Review: *Novel CHA2DS2-VASc-HSF is Superior to CHADS2 and CHA2DS2-VASc Score to Predict the Risk of Severe Coronary Artery Disease*

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Novel CHA_2DS_2-VASc-HSF is Superior to $CHADS_2$ and $CHA2DS_2$-VASc Score to Predict the Risk of Severe Coronary Artery Disease

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Abstract

BACKGROUND: Various risk scoring methods are available to predict the severity of coronary artery disease (CAD). However, the majority of them are complex and require advanced technologies, thus limiting its usage in primary care settings. CHA_2DS_2-VASc-HSF is a novel risk scoring which we develop from CHA_2DS_2-VASc score.

AIM: We hypothesize that CHA_2DS_2-VASc-HSF is predictive for the risk of severe CAD, and we compare its validity with previously established $CHADS_2$ and CHA_2DS_2-VASc score.

MATERIALS AND METHODS: A total of 210 patients who underwent elective coronary angiography were enrolled in our study. Anthropometric, laboratory, angiographic findings, and patient history were obtained from medical records and used to calculate CHA_2DS_2-VASc-HSF score. Severe CAD defined as coronary artery occlusion with the Gensini score of ≥20. Statistical analyses were done using SPSS 25.0 and MedCalc 18.2.1.

RESULTS: This research showed that the patient with severe CAD has significantly higher $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF score compared to normal and mild CAD ($p < 0.001$). $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF correlated significantly with the CAD severity ($r = 0.315$, $p \leq 0.001$; $r = 0.395$, $p \leq 0.001$; $r = 0.612$, $p \leq 0.001$, respectively). CHA_2DS_2-VASc-HSF may predict the risk of severe CAD independent from other variables (odds ratio = 2.540; 95% confidence interval = 1.794–3.595; $p = 0.002$) with the cutoff value of ≥2.5 (sensitivity = 81.4% and specificity = 68.1%). Pairwise comparison of receiver operating characteristic curves showed that CHA_2DS_2-VASc-HSF was superior to predict severe CAD.

CONCLUSIONS: CHA_2DS_2-VASc-HSF scores may predict the risk of severe CAD better than $CHADS_2$ and CHA_2DS_2-VASc score. This score may easily be used in primary care physicians to predict the risk of severe CAD and provide an early referral to the cardiologist.

Introduction

Coronary artery disease (CAD) remained the top cause of mortality and morbidity for a person aged 35 and over worldwide [1], [2]. Failure to detect CAD and provide early treatment may cause CAD treatment to become a more expensive and higher mortality rate [2]. It is estimated that around one-third of the middle age's population in the USA will suffer from CAD manifestation [3]. In Indonesia, the Indonesian Ministry of Health also showed that CAD is the leading cause of morbidity, which is responsible for 12.9% of death [4].

Determining the best risk factor assessment for CAD is extremely important for early prevention and treatment. The screening for CAD using angiography is easily available in developed countries with short waiting lists. However, in developing countries, the awareness and accessibility of cardiovascular disease screening are still low [5]. To obtain cost-effective prevention and treatment of CAD at the patient level, stratification of the cardiovascular risk using a simple method is extremely important. Cardiovascular risk screening will have a relevant implication for decision making in early referral and healthcare resource allocation [6].

At present, $CHADS_2$ and CHA_2DS_2-VASc scores have been established as clinical predictors for cardiac thromboembolism and indication of antithrombotic therapy [7]. Both $CHADS_2$ and CHA_2DS_2-VASc component has similarities with the risk factors of CAD development [8]. The components within the $CHADS_2$ score also had been proven in large cohort studies to be associated with CAD in with ischemic stroke patients [9], while CHA_2DS_2-VASc is the refinement of $CHADS_2$ score, which has been proven to outperform its predecessor in the various patient group, including AF patient who received elective electrical cardioversion [10]. This suggests CHA_2DS_2-VASc score may predict the risk for both cerebrovascular and cardiovascular diseases. However, these scores did not include the major risk factors of CAD such as smoking, hyperlipidemia, and family histories. Hence, this

research aims to improve the validity of the CHA_2DS_2-VASc score by including new major risk factor of CAD which are hyperlipidemia (H), smoking (S), and family history of CAD (F) and compare it with the previous $CHADS_2$ and CHA_2DS_2-VASc score to predict severe CAD in the patients.

