Prediction of ventricular arrhythmia in phospholamban p.Arg14del mutation carriers–reaching the frontiers of individual risk prediction

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Aims	This study aims to improve risk stratification for primary prevention implantable cardioverter defibrillator (ICD) implantation by developing a new mutation-specific prediction model for malignant ventricular arrhythmia (VA) in phospholamban (*PLN*) p.Arg14del mutation carriers. The proposed model is compared to an existing PLN risk model.
Methods and results	Data were collected from *PLN* p.Arg14del mutation carriers with no history of malignant VA at baseline, identified between 2009 and 2020. Malignant VA was defined as sustained VA, appropriate ICD intervention, or (aborted) sudden cardiac death. A prediction model was developed using Cox regression. The study cohort consisted of 679 *PLN* p.Arg14del mutation carriers, with a minority of index patients (17%) and male sex (43%), and a median age of 42 years [interquartile range (IQR) 27–55]. During a median follow-up of 4.3 years (IQR 1.7–7.4), 72 (10.6%) carriers experienced malignant VA. Significant predictors were left ventricular ejection fraction, premature ventricular contraction count/24 h, amount of negative T waves, and presence of low-voltage electrocardiogram. The multivariable model had an excellent discriminative ability {*C*-statistic 0.83 [95% confidence interval (CI) 0.78–0.88]}. Applying the existing PLN risk model to the complete cohort yielded a *C*-statistic of 0.68 (95% CI 0.61–0.75).

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Conclusion   This new mutation-specific prediction model for individual VA risk in *PLN* p.Arg14del mutation carriers is superior to the existing PLN risk model, suggesting that risk prediction using mutation-specific phenotypic features can improve accuracy compared to a more generic approach.

Graphical Abstract
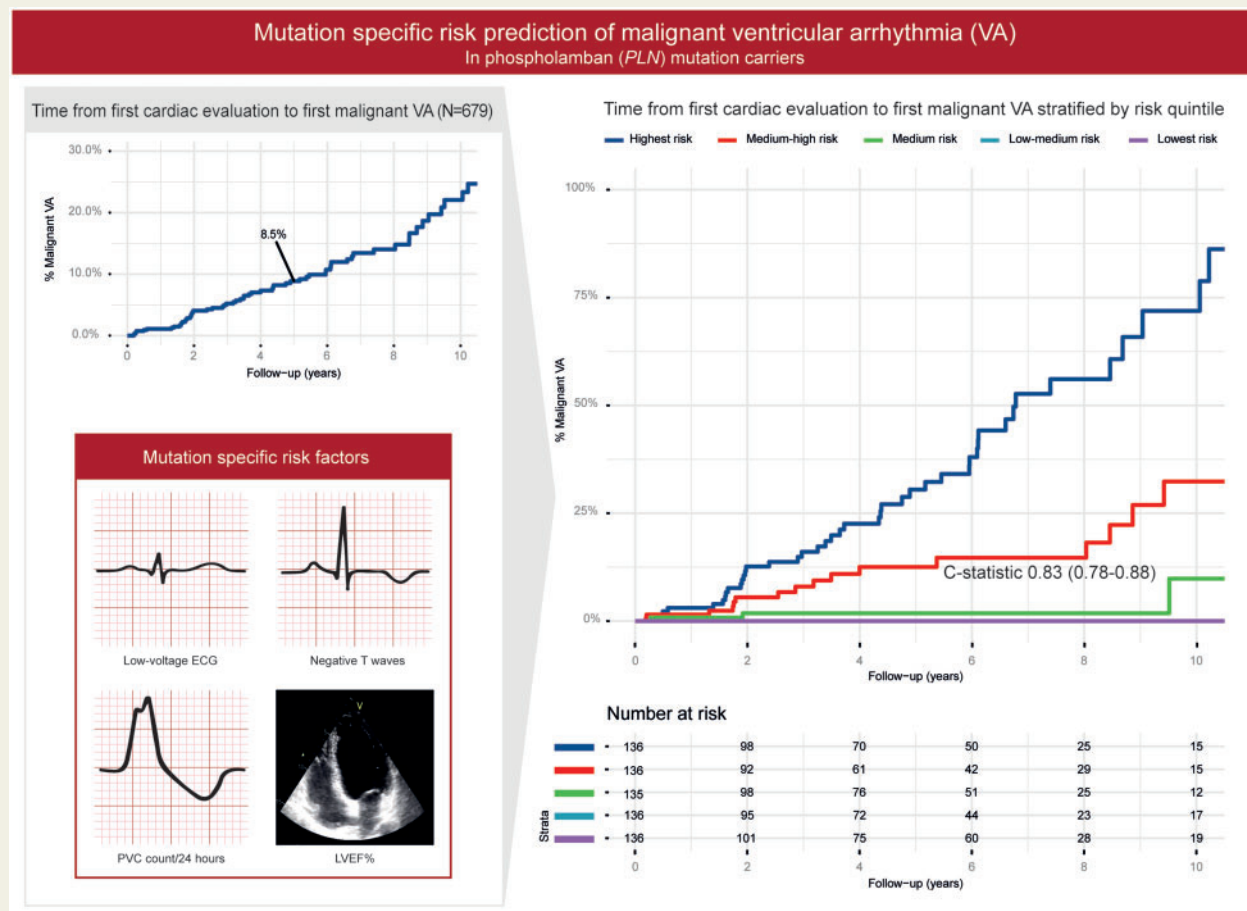
Malignant VA risk prediction in PLN p.Arg14del carriers. With the mutation specific risk factors low and high risk groups can be identified. PLN, Phospholamban; VA, Ventricular arrhythmia.

