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REVIEW ARTICLE

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Fragmented QRS is associated with ventricular arrhythmias in heart failure patients: A systematic review and meta-analysis

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Abstract

Introduction: Many primary prevention heart failure (HF) patients with an implantable cardiac defibrillator (ICD) rarely experience life-threatening ventricular arrhythmias (VA). New strategies are required to identify patients most at risk of VA and sudden cardiac death who would benefit from an ICD. One potential method is the detection of fragmented QRS (fQRS) on the electrocardiogram. The aim was to assess the predictive capacity of fQRS for VA and mortality in ischemic (ICM) and non-ischemic cardiomyopathy (NICM) primary prevention HF patients.

Methods and Results: A systematic review and meta-analysis of studies examining fQRS in HF patients with or without an ICD who met primary prevention indications with reduced ejection fraction ≤40%. Outcome measures were VA (or appropriate ICD therapy) and all-cause mortality. Ten studies involving 3885 patients were included for analysis. Most patients were male with non-fQRS patients being significantly younger (−1.5[−2.66, −0.42], $p = .03$). Diabetes was more likely in fQRS patients (1.12[1.01, 1.25], $p = .03$) while non-fQRS patients were 28% more likely to have a history of atrial fibrillation (0.82[0.67,1.00], $p = .05$). Ventricular arrhythmias were significantly 1.5 times more likely in patients with fQRS (1.51[1.02, 2.25], $p = .04$). HF patients were 1.7 times more likely to die of any cause if fQRS was present (1.68[1.13, 2.52], $p = .01$). NICM patients with fQRS have a significant 2.6-fold increased incidence of death compared with ICM patients (2.55[1.63, 3.98], $p < .0001$).

Conclusion: fQRS is associated with VA and all-cause mortality and may be a novel marker in the risk stratification of primary prevention HF patients indicated for ICD implantation.

KEYWORDS
electrocardiogram, fragmented QRS, heart failure, implantable cardiac defibrillator, sudden cardiac death, ventricular arrhythmia

1 | INTRODUCTION

Heart failure (HF) affects ~38 million people worldwide, with the incidence expected to rise by 46% by 2030 in the United States alone (Atherton et al., 2018; Mozaffarian et al., 2016). Half of all HF patients die within 5 years of diagnosis due to pump failure associated with reduced left ventricular ejection fraction (LVEF≤35%) (Ponikowski et al., 2016), or sudden cardiac death (SCD) (Ponikowski et al., 2016). Modern

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treatment strategies include risk factor modification, medications to enhance heart function, early revascularization, and implantable cardiac defibrillators (ICD) (Atherton et al., 2018; Ponikowski et al., 2016).

While most HF patients have no previous history of documented ventricular arrhythmias (VA), they have a fivefold increased risk of developing them (Priori et al., 2015). Primary prevention ICDs protect HF patients against ventricular arrhythmias that cause SCD. However, a number of studies show that up to 80% of ICD patients never experience sustained arrhythmias (Engstrom et al., 2020), suggesting the current guidelines about who should receive a device may need refinement (Disertori et al., 2020). New criteria are required to identify patients who are at risk for VA and require an implantable device.

One potential method is the detection of fragmented QRS (fQRS) on the electrocardiogram (ECG). This notching and slurring in the QRS, first described in 1969 (Flowers et al., 1969), represents inhomogeneous ventricular activation and conduction due to scar/fibrosis (Das & Zipes, 2009). The resultant slowing of terminal conduction promotes re-entrant circuits and a substrate for VA to occur (Das et al., 2009). fQRS has previously been shown to be an arrhythmogenic marker in congenital and familial acquired cardiomyopathies and syndromes (Supreeth & Francis, 2020). However, the use of fQRS as a VA marker in HF patients is unclear (Supreeth & Francis, 2020). The aim of this systematic review and meta-analysis was to assess the predictive capacity of fQRS for VA and its association with mortality in primary prevention HF patients.

2 | METHODS

2.1 | Systematic review

This systematic review was conducted and is reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Appendix S1). The protocol was registered and published with PROSPERO, an international register for systematic reviews (CRD42021226505).

2.2 | Search strategy

All studies that examined fQRS and VA (ventricular tachycardia (VT) or ventricular fibrillation (VF)), in primary prevention HF patients with or without an ICD in situ, were included. An independent search was conducted in Scopus, CINAHL, EMCARE, and MEDLINE from commencement to October 2020 (Appendix S2). Reference lists of full-text studies were hand-searched to identify additional studies, and corresponding authors of two papers were contacted for additional data.

2.3 | Inclusion criteria

Studies were included if they met the following:

1. Retrospective or prospective cohort, cross-sectional and longitudinal studies that described the occurrence or frequency of VA and the presence of fQRS at baseline, with a follow-up period ≥12 months. Ventricular arrhythmias included VT and VF or SCD classified as arrhythmic where (i) appropriate ICD therapy was delivered including shock and/or anti-tachycardia pacing (ATP) or shock alone, or (ii) unexpected death occurring within 1 h of cardiac symptoms in the absence of progressive cardiac deterioration, or (iii) unexpected death during sleep, or (iv) unexpected death within 24 h after the patient had been seen alive based on a modified Hinkle-Thaler system (Hinkle & Thaler, 1982).
2. ECG analysis showing fQRS as defined by (Das et al., (2009), that is, QRS <120 ms with an additional R wave or notching at the lowest point of the S/R wave, or the existence of >1 R wave in two or more successive leads corresponding to a coronary artery territory (Das et al., 2009). Fragmented wide-QRS (f-wQRS) >120 ms as described above with the additional presence of two or more notches in the R or S wave were also included (Das et al., 2009).
3. Primary prevention indication, that is, reduced LVEF ≤40% with no previous history of sustained VA, with or without an ICD or cardiac resynchronization therapy (CRT) in situ, and with either ischemic (ICM) and/or non-ischemic cardiomyopathy (NICM) (JCS Joint Working Group, 2012). Studies that included secondary prevention patients that had documented sustained VA, or a history of unexplained loss of consciousness with or without an ICD/CRT in situ, were included if primary prevention patients made up at least 70% of the total study population, which is representative of the current ICD population seen clinically (Kremers et al., 2013).

