"A COMPARATIVE STUDY TO DETERMINE THE ROLE OF SHEAR WAVE ELASTOGRAPHY OF BRAIN PARENCHYMA IN PRETERM AND TERM NEONATES"

By

Dr. JAYENDRA MANNAN V

DISSERTATION SUBMITTED TO SRI DEVARAJ URS ACADEMY OF HIGHER EDUCATION AND RESEARCH, KOLAR, KARNATAKA

In partial fulfilment of the requirements for the degree of

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IN

RADIODIAGNOSIS

Under the Guidance of

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A COMPARATIVE STUDY TO DETERMINE THE ROLE OF SHEAR WAVE ELASTOGRAPHY OF BRAIN PARENCHYMA IN PRETERM AND TERM NEONATES ABSTRACT BACKGROUND The ultrasound-based method known as shear wave elastography makes tissue stiffness measurement quantifiable and non-invasive. The purpose of this study was to assess the stiffness of the neonatal brain in term and preterm neonates using 2-dimensional shear wave elastography and to investigate potential stiffness variations between these groups. METHODOLOGY This prospective study carried out over a period of one year involving 41 term and 41 preterm infants. Patients with suspected congenital malformations, Central nervous system infections, cerebral hemorrhage, Hydrocephalus, Periventricular leukomalacia and insufficient fontanel space were excluded from the study. Comparison of continuous variable (gestational age, SWE values for thalamus, periventricular white matter) across the groups (term vs pre-term group) was performed using the student's t test. Chi square test will be used to compare categorical variables (sex, etc.) between research groups. A P-value of less than 0.05 was deemed statistically noteworthy. RESULTS The mean thalamus SWE (kPa) was higher in term deliveries (8.825 ± 0.3754) compared to preterm 7.805±0.5901 (P < 0.001). The mean periventricular white matter SWE (kPa) was higher in term deliveries (7.298 ± 0.4300) compared to preterm, 6.538±0.5300 (P < 0.001). The cut-off value of SWE of mean thalamus, kPa ≥ 8.35 predicted the preterm delivery with 95% sensitivity and 87.5% specificity. The cut-off value of SWE of mean periventricular white matter, kPa) ≥ 6.85 predicted the preterm delivery with 87.5% sensitivity and 72.5% specificity. CONCLUSION Preterm neonates had stiffer thalamus and periventricular white matter than term neonates, with the thalamus having stiffer values than the periventricular white matter. The mean thalamus and mean periventricular white matter stiffness cut off values that were most effective in identifying preterm were 8.35 kPa and 6.85 kPa, respectively. INTRODUCTION Birth before the 37th week of pregnancy is known as prematurity, and it is a major global health issue.[1] Among the neurologic aftereffects, cerebral palsy poses a 5% to 10% risk to preterm newborns, while cognitive, behavioral, or communication impairments pose a 50% risk.[2–9] Reduced gestational age is linked to an increase in mental and neuro-motor deficits in extremely preterm infants.[5] Premature births can cause a wide range of disabilities in their victims, from moderate developmental delays to complete neurological destruction. Healthy preterm newborns show changes in their brain structure even in the absence of obvious neurological injury, which may explain why they are more likely to experience cognitive impairments, neuro-motor abnormalities, and neuro-developmental problems. In recent years, Not in the focus on trying as per the GI on the important of the aspect in the non variable sources..[10] As with many non since, an improved in on of disease pathogeneses and prognoses requires an understanding of the stiffness of brain tissues.[11] In this regard, it is important to be aware of the rigidity of the newborn brain in order to comprehend the neurologic deficiencies resulting from preterm. Understanding the stiffness of brain tissues is necessary to increase our understanding of disease pathogeneses and prognoses, as is the case with many organ systems.[11] In this sense, understanding the neurologic abnormalities resulting from preterm birth requires an awareness of the rigidity of the newborn brain. The pediatric brain can be imaged with low-cost, portable, high-resolution, & radiation-free conventional cranial ultrasonography (US). However, compared to CT and MRI, grayscale and CDI of parenchyma of brain has a poorer diagnostic sensitivity and specificity, much like US imaging of other organ systems.[12] It has been demonstrated that elastography increases the sensitivity and specificity of US in identifying pathology in several organ systems—cirrhosis, in particular.[13-16] Both intraoperative US elastography and brain MR elastography have shown increased stiffness in the brain masses and altered parenchymal stiffness in the context of different intracranial diseases.[17] ARFI) is used in the comparatively new technique where, tissue stiffness is measured using ultrasound SWE). Compared to other ultrasound-based elastography techniques like strain elastography, the ARFI technique is intrinsically less operator-dependent since it causes interior tissue deformation (shear waves). SWE enables quantitative stiffness assessment and correlation with grayscale images at the same time.[18] SWE has shown promise as a safe and effective method to assess diseases impacting several organ systems in the juvenile population, including the musculoskeletal system, central neurological system, and gastrointestinal system (mostly liver illness).[19] The main instance of the of in at the is on youUnderstanding the stiffness of brain tissues is necessary to increase our understanding of disease pathogeneses and prognoses, as is the case with many organ systems.[11] In this sense, understanding the neurologic abnormalities resulting from preterm birth requires an awareness of the rigidity of the newborn brain. The pediatric brain can be imaged with low-cost, portable, high-resolution, & radiation-free conventional cranial ultrasonography (US). However, compared to CT and MRI, grayscale and CDI of parenchyma of brain has a poorer diagnostic sensitivity and specificity, much like US imaging of other organ systems.[12] It has been demonstrated that elastography. REVIEW OF LITERATURE There are significant organizational events and fast growth throughout the third trimester,, which may account for premature infants' greater brain susceptibility. These events include the appropriate alignment and lamination of the growing cortex as well as the development of new circuits at the system level. Cellular processes that occur at different times in distinct parts of the brain include ramification of axon, dendritic arborization, proliferation of glial synaptogenesis & differentiation. Consequently, this developmental trajectory can be derailed and subsequent stages of neurodevelopment affected if these events are interrupted by injury or incorrect signaling associated with preterm birth. The two main methods used to identify neurological damage in newborns are MRI) and ultrasonography (USG). Utilization of computed tomography is typically discouraged due to ionizing radiation. Magnetic resonance imaging is thought to be one of the best imaging technique on locating abnormalities in the brain. Understanding the stiffness of brain tissues is necessary to increase our understanding of disease pathogeneses and prognoses, as is the case with many organ systems.[11] In this sense, understanding the neurologic abnormalities resulting from preterm birth requires an awareness of the rigidity of the newborn brain. The pediatric brain can be imaged with low-cost, portable, high-resolution, & radiation-free conventional cranial ultrasonography (US). However, compared to CT and MRI, grayscale and CDI of parenchyma of brain has a poorer diagnostic sensitivity and specificity, much like US imaging of other organ systems.[12] It has been demonstrated that elastograph. Since ultrasonography can be done cheaply at the bedside and provides quick disease diagnosis in severely unwell newborns, it is a complementary and vital imaging modality. Another benefit of ultrasound is that it makes serial imaging possible, something that is frequently cannot do due to long admission times, transportation costs, and other issues. Ultrasound has some

LIST OF ABBREVIATIONS

Kpa	Kilo pascal
WM	White matter
GA	Gestational age
US	Ultrasound
MRI	Magnetic resonance imaging
cUS	Cranial ultrasonography
SWE	Shear wave elastography
AUC	Area under ROC curve
ROC	Receiver operating characteristic curve
ARFI	Acoustic Radiation Force Impulse
Pre-OLS	Pre oligodendrocytes
RTE	Real time elastography
CE	Compression elastography
TE	Transient elastography
VTIQ	Virtual Touch tissue imaging & quantification
ARFI	Acoustic Radiation Force Impulses
ASQ	Acoustic structure quantification
ROI	Region of interest
SWE	Shear wave elastography
SWV	Shear wave velocity
USE	Ultrasound elastography
PWMLs	Punctate white matter lesions
GMH -IVH	Germinal matrix and intraventricular hemorrhage
PVHI	periventricular hemorrhagic infarction
PVL	Periventricular leukomalacia
cPVL	cystic periventricular leukomalacia

FOV	Field of vision
VTq	Virtual touch quantification
TI	Thermal Index
E	Young's modulus
2D-SWE	Two-dimensional shear wave elastography
CT	Computed tomography

ABSTRACT

Introduction: Birth before the 37th week of pregnancy is known as prematurity, and it is a major global health issue. Premature births can cause a wide range of disabilities in their victims, from moderate developmental delays to complete neurological destruction. Among the neurologic aftereffects, cerebral palsy poses a 5% to 10% risk to preterm newborns, while cognitive, behavioral, or communication impairments pose a 50% risk. As is the case with many organ systems, a greater understanding of the pathogeneses and prognoses of disease requires an understanding of the stiffness of brain tissues. In this way, knowledge of the stiffness of the newborn brain is necessary to comprehend the neurologic disorders resulting from preterm birth. The purpose of this study was to assess the stiffness of the neonatal brain in term and preterm neonates using 2-dimensional shear wave elastography and to investigate potential stiffness variations between these groups.

Aim:

1. To assess the stiffness of the neonatal brain using the SWE method in term and preterm neonates.
2. To evaluate possible differences in elasticity between groups.
3. To derive a cut off reference range for evaluating neonatal brain stiffness between preterm and term neonates.
4. To predict possibility of future brain injuries related to prematurity.

Methods: This prospective study carried out over a period of 18 months involving 41 term and 41 preterm infants. Patients with suspected congenital malformations, Central nervous system infections, cerebral hemorrhage, Hydrocephalus, Periventricular leukomalacia and insufficient fontanel space were excluded from the study. Comparison of continuous variable

(gestational age, SWE values for thalamus, periventricular white matter) across the groups (term vs pre-term group) was performed using the student's t test. Chi square test will be used to compare categorical variables (sex, etc.) between research groups. A P-value of less than 0.05 was deemed statistically noteworthy.

Results: The mean thalamus SWE (kPa) was higher in term deliveries (8.825 ± 0.3754) compared to preterm 7.805±0.5901 (P < 0.001). The mean periventricular white matter SWE (kPa) was higher in term deliveries (7.298 ± 0.4300) compared to preterm, 6.538±0.5300 (P < 0.001). The cut-off value of SWE of mean thalamus, kPa < 8.35 predicted the preterm delivery with 95% sensitivity and 87.5% specificity. The cut-off value of SWE of mean periventricular white matter, kPa) < 6.85 predicted the preterm delivery with 87.5% sensitivity and 72.5% specificity.

Conclusion: Preterm neonates had stiffer thalamus and periventricular white matter than term neonates, with the thalamus having stiffer values than the periventricular white matter. The mean thalamus and mean periventricular white matter stiffness cut off values that were most effective in identifying preterm were 8.35 kPa and 6.85 kPa, respectively.

Keywords: Neonatal brain, congenital malformations, Brain stiffness, Shear wave elastography, Prematurity complications.

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INTRODUCTION

INTRODUCTION

Birth before the 37th week of pregnancy is known as prematurity, and it is a major global health issue.[1] Among the neurologic aftereffects, cerebral palsy poses a 5% to 10% risk to preterm newborns, while cognitive, behavioral, or communication impairments pose a 50% risk.[2–9] Reduced gestational age is linked to an increase in mental and neuro-motor deficits in extremely preterm infants.[5] Premature births can cause a wide range of disabilities in their victims, from moderate developmental delays to complete neurological destruction. Healthy preterm newborns show changes in their brain structure even when there are no overt neurological injury, which may explain why they are more likely to experience cognitive impairments, neuro-motor abnormalities, and neuro-developmental problems. In recent years, Studies have generally tended to focus on trying to comprehend the fundamental processes behind these detrimental neurologic impacts.[10]

Similar to numerous organ systems, an improved knowledge of disease pathogeneses and prognoses requires an understanding of the stiffness of brain tissues.[11] In this regard, it is important to be aware of the rigidity of the newborn brain in order to comprehend the neurologic deficiencies resulting from preterm.

Understanding the stiffness of brain tissues is necessary to increase our understanding of disease pathogeneses and prognoses, as is the case with many organ systems.[11] In this sense, understanding the neurologic abnormalities resulting from preterm birth requires an awareness of the rigidity of the newborn brain.

The pediatric brain can be imaged with low-cost, portable, high-resolution, & radiation-free conventional cranial ultrasonography (US). However, compared to CT and MRI, grayscale and CDI of parenchyma of brain has a poorer diagnostic sensitivity and specificity, much like US imaging of other organ systems.[12] It has been demonstrated that

elastography increases the sensitivity and specificity of US in identifying pathology in several organ systems—cirrhosis, in particular.[13-16] Both intraoperative US elastography and brain MR elastography have shown increased stiffness in the brain masses and altered parenchymal stiffness in the context of different intracranial diseases.[17]

ARFI) is used in the comparatively new technique where, tissue stiffness is measured using ultrasound SWE). Compared to other ultrasound-based elastography techniques like strain elastography, the ARFI technique is intrinsically less operator-dependent since it causes interior tissue deformation (shear waves). SWE enables quantitative stiffness assessment and correlation with grayscale images at the same time.[18] SWE has shown promise as a safe and effective method to assess diseases impacting several organ systems in the juvenile population, including the musculoskeletal system, central neurological system, and gastrointestinal system (mostly liver illness).[19]

The main objective of the present study is to determine the role of wave shear elastography of brain parenchyma among the preterm and term neonates.

AIMS & OBJECTIVES

AIMS AND OBJECTIVES

1. To assess the stiffness of the neonatal brain using the SWE method in term and preterm neonates.
2. To evaluate possible differences in elasticity between groups.
3. To derive a cut off reference range for evaluating neonatal brain stiffness between preterm and term neonates.
4. To predict possibility of future brain injuries related to prematurity.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

There are significant organizational events and fast growth throughout the third trimester., which may account for premature infants' greater brain susceptibility. These events include the appropriate alignment and lamination of the growing cortex as well as the development of new circuits at the system level. Cellular processes that occur at different times in distinct parts of the brain include ramification of axon, dendritic arborization, proliferation of glial synaptogenesis & differentiation. Consequently, this developmental trajectory can be derailed and subsequent stages of neurodevelopment affected if these events are interrupted by injury or incorrect signaling associated with preterm birth.

The brain's developmental events during the premature period

It is critical to comprehend the background of both brain damage and dysmaturation before examining the anomalies in the neuropathology of the brain in preterm babies. The setting here is the amazing sequence of brain development processes that take place in the final 15 weeks of pregnancy in the human body.[20,21] As a result, in the cerebral white matter, axon sheathing begins at around 30 weeks of gestation for Pre-oligodendrocytes (pre-OLs) is the main cellular target in damage to the cerebral white matter and the predominant type of the oligodendroglial lineage during this time.[22,23] Axonal ensheathing is a necessary step in the process of subsequent myelination, which is a post-term event of the cerebrum. This mechanism is essential during the premature period for axonal growth and differentiation, which in turn leads to the development of the thalamus, basal ganglia, cerebral cortex, cerebral white matter, and farther-reaching gray matter sites. The involved mechanisms and structural specifics have already been explored elsewhere.[21,24-33] As a consequence of damage to the cerebral white matter in preterm babies, where impaired pre-OL development is a

significant component, initially, normal pre-OL development is necessary for these developmental events. This leads to dysmaturation of the cerebral cortex, thalamus, and basal ganglia in addition to cerebral white matter. During this stage of development, the cerebellum is also rapidly maturing, primarily due to a layer of neural progenitors on its surface that are proliferating quickly.[34,35] Cerebellar growth is disrupted when these proliferating cells sustain damage or are hindered by external stimuli.[14,36]

One typical conclusion of a clinical significance in pre-mature infants is cerebellar underdevelopment, which may be the outcome.[37]

The Pathophysiology of Brain Damage in the premature Stage

The focus of the AAP study on the neuropathology of brain injury in preterm infants is on overt forms of injury, such as cystic periventricular leukomalacia (c-PVL) and severe GMH-IVH. These lesions are becoming less common yet still significant.[38] PVL is composed of two distinct components: the leukomalacia component of PVL, It is a focal periventricular necrosis in which every cell is lost, and the diffuse white matter gliosis, which is a disruption of the pre-OLs combined with microgliosis and astrogliosis in the cerebral white matter.[39,41] In the diffuse component of PVL, the pre-OL disturbance is characterized by acute cell death, which is followed by subacute and chronic pre-OL pool replenishment. Crucially, though, these pre-OLs are unable to distinguish between and encase white matter axons. The consequences include poor growth of the previously identified gray matter structures and myelination failure. According to neuropathologic research, in autopsied premature newborns, half or less of the white matter injury is caused by PVL.[39,40] Large enough focal necroses to form cysts are extremely rare; they make up no more than 5% of white matter injuries found after death. Sporadic necroses leading to small patches of gliosis are more common; some of these can be seen on MRI scans as punctate white matter lesions

(PWMLs). Interestingly, though, about half of the white matter damage found in premature children who had autopsies consisted of diffuse white matter gliosis rather than focal necroses, and this makes the condition inappropriately referred to as PVL. Crucially, there is evidence of the distinctive surplus of pre-OLs and the halt of their maturation in this non-necrotic kind of white matter injury.[40] And hence, Despite this even lesser form of white matter injury, one would predict the dysmatorial consequences on white and gray matter previously documented.