Introduction

Hereditary cardiomyopathies are a leading cause of sudden cardiac death (SCD) in young adults.[1] In the past years, substantial progress has been made in elucidating the genetic variants that contribute to the development of cardiomyopathy. Predominantly, alterations in genes coding for cytoskeletal, sarcomeric, desmosomal, and Z-disk proteins were found to be associated with the development of cardiomyopathy. Furthermore, variants in genes encoding calcium modulators are known to be associated with cardiomyopathies,[2] including the gene encoding phospholamban (*PLN*), a protein essential for calcium homeostasis. Multiple pathogenic *PLN* variants are associated with the development of cardiomyopathy.[3–8] The pathogenic variant in *PLN*, which has been studied most extensively, is c.40-42delAGA;p.Arg14del,[9] which leads to a deletion of arginine 14 in the coding region of *PLN* and is associated with both dilated cardiomyopathy (DCM) and arrhythmogenic right ventricular cardiomyopathy (ARVC).[10] This variant has been found in several European countries, the USA, Canada, and China[11–13] and is one of the most prevalent single cardiomyopathy-related gene alterations in the world, in particular in the Netherlands.[14] The p.Arg14del variant in PLN is characterized by a low-voltage electrocardiogram (ECG), repolarization abnormalities, development of cardiomyopathy, end-stage heart failure, ventricular arrhythmias (VA), and premature

death. Affected individuals have a poor prognosis and high mortality from late adolescence onwards.[4,10]

Previously, two risk factors were identified that contribute to the prediction of malignant VA in p.Arg14del mutation carriers, i.e. left ventricular ejection fraction (LVEF <45%) and occurrence of sustained or non-sustained VA.[10] These risk factors appeared to be more accurate than the general DCM criteria for primary prevention implantable cardioverter defibrillator (ICD) implantation.[15] However, these risk factors were explored in a mixed cohort of carriers with and without sustained VA at baseline. Furthermore, the sensitivity and specificity of the identified risk factors remained limited and accurate quantification of individual risk is not possible. In addition to this *PLN* p.Arg14del specific risk model, an ARVC risk model for the prediction of malignant VA was recently published, designed to guide primary prevention ICD implantation in ARVC patients fulfilling the 2010 Task Force criteria.[16] This model might also be valid in all p.Arg14del carriers as carriers can develop an ARVC phenotype.

This multicentre cohort study aims to improve risk stratification for primary prevention ICD implantation by developing a new prediction model for sustained VA in p.Arg14del mutation carriers without previous sustained VA. The proposed model will be compared to the existing *PLN* and ARVC models.

Methods

Study design

The prediction model was developed using data from a retrospective multicentre longitudinal cohort study and reported according to the TRIPOD statement.[17] The study conformed to the principles of the Helsinki declaration. Design of the registry and collected variables were published earlier.[18]

Study population

The study cohort consists of index patients and relatives in whom the pathogenic p.Arg14del variant was identified for diagnostic purposes or cascade screening after genetic counselling in three Dutch University Hospitals and one Spanish University Hospital, between 2009 and May 2020. Genetic analysis of *PLN* was performed in index patients with clinical characteristics and family history or area of birth suggestive for a pathogenic *PLN* variant. Genetic analysis and counselling were also offered to relatives who were at risk of being p.Arg14del mutation carriers.

Data collection

All data were collected via chart review from first clinical contact to last follow-up with a cardiologist or clinical geneticist. All data were entered in electronic case report forms in compliance with good clinical practice. Follow-up was performed in both university and non-university hospitals. Baseline was defined as first-ever clinical contact and follow-up ended at the last available cardiology department visit. Data within 1 year of first clinical contact were considered baseline data.

Clinical outcomes

The primary outcome is malignant VA, defined as a composite endpoint of sustained ventricular tachycardia (VT), ventricular fibrillation (VF), appropriate ICD intervention, or (aborted) SCD. Sustained VT is defined as a VT which lasts ≥30 s, or <30 s when terminated electrically or pharmacologically. Appropriate ICD intervention is classified as ICD therapy (antitachycardia pacing or shock) for VF/VT. Aborted SCD is defined as basic life support for cardiac arrest with return of stable circulation. SCD is defined as death (with or without documented VF) within 1 h of acute symptoms or an unexplained death with no antecedent history of worsening symptoms. Carriers were censored if one of the endpoints occurred.

Predictor variables

Possible predictor variables were based on predictors for malignant VA in ARVC and DCM because p.Arg14del mutation carriers may display both ARVC or DCM phenotypes. Furthermore, possible predictors from the 2014 PLN p.Arg14del cohort study were included as possible predictors.[10] All prespecified predictors and their definitions are displayed in Supplementary material online, *Table S1*. The final number of predictors chosen was based on the number of events, with a 10:1 ratio of events per considered predictor.

Missing data

As a result of the retrospective design, there were absence of diagnostic protocols and in some cases lack of clinical evaluation resulting in multiple variables with missing data. Missing data were considered missing at random and accounted for by multiple imputation. Imputation models for left and right ventricular ejection fraction included the qualitative assessment of ejection fraction. A total of 100 imputed datasets were generated.