2.4 | Exclusion criteria

Studies that focused on hypertrophic obstructive cardiomyopathy, Brugada, congenital heart disease, arrhythmogenic right ventricular cardiomyopathy, long QT, short QT, noncompaction cardiomyopathy, and Chagas were excluded. Other methodology of fQRS such as vectorcardiography, magnetocardiography, magnetic field imaging, signal-averaged ECG, and 120-lead body surface potential mapping was also excluded. Non-English language publications, review articles, case studies, conference abstracts, and animal studies were not included.

2.5 | Study selection

Two investigators (NE and HL) screened the titles and abstracts of all retrieved citations to identify studies meeting the inclusion criteria. Full texts of eligible studies were retrieved and reviewed by the same two investigators for inclusion and relevance with mutual agreement.

2.6 | Data extraction

Data were extracted for general characteristics (authors, year, title, journal, publication type); study characteristics (design, sample size,

follow-up time, fQRS definition); patient characteristics (age, gender, comorbidities, medications); clinical characteristics (cardiomyopathy type, New York Heart Association (NYHA) class, LVEF, ICD status); and outcome data (VA, ICD therapy, mortality). When assessing VA, if appropriate shock only was reported, this was combined with ICD therapy of both shock and ATP.

2.7 | Quality assessment

A modified Newcastle-Ottawa scale, including assessments of indication/etiology, representativeness of patient cohort, research methodology, detail of ECG analysis, VA definition, adequacy of follow-up, reporting of loss to follow-up, and detail of coronary artery territory location, was used for quality assessment (Appendix S3). Each study was assessed as low, moderate, or high risk of bias.

2.8 | Meta-analysis

The meta-analysis was conducted in accordance with the Meta-Analysis of Observational Studies in Epidemiology (MOOSE) Group guidelines (Appendix S4), using Review Manager software (V5.4.1). A random-effects meta-analysis was undertaken to account for inherent variability. Proportions or count data were converted to hazard ratios (HR) using the methodology of Parmar and colleagues (Parmar et al., 1998). Outcome measures analyzed between fQRS and non-fQRS patients were as follows: (1) VA (including appropriate ICD shock), (2) all-cause mortality, and (3) composite endpoint of VA and/or all-cause mortality. Subgroup analyses included (1) primary prevention patients *vs* primary and secondary prevention patients, (2) NICM *vs* ICM patients, and (3) fQRS 12-lead ECG coronary artery territory location. Outcomes are reported as HR with 95% confidence intervals. Statistical significance was defined as $p < .05$. Statistical heterogeneity was determined by I^2 statistic ($I^2 < 25\%$, low; $I^2 = 25$–50%, moderate; $I^2 > 50\%$, substantial).

3 | RESULTS

3.1 | Study characteristics

The search strategy yielded 1,111 articles of which 211 were duplicates, leaving 900 for title/abstract assessment. No additional articles were obtained through contact with authors or reference list searching. Based on eligibility criteria, 848 articles were excluded by title/abstract, leaving 52 for full-text evaluation. A total of 26 were excluded because of specific etiology and 10 due to ineligible methodology and outcomes. Five studies were excluded due to the patient cohort having predominantly secondary prevention indications (≥30%), while one study used the same patient cohort in two separate articles, leaving 10 studies involving 3,885 patients for analysis (Figure 1). A full description of included studies is shown in Table 1. According to the modified Newcastle-Ottawa quality assessment scale, seven studies had a moderate risk of bias, and three were low risk. Heterogeneity was high for both the primary and secondary outcomes of VA ($I^2 = 92\%$) and all-cause mortality ($I^2 = 91\%$). Follow-up time ranged from 14 to 50 months (Table 1).

3.2 | Patient cohort

Primary prevention patients comprised 100% of the study cohort in six studies (Brenyo et al., 2012; Cheema et al., 2010; Forleo et al., 2011; Özcan et al., 2014; Ozcan et al., 2013; Vandenberk et al., 2017), with the remaining four having 71%–91% primary prevention indications (Table 2) (Claridge et al., 2017; Kucharz & Kułakowski, 2020; Igarashi et al., (2017); Sha et al., 2011). ICM was the sole etiology in Brenyo et al. (2012), while Igarashi et al. (2017) and Sha et al. (2011) included only NICM patients. The remaining studies had mixed indications with ICM accounting for ~47%–77% of the study population (Brenyo et al., 2012; Cheema et al., 2010; Forleo et al., 2011; Kucharz & Kułakowski, 2020; Özcan et al., 2014; Ozcan et al., 2013; Vandenberk et al., 2017). In six studies, ICDs were implanted in the whole cohort (Cheema et al., 2010; Claridge et al., 2017; Forleo et al., 2011; Kucharz & Kułakowski, 2020; Özcan et al., 2014; Ozcan et al., 2013; Vandenberk et al., 2017), while three studies had a mix of ICD and non-ICD patients (Brenyo et al., 2012; Cheema et al., 2010; Sha et al., 2011).

