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Preoperative Prediction Models for 30-Day All-Cause Mortality After Mitral Valve Repair in Dogs: A Single-Center Retrospective Cohort Study

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ABSTRACT

Background: Mitral valve repair (MVR) has emerged as a novel surgical intervention for dogs with myxomatous mitral valve disease (MMVD). However, no objective risk assessment method has been established for these cases.

Objectives: The primary aim of this study was to develop and evaluate preoperative prediction models for 30-day postoperative mortality in dogs undergoing MVR. The secondary aim was to assess the association between short-term predictive risk and long-term mortality following MVR.

Animals: A total of 2089 client-owned dogs with MMVD that underwent MVR between 2016 and 2023 were included.

Methods: This was a single-center retrospective cohort study. Preoperative variables including demographic data, routine blood test results, diagnostic imaging examination data, and medication history were selected as predictor candidates. Prediction models for 30-day all-cause mortality were developed using these variables and shrinkage estimation methods, and the model performances were evaluated. The association between the predicted probabilities and 2-year cumulative all-cause mortality was assessed using Cox proportional hazards analysis.

Results: The 30-day all-cause mortality rate after MVR was 4.9% (102/2089). The best preoperative prediction model for 30-day all-cause death demonstrated low-to-moderate discrimination abilities (c-statistics, 0.654) and good calibration performance (slope = 1.003; intercept = 0.007; E_{avg} = 0.002) in internal validation. The quartile grouping of the predicted 30-day all-cause mortality risk was associated with 2-year mortality.

Conclusions and Clinical Importance: The preoperative prediction model for short-term mortality in dogs undergoing MVR demonstrated acceptable predictive performance. The prediction model may provide an objective preoperative risk assessment in dogs undergoing MVR at this center.

Abbreviations: ACEi, angiotensin converting enzyme inhibitors; ACVIM, American college of veterinary internal medicine; APTT, activated partial thromboplastin time; CHF, congestive heart failure; CI, confidence interval; CKCS, Cavalier king Charles spaniels; Emax, peak velocity of early diastolic transmitral flow; LA/Ao, left-atrial to aortic ratio; LVIDDn, left ventricular end diastolic diameter normalized for body weight; MMVD, myxomatous mitral valve disease; MVR, mitral valve repair; Tbil, total bilirubin; TP, total protein; VHS, vertebral heart score.

Reo Tanoshima and Masami Uechi contributed equally to this article.

1 | Introduction

Canine myxomatous mitral valve disease (MMVD) is a highly prevalent and progressive disease in small breed middle-aged and older dogs [1]. Congestive heart failure (CHF) can develop as the disease progresses, resulting in pulmonary edema, arrhythmias, and other fatal consequences [1]. A randomized controlled trial demonstrated that, despite standard medical therapy, the median survival time of dogs with MMVD who have progressed to CHF is limited to 7–8 months [2].

Surgical interventions such as mitral valve repair (MVR) have emerged as alternative treatment options [3–6]. MVR provides an improved survival benefit compared to standard medical therapy at our facility, with 73.2% of dogs with ACVIM stage C that undergo MVR having a survival rate of over 36 months (unpublished data). However, MVR is highly invasive, requires advanced medical equipment, and is expensive. A single-center retrospective study showed that 6.3% (3/48) of dogs that underwent MVR died within 8 days of surgery due to perioperative bleeding and thrombosis [7]. Furthermore, a small-scale study showed that dogs in American College of Veterinary Internal Medicine (ACVIM) stage D MMVD had a higher perioperative mortality after MVR, suggesting a potential association between disease severity and short-term risk [5].

Although the ACVIM consensus guidelines for canine MMVD recommend surgical intervention based on disease severity and center performance, specific eligibility criteria have not yet been determined, and decision-making of management options often remains clinician dependent currently. The indications for MVR should be determined by weighing its effectiveness against its risks, and a prediction model can be useful to help guide treatment decision-making by providing an objective risk probability assessment [8]. In human medicine, several prediction models have been proposed to calculate 30-day mortality probabilities after cardiac surgery [9–11]. However, no objective risk assessment methods have been developed for cardiac surgery in veterinary medicine.

To provide quantitative risks and support decision-making for MVR, this study investigates a potential prediction model based on a retrospective cohort at a single center. The main purpose of this study was to develop a predictive model for 30-day postoperative mortality in dogs undergoing MVR for MMVD using preoperative factors and to internally validate its predictive performance. Furthermore, we evaluated the association between the short-term predictive risk and long-term survival.

2 | Materials and Methods

2.1 | Source of Data and Participants

The findings of this study are in accordance with the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis reporting guidelines [12, 13]. Data were retrospectively collected from medical and surgical records at JASMINE Veterinary Cardiovascular Medical Center, Yokohama, Japan. Dogs undergoing MVR between June 1, 2016, and June 30, 2023, at the center were included in the study. Dogs that traveled from abroad were excluded because their follow-up schedules often varied due to individual circumstances, making accurate outcome tracking difficult. Additionally, differences in medications and postoperative care environments, such as long flights, quarantine, and dietary changes, could affect outcomes and compromise the accuracy of the prediction model. Dogs with mitral valve dysplasia were also excluded from the analysis because their pathology, patient characteristics, prognosis, and degree of regurgitation control after MVR differ substantially from those with MMVD. In the analysis cohort, several dogs with ACVIM MMVD stage B1 underwent MVR. Although these dogs did not meet the cardiac remodeling criteria for ACVIM MMVD stage B2 and were classified as stage B1, MVR was deemed appropriate by clinicians in cases of subjectively severe mitral regurgitation or suspected chordae tendineae rupture on echocardiography, both of which indicated a high risk of progressing to heart failure [14, 15]. MVR was performed only when the owners fully understood and accepted the associated surgical risks. All MVR procedures were performed by two experienced surgeons using cardiopulmonary bypass and hypothermic management, as previously reported [3]. This research project was approved by the ethics committee of our institution (approval number: 230920-7).

2.2 | Outcome and Predictors

The primary outcome was the 30-day all-cause mortality after MVR. The secondary outcome was the 2-year cumulative all-cause death after MVR. Preoperative predictor candidates were prespecified through discussions among the authors, referencing previous studies in human medicine [9–11] and clinical knowledge. Factors with a missing data rate of more than 15% and those prone to measurement error due to breed differences were not included in the candidates. The selected factors were as follows: *Signalment*—age at surgery (year), sex (intact or spayed female, and intact or castrated male), breed (Chihuahua, Pomeranian, Cavalier King Charles Spaniel [CKCS], Toy poodle, mixed breed, and other breed), body weight (kg), and MMVD ACVIM stage (B1/B2, C and D) [1]; *Laboratory blood tests*—packed cell volume (PCV, %), white blood cell ($\times 10^2/\mu L$), c-reactive protein (mg/dL), total protein (TP, g/dL), albumin (g/dL), glucose (mg/dL), blood urea nitrogen (mg/dL), creatinine (mg/dL), total bilirubin (Tbil, mg/dL), sodium (mEq/L), potassium (mEq/L), chloride (mEq/L), activated partial thromboplastin time (APTT, sec), prothrombin time (sec), activated clotting time (sec), and fibrinogen (mg/dL); *Diagnostic Imaging*—left-atrial to aortic ratio (LA/Ao), left ventricular end diastolic diameter normalized for body weight (LVIDDn), fractional shortening percent (FS%), peak velocity of early diastolic transmitral flow (Emax, m/s), peak tricuspid regurgitation velocity (m/s), peak aortic jet velocity (m/s), and vertebral heart score (VHS); *Use of preoperative medications (yes/no)*—furosemide, torasemide, spironolactone, angiotensin converting enzyme inhibitors (ACEi), and amlodipine. Preoperative data were collected within 90 days prior to surgery. If multiple results were available during this period, the most recent preoperative results were used.