Statistical analysis

SPSS Version 24.0.0.1 (IBM Corp., Armonk, NY, USA), R version 3.5.1, and RStudio Version 1.1.383 (RStudio, Boston, MA, USA) with packages rms, survminer, riskRegression, and mice were used for analysis. Continuous variables are expressed as mean ± standard deviation (SD) if normally distributed; median ± interquartile range (IQR) of 25–75% is used if the data were skewed. Categorical variables are reported as percentages (counts/total counts). Cox proportional hazards models were used to evaluate the effect of possible predictors while taking the time to event into account. To correct for family clustering, a frailty term for family id was used. Proportional-hazard assumptions were verified as well as linearity of the association for continuous predictors. The model was fitted using stepwise backward selection based on Akaike's Information Criterion (AIC) where, in each step, candidate predictors that do not significantly lead to information loss of the model when deleted, e.g. significant difference in AIC value, were deleted. Stepwise selection was performed in each imputed dataset, where the final model consisted of variables selected in >50% of datasets. Results were pooled using Rubin's rules. Discrimination of the model was described with Harrell's *C*-statistic. Apparent *C*-statistic was estimated by fitting the final model on the original data. The model was internally validated using bootstrap sampling, 1000 bootstraps, to correct for overfitting. Predicted and observed outcomes were graphically evaluated with a calibration plot. Universal shrinkage factors were estimated using the calibration slope of the linear predictor. The ARVC model was applied to the complete PLN p.Arg14del cohort, regardless of phenotype, as carriers may display an ARVC (-like) phenotype and risk prediction with the ARVC model might be suitable for all PLN p.Arg14del carriers. Further details on model presentation, comparison to existing models and clinical utility methods can be found in the Supplementary material online.

Results

Study cohort

The final study cohort consists of 679 p.Arg14del mutation carriers (*Figure 1*). Most of the excluded carriers were only genetically counselled at participating centres without any cardiologic data available.
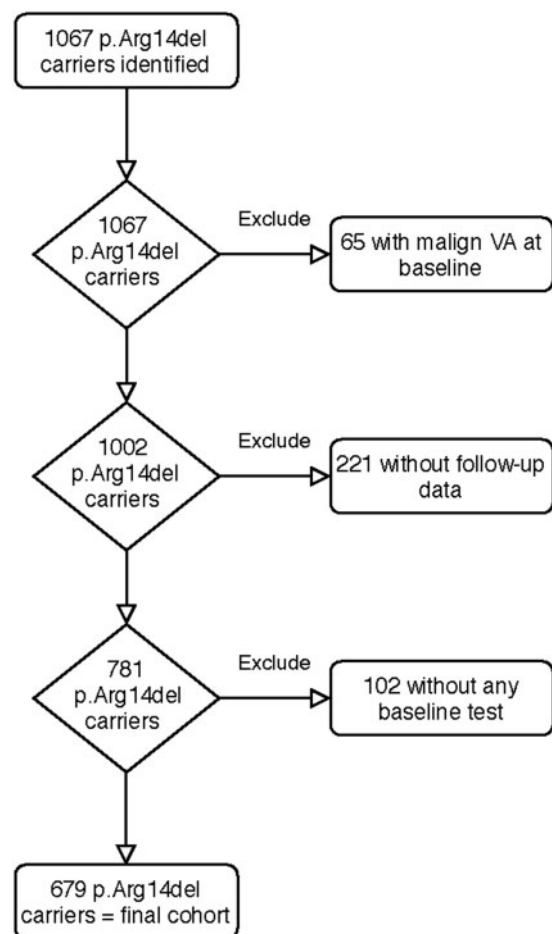
Figure 1 Flowchart of participant inclusion in the study. Diagram summarizing the inclusion and exclusion of study participants carrying the pathogenic *PLN* p.Arg14del variant. A baseline test should include at least an electrocardiogram, cardiac ultrasound, or magnetic resonance imaging. VA, ventricular arrhythmia.

Table 1 Baseline characteristics

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p.Arg14del mutation carriers, *n*	679
Demographics	
Age at presentation (years)	42 (27-55)
Male sex	294 (43)
Caucasian ethnicity	679 (100)
Proband	113 (17)
History	
Cardiac syncope <6 months before presentation	4 (0.6)
NYHA class ≥ II	62 (9)
1st degree family member with malignant VA	91 (13)
Presentation reason: family screening vs. symptomatic or abnormal test result	574 (85)
Fulfilment of 2010 ARVC TFC at baseline	28 (4)
ECG/continuous rhythm monitoring	
Atrial fibrillation/flutter	56 (8)
Low-voltage ECG (*n* = 618)	95 (15)
TWI in ≥3 precordial leads (*n* = 559)	77 (14)
TWI in ≥2 inferior leads (*n* = 559)	49 (9)
NSVT	67 (10)
24 h PVC count >500 (*n* = 406)	125 (31)
Imaging	
LVEF <45% (*n* = 627)	105 (17)
Median LVEF (%) (*n* = 532)	54 (48-58)
RV dysfunction (*n* = 608)	62 (10)
Median RVEF (%) (*n* = 254)	50 (45-55)
LGE on MRI (*n* = 262)	77 (29)

Values are given as *n* (%) or median (interquartile range).
ECG, electrocardiogram; LGE, late gadolinium enhancement; LVEF, left ventricular ejection fraction; MRI, magnetic resonance imaging; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; RV, right ventricular; RVEF, right ventricular ejection fraction; PVC, premature ventricular contraction; TFC, Task Force criteria; TWI, T-wave inversion; VA, ventricular arrhythmia.

Twenty (3%) of the 679 carriers were Spanish. The majority of the final cohort (83%) were family members of an index patient and most subjects were asymptomatic at baseline (85%). Almost half were male (43%), and the median age was 42 years (IQR 27–55). At baseline, only 10 (1%) already had an ICD, or received an ICD within 1 month. Finally, 28 (4%) p.Arg14del mutation carriers had an ARVC diagnosis by the Task Force criteria at baseline. Baseline characteristics are shown in *Table 1*.

