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CLINICAL RESEARCH
Heart failure and cardiomyopathies

A novel tool for arrhythmic risk stratification in desmoplakin gene variant carriers

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Abstract

Background and Aims Pathogenic desmoplakin (*DSP*) gene variants are associated with the development of a distinct form of arrhythmogenic cardiomyopathy known as DSP cardiomyopathy. Patients harbouring these variants are at high risk for sustained ventricular arrhythmia (VA), but existing tools for individualized arrhythmic risk assessment have proven unreliable in this population.

Methods Patients from the multi-national DSP-ERADOS (Desmoplakin SPecific Effort for a RAre Disease Outcome Study) Network patient registry who had pathogenic or likely pathogenic *DSP* variants and no sustained VA prior to enrolment were followed longitudinally for the development of first sustained VA event. Clinically guided, step-wise Cox regression analysis was used to develop a novel clinical tool predicting the development of incident VA. Model performance was assessed by *c*-statistic in both the model development cohort ($n = 385$) and in an external validation cohort ($n = 86$).

Results In total, 471 *DSP* patients [mean age 37.8 years, 65.6% women, 38.6% probands, 26% with left ventricular ejection fraction (LVEF) < 50%] were followed for a median of 4.0 (interquartile range: 1.6–7.3) years; 71 experienced first sustained VA events {2.6% [95% confidence interval (CI): 2.0, 3.5] events/year}. Within the development cohort, five readily available clinical parameters were identified as independent predictors of VA and included in a novel DSP risk score: female sex [hazard ratio (HR) 1.9 (95% CI: 1.1–3.4)], history of non-sustained ventricular tachycardia [HR 1.7 (95% CI: 1.1–2.8)], natural logarithm of 24-h premature ventricular contraction burden [HR 1.3 (95% CI: 1.1–1.4)], LVEF < 50% [HR 1.5 (95% CI: .95–2.5)], and presence of moderate to severe right ventricular systolic dysfunction [HR 6.0 (95% CI: 2.9–12.5)]. The model demonstrated good risk discrimination within both the development [*c*-statistic .782 (95% CI: .77–.80)] and external validation [*c*-statistic .791 (95% CI: .75–.83)] cohorts. The negative predictive value for *DSP* patients in the external validation cohort deemed to be at low risk for VA (<5% at 5 years; $n = 26$) was 100%.

Conclusions The DSP risk score is a novel model that leverages readily available clinical parameters to provide individualized VA risk assessment for *DSP* patients. This tool may help guide decision-making for primary prevention implantable cardioverter-defibrillator placement in this high-risk population and supports a gene-first risk stratification approach.

Structured Graphical Abstract

Key Question

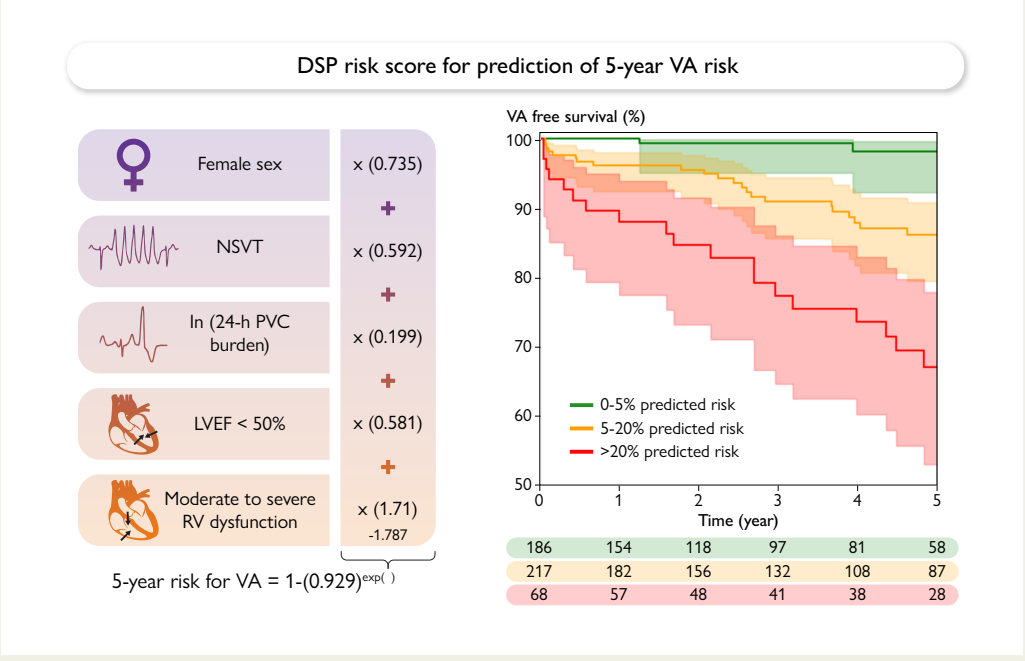
Patients harbouring pathogenic/likely pathogenic desmoplakin (DSP) variants are at high risk for sustained ventricular arrhythmia (VA), but existing tools for individualized arrhythmic risk assessment have proven unreliable. How should clinicians assess arrhythmic risk?

Key Finding

Five readily available clinical parameters were included in a novel DSP risk score: female sex, history of non-sustained ventricular tachycardia, 24-h premature ventricular contraction burden, left ventricular ejection fraction <50%, and presence of right ventricular systolic dysfunction. The model displayed excellent risk discrimination in both derivation and validation cohorts.

Take Home Message

The DSP risk score is a novel model, which provides individualized VA risk assessment. This tool may help guide decision-making for primary prevention implantable cardioverter-defibrillator placement and supports a gene-first risk stratification approach.



The desmoplakin risk score provides individualized predictions of 5-year ventricular arrhythmia risk in patients with pathogenic/likely pathogenic (P/LP) desmoplakin variants based on five readily available clinical risk factors (www.dsp-risk.com). The desmoplakin risk score demonstrated strong discrimination of ventricular arrhythmia risk (*c*-statistic .79 during external validation) and accurately stratifies patients into low- (0%–5% risk at 5 years), intermediate- (5%–20% risk at 5 years), and high-risk (>20% risk at 5 years) groups for the purposes of guiding primary prevention implantable cardiac defibrillator decision-making. DSP, desmoplakin; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contraction; RV, right ventricular; VA, ventricular arrhythmia.