Patients in the non-fQRS cohort were significantly younger than fQRS patients (62.6 ± 13.7 *vs* 60.7 ± 12.9 years), with a mean difference of ~1.5 years (−1.5[−2.66, −0.42], $p = .007$). All studies had a higher proportion of males (67.2%–97%), and males were more likely to have fQRS (Table 2). There was no difference in LVEF, or incidence of coronary artery disease, hypertension, or renal failure between fQRS and non-fQRS cohorts. The non-fQRS patients were 28% more likely to have a history of atrial fibrillation; however, this was not statistically significant (0.82[0.67, 1.00], $p = .05$). Diabetes was significantly more likely if fQRS was present (1.12[1.01, 1.25], $p = .03$). Medications including beta-blockers, angiotensin-converting enzyme inhibitors, aspirin, and Class III antiarrhythmic drugs showed similar use in both groups; however, fQRS patients were 27% more likely to be on a statin (1.27[1.05, 1.55], $p = .02$).

3.3 | Ventricular arrhythmias

The association between fQRS and incidence of VA was reported in eight studies (Figure 2a) (Brenyo et al., 2012; Cheema et al., 2010; Forleo et al., 2011; Igarashi et al., 2017; Kucharz & Kułakowski, 2020; Özcan et al., 2014; Ozcan et al., 2013; Vandenberk et al., 2017). Of the 3,627 patients where VT/VF occurred, arrhythmias were significantly ~1.5 times more likely in fQRS patients (1.51[1.02, 2.25], $p = .04$). A sensitivity analysis omitting studies that also included secondary prevention patients resulted in the same hazard ratio, however, did not reach statistical significance (1.51[0.98, 2.31], $p = .06$) (Figure 2b).

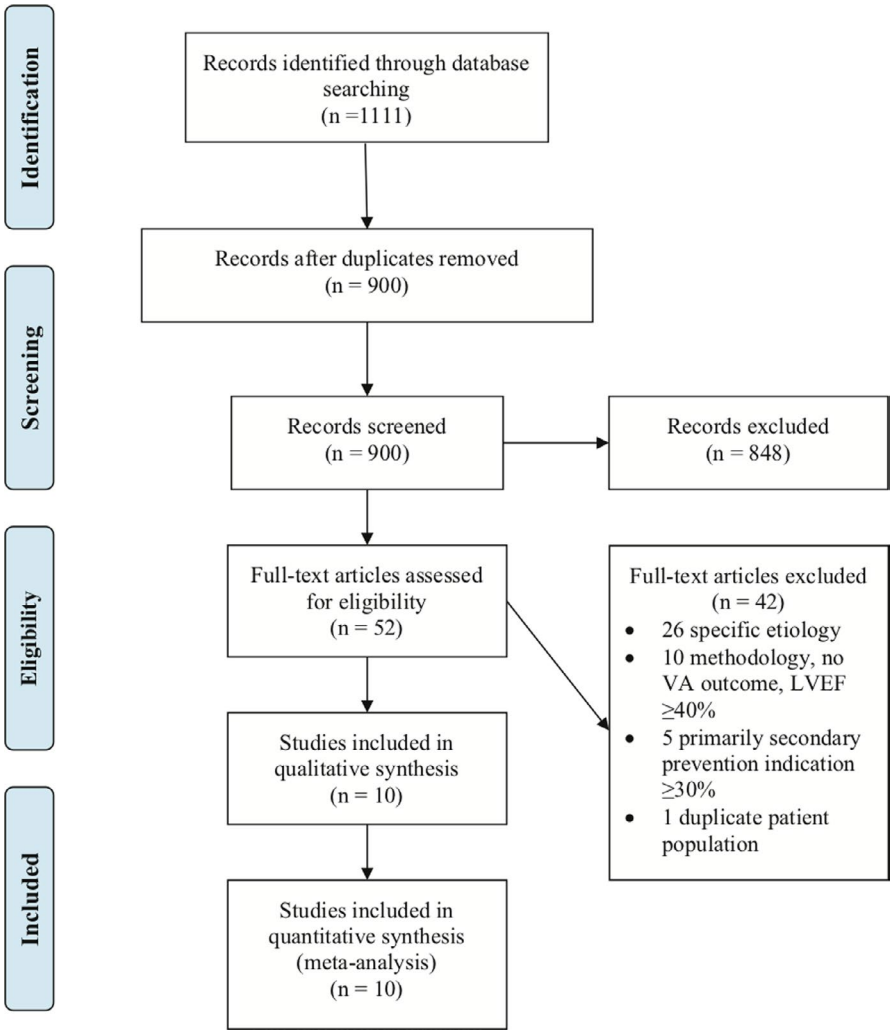

FIGURE 1 PRISMA flow diagram of study selection process. LVEF, left ventricular ejection fraction; VA, ventricular arrhythmias

TABLE 1 Study characteristics and risk of bias

Author, Year	Study Type	Sample Size	Follow-up (months)	Risk of bias
Kucharz and Kułakowski, 2020	Retrospective, single-center cohort study	365	34.5 ± 18	Low
Claridge et al., 2017	Prospective, single-center cohort study	130	33.5 ± 24	Moderate
Vandenberk et al., 2017	Retrospective, single-center cohort study	407	50.5 ± 38	Moderate
Igarashi et al. 2017	Retrospective, multi-center cohort study	137	18	Moderate
Ozcan et al., 2014	Retrospective, single-center cross-sectional	215	23.5 ± 12.1	Moderate
Ozcan et al., 2013	Retrospective, single-center cohort study	227	44.8 ± 16.9	Moderate
Brenyo et al., 2012	Retrospective, RCT study	1040	20	Low
Forleo et al., 2011	Retrospective, single-center cohort study	394	23.6 ± 17.5	Moderate
Sha et al., 2011	Retrospective, single-center cohort study	128	14 ± 5	Moderate
Cheema et al., 2010	Retrospective, multi-center cohort study	842	40 ± 17	Low

Abbreviation: RCT, Randomized controlled trial.