The Significance of Identifying Brain Underdevelopment During the Neonatal Stage

Given the mounting evidence that therapies carried out during the neonatal period, in childhood, and after can potentially prevent or at least mitigate long-term dysmaturation, it is especially critical to identify brain dysmaturation in premature infants.[21] A substantial body of clinical and pre-clinical research suggests that certain therapies can focus on events whose developmental trajectory has been changed since gray and white matter structures continue to actively develop after the preterm period.[20,21] Because of this, Ultimately, the detection of brain dysmaturation at the newborn period should serve as a catalyst for the implementation of neuro-restorative interventions, which can include growth factors, environmental enrichment, or particular pharmaceutical treatments like diet.[41]

Imaging in neonates through anterior fontanelle

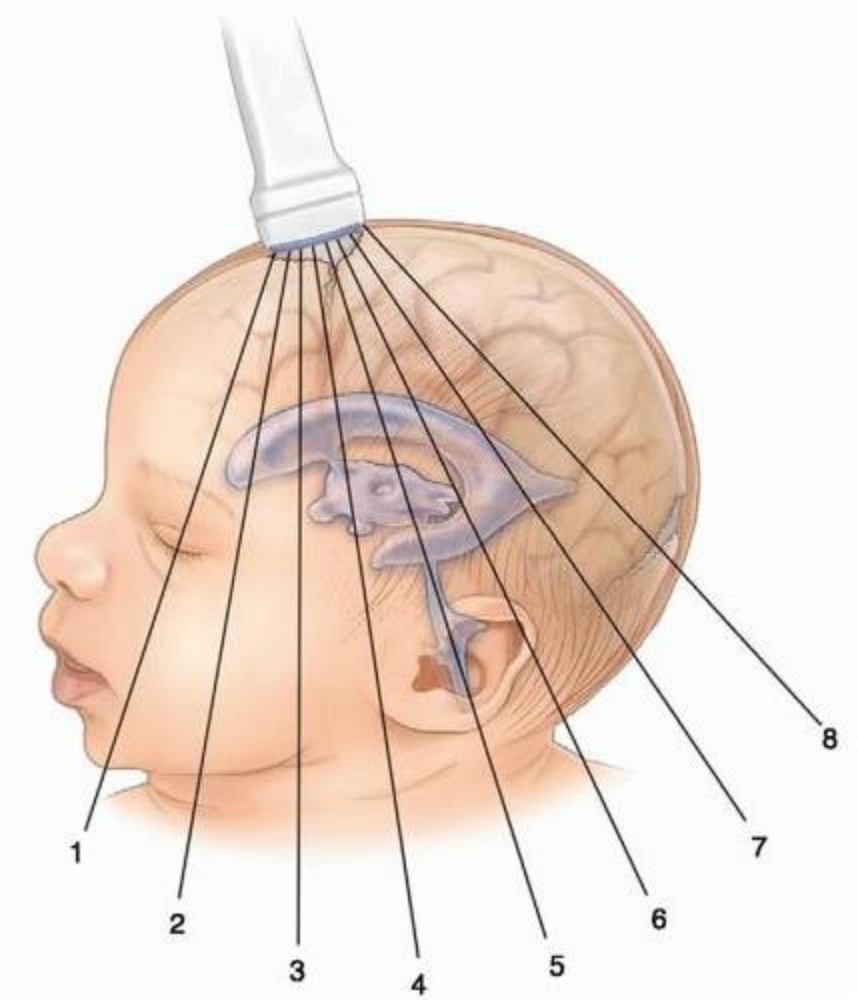

Figure 1: Coronal plan (1-8). Coronal imaging through the anterior fontanella

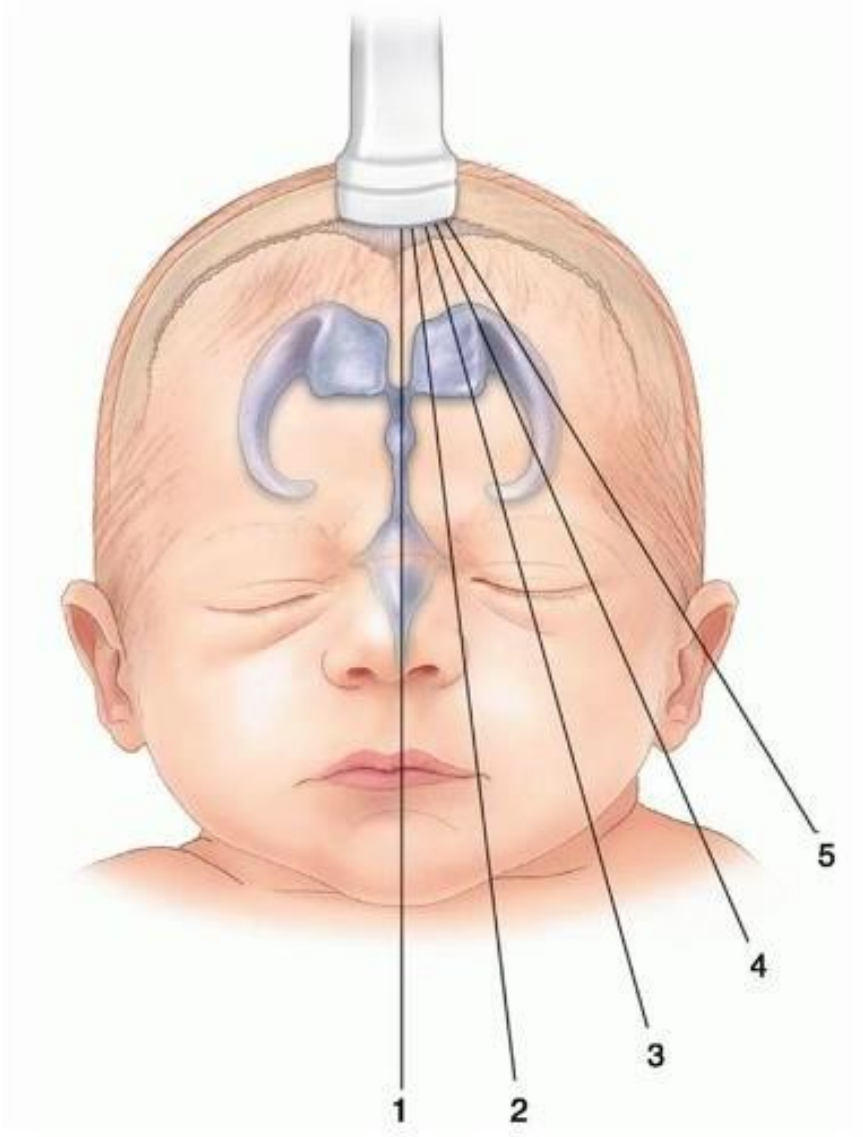

Figure 2: Sagittal scan imaging planes through anterior fontanelle

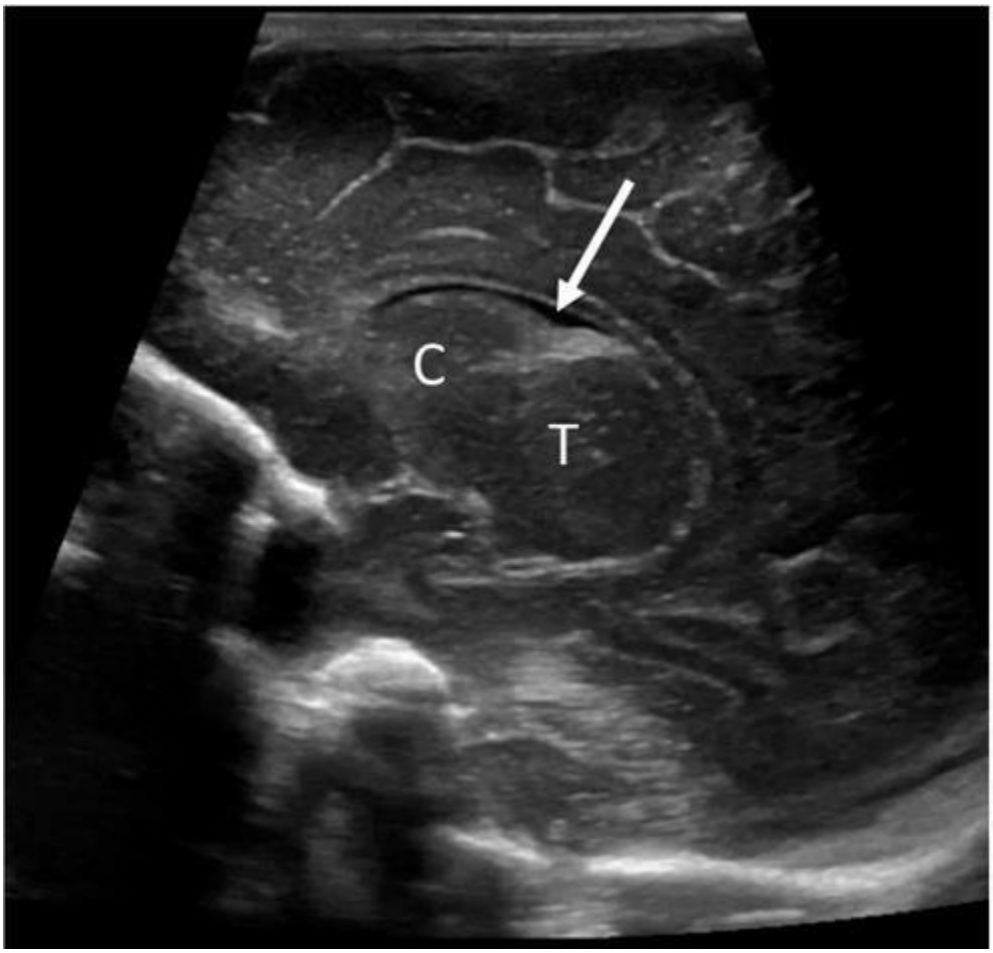

Figure 3: This is a Parasagittal scan at the level of the caudothalamic groove. Head of the caudate nucleus (C) is seen anterior to the thalamus (T). Between these two structures is the caudothalamic groove or notch (arrow), which contains the anterior extent of the choroid plexus (CP).

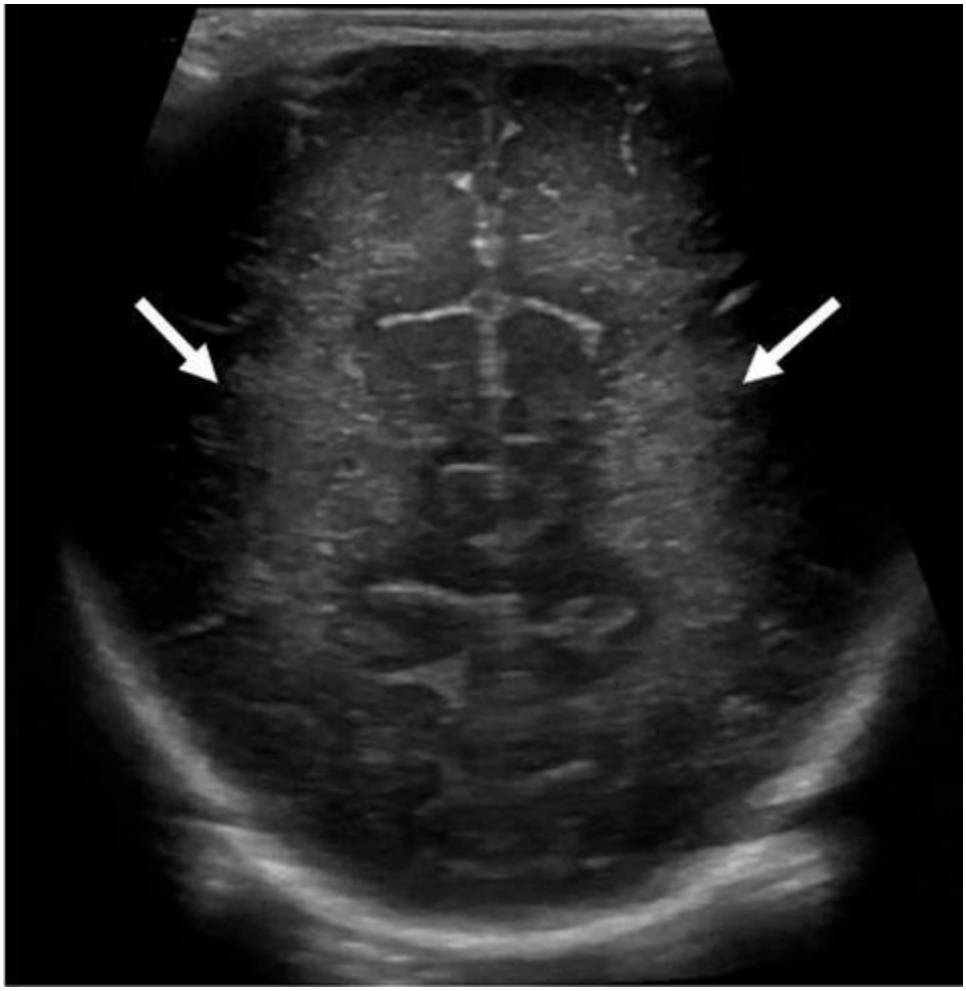

Figure 4: A coronal picture obtained posterior to the occipital horns of the lateral ventricles displaying the occipital brain and normal echogenic periventricular white matter (arrows).

The two main methods used to identify neurological damage in newborns are MRI) and ultrasonography (USG). Utilization of computed tomography is typically discouraged due to ionizing radiation. Magnetic resonance imaging is thought to be one of the best imaging technique on locating abnormalities in the brain. However, Its application to newborns is limited by its lengthy hospitalization periods and the requirement that move patients who can become unstable to MRI rooms. In addition, it is expensive and frequently

necessitates anesthesia, increasing the danger. Because of these difficulties, physicians usually use ultrasonography. Since ultrasonography can be done cheaply at the bedside and provides quick disease diagnosis in severely unwell newborns, it is a complementary and vital imaging modality. Another benefit of ultrasound is that it makes serial imaging possible, something that MRI frequently cannot do due to long admission times, transportation costs, and other issues.

Ultrasound has some drawbacks, such as a lesser sensitivity for diagnosis and prognosis and the requirement for an expert operator to be present. But these restrictions are being quickly overcome, and ultrasonography's potential applications are growing. High-resolution pictures, for instance, are produced using high-frequency ultrasonography (18 to 20 Hz probes can have a resolution of 150 μm). Better Doppler techniques, such ultrafast Doppler, have the potential for functional imaging and produce a significantly greater temporal resolution. Tissue perfusion can be measured with contrast-enhanced ultrasonography.

The sensitivity of predictive and diagnostic value of traditional grayscale ultrasonography can be improved by elastography. The method of elastography is used to measure a tissue's stiffness. With elastography, as opposed to traditional grayscale ultrasonography, the tissue under evaluation is measured quantitatively or semi-quantitatively. Elastography may be especially well adapted for the purpose of studying the brain damage, even though its application is still in its infancy. This is because several alterations linked to brain injury, such as edema, intracranial pressure, and perfusion abnormalities, can affect stiffness. Because the stiffness of the brain tissue varies with development, elastography in neonates may represent both normal and pathological development.

Tissue stiffness is measured using a series of techniques referred to as

elastography, and it is expressed in terms of the Young's modulus (E), a physical property that expresses the connection among the relative change in tissue dimension that results from the applied force per unit area, or stress, and the strain. There are two varieties of ultrasonic elastography techniques: dynamic, or shear wave based, and quasi-static, or strain based.

The kinds of mechanical stimuli that are external to these procedures characterize them.. In strain-based elastography, endogenous mechanical force-such as carotid pulsation-or probe pressure are used to provide force. Shear-wave based elastography uses an imaging technology that creates a shear wave in the tissue. Tissue's mechanical characteristics are estimated using the tissue's reaction to these mechanical stimuli in both methods. Strain imaging makes use of direct relationship $E= \sigma/\varepsilon$, where σ represents externally induced stress and ε represents strain, is known as Hooke's Law. Since the force exerted on the tissue of interest is typically unknown, clinical strain imaging equipment typically does not compute Young's modulus. Shear wave imaging systems compute Young's modulus using the formula $E=3\rho cs2$, where cs is the shear wave speed and ρ represents tissue density. Apart from the automated computation techniques provided by most providers, an ultrasonic operator can translate between kPa and m/s as well as m/s and kPa. Second, after the ultrasound exam is complete, the majority of ultrasound systems show a table with stiffness values in both kPa and m/s.

Elasticity is the ability of a substance or item to return to its original shape after being compressed or stretched. Both the molecular makeup and the structural arrangement of the tissue's constituent parts affect the elasticity of soft tissue.[42] Tissue elastic properties may be modified by significant changes in both compositional and organizational features that occur under pathologic circumstances. Changes in tissue elasticity make it possible to identify the extent of damage, grade a lesion, and show the presence of anomalies in the tissue. Biomechanical characteristics can be characterized using ultrasound elastographic

techniques.[43,44] Quantitative 2-dimensional shear wave elastography (SWE) is being applied by numerous manufacturers using common, accessible ultrasound devices. The excitation mechanism for SWE is an acoustic radiation force impulse.[45,46] Real-time B-mode picture guidance is the primary benefit of this method. which makes it possible to position regions of interest (ROIs) after the elastographic map is acquired in the right location.[47]

An innovative ultrasonographic technique called brain elastography holds the promise of providing operational perceptions of the developing newborn brain. This method deforms a tissue to assess mechanical stiffness by applying an external load, physiological stress, or an auditory stimulus.[48] Strain elastography detects axial displacements of tissue that is deforming in relation to stiffness that is semi-quantitative which measures by using external stressing of manual compression or internal physiological processes, such as heartbeat or breathing. In the region of interest, shear waves propagate laterally thanks to SWE). by deforming a tissue with the help of high intensity ultrasonic pulses, an acoustic radiation force. The tissue stiffness can be measured by measuring at speed of which the waves generates. The use of acoustic force in a comparable manner is shown in ARFI) imaging with VTQ), which measures tissue stiffness based on tissue displacement along the ultrasound beam's axis. elastography of brain has been used to assess stiffness of brain in infants as a means of assessing normal neurodevelopment and diagnosing illness.[49,50,51] Many elastography methods have been used, such as strain elastography and SWE. One of the difficulties in comprehending the physiological significance of the data and moving the field forward is the variety of scan methods for detecting brain elasticity using SWE application of brain elastography in clinical settings for medical treatment.

Technical Background Shear Wave Elastography (SWE)

Conventional B mode picture production uses compressive acoustic waves, which pass through soft tissue at high speeds (1450–1550 m/s). Shear wave elastography, on the other hand, uses mechanical shear waves, which move more slowly (1–10 m/s). Tissue stiffness affects the velocity at which shear waves propagate. Compressive acoustic waves are employed in commercially available shear wave elastography devices for both tracking and inducing shear waves. Shear waves generated by acoustic waves move in a direction opposite to compressive waves. The ultrasound probe monitors the motion of the tissue caused by these waves at several points, allowing for the determination of the shear wave's velocity. SWS) could be utilised in algebraically derive Young's-modulus. SWS is applicable a wide range of tissues and applications.

Shear wave elastography is a quantitative process that may be obtained commercially and is led by ultrasound pictures. One of the benefits of this approach is that it doesn't require much training, and the exam takes less than five minutes. The research done by Ophir et al., who presented elastograms derived from tissue displacement under pressure correlation analysis, is the foundation for the static elastography technique.[52] Dynamic elastography (likewise referred to as real-time elastography, or RTE) was invented at the start of the new century. It entailed overlaying the crucial B-mode with color, values of elasticity in real time. The strain picture is created when the tissue under investigation is subjected to mechanical pressure. This causes a change in the echo frequency pattern. Stiffness of tissues maintain a constant distance from the frequency peaks, while elastic tissues get closer to them. Typically, orange-red represents easily flexible tissue, yellow-green represents intermediately malleable tissue, and blue represents rigid structures. The outcome of strain elastography is qualitative and color-coded. At the very least, the strain ratio may be utilized to calculate the stiffness ratio between the surrounding and ROI regions. The foundation of

dynamic Utilization with shear waves is a focused impulse that enters the tissue as a shock wave and compresses it at a speed of 1540 m/s (virtual touch). Shear waves are released during the relaxation process after compression. The environment's stiffness affects how shear waves spread. The acoustic radiation force impulse, or ARFI, is a second ultrasonic pulse that may be used to measure the shear wave speed, which is around 1–10 m/s.[53,54] For liver elastography, transient elastography (TE) with FibroScan© (Echosens, Paris, France) combines shear waves at 50 Hz produced by specific external impulse vibrations with ultrasound at around 5 MHz. The average of ten consecutive measurements yields the result, which is expressed in kPa.[55] The restriction in obese people and the absence of visual control over the location of the pulse in individuals and cases of ascites are the drawbacks of this well-standardized approach. Nowadays, most contemporary ultrasound instruments with conventional transducers support ARFI, which is widely available. It's important to distinguish between ARFI quantification (such as VTQ), Siemens; Elast PQ, Philips) and ARFI imaging, which are qualitative methods that portray tissue deformation as two-dimensional images (point shear wave elastography, SWE). Using B-mode imaging, the region of measurement is identified and designated as a region of interest. Shear wave elastography (2DSWE), in which a quantification box (Q-Box) receives the impulses at various depths of tissue, is one of the previous ARFI expansions.

