Cape Peninsula University of Technology

THE SIGNIFICANCE OF RENAL RESISTIVE INDEX AS A NON-INVASIVE MARKER IN RENAL DYSFUNCTION.

by

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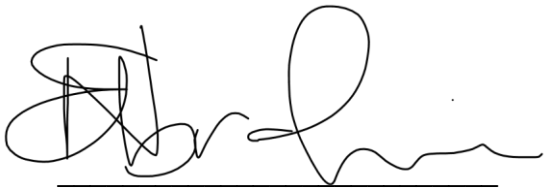
DECLARATION

I, Naazneen Ebrahim, declare that the contents of this thesis represent my own unaided work, and that the thesis has not previously been submitted for academic examination towards any qualification. Furthermore, it represents my own opinions and not necessarily those of the Cape Peninsula University of Technology.



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ABSTRACT

Introduction: A major worldwide health problem, chronic kidney disease (CKD), is characterised by a progressive loss of renal function. The asymptomatic nature of CKD in its early stages increases the likelihood of development to later stages and delays detection. Prompt identification and suitable treatment measures, such as pharmacological and nutritional adjustments, can greatly impede the advancement of the illness and lessen its consequences. Within the field of medical diagnostics, imaging methods are essential for the identification, treatment and management of CKD. Because it is the most effective modality for diagnosis and is non-invasive, ultrasound imaging stands out among the others.
A key method in renal imaging, grey-scale ultrasound imaging, produces two-dimensional images that are necessary for assessing renal architecture and identifying size differences. Furthermore, colour Doppler is used to demonstrate renal perfusion and to provide important information on renal vascularisation. In addition, Spectral Doppler analysis, used to measure the blood flow velocities within the renal arteries, evaluates hemodynamic parameters that are essential for a thorough assessment of CKD. When taken as a whole, these ultrasound imaging methods provide a comprehensive toolset for the timely identification and efficient treatment of CKD, highlighting their vital significance in modern nephrology.

Purpose: The purpose of the thesis was to report the findings of Doppler ultrasound studies of the renal resistive indices of patients who present with renal dysfunction, according to biochemical results at an academic hospital in Johannesburg, South Africa. This was to address the current knowledge gap surrounding the routinely requested Doppler renal ultrasound studies.

Methods: A cross-sectional study of 100 patients presenting with renal dysfunction, as determined by biochemical markers, was carried out. These patients were referred for a renal Doppler ultrasound examination by the nephrology clinic. The study was carried out during the period of December 2022 and February 2023. All participants involved in the study provided informed consent prior to their participation. The study was conducted in adherence to ethical principles to ensure the integrity and ethical compliance of the research process. The ultrasound component of the investigation used a Siemens Acuson Redwood ultrasound machine to carry out the renal ultrasound examinations, and involved using a 3.5 MHz curvilinear probe to image in grey-scale, colour Doppler and spectral Doppler modes. The biochemical markers used in the study were GFR_MDRD, GFR-EPI, urea and creatinine. All of the above contributed to the independent variables of this study. The dependent variables of this study included the kidney sizes, echogenicity of the kidneys, the renal resistive index

(RRI) and other pathology noted during the ultrasound examination. Data were analysed by a statistician of the Cape Peninsula University of Technology using SPSS version 28. Descriptive analysis, Spearman's correlation analysis and inferential statistical analysis, Generalised linear models (GLMs), were used to test the relationship between independent variables and dependant variables.

Results: There were one hundred (n = 100) participants, ages ranging from 18 to 90 years, comprising 52% females and 48% males with clinical indications of chronic kidney disease (50%), acute kidney injury (AKI) (20%), diabetes mellitus (10%), renal dysfunction (10%) and nephropathy (10%).
Correlation results of ultrasound findings and biochemical results of the study showed that, presence of an elevated RRI (> 0.7) is a distinctive trait seen across a broad spectrum of participants with renal dysfunction rather than being restricted to a particular age.
A raised RRI seen in the ultrasound results was not necessarily linked to the clinical indications. The biochemical markers GFR-MDRD, GFR EPI and urea were not linked to kidney size with p-values of 0.242, 0.319 and 0.649, respectively, when their levels indicated renal dysfunction. The study results demonstrated that kidney echogenicity, as opposed to ultrasound parameters such as kidney size and cortical thickness, was a more sensitive method of evaluating renal dysfunction in patients. Spearman's correlation analysis showed a weak negative correlation between renal resistive index and GFR_MDRD and GFR-EPI (r = -0.104 and -0.102 for right and left kidney, respectively) and a weak positive correlation between the RRI and urea (r = 0.073 and 0.010 for right and left kidney, respectively) and creatinine (r = 0.111 and 0.017 for right and left kidney, respectively).

Conclusion: Notably, all individuals diagnosed with renal dysfunction (n = 100) exhibited a raised RRI. These findings suggest that an elevated RRI may serve as a reliable marker for renal dysfunction. Further research is warranted to explore the underlying mechanisms of the disease and to further evaluate the potential of RRI as a diagnostic tool in clinical settings.

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DEDICATION

To my mum, Miriam Ebrahim -

Thank you for all your support, endless sacrifices, and boundless love.

Miriam Ebrahim

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ABBREVIATIONS AND ACRONYMS

ACEI	Angiotensin converting enzyme inhibitor
ACR	Urine albumin to creatinine ratio
AKD	Acute kidney disease
AKI	Acute kidney injury
ARB	Angiotensin receptor antagonist
ATN	Acute tubular necrosis
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemiology collaboration
CT	Computed tomography
CVD	Cardiovascular disease
DM	Diabetes mellitus
DUS	Doppler ultrasound
eGFR	Estimated glomerular filtrate rate
EDV	End diastolic velocity
ESRD	End-stage renal disease
FBS	Fasting blood sugar
GFR	Glomerular filtrate rate
GLzdM	Generalized linear model
Hz	Hertz
ICU	Intensive care unit
IGFBP7	Insulin-like growth factor binding protein 7
IVC	Inferior vena cava
KDIGO	Kidney disease: Improving global outcomes
KIM-1	Kidney injury molecule-1
KUB	Kidneys, ureters and bladder
LP	Lower pole
MDRD	Modified diet in renal disease equation
MP	Mid pole
MRI	Magnetic resonance imaging
NGAL	Neutrophil gelatinase-associated lipocalin
NKF-KDOQI	National Kidney Foundation's Kidney Disease Outcomes Quality Initiative
PCR	Output to creatinine ratio
PDI	Pulse Doppler imaging
POPIA	Protection of Personal Information Act

PRF	Pulse repetition frequency
PSV	Peak systolic velocity
RBCs	Red blood cells
RRI	Renal resistive index
RRT	Renal replacement therapy
TIMP2	Tissue inhibitor of metalloproteinases 2
UP	Upper pole
US	Ultrasound
WMA	World Medical Association

CHAPTER 1
INTRODUCTION

This chapter includes an overview of the thesis and delivers a brief introduction to the study. The topics that are discussed in this chapter include the pathogenesis of chronic kidney disease, ultrasound as an imaging modality, the background and rationale of the study, the research question, aims and objectives, and an overview of the methodology.

1.1 Pathogenesis of chronic kidney disease

Chronic kidney disease (CKD) is known as one of the world's major health problems and may be a silent killer when not detected, as it can be easily masked by other conditions (Makusidi et al., 2014). It may not always be possible to be assessed by a nephrologist which allows latent kidney disease to continue, although under controlled conditions. CKD may also develop without the underlying condition being detected or treated and the disease is known to progress to end-stage renal disease (ESRD) in most cases. According to Petrucci *et al.* (2018), there are various clinical features and complications that contribute to the progression of ESRD which include:

- Infectious diseases such as pyelonephritis and tuberculosis
- Immune and inflammatory diseases such as primary and hepatitis C virus-related glomerulonephritis
- Vascular disease such as chronic ischemic nephropathy
- Congenital and hereditary disease such as congenital cystic dysplasia and polycystic disease
- Metabolic diseases which include diabetes mellitus (DM) and hyperuricemia
- Systemic diseases such as vasculitis, collagen disease and myeloma.

For patients presenting with symptoms of CKD it is of utmost importance to determine the cause and to strive to reverse the condition, if possible. For this, a detailed patient history is essential for both the diagnostic assessment and therapeutic management of CKD. Clinicians may identify underlying aetiologies, stratify illness severity and customise treatment plans to improve patient outcomes by clarifying relevant clinical data.

1.2 Ultrasound as an imaging modality

Ultrasound is usually the first step taken in terms of imaging the kidneys. Ultrasound imaging is cost effective and a safer imaging modality compared to computed tomography (CT) and magnetic resonance imaging (MRI). Granata et al. (2014) support the use of renal ultrasound

imaging due to it being a reliable, sensitive imaging modality of low cost and having acquired a strategic importance in detecting renal pathology. Granata et al. (2014) further contributes to the existing literature that renal ultrasound imaging has several benefits such as multiplanar imaging, excellent spatial resolution and real-time visualisation. It makes it possible to evaluate the size, shape, echogenicity (soft tissue differentiation) and vascularity of the kidneys which make it easier to detect and identify a variety of structural abnormalities such renal cysts, tumours, hydronephrosis and calculi. Furthermore, Doppler ultrasonography offers insightful data on vascular anomalies and renal perfusion, improving diagnostic precision and directing treatment approaches.

Ultrasound imaging, in particular the kidneys, ureters and bladder (KUB) ultrasound, has gained popularity in nephrology as a vital tool for the thorough assessment of renal disorders. Nephrology has made ultrasound imaging a crucial component of its practice. Grey-scale imaging, spectral Doppler and colour Doppler ultrasound are all important tools for assessing renal health; however, not all patients undergoing renal ultrasound examinations have Doppler studies conducted because these tests are not routinely done. For example, the guidelines at the research site often propose a renal Doppler ultrasound examination to exclude renal artery stenosis in patients with hypertension or to exclude renal vessel patency when it is a clinical concern.

The purpose of this study was therefore to establish whether Doppler ultrasound should routinely be done for all patients with renal dysfunction.

1.3 Background and rationale of the study

The nephrology department at an academic hospital in Gauteng province of South Africa refers a considerable number of patients, both as in-patients and as attendees of out-patient nephrology clinics. Medical doctors, particularly nephrologists, often refer patients for KUB ultrasound examinations, including renal Doppler ultrasound.

This study aimed to clarify the importance of the renal resistive index (RRI) as a non-invasive diagnostic tool in patients presenting with renal dysfunction. There is a current knowledge gap on the justification for routine requests for renal Doppler ultrasound examinations, particularly in patients displaying ultrasound abnormalities and patterns of renal dysfunction. By thoroughly evaluating the efficacy of the RRI in patients who present with renal dysfunction, this knowledge gap may be addressed and contribute to a more nuanced understanding of its diagnostic significance. To date, there is limited literature on the association between RRI, biochemical evidence of renal dysfunction and ultrasound-detected structural renal abnormalities. The study investigated the diagnostic use of RRI in the context of various ultarsound abnormalities and renal dysfunction patterns by closely examining the relationship between RRI and renal dysfunction in patients undergoing renal Doppler

ultrasound examinations. It was envisaged that the results of this study would improve the understanding of the role of RRI in the setting of renal dysfunction, enhance the knowledge of heath care workers in the clinical environment, resulting in the modification of the requirements for requesting a renal Doppler ultrasound examination.

1.4 Research question

Patients from the nephrology department, this includes outpatient nephrology clinic and ward patients, are referred for ultrasound at a tertiary academic hospital in Gauteng province of South Africa, and renal Doppler investigations are also requested. At this stage, all renal patients have renal Doppler studies regardless of their clinical history or biochemical results. This has led to the research question:

> *Is there a statistically significant association between the ultrasound findings and biochemical markers in patients presenting with renal dysfunction?*

1.5 Overview of the methodology

A quantitative cross-sectional observational study, which included 100 participants, was conducted at a tertiary academic hospital in Gauteng province of South Africa between the period December 2022 and February 2023. The main aim of the study was to determine whether patients with renal dysfunction, according to biochemical markers, who were referred by the nephrology department had an elevated RRI. Variables included in the study were biochemical markers, viz. GFR-MDRD, GFR EPI, urea and creatinine, as well as renal ultrasound parameters, viz. renal size, echogenicity, cortical thickness and the mean RRI of segmental arteries. The intent was to determine an association between abnormal renal function tests and specifically RRI in patients presenting with renal dysfunction.

1.5.1 Data collection and analysis

A methodical procedure was used for gathering clinical data which included thorough clinical medical history, presenting symptoms, demographic data and biochemical data like GFR-MDRD, GFR EPI, urea and creatinine.

The Siemens Acuson Redwood ultrasound machine was used for the ultrasound component of the study. It involved grey-scale, colour Doppler and spectral Doppler imaging using a 3.5 MHz curvilinear probe. Results collected from the renal ultrasound examination were kidney sizes (right and left), echogenicity of the kidneys (right and left), cortical thickness of the kidneys (right and left) and the RRI of the segmental artery of the upper, lower and mid pole of the right and left kidney from which the mean RRI was then calculated. These results formed the ultrasound report.

Data were analysed by a statistician of the Cape Peninsula University of Technology using SPSS version 28. Descriptive statistical analysis (percentages), inferential statistical analysis, generalised linear model (GLMs) and Spearman's analysis were used to test the relationship between independent variables and dependant variables.

1.5.2 Ethical considerations

All patients provided informed consent prior to participating in the research study and received thorough information regarding the research study Appendix A). The research study was approved by the Research Ethics Committee at the Faculty of Health and Wellness Sciences at Cape Peninsula University of Technology (Ethical clearance number: CPUT/HWS-REC 2022/H23) and the tertiary academic hospital in Gauteng province of South Africa. During the research study all ethical standards were met by obtaining informed consent from participants and implementing measures to protect patient confidentiality such as safeguarding electronically stored information restricting access to only authorised personnel. All of these steps together ensured that patient privacy was strictly upheld for the length of the research. By following these guidelines, researchers may protect study participants' rights and privacy while upholding ethical standards and their credibility in their pursuits.