3.4 | All-cause mortality

All-cause mortality was reported in seven studies (Brenyo et al., 2012; Cheema et al., 2010; Forleo et al., 2011; Özcan et al., 2014; Ozcan et al., 2013; Sha et al., 2011; Vandenberk et al., 2017) and was significantly 1.7 times more likely in fQRS patients (1.68[1.13, 2.52], p = .01) (Figure 3a). When fQRS was isolated to ECG lead territories, fQRS found in the lateral leads was associated with 39% increased mortality risk, while inferior and anterior lead fQRS showed 21% and 33% increases, respectively, with no territory

TABLE 2 Patient Characteristics

Author, Year	Male Gender	Primary Prevention	ICM	NICM	NYHA Class	LVEF (%)*	ICD implanted
Kucharz and Kułakowski, 2020	306 (83.4%)	259 (70.6%)	273 (74%)	94 (26%)	I 10 (6%) II 68 (41%) III 84(50.6%) IV 4 (2.4%)	27.7±9.5	Yes 100%
Claridge et al., 2017	58(80.6%)	93 (71.5%)	72 (55.4%)	58 (44.6%)	N/A	N/A	Yes 100%
Vandenberk et al., 2017	343 (84.3%)	407 (100%)	215 (52.8%)	192 (47.2%)	I 95 (23.4%) II 156 (38.3%) III 156 (38.3%)	28.3±10.3	Yes 100%
Igarashi et al., 2017	92 (67.2%)	137 (79.6%)	0 (0%)	137 (100%)	I 0 II 25 (18.2%) III 84 (61.3%) IV 23 (16.8%)	29.2±9.7	Yes CRT-P or CRT-D (no breakdown)
Ozcan et al., 2014	156 (72.5%)	215 (100%)	102 (47.4%)	113 (52.5%)	76 (35.3%) 112 (52.1%) 27 (12.5%)	27.7±3.5	Yes 100%
Ozcan et al., 2013	156 (68.7%)	227 (100%)	142 (62.5%)	85 (37.4%)	I 0 II 83 (36.5%) III 104 (45.8%) IV 40 (17.6%)	26.5±0.06	Yes 100%
Brenyo et al., 2012	1009 (97%)	100%	1040 (100%)	0 (0%)	N/A	N/A	Yes ICD–693 (66.6%) Non-ICD 347 (33.3%)
Forleo et al., 2011	334 (84.8%)	100%	242 (61.4%)	115 (29.2%)	3 (2–3)†	27±9	Yes 100%
Sha et al., 2011	87 (68%)	90.6% LVEF<40%	0 (0%)	128 (100%) IDCM	N/A	30±6	Yes ICD–10 (7.8%) Non-ICD 118 (72.2%)
Cheema et al., 2010	655 (77.8%)	842 (100%)	644 (76.5%)	198 (23.5%)	N/A	27±6.3	Yes ICD–435 (51.7%) Non-ICD 407 (48.3%)

Abbreviations: CRT-D, cardiac resynchronization therapy defibrillator; CRT-P, cardiac resynchronization therapy pacemaker; ICD, implantable cardiac defibrillator; ICM, ischemic cardiomyopathy; IDCM, idiopathic dilated cardiomyopathy; LVEF, left ventricular ejection fraction; N/A, not applicable; NICM, non-ischemic cardiomyopathy; NYHA, New York Heart Association.

*Mean ± standard deviation.

†Median (interquartile range).

