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From Sorbonne Université, APHP, Groupe Hospitalier Pitié-Salpêtrière, Institut de Cardiologie, Paris, France

*: these authors contributed equally.

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Address for correspondence:

Dr. Mikael Laredo

Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière,

47-83 boulevard de l'Hôpital, 75013 Paris, France.

Email : mik.laredo@gmail.com Phone: +33 1 42 16 30 54; Fax: +33 1 42 16 30 56

Unstructured abstract (250 words)

The new 5-years ventricular arrhythmia (VA) occurrence risk model is a major breakthrough for arrhythmic-risk stratification in the challenging ARVC population. In the original study, the model resulted in a 20.6% reduction in implantable cardioverter-defibrillator (ICD) placement as compared with the 2015 consensus, for the same protection level. However, only internal validation was performed, limiting generalization. Here, we externally validated the model in a European tertiary care cohort of 128 ARVC patients with restrictive indications for primary prevention ICD placement. Overall, 74% were men, none had VA history and a single patient had an ICD at baseline. Median age at diagnosis was 38 years (interquartile range [IQR] [28–50]). During a median follow-up of 7.8 years [IQR (6.1–9.7)], 15 (12%) patients experienced VA. The model provided good discrimination, with a C-index for 5-year VA risk prediction of 0.84 [95% confidence interval (0.74–0.93)] (Figure 1). However, the model led to an overestimation of the 5-year VA risk when applying thresholds <50%. With a <10% predicted risk, no patient showed VA. With a 7.5% predicted risk, the ICD:VA ratio was 6.3 versus 3.4 in original study. The model still outperformed the 2015 International Task Force Consensus. Overall, in a relatively large European ARVC cohort with restrictive indications for ICD placement, the ARVC model for VA prediction successfully identified ARVC patients with VA during follow-up. Yet, our study underlines the need for careful threshold selection considering the model's associated risk overestimation in low- to intermediate-risk patients.

60-words summary

We externally validated the new prediction model of 5-years risk of ventricular arrhythmia (VA) occurrence in arrhythmogenic right ventricular cardiomyopathy (ARVC) from John Hopkins in a European cohort of 128 patients. The model provided good discrimination, with a C-index for 5-year VA risk prediction of 0.84, yet at the cost of a significant risk overestimation in low- to intermediate-risk patients.

Introduction

Selecting candidates for implantable cardioverter-defibrillator (ICD) placement in patients with arrhythmogenic right ventricular cardiomyopathy (ARVC) is challenging.[1] Recently, Cadrin-Tourigny and colleagues developed a 7-variable prediction model for ventricular arrhythmia (VA) occurrence with a large multicenter cohort of 528 patients with ARVC and no VA history (41% had an ICD at baseline). Predictors included male sex, age, recent cardiac syncope, prior non-sustained ventricular tachycardia (NSVT), 24-h premature ventricular contraction (PVC) count, T-wave inversion (TWI) in inferior and anterior ECG leads, and right ventricular ejection fraction.[2] Bootstrapping-based internal validation was satisfactory, with a C-index of 0.77 and a calibration slope of 0.93. In the original study and in a recent external validation study, the proportion of ICD carriers at baseline reached 40%, with implications on subsequent ICD intervention rate during follow-up. Here, we externally validated the ARVC risk score in a European tertiary care cohort with restrictive indications for primary prevention ICD placement.

Methods

In a single tertiary care center, patients with a definite ARVC diagnosis according to the 2010 revised Task Force Consensus (TFC)[4], absence of VA at diagnosis and available 5-year follow-up data were retrospectively included. Data collection was based on screening of the digitalized patient files, and occurred after the design of the present study. ARVC diagnosis was retrospectively assessed according to the 2010 revised TFC[4] at the time of data collection, using the data available at the time of diagnosis ± 3 years. Both RVEF and LVEF were derived from magnetic resonance imaging and echocardiography studies. When both imaging modalities were performed, the value obtained by MRI was chosen. Mutations screening for desmosomal genes *PKP2*, *DSG2*, *DSP*, *JUP* and *DSC2* involved the Sanger or next-generation sequencings. Patients were followed routinely by their treating

electrophysiologist or cardiologist. Ventricular arrhythmia was defined as a composite of sudden cardiac death (SCD), sustained ventricular tachycardia, or appropriate ICD intervention. Rapid VT was defined as VT with cycle length <240 ms. Continuous data are reported as median [interquartile range (IQR)] and categorical variables are presented as number (%). Comparative statistics involved the Chi-square and the Wilcoxon tests. Survival curves were created with the Kaplan-Meier method, with comparisons involving the Log-Rank test. Regression analyses were performed with the Cox proportional-hazards model, estimating hazard ratios (HRs) and 95% confidence intervals (CIs). Tests were two-sided, with $p<0.05$ denoting statistical significance. Statistical analyses were performed with IBM SPSS v23 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics of the 115 included patients are shown in the Table.