1.6 Conclusion

Chapter 1 serves as the compass, plotting the course of the investigation. It not only informs the reader, but also paves the way for insight that will come in the subsequent chapters of this thesis through a nuanced exploration of the pathogenesis of CKD, the significance of ultrasound as an imaging tool, the rationale guiding the study, the formulation of the research question, the delineation of the study aims and objectives, and a comprehensive overview of the chosen methodology.

CHAPTER 2
LITERATURE REVIEW

Chapter 2 presents a comprehensive literature review of the study and delves into the core principles and prior research relevant to the use of ultrasound in assessing renal function, with a particular focus on CKD. The chapter also explores the Physics of Ultrasound including grey-scale imaging, Doppler ultrasound and the renal resistive index.
The chapter then examines the biochemical markers in renal dysfunction and lastly reviews previous studies.
Ultrasound imaging is a practice and terrain of research in a field that is constantly evolving and has generally created a positive impact on medicine. The first imaging modality of choice by clinicians to assess the kidneys is ultrasound as results are available immediately. High-frequency sound waves are used in the non-invasive imaging technique of ultrasound to view internal anatomical structures and functioning in real-time. Sidappa et al. (2013) states that ultrasound is a vital tool for safe, precise and quick medical imaging modality, since it uses sound wave echoes to provide essential information without the use of ionising radiation. Renal ultrasound is being promoted as the initial imaging modality of choice for the kidneys by clinicians because there is no patient preparation required, it is safe and non-invasive, there is easy accessibility of the visualisation of the kidneys and an immediate report (Sidappa et al., 2013).
Patients are referred daily to the ultrasound department for ultrasound examinations, including grey-scale imaging, colour and spectral Doppler analyses. Grey-scale ultrasound is typically employed for diagnostic purposes. Most diagnostic ultrasound procedures can be completed solely with grey-scale ultrasonography. However, colour and spectral Doppler ultrasound are additional tools to assess vasculature. This study intends to assess the value of diagnostic ultrasound imaging in nephrology and how it is used in clinical practice.
A non-invasive medical imaging procedure called renal ultrasound is used to visualise the kidneys and urinary bladder in real-time. In order to offer a thorough evaluation of kidney function, renal ultrasound is frequently utilised in conjunction with other diagnostic tests such as blood tests and urine analyses. Kidneys are retroperitoneal organs and are assessed by ultrasound for pathologies such as kidney stones, cysts, tumours and infections, with a diagnostic report being quickly available and guiding medical decisions and treatment plans (Sidappa et al., 2013).
The kidney anatomy is explained by Trunz and Balasubramanya (2021). The kidneys, located in the retroperitoneum, receive approximately 20% of the cardiac output. The superior mesenteric artery is inferior to the abdominal aorta which is the source of the arterial supply for each kidney's single renal artery. The principal renal arteries are between 4 and 6

cm long and between 5 and 6 mm wide. The right renal artery originates from the anterolateral aorta and is thought to be longer than the left renal artery. It then travels inferiorly, posterior to the inferior vena cava (IVC), until it reaches the right kidney. The left renal artery progresses more towards the side of the aorta and takes a nearly horizontal path to reach the left kidney, situated behind the left renal vein. The renal arteries also give rise to small branches that supply the adrenal gland, renal capsule and the upper part of the ureter. There are five segments to the renal artery: apical, superior, middle, inferior and posterior. The end arteries for the renal parenchyma are provided by the segmental arteries which are further divided into lobar, interlobar, arcuate and interlobular arteries. The interlobular arteries supply the afferent glomerular arterioles which feed into the glomeruli.

The renal veins lie anterior to the renal arteries at the hilum. The right renal vein is shorter than the left renal vein and measures 2 to 4 cm in length. The left renal vein is approximately 6 to 10 cm in length. The left renal vein travels medially between the superior mesenteric artery and aorta before entering the IVC. The left renal vein usually receives blood from the left adrenal and gonadal veins along its course, and frequently, from the lumbar veins. The shorter lateral vein of the right renal vein empties into the IVC.

O'Neill (2014a) explains that, because of the physical location of the kidneys, ultrasound is frequently the only imaging technique needed to evaluate the kidneys. As part of the renal ultrasound evaluation, kidney size, shape, echogenicity, urinary space (including the lower urinary tract), the vasculature and the presence of masses are assessed.

In nephrology, ultrasound is extremely useful for anything from diagnosis to invasive kidney surgery guiding. This study intends to enhance the understanding of ultrasound in the diagnosis and treatment of renal disease. Ultrasound can play a major role in the diagnosis of CKD and the referral to the nephrologist. Referral to the nephrologist is essential for management of the kidneys such as kidney replacement therapy and transplant evaluation.

2.1 Introduction to the physics of ultrasound

According to Oglat et al. (2018), the term *ultrasound* refers to the propagation of sound wave pulse frequencies in a medium that are above the range of actual human hearing. Audible sound waves have a frequency ranging from 20 to 20 000 Hz. In the medical industry, diagnostic ultrasound is a technique that uses ultrasonic energy with frequencies ranging from 1 MHz to 30 MHz, and the acoustic characteristics of the body's organs or phantoms to create an image from continuously moving tissue (Sanders & Winter, 2016).

Ultrasound transducers perform two key functions. Firstly, they convert electrical energy into sound energy during transmission and secondly, they transform the reflected pulse into electricity upon reception (Edelman, 2012). Diagnostic ultrasound functions on the pulse-echo principle and its essential functional unit is the piezoelectric crystal. This crystal has the

unusual capacity to translate mechanical vibrations into electrical oscillations and vice versa. Sound waves are produced when the crystal is mechanically deformed by an alternating electric current. On the other hand, sound waves cause the crystal to distort and produce electrical impulses when they strike it. Its dual capability makes it possible for a single crystal to produce and receive sound waves simultaneously. When the piezoelectric crystal is first subjected to an alternating electrical field, it vibrates and produces a brief, powerful sound pulse. The transducer then switches to a “listening” mode after that. Resonant waves reflected from different surfaces come back to the crystal and set it vibrating again. A picture is then rebuilt using the electrical impulses that are created from these vibrations (Graham et al., 2011).

Diverse types of transducers are employed for various ultrasound examinations. For instance, a curvilinear ultrasound transducer is suitable for imaging the kidneys, ureters and bladder. In the present study, a curvilinear ultrasound transducer (probe) was utilised for this purpose (Edelman, 2012). According to Kaptein and Kaptein (2017), a curvilinear transducer with a 3.5 MHz is utilised to image the adult kidneys in ultrasound depending on the size of the patient.

Shikri (2014) explains that the frequency of a curvilinear 3 to 5 MHz transducer in medical ultrasound imaging is inversely related to both image resolution and depth of penetration. Because of its low-frequency this transducer is more suited for imaging deeper body structures. These transducers generate sound waves with longer wavelengths that can penetrate tissues more efficiently which makes them perfect for illuminating deeper-lying organs and structures like the liver and kidneys. However, because lower frequency sound waves have longer wavelengths and can enter deeper structures, these transducers produce images with less detail and less accurate information about tissue boundaries.

A large field of view is made possible by the shape of the curvilinear transducer in ultrasound imaging. It enables a wider scanning area without the need for excessive physical movement of the transducer by bending the array of elements of the transducer. In situations where the operator wants to see larger anatomical structures or conduct scans that span a large area such as abdominal imaging this shape is especially helpful. A panoramic view of the internal organs or structures being investigated is provided by the curved design which reduces the need to move the transducer, and enables efficient and thorough coverage (Shriki, 2014).

According to Patey and Corcoran (2020), the initial step in the diagnostic ultrasound procedure involves producing the ultrasound waves through the utilisation of piezoelectric crystals (lead zirconate titanate). These crystals consist of electric dipoles arranged in a random manner. When an external electric force is applied, causing the crystal to deform, the dipoles realign, resulting in the creation of a net charge across the crystal. Applying a voltage to the crystal induces a change in the arrangement of the dipoles, leading to the overall

deformation of the crystal. As a result, piezoelectric crystals can both initiate and receive ultrasound waves. The deformation of these crystals within the probe generates a pressure front which subsequently travels through tissues as an acoustic wave. This wave creates alternating regions of compression and rarefaction (lowered density) as it progresses. Shriki (2014) explains that ultrasound waves are typically composed of various frequencies and are rarely waves of a single frequency.

Period and frequency are the two most well-known ultrasound acoustic parameters. Period is the amount of time needed for a wave to finish one cycle. It can also be defined as the amount of time between the beginning of one cycle and the beginning of the following cycle. Period in ultrasonography is the interval between the beginning of one peak and the following peak, including any valleys (Shriki, 2014). Frequency as one Hertz is equal to one cycle per second, while frequency is the number of cycles per second. Ultrasound has an extremely high frequency; hence its frequency is expressed in megahertz (Patey & Corcoran, 2020). Although the density and flexibility of the tissue affect the speed of propagation through the tissues, the average speed of sound waves in body tissue is 1540 m/s (Patey & Corcoran, 2020).

2.2 Grey-scale imaging

The lower lateral ribs and mid axillary line should be used to guide the scanning of the kidneys in a sagittal and transverse plane. The cortex, medulla and renal pelvis should be seen by fanning through the entire kidney (Kaptein & Kaptein, 2017). When assessing the kidneys by using grey-scale ultrasound, the following technique is used with a 3.5 MHz curvilinear probe: The renal lengths in a sagittal plane are measured from the largest pole to pole distance. In a sagittal plane, the renal cortex is measured at the midpoint of the kidney. The measurement should be made across a medullary pyramid and perpendicular to the renal capsule to determine the shortest path between the renal capsule and the base of the medullary pyramid (Beland et al., 2010).

When using diagnostic ultrasound to image the kidneys for conditions such as CKD, the following is to be evaluated in a longitudinal plane:

- The size of the kidneys
- The cortical thickness of the kidneys
- The echogenicity of the kidneys (Petrucci et al., 2018).

2.2.1 Size of the kidney

When measuring the length of the kidneys is it important to have a clear understanding of "normal" kidney length. Previous studies have shown that the normal kidney length is approximately 11 cm and a normal range is between 10 and 12 cm. The left kidney may be longer in length than the right kidney and women may have smaller kidneys than men by approximately 0.5 cm (Faubel et al., 2013). In this study, a renal of length of between 9 and 12 cm was considered normal.

According to O'Neill (2014a), measuring the size of the kidneys thoroughly is significant, since it affects clinical decisions. The maximum length should be reported after doing a measurement multiple times for accuracy. O'Neill (2014a) further states that kidney length in adults should be between 10 and 12 cm whereas Spatola and Andrulli (2016) state the normal renal ultrasound illustrates kidneys of 11 to 12 cm in length, with the left kidney being approximately 3 mm longer than the right kidney. Authors emphasise the importance of the size of the kidneys in the longitudinal plane. Faubel et al. (2013) emphasise that the length of the kidneys is useful in the assessment of patients with AKI and may help distinguish AKI from CKD. Kidney sizes that are less than 8 cm (small) in size point to a CKD diagnosis, but either AKI or CKD can cause normal or increased kidney size. Acute parenchymal illnesses and infiltrative diseases are two potential causes of large kidneys in AKI. Spatola and Andrulli (2016) emphasise that the measurement of the kidneys is an important factor, as there is a decrease in size of the kidneys as GFR declines.

Makusidi et al. (2014) also explain that renal length is of great importance in the diagnosis, treatment and prognosis of renal disease, as there has been documented significant correlation between the renal volume and length with glomerular filtration rate (GFR). The authors have concluded that the length of the kidney obtained by using ultrasound is more sensitive than kidney volume in the prediction of renal function in patients with CKD.

According to Singla et al. (2022), kidney size and volume can help nephrologists determine the stage of kidney disease. Kidney failure is associated with kidney lengths of less than 8 cm. The most likely cause of the kidney volume or length loss is atrophy or fibrosis. Although bilateral hypotrophic kidneys with dwindling volumes may indicate serious illness such as CKD, a unilateral decrease could be a clear sign of hypoperfusion as in the case of renal artery stenosis. Fluid retention, inflammation, protein build-up, acute tubular necrosis or tumours are all linked to increased kidney volume.

2.2.2 Cortical thickness of the kidney

Cortical thickness should be evaluated in the longitudinal plane of the kidney. O'Neill (2014a) states that the cortical thickness, which is measured from the base of the medullary pyramid

to the margin of the kidney, should be assessed in addition to length. It should typically be between 7 and 10 mm though this can vary within a kidney, with the poles being thicker. In this study, cortical thinning was defined as a thickness of less than 10 mm. The parenchymal thickness should be 1.5 to 2.0 cm but fluctuates within the kidney, must be used when the medullae are not visible. The parenchymal thickness, which is known to be the distance between the kidney capsule and the base of the mesorenal pyramid, is known to correlate with the GFR. This parenchymal thickness is measured in a longitudinal plane.
An indication of cortical thinning is frequently highlighted with lobulation. The parenchymal thickness measurement was not used in this study. Hanamura et al. (2012) added that the renal length and cortex area showed a weak relationship with renal function, as kidney sizes are often affected by patient body size and certain disease conditions such as diabetic nephropathy and other pathology. They concluded the RRI measured was the best marker of CKD and showed good correlations with renal function and histological damage scores.

2.2.3 Echogenicity of the kidney

In ultrasound imaging, echogenicity refers to the homogeneity vs heterogeneity, as well as the echogenicity of an anatomical structure. Homogenous (even texture) vs heterogenous (uneven texture) structures are useful markers for normal vs abnormal morphology. Common terminology used to describe the echogenicity of the renal structures is less echogenic (hypoechoic) or more echogenic (hyperechoic) which refers to whether the area is dark grey, mid-grey or light/bright grey, respectively.
O'Neill (2014a) notes that when assessing the kidneys in grey-scale, the medulla pyramids are less echogenic than those of the cortex. The cortex is less echogenic than the liver or spleen. Echogenicity of abdominal structures are assessed qualitatively. In CKD, the echogenicity of the kidneys increases as the cortical thickness decreases.
Supported by Spatola and Andrulli (2016), the renal cortex is isoechoic to the parenchyma of the liver and spleen in CKD. Increased echogenicity is non-specific and has been linked to glomerulosclerosis, tubular atrophy, inflammation and interstitial fibrosis in histologic studies. A decrease in echogenicity of the kidneys usually results from oedema. Bwemelo et al. (2019) state that the evaluation of kidney echogenicity is critical, as changes in renal echogenicity show a strong correlation with renal function when paired with biochemical indicators.