2.3 | Summary of Analysis Methods

First, the predictive contributions of all prespecified predictor candidates for 30-day all-cause mortality were calculated and

ranked. Next, five prediction models were arbitrarily developed based on different combinations of predictors and these regression coefficients were calculated by two shrinkage estimation methods. The predictive performance (discrimination and calibration abilities) of these models were internally validated using the bootstrap resampling method. Among these prediction models, the predictive performances were compared to identify the best-performing model (called "final model"). Additionally, a web-based calculator was implemented using the final model. Finally, the analytic cohort was divided into quartile groups based on the 30-day mortality risk probabilities calculated using the final model. The association between quartile short-term risk groups and 2-year cumulative mortality was then evaluated using survival analysis. The analysis flow is summarized in Figure 1.

Continuous variables were visualized using a histogram to confirm data distribution and sparsity. Categorical variables were summarized in a contingency table with the primary outcome. Patient characteristics are described as median and interquartile range for continuous data and as proportions for categorical data. Multicollinearity among predictor candidates was assessed using a generalized variance inflation factor. All generalized variance inflation factors were less than five, and multicollinearity was considered to not affect the estimation. We did not perform an a priori sample size calculation due to the retrospective design of the study. Instead, all available data from the retrospective review were utilized to enhance statistical accuracy. The missing data for several predictors were addressed through imputation using the missForest method [16].

2.4 | Model Development and Validation

Multivariable binary logistic regression was used to predict the 30-day postoperative all-cause mortality. First, the predictive contributions of all predictor candidates were estimated as standardized odds ratios (ORs) using a multivariate binary logistic regression model using the ridge method [17] to compare the scale-independent predictive contributions of each variable. This enabled the ranking of the predictive contribution of each variable to the outcome. Based on these results, we developed five prediction models: (1) a model incorporating all prediction variables (full model); (2) a model composed of the top 11 variables based on predictive contribution (top11); (3) a top 11 model with additional clinically important variables (top11 + A); (4) a top 11 model with other clinically important variables (top11 + B); and (5) a model combining top11 + A and top11 + B (top11 + A + B). The regression coefficients for each prediction model were estimated using both lasso [18] and ridge [17] methods. These shrinkage estimations are used to improve the predictive performance and reduce overfitting, particularly in situations with rare events and a relatively high number of predictors [19]. Hyperparameter tuning for these shrinkage estimations was determined using 10-fold cross-validation.

The prediction performance of each model was assessed based on discrimination and calibration. Discrimination, which refers to the model's ability to differentiate between patients who died within 30 days of MVR, was evaluated using C-statistics, which ranged from 0 to 1. Perfect discrimination is indicated by a C-statistic of 1, whereas a value of 0.5 indicates a performance no better than chance. Calibration, which reflects the consistency of the predicted probability and observed outcome proportions, was assessed using the calibration slope (the ratio of predicted to observed risk, with an ideal value of 1), calibration intercept (the difference between the mean predicted probability and the mean observed outcome, with an ideal value of 0), and E_{avg} (the mean absolute difference between the individual predicted probabilities and observed outcomes, with an ideal value of 0). Internal validation of prediction performance, particularly regarding model overfitting, was performed using a bootstrapping method. The modeling process (hyperparameter tuning and coefficient estimation) and calculation of the prediction performance were iterated using 500 bootstrap resamples, and the bias-corrected

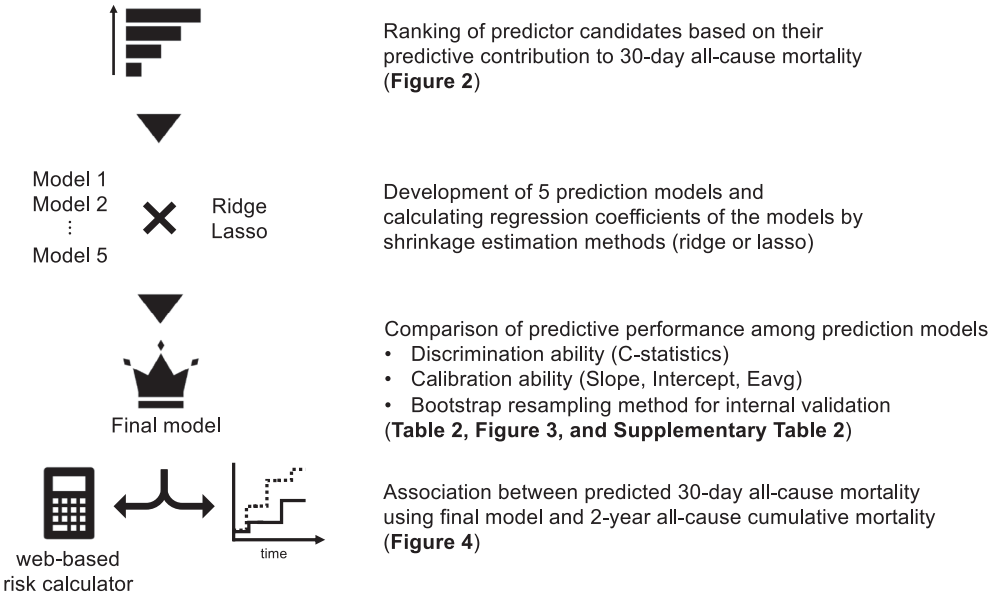

FIGURE 1 | Graphical presentation of the overall analysis flow.

prediction performance was calculated. Based on the results of these predictive performances, a "final model" for clinical use was selected from 10 different prediction sets (five prediction models × two estimation methods) and implemented as a web-based online calculator.

2.5 | Survival Analysis

The entire analytic cohort was stratified into quartiles based on the 30-day mortality risk probabilities predicted by the final model. Survival analysis was subsequently performed to assess the relationship between risk quartile groups and 2-year cumulative all-cause mortality following MVR. The analytic cohort was restricted to patients who survived for over 30 days after MVR, with survival analysis starting at 30 days after MVR. Survival curves were plotted using the Kaplan–Meier method. A multivariate Cox proportional hazards analysis was conducted after visually confirming that the proportional hazards assumption was not violated using the Schoenfeld residual plot. Age, MMVD ACVIM stage, and year of MVR (as a surrogate for surgical quality) were selected as covariates for adjustment after confirming that these covariates were not included as predictors in the final model. A right-censor was defined as the earliest date of either all-cause death, last follow-up (the last recorded date of body weight), or 2 years after MVR. Since this survival analysis was exploratory, the calculated *p* values and confidence intervals (CIs) were not adjusted for multiplicity, and no confirmatory hypothesis testing was conducted.

