et al.(57)	Compounded	↓ ≥1 NYHA and ↑ ≥5% LVEF or ↓ ≥15% LVESV	178/199 (89.5%)
Nesti et al.(58)	Volumetric	↓ ≥15% LVESV or ↑ ≥10% LVEF	106/178 (59.5%)
Pan et al.(59)	Volumetric	↓ ≥15% LVESV	50/82 (61%)
Park et al.(60)	Volumetric	↑ >5% LVEF and/or ↓ ≥15% LVESV	81/125 (64.8%)
Pastore et al.(61)	Symptomatic Volumetric	↓ ≥1 NYHA ↓ ≥15% LVESVi	36/66 (54.5%) 31/66 (47%)
Raj et al.(62)	Compounded	↑ ≥5% LVEF and ↓ ≥1 NYHA	64/93 (68.8%)
Rickard et al.(63)	Volumetric	↓ ≥10% LVESV	52/99 (52.5%)
Rickard et al.(64)	Volumetric	↑ ≥20% LVEF	32/233 (13.7%) - SR
Sabbag et al.(65)	Volumetric	↑ ≥5% LVEF and/or ↓ ≥10% LVESVi	152/239 (63.6%)
Sassone et al.(66)	Volumetric	↓ ≥15% LVESV	133/243 (54.7%)
Sebag et al.(67)	Symptomatic Volumetric	↓ ≥1 NYHA ↑ ≥10% LVEF and/or ↓ ≥15% LVESV	65/85 (76%) 45/85 (53%)
Serdoz et al.(68)	Volumetric Compounded	↑ ≥10% LVEF (R) NYHA I and LVEF>50% (SR)	36/75 (48%) - R 13/75 (17%) - SR 49/75 (64%) - CR*
Shen et al.(69)	Volumetric	↓ ≥15% LVESV	43/100 (43%)
Storkas et al.(70)	Symptomatic Volumetric	↓ ≥1 NYHA or ↓ ≥10% MLFHQ or ↑ ≥10% 6MWT ↓ >15% LVESV	60/68 (88%) 44/68 (65%)
Tian et al.(71)	Compounded	↑ >5% LVEF and ↓ ≥1 NYHA (R) ↑ >20% LVEF or final LVEF≥50% and NYHA I or II (SR)	31/58 (53.4%) - R 10/58 (17.2%) - SR 41/58 (70.6%) - CR*
Toniolo et al.(72)	Symptomatic Volumetric	↓ ≥1 NYHA (pt in NYHA III–IV) or stable NYHA (pt in NYHA I–II) ↓ ≥15% LVESVi	138/197 (70%) 90/197 (46%)
Van't Sant et al.(73)	Volumetric	↓ ≥15% LVESV	115/227 (50.7%)
Yang et al.(74)	Volumetric	↑ ≥5% LVEF in patients with LVEF [36%-49%] (R) ↑ ≥50% LVEF (SR)	29/114 (25.4%) - R 27/114 (23.6%) - SR
Yeim et al.(75)	Symptomatic	↓ ≥1 NYHA	69/96 (72%)
Yin et al.(76)	Volumetric	≥5% absolute increase in LVEF or RVFAC	35/54 (65%)
Yu et al.(77)	Volumetric	↑ ≥10% LVEF or ↑ ≥15% LVEF (relative)	138/227 (60.8%)
Zhang et al.(78)	Volumetric	↓ ≥15% LVESV	27/45 (60%)
Zhang et al.(79)	Volumetric	↓ ≥5mm LVEDD	21/30 (70%)

Caption:
CR: combined response; D: Derivation; LVEDD: left ventricular end-diastolic diameter; LVEDV: left ventricular end-diastolic volume; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVESVi: left ventricular end-systolic volume index; LVESV: left ventricular end-systolic volume; MLFHQ: Minnesota Living with Heart Failure Questionnaire; NR: not reported; NYHA: New York Heart Association class; pt: patients; R: Response; RVFAC: right ventricular fractional area change; SR: super response; V: Validation. 6MWT: Six-Minute Walk Test.
** CR was defined as the combination of response and super response, assuming that super responders were also responders.*

Bias reporting

All studies were classified as having a high RoB (62; 100%). Regarding each domain, RoB was especially high in domains two (attrition) and five (confounding), respectively with 51 (82%) and 49 (79%) studies. Bias due to outcome measurement was low in 60 studies (97%), while 42 (68%) showed low bias in statistical analysis and reporting. Detailed results of the RoB assessment are depicted in Supplemental Figures SF1 and SF2. The agreement between reviewers within each independent domain was 67%, 80%, 53%, 93%, 33%, and 60%, respectively for domains one through six. The mean reviewer agreement across domains was 62%. The overall RoB agreement was 100%.

Discussion

Our review aimed to assess the value of pre-implantation standard ECG parameters in predicting response to CRT using primary studies, and, from our point of view, has the merit of systematizing literature on this specific topic for the first time.