2.2.4 Shape of the kidney

In terms of assessing the shape of the kidneys the renal outline of the kidneys is assessed. According to O'Neill (2014a), a lobular renal outline is typically a sign of cortical thinning, and

swelling of the kidney brought on by inflammation or infiltration is frequently followed with a decrease in aspect ratio, resulting in a more globular shape.

2.2.5 Urinary bladder

Kaptein and Kaptein (2017) explain that the curvilinear probe is used to assess the bladder. The probe is positioned above the symphysis pubis and guided caudally towards the cervix or prostate. Grey-scale ultrasound is quite useful for evaluating the urinary bladder. Bladder ultrasound may detect bladder lesions, bladder wall thickness, a urinary obstruction that is not clinically suspected and much more. Tublin et al. (2003), however, state that with grey-scale imaging, basic anatomy, renal length, cortical thickness and visualisation of the collecting system are the only pieces of information that can be obtained; often these findings are normal despite renal function being abnormal.

More than grey-scale imaging is needed for assessing renal pathology with declining renal function. Doppler imaging is preferred in this case. Although ultrasound is acknowledged for its safety, precision, non-invasiveness and widespread accessibility as an imaging technique, authors have voiced their hesitancy regarding its suitability as the optimal parameter for assessing and tracking renal function in CKD. The utilisation of grey-scale imaging is employed to examine the echogenicity, dimensions and cortical thickness of the kidneys; however, there have only been a few practical uses of ultrasound parameters such as renal cortical and parenchymal thicknesses in the diagnosis of patients. Kodikara et al. (2020) claim that despite a few preliminary studies evaluating renal cortical and parenchymal thickness, none of them have evaluated the correlation with etiological factors or the severity of CKD.

2.2.6 Introduction to Doppler ultrasound

According to Meola et al. (2021), the term *Doppler effect* refers to the frequency variation that is seen when a fixed source of ultrasound pulses strikes moving red blood cells (RBCs) in vessels. The Doppler equation can be used to analyse the backscattering caused by red blood cells circulating in the vessels, and it can be visualised using either a colorimetric map (colour and power Doppler) or spectral analysis.

The Doppler equation states that:

$\Delta F = (2F0 \times V \times \cos\theta)/c$

where ΔF is the Doppler shift, F0 is the pulse frequency, V is the blood flow velocity towards or away from the transducer, cos is the cosine function of the angle of incidence between the pulse wave and vectorial direction of the beam, and c is the ultrasonic speed in soft tissue (1 540 cm/s).

Gameraddin (2019) explains that Doppler ultrasound of all varieties is frequently utilised in medical imaging because of its benefits of high measurement accuracy, non-invasiveness, accessibility and absence of adverse biological effects. There are currently three types: power Doppler, pulse-wave Doppler and colour Doppler. Pulse-wave (spectral Doppler) and colour-flow modes are the two methods for estimating blood flow velocities and direction of blood flow, respectively. Colour-flow mode assesses the vessel; it identifies blood flow and the direction of blood flow. Both approaches rely on Doppler-shift frequencies (Oglat et al., 2018).

2.2.7 Colour Doppler

To illustrate the speed and direction of blood flow through vessels, colour Doppler converts Doppler shifts into a spectrum of colours to create images of blood vessels. The Doppler shift is the variation between the incident frequency and the reflected frequency. A positive Doppler shift happens when the reflector moves away from the probe, and a negative shift happens when the reflector moves in the opposite direction of the ultrasound source (Gameraddin, 2019).

According to Meola et al. (2021), a region of interest (colour box) is acquired with the colour Doppler dataset superimposed on the grey scale field. Brightness points are representations of echoes from stationary reflectors in this area. Instead, the mean flow-velocity variations are assessed by an autocorrelation detector using the echoes from moving scatterers, and they are represented as colour pixels. Traditionally, it has been assumed that the colours blue and red show positive and negative Doppler shifts, respectively. According to Petrucci et al. (2018), colour Doppler provides useful but not diagnostic information on parenchymal perfusion. Colour Doppler can detect the presence or absence of blood flow, as well as the speed and direction of flow in veins and arteries, while spectral Doppler is utilised to analyse blood velocity variations in the primary renal artery over time. Different red and blue saturations are used to represent velocity grading; lighter hues such as light blue or yellow are associated with faster speeds.

Practical guidelines to be followed when using colour Doppler are the following:

- A setup key should be selected, as this improves Doppler parameters.
- Power is applied to the study area before adjusting the colour gain.
- Ascertain that the focus of the investigation is set at the region level. To improve the colour signal, the gain is increased and beam steering adjusted to achieve a suitable beam angle for the chosen vein or artery.
- The pulse repetition frequency (PRF) needs to be changed to synchronise the flow status. Low flows or velocities make a low PRF sensitive, but it can also lead to aliasing

which is an artefact. A high PRF reduces aliasing and makes the system more resistant to low flows and speeds.

- Ascertain that the colour flow area is the appropriate size as a faster frame rate.
- A resolution could be achieved with a smaller colour flow ‘box’ or region (Gameraddin, 2019).

2.2.8 Power Doppler imaging

Meola et al. (2021) explain that an alternative approach called power Doppler imaging (PDI) calculates the overall strength of the Doppler shift at each colour-boxed point. Power mode does not significantly change with flow direction, is angle-independent and sensitive to sluggish flows. The pseudo-angiographic effect of the PDI is caused by an increase in picture persistence. PDI is a great test for visualizing the blood flow in superficial veins because of its sensitivity. The main restriction on PDI is the clutter brought on by the pulsatile arteries and probe sliding. Spatial-temporal clutter filtering has significantly improved CDI-PDI sensitivity in microvascular blood flow analysis on the most recent platform without the need for a contrast agent amplifier.

2.2.9 Spectral Doppler

Spectral analysis is used to determine the blood flow velocity within vessels in real-time. Petrucci et al. (2018) explain that spectral Doppler is used to analyse the blood flow velocity changes in the renal veins and arteries, as the velocities measured are the peak systolic velocity (PSV) and end-diastolic velocity (EDV). The use of Doppler is improving ultrasound assessments for renal dysfunction by assessing the change in intrarenal waveforms that are associated with several types of intrinsic renal disorders, urinary obstruction and renal vascular disease (Tublin et al., 2003).

Practical guidelines to be followed when using spectral Doppler are as follows:

- A setup key should be selected, as this improves Doppler parameters.
- Power is applied to the study area before adjusting the colour gain.
- Ascertain that the focus of the investigation is set at the region level. To improve the colour signal, the gain is to be increased and adjust beam steering to achieve a suitable beam angle for the chosen artery or vein.
- Increase or decrease the pulse repetition frequency (PRF) to synchronise the flow status. Low flows or velocities make a low PRF sensitive, but it can also lead to aliasing which is an artefact. A high PRF makes the system less susceptible to aliasing and more resilient to low flows and speeds. Always ascertain that the colour flow area is the appropriate size as a faster frame rate. A higher resolution could be achieved with a smaller colour flow ‘box’ or region (Gameraddin, 2019).

In summary, colour Doppler analysis is used to indicate the absence or presence of blood flow within the kidneys, whilst spectral Doppler is used to determine the blood flow velocity within vessels in real-time. Doppler ultrasound is used as a predictor of the progression of renal dysfunction (Kawai et al., 2011). Trunz and Balasubramanya (2021) explain that renal Doppler is a useful tool for evaluating a wide range of renal pathology. Renal Doppler ultrasound demonstrates the vascular anatomy and may detect renal artery thrombosis, renal artery stenosis and renal vein thrombosis. The American College of Radiology has classified renal Doppler ultrasound as a first-line imaging modality due to its many advantages, particularly in patients with renal impairment and renal transplant patients when contrast media with CT and MRI may be challenging.

2.2.10 Renal resistive index (RRI)

Spatola and Andrulli (2016:243) postulate that the "Renal Resistive Index (RRI) is a semi-quantitative index derived by Doppler evaluation of renal vascular bed". The most commonly used parameter in renal Doppler ultrasound is the RRI which is calculated from the Doppler flow-velocity waveform as (peak systolic velocity - end-diastolic velocity)/peak systolic velocity (Cauwenberghs & Kuznetsova, 2016).

According to O'Neill (2014b), the renal resistive index is calculated as follows:

$$RRI = \frac{\text{peak systolic velocity - end diastolic velocity}}{\text{peak systolic velocity}}$$

2.2.10.1 Peak systolic velocity

The normal limits of the RRI is in the range of 0.40 to 0.70, increasing with age; however, showing a difference between two kidneys less than 5-8% (Spatola & Andrulli, 2016). In this study, an RRI of 0.40 to 0.70 was regarded as normal, whereas an RRI of more than 0.70 was regarded as elevated.

Petrucci et al. (2018) explain that *kinematic viscosity*, *hydraulic resistance* and *wall elasticity* are three terms that collectively describe the forces that oppose the pulsatile blood flow into the arteries and are represented by the RI. In a young patient, a resistive index of 0.60 is regarded to be within the normal range; however, a resistive index of 0.70 might be seen as the top limit of normal.

Gopalakrishnan et al. (2019) state that renal Doppler ultrasound is one of the strongest non-invasive methods for determining correlations between biochemical indicators and alterations in the kidneys.

2.3 Biochemical markers in CKD

According to Lopez-Giacoman and Madero (2015), the main focus is on biomarkers that measure kidney function in order to diagnose, assess and treat chronic kidney disease (CKD). This disease frequently develops over a long period of time with a long latent phase during which the disease is clinically silent. Glomerular filtration rate or GFR is still the most accurate measure of kidney health. Due to the time-consuming nature of measuring GFR, equations that consider endogenous filtration, indicators like serum creatinine (SCr) and cystatin C (CysC) are commonly used to determine GFR. The decline in kidney function may be preceded by other indications such as albuminuria which has demonstrated substantial connections with disease development and prognosis.

2.3.1 Creatinine

Creatinine is the easiest to measure and most often used as an indication of renal function. It is derived from creatine which muscles use as a store of rapid energy. The anhydride form of creatinine spontaneously and irreversibly converts from creatine. Along with being freely filtered and hardly reabsorbed, the proximal tubule also releases 20 to 30% of creatinine. One of the most used techniques for measuring creatinine levels is the Jaffe reaction which relies on the observation of a colour change because of the reaction between creatinine and alkaline pictrate. Chromatographic analysis is another technique for calculating creatinine levels. It is well known that the chromatographic approach is more precise than the Jaffe method (Treacy & Brown, 2018). Lopez-Giacoman and Madero (2015) explain that, since creatinine is readily filtered, a sizeable portion of the creatinine seen in urine comes from proximal tubular secretion. One of the requirements for applying estimating equations based on SCr is constant renal function.

2.3.2 Glomerular filtrate rate (GFR)

The best marker for determining renal function is still eGFR. Millions of glomeruli participate in the eGFR filtration process. When passing through the kidney, the volume and composition of the filtrate alter. GFR is indirectly calculated using the clearance of filtration indicators which the kidney can only eliminate by glomerular filtration. Both plasma and urine approaches can be used to assess the ability of the kidney to remove endogenous or foreign substances from the body (Lopez-Giacoman & Madero, 2015).

Based on the glomerular filtration rate (GFR), CKD is classified. GFR testing is a fundamental step in the diagnosis of CKD. *Negative glomerulus tubular feedback* and *glomerulus tubular balance* are terms used to describe the crucial roles that renal tubules and glomerular filtration rates play in sustaining renal function. To keep fluid equilibrium, the renal tubules and glomerulus are essential. A feedback mechanism that results in a reduction in the Nephron's filtration rate will eventually be triggered by any circumstance that results in an increase in fluid and Na in the macula densa (distal tubule) (Sutikno & Baskoro, 2020). According to Naicker (2012), when using the suggested African-American ethnic factor (4th variable) of the Modified Diet in Renal Disease equation, an MDRD eGFR study on black South African CKD patients at Chris Hani Baragwanath Hospital in Soweto, Johannesburg, using a standardised creatinine assay, revealed an overall eGFR median positive bias of 27%. In the absence of the factor, the median positive bias decreased to 5% overall. Consequently, the National Health Laboratory Service (NHLS) laboratories use the same Modified Diet in Renal Disease formula to calculate eGFR for people of both races; ethnicity is not taken into account.

The NHLS laboratory results form states the following:

> *In individuals with GFR > 60mL/min/1.73m^2, a Modified Diet in Renal Disease - derived calculation of the GFR may dramatically underestimate real GFR. Additionally, it could not be accurate if you're over 18 or under 70, pregnant, have major co-morbid diseases, have acute renal failure, have aberrant body habits or a strange diet, or have horrible oedema. The MDRD-eGFR utilised here does not consider the racial ethnic component.*

At GFR > 60 mL/min/1.73 m^2, the CKD-EPI formula estimates GFR more precisely than the Modified Diet in Renal Disease formula, making it possible to identify patients with mild renal impairment. Using the KDIGO 2012 recommendations, the severity of renal impairment can be graded. The CKD-EPI calculation utilised in this study does not include a racial bias correcting element.

According to Krstic et al. (2016), the first equation used to calculate GFR using SCr, age, race, sex and body size is the Modification of Diet in Renal Disease (MDRD) equation. Additionally, a new CKD-EPI creatinine equation from 2009 that estimated GFR using a huge database of participants with and without renal disease and its wide range made it more universal than the MDRD equation. Because it may be used for a more diverse population that is significant for clinical practice, compared to the MDRD equation, this equation is more precise.