2.6 | Statistical Software

All data handling and statistical analyses were performed using R ver. 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). The "missForest" package was used for missing data imputation. The "glmnet" package was used for prediction model development with lasso and ridge estimation. Predictive performances were calculated using the "val.prob.ci.2" package [20]. A web-based online calculator was developed using the "shiny" package.

3 | Results

3.1 | Study Cohort Characteristics

A total of 2089 dogs were analyzed in this study. The all-cause mortality rate 30 days after MVR was 4.9% (102/2089). In this analysis cohort, the overall median age was 10.8 (interquartile range, 9.4–12.1) years, and the median body weight was 3.6 (interquartile range, 2.8–4.8) kg. Intact and spayed females accounted for 45.9% (963/2089), while the remaining were intact and castrated males (53.9%, 1126/2089) in the analysis cohort. The MMVD ACVIM stages were B1 (0.2%, 4/2089), B2 (31.0%, 647/2089), C (52.0%, 1087/2089), and D (16.8%, 351/2089). Stages B1 and B2 were more frequently observed in 30-day survivors (31.7%, 630/1987) compared to nonsurvivors (20.6%, 21/102). In contrast, stage D was more frequently observed in nonsurvivors (25.5%, 26/102) than in survivors (16.4%, 325/1987). Breeds included Chihuahuas (45.5%, 951/2089), mixed breeds (12.3%, 256/2089), toy poodles (11.1%, 231/2089), CKCS (5.1%, 107/2089), and other breeds (20.5%, 428/2089). Baseline demographic data are summarized in Table 1. Other baseline data, including breed details, laboratory examinations, diagnostic imaging examinations, and medication histories before missing data imputation, are summarized in Table S1.

3.2 | Development and Evaluation of Prediction Models

The predictive contributions of all predictor candidates for 30-day all-cause mortality after MVR, expressed as standardized ORs, are shown in Figure 2. Standardized ORs greater than 1 indicate a positive relationship with the outcome, whereas those less than 1 indicate a negative relationship. Tbil levels, TP levels, VHS, and LA/Ao were the four most predictive variables, whereas electrolytes, creatinine, peak tricuspid regurgitation velocity, FS%, peak aortic jet velocity, and LVIDDn were the least predictive variables.

A total of 10 clinical prediction sets (five prediction models × two estimation methods) were developed to estimate the probability of 30-day all-cause death following MVR. Five prediction models were included: a model incorporating all predictive variables (full model), a model comprising the top 11 variables ranked by predictive contribution (top11), and combinations of the top 11 model with additional clinically important variables (top11 + A, top11 + B, and top11 + A + B). The top 11 variables were Tbil, TP, VHS, LA/Ao, APTT, ACEi use, breed, amlodipine use, albumin, sex, and body weight. The clinically important variables in Set A were MMVD stage, C-reactive protein levels, LVIDDn levels, and serum glucose levels. The clinically important variables in Set B were prothrombin time, furosemide use, torasemide use, and spironolactone use. The apparent and bias-corrected prediction performances of each model are summarized in Table 2. Model performance was compared using C-statistics, calibration slope, calibration intercept, and E_{avg}. The discrimination of the full model was lower than that of the other models (bias-corrected C-statistics of the lasso and ridge estimations were 0.624 and 0.631, respectively). Among the remaining models, the bias-corrected E_{avg} was the lowest (best) at 0.002 for the top 11 (lasso estimation), top 11 + B (lasso estimation), and top 11 + A + B (lasso estimation). Considering the calibration slope, calibration intercept, and practicality of using fewer predictors in clinical settings, the top 11 model (lasso estimation) was deemed relatively superior and selected as the final model (Bias-corrected estimate: C-statistics, 0.654; calibration slope, 1.003; calibration intercept, 0.007; E_{avg}, 0.002). Due to the nature of lasso estimation, the coefficients for several relatively less important predictors in the final model are shrunk to zero. The apparent calibration plot and coefficients of the final model are shown in Figure 3 and Table S2, respectively.

3.3 | Practical Application of Prediction Model

The probability (%) of 30-day postoperative all-cause death in dogs that underwent MVR can be calculated using the

TABLE 1 | Baseline cohort characteristics stratified by 30 days survival after mitral valve repair.

Characteristics[a]	Dogs at 30 days after mitral valve repair			
	Overall ($n = 2089$)	Survivors ($n = 1987$)	Nonsurvivors ($n = 102$)	Missing[b] (%)
Demographic characteristics				
Age (year)	10.80 [9.40, 12.10]	10.80 [9.30, 12.10]	10.85 [9.70, 12.07]	0
Sex				0
Female	72 (3.4)	71 (3.6)	1 (1.0)	
Spayed Female	891 (42.7)	853 (42.9)	38 (37.3)	
Male	336 (16.1)	320 (16.1)	16 (15.7)	
Castrated Male	790 (37.8)	743 (37.4)	47 (46.1)	
Breed[c]				0
Chihuahua	951 (45.5)	903 (45.4)	48 (47.1)	
Mix	256 (12.3)	249 (12.5)	7 (6.9)	
Toy poodle	231 (11.1)	221 (11.1)	10 (9.8)	
Pomeranian	116 (5.6)	109 (5.5)	7 (6.9)	
CKCS	107 (5.1)	99 (5.0)	8 (7.8)	
Other	428 (20.5)	406 (20.4)	22 (21.6)	
Body weight (kg)	3.58 [2.78, 4.80]	3.58 [2.80, 4.78]	3.54 [2.60, 5.72]	0
MMVD ACVIM stage				0
B1	4 (0.2)	4 (0.2)	0 (0.0)	
B2	647 (31.0)	626 (31.5)	21 (20.6)	
C	1087 (52.0)	1032 (51.9)	55 (53.9)	
D	351 (16.8)	325 (16.4)	26 (25.5)	

Abbreviations: ACVIM, American College of Veterinary Internal Medicine; CKCS, Cavalier King Charles Spaniel; MMVD, Myxomatous mitral valve disease.
[a]Categorical variables are presented as numbers (percentages). Continuous variables are reported as medians [interquartile ranges].
[b]Missing data rates for each characteristic are represented as a percentage.
[c]All the identified breeds are listed in Table S1.

coefficients of predictors from the final model. A web-based risk calculator was developed and is accessible via the link below:https://shimon-furusato.shinyapps.io/prediction_model_for_canine_mitralvalverepair/

3.4 | Association Between Short-Term Risk Prediction and Long-Term Mortality

The distribution of the predicted probabilities of 30-day mortality after MVR, calculated using the final model, was divided into quartiles: First (0.53%–2.77%), second (2.77%–3.92%), third (3.92%–5.71%), and fourth (5.71%–82.31%; Figure S1). Among the patients who survived 30 days postoperatively, the Kaplan–Meier curve for cumulative all-cause death revealed clear differences among the first, second, third, and fourth quartile groups (Figure 4). The 1-year all-cause mortality rates were 2.60% for the first quartile, 6.01% for the second quartile, 4.09% for the third quartile, and 6.07% for the fourth quartile. The 2-year all-cause mortality rates were 8.94% for the first quartile, 12.93% for the second quartile, 11.67% for the third quartile, and 16.3% for the fourth quartile. In a multivariable Cox proportional hazards analysis adjusted for age, MMVD stage, and year of MVR, the hazard ratios (95% CI), referenced to the first quartile, were 1.86 (1.16–2.96) for the second quartile, 1.54 (0.94–2.50) for the third quartile, and 2.00 (1.24–3.22) for the fourth quartile.

