MORPHOMETRIC STUDIES ON SEXUAL DIMORPHISM, VARIATIONS AND DIMENSION OF FORAMEN TRANSVERSARIUM IN A KWAZULU-NATAL POPULATION, SOUTH AFRICA

By

AUNG KHAING ZAW

215080633

UNIVERSITY OF KWAZULU-NATAL

A dissertation submitted in fulfilment of the requirement for the degree of Master of Medical Sciences in Anatomy

In the Discipline of Clinical Anatomy, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

2019

PREFACE

This research was carried out in the Discipline of Clinical Anatomy, School of Laboratory Medicine and Medical Sciences, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa from 2016 to 2019, under the supervision of Professor O. O. Azu, Dr E. C. S. Naidu and Dr C. Rennie.

Candidate______________________ Date 22. 11. 2019

Supervisor ______________________ Date 22. 11. 2019

Co-supervisor[1] ______________________ Date 22. 11. 2019

Co-supervisor[2] ______________________ Date 22. 11. 2019

DECLARATION

I, Dr Aung Khaing Zaw with student number 215080633 declare;

1. That this thesis is the product of my research work
2. That it has not been submitted to UKZN or any other institution for purpose of obtaining an academic qualification, whether by myself or any other party
3. That this thesis does not contain other person's writing, data. Pictures or other information, unless specifically acknowledged as being sourced from other persons or researchers.
4. Where other written sources have been quoted then;
   - i. Their words have been re-written, but the general information attributed to them has been referenced
   - ii. Where their exact words have been used then it has been properly referenced in the reference section

-------------- ------------- **22. 11. 2019**

Aung Khaing Zaw Date

DEDICATION

This work is dedicated to my wife, Dr Khin Su-Le Han, my mother, Tin Mya, my father (of blessed memory), Than Hlaing, my parents-in-law, Dr Khine Swe Swe Han & Khin Aung Han, my brother, Dr Tint Htoo Naing and my brother-in-law, Dr Pye Maung Han.

ACKNOWLEDGEMENT

I thank the Lord Buddha for teaching me the righteous way of living and hardworking.

My sincere appreciation goes to my supervisor Prof O.O. Azu and my co-supervisors Dr E. C. S. Naidu and Dr C. Rennie for their mentorship and tutelage throughout out this program and for their professional expertise to fulfil my master degree in clinical anatomy.

Special appreciation to my wife for her unflinching support, my parents-in-law, my brother-in-law, my mother, my aunts and my little brother for their courage, support and understanding. In loving memory of my dad, you are always on my mind and thanks for everything.

I appreciate the efforts and assistance of Mr. Ugochukwu offor and Dr Koffi Kuame to the completion my project.

I am most indebted to Mr. Samuel Olojede and Mr. Lawal Sodiq who offered their precious time to work on my thesis and encouraged me to finish my dissertation.

My unalloyed appreciation goes to Mr. Partson Tinarwo (Biostatistician) for his contribution to the statistical analysis of this research work. I am grateful to all staff members of Clinical Anatomy discipline who have in one way or the other contributed to the completion of this Master’s program.

Thanks to the Dean and the members of staff from college of health sciences.

TABLE OF CONTENT

Content Page

LIST OF FIGURES

List of figures from manuscript

LIST OF TABLES

LIST OF ACRONYMS AND ABBREVIATIONS

AM	Anterior margin
APD	Anteroposterior diameter
BREC	Biomedical Research Ethics Committee
C1	Cervical vertebral one
C2	Cervical vertebral two
C3	Cervical vertebral three
C6	Cervical vertebral six
C7	Cervical vertebral seven
CT	Computed tomography
DF	Double foramen
DFT	Double foramen transversarium
FT	Foramen transversarium
FURD	Foramen-uncus ridge distance
HFT	Hypoplastic foramen transversarium
IFD	Interforaminal distance
KZN	KwaZulu-Natal
MB	Markus Bader
MRI	Magnetic Resonance Imaging
MSCs	Musculoskeletal conditions
PM	Posterior margin
TD	Transverse diameter
TFT	Triple foramen transversarium
TVAI	Traumatic vertebral artery injury
UKZN	University of KwaZulu-Natal
V1	Vertebral artery in pre foraminal
V2	Vertebral artery in foraminal
V3	Vertebral artery in dura
V4	Vertebral artery in intradural
VA	Vertebral artery
VV	Vertebral vein

ABSTRACT

The foramen transversarium (FT) of the cervical vertebrae serves as an essential landmark in medical imaging procedure and surgery, owing to their anatomical structure in relation to the associated neurovascular bundles. The aim of this study was to analyse the morphometric parameters and variations of the FT with regards to sexual dimorphism, laterality and age within the KwaZulu-Natal (KZN) population, South Africa.

One hundred and thirty (130) dried human typical cervical bones from KZN population of known sex and age (67 males and 63 females with age ranges from 12 to 89) without any degeneration or deformity were sourced from the bone collection at the Discipline of Clinical Anatomy, Nelson Mandela School of Medicine, University of KwaZulu-Natal (UKZN). The morphometric analyses were performed using Markus Bader (MB) Ruler, the digital screen ruler and subjected to RStudio statistical analysis.

The results indicated that the morphometric parameters of the FT were greater in males compared to females ($p< 0.05$). The values of the right sides were higher than that on the left sides except, for the transverse diameter where higher values were observed on the left side of male specimens. Based on the shape of normal FT inspection, the type 1 was predominant (43.85%) shapes, followed by type 3 (23.08%) and least common were type 2 and type 7 (0.77%) on the left side. Type 1 had the higher value (46.16%) on the right side, followed by type 3 (20%) and, type 2 was the least in this study. The variation in number of FT in relation to sex revealed the presence of normal foramen (62.31%, male with 30.77% and female with 31.54%) and double foramen (36.92%, male with 20% and female with 16.92%). More so, it was also observed that, the frequency of bilateral double foramen was common in males (11.54%) compared to females (6.92%).

The result of this study has demonstrated that risk of injury to neurovascular structures associated with FT may be common on the left side, in female and especially in age groups less than < 20 and ≥ 60 years of age.

Keywords: Foramen Transversarium, Cervical vertebrae, Variations, Sexual Dimorphism, Morphometric

CHAPTER ONE

CHAPTER ONE

1. Introduction

Musculoskeletal conditions (MSCs) of the neck region and upper extremity of the body are most frequent job-related disorders globally (Hoe *et al.*, 2018). MSCs such as low back pain, neck pain, bone fractures and osteoarthritis have been reported as major contributors to disability worldwide (Briggs *et al.*, 2018). Different degree of pains, functional disability and limitations to mobility are features of MSCs.

The major structures affected by these conditions are muscles, nerves, arteries and bones. Literature have reported that the cases of neck pain could be mechanical or musculoskeletal in origin (Barnsley, 2015), indicating that they arise through involvement of cervical structures by neoplastic, inflammatory, or infectious diseases.

Foramen transversarium (FT) are bony features of the cervical vertebrae, which are found in the transverse process of cervical vertebrae. These foramina are anatomically relevant as they provide bony passages for several anatomical structures such as the vertebral artery (VA), vertebral vein (VV) and sympathetic nerves. Literature have documented anatomical variations based on shape, size, absent, duplicated as well as hypoplastic forms (Aziz and Morgan, 2018).

The variation of the vertebral column is affected by diversity of embryological malformations. These developmental malformations result into developmental variation, error in fusion, segmentation abnormality and malformation in vertebrae. The extent of these anomalies may be manageable or chronic with systemic complications (Chaturvedi *et al.*, 2018). It is therefore necessary to be aware of the outcome, complications and the cost effects of the spine surgery as a result of vertebral column associated injuries or deformity in order to curtail the upsurge in MSCs (Yeramaneni *et al.*, 2016).

1.1 Vertebral column

There are 33 identifiable vertebrae in a human being, which are further divided into five groups; cervical, thoracic, lumbar, sacral and coccygeal vertebrae based on their features and position. The cervical vertebrae are seven in number, thoracic are 12, lumbar are five, sacral are five in number but fused together to form one bone known as the sacrum and there are four coccygeal that are fused together as well to form the coccyx. Structurally, characteristics of a typical vertebra are vertebral body and a posterior vertebral (neural) arch. The vertebral arch of each vertebra possesses the pedicles, laminar and processes (transverse, spinous, superior and inferior articular processes) (Drake *et al.*, 2014). (Figure 1)

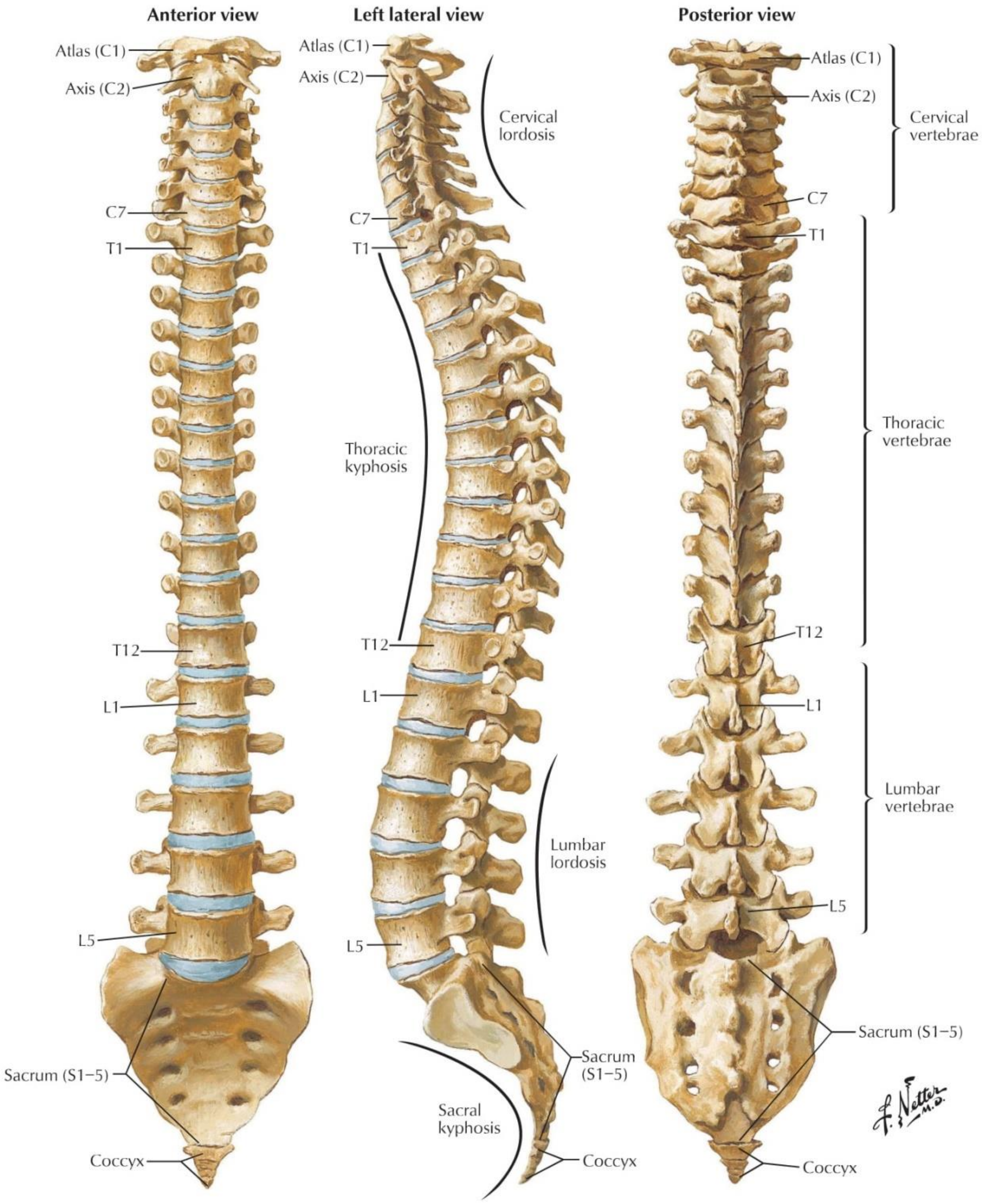

Figure 1: The vertebral column adapted from Netter (2014)

1.2 Anatomy of cervical vertebra

The cervical vertebrae are the first set of the bones in the vertebral column, it comprises of seven bones starting from the base of the skull (Newell, 2008). It continues with thoracic vertebrae below and due to its features, it is the most mobile region of the column (Arıncı and Elhan, 2014).

It presents with different characteristics that differentiate it from other vertebral bones. Between the arch and body of the vertebrae, there is an opening called vertebral foramen (Ratliff and Cooper, 2003). Adult cervical bones possess a significant feature, the foramen transversarium (FT) which set them apart from the rest of the vertebrae (Akhtar *et al.*, 2015).

Cervical vertebrae are divided into typical and atypical. The third, fourth, fifth and sixth have similar features viz. a small, broad vertebral body, short and bifid spinous process, hence considered as typical. Additionally, first, second and seventh also present special characteristics and are referred to as atypical. The first cervical vertebra possesses a transverse process that is longer than other cervical vertebrae except the seventh cervical vertebra. Furthermore, there is absence of the vertebral body in the first cervical vertebra. The second cervical vertebra presents a conical projection on the superior surface of the body known as the dens, with large ovoid articular facets on both sides. There is a long spinous process present in the seventh cervical vertebra in addition to other features (Standring, 2008). (Figure 2)

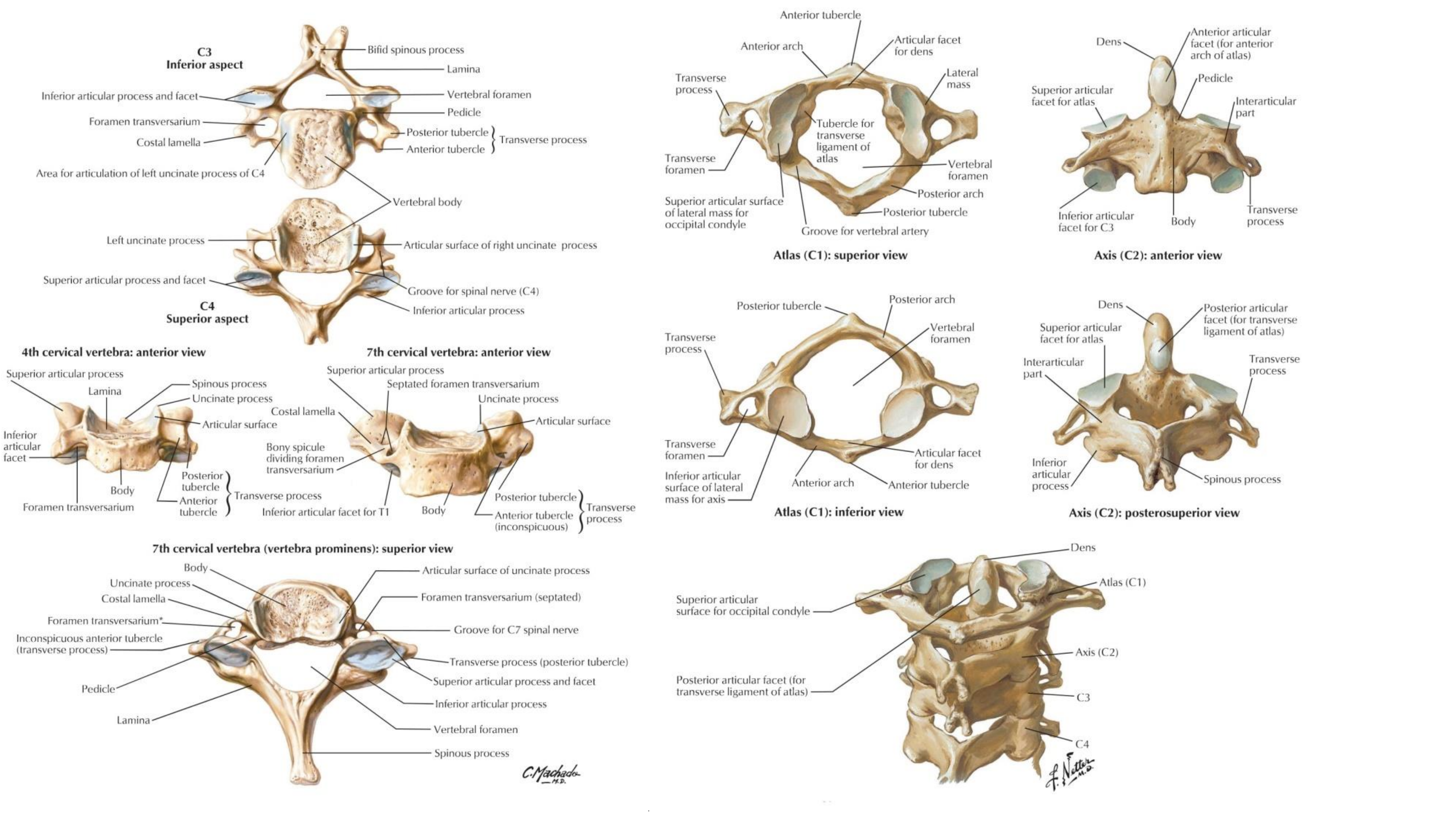

Figure 2: Diagram of the typical and atypical cervical bones adapted from Netter (2014)

1.3 Embryology of vertebrae

The vertebral column presents the most well-arranged vertebral body, in which series of segmental organization of vertebral bones, joints and ligaments are found. During the developmental period from week 4, the vertebrae are derived from the primitive streak, which give rise to the part of embryonic paraxial mesoderm known as the somites (Scaal, 2016).

