Identifying Significant Cranial Angles for Predicting Normal vs. Syndromic Craniosynostosis Patients using A Simple Logistic Regression and Stepwise Multiple Logistic Regression Approach

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Abstract

Previous research in identifying significant angles for early detection of syndromic craniosynostosis was proposed by making a comparison with a 95% confidence interval of the angular mean from the non-syndromic patients. Depending on the number of variables and population studied, this method requires one-by-one comparisons, is time-consuming, and is not robust to outliers. We proposed the use of a logistic regression model to identify the significant cranial angles that can well discriminate between syndromic and non-syndromic patients. 12 angular measurements of 39 patients (17 patients with SC and 22 normal patients aged between 0 to 12 years) who sought treatment at the University Malaya Medical Centre from 2012 to 2020 were obtained from the previous study. 13 regression models (12 simple regression and 1 multiple regression) were produced using simple and multiple stepwise logistic regression. The significant angles were obtained from the best model, which was chosen by comparing their p-value and the Akaike Information Criterion. Results from the simple and multiple logistic regression yield TS-Ba-O (P<0.05) and ACF-DS-Ba (P<0.05) as important factors in discriminating the patient's condition. The stepwise multiple logistic regression model, however suggested one more significant variable; the Na-S-SO (P<0.05). Compared to the previous study, TS-Ba-O was also captured as a significant angle using confident interval methods. The logistic regression model may serve as a promising method to identify cranial angles associated with abnormalities in a patient's cranial growth.

Keywords: *Syndromic craniosynostosis, stepwise regression*

1. Introduction

Craniosynostosis is a disorder where the sutures (growth seams) of an infant's skull close too early, interfering with proper brain and skull growth (Ferreira et al., 2022). It can develop as a single incident leading to non-syndromic craniosynostosis, or it can develop along with other defects in well-defined patterns that constitute clinically recognized syndromes. As part of a wider constellation of related defects, syndromic craniosynostosis (SC) frequently involves many sutures. Apert, Crouzon, and Pfeiffer syndromes are three common genetic syndromes related to SC. In most cases, syndromic forms of craniosynostosis result from mutations in genes from the Fibroblast Growth Factor Receptor (FGFR) family and the connected molecular pathways. However, it is also possible for these conditions to be caused by other gene variants and a variety of chromosomal abnormalities, often in conjunction with intellectual disability (ID) and other physical anomalies (Zollino et al., 2017). This syndrome may result in hypertelorism, midface hypoplasia, eye ptosis, and hand or foot abnormalities (Tudor-Green et al., 2014). Surgery for SC patients primarily tries to prevent or treat functional problems related to SC (such as elevated ICP, orbital, and airway pressure).

Surgery can be broadly categorized into many subgroups, such as specialized functional-based indications or combination functional interventions, and the procedures may incorporate distraction osteogenesis (Hart et al., 2021). Most types of craniosynostosis and the numerous surgical procedures used to treat them result in changes to appearance, cephalic indices, and functional and neurologic consequences. However, in some cases, increased intracranial pressure and further craniofacial abnormalities, also known

as re-synostosis, may result from either the rapid development of bone following surgery or the fact that the type of surgical procedure itself was already inaccurate (Esparza et al., 2008; Hermann et al., 2016). Rates of reoperation after craniosynostosis correction, either for cosmetic reasons or re-synostosis, have also been studied by many researchers (Agrawal et al., 2006; Foster et al., 2008). Foster, Frim, and McKinnon (2008) conclude in their research that children with syndromic conditions had greater re-synostosis rates compared to non-syndromic patients. When the original procedure was performed after the patient had reached the age of one year, re-synostosis was shown to be more common. Consequently, it is crucial to identify functional discrepancies as soon as possible and to follow up thoroughly to stop the additional developmental decline, which might cause patients' growth to become seriously hampered.