Keywords DSP • VA • DSP cardiomyopathy • ICD • Sudden cardiac death • Risk prediction • ACM • ARVC

Introduction

Desmoplakin (DSP) is a cardiac desmosomal protein that plays a critical role in myocardial force transmission,[1] and pathogenic variants in its encoding gene (*DSP*) are an important cause of arrhythmogenic cardiomyopathies.[2,3] While traditionally associated with the development of arrhythmogenic right ventricular (RV) cardiomyopathy (ARVC), DSP-related disease is characterized by several unique features and has become increasingly recognized as a distinct clinical entity.[4–6] Desmoplakin variant carriers demonstrate high rates of left ventricular (LV) pathology including both LV systolic dysfunction and LV myocardial fibrosis, suffer from episodes of inflammatory myocardial injury, and are at particularly increased risk for life-threatening ventricular arrhythmias (VA).[4–7] Implantable cardioverter-defibrillators (ICDs) are thus an essential tool for preventing DSP-related sudden cardiac death (SCD).[8] However, while current guidelines agree upon the benefits of offering an ICD for secondary prevention of sustained VA,[8–10] the indications for prophylactic ICD use in patients with P/LP *DSP* variants are less clear.

The 2019 ARVC risk calculator is a validated, patient-specific risk prediction tool designed to assist clinicians in decision-making regarding the use of primary prevention ICDs in ARVC.[11] However, while this tool reliably predicts sustained VA events in patients with classical ARVC,[12–14] it has demonstrated poor performance in both patients with left-sided disease[15,16] and those with P/LP *DSP* variants.[17,18] The inability to provide dependable risk assessment therefore represents a major deficiency in the clinical care of these patients. While genotype-tailored strategies have demonstrated benefit in other forms of arrhythmic cardiomyopathy,[19–21] the rarity of patients with *DSP* variants described in the current literature has thus far limited the development of DSP-specific risk models.

With this goal in mind, we identified *DSP* patients without sustained VA prior to enrolment from within the DSP-ERADOS (Desmoplakin SPecific Effort for a RAre Disease Outcome Study) cohort of patients with P/LP *DSP* variants. Using readily available clinical variables, we developed and validated the DSP risk score, a clinical tool providing personalized VA risk assessment for *DSP* patients being considered for primary prevention ICD implantation.

Methods

This study conformed to the Declaration of Helsinki and was approved by local ethics and/or institutional review boards. To maintain patient confidentiality, data and study materials have not been made publicly available, but a limited data set may be made available upon reasonable request.

Study population

This was a retrospective analysis of patients from the *DSP* registry maintained by the DSP-ERADOS Network group.[5] This international collaboration includes 26 academic institutions across nine countries, with each institution functioning as an independent, prospective, observational patient registry. Individuals seen at one of these institutions before 1 March 2023 were entered in the registry if they harboured a P/LP variant in the *DSP* gene in accordance with the American College of Medical Genetics and Genomics (ACMGG) criteria.[22] The study population thus includes both proband patients (defined as the first affected individual in a family seeking medical attention) and relatives in whom the P/LP *DSP* variant was identified for diagnostic purposes or cascade screening. Registry patients were included in the current study if they (i) underwent ambulatory cardiac monitoring at the time of their initial evaluation, (ii) underwent either echocardiographic or cardiac magnetic resonance (CMR) imaging at the time of their initial evaluation, and (iii) had clinical follow-up available for longitudinal outcome ascertainment. Patients were excluded from this study if they had a history of sustained VA prior to enrolment or if sustained VA was their presenting symptom. Given the gene-first nature of this cohort, we refer to participants of this study as *DSP* patients throughout the manuscript.

The overall cohort was divided into two groups along institutional lines for model development and external model validation. Briefly, contributing centres were selected as part of the external model validation cohort such that this cohort (i) comprised ∼20% of the overall patient cohort and (ii) reflected the diverse geographic locations of the DSP-ERADOS Network. Specific institutions comprising each of the two cohorts are shown in *Figure 1*.

Data collection

Data were collected independently at each institution according to a set of standardized definitions (see Supplementary data online, *Table S1*). Enrolment (time = 0) of *DSP* patients was defined as the first clinical evaluation of the patient at which initial work-up including echocardiography or CMR imaging and ambulatory cardiac monitor was either available or obtained within the next 90 days. Available demographics, patient medical history, genetic test results, and baseline cardiac instrumental exams, including 12-lead electrocardiogram (ECG), echocardiography, CMR, and ambulatory cardiac monitor, were retrieved for each patient, if available. All *DSP* genetic variants initially considered P/LP underwent centralized expert review by specialists in cardiac genetics (B.M. and C.A.J.), in accordance with the ACMGG guidelines and a previously published arrhythmogenic cardiomyopathy variant protocol.[22,23] Moderate to severe RV systolic dysfunction was defined as the presence of RV ejection fraction (RVEF) < 40% on CMR or RV fractional area change < 33% on echocardiography (if CMR was not available); further RV functional categorizations are presented in Supplementary data online, *Methods S1*. While protocolized quantitation of late gadolinium enhancement (LGE) burden on CMR was not available in this multinational cohort, high-risk LGE pattern was defined as previously published[24] according to the distribution of LGE involvement: (i) subepicardial, (ii) transmural, or (iii) involving both interventricular septum and LV free wall.

Outcomes

The primary outcome of this study was the development of a first sustained VA event, defined as a composite of sustained ventricular tachycardia (VT)

(lasting ≥30 s at ≥100 b.p.m. or with haemodynamic compromise requiring cardioversion), ventricular fibrillation/flutter, sudden cardiac arrest (SCD), or appropriate ICD interventions including both ICD shock or anti-tachycardia pacing for sustained VA. We additionally defined life-threatening VA (LTVA) events as a composite of SCD, aborted SCD, ventricular fibrillation, or fast sustained VT (≥250 b.p.m.). Secondary outcomes used for competing risk analysis included heart transplantation and overall mortality. Outcomes were adjudicated locally at each centre via review of ECG, ICD interrogations, and patient medical records.

Statistics

Analyses were performed in Python version 3.9.13 using the open-source Pandas and Lifelines statistical code libraries. Baseline characteristics were presented as mean ± standard deviation for continuous variables and as proportions for categorical variables; continuous variables that did not follow normal distributions were presented as median with interquartile range (IQR). Unpaired Student's *t*-test, proportional *Z*-test, and Mann–Whitney *U* test were used to test differences between patients who did and did not develop sustained VA for normally distributed continuous, categorical, and non-normally distributed continuous variables, respectively.

