JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY VOL. 82, NO. 14, 2023

PUBLISHED BY ELSEVIER

Validation of Risk Stratification for Cardiac Events in Pregnant Women With Valvular Heart Disease

Swaraj Nandini Pande, MS,[a] J. Yavana Suriya, MD,[a] Sachit Ganapathy, PhD,[b] Ajith Ananthakrishna Pillai, DM,[c] Santhosh Satheesh, DM,[c] Nivedita Mondal, MD,[d] K.T. Harichandra Kumar, MSc, PhD,[b] Candice Silversides, MD, SM,[e] Samuel C. Siu, MD, SM, MBA,[e,f] Rohan D'Souza, MD, PhD,[g] Anish Keepanasseril, MD[a]

ABSTRACT

BACKGROUND Most risk stratification tools for pregnant patients with heart disease were developed in high-income countries and in populations with predominantly congenital heart disease, and therefore, may not be generalizable to those with valvular heart disease (VHD).

OBJECTIVES The purpose of this study was to validate and establish the clinical utility of 2 risk stratification tools—DEVI (VHD-specific tool) and CARPREG-II—for predicting adverse cardiac events in pregnant patients with VHD.

METHODS We conducted a cohort study involving consecutive pregnancies complicated with VHD admitted to a tertiary center in a middle-income setting from January 2019 to April 2022. Individual risk for adverse composite cardiac events was calculated using DEVI and CARPREG-II models. Performance was assessed through discrimination and calibration characteristics. Clinical utility was evaluated with Decision Curve Analysis.

RESULTS Of 577 eligible pregnancies, 69 (12.1%) experienced a component of the composite outcome. A majority (94.7%) had rheumatic etiology, with mitral regurgitation as the predominant lesion (48.2%). The area under the receiver-operating characteristic curve was 0.884 (95% CI: 0.844-0.923) for the DEVI and 0.808 (95% CI: 0.753-0.863) for the CARPREG-II models. Calibration plots suggested that DEVI score overestimates risk at higher probabilities, whereas CARPREG-II score overestimates risk at both extremes and underestimates risk at middle probabilities. Decision curve analysis demonstrated that both models were useful across predicted probability thresholds between 10% and 50%.

CONCLUSIONS In pregnant patients with VHD, DEVI and CARPREG-II scores showed good discriminative ability and clinical utility across a range of probabilities. The DEVI score showed better agreement between predicted probabilities and observed events. (J Am Coll Cardiol 2023;82:1395–1406) © 2023 by the American College of Cardiology Foundation.

Listen to this manuscript's audio summary by Editor-in-Chief Dr Valentin Fuster on www.jacc.org/journal/jacc.

From the [a]Department of Obstetrics and Gynaecology, Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, India; [b]Department of Biostatistics, Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, India; [c]Department of Cardiology, Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, India; [d]Department of Neonatology, Jawaharlal Institute of Post-graduate Medical Education and Research (JIPMER), Puducherry, India; [e]Division of Cardiology, University of Toronto Pregnancy and Heart Disease Program, Mount Sinai and Toronto General Hospitals, University of Toronto, Toronto, Ontario, Canada; [f]Division of Cardiology, University of Western Ontario, London, Ontario, Canada; and the [g]Department of Obstetrics and Gynaecology and Health Research Methods, Evidence and Impact, McMaster University, Hamilton, Ontario, Canada.

Garima V. Sharma, MD, served as Guest Associate Editor for this paper. Christopher M. O'Connor, MD, served as Guest Editor-in-Chief for this paper.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received May 8, 2023; revised manuscript received July 13, 2023, accepted July 21, 2023.

ISSN 0735-1097/$36.00 https://doi.org/10.1016/j.jacc.2023.07.023

ABBREVIATIONS AND ACRONYMS

LMIC = low-to-middle-income countries

VHD = valvular heart disease

Cardiac disease represents a heterogeneous group of congenital and acquired heart lesions and is a leading cause of pregnancy-related mortality and severe morbidity in both high- and low-to-middle-income countries (LMICs).[1,2] It is estimated that one-third of pregnancy-related deaths globally are from cardiovascular disorders, of which up to two-thirds could be prevented.[1,3] Acquired (rheumatic) valvular heart disease (VHD) is responsible for a disproportionately higher proportion of pregnancy-related deaths and severe illness than congenital heart disease in LMICs. Risk stratification of pregnancies with VHD is crucial, especially in LMICs, to facilitate early referral to multidisciplinary cardio-obstetrics teams in tertiary referral centers and to improve pregnancy outcomes.

SEE PAGE 1407

Various risk stratification scores have been developed and validated for pregnancies with cardiac disease. However, many of these were developed in high-income settings, where congenital heart disease is more prevalent. VHD, especially rheumatic VHD, comprised only a small proportion of these development and validation cohorts.[4-6] To address this, the DEVI score was developed and internally validated in a homogenous group of pregnant patients with VHD in a middle-income setting.[7] This score showed excellent discrimination and good calibration in the original study. However, before recommending its use in routine clinical practice, evaluating its performance through temporal validation in a cohort of cases from the same setting, at a different period, or external validation in a different setting or population is essential.[8,9]

Our primary objective was to perform temporal validation and assess the clinical utility of a VHD-specific risk assessment tool, the DEVI score, in a cohort of pregnant patients with VHD. Our secondary objective was to describe the performance and clinical utility of a generalized risk assessment tool, the CARPREG-II score, for risk assessment in patients with VHD from a middle-income setting.

METHODS

STUDY DESIGN AND SETTING. This prospective cohort study was conducted in a tertiary care center in the South-Eastern coastal region of India from January 2019 to April 2022. This center has approximately 15,000 to 17,000 births annually and primarily cares for high-risk pregnancies from rural areas. A waiver of consent was sought from January 2019 to December 2019, and Institutional Ethics approval was obtained from the Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India (IEC/JIP/2019/458) for the remainder of the study period.

STUDY POPULATION. This study cohort included consecutive pregnant individuals of South-Indian descent, older than 18 years of age, with VHD diagnosed before conception or during pregnancy who were treated in the tertiary center. The lesion type and severity were assessed echocardiographically in each patient at the time of the first antenatal visit. Grading of the VHD was based on the European Association of Echocardiography and American Society of Echocardiography recommendations.[10,11] Pulmonary hypertension was diagnosed with right ventricular systolic pressure of more than 40 mm Hg on echocardiographic assessment or with mean pulmonary artery pressure of more than 25 mm Hg at cardiac catheterization.[7]

At this institution, pregnant patients with heart disease undergo a cardiac evaluation at their first antenatal (booking) visit and are followed throughout pregnancy until 6 weeks postpartum by a multidisciplinary team comprising a consultant-led obstetrics team (no less than every 2 weeks till 32 weeks and then weekly till admission/birth) and cardiology team (seen once a month or sooner based on cardiac status). Patients underwent a cardiac and obstetric evaluation at each visit, followed by echocardiography and obstetric ultrasound if clinically indicated. Additionally, all had an in-hospital evaluation by both teams in the immediate postpartum period and were discharged after an observation period of 3 to 5 days postpartum.

