Baseline QRS Area and Reduction in QRS Area Are Associated with Lower Mortality and Risk of Heart Failure Hospitalization after Cardiac Resynchronization Therapy

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Keywords

Heart failure · Patient selection · Prognosis · Cardiac resynchronization therapy

Abstract

Introduction: Cardiac resynchronization therapy (CRT) is an established treatment for heart failure in selected patients. However, current guideline indications do not accurately predict individual prognosis with CRT, and up to 30% are nonresponders. Previous studies have shown that QRS area reduction following CRT is associated with improved survival. This study evaluates the incremental value of using QRS area derived from digital electrocardiogram (ECG) recordings, preoperatively and during CRT pacing. **Methods:** Medical records of 445 patients receiving CRT implants at a large-volume tertiary care center in Sweden were retrospectively evaluated. Digital ECG before and after CRT implantation were collected, and ECG parameters were analyzed in relation to a primary composite endpoint of heart failure hospitalization or death from any cause. **Results:** 147 patients (33%) reached the primary endpoint (93 deaths and 103 heart failure hospitalizations) over a median follow-up time of 2.7 years. A larger preimplant QRS area (HR, 0.89; [0.85–

0.93]; $p = <0.0001$; adjusted HR, 0.93; [0.88–0.98]; $p = 0.011$) and a larger QRS area reduction (HR, 0.92; [0.88–0.96]; $p = <0.0001$; adjusted HR, 0.95; [0.90–0.99]; $p = 0.042$) postimplant correlated with a reduced risk of reaching the primary endpoint. This association was seen in patients with native left bundle branch block morphology, nonspecific intraventricular conduction delay, or paced ECG morphology but not in patients with right bundle branch block. **Conclusion:** Larger preimplant QRS area and QRS area reduction were associated with better clinical outcome following CRT in this retrospective material. This knowledge could help optimize patient selection and postoperative management.

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Introduction

Cardiac resynchronization therapy (CRT) can offer significant benefits to heart failure patients with systolic heart failure and ventricular conduction abnormalities, resulting in left ventricular dyssynchrony [1–3]. However, identifying patients likely to benefit from CRT and estimating their prognosis following implantation remains a challenge [4]. The present guidelines for patient

selection are based on the parameters that can only partially identify patients with a measurable positive response to CRT, and up to half of the treated patients do not show signs of structural heart improvement, such as reverse remodeling or a significant reduction in left ventricular end-systolic volume [1, 5].

Thus, there is a need for alternative ways of assessing patient suitability and estimating prognosis following implantation. In this context, native electrocardiogram (ECG) patterns and changes in ECG morphology during CRT have been studied extensively. It has been shown that patients with true left bundle branch block (LBBB) have a better outcome post-CRT than patients with other conduction abnormalities [6, 7]. Likewise, postoperative reduction in QRS duration is a favorable prognostic sign, even though the association to reverse remodeling is not linear [8]. QRS area has been proposed as a more sensitive marker for dyssynchrony than QRS duration and morphology, and observational studies have shown promising results. However, these studies have required substantial manual work to transform PDF files with ECG recordings into digital measurements [9–13]. Using automated digital ECG analysis, QRS area and other measurements can be easily analyzed and used to predict CRT response and clinical outcome. The present study sought to assess the association between the preimplant QRS area, changes in the QRS area, and relevant clinical outcomes such as total mortality and heart failure hospitalization.

Materials and Methods

Study Population and Data Collection

Medical records of all consecutive patients receiving CRT implants (CRT pacemaker or CRT with an additional function of an implantable cardioverter-defibrillator (ICD)) from January 2015 through September 2020 at Skåne University Hospital in Sweden, a large-volume tertiary care center with a primary uptake area of 1.7 million people, were retrospectively evaluated. Patients fulfilling guideline criteria for CRT and having their device implanted successfully were included. Failure to establish transvenous CRT, undergoing an early explant (within 30 days), follow-up outside the Southern Region of Sweden, a narrow QRS complex (<120 ms) before CRT, or no digital ECG before and/or after CRT implantation excluded patients from analyses. Ethical approval was provided by the Swedish Ethical Review Authority.

