Journal of Advanced Research in Applied Sciences and Engineering Technology

Journal homepage:
https://semarakilmu.com.my/journals/index.php/applied_sciences_eng_tech/index
ISSN: 2462-1943

Abnormalities Detection in Apert Syndrome using Hierarchical Clustering Algorithms

Nur Syahirah Zulkipli[1], Siti Zanariah Satari[1,*], Wan Nur Syahidah Wan Yusoff[1]

[1] Pusat Sains Matematik, Universiti Malaysia Pahang Al-Sultan Abdullah, Lebuhraya Persiaran Tun Khalil Yaakob, 26300 Kuantan, Pahang, Malaysia

ARTICLE INFO

Article history:
Received 25 September 2023
Received in revised form 20 November 2023
Accepted 7 April 2024
Available online 5 May 2024

Keywords:

Craniosynostosis; Abnormalities; Outlier detection; Clustering algorithms; Circular data

ABSTRACT

Craniosynostosis syndrome is a congenital condition occurring due to the abnormal development of the skull, leading to abnormalities in skull morphology. Apert syndrome is one of common craniosynostosis syndrome in Malaysia and this syndrome can be categorized as the severe craniofacial disorders. The abnormalities of skull morphological in Apert syndrome patient can be identified as outliers which are investigated in this study. This study presents a skull morphological analysis based on a case study involving six paediatric patients diagnosed with Apert syndrome, alongside 22 control patients aged 0 to 12 years, all of whom underwent treatment at the University Malaya Medical Centre (UMMC). The computerized tomography scan (CTSCAN) data is provided by UMMC recorded from year 2012 until 2020 and the data is measured using MIMICS software by taking the measurement of cranial angles. The clustering-based procedures will be applied to identify the abnormalities in skull angle dataset. There are 12 skull angles and these angles are analysed using hierarchical clustering algorithms for identifying the outliers or abnormalities. The objective is to detect the abnormalities and determine the skull angles that associated with Apert syndrome (AS) in Malaysia population using clustering-based procedure. The abnormalities in Apert syndrome datasets are successfully detected by the algorithms and this study found that there are skull angles with specific location of angles are associated with Apert syndrome. This study also found that the location of skull angles for patients age 0-24 months old and >24 months old are different. The findings of this study can assist the surgical team in directing additional focus towards specific regions of the skull during the planning of interventions. This guidance has the potential to optimize surgical outcomes and reduce the risk of potential complications.

[*] *Corresponding author.*
E-mail address: zanariah@ump.edu.my

https://doi.org/10.37934/araset.44.2.135174

1. Introduction

Apert syndrome is broadly acknowledged as a congenital anomaly that leads to craniofacial malformation and the presence of bilateral syndactyly in the hands and feet. This syndrome also known as acrocephalosyndactyly and named as Apert syndrome synonymous with the name of French paediatrician, Eugène Apert who is familiar in exploring this syndrome [1]. Apert syndrome is caused by one of the two specific point mutations in the fibroblast growth factor receptor 2 (FGFR2), i.e., Ser252Trp and Pro253Arg [2-4]. Additionally, it is marked by profound syndactyly in the hands and feet, abnormalities in craniofacial structure and craniosynostosis [2-6]. Apert syndrome is one of well-known craniosynostosis syndrome in Malaysia other than Crouzon and Pfeiffer.

Craniosynostosis syndrome is a birth defect that occurs when the natural growth of the skull is disrupted, leading to the premature fusion of skull sutures before the infant's brain has reached full development. This can lead to an altered head shape, increased distance between the eyes with protrusion, and underdevelopment of the midface [7]. Moreover, Rostamzad *et al.,* [8] found that horizontal strabismus which is eyes misalignment and astigmatism are the ocular abnormalities that frequently happen in Apert syndrome. Skull abnormalities can also lead to potential complications, including intracranial hypertension, visual impairment, and potential constraints on brain development [9-11]. Hariri *et al.,* [12] emphasized the necessity for comprehensive management planning for this syndrome, ensuring optimal care and effective functional rehabilitation. Apert, Crouzon and Pfeiffer syndromes are reported as the syndromic craniosynostosis that among the various complex craniomaxillofacial malformation [13]. Moreover, surgical treatment is required to prevent or fix the complications that occur because of the craniosynostosis [14]. Surgical technique such as posterior cranial distraction (PSD) is a convincing treatment for syndromic craniosynostosis patients [15].

Abnormalities or also commonly called as outliers can be defined as a rare or statistically unusual event. Thus, Apert syndrome can be classified as abnormalities since it is rare and unfrequently happen to everyone. The aim of this study is to investigate the skull angles that associated with Apert syndrome (AS) in Malaysia population using clustering-based procedure. Hierarchical clustering algorithms such as single-linkage (SL), complete-linkage (CL) and average-linkage (AL) will be used to identify the abnormalities in AS dataset. Hierarchical clustering algorithms are commonly used in detecting the abnormalities or also called outliers since these algorithms are sensitive to the outliers. The data involves with 12 skull angles as an angular variable or commonly known as a circular variable, and hence the circular similarity distance will be used in the clustering algorithms. In short, there are two circular similarity distances and three hierarchical clustering algorithms will be used to detect the abnormalities in AS for patients of age 0-24 months and >24 months, respectively. The craniofacial landmarks of human skull from Rooppakhun *et al.,* [16] and Hirunpat *et al.,* [17] were utilized as references for this study. At the end of this study, the skull angles that associated with this syndrome will be shown.

