Supplementary

TRIPOD Checklist: Prediction Model Development and Validation

Section/Topic	Item		Checklist Item	Page
Title and abstract				
Title	1	D;V	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted.	1
Abstract	2	D;V	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	3
Introduction				
Background and objectives	3a	D;V	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	5
	3b	D;V	Specify the objectives, including whether the study describes the development or validation of the model or both.	5
Methods				
Source of data	4a	D;V	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	6-7
	4b	D;V	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	6-7
Participants	5a	D;V	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres.	6-7
	5b	D;V	Describe eligibility criteria for participants.	6-7
	5c	D;V	Give details of treatments received, if relevant.	NA
Outcome	6a	D;V	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	6-8
	6b	D;V	Report any actions to blind assessment of the outcome to be predicted.	6-8
Predictors	7a	D;V	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	7-11
	7b	D;V	Report any actions to blind assessment of predictors for the outcome and other predictors.	7
Sample size	8	D;V	Explain how the study size was arrived at.	6-7 Supplementary method
Missing data	9	D;V	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	NA
Statistical analysis methods	10a	D	Describe how predictors were handled in the analyses.	7-11
	10b	D	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	7-11
	10c	V	For validation, describe how the predictions were calculated.	7-11
	10d	D;V	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	7-11
	10e	V	Describe any model updating (e.g., recalibration) arising from the validation, if done.	NA
Risk groups	11	D;V	Provide details on how risk groups were created, if done.	NA
Development vs. validation	12	V	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors.	7-11

https://dx.doi.org/10.21037/qims-20-1211

Results				
Participants	13a	D;V	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	12 Supplementary method
	13b	D;V	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	12 Table 1&2
	13c	V	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1
Model development	14a	D	Specify the number of participants and outcome events in each analysis.	12 Table 1 Figure1
	14b	D	If done, report the unadjusted association between each candidate predictor and outcome.	NA
Model specification	15a	D	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	12-14 Supplementary Table
	15b	D	Explain how to the use the prediction model.	12-14
Model performance	16	D;V	Report performance measures (with CIs) for the prediction model.	12-14, Table 3&4 Figure 2&3
Model-updating	17	V	If done, report the results from any model updating (i.e., model specification, model performance).	NA
Discussion				
Limitations	18	D;V	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	16
Interpretation	19a	V	For validation, discuss the results with reference to performance in the development data, and any other validation data.	14-16
	19b	D;V	Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence.	14-16
Implications	20	D;V	Discuss the potential clinical use of the model and implications for future research.	14-16
Other information				
Supplementary information	21	D;V	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Supplementary material
Funding	22	D;V	Give the source of funding and the role of the funders for the present study.	17

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V. We recommend using the TRIPOD Checklist in conjunction with the TRIPOD Explanation and Elaboration document.

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Method

Diagnosis protocol of calciphylaxis

Calciphylaxis diagnosis protocol was based on "Criteria for Diagnosis of Calciphylaxis" described in McCarthy et al. (11). One patient with risk factors and clinical conditions would receive multidisciplinary discussion including nephrology, dermatology, radiology, and pathology departments with experienced doctors.

In this study, we retrospectively reviewed our institutional datasets for patients with initial diagnosis of calciphylaxis. If one finally diagnosed as calciphylaxis, we included as calciphylaxis patients. If one with possible calciphylaxis but finally ruled out, we included as suspected calciphylaxis patients. Viscera calciphylaxis was not included in analysis. Finally, 32 patients were diagnosed according to reported diagnosis protocol(calciphylaxis) (11), and 15 patients were identified as suspected calciphylaxis from October 1, 2017, to November 30, 2019.

In the next step, we searched CT scan data involving lesion location. For example, if one patient had ulceration in right leg, we would find lower extremities non-contrast CT images in Picture Archiving and Communication Systems. All CT scan followed routine CT scan protocols. All images and masks were resampled to form isotropic voxels of unit dimension with 1 voxel corresponding to 1 mm^3 to ensure comparability. By centering the image at the mean with a standard deviation and re-charting the histogram to conform to $l \pm 3r$ (l: the average gray level within the VOI; r: the gray-level standard deviation), image normalization was realized.