Baseline evaluation consisted of a standard clinical evaluation, i.e., echocardiography, ECG (12-lead ECG), blood tests (hemoglobin, NT-proBNP, creatinine, and eGFR), anamnesis, and physical examination. Data were retrospectively gathered from individual assessments of medical records by the first author (S.M.). Heart failure etiology was considered ischemic in origin if a patient had a previous myocardial infarction, percutaneous coronary inter-

vention, and coronary artery bypass grafting in their medical history. The primary composite endpoint was heart failure hospitalization or death by any cause.

Electrocardiographic Analysis

Digital 12-lead ECG data before and after CRT implantation were collected via the hospital's digital ECG database. ECG analysis was performed with University of Glasgow Resting ECG Analysis Program (version 30.3.0).

Following Glasgow analysis, ECG morphology was assessed and divided into 4 groups: LBBB, paced (pacemaker prior to CRT implantation), intraventricular conduction delay (IVCD), and right bundle branch block (RBBB). The assessment was made by an experienced electrophysiologist using standard definitions of LBBB, IVCD, and RBBB [14]. Another experienced electrophysiologist validated this categorization, and the interindividual correlation coefficient was 0.95.

Vectorcardiograms were derived from the XML files using customized MATLAB software (MathWorks, Inc., Natick, MA, USA) using the Kors matrices. The QRS area was calculated from the median beat from 10-s recordings. The software automatically detected QRS onset and end and thereby QRS duration. Each software detection was visually examined and corrected if needed. A paced morphology was determined by the presence of a ventricular pacemaker spike and typical appearance of the paced QRS complex. The QRS area was calculated as $(QRSX^2 + QRSY^2 + QRSZ^2)^{1/2}$, with QRSX/Y/Z being the integral between the ventricular deflection and the baseline from onset to the end of the QRS complex in the X, Y, and Z leads, respectively.

Statistical Analysis

All statistical analyses were performed with IBM SPSS Statistics (version 26.0, SPSS Inc., Chicago, IL, USA). Continuous, normally distributed variables are presented as mean and standard deviation and nonnormally distributed variables as median and interquartile range. Normality was tested by visual inspection of histogram bars and using the Kolmogorov-Smirnov test as needed. Categorical data are presented as numbers and percentages. Between-group comparisons were performed with Student's *t* test, Fisher's exact test, χ^2 -test, or Mann-Whitney U test as appropriate.

Cox and logistic regression analyses with log-rank test were used to evaluate the association of ECG parameters with the primary endpoint. Multivariate regression analyses included parameters known to be associated with CRT outcome (ECG morphology, age, gender, CRT pacemaker or CRT with an additional function of an ICD, secondary ICD indication, New York Heart Association class, ischemic etiology, left ventricular ejection fraction, diabetes, atrial fibrillation, NT-proBNP, and eGFR). A *p* value <0.05 was considered statistically significant.

Results

Study Population and Baseline Characteristics

629 CRT implantations between January 2015 and September 2020 were identified. As Figure 1 illustrates, sufficient digital ECG data were available for 445 patients meeting inclusion criteria. Baseline demography corre-

Fig. 1. Patient data selection.

lated well to contemporary CRT cohorts and is presented in Table 1. In brief, the median age at implantation was 73 years (65.3–77.6), 20% of patients were female, with a median left ventricular ejection fraction of 27% (22.0–30.0), and an ischemic etiology was present in 44% of patients.

Median time to death or end of follow-up was 2.7 years (1.7–3.9). A total of 147 patients reached the combined primary endpoint: death ($n = 93$) and/or heart failure hospitalization ($n = 103$) during follow-up. Prior to implantation, the median QRS area was 118 μVs (91–148), and during biventricular pacing, the median QRS area was 74 μVs (54–96), resulting in a median reduction of 35% (16–55).

Both the preimplant QRS area and the QRS area reduction during CRT were analyzed for an association with the primary endpoint. Results for univariate and adjusted analyses are presented in Table 2. When the QRS area reduction was dichotomized based on the median value (= 35% relative reduction), patients with larger QRS area reduction had a 52% lower risk of reaching the primary endpoint. The corresponding Kaplan-Meier estimate is shown in Figure 2. A multivariate Cox regression model (adjusted for clinically relevant variables) using the dichotomized variable is presented in Table 3.