In planning the surgical intervention, a patient's age during surgery is not the only factor. Finding exact landmarks and measurements to enhance when correcting an SC patient's skull could significantly contribute to minimizing the risk of relapse and other consequences. The development in finding landmarks for enhancement from previous research involves a simple comparison between normal and syndromic patients (Ali et al., 2015; Bouw et al., 2015; Reitsma et al., 2012). The use of statistical analysis might offer a different way for surgical teams and researchers to identify the correct landmark for enhancement. Previous research in identifying significant angles for early detection of syndromic craniosynostosis (SC) among the Malaysian population has been proposed so far only once by Zulkilpi (2022), in which the method is by making a comparison with the 95% confidence interval (CI) of the angular mean from the non-SC patients (Zulkipli et al., 2022). An angle is reported as significant and requires surgical intervention if it falls outside of the confident interval range calculated from the non-SC patient's angle. Depending on the number of variables and population studied, this method requires one-by-one comparison, is time-consuming, and is not robust to outliers. The mean value is sensitive to outliers, and their influence might not be adequately captured by confidence intervals alone. Outliers can significantly affect the mean and may distort the interpretation of results (Armitage et al., 2008). Furthermore, mean and CI do not provide information about the shape of the underlying distribution. Data with different distributions (e.g., skewed, multimodal) could have similar means and confidence intervals, but they may represent fundamentally different patterns (Witte & Witte, 2010). To further enhance the efficacy of skull anomaly identification for SC conditions, more sophisticated statistical methods are necessary.

Therefore, in this paper, by using the same data set, we propose the use of two regression techniques; (1) simple logistic regression, and (2) reduced multiple logistic regression by the stepwise method to identify the significant angles. By examining the relationship between one or more current independent variables, a logistic regression model forecasts a binary (0 or 1 outcome) dependent data variable, which in this case will be the patient's condition, either syndromic or normal. It assumes a linear (straight line) relationship with the logit (the natural logarithm of the odds) of the outcome rather than modeling a linear relationship between the independent variable and the probability of the outcome, which is unnatural because it would allow predicted probabilities outside the range of 0-1 (Dobson et al., 2008). Over the years, logistic regression has been widely used in research involving the medical field, especially for studies of SC patients and complications post-surgery. Instead of focusing on specific landmarks, most researchers focus on more general causes of the complication, such as timing or age during surgery (Abraham et al., 2018; Utria et al., 2015). So far, no research has been done to find landmarks and measurements to manipulate during the surgical treatment of SC patients using logistic regression.

Logistic regression analysis can be presented as simple (one dependent variable and one independent variable, or what some may call a covariate) or multiple (one dependent variable and two or more covariates). Although fitting simple and multiple logistic regression for the same data set may provide the same result, in some cases, the result might be slightly different. Hence, we fit both and compare the results. For simple logistic regression, the significant variable can easily be selected by comparing the P-value. However, different approaches require for selection of significant variables in multiple logistic regression model. The method will be discussed in detail in section 3, while in section 4, the results and discussion from the regression analysis are presented. At the end of this study, possible skull angles that could be most related to

SC patients will be highlighted, and their application in cranial growth prediction among these patients is discussed in section 5.

2. Objectives

The purpose of this study is to identify the significant cranial angles that can well discriminate between syndromic and non-syndromic patients. These angles are believed to be the area that every surgeon needs to focus on during surgical intervention. Finding the right area would improve the outcome, predict the necessity for major surgery, reduce the need for secondary procedures to address inadequate corrections of deformity, and be expanded for the development of advanced interventional instruments in the craniofacial field in the future.

3. Materials and Methods

Twelve angular measurements in degree unit of 39 patients (17 patients with SC and 22 normal patients aged between 0 to 12 years) who were treated at the University Malaya Medical Centre (PPUM) from the year 2012 to 2020 were obtained from past study (Zulkipli et al., 2022). The angles were measured from each patient's computed tomography (CT) scan image by using Mimics software. Table 1 shows a glimpse of the dataset and the description for each angular measurement is stated in Table 2. Our dependent variable is our patient's condition which to be either normal ($Y_i = 0$) or syndromic ($Y_i = 1$).

13 regression models (12 simple regression and 1 multiple regression) were fitted using the simple and multiple stepwise logistic regression. For simple regression model, we compare the Akaike's Information Criterion (AIC) and the P-value of each 12-regression model while for multiple logistic regression, the variable was selected by using stepwise method and we chose a multiple model with appropriate P-value of all variables included in the model as our final model. Logistic regression estimates the probability, Y_i that the ith case ($i = 1, \ldots, n$) is in one of the categories from the outcomes where:

$$\log\left(\frac{Y_i}{1 - Y_i}\right) = A + B_1 X_1 + B_2 X_3 + \cdots + B_m X_m \tag{1}$$

with A as the intercept term, $B_1, B_2, \ldots, B_m$ are the regression coefficients corresponding to each predictor $X_1, X_2, \ldots, X_m$ for m numbers of predictor. Maximum likelihood estimates of the parameters B are obtained by maximizing the log-likelihood function. According to (Dobson et al., 2008), the log-likelihood function can be written as:

$$l(\pi; y) = \sum_{i=1}^{N}\left[y_i \log \pi_i + (n_i - y_i)\log(1 - \pi_i) + \log\binom{n_i}{y_i}\right] \tag{2}$$