Missing data were considered to be missing at random and imputed using multiple imputation with chained equations; a more detailed description of imputation and missingness is presented in Supplementary data online, *Methods* - Data Inputation .

Model development

The DSP risk score was developed in accordance with the Transparent Reporting of a multivariable Prediction model for individual prognosis or Diagnosis (TRIPOD) statement.[25] The association between potential arrhythmic risk factors in patients with *DSP* variants and the primary outcome of first sustained VA was assessed using Cox regression, and both univariable and multivariable hazard ratios (HRs) are reported. Proportional hazard assumptions were verified using scaled Schoenfeld residual testing. Conversion of variables from continuous to dichotomous values was decided based upon graphical assessment of the hazard for sustained VA over different clinically relevant ranges of those variables. Candidate variables known to have strong associations with VA based on previously published work[4,5,7,8,11,12] were considered iteratively for addition to the prediction model (a complete list is included in Supplementary data online, *Methods S2*). The continued predictive benefit of each added variable was assessed using log-likelihood ratio testing, and model development was finalized once the test *P*-value exceeded .1 or the addition of five predictive variables (allowing for ∼10 sustained VA events per variable), whichever came first. Given the high missingness in CMR-derived data, non-CMR variables were preferentially selected for inclusion. While this study was not adequately powered to develop and externally validate an independent model for the prediction of LTVA events, we assessed the proportion of predicted arrhythmic risk that was comprised of LTVA events using Cox regression over the combined DSP cohort with the previously developed DSP risk score prognostic index as the sole predictor of LTVA.

Model performance was assessed using concordance-based *c*-statistics in both the development and external validation cohorts. Here, 95% confidence intervals (CIs) were assessed using five-fold cross-validation. Optimism correction was not used. Model calibration was assessed graphically as a comparison between predicted and observed rates of sustained VA within the overall cohort. We also assessed the clinical utility of the model for prospective risk stratification and ICD decision-making by dividing patients into the following risk groups: (i) low-risk, defined as predicted 5-year VA risk < 5%, (ii) intermediate-risk, defined as predicted 5-year VA risk between 5% and 20%, and (iii) high-risk, defined as predicted 5-year VA risk > 20%. The cumulative survival free from sustained VA was estimated using the Kaplan–Meier method. Event rates are reported as averages over the 5-year period following the initial patient evaluation. Follow-up duration was calculated from the date of initial evaluation to the date of the study outcome or censoring, which was defined as death from any other cause, heart transplantation, or the most recent follow-up visit at which the outcomes could be ascertained. Log-rank testing was used to assess differences in survival curves between subgroups. Competing risk analysis was also performed using an Aalen–Johansen risk estimator and incident VA, heart transplantation, and mortality as competing risks. We calculated sensitivity, specificity, positive (PPV), and negative (NPV) predictive values for sustained VA events at 5 years at these clinically relevant risk-group cut-offs based on previously published methods for estimating these metrics in survival data.[26]

Results

Patient characteristics and outcomes

The overall cohort comprised 471 *DSP* patients followed for a median of 4.0 (IQR: 1.6–7.3) years. The average age of these patients was 37.8 ± 17.2 years, 309 (65.6%) were women, and 182 (38.6%) were probands. There were 211 different P/LP *DSP* variants (see Supplementary data online, *Table S2*); variants were truncating in 408 patients (86.6%) and missense in 58 patients (12.3%). Echocardiography was available for 424 (90.0%) patients, and CMR evaluation was performed in 387 (82.2%) patients. Baseline patient characteristics stratified by the presence or absence of VA outcome are presented in *Table 1*. Baseline characteristics for patients included in the model development vs. external model validation cohorts, and by contributing centres of the DSP-ERADOS Network, are presented in Supplementary data online, *Tables S3* and *Table S4*, respectively.

Sustained VA was experienced by 71 (15.1%) patients at a median of 3.9 (IQR: 1.6–6.7) years following enrolment. Initial sustained VA events included 10 aborted SCD events (14.1%), 13 ICD interventions for fast VA (VF or VT ≥ 250 b.p.m.) (18.3%), 28 ICD interventions for slower VT (<250 b.p.m.) (39.4%), and 20 spontaneous sustained VT events (<250 b.p.m. or self-terminating after 30 s) (28.2%). Life-threatening VA occurred in 26 DSP patients, including three patients in which a slower sustained VA event occurred prior to the LTVA (see Supplementary data online, *Figure S1*). Five (1.1%) patients died during follow-up. Fourteen (3%) patients underwent cardiac transplantation. Within the development and external model validation cohorts, 53 (13.8%) and 18 (20.9%) patients experienced sustained VA, respectively. Overall, 2.6% (95% CI: 2.0–3.5) of patients experienced a sustained VA event per year (*Figure 2*). Compared with patients who did not experience sustained VA events during follow-up, patients who did were more likely to be female (77.5% vs. 63.5%, $P = .02$), were more likely to be probands (59.2% vs. 38.6%, $P = .0001$), had greater numbers of T-wave inversions (TWIs) in inferior and anterior ECG leads (3 (IQR: 0–4) vs. 1 (IQR: 0–2), $P < .0001$], had greater burdens of both non-sustained ventricular tachycardia (NSVT) (13.2% vs. 39.4%, $P < .0001$) and premature ventricular contractions (PVCs) [2000 (IQR: 800–4500) vs. 300 (IQR: 5–1700), $P < .0001$], and had both lower LV ejection fraction (LVEF) (47 ± 14% vs. 55 ± 11%, $P < .0001$) and higher rates of moderate to severe RV dysfunction (12.7% vs. .8%, $P < .0001$). At the end of follow-up, ICDs were implanted in 184 (39.1%) patients, including 57 (80.3%) patients who did and 127 (31.8%) patients who did not experience a first sustained VA event.