This review highlights two major key points: 1) the difficulty in evaluating response to CRT, arising from the heterogeneity in patient selection and the variety of response criteria; and 2) the need to move beyond traditional ECG predictors.

Electrocardiographic predictors

Our review shows that classical predictors, such as baseline QRSd and LBBB morphology are good markers in predicting response to CRT. We found that the benefit of CRT appears to be restricted to patients with QRS >150ms (but not longer than 178ms), and that this benefit disappears for QRSd ≤120ms, which is supported by guidelines changes that recognize the limited use of CRT in these patients(83). Equally, our findings suggest that LBBB is not only a good predictor of response but can also predict super response to CRT. Also, we have found that the ESC 2013 and Strauss criteria have the highest sensitivity while the AHA definition has the highest specificity in predicting response to CRT, suggesting that the highly stringent AHA definition might limit access to therapy(85). These different definitions, however, reflect not only how difficult it is to define LBBB but, more importantly, how it can impact patient selection as potential responders may be denied CRT, while others who may not benefit can receive this therapy; this was shown in the study by Van Stipdonk et

al.(86) who found that only 14% of patients could be classified as LBBB using the AHA and ESC definitions.

More importantly, our review shows that the role of standard ECG can go beyond the classical predictors described above and can provide additional predictive value. QRS notching and fragmentation results from the heterogeneous ventricular activation and dyssynchronous contraction(87), and was initially described as a predictor of cardiac events and HF hospitalizations in patients with cardiac disease(88). Our results show that notched/fragmented morphologies and fragmentation duration can be good predictors of non-response, in line with the findings of Balci et al.(89) that found that a notched QRS duration >67.5ms was an independent predictor of non-response to CRT; however, the study by Rickard et al.(63) did not corroborate these findings. In contrast, our findings also suggest that the presence of nQRS in lateral leads or mid-QRS notching (in at least one lead) could predict response to CRT due to initial high septum activation resulting in conduction through the whole ventricular tissue and leading to more mechanical dyssynchrony, coinciding with a functional line of block toward the apex of the LV, and therefore the target of CRT(90, 91).

It is speculated that the presence of S-waves in right precordial leads might indicate conduction disturbance in the LV and that it is associated with smaller left atrium diameters, probably representing less left atrial remodeling and therefore within scope for CRT(92, 93). Likewise, while the mechanism behind the presence of an S wave in V6 in patients with complete LBBB is not yet fully understood, Leonelli et al.(94) speculate that an S wave in V6 may represent a more posterosuperior late LV vector due to biventricular enlargement while based on Upadhyay et al.(95) it could be related to widespread diffuse LBBB lesion indicating intramyocardial disease, leading to poor outcome. Even though our results found a significant association of this parameter in predicting (non)response, Poposka et al.(11) found no such significance in multivariate models.

Finally, literature suggests that LAD in the presence of LBBB is an independent predictor of poor prognosis(96) and that patients without LAD seem to benefit more from CRT(97), with our review showing a marginal value of LAD in the prediction of response to CRT, despite one study showing higher odds of response(39). Similarly, we found that the PR interval had a limited role in response prediction, although it was suggested that patients with PR intervals between 150-170ms were more likely to

respond. Current literature seems to corroborate these findings, with patients with prolonged PR intervals showing worse outcomes when compared to those with a 'normal' PR interval(98, 99), although Kutyifa et al.(100) reported that a PR interval ≥ 230ms was able to identify responders with non-LBBB patterns. Figure 2 below summarizes the key electrocardiographic parameters, which are useful in assessing response to CRT.

Response outcomes

Our results are in line with those reported in the literature, showing similar response rates (101) and a significant disagreement around the definition of response(102).
Our study shows higher response rates in studies using symptomatic criteria when compared to those using volumetric criteria, although the agreement between these parameters is good(103). Volumetric criteria are considered not to be reliable predictors of outcome and symptomatic criteria are patient-dependent, therefore making it difficult to obtain a consistent measure(99). However, our study showed compounding symptomatic and volumetric criteria yields the highest response proportions, suggesting that this could be a more sensible approach when trying to assess response.

Bias

In this systematic review, we found a significant heterogeneity in inclusion criteria, with most studies including patients with mild to severe HF (NYHA II-IV) mostly with LVEF ≤35% and varying QRSd cut-offs. A potential explanation for this heterogeneity might be that most studies have an inclusion period that spans over several years (and, sometimes, using populations with devices implanted almost 10 years before the study was published), are based on retrospective cohorts, and use a convenience sampling often from single centers, possibly to make the study sample as large as possible.

Heterogeneity is reflected in the ill-defined inclusion criteria found in some studies(22, 23, 25, 27, 32, 34, 35, 38, 45, 51, 57, 60, 65, 67, 69, 73, 74, 76). This, combined with the relatively small samples, could explain the overall high RoB of the studies included in our review. On that note, it is important to say that only a small number of studies had a low RoB regarding study participation and attrition, with some studies failing to describe the target population in detail, not giving information regarding exclusion criteria or not describing how missing data was handled, thus contributing to the high

risk of selection and attrition bias. Interestingly, the moderate or high RoB shown in all the studies analyzed stresses the potential RoB for the relationship between predictors and outcome, ultimately impacting the generalization of results.