Outcomes

During a median follow-up of 4.3 years (IQR 1.7–7.4), 72 (10.6%) p.Arg14del mutation carriers experienced the composite endpoint of malignant VA, with a crude event rate of 2.0% per year. The Kaplan–Meier estimate of 5-year event rate was 8.5% [95% confidence interval (CI) 6–11%], with events occurring throughout follow-up (*Figure 2*).

The primary composite outcome of malignant VA consisted of 37 appropriate ICD therapies, 25 sustained VT/VF, 6 SCD, 3 aborted

SCD, and 1 VT storm. Arrhythmia characteristics were available in 51/72 (71%), of which 48/51 (94%) were sustained VT >190 b.p.m., VF, or (aborted) SCD. Arrhythmia characteristics are reported in Supplementary material online, *Table S2*. During follow-up, 148 patients received an ICD for primary or secondary prevention. At the end of follow-up, 44 (6%) p.Arg14del mutation carriers had died, 37 of a cardiac cause and 7 of a non-cardiac cause. Of the cardiac deaths, 25 were due to heart failure, 10 were due to SCD, and 2 were due to miscellaneous causes (after valve replacement procedure and left ventricular assist device failure). Characteristics of the patients with SCD are given in Supplementary material online, *Table S3*. Heart transplantation was performed in 17 carriers, and 12 received a left ventricular assist device.

Model development

Each predictor was tested for linearity with the martingale residuals (diagnostic plots depicted in Supplementary material online, *Figure S1*). For 24-h premature ventricular contraction (PVC) count, the log linear conversion performed the best. T-wave inversion was used as a continuous variable, where the amount of precordial and inferior
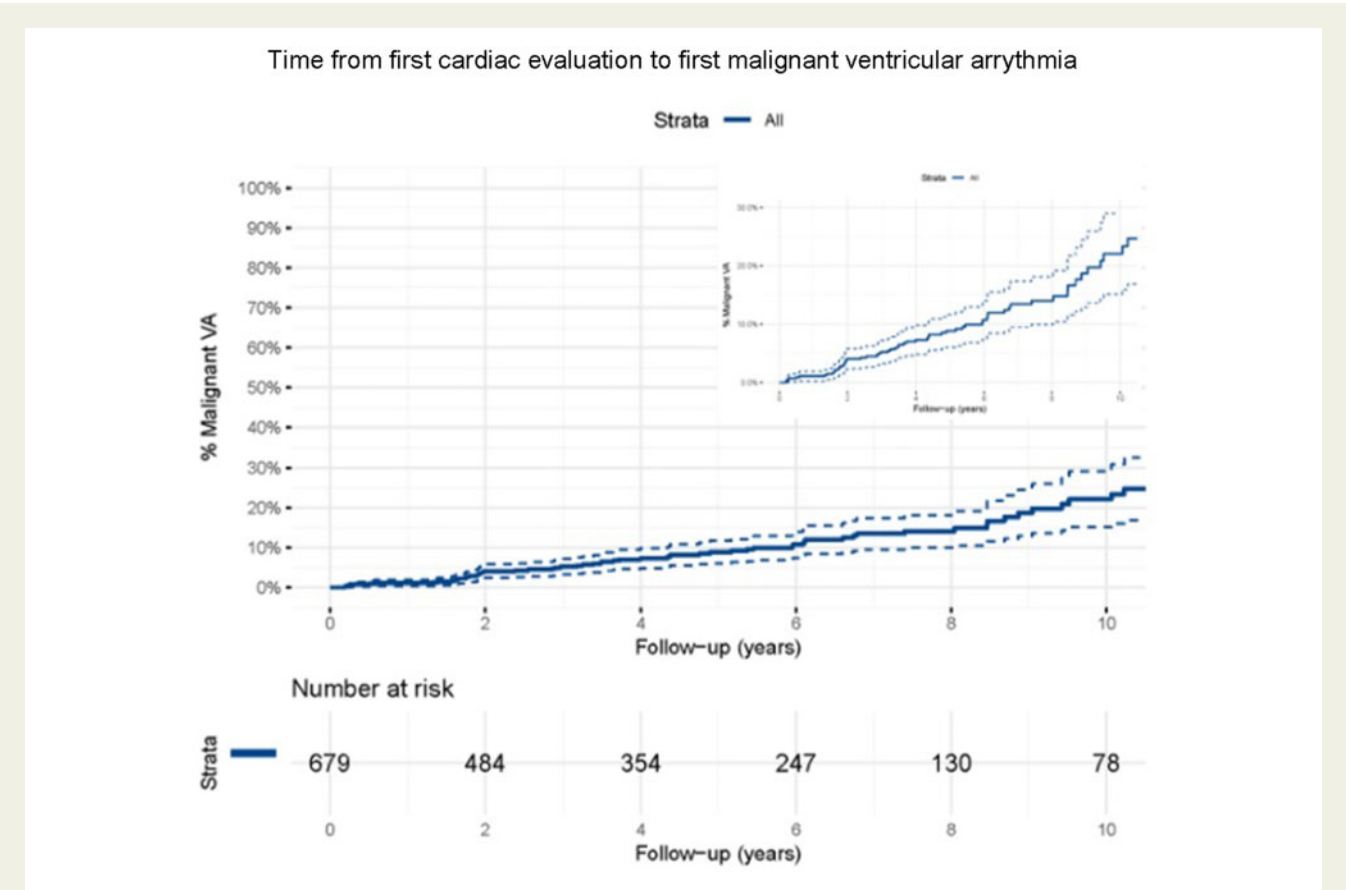
Figure 2 Survival analyses. Kaplan–Meier analysis with percentage of carriers with malignant ventricular arrhythmia (*y*-axis) and follow-up duration in years (*x*-axis). Upper right side is the Kaplan–Meier curve where the y-axis is zoomed in from 0-30%. VA, ventricular arrhythmia.