To inform model development and confirm the relevance of the most important risk factors, relationships between clinically relevant cut-offs of continuous variables and HRs for sustained VA events were assessed graphically (*Figure 3*). Hazard for sustained VA events increased linearly with both the logarithm of 24-h PVC count and the number of inferior and anterior ECG leads with TWI. Hazard for sustained VA events increased sharply below an LVEF of 50% but remained

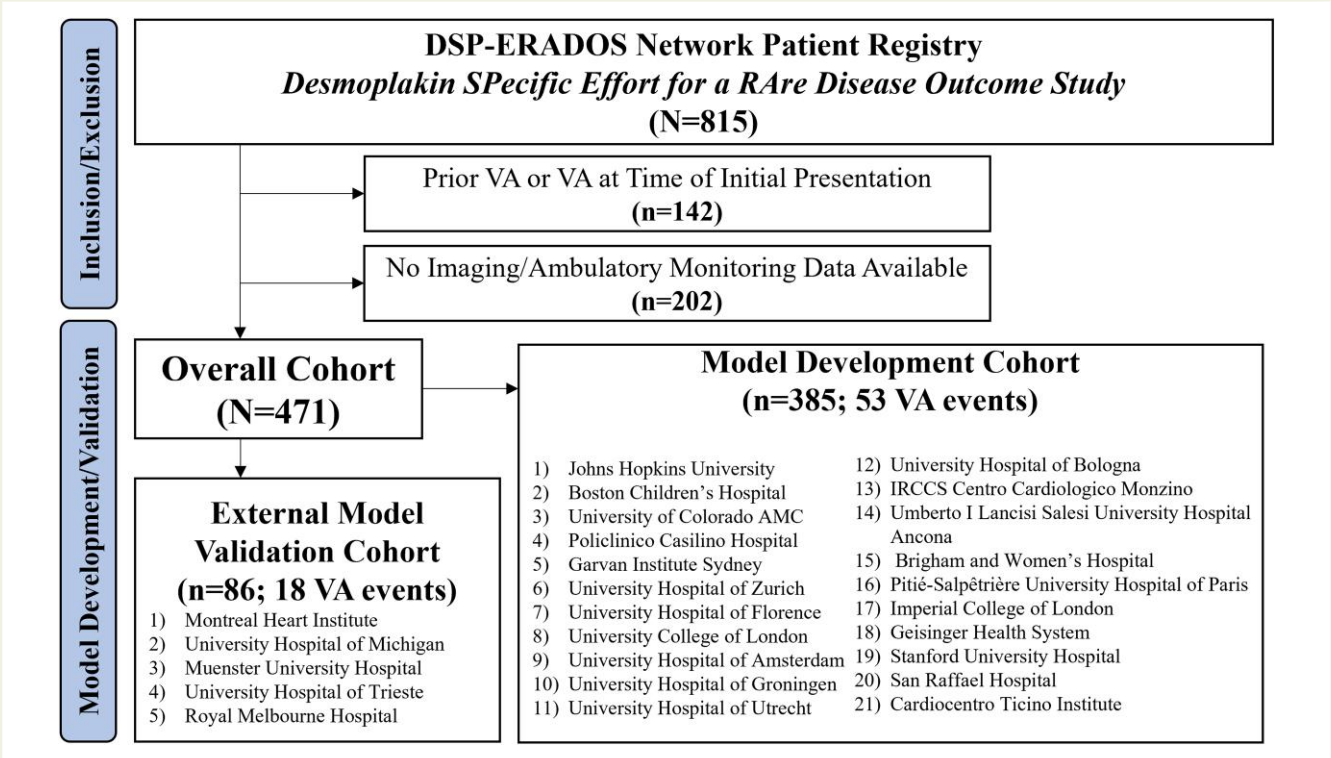


Figure 1 Flowchart showing patient selection for the model development and external model validation cohorts. VA, ventricular arrhythmia

relatively constant even for more severely reduced LVEF. Both moderate and severe RV dysfunction demonstrated increased hazards for sustained VA. Based on these results, we performed univariable and multivariable Cox regression between potential arrhythmic risk factors and incident VA (*Table 2*). Here, female sex, history of NSVT, presence of moderate or severe RV dysfunction, and the log of the burden of PVCs were strongly associated with incident VA on both univariable and multivariable Cox regression. Both LVEF < 50% and the number of inferior and anterior ECG leads with TWI were significantly associated with incident VA on univariable analysis. However, while there was a trend towards an association between LVEF < 50% and incident VA on multivariable analysis ($P = .07$), there was no association between number of inferior and anterior ECG leads with TWI and incident VA after adjustment for other risk factors. A competing risk assessment was performed as a sensitivity analysis using heart transplant and mortality as competing risks but did not impact results.

The desmoplakin risk score

Based upon a step-wise addition of variables to the model, the finalized DSP risk score (available at www.DSP-risk.com) included five clinical and imaging-based risk factors: female sex, history of NSVT, LVEF < 50%, moderate or severe RV dysfunction (RVEF < 40% on CMR or RV fractional area change < 33% on echocardiography), and the natural logarithm of the total 24-h PVC count. Analysis of other potential arrhythmic risk predictors is presented in Supplementary data online, *Methods S2* and for LVEF as a continuous risk predictor in Supplementary data online, *Methods S3*. Here, the risk of sustained VA events at 5 years from the time of initial evaluation is calculated according to Equation (1).

$$5\text{ year risk for sustained VA} = 1 - (0.929)^{\exp(\mathrm{PI})}. \quad (1)$$

Here, PI represents the prognostic index, which is calculated according to Equation (2). Here, dichotomous predictors are defined numerically as 1 (if the predictor is present) or 0 (if the predictor is absent).

$$\begin{aligned}\mathrm{PI} = {} & 0.735 * (\text{female sex}) + 0.592 * (\text{NSVT}) \\ & + 0.581 * (\text{LVEF} < 50\%) + 1.71 * (\text{Mod/Sev RV dysfunction}) \\ & + 0.199 * \ln(\text{24 h PVC count}) - 1.787. \end{aligned} \quad (2)$$

Other risk factors considered for model addition included the number of TWI on inferior and anterior ECG leads, patient age, and the presence of high-risk LGE pattern on CMR, but these did not meet our pre-specified statistical criteria ($P < .1$ during log-likelihood ratio testing and >10 events per predictive variable).

Sub-analysis of the DSP risk score examining the proportion of arrhythmic risk comprised of LTVA yielded Equation (3).

$$5\text{ year risk for LTVA} = 1 - (0.975)^{\exp(\mathrm{PI})}. \quad (3)$$

The DSP risk score demonstrated good discrimination, with *c*-statistics of .782 (95% CI: .765–.799) during model development and .791 (95% CI: .751–.830) during external validation. Prediction of LTVA over the combined DSP cohort using the DSP risk score prognostic index also had strong discrimination, with *c*-statistic of .752 (95% CI: .735–.768). Desmoplakin risk score calibration in the development and external validation cohorts (see Supplementary data online, *Figure S2*) and after stratification of proband/family member status (see Supplementary data online, *Figure S3*) was good. Model performance was good for both male [$n = 162$; *c*-statistic .780 (95% CI: .753–.807)] and female patients [$n = 309$; *c*-statistic .765 (95% CI: .760–.770)]; differences in patient characteristics by sex are presented in Supplementary data online, *Table S5*.

