

Predicting adverse cardiovascular outcomes in post-coronary artery bypass grafting patients using novel ECG frequency analysis of the QRS complex

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Abstract

Background: A novel metric called Layered Symbolic Decomposition frequency (LSDf) has been shown to be an independent predictor of ventricular arrhythmia and mortality in patients receiving implantable cardioverter-defibrillator (ICD) devices. This novel index studies the fragmentation of the QRS complex. However, its generalizability to predict cardiovascular events for other cardiac procedures is unknown. Herein, we investigated the applicability of LSDf as a predictive measure for major adverse cardiovascular events (MACE) in patients receiving coronary artery bypass grafting (CABG).

Methods and Results: One hundred ninety-five patients had high-resolution ECG recorded prior to CABG surgery in 2012/2013 and were followed for a mean duration of 7.32 ± 0.32 years for postoperative cardiovascular outcomes. These outcomes were described as a modified composite of MACE defined as hospitalization for heart failure, ventricular tachycardia, ventricular fibrillation, and cardiovascular death including stroke and cardiac arrest. One hundred seventy-two patients were included for analysis and 18 patients experienced a postoperative cardiovascular outcome. These patients had significantly increased age (71.3 vs. 64.6 years, $p = .007$), prolonged QRS duration (113.22 vs. 97.35 ms, $p = .003$), reduced left ventricular ejection fraction (42.7% vs. 56.5%, $p < .001$), and lower LSDf percent (13.5% vs. 16.9%, $p = .002$). Patients with an LSDf below 13.25% were 4.8 (OR 1.7–13.5, $p < .001$) times more likely to experience a MACE and up to 19.4 (OR 4.2–90.3, $p < .001$) times more likely to experience a MACE when older than 70 years and an ejection fraction below 50%.

Conclusion: Layered Symbolic Decomposition frequency may be an applicable metric to predict long-term cardiovascular outcomes in patients with ischemic heart disease.

KEYWORDS

coronary artery bypass grafting, major adverse cardiovascular events, signal averaging, signal processing

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1 | INTRODUCTION

Coronary artery bypass grafting (CABG) is one of the most commonly performed cardiovascular procedures for the management of coronary artery disease (CAD), with approximately 400,000 cases completed on an annual basis in the United States alone (Alexander & Smith, 2016; Cassar et al., 2009). Long-term outcomes of patients receiving CABG surgery have shown survival advantages over patients receiving beta-blockers and antiplatelet medical therapy, with pronounced survival benefits for individuals that experience a number of clinical characteristics defined as high risk (Yusuf et al., 1994). While observable survival benefits are evident in the long-term for CABG patients, approximately one third report re-admission within 2 years post-procedure as a result of major adverse cardiovascular events (MACE) including stroke, acute myocardial infarction, or arrhythmia, with heart failure accounting for up to 65% of mortality within the first 30 days post-CABG (Herlitz et al., 2004; Loponen et al., 2007; Palmerini et al., 2014).

The use of electrocardiogram (ECG) features of ventricular depolarization to predict MACE events could be considered for risk-stratification in a CABG patient population. Abnormal features in the QRS complex including prolonged QRS duration (≥ 120 ms) and fragmentation have been well documented as increased risk factors for ventricular arrhythmias and sudden cardiac death, specifically in the presence of heart failure; the prognostic impact of these factors for MACE has similarly been reflected in a CABG population (Erdoğan et al., 2012; Kashani & Barold, 2005).