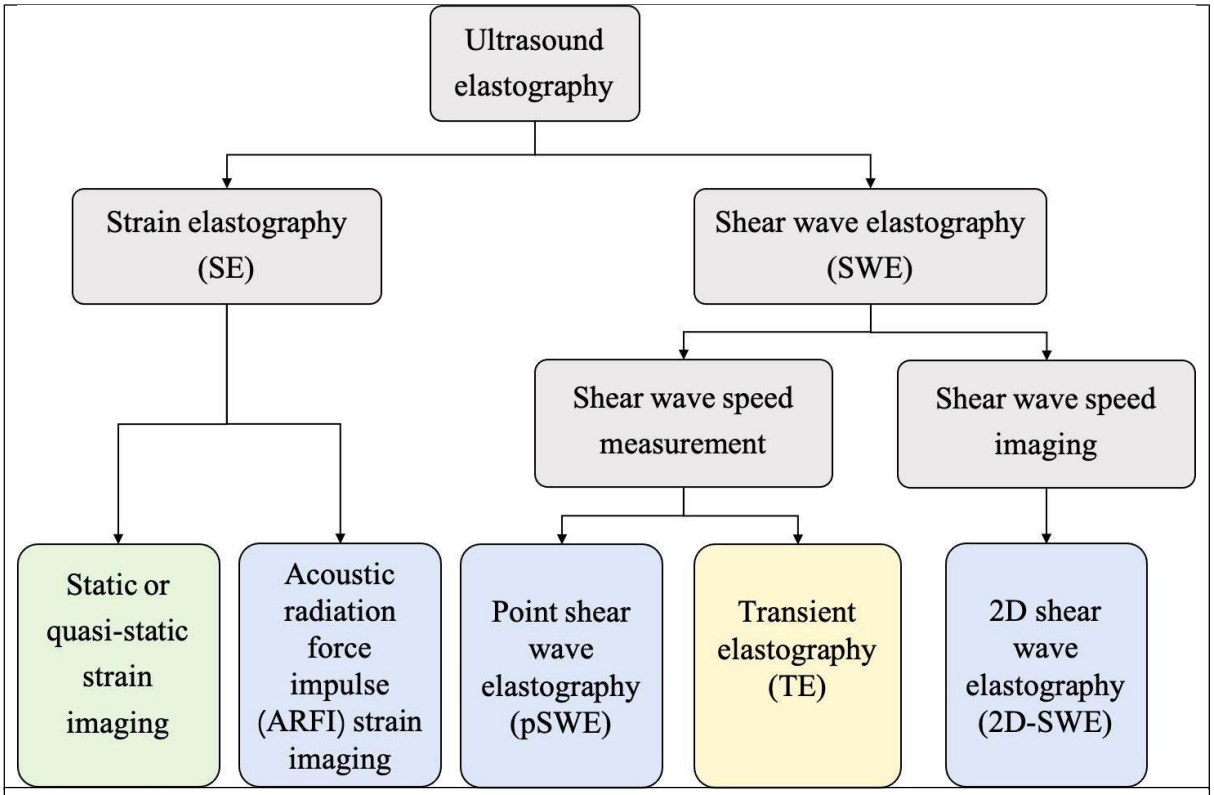

Figure 5: Flow chart of ultrasound elastography

2D Shear Wave Elastography

This method uses the force of sonic radiation to move tissue in various locations. Real-time tracking the way that the shear wave propagates is achieved at high frame rate imaging at various spots in the image, making it easier to discern the resulting shear wave front. An elastogram, or quantitative elasticity image, is displayed as a colored coded display map. The quantitative data may be obtained as the algebraically determined Young's-modulus in kilopascal or propagation of the shareware at speed in m/sec. Anatomic features such as blood vessels can be distinguished from one another by the operator by overlaying real-time tissue stiffness color maps on top of the B-mode image. With a linear probe, the maximum elastogram size is 2-3 cm in side length, and with a convex probe, it is 9 × 4 cm. Many ultrasound systems, such as Siemens' VirtualTouchTMImaging Quantification (VTIQ/ARFI), Philips' Shear Wave Elastography, SuperSonic Imagine's Shear WaveTM Elastography, GE Healthcare's 2D-SWE, and Toshiba's Acoustic Structure Quantification (ASQ), are

compatible with this approach. The graphic below shows an example of a 2D-SWE application on a phantom.

The operator may identify anatomic structures, including blood vessels, by superimposing real-time tissue stiffness color maps on top of the B-mode image. The maximum elastogram size for a linear probe is 2-3 cm in side length, and for a convex probe, it is 9 × 4 cm. This method works with a wide range of ultrasound devices, including GE Healthcare's 2D-SWE, Toshiba's Acoustic Structure Quantification (ASQ), Philips' Shear Wave Elastography, SuperSonic Imagine's Shear WaveTM Elastography, Siemens' VirtualTouchTMImaging Quantification (VTIQ/ARFI), and many more. An illustration of a 2D-SWE application on a phantom is provided in the graphic below.

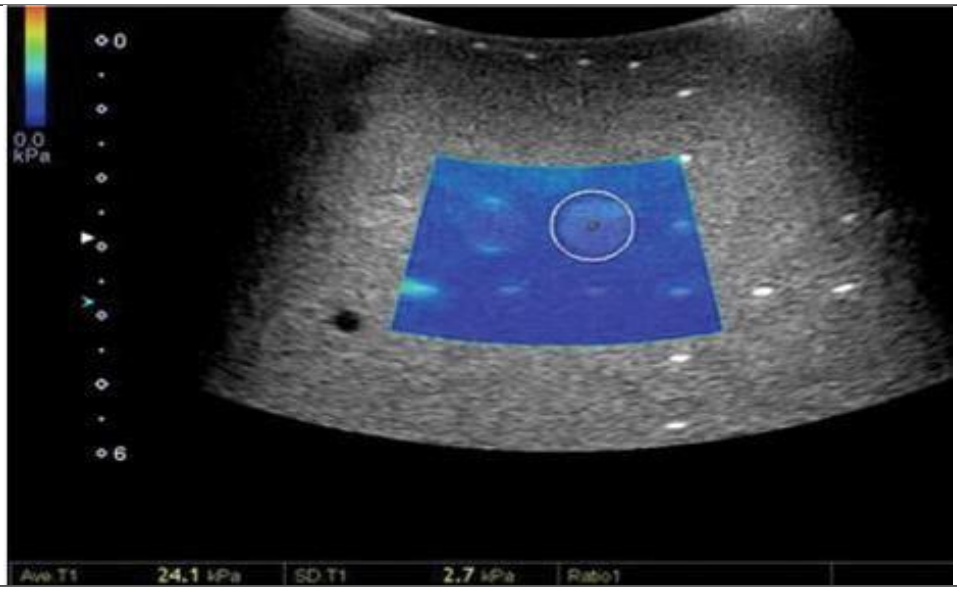

Figure 6: 2D acquisition of SWE using a phantom. Elastographic field of vision (FOV) is indicated by a blue box, and region of interest is decoded by a circle. The image's bottom shows the tissue stiffness in kPa

2D acquisition of SWE using a phantom. Elastographic field of vision (FOV) is indicated by a blue box, and region of interest shown by a circle. The image's bottom shows the tissue stiffness in kPa. The user has the ability to modify the color scale. Compared to red parts, blue areas are less rigid.

2D SWE acquisition with a phantom which has a blue box that represents the elastographic field of vision (FOV), while a circle represents the decoded region of interest. The tissue's stiffness is shown at the bottom of the picture, in kPa. Users have the ability to modify the color scale. Compared to red parts, blue areas are less stiff.

Biomechanical characteristics may be characterized using ultrasound elastographic techniques. Numerous producers are including quantitative 2-dimensional shear wave elastography (SWE) on conventional and widely used ultrasound equipment that are available, using an acoustic radiation force impulse as the excitation mechanism. This method's primary benefit is real-time B-mode picture guiding, which enables the placement of regions of interest (ROIs) at the appropriate position following the acquisition of the elastographic map. The feasibility, reliability, and reproducibility of the acoustic mechanical waves employed in the excitation techniques for calculating the velocity of shear waves have been demonstrated in various anatomic regions. Solid tumors like those of the breast, thyroid, and prostate, liver cirrhosis, vascular atherosclerosis, and musculoskeletal diseases are well-known instances. As a result, suggestions and Clinical practice recommendations pertaining to thyroid nodule treatment, breast masses, liver fibrosis, and the prostate now include elastography. Regarding the clinical utility of brain elastographic techniques in neonates, guidelines have not yet been established. Brain ultrasonography elastography research is rare and primarily experimental.

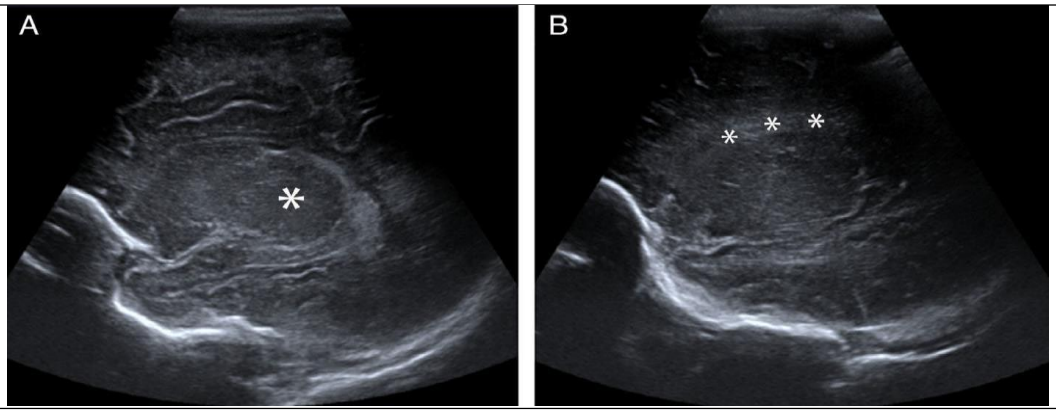

Figure 7: B-mode ultrasound images of the neonatal brain in sagittal perspective. Asterisks designate which shows thalamus (A) & frontal corona radiata (B) as the elastography target locations.

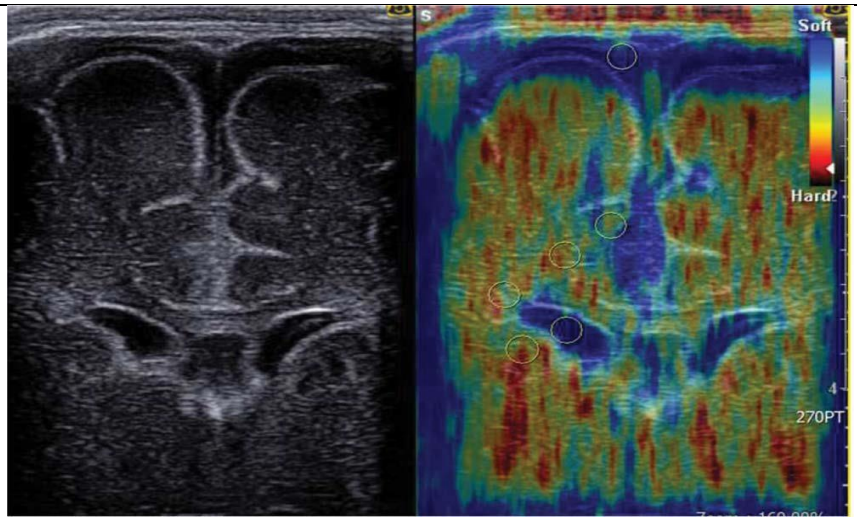

Figure 8: Anatomical locations & elastographic image shows small ROI (3 × 3 mm) positioned for obtaining quantitative measurements shear wave values corresponding to the frontal corona radiata (top row) and thalamus (bottom row)

Brain elastography in a newborn. On the left is coronal B-mode ultrasound image of a brain. The identical picture with an overlay in color illustrating the tissue's elasticity is seen on the right. The intracranial structures are surrounded by rounded zones of interest. Red represents the least elastic tissue and blue represents the most elastic tissue.

Scale for Elastographic Color Grading Scale

Interpretation of Score: The Intracranial Structure's Elastographic Appearance

1. Softest and most elastic Mostly blue colored
2. More pliable, primarily soft Green with up to 50% blue
3. Moderately elastic Mostly green
4. Less flexible, primarily rigid Green with up to 50% red
5. Hardest and least elastic mostly red

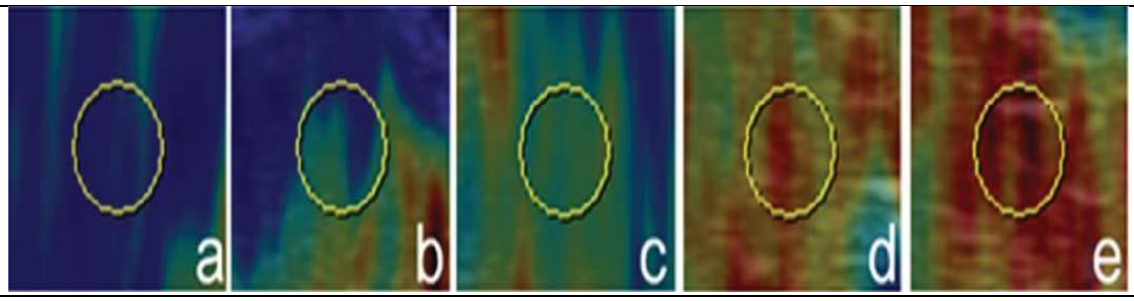

Figure 9: **Scale for Elastographic Color Grading.** ***A 5-point color scale (a–e) is shown, corresponding to elastographic scores of 1 to 5. A score of 1(a) indicates the most elasticity (softest tissue), and a score of 5 (e) indicates the least elasticity (hardest tissue)***

The imperfect development of cranial structures in premature neonates increases the risk of cognitive impairment, neuromotor deficits, and neurodevelopmental abnormalities .In addition to being convenient and inexpensive, with the improvement of probe resolution, ultrasonography has high diagnostic usefulness in the diagnosis of neonatal cranial diseases, and may be combined with colour Doppler imaging in order to evaluate the operational state of intracranial cerebral blood flow .Ultrasonography is currently the preferred method for the routine screening of neonatal early cranial diseases. However, the clinical ultrasound examination techniques currently and commonly used are susceptible to the subjective

judgment of different operators. Thus, the provision of more quantitative analysis data would enhance the specificity and sensitivity of ultrasonography in neonatal cranial applications.

The SWE is a method of ultrasonography that has emerged in recent years. This technique acts based on principles of acoustic radiation force emitted by the probe of ultrasound in the tissue region of interest, and then measures the propagation of shear wave velocity in the tissue and automatically calculates Young's modulus value ($E=3\rho c^2$, where E represents the tissue elastic modulus, ρ represents the tissue density, and c represents the shear wave propagation velocity to quantitatively assess tissue stiffness. Currently, SWE is widely used clinically; however, its application to neonatal cranial brain research is still in the preliminary stage.

Neuronal cell bodies are concentrated in the brain's gray matter, while nerve fiber aggregation occurs in the white matter. When the thalamic elastic stiffness values are higher than the white matter stiffness values in the neonatal period, In contrast to the brain's white matter structure, the gray matter structure is denser. The process of the central nervous system developing is incredibly intricate and ongoing that involves a dynamic balance amongst cell proliferation, myelin formation ,synaptogenesis, differentiation, migration and apoptosis of brain neurons and glia. Examinations of correlations between brain tissue stiffness and the degree of cerebral vascular development and cerebral blood perfusion pressure have shown that the denser the neuronal cells, the higher the value of brain tissue stiffness.

There are some advantages and disadvantages of SWE in evaluation of brain tissue stiffness. Stiffness measurements do not take a matter of minutes by SWE, and intraoperative ultrasonography is a relatively safe approach. Additionally, SWE may provide dynamic real-time images while not impacted by brain shift . Furthermore, the major flaws of using SWE to evaluate brain tissue stiffness including, stiffness values that may not be acquired when

shear wave propagation is prevented by depth and/or obstacles., different ultrasonography operators may result in distinct results due to their different skills.

Ultrasonography safety is monitored using two metrics: mechanical index (MI) linked to cavitation effects and thermal index (TI) related to heating effects. It is best to maintain both indexes as low as feasible. When performing elastography with acoustic displacement techniques (ARFI, SWE), potential dangers resulting from the energetic ultrasonic push pulse must be taken into account.[56] The focal point of the examined zone has the greatest temperature. The length of the scan and the number of pulse sequences cause the heating to grow. In the worst-case scenario, an estimated 1.2 °C temperature rise was calculated using a very powerful ARFI (Fahey et al. 2015).[53] However, SWE did not reveal any histologically detrimental consequences in a 2D investigation conducted on mice.[57] However, if the scanning process took more than 30 minutes, some brief, restricted impacts were noted. When adjusting the output for ARFI, the as low as reasonably attainable (ALARA) concept should be used. Additionally, scanning times should be kept to a minimum, particularly when dealing with sensitive tissue (such as ischemic brain tissue or torsion of the ovary or testicles).

To guarantee that there is no interference with neuronal migration, neurotransmitter levels, or function, any potential heating or mechanical damage to the brain's tissue during brain ultrasonography should be kept to a minimum. After long-term heat or mechanical exposure to elastography, no histological alterations in the mouse model's brain were seen. Even so, after only 10 minutes of exposure to a continuous elastography pulse, changes in the brain's signaling pathways may be observed; nevertheless, these effects seem to return to normalcy three months later.[57]

Two studies have investigated the viability of ultrasound elastography in pediatric brain imaging, carried out by skilled pediatric radiologists; still, numerous inquiries are yet

open.[58,59] The technique's generalizability has not been investigated. Most pediatric ultrasound examinations are routinely performed by sonography technologists, who are not trained pediatric radiologists, in many countries. Furthermore, the research previously mentioned assessed only normal brain parenchyma. There are currently very few published papers that describe SWE findings in pediatric cerebral pathology patients. Many test methods may be used to understand the mechanical properties of brain tissue. Shear, compression, indentation, and tensile testing are the most often used techniques among them. The mechanical characteristics of brain tissue are also assessed utilizing a range of radiologic imaging techniques, comprising magnetic resonance elastography (MRE) and surface wave electromyography (SWE).[11] Tissue examination in vivo is possible with both MRE and SWE. Compared to in vitro examination, in vivo evaluation is a more favorable approach.[60] The intact tissue structure, blood perfusion, hydration, and controlled tissue temperature are the benefits of in vivo testing. Because of these variables, the tissue is analyzed in its native state. An other significant finding was that the thalamus's elasticity exceeded the periventricular white matter stiffness in both groups. Studies using strain elastography and acoustic radiation force impulse elastography to assess the human newborn brain are scarce.[59,61,62] In term neonates, it has been discovered that the thalamus has greater elasticity values than the white matter, despite variations in normal values amongst authors. Elastography was used by Dirrichs et al.[63] to show reduced SWE values in children with hydrocephalus following drainage in patients with known brain diseases. Early reports indicated that periventricular parenchyma's SWE may be carried out in children with hydrocephalus and premature infants with success.[64] Compared to full-term newborns, preterm infants had lower thalamic and periventricular parenchymal stiffness evaluated using 2D SWE.[59]"An increase in stiffness brought on by cerebral edema may be utilized to quantify anoxic brain damage".[64] The authors postulated that although there are early

neonatal reference studies, further reference studies are necessary, and that USE may be applied in the future as a neurodevelopmental prognostic marker.[65]

Neonates have open windows in their skulls, known as the anterior and posterior fontanels, which allow for interference-free measuring of brain regions because the skull bones are not joined at birth.[66] Clinical ambiguities regarding nosologic diseases that cause pathologic alterations in the brain parenchyma's physical characteristics may be significant throughout the newborn period. Therefore, in circumstances like the monitoring of hydrocephalus, quantitative elastography may be useful in addition to other methods.[67] & as predictor for the neurodevelopmental consequences in premature newborns in whom Magnetic resonance imaging (MRI) data may be ambiguous or negative. Stiffness variations may result from modifications in myelinization, neuronal size, and glial proliferation.[68,69] The brain parenchyma's flexibility is the result of several factors coming into equilibrium. On the other hand, a decrease in brain parenchymal stiffness is predicted to occur when there is a lack of myelinization, and an increase is anticipated in cases of intracranial hypertension, a rise in neuronal size, or glial proliferation. Parenchymal edema, according to some writers, may also be significant and cause a drop in the stiffness levels. Brain ultrasonography elastography research is rare and primarily experimental.[64,70,71] Studies on strain elastography[50] and acoustic radiation force impulse elastography, which assess the human infant brain, are scarce.[59,61-63] It has been discovered that the thalamus has greater elasticity values than the white matter in term neonates, despite variations in normal values amongst authors. Elastography was used by Dirrichs et al.[56] to detect reduced SWE values in children with hydrocephalus following drainage in patients with known brain illness. Few investigations have been conducted in the pediatric age group, particularly in the newborn period, despite the fact that research revealing the mechanical properties of healthy brain tissue adults has been conducted.[16,17] Because of this, it is still unclear how the brain's

mechanical characteristics alter during the early stages of development.