Vassalotti et al. (2016) also explain why estimated glomerular filtration rate-based CKD identification is more accurate than serum creatinine-based CKD identification. Both the more conventional Modification of Diet in the Renal Disease Study computation and the

Chronic Kidney Disease Epidemiology Collaboration equation are used to compute glomerular filtration rate. Recent research indicates that the Chronic Kidney Disease Epidemiology Collaboration equation is more accurate at predicting prognoses than the older Modification of Diet in the Renal Disease Study equation.
According to Levin (2013), the following are the primary benefits of switching to the CKD-EPI creatinine equation:

- The CKD-EPI equation is more accurate with GFR > 60 ml/min/1.73 m^2, and GFR > 90 ml/min/1.73 m^2 is reportable.
- It is less influenced by ethnicity and suitable for usage without racial or ethnic correction.
- It is a considerable downgrading from Stage 3a (GFR 45-59) using the MDRD equation to Stage 2 (GFR 60-89) using the CKD–EPI equation.
- The CKD-EPI classification is more accurate than MDRD when compared to the gold standard techniques of estimating GFR, especially in younger persons and women with high GFRs.

2.3.3 Confirmatory results and other urinary biomarkers of kidney disease

According to Levey et al. (2015), confirmatory testing should be pursued in order to predict GFR more accurately in clinical situations where it is anticipated that eGFRcr will not be precise enough for clinical decision making. Among these is calculating GFR based on serum cystatin C levels. An alternate endogenous filtration marker that has gained popularity recently is cytostatin C43.
Cystatin C, a 13,300 dalton serum protein, is widely catabolised, freely filtered and reabsorbed by the renal tubule. All cells with nuclei make it and it is dispersed throughout the extracellular fluid. Creatinine is more affected by muscle mass and nutrition than cystatin C serum concentrations (Levey et al., 2015).
According to Treacy et al. (2019), the renal function indicator cystatin C may be preferable to creatinine. It is a small protein (approximately 13 kDa) produced by all nucleated cells; therefore, it is less dependent on muscle mass, even if it may be increased in hyperthyroidism, corticosteroid use and rapid cell turnover (18, 19). Typically, turbidimetric or nephelometric immunoassay methods are used to quantify cystatin C. Treacy et al. (2019) further explain that the method commonly used for measuring cystatin C typically has fewer sources of interference compared to creatinine methods. However, as it is an immunoassay, there is still a chance that heterophilic antibodies could interfere with the results. The turbidity of the assay can also impair nephelometric and turbidimetric methods, particularly when triglyceride levels are high. This method is automated and, while it might be more expensive than creatinine testing, it is still more cost-effective than other commonly available analytes

like 25-hydroxyvitamin D or B-type natriuretic peptide. Comparing cystatin C values among different assays is not possible due to a lack of standardisation, making it impossible to directly compare values obtained through different methods.
Treacy et al. (2019) go on to state that, even though research has not conclusively demonstrated the clinical benefits of routine cystatin C testing over creatinine, there are some clinical circumstances in which cystatin C may be helpful. Patients with disorders that affect muscle mass and those with eGFR values between 60 and 90 mL/min/1.73 m^2 without albuminuria are included in this category. Cystatin C may be a more accurate indicator of CKD in these circumstances. Additionally, compared to creatinine, cystatin C levels in the bloodstream fluctuate more quickly due to their shorter half-life. Notably, cystatin C can identify acute kidney injury (AKI) earlier than creatinine, especially in patients who are critically unwell.

2.3.4 Neutrophil gelatinase-associated lipocalin/lipocalin-2 (ngal)

Lopez-Giacoman and Madero (2015) explain a well-established marker for acute kidney injury. Neutrophil gelatinase-associated lipocalin (NGAL) is a 25 kDa lipocalin iron-carrying protein that is expressed by tubular renal epithelial cells after tubulointerstitial injury. NGAL is a member of the superfamily of lipocalins, a well-defined group of proteins.

2.3.5 Kidney injury molecule 1 (KIM-1)

Kidney injury molecule-1 (KIM-1) is a type 1 transmembrane protein whose expression is increased in response to kidney damage. KIM-1 functions as an early biomarker for proximal tubular damage, since it is expressed in the urine within the first 12 hours of tubular injury. Experimental and clinical studies have demonstrated that fibrosis and inflammatory areas exhibit high levels of KIM-1 expression. KIM-1 has been associated with decreased urinary KIM-levels in type 1 diabetes mellitus patients whose microalbuminuria has disappeared, interstitial fibrosis in human allografts and robustly expressed renal tubules of mice with polycystic kidney disease (Lopez-Giacoman & Madero, 2015).

2.3.6 Urinary interleukin-18 (IL-18)

A urine marker of AKI is urinary IL-18. It may be linked to increased white blood cell infiltration into the renal parenchyma and is expressed by proximal tubular epithelial cells, monocytes and macrophages. It is useful for detecting acute tubular necrosis (ATN) which is more prevalent in this ailment but not noticeably so in other renal diseases. IL-18 may also be increased in a number of illnesses that are not related to the kidneys, including pulmonary

disease and myocardial infarction. In recent research, the combined effects of urinary KIM-1 and IL-18 have been examined to determine how well they predict AKI. ELISA is one of the immunoassays used to test IL-18 (Treacy et al., 2019).

2.3.7 Tissue inhibitor of metalloproteinases 2 (TIMP2) and insulin-like growth factor binding protein 7 (IGFBP7)

Tissue inhibitor of metalloproteinases 2 (TIMP2) and insulin-like growth factor binding protein 7 (IGFBP7) are responsible for inducing cell-cycle arrest, a common response to kidney injury. These two molecules, TIMP-2 and IGFBP-7, act to inhibit cyclin-dependent protein kinase complexes, temporarily halting the G1 phase of the cell cycle. Their application as biomarkers has gained FDA approval for use alongside clinical assessment in ICU (intensive care unit) patients facing acute cardiovascular and/or respiratory challenges. These biomarkers were initially identified in critical care scenarios as noted by Zhang and Parikh (2019). Treacy et al. (2019) further highlight that TIMP-2 and IGFBP7 are expensive and are not consistently accessible across various analytical systems. Direct comparisons of results are only valid when conducted within the same laboratory and utilising the same methodology, since standardisation is lacking among different assay manufacturers and laboratories.

2.3.8 Urinary albumin and protein

Albumin and protein found in the urine could both indicate the presence of and contribute to the development of renal disease. Concentrating only on albumin could result in missing tubular or overflow proteinuria. However, it has been found that albumin closely correlates with the development of glomerular disease linked to hypertension and renal disease in people with diabetes. Numerous techniques such as colorimetric, electrophoretic or nephelometric assays can be used to assess protein. Proteins under 5 kDa are often completely filtered, followed by those up to 66 kDa which are partially filtered and those greater than 66 kDa which are typically kept (Treacy et al., 2019).
Treacy et al. (2019) state that although small proteins like A1M are primarily filtered at the glomerulus, approximately 99% are reabsorbed by proximal tubule cells in healthy conditions. An elevation in the A1M:creatinine ratio in urine suggests compromised tubular function. Similarly, while around 99% of albumin is reabsorbed by proximal tubule cells under normal circumstances, it is predominantly prevented from entering the glomerular filtrate and retained by the glomerulus. Its presence in urine, often expressed as its creatinine ratio, indicates significant glomerular damage. Transferrin found in urine can also be used for this. To find distal tubule leakage caused by infection or inflammation, urine immunoglobulins can

be examined. However, significant glomerular proteinuria or haematuria could also cause their levels to rise. A protein selectivity index can help identify the site of injury inside the nephron, although its usefulness in real-life is typically constrained.
Renal illness is not usually linked to protein in the urine. Overflow proteinuria happens when the capacity for reabsorption of the tubules is reached and levels of minute proteins in the plasma are filtered. Myoglobin, which is seen with muscle damage, Bence Jones proteins, which are found with amyloidosis and plasma cell neoplasms, and lysozyme, which is seen with leukaemia, are some examples of these proteins. However, the presence of these proteins in excess in the tubule lumen is linked to renal disease. The primary protein found in healthy individuals' urine is the acidic protein Tamm-Horsfall glycoprotein which is secreted by the tubules (Treacy et al., 2019).

2.4 Chronic kidney disease (CKD)

A serious consequence of renal dysfunction is chronic kidney disease (CKD). If untreated, CKD can progress to kidney failure. The literature reviewed focuses on CKD.
The kidneys, two bean-shaped organs that are located retroperitoneal in the human body, filter waste products and poisonous substances from the blood. Human kidneys that are damaged and unable to properly filter the blood are said to have CKD (Ullah & Jamjoom, 2023). CKD is known as one of the world's major health problems and may be a silent killer when not detected, as it can be easily masked by other conditions (Makusidi et al., 2014). CKD is known as the 16th leading cause of death worldwide and affects between 8-16% of the population worldwide.
In a recent update on the epidemiology of CKD, Kovesdy (2022) notes that particularly more than 10% of the general population suffers from CKD, a degenerative condition that is prevalent in elderly persons and women, as well as patients with diabetes and hypertension who are members of racial minorities. In the United States, the age-adjusted prevalence of CKD stages 1 to 4 was 13%, 16.5% and 15.3%, respectively, among non-Hispanic Whites, non-Hispanic Blacks and Mexican Americans in 2015 and 2016.
Typically, biochemical and urine tests are used in regular screening to identify CKD patients. A thorough patient history is important. Patients may appear with symptoms of albuminuria, haematuria, flank pain, nocturia or decrease urine output. Patients with advanced CKD describe symptoms like poor appetite, exhaustion, nausea, metallic taste in the vomit, unintentional weight loss and peripheral oedema (Chen et al., 2019).
Risk factors that are associated with CKD include diabetes mellitus, hypertension, cardiovascular disease (CVD), proteinuria, anaemia and the administration of angiotensin receptor blockers (ARBs) (Inaguma et al., 2017).

According to Lewis (2012), CKD is divided into five stages. Stage 1 is designated to patients with persistent proteinuria or haematuria or structural abnormalities. These patients have impaired renal excretory functions of GFR greater than 90ml/min (GFR > 90ml/min), whereas stages 2 to 5 are patients with varying degrees of GFR decline. It is in stage 5 that CKD is established and called “end-stage renal disease” (ESRD). Lewis (2012:7) also explains CKD can be diagnosed when “the MDRD-derived estimated glomerular filtrate rate (eGFR) is less than 60ml/min on at least two occasions over a period of no less than 90 days or the urine albumin to creatinine (ACR) is greater than 30 mg/mmol or the urine protein to creatinine ratio (PCR) is greater than 50 mg/mmol”.

When the eGFR falls below 30 mL/min/1.73 m^2, the Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend sending patients with CKD to a nephrologist. Further reasons for referral encompass instances like having over 20 red blood cells per high-power field without a known cause, red blood cell casts noticed in urine microscopy or other indications of glomerulonephritis. Referral is also advised in cases of CKD accompanied by uncontrolled hypertension, continuous hypokalaemia or anaemia necessitating erythropoietin replacement, repeated or extensive kidney stones, hereditary kidney ailments, acute kidney injury and rapid progression of CKD (Chen et al., 2019).

According to Petrucci et al. (2018), the course of ESRD is influenced by a variety of clinical traits and consequences. Congenital and hereditary diseases such as congenital cystic dysplasia and polycystic disease, infectious diseases including pyelonephritis and tuberculosis, immune and inflammatory diseases such as primary and hepatitis C virus-related glomerulonephritis, vascular disease including chronic ischemic nephropathy, metabolic diseases such as diabetes mellitus (DM) and hyperuricemia, as well as systemic diseases (vasculitis, collagen disease and myeloma) are among these clinical conditions. Inaguma et al. (2017) explain that diabetes mellitus, hypertension, cardiovascular disease (CVD), proteinuria, anaemia and the use of angiotensin receptor blockers (ARBs) are some of the risk factors linked to CKD.

The Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation, according to Levey et al. (2015), first offered a conceptual module about CKD in 2002 and then revised it in 2005. Prognosis, therapy and factors that affect the progression and consequences of CKD have all been changed in the stage categorisation of this module: from complications arising in a healthy kidney to an increased risk of kidney damage, decreased GFR and eventually kidney failure. This module comprises primary, secondary and tertiary preventative programmes aimed to modify disease progression. Levey et al. (2015) further explain that the NKF-KDOQI released its first guidelines in 2002, defining CKD as having kidney disease for at least three months (affecting either the right or left kidney, or both) and having an estimated glomerular filtration rate of less than 60 mL min/1.73 m^2.

Kidney Disease: Improving Global Outcomes (KDIGO), a global initiative, aims to develop and put into practise clinical practice recommendations for kidney disease patients. In March 2012, KDIGO published its guidelines for diagnosing and managing acute kidney injury (AKI). These guidelines cover a wide range of topics, including the definition and classification of AKI, its general prevention and treatment, with recommendations for avoiding contrast-induced AKI in particular and the management of renal replacement therapy (RRT) in patients with AKI (Palevsky et al., 2013).

Acute kidney disease (AKD), which is defined as AKI or GFR 60 mL/min/1.73 m^2 for less than three months, or a 35% decline in GFR, or structural kidney damage lasting less than three months, or a 50% increase in serum creatinine levels for less than three months, according to Palevsky et al. (2013), is a condition that affects the kidneys. The broad scope of the guidelines cover a wide range of topics, including definition, staging, prevention, non-dialytic care and short-term renal replacement therapy (RRT) management. Referral to nephrology is essential for management of the kidneys such as kidney transplant evaluation and replacement therapy. Ullah and Jamjoom (2023) explain that CKD patients frequently progress to its chronic stages, since it is frequently destructive, expensive, burdensome and even dangerous, especially in countries with little resources.

2.4.1 Understanding chronic kidney disease

Lewis (2012) explains that the glomerulus and renal tubule make up a nephron and each kidney contains thousands of these nephrons. The tubule manages the processing of electrolytes and water, whereas the glomerulus functions as a filter. Afferent and efferent arterioles allow blood to enter and exit the kidneys, respectively.