Table 1 Baseline characteristics of patients included in the overall cohort, stratified according to their subsequent development or survival free from sustained ventricular arrhythmia

Variable	All patients (*N* = 471)	VA free survival (*n* = 400)	Incident VA (*n* = 71)	*P*-value
Age (years)	37.8 (±17.2)	37.9 (±17.4)	37.3 (±15.8)	.78
Female Sex	309 (65.6%)	254 (63.5%)	55 (77.5%)	.02
Non-White ethnicity	31 (6.6%)	25 (6.2%)	6 (8.5%)	.49
History of cardiac syncope	46 (9.8%)	36 (9.0%)	10 (14.1%)	.18
Symptomatic dyspnoea	98 (20.8%)	78 (19.5%)	20 (28.2%)	.10
Proband status	182 (38.6%)	140 (35.0%)	42 (59.2%)	.0001
Missense variant	58 (12.3%)	49 (12.2%)	9 (12.7%)	.92
Truncating variant	408 (86.6%)	346 (86.5%)	62 (87.3%)	.85
Non-sense	194 (41.2%)	162 (40.5%)	32 (45.1%)	.47
Frameshift	183 (38.9%)	158 (39.5%)	25 (35.2%)	.49
Splice	31 (6.6%)	26 (6.5%)	5 (7.0%)	.87
Deletion/duplication	5 (1.1%)	5 (1.2%)	0 (.0%)	.34
Number of ECG leads with T-wave inversion	1 [0–3]	1 [0–2]	3 [0–4]	<.0001
NSVT on ambulatory monitor	81 (17.2%)	53 (13.2%)	28 (39.4%)	<.0001
24-h PVC count	500 [12–2346]	300 [5–1699]	2000 [798–4519]	<.0001
PVC count/24 h > 500	235 (49.9%)	174 (43.5%)	61 (85.9%)	<.0001
LVEF	53.8 (±11.9)	55.0 (±11.1)	47.2 (±13.7)	<.0001
LVEF < 50%	121 (25.9%)	83 (21.0%)	38 (53.5%)	<.0001
Moderate to severe RV dysfunction	12 (2.6%)	3 (.8%)	9 (12.7%)	<.0001
CMR evaluation	387 (82.2%)	331 (82.8%)	56 (78.9%)	.43
Any LGE	245 (63.3%)	200 (60.4%)	45 (80.4%)	.038
High-risk LGE pattern	185 (47.8%)	145 (43.8%)	40 (71.4%)	.001
Right ventricular LGE	32 (8.3%)	23 (6.9%)	9 (16.1%)	.03

Variables are expressed as frequency (%), mean ± standard deviation, or median [IQR], as appropriate.
CMR, cardiac magnetic resonance; ECG, electrocardiogram; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contraction.

The DSP risk score was able to effectively stratify patient risk (*Structured Graphical Abstract*). Observed rates of sustained VA events were .4%/year (95% CI: .1–1.6) in those predicted to be at low-risk ($n = 186$, 39.5%), 2.8%/year (95% CI: 1.9–4.1) among those predicted to be intermediate-risk ($n = 217$, 46.1%), and 6.6%/year (95% CI: 4.5–9.4) among those predicted to be at high risk ($n = 68$, 14.4%). Log-rank testing showed significant differences between all predicted risk groups ($P < .0001$). Within the external testing cohort ($n = 87$), we assessed the clinical utility of using these risk groups to determine a patient's hypothetical appropriateness for ICD implantation (*Table 3*). No *DSP* patients prospectively determined to be low risk ($n = 26$, 30.2%) had sustained VA events at 5 years, resulting in an NPV of 100%. Specific characteristics of patients in each of the three risk groups are presented in Supplementary data online, *Table S6*.

We performed a sub-analysis examining the role of high-risk LGE pattern for the prediction of sustained VA events in the subset of patients with available CMR data ($n = 387$). High-risk LGE pattern was correlated with other risk predictors included in the DSP risk score (see Supplementary data online, *Figure S4*). While high-risk LGE pattern was strongly associated with sustained VA events on univariable Cox regression [HR 2.9 (95% CI: 1.6–5.5), $P = .0009$) within the development cohort ($n = 321$), this association was no longer significant after controlling for other risk factors [HR 1.54 (95% CI: .82–2.92), $P = .18$]; addition of high-risk LGE to the model could not be justified based on log-likelihood ratio testing ($P = .86$). In the low-risk group (5-year risk for VA < 5%; $n = 149$), only 1 of 51 patients (2%) with high-risk LGE pattern experienced a sustained VA event. This patient also had PVC/24 h > 1000 and their VA event occurred 6.1 years following their initial evaluation. Given the signal for additive prognostic information, we performed an additional Bayesian analysis of high-risk LGE pattern in the low- and intermediate-risk groups (5-year VA risk < 20%; $n = 335$) (see Supplementary data online, *Methods S4* and *Table S7*); positive and negative likelihood ratios were 1.7 and .5, respectively, for patients with or without high-risk LGE.

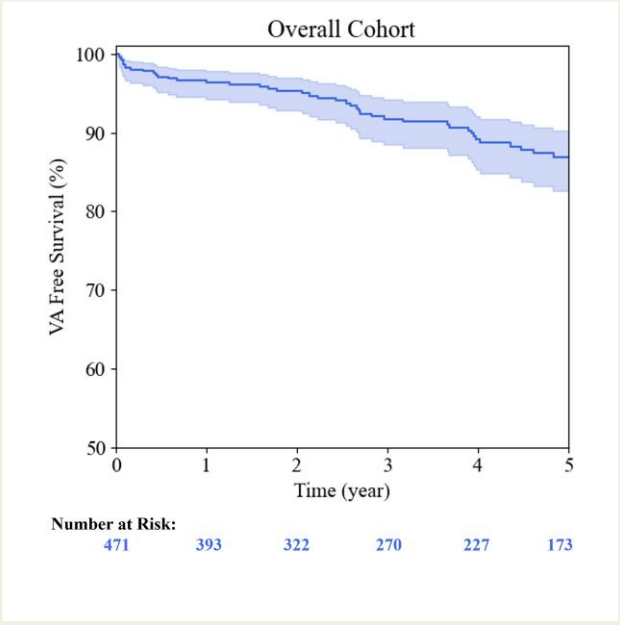


Figure 2 Kaplan–Meier curve showing survival free from sustained ventricular arrhythmia events in the overall cohort. Lighter shading represents 95% confidence intervals

Discussion

In this study, we present the first clinical tool for assessing individualized sustained VA risk in *DSP* patients without prior VA events and validate its performance in a distinct external cohort. This tool, which we term the DSP risk score, was able to reliably distinguish between those patients with incident-sustained VA during 5-year follow-up and those who survived free of sustained VA based upon five readily available clinical parameters: female sex, history of NSVT, LVEF < 50%, moderate or severe RV dysfunction, and the natural logarithm of the total 24-h PVC count. For those *DSP* patients deemed to have low baseline risk (<5% risk for sustained VA at 5 years), the DSP risk score demonstrated excellent NPV.