DATA COLLECTED. The research team members gathered and verified data on the baseline, predictor, and outcome variables until hospital discharge, as described in the following text.

Baseline variables. Clinical and demographic details gathered included maternal age, parity, age at diagnosis, medications during the course of pregnancy, modified World Health Organization Classification, and NYHA functional class at the time of first antenatal visit during pregnancy, childbirth, and in the postpartum period.

Predictor variables. Prior history of adverse cardiac events (heart failure, arrhythmia, infective endocarditis, and thromboembolic events), location, type of lesion (stenotic, regurgitant, or both), and severity of valve involvement (mild, moderate, severe),[10,11] any cardiac intervention(s) before conception as well as the details of the procedures, cardiac

medications at the time of booking, NYHA functional class (I to IV) or cyanosis, systemic ventricular dysfunction, mechanical valves, pulmonary hypertension, any associated high-risk aortopathies, or coronary artery disease were noted for assessing the CARPREG-II or DEVI score.

Outcome variables. The primary outcome was a composite of adverse cardiac events, defined as the occurrence of one or more of the following: 1) cardiac death; 2) cardiac arrest; 3) heart failure (clinical symptoms of acute onset dyspnea with signs of fluid retention such as crepitations in lung bases); 4) valvular or extravalvular thrombotic events or cerebrovascular accidents such as stroke or transient ischemic attack (following evaluation with clinical examination and neuro-imaging); and 5) new-onset or recurrent arrhythmias requiring treatment.

Other cardiac outcomes reported include a decline in ≥2 NYHA functional classes and the need for emergency invasive cardiac interventions.[5,7] We also gathered data on the pregnancy-specific complications developing during or after pregnancy, details of labor and childbirth, and fetal/neonatal outcomes such as birth weight, admission to the neonatal intensive unit, and neonatal death. All data were entered in a REDCap database created for the study.[12]

TABLE 1 Baseline Characteristics of the Study Population[a]

Maternal age, y	26.0 ± 4.5
Nulliparous	234 (40.6)
Multiple pregnancy	4 (0.7)
Diagnosed in index pregnancy	145 (25.1)
Prior cardiovascular event[b]	59 (10.2)
NYHA functional class III/IV, prepregnancy	7 (1.2)
NYHA functional class III/IV, during pregnancy[c]	70 (12.1)
Prior cardiac intervention[d]	163 (28.2)
On cardiac medications	
Diuretic agents	337 (58.4)
Digoxin	56 (9.7)
Beta-blockers	245 (42.5)
Prosthetic heart valve[e]	66 (11.4)
Use of anticoagulant[f]	90 (15.6)
Pulmonary hypertension[g]	108 (18.7)
Anemia at admission[h]	407 (70.5)
Hypothyroidism	74 (12.8)

Values are mean ± SD or n (%). [a]Among 577 pregnancies. [b]Prior cardiovascular events are defined as the occurrence of 1 or more of the following: heart failure (n = 26), arrhythmia (n = 21), infective endocarditis (n = 6), and thromboembolic events (n = 11). [c]Worsening by ≥2 NHYA functional classes. [d]Prior cardiac intervention such as balloon valvotomy or closed mitral valvotomy, valve repair (tricuspid or mitral). [e]It includes 14 pregnancies following bioprosthetic heart valve replacement. [f]Anticoagulants used include oral Coumadin derivatives (warfarin and acenocoumarol) and heparin (unfractionated heparin and enoxaparin). [g]Pulmonary hypertension is defined as right ventricular systolic pressure ≥40 mm Hg on echocardiography or the mean pulmonary artery pressure ≥ 25 mm Hg. [h]Hemoglobin level <10 g/dL.

STATISTICAL ANALYSIS. Categorical variables were expressed as frequencies and percentages. Depending on data distribution, continuous variables were expressed as mean ± SD or median (IQR). Statistical analysis was performed using STATA 17.0 (Stata Corp); the level of significance was set at <0.05 (2-sided).

The individual risk for the cases was calculated using the beta coefficients of the logistic regression output from the CARPREG-II, and DEVI scores were derived. Expected risk for individual patients was calculated using the beta coefficients from the logistic regression analyses as given in the original papers.[5,7] All patients were stratified into one of the risk classes based on the modified World Health Organization classification by the European Society of Cardiology.[13]

Performance was assessed based on 2 parameters—discrimination and calibration. Discrimination was evaluated by estimating the C-statistic with its 95% CI; C-statistic <0.60 indicates poor discrimination, 0.60 to 0.75 means moderate discrimination, and >0.75 is deemed acceptable discrimination.[14] The comparison of the AUC or C-statistics was done using the package "roccomp" in STATA, which tests the equality of the AUCs. A calibration plot was generated to assess the agreement between the observed and the predicted risk of the adverse composite outcome. Using a calibration plot, we evaluated each model's calibration in the large that shows the overall calibration and the slope, denoting the agreement between the observed and predicted levels of risk. Perfect calibration is represented as a 45° straight line with a slope of 1 and an intercept of 0. The calculated calibration-in-the-large (predicted risks are underestimated if >0 or overestimated if <0) and the calibration slope (predicted risks that are too extreme if <1 or not extreme enough if >1) were also noted.

To evaluate the clinical utility of the models, we determined their net benefit using the decision curve analysis approach.[15] Net benefit is a measure that combines the benefits and harms of using a model for clinical decision support. In the context of VHD in pregnancy, the benefit of using either of the models is to identify patients likely to experience a composite adverse cardiac outcome and to avoid unnecessary referral to a high-risk or tertiary care setting leading to overcrowding, personal burden, as well as cost and impact on health system resources. The net benefit of the models was assessed over a range of probability thresholds instead of alternative approaches, ie, either managing all pregnant patients with VHD as if they will have a composite adverse cardiac outcome (or referral to high-risk care setting for all) or

managing all those with VHD as if they will not have a composite adverse cardiac outcome (routine antenatal care for all).

If a lower threshold is used, more patients may be referred to the high-risk care setting, resulting in more unnecessarily receiving specialized care in a tertiary hospital, increasing resource use and costs to patients and health care systems. A higher threshold may be appropriate in high-prevalence but low-resource settings. This will result in fewer patients being stratified to a high-risk or specialized care setting and benefiting from targeted interventions because of resource limitations. The optimal threshold for risk stratification may depend on the health service infrastructure, resources, and preference of clinicians and the pregnant patients/family in a particular setting, thereby continuing care in a hospital nearby to home than a tertiary center, so it is difficult to put forward a single optimal probability threshold for risk stratification for all settings. A decision curve plot represented the net benefit as a function of the probability threshold and provided the results for multiple plausible risk thresholds.[16]

PATIENT AND PUBLIC PARTICIPATION IN RESEARCH. Patients or the public were not involved in this research's design, conduct, reporting, or dissemination plans.