2. Methodology

2.1 Data Collection

The data collected are consist of 12 skull angles of six AS patients and 22 control patients in Malaysia from age of 0-24 and >24 months old. Table 1 summarized the skull angles used in this study together with the landmark descriptions. Hence, there are 12 skull angle datasets used in this study.

Table 1
Skull angles and landmark descriptions used in this study

Skull Angle	Abbreviation	Landmarks Description
Angle1	ACF-DS-Ba	Anterior cranial fossa-Dorsum sellae-Basion
Angle2	ACF-DS-C	Anterior cranial fossa-Dorsum sellae-Posterior margin of the clivus
Angle3	Ba-Cl-Sp	Basion-Posterior clinoid process-Sphenoid
Angle4	Ba-S-Na	Basion-Sella-Nasion
Angle5	Cl-Ba-Sp	Posterior clinoid process-Basion-Sphenoid
Angle6	Cl-Sp-Ba	Posterior clinoid process-Sphenoid-Basion
Angle7	Na-Ba-O	Nasion-basion-opisthion
Angle8	Na-Apex point DS-Ba	Nasion-Apex points of the dorsum sellae-Basion.
Angle9	Na-SO-Ba	Nasion-[Spheno-occipital Synchondrosis]-Basion
Angle10	Na-S-SO	Nasion-Sella-[Spheno-occipital Synchondrosis]
Angle11	S-SO-Ba	Sella-[Spheno-occipital Synchondrosis]-Basion
Angle12	TS-Ba-O	Tuberculum sellae-Basion-Opisthion

The age group is categorized into two subgroups; 0-24 and >24 months old. The number of patients according to age group for both control and AS groups are shown in Table 2. The sample size for age group 0-24 months old is n=11 and n=17 for age group >24 months old with AS. Note that, all the control patients are without any known associated abnormalities. The control patients are matched to the AS patients by age. Hence, the abnormalities in this study refer to the AS data from each skull angle dataset.

Table 2
Number for control patient and AS patient by age group

Age group (months)	Patients		Total
	Control	Apert Syndrome (AS)	
0-24	7	4	11
>24	15	2	17
Total	22	6	28

The computerized tomography scan (CTSCAN) data is provided by University of Malaya Medical Centre (UMMC) recorded from year 2012 until 2020 and the skull angle is measured using MIMICS software as visualized in Figure 1. Skull angle data which measure in degree unit $(0°, 360°)$ are collected from UMMC in August 2020. The data consist of skull angle data from normal and abnormal skulls. Normal skull refers to the skull of control patient. Meanwhile, abnormal skull refers to the skull of patient with AS. Figure 1 (a) shows the landmark points used to measure the skull angles in Table 1. Meanwhile, Figure 1 (b) is the example of the CTSCAN image from patient with AS that used during the process of data collection by measuring the skull angle using MIMICS software.