To choose covariates for multiple regression, a few factors must be considered to build a simple model with higher efficiency, such as multicollinearity and the significance of variables. It might be challenging to isolate each variable's independent influence on the response variable when two or more predictor variables have a strong correlations which is also known as multicollinearity (Weissfeld & Sereika, 1991). These correlated variables not only provide redundant information, which complicates the model, but also might lower the predictive accuracy of the model. In this study, we use the Variance Inflation Factor (VIF) to detect multicollinearity among the predictor variables. The variance inflation for independent variables X_j is computed as (John, 1983):

$$VIF_j = \frac{1}{(1 - R_j^2)}, j = 1, 2 \ldots, p \tag{3}$$

Where p is the number of predictor variables, R_j^2 is the square of the multiple correlation coefficient of the jth variable with the remaining $p - 1$ variable. The value of VIF, $0 < VIF < 5$ implies that there is no evidence of a multicollinearity problem.

Aside from multicollinearity checking, significant angles were obtained from the best model using the stepwise regression method. Stepwise logistic regression is the step-by-step iterative construction of a regression model that involves the selection of independent variables to be used in a final model. It involves adding or removing potential explanatory variables in succession and testing for statistical significance after each iteration (Chowdhury & Turin, 2020). It is necessary to provide a stopping rule or selection criterion for the inclusion or exclusion of variables in all stepwise selection techniques, depending on the goals of the analysis.

Since our focus is to only find the significant variables without necessarily presenting the final model, we choose p values less than 0.05 as our selection criterion. P-value is a measure that aids in assessing the volume of evidence contradicting a null hypothesis. The null hypothesis states that there is no significant effect or relationship in the data, while the alternative hypothesis suggests the presence of some effect or relationship (Huberty, 1991). In other words, it tells you how likely the observed data would be if the null hypothesis were correct. Suppose the p-value is very small (typically below a predetermined significance level, often denoted as alpha, e.g., 0.05). In that case, it suggests that the observed result is unlikely under the null hypothesis and provides evidence against it (Sedgwick, 2014).

Although our focus is only on the significant variables, there is no reason to take the model's performance for granted in each iteration. Therefore, we also check on Akaike's Information Criterion (AIC). AIC calculates the relative information loss compared to other model candidates. The ideal model is thought to perform better with less information loss (Del Giudice, 2020). The AIC values were calculated using the formula such follows;

$$AIC = 2k - 2\ln(\mathcal{L}) \qquad (4)$$

where,

k is the number of free parameters in the model,

$\mathcal{L}$ is the maximized likelihood of a fitted model.

Table 1 First five rows of the patient's angular data set in degree unit

Patient	ACF-DS-Ba (°C)	ACF-DS-C (°C)	Ba-Cl-Sp (°C)	Ba-S-Na (°C)	Cl-Ba-Sp (°C)	Cl-Sp-Ba (°C)	Na-Ba-O (°C)	Na-Apex point DS-Ba (°C)	Na-SO-Ba (°C)	Na-S-SO (°C)	S-SO-Ba (°C)	TS-Ba-O (°C)
1	119.64	112.09	124.19	123.28	36.45	30.55	167.23	111.84	165.50	124.61	175.64	159.18
2	130.88	115.02	126.72	135.62	39.68	21.32	169.64	123.41	155.90	125.94	163.53	126.63
3	140.95	139.83	152.81	151.22	13.72	13.20	156.05	124.95	149.88	133.50	167.97	131.48
4	134.16	142.55	137.79	141.52	39.78	38.49	165.12	117.55	151.18	118.18	154.00	139.10
5	120.78	123.32	125.99	125.61	24.23	36.40	163.72	116.8	148.07	114.10	158.84	136.96