RESULTS

There were 41,947 births during the study period, of which 892 (2.1%) occurred in patients with cardiac disease. Of these, 577 (62.7%) pregnancies occurred in 512 individuals with VHD and were included in the analysis. Only 27 of these (5.3%) were congenital heart disease. Many patients with VHD (145; 28.4%) were diagnosed during pregnancy. **Table 1** shows the baseline characteristics of the study population. A history of prior cardiovascular events was present in 59 (10.2%) pregnancies, NYHA functional class III/IV was present in 7 pregnancies, and a large proportion were on beta-blockers—atenolol or metoprolol (n = 245; 42.5%)—and diuretic agents (n = 337; 58.4%). In 98 (17.0%) pregnancies, the first antenatal visit occurred later (after 20 weeks). The nature of valve lesions is shown in **Table 2**. Mitral regurgitation was the predominant lesion (n = 278; 48.2%). Among those with isolated lesions (n = 165 pregnancies), 44 were complicated with isolated mitral stenosis and 121 had isolated mitral regurgitation. Worsening by ≥2 NYHA functional classes to class III/IV was noted in 70 pregnancies. Balloon mitral valvotomy was performed in 21 pregnancies in the late second or early third trimester (24-34 weeks). Prosthetic mechanical heart valve replacement was performed during the index pregnancy: 1 in the antepartum period (second trimester), and 7 as concurrent valve replacements with cesarean births. They were primarily performed for refractory pulmonary edema after discussion with the multidisciplinary team, given the patients' critical condition.

TABLE 2 Distribution According to the Valvular Lesions (n = 577)[a]

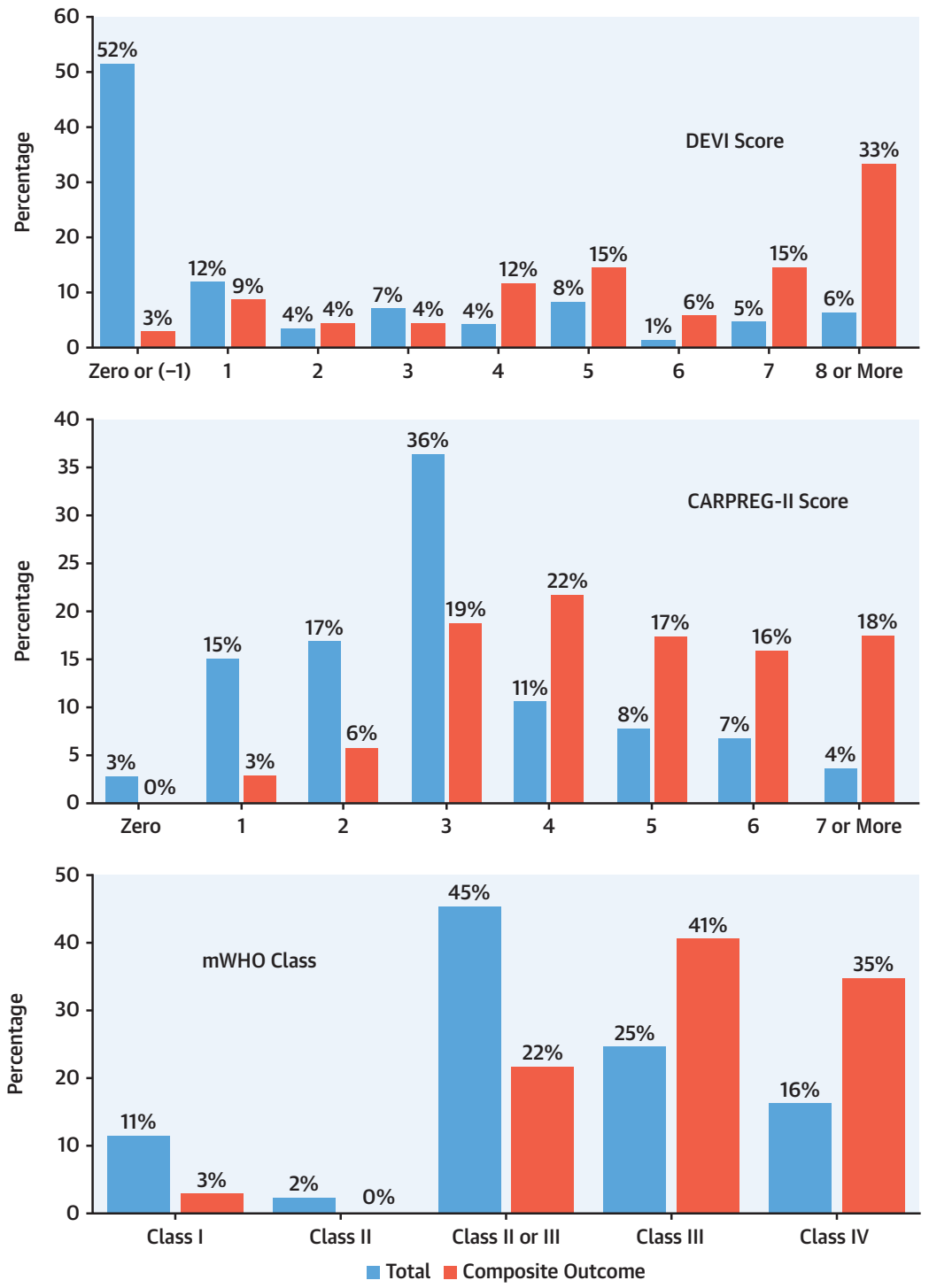
Mitral stenosis	
Moderate	82 (14.2)
Severe	95 (16.5)
Mitral regurgitation	
Moderate	144 (25.0)
Severe	134 (23.2)
Aortic stenosis	
Moderate	9 (1.6)
Severe	7 (1.2)
Aortic regurgitation	133 (23.1)
Tricuspid regurgitation[b]	259 (44.9)
Severe	42 (7.3)
Others[c]	18 (3.1)

Values are n (%). [a]The number of lesions is >577 because 289 (50.1%) had multivalvular lesions. [b]Tricuspid regurgitation was secondary to the mitral valve lesion, with moderate tricuspid regurgitation in 62 (10.8%) and severe tricuspid regurgitation in 62 (7.3%) patients. [c]Includes tricuspid stenosis (n = 2), pulmonary regurgitation (n = 5), and pulmonary stenosis (n = 11).

PRIMARY OUTCOMES. One or more composite adverse cardiac events occurred in 69 (12.1%) pregnancies during pregnancy or the early postpartum period (**Figure 1**). The most common adverse event was heart failure (n = 52; 9.0%), most of which (69.0%) occurred in the antenatal period. Arrhythmia requiring treatment occurred in 25 (4.3%) cases. There were 2 cases each of stroke and infective endocarditis. There were 3 (1.8%) maternal deaths during the study period, 2 among those with mechanical heart valves (1 each from valve thrombosis and refractory supraventricular arrhythmia), and the third was secondary to infective endocarditis in a patient with severe mitral regurgitation (Supplemental Table 1).