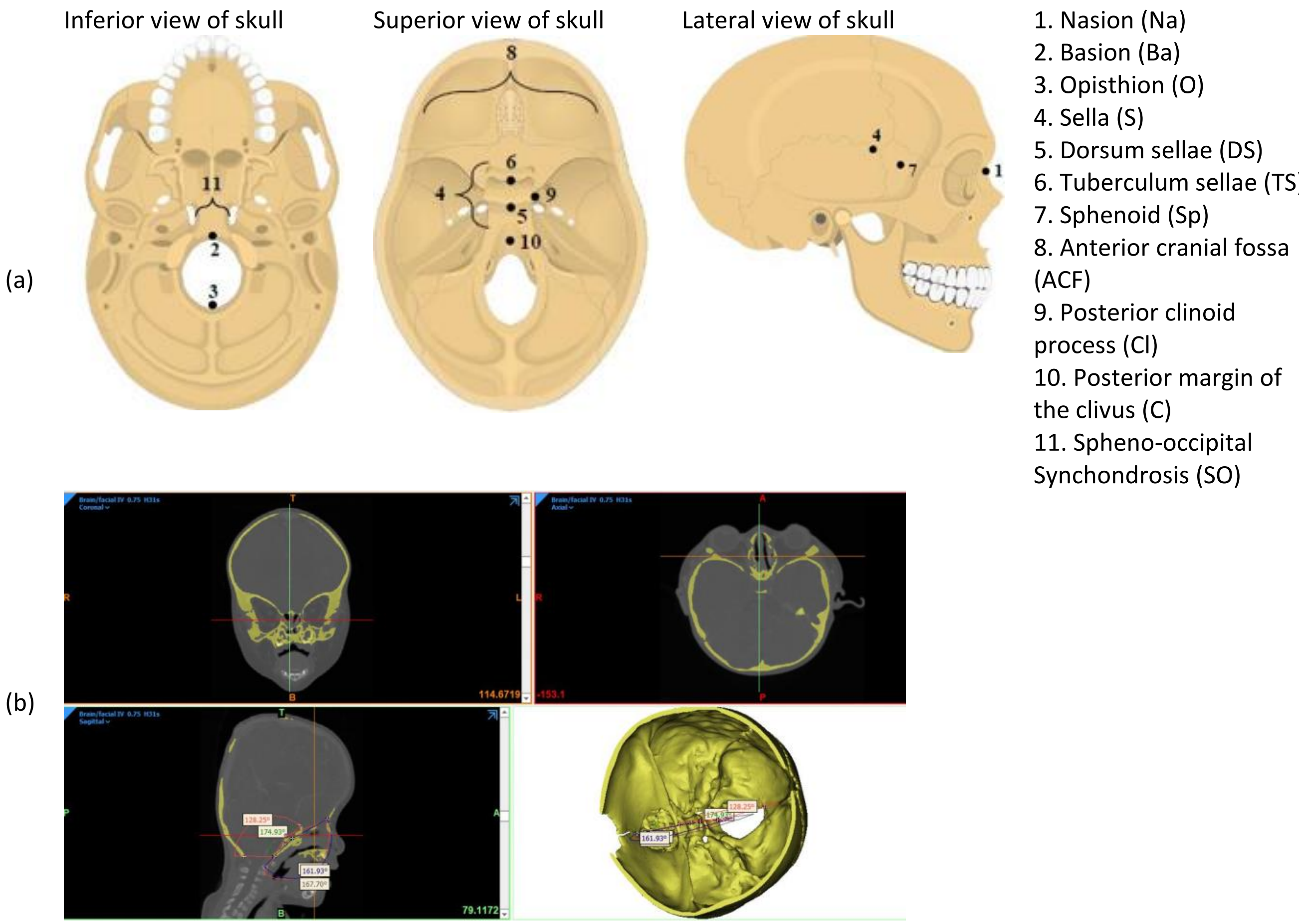


Fig. 1. (a) The landmark points (b) The example of angular measurements of patient with AS for measured using Mimics software

2.2 Abnormalities Detection in Apert Syndrome using Clustering-Based Procedure

The clustering-based procedure is well-known for outlier detection methods as it can be utilized to detect outliers or abnormalities in data by classify the inliers and outliers' clusters. In order to find the skull angles that associate with AS, the dataset will be analysed using hierarchical clustering algorithms. In this study, three different hierarchical clustering algorithms and circular similarity distances will be used for identifying outliers or abnormalities in AS dataset. According to Sebert *et al.,* [18], clustering methods such as hierarchical clustering are sensitive to outliers. Agglomerative clustering is commonly used to classify observations in clusters by determining their similarity. Thus, the measure of similarity between circular observations is important to classify the observations into their own cluster. The similarity measurement between circular observations can be determined by using circular similarity distance.

This study aims to use the circular similarity distances from Chang-chien distance deployed from Chang-chien *et al.,* [19] and Satari distance proposed by Satari [20] to measure the similarity distance in the clustering algorithms. Chang-chien *et al.,* [19] and Satari [20] utilized the circular distance defined by Jammalamadaka and Sengupta [21] in their formula. The formula of Satari and Chang-chien similarity distances are given in Eq. (1) and Eq. (2).

Satari distance:

$$d_{ij(Satari)} = \sum_{k=1}^{p}\left(\pi - \left|\pi - \left|\theta_{ik} - \theta_{jk}\right|\right|\right). \quad (1)$$

Chang-chien distance:

$$d_{ij(Chang\text{-}Chien)} = \sqrt{\sum_{k=1}^{p}\left(1 - cos(\theta_{ik} - \theta_{jk})\right)^{2}} . \quad (2)$$

The hierarchical clustering such as single-linkage (SL), complete-linkage (CL) and average-linkage (AL) will be used to identify the outliers in each 12 skull angles dataset from AS patients age 0-24 and >24 months old. In short, six clustering algorithms will be used in this study listed as follows.

i. SL-Satari
ii. SL-Chang
iii. CL-Satari
iv. CL-Chang
v. AL-Satari
vi. AL-Chang

The outliers will be detected by cutting the dendrogram as a final output from the hierarchical clustering at a certain height so that the outliers can be separated from the inliers. Hence, to detect the outliers, the cutting rule proposed by Satari [20] will be used as a cut of point between inliers and outliers as given in Eq. (3).

$\bar{h} + 2.06_{s_h}$, at 95% confidence interval (3)

where $\bar{h}$ is the average heights of the cluster tree for all $N-1$ clusters, N is a total number of cluster which contain single observations, and s_h is the circular standard deviation of the heights given by Eq. (4).

$$s_h = \sqrt{-2log\bar{R}_h} \quad (4)$$

where $\bar{R}_h$ is the mean resultant length of the height for $N-1$ clusters.

Three performance measures defined by Sebert *et al.,* [18] will be used in this study to evaluate the clustering algorithms in detecting the outliers in AS dataset. The performance measures defined as follows:

i. Probability of all outliers are successfully detected, *pout*.

$$pout = 'success' \ / \ out \tag{5}$$

where *‘success’* is the number of observations that clustering-based procedure successfully identified all the outliers and *out* is the number of outliers. The closer the *pout* value to 1, the clustering algorithms successfully identified most of the outliers (AS data).

ii. Probability of outliers are falsely detected as inliers (masking effect), *pmask*.

$$pmask = 'failure' \ / \ out \tag{6}$$

where *‘failure’* is the number of outliers in dataset that detected as inliers and *out* is the total number of outliers. The *pmask* value ranges from 0 to 1, with a value close to 0 indicating that there are no outliers were detected as inliers.

iii. Probability of inliers detected as outliers (swamping effect), *pswamp*.

$$pswamp = 'false' \ / \ (n - out) \tag{7}$$

where *‘false’* is the number of inliers in all data set that detected as outliers, *n* is total number of observations and *out* is total number of outliers. The *pswamp* value ranges from 0 to 1, with a value close to 0 indicating that no inliers were detected as outliers.