During embryogenesis, each somite gives rise to the dermomyotome, which differentiates into the three major components; the dermis of the skin, the skeletal muscle and the sclerotome that further gives rise to the components of vertebral and the associated joints (Fleming *et al.*, 2015).

Furthermore, the medially positioned sclerotome develops into major parts of the somite. The somite migrates to surround the midline notochord and neural tube. The cells differentiate first into chondrocytes that deposit a cartilage intermediate, and then into osteoblasts that replace the cartilage with bone by a process known as endochondral ossification to give rise to the vertebral arches, the dorsal part around the spinal cord and the centra which is the ventral portion that surround the notochord (Peters *et al.*, 1999; Nakashima *et al.*, 2002; Chal and Pourquié, 2009). The development of vertebrae commences at the 4th week of embryonic life with an indication of precartilage stage marking the first stage then proceed with the chondrification stage which indicates the second stage at around 6th week of intrauterine life and to the last stage, the ossification stage at after 10th week of gestational age (Pansky, 1982; Skórzewska *et al*., 2013). There are three primary observable ossification centres during embryological period which are; one centre at the centrum and one centre each in the half of the vertebral arch. More so, five secondary ossification centres are present at puberty in the following areas; one secondary ossification centre seen at each of the tips of transverse process, one centre at the tip of spinous process and remaining two secondary ossification centres are located at annular epiphyses of upper and lower part of vertebral body (Pansky, 1982).

The VA as one of the contents of the FT begins its development during the intrauterine life approximately day 32 and completed by day 40 between the 12.5- and 16-mm stages (Sim *et al.*, 2001, Padget, 1948). (Figure 3)

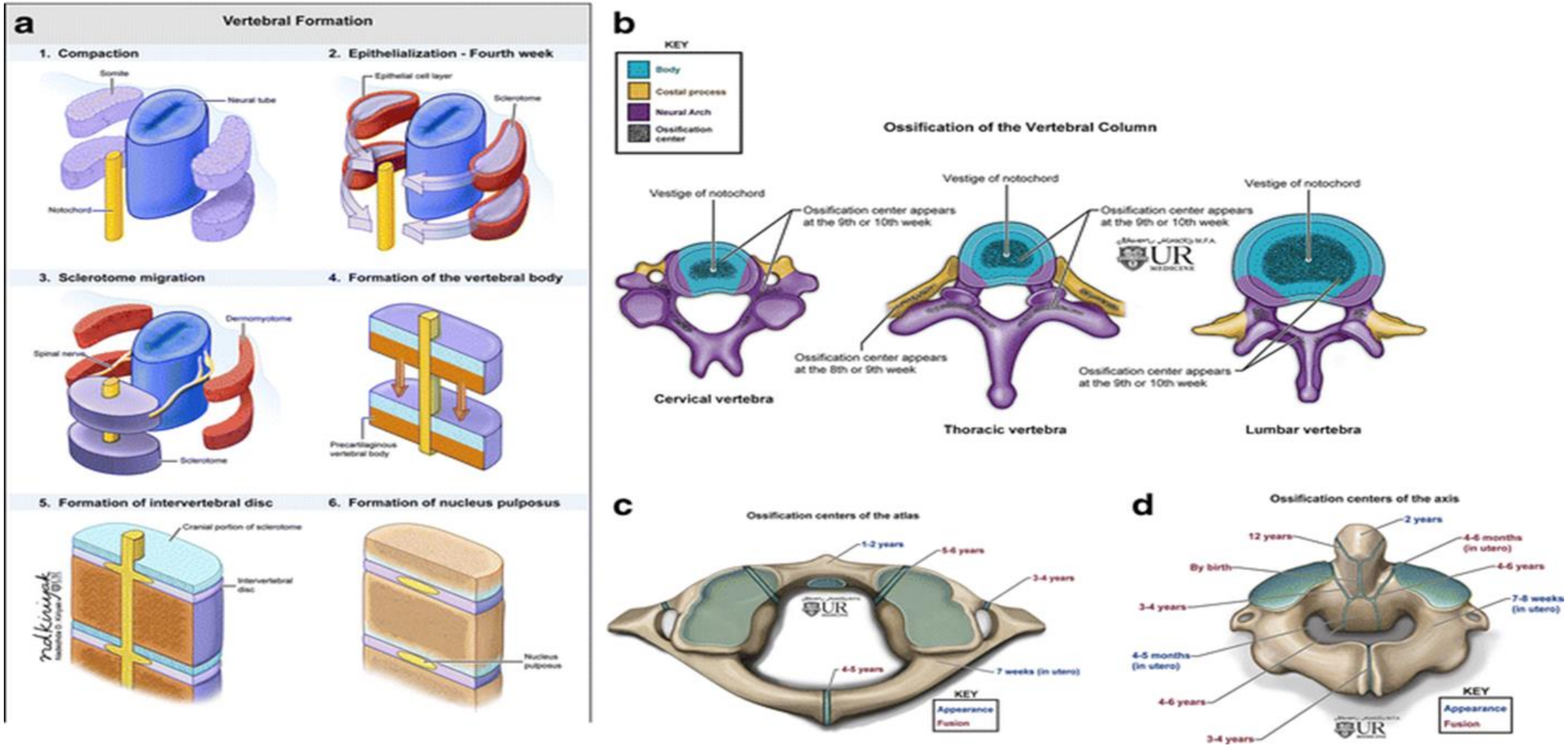

Figure 3: The development of vertebral column adapted from Chaturvedi *et al*. (2018)

1.4 Variations of foramen transversarium

The FT is an important characteristic of the cervical bones (Patra *et al.*, 2015). These foramina present variations in shape, size and in some cases are small, duplicated or even absent (Yadav *et al.*, 2014). VA begins its course at the FT of the sixth cervical vertebra, however, Jovanovic (1990) observed that in 5% of their Canadian sample that occasionally, the VA may begin its course at the seventh cervical foramen.

1.4.1 Shape of foramen transversarium

The shape of FT was classified into five types (type 1 to type 5) according to Taitz *et al.* (1978), while additional classification (type 6 and type 7) were observed by Kimura *et al*. (1985) and Ambali and Jahav, (2017). Type 1 is round, type 2 is elliptical antero-posterior, type 3 elliptical transverse, type 4 elliptical oblique right to left, type 5 elliptical oblique left to right, type 6 irregular and type 7 absent of foramen.

A recent study on the shape of FT revealed that the most common shape was found to be a round FT in the Indian population while the least common shape was found to be elliptical with the main diameter measured antero-posteriorly (Sunitha *et al.*, 2016).

1.4.2 Variation in number of foramen transversarium

Literature have reported different results on the variations of FT, from radiological and bone examinations. Presence of different anatomical variations of FT such as triplicated, duplicated variations has been reported (Kimura *et al.*, 1985; Murlimanju *et al.*, 2011; Zibis *et al.*, 2016). Variations of the FT in relation to the content occupying its length are of clinical significance. Significantly, knowledge about the variations and course of VA, the major content of FT is required in spine surgery because an unpredicted course of VA may lead to a severe clinical condition (Smith *et al.*, 1993).

1.4.2.1 Duplication of the foramen transversarium

Duplication of the FT (double FT) has been largely documented (Zibis *et al.*, 2016). In a study that examined 480 FT, 34 (7.08%) vertebrae with duplication of FT was found in the Indian population (Taitz *et al.*, 1978). In a similar study by Kaya *et al.* (2011) that was carried out in an Ancient Byzantine Jewish population, five out of 22 vertebrae which account for 22.73 % double FT (DFT) was observed. This DFT was unilateral in three (13.63%) and bilateral in two (9.09%) of all the vertebrae considered as well.

Additionally, 15 out of 222 vertebrae with bilateral duplication of FT which accounts for 6.76% was also observed in a Turkish population (Aydınlıoğlu *et al.*, 2001). Similarly, in another study that examined 2000 Tlatelolco Mexican samples, 262 DFT that amounts to 12.41% were recorded (Esquivel, 1975). In another study that considered 100 vertebrae of Japanese population, DFT in 11 (11%) of the vertebrae (Kimura *et al.*, 1985). A recent study by Sangari *et al.* (2015) in 71 vertebrae of unknown race reported the cases of 17 vertebrae (24%) with unilateral duplication and one vertebra (1.04 %) with bilateral duplication of the foramen. The one case (1%) of FT duplication out of 100 vertebrae of polish population was also documented by Wysocki *et al.* (2003) . Asvat (1997) documented DFT cases in 31.33% (94 out of 300 samples) South African Black population and in 56% (56 out of 100 samples) South African White population.

1.4.2.2 Triple foramen transversarium

Triple foramen transversarium (TFT) is a form of multiple foramina resulting from double rib bone element from the same side fusing to the original transverse process (Kimura *et al.*, 1985). Taitz *et al.* (1978) reported that the TFT is a rare variation and in their Indian sample it was found on the left side in one out of 480 vertebrae (0.21%). Murlimanju *et al.* (2011) also found one (0.27%) vertebra out of 363 with triplication in an Indian population specimen. In addition, Rathnakar and Remya (2013) found one (0.71%) out of 140 vertebrae with a TFT on the right side.

1.4.2.3 Hypoplastic foramen transversarium

Hypoplastic foramen transversarium (HFT) refers to bilateral or asymmetric narrowing of the FT. Taitz *et al.* (1978) reported eight out of 480 vertebrae (1.67%) in Indian samples found to be HFT. In another report, Nagar *et al.* (1999) only found one in a sample out of 709 cervical vertebrae of Jewish population studies accounting for 0.14 %.

In addition, Kaya *et al.* (2011) reported one out of 22 cervical vertebrae (4.54%) were HFT in Ancient Byzantine Jewish population . Recently, Yadav *et al.* (2014) found one (0.83%) of the cervical vertebra with a HFT unilaterally, and one (0.83 %) cervical vertebra with a HFT bilaterally in 120 specimens from the Indian population. Sangari *et al.* (2015) observed five vertebrae (7.04 %) with a HFT unilaterally, in a sample of 71 vertebrae of unknown ethnicity. These reports suggest that cervical vertebra with HFT is rare.

1.4.2.4 Absence of foramen transversarium

Studies have documented the absence of FT. Absence of FT 18 (0.9%) out of 2000 vertebrae were reported in a study by Esquivel (1975) on Tlatelolco samples. In addition, Kimura *et al.* (1985) documented 18 (18%) out of 100 cases of absence of FT in Japanese population, where a single case (1%) out of 100 vertebrae of the Polish population was reported by Wysocki *et al.* (2003). Taitz *et al.* (1978) documented four (0.83%) cases out of 480 vertebrae that lack FT in Indian race.

1.5 Clinical relation of foramen transversarium and vertebral artery

VA is the major component occupying the FT with other structures such as sympathetic chain and vertebral vein (VV). The VA originate from the subclavian artery and divided into four parts; V1 (from the subclavian artery to the FT of C6), V2 (passes inside C6–C1 FT), V3 (from the superior aspect of the arch of the C1 to the foramen magnum) and V4(intradurally from the foramen magnum to combine with the VA from opposite side). The VA is the most vulnerable to injury anterior to C7, laterally along C3 to C7, and posteriorly at C1 and C2. Injuries of VA may lead to pathologies such as cerebral ischemia, pseudoaneurysm, thrombosis and embolism. Similarly, traumatic vertebral artery injury (TVAI), a serious clinical condition with difficult diagnosis with regard to VA injury has been identified as one of the VA injuries (Peng *et al.*, 2009).

Regarding the injuries to the divisions of VA, V2 segment is the most commonly affected in adult TVAI (Herrera *et al.*, 2008), while upper V2 and V3 are implicated in infants and children (Wang and Orbach, 2008). (Figure 4)

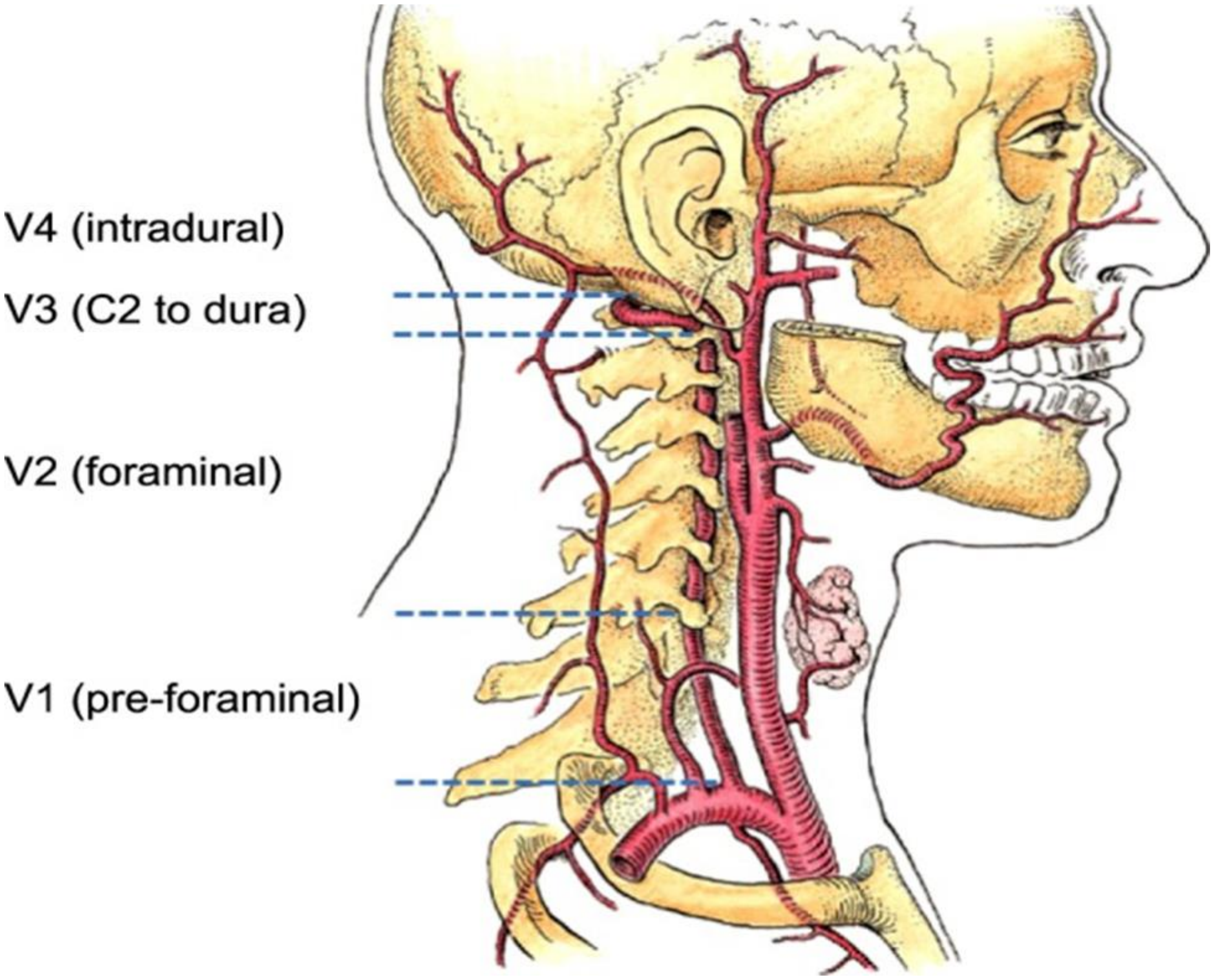

Figure 4: Illustration of the segments of vertebral artery **a**dapted from Shin *et al*. (2014)

The FT protects the V1 and V2 segments of VA. An MRI study by Eskander *et al.* (2010) which examined 250 patients revealed that 8% of the patient's VAs had their segments lying outside the FT.