Table 2 Descriptions of 12 Cranial Angles

Cranial angle	Landmark description
ACF-DS-Ba	Anterior cranial fossa-dorsum sellae-Basion
ACF-DS-C	Anterior cranial fossa-dorsum sellae-Posterior margin of the clivus
Ba-Cl-Sp	Basion-Posterior clinoid process-Sphenoid
Ba-S-Na	Basion-Sella-Nasion
Cl-Ba-Sp	Posterior clinoid process-Basion-Sphenoid
Cl-Sp-Ba	Posterior clinoid process-Sphenoid-Basion
Na-Ba-O	Nasion-Basion-Opisthion
Na-Apex point DS-Ba	Nasion-Apex points of the dorsum sellae-Basion

Na-SO-Ba	Nasion-[Spheno-occipital Synchondrosis]-Basion
Na-S-SO	Nasion-Sella-[Spheno-occipital Synchondrosis]
S-SO-Ba	Sella-[Spheno-occipital Synchondrosis]-Basion
TS-Ba-O	Tuberculum sellae-Basion-Opisthion

4. Results and Discussion

Table 3 shows the mean and standard deviations for the craniofacial angle of normal patients and syndromic patients. The syndromic patient had significantly larger values for angles Cl-Sp-Ba and Na-S-SO than normal patients while the normal patient had significantly larger values in ACF-DS-Ba, ACF-DS-C, Ba-Cl-Sp, Ba-S-Na, Cl-Sp-Ba, Na-Ba-O, Na-Apex point DS-Ba, Na-SO-Ba, S-SO-Ba and TS-Ba-O than syndromic patients.

Table 3 Summary statistics for 12 angles

Variables	Normal Patients n=22		Syndromic Patients n=17		Difference
	Mean (℃)	SD	Mean (℃)	SD	
ACF-DS-Ba	132.49	8.24	125.70	8.74	-6.79
ACF-DS-C	130.74	8.79	124.40	9.65	-6.34
Ba-Cl-Sp	133.15	9.11	123.43	13.94	-9.72
Ba-S-Na	135.77	6.92	134.79	13.92	-0.98
Cl-Ba-Sp	25.60	8.21	31.38	11.51	5.78
Cl-Sp-Ba	23.55	7.91	21.76	9.11	-1.79
Na-Ba-O	163.10	8.75	152.88	16.71	-10.21
Na-Apex point DS-Ba	121.43	7.84	114.31	12.53	-7.11
Na-SO-Ba	150.92	12.35	144.21	13.62	-6.71
Na-S-SO	124.97	10.78	133.62	16.08	8.64
S-SO-Ba	164.20	9.46	162.90	13.28	-1.29
TS-Ba-O	139.79	9.66	126.94	14.31	-12.84

Table 4 describes the result of 12 simple logistic regression model fitted with different angle as variable. This method suggested that TS-Ba-O ($P < 0.01$), Na-Ba-O ($P < 0.03$), ACF-DS-Ba ($P < 0.03$), Ba-Cl-Sp ($P < 0.03$), and ACF-DS-C ($P < 0.05$) as the significant predictors to predict patient's condition separately using each model. We may check this result by combining all the angle chosen, fit regression model using multiple logistic regression and compare the P-value but since this result will be compare with result from stepwise multiple logistic regression, the checking is not necessary.

Table 4 Model summary for 12 regression models using simple logistic regression

Regression Model	Variable	coefficients	SE	P-value	AIC
Model 1	ACF-DS-Ba	-0.10054	0.04599	0.0288	51.392
Model 2	ACF-DS-C	-7.56E-02	3.81E-02	0.0471	52.992
Model 3	Ba-Cl-Sp	-0.07867	0.03455	0.0228	50.739
Model 4	Ba-S-Na	-0.009284	0.031497	0.768	57.336
Model 5	Cl-Ba-Sp	0.06153	0.03531	0.0814	54.107
Model 6	Cl-Sp-Ba	-0.02655	0.03979	0.505	56.969
Model 7	Na-Ba-O	-0.06312	0.02878	0.0283	51.618
Model 8	Na-Apex point DS-Ba	-7.62E-02	3.96E-02	0.054	52.665
Model 9	Na-SO-Ba	-0.04168	0.02695	0.122	54.816
Model 10	Na-S-SO	0.05167	0.02781	0.0632	53.376
Model 11	S-SO-Ba	-1.07E-02	2.94E-02	0.716	57.29
Model 12	TS-Ba-O	-0.09043	0.03355	0.00704	47.46