Table 2 Univariable hazard ratios of pre-specified predictors and multivariable hazard ratios of the predictors in the final model after backwards stepwise selection
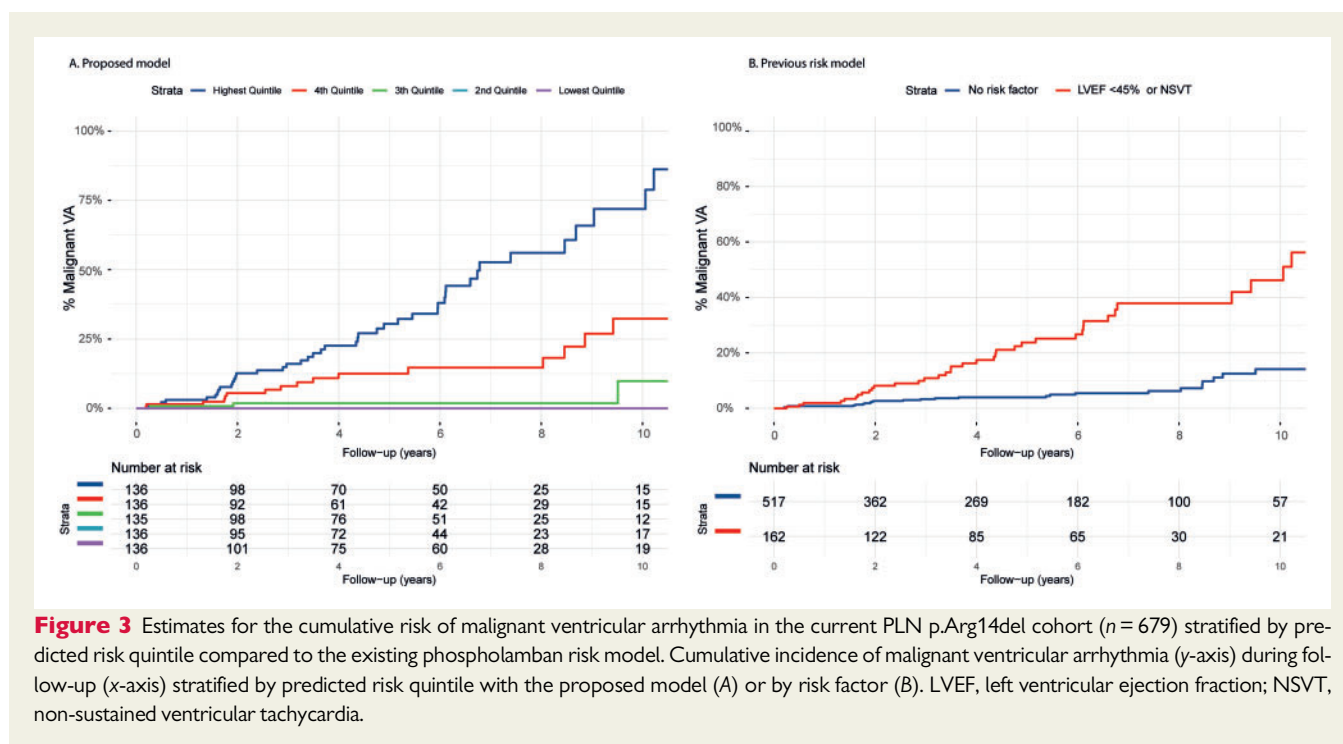
	Univariable			Multivariable		
	HR	95% CI	*P*-value	HR	95% CI	*P*-value
NYHA class ≥II	4.0	2.4-6.8	<0.001	–	–	–
Negative T waves inferior or precordial (per 1 increase)	1.2	1-1.3	0.007	1.1	0.98-1.2	0.11
Low-voltage ECG	3.9	2.3-6.6	<0.001	1.8	1.0-3.4	0.043
Prior NSVT	1.5	0.77-2.8	0.25	–	–	–
24 h PVC count (per 1 log increase)	1.5	1.3-1.7	<0.001	1.4	1.2-1.6	<0.001
LVEF (per 1% decrease)	1.08	1.05-1.09	<0.001	1.04	1.01-1.06	<0.001
RV dysfunction	4.9	2.6-9	<0.001	–	–	–

Hazard ratios were corrected for family clustering using a frailty model.
CI, confidence interval; ECG, electrocardiogram; HR, hazard ratio; LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia; NYHA, New York Heart Association; RV, right ventricular; PVC, premature ventricular contraction.

leads with T-wave inversion was counted. With 72 events, 7 candidate predictors were considered for the multivariable model, chosen from different diagnostic domains. Univariable hazard ratios of these pre-specified predictors and multivariable hazard ratios of the predictors selected in the final model are reported in *Table 2*. Univariable hazard ratios of all predictors are shown in Supplementary material online, *Table S4*. New York Heart Association class and right ventricular dysfunction are significant univariable predictors but are not selected for the multivariable model as their exclusion from the model does not significantly decrease the performance of the model. Final selected predictors are number of negative T waves, presence of low-voltage ECG, PVC count/24 h, and LVEF. The risk formula of

Figure 3 Estimates for the cumulative risk of malignant ventricular arrhythmia in the current PLN p.Arg14del cohort (*n* = 679) stratified by predicted risk quintile compared to the existing phospholamban risk model. Cumulative incidence of malignant ventricular arrhythmia (*y*-axis) during follow-up (*x*-axis) stratified by predicted risk quintile with the proposed model (*A*) or by risk factor (*B*). LVEF, left ventricular ejection fraction; NSVT, non-sustained ventricular tachycardia.

the final model can be found in the Supplementary material online. With the final multivariable model, we calculated the predicted 5-year malignant VA risk of each carrier in the dataset. After dividing the population into quintiles of predicted risk, a clear distinction in risk between the risk groups is shown in *Figure 3* with the lowest risk quintiles having a very low malignant VA rate.