4 | Discussion

This study evaluated preoperative factors, including signalment, routine examination results, and medication histories, as short-term prognostic factors for MVR. Using these prediction candidates, short-term prognosis prediction models were developed and demonstrated good calibration performance. Furthermore, this study found an association between predicted short-term mortality risk and 2-year all-cause death, after adjusting for age, MMVD ACVIM stage, and year of MVR.

The key strengths of this study include the relatively large (2089 cases) sample size for the veterinary literature and the incorporation of several advanced statistical methods, such as missing data imputation to maximize data utilization and shrinkage estimation to address overestimation. Although there are no

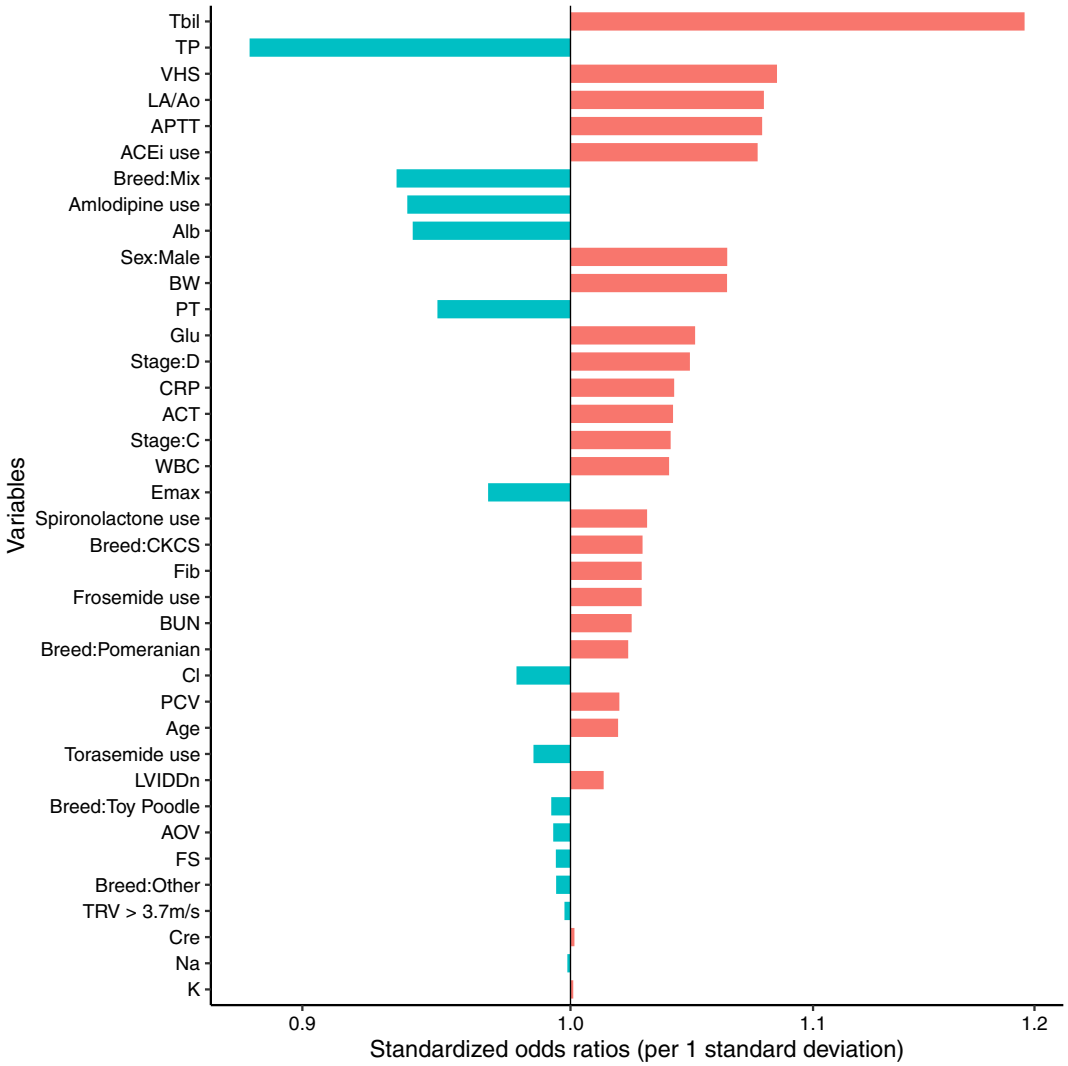

FIGURE 2 | Predictive contributions of all predictor candidates estimated as standardized odds ratios using a multivariable binary logistic regression model with ridge estimation for 30-day postoperative mortality. ACEi, angiotensin-converting enzyme inhibitor; Alb, serum albumin; AOV, peak aortic jet velocity; APTT, activated partial thromboplastin time; ACT, activated clotting time; BUN, blood urea nitrogen; BW, body weight; CKCS, Cavalier King Charles Spaniel; Cl, chloride; Cre, serum creatinine; CRP, C-reactive protein; Emax, peak velocity of early diastolic transmitral flow; Fib, fibrinogen; FS, fractional shortening percent; Glu, serum glucose; K, potassium; LA/Ao, left-atrium to aorta ratio; LVIDDn, left ventricular end diastolic diameter normalized for body weight; Na, sodium; PT, prothrombin time; Stage, myxomatous mitral valve disease stage; Tbil, total bilirubin; TP, total protein; TRV > 3.7 m/s, tricuspid regurgitation velocity greater than 3.7 m/s; VHS, vertebral heart score; WBC, white blood cell. Breeds refer to Chihuahua. Stage refers to B1 and B2.

consensus criteria for the sample size needed to develop the prediction model, the present study considered that at least 100 samples for each event and nonevent were sufficient to ensure a reliable assessment of predictive performance, based on a simulation study [21].