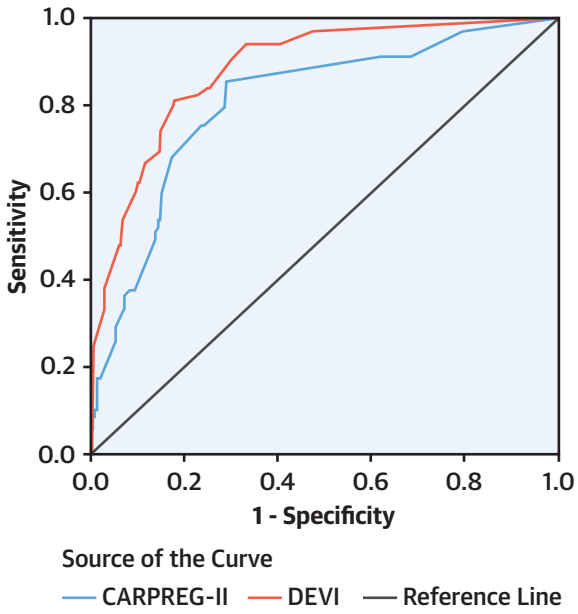
MODEL PERFORMANCE. Temporal validation of the DEVI score. In response to our primary objective, the AUC for the DEVI score, as seen in **Figure 2**, was 0.884 (95% CI: 0.844-0.923), indicating the excellent ability to discriminate those with and without adverse cardiac outcome. The DEVI score also showed fair agreement between predicted and observed risks overall, with a calibration, y = 0.997x - 0.727, with lower actual observed outcomes at higher expected probabilities (an overestimate) as shown in **Figure 3A**. The decision curve analysis (**Figure 4**) revealed the benefits of using the DEVI score to

FIGURE 1 **Incidence of Adverse Cardiac Events and the Risk Stratification Scores**



The percentages associated with the "total" represent the proportion of each risk group as a function of the total number of study population **(blue bars)**. The percentages associated with the "composite outcome" represent the frequency of one or more outcome events within the risk groups **(red bars)**. CARPREG-II = Cardiac Disease in Pregnancy; DEVI = Adverse Cardiac Events in Valvular Heart Disease in Pregnancy score; mWHO = modified World Health Organization.

FIGURE 2 Receiver-Operator Characteristic Curve for Risk Stratification Models



The area under the receiver-operator characteristic curve for DEVI score **(red)**, CARPREG-II score **(blue)**, and the reference line **(black)**. The AUC for the DEVI score was 0.884 (95% CI: 0.844-0.923), and for CARPREG-II was 0.808 (95% CI: 0.753-0.863), showing good discrimination. Abbreviations as in Figure 1.

predict which pregnant patients with VHD are at risk of composite adverse cardiac outcomes for predicted probability thresholds between 0.1 to 0.5. This implies that for thresholds below 0.1 and above 0.5, the score offers no net benefit compared with managing all pregnant patients with VHD as if they will (suggesting universal referral to tertiary centers) or will not (suggesting routine care for all) have adverse outcomes, respectively.

External validation of the CARPREG-II score in a VHD population. The AUC for CARPREG-II was 0.808 (95% CI: 0.753-0.863), suggesting good discriminatory ability for composite adverse cardiac outcomes (Figure 2). In terms of calibration, the slope of the CARPREG-II score was 0.808, with an intercept of −0.455 (Figure 3). Finally, the predicted probability thresholds for CARPREG-II were between 0.1 and 0.4, implying that for thresholds below 0.1 and above 0.4, the CARPREG-II score offers no net benefit about where the patient should be managed to prevent adverse outcomes (Figure 4).

The comparison of the discriminative capacity of DEVI and CARPREG-II scores showed the area under the curve to be significantly different in the study population (chi-square 7.06; P value = 0.008) is shown in Figure 2. Although both scores showed fair agreement between predicted and observed risks overall, the DEVI score showed lower actual observed outcomes at higher expected probabilities (overestimated risk at higher probabilities), and the CARPREG-II score showed higher expected probabilities (overestimate) at both the extremes and lower predicted probabilities (underestimate) in the middle (Figure 3).

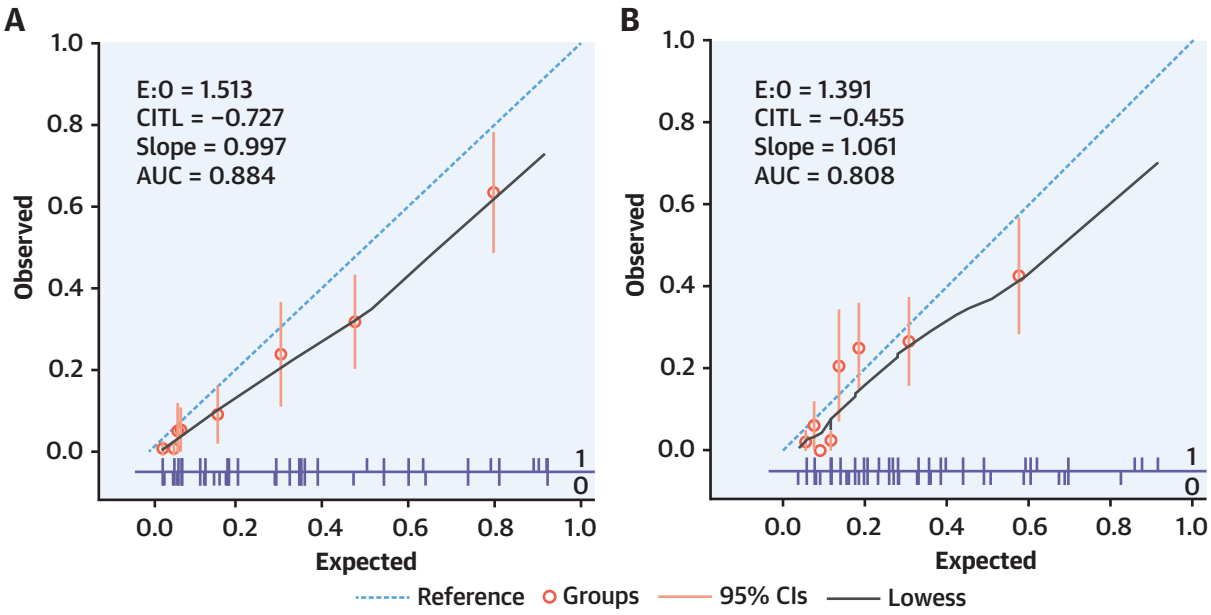
LABOR, DELIVERY, AND FETAL/NEONATAL OUTCOMES. A total of 49 (8.5%) pregnancies resulted in miscarriages, including 12 medical terminations of pregnancy (Table 3). In assessing the pregnancy outcomes, those who continued past 20 weeks were included; the mean gestational age at birth was 38.0 weeks, and the cesarean rates were 25.1% (n = 132). Small-for-gestational-age infants accounted for 179 (33.9%), and there were 15 perinatal losses, of which 11 (2.1%) were stillbirths, and 4 (0.8%) were neonatal deaths. The median duration of hospital stays, including the antenatal period, was 9 days (IQR: 6-16 days).