The skull angles that associate with AS are determine by considering the high value of *pout* and low value of *pmask* and *pswamp* from the performance of the clustering algorithms in detecting the outliers which refer to the dataset from AS.

3. Results and Discussion

The performance measures of the clustering algorithms in identifying the abnormalities in 12 skull angle datasets are summarized in Table 3 and Table 4. The clustering algorithms successfully identified most of the outliers (AS data) with low masking and swamping effect. It is found that only a few skull angles are associated with AS. Table 3 shows the angles associated with this syndrome for age group 0-24 months old are Angle5 (Posterior clinoid process-Basion-Sphenoid), Angle6 (Posterior clinoid process-Sphenoid-Basion), Angle7 (Nasion-Basion-Opisthion) and Angle12 (Tuberculum sellae-Basion-Opisthion).

Table 3
Performance measures based on *pout, pmask* and *pswamp* with the promising clustering algorithms for age group 0-24 months old

Skull Angles	Clustering Algorithms	*pout*	*pmask*	*pswamp*
Angle5	SL-Satari	0.5000	0.5000	0.0000
	SL-Chang	1.0000	0.0000	0.2857
	AL-Satari	0.5000	0.5000	0.0000
	AL-Chang	0.5000	0.5000	0.0000
Angle6	SL-Satari	0.5000	0.5000	0.0000
	SL-Chang	0.5000	0.5000	0.1429
	CL-Satari	0.5000	0.5000	0.1429
	CL-Chang	0.5000	0.5000	0.1429
	AL-Satari	0.5000	0.5000	0.1429
	AL-Chang	0.5000	0.5000	0.1429
Angle7	CL-Satari	1.0000	0.0000	0.1429
	CL-Chang	1.0000	0.0000	0.1429
	AL-Satari	1.0000	0.0000	0.1429
	AL-Chang	1.0000	0.0000	0.1429
Angle12	SL-Satari	1.0000	0.0000	0.1429
	SL-Chang	1.0000	0.0000	0.1429
	CL-Satari	1.0000	0.0000	0.1429
	CL-Chang	1.0000	0.0000	0.1429
	AL-Satari	1.0000	0.0000	0.1429
	AL-Chang	1.0000	0.0000	0.1429

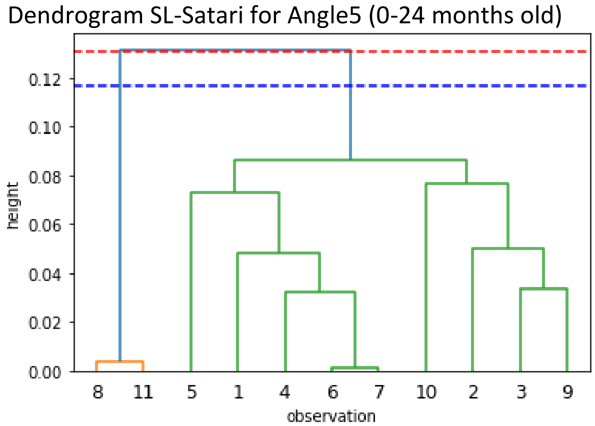
Table 4 shows the summary of the skull angles that associate with AS for age group >24 months old. Table 4 visualised that Angle1 (Anterior cranial fossa-Dorsum sellae-Basion), Angle2 (Anterior cranial fossa-Dorsum sellae-Posterior margin of the clivus), Angle3 (Basion-Posterior clinoid process-Sphenoid), Angle5 (Posterior clinoid process-Basion-Sphenoid), Angle7 (Nasion-Basion-Opisthion), Angle8 (Nasion-Apex points of the dorsum sellae-Basion) and Angle11 (Sella-[Spheno-occipital Synchondrosis]-Basion). The other skull angles with the *pout* values are less than 0.5000 and *pmask* and *pswamp* values are more than 0.5000 are not considered to be associated with AS.

Table 4
Performance measures based on *pout, pmask* and *pswamp* with the promising clustering algorithms for age group >24 months old