During a median follow-up of 7.8 years [IQR (6.1–9.7)], 15 (12%) patients experienced VA. In these patients, the first VA event consisted of sustained VT in 6 (40%) patients, rapid VT in 2 (13%), SCD in 4 (72%) and appropriate ICD therapy in 2 (13%). Three out of 4 patients who experienced SCD were resuscitated with documented ventricular fibrillation. An ICD was implanted in 16 (14%) patients during follow-up, after a VA event in 3 and in primary prevention in 13. Among the latter, 7 experienced VA during follow-up

The estimated cumulative rate of survival without VA at 5 years was 88.7% [95% CI (81.3–93.2)] as compared with 73.6% [95% CI (69.4–78.0%)] in the original study.[2]

Baseline variables significantly associated with VA occurrence during follow-up included: history of cardiac syncope [Odds-ratio (OR) 4.0, 95% IC (1.4-11.1), p=0.07], NSVT [OR 3.7, 95% CI (1.3-10.9), p=0.02], number of anterior/inferior ECG leads with TWI [OR 1.4, 95% CI (1.1-17), p=0.001], RVEF [OR per % decrease 1.1, 95% CI (1.0-1.2),

p<0.001], LVEF [OR per % decrease 1.1, 95% CI (1.0-1.1), p=0.01], and the 5-year-risk score [OR per % increase 1.1, 95% CI (1.0-1.1), p<0.0001].

Male-sex [OR 1.0, 95% CI (0.9-1.0), p=0.2], age [OR per 1-year increase OR 1.0, 95% CI (0.9-1.0), p=0.2] and PVC count (ln) [OR 1.2, 95% CI (1.0-1.5), p=0.05] did not reach statistical significance. In a multivariable analysis including the 5-year-risk score and LVEF, only the former remained statistically significant [adjusted OR per % increase 1.05, 95% IC (1.0-1.1), p<0.0001].

Applied to our population, the ARVC risk model provided good discrimination, with a C-index for 5-year VA risk prediction of 0.84 [95% CI (0.74–0.93)] (Supplemental Figure 1). However, the model led to an overestimation of the 5-year VA risk when applying thresholds <50% (Figure A). With a <10% predicted risk, no patient showed VA (Figure 1A). With a 7.5% predicted risk, the ICD:VA ratio was 6.3 versus 3.4 in the original study, for a protection rate of 100% versus 99.3% (Figure 1B). The score threshold associated with the best performance was as high as 37%, with corresponding values of sensitivity/specificity of 80% and 79%. The model still outperformed the 2015 International Task Force Consensus, with an ICD:VA ratio of 3.3 versus 5.3 for the same level of protection (97%)[5], and the 2019 HRS expert consensus Class IIa & IIb criteria - excluding 1 major criterion corresponding to electrophysiological study results[1].

Discussion

ICDs are efficient to prevent VA-related SCD, but they are associated with high rates of complications in young patients with ARVC. Despite considerable efforts, guidelines for ICD placement are still based on expert consensus, which results in a significant number of unnecessary implantations.[1] In the original study, the new prediction model performed well and would have resulted in a 20.6% reduction in ICD placement as compared with the 2015 consensus, for the same level of protection (89.9%)[2]. However, only internal boostrapping-

based validation was performed in this study, which limits generalization. In our own cohort of ARVC patients with no VA history, the model successfully discriminated patients with VA during follow-up but at a cost of significant risk overestimation in low- to intermediate-risk patients. First, the low number of events, especially in the low- to intermediate-risk groups, warrants caution regarding the validity of this result. Yet, a small number of events was consistently observed in all risk groups <50%. A possible explanation may be an interaction between population baseline characteristics and outcomes definition rather than a flaw intrinsic to the score. Indeed, survival without VA, which includes ICD appropriate interventions, was consistently higher in our population, which reflects that our population counted only 1% of ICD carriers at baseline versus 41% in the original study and thus less appropriate ICD interventions during follow-up. Whether ICD interventions are a surrogate of SCD prevention or whether some VTs interrupted by ICDs would have otherwise been asymptomatic and self-terminating is certainly debatable and reaches beyond the scope of the present work.