Materials and Methods

Study design

This cross-sectional study involves 210 consecutive patients who underwent coronary angiography in the Cardiology Department of Ramelan Navy Hospital Surabaya during 1 year period between January-December 2018. Coronary artery occlusion was assessed from angiograms using the Gensini score. Patients with infectious processes within 2 weeks before catheterization, hepatic dysfunction, thyroid dysfunction, cancer, and chronic kidney disease were excluded from the study. This study had received ethical clearance (No.06/EC/KERS/2019) from the local ethics committee. Informed consents were obtained and details which disclose patients' identity were omitted.

Risk factor data collection

Clinical findings, 12-lead electrocardiogram, and echocardiographic examination were performed based on the American Society of Echocardiography guidelines [11]. The standard laboratory was performed to measure fasting blood glucose (FBG), total cholesterol, and renal function tests from the blood samples [12].

CHA_2DS_2-VASc-HSF score consists of congestive cardiac failure (C), hypertension (H), age >75 years (A), diabetes mellitus (D), stroke (S), vascular diseases (V), age 65–74 years (A), sex category (Sc), hyperlipidemia (H), smoking (S), and family history of cardiovascular disease (F) were obtained by medical record thorough examination. Congestive cardiac failure (C) score was given if left ventricular ejection fraction was reduced (<45%) from echocardiography examination. Hypertension (H) was defined as systolic blood pressure >140 mmHg or diastolic <90 mmHg for repeated measurement, or when the patient was taking antihypertensive medications. Diabetes mellitus (D) Type 2 was defined FBG >126 mg/dl, previous diabetes diagnosis, or when the patient was taking anti-diabetic medications. Stroke (S) was defined as the history or current diagnosis of stroke or TIA which was given by the patients. Vascular disease (V) was defined from the existence of a pathologic condition which causes stenosis of at least 50% in the non-coronary artery. Hyperlipidemia (H) defined as a cholesterol level of more than 200 mg/dL based on the National Cholesterol Education Program or when the patient is consuming of lipid-lowering medications. Cigarette smoking (S) was defined as the habit of smoking of more than five cigarettes per-day without a quit attempt for a minimum of 1 year. Family history of cardiovascular disease (F) was defined as the presence of cardiovascular disease or sudden cardiac-related death of the first degree-relative.

CHA_2DS_2-VASc-HSF scoring

CHA_2DS_2 score was calculated by adding 1 point for the presence of chronic heart failure, age >75 years, DM and hypertension by assigning 2 points for the history of stroke or TIA. In the CHA_2DS_2-VASc score, age 65–74 was assigned for 1 point (A) and age >75 years (A_2) was assigned for 2 points. The CHA_2DS_2-VASc-HSF score put 1 point for the finding of hyperlipidemia (h), smoking (S), and family history of the cardiac disease (F).

Coronary angiography and Gensini scoring

Judkins technique 4 with 5-F catheters was used to perform cannulation of coronary arteries. Kodak 35-mm cinefilm was used to record the images at 30 frames/s. Computer-assisted coronary angiography analysis system was used to detect coronary stenosis (Mipron 1; Kontron, Tokyo, Japan). One minute after the injection of ISDN (2.5 mg/5 mL for 20 s) through the Judkins catheter, several projections were taken to observe the coronary angiography. Coronary atherosclerosis severity was measured using the Gensini scoring method, as described previously [12].

Calculation of the Gensini score was done for each patient through the severity score assignment based on coronary occlusion. Narrowing between 1 and 25% will be scored 1, 26–50% will be scored 2, 51–75% will be scored 3, 75–90% will be scored 8, 91–99% will be scored 16, and 100% will be scored 32. The score is then multiplied based on the location and importance of the artery. We multiply by factor 5 for left main coronary artery occlusion, 2.5 for both proximal circumflex artery and proximal left anterior descending artery, 1.5 for a mid-left anterior descending artery, and 1 mid or distal circumflex artery, for distal left anterior descending artery and the right coronary artery. The multiplication factor for any other branch is 0.5 [3].