A QRS signal processing metric called Layered Symbolic Decomposition frequency (LSDf) has been found to effectively stratify arrhythmia risk and cardiac mortality in an ICD cohort over a long follow-up period (Chow et al., 2019). The LSD algorithm decomposes high-resolution biological signals that do not require a basis reference sinusoidal wave of the FFT, unlike other common approaches to signal processing. The index reports the relative proportion of low-frequency signals to high-frequency signals, which correspond to fragmentation in the QRS complex. LSD proved significantly more reproducible than other spectral analysis techniques such as FFT, Mortlet, Mexican Hat, or Hilbert–Huang transform making this ideal for clinical use (Torbey et al., 2015). It was previously determined that patients reporting $< 13.25\%$ match to the dominant frequency had significantly poorer survival outcomes over long-term follow-up (log-rank $p < .001$) (Chow et al., 2019). As an independent predictor of arrhythmia and mortality in ICD patients, the purpose of this study is to determine the applicability of LSDf as a novel feature in the prediction of adverse outcomes in the long-term follow-up of routine post-CABG patients. We hypothesize that LSDf $< 13.25\%$ will still associate with MACE outcomes in this population of relatively healthy revascularized patients following CABG procedure.

2 | METHODS

2.1 | Patient population

The study protocol was approved by the Queen's University Health Sciences & Affiliated Teaching Hospitals Research Ethics Board (HSREB). Patients underwent CABG surgery in 2012/2013 with all procedures completed at Kingston General Hospital, Kingston, ON. High-resolution ECG recordings were available in our stored electronic databases in patients receiving CABG and consent to ongoing research participation provided at time of recording was verified. Our exclusion criteria were defined as any cases of emergency CABG, hemodynamically unstable patients, or evidence of continuous cardiac pacing.

2.2 | Frequency analysis of high-resolution ECGs using LSDf

Ten-minute, high-resolution (1,000 Hz), orthogonal recordings captured on SpiderView Digital Holter Recorder (Sorin, ELA Medical) were used for signal averaging analysis computed by ad-hoc developed software. LSDf was calculated by an automated algorithm from the most common QRS morphology. With this method, the frequency characterization of the QRS complex is quantified by this index which can capture the relative amount of energy in the 40–150 Hz relative to the energy over the 1–300 Hz range (Torbey et al., 2015). The result quantifies that the lower the LSDf index, the more fragmented the signal-averaged QRS morphology appears due to more energy found within the higher frequency range (> 150 Hz). Particularly, this algorithm uses a tree data structure to analyze a biological signal in several layers. The root is used to represent the lowest frequency components of the signal, whereas the leaves represent the highest frequency components (Chow et al., 2019). Data were collected prior to CABG procedures in 2012/2013 (Seaborn, 2014). The LSD algorithm previously described by Torbey et al. (2015) was used to analyze the ECG recordings, specifically decomposing minute deflections hidden within the averaged QRS segment to create the LSDf metric blinded to patient outcome (Chow et al., 2019; Torbey et al., 2015).

2.3 | Follow-up and outcomes

Routine follow-up was completed at Kingston General Hospital and reported in the electronic health record databases. A retrospective review of clinical outcomes post-CABG was completed by searching of health records supplemented by telephone interviews with patients and/or their primary care physician if necessary. Preliminary assessment of postoperative risk was determined for patients according to baseline demographics in accordance to EuroSCORE guidelines

(Nashef et al., 1999). Objective risk factors pertinent to eligible participants of the current study include age, sex, presence of chronic pulmonary disease (COPD), history of cardiac surgery, neurological dysfunction, serum creatinine, LV dysfunction, acute myocardial infarct, and pulmonary hypertension. Postoperative MACE was defined as compositive of new onset of heart failure (defined as hospital admission or ejection fraction $\leq 40\%$), ventricular fibrillation, ventricular tachycardia, newly implanted cardioverter-defibrillators, and cardiac-related mortality including cardiac arrest and stroke. Mortality from non-cardiovascular or unknown causes was excluded.

2.4 | Secondary analysis

Databases were inspected for left ventricular ejection fraction (LVEF) documented pre-CABG by most recent echocardiograms records, with the latest value appropriate for use provided within 6 months prior to CABG procedure. Resting 12-lead ECG QRS duration calculated by automated ECG analysis (Mac VU360 EKG Machine, GE Healthcare) at the time of procedure and patient age was included based on prior association with MACE (Erdoğan et al., 2012; Lee et al., 2018). Stratification of patient risk for analysis was based on predetermined threshold values and clinical judgments rather than maximized sensitivity and specificity combinations as determined from Youden's Statistic.