Model validation

Internal validation with bootstrapping resulted in an optimism corrected *C*-statistic of the final model of 0.83 (95% CI 0.78–0.88), corresponding to a strong model. Visualization of calibration is represented in Supplementary material online, *Figure S2*. Agreement between predicted and observed 5-year malignant VA risk was excellent. With bootstrapping we calculated a calibration slope of 0.913.

Performance of existing risk models

Applying the previous PLN risk model in the current cohort yielded a *C*-statistic of 0.68 (95% CI 0.61–0.75). *C*-statistic of the proposed model was significantly higher (delta 0.11, *P* = 0.002). Applying the ARVC risk model to the complete current cohort of p.Arg14del mutation carriers regardless of ARVC diagnosis yielded a *C*-statistic of 0.74 (95% CI 0.68–0.80). *C*-statistic of the proposed model was significantly higher (delta 0.07, *P* = 0.006). Although more patients had right and left ventricular involvement, only a fraction of carriers had a Task Force-compatible ARVC diagnosis at baseline, and therefore, these results are probably not surprising; further results on the comparison with the ARVC model are provided in Supplementary material online, *Figures S3 and S4*. Calibration is shown in Supplementary material online, *Figure S2*, and high- and low-risk groups can be

distinguished; however, calibration was not ideal with comparable observed outcomes in the medium-high- and high-risk quintiles.

Clinical utility

We explored scenarios where ICD implantation is based on the outcome of the prediction models. *Figure 4* shows carriers with a predicted risk greater than the risk threshold that would be implanted with an ICD. As visualized, the proposed model leads to less false positives (ICD, no VA) or false negatives (No ICD, VA) compared to the existing PLN model. For example, by applying the proposed model to the study cohort (*n* = 679) with a risk threshold of >10% would result in 161 carriers receiving an ICD, with 42 having a malignant VA compared to 162 carriers with ICD, with 37 having a malignant VA with the existing model. Additionally, we compared diagnostic performance (e.g. sensitivity/specificity) of the risk models and potential cut-offs in Supplementary material online, *Table S5*. Not surprisingly, diagnostic performance was heavily dependent on the chosen risk threshold. Sensitivity and specificity of the previous PLN model was 66.1% and 80%, respectively. Sensitivity and specificity of the proposed model ranged from 58.9% to 98.2% and 53.9% to 88.1%, depending on the risk threshold.

With the proposed risk model, several risk thresholds seem viable and factors other than malignant VA risk should be considered when deciding on a threshold for an individual patient. However, if one would adhere to the generally accepted risk threshold >5% in 5 years (i.e. 1%/year) to justify implantation of an ICD,[19] the proposed model would result in 246 carriers being treated with an ICD, with 52 of them experiencing a malignant VA. Even more relevant, this risk threshold would result in 4 false negatives, while 433 ICD implantations are avoided compared to treating all carriers. Individual risk

prediction can be made with an online calculator available at https://plnriskcalculator.shinyapps.io/final_shiny/ or nomogram (*Figure 5*).

Discussion

Main findings

While the event rate of incident malignant VA is significant in individuals with the *PLN* p.Arg14del variant, over 90% remain event-free at 5 years. Therefore, risk stratification is needed before ICD implantation to avoid unnecessary ICD implantations while protecting the majority of carriers from SCD (*Graphical abstract*).

In this study, we developed and internally validated a new prediction model for malignant VA in *PLN* p.Arg14del mutation carriers without prior malignant VA. Discriminative ability was excellent and calibration was adequate with agreement between predicted and observed risk (Supplementary material online, *Figure S2*). Using the proposed model is superior to using the existing models with a significantly higher discriminative ability (*C*-statistic) and less false positives or false negatives demonstrated in the scenario analyses. This suggests that a mutation-specific prediction model improves performance for this mixed phenotype population of *PLN* p.Arg14del mutation carriers, compared to applying phenotypic driven models for DCM and ARVC to all PLN p.Arg14del mutation carriers. For DCM, no direct comparison was made as the existing *PLN* p.Arg14del model has LVEF <45% as risk factor; thus, the comparison with the DCM model with LVEF <35% as risk factor was deemed redundant. The proposed model has more selected predictors than the previous *PLN* model. Adding PVC count, amount of negative T waves, and presence of low-voltage ECG as predictors can account for the increased model performance with the proposed model. The greatest clinical utility of this model lies in the individual estimations of 5-year risk derived with the nomogram or online calculator. While the acceptable risk threshold for an individual patient is also dependent on other factors, such as the country's health system, shared decision-making, and non-SCD mortality risk, we suggest that a 5-year malignant VA risk of >5% should be the minimum to consider ICD therapy. Above this risk threshold, ICD implantation can be considered, with stronger recommendation with increasing predicted risks. Moreover, with a lower risk threshold, ICD harm probably outweighs ICD benefit given the fact that previous studies in inherited cardiomyopathies have shown a significant burden of ICD-related complications (27%) or inappropriate shocks (14%) in ICD-treated patients.[20]