Plasma enters the capsule space through microscopic filtering slits between endothelial cells (also referred to as podocytes) when there is hydrostatic pressure. The fluid that has been filtered as a result (filtrate) drains into the proximal convoluted tubule. Glomerular filtration rate, or GFR, is used clinically as a gauge of kidney health, since it reflects the rate at which the kidneys can produce filtrate in relation to both an adequate blood supply and the integrity of the glomerular capillary tuft.

The glomerulus is harmed by pathological kidney diseases which also result in sclerosis. Blood vessels are replaced by amorphous collagen deposits throughout this process. This is also known as fibrosis which obstructs blood flow and stops filtration. These glomeruli never recover when this occurs. The quantity of functional glomeruli declines as the sclerotic process advances, lowering GFR. In end-stage renal illness, the total function of the remaining glomeruli is insufficient to preserve health because the number of sclerosed glomeruli is so low. Hemodynamic changes within the kidney are currently maintaining renal excretory function. Even when hormones are used, when blood is directed to the preserved

glomeruli, an increase in blood flow leads to hypertension which can occasionally get worse and speed up glomerulosclerosis. Glomerulosclerosis causes the rest of the glomeruli to fail, resulting in CKD and ESRD (Lewis, 2012).

2.4.2 Significant use of grey-scale ultrasound in CKD

Kuo et al. (2019) state that the primary utility of kidney ultrasound imaging entails ruling out reversible causes of acute kidney injury such as urinary blockage or diagnosing irreversible chronic kidney disease (CKD) which disqualifies needless testing like a kidney biopsy. Increased renal parenchymal echogenicity is seen in acute kidney disease in grey-scale ultrasound. The disease has been linked to inflammatory conditions such as acute interstitial nephritis, acute tubular necrosis, acute glomerulonephritis and HIV nephropathy. Echogenicity and lessened renal cortex thickness are other important signs of acute kidney injury (Gameraddin, 2019).

Ahmed et al. (2019) elaborate that CKD refers to the progressive deterioration of kidney function due to structural or functional irregularities within the kidneys which can worsen over time. As the damage advances, the kidneys cease to operate effectively, regardless of whether the GFR decreases or not. This condition is evident through either pathological deviations or alterations in markers that signify kidney impairment, along with anomalies in imaging tests. A comprehensive diagnostic evaluation relies on ultrasound findings like longitudinal length, echogenicity, parenchymal thickness and cortical thickness. These specific ultrasound characteristics play a crucial role in the early identification of kidney ailment, gauging the extent of renal parenchymal deterioration and its potential for recovery, as well as aiding in the decision-making process regarding the necessity of a renal biopsy. Renal length and cortical thickness can also be used to assess renal function and based on this information, crucial clinical decisions can be made. In order to track the development of renal disease or to determine whether it is normal, repeated sonographic examinations are carried out. Although measuring renal longitudinal length is sufficient in people with normal kidney function, measuring renal parenchymal volume is quite accurate in patients with end-stage renal disease.

2.4.3 Significant use of spectral Doppler ultrasound in CKD

Gameraddin (2019) states that Doppler ultrasonography is useful in identifying CKD and ESRD progression. The RRI correlates significantly with the presence of proteinuria which results in patients with macroalbuminuria (300lg/mg creatine) compared to patients with a normal macroalbuminuria. An RRI value of 0.70 was noted to be an independent risk factor for patients with worsening renal function (Spatola & Andrulli, 2016; Granata et al., 2014). Agarwal (2015) explains further that when there is poor vascular compliance, the peak

systolic pressure rises and when transmitted to the microcirculation, damage to the capillary bed occurs, leading to adverse downstream events such as progression to ESRD; it is then when a high renal vascular resistance is present with a low renal blood flow and the RRI may be elevated as well. Greater microvascular disease and an elevated RRI may indicate disease specific to the tubulointerstitial compartment.

With reference to acute kidney injury (AKI), the RRI value is known to be a valid tool in differentiating between pre-renal and renal failure, allowing the prediction of the renal response to vaso-active agents. The RRI value 0.7 in non-diabetic and diabetic kidney disease is known to predict CKD progression to ESRD even when renal dysfunction is mild to moderate (Spatola & Andrulli, 2016). Granata et al. (2014) support the view that a RRI value is a good predictor of the onset of AKI. Ghafoori and Shiva (2007) also support that the resistive index (RI) measurement of Doppler ultrasonography is a valid indicator of renal function in renal parenchymal disease.

Doppler ultrasound (DUS) has significantly contributed more than any other parameters such as protein urea and hypertension in identifying nephropathies in type 2 diabetes mellitus (T2-DM). The RRI index is a sensitive marker of renal damage when diabetic nephropathy is present and diagnosed by a persistent proteinuria of 500 mg per 24 hours. Granata et al. (2014) also add that an increased RRI is closely related to arteriosclerotic lesions in people with type 2 diabetes mellitus who have normal renal function. The presence of a raised RRI suggests the diagnosis of diabetic nephropathy which reduces the need for a renal biopsy. Granata et al. (2014:4) state that “RRI is considered a marker of progression of renal damage, and an RRI value 0.80 is an important indicator of irreversible damage in patients with chronic renal failure”. An elevated RRI is linked to a lower chance of better renal function when RAS is present. The tardus parvus is caused by RAS because there is an increase in blood flow resistance towards the peripheral arteries when RAS is present (Al-Katib et al., 2017).

2.5 Previous studies

A significant study by Kim et al. (2017) explains that RRI correlates well with renal arteriosclerosis and appears to be a good indicator of renal vascular resistance. Previous studies by Rademacher et al. (2002), Sugura and Wada (2009) and Kim et al. (2017) have noted that rising RRI readings are connected to the development of renal disease. According to Kim et al.’s (2017) study, regardless of whether an ACEI or ARB is being used, an increased resistive index of 0.79 or more is recognised to be a useful predictor for renal advancement in individuals with intermediate renal function.

According to a study by Sutikno and Baskoro (2020), comparing the renal intraparenchymal RRI and renal cortical echogenicity based on GFR in patients with CKD, the RRI was more sensitive and specific than the renal cortical echogenicity in terms of diagnosing patients with CKD.

Kawai et al. (2011) have concluded that RRI may be a very helpful instrument to assess the pathophysiology of renal injury and forecast a prognosis, according to their study that was conducted. That study has also discovered that the RRI increases when eGFR decreases. According to reports, there is a strong correlation between organ damage and the RRI.

In a study by Provenzano et al. (2020), which included non-dialysis patients who had been diagnosed with CKD based on the estimated glomerular function rate less than the typical 60mL/min/1.73 m^2, the usefulness of RRI to physicians was investigated. According to the study findings, independent of eGFR, the RRI was higher in patients with CKD, diabetes and cardiovascular disease. However, Provenzano et al. (2020) concluded that additional research was required to determine whether an RRI denoted a more intricate pathway of intrarenal injury.

Previous research on the velocity of blood flow through a damaged glomerulus (renal disease) has revealed that when the glomerular filtrate rate is reduced, RRI is increased. It is important to note that the studies mentioned above are not consistent in scanning the same renal area.

Additionally, earlier studies provided additional clarity regarding the ultrasound imaging method. Using samples from the interlobar and segmental arteries, Kim et al. (2017) documented the parenchymal peak systolic and end diastolic frequency changes, whereas Sutikno and Baskoro (2020) used samples from the interlobar arteries of the lower, mid and upper poles of the kidneys. Three distinct segmental arteries were sampled in both kidneys by Kawai et al. (2011).

Patients are regularly referred to the ultrasound department for various ultrasound examinations, including grey scale imaging, colour analysis and spectral Doppler analysis. Renal ultrasonography, often used alongside blood tests and urine analyses, is commonly employed to comprehensively assess kidney function. Ultrasound is highly valuable in nephrology, aiding in everything from diagnosis to guiding invasive kidney surgeries. It is frequently the sole imaging method required for kidney evaluation. During ultrasound evaluations, factors such as kidney size, shape, echogenicity, urinary space (including the lower urinary tract), vasculature and the presence of masses are all examined.

CKD is a major global health concern that often goes unnoticed due to its association with other diseases, earning it the label of a “silent killer”. It ranks as the 16th leading cause of death globally and affects 8-16% of the world’s population, often remaining undetected. The progression to end-stage renal disease (ESRD) is influenced by various clinical factors and

outcomes. In previous studies, it has been found that the RRI is more specific than the echogenicity of the renal cortex in diagnosing CKD. Elevated renal vascular resistance can lead to an increased RRI. The RRI is a significant biomarker that predicts mortality in CKD patients with reduced vascular compliance.

This study emphasises the importance of ultrasound in nephrology and its clinical application. It underscores how ultrasound aids in diagnosing and treating renal disease, particularly CKD, and highlights its role in referring patients to nephrologists.

CHAPTER 3
RESEARCH DESIGN AND METHODOLOGY

Chapter 3 provides a thorough description of the methodology that was used for the study. The description provides details of the research strategy the researcher's responsibilities, the boundaries of the research environment, the study population, sample size determination, nuances of data collection processes, and the technique utilised in data analysis.
It is stated by Kesmodel (2018) that there are many uses for cross-sectional studies, as a cross-sectional design is the most pertinent design when determining the prevalence of diseases, patient and healthcare professional attitudes and knowledge and in validation and reliability studies. The utilization of a cross-sectional study design aligns seamlessly with the overarching objectives and research aims of this present research study, thereby substantiating its appropriateness as the chosen methodological approach for this research study. Due to a quantitative cross-sectional research designs inherent fit with the research's goals and design, a quantitative cross-sectional study was selected as the preferred methodology.
A cross-sectional observational study, utilising grey-scale and Doppler ultrasound imaging, was conducted on patients presenting with renal dysfunction within the Gauteng province of South Africa. The study was approved by the Faculty of Health and Wellness Sciences Research Ethics Committee (FHWS-REC) at the Cape Peninsula University of Technology (Ethical clearance number: CPUT/HWS-REC 2022/H23) (Appendix C). Renal patients were recruited by the principal investigator of the study and the ultrasound examinations were conducted at a tertiary academic hospital in Gauteng, South Africa. Patients attending the nephrology clinic and ward, who were referred for an ultrasound examination, were recruited as study participants. The primary indication for referral was abnormal biochemical markers suggestive of renal dysfunction. Data for this study were collected between the period December 2022 and February 2023.

3.1 Aim of the study

The aim of the study was to determine whether there was an association between the ultrasound findings and the biochemical variant evidence in adult patients presenting with renal dysfunction at an academic hospital in Johannesburg, South Africa.

3.2 Research objectives

The research objectives of this study were to:

1. Determine whether there was an association between the renal resistive index and the biochemical variant evidence in patients presenting with renal dysfunction.
2. Determine whether there was an association between the renal ultrasound findings (size, echogenicity, cortex thickness) and biochemical variant evidence of renal dysfunction.

3.3 Ethical considerations

The study was approved by the Faculty of Health and Wellness Sciences Research Ethics Committee at Cape Peninsula University of Technology (Appendix C: (Ethical clearance number: CPUT/HWS-REC 2022/H23) and the tertiary academic hospital in Johannesburg, South Africa (see Appendix B). The Protection of Personal Information Act (POPIA) factors were taken into account when conducting this investigation. The study was conducted in accordance with the Declaration of Helsinki which is the World Medical Association's best-know policy (2022). According to the Declaration of Helsinki (2022), clinical research must be based on laboratory and animal studies, as well as other scientifically verified facts. Clinical research should conform to the moral and scientific principles that guide medical research. Only those who are scientifically qualified and working under a licenced medical practitioner should do clinical research.
In the instance of this research, careful attention was focused on ensuring full compliance with relevant ethical considerations. The data that were obtained from this study were collected for the sole purpose of this research study and publication.

3.3.1 Privacy, confidentiality and anonymity

Every precaution was taken to protect research participants' privacy and the confidentiality of their personal data. Patient privacy was ensured from the time of recruitment till the end of the examination. The use of "study numbers" and "patient hospital numbers" was employed rather than patient identification or names. Study numbers were not related to the patient but rather the order at which the patient was scanned, while hospital numbers were used to access data. This could not ensure participant anonymity, as the participants were known to the principal researcher. However, only the principle researcher had access to the participant identifiers, ensuring participant confidentiality and privacy.

3.3.2 Data protection

The data were entered into an Excel spreadsheet and stored in an encrypted location (Excel spreadsheet on a password-protected laptop where only the researcher was able to access it and share it with the supervisors.

To prevent participants from being recognised, the researcher excluded any personally identifiable information from the research data such as the names, surnames or identity numbers of the participants. Sensitive information was not collected or recorded, only as simply the data required for the study were gathered. The study data will not be retained for any longer than is required. The Excel spreadsheet used for data collection will be discarded following the completion of the study.

3.3.3 Informed consent

Written informed consent was sought from each participant who participated in the research study. The informed consent forms were available in four languages, viz. English, Afrikaans, isiZulu and isiXhosa (Appendix A). This was written in layman's language. The participant's written permission was obtained which allowed for the ultrasound examinations to be conducted, and the results of the study to be recorded and published.

Subject participation was voluntary and not coerced for anyone to take part in the study. Participants also had the right to refuse to take part in the study or withdraw at any time during the study. The participants were reassured that their medical treatment and management would not have been impacted if this had occurred.

3.4 Research setting

3.4.1 Study site

A tertiary academic hospital in Johannesburg, South Africa, served as the site of this study. It is one of the main hospitals in Johannesburg, with 1 088 beds and acts as a referral centre for other hospitals in Gauteng. The hospital has a specialised Nephrology Unit from which the participants were recruited. The ultrasound examinations were carried out in the ultrasound department in a secure ultrasound room with closed doors in which only the researcher and patient were present. The hospital ultrasound department consists of various functional areas which were utilised during the research study, namely:

- *Reception area*: Clerical duties were performed in this area such as patient bookings, interacting with patients and data entry into the computer.
- *Waiting room:* In this area, the patients spent time after registration until called to the ultrasound room for the ultrasound service. It is in this area that patients were also

prepped for certain ultrasound examinations such as filling of the urinary bladder for pelvic examinations. In this research study, no specific preparation was needed. The patient in the waiting area were given the information leaflet to read so that the patient will be aware of the study before being asked to volunteer. If the patient agreed to participate in the study, then they were given an informed consent form to peruse and sign. (Appendix A: Patient Informed Consent [English, Afrikaans, Zulu and Xhosa]).