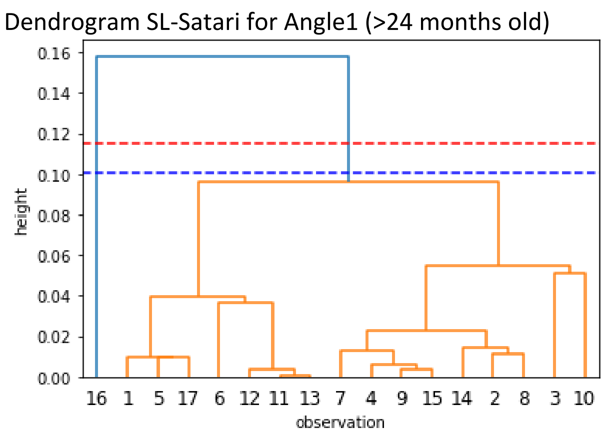
Skull Angles	Clustering Algorithms	*pout*	*pmask*	*pswamp*
Angle1	SL-Satari	0.5000	0.5000	0.0000
	CL-Satari	1.0000	0.0000	0.4000
	CL-Chang	1.0000	0.0000	0.4000
	AL-Satari	0.5000	0.5000	0.0000
	AL-Chang	0.5000	0.5000	0.0000
Angle2	SL-Satari	1.0000	0.0000	0.3333
	CL-Satari	1.0000	0.0000	0.3333
	CL-Chang	1.0000	0.0000	0.3333
	AL-Satari	1.0000	0.0000	0.3333
	AL-Chang	1.0000	0.0000	0.3333
Angle3	SL-Satari	1.0000	0.0000	0.3333
	SL-Chang	1.0000	0.0000	0.3333
	AL-Satari	1.0000	0.0000	0.1333
	AL-Chang	1.0000	0.0000	0.1333
Angle5	SL-Satari	1.0000	0.0000	0.2000
	SL-Chang	1.0000	0.0000	0.2667
	CL-Satari	1.0000	0.0000	0.2000
	CL-Chang	1.0000	0.0000	0.2000
	AL-Satari	1.0000	0.0000	0.2000
	AL-Chang	1.0000	0.0000	0.2000
Angle7	SL-Chang	1.0000	0.0000	0.4000
	CL-Satari	1.0000	0.0000	0.4000
	CL-Chang	1.0000	0.0000	0.4000
Angle8	SL-Satari	0.5000	0.5000	0.0000
	SL-Chang	0.5000	0.5000	0.0000
	CL-Satari	0.5000	0.5000	0.0000
	CL-Chang	0.5000	0.5000	0.0000
	AL-Satari	0.5000	0.5000	0.0000
	AL-Chang	0.5000	0.5000	0.0000
Angle11	SL-Satari	0.5000	0.5000	0.0000
	CL-Satari	1.0000	0.0000	0.4000
	CL-Chang	1.0000	0.0000	0.4000
	AL-Satari	0.5000	0.5000	0.0000
	AL-Chang	1.0000	0.0000	0.4000

The outliers are detected and visualized in dendrogram by cutting at a certain height using 95% confidence interval of cutting rule. Figure 2 shows the examples of dendrogram which visualized the cutting height of cut of point to separate the inliers and outliers. This study used red line which represent the cutting rule at 95% confidence interval as cut of point to identify the outlier. The observations that exceed the cutting height were considered as outliers.

Journal of Advanced Research in Applied Sciences and Engineering Technology
Volume 44, Issue 2 (2025) 135-174



Cutting Height 95% CI (Red line): 0.0831
Cutting Height 90% CI (Blue line): 0.0740



Cutting Height 95% CI (Red line): 0.1155
Cutting Height 90% CI (Blue line): 0.1007

Fig. 2. The example of dendrogram for SL-Satari for Angle5 dataset for age group 0-24 months old and for Angle1 dataset for age group >24 months old

Table 5 shows the summary of skull angles that associated with AS by clustering algorithms. SL-Satari and SL-Chang were found that Angle5, Angle6 and Angle12 associated with AS for age group 0-24 months.

Table 5
Summary of skull angles that associated with Apert syndromes

Clustering	Algorithms	Age group	
		0-24 months old	>24 months old
Single-linkage	SL-Satari	Angle5, Angle6, Angle 12	Angle1, Angle2, Angle3, Angle5, Angle8, Angle11
	SL-Chang		Angle3, Angle5, Angle7, Angle8
Complete-linkage	CL-Satari CL-Chang	Angle6, Angle7, Angle 12	Angle1, Angle2, Angle5, Angle7, Angle8, Angle11
Average-linkage	AL-Satari AL-Chang	Angle5, Angle6, Angle7, Angle 12	Angle1, Angle2, Angle3, Angle5, Angle8, Angle11

Meanwhile, CL-Satari and CL-Chang found Angle6, Angle7 and Angle12 associated with AS for age group 0-24 months. AL-Satari and AL-Chang found Angle5, Angle6, Angle7 and Angle12 were associated with AS for age group 0-24 months. The locations of aforementioned skull angles for group age 0-24 months old are visualized in Figure 3.