Statistical analyses

Data analyses were performed using SPSS Statistics 25.0 and MedCalc 18.2.1. Continuous variables, presented as mean ± standard deviation (SD), were compared using ANOVA test. Correlation between

parametric variables was obtained using Spearman's Rho followed by logistic regression. Specificity and sensitivity were obtained from the receiver operating characteristic (ROC) curve and cutoff point analysis. Area under the curve (AUC) comparison was done using the pairwise comparison method as described previously [13].

Results

Clinical characteristics of the patients

The total of 210 patients was involved in this study. Table/Figure 1 shows the characteristics of the participant, which grouped based on the CAD severity. Of the 210 patients, 70 patients had normal angiogram (Gensini score = 0, 33.3%), 48 patient had mild CAD (Gensini score = 1–19, 22.9%), and 92 patients had obstructive/severe CAD (Gensini score >20, 43.8%). The comparison of the baseline demographics and characteristics of the three groups (normal coronary arteries, mild CAD, and severe CAD) is presented in Table 1.

From Table 1, significant differences between severe CAD and normal angiography groups were observed on the age, FBG, ureum, and creatinine which are the CAD risk factors. $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF score also significantly higher on the patient with severe CAD compared to the patient with normal angiography.

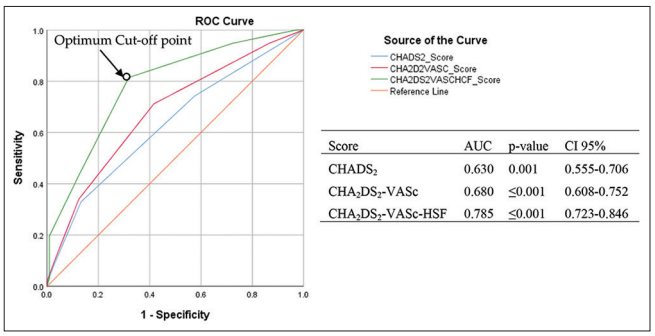

Figure 1: Receiver operating characteristic curve of $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF score to predict severe CAD. AUC: Area under the curve; CI: Confidence interval

Correlations between multiple variables with CAD severity

The correlation test was used to identify the factors associated with the severity of CAD. Table 2 shows the results of Spearman's correlations between Gensini score and multiple independent variables in the in subjects. Spearman's correlation analysis showed that the highest correlation was identified on the CHA_2DS_2-VASc-HSF score with Gensini score, which showed a moderate to strong correlation (r = 0.612, p = ≤ 0.001).

Logistic linear regression analysis of the variables to predict severe CAD

Univariate and multivariate logistic linear regression analysis was done on various variables in predicting the outcome (severe CAD) as presented in Tables 3 and 4. The analysis from Tables 3 and 4 showed that $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF were significant predictors for severe CAD.

Specificity and sensitivity test using ROC curves

From the ROC curves in Figure 1, it is suggested that CHA_2DS_2-VASc-HSF score has higher AUC compared to $CHADS_2$ and CHA_2DS_2-VASc score. Optimum cutoff point analysis showed that the CHA_2DS_2-VASc-HSF score ≥2.5 provided the highest predictive value for severe CAD (sensitivity = 81.4% and specificity = 68.1%). Pairwise comparison from Table 5 showed that the CHA_2DS_2-VASc-HSF score was found to be the best scoring scheme to predict severe CAD compared to $CHADS_2$ and CHA_2DS_2-VASc score.