Sample size consideration

For training, we used 70% (19 patients with 40 lesions) randomly chosen calciphylaxis patients and all CKD-non-calciphylaxis patients (41 patients with 82 patches) to form training cohort. To balance the case-to-noncase ratio as 1:1, we used SMOTE method to up-sample the calciphylaxis cases, which is a re-sampling technique commonly used in datasets. We applied 5-fold cross-validation on training data set to prove model performance. Eight features were selected after PCC and Relief, which making an event-per-predictor ratio >20. Therefore, we believed that there was no big concern on the overfitting issue of our model at this sample size.

For test, we used method introduced by Shein-Chung Chow and colleagues (19).

$$N_{\text{positive}} = N_{\text{negative}} = 2\left(\sigma \frac{z_{\alpha/2} + z_{\beta}}{\mu_{\text{positive}} - \mu_{\text{negative}}}\right)^2$$

where, N is the sample size for the validation group. Desired two-sided significance level of $\alpha = 0.05$ ($z_{\alpha/2}=1.96$) and power of $1-\beta = 95\%$ ($z_{\beta}=1.64$).

LR model: The sample sizes in the training groups were $n_{positive}= 82$(SMOTE) and $n_{negative}= 82$, with means of $\mu_{positive}=0.3927$ and $\mu_{negative}=0.6075$ respectively, and with a standard deviation of $\sigma=0.1369$. The minimum number of validation samples:

$$N_{\text{positive}} = N_{\text{negative}} = 2\left(\sigma \frac{z_{\alpha/2} + z_{\beta}}{\mu_{\text{positive}} - \mu_{\text{negative}}}\right)^2 \approx 11$$

SVM model: The sample sizes in the training groups were $n_{positive}= 82$(SMOTE) and $n_{negative}= 82$, with means of $\mu_{positive}=0.1688$ and $\mu_{negative}=0.8133$ respectively, and with a standard deviation of $\sigma=0.3948$. The minimum number of validation samples:

$$N_{\text{positive}} = N_{\text{negative}} = 2\left(\sigma \frac{z_{\alpha/2} + z_{\beta}}{\mu_{\text{positive}} - \mu_{\text{negative}}}\right)^2 \approx 10$$

Test dataset in our study included 18 calciphylaxis-positive and 20 calciphylaxis-negative lesions, which exceeded the minimum required sample sizes.

References

19. Chow S, Shao J, Wang H. Sample size calculations in clinical research. 2nd Ed. Chapman &Hall//CRC Biostatistics Series 2008.

 https://dx.doi.org/10.21037/qims-20-1211

Table S1 Features and coefficients of models

Features	Coef in model (SVM)	Coef in model (LR)
wavelet-LLH_glszm_GrayLevelVariance	1.330	1.187
wavelet-LLH_glcm_Imc2	2.930	2.524
wavelet-HLH_firstorder_Skewness	0.703	0.578
wavelet-HHH_glszm_LargeAreaLowGrayLevelEmphasis	0.594	0.316
original_firstorder_Kurtosis	-0.300	0.148
wavelet-LLL_firstorder_90Percentile	1.982	1.485
wavelet-LHH_firstorder_Median	3.460	2.168
wavelet-LLH_glcm_Imc1	–4.422	–3.164

Coef, coefficients.

Table S2 Results of Delong tests

ROC 1	ROC 2	p-value
LR	Bone scintigraphy	<0.01
LR	Plain radiograph	<0.01
SVM	Bone scintigraphy	0.02
SVM	Plain radiograph	<0.01

LR, Logistic Regression; SVM, Support Vector Machine; AUC, Areas under the ROC curves; ROC, Receiver operating characteristic.

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