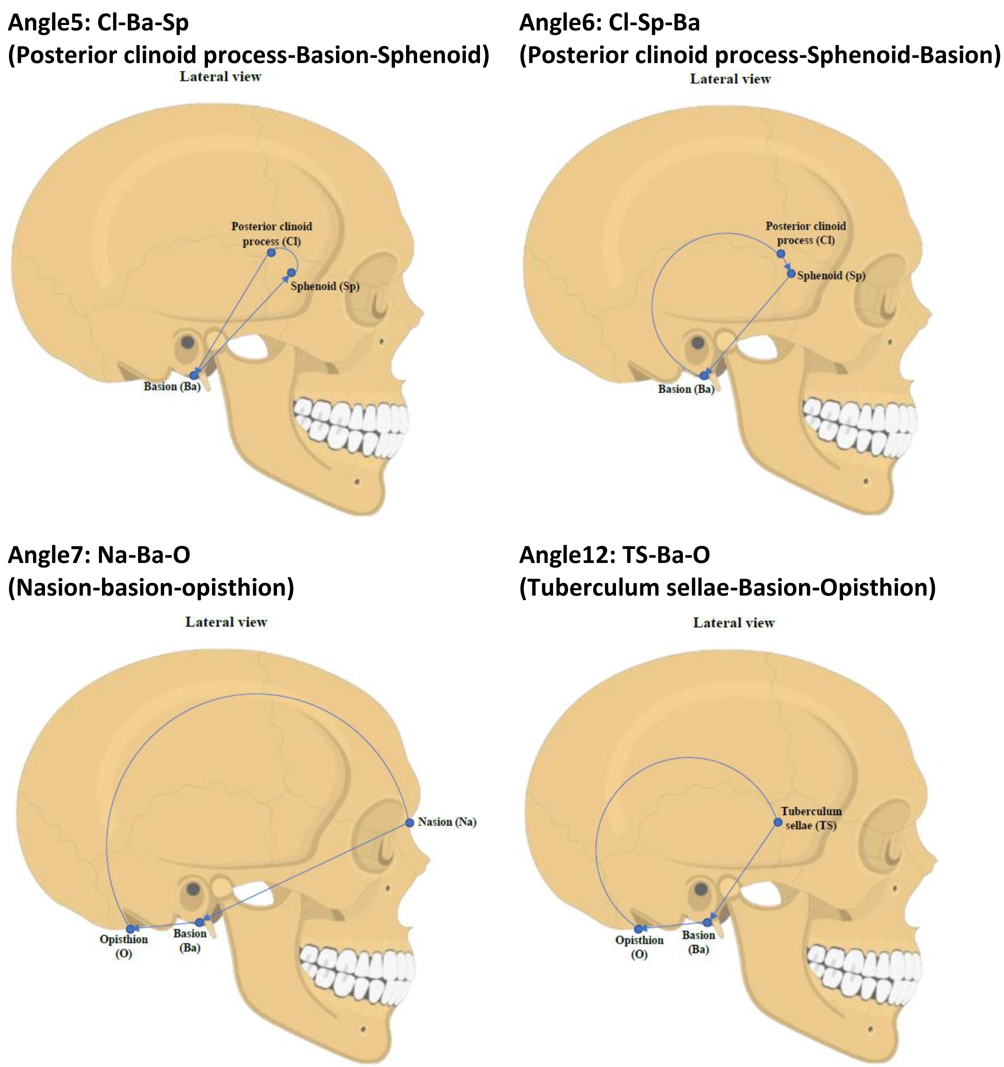


Fig. 3. The location of skull angles that associated with Apert syndrome for age group 0-24 months old

Table 5 shows that Angle1, Angle2, Angle3, Angle5, Angle8 and Angle11 associated with AS for age group >24 months by using SL-Satari. Meanwhile, SL-Chang found that Angle3, Angle5, Angle7 and Angle8 associated with AS for age group >24 months. Besides that, CL-Satari and CL-Chang were found Angle1, Angle2, Angle5, Angle7, Angle8 and Angle11 were associated with AS for age group >24 months. Lastly, AL-Satari and AL-Chang found Angle1, Angle2, Angle3, Angle5, Angle8 and Angle11 were associated with AS for age group >24 months. The locations of aforementioned skull angles for group age >24 months old are visualized in Figure 4.