Variations in size and number of FT have been implicated in several conditions such as, fainting attack, migraine and headache which have been attributed to the entrapment of VA (Ebraheim *et al.*, 1996; Caovilla *et al.*, 2000; Malik *et al.*, 2010).

The variations in FT are in connection with the breadth and the course of the neurovascular bundles that are found there (Das *et al.*, 2005) as well as tortuosity of VA (Aydınlıoğlu *et al.*, 2001). This leads to clinical conditions such as vertebrobasilar insufficiency (Kaya *et al.*, 2011), hearing impairment and neurological symptoms as a result of spasm of either VA or basilar artery (Taitz *et al.*, 1978; Das *et al.*, 2005; Kaya *et al.*, 2011). Movement of the head result from factors such as compression of thyroid cartilage, abnormal bony outgrowths, thickened musculoskeletal structures and absence of FT have been identified as other contributing factors to the cause of vertebrobasilar insufficiency (Tsutsumi *et al.*, 2008). In addition, the pattern of blood flow may be altered owing to the relation between the VA blood flow and the dimensions of FT (Kotil and Kilincer, 2014).

The VA is the major structure found in the FT and it is an important structure in the formation of FT, therefore variations in the course, size and presence of VA will considerably have effect on the variations of FT. In order to determine the extent and the course of the contents of FT, the radiologists, surgeons and physicians require better anatomical understanding about the variations of FT (Murlimanju *et al.*, 2011). Sañudo *et al.* (2003) reported that 10% cases of malpractice involving physicians are based on inadequate knowledge about anatomical variations.

1.6 Problem statement

Knowledge of variations in FT of the cervical vertebrae size and shape are of importance due to its clinical implications, however there has been few studies on sexual dimorphism. The morphometric parameters and variations of FT were previously documented by Malik *et al*., (2010) and these variations maybe of clinically significant. Interestingly, Sañudo *et al.* (2003) reported that approximately 10% of surgical errors by the physicians are due to lack of knowledge in anatomical variation. Recently, several studies on the variations on FT were largely based on using the vernier calliper (Sunitha *et al*., 2016; Guerra *et al*., 2017) as well as CT scan (Sanchis-Gimeno *et al*., 2018; Zibis *et al*., 2018; Tellioglu *et al*., 2018) as a tool for the measurement of FT diameter in bone specimens. Sexual dimorphism is essential in forensic medicine, and to determine the accuracy of particular bone. Malik *et al*., (2010) found significant differences between morphometric parameters in male and female foramen transversarium (FT), with smaller female FT dimensions. The knowledge about the course of VA as the major content of the FT is of serious indication for the screw placement in fixation (Pruthi *et al.*, 2014). Lesion or damage to VA during the surgical manoeuvres around the cervical vertebrae may result in serious clinical conditions. Additionally, the case of hypoplastic VA may alter the pattern of blood flow (Barbagallo *et al.*, 2014). To the best of our knowledge, no or little study has compared the morphometric parameters and variations of FT with respect to age and sex.

1.7 Aim

The aim of this study was to analyse the morphometric parameters and variations of the foramen transversarium (FT) with regards to sexual dimorphism and age of KwaZulu-Natal population, South Africa.

1.8 Objectives

The specific objectives of this study were to;

i. measure the size of the foramen transversarium (FT)

ii. classify the anatomical variations of the FT

iii. compare the anatomical variations according to sex, age and laterality

1.9 Research question

a. Would the FT variations be rare or common in KZN?

b. Would the variations be similar between sex, age and laterality groups?

c. Would the result be different from previous work?

1.10 Significance of study

Different variation and anomalies regarding the morphometric and anatomical parameters of FT may result in entrapment of associated neurovascular structures during movements (Mulla and Pundge, 2015). This compression may result in common MSCs such as neck pain, severity of cerebrovascular conditions, migraines and shoulder pain (Sultana *et al.*, 2015). Imperatively, investigations on the FT variation and morphometric parameters are of clinical significance because of the diameter of FT, associated structures, especially VA blood flow and that of the FT (Kotil and Kilincer, 2014). Therefore, morphometric and anatomical investigation of the FT variations with respect to age, sex and laterality is of clinically significant in radiological assessment, clinical diagnosis and management of MSCs associated with musculoskeletal structures.

Materials and Method

Materials

One hundred and thirty (130) dried human cervical bones without any degeneration or deformity were used for this study. The typical cervical bones from the KwaZulu-Natal population that included 67 Males and 63 Females with an age range from 12 to 89 years of age were sourced from the bone collection at Discipline of Clinical Anatomy, Nelson Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa. All the intact cervical vertebrae without any traumatic disorders, deformity or degeneration were included in this study. Ethical approval for this investigation was received from Biomedical Research Ethics Committee of the University of KwaZulu-Natal, Durban, South Africa (class approval number BREC: BCA356/14) (Appendix 1). The following tools were utilised: a) cardboard box and plastic bag to store bone samples b) white board to use as background or base, 15cm and 150mm length ruler c) tripod with 360 degree panning head, 90 degree tilt and bubble level for optimal position control d) smart phone camera, smart phone holder to attach to tripod, e) bluetooth camera remote (selfie stick) and f) prestik (reusable rubber-like temporary adhesive) to stabilize and lie the bone on horizontal plane.

General methodology and study design

The morphometric analysis, the age, sex and related information about these bones were assessed and documented. The age division criteria based on teenage (> 20), youth (20-< 40), middle age (40-< 60) and old age (≥ 60) (Levinson 1986; Briner 2006). Prior to the setup of the bone sample, two challenges were observed, in order to place the cervical vertebra in a horizontal plane. The first challenge, was that some of the spinous process of the cervical vertebrae were angulated. Second one, was that some of the FT were also angulated. This caused the bone sample to be unstable to place in a horizontal plane. Therefore, prestik (reusable rubber-like temporary adhesive) was placed on the underlying white board, thereby stabilising the cervical vertebral body on it.

The smart phone camera was set up with smart phone holder mounted to the tripod. The panning head of tripod was tilted into 90 degree, then checked the bubble level of tripod to confirm the optimal position of the horizonal plane set up. Also, the grid line setting of the camera was turned on to help the optimal position. Lastly, the Bluetooth camera remote was used to reduce the disturbance of the camera set up.

In the light of the above challenges, three photos in different angles for each cervical vertebra were taken. First angle - the line of cervical vertebral body was placed parallel to the underlying board in a horizontal plane and mainly focused on cervical vertebral body. Second and third angles - the line of FT was placed parallel to background white board, then focused on left FT and right FT. (Figure 6)

The Paint app was implored to assess the photos of cervical vertebra and two horizontal lines were drawn in the first photo. One at the anterior margin of cervical vertebral body and the other at the posterior margin of cervical vertebral body. Sample number were added in the first photo and, sample number and side (left or right) were added in the second and third photos. Morphometric analyses were performed using Markus Bader (MB) Ruler, the digital screen ruler, millimetre (mm), in accordance with a recent study by Hazar *et al.* (2015). (Figure 7)

The first photo was used to measure the interforaminal diameter (IFD), foramen-uncus ridge distance (FURD), anterior margin (AM) and posterior margin (PM) and to observe the shape and number variations of FT. The second and third photos were used to measure the antero-posterior diameter (APD) and transverse diameter (TD), and to observe the shape and number variations of FT.

Study design

The summary of the sample and design of the study is outlined below in the Figure 5.

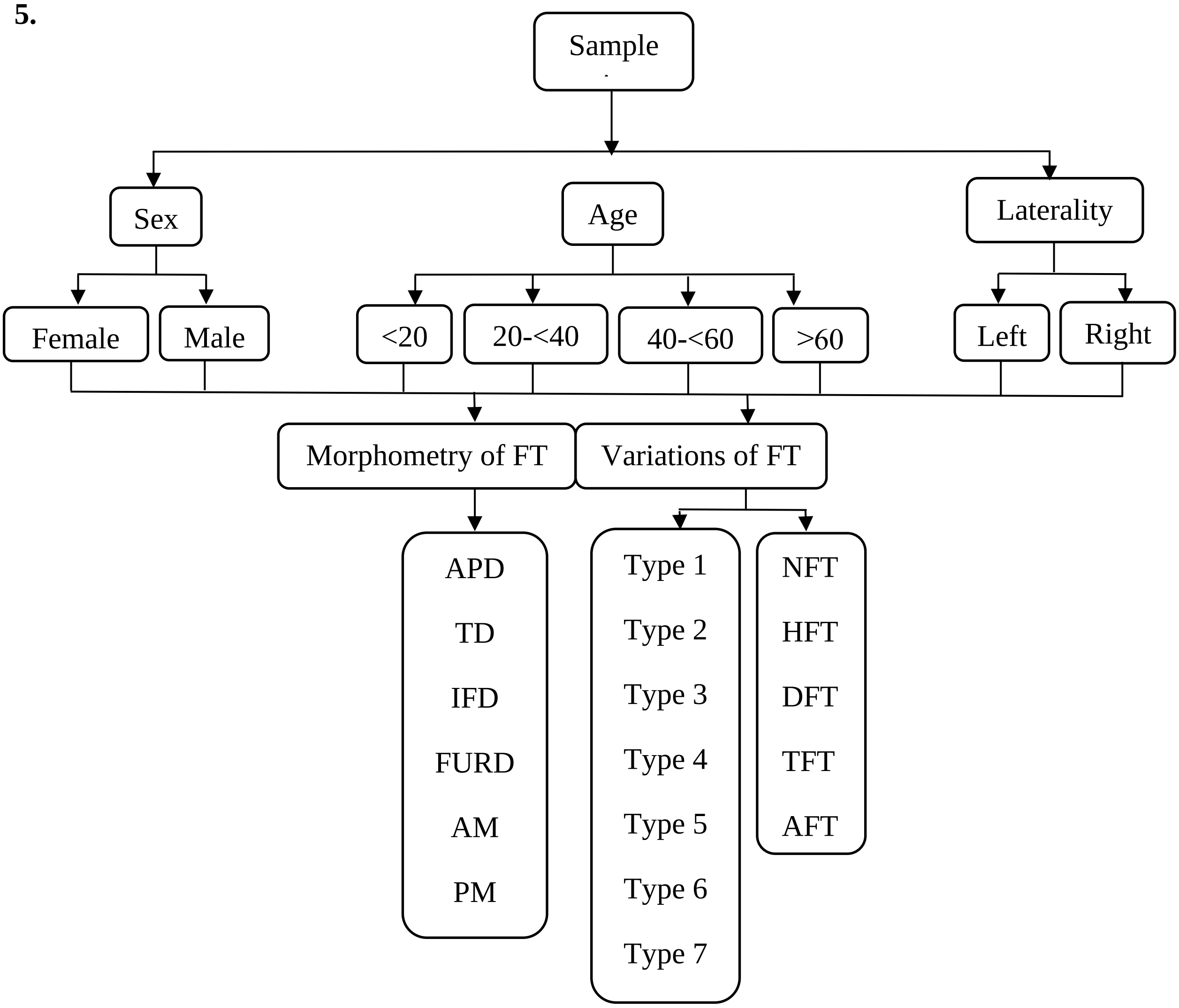

Figure 5: Study design

Key: foramen transversarium (FT), anteroposterior diameter (APD), transverse diameter (TD), interforaminal distance (IFD), foramen-uncus ridge distance (FURD), anterior margin (AM), posterior margin (PM), Type 1 - round, Type 2 - elliptical (anteroposterior), Type 3 - elliptical (Transverse), Type 4 - elliptical (oblique: right to left), Type 5 - elliptical (left to right), Type 6 - irregular, Type 7 - absent of foramen transversarium, normal foramen transversarium (NFT), hypoplastic foramen transversarium (HFT), double foramen transversarium (DFT), triple foramen transversarium (TFT), absent of foramen transversarium (AFT)

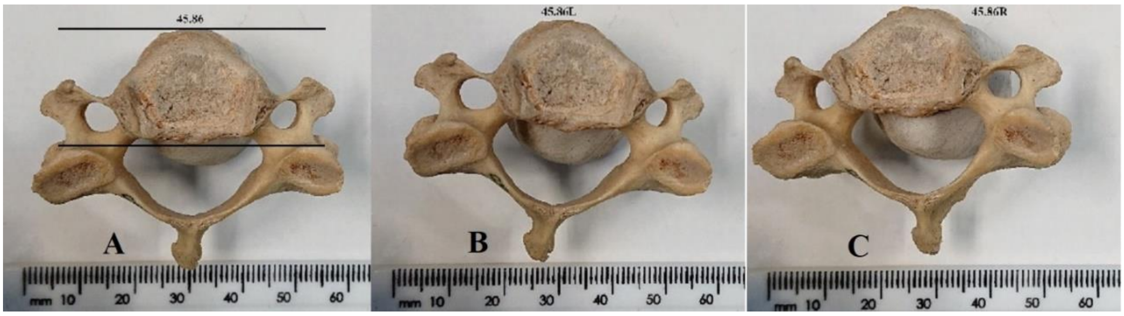

Figure 6: The three different angles of cervical vertebra, A – vertebral body in horizontal plane with two horizontal lines and sample number, B – left foramen transversarium in horizontal plane with sample number and side, C – right foramen transversarium in horizontal plane with sample number and side

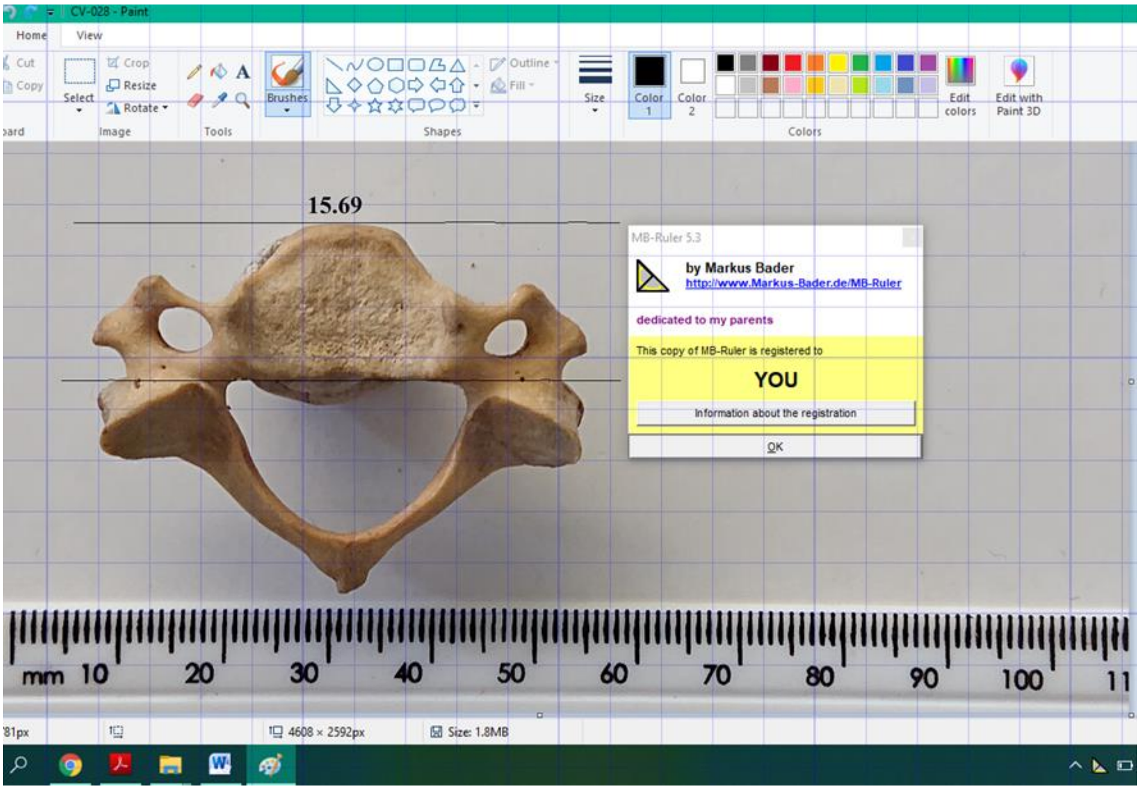

Figure 7: MB RULER used for morphometric parameters

Variations of the foramen transversarium

The variations and shapes of the FT were assessed using visual inspection on the bones that fell into the inclusion criteria after which the bones were stabilized on a smooth horizontal plane with the camera on tripod stand in horizontal plane. This study adopted the classification described by Taitz *et al*. (1978). The classification utilized both the shape and the main diameter (i.e. anteroposterior-length, transverse-breath) of which five types were identified viz. Type 1, the round, type 2, the elliptical anteroposterior, type 3, the elliptical in transverse, type 4, the elliptical oblique from right to left, type 5, the elliptical oblique from left to right (Taitz *et al*., 1978). Type 6, the irregular in shape and type 7, the absence of FTs were added (Kimura *et al*., 1985; Ambali and Jahav, 2017). The images of the bones were taken three times in order to eliminate intra-observer bias.