One technique for figuring out the brain's elastic characteristics is shear wave elastography.[11] Shear wave elastography is a quantitative, non-invasive technique that uses ultrasound to evaluate tissue stiffness through acoustic palpation. The investigated tissue propagates transversely radiating shear waves that reflect tissue elasticity when transducer creates a regionalized force of acoustic radiation that moves via the tissue. For linearly isotropic tissues, the square of the shear wave speed equals the elastic modulus (E) (E53qcs2, where cs is the shear wave velocity and q is the tissue density). With the ability to measure quantitative elasticity scores, the elastic modulus (in kilopascals) may be computed from the velocity data and shown in a color-coded graphic.[73,74] SWE has been widely employed in the past few years to assess a wide range of tissue and organ disorders, including those of the liver, breast, thyroid, lymph nodes, and prostate.[75,76] The three main SWE techniques for noninvasive tissue stiffness-based assessment are transient elastography, point SWE, and 2-dimensional (2D) SWE.[74,76]

The development of cerebral stiffness in both term and preterm infants based on age has been demonstrated in number of investigations. In white matter areas, cortical & subcortical andterm infants' brain stiffness was shown to be higher than that of preterm infants' using ARFI with VTQ, as reported by Su et al.[61] Albayrak and Kasap demonstrated similar findings with SWE, indicating that term newborns exhibited more cerebral stiffness than preterm infants.[59] The greater stiffness in term neonates is connected with stronger myelination and possibly a larger water content in preterm brains' than compared to term neonatal brains; nevertheless, more mechanistic investigations are required to fully comprehend the relationship between physiologic growth and the chronological evolution of cerebral stiffness. Surprisingly, biomechanical testing and magnetic resonance elastography have produced contradicting results, suggesting that brain regions with myelin sheaths are

less rigid than those without. It is essential to first ascertain the direction of white matter tracts in a region of interest since anisotropy, or the orientation of these tracts, influences the elasticity results. Additionally, data point to regional differences in brain flexibility in term and preterm brains. Strain elastography was employed by Kim et al.[58] to assess stiffness in the caudate, subcortical, periventricular, and each of the cortical gray matter and white matter.

In comparison to term group, in the preterm group, there was a substantial decrease in brain parenchymal stiffness values in the thalamus and periventricular white matter. Moreover, a strong favorable association has been seen between the stiffness values and the delivery week. Another important observation is that of the elasticity of thalamus is greater than that of the periventricular white matter stiffness.

The SWE approach has been applied by several researchers to assess brain illnesses in the past few years. Applying the intraoperative 2D SWE approach, Chauvet et al.[17] assessed the elasticity of the healthy brain tissue around tumors in 63 individuals as well as brain tumors. Using SWE, they were able to determine the elasticity values that differed between tumoral and normal brain tissue. Additionally, they discovered that the elasticity values varied significantly depending on the kind of brain tumor. These findings suggest that the intraoperative SWE approach gives surgeons more knowledge regarding the tumor's diagnosis and extent. Xu et al.[71] found that the stiffness of mice's brains varied across hemispheres after the middle cerebral artery blockage using the 2D SWE approach. It was proposed that these variations were related to diaschisis in the contralateral hemisphere and blockage in the ipsilateral hemisphere, which caused ischemia and edema. In a further investigation, Xu et al.[72] employed this technique on rats and mice undergoing brain surgery or mild traumatic brain damage. 24 hours after a moderate traumatic brain injury, they noticed changes in interhemispheric stiffness. They theorized that these abnormalities were

brought on by the edema and bleeding in the traumatized hemisphere as well as a reduction in blood flow in bilateral hemispheres.[72]Chen et al.'s study[77] evaluated babies in the preterm and term groups who had hypoxic ischemic encephalopathy and those who did not. The cerebral falx, thalamus, and both parietal lobes were measured. The parietal lobe stiffness values of the preterm group without HIE were discovered to be more than those of the term group without such encephalopathy. Compared to the term group with the same condition, the preterm group with HIE had higher elasticity values in the right thalamus and bilateral parietal lobes. Su et al.[61] found that the term group had increased stiffness values in all areas from the thalamus ,parietal white matter, cerebellum, and cerebral falx in their series of healthy term and preterm infants. In healthy term newborns, Chen et al.'s research[77] revealed that the thalamus had a increased rigidity than the parietal white matter. In line with this, Su et al.[61] reported that in both term and preterm newborns, Compared to the parietal white matter, the thalamus was more stiffer. Consistent with those investigations, we also discovered that the thalamus had a higher stiffness value than the periventricular white matter. Brain elasticity measurements were used to diagnose preterm in both of those trials, although there was no threshold value. This work presented thalamic and periventricular white matter stiffness threshold values to indicate preterm for the first time to our knowledge. Numerous hypotheses have been put out to explain why brain tissue changes depending on location or stiffens with age. Using MRE, Green et al.'s investigation on adult human brains revealed white matter was less stiff than gray matter.[78] Furthermore, we discovered that the thalamus, which is primarily composed of gray matter mass, has a stiffer structure than the white matter surrounding the periventricular area. A decline in the elasticity properties of the human brain owing to age was reported by Sack et al,[12] who utilized MRE to evaluate variations in participants' elasticity of the brain values according to their age and sex between the ages of 18 and 88. They speculated the possibility that parenchymal liquefaction is the

reason for this decline as a result of aging. Women's temporal and occipital lobes were discovered to be more rigid than men's in the same age group by Arani et al.[79]

There aren't much research that employ MRE to look at the developing human brain in the literature. However, there aren't many in vitro and in vivo experimental animal studies that examine the stiffness of the early child's brain. In experiments conducted at 1.25% shear strain across a frequency range of 20–200 Hz, Thibault and Margulies[80] found that adult brain tissue was significantly stiffer than that of pig juvenile brain tissue. Adult and adolescent tissue did not significantly differ from one another, even at 2.5% shear strain. These findings demonstrate the nonlinear nature of brain tissue, with adult tissue being stiffer than pediatric tissue at very small stresses but not at big strains when measured at a significant deformation.. The newborn phase in pigs roughly equal to two weeks after birth in rats. Using MRE, Pong et al.'s recent work[81] examined the stiffness of the brain in neonatal rats aged one to six weeks. In their experiment, they simultaneously and histologically examined myelination and cell density. They looked the consequences of aging and geography regarding the brain's physical characteristics in addition to the factors that drove these changes. Week one and week two of pregnancy, the cortical gray matter's shear modulus steadily increased, steadied between weeks 2 and 4, and then gradually fell until week 6. Deep gray matter's shear modulus steadily rose from week 1 through week 4, after which it steadily decreased to week 6. They found that the early postnatal weeks, when the brain tissue's shear modulus grew, corresponded to human early childhood, whereas the later postnatal weeks, when the brain tissue's shear modulus steadily fell, corresponded to the human adolescent period. According to their research, deep gray matter has lower stiffness values than cortical gray matter, and the reason for this difference may be that deep gray matter contains more myelin.[81,82] They did, however, also disclose a study demonstrating that brain elasticity values are decreased by demyelination, But they also disclosed a study

demonstrating how brain elasticity is decreased by demyelination. [83] And the precise implications of myelin on stiffness remain unclear.[81] Finally, they proposed that there is no direct correlation between the values of brain stiffness and histologic features, and that factors other than myelination that influence brain stiffness include cell death ,vascular development and perfusion pressure ,brain growth and dendritic pruning.[82,84] The newborn rats, who were one to six weeks old, were similar to people who were two to twelve years old, according to a study by Pong et al. [81] All aforementioned research included human age groups ranging from childhood to adulthood, based on these reference values. As far as we are aware, no research has been done in the literature to examine the brain's rigidity during the preterm and term neonatal stages. Apart from these variables, the development of the neonatal brain involves an intricate sequence of microstructural and macrostructural occurrences, encompassing not only the myelinization of the brain but also the proliferation and migration of neurons and glia, as well as the associational development of neural circuits and cortical layers.[85] Because of this, the development process changes according to the gestational week,, may also have an impact on brain stiffness during the newborn era. We believe that the changes in brain stiffness that arise from gestational developing stages during the newborn era may be a complicated process that combines the common outcomes of all of the developmental stages and modifications that have been discussed above. A deeper understanding of this mechanism will require additional research, including more thorough histologic analyses. Furthermore, there is currently no standard procedure for brain elastography in babies. The association between regionally diverse brain elasticity and the health of the developing brain needs to be better understood. Furthermore, it is challenging to compare studies due to vendor variations in quantitative elasticity of brain or semi-quantitative computations. Apart from customizing the process to the specific clinical question, future protocol designs will need to account for these considerations. Additional

investigation is required to comprehend the possible influence of technical fluctuations on the diagnostic efficacy of brain elastography as well as biological and histological associations of brain elasticity measurements. If a comparison is done across patients or over an extended length of time in the same patient, the same scan parameters should be used consistently when initiating prospective clinical research utilizing this method.

Brain Imaging and Its Effects on Families

Parents and their young adult preterm offspring are interested in learning about NICU occurrences that could affect their life in the long run.[86] Sophie et al[87] examined the effects of prenatal and neonatal factors related to the delivery and hospitalization of their preterm child and found that mothers experienced significant stress regarding the results of cUS at 7 years of age. Maternal anxiety was reduced more when MRI data was used than when cUS data was used in the largest study on this subject to date. Poor explanation of the reasoning behind or findings from neuroimaging has frequently been the source of parents' concerns about MRIs in their premature newborn.[88] Thus, it is important for caregivers to emphasize the importance of effectively communicating any results, particularly those from neuroimaging.[89,90]

In fact, encouraging results about brain imaging of the preterm infant present a vital chance to assist the families under our care, not "waste." The moment has come for neonatal physicians to use neuroimaging to better understand brain injury and recovery in growing brains.

MATERIALS & METHODS

MATERIALS AND METHODS

Source of Data

This is a hospital-based, prospective comparative study conducted in the department of Radio-Diagnosis, at R.L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, over a period of 18 months from September 2022 to February 2024. The study included consecutive neonates referred for ultrasound examination to the radiodiagnosis department.

Methodology

A total of 82 neonates were included referred for ultrasound examination to the department of Radio-Diagnosis at the R.L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar. The study was conducted following approval from the institutional ethical committee. A written consent form was obtained from parents fulfilling the inclusion criteria after explaining the objective, procedure, and expected outcome in detail before the start of the study. The patients were included in the study based on the inclusion and exclusion criteria mentioned as follows:

Inclusion Criteria

1. Case - Preterm neonatal infants with gestational age which is less than 37 weeks (33 weeks to 37 weeks).
2. Control - Term infants with normal brain parenchyma.(from 37+ weeks to 40 weeks)

Exclusion Criteria

1. Patients with suspected congenital malformations

2. Central nervous system infections
3. Cerebral hemorrhage
4. Hydrocephalus
5. Periventricular leukomalacia.
6. An insufficient fontanel space.

Sample Size

Eda Albayrak et al. has reported the mean (SD) Shear Wave Elastography values among term and pre-term babies as follows:

Parameter	Term	Pre-term	Sample size required
Thalamus - right	9.03 ± 1.84	8.00 ± 1.43	41 in each group
Thalamus - left	9.14 ± 1.66	7.98 ±1.21	41 in each group
Thalamus – mean	9.09 ± 1.50	8.0 ± 1.10	26 in each group
Periventricular white matter – right	7.2 ± 1.24	6.29 ± 1.50	36 in each group
Periventricular white matter – left	7.33 ± 1.6	6.30 ± 1.21	36 in each group
Periventricular white matter - Mean	7.26 ± 0.99	6.3 ± 1.23	24 in each group

Assuming a 95% Confidence Limit for Alpha Error, 80% Power, and a 1:1 Pre-Term Group Ratio.

The necessary sample size to identify the variation in mean shear wave elastography between the two-study group was taken to be 82 subjects (41 subjects in term group and 41 subjects in pre-term group)

The sample size was derived from the following formula:

Sample size (n) = $\frac{2S_p^2 [Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}]^2}{\mu_d^2}$; $S_p^2 = \frac{S_1^2 + S_2^2}{2}$

where, S_1: Standard deviation in the first group

S_2: Standard deviation in the second group

μ_d : Mean difference between the samples

α: Significance level

1-β: Power

Ethical considerations:

Institution's human ethics committee approved this study. All participants were provided with written informed consent, and only those willing to sign the consent were allowed to take part in the study. Before getting consent, the participants were informed about risks and advantages of study as well as voluntary nature of participation. Privacy of study participants was protected at all times.

Method of Collection of Data

Informed consent will be taken from all the patients. Once a patient satisfies the inclusion criteria for this study, a detailed history will be taken from the patient referred to the Department of Radiodiagnosis. Any previous imaging studies if available will be reviewed. SWE findings and diagnosis will be recorded in the proforma. All patients will be subjected to B-mode sonography and elastography in the supine position. Neuro-sonography and elastography will be performed using PHILIPS EPIQ 5 system equipped with shear wave point quantification ELASTPQ , using curvilinear broadband transducer C5-1MHz. The measurements will be repeated three times, and the mean stiffness value of thalamus & peri-ventricular white matter will be calculated and measured in kilopascal (kp). Clinical follow-up for the available patients will be done.

Figure 10: Philips EPIQ5 USG machine.

Figure 11 : C 1-5 MHz convex transducer (equipped with shear wave point quantification, ELASTPQ)

For determining the elasticity, we used shear wave elastography. This technique generates shear waves inside the tissue using a focused ultrasound beam. A fixed rectangle of size 0.5 x 0.5 cm is chosen as the region of interest and is placed in the middle third portion of the thalamus & peri-ventricular white matter. After image stabilization, the probe is held steady for 3–5 seconds for framing.

Statistical Analysis

The present study included both qualitative and quantitative variables. Quantitative factors were represented by mean ± SD and median (QR), while qualitative variables were denoted by numbers (%). The Kolmogorov-Smirnov test that was used to determine whether the data were normal. The two numerical variables were compared using parametric independent t-tests. The relationship between two independent qualitative variables was ascertained utilising the Chi square test. To ascertain the cut-off value and the predictive power of the periventricular white matter and thalamus stiffness in determining a meaningful preterm classification in predicting patient outcomes, Receiver Operating Characteristic (ROC) analysis was utilized.

A 95% confidence level was considered for all tests. The data analysis was performed using SPSS 20.

RESULTS

RESULTS

Gender	Group		Total
	Preterm	Term	
F	22	19	41
	55.0%	47.5%	51.3%
M	18	21	39
	45.0%	52.5%	48.8%
Total	40	40	80
	100.0%	100.0%	100.0%

Table 1: Gender-wise distribution of preterm and term babies

*Chi Square test (P-value = 0.502)

Table 1 shows the gender-wise distribution of term and preterm babies. No significant association was observed between gender and term/preterm delivery (P-value = 0.502).