Advanced statistical approaches allowed us to evaluate comprehensive preoperative factors for risk prediction while maintaining high estimation accuracy. To address missing data, we implemented missing data imputation. This approach prevented the sample size reduction and mitigated estimation bias often introduced by complete case analysis [22], ensuring that the analysis remained robust. Additionally, to address sparse data bias [23, 24], where regression coefficients are inflated due to an insufficient number of outcomes for certain predictor combinations, we employed shrinkage methods, including lasso and ridge estimation. These shrinkage methods effectively mitigate sparse data bias and reduce the risk of spurious results, strengthening the validity and robustness of our predictive model.

This study found that serum Tbil, serum TP, VHS, and LA/Ao were the top four predictors of short-term mortality in dogs after MVR. Although these results are interesting for exploring the underlying biological and medical mechanisms, the interpretation of these statistical findings should be approached with caution. The conclusions drawn from the identified predictors in this study are limited to their statistical association with the outcome and their predictive strength. Prediction is not the same as causal inference; therefore, identified predictors do not imply causation of the outcome. In other words, even if we intervene and alter the value of certain predictors, the outcome may not

TABLE 2 | Predictive performance for each prediction model.

Model	Method	Estimate	C-statistics	Calibration slope	Calibration intercept	E_{avg}
full	lasso	apparent	0.700	1.363	0	0.005
		bias-corrected	0.624	0.981	0.011	0.003
	ridge	apparent	0.712	1.656	0	0.009
		bias-corrected	0.631	1.227	0.011	0.005
top 11	lasso	apparent	0.696	1.209	0	0.003
		bias-corrected	0.654	1.003	0.007	0.002
	ridge	apparent	0.695	1.288	0	0.005
		bias-corrected	0.655	1.087	0.007	0.003
top 11 + A	lasso	apparent	0.701	1.236	0	0.004
		bias-corrected	0.649	0.985	0.009	0.004
	ridge	apparent	0.702	1.323	0	0.005
		bias-corrected	0.652	1.07	0.009	0.003
top 11 + B	lasso	apparent	0.705	1.26	0	0.003
		bias-corrected	0.655	1.018	0.009	0.002
	ridge	apparent	0.706	1.404	0	0.005
		bias-corrected	0.657	1.159	0.009	0.003
top 11 + A + B	lasso	apparent	0.706	1.279	0	0.003
		bias-corrected	0.648	0.994	0.011	0.002
	ridge	apparent	0.71	1.436	0	0.006
		bias-corrected	0.654	1.148	0.01	0.004

Note: The full model included the following variables: age, breed, sex, MMVD stage (B1/B2, C, and D), body weight, vertebral heart score (VHS), left-atrium to aorta ratio (LA/Ao), left ventricular end diastolic diameter normalized for body weight (LVIDDn), fractional shortening percent, peak velocity of early diastolic transmitral flow, tricuspid regurgitation velocity > 3.7 m/s, peak aortic jet velocity, activated partial thromboplastin time (APTT), prothrombin time, fibrinogen, activated clotting time, PCV, white blood cell, total protein, albumin, serum glucose, blood urea nitrogen, creatinine, total bilirubin (Tbil), C-reactive protein, sodium, potassium, chloride, furosemide use, torasemide use, spironolactone use, angiotensin converting enzyme inhibitors (ACEi) use, and amlodipine use. *The top 11 variables* were Tbil, total protein, VHS, APTT, LA/Ao, ACEi use, breed, amlodipine use, albumin level, sex, and body weight. *The set A variables* were MMVD stage, C-reactive protein level, LVIDDn, and serum glucose level. *The set B variables* were prothrombin time, furosemide use, torasemide use, and spironolactone use. *C-statistics*, or discrimination, represent the model's ability to differentiate between patients who died within 30 days of MVR, with values ranging from 0 to 1. C-statistic of 1 indicates perfect discrimination, while 0.5 signifies performance equivalent to chance. Calibration, reflecting the agreement between predicted probabilities and observed outcomes, was evaluated using the *calibration slope* (ratio of predicted to observed risk, ideal value: 1), *calibration intercept* (difference between mean predicted probability and mean observed outcome, ideal value: 0), and E_{avg} (mean absolute difference between individual predicted probabilities and observed outcomes, ideal value: 0).

change, as these predictors could merely serve as surrogates for factors that truly influence the outcome.

In the present study, absolute serum Tbil concentration was positively associated with 30-day mortality, with each standard deviation increase in Tbil (0.1 mg/dL) corresponding to an around 1.2-fold increase in the standardized OR. In human cardiac surgery, a systematic review revealed that higher preoperative Tbil concentration (mean difference, 0.042 mg/dL) and right atrial pressure (mean difference, 4.65 mmHg) were risk factors for postoperative hyperbilirubinemia [25]. Additionally, postoperative hyperbilirubinemia was strongly associated with in-hospital mortality (OR, 9.90; 95% CI, 5.00–19.60) in the same study [25]. Furthermore, a retrospective study reported that each 1 μmol/L (0.06 mg/dL) increase in Tbil was independently associated with a 1.42 (95% CI, 1.04–1.94) times higher hazard ratio for mortality in dogs with acquired cardiac disease [26]. Interestingly, most patients in that study [26] and the present study had Tbil levels within the reference range. A similar relationship between poor prognosis and slight Tbil changes was observed in human patients with heart failure and reduced ejection fraction [27]. Based on these findings, even slight elevations in preoperative Tbil levels within the reference interval may indicate poorer conditioning and be associated with a poorer prognosis. A retrospective study demonstrated that MMVD ACVIM stage severity was positively associated with the degree of caudal vena cava dilation in dogs without right heart disease [28], suggesting that MMVD severity may be related to systemic congestion. The prognostic value of preoperative Tbil may be explained by the relationship between cardiac dysfunction and systematic congestion. However, artificial hemolysis or hyperlipidemia in blood samples can cause falsely elevated Tbil levels [29]. Further prospective studies with controlled blood collection and measurement methods are necessary to elucidate the detailed mechanisms of Tbil and its prognostic associations.

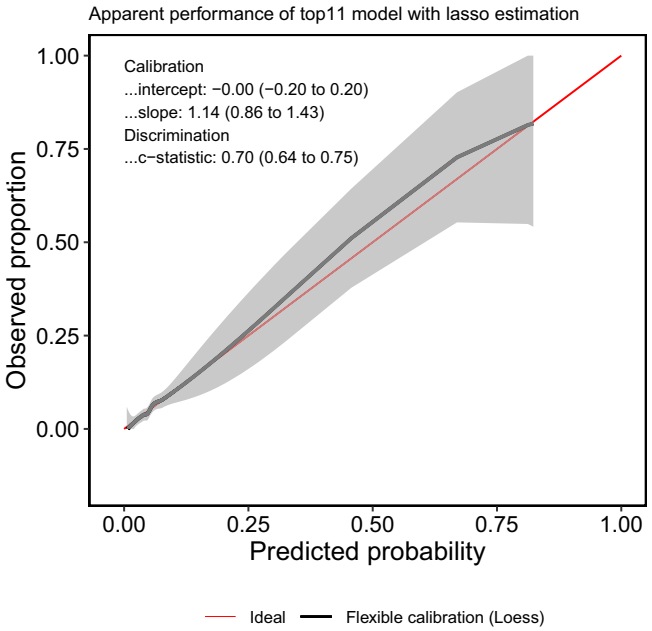

FIGURE 3 | Apparent calibration plot of the prediction model (final model) using lasso estimation for 30-day all-cause mortality in dogs after MVR. The plot compares the observed proportions of 30-day mortality with the predicted probabilities. The red line represents perfect calibration (ideal line), while the black line shows the flexible calibration using a Loess smoother. The shaded area represents the 95% confidence interval (CI) for the calibration curve. Apparent calibration metrics include an intercept of 0.00 (95% CI: −0.20 to 0.20) and a slope of 1.14 (95% CI: 0.86–1.43). The apparent discrimination ability of the model is reflected by a c-statistic of 0.70 (95% CI: 0.64–0.75).

