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Scaphocephaly in a select South African population: a morphometric analysis of the cranial fossae and ventricular access points

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PREFACE

This study is a representation of original work by the author and has not been submitted to other universities in any form. The work is under review in accredited journals in line with the thesis guidelines of the University of KwaZulu-Natal. Acknowledgement in the text has been made where the work of others was used.

The research described in this project was supervised by Prof L. Lazarus (Department of Clinical Anatomy, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, South Africa), Prof A. Madaree (Department of Plastic and Reconstructive Surgery, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, South Africa), and Dr R. Harrichandparsad (Department of Neurosurgery, School of Clinical Medicine, College of Health Sciences, University of KwaZulu-Natal, South Africa), and was conducted in the above-mentioned institution (on the Westville Campus) and Inkosi Albert Luthuli Central Hospital, Durban, KwaZulu-Natal, South Africa.

DECLARATION

I, Ms Vensuya Bisetty, declare that:

i. The work described in this thesis has not been submitted to the University of KwaZulu-Natal or other tertiary institutions for purposes of obtaining an academic qualification, whether by myself or any other party.

ii. This dissertation does not contain another person's data, graphs, tables or other information unless specifically acknowledged as being sourced from other persons.

iii. This dissertation does not contain another person's writing unless specifically acknowledged as being sourced from other persons. Where other written sources have been quoted, the information used has been referenced accordingly.

iv. The research reported in this thesis unless where otherwise indicated, is my original work. My contribution to the project was as follows:

- Development and design of research topic and protocol
- Conduction of research methodology
- Collection and analysis of data
- Interpretation of data obtained
- Formulation of manuscript
- Write-up of final thesis

v. The contribution of others to this project was as follows:

Prof L Lazarus (Supervisor), Prof A Madaree (Co-Supervisor) and

Dr R Harrichandparsad (Co-Supervisor):

- Development and refining of research design and plan
- Assistance with analysis of data and statistical analysis
- Review of manuscript and thesis before submission

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Dr Rohen Harrichandparsad

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TABLE OF CONTENTS

TITLE PAGE ..... **i**

PREFACE ..... **ii**

DECLARATION ..... **iii**

ACKNOWLEDGEMENTS ..... **iv**

TABLE OF CONTENTS ..... **v**

LIST OF FIGURES ..... **ix**

LIST OF TABLES ..... **xi**

LIST OF ACRONYMS AND ABBREVIATIONS ..... **xii**

ABSTRACT ..... **xiii**

CHAPTER 1: INTRODUCTION **1**

1.1. Introduction 1

1.1.1. Research questions 4

1.1.2. Aims 4

1.1.3. Objectives 4

1.2. Literature Review 5

1.2.1. Gross Anatomy 5

1.2.2. Embryology 7

1.2.3. Craniosynostosis 8

1.2.4. Scaphocephaly 10

1.2.5. Morphometry of the cranial base and fossae in scaphocephaly 15

1.2.6. Select ventricular access points used in neurosurgery 18

1.3. Materials and Methods 27

1.3.1. Patients 27

1.3.2. Image acquisition & analysis 28

1.3.3. Subset 1: Morphometry of the cranial fossae in scaphocephaly 28

1.3.4. Subset 2: Morphometry of Kocher's & Frazier's Points in scaphocephaly 29

1.3.5. Variables 30
1.3.6. Sample size 31
1.3.7. Statistical analysis 31
1.3.8. Ethical Considerations 32
1.4. Structure of Thesis 33
1.4.1. Chapter 1: Introduction 33
1.4.2. Chapter 2: Scientific Manuscript 1 33
1.4.3. Chapter 3: Scientific Manuscript 2 33
1.4.4. Chapter 4: Synthesis 34
1.5. References 34
CHAPTER 2: SCIENTIFIC MANUSCRIPT 1 40
Title page 41
2.1. Abstract 42
2.2. Introduction 43
2.3. Materials and Methods 44
2.3.1. Patients 44
2.3.2. Image acquisition & analysis 44
2.3.3. Morphometry of the cranial fossae 45
2.3.4. Statistical analysis 49
2.4. Results 49
2.4.1. Morphometry of the cranial fossae 50
2.5. Discussion 55
2.5.1. Morphometry of the cranial fossae 56
2.5.2. Comparison by Age, Sex, Population group & Degree of severity 57
2.6. Declarations 59
2.6.1. Acknowledgements 59
2.6.2. Author contributions 59
2.6.3. Conflict of Interest 59
2.6.4. Ethical Approval 59
2.7. References 60
CHAPTER 3: SCIENTIFIC MANUSCRIPT 2 62

Title page 63

3.1. Abstract 64

3.2. Introduction 65

3.3. Materials and Methods 67

3.3.1. Patients 67

3.3.2. Image acquisition & analysis 68

3.3.3. Morphometry of Kocher's & Frazier's Points 68

3.3.4. Statistical analysis 72

3.4. Results 72

3.4.1. Demographic data 72

3.4.2. Morphometric analysis of Kocher's and Frazier's points in patients with scaphocephaly 73

3.5. Discussion 76

3.5.1. Morphometric analysis of Kocher's point 77

3.5.2. Morphometric analysis of Frazier's point 78

3.6. Conclusion 79

3.7. Disclosures 79

3.8. References 80

CHAPTER 4: SYNTHESIS 83

4.1. Synthesis 84

4.1.1. Manuscript 1 - Morphometric analysis of the cranial fossae in scaphocephalic patients: An anatomical basis 84

4.1.2. Manuscript 2 - A morphometric analysis of Kocher's and Frazier's points in a select South African scaphocephalic population 85

4.2. Limitations 87

4.3. Recommendations 87

4.4. Conclusions 88

4.5. References 89

APPENDICES 90

Appendix A: Journal submission 90

Appendix B: Post-hoc analyses 91
Appendix C: Full ethical approval 92
Appendix D: UKZN Gatekeeper permission 93
Appendix E: IALCH Gatekeeper permission 94
Appendix F: DOH Permission 96
Appendix G: Data sheet 1 sample 97
Appendix H: Data sheet 2 sample 98
Appendix I: Data sheet 3 sample 99
Appendix J: Data sheet 4 sample 100
Appendix K: Data sheet 5 sample 101
Appendix L: Data sheet 6 sample 102
Appendix M: Data sheet 7 sample 103
Appendix N: Data sheet 8 sample 104
Appendix O: Turnitin report 105

LIST OF FIGURES

Figure	Caption	Page
Chapter 1		
Figure 1	Classification of Craniosynostosis.	9
Figure 2	Deformation of the skull due to premature fusion of the sagittal suture. *(Adapted from Kajdic et al., 2017)*	10
Figure 3	**(A)** Anterior sagittal craniosynostosis with frontal bossing. Arrows indicate areas of compensatory growth; **(B)** Posterior sagittal craniosynostosis- Occipital-knob deformity; **(C)** Posterior sagittal craniosynostosis- Golf-tee deformity; **(D)** Posterior sagittal craniosynostosis- Bathrocephaly; **(E)** Complete sagittal craniosynostosis. Arrows indicate areas of compensatory growth. *(Adapted from Jane et al., 2000)*	11
Figure 4	Computed tomographic representations of the types of sagittal craniosynostosis. *(Adapted from David et al., 2009)*	13
Figure 5	Morphometric analysis of the cranial base on a 3D-CT scan of a healthy individual. *(Adapted from Calandrelli et al., 2020)*	16
Figure 6	Ventricular access via Kocher's point. *(Adapted from Morone et al., 2019)*	21
Figure 7	Ventricular access via Frazier's point. *(Adapted from Morone et al., 2019)*	23
Chapter 2		
Figure 1	Anterior cranial fossa (ACF) parameters on axial CT scan of a normal patient [length= LS* to ITF, width= ITF to ITF]. **KEY:** LS*= Transcended point of midpoint of limbus sphenoidale, ITF= Inner table of frontal bone.	46
Figure 2	Middle cranial fossa (MCF) parameters on axial CT scan of a normal patient [length= GWS to PT, width= PF to ITT]. **KEY:** GWS= Midpoint of curvature of greater wing of sphenoid bone, PT= Petrous part of temporal bone, PF= Midpoint of floor of pituitary fossa, ITT= Inner table of temporal bone.	47

Figure 3	Posterior cranial fossa (PCF) parameters on axial CT scan of a normal patient [length= DS* to ITO, width= ITP to ITP]. **KEY:** DS*= Transcended point of midpoint of posterior margin of dorsum sellae, ITO= Inner table of occipital bone, ITP= Inner table of parietal bone.	48
Figure 4	Post-hoc analysis results showing differences between severity and control groups for **(A)** anterior cranial fossa (ACF) length and **(B)** posterior cranial fossa **(**PCF) length.	55
Chapter 3		
Figure 1	CT head scan of a patient with scaphocephaly. **(A)** Sagittal image showing Kocher's point placed 1cm anterior to the coronal suture along the right midpupillary line, **(B)** Axial image showing midpupillary line, **(C)** Coronal image showing midpupillary line. **KEY:** KP= Kocher's Point, cs= coronal suture.	69
Figure 2	CT head scan of a patient with scaphocephaly. **(A)** Sagittal image showing extrapolated point into the midline, **(B)** Axial image showing extrapolated point, **(C)** Coronal image showing Kocher's point and extrapolated point. **KEY:** EP= Extrapolated Point, KP= Kocher's Point.	69
Figure 3	CT head scan of a patient with scaphocephaly. **(A)** Sagittal image showing measurement between the nasion and the extrapolated point, **(B)** Axial image showing extrapolated point, **(C)** Coronal image showing measurement between Kocher's point and the extrapolated point. **KEY:** n= nasion, EP= Extrapolated Point, KP= Kocher's Point.	69
Figure 4	CT head scan of a patient with scaphocephaly. **(Left)** Sagittal image showing occipital horn most prominently, **(Right)** Axial image showing crosshairs angled along the length of the right lateral ventricle (on image showing the lateral ventricle most clearly).	70
Figure 5	CT head scan of a patient with scaphocephaly. **(Left)** Sagittal image showing trajectory and Frazier's point on the outer surface of the skull, **(Right)** Axial image showing Frazier's point. **KEY:** FP= Frazier's Point.	71
Figure 6	CT head scan of a patient with scaphocephaly. **(Left)** Sagittal image showing measurement between the inion and extrapolated point, **(Right)** Axial image showing measurement between Frazier's point and the extrapolated point. **KEY:** FP= Frazier's Point, EP= Extrapolated Point, i= inion.	71
Figure 7	Correlation between the parameters for Kocher's and Frazier's points and age and CI. **KEY:** P=Posterior, KP= Kocher's Point, ML= Midline, FP= Frazier's Point.	75

LIST OF TABLES

Table	Title	Page
Chapter 1		
Table 1	Length (mm) of the cranial fossae in scaphocephalic and healthy individuals	17
Table 2	Variously described/used definitions of Kocher's point in the consulted literature	20
Table 3	Parameters of the anterior entry point (Kocher's Point) in the literature	22
Table 4	Parameters of the posterior entry point (Frazier's Point) in the literature	24
Chapter 2		
Table 1	Demographic data and anatomical profile of the study population	50
Table 2	Maximal cranial fossae dimensions in patients with scaphocephaly *vs.* control group	51
Table 3	Maximal cranial fossae dimensions in patients with scaphocephaly compared to controls by age	53
Table 4	Maximal cranial fossae dimensions in patients with scaphocephaly compared to controls by sex	54
Table 5	Maximal cranial fossae dimensions in patients with scaphocephaly compared to controls by the degree of severity	54
Chapter 3		
Table 1	Morphometric analysis of Kocher's and Frazier's points in patients with scaphocephaly	74

LIST OF ACRONYMS AND ABBREVIATIONS

ACF	Anterior cranial fossa
AP	Anteroposterior
CSF	Cerebrospinal fluid
CT	Computed Tomography
DICOM	Digital Imaging and Communications in Medicine
MCF	Middle cranial fossa
ICP	Intracranial pressure
IALCH	Inkosi Albert Luthuli Central Hospital
ICC	Intraclass correlation coefficient
NRF	National Research Foundation
PACS	Picture Archiving and Communications System
PCF	Posterior cranial fossa
SD	Standard deviation
UKZN	University of KwaZulu-Natal

ABSTRACT

Scaphocephaly is a cranial deformity that results from premature fusion of the sagittal suture and is characterized by an elongated and narrowed skull. Patients with this condition present with varying clinical features including frontal bossing and occipital protrusion. This study comprised two subsets, analysing different aspects related to this cranial deformity. Most morphological and morphometrical studies in patients with scaphocephaly focus on the cranial vault. Literature on the morphometry of the cranial base and its fossae in these patients is sparse. Therefore, the first subset aimed to analyse and compare the morphometry of the cranial fossae in patients with scaphocephaly. Due to varying cranial morphology among patients with these deformities, ventricular access using conventional techniques is often a challenge. Although ventricular access may not be frequently required in paediatric scaphocephalic patients, it is vital that an ideal location of the access points be established for safe ventricular catheterization. Accordingly, the second subset aimed to document the morphometry of Kocher's and Frazier's points in scaphocephalic patients using known craniometric and surface anatomical landmarks.

Dimensions of the anterior, middle and posterior cranial fossae (ACF, MCF and PCF) were measured using select anatomical landmarks on computed tomography (CT) scans of 24 consecutive patients diagnosed with scaphocephaly between 2014 and 2020, and 14 non-affected/ normal paediatric patients selected as controls. Parameters of Kocher's and Frazier's points were measured in relation to known cranial surface anatomical landmarks on scans of the scaphocephalic patients utilized in subset 1. The study found that ACF and PCF are most affected in scaphocephalic patients, with elongation along the anteroposterior (AP) plane (lengths) (ACF, p=0.041 and PCF, p=0.018). Minimal changes were observed in the transverse plane (widths) in scaphocephaly versus non-affected/normal controls. Regarding subset 2, Kocher's point was located between 91.6mm and 140mm posterior to the nasion, and between 20.5mm and 34.6mm lateral to the midline in patients with scaphocephaly. Frazier's point was located between 60.9mm and 82.8mm superior to the inion, and 25.9mm and 41.4mm lateral to the midline. Parameters measured in the AP plane were found to be more affected than those measured lateral from the midline.

This study contributes to the literature by providing novel morphometric data based on a select South African population. Data obtained could aid craniofacial surgeons in understanding which cranial fossa is most affected in scaphocephaly and to what extent, to decide on the most appropriate method of treatment. Additionally, the study concluded that the traditional landmarks

used for ventricular access are relatively unreliable in scaphocephalic patients. This study provides data for neurosurgical consideration regarding ventricular catheterization procedures in patients with scaphocephaly.

CHAPTER 1: INTRODUCTION

1.1.Introduction

Craniosynostosis, a congenital abnormality, is characterized by an abnormal head shape resulting from the premature fusion of one or more cranial sutures (Heuzé *et al.*, 2010; Van Veelen-Vincent *et al.*, 2010; Ciurea *et al.*, 2011). Sagittal synostosis refers to the early closure of the sagittal suture. The resultant head shape is described by the term *scaphocephaly*, denoting a long narrow 'boat-shaped' skull (Ruiz-Correa *et al.*, 2006; David *et al.*, 2012; Ghizoni *et al.*, 2016). The excessive skull length compensates for the restricted growth of the skull width, resulting in a reduced cephalic index (CI) of <70% (Van Veelen-Vincent *et al.*, 2010; Massimi *et al.*, 2012; Tatum *et al.*, 2012). Scaphocephaly (also called sagittal synostosis or sagittal craniosynostosis) may be accompanied by additional morphological changes including frontal bossing, biparietal narrowing, temporal protrusion, sagittal ridging, coronal constriction, anteroposterior elongation, and occipital protuberance (David *et al.*, 2009; Van Veelen-Vincent *et al.*, 2010; Ghizoni *et al.*, 2016; Calandrelli *et al.*, 2019). In some cases, it may also present with elevated intracranial pressure (ICP) (Ciurea *et al.*, 2011; Tatum *et al.*, 2012; Seeberger *et al.*, 2016; Satanin *et al.*, 2019). The cranial dysmorphism in scaphocephaly varies considerably amongst affected individuals, depending on the age of onset, anatomical location, presence of prominent anatomical features, degree of premature suture closure and compensatory growth, as well as the severity of the deformity (Jane *et al.*, 2000; Ruiz-Correa *et al.*, 2006; David *et al.*, 2009; Massimi *et al.*, 2012; Tatum *et al.*, 2012; Calandrelli *et al.*, 2019). Scaphocephaly is the most prevalent form of craniosynostosis, contributing to more than half of all reported cases (Ruiz-Correa *et al.*, 2006; Heuzé *et al.*, 2010; Ciurea *et al.*, 2011). The overall incidence of scaphocephaly has been estimated to be between 1 in 2000 and 1 in 7000 live births, with a 2-4:1 male predilection (Ciurea *et al.*, 2011; Massimi *et al.*, 2012; Tatum *et al.*, 2012; Kajdic *et al.*, 2017; Calandrelli *et al.*, 2020).

The exact etiology of scaphocephaly remains unclear but can be ascribed to environmental and genetic influences (Massimi *et al.*, 2012). Controversy in the literature exists with regards to cranial vault and base involvement in craniosynostosis. The cranial base was postulated by Moss (1959) to be the primary site of abnormality in children with craniosynostosis. Moss (1959) thought that the altered cranial base was responsible for transmitting tensile forces through the dura mater, which ultimately led to the premature fusion of calvarial sutures. Contrarily, Eaton *et al.* (1997) found that the morphology of the endocranial base is subjected to change by deformities

of the cranial vault and suggested that the endocranial base is not the primary anomaly in individuals with sagittal synostosis.

Morphologic and morphometric studies on the cranial vault in scaphocephaly are abundant in the literature. However, there is sparse literature available with regard to the morphometry of the cranial base and its fossae in the aforementioned population. In sagittal synostosis, disproportionate growth of the cranial base along the anterior-posterior axis is expected, with little or no change along the medial-lateral and superior-inferior axes (Richtsmeier *et al.*, 1991). The characteristic narrow, elongated deformation is observed at both the level of the vault and base (Bendon *et al.*, 2014; Beez *et al.*, 2017). The base appears to be less severely affected as compared to the vault; however, the clinical impact of deformity at the skull base remains unknown (Bendon *et al.*, 2014).

This study comprises two subsets. The first aspect of this study provides basic morphometric anatomical measurements of the cranial fossae in scaphocephaly and control patients, within a select South African population. The comparison of measurements will provide information on the extent of the deformity at the level of the cranial fossae in patients with scaphocephaly. These measurements will aid craniofacial surgeons in the systematic assessment of scaphocephaly, by enabling a more precise understanding of which cranial fossa is most affected and the extent to which it is affected. This may influence the decision on the most appropriate method(s) of corrective treatment.

The second component of this study focuses on two neurosurgical landmarks indicated for ventricular catheterization viz. Kocher's and Frazier's points, in patients with scaphocephaly.

Ventricular access during neurosurgery is often required (Morone *et al.*, 2019). A ventriculostomy is a routinely used emergency neurosurgical procedure that entails the catheterization of one of the cerebral ventricles for diagnostic and therapeutic purposes (Techataweewan *et al.*, 2017; Morone *et al.*, 2019). Some of the common indications for emergency ventricular access include hydrocephalus, intracranial hypertension (ICH), subarachnoid and intracranial haemorrhage, and traumatic brain injury (Rehman *et al.*, 2013; Techataweewan *et al.*, 2017; Lee *et al.*, 2020). Surface anatomical landmarks on the cranium are used to identify the optimal entry site for ventricular cannulation (Techataweewan *et al.*, 2017). Various modalities are available to facilitate ventricular catheter placement; however, due to its simplicity and efficiency in time-sensitive emergencies, the freehand pass technique remains a highly preferred method by

neurosurgeons (Sarrafzadeh *et al.*, 2014; Robertson *et al.*, 2017; Techatweewan *et al.*, 2017, Raabe *et al.*, 2018; Lee *et al.*, 2020).

Numerous access points have been described in the literature, each accessing different parts of the lateral ventricles, depending upon the indications for ventricular cannulation (Mortazavi *et al.*, 2013; Morone *et al.*, 2019; Roka, 2021). This study only focuses on Kocher's and Frazier's points. Kocher (1984, p. 50) initially described a frontal entry point as being situated "…2.5cm from the median line and 3cm forward of the pre-central fissure." The literature review has revealed that Kocher's point is the most common anterior entry site and is now variously defined as being between 10 to 13cm posterior to nasion and 1.5 to 4cm lateral to the midline at the mid-pupillary line, and approximately 1 to 2cm anterior to the coronal suture (Kocher, 1984; Ozedemir *et al.*, 2014; Ikeda *et al.*, 2017; Kirkman *et al.*, 2017; Techataweewan *et al.*, 2017; Morone *et al.*, 2019; Lee *et al.*, 2020). Frazier's point, a common posterior access site, is located approximately 3 to 4cm lateral to the midline and 6 to 7cm above the inion (Frazier, 1928; Lee *et al.*, 2008; Mortazavi *et al.*, 2013; Morone *et al.*, 2019).

Despite being a simple and commonly performed procedure, ventricular cannulation via the freehand method has been found to be relatively inaccurate, with catheter misplacement rates of up to 45% (Techataweewan *et al.*, 2017; Morone *et al.*, 2019). Catheter misplacement has been attributed to variations in cranial morphology and ventricular anatomy, surgical experience, size of the burr hole, and techniques employed (Sarrafzadeh *et al.*, 2014; Techataweewan *et al.*, 2017; Lee *et al.*, 2020; Deora *et al.*, 2020). A lack of standardization regarding the entry points may also contribute to the misplacement of the ventricular catheter (Lee *et al.*, 2008). To avoid serious morbidities and mortality, it is critical that the ventricular catheter not be misplaced (Kirkman *et al.*, 2017; Lee *et al.*, 2020). Neurosurgeons may encounter greater challenges when performing ventriculostomy procedures on patients presenting with cranial abnormalities (Nigim and Kasper, 2013). The many morphological variations in scaphocephaly make it difficult to precisely identify the standard surface anatomical landmarks used in the freehand pass technique and may influence the accuracy of ventricular catheter placement in such patients.

The ideal cranial entry point, trajectory insertion, and catheter length play a vital role in ensuring successful ventricular catheter placement (Low *et al.*, 2010; Kemp *et al.*, 2014; Meybodi *et al.*, 2017). Many studies have focused on optimizing the trajectory and catheter length but there have been few studies that attempted to specifically validate or update these historical cranial ventricular access points, despite ventricular catheterization being a ubiquitous neurosurgical

procedure (Meybodi *et al.* 2017; Deora *et al.*, 2020). Furthermore, the majority of the literature that neurosurgeons rely on for external ventricular drainage is based on adult experience, and the knowledge from which has to be extrapolated to a paediatric population (Kulkarni, 2009). There is a paucity of literature regarding the ideal entry points for ventricular access in a paediatric population, much less, a scaphocephalic paediatric population.

This second subset of the study will provide an ideal range at which Kocher's and Frazier's point can be located in patients with scaphocephaly, if ventricular catheterization is required. The findings of this study have the potential to equip neurosurgeons with the data required to modify the approaches typically used in ventricular cannulation to suit patients with scaphocephaly. This study is warranted as both parts have not yet been fully explored in the literature. This study will contribute to the literature by providing data based on a select South African population.

1.1.1. Research questions

- Subset 1- What would the dimensions of the anterior, middle, and posterior cranial fossae (ACF, MCF and PCF) be in scaphocephalic patients as compared to normal?
- Subset 2- Where would Kocher's point and Frazier's point, both being important ventricular access sites in neurosurgery, be located on the skulls of scaphocephalic patients? What would be the location of both these points in patients with scaphocephaly when compared to the described craniometric points in the literature?

1.1.2. Aims

- Subset 1- To analyse and compare the morphometry of the ACF, MCF and PCF in scaphocephalic and control patients in a select South African population.
- Subset 2- To document the location of Kocher's and Frazier's points in a select South African scaphocephalic population using known craniometric and anatomical surface landmarks.

1.1.3. Objectives

- Subset 1- To calculate the dimensions, i.e., length and width of the ACF, MCF and PCF in scaphocephalic and normal patients using fixed anatomical landmarks.
- To compare the aforementioned variables against age, sex, population group and the degree of severity.

- Subset 2- To define the positions of the anterior and posterior entry sites for ventricular catheter placement using known craniometric landmarks, and to measure the craniometric dimensions of the entry sites relative to cranial surface anatomical landmarks in patients with scaphocephaly.
- To compare the aforementioned variables against age, population group, and the degree of severity.