Table 1: Characteristics of the patients based on CAD severity

Variables*	CAD severity			p-value
	Normal angiogram (n=70)	Mild CAD (n=48)	Severe CAD (n=92)	
Age (years)	50.97 ± 8.95[b,c]	53.87 ± 10.90[a]	54.65 ±9.13[a]	≤0.001
SBP (mmHg)	131.81 ± 26.17	123.00 ± 16.67	130.90 ± 23.05	0.691
DBP (mmHg)	72.81 ± 10.86	76.53 ± 9.12	77.58 ± 9.23	0.463
Weight (kg)	69.48 ± 12.43	65.27 ± 7.70	70.03 ± 9.88	0.369
Height (m)	164.06 ± 8.59	164.33 ± 3.90	165.45 ± 5.79	0.208
BMI (kg/m^2)	25.67 ± 3.26	24.22 ± 3.28	25.55 ± 3.15	0.341
Hb (g/dL)	14.01 ± 1.11	13.63 ± 1.73	14.60 ± 3.75	0.474
WBC (cells/µL)	7434.2 ± 1725.5	6746.0 ± 1624.1	7350.1 ± 2108.5	0.292
HCT (%)	41.63 ± 3.64	41.20 ± 4.89	42.46 ± 4.36	0.897
Platelet (×10^3 cells/µL)	273.00 ± 78.55	271.66 ± 47.73	258.12 ± 52.97	0.268
PT (s)	13.31 ± 1.28	13.56 ± 2.67	13.56 ± 3.46	0.301
APTT (s)	32.56 ± 3.23	31.33 ± 6.19	33.39 ± 5.27	0.097
FBG (mg/dL)	108.06 ± 37.97[c]	114.13 ± 32.82	112.45 ± 34.39[a]	0.032
Ureum (mg/dL)	12.45 ± 3.15[b,c]	16.81 ± 5.20[a]	16.45 ± 7.70[a]	0.005
Creatinine (mg/dL)	1.00 ± 0.31[b,c]	1.27 ± 0.25[a]	1.16 ± 0.26[a]	0.005
Ejection fraction (%)	57.65 ± 18.31	64.73 ± 5.96	52.15 ± 16.85	0.474
$CHADS_2$ Score	0.68 ± 0.65[b,c]	0.60 ± 0.99[a]	1.08 ± 0.94[a]	≤0.001
CHA_2DS_2-VASc Score	1.32 ± 0.83[b,c]	1.47 ± 1.06[a]	1.95 ± 1.04[a]	≤0.001
CHA_2DS_2-VASc-HSF Score	2.06 ± 0.77[b,c]	2.33 ± 1.23[a,c]	3.43 ± 1.20[a,b]	≤0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index, Hb: Hemoglobin; WBC: White blood cells; HCT: Hematocrit; PT: Prothrombin time; APTT: Activated partial thromboplastin time; FBG: Fasting blood glucose; SD: Standard deviation. Values are presented as a mean±SD; different annotation showed a significant difference (p<0.05) for the *post hoc* LSD test to normal angiogram (a), mild CAD (b) and severe CAD (c).

Discussion

The major findings of this research were: (1) CHA_2DS_2-VASc-HSF score was significantly increased both mild and severe CAD patients, (2) the $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF scores have positive and significant correlation with CAD severity measured by Gensini score, (3) $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF are significant predictors for severe CAD, the highest odds ratio was found on the CHA_2DS_2-VASc-HSF score, and (4) CHA_2DS_2-VASc-HSF was the best score to predict severe CAD with the cutoff point of ≥2.5.

Table 2: Spearman's correlations between various independent variables with CAD Gensini score

Variables*	Correlation coefficient (r)
Age (years)	0.276**
FBG (mg/dL)	0.180*
Ureum (mg/dL)	0.232**
Creatinine (mg/dL)	0.204**
WBC	0.236**
Ejection fraction (%)	–0.215**
CHA_2DS_2	0.315**
CHA_2DS_2-VASc	0.395**
CHA_2DS_2-VASc-HSF	0.612**

*Significant correlation at p<0.05, **Significant correlation at p<0.01. FBG: Fasting blood glucose; WBC: White blood cells.

Table 3: Univariate regression analysis for the predictors of severe CAD

Variables	Odds ratio	95% CI	p-value
Age (years)	1.036	1.007–1.066	0.013
SBP (mmHg)	1.003	0.992–1.015	0.585
DBP (mmHg)	1.015	0.990–1.042	0.242
BMI (kg/m^2)	1.016	0.933–1.106	0.721
Hb (g/dL)	1.072	0.861–1.335	0.551
WBC (cells/μL)	1.000	1.000–1.000	0.676
HCT (%)	0.995	0.899–1.102	0.929
Platelet (× 10^3 cells/μL)	1.000	1.000–1.000	0.615
FBG (mg/dL)	1.009	1.001–1.017	0.024
Ureum (mg/dL)	1.103	1.045–1.164	≤0.001
Creatinine (mg/dL)	5.000	1.756–14.233	0.005
Ejection fraction (%)	0.390	0.059–2.563	0.474
CHA_2DS_2 score	1.834	1.304–2.580	≤0.001
CHA_2DS_2-VASc score	1.962	1.455–2.644	≤0.001
CHA_2DS_2-VASc-HSF score	2.716	1.996–3.696	≤0.001