2.5 | Statistical analysis

Kaplan–Meier curves were employed in the analysis of the a priori LSDf 13.25% cut point. Log-rank (Mantel–Cox) analysis was completed to compare survival distributions of patients stratified above or below this LSDf threshold. Receiver operating characteristic (ROC) curves were created to represent a variety of clinical and electrophysiological features, including the novel LSDf metric. The point capturing optimal sensitivity and specificity on the ROC curves was determined using Youden's J statistic for secondary analysis variables. The accuracy of these features to the onset of postoperative MACE was also assessed using the area under the curve (AUC). Pearson Chi-square tests and risk estimates were completed for LSDf and secondary analysis variables, where abnormalities and increased risks were defined as LSDf $< 13.25\%$, age > 70 years, QRS duration > 110 ms, and LVEF $< 50\%$.

3 | RESULTS

3.1 | Patient characteristics

A total of 195 patients receiving CABG in 2012/2013 were eligible to participate; of these patients, 23 were excluded for follow-up

evaluation due to loss of original high-resolution ECG recordings collected at the time of surgery or evidence of continuous cardiac pacing at the time of recording. A final inclusion of 172 patients was eligible for the study and a review of clinical outcomes was completed in February 2020, with a mean follow-up period of 7.32 ± 0.32 years. The mean age of patients was 65.3 ± 9.91 years at the time of consent with predominantly male patients enrolled ($n = 138$, 80.2%). Over the follow-up period, a total of 18 patients (10.5%) experienced postoperative cardiovascular outcomes described previously. The remaining 154 patients did not report experiencing any outcome during the follow-up period or reported outcomes unrelated to our area of interest (i.e., mortality due to metastatic cancer). Patient demographics collected at baseline are described in Table 1.

3.2 | Survival analysis of LSDf

Over the follow-up period, patients were stratified based on their LSDf value, with 13.25% as the threshold as determined from previous ICD cohort (Figure 1). The log-rank (Mantel–Cox) comparing the mean survival time for patients with an LSDf value below 13.25% was significantly lower ($p = .001$) compared to patients with an LSDf above 13.25%.

3.3 | Receiver operating characteristic analysis

Receiver operating characteristics (ROC) analysis was completed for age, left ventricular ejection fraction (LVEF), QRS duration, and LSDf to determine the ability of predicting long-term postoperative cardiovascular outcome (Figure 2). Ejection fraction had the greatest area under the curve (0.812, $p < .001$), with sensitivity and specificity reporting at 0.714 and 0.833, respectively. The area under the curve (AUC) for our novel LSDf metric was 0.704 ($p = .005$) compared to age with AUC = 0.685 ($p = .010$) and QRS duration AUC = 0.631 ($p = .069$). In comparing these three predictors, LSDf had the greatest Youden's index with maximum sensitivity 0.851 and specificity 0.556 (Table 2). Along with LSDf, statistical significance for outcome prediction was apparent for age and LVEF (Table 2).

3.4 | Evaluation of LSDf with high-risk variables for MACE (secondary analysis)

Patients with abnormal values outlined for LSDf and secondary analysis variables age, QRS duration, and LVEF had greater MACE frequency compared to patients with normal/low-risk values (Table 3). Risk estimates completed for these patients with LSDf below 13.25% were 4.80 times more likely to experience a MACE and increased up to 19.36 times if patients were also older than 70 years and had an ejection fraction below 50% (Table 4).