Clinical implications

Clinically, the possibility of using simple ECG criteria that can accurately predict response is of immense value in selecting patients who are more likely to benefit from CRT. The ubiquitous, inexpensive, and non-invasive nature of the test enhances its practicality and utility, and by basing shared decision-making on robust evidence healthcare providers can more effectively optimize patient outcomes. For patients and healthcare systems, expediting the selection process while reducing the potential for iatrogeny and costs offers substantial benefits. The ability to quickly and accurately determine which patients will benefit most from CRT helps avoid unnecessary procedures and associated complications, leading to a more efficient resource allocation. Nevertheless, ECG criteria have to be reproducible and easy to use in order to be useful in clinical practice. As such, it is expected that computer-aided automation and artificial intelligence will play a vital role in CRT response prediction(104), especially if based in simple, easily accessible tests.

Limitations

Our findings should be interpreted in the light of some limitations. Firstly, the lack of a unique definition of response and different response assessment cut-offs made impossible a quantitative synthesis of the results. Likewise, parameters such as LV lead position and medical therapy, which are known to affect response, were not evaluated in the current study. Secondly, the class of indication and level of evidence was not described in any of the studies and, as such, indication for CRT was assumed but it was not possible to ascertain if the guidelines followed impacted response. A third caveat resides in the fact that we wanted to assess only the predictive capability of the pre-implantation ECG as a tool for patient selection in a way that replicates a real clinical context; as a result, ECG criteria that involve post-implantation assessment were not considered. Additionally, none of the studies included alternative LV pacing sites, and therefore caution is warranted when replicating these findings in future studies. Finally, despite QUIPS being from our perspective the more appropriate tool for RoB assessment in studies of prognostic factors, some domains of this tool

may be problematic to interpret, depending on the complexity of the research area, and can potentially contribute to agreement issues (105-107).

Conclusion

Our review aimed at assessing the value of pre-implantation standard ECG parameters in predicting response to CRT using primary studies, and, from our point of view, has the merit of systematizing literature in this specific topic for the first time.

This review highlights two major key points: 1) the difficulty in evaluating response to CRT, arising from the heterogeneity in patient selection and the variety of response criteria; and 2) the need to move beyond traditional ECG predictors.

Clinically, the possibility of using simple ECG criteria that can accurately predict response is of immense value in selecting patients who are more likely to benefit from CRT. The ubiquitous, inexpensive, and non-invasive nature of the test enhances its practicality and utility, and by basing shared decision-making on robust evidence healthcare providers can more effectively optimize patient outcomes. For patients and healthcare systems, expediting the selection process while reducing the potential for iatrogeny and costs offers substantial benefits. The ability to quickly and accurately determine which patients will benefit most from CRT helps avoid unnecessary procedures and associated complications, leading to a more efficient resource allocation.

Although traditional predictors, such a QRS duration and morphology are relevant in predicting response to CRT, contemporary predictors such as QRS notching or fragmentation, show great potential in identifying responders but more research warranted, particularly in large prospective studies, to confirm their prognostic value.

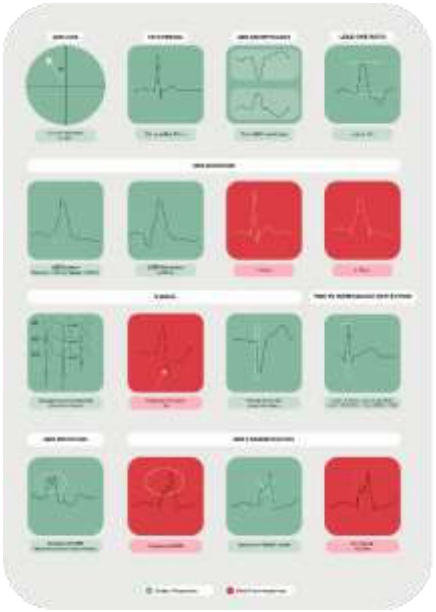


Figure 2: Key electrocardiographic parameters useful in assessing response to CRT.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All authors reviewed the results, approved the final version of the manuscript, and consented for publication.

Funding

PDC was supported by the Fundação para a Ciência e a Tecnologia, I.P, through grant number UI/BD/151574/2021 (DOI: 10.54499/UI/BD/151574/2021). The content of the project is solely the responsibility of the authors and does not necessarily represent the official views of the funders. The funders and industry did not have any role in the data analysis or the article contents.

Authors' Contribution

PDC and MMS were responsible for the conception and design of the study. PDC, DFS, MCP, FMS and JPB were responsible for the data collection and processing. PDC, MMS and PPR were responsible for the data analysis and interpretation of results. PDC and DFS were responsible for the literature review. PDC was responsible for the draft manuscript preparation. All authors were responsible for the critical review and editing of the manuscript.