Another group has recently externally validated the score in cohort of 140 patients.[3] This study findings are that the ARVC risk score discriminated well patients with VA during follow-up, was superior to TFC and HRS criteria, but similarly to our study, applying a higher risk score threshold – 10% – was associated with better performance. The proportion of ICD carriers at baseline is unknown in this study, yet the 46% VA-rate suggests it is high. In our center, we have restrictive indications for ICD implantation in primary and secondary prevention in ARVC. Only patients with severe RV dysfunction, LV dysfunction and not-well tolerated monomorphic or polymorphic VAs receive an ICD. This is translated into the 1% proportion of ICD carriers at baseline and in the lower event-rate during follow-up. Therefore, our study adds evidence for the clinical utility of the ARVC risk score and

threshold selection, particularly in patients without an ICD, who are likely to represent a growing body of ARVC patients.

Limitations to the present work include 1) a relatively small population and number of events, especially in the low- to intermediate-risk groups, which warrants caution regarding survival estimates in these subgroups and precluded valid multivariable analyses including the risk model variables, 2) similar demographical characteristics than the original study's population, with a high prevalence of male sex and *PKP2* mutations, limiting the benefits of this study regarding generalization to the variety of arrhythmogenic cardiomyopathy phenotypes and 3) the availability of electrophysiological study results in a very small number of patients, which hampered the performance of 2019 HRS expert consensus Class IIa&IIb criteria and prevents face-to-face comparision of the latter to the ARVC risk model in our population.[1]

Overall, applied to a single-center cohort of patients with ARVC and no VA history, the ARVC risk score identified ARVC patients with VA during follow-up, which further reinforces its clinical utility. However, use of the model led to risk overestimation in most low- to intermediate-risk patients, which underlines the need for careful threshold selection.

Figure Legends

Figure 1. A. Kaplan-Meier representation of ventricular arrhythmia (VA)-free survival in our population. The population was divided according to their predicted 5-year VA risk by the ARVC risk score. **B.** Outcomes of patients based on the VA-risk predicted by the ARVC risk model. Ratio of implantable cardioverter-defibrillator (ICD) to VA (ICD:VA) was defined as: (number of patients with an ICD)/(number of patients with VA and an ICD). Protection rate was defined as : 100*[(Total number of patients) – (n° of patients with VA and an ICD) / (Total number of patients)].

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Supplemental Material

Supplemental Figure 1. Receiving operator channel curve of the ARVC risk score to predict the 5-year-risk of ventricular arrhythmia occurrence in an external cohort. The C-index is 0.84 (95% confidence interval (0.74–0.93)

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*: these authors contributed equally.

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Address for correspondence:

Dr. Mikael Laredo

Institut de Cardiologie, Groupe Hospitalier Pitié-Salpêtrière,

47-83 boulevard de l'Hôpital, 75013 Paris, France.

Email : mik.laredo@gmail.com Phone: +33 1 42 16 30 54; Fax: +33 1 42 16 30 56

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Supplemental Material

Supplemental Figure 1. Receiving operator channel curve of the ARVC risk score to predict the 5-year-risk of ventricular arrhythmia occurrence in an external cohort. The C-index is 0.84 (95% confidence interval (0.74–0.93)

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Table: Baseline clinical characteristics.

Characteristics	**Overall (n=115)**	**No sustained VA (n=100)**	**Sustained VA (n=15)**	**P-value**
Age at diagnosis, years	38.2 (27.6-49.9)	39.3 (28.6-50.7)	29.5 (21.4-39.5)	0.10
Male sex	84 (73)	70 (70)	14 (93)	0.11
Proband	88 (77)	76 (76)	12 (80)	0.73
Definite ARVC diagnosis	115 (100)	100 (100)	15 (100)	
Pathogenic mutation*	37 (34)	28 (30)	9 (69)	0.02
PKP2	24**	17	7	
DSG2	8**	6	2	
DSP	4	3	0	
DSC2	1	1	0	
History of cardiac syncope	23 (20)	16 (16)	7 (47)	0.01
TWI in the inferior and/or anterior ECG leads	30 (26)	20 (20)	10 (67)	0.0003
Non-sustained VT	44 (38)	23 (20)	10 (67)	0.02
24-h PVC count, n	750 (33-2291)	750 (24-2345)	1200 (750-7905)	0.13
RVEF, %	50 (44-50)	50 (44-50)	40 (38-50)	0.003
LVEF, %	60 (55-65)	60 (56-66)	56 (52-62)	0.04
Treatment at baseline				
ICD	1 (0.9)	1 (1)	0 (0)	-
Beta-blockers	77 (67)	68 (68)	9 (60)	0.58
Sotalol	10 (9)	7 (7)	3 (20)	0.26
Flecainide	44 (38)	35 (35)	9 (60)	0.16
Amiodarone	3 (3)	1 (1)	2 (13)	0.07