1.2.Literature Review

1.2.1. Gross Anatomy

1.2.1.1. Cranium

Cranial sutures are fibrous joints found between the membranous bones (two frontal, two parietal, and one occipital) of the cranial vault (Johnson and Wilkie, 2011). The calvarium is comprised of four major sutures – metopic, sagittal, coronal, and lambdoid - and three minor sutures viz. frontonasal, temporal squamosal, and frontosphenoidal. The frontal bones are separated by the metopic suture and the parietal bones via the sagittal suture. The coronal suture separates the frontal from the parietal bones, and the lambdoid suture separates the occipital from the parietal bones (Johnson and Wilkie, 2011; Ghizoni *et al.* 2016). The bones of the newborn skull meet at the intersection of the sutures, forming spaces called fontanelles. The cranial sutures and fontanelles permit movement of the cranial bones to facilitate the passage of the newborn's skull through the birth canal during parturition (Johnson and Wilkie, 2011; Nagaraja *et al.*, 2013; Ghizoni *et al.* 2016; Kajdic *et al.*, 2017). The posterior fontanelle closes three months after birth, the sphenoidal in the third month, and the anterior fontanelle usually closes within 18 months of birth, whilst the posterolateral fontanelle remains open until the second year (Gray and Standring, 2016). Postnatally, the cranial vault sutures allow enlargement of the calvaria to accommodate the growing brain (Johnson and Wilkie, 2011; Ghizoni *et al.* 2016; Kajdic *et al.*, 2017). These sutures fuse over time and are rendered immovable. The timing of the closure of each suture varies (Anderson and Kharazi, 2019). The metopic suture typically fuses between 3 to 9 months of age. Closure of the sagittal suture usually commences at 22 years of age, followed by the coronal suture at 24 years and the lambdoid suture at 26 years. In most cases, these sutures may become fully closed only at 35, 41, and 47 years of age, respectively (Som and Curtin, 2011; Anderson and Kharazi, 2019).

The cranial base is made up of 5 bones viz. paired frontal, ethmoid, sphenoid, paired temporal and occipital, and forms the floor of the cranial cavity. The internal cranial base is divided into three distinct regions viz.:

a) The anterior cranial fossa (ACF), which is formed by the frontal, ethmoid, and sphenoid bones, contains the frontal lobes of the cerebral hemispheres. The boundaries are formed anteriorly and laterally by the frontal bone. The floor of the ACF is made up of the orbital plate of the frontal bone, cribriform plate and crista galli of the ethmoid bone, and the lesser wings, jugum sphenoidale, and prechiasmatic sulcus of the sphenoid bone (Moore *et al.*, 2010; Gray and Standring, 2016).

b) The middle cranial fossa (MCF) consists of the sphenoid and temporal bones. It is bounded anteriorly by the posterior aspect of the greater and lesser wings of the sphenoid bone, posteriorly by the superior border of the petrous part of the temporal bone, laterally by the squamous part of the temporal bone and greater wing of the sphenoid bone, and medially by the lateral aspect of the sphenoid body, including the carotid sulcus, sella turcica and dorsum sellae (Moore *et al.*, 2010; Gray and Standring, 2016).

   The MCF is comprised of a central part and two lateral parts, both of which are characterized by numerous bony landmarks. The central part is formed by the body of the sphenoid bone and is marked by a saddle-shaped depression, known as the pituitary (hypophysial) fossa or the sella turcica, which houses the pituitary gland. The anterior border of the sella turcica is formed by a bony protuberance called the tuberculum sellae, which continues anteriorly with the prechiasmatic sulcus. The posterior border is formed by a vertical pillar of bone called the dorsum sellae. The anterior clinoid processes, which arise from the lesser wings of the sphenoid bone, and posterior clinoid processes, which are the superolateral expansions of the dorsum sellae, surround the sella turcica. The lateral parts of the MCF, which are formed by the greater wings of the sphenoid bone, and the squamous and petrous parts of the temporal bones, support the temporal lobes of the brain. There are also many foramina present in the MCF, including the optic canals, superior orbital fissure, foramen rotundum, foramen ovale, foramen spinosum, hiatus for the greater petrosal nerve, hiatus for the lesser petrosal nerve and the carotid canal (Moore *et al.*, 2010; Gray and Standring, 2016).

c) The posterior cranial fossa (PCF) is formed by the sphenoid, temporal, and occipital bones and accommodates the cerebellum, pons, and medulla oblongata. The boundaries of the PCF

are formed anteriorly by the dorsum sellae, posterior aspects of the sphenoid body, and the basilar part of the occipital bone; posteriorly by the squamous part of the occipital bone; and laterally by the petrous and mastoid parts of the temporal bones and by the condylar parts of the occipital bone (Moore *et al.*, 2010; Gray and Standring, 2016).

The PCF contains several foramina and osseous landmarks. The foramen magnum is the most pre-eminent feature in the floor of the PCF. Some of the other major foramina in the PCF include the internal acoustic meatus, jugular foramen, and the hypoglossal canal. The squamous part of the occipital bone presents a median ridge termed the internal occipital crest, which extends posteriorly from the foramen magnum to an internal occipital protuberance. The PCF also contains many visible grooves and depressions for the dural venous sinuses (Moore *et al.*, 2010; Gray and Standring, 2016).

1.2.1.2. The ventricular system

The ventricular system of the human brain is composed of four interconnecting cerebrospinal fluid (CSF)-filled cavities called ventricles, which are the adult derivatives of the central lumen of the embryonic neural tube. CSF is produced by the choroid plexus located within the ventricles. The lateral ventricle is a large C-shaped structure found within each of the cerebral hemispheres. The lateral ventricle can be divided anatomically into a body and three horns viz. frontal (anterior), occipital (posterior), and temporal (inferior), which project into the frontal, occipital and temporal lobes of the brain, respectively (Gray and Standring, 2016; Mortazavi et al., 2013; Gray and Standring, 2016; Kumar *et al.*, 2017). Near its rostral end, the lateral ventricle communicates with the third ventricle via the interventricular foramen. The third ventricle is a narrow midline cavity situated between the left and right thalamus and the hypothalamus. The third ventricle communicates caudally with the cerebral aqueduct of Sylvius, which is continuous with the fourth ventricle. The fourth ventricle is a wide cavity located between the brainstem and cerebellum, which is continuous caudally with the central canal of the spinal cord. The median aperture and two lateral apertures, found along the medial and lateral walls of the fourth ventricle, respectively, allow for the exit of CSF from the ventricular system (Gray and Standring, 2016; Kumar *et al.*, 2017).

1.2.2. Embryology

1.2.2.1. Cranium

The neurocranium refers to the protective casing that surrounds the brain and is divided into two parts, viz. the membranous part that forms the cranial vault and the cartilaginous part that forms

the base. The membranous portion is derived from neural crest cells and paraxial mesoderm. Mesenchyme from these two sources envelopes the brain and undergoes intramembranous ossification to form flat bones, which then ossify with needle-like spicules that radiate from the primary ossification centres towards the periphery. The cartilaginous portion consists of many separate cartilages. Cartilages that arise from neural crest cells and lie anterior to the pituitary fossa form the prechordal part. Cartilages lying posterior to this limit form the chordal part and arise from paraxial mesoderm. Fusion of these cartilages via endochondral ossification results in the formation of the cranial base (Nagaraja *et al.*, 2012; Sadler, 2012).

1.2.2.2. The ventricular system

The cerebral ventricles are the adult derivatives of the central lumen of the embryonic neural tube. The ventricular system extends from the lumen in the spinal cord to the fourth ventricle in the rhombencephalon, through the narrow aqueduct of the mesencephalon, and to the third ventricle in the diencephalon. The interventricular foramina connect the third ventricle to the lateral ventricles. The choroid plexus, which is located within the ventricles, is responsible for the production of CSF (Nagaraja *et al.*, 2012; Sadler, 2012).

1.2.3. Craniosynostosis

Craniosynostosis is a condition characterized by the premature fusion of one or more cranial sutures. An occurrence of early sutural closure may result in a multitude of morphological and functional changes regarding craniofacial development (Van Veelen *et al.*, 2010; Ciurea *et al.*, 2011). It may also result in varying degrees of craniocerebral volumetric disproportions (Ciurea *et al.*, 2011). In severe cases, craniosynostosis may be accompanied by elevated intracranial pressure (ICP) as well as sensory, respiratory, and neurological dysfunction (Kajdic *et al.*, 2017). It is assumed that skull growth is restricted by craniosynostosis and may predispose to raised ICP (Seeberger *et al.*, 2016).

The classifications of craniosynostosis vary depending on the underlying mechanism, the number of fused sutures, or the presence of other disorders. Primary craniosynostosis is the result of a primary defect in the ossification process whilst secondary craniosynostosis occurs due to known systemic diseases, with hematologic or metabolic dysfunction. Secondary craniosynostosis may also develop in newborns with microcephaly due to lack of brain growth or after shunt placement in children with hydrocephalus. The term ‘simple craniosynostosis’ is used to describe the premature closure of a single suture; conversely, ‘complex craniosynostosis’ refers to early fusion involving several sutures of the skull. Craniosynostosis is further classified into syndromic, where

it occurs with other dysmorphisms including Apert, Crouzon, or Pfeiffer syndrome, and non-syndromic, where it develops as an isolated disease (Van Veelen-Vincent *et al.*, 2010; Ghizoni *et al.*, 2016; Kajdic *et al.*, 2017) (Fig. 1). Non-syndromic craniosynostosis is more commonly encountered and typically involves a single suture, whereas multiple sutures are affected in syndromic craniosynostosis (Van Veelen-Vincent *et al.*, 2010).

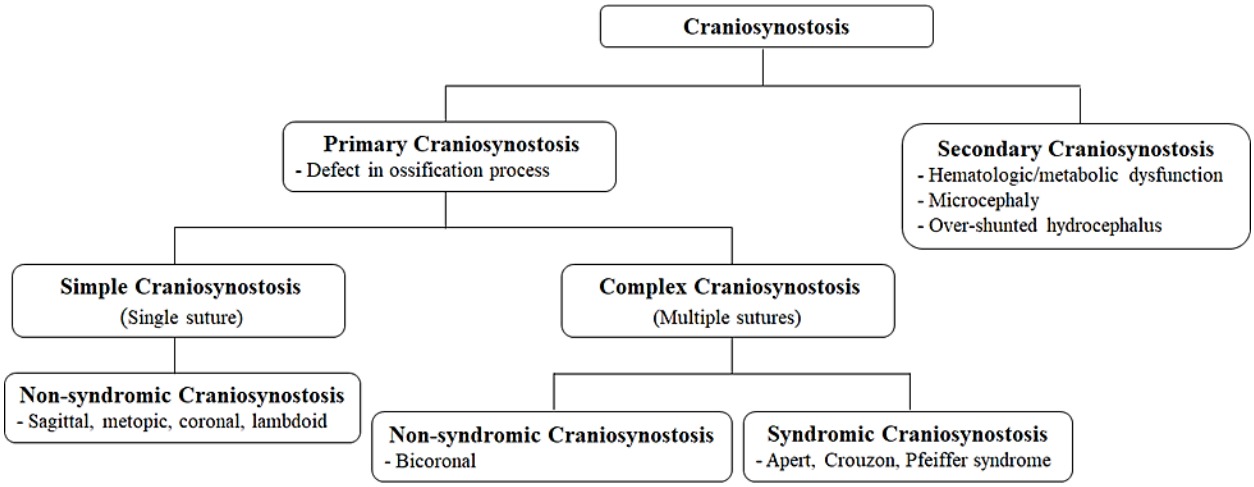


Figure 1: Classification of Craniosynostosis.

The predisposing factors for craniosynostosis are either environmental (*in-utero* head constraint, abnormal position, oligohydramnios, prenatal exposure to teratogens, maternal smoking, and antiepileptic drugs such as valproic acid and phenytoin) or genetic (single-gene mutations, chromosome abnormalities, and polygenic background) (Johnson and Wilkie, 2011; Kajdic *et al.*, 2017). Genetic causes contribute to approximately 20% of all craniosynostoses and are usually associated with complex craniosynostosis and extracranial complications. Most genetically linked craniosynostoses are characterized by autosomal dominant inheritance or, in some cases, new mutations. Craniosynostosis has an estimated incidence of 1 in 2100-2500 live births (Johnson and Wilkie, 2011; Kajdic *et al.*, 2017).

Virchow (1951) originally described the relationship between premature fusion of cranial sutures and skull morphology (Van Veelen-Vincent *et al.*, 2010). According to the observations by Otto (1830) and Virchow (1951) on compensatory changes associated with single suture synostosis, premature fusion inhibits skull growth at right angles to the obliterated suture but enhances growth in the direction parallel to it in order to accommodate the growing brain. Craniosynostosis follows an additional three rules involving compensatory growth viz.

1) Compensatory growth is greatest at adjacent sutures.
2) Compensatory growth is symmetrical if the adjacent suture is roughly parallel to the fused suture.

3) If the adjacent suture is parallel to the fused suture, compensatory growth occurs from the bone distal to the fused suture (Jane *et al.*, 2000; Massimi *et al.*, 2012).

1.2.4. Scaphocephaly

Scaphocephaly (sagittal synostosis or sagittal craniosynostosis) is the morphological consequence of premature fusion of the sagittal suture, the suture joining the paired parietal bones in the median plane (David *et al.*, 2009; Heuzé *et al.*, 2010; Singh *et al.*, 2014; Seeberger *et al.*, 2016). Progression of sagittal synostosis along the sagittal arch may involve the metopic suture and/or the minor sutures of the cranial base (ethmoido-frontal sutures) as well as the anterior fontanelle (David *et al.*, 2012; Calandrelli *et al.*, 2020). Scaphocephaly is the most frequently encountered form of simple non-syndromic craniosynostosis, accounting for more than 50% of all reported cases (Ruiz-Correa *et al.*, 2006; Heuzé *et al.*, 2010; Ciurea *et al.*, 2011). According to the literature, scaphocephaly has a general incidence ranging from 1 in 2000 to 1 in 7000 births, with a male to female predominance of 2-4:1 (Ciurea *et al.*, 2011; Massimi *et al.*, 2012; Tatum *et al.*, 2012; Kajdic *et al.*, 2017; Calandrelli *et al.*, 2020).

The term 'scaphocephaly', derived from Greek words *skaphe* meaning 'boat' and *kephale,* meaning 'head', describes the distinct shape of a narrow, elongated skull, resembling an inverted boat (David *et al.*, 2012; Ghizoni *et al.*, 2016). The resultant skull shape occurs due to impaired transverse growth and compensatory anteroposterior growth (Kajdic *et al.*, 2017) (Fig. 2). The typical findings that may accompany scaphocephaly include frontal bossing, biparietal narrowing, temporal protrusion, sagittal ridging, coronal constriction, anteroposterior elongation, changes in the cervico-occipital angle, and occipital protuberance (David *et al.*, 2009; Van Veelen-Vincent *et al.*, 2010; Ghizoni *et al.*, 2016; Calandrelli *et al.*, 2019).

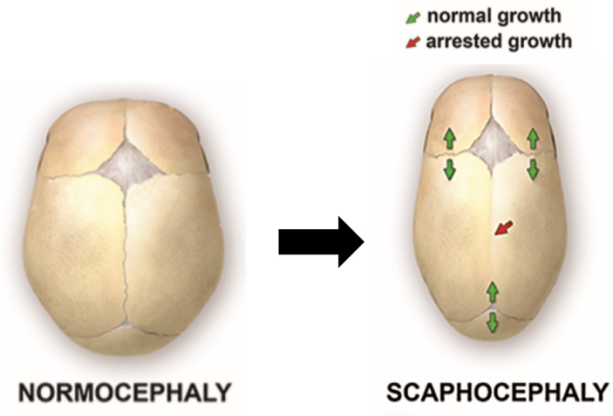


Figure 2: Deformation of the skull due to premature fusion of the sagittal suture.
(Adapted from Kajdic et al., 2017)

According to the literature reviewed, increased ICP is sometimes a complication in scaphocephaly, with an approximate incidence of 4.5-44% (Ciurea *et al.*, 2011; Tatum *et al.*, 2012; Seeberger *et al.*, 2016; Satanin *et al.*, 2019). Intracranial hypertension (ICH) may develop from intracranial venous congestion as changes regarding the sagittal suture in scaphocephaly may impede the absorptive ability of arachnoid granulations (Hassler and Zentner, 1990). The clinical manifestations of ICH in scaphocephaly vary. Some of the characteristic symptoms and signs include headache/vomiting, irritability, school/personality changes, papilledema, oculomotor paresis, severe frontal/occipital bossing, and towering of the head, and supraorbital retrusion (Seruya *et al.*, 2011; Ciurea *et al.*, 2011). In some cases, especially in older children with a delayed presentation of scaphocephaly (>18-24 months of age), ICH may present without any signs or symptoms (Ellenbogen *et al.*, 2012).

There are many morphologic variations in scaphocephaly. This is dependent on the age of onset, specific location, degree of premature suture closure and compensatory growth, and severity of the deformity (Jane *et al.*, 2000; Ruiz-Correa *et al.*, 2006; Tatum *et al.*, 2012; Calandrelli *et al.*, 2019). Sagittal craniosynostosis may be clinically differentiated into three main variants:

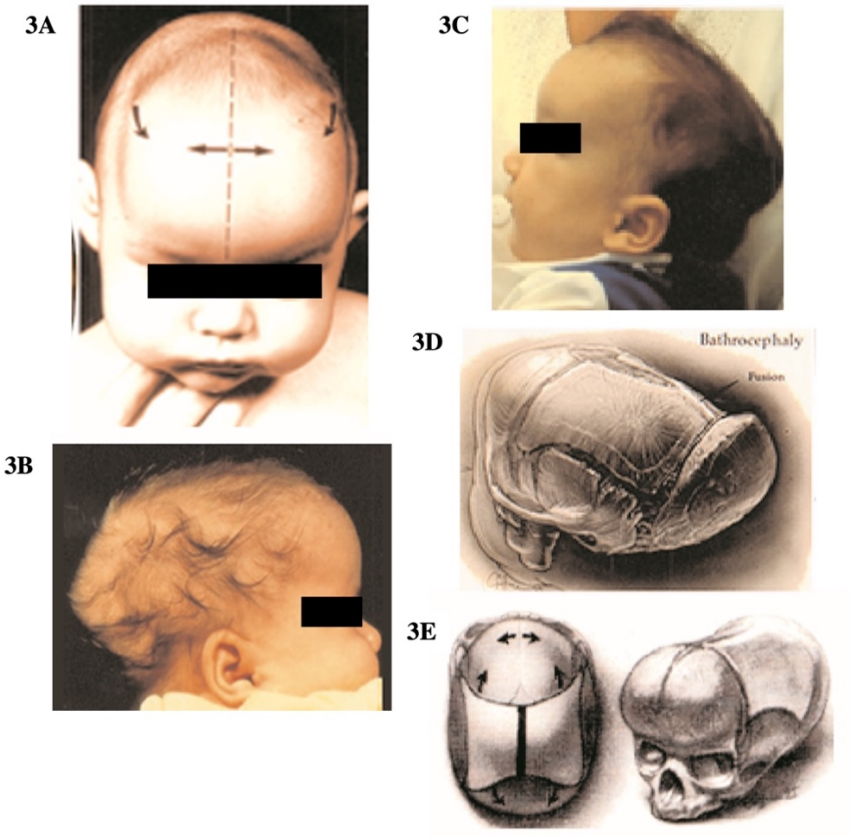


Figure 3: (A) Anterior sagittal craniosynostosis with frontal bossing. Arrows indicate areas of compensatory growth; **(B)** Posterior sagittal craniosynostosis- Occipital-knob deformity; **(C)** Posterior

sagittal craniosynostosis- Golf-tee deformity; **(D)** Posterior sagittal craniosynostosis- Bathrocephaly; **(E)** Complete sagittal craniosynostosis. Arrows indicate areas of compensatory growth.
(Adapted from Jane et al., 2000)

(i) *Anterior sagittal craniosynostosis* results from the early closure of the anterior portion of the sagittal suture. The resultant compensatory growth causes a noticeable frontal bossing (Fig. 3A). The occipital region is not always affected (Jane *et al.*, 2000; Massimi *et al.*, 2012).

(ii) *Posterior sagittal craniosynostosis* results from the premature fusion of the posterior portion of the sagittal suture and occurs less frequently than the anterior form. The anterior region of the skull usually presents as normal (Jane *et al.*, 2000; Massimi *et al.*, 2012). It may be further classified into three variants:

a) The so-called *'occipital knob'*, the most basic deformity, is characterized by a narrowing of the posterior regions of the skull with protuberance of the occipital bones (Fig. 3B). Since the occipital bone is located distal and perpendicular to the fused suture, it consequently becomes the site of compensatory growth (Jane *et al.*, 2000; Massimi *et al.*, 2012).

b) The so-called *'golf tee'* deformity occurs in more severe cases of posterior sagittal craniosynostosis. It is characterized by the narrowing and more prominent protrusion of the posterior part of the skull (Fig. 3C). This may be accentuated by the compensatory growth of the parietal bones (Jane *et al.*, 2000; Massimi *et al.*, 2012).

c) *Bathrocephaly* manifests as a podium (step-like platform) in the occipital region. The posterior portion of the parietal bone slopes inferiorly while the occipital bone protrudes superiorly (Jane *et al.*, 2000) (Fig. 3D).

(iii) *Complete sagittal craniosynostosis* is the most extreme form. It presents a complete fusion of the sagittal suture, resulting in both anterior and posterior skull deformation (Jane *et al.*, 2000; Massimi *et al.*, 2012) (Fig. 3E).

Sagittal craniosynostosis may also be classified into types based on the presence of a dominant feature, i.e., the *anterior type* presents with a transverse retrocoronal band, the *central type* with a prominent sagittal ridge, and the *posterior type* with a prominent occiput. If no dominant feature is presented, it may be referred to as the *complex type* (Jane *et al.*, 2000; David *et al.*, 2009; Massimi *et al.*, 2012) (Fig. 4). According to David *et al.* (2009), the posterior type is the most common, followed by the central, the anterior, and the complex type.

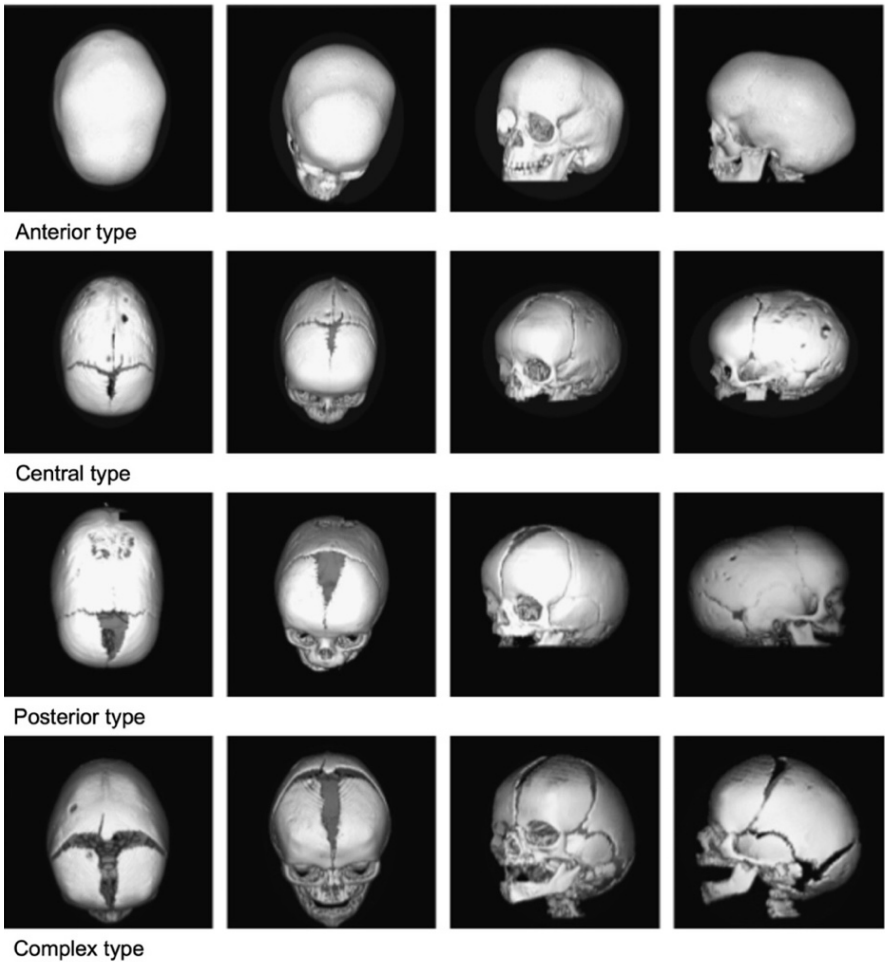


Figure 4: Computed tomographic representations of the types of sagittal craniosynostosis. *(Adapted from David et al., 2009)*

The cephalic index (CI), representing the ratio of the maximum width of the cranium to its maximum length, is used to quantify the abnormal skull shape associated with sagittal craniosynostosis as well as the severity of the deformity (Ruiz-Correa *et al.*, 2006; Bendon *et al.*, 2014; Calandrelli *et al.*, 2019). It is calculated by dividing the maximum cranial width by the maximum cranial length and multiplying by 100 (Bendon *et al.*, 2014; Calandrelli *et al.*, 2019). The maximum cranial width is measured as the distance between one euryon (defined as the point on either parietal bone marking either end of the greatest transverse diameter of the skull) and the other (EU-EU), and the maximum cranial length is measured as the distance between the glabella and the opisthocranium (G-OP) (Ruiz-Correa *et al.*, 2006). Scaphocephaly is characterized by a relatively low CI of less than 70% as compared to the normal range of 75.9-83.4% in males and 76.1-84.2% in females (Massimi *et al.*, 2012; Tatum *et al.*, 2012; Bendon *et al.*, 2014).