DISCUSSION

MAIN FINDING. In this cohort study conducted among pregnancies in patients with VHD in a middle-income setting, 12% of pregnancies were complicated by at least 1 adverse cardiac event. Temporal validation of the DEVI score suggested excellent discriminatory properties (the ability to rank patients to risk) and overall fair agreement between observed and calculated risk (calibration), with a tendency to overestimate risk at higher probabilities. Although the CARPREG-II score also demonstrated good discriminatory properties (Central Illustration), it overestimated the risk at higher and lower calculated probabilities and underestimated the risk at middle computed probabilities. The net benefit is observed between the lower threshold of 10% and an upper threshold probability of 50% in the DEVI score compared with 40% using the CARPREG-II score.

INTERPRETATION. VHD is associated with a high incidence of adverse cardiac and obstetric outcomes. A systematic review of moderate and severe VHD reported high rates of maternal mortality (1% with moderate mitral stenosis [MS] vs 3% with severe MS), heart failure (18% vs 37%), and new or recurrent arrhythmias (18% vs 16%). Moderate and severe MS were also associated with high stillbirth rates (4%-5%) and neonatal death (2%). In comparison, our study had fewer adverse cardiac and obstetric events; this may be because of the following: 1) a wider range of

FIGURE 3 Calibration Plots for DEVI Score and CARPREG-II Score Models



(A) DEVI score; **(B)** CARPREG-II score. A calibration plot for each score with the 8 different percentile groups (represented as groups with 95% CI) of predicted probabilities is shown in the image. The **reference line** indicates a perfect relationship between predicted and observed probabilities, and the fitted curve using the Lowess method shows the observed relationship. C-statistics is the area under the receiver-operating characteristics curve. DEVI score also showed fair agreement between predicted and observed risks overall, with lower actual observed outcomes at higher expected probabilities (an overestimate). CARPREG-II score showed higher expected probabilities (overestimate) at both the extremes and lower predicted probabilities (underestimate) in the middle. CITL = calibration in the large; E/O = ratio of expected to observed; other abbreviations as in Figure 1.

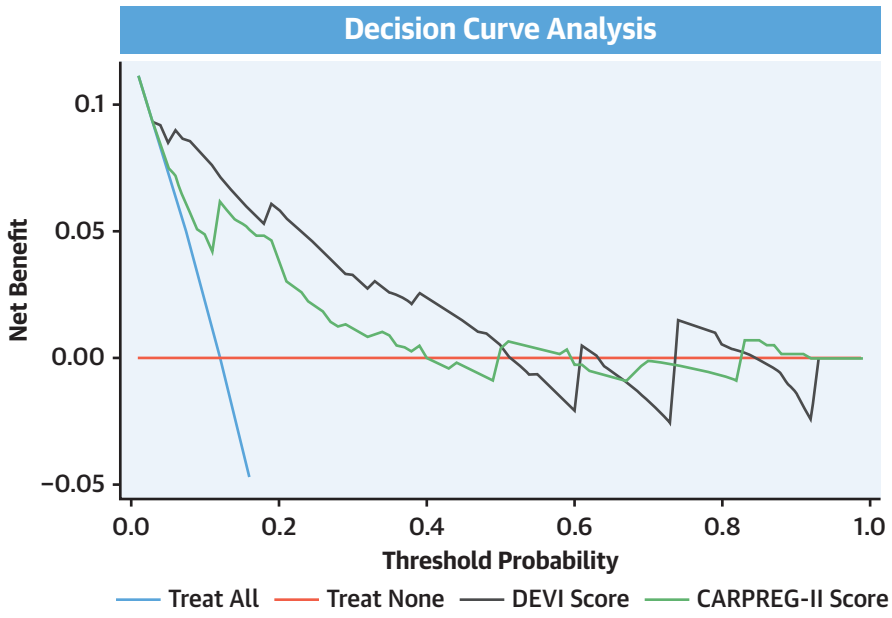
severity in the primary cardiac lesions; 2) a high proportion of patients on beta-blockers during pregnancy; and 3) an increasingly experienced multidisciplinary team caring for pregnant patients with cardiac care.[17] In 28% of the pregnancies, the diagnosis of VHD was made during pregnancy. This is common in LMICs, where between 25% and 53% of diagnoses of VHD are made during pregnancy.[7,18] Mitral valve lesions, especially mitral regurgitation, were the most common valvular lesions. Although mitral regurgitation is generally well tolerated in pregnancy, as substudy from the CARPREG group shows that not all have a lower risk, especially those with concomitant risk factors.[19]

There are some fundamental differences between this study cohort and the CARPREG-II cohort, which may explain the lower rate of cardiac events in this study (12.1% vs 15.8%). First, the greater need for interventions during pregnancy (5.0% vs 1.2%) and the higher use of heart failure medications (beta-blockers or diuretic agents) indicate the difference in the protocols followed. Second, there was a difference in the duration of capture of adverse cardiac events (3-5 days postpartum in our study vs up to 6 days postpartum in the CARPREG-II study).[5] Finally, although the composite adverse event rate was lower in our study, maternal deaths were higher (1.8% vs 0.3%).[5]

The incidence of SGA infants (34.1%) was high, similar to the data from LMICs.[20] These high rates may be linked to the socioeconomic strata in which VHD is more common, and medication such as beta-blockers and the severity of disease processes in these patients may also contribute. Miscarriages accounted for 8.5% of all pregnancies, higher than reported in CARPREG-II (<5%).[5] The cesarean rates were 25.1%, similar to the study from the Netherlands (25%) and lower than the report from the ROPAC (Registry Of Pregnancy And Cardiac disease) investigators (52% among those with mitral valve disease).[21,22] As most of them underwent cesarean sections for obstetric indications, this may be attributed to the difference in labor ward protocols and indications and thresholds for performing cesarean sections.

VHD remains the most common cardiac lesion complicating pregnancy in LMICs.[1] Many pregnant patients with VHD live in rural regions and depend

FIGURE 4 Decision Curve Analysis of DEVI Score and CARPREG-II Score



The Decision Curve Analysis revealed the benefits of using the DEVI score in predicting pregnant patients with valvular heart disease at risk of composite adverse cardiac outcomes for predicted probability thresholds between 0.1 and 0.5. whereas it was between 0.1 and 0.4 for the CARPREG-II score. Abbreviations as in Figure 1.

primarily on the available primary health centers for antenatal and peripartum care. Diagnosing a high-risk condition such as VHD before or during pregnancy results in referrals to tertiary or regional centers for advanced cardio-obstetrics care, where better diagnostic and interventional facilities are available. These referrals result in a considerable resource and economic burden to health care systems, and distress, inconvenience, and increased costs to patients and families with strained financial resources.[1,3,7,23] Risk stratification that relies on readily-available data and is based on a personalized approach performed in a primary care setting (as shown in the Clinical Scenario in Figure 5) could facilitate necessary and timely referrals to specialized care centers, thereby reducing the negative effects on families and health care systems, especially in LMICs.