Table 5 Step by step stepwise multiple logistic regression model summary

Step	Step 1		Step 2		Step 3	
	Coefficient	P-value	Coefficient	P-value	Coefficient	P-value
Intercept	11.81336	0.00834	34.38236	0.00429	35.19958	0.0228
TS-Ba-O	-0.09043	0.00704	-0.11276	0.00661	-0.10354	0.0329
ACF-DS-Ba			-0.15166	0.02076	-0.3153	0.012
Na-S-SO					0.14565	0.0323
No. of variables	1		2		3	
AIC	47.46		41.707		35.705	

For stepwise multiple logistic regression, the most statistically significant predictors with the lowest P-values (TS-Ba-O ($P < 0.01$)) in the simple logistic regression method will be the first angle to enter our multiple logistic regression model. For the next variable, we apply stepwise logistic regression, where other angles, one by one, will be fit into the model together with the first angle chosen, but the final model with both the first and second variables will be chosen. We then proceed by adding the third variable to our final model from the second step. The step continues until no new angle is added and the p value remains at a significant level for all the angles included in the previous step. From Table 5, the second step included both TS-Ba-O ($P < 0.01$) and ACF-DS-Ba ($P < 0.03$). The AIC value for the second model ($AIC = 41.707$) was smaller than the first model ($AIC = 47.46$) indicating that the model lost less information than the first model which implies that this model is significantly better than the first model. Note that the second variable entered with the lowest p value in the multiple regression model is not the same as the second lowest p value from the simple regression result. This proves that simple regression and multiple regression do not necessarily provide the same result. The third step included TS-Ba-O ($P < 0.04$), ACF-DS-Ba ($P < 0.02$), and Na-S-SO ($P < 0.04$) with slightly smaller AIC ($AIC = 35.705$). The iteration ends at the third step since adding more variables will increase the P-values of each variable in the model.

Both simple and multiple logistic regression demonstrated that TS-Ba-O and ACF-DS-Ba are important factors in classifying a patient's condition. Multiple logistic regression, however, suggested one more variable to be significant, which is Na-S-SO, which was not captured using simple logistic regression, while simple logistic regression identified three more variables: Na-Ba-O, Ba-Cl-Sp, and ACF-DS-C. The regression coefficient and the VIF of the independent variables for multiple logistic regression are presented

in Table 6. The VIF showed that there was no evidence of a multicollinearity problem among the predictor variables.

Table 6 VIF analysis of variables from multiple logistic regression model

Variables	Coefficient	VIF
TS-Ba-O	-0.10354	1.561
ACF-DS-Ba	-0.3153	3.245
Na-S-SO	0.14565	3.925

Compared to the previous study (Zulkipli et al., 2022), TS-Ba-O were also captured as significant angles by using CI methods. This implied that more focus should be put on that facial angle, as both methods agree on their significance for detection. However, in this study, we proposed two more angles, which are ACF-DS-BA and Na-S-SO. The method presented in this paper is an improvement from a previous study, as logistic regression handles outliers better than mean comparison.

5. Conclusion

This research aims to identify the cranial angles that are associated with syndromic craniosynostosis in Malaysia by comparing simple logistic regression and stepwise logistic regression analysis. 12 simple logistic regression models and 1 multiple logistic regression model were fitted, and the result was observed.

The findings from both simple and multiple logistic regression indicated that the variables TS-Ba-O and ACF-DS-Ba are crucial in classifying the state of the patient. While Na-S-SO was proposed by multiple logistic regression to be another relevant variable, simple logistic regression identified three other factors: ACF-DS-C, Na-Ba-O, and Ba-Cl-Sp. Also, worth noticing that the estimated model obtained by multiple logistic regression was;

$$\log\left(\frac{Y_i}{1-Y_i}\right) = 35.19958 - 0.10354(\text{TS\_Ba\_O}) - 0.3153(\text{ACF\_DS\_Ba}) + 0.14565(\text{Na\_S\_SO}) \tag{5}$$

More data is needed to verify this model for future applications, and the estimated model can be further improved by using more advanced statistical methods. This work is new in that it presents significant angles for the early diagnosis of SC. However, SC itself is too general and can be narrowed down to a few syndromes, such as Apert, Pfeiffer, and Crouzon. The same method can be applied to find the significant angles for each syndrome if enough data are collected.

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7. References

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