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; BMI: Body mass index, Hb: Hemoglobin; WBC: White blood cells; HCT: Hematocrit; PT: Prothrombin time; APTT: Activated partial thromboplastin time; FBG: Fasting blood glucose.

Table 4: Multivariate regression analysis for the predictors of severe CAD

Variables	Odds ratio	95% CI	p-value
With $CHADS_2$ score			
Age (years)	1.017	0.985–1.049	0.298
FBG (mg/dL)	1.002	0.994–1.011	0.588
Ureum (mg/dL)	1.067	1.008–1.130	0.026
Creatinine (mg/dL)	2.828	0.893–8.960	0.077
$CHADS_2$ Score	1.572	1.009–2.345	0.046
With CHA_2DS_2-VASc score			
Age (years)	1.008	0.976–1.042	0.613
FBG (mg/dL)	1.002	0.994–1.010	0.601
Ureum (mg/dL)	1.065	1.006–1.129	0.032
Creatinine (mg/dL)	2.323	0.731–7.380	0.153
CHA_2DS_2-VASc score	1.569	1.098–2.240	0.013
With CHA_2DS_2-VASc-HSF score			
Age (years)	0.997	0.962–1.033	0.871
FBG (mg/dL)	0.997	0.989–1.006	0.516
Ureum (mg/dL)	1.065	0.998–1.137	0.056
Creatinine (mg/dL)	1.511	0.421–5.419	0.527
CHA_2DS_2-VASc-HSF Score	2.540	1.794–3.595	0.002

FBG: Fasting blood glucose; CI: Confidence interval.

The severe CAD may be fatal if remained undiagnosed and developed further into coronary total occlusion, which caused myocardial infarction. Hence, early detection of severe CAD is extremely important to prevent the mortality and morbidity of the patients [3]. Coronary angiography is the gold standard to diagnose the severity of stable CAD. However, early coronary angiography screening is lacking in developing countries [14]. Hence, clinicians need reliable, simple, objective, and quantitative tools to identify these risk stratifications to refer the patient for early screening, modify the risk factor, and provide early treatment [15]. Several scoring systems which involve major risk factors such as European SCORE and Framingham risk score (FRS) have been developed to assess the risk of CAD [16]. FRS is the most widely used score, which estimates the 10-year risk of developing CAD risk. However, this score cannot assess the severity of CAD. Furthermore, FRS also overestimates cardiovascular mortality rates in a low-risk population and underestimates it at the high-risk populations [17], [18]. Due to its multiplicity and complexity, FRS, SCORE, and other scoring systems are considered to be unpractical for daily use for primary care physician [19], [20]. Hence, alternatives scoring such as that $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF may offer a better alternative, which is easily be applied by the physician without any additional cost.

This study showed that $CHADS_2$, CHA_2DS_2-VASc, and CHA_2DS_2-VASc-HSF are having a positive and significant correlation with CAD severity measured by Gensini score. The highest correlation was found on the CHA_2DS_2-VASc-HSF score. This was in accordance with the previous research that showed both $CHADS_2$ and CHA_2DS_2-VASc score are significantly correlated with the Gensini score with almost similar r-value ($r = 0.383$, $p < 0.001$; $r = 0.300$, $p = 0.001$) [15]. When CHA_2DS_2-VASc score is modified by adding hyperlipidemia (H) and smoking (S), a stronger and significant correlation was found between CHA_2DS_2-VASc-HS score and Gensini score ($r = 0.813$, $p < 0.001$) [21]. Similar to this research, CHA_2DS_2-VASc-HSF also has a stronger and significant correlation with the severity of CAD measured by syntax score in NSTEMI patients compared to $CHADS_2$ and CHA_2DS_2-VASc [22]. This suggested that CHA_2DS_2-VASc-HSF score has a superior association with CAD severity compared to $CHADS_2$ and CHA_2DS_2-VASc score.