	All patients (n = 172)	Postoperative MACE (n = 18)	No outcome, unrelated events (n = 154)	p-value
Age at consent (years)	65.3 (9.91)	71.3 (9.41)	64.66 (9.78)	.007*
Female sex	34 (19.8%)	6 (33.3%)	28 (18.2%)	.132
Mean aortic pressure (S)	130.44 (19.98)	127.72 (15.28)	130.76 (20.48)	.543
Mean aortic pressure (D)	70.37 (10.22)	67.72 (10.23)	70.68 (10.21)	.246
Mean number of grafts	2.95 (0.87)	2.83 (0.98)	2.96 (0.86)	.231
CABG with valve replacements	18 (10.5%)	4 (22.2%)	14 (9.09%)	.551
EuroSCORE	1.64 (0.09)	2.72 (1.23)	1.51 (1.06)	<.001*
Comorbidities				
Type 2 diabetes	55 (32.0%)	7 (38.9%)	48 (31.1%)	.494
COPD	31 (18.0%)	5 (27.8%)	26 (16.9%)	.253
Renal insufficiency	45 (26.1%)	5 (27.8%)	40 (26.0%)	.919
Obesity (BMI ≥ 30)	66 (38.4%)	7 (38.9%)	59 (38.3%)	.935
Hyperlipidemia	67 (38.9%)	6 (33.3%)	61 (39.6%)	.567
Hypertension	123 (71.5%)	13 (72.2%)	110 (71.4%)	.930
Mean QRS duration (ms)	99.01 (21.8)	113.22 (31.3)	97.35 (19.9)	.003*
Mean left ventricular ejection fraction (%)	55.1 (11.8)	42.7 (11.5)	56.5 (11.0)	<.001*
Mean LSDf (%)	16.5 (4.31)	13.5 (5.73)	16.9 (3.99)	.002*

Note: Table values are counts or mean (standard deviation).

*Statistically significant $p < .05$, determined using independent samples t test (2-tailed), equal variances assumed

TABLE 1 Clinical characteristics of eligible CABG patients

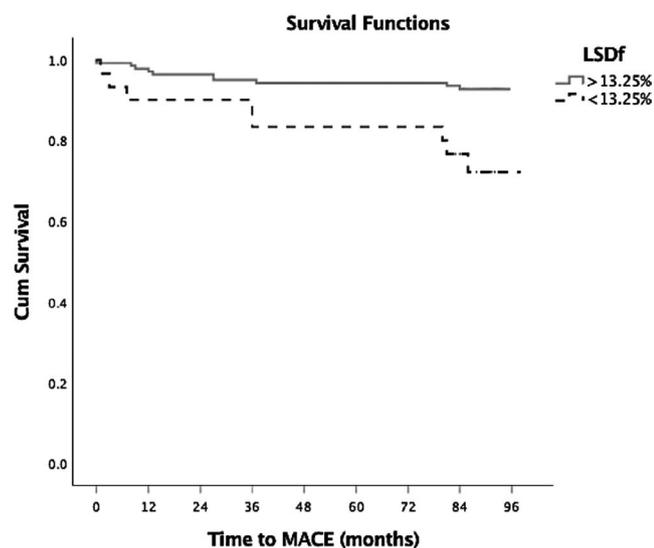


FIGURE 1 Kaplan-Meier survival curve for LSDf 13.25% cut-point over follow-up period

4 | DISCUSSION

This retrospective study was designed to determine the applicability of LSDf as a predictive metric of MACE in a relatively healthy cohort of cardiac patients compared with our prior study of ICD recipients. Among the various cardiac risk assessment guidelines available today, the European System for Cardiac Operative Risk Evaluation (EuroSCORE) and the Society of Thoracic Surgeons (STS) risk scores are the two in most widespread use (Nashef et al., 1999; Shahian et al., 2009). Between both of these scores, age, LV dysfunction (ejection fraction), COPD, renal function, and history of MI are some examples of preoperative clinical characteristics of interest considered for risk evaluation purposes. At baseline, our cohort of patients fall within the low-risk classification according to the EuroSCORE (with risk assessments mean of 1.64 ± 0.09) despite a final observed 10.46% MACE rate reflective of event rates for patients described as high risk (Nashef et al., 1999). Although we do observe a significantly greater assigned EuroSCORE for patients eventually reporting