Prior studies

Event rate of malignant VA was lower in this study compared to the 2014 p.Arg14del cohort of the previous model (crude annual rate 2% vs. 5.4%).[10] We hypothesize ascertainment bias playing a role, with increasing inclusion of asymptomatic family members, 85% in this study vs. 58% in the previous report.[21] In addition, we excluded carriers with malignant VA at baseline who are more likely to develop new malignant VA. Malignant VA rate was also lower than the ARVC risk model cohort (2.0% vs. 5.6% annual event rate).[22] This was expected as included patients in the ARVC cohort were generally more severely affected because they had to fulfil the strict 2010 Task Force criteria.[23] Risk stratification models have proven to be useful
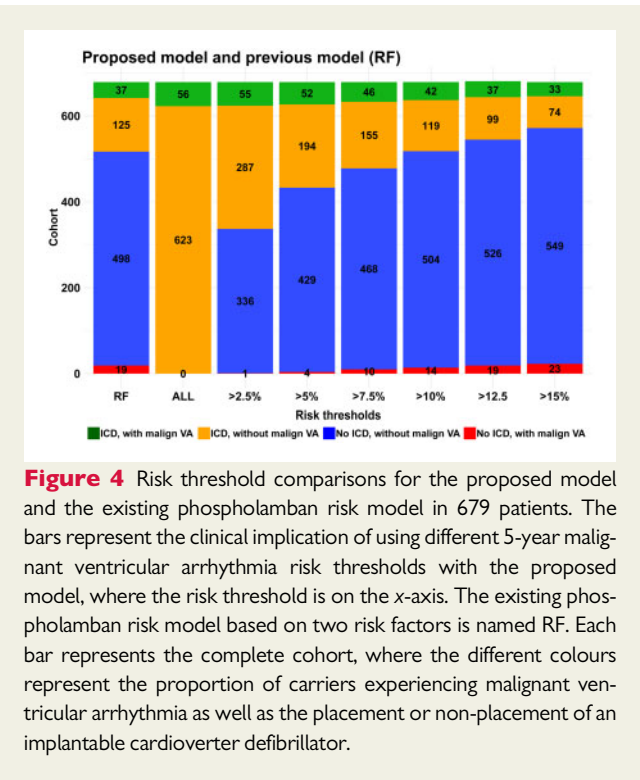

Figure 4 Risk threshold comparisons for the proposed model and the existing phospholamban risk model in 679 patients. The bars represent the clinical implication of using different 5-year malignant ventricular arrhythmia risk thresholds with the proposed model, where the risk threshold is on the *x*-axis. The existing phospholamban risk model based on two risk factors is named RF. Each bar represents the complete cohort, where the different colours represent the proportion of carriers experiencing malignant ventricular arrhythmia as well as the placement or non-placement of an implantable cardioverter defibrillator.

clinical tools for arrhythmic risk prediction in hypertrophic cardiomyopathy (HCM) and ARVC.[16,24] Discriminative ability of the proposed model was at least similar to these tools, with a *C*-statistic of 0.83 vs. 0.70 and 0.77 of the HCM and ARVC models, respectively. Earlier research demonstrated gene and mutation-specific differences in disease manifestation and age-related penetrance.[25] We hypothesize that gene- or maybe even mutation-specific risk stratification, whenever possible, is a potential superior approach.

Limitations and future directions

The prediction model is not suited for patients <16 years old because of the natural evolution of T waves during childhood. In addition, using our mutation-specific approach, it is uncertain that this risk model is suitable for other PLN variants as they might develop different phenotypes. Due to the retrospective design, not all patients were evaluated or treated based on a standardized protocol. In some patients, first contact with a cardiologist preceded the genetic diagnosis. Currently, all newly identified carriers will undergo extensive testing but in the early days, in some patients even before the discovery of *PLN* p.Arg14del as a pathogenic mutation, not all tests would have been considered as we do today, resulting in missing data. For instance, the amount of data on the presence of late gadolinium enhancement (LGE) was insufficient to consider it as a predictor for the main analysis. In a sub-analysis, presence of LGE was a univariable significant predictor of malignant VA (hazard ratio 9.6, 95% CI 3.1–29.0, *P* < 0.001). However, LGE was not selected for the multivariable model as leaving LGE out of the model did not decrease model performance significantly, likely because of significant overlap of predictive ability with other predictors such as low-voltage ECG and LVEF. In a future iteration of the prediction model, LGE can be further
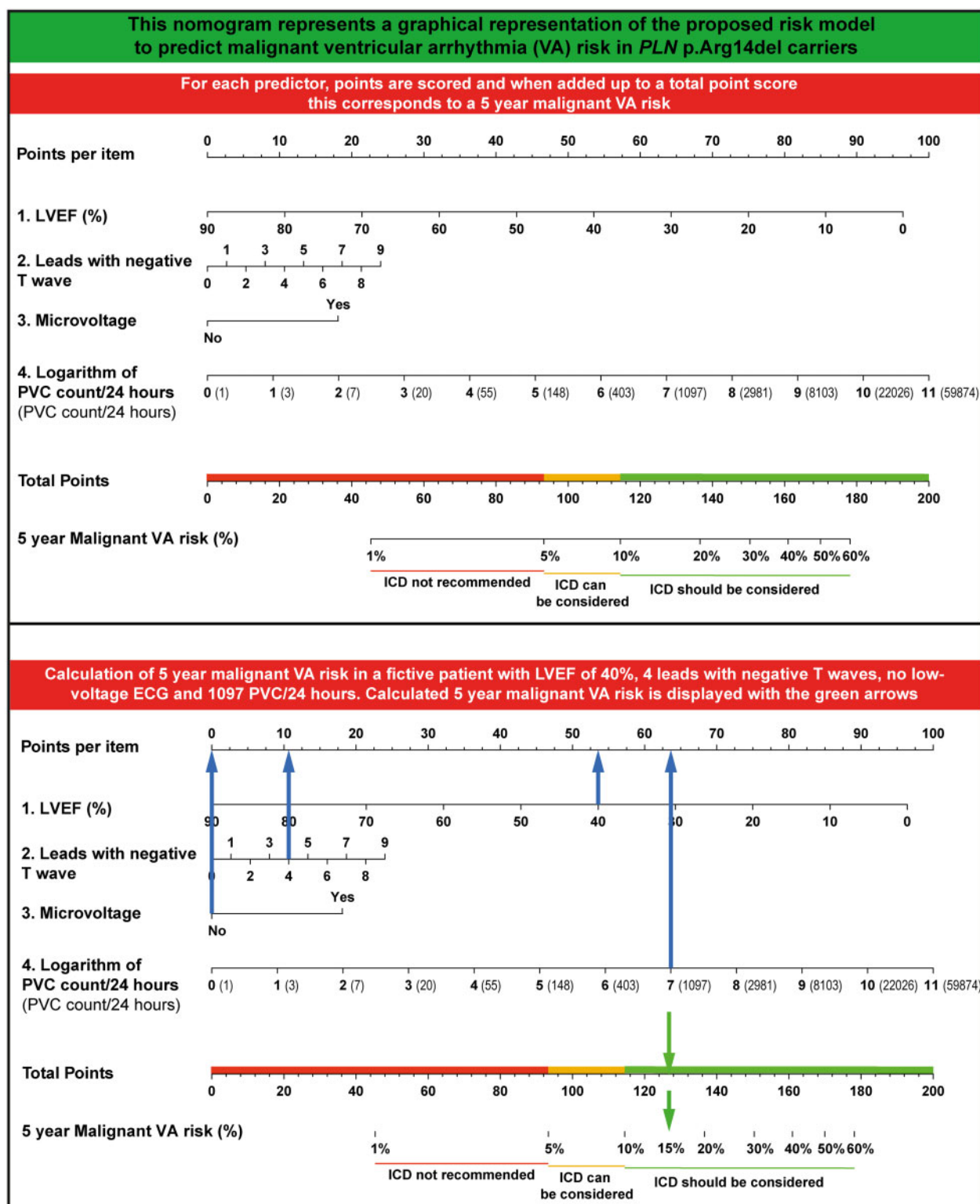
Figure 5 Nomogram to predict 5-year malignant ventricular arrhythmia risk.