Our study found that decreased serum TP and albumin levels were also associated with short-term mortality. Hypoalbuminemia is associated with various pathological conditions, including chronic inflammation, malnutrition, or cardiac cachexia [30, 31]. A meta-analysis of human patients undergoing cardiac surgery found that hypoalbuminemia was associated with all-cause mortality and an increased risk of postoperative complications [32]. Preoperative comorbidities or chronic conditions may negatively affect the outcomes of highly invasive surgeries.

In the present study, VHS and LA/Ao were positively correlated with 30-day mortality after MVR. A post hoc analysis of a randomized controlled study revealed that the VHS gradually increased until onset of CHF, suggesting that the VHS reflects disease progression in dogs with MMVD stage B2 [33]. In addition, VHS improved the prediction model performance of all-cause death in dogs with MMVD stage B2 and C [34]. Furthermore, increased LA/Ao was identified as a risk factor for cardiac-related death in both asymptomatic and symptomatic dogs with MMVD [35–37]. These findings support the role of VHS and LA/Ao as key prognostic predictors of short-term mortality through disease progression in dogs undergoing MVR.

On the other hand, FS% had relatively low predictive values compared to other diagnostic imaging variables. One possible explanation may be the nonlinear relationship between FS% and MMVD severity. Specifically, ejection from the left ventricle increases with the progression of mitral regurgitation, but declines in the decompensated phase due to impaired contractile function [38–40]. However, the nonlinear term was not

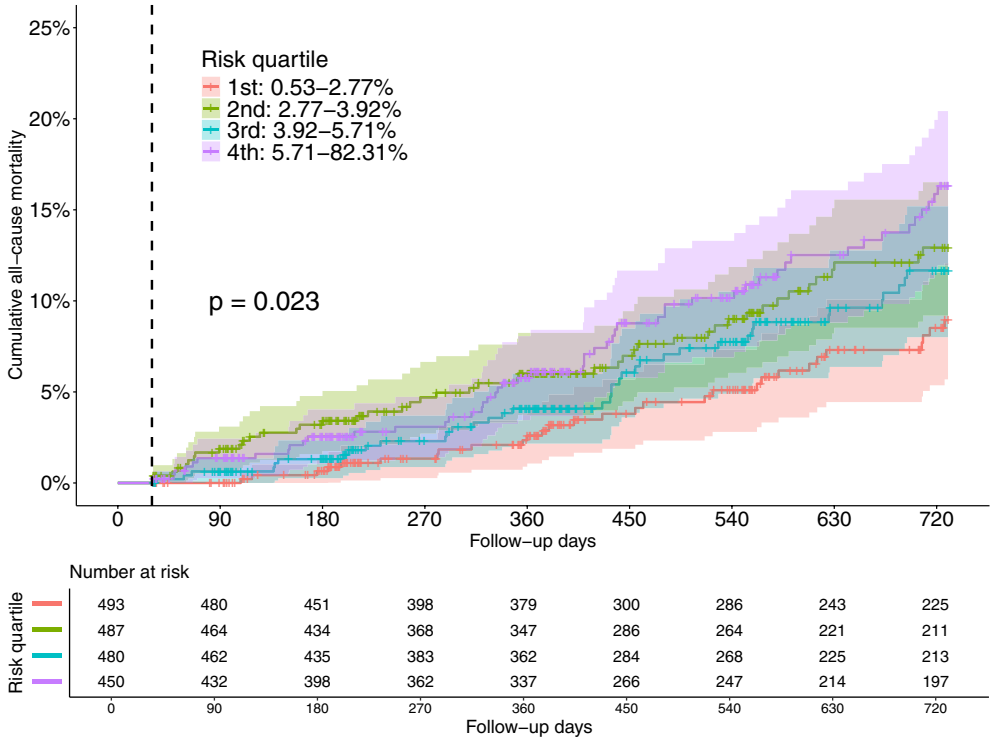

FIGURE 4 | Kaplan–Meier survival curves stratified by risk quartiles for 2-year cumulative all-cause mortality in dogs who survived more than 30 days after MVR. The quartiles were based on predicted 30-day mortality risk, with ranges of first quartile: 0.53%–2.77%, second quartile: 2.77%–3.92%, third quartile: 3.92%–5.71%, and fourth quartile: 5.71%–82.31%. The shaded areas represent the 95% confidence intervals for each quartile. A difference was observed between the quartiles (log-rank $p = 0.023$). The vertical dotted line represents the 30-day time point after MVR.

included in the models due to the limited sample size, which may have resulted in an underestimation of the predictive value of FS%.

Similarly, LVIDDn, an indicator of left ventricular filling pressure or volume overload [39], had an unexpectedly low predictive value. Although the reasons for this are unclear, several factors may have affected the estimation results. The time lag between the last preoperative diagnostic imaging examination and the day of MVR might have influenced the results. Diagnostic imaging examinations were sometimes conducted up to 90 days before the procedure rather than on the day of surgery. During this period, LVIDDn might have fluctuated greatly owing to medical treatments, such as diuretics, leading to a potential discrepancy between the preoperative measurement and the actual status on the day of surgery.

The prediction models in the present study demonstrated low-to-moderate discrimination performance. These results are not unexpected because short-term prognosis after MVR is influenced not only by preoperative conditions but also by intraoperative factors. Several studies have shown that the performance of clinical prediction models for cardiac surgery improves with the inclusion of intraoperative factors [41, 42]. Similarly, the present study showed improvements in the performance of our prediction models, both in discrimination and calibration abilities, by incorporating the cardiopulmonary bypass time and aortic cross-clamp time (data not shown). However, the primary focus of the study lies in evaluating the surgical risk preoperatively; therefore, the prediction models included in this study did not incorporate intraoperative or postoperative factors.

The final model demonstrated good calibration abilities, including calibration slope, calibration intercept, and E_{avg}. A calibration slope of less than 1 indicated model overfitting [20]. In general, a lower number of events relative to the number of variables, as observed in our dataset, can lead to overfitting. To mitigate this issue, shrinkage estimation methods were applied. The bias-corrected calibration slope in the final model was close to 1, indicating minimal overfitting. Additionally, the calibration intercept and E_{avg} demonstrated strong performance, indicating a high consistency between the predicted probability and observed outcome proportions.