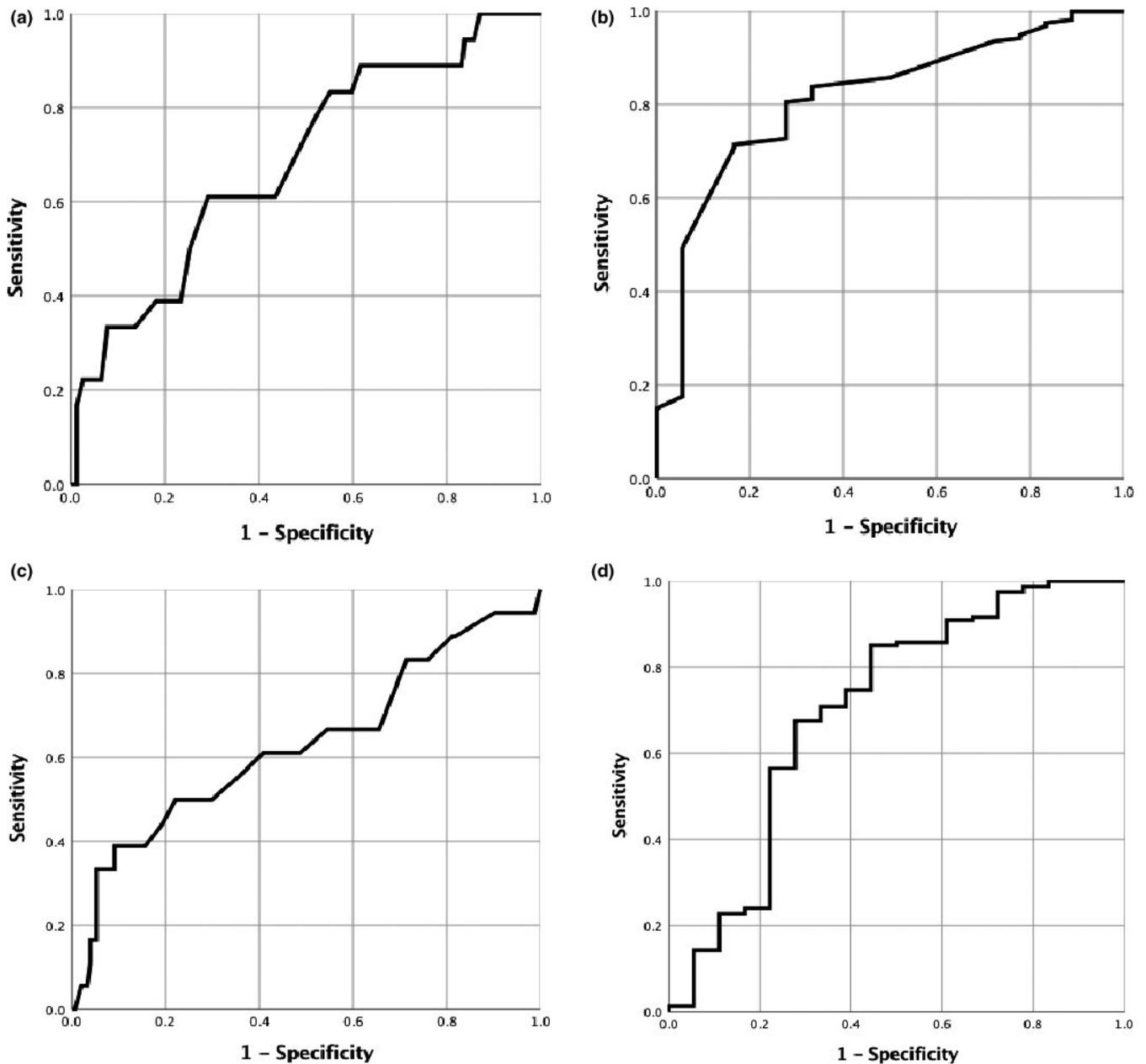


FIGURE 2 Receiver operating characteristic curves for (a) age, (b) LVEF, (c) QRS duration, and (d) LSDf