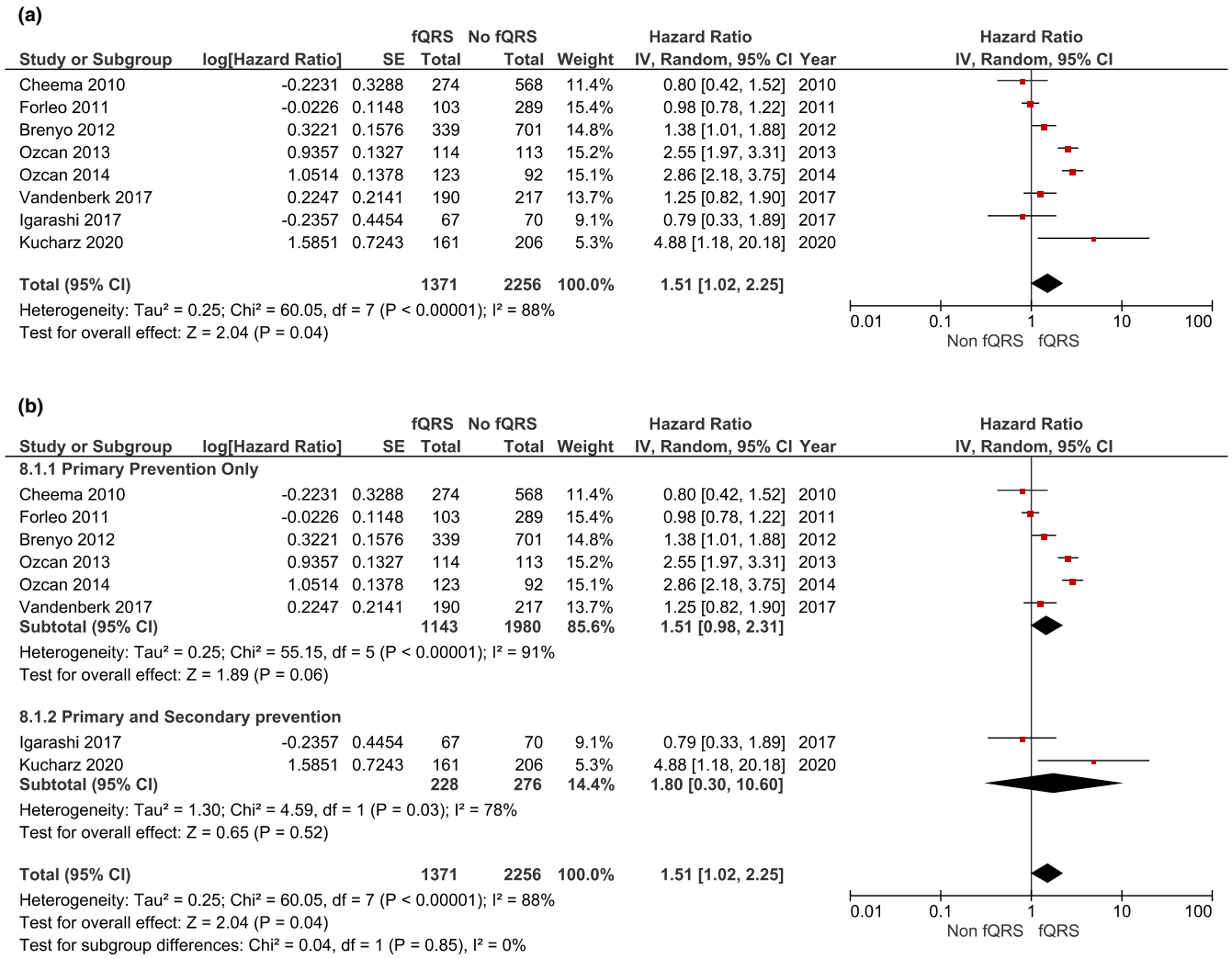

FIGURE 2 Forest plot demonstrating the association between fQRS and ventricular arrhythmias in heart failure patients (a), including subgroup analysis of primary prevention only compared to primary and secondary prevention patients (b). CI, confidence interval; fQRS, fragmented QRS

demonstrating a statistical association with all-cause mortality (Figure 3b). A comparison of NICM and ICM groups showed NICM patients with fQRS had a significant 2.6-fold increased risk of death (2.55[1.63, 3.98], $p < .0001$), whereas in ICM patients the presence of fQRS did not increase mortality (1.10[0.79, 1.53], $p = .58$) (Figure 4).

3.5 | All-cause mortality and ventricular arrhythmias

The composite endpoint of all-cause mortality and VA was assessed in 817 patients across four studies (Claridge et al., 2017; Forleo et al., 2011; Özcan et al., 2014; Sha et al., 2011). Patients with fQRS were ~2.2-times more likely to have VA or die of any cause; however, this association was not significant (2.17 [0.95, 4.98], $p = .07$) (Figure 5).

4 | DISCUSSION

Despite significant advances in cardiac research, imaging and testing, the identification of patients at risk of sudden death from ventricular arrhythmias (VAs) remains challenging (Priori et al., 2015). One possible independent risk parameter that has attracted much interest is fragmentation of the QRS (fQRS). The complex originates from a conduction delay and disrupted ventricular depolarization due to regional myocardial scarring that can form an arrhythmogenic substrate for lethal VA (Das & Zipes, 2009). Our meta-analysis indicates that fQRS is significantly associated with VA in HF patients with ischemic and non-ischemic cardiomyopathy (Figure 2a). Patients exhibiting fQRS were also significantly 1.7 times more likely to die of any cause (Figure 3a), with the incidence of death significantly higher in NICM patients (Figure 4). Patients with and without fQRS were comparable with regards to EF, comorbidities, and medications, except for diabetes which was significantly more likely in