The associations between the preimplant QRS area and the QRS area reduction were also evaluated for the individual components of the primary endpoint, and the

results were consistent. Baseline QRS area over 118 μVs was associated with a 53% reduction in the risk of death ($p = 0.001$) and a 57% reduction ($p < 0.001$) in the risk of hospitalization for heart failure. Patients with QRS area reduction more than the median had a 51% ($p = 0.001$) reduction in the risk of death and a 54% ($p < 0.001$) reduction in the risk of hospitalization for heart failure.

QRS Area in Different ECG Morphologies

Changes in QRS area and QRS duration were explored by stratifying for the four major groups of QRS morphology, as shown in Figure 3. At baseline, the QRS area was similar for patients with LBBB and paced QRS, but significantly smaller for patients with IVCD or RBBB. QRS duration was longer for patients with paced QRS, but similar for the other three groups. A numerical reduction in QRS duration post-CRT was evident in all groups, but it was only statistically significant for LBBB and paced QRS morphology.

There was no interaction between baseline ECG morphology and baseline QRS area ($p = 0.19$), but there was an interaction between the baseline ECG morphology and the QRS area reduction ($p < 0.001$), with a larger reduction in patients with LBBB than the other groups. When the univariate Cox regression analysis for the primary endpoint was performed, the hazard ratios for QRS area (per 10 μVs) were similar for patients with LBBB (HR, 0.90; [0.85–0.96]; $p < 0.001$), paced QRS (HR, 0.87;

Table 1. Baseline characteristics

Baseline characteristics, mean $\pm$ SD or median (IQR)	(<i>n</i> = 445)
Age at implantation, years (IQR)	72.7 (65.3–77.6)
Female gender, <i>n</i> (%)	89 (20.0)
CRT-P or CRT-D, <i>n</i> (%)	
CRT-P	139 (31.2)
CRT-D (primary prophylactic)	268 (60.2)
CRT-D (secondary prophylactic)	38 (8.5)
LVEF, % (IQR)	27.0 (22.0–30.0)
NYHA class	
II	126
III	281
IV	35
Ischemic etiology, <i>n</i> (%)	196 (44.0)
Hypertension, <i>n</i> (%)	302 (68.2)
Diabetes, <i>n</i> (%)	145 (32.7)
Previous PCI, <i>n</i> (%)	149 (33.6)
Previous CABG, <i>n</i> (%)	88 (19.9)
Atrial fibrillation, <i>n</i> (%)	
Chronic or persistent	125 (28.2)
Paroxysmal	103 (23.3)
No	215 (48.5)
Hemoglobin, mg/L (SD)	133 (16.9)
NT-proBNP, ng/L (IQR)	1,794 (734–4,170)
Creatinine, g/dL (IQR)	105 (84.5–138)
eGFR, mL/min/m ² (SD)	53.2 (19.6)
Beta blocker use, <i>n</i> (%)	376 (84.5)
ACE-inhibitor or angiotensin-receptor blocker use, <i>n</i> (%)	338 (76.0)
Sacubitril/Valsartan use, <i>n</i> (%)	53 (11.9)
Aldosterone antagonist use, <i>n</i> (%)	247 (55.5)
Loop diuretic use, <i>n</i> (%)	296 (66.5)
Class I or III antiarrhythmic use, <i>n</i> (%)	19 (4.3)
Digoxin use, <i>n</i> (%)	38 (8.5)
Anticoagulant use, <i>n</i> (%)	228 (51.2)
Previous pacemaker or ICD, <i>n</i> (%)	127 (28.5)
Median time, death, or follow-up (IQR)	2.7 (1.7–3.9)
ECG morphology, <i>n</i> (%)	
LBBB	248 (55.7)
Paced	69 (16.0)
IVCD	104 (24.2)
RBBB	18 (4.2)
All ECG morphology subgroups	
QRS duration pre, ms (SD)	163 (19.6)
QRS duration post, ms (SD)	152 (22.9)
QRS duration reduction, ms (SD)	11.1 (25.1)
QRS area pre, μ Vs (IQR)	122 (91–148)
QRS area post, μ Vs (IQR)	74 (54–96)
QRS area reduction (relative %) (IQR)	35 (16–55)
LBBB	
QRS duration reduction, ms (SD)	17.0 (22.1)
QRS area reduction (relative %) (IQR)	41 (35–42)
Paced	
QRS duration reduction, ms (SD)	17.3 (26.0)
QRS area reduction (relative %) (IQR)	44 (28–42)
IVCD	
QRS duration reduction, ms (SD)	0.9 (2.3)
QRS area reduction (relative %) (IQR)	20 (6–21)
RBBB	
QRS duration reduction, ms (SD)	8.0 (16.6)
QRS area reduction (relative %) (IQR)	31 (8–51)