The etiology of scaphocephaly is unknown; however, it may be attributed to environmental factors including intrauterine fetal head constraint due to multiple births, maternal age > 35 years, maternal race, maternal smoking, high altitude maternal residence, paternal occupation, use of nitrosatable drugs, fertility treatments or a birth weight > 4kg (Heuzé *et al.*, 2010; Massimi *et al.*, 2012). Scaphocephaly is often observed in premature infants (Tatum *et al.*, 2012; Kajdic *et al.*, 2017). The genetic basis remains obscure (Heuzé *et al.*, 2010). Scaphocephaly is generally an isolated event; however, familial cases do occur in up to 6% (Van Veelen-Vincent *et al.*, 2010; David *et al.*, 2012; Massimi *et al.*, 2012). Twins are more likely to develop scaphocephaly as compared to singletons, with monozygotic twins being at a higher risk. This suggests the involvement of both environmental and genetic factors (Van Veelen-Vincent *et al.*, 2010; Massimi *et al.*, 2012).

The involvement of the cranial vault and base in craniosynostosis is a source of debate in the literature. Moss (1959) proposed that the cranial base was the primary site of abnormality in craniosynostosis children. The altered cranial base was thought to be responsible for transmitting tensile forces through the dura mater, resulting in premature fusion of calvarial sutures. Eaton *et al.* (1997), on the other hand, discovered that deformities of the cranial vault influence the morphology of the endocranial base, implying that the endocranial base is not the primary anomaly in people with sagittal synostosis.

There is controversy in the literature regarding intracranial volume in scaphocephaly. Satanin *et al.* (2019) stated that the intracranial volume in scaphocephaly is relatively normal despite abnormal skull growth. According to Seeberger *et al.* (2016), scaphocephalic individuals present with an intracranial volume larger than, less than, or within the normal range.

Even though skull elongation results in the corresponding elongation of the lateral ventricles, the ventricular anatomy in scaphocephaly remains relatively normal (David *et al.*, 2012).

The three-dimensional (3D) Computed Tomography (CT) scan is the preferred diagnostic imaging technique used in scaphocephaly as it is rapid and provides extensive information on the changes in cranial morphology. The use of 3D-CT scans is highly beneficial in surgical planning as well as post-operative evaluation (Ciurea *et al.*, 2011). Surgical intervention for scaphocephaly is usually directed at the cranial vault and a multidisciplinary approach is often required (Ciurea *et al.*, 2011; Bendon *et al.*, 2014). Common indications for surgery in scaphocephaly include cosmetic improvement, ICH, visual impairment, and mental retardation (Ciurea *et al.*, 2011;

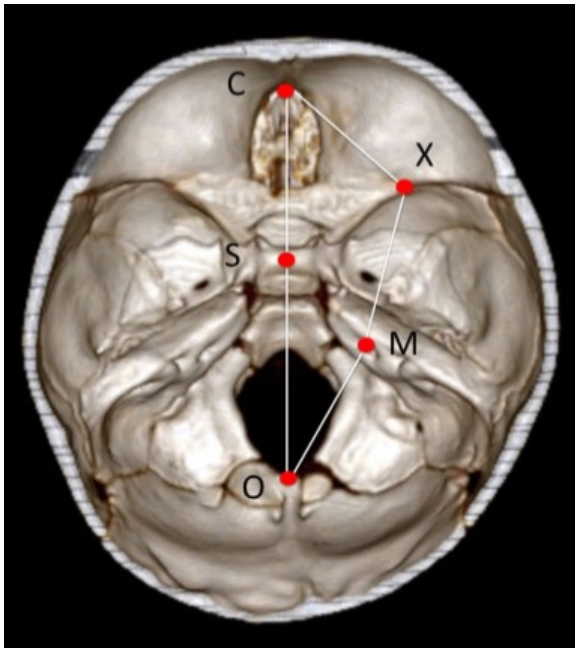
Massimi *et al.*, 2012). The optimal time for surgical intervention is between 3 and 12 months of age, as the infant skull is still fairly malleable. This allows for easier shaping of bone, thus resulting in improved outcomes (Massimi *et al.*, 2012; Ghizoni *et al.*, 2016). There are many surgical procedures used in the treatment of scaphocephaly ranging from a simple endoscopic resection of the sagittal suture to total reconstruction of the skull (Ciurea *et al.*, 2011; Ghizoni *et al.*, 2016). Other methods include the use of springs and distraction devices. Open methods include lateral vault panel remodeling, and subtotal and total vault remodeling (Madaree and Morris, 2021). It is imperative that the age of the patient, degree of suture fusion, and severity of the deformity be taken into account when deciding on surgical approaches (Heuzé *et al.*, 2010).

1.2.5. Morphometry of the cranial base and fossae in scaphocephaly

The relationship between scaphocephaly at the cranial vault and cranial base in sagittal craniosynostosis was investigated by Bendon *et al.* (2014). There is scant knowledge regarding deformity at the base because the CI cannot be clinically determined, as in the case with the vault. The studies by Bendon *et al.* (2014) and Beez *et al.* (2017) found that the narrow, elongated deformation characteristic of scaphocephaly is observed at both the level of the vault and base. The base appears to be less severely affected as compared to the vault; however, the clinical impact of deformity at the skull base remains unknown (Bendon *et al.*, 2014).

1.2.5.1. Length of cranial fossae

The study by Calandrelli *et al.* (2020) utilized endocranial landmarks on 3D-CT scans to measure the base of the skull and hemifossae. The subjects were classified into three groups based on the severity of the deformity, which was determined by calculating the CI and vertical longitudinal index (VLI). Calandrelli *et al.* (2020) measured the lengths of the ACF, MCF and PCF, bilaterally; ACF length= CX, MCF length= XM and PCF length= MO (Fig. 5).



***Landmarks: C**= anterior edge of crista galli; **S**= center of sella turcica; **O**= opisthion; **X**= xiphoid of the lesser wing of sphenoid; and **M**= internal acoustic meatus.*

*Landmarks C, S, O divide the base of the skull into two hemibases. Bilateral **CX**, **XM,** and **MO** lengths were measured and represent the size of the ACF (CX), MCF (XM), and PCF (MO).*

Figure 5: Morphometric analysis of the cranial base on a 3D-CT scan of a healthy individual. *(Adapted from Calandrelli et al., 2020)*

Calandrelli *et al.* (2020) found symmetry of the ACF, MCF, and PCF together with an increase in the anterior and middle lengths of the cranial base, which may be indicative of the skull elongation in scaphocephaly. The increase of the MCF length was observed more frequently than the ACF. The PCF lengths were comparable in all groups (Table 1).

Table 1: Length (mm) of the cranial fossae in scaphocephalic and healthy individuals

Author	Year	Sample size	Gender	Age (months)	Patient (Scaphocephaly)	Control (Healthy)
					ACF	
Calandrelli *et al.*	2020	130 (66 affected subjects, 64 age-matched healthy subjects)	13 Females 53 Males	*Mild* (mean): 4.17 *Moderate* (mean): 4 *Severe* (mean): 4.1	*Mild* Right= 39.95 Left= 39.88 *Moderate* Right= 39.57 Left= 39.52 *Severe* Right= 37.40 Left= 37.42	Right= 36.00 Left= 36.16
					MCF	
					Mild Right= 39.48 Left= 39.50 *Moderate* Right= 40.39 Left= 40.15 *Severe* Right= 39.48 Left= 39.47	Right= 37.91 Left= 37.79
					PCF	
					Mild Right= 35.51 Left= 35.56 *Moderate* Right= 35.44 Left= 35.60 *Severe* Right= 35.04 Left= 35.12	Right= 35.53 Left= 35.54

1.2.6. Select ventricular access points used in neurosurgery

Access to the cerebral ventricular system is often required during neurosurgery (Mortazavi *et al.*, 2013). A ventriculostomy is one of the most frequently performed procedures by a neurosurgeon. It entails the drilling of a burr hole in the cranium and the insertion of a temporary or permanent catheter into one of the ventricles of the brain (Techataweewan *et al.*, 2017; Morone *et al.*, 2019; Ganau *et al.*, 2021). Ventricular cannulation is usually performed for diagnostic or therapeutic purposes in ICP monitoring and CSF drainage (Techataweewan *et al.*, 2017; Morone *et al.*, 2019; Ganau *et al.*, 2021). However, the clinical applicability varies. Ventricular catheter placement is regarded as the gold standard for the treatment of hydrocephalus and the monitoring of ICP (Rehman *et al.*, 2013; Techataweewan *et al.*, 2017; Lee *et al.*, 2020). It is also used in the intraventricular administration of drugs and monitoring of carcinomatous and fungal meningitides (Rehman *et al.*, 2013).

Traditionally, surface anatomical landmarks are used to facilitate the identification of the burr hole location and safe insertion of the catheter into the ventricle (Techataweewan *et al.*, 2017; Morone *et al.*, 2019; Vigo *et al.*, 2020). Over time, numerous devices have been deemed technically accurate and safe for ventricular catheter placement, including endoscopy, ultrasound, neuronavigation, stereotaxic devices, and mechanical guides (Sarrafzadeh *et al.*, 2014; Techataweewan *et al.*, 2017, Raabe *et al.*, 2018). These techniques are, however, time-consuming, costly, and not readily accessible in many healthcare institutions (Lee *et al.*, 2008; Raabe *et al.*, 2016). During emergencies, neurosurgeons often practice ventricular cannulation as a life-saving procedure, where the freehand pass technique using anatomical landmarks is the only available method (Techataweewan *et al.*, 2017; Morone *et al.*, 2019; Vigo *et al.*, 2020).

Various cranial entry points have been described in the literature, each using anatomical landmarks to reach different parts of the lateral ventricle. The Kocher's, Kaufman's, Paine's, Menovksy's, and Tubbs' points are described as frontal horn access sites, whilst Keen's, Frazier's, Dandy's, and Sanchez's points are described as occipital horn access sites (Mortazavi *et al.*, 2013; Morone *et al.*, 2019; Vigo *et al.*, 2020). These entry points are positioned as such that they avoid penetration of the eloquent cortex (Kemp *et al.*, 2014). The part of the ventricle that is accessed is dependent upon the indication for ventricular catheter placement (Morone *et al.*, 2019). For successful ventricular cannulation, it has been suggested that the ventricular catheter tip be positioned away from the ventricular wall and choroid plexus (Kemp *et al.*, 2014). Many agree that the frontal horn is usually the termination site of the ventricular catheter as it is

away from the choroid plexus (Kemp *et al.*, 2014; Lind *et al.*, 2008a; Ozdemir *et al.*, 2014; Techataweewan *et al.*, 2017).

For the purpose of this study, the focus is only on the most commonly used anterior and posterior entry points in a neurosurgical setting, which are Kocher's point and Frazier's point (Mortazavi *et al.*, 2013; Morone *et al.*, 2019; Vigo *et al.*, 2020). In ventricular access via Kocher's and Frazier's points, the optimal location of the ventricular catheter tip is within the frontal horn of the ipsilateral lateral ventricle, just anterior to the interventricular foramen (Ozdemir *et al.*, 2014; Techataweewan *et al.*, 2017). This positioning reduces the risk of obstruction by the choroid plexus (Mortazavi *et al.*, 2013). There is inadequate evidence to recommend the anterior entry site over the posterior and vice versa, therefore both entry points are suitable for ventricular cannulation, especially in paediatric patients requiring treatment for hydrocephalus (Kemp *et al.*, 2014). The approach also depends on the surgeon's preference (Lind *et al.*, 2008a).

1.2.6.1. Kocher's point

This point is assumed to be named after the Swiss neurosurgeon, Emil Theodor Kocher (Mortazavi *et al.*, 2013). Kocher's point or the coronal point, as it is also known, is the most common anterior entry point for acute and long-term ventricular catheter placement (Kumar *et al.*, 2017; Techataweewan *et al.*, 2017). According to Kocher (1984, p. 50), the entry point is "…2.5cm from the median line and 3cm forward of the pre-central fissure." (Table 2). However, there is a lack of universal consensus regarding the exact location of this point (Techataweewan *et al.*, 2017). Various definitions have since been described and used in the consulted literature, i.e., Kocher's point is located between 10 to 13cm posterior to nasion and 1.5 to 4cm lateral to the midline at the midpupillary line, and approximately 1 to 2cm anterior to the coronal suture (Woernle *et al.*, 2011; Mortazavi *et al.*, 2013; Kirkman *et al.*, 2017; Techataweewan *et al.*, 2017; Raabe *et al.*, 2018; Morone *et al.*, 2019; Roka, 2021) (Table 2) (Fig. 6). The point is located lateral to the superior sagittal sinus and bridging veins, and anterior to the primary motor cortex. This location is important as these are vital areas that should be avoided (Kumar *et al.*, 2017; Mortazavi *et al.*, 2013; Morone *et al.*, 2019; Vigo *et al.*, 2020). The variability in the definition of Kocher's point may be partially dependent on the population group and cranial vault shape of the patient sample used in the definition (Techataweewan *et al.*, 2017).

Table 2: Variously described/used definitions of Kocher's point in the consulted literature

Author	Year	Definition of Kocher's point
Kocher	1984	2.5cm from the median line and 3cm forward of the pre-central fissure.
Woernle *et al.*	2011	Situated approximately 13cm posterior to the nasion, was measured to verify the coronary suture. Then, following the coronary suture, the right mediopupillar line was crossed after approximately 3cm. Based on this point, the location for the burr hole was selected at 1 to 2cm precoronally.
Mortazavi *et al.*	2013	It is located 1to 2cm anterior to the coronal suture in the midpapillary line, or 11cm posterior from the glabella and 3 to 4cm lateral from midline
Kirkman *et al.*	2017	11cm posterior to the nasion, and 2.5cm lateral to the midline.
Techataweewan *et al.*	2017	10 and 13cm posterior to nasion and 2.5 to 3cm lateral to the midline at the mid-pupillary line, or at least one cm anterior to the coronal suture.
Raabe *et al.*	2018	Varies from 1.5cm lateral to the midline, and from 10 to 12.5cm behind the nasion.
Morone *et al.*	2019	11cm superior and posterior from the nasion and 3cm lateral to midline. This location generally lies along the midpupillary line and is 1 to 2cm anterior to the coronal suture.
Roka *et al.*	2021	This point is 1 or 2cm anterior to the coronal suture or 11 to 12cm posterior and superior from the root of the nose and 3cm lateral to the midline corresponding to the midpupillary line.

Kocher's point can also be defined by the intersection of two orthogonal lines; an anteroposterior midpupillary line and a horizontal line commencing at the midpoint between the external auditory meatus and the medial canthus of the ipsilateral eye (Mortazavi *et al.*, 2013). Catheterization of the patient's right side is preferred over the left as it usually corresponds to the non-dominant hemisphere. Accurate placement of an external ventricular drain (EVD) can be achieved by directing the catheter at an angle that is perpendicular to the intersection of the imaginary lines drawn from the ipsilateral medial canthus and external auditory meatus (Ikeda *et al.*, 2017; Morone *et al.*, 2019). The catheter should be passed to a depth of approximately 6cm below the skin surface or until the frontal horn of the ipsilateral lateral ventricle is penetrated (Morone *et al.*, 2019).

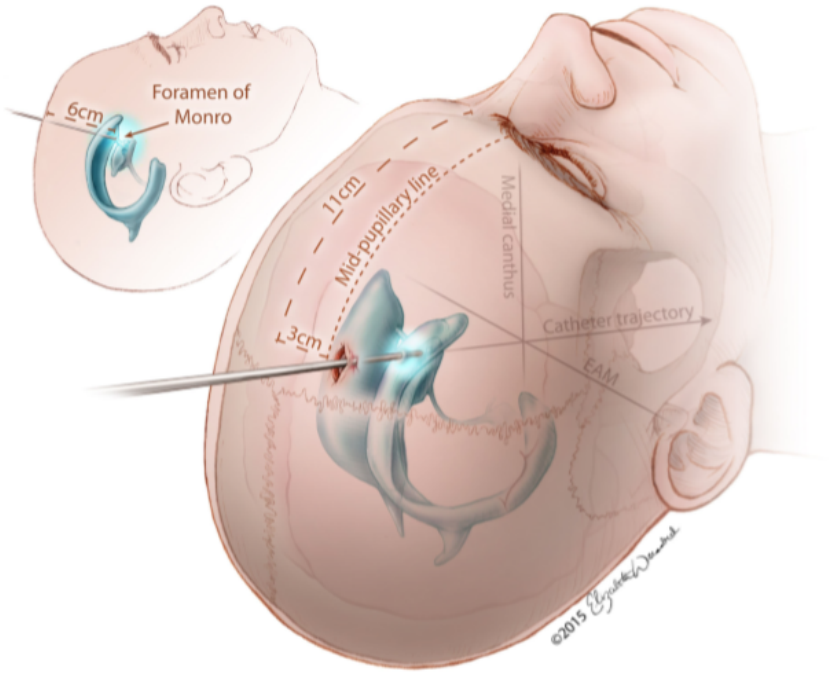


Figure 6: Ventricular access via Kocher's point. *(Adapted from Morone et al., 2019)*

Kocher's point is usually defined in relation to the nasion, midline, and coronal suture. The Turkish study by Ozdemir *et al.* (2014) investigated the distance between the nasion and the coronal suture. The study had found the ideal position for the anterior entry point to be 30mm lateral to the midline and 110mm posterior to the nasion in the Turkish population. The study by Ikeda *et al.* (2017) reported on the anterior access point in a Japanese population, ranging between 13.5±2.5mm and 43.5±6.1mm from the midline. Lee *et al.* (2020) evaluated the accuracy of EVD placements and found that outcomes were favourable when placed 34.69±3.61mm lateral to the midline and 14.66±6.62mm anterior to the coronal suture. On the basis of the findings of these studies, the lateral craniometric dimension was the most constant of the three dimensions used in the anterior approach. It was found to be between 10 to 49.6mm lateral to the midline (Ozdemir *et al.*, 2014; Ikeda *et al.*, 2017; Lee *et al.*, 2020). The findings of the studies conducted by Ozdemir *et al.* (2014) and Lee *et al.* (2020) were based on an adult population, whilst the findings by Ikeda *et al.* (2017) were based on both an adult and paediatric population. However, no data specific to the paediatric group is provided by Ikeda et *al.* (2017) (Table 3).

Table 3: Parameters of the anterior entry point (Kocher's Point) in the literature

Author	Year	Country	Sample size	Age group/range	Modality	Parameter		
						Posterior to nasion (mean±SD) (mm)	Lateral to midline ((mean±SD) (mm)	Anterior to coronal suture (mean±SD) (mm)
Ozdemir *et al.*	2014	Turkey	60	Adult	Cadavers/Dry skulls	110	30	-
Ikeda *et al.*	2017	Japan	158	12-85 years	CT scans	-	13.5±2.5 – 43.5±6.1	-
Lee *et al.*	2020	Singapore	77	Adult	CT scans	-	34.69±3.61	14.66±6.62

1.2.6.2. Frazier's Point

Frazier's point (also known as the parieto-occipital point) is a common posterior access site used primarily for long-term CSF diversion via an internalized shunting system (Lee *et al.*, 2008; Mortazavi *et al.*, 2013; Kumar *et al.*, 2017). It is thought to be named after Doctor C.H. Frazier (Frazier, 1928), who described the point as a surface landmark for extradural trigeminal nerve transection. In recent times, the point is utilized in posterior cranial fossa surgery, when urgent diversion of CSF is required to relieve elevated ICP. Frazier's point is reported to lie 3 to 4cm lateral to the midline and 6 to 7cm above the inion, corresponding to a region of the parietal bone above the lambdoid suture (Woernle *et al.*, 2011; Mortazavi *et al.*, 2013; Kumar *et al.*, 2017; Morone *et al.*, 2019) (Fig. 7). The ventricular catheter is aimed medially and superiorly to the point that lies 4cm above the contralateral medial canthus and is passed to an initial depth of 5cm. The catheter stylet is removed once CSF is encountered, and the catheter is soft-passed an additional 5cm (total 10cm), positioning it entirely within the body of the ventricle (Mortazavi *et al.*, 2013; Morone *et al.*, 2019) or the occipital horn of the ipsilateral lateral ventricle (Ellenbogen *et al.*, 2012).

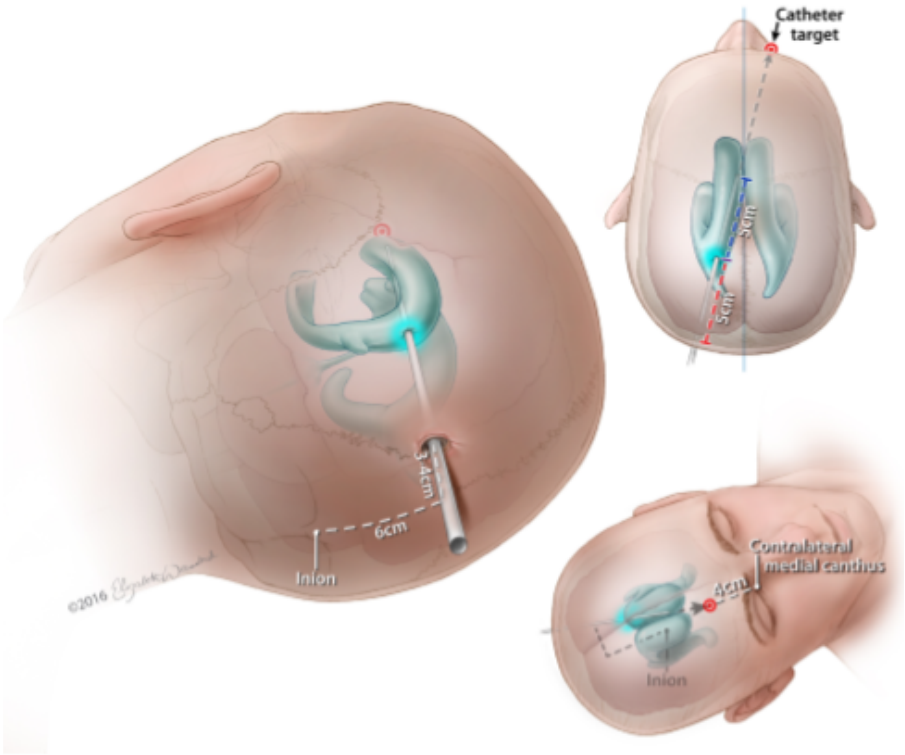


Figure 7: Ventricular access via Frazier's point. *(Adapted from Morone et al., 2019)*

Table 4: Parameters of the posterior entry point (Frazier's Point) in the literature

Author	Year	Country	Sample size	Age group/range	Modality	Parameter	
						Superior to inion distance (mean±SD) (mm)	**Lateral to midline distance (mean±SD) (mm)**
Shimizu et al.	2004	Japan	44	Adult	CT scans	68.6	-
Lee et al.	2008	Singapore	10	Adult	MRI scans	60	40
Lind et al.	2008b	Australia and New Zealand	11	Adult	MRI scans	60	30 or 40
Meybodi et al.	2017	Iran	15 (Hydrocephalus)	Adult	CT scans	Right= 63.7 Left= 62.2	Right= 25.4 Left= 25.4
Deora et al.	2020	India	150 (100 hydrocephalus and 50 non-hydrocephalus)	Adult and Paediatric	MRI scans	***Hydrocephalus:*** Flat occiputs= 49±10.10 Little round occiputs= 54±8 Round occiputs= 50±8.5 Very round occiputs= 54±10.7 **Non-hydrocephalus:** Flat occiputs= 55±6.9 Little round occiputs= 53±5.4 Round occiputs= 58±7.6 Very round occiputs= 52±10.1	40

Studies conducted by Shimizu *et al.* (2004), Lee *et al.* (2008) and Lind *et al.* (2008b) analysed, the ideal trajectory for ventricular cannulation in adults. The study conducted by Shimizu *et al.* (2004) in a Japanese population found correct placement of the catheter when burr holes were located approximately 68.6mm superior to the inion. Lee *et al.* (2008) and Lind *et al.* (2008b) had favourable outcomes when burr holes were sited 60mm superior to the inion and 40mm lateral to the midline, and 60mm superior to the inion and 30mm- or 40mm lateral to the midline, respectively. A study by Meybodi *et al.* (2017) aimed to revalidate the craniometric dimensions of posterior burr hole sites for the insertion of ventricular catheters in hydrocephalic patients. The study had found the ideal site to be 63.7mm above the inion and 25.4mm lateral to the midline when the right lateral ventricle was accessed, and 62.2mm above the inion and 25.4mm lateral to the midline when the left was accessed (Meybodi *et al.*, 2017). A part of the study by Deora *et al.* (2020) investigated the variation of the occipital trajectory with skull shape and the ideal entry point in non-hydrocephalus and hydrocephalus patients. The lateral distance from the midline was kept constant at 40mm. The study found that the vertical dimension of the entry point varied according to the shape of the occiput in each patient group (Deora *et al.*, 2020). The superior to inion distance was higher in non-hydrocephalus patients as compared to hydrocephalus patients for all occiput shape groups. The study by Deora et *al.* (2020) was the only study in the consulted literature on Frazier's point to have included both adults and paediatric patients in their study population. These results, however, are based on the combined population, and no data specific to the paediatric group is provided (Table 4).