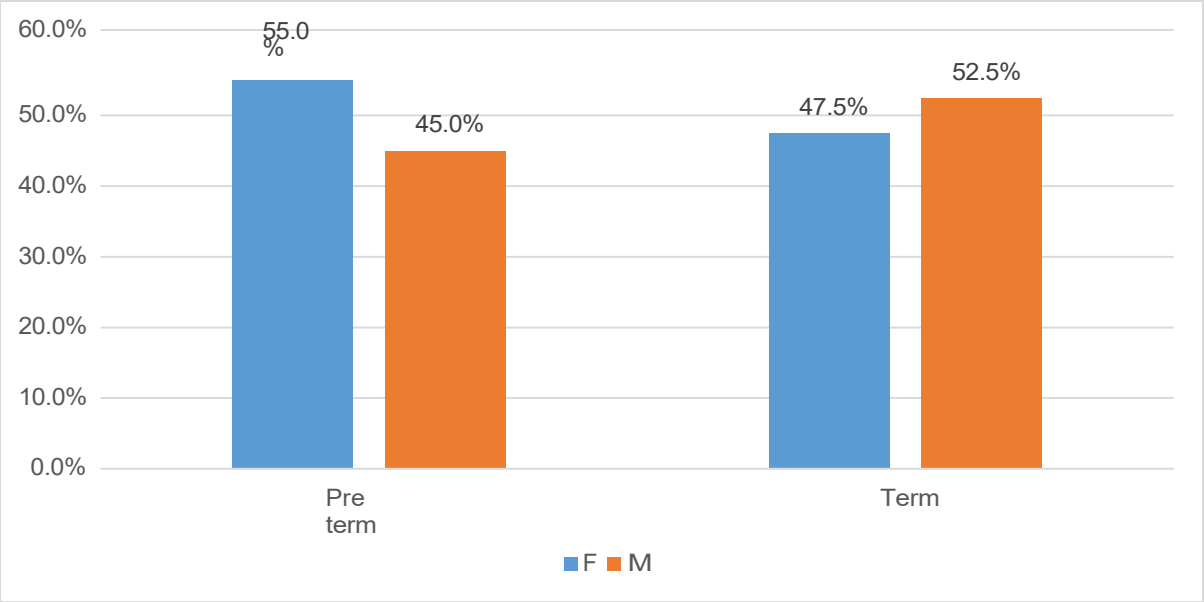

Figure 12 : Gender-wise distribution of term and preterm babies (Blue – Female, Orange - Male)

	Group	N	Mean	Std. Deviation	P- Value
Birth Week	Preterm	40	35.88	1.09	P<0.001
	Term	40	38.93	.797	
Age(days)	Preterm	40	2.90	1.411	0.001
	Term	40	4.30	2.015	
Birth weight	Preterm	40	2.570	.4625	P<0.001
	Term	40	3.093	.2768	

Table 2: Comparison of mean birth parameters between term and preterm babies

Table 2 depicts the comparison of the mean gestational age between preterm and term deliveries. The mean gestational age of term infants (38.93±0.797 weeks) was significantly higher compared to preterm infants (35.88±1.09 weeks), with a statistical significance of P < 0.001. Additionally, mean maternal age and birth weight were also observed to be higher in term deliveries (see Table 2)

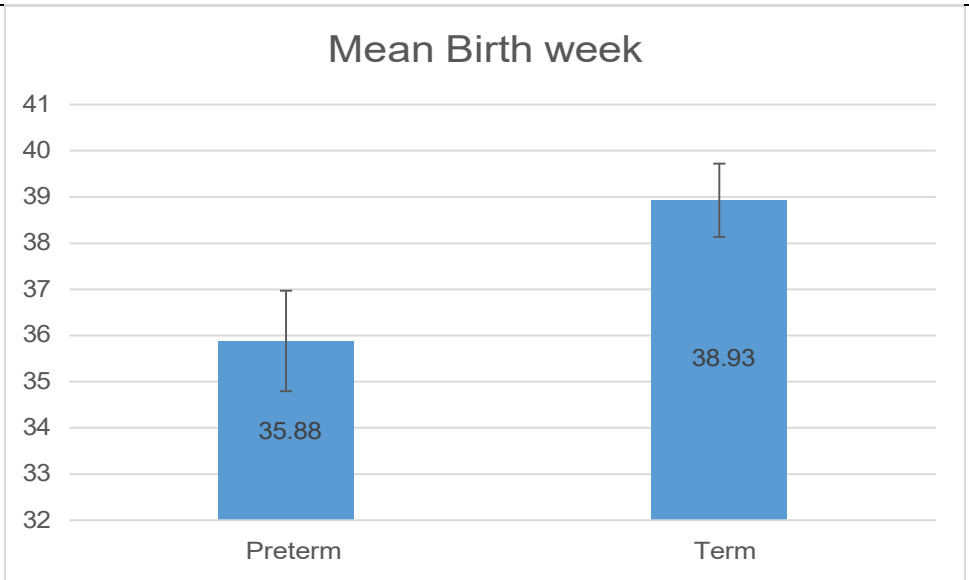

Figure 13 : Bar chart showing Mean birth week

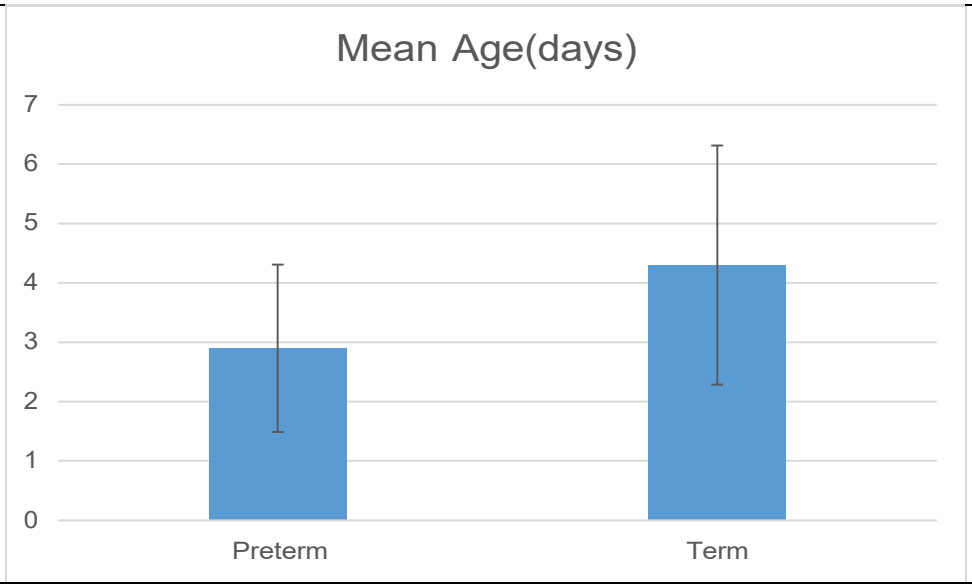

Figure 14 : Bar chart showing***Mean Age (days)***

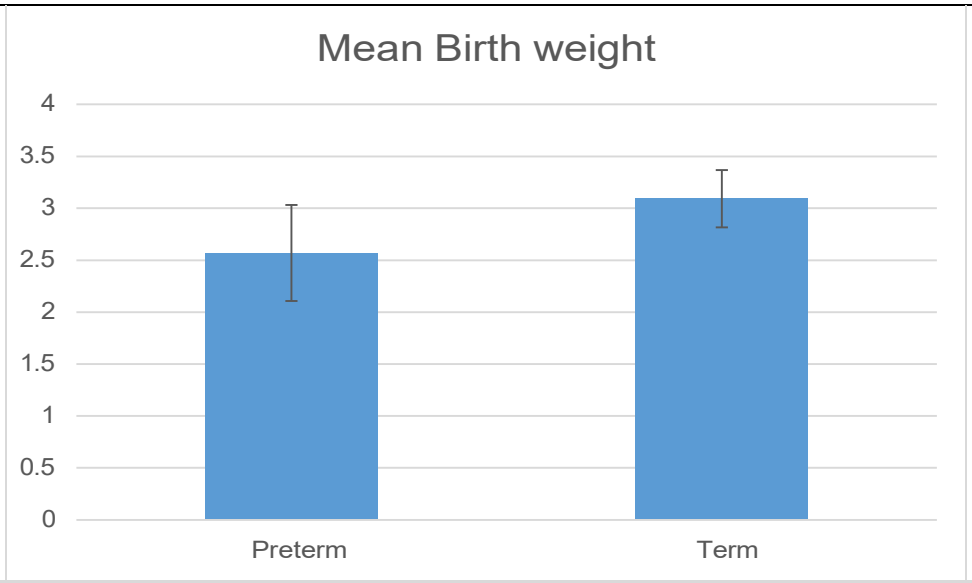

Figure 15 : Bar chart showing***Mean Birth weight***

	Group	N	Mean	Std. Deviation	P- Value
SWE of Right Thalamus, kPa	Preterm	40	7.788	.7367	P<0.001
	Term	40	9.095	.5411	
SWE of Left Thalamus, kPa	Preterm	40	7.870	.5644	P<0.001
	Term	40	9.068	.5346	
SWE of Mean Thalamus	Preterm	40	7.805	.5901	P<0.001
	Term	40	8.825	.3754	
SWE of Right Periventricular White Matter, kPa	Preterm	40	6.490	.5943	P<0.001
	Term	40	7.260	.5012	
SWE of Left Periventricular White Matter, kPa	Preterm	40	6.608	.5797	P<0.001
	Term	40	7.302	.5877	
SWE of Mean Periventricular White Matter, kPa	Preterm	40	6.538	.5300	P<0.001
	Term	40	7.298	.4300	

Table 3: The shear wave elastography (SWE) values for the right and left thalamus (kPa), the mean thalamus SWE (kPa), the SWE values of right and left periventricular white matter (kPa), and the mean periventricular white matter SWE (kPa).

Table 3 presents the shear wave elastography (SWE) values for the right and left thalamus (kPa), the mean thalamus SWE (kPa), the SWE values of right and left periventricular white matter (kPa), and the mean periventricular white matter SWE (kPa).

The SWE values of the right (9.095 ± 0.5411) and left (9.068 ± 0.5411) thalamus (kPa) were higher in term deliveries compared to preterm ($P < 0.001$).

The mean thalamus SWE (kPa) was higher in term deliveries (8.825 ± 0.3754) compared to preterm ($P < 0.001$).

The SWE values of the right (7.260 ± 0.5012) and left (7.302 ± 0.5877) periventricular white matter (kPa) were higher in term deliveries compared to preterm ($P < 0.001$).

The mean periventricular white matter SWE (kPa) was higher in term deliveries (7.298 ± 0.4300) compared to preterm ($P < 0.001$).