- *Ultrasound room:* The ultrasound examination was performed in the ultrasound room. Patients were escorted to the ultrasound room after registration and signing of consent if consent was granted for the examination. If the patient refused to participate, the renal Duplex examination was still performed as requested by the referring clinician.
- *Reporting room:* The ultrasound study was reported on using XRE and completed ultrasound reports were kept on the PAC system. The request form for an ultrasound was put into the box and picked up the following day to be stored.

3.5 Sample selection

3.5.1 Inclusion criteria

Patients with the following conditions were included:

- Acute kidney injury
- Suspected acute on CKD (AOCKD)
- Suspected CKD
- Reduced glomerular filtrate rate < suspected CKD - (<GFR) less than 60 ml/min/1.73 m^2

3.5.2 Exclusion criteria

Patients with the following clinical history were excluded:

- Renal transplant
- Undergoing dialysis treatment

3.5.3 Sample size determination

Convenience sampling was employed in this cross-sectional observational study, A good sample is one that statistically represents the target population and is sizable enough to provide an answer to the research issue (Majid, 2018).

The following formula was used:

$$n = \frac{z2.\sigma.(1-\sigma)}{\varepsilon 2}$$

The study used a confidence level of 95% (Bryan-Jones et al., 1983).

Therefore:

n = $\frac{(1.96)2(0.5)\ (1-0.5)}{(0.1)2}$

= 96

n - Sample size

σ - Standard deviation = 0.5

ε - Margin of error = 0.1

z - z value = 1.96

In accordance with the above formula, the research study included a total of 100 participants.

3.6 Study variables

A distinction between independent and dependent variables was established for this study as listed in Table 3.1. The controlled independent variables functioned as the causal agents to have an impact on the dependent variables. The observed result was known as the "dependent variable".

Table 3.1: Independent and dependent variables

Independent variables	Dependent variables
• Demographic factors such as age and gender (male and female) • Clinical indications • Biochemical results: urea, creatinine, GFR-MDRD and GFR-EPI	• Kidney sizes • Echogenicity of the kidneys • Cortical thickness • Renal resistive index • Other pathology noted during the ultrasound examination

3.7 Data collection

During the data collection phase, a wide range of data, including clinical information, demographic details, biochemical results and ultrasound observations. The ultrasound request formed a source from which data were obtained including the participant's age, gender and medical and clinical history. Some request forms also contained the biochemical data such as urea, creatinine and eGFR. Lab Track, a fully featured medical practice management software package designed to provide laboratory results of patients, was used to obtain the participant's laboratory results that were not available on the ultrasound request form. Participants' ultrasound reports were obtained from the Picture Archiving and

Communication System (PACS) which included information regarding the bipolar length of the kidneys (cm), kidney echogenicity, renal cortical thickness (cm) and the mean RRI.

3.7.1 Data management plan

The data management plan included 4 stages

- Data collection (from source 1 and source 2)
- Data storage
- Management of data and
- Sharing of data.

Data collection source 1 (ultrasound request form)

Clinical parameters were collected from the ultrasound request form as provided by the referring clinician which included:

- Age of patient
- Gender
- Detailed clinical history
- Laboratory results

Data collection source 2 (Ultrasound scan results)

Data collected were as follows

- Kidney size (left and right)
- Echotexture of the kidneys
- Cortical thickness
- The RRI of the right and left kidney in the upper, mid, and lower pole

Storage of data

- Automatic storage of ultrasound images from ultrasound machine to PACS, password protected.
- Ultrasound report compiled by researcher stored onto PACS, password protected. Data was retrieved from PACS and stored on an external hard drive.
- Ultrasound report analysis

Managing Data

Data was recorded on a “Data collection sheet ” and was captured electronically in

Microsoft Excel by the researcher. A statistician was consulted to analyse the data.

Sharing data

This stage involved the write up of the study results. Raw data was not shared. Results of the study will be published.

3.7.2 Reliability and validity

The principal researcher performed all RRI measures as part of the renal ultrasound examinations. All RRI measurements was be performed using the same ultrasound machine, in the same standard ultrasound protocol in a reproducible manner to ensure reliable results.

3.8 Materials and methods

The Siemens Acuson Redwood ultrasound machine with grey-scale imaging, Doppler facilities (colour and spectral Doppler) and a 3.5 MHz multifrequency curvilinear transducer with coupling gel was used to interrogate the participants' renal system.

3.8.1 Ultrasound technique

The examination was performed with the patient in the supine position on the examination bed.

3.8.1.1 Grey-scale ultrasound

Grey-scale imaging was used to assess kidney size (bipolar length), renal echogenicity, cortical thickness and to demonstrate any structural abnormality (if present). The bipolar length, measured from the upper to lower pole of the kidney and renal cortex was measured in centimetres (cm) as seen in Figure 3.1.

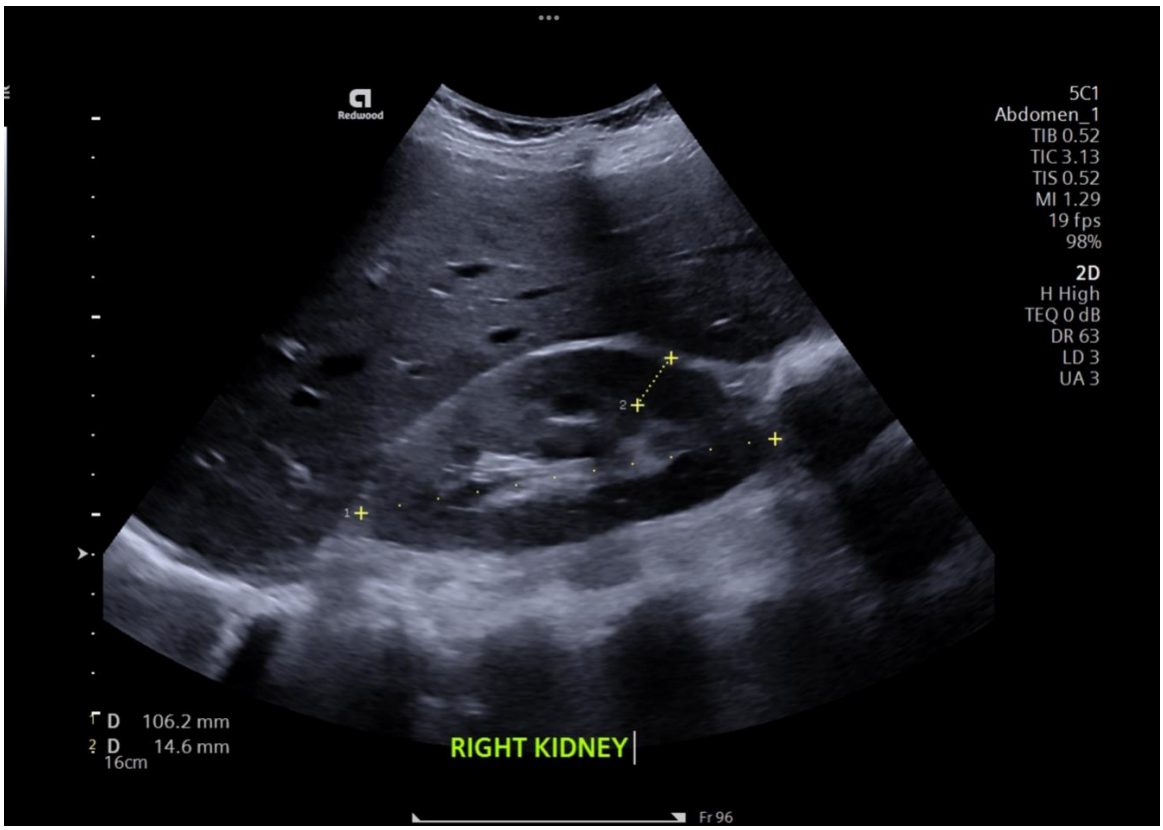

Figure 3.1: Grey scale ultrasound image of the right kidney in the longitudinal plane (1). Measurement of the maximal upper pole-to-lower pole distance at 10.62 cm (2). Measurement of the renal cortex at 1.46 cm. (Source: Permission granted by patient)

3.8.1.2 Colour Doppler

The purpose of colour Doppler was to assess patency of the segmental arteries as seen in Figure 3.2 depicted by the blue/red colours filling the vessels. This was achieved through a system of steps that are listed below.

1. Colour Doppler was activated where a colour box was placed over the selected vessels.
2. The focus was set at the region level to improve the colour signal, the gain was increased and adjusted together with beam steering to have achieved a suitable beam angle for the chosen artery, the segmental artery.
3. The pulse repetition frequency (PRF) was adjusted to synchronise the flow status.

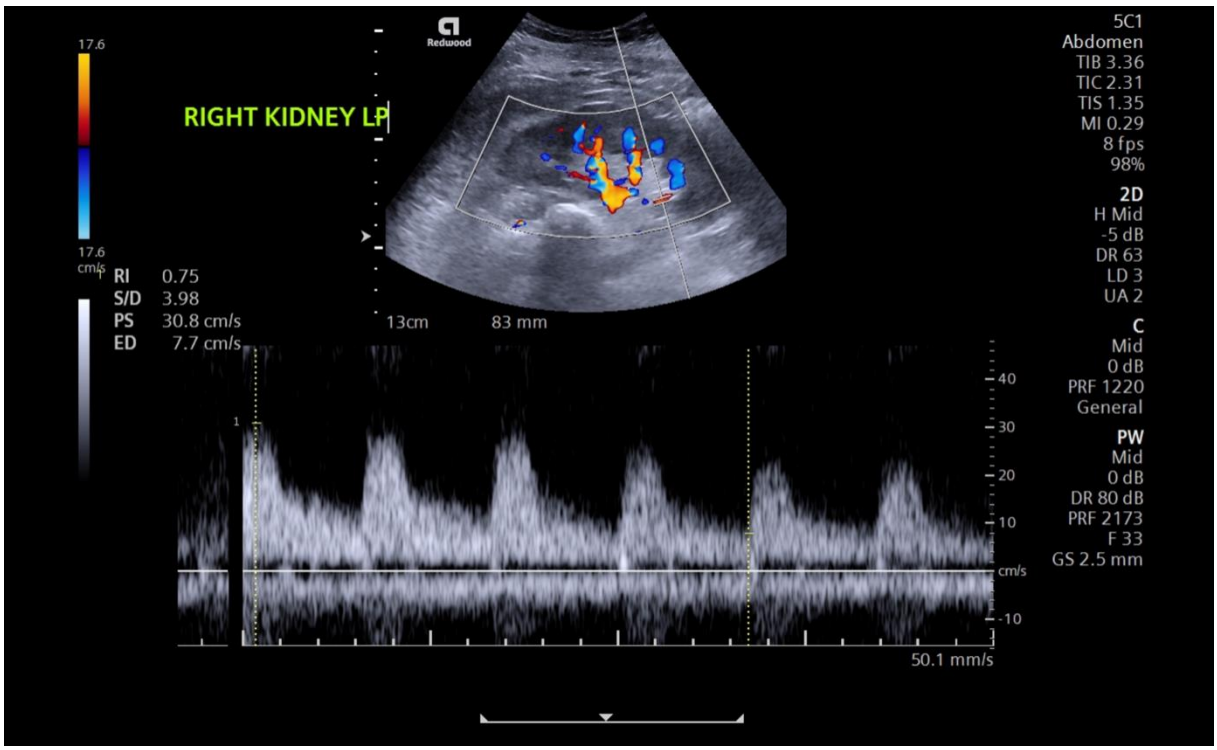

Figure 3.2: Colour (red/blue filling of the vessels) and spectral Doppler analyses of the segmental artery of the lower pole of the right kidney with greater than three reproducible waveforms. PSV (peak systolic velocity) = 30.8 cm/s, EDV (end-diastolic velocity) = 7.7 cm/s. (Source: Permission granted by patient)

3.8.1.3 Spectral Doppler

Spectral Doppler analysis was performed to determine the RRI, where the peak and end-diastolic velocities was measured across three waveforms of the segmental artery as seen in Figure 3.2. This was achieved by following the steps below.

1. The Doppler cursor was placed over the artery that was to be examined.
2. The gain was increased to remove any noise.
3. Beam steering was used to achieve a beam angle of less than 60 degrees. Reverberation and acoustic shadowing are two examples of artefacts that can be lessened by using a beam angle less than 60 degrees.
4. The PRF was adjusted accordingly to 1.5 kHz.
5. A sample volume of 2.5 mm was used.
6. The sample volume was placed over the vessel of interest and the pulsed wave Doppler was activated.
7. The update button was turned on and the auto trace features were enabled.
8. Doppler sampling of the segmental arteries in the upper, middle and lower poles of the kidneys was performed.

9. The RRI from three to five reproducible waveforms was averaged to arrive at a mean RRI for each kidney.
10. The renal resistive indices acquired from the upper, middle and lower poles were added up, and the total amount of sampled locations amount was then divided by three to obtain the mean RRI.

3.9 Data collection

The ultrasound data was captured in a report which included:

- Renal size (bipolar length) in centimetres
- Renal echogenicity
- Any anatomical abnormality such as renal cysts, lesions, calculi or hydronephrosis
- The renal resistive index of the segmental artery in the upper, mid and lower poles of the kidneys
- The mean RI of the kidneys
- Assessment of the urinary bladder
- Free fluid (if any) noted in the abdomen or pelvis during the ultrasound examination

3.9.1 Renal size in length (cm)

The normal measurements of the adult kidney range from 9-12 cm in length with the left kidney being approximately 3 mm longer than the right kidney (Curry & Prince, 2020; Spatola & Andrulli, 2016). These guidelines formed the protocol of the research site which was followed in this study: kidney lengths between 9 and 12 cm were considered to be within normal ranges. Faubel et al. (2013) mention that kidney sizes that are < 8cm (small) point to a CKD diagnosis, but either AKI or CKD can cause normal or increased kidney size. Patient body habitus was also taken into consideration when measuring renal length, as renal size may be increased in patients with increased body habitus (Curry & Prince, 2020).
Adult kidney lengths should range from 10 to 12 cm, according to O'Neill (2014a), while according to Spatola and Andrulli (2016), a normal renal ultrasonography shows kidneys that are 11 to 12 cm long, with the left kidney being about 3 mm longer than the right kidney.