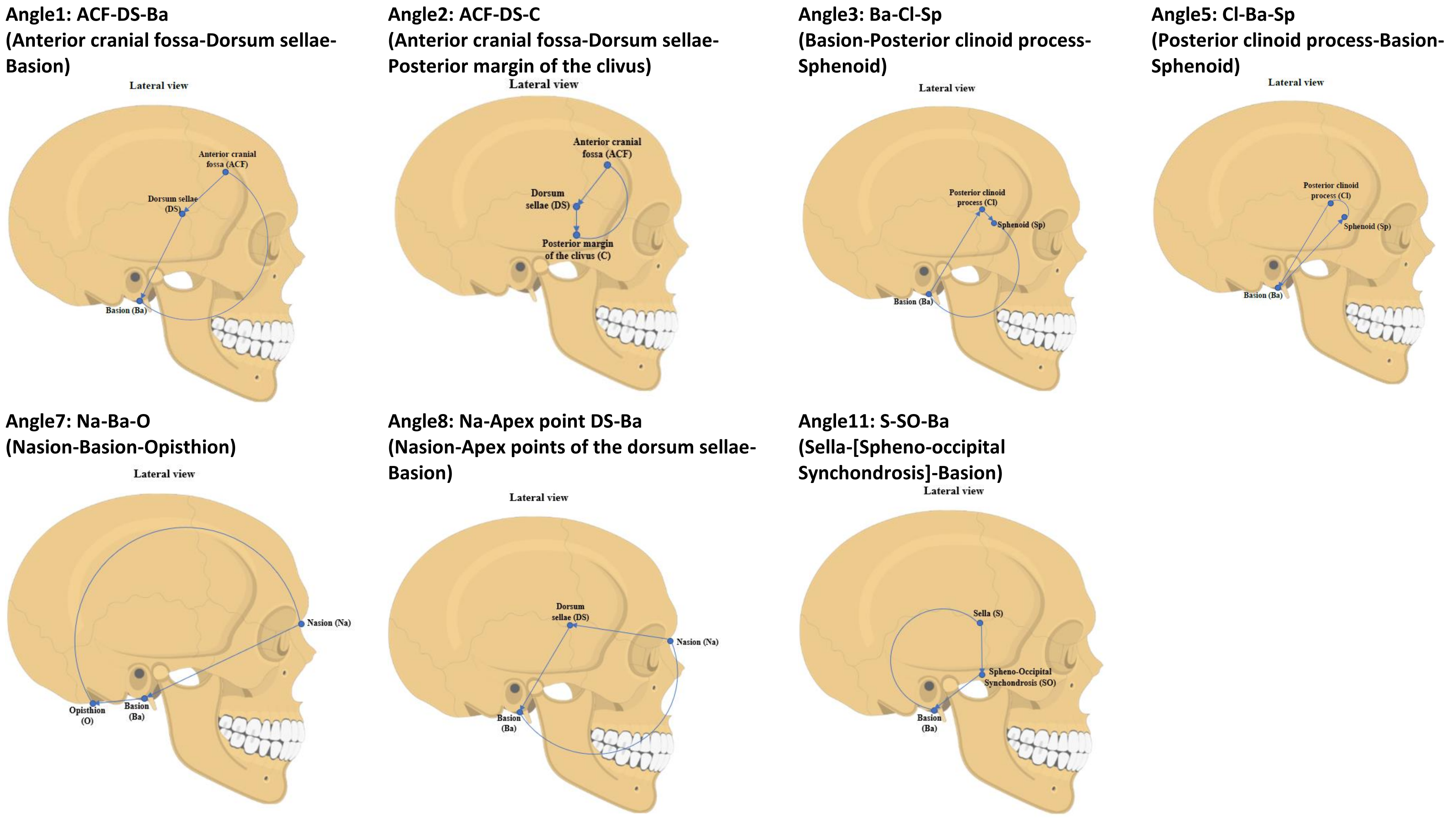


Fig. 4. The location of skull angles that associated with Apert syndrome for age group >24 months old

4. Conclusions

This study seeks to explore the skull angles correlated with Apert syndrome (AS) within the Malaysian population by employing a clustering-based procedure. In order to confirm the skull angles that truly associated with AS, six clustering algorithms were used and these clustering algorithms are able to detect the abnormalities in the datasets that contain control data and AS data for age group 0-24 months old and >24 months old. Generally, this study found that there are skull angles with specific location of angles are associated with this syndrome. This study also found that the location of skull angles for patients age 0-24 months old and >24 months old are different.

For age group 0-24 months old, the skull angles that associate with this syndrome are Angle5 (Posterior clinoid process-Basion-Sphenoid), Angle6 (Posterior clinoid process-Sphenoid-Basion), Angle7 (Nasion-Basion-Opisthion) and Angle12 (Tuberculum sellae-Basion-Opisthion). On the other hands, there are seven skull angles that found to be associated with this syndrome for age group >24 months old. Generally, the skull angles that associate with AS for age group >24 months old are Angle1 (Anterior cranial fossa-Dorsum sellae-Basion), Angle2 (Anterior cranial fossa-Dorsum sellae-Posterior margin of the clivus), Angle3 (Basion-Posterior clinoid process-Sphenoid), Angle5 (Posterior clinoid process-Basion-Sphenoid), Angle7 (Nasion-Basion-Opisthion), Angle8 (Nasion-Apex points of the dorsum sellae-Basion) and Angle11 (Sella-[Spheno-occipital Synchondrosis]-Basion).

In conclusion, the finding from this study will give the information regarding with the Apert syndrome and can assist the surgical team in directing additional focus towards specific regions of the skull during the planning of interventions. Therefore, the potential morbidity can be reduced and help the surgical team to optimize the surgical outcomes. Lastly, the scope of this study also can be extended with other craniosynostosis syndromes such as Crouzon and Pfeiffer syndromes particularly in Malaysia.

Acknowledgement
The authors express their gratitude to the associate editors and referees for their diligent review and insightful suggestions, which contributed to enhancing the quality of this paper. The Universiti Malaysia Pahang Al-Sultan Abdullah (UMPSA) and Ministry of Higher Education Malaysia are acknowledged for the financial support received for this study. (UMP Internal Grant: PGRS210328, RDU1901168 and FRGS/1/2019/STG06/UMP/02/6).

References

[1] Lee, Dennis S., and Kevin C. Chung. "Eugene Apert and his contributions to plastic surgery." *Annals of plastic surgery* 64, no. 3 (2010): 362-365. https://doi.org/10.1097/SAP.0b013e3181b0bb53

[2] Athanasiadis, A. P., M. Zafrakas, P. Polychronou, L. Florentin-Arar, P. Papasozomenou, G. Norbury, and J. N. Bontis. "Apert syndrome: the current role of prenatal ultrasound and genetic analysis in diagnosis and counselling." *Fetal diagnosis and therapy* 24, no. 4 (2009): 495-498. https://doi.org/10.1159/000181186

[3] Martelli Jr, Hercilio, Lívia Maris Ribeiro Paranaíba, Roseli Teixeira De Miranda, Julian Orsi Jr, and Ricardo D. Coletta. "Apert syndrome: report of a case with emphasis on craniofacial and genetic features." *Pediatric Dentistry* 30, no. 6 (2008): 464-468.