Regardless of being highly favoured by neurosurgeons, the freehand pass technique is a relatively inaccurate procedure, with rates of misplacement ranging from 4 to 45% (Techataweewan *et al.*, 2017; Morone *et al.*, 2019). Misplacement of the catheter may be due to variations in anatomy, i.e., cranial morphology, ventricular size, ventricular distortion secondary to trauma and choroid plexus distance (Sarrafzadeh *et al.*, 2014; Techataweewan *et al.*, 2017; Lee *et al.*, 2020). Freehand ventricular cannulation in neonates and younger paediatric patients proves challenging due to the presence of small ventricles. This is the case for patients with slit ventricles as well. The accuracy in catheter placement may also depend on surgical experience, size of the burr hole, and the techniques used (Low *et al.*, 2010; Sarrafzadeh *et al.*, 2014). The lack of standardization regarding the entry points also plays a role in the misplacement of the ventricular catheter (Lee *et al.*, 2008)

The misplaced ventricular catheter tip may often be located in the third ventricle, subarachnoid space, and brain tissue (Kirkman *et al.*, 2017). Passage of the catheter tip into the basal ganglia, internal capsule, fornix, thalamus, choroid plexus, and vessels such as the superior thalamostriate vein or the posterior medial choroidal arteries may result in direct injury. There are also reports of misplacement into the brainstem, Sylvian fissure, interpeduncular, or suprasellar cistern as well as into the basal cisterns (Raabe *et al.*, 2018).

The ideal cranial entry point, trajectory insertion, and catheter length play a vital role in ensuring successful ventricular catheter placement (Low *et al.*, 2010; Kemp *et al.*, 2014; Meybodi *et al.*, 2017). For this feat, many authors advocate pre-operative planning using radiological imaging as well as tailoring the approaches for each patient individually (Low *et al.*, 2010; Shimizu *et al.*, 2014; *Deora et al.*, 2020). This should be done regardless of the level of neurosurgical experience (Low *et al.*, 2010; Shimizu *et al.*, 2014).

1.2.6.3. Ventricular access in children

According to Kulkarni (2009), most of the existing literature that is relied upon for external ventricular drainage is based on adult experience, the knowledge from which has to be extrapolated to a paediatric population. A qualitative study conducted by Lind *et al.* (2008a) reported that most neurosurgeons had adjusted their landmarks and techniques for ventricular catheterization in children compared to adults, whilst others did not.

1.2.6.4. Ventricular access in scaphocephaly

It is crucial that ICP be monitored even if subtle elevation is clinically suspected, especially in older scaphocephalic patients where ICH may, sometimes, present as asymptomatic (Seruya *et al.*, 2011; Ellenbogen *et al.*, 2012). In the event of elevated ICP during the surgical repair of scaphocephaly, a ventriculostomy is used to monitor ICP and drain CSF simultaneously, thus protecting the brain from further elevations in pressure. The ventricular catheter is removed before closure, provided that ICP has returned to normal. If elevation in ICP persists, the ventricular drain is left in place for post-operative monitoring (Ellenbogen *et al.*, 2012).

Although hydrocephalus occurs less frequently in individuals with non-syndromic isolated sagittal craniosynostosis as compared to syndromic multiple suture craniosynostosis, the occurrence is not impossible. The optimal treatment for hydrocephalus in a population with craniosynostosis is unascertained (Bonfield *et al.*, 2021). For this reason, ventricular access will be required for CSF diversion or drainage.

1.3.Materials and Methods

1.3.1. Patients

This retrospective study was conducted using pre-operative CT head scans that were obtained from the database of the Department of Plastic and Reconstructive Surgery and the Department of Neurosurgery at the Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa. The scans comprised a patient group of 24 consecutive paediatric patients with a CT-confirmed diagnosis of scaphocephaly, who presented to the craniofacial clinic at IALCH between January 2014 and June 2020; and a control group of 14 non-affected/normal paediatric patients, who underwent clinically indicated CT scanning of the head for non-head-shape indications, and who had comparable CT scan information available. Only those that had met the inclusion criteria were selected for analysis. This study is comprised of two subsets.

1.3.1.1. Inclusion criteria

Patient group

- Female and male paediatric patients with a CT-confirmed diagnosis of scaphocephaly (isolated sagittal synostosis) who had presented to the craniofacial clinic at IALCH between January 2014 and June 2020.

Control group

- Non-affected/normal paediatric patients below the age of 9 years, who underwent clinically indicated CT scanning of the head for non-head-shape indications, and with comparable CT scan information available.
- Fine-cut CT scans with a slice thickness of 0.6mm.

1.3.1.2. Exclusion criteria

Patient group

- Paediatric patients with multiple suture involvement.
- Paediatric patients diagnosed with syndromic sagittal synostosis.
- Paediatric patients with insufficient CT scan information and CT scans of poor-quality images where distinct anatomy could not be clearly defined.

Control group

- Paediatric patients with an abnormal skull shape, a diagnosis of craniosynostosis and hydrocephalus.
- Paediatric patients not within the designated age groups, i.e., patients aged 9 years and above.

- Paediatric patients with insufficient CT scan information and CT scans of poor-quality images where distinct anatomy could not be clearly defined.
- CT scans with a slice thickness < or > 0.6mm.

1.3.2. Image acquisition & analysis

Medical records were accessed via the hospital's information management system and reviewed to identify suitable patients. Axial CT scans of selected patients were retrieved from the Picture Archiving and Communication System (PACS) and saved onto a hard drive in DICOM (Digital Imaging and Communication in Medicine) format. CT images were acquired in the clinical routine with either a 128-slice SOMATOM Definition AS scanner or SOMATOM Definition Flash CT Scanner (Siemens Healthineers, Forcheim, Germany). The scans of the patient group had a slice thickness ranging from 1 to 5mm. All CT scans of the control group were fine-cut and had a slice thickness of 0.6mm. The acquired axial images from CT were reformatted into sagittal and coronal planes in the 3D-multiplanar reconstruction view and analysed using the Horos software version 3.3.6 (Horos Project, Annapolis, MD, USA), on an offline MacBook Pro workstation (Apple, Cupertino, CA, USA). The CT scan images were automatically calibrated by the Horos software; they were standardized to a 1cm reference scale. Calibration was manually verified. CT scans were aligned parallel to the orbitomeatal plane. This plane was defined by a line passing through the outer canthus of the eye and the midpoint of the external acoustic meatus (Otake *et al*., 2018). All measurements were performed on CT images using the length tool in subset 1 and the open polygon tool in subset 2. The measurements pertaining to both parts of this study were taken three times by the candidate (during intra-observer analysis) as well as by a second observer (during inter-observer analysis) to ensure accuracy and reliability.

To avoid repetition, figures for materials and methods have not been included in this chapter. They have been included within the relevant manuscripts in Chapters 2 and 3.

1.3.3. Subset 1: Morphometry of the cranial fossae in scaphocephaly

1.3.3.1. Identification of Anatomical Landmarks & Morphometric analysis

CT scans of both groups were analysed in the axial plane and fixed anatomical landmarks characteristic of each cranial fossa were selected to obtain maximum anteroposterior and transverse diameters for length and width measurements, respectively. Landmarks were chosen by a plastic surgeon (A.M), neurosurgeon (R.H) and an anatomist (L.L) on the basis of being easily identifiable, able to characterize the morphology of the fossae for measurements to be best

taken, as well as reproducible. Linear measurements were performed on the bone window setting, using the length tool.

ACF Length: The midpoint of the limbus sphenoidale was identified and labelled using the point tool. This point was taken as a reference landmark and transcended to the level at which the ACF was observed to be at its maximal length. The maximum anteroposterior diameter of the ACF was measured as a perpendicular from the transcended point to the inner table of the frontal bone. The measurement was taken on a slice above and below the selected slice to confirm that the maximum length was obtained.
ACF Width: At the same level at which the maximum length was obtained, the maximum transverse diameter of the ACF was measured as the lateral distance between the points on the inner tables of the frontal bones that were most remote from each other in the ACF.

MCF Length: The anteroposterior diameter of the MCF was measured as a perpendicular from the midpoint of the curvature of the greater wing of the sphenoid bone to the petrous part of the temporal bone; at the level of the floor of the pituitary fossa. This was done on both, the right and left sides.
MCF Width: At the same level, the transverse diameter of the MCF was measured as a perpendicular from the midpoint of the floor of the pituitary fossa to the inner table of the temporal bone. This was done on both, the right and left sides.

PCF Length: The midpoint of the posterior margin of the dorsum sellae was identified and labelled using the point tool. This point was used as a reference landmark and transcended to the level at which the PCF was observed to be at its maximal length. The maximum anteroposterior diameter of the PCF was measured from the transcended point to the inner table of the occipital bone. The measurement was taken on a slice above and below the selected slice to confirm that the maximum length was obtained.
PCF Width: At the same level at which the maximum length was obtained, the maximum transverse diameter of the PCF was measured as the lateral distance between the points on the inner tables of the parietal bones that were most remote from each other in the PCF.

1.3.4. Subset 2: Morphometry of Kocher's & Frazier's Points in scaphocephaly

Ventricular catheterization is usually performed on the right side by default as it corresponds to the non-dominant hemisphere; therefore, the measurements regarding these points were only taken on the right side. Curvilinear measurements were performed on the brain window setting,

using the open polygon tool. The open polygon tool was used because it is able to measure curvilinear distances more accurately.

Kocher's Point: The midpupillary line, a standard craniometric landmark, on the right side was located in the axial and coronal planes. In the sagittal plane, a point was placed 1cm anterior to the coronal suture in the right midpupillary line (a distance of 1cm anterior to coronal suture is preferred as it avoids the motor cortex). This point was regarded as the ideal frontal entry point or the so-called "Kocher's point". This point was then extrapolated into the midline. The distance posterior to the nasion was measured between the nasion and the extrapolated point, in the sagittal plane. The lateral distance from the midline was measured between the frontal entry point (Kocher's point) and the extrapolated point, in the coronal plane.

Frazier's Point: In the axial plane, the image showing the lateral ventricle most clearly was identified, this was a slice just above both thalami. The crosshairs were angled along the length of the right lateral ventricle, with the ideal target being the frontal horn, until the occipital horn was seen most prominently. By using this method, the crosshairs were positioned within the body of the lateral ventricle, with the frontal and occipital horns in the same plane. In the sagittal plane, a trajectory was constructed posteriorly, from the frontal horn to the parietal bone, in the middle of the lateral ventricle along its longest plane and at a tangent to the thalamus. The endpoint of the trajectory on the outer surface of the skull was regarded as the ideal occipital entry point or the so-called "Frazier's point". This point was then extrapolated into the midline. The distance superior to the inion was measured from the inion to the extrapolated point, in the sagittal plane. The lateral distance from the midline was measured between the occipital entry point (Frazier's point) and the extrapolated point, in the axial plane. The point of attachment of the tentorium cerebelli was used as a marker to help locate the inion. A lower-lying tentorium cerebelli was excluded, radiographically.

1.3.5. Variables

Demographic factors: Demographic information, including age, sex, and population group was documented. Due to the lack of an age-matched control group, the patients and controls were grouped by age for the relevant comparative analyses. There were four groups, i.e., <1 year, 1-<3 years, 3-<6 years, and 6-<9 years. According to Statistics South Africa (2020), the population is categorized into four subgroups, viz. Black, Coloured, Indian and White. In this study, there were no patients in the Coloured subgroup.

Degree of severity: The CI was used to quantify the head shape of all patients and was calculated according to the following equation: cephalic width/cephalic length x 100. The distance between the most anterior and posterior points of the outer table of the skull was measured in the transverse plane to calculate the cephalic length. The cephalic width was measured as the distance between the outer skull tables at the widest points of the skull in the transverse plane (Waitzman *et al.*, 1992). Scaphocephalic patients were categorized into 3 groups according to the degree of severity for the relevant analyses, i.e., >70% [Mild], 65-70% [Moderate] and 60-65% [Severe]. Patients in the control group had an open suture with a CI >70%.

1.3.6. Sample size

Patient group: Pre-operative CT scans of all consecutive patients with a CT-confirmed diagnosis of scaphocephaly, presenting to the craniofacial clinic at IALCH from January 2014 to June 2020, and which met the inclusion criteria. Of the 37 patients with scaphocephaly that were identified, 24 had met the inclusion criteria of the patient group.

Control group: Pre-operative CT scans of non-affected/normal patients below the age of 9 years, undergoing clinically indicated CT scanning of the head for non-head-shape indications, with comparable CT scan information available, and which met the inclusion criteria. Of the 39 non-affected/normal patients that were identified, 14 had met the inclusion criteria of the control group.

1.3.7. Statistical analysis

Statistical data analysis was conducted using R Statistical computing software of the R Core Team, 2020, version 3.6.3 (R Studio, Boston, MA, USA). Results were presented in the form of descriptive and inferential statistics. Descriptive statistics were expressed as the minimum, maximum, quartiles, interquartile range, means and standard deviation. Categorical variables were described as counts and percentage frequencies. Multidimensional numerical variables were presented as correlation plots. Correlation analysis was also applied to determine the association between different numerical measurements. Depending on the distribution of the numerical variables between two independent groups, mean or median differences were assessed using either the t-test or Wilcoxon, respectively. The ANOVA and the Kruskal Wallis tests were used as appropriate to assess the mean difference of numerical variables across at least three levels of a categorical variable. In the case of significant mean difference, post-hoc tests were conducted using Tukey's HSD single-step multiple comparison procedure and similarly with Dunn test for

a significant difference in the medians. In the case of pairwise comparison of the groups, the t-test or Rank sum test was used as appropriate. To determine the association between categorical variables, a Chi-Square Test was used and when the distribution of the cross-tabulations contained an expected value of less than five, a Fisher's exact test was applied. All inferential statistical analysis tests were conducted at 5% levels of significance. To determine the reliability of the morphometrical data, intra-observer error and inter-observer error were calculated and represented as intraclass correlation coefficient (ICC) values. All statistical methods and analyses were carried out in consultation with a university statistician.

1.3.8. Ethical Considerations

The relevant gatekeeper permissions were sought, and ethical approval was obtained from the Biomedical Research Ethics Committee (BREC) of the University of KwaZulu-Natal (UKZN) (BREC/00002084/2020). This study involved the use of retrospective CT scans and, therefore, did not pose any risk to the patients.

1.3.8.1. Confidentiality & Management of Data

Patient identification data was anonymised to maintain confidentiality. All data is saved in password-protected folders on a hard drive that is stored in a locked cupboard and is only accessible by the investigators. Data will be destroyed after a period of 5 years.

1.4.Structure of Thesis

This thesis was prepared in accordance with the guidelines outlined by the College of Health Sciences, University of KwaZulu-Natal, South Africa. Specific methodologies employed for each subset of the study are detailed in the respective manuscripts to address the objectives. Harvard referencing was used in this thesis with the exception of the manuscripts, which have been structured, formatted, and referenced according to the author guidelines of the respective scientific journals. References cited in each chapter are listed at the end of the respective chapter. The structural outline of the thesis is as follows:

1.4.1. Chapter 1: Introduction

This chapter presented a background and comprehensive literature review on scaphocephaly, the cranial fossae and select ventricular access points as well as an overview of the study. The aims, objectives, research questions as well as an overview of the methodology were included in this chapter. Figures for materials and methods were not included in this chapter as they have been included within the respective manuscripts in the forthcoming chapters.

1.4.2. Chapter 2: Scientific Manuscript 1

This chapter comprised of an original scientific manuscript titled: Morphometric analysis of the cranial fossae in patients with scaphocephaly: An anatomical basis. This manuscript analysed the basic morphometry of the cranial fossae, viz. maximum lengths and widths of the anterior, middle and posterior cranial fossae in patients with scaphocephaly (n=24), and controls (n=14) within a select South African population (Subset 1). The results were compared across demographics to determine statistically significant relationships.

This manuscript was submitted to the *Journal of Craniofacial Surgery* for review and possible publication (awaiting manuscript number: Appendix A).

1.4.3. Chapter 3: Scientific Manuscript 2

This chapter comprised a second original scientific manuscript titled: A morphometric analysis of Kocher's and Frazier's points in a select South African scaphocephalic population. This manuscript analysed and documented the morphometry of Kocher's and Frazier's points in patients with scaphocephaly (n=24), using known craniometric and surface anatomical landmarks

(Subset 2). The results were compared on the basis of demographic variables to determine statistically significant relationships.

This manuscript was submitted to the *Journal of Neurosurgery: Pediatrics* for review and possible publication (Manuscript number: PEDS21-586).

1.4.4. Chapter 4: Synthesis

This chapter further discussed the main findings of Chapters 2 and 3 and concluded the findings of the morphometry of the cranial fossae as well as the location of Kocher's and Frazier's Points in patients with scaphocephaly in a select South African population. The limitations encountered and recommendations for future research have been highlighted and elucidated in this chapter. Following Chapter 4 are the appendices.

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CHAPTER 2: SCIENTIFIC MANUSCRIPT 1

Chapter 1 provided a review of published literature on scaphocephaly, the cranial fossae and select ventricular access points. This review demonstrated that literature on the morphometry of the cranial base and its fossae in patients with scaphocephaly is scarce. Additionally, no previous study has analysed the morphometry and documented the possible locations of Kocher's and Frazier's points in patients with scaphocephaly.

Contributions of this chapter

This chapter is comprised of a scientific manuscript that analysed and compared the basic morphometry of the cranial fossae, viz. the maximum lengths and widths of the anterior, middle and posterior cranial fossae in patients with scaphocephaly, and controls within a select South African population. The results of this study were compared across demographics to determine statistically significant relationships.

The following manuscript has been submitted and is currently under review by the scientific journal:

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Authors: V Bisetty, R Harrichandparsad, L Lazarus, A Madaree
Journal: Journal of Craniofacial Surgery
Manuscript Number: Pending (Appendix A)

Please note: This manuscript has been written, formatted, and presented according to the author guidelines outlined by the *Journal of Craniofacial Surgery*. The American Medical Association (AMA) manual of style was used for reference formatting, as required by the journal. In addition, the journal requires that the figures and tables be separated from the main text; however, the author has incorporated figures and tables into the main text for the purpose of ease of reference during the examination process.

Morphometric analysis of the cranial fossae in scaphocephalic patients: An anatomical basis

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2.1.Abstract

Scaphocephaly is the morphological consequence of premature sagittal suture fusion. Morphologic and morphometric studies on the cranial vault in scaphocephaly flourish in the literature. However, few studies are available on the cranial base in a scaphocephalic population, let alone the morphometry of its fossae. Therefore, this study aimed to analyse and compare the morphometry of the anterior, middle, and posterior cranial fossae (ACF, MCF and PCF) in patients with scaphocephaly.

The length and width of the ACF, MCF and PCF were measured using fixed anatomical landmarks on the two-dimensional (2D) computed tomography (CT) scans of 24 consecutive patients diagnosed with isolated sagittal synostosis between 2014 and 2020, and 14 controls.

A comparison of the results between patients with scaphocephaly and the controls showed that the ACF and PCF lengths increased significantly (p=0.041 and p=0.018) in patients with scaphocephaly. No differences in the MCF lengths were observed (p=0.278; 0.774). When compared by the degree of severity, the ACF and PCF lengths were significantly larger (ANOVA, p=0.033; post-hoc, p=0.013 and ANOVA, p=0.015; post-hoc, p=0.036) in scaphocephalic patients within the severe group as opposed to the control group.

The morphometric data obtained indicate a preponderance of deformity in the ACF and PCF with elongation along the anteroposterior (AP) plane (lengths) in scaphocephalic patients. Minimal changes were observed in the transverse plane (widths) in scaphocephaly versus controls. This data could aid craniofacial surgeons in understanding the affectation of the cranial fossae and influencing the decision on the most suitable method of corrective modality.

Keywords: Scaphocephaly, sagittal, morphometry, cranial fossae

2.2.Introduction

Sagittal synostosis or scaphocephaly is the most common type of non-syndromic craniosynostosis and accounts for 40-60% of all reported cases.[1–4] It has an overall estimated incidence of approximately 1 in 2000 to 7000 live births, with a distinct male to female predominance of 2-4: 1.[2,3,5–7] Scaphocephaly is characterized by the premature fusion of the sagittal suture and its resultant abnormal skull shape, which is typically elongated in the anteroposterior (AP) direction and shortened in the transverse direction.[2,6,8] This cranial deformity is reflected by a relatively small cephalic index (CI) of <70%.[3,5] Some of the secondary morphological changes that may accompany scaphocephaly include frontal bossing, biparietal narrowing, temporal protrusion, sagittal ridging, coronal constriction, changes in cervico-occipital angle and occipital protuberance.[4,9] The cranial morphology in scaphocephaly varies considerably amongst affected individuals, depending on the anatomic location, presence of prominent anatomic features, age of onset, degree of premature suture closure and compensatory growth, as well as the severity of deformity.[1,3,5,9,10]

The etiology of sagittal craniosynostosis is still largely unknown; however, environmental and genetic factors are thought to be implicated.[3] Controversy in the literature exists with regards to the cranial vault and base involvement in craniosynostosis. Moss[11] postulated the cranial base to be the primary site of abnormality in children with craniosynostosis; the altered cranial base was thought to be responsible for transmitting tensile forces through the dura mater, which ultimately led to the premature fusion of sutures. Conversely, the study by Eaton *et al.*[12] concluded that the morphology of the endocranial base is subjected to change by deformities of the cranial vault and suggested that the endocranial base is not the primary anomaly in individuals with sagittal synostosis.

Numerous studies on the morphology and morphometry of the cranial vault in scaphocephaly are reported in the literature. However, few studies are available on the cranial base in this population, let alone the morphometry of its fossae. As with the vault, disproportionate growth of the cranial base in sagittal synostosis occurs along the anterior-posterior axis with little or no change along the medial-lateral and superior-inferior axes.[13] The characteristic narrow, elongated deformation is observed at the levels of the vault and base.[8,14] The base appears to be less severely affected compared to the vault; however, the clinical impact of deformity at the skull base remains unknown.[8]

This study provides baseline morphometric anatomical measurements of each cranial fossa in scaphocephalic patients. The comparison of measurements between scaphocephaly and control

patients will provide information on the extent of deformity at the level of each cranial fossa in scaphocephaly. This morphometric data will aid craniofacial surgeons in the systematic assessment of scaphocephaly by enabling a more precise understanding of which cranial fossa is most affected and the extent to which it is affected. This may help in deciding on the appropriate method of corrective treatment.

The aim of this study was to analyse and compare the morphometry of the anterior, middle, and posterior cranial fossae (ACF, MCF and PCF) in scaphocephaly and control patients in a select South African population, with the objectives being (i) to measure the true length and width of the ACF, MCF and PCF in scaphocephaly and control patients using fixed anatomical landmarks, and (ii) to compare the afore-mentioned variables by age, sex, population group and the degree of severity.