Competing interests

PDC has previously received consultancy fees from Medtronic and Ela Medical. FMS has previously received consultancy fees from Medtronic, Microport and Abbot. AHR and MMO have previously received consultancy and speaking fees from Medtronic, Boston Scientific, Microport and Abbot. The remaining authors declare that they have no known conflicts of interest.

Availability of data and material

All research data supporting the results of your manuscript is available as Supplementary material and appended to this submission.

Acknowledgments

The authors wish to thank Joana Morgado (joana.morgado.matos@gmail.com) for her valuable assistance in designing the illustrations for this paper.

Ethics in publishing

1. Does your research involve experimentation on animals?:

No

2. Does your study include human subjects?:

No

3. Does your study include a clinical trial?:

No

4. Are all data shown in the figures and tables also shown in the text of the Results section and discussed in the Conclusions?:

Yes

References

1. Roger VL. Heart Failure Epidemic. Circulation. 2018;138(1):25-28.
2. Meyer S, Brouwers FP, Voors AA, et al. Sex differences in new-onset heart failure. Clinical Research In Cardiology. 2015;104(4):342-50.
3. Virani SS, Alonso A, Benjamin EJ, et al. Heart Disease and Stroke Statistics-2020 Update: A Report From the American Heart Association. Circulation. 2020;141(9):e139-e596.
4. van Riet EE, Hoes AW, Limburg A, et al. Prevalence of unrecognized heart failure in older persons with shortness of breath on exertion. Eur J Heart Fail. 2014;16(7):772-7.
5. Braunschweig F, Cowie MR, Auricchio A. What are the costs of heart failure? Europace. 2011;13 Suppl 2:ii13-7.
6. Wang Z, Wu Y, Zhang J. Cardiac resynchronization therapy in heart failure patients: tough road but clear future. Heart Fail Rev. 2021;26(3):735-45.
7. Herweg B, Welter-Frost A, Vijayaraman P. The evolution of cardiac resynchronization therapy and an introduction to conduction system pacing: a conceptual review. Europace. 2021;23(4):496-510.

8. O'Brien T, Park MS, Youn JC, et al. The Past, Present and Future of Cardiac Resynchronization Therapy. Korean Circ J. 2019;49(5):384-99.
9. Palmiero G, Florio MT, Rubino M, et al. Cardiac Resynchronization Therapy in Patients with Heart Failure: What is New? Heart Fail Clin. 2021;17(2):289-301.
10. Noheria A, Sodhi S, Orme GJ. The Evolving Role of Electrocardiography in Cardiac Resynchronization Therapy. Curr Treat Options Cardiovasc Med. 2019;21(12):91.
11. Poposka L, Boskov V, Risteski D, et al. Electrocardiographic Parameters as Predictors of Response to Cardiac Resynchronization Therapy. Open Access Maced J Med Sci. 2018;6(2):297-302.
12. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
13. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. BMJ. 2021;372:n160.
14. Ouzzani M, Hammady H, Fedorowicz Z, et al. Rayyan - a web and mobile app for systematic reviews. Systematic Reviews. 2016;5(1):210.
15. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing bias in studies of prognostic factors. Ann Intern Med. 2013;158(4):280-6.
16. Grooten WJA, Tseli E, Äng BO, et al. Elaborating on the assessment of the risk of bias in prognostic studies in pain rehabilitation using QUIPS—aspects of interrater agreement. Diagnostic And Prognostic Research. 2019;3(1):5.
17. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Research Synthesis Methods. 2020;n/a(n/a).
18. Adelstein EC, Saba S. Usefulness of Baseline Electrocardiographic QRS Complex Pattern to Predict Response to Cardiac Resynchronization. American Journal of Cardiology. 2009;103(2):238-42.
19. Antonio N, Lourenco C, Teixeira R, et al. Cardiac resynchronization therapy is effective even in elderly patients with comorbidities. Journal of Interventional Cardiac Electrophysiology. 2010;27(1):61-68.
20. Assadian Rad M, Tabarzan Baboli N, Barzigar A, et al. The role of the fragmented QRS complexes on a routine 12-lead ECG in predicting non-responsiveness to cardiac resynchronization therapy. Anatolian Journal of Cardiology. 2015;15(3):204-8.
21. Atwater BD, Babatunde A, Swan C, et al. ECG myocardial scar quantification predicts reverse left ventricular remodeling and survival after cardiac resynchronization therapy implantation: A retrospective pilot study. Journal of Electrocardiology. 2015;48(4):565-70.
22. Bani R, Checchi L, Cartei S, et al. Simplified Selvester Score: a practical electrocardiographic instrument to predict response to CRT. Journal of Electrocardiology. 2015;48(1):62-68.
23. Bertaglia E, Migliore F, Baritussio A, et al. Stricter criteria for left bundle branch block diagnosis do not improve response to CRT. Pacing and Clinical Electrophysiology. 2017;40(7):850-56.
24. Bonakdar HR, Jorat MV, Fazelifar AF, et al. Prediction of response to cardiac resynchronization therapy using simple electrocardiographic and echocardiographic tools. Europace. 2009;11(10):1330-37.
25. Bouwmeester S, Mast T, Prinzen F, et al. Predictive value of left atrial remodeling for response to cardiac resynchronization therapy. Journal of Ultrasonography. 2022;22(90):E168-E73.
26. Brunet-Bernard A, Marechaux S, Fauchier L, et al. Combined Score Using Clinical, Electrocardiographic, and Echocardiographic Parameters to Predict Left Ventricular Remodeling in Patients Having Had Cardiac Resynchronization Therapy Six Months Earlier. American Journal of Cardiology. 2014;113(12):2045-51.
27. Caputo ML, van Stipdonk A, Illner A, et al. The definition of left bundle branch block influences the response to cardiac resynchronization therapy. International Journal of Cardiology. 2018;269:165-69.