[4] Hutson Jr, Larry R., Elizabeth Young, and Lindhe Guarisco. "Tracheal anomalies complicating ventilation of an infant with Apert syndrome." *Journal of clinical anesthesia* 19, no. 7 (2007): 551-554. https://doi.org/10.1016/j.jclinane.2007.02.015

[5] Lu, Xiaona, Antonio Jorge Forte, Rajendra Sawh-Martinez, Robin Wu, Raysa Cabrejo, Derek M. Steinbacher, Michael Alperovich, Nivaldo Alonso, and John A. Persing. "Normal angulation of skull base in Apert syndrome." *Journal of Cranio-Maxillofacial Surgery* 46, no. 12 (2018): 2042-2051. https://doi.org/10.1016/j.jcms.2018.09.026

[6] Munarriz, Pablo M., Beatriz Pascual, Ana M. Castaño-Leon, Ignacio García-Recuero, Marta Redondo, Ana Martínez de Aragón, and Ana Romance. "Apert syndrome: Cranial procedures and brain malformations in a series of patients." *Surgical Neurology International* 11 (2020). https://doi.org/10.25259/SNI_413_2020

[7] Cha, Bong Kuen, Dong Soon Choi, In San Jang, Hyun Tae Yook, Seung Youp Lee, Sang Shin Lee, and Suk Keun Lee. "Aberrant growth of the anterior cranial base relevant to severe midface hypoplasia of Apert syndrome." *Maxillofacial Plastic and Reconstructive Surgery* 40 (2018): 1-8. https://doi.org/10.1186/s40902-018-0179-8

[8] Rostamzad, Parinaz, Zehra F. Arslan, Irene MJ Mathijssen, Maarten J. Koudstaal, Mieke M. Pleumeekers, Sarah L. Versnel, and Sjoukje E. Loudon. "Prevalence of ocular anomalies in craniosynostosis: a systematic review and meta-analysis." *Journal of Clinical Medicine* 11, no. 4 (2022): 1060. https://doi.org/10.3390/jcm11041060

[9] Delashaw, Johnny B., John A. Persing, William C. Broaddus, and John A. Jane. "Cranial vault growth in craniosynostosis." *Journal of neurosurgery* 70, no. 2 (1989): 159-165. https://doi.org/10.3171/jns.1989.70.2.0159

[10] Kabbani, Haidar, and Talkad S. Raghuveer. "Craniosynostosis." *American family physician* 69, no. 12 (2004): 2863-2870.

[11] Bristol, Ruth E., Gregory P. Lekovic, and Harold L. Rekate. "The effects of craniosynostosis on the brain with respect to intracranial pressure." In *Seminars in pediatric neurology*, vol. 11, no. 4, pp. 262-267. WB Saunders, 2004. https://doi.org/10.1016/j.spen.2004.11.001

[12] Hariri, Firdaus, Zainal Ariff Abdul Rahman, Nor Faizal Ahmad Bahuri, Mohd Nazri Azmi, Norli Anida Abdullah, and Dharmendra Ganesan. "Crouzon syndrome: a case series of craniomaxillofacial distraction osteogenesis for functional rehabilitation." *Journal of Oral and Maxillofacial Surgery* 76, no. 3 (2018): 646-e1. https://doi.org/10.1016/j.joms.2017.11.029

[13] Hariri, F., M. F. Abdullah, K. B. C. Adam, N. F. A. Bahuri, J. Kulasegarah, A. M. Nathan, F. Ismail *et al.,* "Analysis of complications following multidisciplinary functional intervention in paediatric craniomaxillofacial deformities." *International journal of oral and maxillofacial surgery* 50, no. 4 (2021): 457-462. https://doi.org/10.1016/j.ijom.2020.08.002

[14] Meulstee, J. W., L. M. Verhamme, W. A. Borstlap, F. Van der Heijden, G. A. De Jong, T. Xi, S. J. Bergé, Hans Delye, and T. J. J. Maal. "A new method for three-dimensional evaluation of the cranial shape and the automatic identification of craniosynostosis using 3D stereophotogrammetry." *International journal of oral and maxillofacial surgery* 46, no. 7 (2017): 819-826. https://doi.org/10.1016/j.ijom.2017.03.017

[15] Khansa, Ibrahim, Annie I. Drapeau, and Gregory D. Pearson. "Posterior Cranial Distraction in Craniosynostosis: A Systematic Review of the Literature." *The Cleft Palate Craniofacial Journal* (2023): 10556656231168548. https://doi.org/10.1177/10556656231168548

[16] Rooppakhun, Supakit, Surasith Piyasin, Natapoom Vatanapatimakul, Yupaporn Kaewprom, and Kriskrai Sitthiseripratip. "Craniometric study of Thai skull based on three-dimensional computed tomography (CT) data." *Journal of the Medical Association of Thailand* 93, no. 1 (2011): 90.

[17] Hirunpat, Siriporn, Nat Wimolsiri, and Nuttha Sanghan. "Normal value of skull base angle using the modified magnetic resonance imaging technique in Thai population." *J Oral Health Craniofac Sci* 2 (2017): 17-21. https://doi.org/10.29328/journal.johcs.1001006

[18] Sebert, David M., Douglas C. Montgomery, and Dwayne A. Rollier. "A clustering algorithm for identifying multiple outliers in linear regression." *Computational statistics & data analysis* 27, no. 4 (1998): 461-484. https://doi.org/10.1016/S0167-9473(98)00021-8

[19] Chang-Chien, Shou-Jen, Wen-Liang Hung, and Miin-Shen Yang. "On mean shift-based clustering for circular data." *Soft Computing* 16 (2012): 1043-1060. https://doi.org/10.1007/s00500-012-0802-z

[20] Satari, Siti Zanariah. "Parameter estimation and outlier detection for some types of circular model/Siti Zanariah binti Satari." PhD diss., University of Malaya, 2015.

[21] Jammalamadaka, S. Rao, Ambar Sengupta, and Ashis Sengupta. *Topics in circular statistics*. Vol. 5. world scientific, 2001. https://doi.org/10.1142/4031