TABLE 2 Predictors of postoperative cardiovascular outcomes from ROC curves, sensitivity, and specificity from Youden's index

Variable	Area under curve (AUC)	Sensitivity	Specificity	Threshold	p-value	95% Confidence interval	
						Lower	Upper
Age	0.685	0.611	0.708	70.5 years	.010*	0.554	0.816
QRSd	0.631	0.389	0.909	115.5 ms	.069	0.476	0.787
LVEF	0.812	0.714	0.833	53.7%	<.001*	0.713	0.911
LSDf	0.704	0.851	0.556	13.56%	.005*	0.553	0.855

*Statistically significant $p < .05$.

TABLE 3 MACE frequencies experienced by patients over follow-up period

Variable	Stratification	MACE frequency (%)	p-value
Age	≥70 years	19.6	.006*
	<70 years	6.0	
QRSd	≥110 ms	30.4	.001*
	<110 ms	7.4	
LVEF	≥50%	3.9	<.001*
	<50%	28.9	
LSDf	≥13.25%	7.0	.001*
	<13.25%	26.7	

*Statistically significant $p < .05$, Pearson Chi-square asymptotic significance (2-sided).

TABLE 4 Odds ratio for (a) individual, (b) two combined, (c) three combined clinical variables (ascending)

Variables	Odds ratio for MACE	95% Confidence interval	
		Lower	Upper
(a)			
Age	3.81	1.39	10.44
LSDf	4.80	1.71	13.49
QRSd	5.49	1.86	16.16
LVEF	9.91	3.29	29.85
(b)			
LSDf, LVEF	9.13	2.72	30.64
LSDf, QRSd	9.16	2.92	28.77
LSDf, Age	10.50	3.04	36.25
Age, LVEF	11.61	3.55	37.99
(c)			
LSDf, Age, QRSd	11.46	2.93	44.79
LSDf, QRSd, LVEF	14.42	3.45	60.37
LSDf, Age, LVEF	19.36	4.15	90.25

cardiac events (2.72 ± 1.23 vs. 1.51 ± 1.06 , $p < .001$), these values still fall within the defined range of low-risk groups (0–2) (Nashef et al., 1999).

While our patients represent a low-risk population, our secondary analysis supports the risk-stratification potential of existing variables including increased age and reduced ejection fraction to facilitate the identification of such patients, presenting with the greatest risk estimation for two combined variables. We propose that the novel metric LSDf can be used to supplement and increase refinement of stratification for a CABG population at baseline assessment, increasing the risk estimation from 11.61 to 19.36 with the addition of this single metric (95% CI 3.55–37.99 and 4.15–90.25, respectively). The significant likelihood of experiencing a

MACE in the current population is likely due to the low event rate observed; however, this is nonetheless consistent and reflective of reduced MACE associated with long-term CABG revascularization patients (Bundhun et al., 2016).

Layered Symbolic Decomposition frequency has previously demonstrated to be a viable reproducible metric to select patients destined for ICD therapy or mortality, and we have successfully shown the ability of the technique to pick up subtle markers in elective CABG patients. While the overall incidence of MACE varies widely across CABG patients, we found that the evaluation of risk using the previously determined LSDf cutoff (13.25%, $p < .05$ derived from an ICD population) was appropriate and efficacious for the current population. The reproducibility of high-risk patient identification in agreement to this threshold demonstrates translational applicability into the clinical setting as a potential general cardiac assessment tool and supports the ongoing efforts in exploring ECG markers for personalized approaches in the prevention of adverse events in cardiac patients.