Compared with existing risk assessment tools, the DSP risk score demonstrated marked improvement in risk stratification for *DSP* patients.[5,17] We believe that this model has the potential to be used as part of everyday shared decision-making discussions of the use of primary prevention ICDs in this important, clinically distinct form of arrhythmogenic cardiomyopathy. To facilitate its use, we have made our model available online at www.DSP-risk.com. The DSP risk score represents an important step forward in arrhythmic risk assessment that is tailored not just to a patient's clinical phenotype but also to his or her underlying genetic substrate.

Desmoplakin-specific risk factors for sustained ventricular arrhythmia

Our findings reinforce the unique nature of DSP-specific VA risk that has been observed by other groups. As in other arrhythmogenic cardiomyopathies, electrophysiologic derangement, including both increased PVC burden and the presence of NSVT on ambulatory monitoring, appears to be important predictors of subsequent VA events. The magnitude of increased VA risk conferred by these findings appears to be very similar across DSP-related disease, ARVC,[11] and phospholamban (*PLN*)-related disease.[21] While RV dysfunction is another known risk factor for sustained VA events in ARVC, the magnitude of risk conferred by its presence was even more pronounced in *DSP* (HR DSP: 6.0; HR ARVC: 1.8).[27] Importantly, this risk factor was much less common in *DSP* patients (moderate to severe RV dysfunction present in 2.6% of patients). Moderate to severe RV dysfunction is thus an infrequent manifestation of *DSP*,[5] and, when paired with the fact that it was identified only in the presence of multiple other VA risk factors, this finding suggests that RV dysfunction may be a marker of more advanced disease [analogous to LV involvement in plakophilin (*PKP2*)-mediated ARVC]. Unlike for patients with other cardiomyopathies in whom LVEF < 30%–35% usually implies increased VA risk (and, as a result, is often used as a cut-off for ICD implantation decisions), we found that *DSP* patients had elevated VA risk at even low levels of LV systolic dysfunction. Here, VA risk increased below an LVEF threshold of 50% and remained stably elevated even for more severely reduced LVEFs. As suggested by prior studies demonstrating the predilection of *DSP* variants to cause LV fibrosis and subsequent systolic dysfunction,[4–7] the importance of LV morphologic and functional evaluation is another distinguishing feature of VA risk assessment in these patients. The ARVC risk calculator, which was derived in a predominantly *PKP2* variant or gene-elusive patient cohort, does not incorporate any direct assessments of LV involvement (either the presence of LGE or LVEF). This has proven to be a limitation for risk stratification of patients with less common ARVC genotypes in which LV involvement is frequent (e.g. *DSP*), and multiple external validation studies have demonstrated unreliable performance of the ARVC risk calculator for patients with LV involvement.[15,18] Finally, in stark contrast to other cardiomyopathies,[28,29] we identified female sex, rather than male sex, as a strong independent risk factor for VA. The underlying mechanism of this association is yet to be fully decoded, but differences in sex hormone levels and history of pregnancy are suspected to play roles.[30]

Of note, while *DSP* patients experiencing incident-sustained VA events were more likely to be probands than those who did not, defining proband status for an individual patient can be difficult from a practical standpoint. Family history may be unknown or ambiguous, particularly given the possibility of SCD as the first manifestation of DSP-related disease. In the era of increasingly widespread, community-based genetic testing,[31] there is also likely to be a shift towards initial identification of phenotype-negative patients or patients with mild phenotype within carrier families. Proband status was thus purposefully excluded as a predictor during the development of the DSP RISK SCORE. Importantly, the DSP risk score demonstrated well-calibrated risk prediction in both proband and family member subgroups (see Supplementary data online, *Figure S3*), suggesting that much of the predictive value of proband status is accounted for by the other included risk predictors. Likewise, we did not include LGE as a quantitative predictor due to the practical difficulties in achieving robust adjudication of this variable across sites. Since focal sub-epicardial LGE occurs early in the disease process with subsequent progression to circumferential LGE,[4] prioritization of LGE as a continuous variable in future studies may help to further refine risk assessment in these patients.

Value of genotype-tailored arrhythmic risk assessment

While patients with P/LP *DSP* variants often fulfil the criteria for the diagnosis of ARVC (due to the presence of a P/LP *DSP* variant fulfilling a major criterion), the poor performance of the ARVC risk calculator