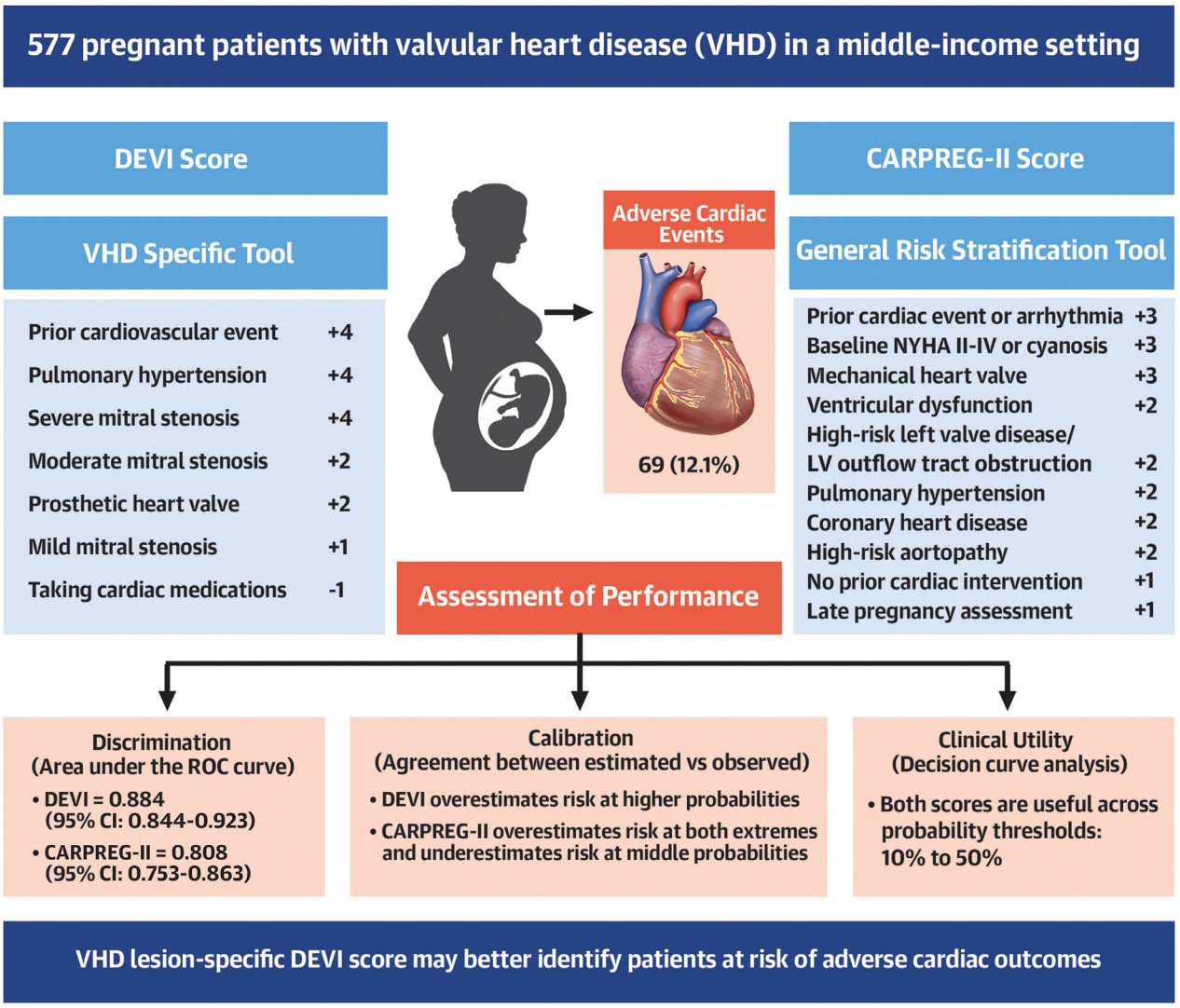
The performance of a clinical prediction rule or a risk stratification model is determined by its ability to *discriminate* those at risk of adverse outcomes from those who are not and accurately estimate the probability of the event (calibration).[14,16] The DEVI and CARPREG-II scores were shown to have almost similar discriminative ability. In contrast, the

TABLE 3 Obstetric, Fetal, and Neonatal Outcomes

Abortions[a]	49 (8.5)
Spontaneous	37 (6.4)
Induced	12 (2.1)
Gestational diabetes[a]	77 (13.3)
Hypertensive disorders[a,b]	50 (8.7)
Preeclampsia	30 (5.2)
Gestational age at delivery, wks[c]	38.0 ± 2.2
Cesarean births[c]	132 (25.1)
Operative vaginal births[c]	132 (25.1)
Stillbirths[d]	11 (2.1)
Mean birth weight,[d] g	2,650.6 ± 604.6
Preterm birth[d]	
At <37 wks	93 (17.7)
At <34 wks	28 (5.3)
Small for gestational age (<10th centile for gestation)	192 (36.1)
Admission to neonatal intensive care unit (NICU)[e]	65 (12.6)
Neonatal death[e]	4 (0.8)
Duration of maternal hospital stay, d[a]	9 (6-16)

Values are n (%), mean ± SD, or median (25th to 75th percentile). [a]Among 577 pregnancies. [b]According to International Society for the Study of Hypertension in Pregnancy 2018 criteria. [c]Among 528 pregnancies that crossed 20 weeks of gestational age. [d]Among 532 births including multiple pregnancies (n = 4), which crossed 20 weeks of gestational age. [e]Among 521 live-born babies, after excluding stillbirth (n = 11).