We investigated whether the $CHADS_2$-VASc-HSF scores could aid clinicians to predict the patient who has higher odds of severe CAD, which need immediate diagnosis and treatments. This research showed that CHA_2DS_2-VASc-HSF has the highest odd

Table 5: Pairwise comparison between receiver operating characteristic curves

Variables	Differences between areas	SE	95% CI	Z- Statistic	p-value
$CHADS_2$ and CHA_2DS_2-VASc	0.0496	0.0227	0.0052–0.941	2.190	0.028
$CHADS_2$ and CHA_2DS_2-VASc-HSF	0.154	0.0320	0.0914–0.217	4.819	≤0.001
CHA_2DS_2-VASc and CHA_2DS_2-VASc-HSF	0.105	0.0255	0.0546–0.154	4.105	≤0.001

SE: Standard error; CI: Confidence interval.

ratio to predict the severe CAD compared to $CHADS_2$ and CHA_2DS_2-VASc. Previously, the $CHADS_2$ score, as one of the rapid and very practical scores for risk stratification for thromboembolism, has also shown able to predict CAD in ischemic stroke patients [23]. The development of $CHADS_2$ into CHA_2DS_2-VASc score also has been shown to have better predictive power for long-term mortality for patients with severe CAD [24]. This suggested that the improvement of CHA_2DS_2-VASc into CHA_2DS_2-VASc-HSF may provide a better prediction for the odds of having severe CAD.

The $CHADS_2$ score is considered as one of the rapid, wide range, and very practical for risk stratification for thromboembolism, which was also developed to predict CAD in ischemic stroke patients [23]. CHA_2DS_2-VASc is the development of the $CHADS_2$ score, which showed better predictive power for long-term mortality for patients with CAD [24]. When compared with TIMI, GRACE score, CHA_2DS_2-VASc showed that the capability to predict severe CAD measured by syntax score [25]. Modification of CHA_2DS_2-VASc into CHA_2DS_2-VASc-HS score also has been shown to improve its predictive value for severe CAD compared to both $CHADS_2$ into CHA_2DS_2-VASc with the sensitivity of 85.2% and specificity of 57.5% at the cutoff value of >2 [13]. In this research, modification of CHA_2DS_2-VASc into CHA_2DS_2-VASc-HSF score also showed a higher AUC area compared to both $CHADS_2$ into CHA_2DS_2-VASc score with the sensitivity of 81.4% and specificity of 68.1% at the cutoff value of >2.5. CHA_2DS_2-VASc-HSF also shown to be the best scoring scheme for severe CAD prediction compared to $CHADS_2$ and CHA_2DS_2-VASc score. This suggests that CHA_2DS_2-VASc-HSF score is a better scoring method which easily used by the physician to screen the patient with angina, which may require referral for coronary angiography and early treatment.

However, this study may yet to be generalized since it only involved a single-center as the source of data. This study also used consecutive samplings from all patients who were admitted for diagnostic coronary angiography. Hence, selection bias might occur. In the future, it is suggested to involve more cardiac center and stratify the sample based on several factors such as race and social status to ensure the validity of the score among various demographic characteristics.

Conclusions

The CHA2DS2-VASc-HSF score can predict the severe CAD with superior validity compared to CHADS2 and CHA2DS2-VASc score. Suggesting that CHA2DS2-VASc-HSF score may be recommended for primary care physicians to easily predict severe CAD and refer them earlier without additional costs.

Authors' Contributions

Conceptualization, A. and M.J.A.; Methodology, R.L.; Software, M.J.A. and R.L.; Validation, A. and B.J.; Formal analysis, M.J.A. and R.L.; Investigation, I.G.P.G.S., M.J.A., and K.A.S; Resources, A. and B.J.; Data curation, I.G.P.G.S. and K.A.S; writing—original draft preparation, I.G.P.G.S. and K.A.S.; writing—review and editing, A. and M.J.A.; visualization, R.L; supervision, A. and B.J.; project administration, R.L.

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