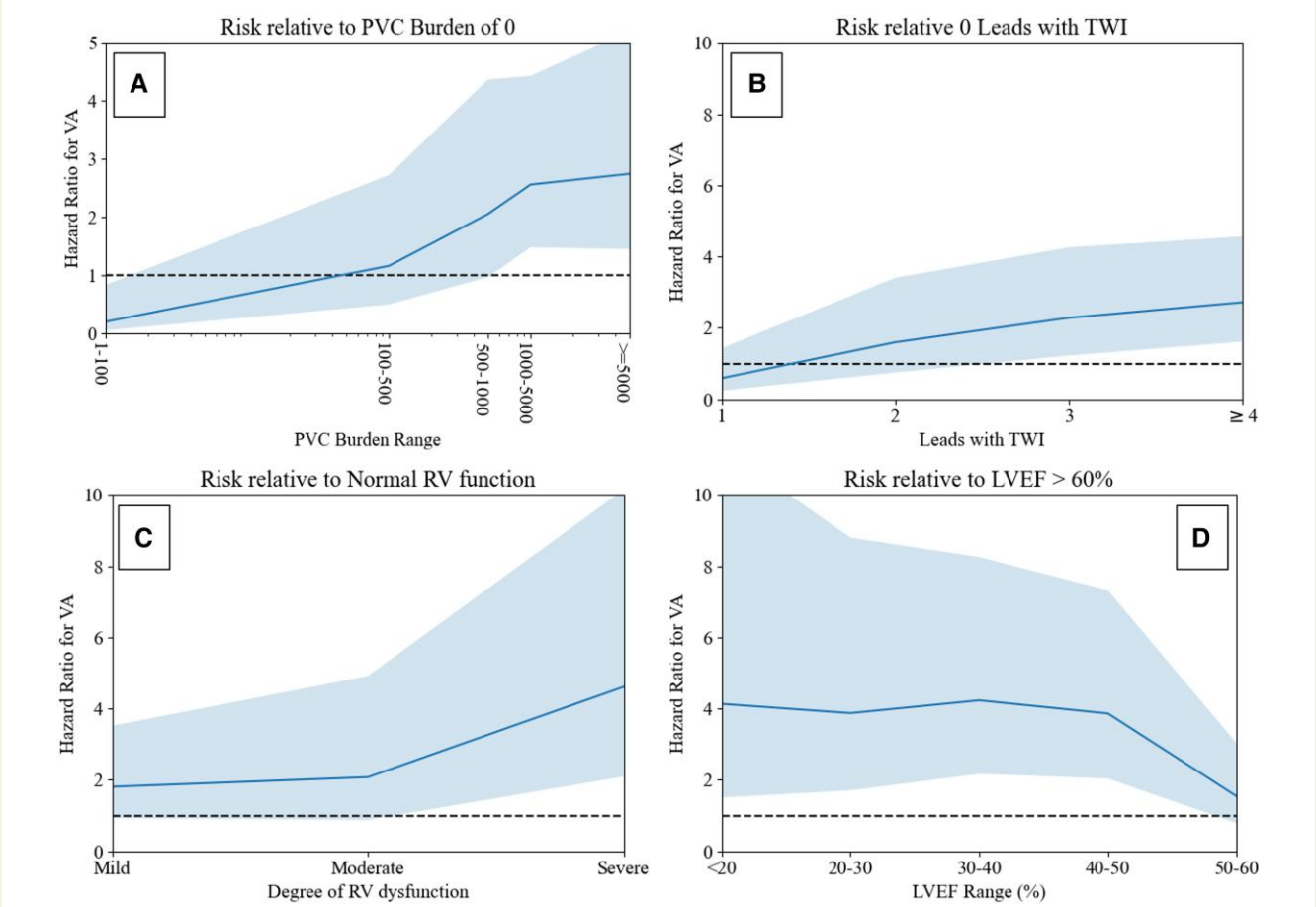


Figure 3 Relationships between the hazard of sustained ventricular arrhythmia events and cut-offs for converting continuous variables to dichotomous variables for (*A*) 24-h premature ventricular contraction burden, (*B*) number of inferior and anterior electrocardiogram leads with T-wave inversion, (*C*) right ventricular systolic dysfunction, and (*D*) left ventricular ejection fraction. In each case, the hazard for ventricular arrhythmia is assessed relative to normal values of the particular variable. LVEF, left ventricular ejection fraction; PVC, premature ventricular contraction; RV, right ventricular; TWI, T-wave inversion; VA, ventricular arrhythmia

within this population highlights the need for genotype-tailored strategies for risk assessment.[17,18] These strategies have demonstrated improved risk prediction in other genetic cardiomyopathies,[32] including those related to filamin C (*FLNC*),[19] lamin A (*LMNA*),[20] and *PLN*.[21] Development of the DSP risk score is thus part of a larger cultural shift away from basing arrhythmic risk stratification on groups of patients with loosely similar clinical phenotype and towards a 'gene-first' approach.[33] However, the way in which this new paradigm impacts the use of ICDs in patients with arrhythmogenic cardiomyopathies remains to be seen. Unlike in hypertrophic cardiomyopathy where specific risk cut-offs derived from analogous risk models have been recommended for deciding ICD eligibility,[10,34] ICD management in ARVC has historically leveraged risk scores as a tool for guiding shared decision-making conversations,[11,12] but regional differences exist.[35] Recent guidelines from the European Society of Cardiology (ESC) on VA and the prevention of SCD[10] highlight a limited set of high-risk genes in dilated cardiomyopathy (including *FLNC*, *LMNA*, and *PLN*) for which mutations plus LVEF < 50% and an additional risk factor should trigger consideration of ICD implantation. While *DSP* was not recognized as a high-risk gene in these guidelines, updated ESC guidelines for the management of cardiomyopathies do recognize *DSP* cardiomyopathy as a high-risk subgroup of both dilated cardiomyopathy and the newly defined phenotype of non-dilated LV cardiomyopathy and suggest consideration of primary prevention ICD in these patients.[36] Our findings likewise demonstrate that *DSP* patients, particularly those with manifestations of disease such as left- or right-sided systolic dysfunction, high PVC burden, or history of NSVT, are at similarly elevated risk for VA compared with these other high-risk genotypes.

The DSP risk score likely represents only the first step in individualized risk assessment for *DSP* patients. As for ARVC patients, many important modifiers to VA risk will require further study. Athletic activity is strongly associated with worsening risk for VA in ARVC,[37,38] but to what extent this remains true in *DSP* patients remains unclear. Incident arrhythmic risk in ARVC has also been shown to decrease over time,[27] but whether this holds true in patients with DSP-related disease requires further study with longitudinal risk modelling. In particular, episodes of myocardial injury are observed in around 9% of *DSP* patients over the course of their disease, and these episodes are followed by a dramatic increase in subsequent arrhythmic risk.[4,5,36,39] The extent to which these episodes parallel the 'hot phases' of increased ectopy seen in ARVC,[40] reflect rapid periods of otherwise normal disease progression, or represent some other distinct mechanism

Table 2 Univariable and multivariable Cox proportional hazard modelling of suspected risk factors for sustained ventricular arrhythmia

Variable	Univariable CPH (95% CI)	*P*-value	Multivariable CPH (95% CI)	*P*-value
Female sex	1.905 (1.091–3.324)	.023	1.914 (1.080–3.394)	.03
NSVT on ambulatory monitor	2.801 (1.738–4.514)	<.0001	1.798 (1.073–3.011)	.03
LVEF < 50%	2.786 (1.742–4.456)	<.0001	1.591 (.958–2.643)	.07
Moderate or severe RV dysfunction	6.503 (3.199–13.216)	<.0001	6.543 (2.866–14.939)	<.0001
ln(24-h PVC count)	1.363 (1.211–1.534)	<.0001	1.266 (1.117–1.436)	<.0001
Number of ECG leads with T-wave inversion	1.150 (1.055–1.254)	.002	.978 (.875–1.092)	.69

Here, only those variables ultimately selected for the DSP risk score were included in multivariable modelling. Presence of LGE on CMR was excluded due to collinearity with LV systolic dysfunction (LVEF < 50%) and higher missingness in CMR data. Hazards are shown along with 95% CIs.
CI, confidence interval; CPH, Cox proportional hazard; ECG, electrocardiogram; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; RV, right ventricular.