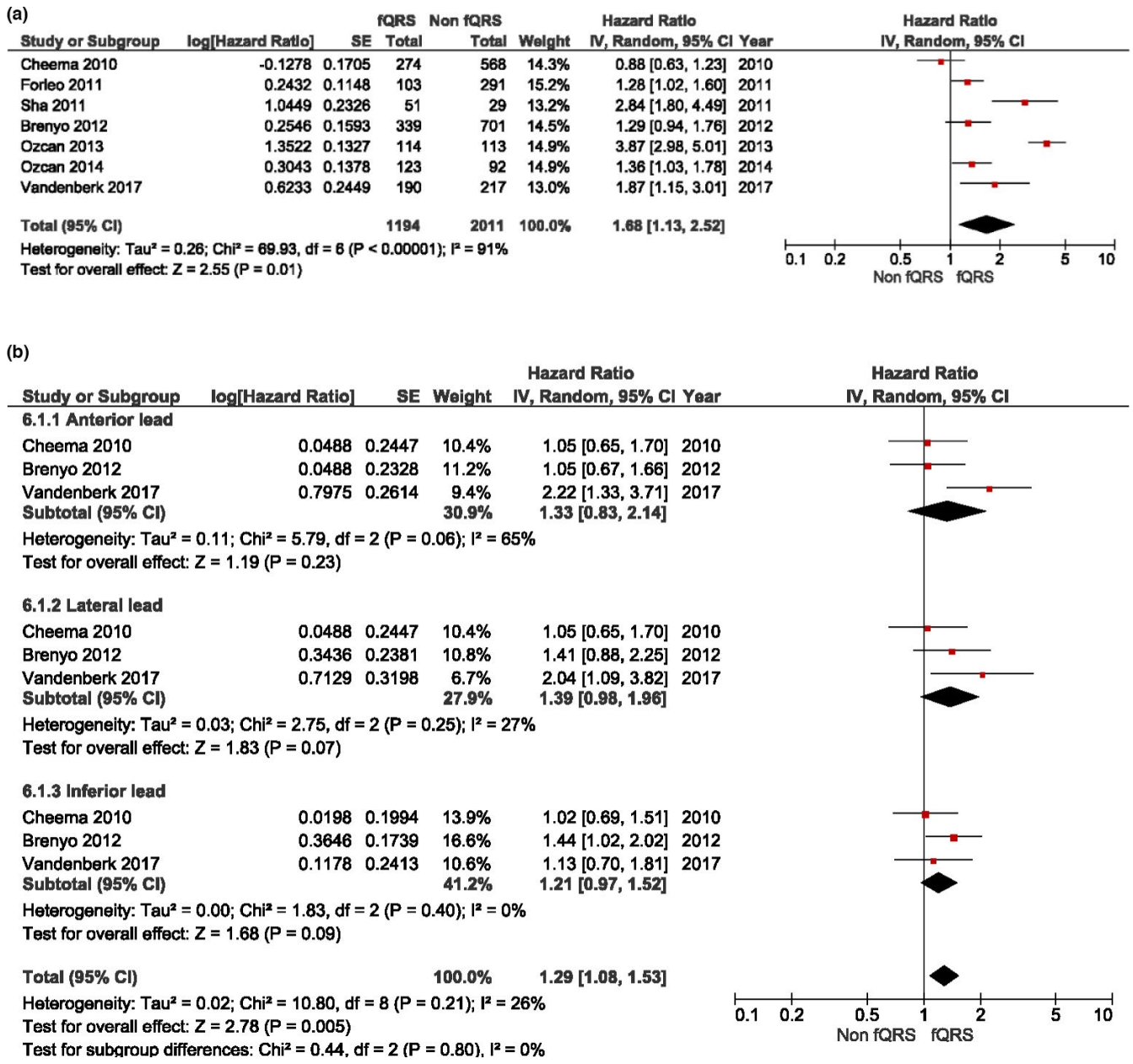

FIGURE 3 Forest plot demonstrating the association between fQRS and all-cause mortality in heart failure patients (a), including subgroup analysis of 12-lead ECG coronary artery territory location (b). CI, confidence interval; ECG, electrocardiogram; fQRS, fragmented QRS

fQRS patients, and a 28% increased likelihood of atrial fibrillation in non-fQRS patients. These results will now be discussed in terms of the structure of the meta-analysis with ventricular arrhythmias and all-cause mortality as primary endpoints.

4.1 | fQRS is associated with ventricular arrhythmias in HF patients

Our meta-analysis provides the first synthesized evidence that fQRS may be significantly associated with VA in a cohort of 3,627 patients with reported VA. The idea of a fragmented QRS complex as a potential VA or ICD indicator was first introduced by Das and colleagues in 2009 (Das et al., 2009). However, individual studies have failed to reach a consensus on its usefulness as a VA risk factor (Brenyo et al., 2012; Cheema et al., 2010; Claridge et al., 2017; Forleo et al., 2011; Igarashi et al., 2017; Kucharz & Kułakowski, 2020; Özcan et al., 2014; Ozcan et al., 2013; Vandenberk et al., 2017). Part of the reason appears to be that many studies were underpowered and different groups used different criteria for the assessment of VA. For example, the studies of Vandenberk (Vandenberk et al., 2017) and Brenyo (Brenyo et al., 2012), comprising 1,440 patients reported ICD shock only as an endpoint. In these studies, ventricular arrhythmias that may have been treated by anti-tachycardia