Morphometry of the foramen transversarium

The left and right sides of FT were measured using MB digital screen ruler to determine the anteroposterior distance (APD) – from anterior border of FT to posterior border of FT, interforaminal distance (IFD) - distance between medial border of right FT to left FT, anterior margin (AM) – from anterior border of FT to anterior margin of vertebral body, posterior margin (PM) - from posterior border of FT to posterior margin of vertebral body, transverse diameters (TD) – from medial border of FT to lateral border of FT and foramen-uncus ridge distance (FURD) - distance from medial border of FT to medial ridge uncus and the data were analysed using RStudio, a programming language for statistical computing and graphics. The results of all measurements obtained were compared according to sex, sides (left and right) and age. (Figure 6-10). Appendix 2; illustrates the data table showing all parameters.

Figure 8: Morphometric parameters

Key: A - anteroposterior diameter, B - transverse diameter, C - interforaminal distance, D - anterior margin distance, E - posterior margin distance, F - foramen-uncus ridge distance and 11.71 - sample number

Figure 9: Materials used to record bone samples

Keys: A - white board with cm and mm showing ruler attached, B - tripod with horizontal head and bubble level, C - Prestik (reusable rubber-like temporary adhesive), D - Bluetooth camera remote (selfie stick), E - smart phone camera, F - smart phone holder to attach to tripod

Figure 10: Setup to record bone samples

Statistical analysis

Morphometric parameters of FT were analysed using descriptive and inferential statistics. The descriptive statistics involved the five number summaries, that is; the minimum, maximum, mean, SD (standard deviation) and quartiles (25%, 50% and 75%). In addition to the descriptive statistics, the coefficient of variation (CV) was reported to provide a measure of how the parameter measures varied around the average. On the other hand, the inferential statistics mainly compared the measurements between sex within age groups and side. In order to assess the differences in the measurements among multiple treatment groups, either t-test were used for normally distributed measurements or non-parametric test Wilcoxon test, in the case of skewed distributions. The data was initially captured into Ms Excel and imported into a Statistical Software called R, version 3.6.1 for statistical analysis. All the tests were conducted at 5% level of significance.

Design of thesis

This thesis entails the preliminary pages followed by Chapter 1, where introduction, literature review, problem statement, aim, objectives, research questions, general methodology, study design and statistical analysis were all discussed. The next chapter, chapter 2, discussed the manuscript; this chapter is arranged in accordance with the journal to which it has been submitted to. Chapter 3 is the final chapter, which synthesized all aspects of the thesis. It described the overview aspects of the chapters.

.

References

Arıncı, K. and Elhan, A., 2014. Vertebrae cervicales. *Anatomi*, 5(1). pp.59-60.

Akhtar, M.J., Madhukar, P.K., Rahman, S. and Kashyap, N., 2015. A morphometric study of foramen transversarium of dried cervical vertebrae. *International Journal of Research in Medical Science*, 3(4), pp.912-916.

Ambali, M.P. and Jadhav, S.D., 2017. Anatomical variations in foramen transversarium of typical cervical vertebrae and its clinical significance. *International Journal of Anatomy and Research*, *5*(1), pp.3426-29.

Asvat, R., 1997. Morphological variations of the cervical vertebrae in samples of South African black and white population groups. *Doctoral Dissertation*, University of Witwatersrand, pp.58-66. URI: http://hdl.handle.net/10539/21334.

Aydınlıoğlu, A., Kavaklı, A., Yeşilyurt, H., Erdem, S. and Eroğlu, C., 2001. Foramen transversarium bipartita. *Van Tıp Dergisi*, 8(4), pp.110-112.

Aziz, J.N. and Morgan, M., 2018. Morphological Study of the Foramen Transversarium of the Atlas Vertebra among Egyptian Population and Its Clinical Significance. *Anatomy Physiology & Biochemistry International Journal*, 4(4), pp.1-5. DOI: 10.19080/APBIJ.2018.04.555642.

Barbagallo, G., Certo, F., Albanese, V. and Visocchi, M., 2014. The impact of complications following cervical spine surgery: a systematic review. *Journal of Neurosurgical Sciences*, 58(2 Supplementary 1), pp.55–64.

Barnsley, L., 2015. Neck pain. *Rheumatology (Sixth Edition)*, 1, pp.567-577.

Briggs, A.M., Woolf, A.D., Dreinhöfer, K., Homb, N., Hoy, D.G., Kopansky-Giles, D. and March, L., 2018. Reducing the global burden of musculoskeletal conditions. *Bulletin of the World Health Organization*, 96(5), pp.366–368. doi:10.2471/BLT.17.204891

Caovilla, H.H., Gananca, M.M., Munhoz, M.S. and Silva, M.L., 2000. Sindrome cervical. *Quadros Clinicos Otoneurologicos Mais Comuns*. *Atheneu Sao Paulo*, 3(11), pp.95-100.

Chal, J. and Pourquié, O., 2009. 3 Patterning and Differentiation of the Vertebrate Spine. *Cold Spring Harbor Monograph Archive*, 53, pp.41-116.

Chaturvedi, A., Klionsky, N.B., Nadarajah, U., Chaturvedi, A. and Meyers, S.P., 2018. Malformed vertebrae: a clinical and imaging review. *Insights Into Imaging*, *9*(3), pp.343-355.

Das, S., Suri, R. and Kapur, V., 2005. Double foramen transversaria: An osteological study with clinical implications. *International Medical Journal*, 12(4), pp.311-313.

Drake, R., Vogl, A. W., Mitchell, A. W., Tibbitts, R. and Richardson, P., 2014. *Gray's Atlas of Anatomy E-Book*, Elsevier Health Sciences.

Ebraheim, N.A., Xu, R. and Yeasting, R.A., 1996. The location of the vertebral artery foramen and its relation to posterior lateral mass screw fixation. *Spine*, 21(11), pp.1291-1295.

Eskander, M.S., Drew, J.M., Aubin, M.E., Marvin, J., Franklin, P.D., Eck, J.C., Patel, N., Boyle, K. and Connolly, P.J., 2010. Vertebral artery anatomy: a review of two hundred fifty magnetic resonance imaging scans. *Spine*, 35(23), pp.2035-2040.

Esquivel, M.T.J., 1975. Anatomical varieties in vertebrae of the Tlatelolco collection. *Annals of the National Museum of Mexico*, 4, pp.71-82. National Museum of Mexico

Fleming, A., Kishida, M.G., Kimmel, C.B. and Keynes, R.J., 2015. Building the backbone: the development and evolution of vertebral patterning. *Development*, 142(10), pp.1733-1744.

Guerra, M.M., Fuentes, P.R., Roa, I., Molinet, G., Robles, F. and Roa, I., 2017. Anatomical variations of the foramen transversarium in cervical vertebrae. *International Journal of Morphology*, *35*(2), pp.719-722. doi:10.4067/s0717-95022017000200053

Hazar, Z., Karabicak, G.O. and Tiftikci, U., 2015. Reliability of photographic posture analysis of adolescents. *Journal of Physical Therapy Science*, 27(10), pp.3123-3126.doi:10.1589/jpts.27.3123

Herrera, D.A., Vargas, S.A. and Dublin, A.B., 2008. Endovascular treatment of traumatic injuries of the vertebral artery. *American Journal of Neuroradiology*, *29*(8), pp.1585-1589.

Hoe, V.C., Urquhart, D.M., Kelsall, H.L., Zamri, E.N. and Sim, M.R., 2018. Ergonomic interventions for preventing work-related musculoskeletal disorders of the upper limb and neck among office workers. *Cochrane Database of Systematic Reviews*, (10). doi:10.1002/14651858.cd008570.pub3

Jovanovic, M.S., 1990. A comparative study of the foramen transversarium of the sixth and seventh cervical vertebrae. *Surgical and Radiologic Anatomy*, 12(3), pp.167-172.

Kaya, S., Yilmaz, N.D., Pusat, S. Kural,C., Kırık, A. and Izcı1, Y., 2011. Double foramen transversarium variation in ancient byzantine cervical vertebrae: preliminary report of an anthropological study. *Turkish Neurosurgery*, 21, pp.534–538. doi:10.5137/1019-5149.JNT.4456-11.1

Kimura, K., Konishi, M. and Hu, S.Y., 1985. Shape and size of the transverse foramina in Japanese. *Okajimas Folia Anatomica Japonica*, 62(2), pp.123-131. doi:10.2535/ofaj1936.62.2_123

Kotil, K. and Kilincer, C., 2014. Sizes of the transverse foramina correlate with blood flow and dominance of vertebral arteries. *The Spine Journal*, *14*(6), pp.933-937.

Malik, S.W., Stemper, B.D., Metkar, U., Yoganandan, N., Shender, B.S. and Rao, R.D., 2010. Location of the transverse foramen in the subaxial cervical spine in a young asymptomatic population. *Spine,* 35(12), pp.E514-E519.

Mulla, N.G. and Pundge, S.J., 2015. Double foramen transversarium-a case report. *International Journal of Current Research and Review*, *7*(16), p.6.

Murlimanju, B.V., Prabhu, L.V., Shilpa, K., Rai, R., Dhananjaya, K.V. and Jiji, P.J., 2011. Accessory transverse foramina in the cervical spine: incidence, embryological basis, morphology and surgical importance. *Turkish Neurosurgery*, 21, pp.384-387. doi:10.5137/1019-5149.JNT.4047-10.0

Nagar, Y., Taitz, C. and Reich, R., 1999. What can we make of these fragments? Excavation at ‘Mamilla’Cave, Byzantine period, Jerusalem. *International Journal of Osteoarchaeology*, 9(1), pp.29-38.

Nakashima, K., Zhou, X., Kunkel, G., Zhang, Z., Deng, J.M., Behringer, R.R. and De Crombrugghe, B., 2002. The novel zinc finger-containing transcription factor osterix is required for osteoblast differentiation and bone formation. *Cell*, *108*(1), pp.17-29.

Netter, F.H., 2014. *Atlas of Human Anatomy Sixth Edition*.

Newell, R.L.M., 2008. The back.In : Standring S, editor. *Gray’s Anatomy, The anatomical basis of clinical practice .40th ed. Churchill Livingstone Elsevier*, pp.713,763 – 73.

Padget, D.H., 1948. The development of the cranial arteries in the human embryo: Contrib. *Embryology*, 32, pp.207-261.

Pansky, B., 1982. *Review of Medical Embryology*. Macmillan.

Patra, A., Kaur, H., Chhabra, U., Kaushal, S. and Kumar, U., 2015. Double foramen transversarium in dried cervical vertebra: An osteological study with its clinical implications. *Indian Journal of Oral Sciences*, *6*(1), pp.7-9.

Peng, C.W., Chou, B.T., Bendo, J.A. and Spivak, J.M., 2009. Vertebral artery injury in cervical spine surgery: anatomical considerations, management, and preventive measures. *The Spine Journal*, 9(1), pp.70-76.

Peters, H., Wilm, B., Sakai, N., Imai, K., Maas, R. and Balling, R., 1999. Pax1 and Pax9 synergistically regulate vertebral column development. *Development,* 126(23), pp.5399-5408.

Pruthi, N., Dawn, R., Ravindranath, Y., Maiti, T.K., Ravindranath, R. and Philip, M., 2014. Computed tomography-based classification of axis vertebra: choice of screw placement. *European Spine Journal*, 23(5), pp.1084-1091.

Rathnakar, P. and Remya, K., 2013. Study of accessory foramen transversaria in cervical vertebrae. *Nitte University Journal of Health Science*, 3(4), pp.97–99.

Ratliff, J.K. and Cooper, P.R., 2003. Cervical laminoplasty: a critical review. *Journal of Neurosurgery: Spine*, 98(3), pp.230-238.

Sanchis-Gimeno, J.A., Blanco-Perez, E., Llido, S., Perez-Bermejo, M., Nalla, S. and Mata-Escolano, F., 2018. Can the transverse foramen/vertebral artery ratio of double transverse foramen subjects be a risk for vertebrobasilar transient ischemic attacks?. *Journal of Anatomy*, *233*(3), pp.341-346.

Sangari, S.K., Dossous, P.M., Heineman, T. and Mtui, E.P., 2015. Dimensions and anatomical variants of the foramen transversarium of typical cervical vertebrae. *Anatomy Research International*, *2015*, pp.1-5. doi:10.1155/2015/391823

Sañudo, J.R., Vázquez, R. and Puerta, J., 2003. Meaning and clinical interest of the anatomical variations in the 21st century. *European Journal of anatomy*, 7(1), pp.1-4.

Scaal, M., 2016, January. Early development of the vertebral column. *In Seminars in Cell & Developmental Biology*, 49, pp.83-91. Academic Press.

Shin, H.Y., Park, J.K., Park, S.K., Jung, G.S. and Choi, Y.S., 2014. Variations in entrance of vertebral artery in Korean cervical spine: MDCT-based analysis. *The Korean Journal of Pain*, 27(3), pp.266.

Sim, E., Vaccaro, A.R., Berzlanovich, A., Thaler, H. and Ullrich, C.G., 2001. Fenestration of the extracranial vertebral artery: review of the literature. *Spine*, 26(6), pp.139-142.

Skórzewska, A., Grzymisławska, M., Bruska, M., Łupicka, J. and Woźniak, W., 2013. Ossification of the vertebral column in human foetuses: histological and computed tomography studies. *Folia Morphologica*, 72(3), pp.230-238.

Smith, M.D., Emery, S.E., Dudley, A., Murray, K.J. and Leventhal, M., 1993. Vertebral artery injury during anterior decompression of the cervical spine. A retrospective review of ten patients. *The Journal of Bone and Joint Surgery. British volume*, 75(3), pp.410-415.

Standring, S., 2008. Gray's Anatomy, The anatomical basis of clinical practice *.40th ed.Churchill Livingstone Elsevier*.