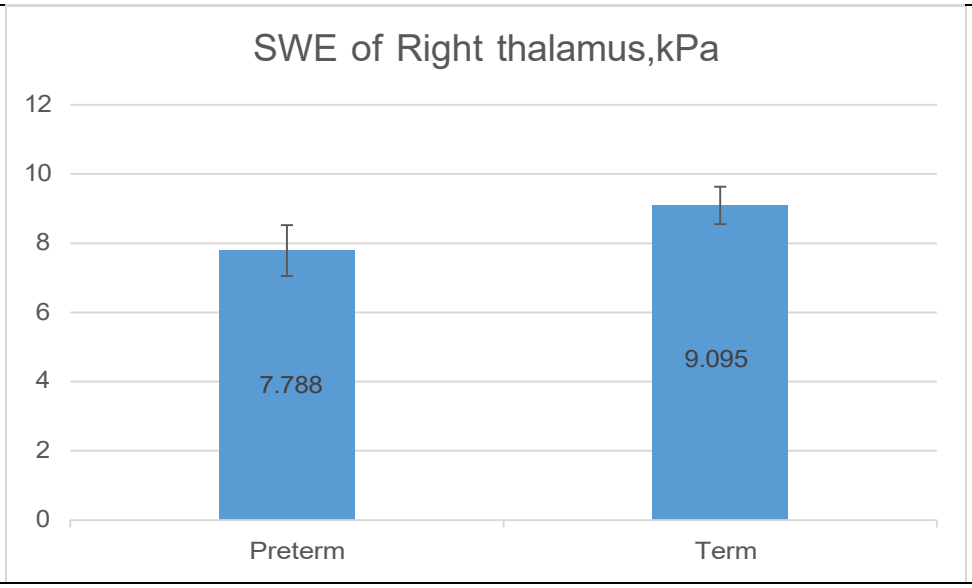

Figure 16 : SWE of right thalamus,kPa

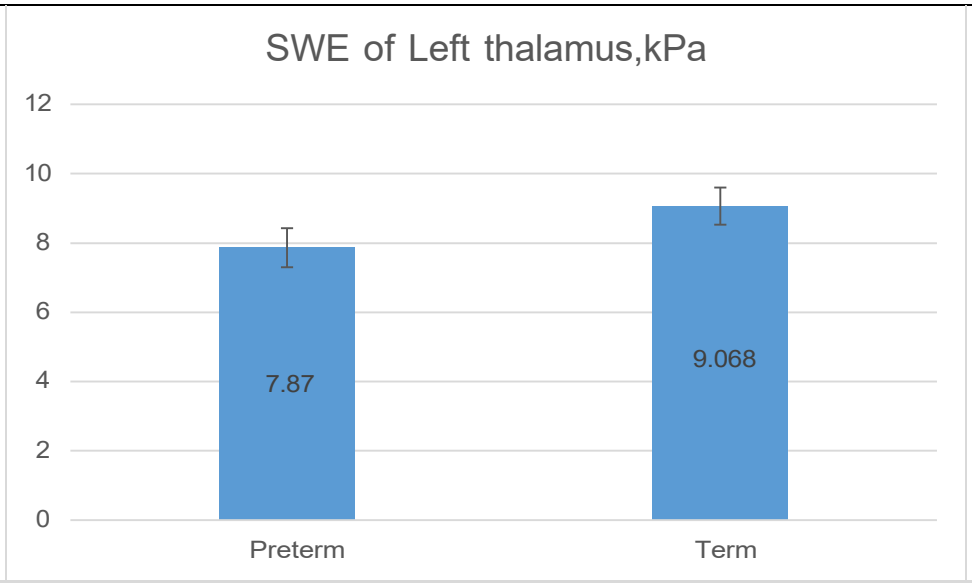

Figure 17 : SWE of left thalamus,kPa

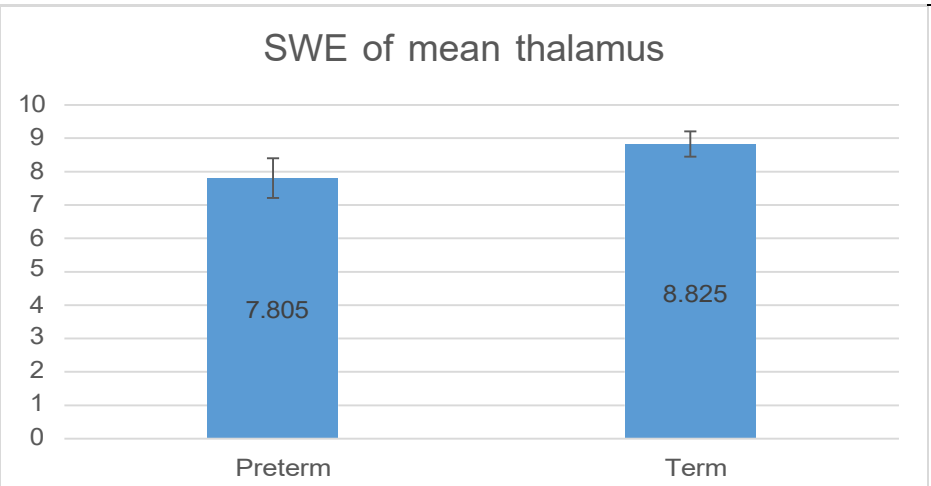

Figure 18 : SWE of mean thalamus,kPa

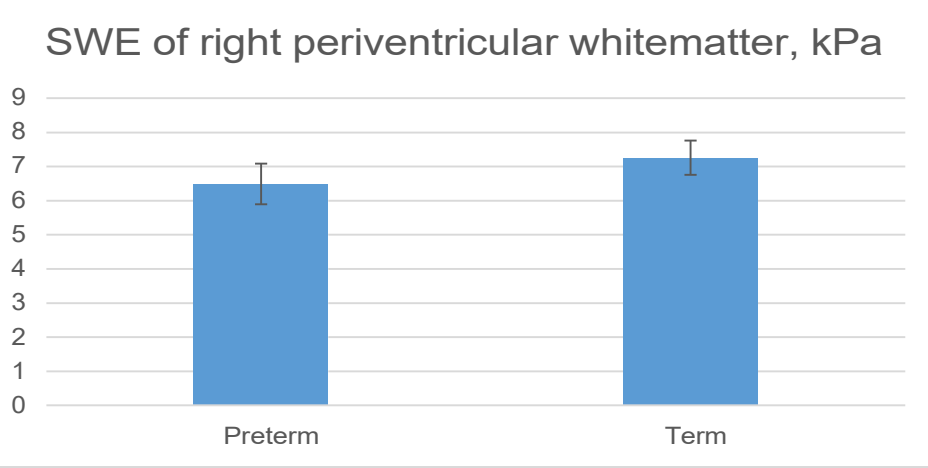

Figure 19 : SWE of right periventricular whitematter ,kPa

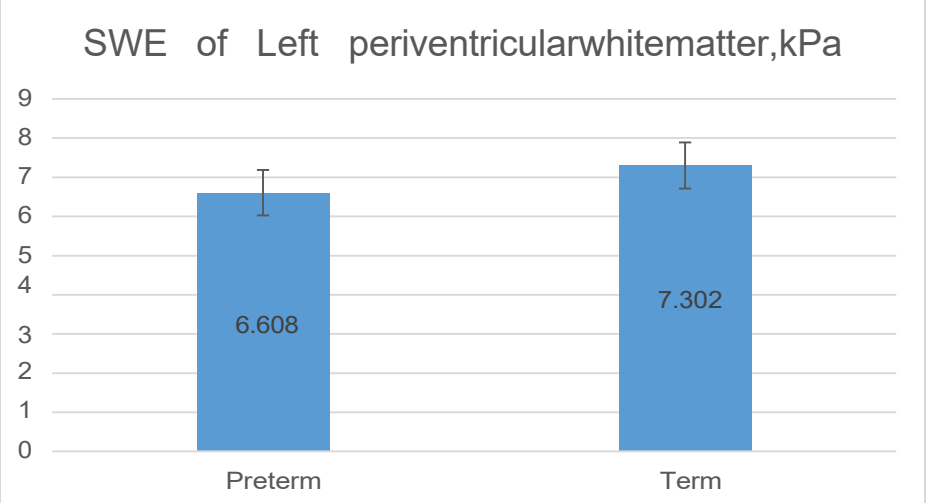

Figure 20 : SWE of left periventricular whitematter ,kPa

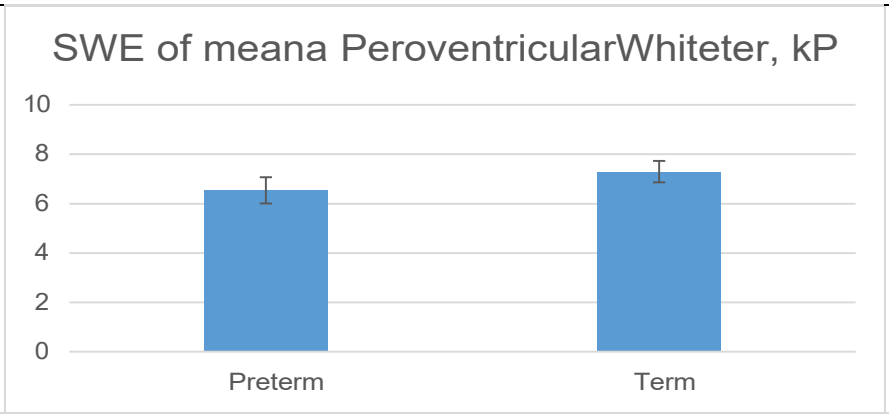

Figure 21 : SWE of mean periventricular whitematter ,kPa

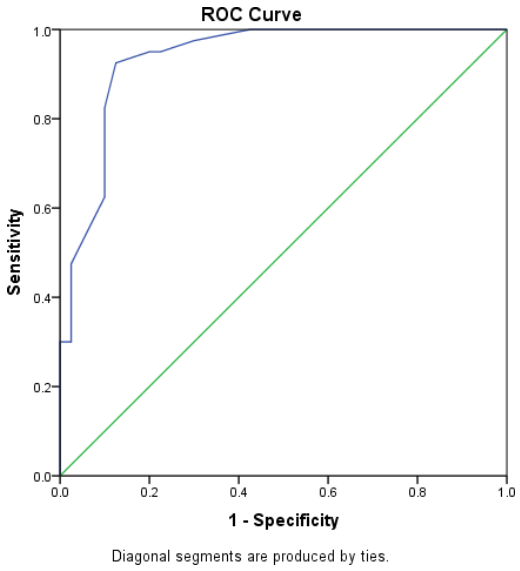

Figure 22: ROC curve constructed for SWE of Right thalamus, kPa

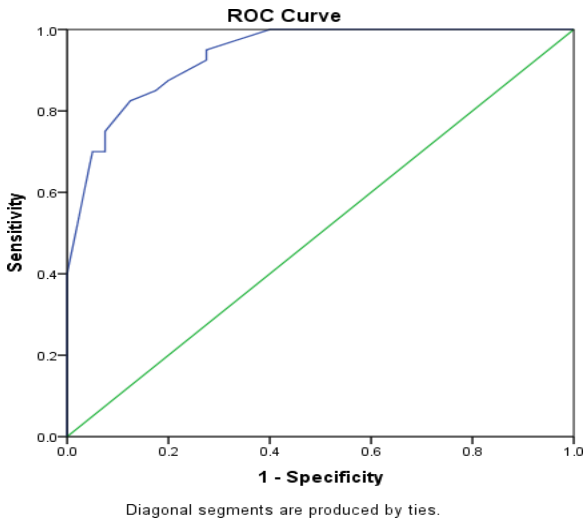

Figure 23: ROC curve constructed for of Left thalamus, kPa

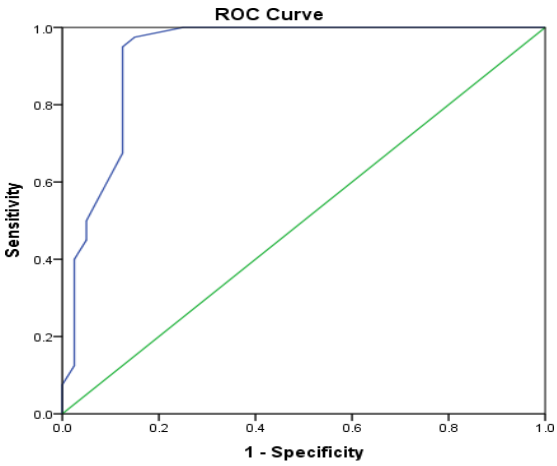

Figure 24: ROC curve constructed for of mean thalamus

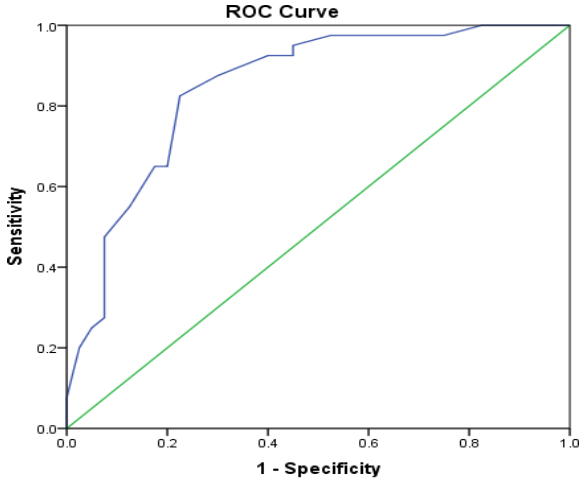

Figure 25: ROC curve constructed for right periventricular white matter, kPa

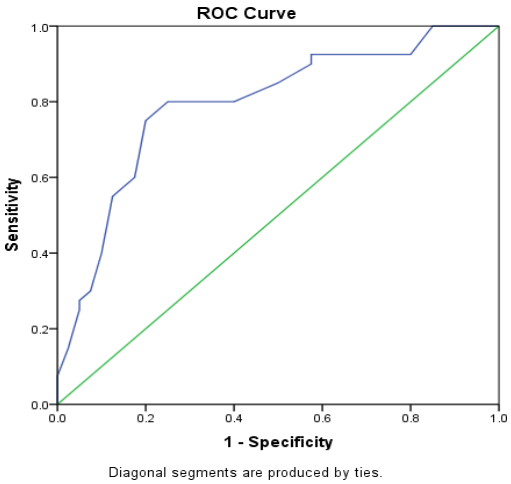

Figure 26: ROC curve constructed for left periventricular white-matter, kPa

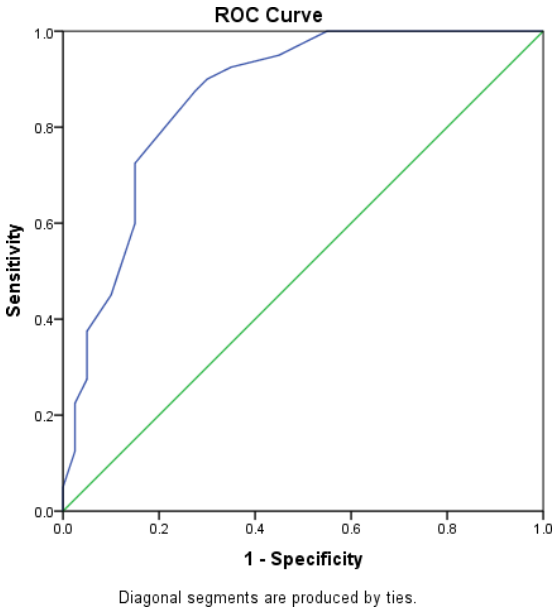

Figure 27: ROC curve constructed for mean periventricular whitematter, kPa

Test Result Variable(s)	AUC	P-Value	Asymptotic 95% Confidence Interval		Cut-off Value	Sensitivity	Specificity
			Lower Bound	Upper Bound			
SWE of Right thalamus ,kPa	0.935	P<0.001	0.881	0.990	8.45	92.5%	87.5%
SWE of Left thalamus,kPa	0.937	P<0.001	0.889	0.985	8.55	82.5%	87.5%
SWE of mean thalamus	0.930	P<0.001	0.868	0.992	8.35	95%	87.5%
SWE of right periventricular white matter, kPa	0.847	P<0.001	0.760	0.933	6.85	82.5%	77.5%
SWE of left periventricular whitematter, kPa	0.794	P<0.001	0.694	0.895	7	75%	80%
SWE OF MEAN PERIVENTRICULAR WHITEMATTER, kPa	0.864	P<0.001	0.783	0.946	6.85	87.5%	72.5%

Table 4: The specifics of the cut-off values for the periventricular white matter and thalamus's stiffness in determining a significant preterm classification.

The specifics of the cut-off values for the periventricular white matter and thalamus's stiffness in determining a significant preterm classification are shown in Table 4.

ROC analysis was conducted on SWE (left & right thalamus, kpa) & (left& right periventricular white-matter, kpa) to predict outcomes for deliveries (i.e term or preterm).

To determine the most appropriate cut-offs for predicting outcomes for term and preterm deliveries (Figure 22 to 27)

A cut-off value of SWE (left & right thalamus, kPa) < 8.45 and < 8.55 respectively predicting the preterm delivery.

A cut-off value of SWE OF Mean thalamus, kPa < 8.35 predicting the preterm delivery with 95% sensitivity and 87.5% specificity

A cut-off value of SWE (left & right periventricular white matter, kPa) < 6.85 and < 7 respectively predicting the preterm delivery.

A cut-off value of SWE OF MEAN PERIVENTRICULAR WHITEMATTER, kPa) < 6.85 predicting the preterm delivery with 87.5% sensitivity and 72.5% specificity.

IMAGES

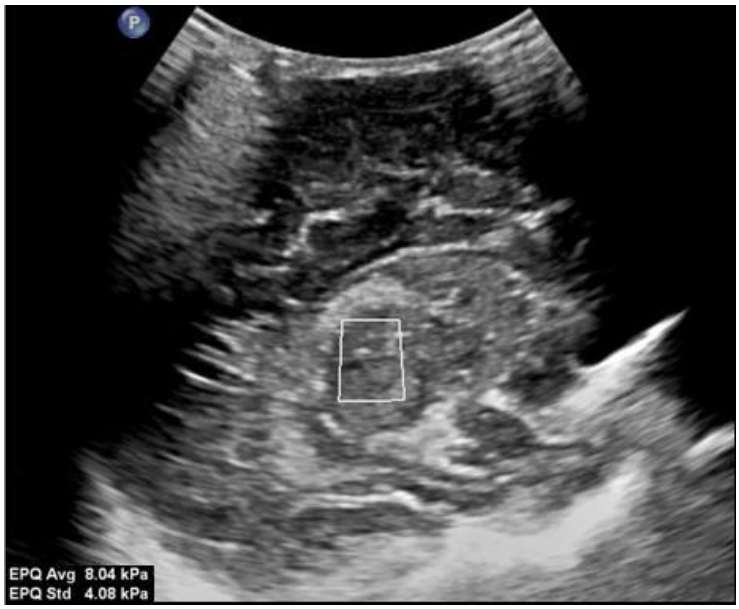

Fig 28: Image from a 3 day old Pre-term neonate . ROI was placed at left thalamus .

Avg SWE value was found to be 8.04 kPa .

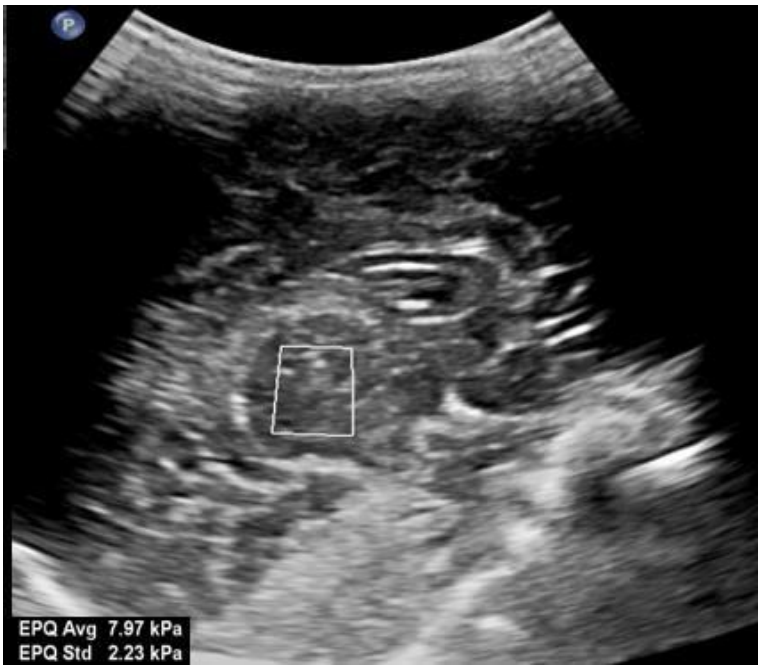

Fig 29: Image from a 3 day old Pre-term neonate. ROI was placed at right thalamus .

Avg SWE value was found to be 7.9 Kpa.

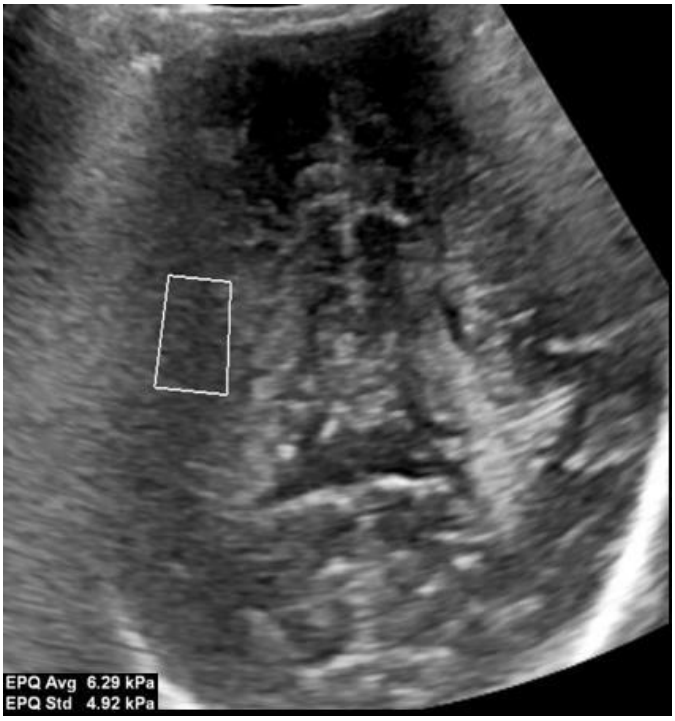

Fig 30: Image from a 1 day old Pre- term neonate.ROI was placed at right peri-ventricular white matter. Avg SWE value was found to be 6.3 kPa.

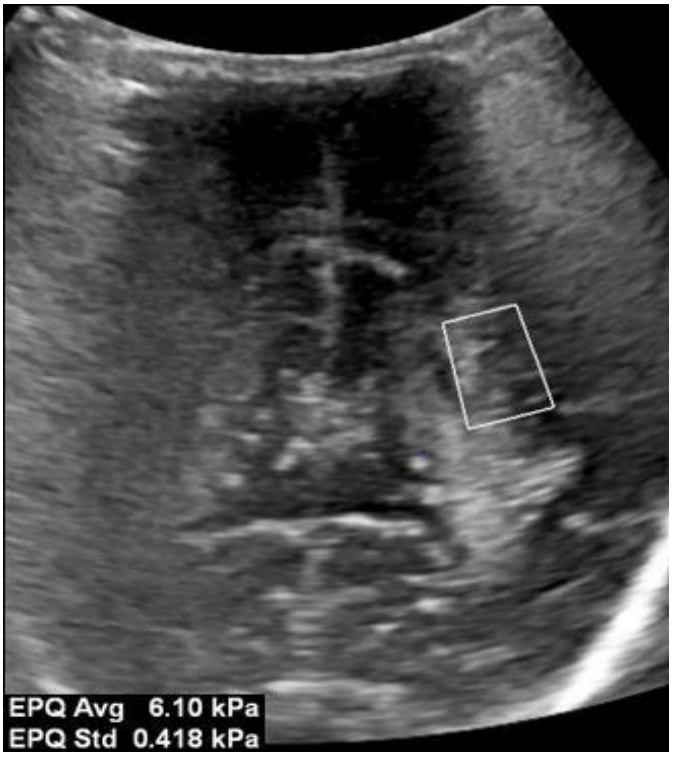

Fig 31: Image from a 1 day old Pre-term neonate.ROI was placed at left peri-ventricular white matter. Avg SWE value was found to be 6.1 kPa.

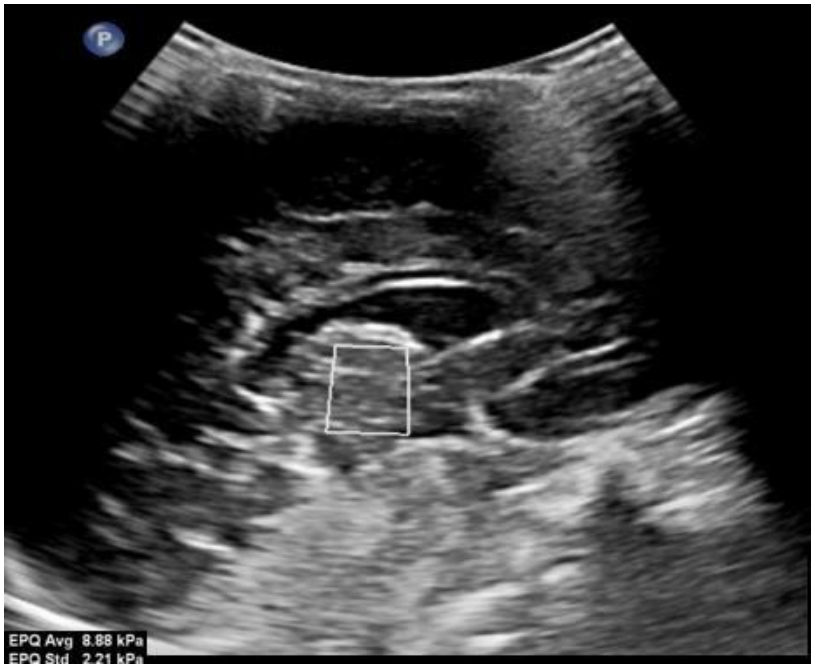

Fig 32: Image from a 3 days Term neonate.ROI was placed at left thalamus. Avg SWE value was found to be 8.8 kPa.

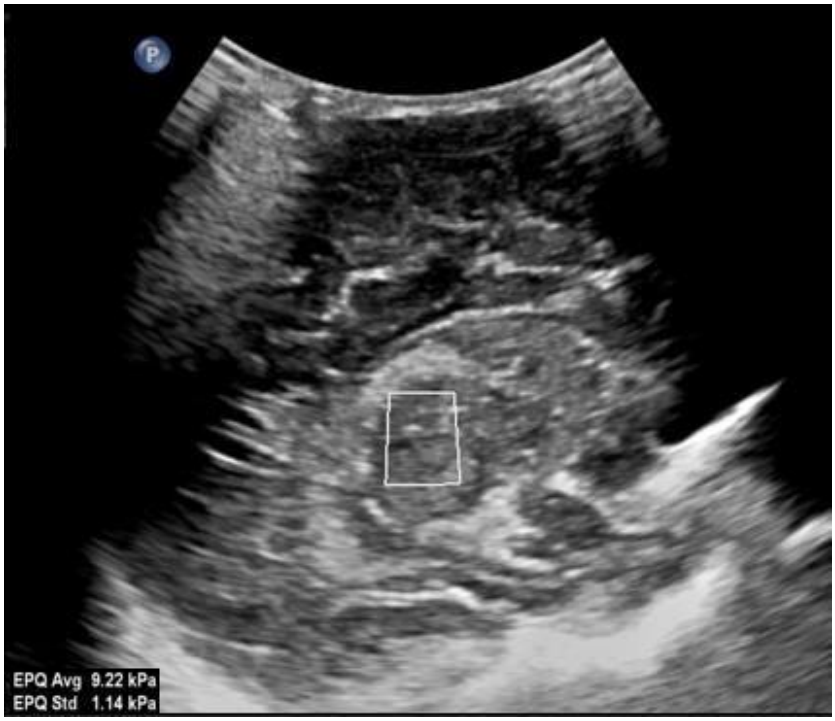

Fig 33: Image from a 3 days Term neonate.ROI was placed at right thalamus. Avg SWE value was found to be 9.2 kPa.

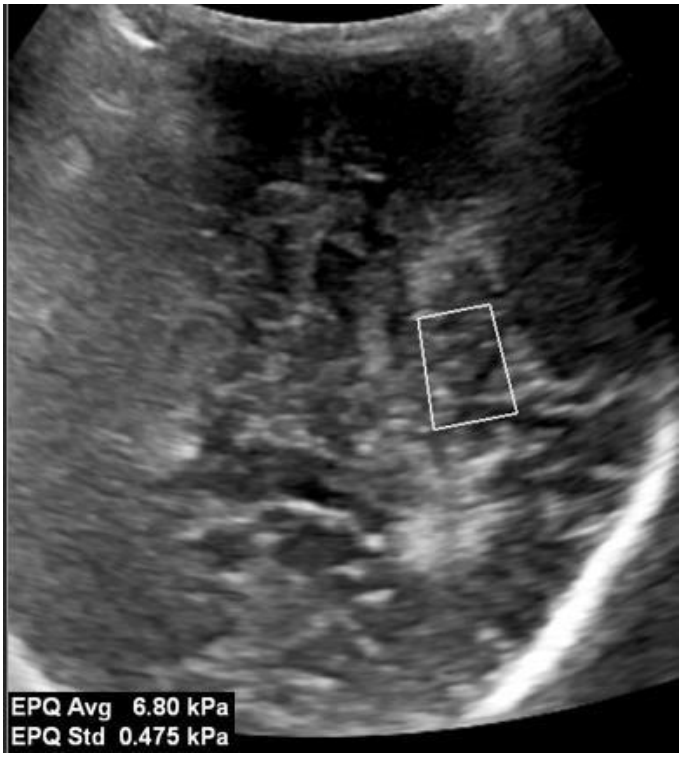

Fig 34: Image from a 3 days old Term neonate . ROI was placed at left peri-ventricular white matter. Avg SWE value was found to be 6.8 kPa.