ACE, angiotensin-converting enzyme; CABG, coronary artery bypass grafting; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association, PCI, percutaneous coronary intervention.

Table 2. Cox regression analysis for prediction of the primary endpoint (hospitalization for heart failure or death)

Parameter	Univariate			Multivariate*		
	<i>p</i> value	HR	95% CI	<i>p</i> value	HR	95% CI
QRS duration pre (per 10 ms)	0.007	0.89	0.82–0.97	0.38	0.95	0.84–1.07
QRS duration pre >150 ms	0.070	0.73	0.51–1.03			
QRS duration post (per 10 ms)	0.15	1.05	0.98–1.13			
Reduction in QRS duration (per 10 ms)	0.001	0.90	0.85–0.96	0.30	0.96	0.87–1.04
QRS area pre (per 10 μ Vs)	<0.0001	0.89	0.85–0.93	0.011	0.93	0.88–0.98
QRS area post (per 10 μ Vs)	0.72	0.99	0.95–1.04			
Relative reduction in QRS area (per 10%)	<0.0001	0.92	0.88–0.96	0.042	0.95	0.90–0.99
QRS area, absolute reduction above median (= 35%)	<0.0001	0.43	0.30–0.60	0.001	0.48	0.31–0.74

* Variables included in the multivariate model were ECG morphology, age, gender, CRT-P or CRT-D, secondary ICD indication, ischemic etiology, NYHA class, LVEF, diabetes, atrial fibrillation, NT-proBNP, and eGFR.

Fig. 2. Kaplan-Meier estimates of survival free of heart failure hospitalization. Based on postimplant QRS area reduction above or below median (cutoff = 35% reduction).

[0.77–0.98]; $p = 0.027$), and IVCD (HR, 0.86; [0.77–0.95]; $p = 0.004$), but not for patients with RBBB (HR, 1.01; [0.70–1.5]; $p = 0.89$). In a similar analysis for QRS area reduction postimplant, hazard ratios (per 10%) were similar for LBBB (HR, 0.90; [0.84–0.95]; $p < 0.001$), paced QRS (HR, 0.95; [0.82–1.1]; $p = 0.47$), and IVCD (HR, 0.96; [0.90–1.02]; $p = 0.21$), but not for patients with RBBB (HR, 1.09; [0.76–1.6]; $p = 0.65$). Preimplant QRS area and QRS area reduction postimplant had an additive value for the prediction of the primary endpoint, and patients with a larger preimplant QRS area in combination with larger QRS area reduction postimplant had the best outcome

(shown in online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000522151).

Discussion

This study investigated the value of ECG parameters in the prediction of clinical outcome following CRT. The main findings show that a larger preimplant QRS area and a larger QRS area reduction were associated with a reduced risk of heart failure hospitalization and death. In addition, the combination of having a larger preimplant QRS area (more

Table 3. Full multivariate model for prediction of the primary endpoint (hospitalization for heart failure or death)

Parameter	Multivariate		
	<i>p</i> value	HR	95% CI
ECG morphology (LBBB reference)			
IVCD	0.65	0.88	0.52–1.49
RBBB	0.51	1.37	0.53–3.52
Paced	0.019	0.46	0.24–0.88
Age (per year)	0.068	0.98	0.95–1.00
Gender (male reference)	0.44	0.79	0.43–1.44
NYHA class (per 1 unit increase)	0.60	1.07	0.84–1.34
Type of device (CRT-D primary prophylactic reference)			
CRT-D (secondary ICD indication)	0.046	1.99	1.01–3.92
CRT-P	0.022	1.81	1.09–3.01
Ischemic etiology	0.008	1.83	1.17–2.83
LVEF baseline (per absolute % increase)	0.99	1.00	0.97–1.03
Diabetes	0.21	1.32	0.86–2.04
Atrial fibrillation			
Paroxysmal	0.92	1.03	0.60–1.76
Chronic	0.037	1.71	1.03–2.82
NT-proBNP (per 100 ng/L increase)	<0.0001	1.009	1.005–1.013
eGFR (per mL/min/m ² increase)	0.19	0.99	0.98–1.005
Relative reduction in QRS area (per 10% reduction)	0.042	0.95	0.90–0.99

LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; and RBBB, right bundle branch block.

Fig. 3. QRS duration and QRS area measurements stratified by native ECG morphology.

than median value) and a larger QRS area reduction was associated with the best outcome. The association was seen in three major subgroups of ECG morphology: LBBB, paced, and IVCD, but not in patients with RBBB. The as-

sociation with the primary endpoint was stronger for pre-implant QRS area and QRS area reduction than it was for the traditional measurement of QRS duration.

Preimplant QRS Area and QRS Area Reduction in Relation to Clinical Endpoints

Several previous studies have observed similar findings to this study regarding the association between preimplant QRS area and clinical outcome following CRT [9–12]. Emerek et al. [9] found that a larger QRS area was associated with survival free from heart transplantation and left ventricular assist device (LVAD) implantation. A study by Okafor et al. [11] similarly found a larger QRS area to be associated with a lower risk of heart failure hospitalization and cardiac and total mortality. As the QRS area has been shown to correlate with electrical dyssynchrony and late activation of the left ventricular lateral wall, the association between a larger preimplant QRS area and a better outcome is not unexpected [15].

The finding that a larger QRS area reduction is associated with better outcome is also consistent with previous research [13, 16]. In a study by van Stipdonk et al. [13], a QRS area reduction was the only independent ECG parameter associated with a primary composite endpoint of all-cause mortality, cardiac transplantation, and LVAD implantation. Ghossein et al. [16] observed that a QRS area reduction was independently associated with a primary composite endpoint of all-cause mortality, heart transplantation, and LVAD implantation. In our material, a QRS area reduction had a slightly weaker association with clinical outcome than the QRS area at baseline. This may reflect that if the level of dyssynchrony is not of a certain magnitude (i.e., large QRS area at baseline), then it is less likely to play a major role for the patient's clinical outcome, even if a significant relative QRS area reduction is achieved post-CRT.

QRS Area and QRS Area Reduction Compared to Conventional ECG Parameters: ECG Morphology and QRS Duration

Current ECG criteria for CRT candidate selection include the presence of LBBB and QRS duration ≥ 150 ms [1]. Our study is in accordance with the previously published research, making a case for including QRS area parameters in patient selection, particularly for patients without a current class I recommendation for CRT [13]. In a prospective study by Maass et al. [17] QRS area outperformed conventional parameters in predicting echocardiographic response to CRT. Similarly, van Stipdonk et al. [13] found that QRS area reduction was more strongly associated with all studied outcomes than QRS duration and LBBB morphology separately. In addition, Emerek et al. [9] found that QRS area was strongly associated with better outcome in patients with a QRS duration

< 150 ms, i.e., without a current class I indication for CRT. The results in the study by Emerek et al. [9] also indicated that QRS area could be more important for the selection of suitable CRT candidates than the presence of true LBBB according to Strauss' criteria. In our study, QRS area was a strong predictor regardless of QRS morphology, with the exception of RBBB, and remained significant in the multivariate model. Furthermore, it was a stronger predictor than QRS duration reduction in the LBBB subgroup. The QRS duration reduction only impacted prognosis in LBBB patients. The finding that QRS area is a stronger parameter than QRS duration in predicting response to CRT is consistent with the studies mentioned above. This is likely a reflection of QRS area being a more sensitive marker for electrical dyssynchrony than QRS duration.