CENTRAL ILLUSTRATION **Validation of Risk-Stratification Models in Pregnant Patients With Valve Disease**

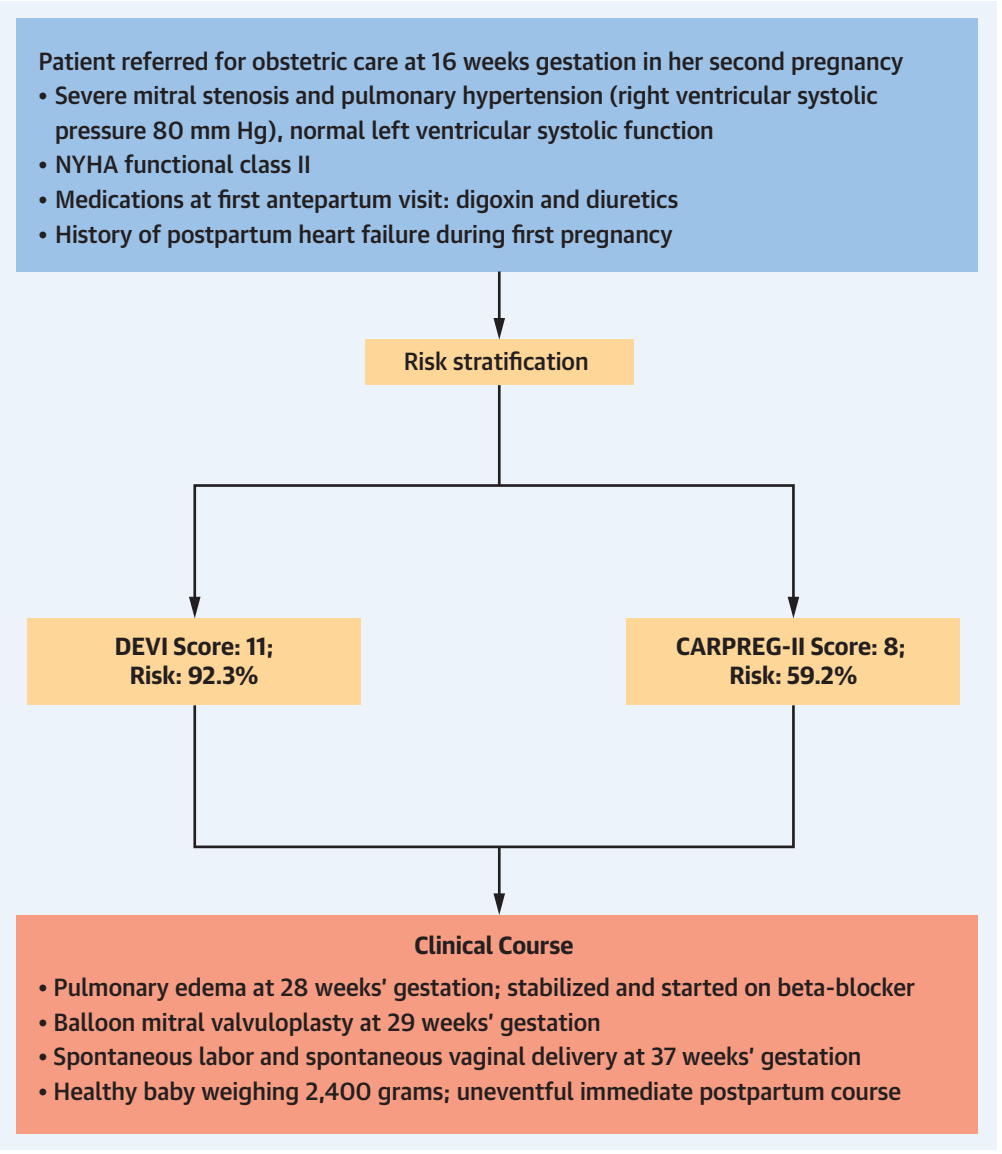


Pande SN, et al. J Am Coll Cardiol. 2023;82(14):1395-1406.

In this cohort of 577 pregnant women with valvular heart disease, risk stratification was performed using the DEVI and CARPREG-II scores to assess the utility of these scoring systems in predicting composite adverse cardiac events during pregnancy and the immediate postpartum period. Individual predicted risk was calculated using the original logistic regression provided in the original studies. Composite cardiac events were observed in 12.1%. Both scores were shown to aid in discriminating women who develop composite cardiac events from those who did not, but the agreement between predicted and observed events was better with the DEVI score. Risk stratification model developed from a homogenous population of pregnant patients with valvular heart disease (VHD), may better identify patients at risk of adverse cardiac outcomes. CARPREG-II = Cardiac Disease in Pregnancy; DEVI = Adverse Cardiac Events in Valvular Heart Disease in Pregnancy score; ROC = receiver-operator characteristic.

calibration was better with the DEVI score, which shows the observed risk to be similar to the predicted risks across various quintiles of thresholds over a broad predicted range. The decision curve analysis of both risk stratification models demonstrated the clinical utility over a range of predicted probabilities. There are several reasons for this: 1) although they are from a similar population, the DEVI score was developed in a homogenous group of VHD from middle-income settings, whereas CARPREG-II was developed from a high-income setting in a cohort with predominantly congenital heart disease, where the

FIGURE 5 Clinical Scenario Showing the Utility of Risk Stratification Models



Calculation for the individual patient in the figure showing an increased risk of the adverse cardiac event with patient requiring urgent balloon mitral valvulotomy, and was able to have vaginal delivery. Expected risk for the patient was calculated using the beta coefficients from the logistic regression analyses in the original papers of DEVI and CARPREG-II scores. Abbreviations as in Figure 1.

risk factors vary from those of VHD; and 2) the DEVI score is primarily aimed at the in-hospital complications, whereas CARPREG-II included complications within 6 months of delivery.

Additional risk factors, such as severe mitral regurgitation, use of anticoagulants, presence of atrial fibrillation, as well as the effect of starting medications and performing interventions during pregnancy, all of which could potentially modify the risk, need to be considered in the future recalibration of the DEVI score. Although the results of this study suggest that lower-risk patients may not need to receive their obstetric care in a tertiary center and can receive it in the community, the validity of the use of the DEVI score in triaging referral to tertiary care will require future studies involving health systems with

both community and tertiary care sites. The risk factors for adverse cardiac outcomes may vary with the type or category of the lesion; thus, a lesion or category-specific (congenital heart disease, and so on) risk stratification score may be more helpful. This may necessitate using advanced statistical packages such as machine learning to overcome the limitations of conventional methods like multicollinearity.[24] Although combining individual risks into coefficient-weighted scores may facilitate risk stratification without the need for calculations, it may reduce discriminative and calibration accuracy. A web-based calculator may further enhance the performance and utilization of the risk stratification scores/rules.[4]

STUDY STRENGTHS AND LIMITATIONS. This prospective study which included consecutive pregnancies with VHD seen at a tertiary referral center with cardio-obstetrics expertise avoided selection bias. Using strict, predetermined definitions based on the developmental cohorts of the DEVI and CARPREG-II scores also reduced outcome classification bias. As recommended in published guidelines, the study assessed both discrimination and calibration accuracy as a strength of the study.[8] In addition, calculating individual probability using the equation from the developmental cohort and using decision curve analysis without a particular cutoff for risk assessment helped in the performance assessment.[15] The study also has some limitations. Lower event rates during the study period than the developmental cohort (mention event rate) may have influenced the calibration. The role of other potential risk-stratification factors such as exercise testing and assessment of hemodynamic and biomarkers such as brain natriuretic peptide levels were not done routinely in our middle-income setting and therefore could not be included in model development or validation. Progression to NYHA functional class III-IV or a worsening by ≥2 NYHA functional classes was considered a significant secondary outcome in the study, but the possibility of these symptoms, albeit less likely to be the result of physiologic changes of pregnancy, could not be ruled out entirely.