2.3.Materials and Methods

2.3.1. Patients

This was a retrospective study conducted using 2-dimensional (2D) pre-operative Computed Tomography (CT) head scans acquired from the database of the Departments of Plastic and Reconstructive Surgery and Neurosurgery at the Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa. Ethical approval for this study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00002084/2020). This study comprised scans of 24 consecutive patients with a radiologically confirmed diagnosis of isolated sagittal synostosis who presented to the craniofacial unit at IALCH between January 2014 and June 2020. Fine-cut CT scans from 14 non-affected/normal pediatric patients, who underwent clinically indicated CT scanning of the head for non-head-shape indications and had comparable CT scan information available, were selected as controls. Only those that had met the criteria for inclusion were selected for analysis. Patients diagnosed with a genetic syndrome and/or multiple suture craniosynostosis were excluded. For controls, patients with an abnormal skull shape or a diagnosis of craniosynostosis or hydrocephalus; and CT scans with a slice thickness < or > 0.6mm, were excluded. CT scans with insufficient information and of poor quality were excluded.

2.3.2. Image acquisition & analysis

Axial CT scans of selected patients were retrieved from the hospital's Picture Archiving and Communication System (PACS) and saved in DICOM (Digital Imaging and Communication in Medicine) format. These CT images were acquired in the clinical routine with either a 128-slice

SOMATOM Definition AS scanner or SOMATOM Definition Flash CT Scanner (Siemens Healthineers, Forcheim, Germany). The slice thickness of the scans of scaphocephalic patients ranged from 1 to 5mm. All control scans were fine-cut and had a slice thickness of 0.6mm. The acquired axial CT images were reformatted into sagittal and coronal planes in the three-dimensional (3D)-multiplanar reconstruction view and analysed using the Horos software version 3.3.6 (Horos Project, Annapolis, MD, USA). The CT scan images were automatically calibrated by the Horos software; calibration was also manually verified. CT scans were aligned in the orbitomeatal plane. Linear measurements were performed on the bone window setting using the length tool. Measurements were taken three times by the first author (during intra-observer analysis) as well as by a second observer (during inter-observer analysis) to ensure accuracy and reliability.

2.3.3. Morphometry of the cranial fossae

2.3.3.1. Identification of Anatomical Landmarks & Morphometric analysis

Fixed anatomical landmarks characteristic of each cranial fossa were selected on the CT scans in the axial plane to obtain anteroposterior and transverse diameters for true maximum length and width measurements, respectively. Landmarks were chosen by a plastic surgeon, neurosurgeon and an anatomist as these were easily identifiable, reproducible and deemed to be the best points to investigate the dimensions being studied.

ACF Length: The midpoint of the limbus sphenoidale was identified as a reference landmark and transcended to the level at which the ACF was observed to be at its maximal length. The midline anteroposterior diameter of the ACF was measured as a perpendicular from the transcended point (LS*) to the inner table of the frontal bone (ITF) (Fig. 1).

ACF Width: The maximum transverse diameter of the ACF was measured as the lateral distance between the points on the inner tables of the frontal bones that were most remote from each other in the ACF (ITF to ITF); at the same level at which the maximum length was obtained (Fig. 1).

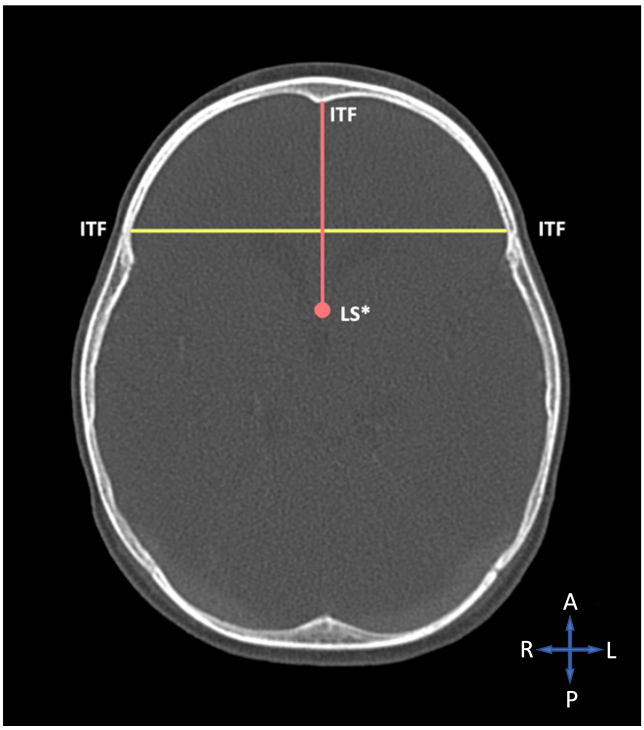

FIGURE 1. Anterior cranial fossa (ACF) parameters on axial CT scan of a normal patient [length= LS* to ITF, width= ITF to ITF]. **KEY:** LS*= Transcended point of midpoint of limbus sphenoidale, ITF= Inner table of frontal bone.

MCF Length: The midline anteroposterior diameter of the MCF, on the right and left sides, was measured as a perpendicular from the midpoint of the curvature of the greater wing of the sphenoid bone (GWS) to the petrous part of the temporal bone (PT); at the level of the floor of the pituitary fossa (Fig. 2).

MCF Width: At the same level, the transverse diameter of the MCF was measured as a perpendicular from the midpoint of the floor of the pituitary fossa (PF) to the inner table of the temporal bone (ITT). This measurement was taken bilaterally (Fig. 2).

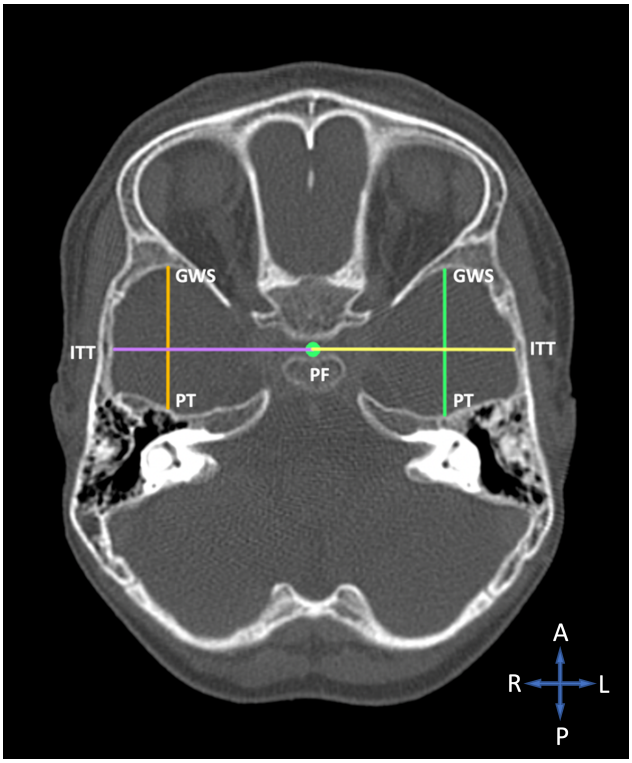

FIGURE 2. Middle cranial fossa (MCF) parameters on axial CT scan of a normal patient [length= GWS to PT, width= PF to ITT]. **KEY:** GWS= Midpoint of curvature of greater wing of sphenoid bone, PT= Petrous part of temporal bone, PF= Midpoint of floor of pituitary fossa, ITT= Inner table of temporal bone.

PCF Length: The midpoint of the posterior margin of the dorsum sellae was identified as a reference landmark and transcended to the level at which the PCF was observed to be at its maximal length. The midline anteroposterior diameter of the PCF was measured as a perpendicular from the transcended point (DS*) to the inner table of the occipital bone (ITO) (Fig. 3).

PCF Width: The maximum transverse diameter of the PCF was measured as the lateral distance between the points on the inner tables of the parietal bones that were most remote from each other in the PCF (ITP to ITP); at the same level at which the maximum length was obtained (Fig.3).

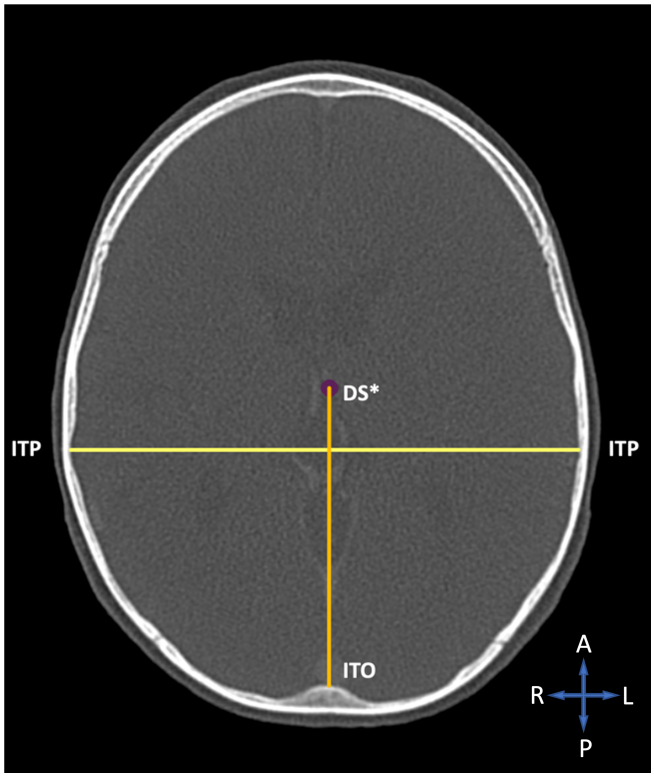

FIGURE 3. Posterior cranial fossa (PCF) parameters on axial CT scan of a normal patient [length= DS* to ITO, width= ITP to ITP]. **KEY:** DS*= Transcended point of midpoint of posterior margin of dorsum sellae, ITO= Inner table of occipital bone, ITP= Inner table of parietal bone.

Demographic information, including age, sex, and population group, was documented. According to Statistics South Africa, population groups are categorized into four main subgroups, viz. Black, Coloured, Indian and White.[15] There were no patients within the Coloured subgroup in this study.

The cephalic index (CI) was used to quantify the head shape of all patients. The CI was calculated according to the following equation: cephalic width/cephalic length x 100. The distance between the most anterior and posterior points of the outer table of the skull was measured in the transverse plane to calculate the cephalic length. The cephalic width was measured as the distance between the outer skull tables at the widest points of the skull in the transverse plane.[16]

Due to the absence of an age-matched control group, the patients and controls were grouped by age for the relevant comparative analyses. There were four groups, i.e., <1 year, 1-<3 years, 3-<6 years, and 6-<9 years. Scaphocephalic patients were stratified into 3 groups according to the degree of severity for the relevant analyses, i.e., >70% [Mild], 65-70% [Moderate] and 60-65% [Severe]. Patients in the control group had an open suture with a CI >70%.

2.3.4. Statistical analysis

Results were presented as descriptive and inferential statistics. Data were assessed for normality and the relevant statistical test performed (t-test or Wilcoxon). For the mean difference of numerical variables across at least three levels of a categorical variable, the ANOVA test and the Kruskal Wallis test were performed as appropriate. In the case of significant mean difference, post-hoc tests were conducted using Tukey's HSD single-step multiple comparison procedure and similarly with Dunn test for significant difference in the medians. The t-test and Rank-sum test were used in the pairwise comparison of the groups. The Chi-Square and Fisher's exact tests were employed for associations between categorical variables. Intra-observer and inter-observer error were calculated and represented as intraclass correlation coefficient (ICC) values to determine the reliability of the morphometric data. All statistical data analyses were carried out with the assistance of a university statistician, using R Statistical computing software of the R Core Team version 3.6.3 (R Studio, Boston, MA, USA). A value of $p<0.05$ was considered statistically significant.

2.4.Results

The demographic information and anatomical profile of the study population are depicted in Table 1. Twenty-four patients with scaphocephaly met the criteria for inclusion in the study. The mean age in this group at the time of the CT scan was 2.47±2.36 years (range: 0.167-7.67 years). Age distributions were as follows: <1 year (n=8), 1-<3 years (n=8), 3-<6 years (n=4) and 6-<9 years (n=4). Four (16.7%) of the patients were female, and 20 (83.3%) were male. The majority of the patients were Black (66.7%), followed by Indian (16.7%) and White (16.7%). The mean CI of the scaphocephalic patients was 67.1±3.51% (range: 60.8-74.5%). With regards to stratification by the degree of severity, 4 (16.7%) patients were attributed to the mild group, 13 (54.2%) to the moderate group and 7 (29.2%) to the severe group. Fourteen non-affected/normal patients were enrolled as controls (mean age: 3.35±2.81 years, range: 0.0833-8.42 years). Age distributions for this group were as follows: <1 year (n=1), 1-<3 (n=8), 3-<6 (n=2) and 6-<9 (n=3). Fifty percent of the control group were females. Thirteen (92.9%) patients were Black, and 1 (7.1%) was Indian. All control patients had an open sagittal suture, with a CI usually above 70% (mean: 74.6±3.65%, range: 70.1%-82.1%) (Table 1).

TABLE 1. Demographic data and anatomical profile of the study population

Demographics/ Anatomical profile	Scaphocephaly (n=24)	Control (n=14)
Age, *n* (%)		
<1 year	8 (33.3)	1 (7.1)
1-<3 years	8 (33.3)	8 (57.1)
3-<6 years	4 (16.7)	2 (14.3)
6-<9 years	4 (16.7)	3 (21.4)
Mean±SD (years)	2.47±2.36	3.35±2.81
Range (years)	0.167-7.67	0.0833-8.42
Sex, *n* (%)		
Female	4 (16.7)	7 (50.0)
Male	20 (83.3)	7 (50.0)
Population group*, *n* (%)		
Black	16 (66.7)	13 (92.9)
Indian	4 (16.7)	1 (7.1)
White	4 (16.7)	0 (0.0)
Degree of severity, *n* (%)		
Mild [>70%]	4 (16.7)	-
Moderate [65-70%]	13 (54.2)	-
Severe [60-65%]	7 (29.2)	-
Mean±SD (years)	67.1±3.51	74.6±3.65
Range (years)	60.8-74.5	70.1-82.1

Abbreviation: SD: Standard deviation.
*Statistics South Africa[15]

2.4.1. Morphometry of the cranial fossae

Overall analysis

Table 2 compares the maximal dimensions of the cranial fossae between scaphocephalic patients and control subjects.

TABLE 2. Maximal cranial fossae dimensions in patients with scaphocephaly *vs.* control group

Dimensions (mm)	Scaphocephaly (*n*=24) (mean±SD)	Control (*n*=14) (mean±SD)	*p*-value[a]	% Change[#]
ACF Length	60.7±5.17	56.9±5.71	**0.041**	**6.8**
ACF Width	94.2±5.76	95.6±8.72	0.568	-1.5
MCF Length (Left)	37.8±5.74	35.9±3.74	0.278	5.3
MCF Width (Left)	42.3±4.29	43.7±6.02	0.410	-3.2
MCF Length (Right)	38.2±5.90	37.7±4.35	0.774	1.3
MCF Width (Right)	41.8±4.20	44.1±6.17	0.179	-5.2
PCF Length	90.7±9.11	83.1±9.33	**0.018**	**9.2**
PCF Width	113±8.67	118±10.5	0.111	-4.2

Abbreviation: ACF: Anterior cranial fossa. MCF: Middle cranial fossa. PCF: Posterior cranial fossa. SD: Standard deviation.

[a] *t*-test

[#] % Change= (mean value of dimension in scaphocephalic patients – mean value of dimension in control group)÷(mean value of dimension in control group) x 100

Bold: Statistically significant results (*p*<0.05)

The following statistically significant anomalies were identified in patients with scaphocephaly; the mean length of the ACF was significantly larger (*p*=0.041) in the scaphocephaly group (60.7±5.17mm) compared to the control group (56.9±5.71mm) by 3.8mm (6.8%), and the mean PCF length was significantly greater (*p*=0.018) in the scaphocephaly group (90.7±9.11mm) than in the control group (83.1±9.33mm) by 7.6mm (9.2%) (Table 2).

No statistically significant differences were found in the left and right MCF lengths between scaphocephalic patients and controls (*p*=0.278; 0.774). The width of the ACF, left and right MCF and PCF between the scaphocephaly and control groups were found to be non-significant (*p*=0.568; *p*=0.410 and *p*=0.179; *p*=0.111) (Table 2).

Comparison by:

Age

Substantial comparisons could not be made since one of the age groups had only a single measurement recorded (Table 3). As a result, the following is reported as descriptive statistics.

For all age groups, a trend was noticed in that the mean values for the ACF, MCF and PCF lengths were generally greater in scaphocephalic patients as compared to the controls.

The mean ACF, MCF and PCF widths were observed to be generally higher in scaphocephalic patients as compared to controls within the <1 year and 3-<6-year age groups but lower when compared to controls in the 1-<3 year and 6-<9-year age groups (Table 3).

Sex

No statistically significant differences between the variables and sex were documented (Table 4).

Population group

Due to the limited sample size and absence of a White subgroup, no statistical analyses involving population groups were conducted (Table 1).

Degree of Severity

It was found that the mean length of the ACF was significantly larger (ANOVA, p=0.033; post-hoc, p=0.013) in scaphocephalic patients within the severe group (64.2±3.63mm) compared to the control group (56.9±5.71mm) (Table 5; Fig. 4A).

A statistically significant difference in the PCF length is reported between patients in the severe group and the control group for PCF length (ANOVA, p=0.015) (Table 5). The mean length of the PCF was significantly greater (post-hoc, p=0.036) in the severe group (96.9±8.90mm) compared to the control group (83.1±9.33mm) (Table 5; Fig. 4B).

Intra-observer reliability

The results of the intra-observer reliability test indicate that the average measurements used are highly reliable as the intraclass coefficients for all intra-rater reliability tests yielded an ICC of 1 viz. ACF length (ICC=1), Right MCF length (ICC=1), Left MCF length (ICC=1), PCF length (ICC=1), ACF width (ICC=1), Right MCF width (ICC=1), Left MCF width (ICC=1), PCF width (ICC=1).

Inter-observer reliability

The inter-observer reliability test yielded the following intraclass coefficients: ACF length (ICC=0.98), Right MCF length (ICC=1), Left MCF length (ICC=1), PCF length (ICC=1), ACF width (ICC=1), Right MCF width (ICC=1), Left MCF width (ICC=1), PCF width (ICC=1); all indicating excellent reliability.

TABLE 3. Maximal cranial fossae dimensions in patients with scaphocephaly compared to controls by age

Dimension (mm)	Age (years)							
	< 1		1-<3		3-<6		6-<9	
	Scaphocephaly (n=8) (Mean±SD)	Control (n=1) (Mean±SD)	Scaphocephaly (n=8) (Mean±SD)	Control (n=8) (Mean±SD)	Scaphocephaly (n=4) (Mean±SD)	Control (n=2) (Mean±SD)	Scaphocephaly (n=4) (Mean±SD)	Control (n=3) (Mean±SD)
ACF Length	56.0±5.51	43.0	62.2±3.64	57.8±4.60	64.3±2.53	57.4±4.08	63.5±2.07	58.8±5.05
ACF Width	88.6±3.25	70.9	95.1±5.17	95.7±4.67	100±2.39	96.4±1.85	97.7±3.41	103±5.75
MCF Length (Left)	33.7±3.31	28.1	37.2±4.10	36.4±2.16	40.2±4.41	32.5±2.82	44.8±7.07	39.5±2.76
MCF Width (Left)	38.7±2.18	30.9	41.3±3.24	43.0±5.01	46.1±2.60	44.1±0.21	47.7±2.03	49.6±3.47
MCF Length (Right)	33.5±1.83	29.6	38.7±4.18	36.8±2.32	41.1±7.14	38.9±7.31	44.1±7.04	42.2±3.21
MCF Width (Right)	37.9±1.93	30.5	41.9±4.04	43.2±4.42	45.4±2.57	44.2±1.76	45.8±1.65	50.9±3.40
PCF Length	82.4±5.29	61.3	91.0±5.84	82.5±5.21	96.5±6.40	79.5±3.63	101±8.63	94.2±5.20
PCF Width	103±3.07	85.0	114±7.01	120±2.98	120±5.86	113±2.03	121±2.33	126±1.90

Abbreviation: ACF: Anterior cranial fossa. MCF: Middle cranial fossa. PCF: Posterior cranial fossa. SD: Standard deviation.

TABLE 4. Maximal cranial fossae dimensions in patients with scaphocephaly compared to controls by sex

Dimension (mm)	Scaphocephaly (*n*=24) (Mean±SD)		Control (*n*=14) (Mean±SD)		*p*-value[a]
	Females	Males	Females	Males	
ACF Length	56.7±4.84	61.5±4.97	56.1±7.58	57.6±3.46	0.425
ACF Width	91.3±3.05	94.8±6.05	92.2±9.65	98.9±6.77	0.543
MCF Length (Left)	33.4±1.20	38.7±5.90	34.9±4.23	36.9±3.18	0.399
MCF Width (Left)	39.5±1.89	42.9±4.44	41.3±6.84	46.1±4.27	0.703
MCF Length (Right)	35.2±3.53	38.8±6.15	37.2±4.52	38.3±4.46	0.555
MCF Width (Right)	39.1±3.47	42.3±4.20	41.3±6.54	46.9±4.66	0.523
PCF Length	87.9±6.41	91.3±9.59	82.5±11.6	83.7±7.28	0.772
PCF Width	108±2.34	113±9.26	114±13.7	122±4.07	0.710

Abbreviation: ACF: Anterior cranial fossa. MCF: Middle cranial fossa. PCF: Posterior cranial fossa. SD: Standard deviation.

[a]ANOVA test conducted for females and males in the scaphocephaly and control groups

TABLE 5. Maximal cranial fossae dimensions in patients with scaphocephaly compared to controls by the degree of severity

Dimension (mm)	Scaphocephaly (*n*=24) (Mean±SD)			Control (*n*=14) (Mean±SD)	*p*-value
	Degree of Severity				
	Mild (*n*=4)	Moderate (*n*=13)	Severe (*n*=7)		
ACF Length	60.7±7.10	58.8±4.59	64.2±3.63[c]	56.9±5.71[d]	**0.033**[a]
ACF Width	98.1(93.6-102)	92.4(90.8-96.3)	96.9(90.7-98.9)	97.1(94.3-99.5)	0.375[b]
MCF Length (Left)	40.8±3.47	37.4±6.72	36.8±4.74	35.9±3.74	0.420[a]
MCF Width (Left)	45.7±4.32	41.0±3.76	42.9±4.61	43.7±6.02	0.318[a]
MCF Length (Right)	40.3±3.04	37.4±6.70	38.6±5.85	37.7±4.35	0.790[a]
MCF Width (Right)	44.4±3.05	40.3±4.23	42.9±4.05	44.1±6.17	0.229[a]
PCF Length	85.4±6.30	89.0±8.65	96.9±8.90[c]	83.1±9.33[d]	**0.015**[a]
PCF Width	124(118-125)	109(104-118)	111(107-117)	121(115-122)	0.030[b#]

Abbreviation: ACF: Anterior cranial fossa. MCF: Middle cranial fossa. PCF: Posterior cranial fossa. SD: Standard deviation.

[a]ANOVA test

[b]Kruskal-Wallis test; Median(Q1-Q3) value is shown due to skewness in the data

[#]Although *p*-value is significant, the post-hoc results did not show any significant differences due to low power of sample

[c] Values in severity group differed significantly from those in control group (footnote *d*) in post-hoc comparisons

Bold: Statistically significant results (*p*<0.05)

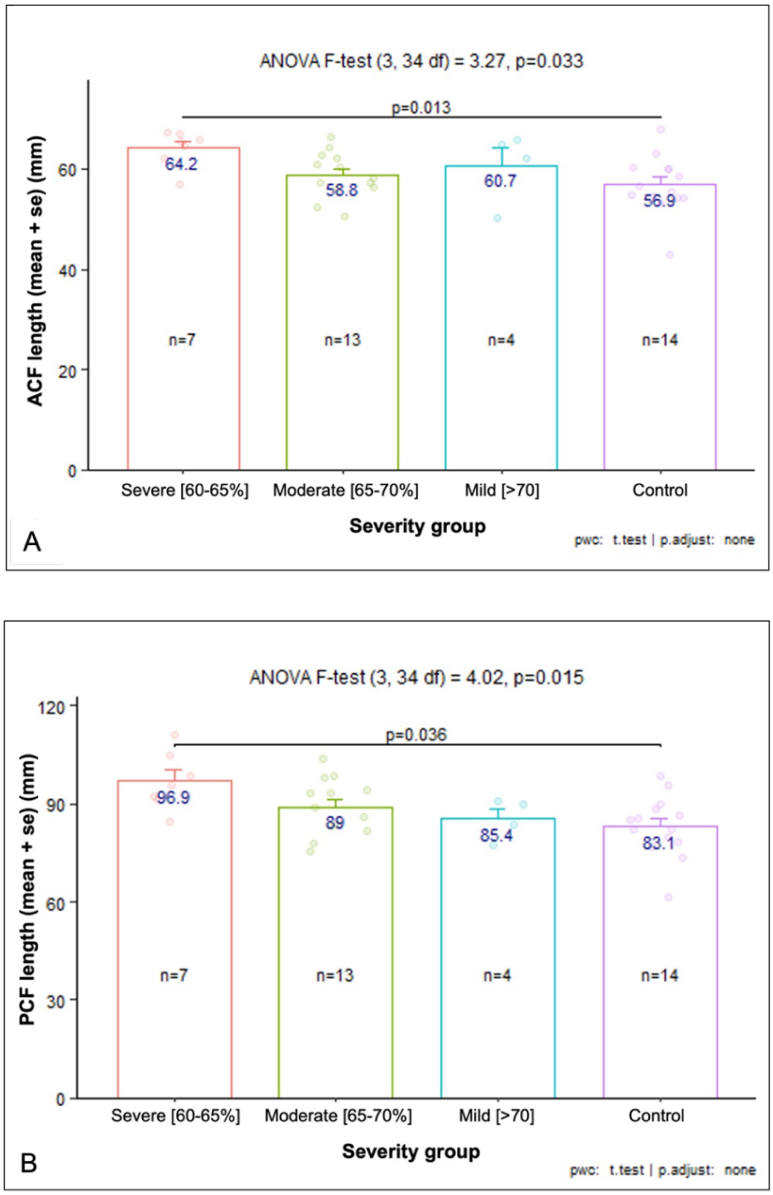

FIGURE 4. Post-hoc analysis results showing differences between severity of scaphocephalic and control groups for **(A)** anterior cranial fossa (ACF) length and **(B)** posterior cranial fossa **(**PCF) length.