Sultana, Q., Avadhani, R., Varalakshmi, K.L. and Shariff, M.H., 2015. Variations of foramen transversarium in atlas vertebrae: a morphological study with its clinical significance. *Nitte University Journal of Health Sciences*, 5, pp.80-83.

Sunitha, N.S., Karpagajothi, J. and Bharathi Rani, S., 2016. Interesting Facts about the Foramen Transversarium of Cervical Vertebra. *IOSR Journal of Dental and Medical Sciences*, 15(1), pp.20-24. DOI: 10.9790/0853-15182024

Taitz, C., Nathan, H. and Arensburg, B., 1978. Anatomical observations of the foramina transversaria. *Journal of Neurology, Neurosurgery & Psychiatry*, 41(2), pp.170-176.

Tellioglu, A.M., Durum, Y., Gok, M., Polat, A.G., Karaman, C.Z. and Karakas, S., 2018. Evaluation of morphologic and morphometric characteristic of foramen transversarium on 3-dimensional multidetector computed tomography angiography. *Turkish Neurosurgery*, *28*(4), pp.557-562.

Tsutsumi, S., Ito, M. and Yasumoto, Y., 2008. Simultaneous bilateral vertebral artery occlusion in the lower cervical spine manifesting as bow hunter's syndrome. *Neurologia medico-chirurgica*, *48*(2), pp.90-94.

Wang, H. and Orbach, D.B., 2008. Traumatic dissecting aneurysm at the vertebrobasilar junction in a 3-month-old infant: evaluation and treatment strategies: Case report. *Journal of Neurosurgery: Pediatrics*, 1(5), pp.415-419.

Wysocki, J., Bubrowski, M., Reymond, J. and Kwiatkowski, J., 2003. Anatomical variants of the cervical vertebrae and the first thoracic vertebra in man. *Folia Morphologica*, 62(4), pp.357-363.

Yadav, Y., Goswami, P. and Bharihoke, V., 2014. An osteological study of foramen trasversarium: variations and clinical aspects. *Journal of Evolution of Medical & Dental Sciences*, 3(68), pp.14562–14566.

Yeramaneni, S., Robinson, C. and Hostin, R., 2016. Impact of spine surgery complications on costs associated with management of adult spinal deformity. *Current Reviews in Musculoskeletal Medicine*, 9(3), pp.327-332. doi:10.1007/s12178-016-9352-9

Zibis, A., Mitrousias, V., Galanakis, N., Chalampalaki, N., Arvanitis, D. and Karantanas, A., 2018. Variations of transverse foramina in cervical vertebrae: what happens to the vertebral artery?. *European Spine Journal*, 27(6), pp.1278-1285. doi:10.1007/s00586-018-5523-2

Zibis, A.H., Mitrousias, V., Baxevanidou, K., Hantes, M., Karachalios, T. and Arvanitis, D., 2016. Anatomical variations of the foramen transversarium in cervical vertebrae: findings, review of the literature, and clinical significance during cervical spine surgery. *European Spine Journal*, 25(12), pp.4132-4139. doi:10.1007/s00586-016-4738-3

CHAPTER TWO

The literature review documented variations in morphometric parameters of foramen transversarium (FT) but have not considered age, sex and laterality in combination. This FT is an important feature of cervical vertebrae because it transmits the vertebral vessels and sympathetic nerve. Therefore, adequate knowledge is required about the variations that exist in terms of laterality, age groups and sex. In view of this, this research manuscript reported the variations in the morphometric parameters with respect to age, sex and laterality of FT in a KwaZulu-Natal population by exploring the following objectives;

i. measure the size of the FT

ii. classify the anatomical variations of the FT

iii. compare the anatomical variations according to sex, age and laterality

This manuscript has been sent to the Anatomical Science International (ANSI) with submission reference ANSI-D-19-00360

CHAPTER TWO

MANUSCRIPT FROM RESEARCH

SEXUAL DIMORPHISM AND MORPHOMETRIC ANALYSIS OF FORAMEN TRANSVERSARIUM IN KWAZULU-NATAL POPULATION

Aung K. Zaw[1], Samuel O. Olojede[1], Sodiq K. Lawal[1,3], Ugochukwu Offor[1], Koffi Kouame[1], Edwin C.S. Naidu[1], Carmen O. Rennie [1], Onyemaechi O. Azu[1,2]

[1]Discipline of Clinical Anatomy, Nelson R. Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa

[2]Department of Anatomy, School of Medicine, University of Namibia, Windhoek, Namibia

[3]Department of Anatomy, St. Francis University College of Health Sciences and Allied Sciences, Ifakara, Tanzania

Corresponding Author: Prof. Onyemaechi Okpara Azu, Department of Anatomy, School of Medicine, University of Namibia, Windhoek, Private bag 13301, Namibia, oazu@unam.na, Azu@ukzn.ac.za, https://orcid.org/0000-0003-0916-7184

ABSTRACT

The foramen transversarium (FT) is a distinguished characteristic of a cervical bones based on the vertebral vessels and sympathetic nerve it transmits which are of great importance in surgical and radiological procedures. The aim of this study was to analyse the morphometric parameters of the FT with regards to sexual dimorphism and age within the KwaZulu-Natal (KZN) population, South Africa.

One hundred and thirty (130) dried human typical cervical bones of KZN population of known sex and age (67 males and 63 females with age ranges from 12 to 89) without any degeneration or deformity were sourced from the bone collection at the Discipline of Clinical Anatomy, Nelson Mandela School of Medicine, University of KwaZulu-Natal (UKZN). The morphometric analyses were performed using Markus Bader (MB) Ruler, the digital screen ruler and subjected to RStudio statistical analysis.

The results of this study indicated that the morphometric parameters of the FT were greater in males compared to females ($p < 0.05$). The values of the right sides were higher than that on the left sides except, for the transverse diameter where higher values were observed in the left side of male specimens. Based on the shape of FT, the type 1 was predominant (43.85%) shapes, followed by type 3 (23.08%) and least common are type 2 and 7 (0.77%) on the left side. Type 1 has the higher value (46.16%) on the right side, followed by type 3 (20%) and type 2 (0.77%) is the least in this study. The variation in FT in relation to sex revealed the presence of normal foramen (62.31%, male with 30.77% and female with 31.54%) and double foramen (36.92%, male with 20% and female with 16.92%). It was observed that the frequency of bilateral double foramen is common in males (11.54%) compared to females (6.92%).

The result of this study has demonstrated that risk of injury to neurovascular structures associated with FT may be common on the left side, in female and especially in age groups less than < 20 and ≥ 60 years of age.

Keywords: Foramen Transversarium, Cervical vertebrae, Morphometric, Sex, Age

Introduction

Musculoskeletal disorders result from injury or damage to the neurovascular bundles, bones and associated structures (Briggs *et al.*, 2018). The vertebral column is one of the structures that are vulnerable to musculoskeletal injury especially the cervical vertebrae among others. The cervical vertebrae form an important component of the vertebral column at the neck region (Singh *et al.*, 2019). The cervical vertebrae presents the vertebral body, vertebral arch, vertebral foramen, articular facet, spinous process and foramen transversarium (FT) as an important anatomical adaptation features (Moore *et al.*, 2013). The FT is an important and noticeable feature of cervical vertebrae that occupy the sympathetic fibres, vertebral vein (VV) and vertebral artery (VA) (Guerra *et al.*, 2017). This foramen is also known as VA foramen with respect to the VA that passes through it (Hsu, 2011), which makes anatomical knowledge regarding the variations of FT essential in diagnosis, radiological assessment and medical imaging interpretation (Murlimanju *et al.*, 2011). Consequently, fracture or injury to the cervical vertebrae and the FT will result in damage or lesion to the associated neurovascular bundles (Dalgic *et al*., 2009). Literature have documented anatomical variations of FT based on shapes and size. Manjunath *et al*. (2018) reported one FT on either side as well as absent or duplicated on one or either sides. A recent study observed extremely narrow, multiple, hypoplastic, duplicated and triplicated FT (Zibis *et al.*, 2016). These variations have consequences on course and dimension of the associated neurovascular vessels (Das *et al.*, 2005), and may alter the position and path of these structures. This leads to clinical conditions such as vertebrobasilar insufficiency (Kaya *et al.*, 2011), hearing impairment and neurological symptoms as a result of spasm of either VA or basilar artery (Taitz *et al.*, 1978; Das *et al.*, 2005; Kaya *et al.*, 2011). Importantly, ignorance of the variations in terms of the shape and size in FT may present devastating outcomes during diagnosis, surgery or interpretation of medical imaging. Besides, previous studies have not considered the combination of age, sex and laterality as regards to the variations of FT.

Imperatively, deeper understanding about the anatomical variations that exists in FT with respect to age and sex is required in order to be able to properly diagnose and accurately interpret results of any musculoskeletal disorders especially in relation to the FT and its contents. Sexual dimorphism is essential in forensic medicine, to analyse the accuracy of a particular bone in determining sex. Malik *et al*., (2010) found significant differences between morphometric parameters in male and female, with smaller dimensions for the foramen transversarium (FT) in female specimens. The knowledge of morphometric parameters and variation of FT in sex, age and side may help in surgical procedures such as screw fixation in cervical region and also for radiological investigations.

In the light of this, this study was designed to assess the morphometric variations of the FT in relation to the age and sex within a KwaZulu-Natal (KZN) population, South Africa.

Materials and Method

Materials

One hundred and thirty (130) dried human cervical bones without any degeneration or deformity were used for this study. The typical cervical bones from the KwaZulu-Natal population that included 67 Males and 63 Females with an age range from 12 to 89 years of age were sourced from the bone collection at Discipline of Clinical Anatomy, Nelson Mandela School of Medicine, University of KwaZulu-Natal, Durban, South Africa. All the intact cervical vertebrae without any traumatic disorders, deformity or degeneration were included in this study. Ethical approval for this investigation was received from Biomedical Research Ethics Committee of the University of KwaZulu-Natal, Durban, South Africa (class approval number BREC: BCA356/14). The following tools were utilised: a) cardboard box and plastic bag to store bone samples b) white board to use as background or base, 15cm and 150mm length ruler c) tripod with 360 degree panning head, 90 degree tilt and bubble level for optimal position control d) smart phone camera, smart phone holder to attach to tripod, e) bluetooth camera remote (selfie stick) and f) prestik (reusable rubber-like temporary adhesive) to stabilize and lie the bone on horizontal plane.

General methodology and study design

The morphometric analysis, the age, sex and related information about these bones were assessed and documented. The age division criteria based on teenage (> 20), youth (20-< 40), middle age (40-< 60) and old age (≥ 60) (Levinson 1986; Briner 2006). Prior to the setup of the bone sample, two challenges were observed when placing the cervical vertebrae in a horizontal plane viz. some of the spinous process and FT of the cervical vertebrae were angulated, thereby making the cervical vertebrae unstable in the horizontal plane. Therefore, Prestik (reusable rubber-like temporary adhesive) was placed on the underlying white board, thereby stabilising the cervical vertebral body on it.

The smart phone camera was set up with smart phone holder mounted to the tripod. The panning head of tripod was tilted into 90 degree, then checked the bubble level of tripod to confirm the optimal position of the horizonal plane set up. Also, the grid line setting of the camera was turned on to help the optimal position. Lastly, Bluetooth camera remote was used to reduce the disturbance of the camera set up.

In the light of the above challenges, three photos in different angles for each cervical vertebra were taken. First angle - the line of cervical vertebral body was placed parallel to underlying board in horizontal plane and mainly focused on cervical vertebral body. Second and third angles - the line of FT was placed parallel to background white board, then focused on left FT and right FT. (Figure 1)

The Paint app was implored to assess the photos of cervical vertebra and two horizontal lines were drawn in the first photo. One at the anterior margin of cervical vertebral body and other at the posterior margin of cervical vertebral body. The sample number was added in the first photo and, sample number and side (left or right) were added in the second and third photos. Morphometric analyses were performed using Markus Bader (MB) Ruler, the digital screen ruler, millimetre (mm), in accordance with a recent study by Hazar *et al.* (2015). (Figure 2)

The first photo was used to measure the interforaminal diameter (IFD), foramen-uncus ridge distance (FURD), anterior margin (AM) and posterior margin (PM). and to observe the shape and number variations of FT. The second and third photos were used to measure the anteroposterior diameter (APD) and transverse diameter (TD), and to observe the shape and number variations of FT.

Variations of the foramen transversarium

The variations and shapes of the FT were assessed using visual inspection on the bones that fell into the inclusion criteria after which the bones were stabilized on a smooth horizontal plane with the camera on tripod stand in horizontal plane. This study adopted the classification described by Taitz *et al*. (1978). The classification utilized both the shape and the main diameter (i.e. anteroposterior-length, transverse-breath) of which five types were identified viz. Type 1, the round, type 2, the elliptical anteroposterior, type 3, the elliptical in transverse, type 4, the elliptical oblique from right to left, type 5, the elliptical oblique from left to right (Taitz *et al*., 1978). Type 6, the irregular in shape and type 7, the absence of FTs were added and included in the classification (Kimura *et al*., 1985; Ambali and Jahav, 2017). The images of the bones were taken three times in order to eliminate intra-observer bias. (Figure 1)

Morphometry of the foramen transversarium

The left and right sides of FT were measured using MB digital screen ruler to determine the anteroposterior distance (APD) – from anterior border of FT to posterior border of FT, interforaminal distance (IFD) - distance between medial border of right FT to left FT, anterior margin (AM) – from anterior border of FT to anterior margin of vertebral body, posterior margin (PM) - from posterior border of FT to posterior margin of vertebral body, transverse diameters (TD) – from medial border of FT to lateral border of FT and foramen-uncus ridge distance (FURD) - distance from medial border of FT to medial ridge uncus and the data were analysed using RStudio, a programming language for statistical computing and graphics. The results of all measurements obtained were compared according to sex, sides (left and right) and age. (Figure 1-4).

Statistical analysis

Morphometric parameters of FT were analysed using descriptive and inferential statistics. The descriptive statistics involved the five number summaries, that is; the minimum, maximum, mean, SD (standard deviation) and quartiles (25%, 50% and 75%). In addition to the descriptive statistics, the coefficient of variation (CV) was reported to provide a measure of how the parameter measures varied around the average. On the other hand, the inferential statistics mainly compared the measurements between sex within age groups and side. In order to assess the differences in the measurements among multiple treatment groups, either t-test were used for normally distributed measurements or non-parametric test Wilcoxon test, in the case of skewed distributions. The data was initially captured into Ms Excel and imported into a Statistical Software called R, version 3.6.1 for statistical analysis. All the tests were conducted at 5% level of significance.