Another limitation may be the treatment paradox, which challenges risk stratification models or the clinical prediction rules.[25] This refers to the differential (possibly more aggressive) treatment of patients at the highest risk, affecting the score's performance. Most patients in our setting return to their communities after delivery and are followed up in nearby health centers. Obtaining data from these centers in a middle-income setting is currently not feasible. Hence, the study period was restricted to 3 to 5 days postpartum, which is reflective of when patients are routinely discharged from the hospital. Acknowledging that many adverse events occur later in the postpartum period, future studies need to consider follow-up in the extended postpartum period.

CONCLUSIONS

In relation to risk-stratification in pregnant patients with primarily rheumatic VHD in a middle-income country, the DEVI and CARPREG-II scores aid in correctly classifying those who develop adverse cardiac outcomes during pregnancy and childbirth (discrimination). The lesion-specific DEVI score showed better agreement between the predicted and observed events (calibration). However, the DEVI score needs to be externally validated in diverse community settings to increase its usability and clinical application.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

The authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Anish Keepanasseril, Department of Obstetrics and Gynaecology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Dhanvantri Nagar, Puducherry 605006, India. E-mail: keepan_r@yahoo.com OR keepanasseril.a@jipmer.edu.in.

PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: VHD in pregnant women is associated with adverse cardiac and obstetrical outcomes, especially in low-to-middle-income settings.

TRANSLATIONAL OUTLOOK: Risk stratification schemes developed from a homogenous population of pregnant patients with VHD may better identify patients at risk of adverse cardiac outcomes than those from more heterogeneous data sets.

REFERENCES

1. French KA, Poppas A. Rheumatic heart disease in pregnancy: global challenges and clear opportunities. *Circulation*. 2018;137(8):817–819.

2. Say L, Chou D, Gemmill A, et al. Global causes of maternal death: a WHO systematic analysis. *Lancet Glob Health*. 2014;2(6):e323–e333.

3. Watkins DA, Johnson CO, Colquhoun SM, et al. Global, regional, and national burden of rheumatic heart disease, 1990-2015. *N Engl J Med*. 2017;377(8):713–722.

4. D'Souza RD, Silversides CK, Tomlinson GA, Siu SC. Assessing cardiac risk in pregnant women with heart disease: how risk scores are created and their role in clinical practice. *Can J Cardiol*. 2020;36(7):1011–1021.

5. Silversides CK, Grewal J, Mason J, et al. Pregnancy outcomes in women with heart disease: the CARPREG II Study. *J Am Coll Cardiol*. 2018;71(21):2419–2430.

6. Siu SC, Evans KL, Foley MR. Risk assessment of the cardiac pregnant patient. *Clin Obstet Gynecol*. 2020;63(4):815–827.

7. Baghel J, Keepanasseril A, Pillai AA, Mondal N, Jeganathan Y, Kundra P. Prediction of adverse cardiac events in pregnant women with valvular rheumatic heart disease. *Heart*. 2020;106(18):1400–1406.

8. Ramspek CL, Jager KJ, Dekker FW, Zoccali C, van Diepen M. External validation of prognostic models: what, why, how, when and where? *Clin Kidney J*. 2021;14(1):49–58.

9. Binuya MAE, Engelhardt EG, Schats W, Schmidt MK, Steyerberg EW. Methodological guidance for the evaluation and updating of clinical prediction models: a systematic review. *BMC Med Res Methodol*. 2022;22(1):316.

10. Lancellotti P, Tribouilloy C, Hagendorff A, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 1: aortic and pulmonary regurgitation (native valve disease). *Eur J Echocardiogr*. 2010;11(3):223–244.

11. Lancellotti P, Moura L, Pierard LA, et al. European Association of Echocardiography recommendations for the assessment of valvular regurgitation. Part 2:mitral and tricuspid regurgitation (native valve disease). *Eur J Echocardiogr*. 2010;11(4):307–332.

12. Harris PA, Taylor R, Minor BL, et al. The REDCap consortium: building an international community of software platform partners. *J Biomed Inform*. 2019;95:103208.

13. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. *Eur Heart J*. 2018;39(34):3165–3241.

14. Nahm FS. Receiver operating characteristic curve: overview and practical use for clinicians. *Korean J Anesthesiol*. 2022;75(1):25–36.

15. Vickers AJ, van Calster B, Steyerberg EW. A simple, step-by-step guide to interpreting decision curve analysis. *Diagn Progn Res*. 2019;3:18.

16. Wynants L, van Smeden M, McLernon DJ, et al. Three myths about risk thresholds for prediction models. *BMC Med*. 2019;17(1):192.

17. Ducas RA, Javier DA, D'Souza R, Silversides CK, Tsang W. Pregnancy outcomes in women with significant valve disease: a systematic review and meta-analysis. *Heart*. 2020;106(7):512–519.

18. Poli PA, Orang'o EO, Mwangi A, Barasa FA. Factors related to maternal adverse outcomes in pregnant women with cardiac disease in low-resource settings. *Eur Cardiol*. 2020;15:e68.

19. Pfaller B, Dave Javier A, Grewal J, et al. Risk associated with valvular regurgitation during pregnancy. *J Am Coll Cardiol*. 2021;77(21):2656–2664.

20. Lee AC, Kozuki N, Cousens S, et al. Estimates of burden and consequences of infants born small for gestational age in low and middle income countries with INTERGROWTH-21(st) standard: analysis of CHERG datasets. *BMJ*. 2017;358:j3677.

21. van Hagen IM, Thorne SA, Taha N, et al. Pregnancy outcomes in women with rheumatic mitral valve disease: results from the registry of pregnancy and cardiac disease. *Circulation*. 2018;137(8):806–816.

22. Petrus AHJ, Jongert BL, Kies P, et al. Evaluation of mode of birth in pregnant women with heart disease. *Eur J Obstet Gynecol Reprod Biol*. 2020;248:150–155.

23. Minja NW, Nakagaayi D, Aliku T, et al. Cardiovascular diseases in Africa in the twenty-first century: gaps and priorities going forward. *Front Cardiovasc Med*. 2022;9:1008335.

24. Chan JY-LLS, Bea KT, Cheng WK, Phoong SW, Hong Z-W, Chen Y-L. Mitigating the multicollinearity problem and its machine learning approach: a review. *Mathematics*. 2022;10:1283.

25. van Geloven N, Swanson SA, Ramspek CL, et al. Prediction meets causal inference: the role of treatment in clinical prediction models. *Eur J Epidemiol*. 2020;35(7):619–630.

KEY WORDS CARPREG-II score, composite adverse cardiac outcome, DEVI score, pregnancy, rheumatic heart disease, risk stratification, valvular heart disease

APPENDIX For a supplemental table, please see the online version of this paper.