28. Celikyurt U, Acar B, Karauzum I, et al. Shorter time to begin of QRS fragmentation predicts non-response to cardiac resynchronization therapy in non-ischemic heart failure patients. Revista Clinica Espanola. 2019;219(5):243-50.
29. Celikyurt U, Agacdiken A, Sahin T, et al. Number of Leads With Fragmented QRS Predicts Response to Cardiac Resynchronization Therapy. Clinical Cardiology. 2013;36(1):36-39.
30. Celikyurt U, Agacdiken A, Sahin T, et al. Relationship between fragmented QRS and response to cardiac resynchronization therapy. Journal of Interventional Cardiac Electrophysiology. 2012;35(3):337-42.
31. Chen JY, Lin KH, Chang KC, et al. The Shortest QRS Duration of an Electrocardiogram Might Be an Optimal Electrocardiographic Predictor for Response to Cardiac Resynchronization Therapy. Int Heart J. 2017;58(4):530-35.
32. Chen K, Su H, Xie C, et al. Prognostic implications of QRS duration in third-degree atrioventricular block patients with heart failure treated with cardiac resynchronization therapy. Int Heart J. 2018;59(6):1320-26.
33. Cvijic M, Zizek D, Antolic B, Zupan I. Electrocardiographic parameters predict super-response in cardiac resynchronization therapy. Journal of Electrocardiology. 2015;48(4):593-600.
34. De Pooter J, El Haddad M, Timmers L, et al. Different Methods to Measure QRS Duration in CRT Patients: Impact on the Predictive Value of QRS Duration Parameters. Annals of Noninvasive Electrocardiology. 2016;21(3):305-15.
35. Del-Carpio Munoz F, Powell BD, Cha YM, et al. Delayed intrinsicoid deflection onset in surface ECG lateral leads predicts left ventricular reverse remodeling after cardiac resynchronization therapy. Heart Rhythm. 2013;10(7):979-87.
36. Domenichini G, Burri H, Valzania C, et al. QRS pattern and improvement in right and left ventricular function after cardiac resynchronization therapy: a radionuclide study. BMC Cardiovascular Disorders. 2012;12.
37. Fabiszak T, Lach P, Ratajczak J, et al. Influence of QRS duration and axis on response to cardiac resynchronization therapy in chronic heart failure with reduced left ventricular ejection fraction: A single center study including patients with left bundle branch block. Cardiology Journal. 2020;27(5):575-82.
38. Feeny AK, Rickard J, Patel D, et al. Machine Learning Prediction of Response to Cardiac Resynchronization Therapy. Circulation: Arrhythmia and Electrophysiology. 2019;12(7).
39. García-Seara FJ, Martínez-Sande JL, Cid B, et al. Influence of the preimplantation QRS axis on responses to cardiac resynchronization therapy. Revista Espanola de Cardiologia. 2008;61(12):1245-52.
40. Gasparini M, Biffi M, Landolina M, et al. The Interplay of PR Interval and AV Pacing Delays Used for Cardiac Resynchronization Therapy in Heart Failure Patients: Association with Clinical Response in a Retrospective Analysis of a Large Observational Study. Journal of Personalized Medicine. 2022;12(9).
41. Ghani A, Delnoy P, Adiyaman A, et al. Predictors and long-term outcome of super-responders to cardiac resynchronization therapy. Clinical Cardiology. 2017;40(5):292-99.
42. Gunduz R, Usalp S. Predictive value of frontal QRS-T angle after cardiac resynchronization therapy. Journal of Electrocardiology. 2021;68:24-29.
43. Guo Z, Liu X, Cheng X, et al. Combination of Left Ventricular End-Diastolic Diameter and QRS Duration Strongly Predicts Good Response to and Prognosis of Cardiac Resynchronization Therapy. Cardiology Research and Practice. 2020;2020.
44. Hsu JC, Solomon SD, Bourgoun M, et al. Predictors of super-response to cardiac resynchronization therapy and associated improvement in clinical outcome: The MADIT-CRT (Multicenter Automatic Defibrillator Implantation Trial with Cardiac Resynchronization Therapy) study. Journal of The American College of Cardiology. 2012;59(25):2366-73.
45. Jiang Z, Qiu Y, Qian Z, et al. An S wave in ECG lead V6 predicts poor response to cardiac resynchronization therapy and long-term outcome. Heart Rhythm. 2020;17(2):265-72.