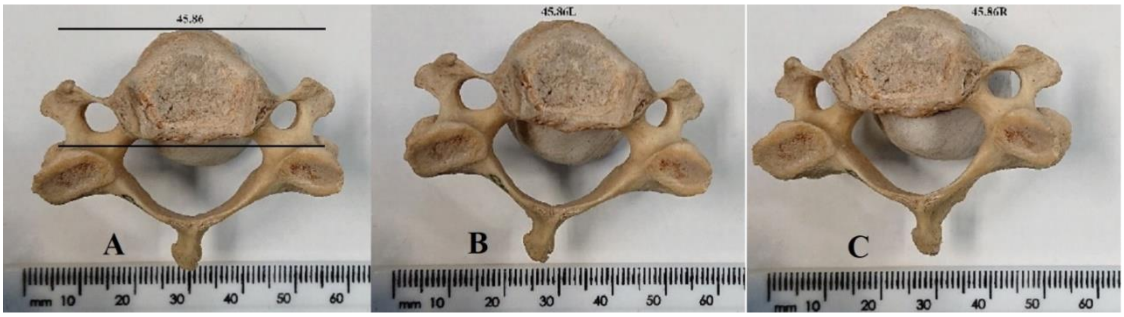

Figure 1: The three different angles of cervical vertebra, A – vertebral body in horizontal plane with two horizontal lines and sample number, B – left foramen transversarium in horizontal plane with sample number and side, C – right foramen transversarium in horizontal plane with sample number and side

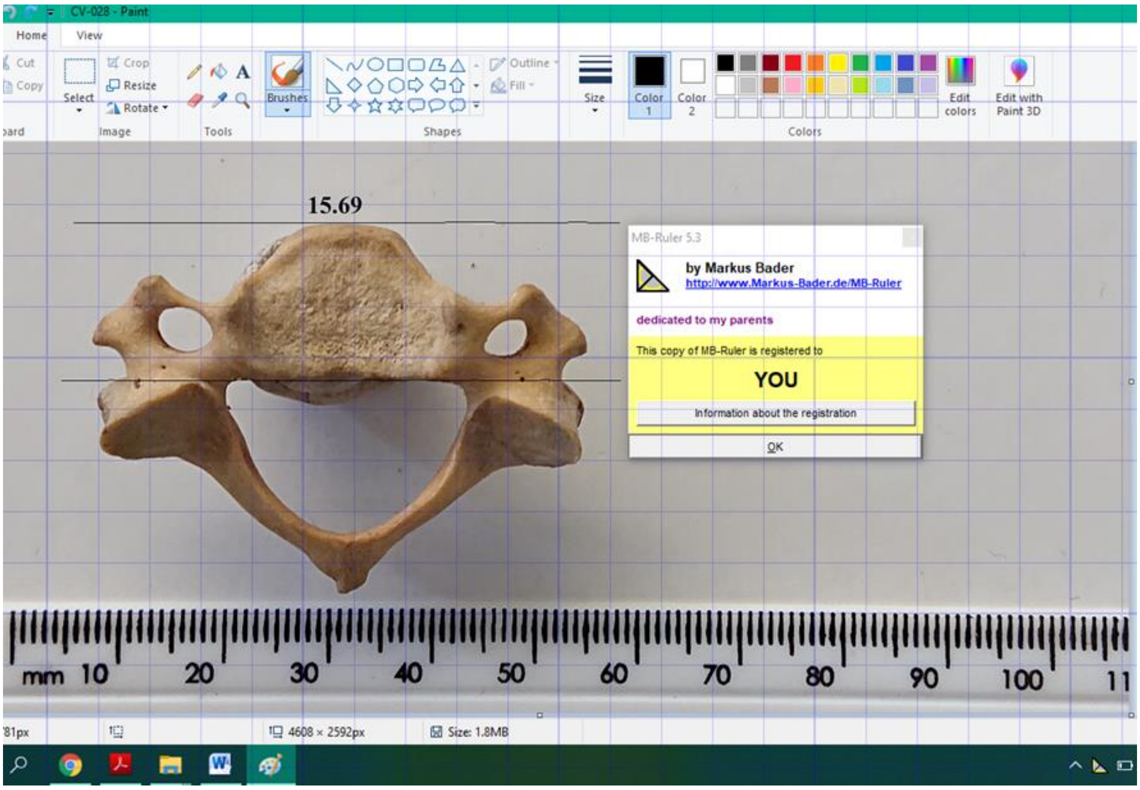

Figure 2: MB RULER used for morphometric parameters

Figure 3: Morphometric parameters

Key: A - anteroposterior diameter, B - transverse diameter, C - interforaminal distance, D - anterior margin distance, E - posterior margin distance, F - foramen-uncus ridge distance and 11.71 - sample number

Figure 4: Setup to record bone samples

Results

Morphometric parameters of foramen transversarium

Anteroposterior diameter (APD)

The APD results are 6.16 mm in male and 5.93 mm in female of right side, 6.25 mm in male and 6.09 mm in female of left side. APD showed no significant difference between male and female, left and right specimens. (Table 1)

Transverse diameter (TD)

The results of TD are 7.02 mm in male and 6.77 mm in female of right side, 7.32 mm in male and 6.89 mm in female of left side. There was a significant difference ($p< 0.05$) in TD of male and female on the left specimens but no significant difference in the right measurements of specimens. There was a slight increase in diameter when comparing the left from the right in male and female specimens (Table 1).

Foramen-uncus ridge distance (FURD)

The FURD values are 4.24 mm in male and 4.16 mm in female of right side, 4 mm in male and 3.75 mm in female of left side. There was no significant difference in FURD of both male and female specimens and also in right and left. There was slight increase in diameter when comparing the right from the left in male and female specimens (Table 1).

Anterior margin (AM)

There was no significant difference in AM of both male and female specimens and also between right and left (Table 1). The results of AM are 9.10 mm and 9.2 in male and female samples of right side, 9.12 mm and 9.14 mm in female samples of left side.

Posterior margin (PM)

The PM result are 3.87 mm in male and 3.71 in female of right side, 3.66 mm in male and 3.32 mm in female of left side. There was no significant difference in PM of both male and female specimens and also in right and left. There was slight increase in diameter when comparing the right from the left in male and female specimens (Table 1).

Interforaminal distance (IFD)

IFD showed significant difference ($p < 0.05$) with increased in diameter of the male when compared with the female specimens (Table 1). The values are 27.9 mm in male and 26.8 mm in female.

Table 1: Morphometric analyses of foramen transversarium mean dimensions of male and female on right and left specimen

	Male	Female	P-value	Male	Female	P-value
Parameters	Right	Right		Left	Left	
APD (mm)	6.16	5.93	0.18	6.25	6.09	0.29
TD (mm)	7.02	6.77	0.23	7.32	6.89	0.02
FURD (mm)	4.24	4.16	0.68	4	3.75	0.14
AM (mm)	9.10	9.02	0.81	9.12	9.14	0.62
PM (mm)	3.87	3.71	0.49	3.66	3.32	0.15
Parameter	Male		Female		P-value	
IFD (mm)	27.91		26.83		0.04	

Keys: anteroposterior diameter (APD), transverse diameter (TD), foramen-uncus ridge distance (FURD), anterior margin (AM), posterior margin (PM), interforaminal distance (IFD), millimetre (mm)

Shape of foramen transversarium

The incidence of various shape types from the most common (type 1; round) to the least common (Type 2; elliptical in anteroposterior, Type 7; absent FT) as presented in the Table 2. (Figure 5-6)

It was evident from table 2 that out of 130 specimens, total of 60 (46.16%) FT were found to be type 1 (round shape) on the right sides of both sexes. This implies that of total of 60

FT, 31 (23.85%) in male and 29 (22.31%) in female on the right side. On the left side, total of 57 (43.85%) FT was found to be type 1 (round shape), 31 (23.85%) found in male and 26 (20%) for female.

Type 2 (elliptical in anteroposterior) is the least common, it occurred only on the left side in one (0.77%) male specimen (Table 2).

The results from table 2 shows total number of 26 (20%) on the right side, accounting for 14 (10.77%) male and 12 (9.23%) female FT was found to be type 3 (elliptical in transverse). Thirty (30) (23.08%) FT on the left side, whereby 16 (12.31%) were found for male and 14 (10.77%) for female.

Occurrence of type 4 (elliptical from right to left oblique) shape of FT were found in 24 (18.46%) specimens on the right side, whereby 12 (9.23%) each were observed both male and female. Whereas, only two (1.54%) FT were found on the left side only in female specimen (Table 2).

In this study, only 3 (2.31%) FT exhibited type 5 (elliptical from left to right oblique) on the right side from one (0.77%) male and two (1.54%) female specimens. Total number of 22 (16.92%) was observed on the left side indicating 12 (9.23%) male and ten (7.69%) female (Table 2).

The results on the shape of FT variations revealed that, a total of 17 (13.07%) type 6 (irregular) shape of FT was found in this study on the right side compared to nine (6.92%) male and eight (6.15%) female on the right. The same total of 17 (13.07%) were also observed on the left side but six (4.61%) for male and 11 for (8.46%) female (Table 2).

In this study, the absence of FT (type 7) was only observed in one (0.77%) male specimen on the left side (Table 2). (Figure 6)

Table 2: Shape of foramen transversarium of Male and Female on right and left specimen

	Right side			Left side		
Shape types	Male	Female	Total	Male	Female	Total
1	31 (23.85%)	29 (22.31%)	60 (46.18%)	31 (23.85%)	26 (20%)	57 (43.85%)
2	0 (0)	0 (0)	0 (0)	1 (0.77%)	0 (0)	1 (0.77%)
3	14 (10.77%)	12 (9.23%)	26 (20%)	16 (12.31%)	14 (10.77%)	30 (23.08%)
4	12 (9.23%)	12 (9.23%)	24 (18.46%)	0 (0)	2 (1.54%)	2 (1.54%)
5	1 (0.77%)	2 (1.54%)	3 (2.31%)	12 (9.23%)	10 (7.69%)	22 (16.92%)
6	9 (6.92%)	8 (6.15%)	17 (13.07%)	6 (4.61%)	11 (8.46%)	17 (13.07%)
7	0 (0)	0 (0)	0 (0)	1 (0.77%)	0 (0)	1 (0.77%)

Key: 1= round, 2= elliptical (anteroposterior), 3= elliptical (transverse), 4= elliptical (oblique: right to left), 5=elliptical (left to right), 6= irregular and 7= absent of foramen transversarium

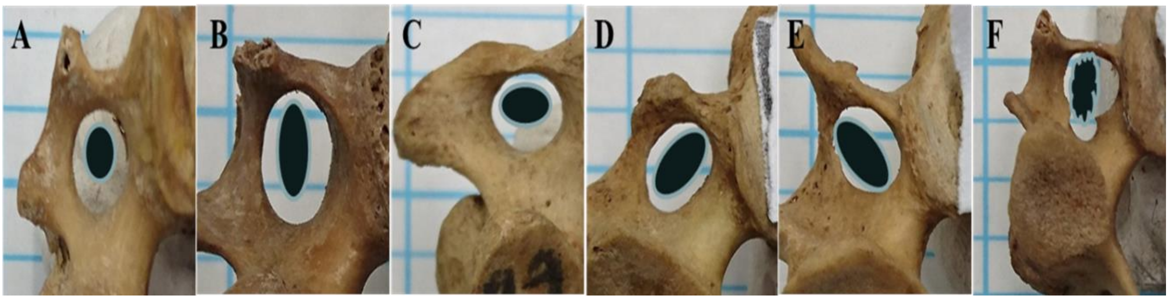

Figure 5: Shapes of the foramen transversarium

Key: A - type 1 (round), B - type 2 (elliptical anteroposterior), C - type 3 (elliptical transverse), D - type 4 (elliptical oblique right to left), E - type 5 (elliptical oblique left to right), F - type 6 (irregular)

Figure 6: type 7 - absent of foramen transversarium on the left side

Variations in number of foramen transversarium

Table 3 illustrates that, out of 130 typical cervical vertebrae, 48 (36.92%) vertebrae with double foramen transversarium (DFT) and one (0.77%) vertebra with absence of FT.

Twenty two (16.92%) vertebrae with DFT were found in female and 26 (20%) vertebrae with DFT were seen in male. Also, one (0.77%) vertebra with no FT was found in male (Table 3).

Two types of double foramen (DF) were found (Figure 7-8)– bilateral DF and unilateral DF. Total of 24 (18.46%), nine (6.92%) bilateral DF were found in female and 15 (11.54%) bilateral DF in male. Total of 24 (18.46%), 13 (10%) unilateral DF were observed in female and 11 (8.46%) unilateral DF in male (Table 4).

Four types of bilateral FT were observed – bilateral complete, bilateral incomplete, left complete and right incomplete, and left incomplete and right complete as shown in the Table 4. (Figure 7)

Four types of unilateral FT were found – left unilateral complete, right unilateral complete, left unilateral incomplete and right unilateral incomplete (Table 4). (Figure 8)

Table 3: Variations in number of foramen transversarium in relation to sex

	Female	%	Male	%	Total	%
Normal FT	41	31.54	40	30.77	81	62.31
HFT	0	0	0	0	0	0
DFT	22	16.92	26	20	48	36.92
TFT	0	0	0	0	0	0
Absence of FT	0	0	1	0.77	1	0.77

Key: FT = foramen transversarium, HFT = hypoplastic foramen transversarium, DFT = double foramen transversarium, TFT = triple foramen transversarium

Table 4: Variations of double foramen transversarium in relation to sex

	Double foramen (DF)	Female	%	Male	%	Total	%
Bilateral DF	Bilateral complete DF	1	0.77	6	4.62	7	5.38
	Bilateral incomplete DF	5	3.85	3	2.31	8	6.15
	Left complete & Right incomplete DF	1	0.77	5	3.85	6	4.62
	Left incomplete & Right complete DF	2	1.54	1	0.77	3	2.31
	Total	9	6.92	15	11.54	24	18.46
Unilateral DF	Left unilateral complete DF	1	0.77	1	0.77	2	1.54
	Right unilateral complete DF	3	2.31	5	3.85	8	6.15
	Left unilateral incomplete DF	5	3.85	3	2.31	8	6.15
	Right unilateral incomplete DF	4	3.08	2	1.54	6	4.62
	Total	13	10	11	8.46	24	18.46

Figure 7: Types of bilateral double foramen transversarium (DFT)

Key: A = bilateral complete DFT, B = bilateral incomplete DFT, C = left incomplete & right complete DFT and D = right complete & left incomplete DFT

Figure 8: Types of unilateral double foramen transversarium

Key: A = left unilateral complete DFT, B = left unilateral incomplete DFT, C = right unilateral complete DFT and D = right unilateral incomplete DFT

Morphometric parameters with respect to sex, age and laterality of foramen transversarium

The morphometric analysis with respect to age, sex and laterality were presented in Table 5. The laterality considered left and right sides of the specimens. The sex considered in this study was male and female. It was evident that in the APD, all the age groups and sex were significantly different ($p < 0.05$) p-value except the right sides of age groups < 20 and 20 to < 40 years in both sexes.

The results on the measurement of TD showed significant difference ($p < 0.05$) on the sides and sex across all age groups. Greater values were observed in age 20-< 40 and 40-< 60 in both male and female and both sides (Table 5).

In the AM measurement, statistically significant difference ($p < 0.05$) were observed on the left sides of ages group < 20, 20-< 40 and ≥ 60 as well as both sides of 40-< 60. Right sides of age groups < 20, 20-< 40 and ≥ 60 were not significant in both males and females (Table 5).

The PM measurements showed significant difference ($p < 0.05$) in all the age groups, both sides and for male and female as revealed in the Table 5.

The result of FURD showed statistically significant difference ($p < 0.05$) for both sides of male and female in age groups < 20, 20-< 40, ≥ 60 and the right sides of both male and female of age group 40-< 60. Additionally, no significant differences were observed on the left sides in male and female of age group 40-< 60 (Table 5).

The IFD showed a significant difference ($p < 0.05$) in all age groups for both left and right sides in both sex except left and right sides of age group 40-< 60 in both male and female (Table 5).