2.5.Discussion

In the literature reviewed, only one study[7] reports on the morphometry of the cranial base and its fossae in scaphocephalic patients. In the present study, the basic morphometry of the cranial fossae, viz. maximum lengths and widths of the ACF, MCF and PCF, was analysed in scaphocephalic patients and controls. To the best of the authors' knowledge, the current study is the first to document such measurements in patients with scaphocephaly.

The study by Calandrelli *et al.*[7] analysed the morphometry of the cranial base and hemi-fossae in patients with isolated sagittal synostosis using landmarks on 3D-CT scan images of the endocranial base. The subjects enrolled in the said study were classified into three groups based on the severity of the deformity, which was determined by calculating the CI as well as the vertical longitudinal index (VLI) and were compared to controls.

Calandrelli *et al.*[7] found that the ACF, MCF, and PCF were symmetrical and that lengths of the anterior and middle cranial base were increased. MCF length was increased in all three severity groups, viz. mild, moderate and severe. Compensatory enlargement of the ACF was only significant in patients with mild and moderate sagittal synostosis. The lengths of the PCF were comparable in all groups. These findings imply that spontaneous calvarial remodeling may contribute to enlargement of the anterior and middle cranial base, probably because the central section of the sagittal suture is usually the first to fuse. The minor elongation of the cranial base in the severe group may be related to the earlier timing of sagittal suture synostosis.[7]

Due to the lack of availability of 3D-CT scan images of the endocranial base, the method used by Calandrelli *et al.*[7] could not be followed in the present study. In addition to this, there is a dichotomy of opinion with regards to the description of the ACF, MCF, and PCF lengths in the literature consulted.[7] The landmarks and measurements used by Calandrelli *et al.*[7] to quantify the length of the ACF, MCF and PCF were not reflective of the true lengths of the cranial fossae as these measurements were captured diagonally. There is also no previous literature investigating the width of the cranial fossae in patients with scaphocephaly. Using the CT material available and in keeping with the objectives, this study opted to measure the true lengths and widths of the cranial fossae. The authors are of the belief that midline AP and transverse diameter measurements between fixed anatomical points best represent lengths and widths, respectively. Anatomical landmarks characteristic of each cranial fossa that was visible on 2D-CT scans were chosen accordingly, between which midline AP and transverse diameters were measured to obtain the true lengths and widths of the cranial fossae, respectively.

Due to the difference in the anatomical landmarks used and measurements made, the findings of this study cannot be compared with those of Calandrelli *et al.*[7]

2.5.1. Morphometry of the cranial fossae

In the current study, the maximal dimensions of the ACF, MCF and PCF were compared between scaphocephalic and control patients. The lengths of the ACF and PCF were significantly longer

in patients with scaphocephaly when compared to controls by 6.8% and 9.2%, respectively (Table 2). The larger lengths of the ACF and PCF may be due to:

(i) compensatory AP expansion of the skull as a result of premature fusion of the sagittal suture

(ii) the varying degrees of the compensatory anterior and/or posterior deformities associated with scaphocephaly, i.e. bossing of the frontal bone and/or protrusion of the occipital bone.

There were no statistically significant differences in the widths of the ACF and PCF between patients in the scaphocephaly and control groups. The differences in MCF lengths and widths between the scaphocephaly and control groups were found to be statistically non-significant.

2.5.2. Comparison by Age, Sex, Population group & Degree of severity

Substantial comparisons could not be made in terms of the age and population groups due to the limited sample size and the lack of age- and population group-matched control group. There were no statistically significant differences documented between the variables and sex.

The maximal dimensions of the ACF, MCF and PCF were compared between scaphocephaly and control patients by degree of severity. Patients were classified into three groups based on the severity of the deformity, which was quantified by calculating the traditional CI. The length of the ACF and PCF was found to be significantly larger in scaphocephalic patients within the severe group as opposed to the control group. This is possible due to, as mentioned earlier, the compensatory AP elongation of the cranium compounded by the associated increased prominence of the frontal bone and/or protuberance of the occipital bone, which may be exacerbated in the severe group. No statistically significant differences were found in the MCF lengths between the three severity groups and the control group. The width of the ACF, MCF (right and left), and PCF were comparable in all groups.

Overall, the current study found that the lengths of the cranial fossae were generally larger in scaphocephalic patients, with only the lengths of the ACF and PCF being statistically significant. The widths of the cranial fossae were generally smaller in scaphocephalic patients, but this did not reach statistical significance. These findings reveal that most of the change occurs along the AP plane, and very little change occurs in the transverse plane. Furthermore, this study highlights that the majority of the changes occur in the ACF and PCF, with very little change in the MCF. This may be due to the fact that the ACF and PCF are not as anatomically bound as compared to the MCF. It is possible that because the ACF has a free border anteriorly and the PCF, posteriorly;

compensatory growth can occur freely at these regions in scaphocephalic patients. On the other hand, due to its anatomical location between the ACF and PCF and the fact that it is bounded by fixed osteological borders, the MCF may be constrained and thus is not subjected to significant compensatory changes.

A significant limitation of the present study is the relatively small sample size in both, scaphocephaly and control groups. Another limitation is the absence of an age-, sex-, and population-matched control group.

This novel study provides an insight into understanding the changes that occur at the cranial fossae in scaphocephalic patients when compared to normal patients. The morphometric dimensions obtained in the present study indicate a preponderance of deformity in the ACF and PCF, especially with elongation along the AP plane (lengths) in scaphocephalic patients. There were very few changes observed in the transverse plane (widths) in scaphocephalic patients compared to the controls. These findings can assist craniofacial surgeons in deciding on the type of corrective surgery to be performed. This study augments the existing literature on sagittal synostosis by providing morphometric data that has not been previously recorded. The majority of the literature available with regards to morphometric analyses in scaphocephaly is based on the skull as a whole. Most of these studies are clinical and relatively descriptive. The present study is one of the first to delineate anatomic regions and obtain such morphometric measurements thereof in patients with scaphocephaly.

2.6.Declarations

2.6.1. Acknowledgements

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2.6.2. Author contributions

V Bisetty: Project development, Data collection, Data analysis, Manuscript writing and editing

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2.6.3. Conflict of Interest

The authors declare that they have no conflicts of interest to report.

2.6.4. Ethical Approval

Ethical clearance was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00002084/2020).

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CHAPTER 3: SCIENTIFIC MANUSCRIPT 2

Chapter 2 provided an analysis of the dimensions of each cranial fossae in scaphocephalic patients versus controls within a select South African population. The morphometric data obtained provided an insight into the anatomical changes that occur at each cranial fossa in patients scaphocephaly compared to normal.

Contributions of this chapter

This chapter constitutes a scientific manuscript that aimed to analyse and document the morphometry of Kocher's and Frazier's points within a select South African scaphocephalic population, using known craniometric and surface anatomical landmarks. The results were compared on the basis of demographic variables to determine statistically significant relationships.

The following manuscript has been submitted and is currently under review by the scientific journal:

Title: A morphometric analysis of Kocher's and Frazier's points in a select South African scaphocephalic population
Authors: V Bisetty, R Harrichandparsad, L Lazarus, A Madaree
Journal: Journal of Neurosurgery: Pediatrics
Manuscript Number: PEDS21-586

This manuscript has been written, formatted, and presented according to the author guidelines outlined by the *Neurosurgery: Pediatrics*. The American Medical Association (AMA) manual of style for reference formatting was followed, as required by the journal. In addition, the journal requires that figures and tables be separated from the main text; however, for ease of reference during the examination process, the author has incorporated figures and tables into the main text.

Title:

A morphometric analysis of Kocher's and Frazier's points in a select South African scaphocephalic population

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3.1.Abstract

Objective: Identifying the standard surface anatomical landmarks used for ventricular access procedures in patients with cranial deformities is often challenging and possibly influences the accuracy of ventricular catheter placement. Although ventricular access may not be frequently required in patients with scaphocephaly, it is imperative that an ideal location of the ventricular access points be established for safe ventricular catheterization in these patients. This study analysed and documented the morphometry of Kocher's and Frazier's points in a select South African scaphocephalic population using known craniometric and anatomical surface landmarks.

Methods: The craniometric dimensions of Kocher's and Frazier's points were measured relative to anatomical and craniometric landmarks on pre-operative Computed Tomography (CT) scans of 24 consecutive patients with a radiologically confirmed diagnosis of isolated sagittal synostosis. The results were compared against age, sex, population group and the degree of severity.

Results: The study provides mean values and ranges for consideration regarding ventricular catheter placement in patients with scaphocephaly. The mean distance of Kocher's point posterior to the nasion and lateral to the midline in scaphocephalic patients was 117±14.1mm (range: 91.6-140mm) and 27.2±3.22mm (range: 20.5-34.6mm), respectively. Statistically significant increases were reported in the mean distance posterior to nasion between patients in the <1 year and older age groups (>1-<9 years) (ANOVA, p<0.001; post-hoc, p=0.001; 0.001; 0.002); and in the mean distance lateral to the midline (ANOVA, p=0.004), between patients in the <1 year and 3-<6-year (post-hoc, p=0.002) and 1-<3-year and 3-<6-year (post-hoc, p=0.030) age groups, respectively. A mean distance of 67.9±4.75mm (range: 60.9-82.8mm) superior to the inion and 32.4±4.61mm (range: 25.9-41.4mm) lateral to the midline was recorded for the location of Frazier's point in patients with scaphocephaly. No statistically significant differences were documented for comparisons by sex, population group and degree of severity.

Conclusions: The study found that the traditional landmarks used for ventricular access are relatively unreliable in patients with scaphocephaly, particularly in those less than one year of age. The parameters measured in the anteroposterior (AP) plane were more affected than those measured lateral from the midline. A patient-tailored approach using neuronavigational techniques is usually recommended in these patients. However, in the event that neuronavigation is unavailable, these findings will allow neurosurgeons to modify the approaches used in ventricular cannulation to suit patients with scaphocephaly.

3.2.Introduction

Sagittal synostosis, also known as scaphocephaly, occurs when the sagittal suture fuses prematurely. The resultant skull shape is long and narrow due to restricted growth in the transverse direction and compensatory growth in the anteroposterior direction.[1–3] Scaphocephaly represents the most common form of craniosynostosis, accounting for approximately 40-60% of all reported cases.[1,2,4] It has an estimated incidence of 1 in 2000 to 7000 live births and affects males predominantly.[1,3,5] The cranial abnormality is characterized by a relatively low cephalic index (CI) of <70 %.[5] Scaphocephaly has variable morphology and is frequently accompanied by secondary deformities, including frontal bossing, biparietal narrowing, temporal protrusion, sagittal ridging, coronal constriction, changes in the cervico-occipital angle and occipital protuberance.[2,6] Variation in morphology depends on the anatomic location, presence of prominent anatomic features, age of onset, degree of premature suture closure and compensatory growth, as well as the severity of the deformity.[4–6] Despite skull elongation resulting in the corresponding elongation of the lateral ventricles, the ventricular anatomy in scaphocephaly remains relatively normal.[7]

Increased intracranial pressure (ICP) is sometimes a complication in scaphocephaly.[1,5] Intracranial hypertension (ICH) may develop in scaphocephaly due to intracranial venous congestion because changes in the sagittal suture can impair the absorptive ability of arachnoid granulations.[8] In some cases, especially in children >18-24 months, ICH may present as asymptomatic.[9] It is crucial that ICP be monitored even if subtle elevation is clinically suspected, especially in older patients with scaphocephaly.[9,10]In the event of elevated ICP during the surgical repair of scaphocephaly, ventricular access may be required to monitor ICP and drain CSF simultaneously, thus protecting the brain from further elevations in pressure.[9] Hydrocephalus occurs less frequently in individuals with non-syndromic isolated sagittal craniosynostosis as compared to syndromic multiple-suture craniosynostosis; however, the occurrence is not impossible. The optimal treatment for hydrocephalus in a population with craniosynostosis is unascertained.[11] For this reason, ventricular access may be required for CSF diversion or drainage.

A ventriculostomy is a routinely used emergency neurosurgical procedure that entails the drilling of a burr hole into the skull and the subsequent catheterization of one of the ventricles of the brain for diagnostic or therapeutic purposes in ICP monitoring and CSF drainage.[12,13] Common indications for emergency ventricular access include hydrocephalus, intracranial hypertension, subarachnoid and intracranial haemorrhage, and traumatic brain injury.[12,14,15] A ventriculostomy is usually performed freehand using cranial surface anatomical landmarks to identify the optimal

entry site for ventricular cannulation.[12] In recent times, various modalities including endoscopy, ultrasound, neuronavigation, stereotaxic, and mechanical guides have been used to facilitate ventricular catheter placement; however, due to its simplicity and efficiency in emergency situations, the freehand pass technique is still a preferred method by neurosurgeons worldwide.[12,15,16]

Numerous ventricular access points have been described in the literature, each accessing different parts of the lateral ventricles, depending upon the indications for ventricular cannulation.[13,17,18] This study only focuses on Kocher's and Frazier's points, common anterior and posterior ventricular horn access sites. Kocher[19(p50)] initially described an entry point as "…2.5cm from the median line and 3cm forward of the pre-central fissure." This entry point is now variously defined in the literature as being between 10 to 13cm posterior to nasion and 1.5 to 4cm lateral to the midline at the mid-pupillary line, and approximately 1 to 2cm anterior to the coronal suture.[12,13,16–18,20,21] Kocher's point is commonly accessed for the placement of an external ventricular drain.[18] Frazier's point, traditionally described by Frazier[22], is located approximately 3 to 4cm lateral to the midline and 6 to 7cm above the inion, just superior to the lambdoid suture.[13,17,18,23] Frazier's point is most often accessed for the placement of ventricular shunts. However, the clinical applicability of these points varies.[18] Inadequate evidence exists to recommend the anterior access site over the posterior and vice versa, therefore both points are suitable for ventricular cannulation.[24]

Although ventricular cannulation via the freehand method is a simple and commonly performed procedure, it has been found to be relatively inaccurate, with catheter misplacement rates of up to 45%.[12,13] Misplacement of the catheter has been attributed to variations in cranial morphology and ventricular anatomy, surgical experience, size of the cranial burr hole, as well as the techniques used.[12,15,25] The lack of standardization regarding the entry points may also contribute to the misplacement of the ventricular catheter.[23] It is essential that misplacement of the ventricular catheter be avoided to prevent serious morbidities and mortality.[15,21] Neurosurgeons may face greater challenges when performing ventriculostomy procedures on patients presenting with scaphocephaly.[26] The many morphological variations in scaphocephaly make it difficult to identify the standard surface anatomical landmarks used in the freehand pass technique and may influence the accuracy of ventricular catheter placement in such patients.

The ideal cranial entry point, trajectory insertion, and catheter length play a vital role in ensuring successful ventricular catheter placement.[24,27,28] Many studies have focused on optimizing the

trajectory and catheter length, but there have been few studies that attempted to specifically validate or update these historic cranial entry points, despite ventricular catheterization being a ubiquitous neurosurgical procedure.[25,28] However, these studies mostly provide morphometric data for just one of the dimensions related to the craniometric point. It must be noted that more attempts have been made to validate and update Kocher's point compared to Frazier's point. Furthermore, a large majority of the literature that the neurosurgical fraternity relies on for external ventricular drainage is based on adult experience, the knowledge from which has to be extrapolated to a paediatric population.[29] There is a paucity of literature regarding the ideal entry points for ventricular access in a paediatric population and much less in a scaphocephalic paediatric population.

Although ventricular access may not be required as often in patients with scaphocephaly, it is important that a range be established, so one is aware of the degree of variation in the entry point location as compared to that which is known. This study will provide a range at which the Kocher's and Frazier's point burr holes can be ideally located in patients with scaphocephaly, should the need for ventricular catheterization arise. The findings will allow neurosurgeons to modify the approaches used in ventricular cannulation to suit patients with scaphocephaly.

The aim of this study was to document the ideal location of Kocher's and Frazier's points in a select South African scaphocephalic population using known craniometric and anatomical surface landmarks.

3.3.Materials and Methods

3.3.1. Patients

This study utilized pre-operative Computed Tomography (CT) head scans of 24 consecutive patients with a radiologically confirmed diagnosis of isolated sagittal synostosis, who presented to the craniofacial clinic at the Inkosi Albert Luthuli Central Hospital (IALCH), Durban, South Africa, between January 2014 and June 2020. Scans of patients diagnosed with syndromic and/or multiple suture craniosynostosis were excluded. CT scans with inadequate information and of poor quality were also excluded. Ethical approval for this retrospective study was obtained from the Biomedical Research Ethics Committee of the University of KwaZulu-Natal (BREC/00002084/2020).

3.3.2. Image acquisition & analysis

Axial CT scans of selected patients were obtained from the database of the Department of Plastic and Reconstructive Surgery at IALCH and saved in DICOM (Digital Imaging and Communication in Medicine) format. CT images were acquired in the clinical routine with either a 128-slice SOMATOM Definition AS scanner or SOMATOM Definition Flash CT Scanner (Siemens Healthineers, Forcheim, Germany). CT scans had a slice thickness of 1-5mm. Acquired axial CT images were reformatted into sagittal and coronal planes in the 3D-multiplanar reconstruction view and analysed using the Horos software version 3.3.6 (Horos Project, Annapolis, MD, USA). CT scan images were automatically calibrated by the Horos software and were standardized to a 1cm reference scale; calibration was manually verified. CT scans were aligned in the orbitomeatal plane. Ventricular catheterization is usually performed on the right side, by default, as it corresponds to the non-dominant hemisphere; therefore, measurements were only taken on the right side. Curvilinear measurements were taken on the brain window setting using the open polygon tool. The open polygon tool was used as it is able to measure curvilinear distances more accurately. Each measurement was taken three times by the first author (during intra-observer analysis) as well as by a second observer (during inter-observer analysis) to ensure accuracy and reliability.

3.3.3. Morphometry of Kocher's & Frazier's Points

3.3.3.1. Kocher's Point

A point was placed 1cm anterior to the coronal suture (to avoid the motor cortex) along the right midpupillary line (regarded as a standard anatomical surface landmark) in the sagittal plane. This point was regarded as the ideal frontal entry point or the so-called "Kocher's point" (Fig. 1A; B; C). The point was then extrapolated into the midline (Fig. 2A; B; C). The distance posterior to the nasion was measured between the nasion and the extrapolated point, in the sagittal plane. The lateral distance from the midline was measured between the frontal entry point (Kocher's point) and the extrapolated point, in the coronal plane (Fig. 3A; B; C).

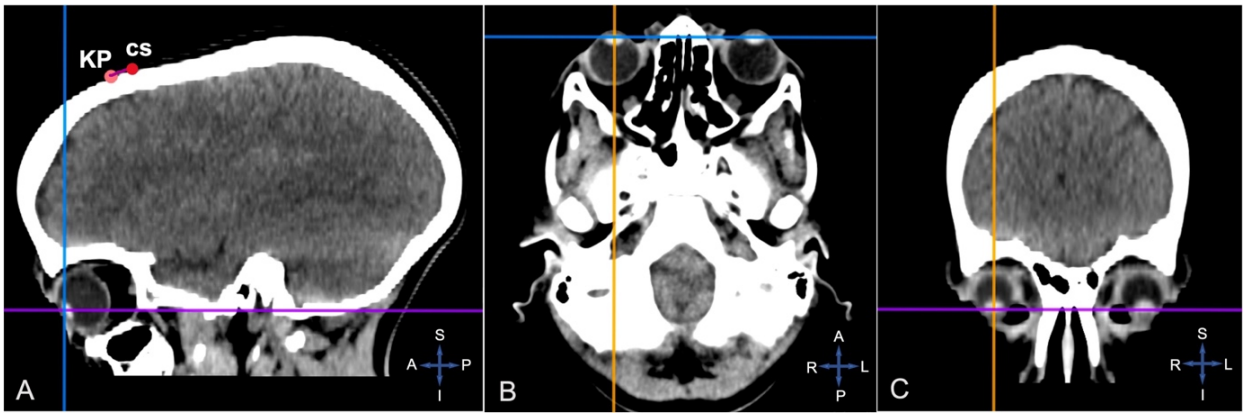

FIG. 1. CT head scan of a patient with scaphocephaly. **(A)** Sagittal image showing Kocher's point placed 1cm anterior to the coronal suture along the right midpupillary line, **(B)** Axial image showing midpupillary line, **(C)** Coronal image showing midpupillary line. **KEY:** KP= Kocher's Point, cs= coronal suture.

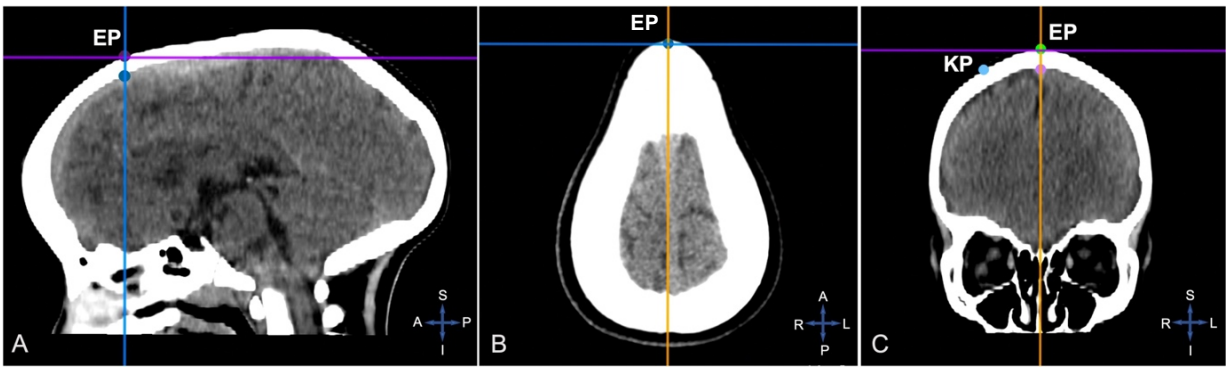

FIG. 2. CT head scan of a patient with scaphocephaly. **(A)** Sagittal image showing extrapolated point into the midline, **(B)** Axial image showing extrapolated point, **(C)** Coronal image showing Kocher's point and extrapolated point. **KEY:** EP= Extrapolated Point, KP= Kocher's Point.

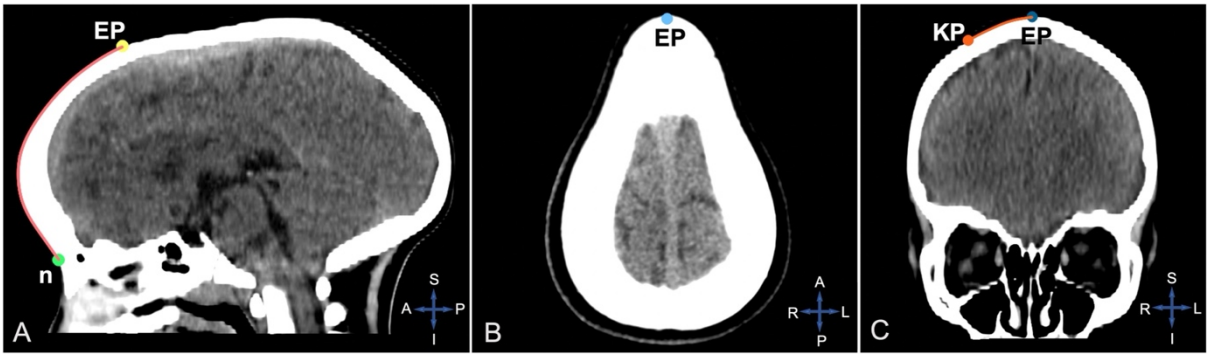

FIG. 3. CT head scan of a patient with scaphocephaly. **(A)** Sagittal image showing measurement between the nasion and the extrapolated point, **(B)** Axial image showing extrapolated point, **(C)** Coronal image showing measurement between Kocher's point and the extrapolated point. **KEY:** n= nasion, EP= Extrapolated Point, KP= Kocher's Point.