46. Kang Y, Cheng LL, Cui J, et al. A new score system for predicting response to cardiac resynchronization therapy. Cardiology Journal. 2015;22(2):179-87.
47. Karaca O, Omaygenc MO, Cakal B, et al. Adjusting the QRS Duration by Body Mass Index for Prediction of Response to Cardiac Resynchronization Therapy: Does One QRS Size Fit All? Annals of Noninvasive Electrocardiology. 2016;21(5):450-59.
48. Kataoka N, Imamura T, Koi T, et al. A Simple Predictive Marker in Cardiac Resynchronization Therapy Recipients: Prominent S-Wave in Right Precordial Leads. Medicina-Lithuania. 2021;57(8).
49. Kuznetsov VA, Malishevskii LM, Todosiychuk VV, et al. Assessment of the relationship of various criteria for left bundle branch block with the response to cardiac resynchronization therapy in chronic heart failure. Kardiologiya. 2020;60(7):78-85.
50. Lin HY, Zhou Y, Xu G. Predictors for Cardiac Resynchronization Therapy Response The Importance of QRS Morphology and Left Ventricular Lead Position. Int Heart J. 2014;55(3):256-63.
51. Lipoldova J, Ozabalova E, Meluzin J, et al. Usefulness of left ventricle dyssynchrony assessment before cardiac resynchronization implantation. Biomedical Papers-Olomouc. 2010;154(1):39-46.
52. Liu X, Hu YR, Hua W, et al. A Predictive Model for Super-Response to Cardiac Resynchronization Therapy: The QQ-LAE Score. Cardiology Research and Practice. 2020;2020.
53. Loutfi M, Nawar M, Eltahan S, et al. Predictors of response to cardiac resynchronization therapy in chronic heart failure patients. Egyptian Heart Journal. 2016;68(4):227-36.
54. Mollema SA, Bleeker GB, van der Wall EE, et al. Usefulness of QRS duration to predict response to cardiac resynchronization therapy in patients with end-stage heart failure. American Journal of Cardiology. 2007;100(11):1665-70.
55. Mollo R, Cosenza A, Coviello I, et al. A novel electrocardiographic predictor of clinical response to cardiac resynchronization therapy. Europace. 2013;15(11):1615-21.
56. Mugnai G, Donazzan L, Tomasi L, et al. Electrocardiographic predictors of echocardiographic response in cardiac resynchronization therapy: Update of an old story. Journal of Electrocardiology. 2022;75:36-43.
57. Nakai T, Mano H, Ikeya Y, et al. Narrower QRS may be enough to respond to cardiac resynchronization therapy in lightweight patients. Heart And Vessels. 2020;35(6):835-41.
58. Nesti M, Perini AP, Bani R, et al. Myocardial Scar on Surface ECG: Selvester Score, but Not Fragmentation, Predicts Response to CRT. Cardiology Research And Practice. 2020;2020.
59. Pan W, Su Y, Zhu W, et al. Notched QRS complex in lateral leads as a novel predictor of response to cardiac resynchronization therapy. Annals Of Noninvasive Electrocardiology. 2013;18(2):181-87.
60. Park MY, Altman RK, Orencole M, et al. Characteristics of Responders to Cardiac Resynchronization Therapy: The Impact of Echocardiographic Left Ventricular Volume. Clinical Cardiology. 2012;35(12).
61. Pastore G, Morani G, Maines M, et al. Patients with right bundle branch block and concomitant delayed left ventricular activation respond to cardiac resynchronization therapy. Europace. 2018;20(11):E171-E78.
62. Raj A, Nath RK, Pandit BN, et al. Lead one ratio: A new electrocardiogram marker for cardiac resynchronization therapy response. Arya Atherosclerosis. 2022;17(1).
63. Rickard J, Bassiouny M, Cronin EM, et al. Predictors of response to cardiac resynchronization therapy in patients with a non-left bundle branch block morphology. Am J Cardiol. 2011;108(11):1576-80.
64. Rickard J, Kumbhani DJ, Popovic Z, et al. Characterization of super-response to cardiac resynchronization therapy. Heart Rhythm. 2010;7(7):885-89.
65. Sabbag A, Morag Y, Beinart R, et al. Do all intra-ventricular conduction defect ECG patterns respond equally to CRT? Journal Of Interventional Cardiac Electrophysiology. 2020;58(1):87-94.