Table 5: Comparison of anatomical variations according to sex, age and laterality

			<20			20-<40			40-<60			≥60		
			Mean(SD)	Max	Min	Mean(SD)	Max	Min	Mean(SD)	Max	Min	Mean(SD)	Max	Min
APD (mm)	Female	Left	6.81(0.24)	7.11	6.53	6.12(0.83)	7.80	4.42	6.12(1.01)	8.90	4.41	5.71(0.94)	7.42	4.73
	Male	Left	6.12(0.71)	7.02	5.20	6.21(1.01)	8.11	4.62	6.33(0.81)	8.33	4.92	6.03(0.61)	6.73	4.91
	Female	Right	5.92(0.23)	6.13	5.70	6.23(1.11)	8.13	3.21	5.81(0.82)	7.52	4.43	5.42(0.93)	7.11	3.82
	Male	Right	6.11(0.62)	6.84	5.41	6.11(0.82)	7.22	4.64	6.23(0.91)	8.43	4.01	6.21(0.92)	7.32	4.64
TD (mm)	Female	Left	7.83(0.64)	8.62	7.12	6.92(1.14)	8.81	4.44	6.74(1.43)	10.03	4.34	6.62(0.91)	8.33	5.71
	Male	Left	7.14(0.54)	7.61	6.42	7.60(1.32)	10.02	5.72	7.23(0.83)	9.13	5.62	7.33(1.11)	8.61	5.13
	Female	Right	7.31(0.52)	8.23	6.73	6.91(1.13)	9.42	3.11	6.83(1.41)	10.03	4.21	6.21(0.92)	8.24	5.54
	Male	Right	7.01(0.91)	7.90	5.61	7.21(1.24)	9.43	4.93	7.03(1.22)	10.44	5.04	7.03(0.93)	8.12	5.63
AM (mm)	Female	Left	6.51(1.02)	8.12	5.63	9.03(1.52)	12.90	6.70	10.33(2.12)	15.01	6.42	10.74(3.11)	18.63	7.42
	Male	Left	8.14(1.03)	9.80	7.32	9.01(2.23)	14.61	6.04	9.12(1.92)	13.83	5.03	10.71(0.93)	11.81	9.61
	Female	Right	7.01(1.63)	9.31	4.91	8.40(1.51)	12.63	5.51	10.21(2.11)	15.32	6.11	10.52(3.34)	18.74	6.54
	Male	Right	7.70(1.32)	9.23	6.32	8.63(1.70)	12.51	6.11	9.34(1.73)	13.11	5.63	10.23(0.71)	11.73	9.73
PM (mm)	Female	Left	2.90(0.41)	3.52	2.31	3.22(1.31)	5.92	1.04	3.82(1.32)	5.94	1.04	3.11(1.33)	6.32	1.62
	Male	Left	3.40(0.82)	4.32	2.64	3.71(1.23)	5.83	1.84	3.71(1.51)	8.01	1.12	3.82(1.82)	7.31	1.71
	Female	Right	3.31(0.84)	4.54	2.21	3.52(1.21)	6.43	1.32	4.11(1.44)	7.22	1.11	3.93(1.64)	7.74	2.24
	Male	Right	4.10(1.23)	5.62	2.32	4.11(1.52)	7.62	2.32	3.71(1.12)	6.23	1.03	4.31(1.31)	6.33	3.02
FURD (mm)	Female	Left	3.93(0.51)	4.54	3.21	3.82(0.83)	5.61	2.41	4.04(1.02)	6.13	2.22	3.22(0.52)	3.92	2.51
	Male	Left	3.42(1.04)	4.70	1.83	4.22(1.30)	6.72	2.32	4.03(0.82)	5.43	2.73	3.91(1.63)	6.91	2.03
	Female	Right	4.41(0.91)	5.93	3.82	4.03(1.01)	6.33	2.24	4.63(0.91)	6.94	3.11	3.73(0.52)	4.83	3.12
	Male	Right	3.93(1.44)	5.71	1.83	4.83(1.42)	7.42	2.41	4.11(0.90)	6.03	2.52	4.24(1.14)	6.11	3.04
IFD (mm)	Female		25.91(0.93)	27.32	25.12	26.71(2.10)	30.81	22.91	27.83(2.02)	31.02	23.94	26.11(2.64)	30.44	22.23
	Male		27.12(1.12)	28.61	25.83	27.92(2.53)	34.11	23.30	27.91(1.72)	31.63	25.01	28.62(1.12)	29.91	27.01

Key: anteroposterior diameter (APD), transverse diameter (TD), foramen-uncus ridge distance (FURD), anterior margin (AM), posterior margin (PM), interforaminal distance (IFD), standard deviation (SD), millimetre (mm)

Discussion

Foramina serve as an essential landmark in medical imaging procedure and surgery, owing to their anatomy in relation to the associated neurovascular bundles. FT of the cervical vertebrae exhibits different variations and better understanding on these variations and their anatomy are clinically relevant (Sethi *et al.*, 2014). In view of this, a study that employed MB ruler to assess the morphometric variations in FT in relation to the age and sex of the specimens in a KwaZulu-Natal population, South Africa was designed.

The results on the morphometric investigation of FT observed different dimension of measurements ranging from; APD, TD, FURD, AM, PM to IFD.

The APD mean measurement in male was 6.2 mm on both right and left sides. In the female, 5.9 mm and 6.1 mm were observed on right and left respectively. The APD measurement showed no significant difference in the male and female, left and right specimens, also the left and right diameter measurement of the male specimens were the same. The APD measurement was approximately 5.3 mm in male and 4.9 mm in female, APD was larger in male than the female which was in agreement with a previous study that reported larger APD measurement of FT in male than in female (Malik *et al.*, 2010).

The mean TD measurements reported for male specimens were 7.0 mm on the right side and 7.3 mm on the left side while 6.8 mm and 6.9 mm on right and left sides respectively for female specimens. This result clearly revealed a significant difference in TD of male and female on the left sides of the specimens but no significant difference on the right side measurement of specimens. The TD measurements in male were larger than female specimens, also, measurements were slightly larger on the left sides of both sexes. Similar results were previously reported, approximately 6.1 mm in male and 5.58 mm in female, 6.44 mm in male and 5.88 mm in female (Malik *et al.*, 2010; Malla *et al.*, 2018).

The results on the mean FURD measurements were 4.2 mm on the right and 4.0 mm on the left side of male specimen while 4.2 mm were recorded for right side of female and 3.8 mm for left side of female. These results indicate that no significant difference in FURD of both male and female specimens and in right and left. This finding correlates with a study that found no statistical significance in measurements of male (6.35 mm) and female (5.98 mm) despite slight differences in measurements (Malla *et al.*, 2018).

The mean AM value for male were 9.1 mm on both right and left sides, while 9.0 mm and 9.1 mm on right and left sides of female specimens respectively. This result showed no significant difference in AM of both male and female specimens and on right and left. The values recorded for PM in male were 3.9 mm and 3.7 mm on right and left sides respectively. In the female specimens, 3.7 mm and 3.3 mm were documented on right and left sides respectively. These results showed that no significant difference in PM of both male and female specimens and on right and left sides. The measurements on IFD were 27.9 mm for male and 26.8 mm for female which showed significant difference in distance of the male when compare with the female specimens.

In terms of sex, the mean value for APD, TD, PM and IFD measurements showed slightly larger values in male compared with the female, which is in accordance with previous study that reported greater morphometric values of FT in male than female specimens (Malik *et al.*, 2010). In terms of laterality, the mean morphometric values were slightly higher on the right sides.

Different shapes of FT that were observed in this study were round, anteroposterior elliptical, transverse elliptical, oblique elliptical (right to left), oblique elliptical (left to right) and irregular shapes. The absence of FT was also found.

It was evident from this finding that the round shape was the most common shape type of FT in this study. Out of 130 specimens, total of 60 (46.16%) FT were found to be type 1 (round shape) on the right sides of both sexes. On the left side, total of 57 (43.85%) FT was found to be type 1 (round shape).

This result is in accordance with previous studies that reported round shape FT as most common type, 32% and 41.32% (Sunitha *et al*., 2016; Guerra *et al*., 2017).

The anteroposterior elliptical (type 2) was the least common shape type; it occurred only on the left side of male which amount to 0.77 %. This finding (2.4%) corroborates with a recent study by Vasuki *et al*. (2018) that reported least frequency of anteroposterior elliptical shape of FT in dry human cervical vertebrae.

Total number of 26 (20%) on the right side of FT was found to be type 3 (elliptical in transverse) and 30 (23.08%) FT was seen on the left side. Interestingly, this result agrees with the report by Sunitha *et al*. (2016) that documented 21% for transverse elliptical shape of FT as well as this shape to be the second most common shape type.

There were 26 records of oblique elliptical (right to left) shape from the result. Total number of 24 (18.46%) specimens on the right side and only two (1.54%) FTs were found on the left side.

The cases of oblique elliptical (left to right) shape of FTs were documented. There were 25 FT observed for this type. Only three (2.31%) FT exhibits type 5 (elliptical from left to right oblique) on the right side and total number of 22 (16.92%) was observed on left side. The frequencies of oblique elliptical shapes both right to left and left to right types are similar considerably and differed from other shape types. A recent study by Kwiatkowska *et al*. (2014) reported similar findings approximately 10%.

The total of 34 were observed for the irregular type of FT. Total number of 17 (13.07%) FT exhibited type 6 (irregular) in this study on the right side and the same total of 17 (13.07%) were also observed on the left side. This result was similar to previous finding by Aziz and Morgan (2018) that documented 10% frequency for the irregular type of FT.

The absence of FT (type 7) 0.77% was observed on the left side of male specimen. This incidence is lower in comparison to previous studies reported by Zibis *et al*. (2018) 8 out of 350 (2.28%) vertebrae in Indo-European race, and Kimura *et al*. (1985) 18 out of 100 vertebrae (18%) in Japanese population where absence of FT was documented.

The shape of FT investigation has shown that, round shape (Type 1) was the most common shape type, while transverse elliptical shape (Type 3) was second in common and anteroposterior elliptical (Type 2) was the least common shape type of FT. This study was also observed the absence of foramen (type 7) in a male specimen on the left side.

The result on the variations of FT in relation to sex was not statistically significant. The presence of DF in male specimens which correlates to the result of this finding that observed higher frequency of DF in male specimen compared to female. There was a case of absence of foramen in male specimen in this study which is in conformity with recent report by Kwiatkowska *et al*. (2014). Previous study by Zibis *et al*. (2018) documented the presence of hypoplastic, duplicated and triplicated FT but in this study, the cases of hypoplastic and triplicated FT were not observed.

This study provides more insight into the variation of DFT in terms of sexual dimorphism. It was evident from this study that, frequency of bilateral DF was higher in male (11.54 %) compared to female (6.92%) specimens while cases of unilateral DF were larger in female (10%) compared to male (8.46%) specimens. This was supported by Patra *et al*. (2015) study, who documented that the bilateral formation (11.33%) was more frequent than unilateral formation (10.67%), although their report did not consider sexual dimorphism. These findings contrary to another similar study that reported that unilateral formation was significantly the most frequent and found no differences were found based on sex (Quiles Guiñau *et al.*, 2016). Presence of DFT observed in this study would provide guide during the screw fixation operation when using posterior approach.

The mean APD were higher in male specimens on both left and right at age groups 40- < 60 and ≥ 60 while only larger on left side in female age < 20. Similar findings were reported by Malik *et al*. (2010), who documented that all measurements were significantly different between males and females, with smaller female dimensions.

The mean value of TD was observed to be larger in male on the left sides across all the age groups but in female specimens it was higher in age group that were < 20. Similar results on the laterality of the TD were reported by Yesender *et al*. (2017).

Different values were observed for the AM distance. The higher values for AM were observed in males on the left side in age group < 20. Additionally, in both sexes were observed the higher values on left sides at age 20-< 40. Similar values were also observed in both sexes on both sides in age group 40-< 60 and ≥ 60. The values of PM were higher in all male specimens on the right sides in all age groups except age group 40-< 60 where the value was larger in females on the right side. Based on the results of morphometric parameters in this study, anatomical variations with respect to sex, age and laterality, the size of the FT may determine the size of the vertebral artery (VA) and the variation in FT will also determine the number of branches of VA. This may influence the outcome of the surgical procedure and radiological assessment.

The FURD were measured and documented. The higher values were observed in the male on the right sides in age groups 20-< 40 and ≥ 60 while larger values were noticed in female on the right sides in age groups < 20, 40-< 60. This result correlates with previous findings that observed higher mean FURD in male than in female (Oh *et al.*, 1996; Curylo *et al.*, 2000; Güvençer *et al.*, 2006; Malik *et al.*, 2010).

The higher values for IFD were observed in male in all age groups except age group 40-< 60 where there was similarity in the distance. Malik *et al*. (2010) reported that mean interforaminal distance was greater in males than in females at each spinal level, which is similar to the findings of this study. The variation in anatomical parameters of FT regarding the sex, age and laterality is of great importance owing to the associated neurovascular structures. In addition, sexual dimorphism has been reported on different morphometric parameters in human body.

Conclusion

In terms of sex, the mean values for APD, TD, PM and IFD measurements showed slightly larger values in males compared with the females. In terms of laterality, the mean morphometric values were slightly higher on the right sides. The shape of FT investigation has shown that, round shape (Type 1) was the most common shape type, while transverse elliptical shape (Type 3) was second in common and anteroposterior elliptical (Type 2) and absence of FT (Type 7) were the least common shape type of FT. The absence of FT (type 7) in a male specimen on the left side was observed in this study. The variation in FT in relation to sex revealed the presence of normal and DF, it was observed that frequency of bilateral DF is common in male compared to female and the cases of bilateral DF was common than unilateral DF. The result of this study has demonstrated that risk of injury to neurovascular structures associated with FT may likely to be more common on the left sides, in female and especially age group < 20 and ≥ 60. This was based on the hypothesis that the diameter of FT was a good marker of VA size, the smaller the diameter of FT, the likelihood of VA hypoplasia.

Acknowledgments

We hereby acknowledge the College of Health Sciences (CHS), University of Kwa-Zulu Natal, Durban, South Africa for CHS funding and Grant from Incentive fund rated researchers, SA national research foundation with grant number Cprr U119257

Conflict of interest

Authors hereby declare no conflict of interest

References

Aziz, J.N. and Morgan, M., 2018. Morphological Study of the Foramen Transversarium of the Atlas Vertebra among Egyptian Population and Its Clinical Significance. *Anatomy Physiology & Biochemistry International Journal*, 4(4), pp.1-5. DOI: 10.19080/APBIJ.2018.04.555642.

Briggs, A.M., Woolf, A.D., Dreinhöfer, K., Homb, N., Hoy, D.G., Kopansky-Giles, D. and March, L., 2018. Reducing the global burden of musculoskeletal conditions. *Bulletin of the World Health Organization*, 96(5), pp.366–368. doi:10.2471/BLT.17.204891

Briner, M., 2006. Erik Erikson page, 1999, on Briner's site about learning theories, USMA Department of Mathematical Sciences. *Center for Assessment and Program Evaluation (CAPE), United States Military Academy at West Point. Accessed*, *24*.

Curylo, L.J., Mason, H.C., Bohlman, H.H. and Yoo, J.U., 2000. Tortuous course of the vertebral artery and anterior cervical decompression: a cadaveric and clinical case study. *Spine*, *25*(22), pp.2860-2864.

Dalgic, A., Okay, O., Nacar, O., Daglioglu, E., Pasaoglu, L. and Belen, D., 2009. Vertebral artery insult at the transverse foramina by gun shot wounds: report of two cases. *Turkish Neurosurgery*, 19(4), pp.413-416.

Das, S., Suri, R. and Kapur, V., 2005. Double foramen transversaria: An osteological study with clinical implications. *International Medical Journal*, 12(4), pp.311-313.

Guerra, M.M., Fuentes, P.R., Roa, I., Molinet, G., Robles, F. and Roa, I., 2017. Anatomical variations of the foramen transversarium in cervical vertebrae. *International Journal of Morphology*, *35*(2), pp.719-722. doi:10.4067/s0717-95022017000200053

Güvençer, M., Men, S., Naderi, S., Kiray, A. and Tetik, S., 2006. The V2 segment of the vertebral artery in anterior and anterolateral cervical spinal surgery: a cadaver angiographic study. *Clinical Neurology and Neurosurgery*, *108*(5), pp.440-445.

Hazar, Z., Karabicak, G.O. and Tiftikci, U., 2015. Reliability of photographic posture analysis of adolescents. *Journal of Physical Therapy Science*, 27(10), pp.3123-3126.doi:10.1589/jpts.27.3123

Hsu, W.K., 2011. Advanced techniques in cervical spine surgery. *The Journal of Bone & Joint Surgery*, *93*(8), pp.780-788.

Kaya, S., Yilmaz, N.D., Pusat, S. Kural,C., Kırık, A. and Izcı1, Y., 2011. Double foramen transversarium variation in ancient byzantine cervical vertebrae: preliminary report of an anthropological study. *Turkish Neurosurgery*, 21, pp.534–538. doi:10.5137/1019-5149.JNT.4456-11.1

Kimura, K., Konishi, M. and Hu, S.Y., 1985. Shape and size of the transverse foramina in Japanese. *Okajimas Folia Anatomica Japonica*, 62(2), pp.123-131. doi:10.2535/ofaj1936.62.2_123

Kwiatkowska, B., Szczurowski, J. and Nowakowski, D., 2014. Variation in Foramina Transversaria of Human Cervical Vertebrae in the Medieval Population from Sypniewo (Poland). *Anthropological Review*, 77(2), pp.175–188. doi:10.2478/anre-2014-0014

Levinson, D.J., 1986. A conception of adult development. *American Psychologist*, *41*(1), pp.3.