evaluated and new predictors might be included, such as strain imaging.[26] We compared clinical characteristics of carriers with complete data vs. carriers with incomplete data to assess the impact of missing data on results. Clinical characteristics of the group with missing data were mostly similar to those of the group without missing data (Supplementary material online, *Table S6*). The only characteristic significantly different was the amount of negative T waves, which was higher in the group with incomplete data [1 (IQR 0–2) vs. 0 (IQR 0–1), *P* < 0.001].

True SCD risk is obscured by ICD implantation in the high-risk (deemed by the treating physician) group of the study cohort. However, removing ICD recipients from the cohort would not be a valid alternative. Firstly, this would lead to insufficient power, but more importantly would lead to new biases. Removing high-risk carriers from this cohort will lead to selection bias and underestimate true SCD risk. Similar issues pertain to other observational datasets where ICD implantation is performed, for example HCM or ARVC.[16,24] For PLN mutations carriers a randomized controlled trial is not feasible. This is why we considered the composite endpoint of malignant VA as a surrogate marker for SCD. While being a serious event, not all carriers experiencing malignant VA would suffer from SCD. This should be kept in mind when choosing the risk threshold. In order to assess robustness of the combined endpoint, we analysed whether predictor effects of ICD therapy were similar to predictors for the other malignant VA endpoints (Supplementary material online, *Table S7*). Similarly, we analysed if predictor effects were different for life-threatening VA [defined as VT >240 b.p.m., VF, or (aborted) SCD] compared to the other VA (Supplementary material online, *Table S8*). Univariable hazard ratios of selected predictors were mostly similar for appropriate ICD therapy vs. other VA, and life-threatening VA vs. other VA. Thus, VA risk prediction with this model is valid but the predicted risk of the model reflects all malignant VA and not only life-threatening VA or SCD. Nearly all carriers who experienced SCD had a significant decrease in LVEF, which can be explained by it being a major risk factor for malignant VA. However, this may also be an indication that malignant VA are more lethal in carriers with a reduced ejection fraction.

We compared the proposed model to the existing *PLN* risk model for phenotypes of DCM (not directly) and ARVC. Importantly, these models were developed in patients with a DCM or ARVC phenotype and were not designed for patients with a DCM or ARVC causing genotype without phenotype. This is one of the reasons why this study cannot be seen as an external validation of the DCM and ARVC models, but rather tested if the model might work for all p.Arg14del mutation carriers, regardless of phenotype. Comparison of the models with only DCM or ARVC positive patients was not possible, as the power was insufficient for these analyses. Finally, external validation of the prediction model is desirable; however, it would currently be challenging to find a large enough cohort.

Conclusion

Based on the largest cohort of *PLN* p.Arg14del mutation carriers, we present a new mutation-specific model for the prediction of individual malignant VA risk. The proposed model is superior to the existing

PLN risk model and will inform decision-making for primary prevention ICD implantation. Furthermore, this is a demonstration that risk prediction using mutation-specific phenotypic features can improve accuracy compared to a more generic approach.

Supplementary material

Acknowledgements

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Data availability

The data underlying this article cannot be shared due to the privacy of individuals who participated in the study. The data will be shared on reasonable request to the corresponding author.

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