66. Sassone B, Gambetti S, Bertini M, et al. Relation of QRS duration to response to cardiac resynchronization therapy. American Journal Of Cardiology. 2015;115(2):214-19.
67. Sebag FA, Martins RP, Defaye P, et al. Reverse Electrical Remodeling by Cardiac Resynchronization Therapy: Prevalence and Clinical Impact. Journal Of Cardiovascular Electrophysiology. 2012;23(11):1219-27.
68. Serdoz LV, Daleffe E, Merlo M, et al. Predictors for Restoration of Normal Left Ventricular Function in Response to Cardiac Resynchronization Therapy Measured at Time of Implantation. American Journal Of Cardiology. 2011;108(1):75-80.
69. Shen X, Nair CK, Aronow WS, et al. A new baseline scoring system may help to predict response to cardiac resynchronization therapy. Archives Of Medical Science. 2011;7(4):627-33.
70. Storkas HS, Hansen TF, Tahri JB, et al. Left axis deviation in patients with left bundle branch block is a marker of myocardial disease associated with poor response to cardiac resynchronization therapy. Journal Of Electrocardiology. 2020;63:147-52.
71. Tian Y, Zhang P, Li X, et al. True complete left bundle branch block morphology strongly predicts good response to cardiac resynchronization therapy. Europace. 2013;15(10):1499-506.
72. Toniolo M, Zanotto G, Rossi A, et al. Long-term independent predictors of positive response to cardiac resynchronization therapy. Journal Of Cardiovascular Medicine. 2013;14(4):301-07.
73. Van't Sant J, Ter Horst IAH, Wijers SC, et al. Measurements of electrical and mechanical dyssynchrony are both essential to improve prediction of CRT response. Journal Of Electrocardiology. 2015;48(4):601-08.
74. Yang M, Li X, Yang D, et al. Cardiac resynchronization therapy improves myocardial conduction. Pace - Pacing And Clinical Electrophysiology. 2019;42(2):238-46.
75. Yeim S, Bordachar P, Reuter S, et al. Predictors of a positive response to biventricular pacing in patients with severe heart failure and ventricular conduction delay. Pace-Pacing And Clinical Electrophysiology. 2007;30(8):970-75.
76. Yin YR, Dimopoulos K, Shimada E, et al. Early and Late Effects of Cardiac Resynchronization Therapy in Adult Congenital Heart Disease. Journal Of The American Heart Association. 2019;8(21).
77. Yu ZQ, Chen XY, Han F, et al. Electro-echocardiographic Indices to Predict Cardiac Resynchronization Therapy Non-response on Non-ischemic Cardiomyopathy. Sci Rep. 2017;7.
78. Zhang H, Dai Z, Xiao P, et al. The left ventricular lead electrical delay predicts response to cardiac resynchronisation therapy. Heart Lung And Circulation. 2014;23(10):936-42.
79. Zhang JH, Zhang Y, Zhou XH, et al. QRS duration shortening predicts left ventricular reverse remodelling in patients with dilated cardiomyopathy after cardiac resynchronization therapy. Acta Cardiologica. 2015;70(3):307-13.
80. Surawicz B, Childers R, Deal BJ, et al. AHA/ACCF/HRS recommendations for the standardization and interpretation of the electrocardiogram: part III: intraventricular conduction disturbances: a scientific statement from the American Heart Association Electrocardiography and Arrhythmias Committee, Council on Clinical Cardiology; the American College of Cardiology Foundation; and the Heart Rhythm Society. Endorsed by the International Society for Computerized Electrocardiology. J Am Coll Cardiol. 2009;53(11):976-81.
81. Cosío FG, Palacios J, Pastor A, Núñez A. The Electrocardiogram. In: Camm AJ, Lüscher TF, Serruys PW, editors. The Esc Textbook Of Cardiovascular Medicine: Oxford University Press; 2009. p. 0.
82. Brignole M, Auricchio A, Baron-Esquivias G, et al. 2013 ESC guidelines on cardiac pacing and cardiac resynchronization therapy: the task force on cardiac pacing and resynchronization therapy of the European Society of Cardiology (ESC). Developed in collaboration with the European Heart Rhythm Association (EHRA). Europace. 2013;15(8):1070-118.
83. Glikson M, Nielsen JC, Kronborg MB, et al. 2021 ESC Guidelines on cardiac pacing and cardiac resynchronization therapy. European Heart Journal. 2021;42(35):3427-520.