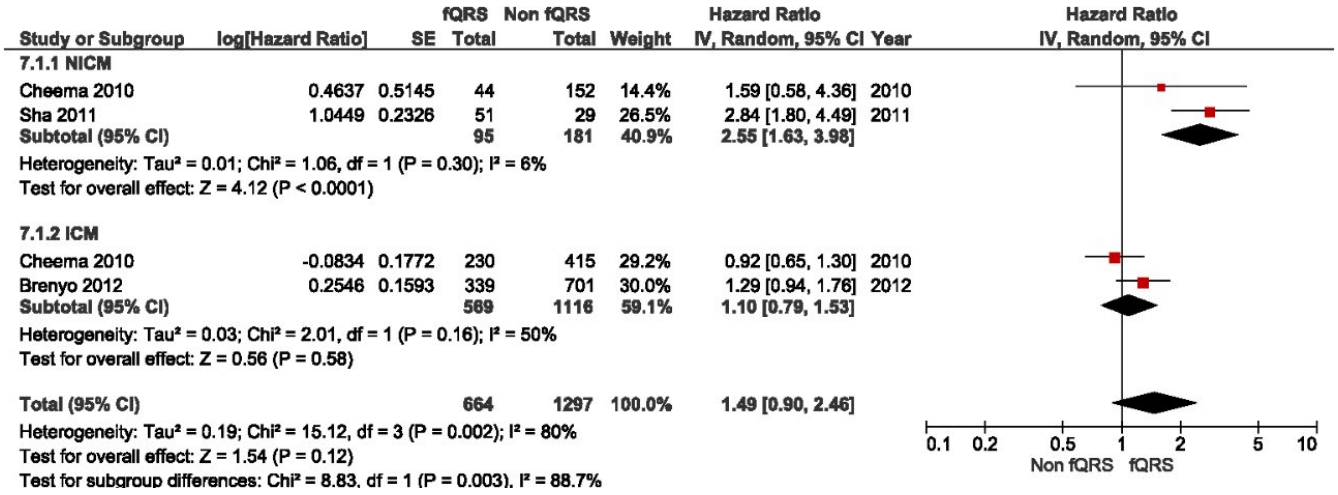

FIGURE 4 Forest plot demonstrating the association between fQRS and all-cause mortality in NICM versus ICM heart failure patients. CI, confidence interval; fQRS, fragmented QRS; ICM, ischemic cardiomyopathy; NICM, non-ischemic cardiomyopathy

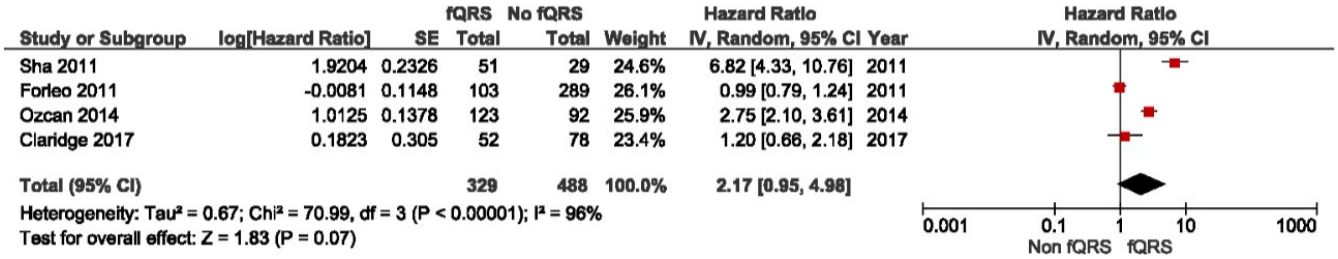

FIGURE 5 Forest plot demonstrating the association between fQRS and the composite endpoint of ventricular arrhythmias or all-cause mortality in heart failure patients. CI, confidence interval; fQRS, fragmented QRS

pacing were not included for analysis, possibly underestimating VA incidence and their association with fQRS. In contrast, Özcan et al., (2014) had considerably higher shock rates than reported by other studies (52%) and is most likely the result of short duration, low-rate detection programming of the ICDs in that study. Future studies should consider detailed specification of programming when evaluating arrhythmias in ICD patients.

Our review encompassed all VAs analyzed, including ICD shocks and ATP, shocks alone, and sudden death criteria for non-ICD patients. While the selection of eligible papers for this review appears to be representative of the current clinical population, unfortunately, not all studies included all variables required for complete analysis. Furthermore, there was no separate analysis of ischemic and non-ischemic cardiomyopathy patients. The inclusion of secondary prevention patients is also a potential confounder in the current meta-analysis; however, secondary prevention patients only represented 3.75% (136) of the total population analyzed. Future studies should include subset analysis if both ICM and NICM, and primary and secondary prevention, patients are included.

Another well-established factor promoting arrhythmias is a wide-QRS complex (>120 ms), which is a marker of slow conduction that may promote re-entrant VT (Kashani & Barold, 2005). In this meta-analysis, six of the eight studies examined the association of fQRS in both narrow and wide-QRS (>120 ms) with VA in heart failure patients (Brenyo et al., 2012; Cheema et al., 2010; Forleo et al., 2011; Igarashi et al., 2017; Kucharz & Kułakowski, 2020; Özcan et al., 2014; Vandenberk et al., 2017). Two studies that reported fQRS was significantly associated with VA also reported increased wide-QRS in the fQRS group (Kucharz & Kułakowski, 2020; Özcan et al., 2014), whereas four studies showed no difference (Brenyo et al., 2012; Cheema et al., 2010; Forleo et al., 2011; Vandenberk et al., 2017), while two did not report. We conclude that future studies should include wide-QRS along with fQRS data to further evaluate the relationship in HF patients.

Our analysis also found that the fQRS patients were significantly 1.5 years older than non-fQRS patients and had a 12% increased incidence of diabetes. Multiple studies have shown that age is not a contributing factor to VA in ICD patients (Santangelo et al., 2021), (Bergau et al., 2017), and we and others have found that comorbidities are not often associated with VA or appropriate ICD therapy (Engstrom et al., 2020). While some studies have demonstrated a link between diabetes and VA (Grisanti, 2018), others have reported the opposite (Juhani Junttila et al., 2020), which may be related to HF severity and the presence of different comorbidities. Further studies involving larger populations are required to clarify the relationship

between age, diabetes, comorbidities, and VA in heart failure patients with and without fQRS.