3.3.3.2. Frazier's Point

In the axial plane, the image showing the lateral ventricle most clearly was identified; this was a slice just above both thalami. The crosshairs were angled along the length of the right lateral ventricle, with the ideal target being the frontal horn, until the occipital horn was seen most prominently (Fig. 4 left; right). By using this method, the y-axis was positioned within the body of the lateral ventricle, with the frontal and occipital horns in the same plane. In the sagittal plane, a trajectory was constructed posteriorly, from the frontal horn to the parietal/occipital bone, in the middle of the lateral ventricle along its longest plane and at a tangent to the thalamus. The endpoint of the trajectory on the outer surface of the skull was regarded as the ideal occipital entry point or the so-called "Frazier's point" (Fig. 5 left; right). This point was then extrapolated into the midline. The distance superior to the inion was measured from the inion to the extrapolated point, in the sagittal plane. The lateral distance from the midline was measured between the occipital entry point (Frazier's point) and the extrapolated point, in the axial plane (Fig. 6 left; right). The point of attachment of the tentorium cerebelli was used as a marker to help locate the inion. A lower-lying tentorium cerebelli was excluded, radiographically.

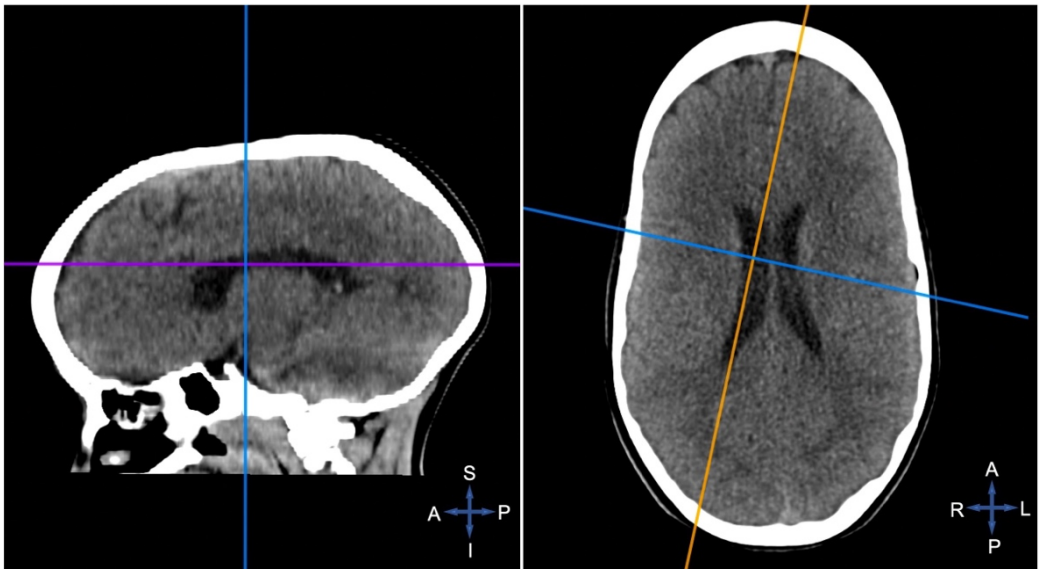

FIG. 4. CT head scan of a patient with scaphocephaly. **(Left)** Sagittal image showing occipital horn most prominently, **(Right)** Axial image showing crosshairs angled along the length of the right lateral ventricle (on image showing the lateral ventricle most clearly).

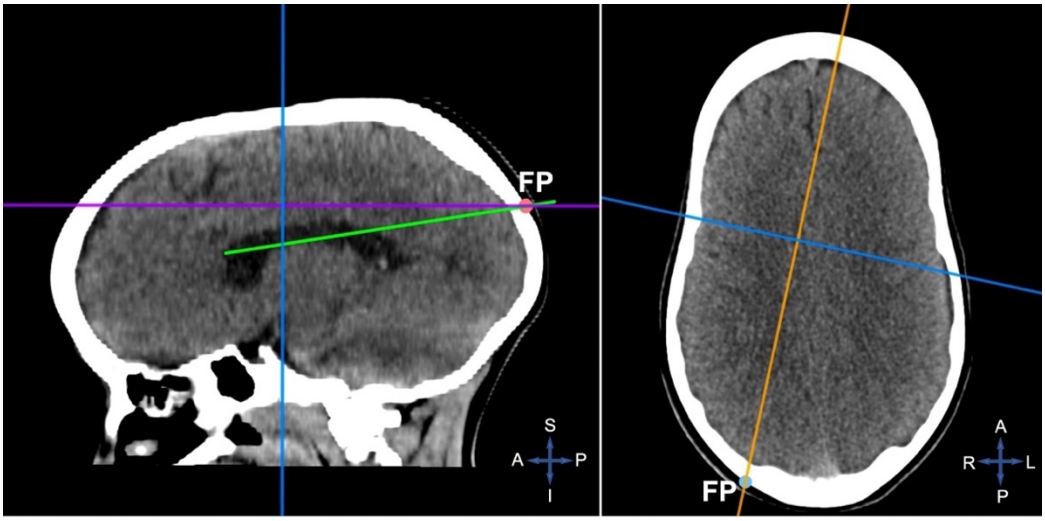

FIG. 5. CT head scan of a patient with scaphocephaly. **(Left)** Sagittal image showing trajectory and Frazier's point on the outer surface of the skull, **(Right)** Axial image showing Frazier's point. **KEY:** FP= Frazier's Point.

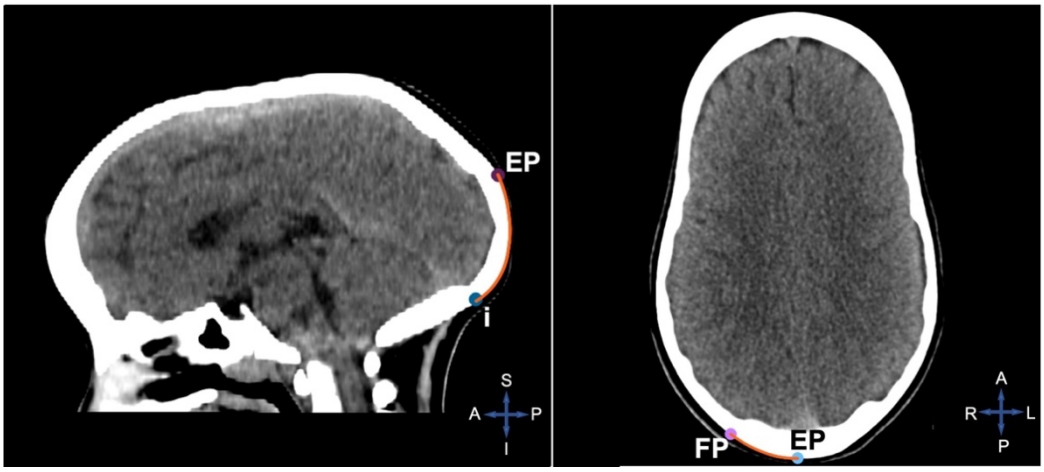

FIG. 6. CT head scan of a patient with scaphocephaly. **(Left)** Sagittal image showing measurement between the inion and extrapolated point, **(Right)** Axial image showing measurement between Frazier's point and the extrapolated point. **KEY:** FP= Frazier's Point, EP= Extrapolated Point, i= inion.

Demographic information, including age, sex, and population group, was documented. According to Statistics South Africa, population groups are categorized into four main subgroups, viz. Black, Coloured, Indian and White.[30] There were no patients within the Coloured subgroup in this study.

The traditional cephalic index (CI) was used to quantify the head shape of all patients. The CI was calculated according to the following equation: cephalic width/cephalic length x 100. The distance between the most anterior and posterior points of the outer table of the skull was measured in the transverse plane to calculate the cephalic length. The cephalic width was

measured as the distance between the outer skull tables at the widest points of the skull in the transverse plane.[31]

Age was categorized into four groups for the relevant comparative analyses, i.e., <1 year, 1-<3 years, 3-<6 years, and 6-<9 years. Scaphocephalic patients were stratified into three groups according to the degree of severity for the relevant analyses, i.e., >70% [Mild], 65-70% [Moderate] and 60-65% [Severe].

3.3.4. Statistical analysis

Descriptive statistics were used to summarize the data. Multidimensional numerical variables were presented as correlation plots. All numerical variables showed no significant departure from normality, and the mean differences between two independent groups were assessed using the t-test. The mean differences across at least three levels of a categorical variable used the ANOVA test, and post-hoc pairwise comparison of the groups was conducted using the t-test. To assess the reliability of the morphometric data, intra-rater and inter-rater error were calculated and represented as intraclass correlation coefficient (ICC) values. All data were analysed with the assistance of a university statistician, using the R Statistical computing software of the R Core Team version 3.6.3 (R Studio, Boston, MA, USA). Statistical significance was set at $p<0.05$.

3.4.Results

3.4.1. Demographic data

A total of 24 patients with scaphocephaly met the study inclusion criteria. The mean age at the time of the CT scan was 2.47±2.36 years (range: 0.167-7.67 years). Age distributions were as follows; <1 year (n=8), 1-3 years (n=8), 3-6 years (n=4) and 6-9 years (n=4). There were 4 (16.7%) females and 20 (83.3%) males. Of the 24 patients, 16 (67.7%) were Black, 4 (16.7%) were Indian, and 4 (16.7%) were White. Patients had a mean CI of 67.1±3.51% (range: 60.8%-74.5%). When stratified according to severity, the mild, moderate and severe groups were made up of 4 (16.7%), 13 (54.2%) and 7 (29.2%) patients, respectively.

3.4.2. Morphometric analysis of Kocher's and Frazier's points in patients with scaphocephaly

Overall analysis of Kocher's point

The mean distance of Kocher's point posterior to the nasion and lateral to the midline (along the midpupillary line) in patients with scaphocephaly was 117±14.1mm and 27.2±3.22mm, respectively (Table 1).

Kocher's point compared by age, sex, population group and degree of severity

The ANOVA test revealed a statistically significant difference in the mean distance posterior to the nasion between the different age groups (p<0.001) (Table 1). The post-hoc analysis indicated a statistically significant increase in the mean distance posterior to nasion between patients in the <1 year and 1-<3-year (p=0.001), 3-<6-year (p=0.001), and 6-<9-year (p=0.002) age groups.

When compared by age, the ANOVA test showed a statistically significant (p=0.004) difference in the distance lateral to the midline (Table 1). The post-hoc analysis identified a statistically significant increase in the mean distance lateral to the midline between patients in the <1 year and 3-<6-year (p=0.002) and 1-<3-year and 3-<6-year (p=0.030) age groups, respectively.

No statistically significant differences were documented for comparisons of the parameters for Kocher's point by sex, population group and degree of severity (Table 1).

Overall analysis of Frazier's point

A mean distance of 67.9±4.75mm superior to the inion and 32.4±4.61mm lateral to the midline was recorded for the location of Frazier's point in patients with scaphocephaly (Table 1).

Frazier's point compared by age, sex, population group and degree of severity

No statistically significant differences were documented when the parameters for Frazier's point was compared by age, sex, population group and degree of severity (Table 1).

TABLE 1. Morphometric analysis of Kocher's and Frazier's points in patients with scaphocephaly

	n	KOCHER'S POINT		FRAZIER'S POINT	
		Parameter (Mean±SD) (Range)			
		Posterior to nasion distance (mm)	Lateral to midline distance (mm)	Superior to inion distance (mm)	Lateral to midline distance (mm)
Total	24	117±14.1 (91.6-140)	27.2±3.22 (20.5-34.6)	67.9±4.75 (60.9-82.8)	32.4±4.61 (25.9-41.4)
Age (years)					
<1	8	101±9.47 (91.6-123)	24.8±2.21 (20.5-28.3)	65.6±2.64 (61.8-68.8)	30.1±4.94 (25.9-40.8)
1-<3	8	124±8.09 (112-136)	26.6±2.49 (21.7-29.5)	69.6±6.55 (62.5-82.8)	32.0±4.32 (25.9-41.4)
3-<6	4	131±6.93 (123-140)	30.6±1.40 (28.9-32.3)	65.9±3.40 (60.9-68.6)	34.5±4.11 (28.4-36.9)
6-<9	4	124±5.77 (118-131)	29.4±3.76 (26.2-34.6)	70.9±2.36 (68.3-74.0)	35.7±3.27 (31.4-38.9)
p-value[a]		**<0.001**	**0.004**	0.150	0.176
Sex					
Female	4	117±11.6 (103-130)	25.3±2.68 (21.7-28.1)	67.1±2.59 (64.7-69.9)	29.0±2.32 (25.9-31.0)
Male	20	118±14.8 (91.6-140)	27.5±3.24 (20.5-34.6)	68.0±5.11 (60.9-82.8)	33.1±4.69 (25.9-41.4)
p-value[b]		0.942	0.207	0.741	0.112
Population group*					
Black	16	120±14.2 (91.6-140)	27.9±3.23 (21.7-34.6)	68.9±4.56 (62.5-82.8)	30.9±3.88 (25.9-38.9)
Indian	4	118±10.6 (103-129)	27.5±2.07 (26.2-30.5)	67.6±5.91 (60.9-74.0)	34.6±3.98 (28.8-37.5)
White	4	106±14.2 (96.7-127)	24.0±2.58 (20.5-26.7)	63.9±2.63 (61.8-67.4)	36.3±5.77 (29.6-41.4)
p-value[a]		0.212	0.089	0.164	0.059
Degree of severity [CI group]					
Mild [>70%]	4	117±12.0 (100-127)	26.4±4.80 (20.5-32.3)	65.9±3.83 (61.8-70.8)	34.6±5.39 (28.4-41.4)
Moderate [65-70%]	13	113±14.4 (91.6-136)	26.7±3.30 (21.7-34.6)	68.0±5.79 (60.9-82.8)	32.2±4.83 (25.9-40.8)
Severe [60-65%]	7	125±13.0 (98.8-140)	28.4±1.93 (24.5-30.6)	68.7±2.93 (65.3-74.8)	31.5±4.03 (26.3-36.6)
p-value[a]		0.218	0.477	0.653	0.582

[a] ANOVA test

[b] *t*-test

*Statistics South Africa

Bold: Statistically significant results, (*p*<0.05)

Correlation analysis

- Kocher's point

Age was reported to have a moderately positive correlation with the distance posterior to nasion (r=0.57; *p*=0.004) and the distance lateral to midline (r=0.61; *p*=0.002) (Fig. 7)

CI was weakly and negatively correlated with the distance posterior to the nasion (r=-0.18; *p*=0.393) and lateral to the midline (r=-0.17; *p*=0.193) (Fig. 7).

- Frazier's point

There was a moderately positive correlation between age and the distance superior to inion (r=0.34; *p*=0.107) and lateral to midline (r=0.46; *p*=0.025) (Fig. 7).

A weak negative correlation between CI and the distance superior to inion was reported (r=-0.28; *p*=0.193). CI had a weak positive correlation with the distance lateral to midline (r=0.25; *p*=0.236) (Fig. 7).

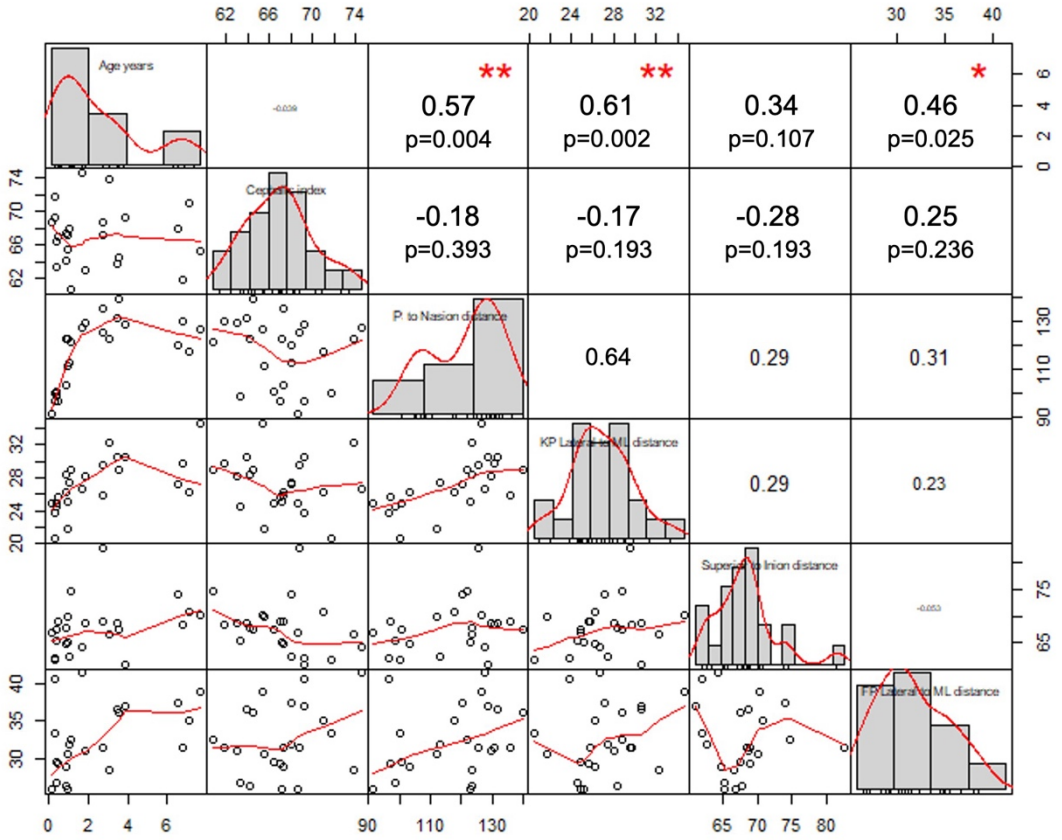

FIG 7. Correlation between the parameters for Kocher's and Frazier's points and age and CI.
KEY: P= Posterior, KP= Kocher's Point, ML= Midline, FP= Frazier's Point.

Intra-rater reliability

The results of an intra-rater reliability test infer that the average measurements used are highly reliable (p<0.001), intraclass coefficients for all intra-rater reliability tests were (ICC=1).

Inter-rater reliability

The inter-rater reliability test yielded the following intraclass coefficients: Posterior to nasion distance (ICC=1), Lateral to midline distance (ICC=0.96), Superior to inion distance (ICC=0.84), and Lateral to midline distance (ICC=0.98); all indicating good to excellent reliability.

3.5.Discussion

This present study analysed the morphometry of Kocher's and Frazier's points in patients with scaphocephaly, using surface anatomical landmarks. To the best of the investigators' knowledge, the current study is the first to document these craniometric points in a scaphocephalic population.

Several cranial entry points have been described in the literature, each of which uses anatomical landmarks to access different parts of the lateral ventricle.[13,17,18,32]. These entry points are positioned so that they do not penetrate the eloquent brain tissue.[24] The part of the ventricle that is accessed is dependent upon the indication for ventricular catheter placement.[13]

The SI units of the traditionally described landmarks have been converted from cm to mm for ease of reference in this study.

Kocher's point was initially described as 25mm from the median line and 30mm forward of the pre-central fissure.[19] However, Kocher's point is now variously defined in the literature as being between 100 to 130mm posterior to nasion and 15 to 40mm lateral to the midline at the mid-pupillary line, and approximately 10 to 20mm anterior to the coronal suture.[12,13,17,18,20,21] A study by Ikeda *et al*.[33] reported on the anterior access points ranging between 13.5±2.5mm and 43.5±6.1mm from the midline. This study was the only study in the literature reviewed that provided morphometric data on Kocher's point to include paediatric patients.

Frazier's point was traditionally described by Frazier[22]; it is located approximately 3 to 4cm lateral to the midline and 6 to 7cm above the inion, just superior to the lambdoid suture.[13,17,18,23] A part of the study by Deora *et al*.[25] investigated the variation of the occipital trajectory with skull shape and the ideal entry point in non-hydrocephalus and hydrocephalus patients. The sample population comprised adults and paediatric patients. The study found that the vertical dimension of the entry point varied according to the shape of the occiput in each patient group;

Hydrocephalus: Flat occiputs= 49±10.10mm; Little round occiputs= 54±8mm; Round occiputs= 50±8.5mm; Very round occiputs= 54±10.7mm. Non-hydrocephalus: Flat occiputs= 55±6.9mm; Little round occiputs= 53±5.4mm; Round occiputs= 58±7.6mm; Very round occiputs= 52±10.1mm. The superior to inion distance was higher in non-hydrocephalus patients as compared to hydrocephalus patients for all occiput shape groups.[25] These results, however, are based on the combined population, and no data specific to the paediatric group is provided.

Furthermore, as mentioned in the introduction, these studies[25,33] provide morphometric data; however, it is only for one dimension related to the relevant craniometric point. The findings of the present study cannot be directly compared to the results of the above-mentioned studies due to this reason, as well as the fact that these studies have been conducted in different populations.

3.5.1. Morphometric analysis of Kocher's point

The results of the present study show that the location of Kocher's point in scaphocephalic patients ranges from 91.6mm to 140mm (mean±SD: 117±14.1mm) posterior to the nasion and 20.5mm to 34.6mm (mean±SD: 27.2±3.22mm) lateral to the midline (Table 1). These findings indicate that considerable variation exists in the distance posterior to the nasion, i.e., in the AP plane among patients. When compared to the traditionally described craniometric point in the consulted literature, these findings show that the range for Kocher's point posterior to the nasion in patients with scaphocephaly falls slightly out of the range for that which is described in the literature. This is possible due to the compensatory AP elongation of the skull that occurs in scaphocephalic patients. It may also be attributed to the varying degrees of frontal bossing that typically accompanies scaphocephaly. The distance from the midline, i.e., in the coronal plane, was found to have remained within the described range. Since the midpupillary line was used as a defining landmark in the lateral dimension, this finding possibly implies that although the skull is narrowed in patients with scaphocephaly, the midpupillary line remains within normal limits. The clinical implication of these findings is that the traditional morphometric points used for ventricular access to the frontal horn are unreliable in scaphocephalic patients, particularly the distance posterior to the nasion. Neuronavigation is therefore recommended in these patients.

A statistically significant increase in the distance posterior to the nasion was reported between patients in the <1 year age group and those in the older age groups (1-<3, 3-<6 and 6-<9 years). A statistically significant increase in the distance lateral to the midline was reported between scaphocephalic patients under three years of age and those over the age of 3 years. Such findings are to be expected because, irrespective of the deformity, the skull size of patients in the <1year

age group is generally smaller than the skull size of patients in the older age groups. This is probably attributed to the fact that the bones of the skull are still fairly malleable in patients under one year of age due to the fontanelles still being opened.

It is worth noting that although the results indicate that the landmarks are less reliable in the <1 year age group, there are alternate ways to perform ventricular cannulation in this age group. The coronal sutures are palpated with ease when the anterior fontanelle is opened. It is, therefore, easier to palpate the coronal suture in children under one year of age, and one does not rely too much on the traditional morphometric points in these patients. In older age groups, the fontanelles would have already closed, making it difficult to palpate the coronal suture; thus, the traditional morphometric points are relied on in these patents (anecdotal communication of R.H).

3.5.2. Morphometric analysis of Frazier's point

In the present study, Frazier's point was located between 60.9mm to 82.8m (mean±SD: 67.9±4.75mm) superior to the inion and 25.9mm to 41.4mm (mean±SD: 32.4±4.61mm) lateral to the midline in scaphocephalic patients (Table 1). The findings show that the location of Frazier's point varies among scaphocephalic patients. On comparison with the traditionally described craniometric point in the literature, the distance superior to the inion was observed to be most affected in patients with scaphocephaly. This is probably due to the compensatory AP expansion of the skull that occurs in these patients. The distance lateral to the midline also varied considerably. This may be attributed to the altered morphology of the occiput due to posterior deformities characteristic of scaphocephaly, including occipital protrusion and narrowing. The clinical implication of this finding is that the traditional morphometric points for occipital ventricular access are not reliable in scaphocephalic patients, particularly the distance superior to the inion. Neuronavigation is therefore recommended in these patients.