84. Strauss DG, Selvester RH, Wagner GS. Defining Left Bundle Branch Block in the Era of Cardiac Resynchronization Therapy. The American Journal of Cardiology. 2011;107(6):927-34.
85. Calle S, Timmermans F, De Pooter J. Defining left bundle branch block according to the new 2021 European Society of Cardiology criteria. Neth Heart J. 2022;30(11):495-98.
86. van Stipdonk AMW, Hoogland R, ter Horst I, et al. Evaluating Electrocardiography-Based Identification of Cardiac Resynchronization Therapy Responders Beyond Current Left Bundle Branch Block Definitions. JACC: Clinical Electrophysiology. 2020;6(2):193-203.
87. Basaran Y, Tigen K, Karaahmet T, et al. Fragmented QRS Complexes Are Associated with Cardiac Fibrosis and Significant Intraventricular Systolic Dyssynchrony in Nonischemic Dilated Cardiomyopathy Patients with a Narrow QRS Interval. Echocardiography. 2011;28(1):62-68.
88. Korhonen P, Husa T, Konttila T, et al. Fragmented QRS in prediction of cardiac deaths and heart failure hospitalizations after myocardial infarction. Ann Noninvasive Electrocardiol. 2010;15(2):130-7.
89. Balci MM, Balci KG, Sen F, et al. Usefulness of notched duration to predict response to cardiac resynchronization therapy. Scandinavian Cardiovascular Journal. 2015;49(4):200-06.
90. Rodriguez LM, Timmermans C, Nabar A, et al. Variable patterns of septal activation in patients with left bundle branch block and heart failure. J Cardiovasc Electrophysiol. 2003;14(2):135-41.
91. Risum N, Strauss D, Sogaard P, et al. Left bundle-branch block: The relationship between electrocardiogram electrical activation and echocardiography mechanical contraction. American Heart Journal. 2013;166(2):340-48.
92. Badran HA, Abdelhamid MA, Ibrahim MT, et al. Left atrium in cardiac resynchronization therapy: Active participant or innocent bystander. J Saudi Heart Assoc. 2017;29(4):259-69.
93. D'Andrea A, Caso P, Romano S, et al. Different effects of cardiac resynchronization therapy on left atrial function in patients with either idiopathic or ischaemic dilated cardiomyopathy: a two-dimensional speckle strain study. Eur Heart J. 2007;28(22):2738-48.
94. Leonelli FM, Bagliani G, De Ponti R, et al. Intraventricular Delay and Blocks. Card Electrophysiol Clin. 2018;10(2):211-31.
95. Upadhyay GA, Cherian T, Shatz DY, et al. Intracardiac Delineation of Septal Conduction in Left Bundle-Branch Block Patterns. Circulation. 2019;139(16):1876-88.
96. Perrotta L, Kandala J, L DIB, et al. Prognostic Impact of QRS Axis Deviation in Patients Treated With Cardiac Resynchronization Therapy. J Cardiovasc Electrophysiol. 2016;27(3):315-20.
97. Brenyo A, Rao M, Barsheshet A, et al. QRS axis and the benefit of cardiac resynchronization therapy in patients with mildly symptomatic heart failure enrolled in MADIT-CRT. J Cardiovasc Electrophysiol. 2013;24(4):442-8.
98. Atwater BD, Emerek K, Sørensen PL, et al. PR Prolongation predicts inadequate resynchronization with biventricular pacing in left bundle branch block. Pacing and Clinical Electrophysiology. 2019;42(11):1477-85.
99. Allison JD, Jr., Biton Y, Mela T. Determinants of Response to Cardiac Resynchronization Therapy. J Innov Card Rhythm Manag. 2022;13(5):4994-5003.
100. Kutyifa V, Stockburger M, Daubert JP, et al. PR interval identifies clinical response in patients with non-left bundle branch block: a Multicenter Automatic Defibrillator Implantation Trial-Cardiac Resynchronization Therapy substudy. Circ Arrhythm Electrophysiol. 2014;7(4):645-51.
101. Fornwalt BK, Sprague WW, BeDell P, et al. Agreement is poor among current criteria used to define response to cardiac resynchronization therapy. Circulation. 2010;121(18):1985-91.
102. Daubert C, Behar N, Martins RP, et al. Avoiding non-responders to cardiac resynchronization therapy: a practical guide. European Heart Journal. 2017;38(19):1463-72.

103. Bleeker GB, Bax JJ, Fung JW-H, et al. Clinical Versus Echocardiographic Parameters to Assess Response to Cardiac Resynchronization Therapy. The American Journal of Cardiology. 2006;97(2):260-63.
104. Simon A, Pilecky D, Kiss LZ, et al. Useful Electrocardiographic Signs to Support the Prediction of Favorable Response to Cardiac Resynchronization Therapy. J Cardiovasc Dev Dis. 2023;10(10).
105. Bollen L, Jacobs WCH, Van der Linden YM, et al. A systematic review of prognostic factors predicting survival in patients with spinal bone metastases. Eur Spine J. 2018;27(4):799-805.
106. den Bakker CM, Anema JR, Zaman AGNM, et al. Prognostic factors for return to work and work disability among colorectal cancer survivors; A systematic review. Plos One. 2018;13(8):e0200720.
107. Bruls VEJ, Bastiaenen CHG, de Bie RA. Prognostic factors of complaints of arm, neck, and/or shoulder: a systematic review of prospective cohort studies. Pain. 2015;156(5):765-88.