Malik, S.W., Stemper, B.D., Metkar, U., Yoganandan, N., Shender, B.S. and Rao, R.D., 2010. Location of the transverse foramen in the subaxial cervical spine in a young asymptomatic population. *Spine*, 35(12), pp.514-519.

Malla, H.P., Kim, S.B., Won, J.S. and Choi, M.K., 2018. Study of the Transverse Foramen in the Subaxial Cervical Spine in Korean Patients With Degenerative Changes: An Anatomical Note. *Neurospine*, *15*(2), pp.163.

Manjunath, M.V., Kavitarati, D. and Sugathan, K.R., 2018. A study of presence of accessory foramina transversaria in dry human cervical vertebrae of South Indian origin. *International Journal of Medical Science and Public Health*, *7*(11), pp.934-938.

Moore, K.L., Dalley, A.F. and Agur, A.M.R., 2013. Clinically Oriented Anatomy 7th edition, *Lippincott Williams & Wilkins*.

Murlimanju, B.V., Prabhu, L.V., Shilpa, K., Rai, R., Dhananjaya, K.V. and Jiji, P.J., 2011. Accessory transverse foramina in the cervical spine: incidence, embryological basis, morphology and surgical importance. *Turkish Neurosurgery*, 21, pp.384-387. doi:10.5137/1019-5149.JNT.4047-10.0

Oh, S.H., Perin, N.I. and Cooper, P.R., 1996. Quantitative three-dimensional anatomy of the subaxial cervical spine. Implication for anterior spinal surgery. *Neurosurgery*, *38*(6), pp.1139-1144.

Patra, A., Kaur, H., Chhabra, U., Kaushal, S. and Kumar, U., 2015. Double foramen transversarium in dried cervical vertebra: An osteological study with its clinical implications. *Indian Journal of Oral Sciences*, *6*(1), pp.7-9.

Quiles Guiñau, L., Gomez Cabrero, A., Miquel Feucht, M., Blanco Pérez, E., Mata Escolano, F. and Sanchis Gimeno, J.A., 2016. Analysis of the cervical double transverse foramen in present Spanish population. *European Journal of Anatomy*, *20*(4), pp.337-346.

Sethi, M., Vasudeva, N. and Mishra, S., 2014. Study of foramen transversaria of first cervical vertebrae and its variations. *OA Anatomy*, *2*, pp.25.

Singh, A.P., Anand, C. and Singh, S., 2019. A study of anatomical variations in transverse foramen of cervical vertebrae for morphological & clinical importance. *International Journal of Contemporary Medical Research*, 6(6), pp.9-11. DOI: http://dx.doi.org/10.21276/ijcmr.2019.6.6.19

Sunitha, N.S., Karpagajothi, J. and Bharathi Rani, S., 2016. Interesting Facts about the Foramen Transversarium of Cervical Vertebra. *IOSR Journal of Dental and Medical Sciences*, 15(1), pp.20-24. DOI: 10.9790/0853-15182024

Taitz, C., Nathan, H. and Arensburg, B., 1978. Anatomical observations of the foramina transversaria. *Journal of Neurology, Neurosurgery & Psychiatry*, 41(2), pp.170-176.

Vasuki, A.M., Jamuna, M., Nirmaladevi, M., Hebzibah, D.J., Radhika, K. and Krishnan, K., 2018. An osteological study of foramen transversarium of cervical vertebrae and its clinical significance. *International Journal of Anatomy & Research*, 6(1.2), pp.4906-4913. DOI: 10.16965/ijar.2017.505

Yesender, M., Devadas, P., Saritha, S. and Vinila, B.S., 2017. Study on the anatomical variations and morphometry of foramen transversaria of the subaxial cervical vertebrae. *International Journal of Anatomy & Research*, *5*(2.1), pp.3708-3712. DOI: 10.16965/ijar.2017.151

Zibis, A., Mitrousias, V., Galanakis, N., Chalampalaki, N., Arvanitis, D. and Karantanas, A., 2018. Variations of transverse foramina in cervical vertebrae: what happens to the vertebral artery?. *European Spine Journal*, 27(6), pp.1278-1285. doi:10.1007/s00586-018-5523-2

Zibis, A.H., Mitrousias, V., Baxevanidou, K., Hantes, M., Karachalios, T. and Arvanitis, D., 2016. Anatomical variations of the foramen transversarium in cervical vertebrae: findings, review of the literature, and clinical significance during cervical spine surgery. *European Spine Journal*, 25(12), pp.4132-4139. doi:10.1007/s00586-016-4738-3

CHAPTER THREE

CHAPTER THREE

3.1 Synthesis

In this study various morphometric parameters were investigated on foramen transversarium (FT) in relation to sex, age and laterality as well as variations of FT.

Using the MB digital screen ruler, almost all the morphometric parameters were slightly higher in the male specimens compared to the mean values from female specimens. Similar results were documented by Malik *et al*. (2010) on 490 human cervical vertebrae employed from Computed Tomography (CT) scan.

This implies that the method used in this present study was reliable and valid.

The results on morphometric parameters in relation to sex in this present study indicates that, the mean value for the antero-posterior diameter (APD), transverse diameter (TD), posterior margin (PM) and interforaminal distance (IFD) measurements showed slightly larger values in male compared with the female, which is in accordance with a previous study that reported greater morphometric values of FT in male than female specimens (Malik *et al* 2010). More so, based on laterality, the mean morphometric values were slightly higher on the right sides. A similar study reported the variations in diameter of vertebral artery (VA) in approximately 75 % (Rohkamm, 2004). The implication of this result is that considerable narrowing of FT may put the patients at the risk of vertebrobasilar insufficiency.

The shape of FT investigation had shown that, round shape (Type 1) was the most common shape type, followed by transverse elliptical shape (Type 3) and, antero-posterior elliptical (Type 2) and absent of FT (Type 7) are the least common shape type of FT. In a recent report, it was observed that the round (type 1) shape of FT was found in 32% which accounts for the most common shape in their study (Sunitha *et al*., 2016). Information on the variations of FT may assist in radiological diagnosis and interpretation as well as computed tomography scans. Additionally, this data may be helpful during intervention on the vertebrae and associated structures in order to ascertain the exact surgical method applicable.

The absence of FT (type 7) was observed in this study in a male specimen on the left side. Similar findings of a case report by Vasudeva and Kumar (1995), which documented absence foramen on the left side. The author attributed the absence of FT to developmental anomalies, especially that of VA being the one of the structures that traverses it. Therefore, the fate of VA and other structures are not clear in this event but Vasudeva and Kumar (1995) deduced that in such situation of absence of FT, the VA probably passes directly from FT of C2 via the vertebral foramen of C1.

Analysis on variation of FT with respect to sex showed the presence of normal foramen, DF and absence of FT. In this study, frequency of bilateral DF is common in male specimens compared to female and the cases of bilateral DF is common than unilateral DF. Previous studies have reported that reasons such as vascular compression, penetrating injuries, trauma, and fractures to FT or to course of the vascular structures are responsible for the variations of FT (Dalgic *et al*., 2009; Murlimanju *et al*., 2011; Guerra *et al*., 2017). Moreover, the size and shape of FT may affect the course and function of the neurovascular structures passing through it (Kwiatkowska *et al*., 2014). Additionally, reasons for these variations in size and numbers such as fainting attack, compression of VA, migraine and headache have been earlier reported (Murlimanju *et al*., 2011; Guerra *et al*., 2017). Importance of these variations to radiologist, physicians and neurosurgeons in diagnosis and monitoring has been documented. The VA transmitting the FT gives substantial blood supply to the brain as well as a branch of basilar arteries that supplies the inner ear. Entrapment of these arteries may lead to neurological disorders or hearing impairments and these makes knowledge about the variations of FT so significant (Murlimanju *et al*., 2011).

The result of this study has demonstrated that risk of injury to neurovascular structures associated with FT is common on the right sides, in female and especially age group < 20. This is based on the hypothesis that diameter of FT is a good marker of VA size, the smaller the diameter of FT, the likelihood of VA hypoplasia.

3.2 Conclusion

The method employed in this study is reliable and valid since the results of this study are in consonant with other studies. This finding showed that measurement on morphometric parameters of FT were greater in males compared with the females. The result on the laterality showed that values of right sides are higher than left sides except in transverse diameter where higher values were observed in the left side of male specimens. Based on the shape of FT inspection, the round shape (Type 1) was predominant shape in this study followed by transverse elliptical shape (Type 3) and, anteroposterior elliptical (Type 2) and absent of FT (Type 7) were the least common shape type of FT. Also observed was the absence of FT (Type 7) on the left side in male specimen. The variation in FT in relation to sex revealed the presence of normal foramen, DF. The frequency of bilateral DF was found to be common in male compare to female and the cases of bilateral DF is more common than unilateral DF.

In conclusion, special consideration should be given to the left sides in the females especially age group < 20 and ≥ 60. Therefore, information regarding morphometric and anatomical variations analyses on FT is clinically significant owing to severe clinical consequences that may arise as a result of trauma or injury to any of the anatomical structures that traverse through it. Therefore, sound knowledge about the variations in FT in terms of sex, age and laterality are of great benefit in diagnostic purposes, especially the medical imaging.

3.3 Recommendation

Future research should employ MB digital screen ruler and compare it with CT scan and Vernier calliper that has been previous employed in order to investigate anatomical variation and morphometric parameters of the FT

References

Dalgic, A., Okay, O., Nacar, O., Daglioglu, E., Pasaoglu, L. and Belen, D., 2009. Vertebral artery insult at the transverse foramina by gun shot wounds: report of two cases. *Turkish neurosurgery,* 19, pp.413-416.

Guerra, M. M., Fuentes, P. R., Roa, I., Molinet, G., Robles, F. and Roa, I., 2017. Anatomical variations of the foramen transversarium in cervical vertebrae. *International Journal of Morphology,* 35, pp.719-722.

Kwiatkowska, B., Szczurowski, J. and Nowakowski, D., 2014. Variation in foramina transversaria of human cervical vertebrae in the medieval population from Sypniewo (Poland). *Anthropological Review,* 77, pp.175-188.

Malik, S. W., Stemper, B. D., Metkar, U., Yoganandan, N., Shender, B. S. and Rao, R. D., 2010. Location of the transverse foramen in the subaxial cervical spine in a young asymptomatic population. *Spine,* 35, pp.514-519.

Murlimanju, B.V., Prabhu, L.V., Shilpa, K., Rai, R., Dhananjaya, K.V. and Jiji, P.J., 2011. Accessory transverse foramina in the cervical spine: incidence, embryological basis, morphology and surgical importance. *Turkish Neurosurgery*, 21, pp.384-387.

Rohkamm, R., 2004. *Color Atlas of Neurology,* Georg Thieme Verlag.

Sunitha, N., Karpagajothi, J. and Bharathi Rani, S., 2016. Interesting Facts about the Foramen Transversarium of Cervical Vertebra. *IOSR Journal of Dental and Medical Sciences,* 15, pp.20-24.

Vasudeva, N. and Kumar, R., 1995. Absence of foramen transversarium in the human atlas vertebra: a case report. *Cells Tissues Organs,* 152(3), pp.230-233.

APPENDIX

Appendix 1

UNIVERSITY OF
KWAZULU-NATAL
INYUVESI
YAKWAZULU-NATALI
RESEARCH OFFICE
Biomedical Research Ethics Administration
Westville Campus, Govan Mbeki Building
Private Bag X 54001
Durban
4000
KwaZulu-Natal, SOUTH AFRICA
Tel: 27 31 2604769 - Fax: 27 31 2604609
Email: BREC@ukzn.ac.za
Website http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx

27 August 2018

Dr Azu O Okpara
Discipline of Clinical Anatomy
School of Laboratory Medicine & Medical Sciences
Nelson R Mandela School of Medicine
Durban
4013
azu@ukzn.ac.za

PROTOCOL: Class Approval in respect of DOCA - NRMSOM cadavers for 2014 to 2016. BREC REF: BCA356/14.

RECERTIFICATION APPLICATION APPROVAL NOTICE

Approved:	23 July 2018
Expiration of Ethical Approval:	22 July 2019

I wish to advise you that your application for Recertification received on 23 August 2018 for the above protocol has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee (BREC) for another approval period. The start and end dates of this period are indicated above.

If any modifications or adverse events occur in the project before your next scheduled review, you must submit them to BREC for review. Except in emergency situations, no change to the protocol may be implemented until you have received written BREC approval for the change.

The committee will be notified of the above approval at its next meeting to be held on 09 October 2018.

Yours sincerely

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc: naidue@ukzn.ac.za

Appendix 2

Data Sheet

No	Sample	Sex	Age	Race	Left Shape	Right Shape	Accessory Foramen		LAPD	RAPD	LTD	RTD	IFD	LFURD	RFURD	LAM	RAM	LPM	RPM
							Left	Right											

Appendix 3

Conference presentation

Zaw, A.K., 2018. Morphometric analysis of foramen transversarium variation in cervical vertebrae in KZN, South Africa. College of health sciences, research symposium (oral presentation).

Funding

College of Health Sciences (CHS), University of Kwa-Zulu Natal, Durban, South Africa for CHS funding and Grant from Incentive fund rated researchers, SA national research foundation with grant number Cprr U119257

Appendix 4

Turnitin report

Turnitin Originality Report

Processed on: 22-Nov-2019 9:51 AM CAT
ID: 1219360853
Word Count: 8964
Submitted: 1

TEXT By AUNG ZAW

Similarity Index	Similarity by Source	
8%	Internet Sources:	4%
	Publications:	6%
	Student Papers:	2%

1% match (publications)
Aristeidis H. Zibis, Vasileios Mitrousias, Kyriaki Baxevanidou, Michael Hantes, Theofilos Karachalios, Dimitrios Arvanitis. "Anatomical variations of the foramen transversarium in cervical vertebrae: findings, review of the literature, and clinical significance during cervical spine surgery", European Spine Journal, 2016

1% match (publications)
Oluwatosin Olalekan Ogedengbe, Sunday Adelaja Ajayi, Omobola Aderibigbe Komolafe, Aung Khaing Zaw et al. "Sex determination using humeral dimensions in a sample from KwaZulu-Natal: an osteometric study", Anatomy & Cell Biology, 2017

1% match (Internet from 18-Jun-2016)
http://dev.biologists.org/content/142/10/1733.full

< 1% match (publications)
Ricardo Becerro de Bengoa Vallejo, Marta Elena Losa Iglesias, Kevin T. Jules. "Tendon Insertion at the Base of the Proximal Phalanx of the Hallux: Surgical Implications", The Journal of Foot and Ankle Surgery, 2012

< 1% match (student papers from 19-Mar-2018)
Submitted to Mansoura University on 2018-03-19

< 1% match (Internet from 18-Feb-2015)
http://www.samj.org.za/index.php/samj/article/view/6967/5454

< 1% match (publications)
Gülay Açar, Mustafa Büyükmumcu, İbrahim Güler. "Computed tomography based analysis of the lamina papyracea variations and morphology of the orbit concerning endoscopic surgical approaches", Brazilian Journal of Otorhinolaryngology, 2019

< 1% match (publications)
Gabrielle G. Tardieu, Bryan Edwards, Fernando Alonso, koichi Watanabe et al. "Aortic arch origin of the left vertebral artery", Clinical Anatomy, 2017

< 1% match (Internet from 27-Jul-2008)
http://www.tfhrc.gov/safety/hsis/pubs/04134/results.htm

< 1% match (Internet from 05-Oct-2018)
https://jnnp.bmj.com/content/jnnp/41/2/170.full.pdf

< 1% match (Internet from 21-Apr-2014)
http://hsag.co.za/index.php/HSAG/rt/printerFriendly/664/821

< 1% match (Internet from 17-Oct-2010)