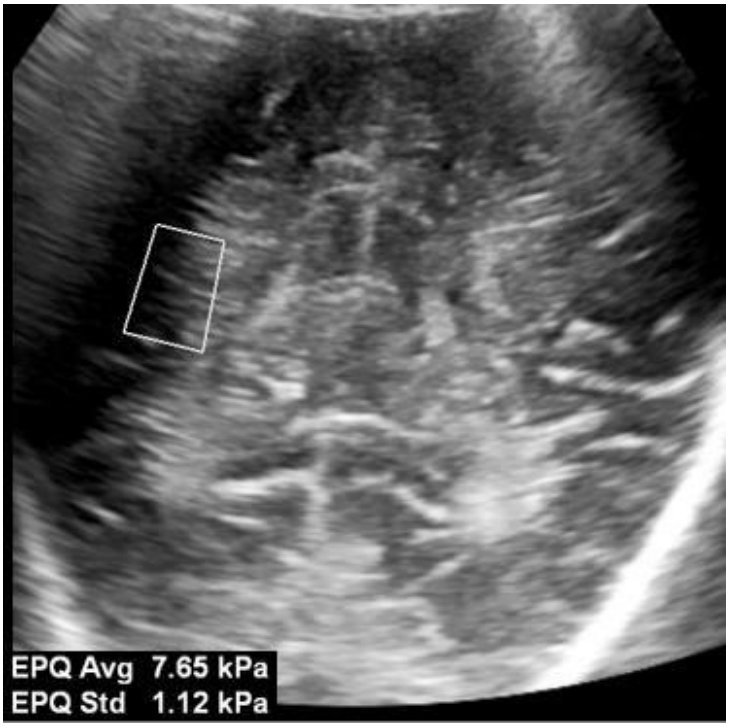

Fig 35: Image from a 3 days old Term neonate.ROI was placed at right peri-ventricular white matter. Avg SWE value was found to be 7.6 kPa.

DISCUSSION

DISCUSSION

Elastography is a new technique used in several organ evaluations. Few studies have used elastography in the newborn brain, despite the fact that sonography is common imaging technique for newborns that are under 30 weeks old gestational age and that at the term-equivalent age, recurrent imaging is indicated.[91] Shear wave elastography may be utilized to assess potential disparities in elasticity between term and preterm infants, as well as to measure stiffness of the brain in each group.

The SWE method was utilized in this work to evaluate the stiffness of the neonatal brain in both preterm and term neonates in order to develop a cut off reference range for measuring newborn brain stiffness between preterm and term neonates.

One novel method being used in many organ evaluations is elastography. Although sonography is a standard imaging tool for babies under 30 weeks gestational age, and recurring imaging is required at the term-equivalent age, few studies have used elastography in the newborn brain.[91] Shear wave elastography can be used to determine the brain stiffness in each group and to evaluate any potential differences in elasticity between term and preterm infants.

In present study, the mean gestational age of term infants (38.93 ± 0.797 weeks) was significantly higher compared to preterm infants (35.88 ± 1.09 weeks), with a statistical significance of $P < 0.001$. Mean maternal age and birth weight were also observed to be higher in term deliveries. No significant association was observed between gender and term/preterm delivery (P-value = 0.502). Enrique Garcés Iñigo conducted a comparable study during which 40 weeks was the median gestational age (interquartile range: 38 - 40 weeks) and the mean gestational age was 39.15 ± 1.42 weeks.[92] 3.33 ± 0.422 kg was the mean weight, while 3.400 kg was the median weight (interquartile range: 3.115–3.618 kg). The

groups that were considered term, pre-term, and extremely pre-term had average gestational ages of 38.4 ± 1.2 weeks, 29.0 ± 3.7 weeks, and 28.3 ± 3.1 weeks, respectively, in the study by Alexander M. El-Ali et al.[93]

Results of the demographic variables examined in this study and similar study by Albayrak and Kasap[94] are as shown in the table below.

		Present Study			**Albayrak and Kasap[67]**		
	Group	Mean	Std. Deviation	P- Value	Mean	Std. Deviation	P- Value
Gestational Age	Preterm	35.88	1.09	<0.001	33.28	2.55	<.001
	Term	38.93	0.797		38.77	0.96	
Gender	Preterm	M	F	0.502	Preterm	M	F
		18/40	22/40			20/42	19/42
	Term	21/40	19/40		Term	21/42	23/42

Table 5 : Results of the demographic variables examined in this study and similar study by Albayrak and Kasap[94].

In the present study, SWE values of the right (9.095 ± 0.5411) and left (9.068 ± 0.5411) thalamus (kPa) were higher in term deliveries compared to preterm, (7.788±0.7367 and 7.870±0.5644). A statistically significant difference was observed (P < 0.001). The mean thalamus SWE (kPa) was higher in term deliveries (8.825 ± 0.3754) compared to preterm 7.805±0.5901 (P < 0.001).

The SWE values of the right (7.260 ± 0.5012) and left (7.302 ± 0.5877) periventricular white matter (kPa) were higher in term deliveries compared to preterm, 6.490±0.5943 and 6.608±0.5797. A statistically significant difference was observed (P < 0.001). The mean periventricular white matter SWE (kPa) was higher in term deliveries (7.298 ± 0.4300) compared to preterm, 6.538±0.5300 (P < 0.001)

In line with our findings, In the periventricular white matter, the mean stiffness was

shown to be lower in all gestational age groups in the study by Alexander M. El-Ali et al.[93] compared to the deep gray nuclei. In both the severe preterm group (1.2 m/s vs. 1.4 m/s, P=0.001) and term group (1.3 m/s vs. 1.5 m/s, P < 0.001), this difference was statistically significant. Nevertheless, This distinction fell short of being statistically significant. (1.3 m/s vs. 1.4 m/s P = 0.12) when all pre-term babies were taken into account. The mean deep gray stiffness varied significantly between the groups (ANOVA, P < 0.01). Additionally, there was a difference (P < 0.01) in the mean stiffness of the deep gray nuclei between the term (1.5 ± 0.3 m/s) and pre-term (1.4 ± 0.2 m/s) groups. There were no discernible variations in white matter stiffness according to gestational age. Between GA <37 weeks (n = 12, white matter = 1.3±0.3 m/s, deep gray nuclei = 1.4±0.4) and GA >37 weeks (n = 8, white matter = 1.2±0.4, deep gray nuclei = 1.5±0.3 m/s) (white matter P-value = 0.40, deep gray nuclei P-value = 0.59), there was no discernible change in brain stiffness.

The authors of the study by Albayrak and Kasap[94] noted that even though the values for the right, left, and mean periventricular white matter stiffness as well as the right side, left side, and mean thalamus stiffness were found to be less at before 33 weeks, only the difference between the left periventricular white matter values was statistically significant. The left and the right of thalamus and the left side and right side of the periventricular white matter did not differ statistically significantly (p 5.772 and. 716, respectively). Nonetheless, a statistically significant difference (p<.001) was seen between the mean periventricular white matter values and the mean thalamus elasticity values in both the preterm and term groups. Compared to the thalamus & the periventricular white matter the stiffness values were substantially less. The study population was categorized as preterm based on the ROC curve analysis if the mean thalamus stiffness and the mean periventricular white matter stiffness were less than the cutoff criteria, which were 6.59 kPa and 8.28 kPa, respectively. The birth week was positively and weakly correlated with the stiffness of the right (r50.272; p5.013),

left (r50.265; p5.015), and mean (r50.349; p5.001) thalamus, as indicated by the Pearson correlation coefficient. Furthermore, a moderate positive correlation was found between the birth week and the mean periventricular white matter stiffness value (r50.419; p<.001), and a weak but noteworthy positive connection was found between the birth week and the right periventricular white matter (r50.34; p5. 002) and left periventricular white matter (r50.348; p5.001).

The SWE findings in the present study and similar study by Albayrak and Kasap[94] are as shown in the table below.

SWE (kPa)		**Present Study**			**Albayrak And Kasap[67]**		
	Group	Mean	Std. Deviation	P-Value	Mean	Std. Deviation	P-Value
Right thalamus	Preterm	7.788	.7367	<0.001	8.00	1.43	0.006
	Term	9.095	.5411		9.03	1.84	
Left thalamus	Preterm	7.870	.5644	<0.001	7.98	1.21	0.001
	Term	9.068	.5346		9.14	1.66	
Mean	Preterm	7.805	.5901	<0.001	8.00	1.10	<0.001
	Term	8.825	.3754		9.09	1.50	
Right periventricular white matter	Preterm	6.490	.5943	<0.001	6.29	1.50	0.003
	Term	7.260	.5012		7.2	1.24	
Left periventricular white matter	Preterm	6.608	.5797	<0.001	6.3	1.21	0/002
	Term	7.302	.5877		7.33	1.6	
Mean	Preterm	6.538	.5300	<0.001	6.3	1.23	<0.001
	Term	7.298	.4300		7.26	0.99	

Table 6 : The SWE findings in the present study and similar study by Albayrak and Kasap

The elasticity of the brain in preterm and term newborns was compared at each step of acquired from the frontal WM, parietal WM, and thalami in the study by Flora Faure et al. [95] using one-way ANOVA. We discovered that preterm infants had considerably less flexibility in the WM (parietal and frontal) than term infants from birth ($p < 0.001$). Overall, it was discovered that the extremely preterm newborns had lower elasticity values than the very preterm infants. Additionally, preterm infants' elasticity in the thalami was considerably lower than that of term newborns. For preterm newborns, the thalamus ($m = 0.28$, $p < 0.001$), parietal WM ($m = 0.46$, $p < 0.001$), and frontal WM ($m = 0.15$, $p < 0.001$) all had positive

linear regression slopes (m) of elasticity values versus gestational. The elasticity found to increase with gestational age.

A clear relationship exists between the level of myelination and the examination of elasticity coefficients and their variations with age and brain area is possible since stiffness increases with myelin content. In fact, a strong association was observed by Weickenmeier et al,[96] between the stiffness (determined by force–displacement characterisation in tissue samples) and the myelin concentration of the bovine brain (based on histological investigation). Myelin may perform a structural role in function of the brain folding and neurodevelopment in addition to facilitating information transfer between neurons by locally altering the brain's mechanical characteristics, according to their theory. A study employing magnetic resonance elastography shown that cuprizone-induced controlled demyelination reduces the elasticity of the brain in mice, supporting the association between stiffness and myelin concentration.[97]

The assessment of elasticity values in white and gray substances has been the subject of rather inconsistent findings in newborn research.[98-101] For a variety of reasons, it is still difficult to obtain accurate measurements of brain elasticity and compare research. First, the ultrasonic producers estimate elasticity using various technologies. The results appear to be more consistent when comparing trials conducted with the same ultrasonic equipment. Additionally, shear waves' velocity varies according to their direction of propagation due to WM mechanical anisotropy, which is caused by the local orientation of myelin fibers and axons. Shear waves typically propagate faster along than across fibers.[102]

It is still challenging to compare studies and get reliable measures of brain flexibility for a number of reasons. The ultrasonic manufacturers first use a variety of technologies to evaluate elasticity. When comparing trials carried out with the same ultrasonic equipment, the outcomes seem more consistent.

Thus, when measuring along these fibers as opposed to across the fibers, the apparent elasticity for a given anatomical position will be higher. The zone of measurement's location and size (frontal or parietal), as well as the plane of acquiring (coronal or sagittal), affect the orientation of the fibers with respect to the direction of shear wave propagation.

Standardizing the imaging planes and SWE measurement locations, as this study has done, supports measurement reproducibility. However, there could be considerable inter-individual variability or even local complex anisotropy in particular brain regions, which could cause the variance of elasticity measures to increase. This may account for the greater range in elasticity values found in the parietal WM as opposed to the frontal WM or thalamic measures in our investigation, as well as the parietal WM's lower interoperator-reproductibility. Though greater than that of the intra-observer study, the bias (mean difference) of the interobserver reproducibility for the frontal WM was still smaller than the observable variations between those with illness and those without. Furthermore, it should be mentioned that myelination occurs continuously, beginning at 20 weeks of gestation and moving from posterior to anterior frontal WM. This explains why parietal WM elasticity values are always higher than frontal WM elasticity values. It also implies that the degree of myelination and the corresponding elasticity value & same location will vary depending on the gestational age at which it is assessed.

Depending on the determined anatomical location in the brain, different stiffness values can be produced. In healthy term newborns, Chen et al.'s research[103] revealed that the thalamus had a increased rigidity that of the parietal white matter.

In line with this, Su et al,[101] reported that in both term and preterm newborns, the thalamus was stiffer than that of the parietal white matter. Consistent with those investigations, we also discovered that the thalamus had a higher stiffness value than the periventricular white matter. Brain elasticity measurements were used to diagnose preterm in

both of those trials, although there was no threshold value. This work presented threshold values for thalamus and periventricular white matter stiffness to indicate preterm for the first time to our knowledge. A number of theories have been put out to explain why the brain tissue becomes rigid with age or location. Using MRE, Green et al.'s work on adult human brains revealed that white matter was less stiff than gray matter.[104] Furthermore, we discovered that the thalamus, which is primarily composed of gray matter mass, has a stiffer structure than the white matter surrounding the periventricular area. Sack et al. [105] reported that age causes a decrease in human brain elasticity values ,who utilized MRE to evaluate difference in brain elasticity values in volunteers between the ages of 18 and 88 as a result of age and sex. They speculated that parenchymal liquefaction may be the source of the decline. as a result of aging. Women's temporal and occipital lobes were discovered to be stiffer than men's in the similar age group by Arani et al.[106] Cortical gray matter (P<.001), periventricular white matter (P<.001), and subcortical white matter (P<.001) all exhibited reduced elasticity than the cortical gray matter in the Kim HG,[102] investigation. In comparison to cortical gray matter (P<.001) and periventricular white matter (P5.004), caudate exhibited reduced flexibility. Both of the peri-ventricular and sub-cortical white matter displayed a median value of 4.0; nevertheless, there is a statistically significant difference in elasticity between the two types of white matter (P5.009). The elastographic values of the caudate and subcortical white matter did not differ significantly (P5.222). While some research has suggested that white matter is more elastic than gray matter,[104,108,109] other studies found no difference,[105] and still others found the reverse trend.[111] A study conducted on human brain tissues ranging in age from 2 months to 50 years[112] revealed an intriguing finding: the younger group had much higher gray matter elasticity than the older group, whereas there were no significant variations in white matter elasticity. Cortical gray matter and corrected GA showed a tendency toward positive connection in this investigation.

Thus, we conjecture that the younger age group covered by this research is the reason for the gray matter's increased flexibility when compared to other locations. Their findings demonstrated that, aside from subcortical white matter, the caudate was noticeably tougher than any other location. This result was in line with a shear wave elastography investigation from the past,[113] in which the research on 41 newborns revealed that the basal ganglia had a greater Virtual Touch tissue quantification value than the parietal white matter (i.e., the basal ganglia are harder than the white matter). It's well knowledge that brain development continues after birth.[114] Our findings indicated positive relationship amongst the cortical gray matter elasticity score and corrected GA, which leads us to believe that the elasticities of the different regions of the brain may vary depending on the neonates' GA. This result was in line with the earlier research that used shear wave elastography.[113]

In that study, preterm newborns (less than 37 weeks) have more flexibility in their parietal white matter and thalamic nuclei than term neonates (37 weeks). Nevertheless, neither the gray matter nor the white matter showed any obvious age pattern. elasticity in an MR elastographic investigation of adults[114] which again shows that neonates and adults have different tissue characteristics and age-related alterations. It is known from research employing shear wave elastography that the orientations of the fibers have an effect on the shear wave's propagation.[115,116] Shear wave elasticity in muscles is higher with muscle fiber orientation when measured perpendicular to that direction compared to when measured parallel to that direction.[115] Only coronal elastographic pictures were measured in this investigation. Depending on the direction of the ultrasonic beam, tissue anisotropy may have had an impact on the elastographic score even though there will only be a little degree of myelination in the newborn white matter. Further investigation, using several orientations to scan the brain, is necessary to confirm the association between brain tissue anisotropy and elasticity.

In the current study, a cut-off value of SWE (left & right thalamus, kPa) < 8.45 and < 8.55 respectively was considered for predicting the preterm delivery. The cut-off value of SWE of mean thalamus, kPa < 8.35 predicted the preterm delivery with 95% sensitivity and 87.5% specificity. A cut-off value of SWE (left & right periventricular white matter, kPa) < 6.85 and < 7 respectively was considered for predicting the preterm delivery. The cut-off value of SWE of mean periventricular white matter, kPa) < 6.85 predicted the preterm delivery with 87.5% sensitivity and 72.5% specificity. The ROC findings in the present study and similar study by Albayrak and Kasap are as shown in the table below.

	Present Study					**Albayrak and Kasap**				
Mean SWE	AUC	P-Value	Cut-off Value	Sensitivity	Specificity	AUC	P- Value	Cut-off Value	Sensitivity	Specificity
Thalamus	0.930	<0.001	8.35	95%	87.5%	0.743	<.001	8.28	67%	75%
Periventricular white matter	0.864	<0.001	6.85	87.5%	72.5%	0.74	<.001	6.59	64%	79.5%

Table 7 : The ROC findings in the present study and similar study by Albayrak and Kasap

CONCLUSION

CONCLUSION

This work demonstrates that quantitative stiffness bedside measurement in premature infants using 2D-SWE is both possible and repeatable. We discovered that preterm newborns had stiffer thalamus and periventricular white matter than term neonates, with the thalamus having stiffer values than the periventricular white matter. The mean thalamus and mean periventricular white matter stiffness cutoff values that were most effective in identifying preterm were 8.35 kPa and 6.85 kPa, respectively. The use of SWE imaging method will enable advancements in monitoring neonatal brain growth from an early postnatal period that are therapeutically meaningful.

Advanced cranial USG and MRI scans have become indispensable tools in the comprehensive understanding of overt brain damage and secondary changes in brain maturation in the developing brain. Our recommendations concern the utilization of various modalities such as neurosonogram, shear wave elastography, and cUS, which offer convenient and frequently urgent information regarding overt brain injury. They are also highly effective in diagnosing GMH IVH, PVHI, and PVL.