Clinical Implications

In the clinical setting, the ability to predict prognosis and inform patients immediately after implantation or at the primary follow-up visit allows for early intervention in ways that could improve the patient's condition before additional disease progression has occurred. The seminal study by Mullens et al. [18] showed that patients with poor response to CRT have a better prognosis if a specific adjustment in device settings and/or other therapies can be identified and that early therapeutic optimization improves survival. Therapeutic optimization in patients with a poor prognosis could include pharmacological adjustments, refinement of device timing by simultaneous ECG analysis, and early intervention in patients who may need an LVAD implantation or a heart transplant prior to disease progression that could inhibit such treatment options (e.g., kidney failure).

This study observed that a larger postimplant QRS area reduction was associated with a larger benefit from CRT. Knowledge about how QRS area reduction predicts clinical outcome could inform new approaches to positioning the left ventricular lead; it is possible that maximizing QRS area reduction through changes in LV lead placement at the time of implantation could further improve response to CRT. A study by Pooter et al. [19] found that a change in the LV lead position simultaneously could increase QRS area reduction and improve the acute hemodynamic response, supporting this hypothesis. Prospective trials are needed in order to further assess the possible role of QRS area reduction in optimizing LV lead positioning.

In the present study, ECG data were exclusively collected from digital 12-lead ECG recordings. In previous

studies, ECG data have been semidigital as data have been converted from printed to digital versions prior to the calculation of ECG parameters. As minor distortions can arise during data transformation, the calculation of QRS area is less precise with this technique, and results may be affected. Therefore, for future, wider clinical application of ECG parameters, calculations based on digital data are preferred as it ensures accurate calculations.

As necessary software and access to digital ECG data are lacking in current medical record systems, integrating QRS area measurements have not been straightforward thus far. If medical record systems incorporate this information in an accessible way, however, information about preimplant QRS area and QRS area reduction as well as other ECG parameters could be used as a complement to current guidelines and parameters, e.g., ECG morphology and QRS duration. In this context, randomized trials that investigate the difference between QRS area measurements and conventional selection parameters are warranted.

Limitations

A retrospective study design is subject to multiple biases (selection, referral, and attrition biases) and prohibits the inclusion of a nontreated control group. Therefore, the absolute benefit of CRT compared to no treatment concerning the primary endpoint cannot be determined in the present study. As sufficient ECG data were not available for all patients, some patients were excluded from ECG analyses. Although previously identified factors that influence CRT outcome were included in the multivariate analyses, there may have been residual bias between the groups that were not accounted for in the statistical models.

The use of transformed 12-lead ECGs rather than vectorcardiograms may have led to patient misclassification. However, 12-lead ECGs are readily available, and by using these instead of special vectorcardiogram recordings, the findings will be much easier to integrate into clinical practice. The agreement between 12-lead QRS area and vectorcardiogram recordings is good [20].

Our cohort was relatively small, and therefore any conclusions regarding subgroups (for instance, various ECG morphology groups) should be drawn with caution. Detailed left ventricular lead positions were not available, but all implanters were experienced and always aimed for a posterolateral/lateral mid- or basal position of the lead. Lead positions may however have a different impact on QRS area and QRS duration in different ECG morphologies, and this may have affected the results.

Conclusions

A larger preimplant QRS area and a postimplant QRS area reduction were independently associated with clinical outcome in terms of survival free from heart failure hospitalization in this cohort of CRT-treated patients. This association was present in patients with LBBB, paced, or IVCD morphologies. These findings are clinically relevant as they suggest that pre- and postoperative QRS area data could improve the prediction of prognosis after CRT. Accurate predictors of prognosis could, in turn, improve patient selection and management following implant.

Statement of Ethics

This study was approved by the Swedish Ethical Review Authority. The requirement of written informed consent was waived by the authority. Approval number: 2020-05843.

Conflict of Interest Statement

R.B. has received speaker fees from Medtronic and BIOTRONIK. P.G.P. is an associate editor of Cardiology. The authors have no additional conflicts of interest to declare.

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Author Contributions

S. Marinko performed data collection, data analysis, and writing of the manuscript. R. Borgquist performed study design, data collection, data analysis, and review of the manuscript. J. Carlson and P.G. Platonov performed data collection, data analysis, and review of the manuscript.

Data Availability Statement

Data are available upon reasonable request from the corresponding author (S.M.). Data are not publicly available as it could compromise the privacy of the study's participants. "All data generated or analyzed during this study are included in this article and its online supplementary material."

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