4.2 | fQRS is associated with all-cause mortality in heart failure patients

Another potentially important clinical finding of our meta-analysis is that during the ~1-to-4-year follow-up, patients with fQRS were significantly 68% more likely to die of any cause (Figure 3a). Mortality is most likely a 'systems failure' comprising a weak heart and many underlying comorbid conditions and mechanisms, some of which we have discussed above, and many that are currently unknown (Engstrom et al., 2020). For example, some comorbidities such as obstructive sleep apnea predispose patients to inappropriate ICD therapy, which may increase mortality risk (Engstrom et al., 2020). It would be interesting to know whether these patients more likely to die developed fQRS and their clinical implications after ICD placement, and these data should be included in future studies.

This meta-analysis also examined mortality differences between fQRS patients with ischemic and non-ischemic cardiomyopathy and found NICM patients with fQRS were significantly 2.55-fold more likely to die than those with ICM etiology (Figure 4). This finding is new. The higher mortality may be due to loss of protection from the presence of an ICD, given NICM patients in the current meta-analysis had ~20% less ICDs compared to the ICM cohort regardless of fQRS. A decade or so ago, higher mortality rates were often reported in ICM patients; however, in recent years, these patients have experienced improved early interventions leading to improved outcomes with reduced myocardial scar (Elgendy Islam et al., 2019). Although the mechanisms for mortality in NICM patients with dilated cardiomyopathy are unknown, differences in pump failure compared to ischemic etiologies may be due to differences in Ca^{2+} cycling kinetics (Morita et al., 2005; Rubart & Zipes, 2005). We conclude that despite the limited number of studies comparing NICM and ICM patients for our meta-analysis, the presence of fQRS in NICM patients shows a possible association with mortality. However, a larger sample size would be required to confirm this relationship and warrants further investigation.

4.3 | Increased atrial fibrillation in non-fQRS patients

The prevalence of AF in chronic HF patients is ~25% (Carlisle et al., 2019). In our analysis, an unexpected finding was that non-fQRS patients had a higher rate of atrial fibrillation than fQRS patients (28% more likely), which was accompanied by a reduced incidence of arrhythmias and mortality. This is contrary to literature findings showing that AF has been associated with a threefold increased risk of VF and a fourfold increased mortality risk (Bardai et al., 2014; Lee et al., 2018). There are a few possible explanations. First, the four studies reporting AF we analyzed had almost double the number of non-fQRS compared with fQRS patients (Cheema et al., 2010; Forleo et al., 2011; Sha et al., 2011; Vandenberk et al., 2017). In addition, the Cheema et al., (2010) study which made up 49% of the total population excluded persistent AF, which is the most diagnosed type representing 40%–50% of cases found in HF (Carlisle et al., 2019). Further studies including HF patients with all AF variants would provide a stronger statistical comparison between groups to assess whether the differences we have seen are applicable to the wider population.

4.4 | Review design and limitations

The strength of this systematic review and meta-analysis is that it synthesizes the most up-to-date evidence of fQRS in 3,885 HF patients across 10 studies. The meta-analysis was conducted in accordance with MOOSE guidelines and a validated methodology was used for data transformation to ensure validity and robustness. However, there are some important potential limitations. Firstly, there was significant heterogeneity and a moderate risk of bias, with all but one of the studies being retrospective in nature, and 80% were single cohort studies. Follow-up time was variable ranging from 14 to 50 months, and there was inconsistent reporting of 12-lead ECG coronary artery territory location, NYHA Class, and medical history. Furthermore, multiple surrogate endpoints were reported for the primary outcome measure, including total ICD therapy (ATP + shock), shock only, and non-ICD indications which contributed to the heterogeneity. The small sample size (817 patients across four studies) and heterogeneity are likely reasons why the composite endpoint of VA and all-cause mortality did not reach statistical significance, despite significant associations for both endpoints individually.

4.5 | Future research and clinical implications

Despite these limitations, these results provide evidence for significant associations between fQRS and VA and mortality in primary prevention HF patients, indicating a potential role for fQRS in patient risk stratification. Further high-quality studies are required that address the following:

1. In addition to VA, total therapy, including ATP and shocks, for ICD patients should be included for analysis with specification of ICD programming. If SCD is an endpoint, VA rate is the preferred assessment (1997).
2. If wide-QRS is included, there should be equivalent representation in both fQRS and non-fQRS cohorts.
3. Subgroup analysis should be performed for primary and secondary prevention patients, ICM and NICM patients, and for comorbidities to elucidate different contributions in relation to fQRS presence.

4. fQRS and origin of ECG lead location, that is, inferior, anterior, or lateral, may identify areas of significance and should be investigated further.
5. The development of fQRS after ICD implantation and/or after HF diagnosis may indicate disease progression and scar and fibrosis maturation which may have further implications for patient care.

Additional evidence addressing these limitations may support the inclusion of fQRS as a diagnostic marker in primary prevention HF patients that could be used to assist in determining patients at risk for VA and therefore candidates for ICD implantation.

5 | CONCLUSION

fQRS shows a significant association with ventricular arrhythmias and all-cause mortality in primary prevention heart failure patients. fQRS may be a novel marker that can be included in risk stratification for ICD use.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

All authors contributed to the concept and design of the systematic review. NE and HL completed data extraction, analysis, and interpretation. NE drafted the manuscript which was edited and approved by all authors.

ETHICAL APPROVAL

No ethical approval is required because data from previous published studies in which informed consent or a waiver of consent was obtained by primary investigators will be retrieved and analysed.

DATA AVAILABILITY STATEMENT

Data analyzed in this study were a synthesis of existing published data, openly available in cited references.

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