3.9.2 Echogenicity of the kidneys

According to Faubel (2014), the medullary pyramids are hypoechoic to the renal cortex on grey scale imaging and the renal cortex should be hypoechoic to the liver and spleen. This study adhered to the above-mentioned guidelines, namely the echogenicity of the renal

cortex was compared to that of the liver and spleen, as these guidelines have been documented in literature and are also noted to be the protocol of the research site.

3.9.3 Cortex measurement of the kidneys (cm)

The normal renal cortical thickness ranges from 7 to 10 mm. A decrease in cortical thickness may be suggestive of early signs of renal failure (Yamashita et al., 2015). These guidelines constituted the protocol implemented at the research site and were utilised in this study.

3.9.4 Mean renal resistive index of the kidneys

Established guidelines written by Petrucci et al. (2018) and Spatola and Andrulli (2016) were utilised regarding the mean RRI. The normal RRI range was established as 0.40 to 0.70. Any RRI value above 0.70 indicated an elevated renal resistive index, while a value of 0.70 was considered as the upper limit of normal.

3.10 Biochemical data

The participants' laboratory biochemical test results were retrieved from the request forms and at Lab Track. The results of the following biomarkers were retrieved:

- Urea
- Creatinine
- GFR-MDRD
- GFR-EPI

The retrieved biochemical data were captured onto an Excel spreadsheet indicating the names and values for each biomarker.

3.10.1 Laboratory analysis

At the time of the examination, no laboratory experiments were being done. Prior to the ultrasound examinations, all laboratory tests were completed and the results were captured from the request forms and at times obtained using Lab Track.

3.10.2 Glomerular filtrate rate

According to Lopez-Giacoman and Madero (2015), the use of prediction equations has been widely employed to estimate GFR from endogenous filtration indicators without the necessity for clearance computation, given the limitations of creatinine as a marker of renal function. The most often utilized endogenous filtration indicators for eGFR are SCr and CysC. In this study, results of GFR_MDRD and GFR-EPI were both used.

3.10.3 Urea

According to Gowda et al. (2010), urea is a substantial nitrogenous by-product of protein and amino acid breakdown that is created by the liver and distributed throughout intracellular and extracellular fluid in the kidneys. Urea is taken out of the blood by glomeruli, then partially reabsorbed with water. Urea nitrogen concentrations in adult human blood should range from 2.1 to 7.1 mmol/L.

3.10.4 Creatinine

The breakdown product of creatine phosphate in muscles, creatinine, is normally created by the body at a consistent rate depending on muscle mass, according to Gowda et al. (2010). Creatinine is the renal function indicator that is most routinely used. The normal range for creatinine in men is 61.9 to 114.9 umol/L, whereas the normal range for women is 53 to 97.2 umol/L. Table 3.2 illustrates the normal range of creatine in men and women. Creatine ranges of > 61.9 to 114.9 µmol/L for men and creatine ranges > 53 to 97.2 µmol/L for women were noted as raised levels of creatine in this study.

Table 3.2: Normal range of creatinine

Gender	Normal range of creatinine
Men	61.9 – 114.9 µmol/L*
Women	53 – 97.2 µmol/L*

*µmol/L: micromoles per litre

3.11 Statistical analysis of data

A GLzdM and a Spearman's analyses were used to test the relationship between independent and dependant variables. A generalised linear model is a versatile class of a statistical model that is used when the response variable may not be normally distributed as in this research study. The response variable, which is the dependent variable, does not follow a normal distribution. In this research study, GLzdM was used to pinpoint and measure the relationship between the independent and dependent variables that served as predictor factors (Corrie, 2023).

Spearman's correlation analysis was also used to evaluate the strength and direction of the association between continuous or ordinal variables. Data were gathered for relevant variables in this research study, and averages and the standard deviation were used to summarise the findings. In addition, Spearman's rank correlation analysis was used to evaluate the relationship between these variables because the data showed non-linearity and did not conform to the assumptions of a linear correlation.

Data obtained were analysed using SPSS version 28. The categorical parameters were summarised as frequencies and percentages, while continuous parameters were summarised as means ± standard deviation. This was done by the statistician of the Cape Peninsula University of Technology.

CHAPTER 4
RESULTS

The aim of this chapter is to present the findings of this research study which have been generated from the research methodology and data collection methods outlined in Chapter 3. The findings that are presented are consistent with the aim of this research study, viz. to ascertain an association of the renal sonographic features (grey scale and Doppler ultrasound) with clinical and biochemical variant evidence of renal dysfunction of the participants. The findings have also included a descriptive analysis of the demographic features (age and gender), the clinical indications (chronic kidney disease, acute kidney injury, diabetes mellitus, nephropathy and renal dysfunction) and the renal sonographic features (kidney size, echo pattern, cortex size and renal resistive index) of the participants. Descriptive statistical analysis included percentage, mean, median and standard deviation, and was presented as a graph, table and pie chart. Inferential statistical analysis included Wald Chi square test with a statistical significance of $p = 0.05$ and Spearman's correlation test.

4.1 Demographic data

Renal ultrasound examinations were conducted on a cohort of 100 participants ($n = 100$) who attended the nephrology clinic between December 2022 and February 2023. The ultrasound examinations were conducted in the ultrasound department in the radiology division of an academic hospital in Johannesburg, South Africa.

4.1.1 Gender of the participants

The gender distribution of the research study participants was 48% male and 52% female as seen in Figure 4.1.

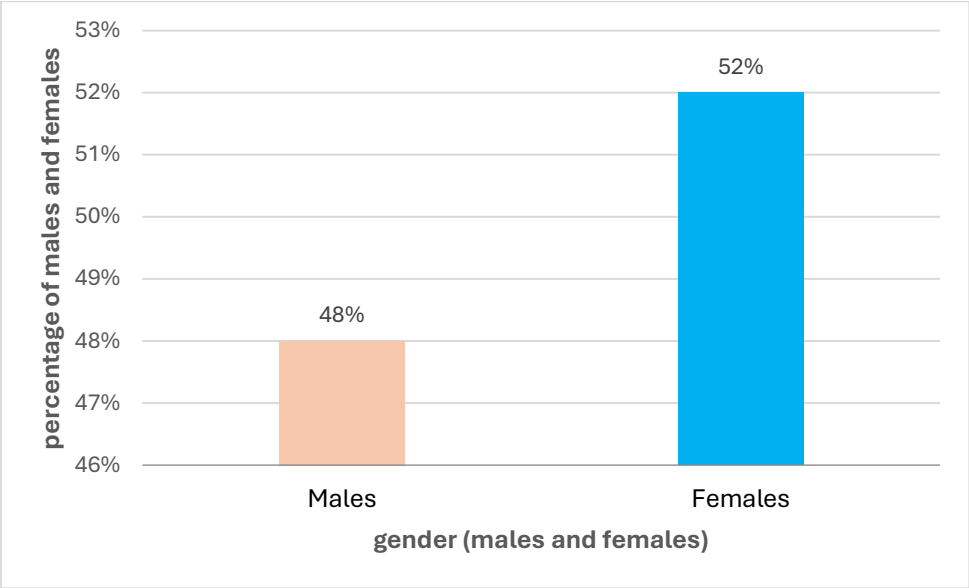

Figure 4.1: Demographic breakdown of 100 participants

4.1.2 Age of the participants

Figure 4.2 provides the participant distribution across different age groups, with 12% of participants falling within the 18-29 age group, 13% of participants in the 30-39 age group, 24% of participants in the 40-49 age group, 23% of participants in the 50-59 age group, 15% of participants in the 60-69 age group, 11% of participants between the ages of 70 and 79, and finally, 2% of participants in the 80-90 age group.

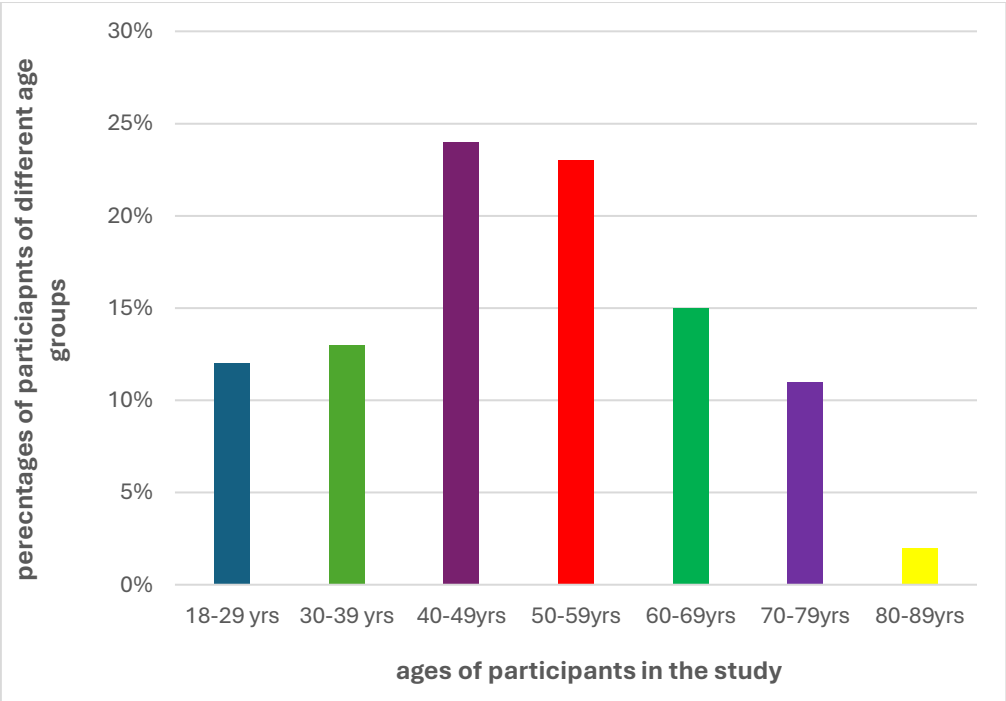

Figure 4.2: Age range of the participants

4.2 Clinical indications for the ultrasound examination

Figure 4.3 demonstrates the distribution of clinical histories presented by the participants. Fifty percent (50%) of the participants had a clinical history of chronic kidney disease (CKD), prompting the request for ultrasound imaging. Additionally, 20% of the referred participants had a clinical history of acute kidney injury (AKI), 10% presented with a history of diabetes mellitus (DM), 10% were diagnosed with newly identified renal dysfunction and the remaining 10% had a clinical history of nephropathy.

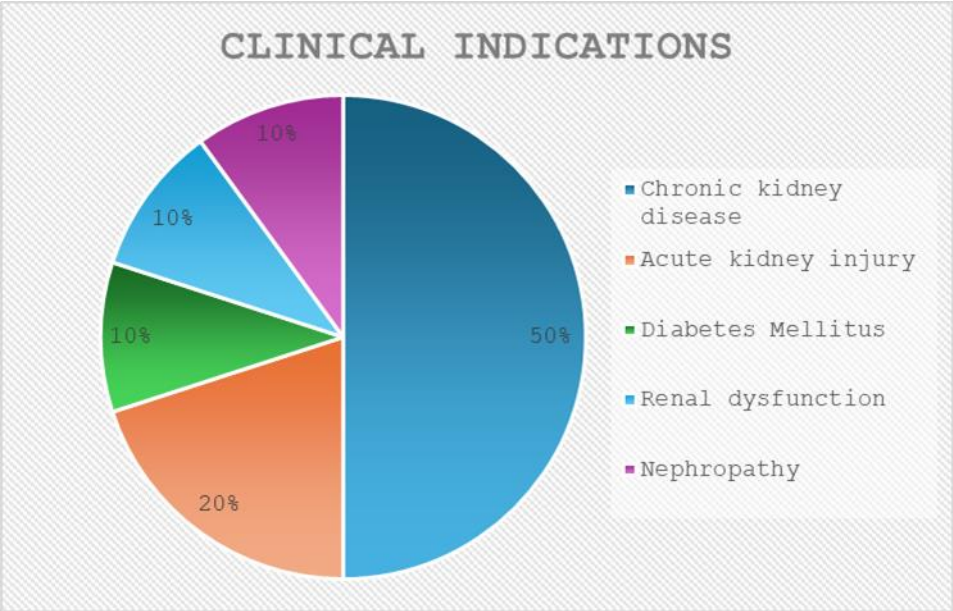

Figure 4.3: Clinical indications for the ultrasound examinations

4.3 Analysis of the dependent variables used in the research study

The dependent variables were:

- Kidney size
- Kidney echogenicity
- Cortex of the kidneys
- Renal resistive index

4.3.1 Kidney size and renal dysfunction: A descriptive analysis

The ultrasound findings showed that 3% of the participants had kidneys that were small in size (< 9 cm) which was concurrently reported as indicative of CKD. A significant portion, 92% of the participants, showed kidneys of normal size (9-12 cm), whereas the remaining 5% of participants showed an increase in kidney size (> 12 cm). Refer to Figure 4.4 below for the analysis of the kidney size for participants with renal dysfunction.