Quartile stratification of short-term mortality risk using the final model was associated with 2-year all-cause mortality even after adjusting for age, MMVD stage, and year of MVR. Specifically, the population with a short-term risk of over 5.71% had two times higher hazard risk for 2-year all-cause mortality than those with a short-term risk of under 2.77%. These findings suggest that short-term risk predictors overlap with long-term risks and that risk stratification using the final model may be useful in identifying long-term high-risk populations in dogs undergoing MVR. Even if dogs with higher short-term survival risk successfully pass the early postoperative period, closer monitoring may still be necessary.

The prediction model may offer valuable and objective information that helps clinicians determine the suitability of surgical interventions, fostering evidence-based decision-making. It may also enhance communication of preoperative risk assessments between clinicians and pet owners, facilitate shared decision-making, and ensure consistent risk evaluation among clinicians, regardless of their experience level. However, it is important to note that while prediction models can assist in clinical decision-making based on limited information, they cannot fully replace the clinician's judgment. Clinicians need to formulate treatment plans comprehensively by considering nonquantifiable aspects of the patient's condition, the clinical course, and their own experience, as they routinely do.

This study had several limitations. First, the number of events was low, with only 102 cases due to low mortality, whereas the total sample size of 2089 dogs was large for this single-center study. Consequently, this sample size was thus considered insufficient to include nonlinear or interaction terms, which may have limited predictive performance. Second, owing to the retrospective nature of the study, preoperative examination methods and treatment strategies were not standardized, potentially reducing prediction accuracy. Third, the generalizability of the model is unknown, as this was a single-center study. The performance of the final model may decrease when applied to other institutions, and further multicenter studies are required to evaluate the external validity of this model. Fourth, the performance of prediction models may decline over time due to changes in the signalment of the target population, as well as improvements in surgical techniques and postoperative care [43, 44]. Therefore, the prediction models must be regularly updated and recalibrated to fit specific clinical settings. The accumulation of high-quality data and multicenter prospective studies is essential to support these efforts.

In conclusion, the developed preoperative prediction model for 30-day all-cause mortality in dogs undergoing MVR demonstrated low-to-moderate discrimination abilities and good calibration performance in internal validation. Quartile grouping of the predicted 30-day all-cause mortality risk was also associated with 2-year mortality in dogs undergoing MVR. The proposed prediction model may support treatment decisions by offering an objective evaluation of the risk associated with MVR in dogs at this center.

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Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

Approved by the Institutional Ethics Committee of JASMINE Veterinary Cardiovascular Medical Center, approval number: 230920-7. Authors declare human ethics approval was not needed.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. B. W. Keene, C. E. Atkins, J. D. Bonagura, et al., "ACVIM Consensus Guidelines for the Diagnosis and Treatment of Myxomatous Mitral Valve Disease in Dogs," *Journal of Veterinary Internal Medicine* 33 (2019): 1127–1140.

2. G. Wess, J. G. Kresken, R. Wendt, et al., "Efficacy of Adding Ramipril (VAsotop) to the Combination of Furosemide (Lasix) and Pimobendan (VEtmedin) in Dogs With Mitral Valve Degeneration: The VALVE Trial," *Journal of Veterinary Internal Medicine* 34 (2020): 2232–2241.

3. M. Uechi, "Mitral Valve Repair in Dogs," *Journal of Veterinary Cardiology* 14 (2012): 185–192.

4. I. Kanemoto, K. Mihara, and K. Sato, "Open-Heart Techniques and Mitral Valve Plasty for Mitral Regurgitation in Toy- and Small-Breed Dogs: A Review," *Open Veterinary Journal* 11 (2021): 14–26.

5. K. Matsuura, T. Yoshida, S. Yamada, et al., "The Outcome of Surgical Mitral Valve Repair With Loop-In-Loop Technique in Dogs With Different Stage Myxomatous Mitral Valve Disease," *Journal of Veterinary Cardiology* 42 (2022): 74–82.

6. K. Mihara, I. Kanemoto, K. Sato, et al., "Effects of Mitral Valve Repair on Valvular Geometry and Hemodynamics in Dogs With Myxomatous Mitral Valve Disease," *Veterinary Surgery* 53 (2024): 415–425.

7. M. Uechi, T. Mizukoshi, T. Mizuno, et al., "Mitral Valve Repair Under Cardiopulmonary Bypass in Small-Breed Dogs: 48 Cases (2006-2009)," *Journal of the American Veterinary Medical Association* 240 (2012): 1194–1201.

8. A. Maiga, F. Farjah, J. Blume, et al., "Risk Prediction in Clinical Practice: A Practical Guide for Cardiothoracic Surgeons," *Annals of Thoracic Surgery* 108 (2019): 1573–1582.

9. A. L. W. Shroyer, L. P. Coombs, E. D. Peterson, et al., "The Society of Thoracic Surgeons: 30-Day Operative Mortality and Morbidity Risk Models," *Annals of Thoracic Surgery* 75 (2003): 1856–1864.

10. S. A. M. Nashef, F. Roques, L. D. Sharples, et al., "EuroSCORE II," *European Journal of Cardio-Thoracic Surgery* 41 (2012): 734–744.

11. D. X. Zhuo, K. C. Bilchick, K. P. Shah, et al., "Maggic, STS, and EuroSCORE II Risk Score Comparison After Aortic and Mitral Valve Surgery," *Journal of Cardiothoracic and Vascular Anesthesia* 35 (2021): 1806–1812.

12. K. G. M. Moons, D. G. Altman, J. B. Reitsma, et al., "Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD): Explanation and Elaboration," *Annals of Internal Medicine* 162 (2015): W1–W73.

13. G. S. Collins, K. G. M. Moons, P. Dhiman, et al., "TRIPOD+AI Statement: Updated Guidance for Reporting Clinical Prediction Models That Use Regression or Machine Learning Methods," *BMJ* 385 (2024): e078378.

14. F. Serres, V. Chetboul, R. Tissier, et al., "Chordae Tendineae Rupture in Dogs With Degenerative Mitral Valve Disease: Prevalence, Survival, and Prognostic Factors (114 Cases, 2001–2006)," *Journal of Veterinary Internal Medicine* 21 (2007): 258–264.

15. J. Sargent, R. Muzzi, R. Mukherjee, et al., "Echocardiographic Predictors of Survival in Dogs With Myxomatous Mitral Valve Disease," *Journal of Veterinary Cardiology* 17 (2015): 1–12.

16. D. J. Stekhoven and P. Bühlmann, "MissForest—Non-Parametric Missing Value Imputation for Mixed-Type Data," *Bioinformatics* 28 (2012): 112–118.

17. S. L. Cessie and J. C. V. Houwelingen, "Ridge Estimators in Logistic Regression," *Applied Statistics* 41, no. 1 (1992): 191–201, https://doi.org/10.2307/2347628.

18. R. Tibshirani, "Regression Shrinkage and Selection via the Lasso," *Journal of the Royal Statistical Society Series B (Statistical Methodology)* 58 (1996): 267–288.