Table 3 Clinical utility of the desmoplakin risk score assessed in the external validation cohort ($n = 86$) at two risk thresholds

	5% predicted 5-year predicted risk for VA	20% predicted 5-year predicted risk for VA
Number below risk threshold	26 (30.2%)	72 (83.7%)
Sensitivity (95% CI)	92% (77–100)	43% (15–71)
Specificity (95% CI)	37% (24–50)	93% (86–100)
PPV (95% CI)	24% (11–38)	49% (18–80)
NPV (95% CI)	100% (100–100)	90% (83–98)
Positive likelihood ratio	1.47	5.93
Negative likelihood ratio	.21	.61

CI, confidence interval; NPV, negative predictive value; PPV, positive predictive value; VA, ventricular arrhythmia.

leading to increased arrhythmic burden is not clear at this time. Finally, specialized imaging such as CMR for assessment of LGE and invasive procedures such as programmed ventricular stimulation for assessment of arrhythmic inducibility[41] and ablation[42] have demonstrated improved risk stratification in intermediate-risk ARVC patients for whom the decision to implant ICD is ambiguous. While we identified a signal suggesting the potential for high-risk LGE pattern to further stratify VA risk predictions provided by the DSP risk score, due to relatively high missingness in CMR (~20%), this study was not powered to fully elucidate the role of LGE assessment in *DSP* patients and further study is required. Although the incidence of sustained VA in low-risk patients with high-risk LGE pattern on CMR was low in the present cohort (only 1 of 51 patients experienced VA), VA was still possible in this important subset of patients. Nuanced clinical judgement that considers high-risk LGE pattern and other potential risk markers not adequately captured by the DSP risk score (e.g. syncope deemed to be very likely arrhythmic) thus remains an essential part of shared decision-making around ICD implantation even in low-risk patients.

Clinical implications

Desmoplakin patients have a higher risk for arrhythmia even relative to patients with other forms of arrhythmogenic cardiomyopathy,[15,17,18] but not all *DSP* patients will go on to have VA events. Distinguishing low-risk patients unlikely to benefit from ICD placement from high-risk patients for whom ICD placement is critical for reducing SCD risk is therefore of paramount importance. The DSP risk score offers prognostic information to help guide decision-making around the placement of primary prevention ICDs. This type of decision is highly personal, however, and patients may have different tolerance for risk based upon their age, sex, lifestyle, or cultural background. For this reason, the DSP risk score assesses VA risk as a continuous variable rather than simply grouping patients into low-, intermediate-, or high-risk categories. The DSP risk score thus seeks to provide clinicians with the data necessary to have more nuanced, data-driven, shared decision-making conversations with their patients.

While there is no concrete risk threshold below which *DSP* patients should not receive an ICD, our model demonstrated excellent NPV in those patients for whom 5-year VA risk was estimated to be below 5%. In fact, no low-risk patients within the external validation cohort ($n = 26$) went on to have incident VA events in the 5 years following their initial evaluation. Thus, patients and clinicians may feel reassured that a decision to withhold or defer ICD placement based upon 5-year DSP risk score prediction below 5% is reasonable.

Limitations

Our study population was drawn from the DSP-ERADOS Network, an international collaboration of academic centres from North America, Europe, and Australia. The method for identifying patients with P/LP DSP variants was defined locally by each contributing centre, and there may be between-centre differences in the clinical indications of enrolled patients. These patients were predominantly White, and our results should consequently be extrapolated with caution to patients from other racial or ethnic backgrounds. Our ascertainment from primarily tertiary care settings may also have created a referral bias that could lead to overestimation of VA risk in a community-derived population. This was a retrospective cohort study with variable patient follow-up time. Some patients may have been lost to follow-up prior to an initial VA event. While this study represents the largest cohort of primary prevention DSP patients published to date, statistical power to analyse potential arrhythmic risk predictors was limited to approximately five variables (based on our requirement for ~10 VA events per added predictor); additional arrhythmic risk predictors may exist and warrant further study. We did not identify a significant association between sustained VA and syncopal events; this could reflect the challenge of retrospective adjudication of the aetiology of syncopal events (e.g. vagal/orthostatic vs. arrhythmic/unexplained). Additionally, family history of SCD was not systematically collected and therefore was not tested as a potential risk factor for sustained VA.

As in similar studies, we used a surrogate composite endpoint that included appropriate ICD therapy to infer risk of SCD. While most clinicians agree that ICD-treated VA represents a severe event, ICD therapies are an imperfect substitute for SCD.[43] Further study examining the utilization of primary prevention ICDs in *DSP* patients and their ultimate impact on adverse clinical arrhythmic outcomes is warranted. Finally, the DSP risk score provides VA risk estimation from the single time of a patient's initial clinical evaluation. Arrhythmic risk in ARVC is known to change over time,[27] and thus *DSP* patients should be re-evaluated periodically. Longitudinal studies are needed to identify the frequency with which clinical re-evaluation of *DSP* patients should be performed.

Conclusion

In this study, we present the DSP risk score, a novel model that leverages readily available clinical parameters to generate individualized assessments of VA risk in patients with P/LP *DSP* variants. The DSP risk score demonstrated good ability to predict incident-sustained VA by 5 years during both model development and subsequent external validation. It has the potential to guide the implantation of primary prevention ICDs in this rare but important form of arrhythmogenic heart disease. This clinical tool thus represents an important step forward in arrhythmic risk assessment that is tailored not just to a patient's clinical phenotype but also to his or her underlying genetic.

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Supplementary data

Supplementary data are available at *European Heart Journal* online.

Declarations

Disclosure of Interest

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Data Availability

To maintain patient confidentiality, data and study materials have not been made publicly available, but a limited data set may be made available upon reasonable request.

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Ethical Approval

This study conformed to the Declaration of Helsinki and was approved by local ethics and/or institutional review boards.

Pre-registered Clinical Trial Number

None supplied.

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