SUMMARY

SUMMARY

A hospital based, prospective comparative study was conducted in the department of Radio-Diagnosis, at R.L. Jalappa Hospital and Research Centre attached to Sri Devaraj Urs Medical College, Tamaka, Kolar, to perform shear wave elastography of neonatal brain.. A total of 82 neonates were included who were referred for ultrasound elastography examination to the department of Radio-Diagnosis. Patients with history of Patients with suspected congenital malformations,Central nervous system infections, Cerebral hemorrhage , Hydrocephalus , Periventricular leukomalacia, an insufficient fontanel space, etc were excluded from the study as they would lead to false positive results

- The mean gestational age of term infants (38.93 ± 0.797 weeks) was significantly higher compared to preterm infants (35.88 ± 1.09 weeks), has a noteworthy statistical correlation of $P < 0.001$.
- Mean maternal age and birth weight were also observed to be higher in term deliveries.
- No significant association was observed between gender and term/preterm delivery (P-value = 0.502)
- SWE values of the right (9.095 ± 0.5411) and left (9.068 ± 0.5411) thalamus (kPa) were higher in term deliveries compared to preterm, (7.788 ± 0.7367 and 7.870 ± 0.5644). There was a statistically significant difference. ($P < 0.001$).
- The SWE values of the right (7.260 ± 0.5012) and left (7.302 ± 0.5877) periventricular white matter (kPa) were higher in term deliveries compared to preterm, 6.490±0.5943 and 6.608 ± 0.5797. This difference was statistically significant ($P < 0.001$).
- The mean thalamus SWE (kPa) was higher in term deliveries (8.825 ± 0.3754) compared to preterm7.805 ± 0.5901 ($P < 0.001$). The mean periventricular white matter SWE (kPa)

was higher in term deliveries (7.298 ± 0.4300) compared to preterm, 6.538 ± 0.5300 ($P < 0.001$)

- The cut-off value of SWE of mean thalamus, kPa < 8.35 predicted preterm with 95% sensitivity and 87.5% specificity.
- The cut-off value of SWE of mean periventricular white matter, kPa) < 6.85 predicted preterm with 87.5% sensitivity and 72.5% specificity.

Shear wave elastography is a non-invasive and quantitative method technique to evaluate the stiffness of brain parenchyma, it has the potential to improve the diagnosis and management of brain injuries in newborns, ultimately leading to better outcomes for these vulnerable patients. Performing SWE on neonates can help us keep a track on the stiffness of brain parenchyma which in-turn helps us in preventing neurological complications that can occur.

LIMITATIONS

LIMITATIONS AND RECOMMENDATIONS

- Major limitation of this study was a small sample size. The findings of this investigation are more likely to contain type II statistical errors, so our findings need to be verified by carrying out a larger, multi-centric randomized trial. As with any technology, there are limitations to the modality that need to be taken into account. There will probably be variation in the measurements obtained from a broad spectrum of the population, and in order to support clinical decision-making and application, a database of typical stiffness ranges should be established. Nonetheless, further measurement standardization is required to enhance trustworthy evaluation throughout multi-site research. Follow-up was the main concern, where most of the patients wont come back for follow-up.

- In the end, we think the SWE imaging technique will enable therapeutically meaningful advancements in the observation of the newborn brain growth from prenatal to postnatal period,SWE of brain parenchyma can be incorporated as a routine method to screen neonates for impending neurological complications. Even though SWE has a lot of potential, there are still several obstacles to be solved. Standardized protocols are necessary, for example, to guarantee that measurements are precise and uniform amongst various machines and operators. Additional high-caliber clinical trials are required to support the use of SWE in neonates. Larger investigations are necessary to confirm its diagnostic accuracy and clinical value, even though pilot findings seem optimistic.

- Despite these challenges, SWE represents a significant advancement in neonatal brain imaging. By providing a safe, non-invasive, and quantitative method to assess brain stiffness, it has the potential to improve the diagnosis and management of brain injuries in newborns, ultimately leading to better outcomes for these vulnerable patients. Positive

results on brain imaging of the preterm infant are not "waste," but rather a vital chance to assist the families under our care. It is now necessary for newborn physicians to use neuroimaging in order to comprehend brain injury and healing.

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BIBLIOGRAPHY

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ANNEXURE

ANNEXURES

ANNEXURE I

PATIENT PROFORMA

SUBJECT EVALUATION

Date:

Time:

Demographic Variables

Hospital number:

Birth week:

Sex :

Age :

Brief History:

Physical Parameters

birth weight of the neonate :

mode of delivery :

APGAR Score :

Shear Wave Elastography:

ROI size:

ROI location:

Elastography values of Thalamus: / / /

Elastography values of Periventricular white matter: / / /

Mean elastography value (in kPa):

ANNEXURE II- INFORMED CONSENT FORM

I Mr./Mrs. _____have been explained in my own understandable language, that my son/ daughter will be included in a study which is**" A COMPARATIVE STUDY TO DETERMINE THE ROLE OF SHEAR WAVE ELASTOGRAPHY OF BRAIN PARENCHYMA IN PRETERM AND TERM NEONATES"**

I have been explained that the clinical findings, elastography findings will be assessed and documented for study purpose.

I have been explained that participation in this study is entirely voluntary, and we can withdraw from the study any time and this will not affect our relation with the doctor or the treatment for the ailment.

I have understood that all the details found during the study are kept confidential and while publishing or sharing of the findings, my details will be masked.

I have principal investigator mobile number for enquiries.

I in my sound mind give full consent for my son/daughter to be a part of this study.

Signature of the parent:

Name:

Signature of the witness:

Name:

Relation to patient:

Date:

Place:

ANNEXURE III - PATIENT INFORMATION SHEET

STUDY TITLE: "A COMPARATIVE STUDY TO DETERMINE THE ROLE OF SHEAR WAVE ELASTOGRAPHY OF BRAIN PARENCHYMA IN PRETERM AND TERM NEONATES"

STUDY SITE: R.L Jalappa Hospital and Research Centre, Tamaka, Kolar.

This is to inform you that, neurosonogram scan and elastography is done for early diagnosis and monitoring of progression of neurological deficits. The neurosonogram scan and elastography can be used as a supplement to existing methods in diagnosing and monitoring of progression of neurological deficits and for planning of the treatment. The patient referred to department of Radiology at R.L Jalappa hospital and research Centre, Tamaka, Kolar to undergo neurosonogram scan &elastography as a part of protocol and of those patients who meet the inclusion criteria will be taken for the study.

We are conducting this study to predict the onset and severity of this condition. If you are willing your son/ daughter will be enrolled in this study and we will do neurosonogram scan and elastography and other relevant investigations which are required for further management.

Your son/ daughter will receive the standard care.
This will facilitate evaluation of brain parenchyma function and can be used as a supplement to existing methods for predicting neurological deficits in an early stage and treating it. It will also benefit other preterm neonates in future.

Your son/ daughter is free to opt-out of the study at any time if you are not satisfied or apprehensive to be a part of the study. Your son/ daughter treatment

and care will not be compromised if you refuse to be a part of the study. The study will not add any risk or financial burden to you if your son/ daughter are part of the study. In case of any complication patient will be treated accordingly.

Your son/ daughter identity and clinical details will be confidential. You will not receive any financial benefit for being part of the study. You are free to contact Dr. JAYENDRA MANNAN .V for any doubt or clarification you have.

Dr. JAYENDRA MANNAN .V
Mobile no: 8660457528
E-mail id: mannan.jayendra77@gmail.com

MASTER CHART

KEY TO MASTER CHART:

M- Male

F- Female

UHID - Unique health identification number

kPa - kilopascal

SWE - Shear wave Elastography

W - Weeks

D - Days

LSCS - Lower segment cesarean section

E-LSCS - Elective Lower segment cesarean section

EM-LSCS - Emergency Lower segment cesarean section

.

SL No.	UHID	BIRTH WEEK (33 -35)	BIRTH WEEK (35-37)	AGE	SEX	BIRTH WEIGHT	Mode of birth	SWE of Right thalamus,kPa	SWE of Left thalamus,kPa	SWE of mean thalamus	SWE of right periventricular whitematter,	SWE of Left periventricularwhite mat ter,kPa	SWE OF MEAN PERIVENTRICULAR WHITEMATTER,
1	323324		37	3 days	M	2.8 Kg	LSCS	7.2	8.6	8.00	6.70	6.70	6.7
2	324118		35	1 day	F	2.5 Kg	LSCS	8.4	7.9	7.90	6.30	6.70	6.5
3	321306		37	1 day	F	3.0 Kg	NORMAL	8.2	8.1	8.20	6.30	6.80	6.5
4	324129		36	4 days	M	2.8 Kg	NORMAL	8.2	8.1	8.10	5.90	5.90	5.9
5	324673		34	5 days	F	2.9 Kg	LSCS	7.9	7.9	7.90	6.70	5.70	6.1
6	324703		37	3 days	F	3.2 Kg	LSCS	8.1	8.5	8.20	6.20	6.20	6.2
7	326713	33 w 5 d		1 day	F	1.6	E LSCS	6.9	7.4	7.20	6.10	5.30	5.8
8	326729		37	3 days	M	2.8 Kg	E LSCS	8.5	8.6	8.60	6.30	6.30	6.3
9	327245		36	4 days	M	2.9 Kg	EM LSCS	7.9	8.3	8.10	7.00	7.40	7.4
10	327247		37	6 days	F	3.2 Kg	EM LSCS	8.9	8.4	8.60	6.70	6.40	6.5
11	327273	32 w 6 d		3 days	M	2.2 Kg	EM LSCS	6.5	6.9	6.70	6.70	6.70	6.7
12	329757		37	1 day	M	3.0 Kg	E LSCS	8.1	7.5	7.80	6.00	6.40	6.2
13	329759		37	1 day	F	2.9 Kg	E LSCS	7.8	7.8	7.80	7.80	7.10	7.3
14	327634	33 w 5 d		3 days	F	2.4 kg	EM LSCS	6.1	6.9	6.50	5.60	6.10	5.8
15	330486		37	3 days	M	2.8 kgs	EM LSCS	8.4	7.6	7.90	6.80	6.20	6.4
16	331268		36	3 days	M	2.8 kgs	EM LSCS	7.8	7.9	7.90	6.20	6.20	6.2
17	331270		37	3 days	F	3.0 kgs	E LSCS	8.3	8.1	8.10	6.20	6.20	6.2
18	303911		37	1 day	M	2.9 kgs	EM LSCS	8.4	8.1	8.20	6.60	6.60	6.6
19	323363		36	3 days	F	3.2 kgs	EM LSCS	8.1	8.5	8.30	6.20	6.90	6.6
20	330260	34 W 6 D		1 day	F	2.2 kgs	EM LSCS	7.1	7.5	7.30	5.60	6.70	6.2
21	330935		37	3 days	F	2.9 kgs	E LSCS	7.9	8.3	7.90	7.60	7.60	7.6
22	330938		37	3 days	M	2.6 kgs	EM LSCS	7.7	7.5	7.60	7.90	7.90	7.9
23	331157	34 w 4 d		1 day	F	2.1 kgs	EM LSCS	7.6	7.3	7.40	5.70	5.90	5.7
24	331264		36	1 day	M	2.9 kgs	E LSCS	8.1	8.1	8.10	6.60	6.60	6.6
25	332166		35	1 day	F	3.0 kgs	EM LSCS	8.1	7.9	7.90	7.10	6.80	6.9
26	332168		36	3 days	F	2.8 kgs	EM LSCS	8.9	8.3	8.60	7.20	7.20	7.2
27	332191		36	3 days	M	2.8 KGS	E LSCS	7.1	8	7.50	6.10	6.60	6.4
28	331826	34 W 3 D		6 days	F	1.6 KGS	EM LSCS	7	7	7.00	5.90	5.90	5.9
29	333009		37 W	6 days	M	2.9 KGS	NORMAL	7.5	7.5	7.5	6.8	7.3	6.9
30	3318876		37	3 DAYS	F	2.1 KGS	EM LSCS	8.2	7.8	8	6.4	6.4	6.4
31	332445	34 W 6 D		4 D	F	1.5 KGS	EM LSCS	6.1	7.7	6.90	5.10	5.90	5.6
32	332407		35	3 DAYS	F	1.9 KGS	EM LSCS	7.1	7.4	7.2	6.1	6.1	6.1
33	328890		36 W 3 D	5 D	M	2.2 KGS	EM LSCS	7.2	7.2	7.2	6.4	7.5	6.9
34	342940		35 W 5 D	3 DAYS	M	2.6 KGS	EM LSCS	7.5	7.5	7.5	6.8	6.8	6.8

SL No.	UHID	BIRTH WEEK (33 -35)	BIRTH WEEK (35-37)	AGE	SEX	BIRTH WEIGHT	Mode of birth	SWE of Right thalamus,kPa	SWE of Left thalamus,kPa	SWE of mean thalamus	SWE of right periventricular whitematter,	SWE of Left periventricularwhite mat ter,kPa	SWE OF MEAN PERIVENTRICULAR WHITEMATTER,
35	347108		36 W 1 D	3 DAYS	M	2.1 KGS	EM LSCS	9.5	9.1	9.3	7.1	6.8	6.9
36	347097		36 W 6 D	3 DAYS	F	2.6 KGS	E LSCS	7.6	7.8	7.7	6.2	6.2	6.2
37	349024		35 W 2 D	3 DAYS	M	2.6 KGS	E LSCS	8.9	8.9	8.9	7.2	7.8	7.4
38	342953	34 W 3 D		3 DAYS	F	1.8 KGS	EM LSCS	7.1	7.1	7.1	6.2	6.8	6.5
39	370744		36 W 4 D	3 DAYS	M	2.6 KGS	EM LSCS	7.8	7	7.4	6.9	6.9	6.9
40	356716		35W 4 D	3 DAYS	F	1.9 KGS	EM LSCS	7.8	8.8	8.2	6.4	6.8	6.6
41	365712		36W 5D	3DAYS	M	2.1KGS	EM LSCS	7.9	8.6	8.3	6.5	6.9	6.5

Sl No.	UHID	BIRTH WEEK	AGE	SEX	BIRTH WEIGHT	Mode of delivery	SWE of Right thalamus,kPa	SWE of Left thalamus,kPa	SWE OF MEAN THALAMUS	SWE right periventricul arw hitematter,kP	SWE Left periventricular w hitematter,kPa	SWE OF MEAN PERIVENTRICU LA R WHITEMATTER
1	323531	39	3 DAYS	M	3.5 Kg	LSCS	9.2	9.2	8.6	7.2	7.9	7.5
2	325721	40	5 DAYS	F	3.2 kg	LSCS	8.8	8.1	8.5	6.9	6.1	6.5
3	325939	39	5 DAYS	M	3.4 kg	LSCS	9.6	8.7	8.5	7.9	7.4	7.3
4	323755	38	4 DAYS	M	3.1 kgs	LSCS	8.5	8.9	8.2	7.4	7.1	7.1
5	326722	39	5 DAYS	F	3.4 kg	NORMAL	8.2	9.1	8.8	7.9	7.1	7.4
6	326749	40	1 DAYS	M	3.4 kg	E LSCS	9.8	9.6	8.6	6.9	7.9	7.6
7	318821	38	3 DAYS	F	2.9 kg	NORMAL	8.5	9.4	9.2	7.3	7.4	7.4
8	327215	39	6 DAYS	F	3.2 kg	E LSCS	8.8	8.7	8.8	7.9	7.3	7.5
9	327218	38	6 DAYS	F	2.9 kg	NORMLA	8.1	8.9	8.5	6.5	6.6	6.6
10	327584	40	5 DAYS	M	3.7 kg	EM LSCS	10.1	9.1	9.6	6.1	7.4	6.9
11	327585	39	5 DAYS	M	3.2 kg	EM LSCS	9.2	8.5	8.5	6.8	6.9	6.9
12	327589	39	6 DAYS	F	3.1 kg	EM LSCS	8.9	8.3	8.6	6.4	7.8	7.1
13	328256	40	3 DAYS	M	3.5 kg	EM LSCS	8.6	8.6	8.6	6.7	7.4	7.1
14	327643	39	1 day	F	2.8 Kg	E LSCS	8.6	9.7	9.10	7.10	6.10	6.8
15	321469	39	3 days	F	2.9 Kg	EM LSCS	9.7	8.6	9.30	7.50	7.50	7.5
16	329557	38	7 DAYS	F	3.2 kg	E LSCS	9.3	8.9	8.4	6.9	6.1	6.5
17	330488	39	3 DAYS	M	3.4 kg	EM LSCS	8.7	9.6	9.2	6.9	6.7	6.7
18	330416	40	6 DAYS	M	3.1 kg	EM LSCS	9.7	9.9	8.5	7.2	6.5	6.9
19	331291	38	8 DAYS	F	3.1 kg	E LSCS	8.5	8.2	8.3	7.9	7.5	7.7
20	330484	39	3 DAYS	M	2.9 kgs	EM LSCS	9.1	9.9	9.4	7.5	7.1	7.3
21	332372	38	3 DAYS	M	2.9 kgs	EM LSCS	8.8	9.5	9.1	6.8	7.1	6.9
22	332419	40	3 DAYS	F	3.1 kgs	E LSCS	8.7	8.3	8.6	6.9	7.8	7.4
23	331303	39	1 DAY	F	3.0 kgs	EM LSCS	9.2	9.1	9.1	6.7	7.5	7.2
24	331307	37 W 5 D	3 DAYS	F	3.3 kgs	EM LSCS	8.9	8.4	8.4	7.3	6.6	6.9
25	331575	38	3 days	M	3.1 kgs	E LSCS	8.7	9.8	8.5	7.3	7.1	7.2
26	338265	39	1 day	F	2.9 kgs	EM LSCS	9.8	9.9	9.1	7.8	7.8	7.8
27	337634	40	3 days	M	3.4 kgs	NORMAL	8.9	8.9	8.9	7.1	7.1	7.1
28	343379	39	7 days	M	3.2 kgs	EM LSCS	8.9	8.9	8.4	8.1	7.4	7.8

Sl No.	UHID	BIRTH WEEK	AGE	SEX	BIRTH WEIGHT	Mode of delivery	SWE of Right thalamus,kPa	SWE of Left thalamus,kPa	SWE OF MEAN THALAMUS	SWE right periventricul arw hitematter,kP	SWE Left periventricular w hitematter,kPa	SWE OF MEAN PERIVENTRICU LA R WHITEMATTER
29	346698	39 W 5D	3 days	F	2.8 kgs	E LSCS	9.6	9.6	9.6	7.2	8.5	8.1
30	338122	38 W 5 D	3 days	F	2.4 kgs	EM LSCS	8.9	9.6	9.1	7.1	7.4	7.3
31	339123	38 W 3 D	7 days	F	3.1 Kgs	E LSCS	9.6	9.1	8.6	7.3	7.7	7.5
32	337677	40 W 1D	7 dayS	M	3.2 Kgs	EM LSCS	10.3	9.6	8.6	7.5	8.2	7.9
33	347074	39 W 2D	3 DAYS	M	2.9 KGS	EM LSCS	9.8	9.1	9.2	6.9	7.2	7.1
34	343838	38 W 2d	7 days	F	3.1 Kgs	E LSCS	9.3	9.2	9.2	7.9	7.9	7.9
35	358084	39 W 2 D	7 days	M	3.2 Kgs	NORMAL	8.9	8.9	8.9	7.1	8.5	8.1
36	326789	39 W 6 D	3 days	M	3.4 Kgs	EM LSCS	9.7	9.1	9.1	8.1	7.5	7.9
37	349855	40 W 4 D	7 Days	M	2.7 kgs	EM LSCS	8.4	8.6	8.5	6.9	6.9	6.9
38	347727	38 W 2 D	3 days	F	2.6 kgs	EM LSCS	8.5	9.9	9.3	7.6	7.6	7.6
39	349614	39 W 2 D	7 days	M	2.9 KGS	EM LSCS	9.6	9.2	9.1	7.8	7.8	7.8
40	327482	38 W 4 D	3 days	M	2.6 kgs	EM LSCS	9.4	8.1	8.5	8.1	6.7	7.2
41	326749	40 W 4 D	3 days	m	2.6 kgs	EM LSCS	9.5	8.6	8.8	8.3	7.9	7.3