19. M. Pavlou, G. Ambler, S. Seaman, M. de Iorio, and R. Z. Omar, "Review and Evaluation of Penalised Regression Methods for Risk Prediction in Low-Dimensional Data With Few Events," *Statistics in Medicine* 35 (2016): 1159–1177.

20. B. Van Calster, D. Nieboer, Y. Vergouwe, et al., "A Calibration Hierarchy for Risk Models Was Defined: From Utopia to Empirical Data," *Journal of Clinical Epidemiology* 74 (2016): 167–176.

21. E. W. Steyerberg, "Validation in Prediction Research: The Waste by Data Splitting," *Journal of Clinical Epidemiology* 103 (2018): 131–133.

22. A. R. T. Donders, G. J. M. G. van der Heijden, T. Stijnen, and K. G. M. Moons, "Review: A Gentle Introduction to Imputation of Missing Values," *Journal of Clinical Epidemiology* 59 (2006): 1087–1091.

23. S. Greenland, J. A. Schwartzbaum, and W. D. Finkle, "Problems due to Small Samples and Sparse Data in Conditional Logistic Regression Analysis," *American Journal of Epidemiology* 151 (2000): 531–539.

24. S. Greenland, M. A. Mansournia, and D. G. Altman, "Sparse Data Bias: A Problem Hiding in Plain Sight," *BMJ* 352 (2016): i1981.

25. X. Chen, M. Bai, W. Zhang, S. Sun, and X. Chen, "The Incidence, Risk Factors, and Prognosis of Postoperative Hyperbilirubinemia After Cardiac Surgery: A Systematic Review and Meta-Analysis," *Annals of Palliative Medicine* 10 (2021): 7247–7257.

26. A. Chong, M. Appleton, D. Casamián-Sorrosal, et al., "Total Bilirubin Is an Independent Predictor of Death in Dogs With Degenerative Valvular Disease and Dilated Cardiomyopathy," *Journal of Veterinary Cardiology* 43 (2022): 10–26.

27. A. P. Ambrosy, M. Vaduganathan, M. D. Huffman, et al., "Clinical Course and Predictive Value of Liver Function Tests in Patients Hospitalized for Worsening Heart Failure With Reduced Ejection Fraction: An Analysis of the Everest Trial," *European Journal of Heart Failure* 14 (2012): 302–311.

28. L. Giraud, N. Fernandes Rodrigues, M. Lekane, et al., "Caudal Vena Cava Point-Of-Care Ultrasound in Dogs With Degenerative Mitral Valve Disease Without Clinically Important Right Heart Disease," *Journal of Veterinary Cardiology* 41 (2022): 18–29.

29. L. Cohn and E. Cote, *Cote's Clinical Veterinary Advisor: Dogs and Cats*, 4th ed. (Elsevier Inc., 2019).

30. P. B. Soeters, R. R. Wolfe, and A. Shenkin, "Hypoalbuminemia: Pathogenesis and Clinical Significance," *JPEN Journal of Parenteral and Enteral Nutrition* 43 (2019): 181–193.

31. D. L. Ineson, L. M. Freeman, and J. E. Rush, "Clinical and Laboratory Findings and Survival Time Associated With Cardiac Cachexia in Dogs With Congestive Heart Failure," *Journal of Veterinary Internal Medicine* 33 (2019): 1902–1908.

32. R. Xu, M. Hao, W. Zhou, et al., "Preoperative Hypoalbuminemia in Patients Undergoing Cardiac Surgery: A Meta-Analysis," *Surgery Today* 53 (2023): 861–872.

33. A. Boswood, S. G. Gordon, J. Häggström, et al., "Temporal Changes in Clinical and Radiographic Variables in Dogs With Preclinical Myxomatous Mitral Valve Disease: The EPIC Study," *Journal of Veterinary Internal Medicine* 34 (2020): 1108–1118.

34. M. Vereb, C. E. Atkins, D. Adin, et al., "Efficacy of a Mitral Regurgitation Severity Index to Predict Long-Term Outcome in Dogs With Myxomatous Mitral Valve Disease," *Journal of Veterinary Internal Medicine* 38 (2024): 51–60.

35. M. Borgarelli, P. Savarino, S. Crosara, et al., "Survival Characteristics and Prognostic Variables of Dogs With Mitral Regurgitation Attributable to Myxomatous Valve Disease," *Journal of Veterinary Internal Medicine* 22 (2008): 120–128.

36. M. Borgarelli, S. Crosara, K. Lamb, et al., "Survival Characteristics and Prognostic Variables of Dogs With Preclinical Chronic Degenerative Mitral Valve Disease Attributable to Myxomatous Degeneration," *Journal of Veterinary Internal Medicine* 26 (2012): 69–75.

37. M. Borgarelli, L. Ferasin, K. Lamb, et al., "The Predictive Value of Clinical, Radiographic, Echocardiographic Variables and Cardiac Biomarkers for Assessing Risk of the Onset of Heart Failure or Cardiac

Death in Dogs With Preclinical Myxomatous Mitral Valve Disease Enrolled in the DELAY Study," *Journal of Veterinary Cardiology* 36 (2021): 77–88.

38. P. O'gara, L. Sugeng, R. Lang, et al., "The Role of Imaging in Chronic Degenerative Mitral Regurgitation," *JACC: Cardiovascular Imaging* 1 (2008): 221–237, https://doi.org/10.1016/j.jcmg.2008.01.011.

39. J. D. Bonagura and K. E. Schober, "Can Ventricular Function Be Assessed by Echocardiography in Chronic Canine Mitral Valve Disease?," *Journal of Small Animal Practice* 50, no. s1 (2009): 12–24.

40. M. J. Hezzell, A. Boswood, W. Moonarmart, and J. Elliott, "Selected Echocardiographic Variables Change More Rapidly in Dogs That Die From Myxomatous Mitral Valve Disease," *Journal of Veterinary Cardiology* 14 (2012): 269–279.

41. T. J. S. Durant, R. A. Jean, C. Huang, et al., "Evaluation of a Risk Stratification Model Using Preoperative and Intraoperative Data for Major Morbidity or Mortality After Cardiac Surgical Treatment," *JAMA Network Open* 3 (2020): e2028361.

42. Y. Liu, J. Xiao, X. Duan, et al., "The Multivariable Prognostic Models for Severe Complications After Heart Valve Surgery," *BMC Cardiovascular Disorders* 21 (2021): 491.

43. G. L. Hickey, S. W. Grant, G. J. Murphy, et al., "Dynamic Trends in Cardiac Surgery: Why the Logistic EuroSCORE Is no Longer Suitable for Contemporary Cardiac Surgery and Implications for Future Risk Models," *European Journal of Cardio-Thoracic Surgery* 43 (2013): 1146–1152.

44. G. L. Hickey, S. W. Grant, C. Caiado, et al., "Dynamic Prediction Modeling Approaches for Cardiac Surgery," *Circulation. Cardiovascular Quality and Outcomes* 6 (2013): 649–658.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.