Data are n (%) or median (IQR). *among 106 patients. **including 1 patient with double *DSG2* and PKP2 pathogenic mutation.

Abbreviations: ARVC: arrhythmogenic right ventricular cardiomyopathy; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; PVC: premature ventricular complex; RVEF: right ventricular ejection fraction; VT: ventricular tachycardia.

Figure

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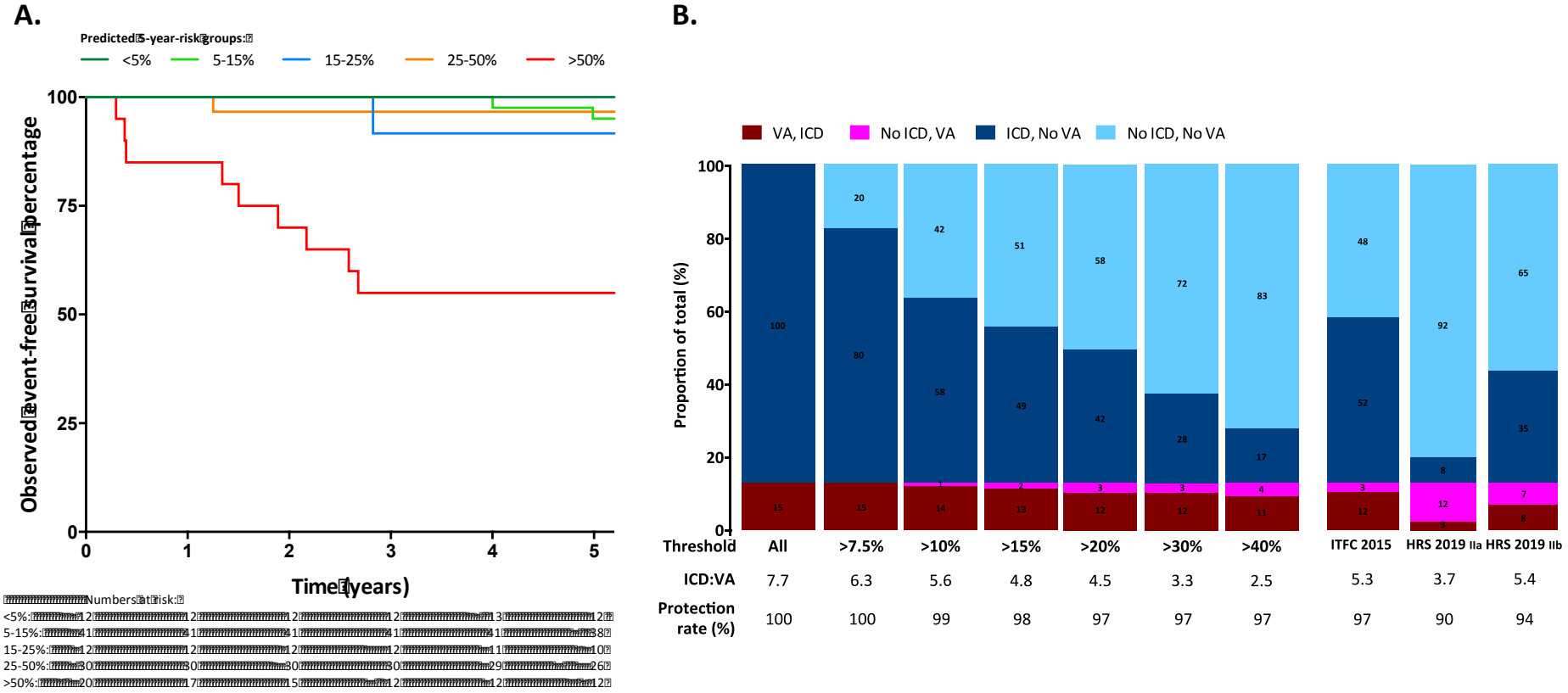

Supplementary Figure S1