An expected trend with regard to the degree of severity was noted, where the mean distance superior to the inion increased as the severity increased. Conversely, the mean distance lateral to the midline increased as the severity decreased. However, this did not reach statistical significance. Although from this observation, it can be inferred that as scaphocephaly increases in severity, the head elongates in the AP plane and narrows in the coronal plane. This increase results in the further dispositioning of these points.

The limitations of the current study include the relatively small sample size as well as the absence of normal data for non-hydrocephalus and non-craniosynostosis patients in the paediatric population to compare findings with.

3.6.Conclusion

This present study employs a novel method and the results obtained are also novel for this particular cohort of patients. The study provides mean values and ranges for consideration in the techniques for ventricular catheter placement in patients with scaphocephaly. The results emanating from this study indicate that the traditional landmarks for ventricular access are relatively unreliable in these patients (particularly in those less than one year of age). This study found that the parameters measured in the AP plane were more affected than those measured lateral from the midline in patients with scaphocephaly. A patient-tailored approach using neuronavigational techniques is usually recommended in these patients. However, in the event that neuronavigation is unavailable, these findings will allow neurosurgeons to modify the approaches used in ventricular cannulation to suit patients with scaphocephaly.

3.7. Disclosures

Sources of Support: National Research Foundation (NRF), Grant number: 122998, Grantee: Vensuya Bisetty. The financial assistance of the NRF towards this research is hereby acknowledged. Opinions expressed and conclusions arrived at, are those of the author and are not necessarily to be attributed to the NRF.

The authors have nothing to disclose.

Acknowledgments: The authors wish to acknowledge Dr Partson Tinarwo for his assistance with statistical analysis.

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CHAPTER 4: SYNTHESIS

Chapter 3 analysed the morphometry of Kocher's and Frazier's points within a select South African cohort of scaphocephalic patients, using known craniometric and surface anatomical landmarks. The study provided novel morphometrical data for consideration in the techniques used for ventricular catheterization procedures in patients with scaphocephaly.

Contributions of this chapter

This chapter elaborated on the main findings of Chapters 2 and 3 and concluded the findings of the morphometry of the cranial fossae as well as the ideal location of Kocher's and Frazier's points in patients with scaphocephaly in a select South African population. Limitations encountered during the study as well as potential areas for future research have been identified and explained.

4.1.Synthesis

This retrospective study comprised two manuscripts: the first manuscript analysed the basic morphometry of the cranial fossae, viz. maximum lengths and widths of the anterior, middle and posterior cranial fossa (ACF, MCF and PCF) in patients with scaphocephaly and controls. The second manuscript analysed the morphometry of Kocher's and Frazier's points in patients with scaphocephaly, using known craniometric and surface anatomical landmarks.

The study sample of Manuscript 1 (n=38) included Computed Tomography (CT) scans of consecutive patients with a radiologically confirmed diagnosis of scaphocephaly who had presented to the craniofacial unit at the Inkosi Albert Luthuli Central Hospital (IALCH) between January 2014 and June 2020; and fine slice CT scans of non-affected/normal paediatric patients, who underwent clinically indicated CT scanning of the head for non-head-shape indications and had comparable CT scan information available. Of the 37 scaphocephalic patients who presented to the clinic during the 6-year period, 24 (n=24) had met the criteria for inclusion in the study. Of the 39 non-affected/normal paediatric patients that were identified, 14 (n=14) met the inclusion criteria for controls. The study sample for Manuscript 2 consisted of the CT scans of the selected scaphocephalic patients (n=24) only.

According to the literature, scaphocephaly is more prevalent in males than in females, with a ratio of approximately 2-4:1 (Ciurea *et al.*, 2011; Massimi *et al.*, 2012; Tatum *et al.*, 2012; Kajdic *et al.*, 2017; Calandrelli *et al.*, 2020). This prevalence is reflected in the scaphocephaly cohort, which comprises 20 males and four females. A cephalic index (CI) of <70% is generally used to describe scaphocephaly (Massimi *et al.*, 2012; Tatum *et al.*, 2012). However, in the present study, four patients with scaphocephaly had a CI between 70-74%. These patients were considered to have presented with a mild form of the deformity. All control patients had a CI >70% and an open sagittal suture.

4.1.1. Manuscript 1 - Morphometric analysis of the cranial fossae in scaphocephalic patients: An anatomical basis

A thorough search of the relevant literature yielded only one article related to the morphometry of the cranial base and its fossae in scaphocephalic patients (Calandrelli *et al.*, 2020), which only investigated the lengths of the cranial fossae. No previous literature reported on the width of the cranial fossae in patients with scaphocephaly. Furthermore, a dichotomy of opinion exists with regards to the description of the ACF, MCF and PCF lengths in the consulted literature.

Calandrelli *et al.* (2020) used endocranial anatomical landmarks to measure the length of the ACF, MCF and PCF. These measurements, however, did not reflect the true lengths of the cranial fossae as they were captured diagonally. This study states that the midline anteroposterior (AP) and transverse diameter measurements between fixed anatomical points better represent lengths and widths, respectively. Therefore, anatomical landmarks characteristic of each cranial fossa were chosen accordingly, between which midline AP and transverse diameters were measured to obtain the true lengths and widths of the cranial fossae, respectively.

This study found that the lengths of the cranial fossae were generally larger in scaphocephalic patients, with only the lengths of the ACF and PCF being statistically significant (p=0.041; p=0.018) (Page 51: Chapter 2, Table 2).When compared by the degree of severity, the ACF and PCF lengths were significantly greater (ANOVA, p=0.033; post-hoc, p=0.013 and ANOVA, p=0.015; post-hoc, p=0.036) in scaphocephalic patients within the severe group as opposed to the control group (Page 54: Chapter 2, Table 5; Page 55: Chapter 2, Fig. 4A and B). The differences in the MCF length in scaphocephalic patients were statistically non-significant (p=0.278; p=0.774) (Page 51: Chapter 2, Table 2). The widths of the ACF, MCF and PCF were generally smaller in patients with scaphocephaly, but this did not reach statistical significance (p=0.568; p=0.410 and p=0.179; p=0.111) (Page 51: Chapter 2, Table 2). These findings reveal that the majority of the changes occur in the ACF and PCF, with very little change in the MCF. Furthermore, this study highlights that most of the change occurs along the AP plane, and very little change occurs in the transverse plane. These changes may be attributed to the compensatory AP growth that occurs in scaphocephaly, together with the varying degrees of frontal bossing and/or occipital protrusion.

4.1.2. Manuscript 2 - A morphometric analysis of Kocher's and Frazier's points in a select South African scaphocephalic population

There is an abundance of literature that focuses on optimizing the ideal trajectory and catheter length with regard to ventricular access, but there have been few studies that attempted to specifically validate or update the cranial entry points, despite ventricular catheterization being a frequently performed procedure in neurosurgery (Meybodi *et al.* 2017; Deora *et al.*, 2020). However, these studies mostly provide data based on an adult population. If the study did comprise a paediatric cohort (Ikeda *et al.*, 2012; Deora *et al.*, 2020), no values were provided and hence there is no specific data with regards to Kocher's and Frazier's points in the literature for the aforementioned population. Therefore, this study infers from the literature on whether the

traditional craniometric points for ventricular access are reliable to use if these procedures were to be performed in patients with scaphocephaly.

Although the methodology employed in Manuscript 2 is complex, it is reproducible as each step is described in detail. In the event of neuronavigation being unavailable, the methodology outlined could be adopted, provided that compatible software is used and the relevant anatomical and craniometric landmarks used to the measure the dimensions of Kocher's and Frazier's points in pre-operative CT scans can be accomplished.

For ease of reference to the literature in this chapter, the SI units of the results from the present study have been converted from mm to cm.

The present study found that Kocher's point is located between 9.16cm and 14cm posterior to the nasion, and 2.05cm and 3.46cm lateral to the midline in patients with scaphocephaly. These findings indicate that considerable variation exists in the distance posterior to the nasion, i.e., in the AP plane among patients with scaphocephaly. When compared to the traditionally described craniometric point in the consulted literature (Page 20: Chapter 1, Table 2), these findings show that the range for Kocher's point posterior to the nasion in patients with scaphocephaly falls slightly out of the range that is described. The distance from the midline, i.e., in the coronal plane, was found to have remained within the described range. A statistically significant increase in the distance posterior to the nasion was reported between patients in the <1 year age group and those in the older age groups (1-<3, 3-<6 and 6-<9 years) (post-hoc, p=0.001; 0.001; 0.002) (Appendix B). A statistically significant increase in the distance lateral to the midline was reported between scaphocephalic patients under three years of age and those over the age of 3 years (post-hoc, p=0.002; 0.030) (Appendix B).

The results of the current study show that Frazier's point is located between 6.09cm to 8.28cm, superior to the inion and 2.59cm to 4.14cm lateral to the midline in patients with scaphocephaly. The findings of the present study show that the location of Frazier's point varies among the South African scaphocephalic population. On comparison with the traditionally described craniometric point in the literature the distance superior to the inion, i.e., in the AP plane, was observed to be most affected in patients with scaphocephaly.

The disposition of these points, especially in the AP plane, is probably due to the compensatory elongation of the skull that occurs in the AP direction in scaphocephalic patients. It may also be

attributed to the varying degrees of the secondary anterior and posterior deformities (frontal bossing and occipital bulging) that typically accompany scaphocephaly.

4.2.Limitations

A significant limitation of both manuscripts of this thesis is the relatively small sample size in both scaphocephaly and control groups. Another limitation is the absence of an age-, sex-, and population-matched control group. These limitations hindered detailed statistical analyses. The small sample size of the control group is attributed to the fact that CT scans are not routinely performed in paediatric patients due to the radiation involved; therefore, obtaining CT material in this regard was difficult.

In addition, there is an absence of normal data for non-hydrocephalus and non-craniosynostosis patients in the paediatric population. Therefore, there were no normal-patient data to compare findings with. It is difficult to obtain radiological material from such patients because, due to the radiation involved, CT scans are not routinely performed in paediatric patients.

4.3.Recommendations

Further studies with a larger sample size are recommended by (i) adjusting the time frame for retrospective analysis (possibly a ten-year retrospective investigation), (ii) including CT scans of scaphocephalic patients from other craniofacial centres in the country (this will also provide a more inclusive representation of a South African scaphocephalic population as the present study provides data based on a single unit) and (iii) including normal-patient reference CT material from other institutions to expand the control database. Future research can be carried out in scaphocephalic patients post corrective craniofacial surgery. This can be used as a possible method to evaluate the results of surgery.

In addition, future studies could investigate the morphometry of Kocher's and Frazier's points in the normal paediatric population as well as in patients with other types of craniosynostosis. Further studies could also be done taking into account the morphology and morphometry of the lateral ventricles in scaphocephalic patients. This study only reported on two of the various craniometric points described for ventricular access; future studies could investigate the morphometry of the other described points in patients with scaphocephaly. This investigation also only provides data on the right side due to the right lateral ventricle being accessed; future studies

may document these points on the left side by accessing the left ventricle and compare those findings with the results obtained from this study.

4.4.Conclusions

This study presents novel morphometric data based on a select South African scaphocephalic population. It provides an insight into understanding the changes that occur at the cranial fossae in scaphocephalic patients when compared to normal. The morphometric dimensions obtained indicate that majority of the deformity presents in the ACF and PCF, especially with elongation along the AP plane (lengths) in patients with scaphocephaly. Very few changes were observed in the transverse plane (widths) in scaphocephalic patients compared to the controls. These findings could assist craniofacial surgeons in deciding on the type of corrective surgery to be performed.

Additionally, the study provides morphometric data for consideration when accessing the ventricles of patients with scaphocephaly. It provides a range at which the Kocher's and Frazier's point burr holes can be ideally located in patients with scaphocephaly. Results emanating from this study show that the traditional landmarks for used ventricular access are not reliable in these patients and must therefore be accommodated for. This study found that the parameters measured in the AP plane were more affected than those measured lateral from the midline in patients with scaphocephaly. The findings of this study will aid neurosurgeons, in-training as well as experienced, in deciding on the best approach for safe ventricular catheterization in patients with scaphocephaly. An individualized treatment approach using guided techniques is usually recommended in these patients. However, in the event that neuronavigation is unavailable, these findings will allow neurosurgeons to modify the approaches used in ventricular cannulation to suit patients with scaphocephaly.

The findings of this study illustrate that most of the changes occur along the same pattern at which the deformity presents. Overall, this study attempted to fill a gap in the literature by providing an anatomical basis of different aspects related to this rare congenital deformity, i.e., the cranial fossae and ventricular access points. This study adds to the existing body of knowledge on sagittal synostosis by providing previously unrecorded morphometric data within a select South African population. In addition to having the potential to aid craniofacial and neurosurgeons, this research contributes to the understanding of the changes that occur with regard to the cranial fossae and ventricular access points in scaphocephaly from an anatomical perspective.

4.5.References

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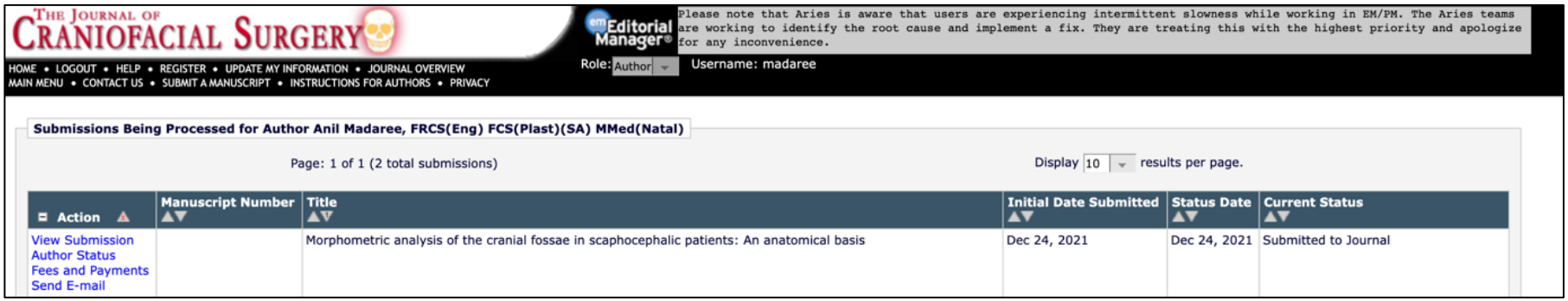
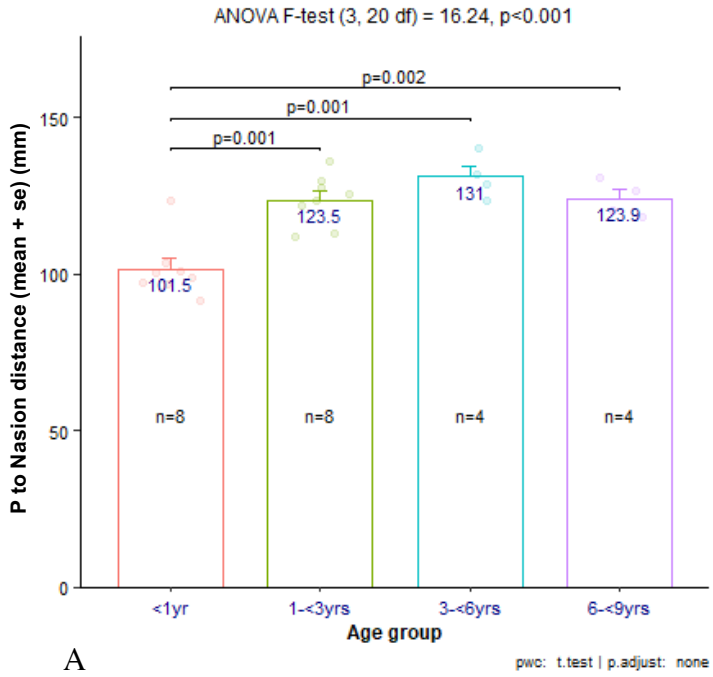
APPENDICES

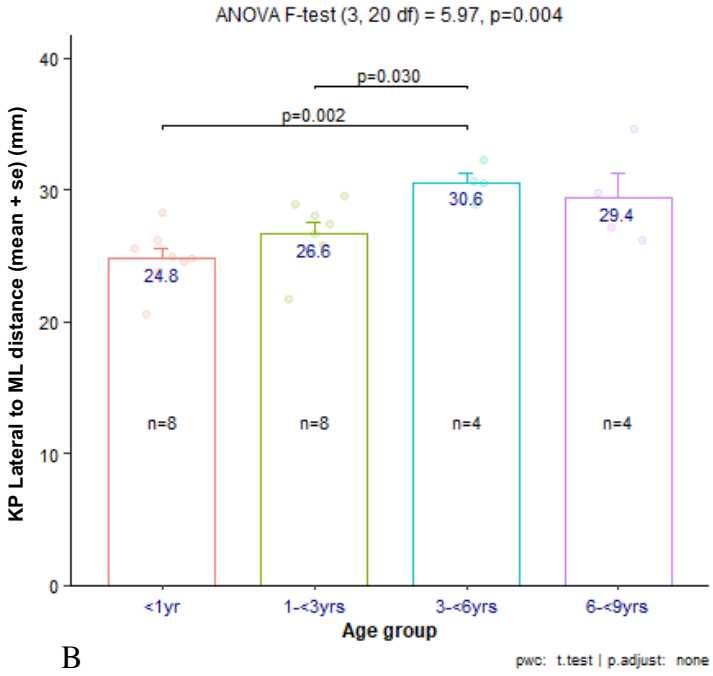
Appendix A: Journal submission



Appendix B: Post-hoc analyses



A



B

Mean distance of Kocher's point compared by age: **A.** posterior to nasion **B.** lateral to midline.

KEY: P= Posterior, KP= Kocher's Point, ML= Midline.

Appendix C: Full ethical approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

13 December 2020

Miss Vensuya Bisetty (216000885)
School of Lab Med & Medical Sc
Westville

Dear Miss Bisetty,

Protocol reference number: BREC/00002084/2020
Project title: Scaphocephaly in South Africa: a morphometric analysis of the cranial fossae and select ventricular access points
Degree: MMedSci

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application.

The conditions have been met and the study is given full ethics approval and may begin as from 13 December 2020. Please ensure that outstanding site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is subject to national and UKZN lockdown regulations dated 10th November 2020, see (http://research.ukzn.ac.za/Libraries/BREC/BREC_Lockdown_Level_1_Guidelines.sflb.ashx). Based on feedback from some sites, we urge PIs to show sensitivity and exercise appropriate consideration at sites where personnel and service users appear stressed or overloaded.

This approval is valid for one year from 13 December 2020. To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on 09 February 2021.

Yours sincerely,

[redacted]

Prof D Wassenaar
Chair: Biomedical Research Ethics Committee

Biomedical Research Ethics Committee
Chair: Professor D R Wassenaar
UKZN Research Ethics Office Westville Campus, Govan Mbeki Building
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Website: http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

Appendix D: UKZN Gatekeeper permission

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

13 November 2020

To whom it may concern

This letter serves to inform that the School of Laboratory Medicine and Medical Sciences grants **V Bisetty (216000885)** permission to conduct the study referenced **BREC/00002084/2020** titled: **Scaphocephaly in South Africa: a morphometric analysis of the cranial fossae and select ventricular access points**. This permission is only valid for the time period stipulated in the BREC application.

Sincerely

[redacted]

Dr A Khathi

Academic Leader Human Body Form and Function Theme

Room E3-408
Department of Human Physiology
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Appendix E: IALCH Gatekeeper permission

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:
INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
OFFICE OF THE MEDICAL MANAGEMENT
Private Bag X03, Mayville, 4058
800 Vusi Mzimela (Bellair) Road, Mayville,4091
Tel: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@ialch.co.za

Reference: BREC/00002084/2020
Enquiries: Medical Management

17 November 2020

Ms V Bisetty (216000885)
School of Lab Medicine & Medical Science
Westville

Dear Ms Bisetty

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **Scaphocephaly in South Africa: a morphometric analysis of the cranial fossae and select ventricular access points.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted]

Dr A Harrichandparsad
Clinical Care Manager
Office of the Medical Manager
IALCH

GROWING KWAZULU-NATAL TOGETHER

KWAZULU-NATAL PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

DIRECTORATE:

INKOSI ALBERT LUTHULI CENTRAL HOSPITAL
Private Bag X03, Mayville, 4058
800 Vusi Mzimela (Bellair) Road, Mayville,4091
Tel: 031 240 1059 Fax: 031 240 1005 Email: Ursula.john@ialch.co.za

OFFICE OF THE MEDICAL MANAGEMENT

Reference: BREC/00002084/2020
Enquiries: Medical Management

17 November 2020

Ms V Bisetty (216000885)
School of Lab Medicine & Medical Science
Westville

Dear Ms Bisetty

Re: Approved Research: Ref No: BREC/00002084/2020: Scaphocephaly in South Africa: a morphometric analysis of the cranial fossae and select ventricular access points.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

[redacted]

Dr A Harrichandparsad
Clinical Care Manager
Office of the Medical Manager

GROWING KWAZULU-NATAL TOGETHER

Appendix F: DOH Permission

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritzburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

NHRD Ref: KZ_202011_029

Dear Ms V. Bisetty
(UKZN)

Approval of research

1. The research proposal titled **'Scaphocephaly in South Africa: A morphometric analysis of the cranial fossae and select ventricular access points'** was reviewed by the KwaZulu-Natal Department of Health (KZN-DoH).

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. *All research conducted in KwaZulu-Natal must comply with government regulations relating to Covid-19. These include but are not limited to: regulations concerning social distancing, the wearing of personal protective equipment, and limitations on meetings and social gatherings.*
   b. *Kindly liaise with the facility manager BEFORE your research begins in order to ensure that conditions in the facility are conducive to the conduct of your research. These include, but are not limited to, an assurance that the numbers of patients attending the facility are sufficient to support your sample size requirements, and that the space and physical infrastructure of the facility can accommodate the research team and any additional equipment required for the research.*
   c. *Please ensure that you provide your letter of ethics re-certification to this unit, when the current approval expires.*
   d. *Provide an interim progress report and final report (electronic and hard copies) when your research is complete to* ***HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200*** *and e-mail an electronic copy to hrkm@kznhealth.gov.za*
   e. *Please note that the Department of Health shall not be held liable for any injury that occurs as a result of this study.*

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

Clutge

Dr E Lutge
Chairperson, Health Research Committee
Date: 02/12/2020

Fighting Disease, Fighting Poverty, Giving Hope

Appendix G: Data sheet 1 sample

Patient ID	Sex	Race	Age (Months)	Cephalic Length (mm)	Cephalic Width (mm)	Cephalic Index (%)

(Data is available on request)

Appendix H: Data sheet 2 sample

Patient ID	Sex	Race	Age (Months)	ACF	
				Length (mm)	Width (mm)

(Data is available on request)

Appendix I: Data sheet 3 sample

Patient ID	Sex	Race	Age (Months)	MCF (Right)	
				Length (mm)	Width (mm)

(Data is available on request)

Appendix J: Data sheet 4 sample

Patient ID	Sex	Race	Age (Months)	MCF (Left)	
				Length (mm)	Width (mm)

(Data is available on request)

Appendix K: Data sheet 5 sample

Patient ID	Sex	Race	Age (Months)	MCF (Left)	
				Length (mm)	Width (mm)

(Data is available on request)

Appendix L: Data sheet 6 sample

Patient ID	Sex	Race	Age (Months)	PCF	
				Length (mm)	Width (mm)

(Data is available on request)

Appendix M: Data sheet 7 sample

Patient ID	Sex	Race	Age (Months)	Kocher's Point	
				Posterior to nasion (mm)	Lateral to midline (mm)

(Data is available on request)

Appendix N: Data sheet 8 sample

Patient ID	Sex	Race	Age (Months)	Frazier's Point	
				Superior to inion (mm)	Lateral to midline (mm)

(Data is available on request)

Appendix O: Turnitin report

Masters Thesis (Vensuya Bisetty)

ORIGINALITY REPORT

8%	3%	8%	0%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Joastin Naidoo, Rohen Harrichandparsad, Lelika Lazarus. "Anatomical Configurations of Dominant Anastomotic Veins of the Superficial Cortical Venous System", Research Square Platform LLC, 2021 Publication	1%
2	"Textbook of Pediatric Neurosurgery", Springer Science and Business Media LLC, 2020 Publication	1%
3	Peter J Morone, Michael C Dewan, Scott L Zuckerman, R Shane Tubbs, Robert J Singer. "Craniometrics and Ventricular Access: A Review of Kocher's, Kaufman's, Paine's, Menovksy's, Tubbs', Keen's, Frazier's, Dandy's, and Sanchez's Points", Operative Neurosurgery, 2020 Publication	1%
4	researchspace.ukzn.ac.za Internet Source	1%
5	archive.org	