The use of ECGs in providing abundant clinical information is a growing area of interest in the field of cardiovascular health. Prolonged QRS duration has been used as a tool for treatment recommendation for cardiac resynchronization therapy (CRT) to improve symptoms of heart failure and reduce the risk for sudden cardiac death (Cleland et al., 2005). The association of prolonged QRS duration and MACE in the current patient population demonstrates consistency for these recommendations. Multiple studies have shown increased QRS duration as an independent predictor of sudden cardiac death and ventricular arrhythmia (Açil et al., 2006; Iuliano et al., 2002; Whitbeck et al., 2014), with one study showing up to a 10% increase in mortality rate for every 10 ms increase in QRS duration (Kalahasti et al., 2003). The end of the QRS complex is a particular area of interest, as ventricular late potentials falling outside the standard QRS duration window may represent areas of diseased myocardium and substrate for reentry ventricular tachycardia. These late potentials are commonly visualized using high-resolution ECGs, where increasing evidence for abnormal signal-averaged electrograms (SAECGs) can be used as a powerful predictor of worse outcomes in arrhythmia patients (Gadaleta & Giorgio, 2012). In relation of electrograms to revascularization procedures, evidence from the Coronary Artery Bypass Graft (CABG) Patch Trial has demonstrated up to two times the mortality rate reported after 2 years post-surgery in patients with abnormal SAECGs at baseline compared to patients with normal electrocardiograms (Curtis et al., 1997; The CABG Patch Trial Investigators & Coordinators, 1993). However, despite early promise late potentials failed to generate widespread clinical adoption outside assessment of arrhythmogenic right ventricular cardiomyopathy. Late potentials do not reflect fragmentation within the QRS, and spectral techniques are poorly reproducible, limiting clinical applicability. Although the evidence for short-term improvement of SAECGs immediately post-CABG remains unclear, postoperative arrhythmic events correlate well to abnormal SAECGs acquired prior to procedure likely related to existing arrhythmogenic substrates (Borbola et al., 1988; Takami & Ina, 2003).

Risk stratification based on simple ECG metrics is desirable, and LSDf could act as a valuable non-invasive marker. With technological advances and personalized approaches in cardiac monitoring becoming increasingly available, identification of these patients through simple ECG markers is of keen interest. The development of “tattoo” electrodes and wearable devices will enable sophisticated ECG analysis from thousands of recorded beats and can notify healthcare providers of patients predisposed to increased risk as various cut points are breached. This will allow more vigorous and targeted monitoring and subsequent delivery of appropriate therapy for patients identified at greater risk.

4.1 | Future directions

The application of this novel LSDf metric has not yet been studied prospectively. Prospective studies collecting patient information from ICD and CABG patients to determine LSDf prior to event occurrence will allow us to validate the optimal threshold determined by the two studies. We acknowledge that the high-resolution ECG is not the standard clinical practice and will require LSDf to be acquired through standard 12-lead ECG recordings for full translation to clinical practice. Future studies are needed to better understand the relationship between LSDf and the underlying pathology it represents.

4.2 | Limitations

This single-center study is retrospective in nature, with the potential for recall bias and missing data. The total number of patients that reported a MACE is limited, reflecting a low-risk group and some combinations of risk factors were rare. High odds ratio is likely attributed to low event numbers, however remain significant despite small sample size.

5 | CONCLUSIONS

This is the second study to investigate the predictive potential of LSDf for adverse cardiovascular outcomes and supports existing research of this metric as a viable risk-stratification tool. Recognized clinical markers such as increased age, reduced LVEF, and prolonged QRS duration are shown to be predictive of poor cardiac outcomes in this cohort of patients and reflect promising utility of LSDf as a supplemental tool for CABG patients.

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CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

AUTHORS' CONTRIBUTION

Authors Hua, Vlahos collected and analysed data. Drs Shariat and Payne provided editorial comment and technical expertise. Dr Redfearn is senior investigator and provided research concept and oversight.

ETHICAL APPROVAL

The study protocol was approved by the Queen's University Health Sciences and Affiliated Teaching Hospitals Research Ethics Board.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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