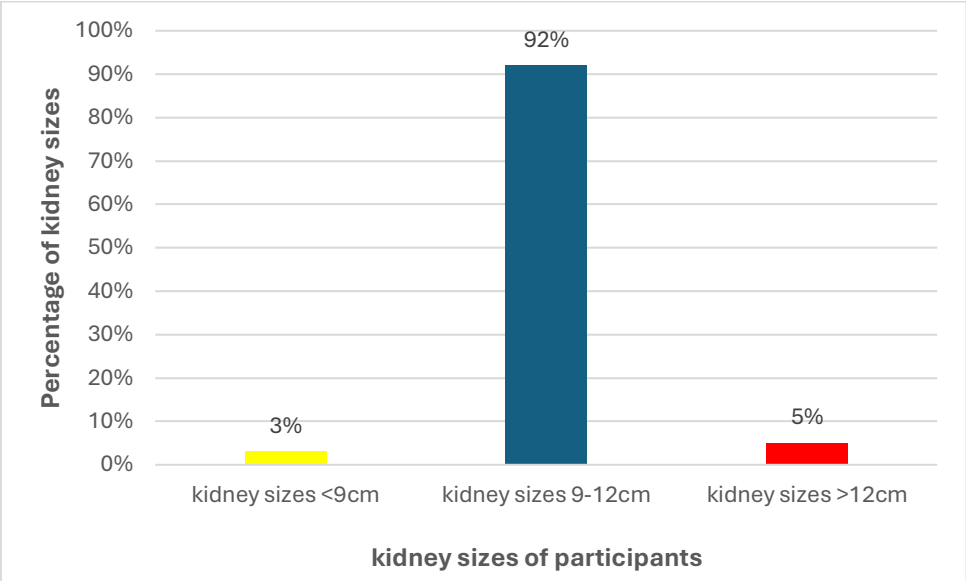

Figure 4.4: Analysis of kidney size in participants with renal dysfunction

4.3.2. Kidney size and renal dysfunction - a linear regression.

The following independent factors were considered in the linear regression analysis to determine whether there was an association between the kidney size and gender, age, GFR-MDRD, GFR-EPI, urea and creatinine.

According to Kumari & Yadav (2018) a linear regression is a statistical method that calculates the value of a dependent variable from an independent variable, assessing the association between the two variables.

In statistics a Walt test was used to assess the significance of independent variables in a model. Type III Tests evaluates the significance of each effect in the model considering all other effects (SAS Institute Inc., 2004).

Table 4.1 which illustrates the Type III Wald Chi-square test that was used to determine whether there was an association between kidney size, gender, age and biochemical markers (GFR-MDRD, GFR EPI, urea).

Table 4.1: Type III Wald Chi-square test.

	Type III Wald Chi-Square	**Degree of Freedom**	**Significance $p < 0.05$**	
GENDER	6.713	1	*.010	Gender is statistically significant.
AGE	.065	1	.799	Age is not statistically significant.
GFR-MDRD	1.369	1	.242	GPR_MDRD is not statistically significant.
GFR EPI	.994	1	.319	GFR EPI is not statistically significant.
Urea	.207	1	.649	Urea is not statistically significant.
Creatinine	15.543	1	*<.001	Creatinine is statistically significant.

* demonstrate significance levels

There was no statistically significant ($p < 0.05$) association between kidney size and age ($p = 0.799$), GFR-MDRD ($p = 0.242$), GFR EPI ($p = 0.319$) and urea ($p = 0.649$). There was statistical significance ($p < 0.05$) of association between kidney size and gender ($p = 0.010$) and creatinine ($p < 0.001$).

4.3.3 Kidney echogenicity and renal dysfunction: A descriptive analysis

The ultrasound results showed 69% of the participants had kidneys with an increased echogenicity (hyperechoic), while 31% had kidneys with a normal echogenicity (Figure 4.5).

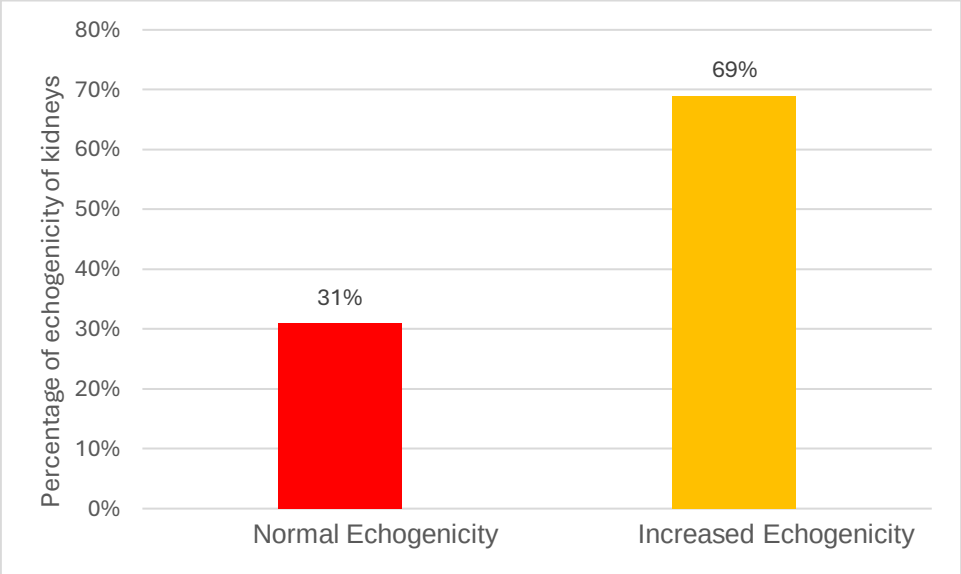

Figure 4.5: Echogenicity of the kidneys in participants with renal dysfunction

4.3.4 Renal cortical thickness and renal dysfunction: A descriptive analysis

The ultrasound findings showed 3% of the participants had kidneys that were characterised by cortical thinning (< 1 cm), while 97% showed kidneys with normal cortical thickness (> 1 cm), constituting the vast majority (Figure 4.6).

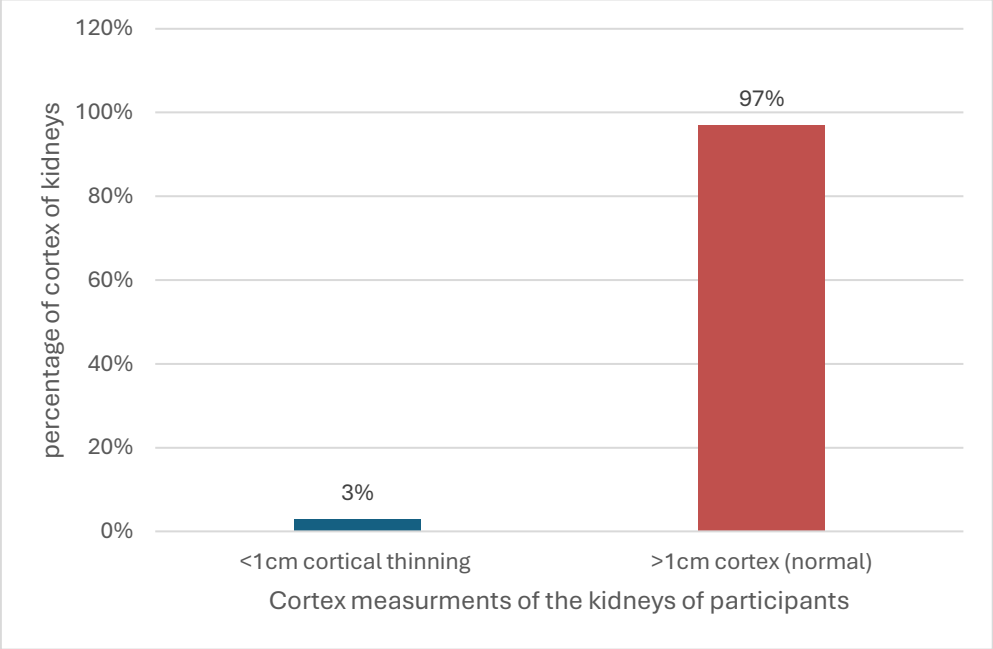

Figure 4.6: Analysis of normal kidney cortex and occurrence of cortical thinning in participants with renal dysfunction

4.4 Renal resistive index (RRI) of patients with clinical and biochemical variant evidence of renal dysfunction

All participants (n = 100) presented with renal dysfunction according to biochemical markers had a raised RRI (Figure 4.7).

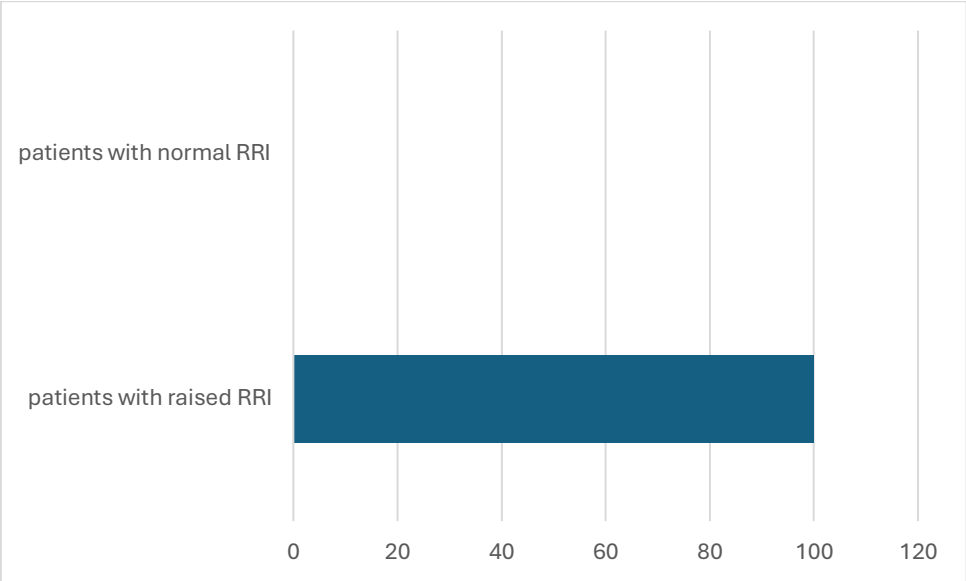

Figure 4.7: Analysis of RRI of participants with clinical and biochemical variant evidence of renal dysfunction

4.4.1 Association between biochemical markers indicative of renal dysfunction and RRI using Spearman's correlation analysis

Table 4.2 below represents the results of the descriptive analysis (minimum, maximum, mean and standard deviation) of the biochemical markers (GFR-MDRD, GFR-EPI, urea and creatinine).

Table 4.1: Descriptive analysis (minimum, maximum, mean and standard deviation) of the biochemical markers (GFR-MDRD, GFR-EPI, urea and creatinine)

	N	Minimum	Maximum	Mean	Std. Deviation
GFR-MDRD	100	1	59	35.44	16.467
GFR-EPI	100	1	60	36.80	17.004
Urea	93	2.7	181.0	17.349	23.8711
Creatinine	100	9.3	2684.0	253.147	386.0299
	Total	100	100.0	100.0	N = 100

Key: N = sample size; GFR-MDRD = Glomerular Filtration Rate Modification of Diet in Renal Disease; GFR-EPI = Glomerular Filtration Rate Epidemiology

The association of the independent variables (GFR-MDRD, GFR-EPI, urea and creatinine) with the mean RRI was the subject of Spearman's rank-order correlation analysis which was used to evaluate the direction and intensity of this relationship as seen in Table 4.3.

Table 4.2: Spearman's and Pearson's correlation between renal resistive index and biochemical markers GFR-MDRD, GFR-EPI, urea and creatinine

		Correlation Coefficient	MEAN	MEAN A
	AGE	Correlation Coefficient	*-.040	*-.074
		Sig. (2-tailed)	**.693	**.464
		N	100	100
	GFRMDRD	Correlation Coefficient	*-.104	*-.102
		Sig. (2-tailed)	**.302	**.314
		N	100	100
	GFREPI	Correlation Coefficient	*-.104	*-.102
		Sig. (2-tailed)	**.302	**.314
		N	100	100
	Urea	Correlation Coefficient	*.073	*.010
		Sig. (2-tailed)	**.486	**.927
		N	93	93
	Creatinine	Correlation Coefficient	*.111	*.017
		Sig. (2-tailed)	**.270	**.864
		N	100	100
N=100				

Key: Sig = significance; N = sample size; GFR-MDRD = Glomerular Filtration Rate Modification of Diet in Renal Disease; GFR-EPI = Glomerular Filtration Rate Epidemiology.

* Spearman's correlation

** Pearson's correlation

According to the results of Spearman's correlation analysis, there was a weak negative correlation between renal resistive index and GFR_MDRD and GFR-EPI (r = -0.104 and -0.102 for right and left kidney, respectively) and a weak positive correlation between the RRI and urea (r = 0.073 and 0.010 for right and left kidney, respectively) and creatinine (r = 0.111 and 0.017 for right and left kidney, respectively).

Pearson's correlation analysis showed no significant significance ($p < 0.05$) in all cases.

4.5 Summary of results

Chapter 4 of this thesis provided a thorough study of the research findings, including an investigation of numerous variables using both linear regression and Spearman's correlation analysis to determine the relationships between variables.

The aim of the study, which involved a total of 100 participants aged 18 to 90, was to investigate the relationship between renal ultrasound characteristics (Doppler and grey scale ultrasound) and the biochemical and clinical markers associated with patients presenting with renal dysfunction.

The cohort's demographics showed that women made up 52% of the cohort, somewhat more than men (48%). The results of this study showed that all patients identified with renal dysfunction had an increased RRI based on ultrasound data.

Participants presenting with CKD in a range of age groups presented with a variety of clinical indications and all had an elevated RRI on ultrasound evaluation. The results of the kidney size analysis showed that there was no statistically significant correlation between kidney size and age, but there was a statistically significant association between kidney size and gender. Thirty-one per cent (31%) of patients with elevated RRI had kidneys with normal echogenicity and 97% of them had kidney cortex values on ultrasound that were within normal ranges.

The results highlighted the potential use of ultrasound imaging as a diagnostic tool in evaluating renal health and dysfunction, as all participants (n = 100) with renal dysfunction had a raised RRI > 0.7.

The following chapter examines the findings of Chapter 4.

CHAPTER 5
DISCUSSION

5.1 Introduction

The study results are reviewed in this chapter, with an emphasis on the associations between the independent and dependent variables. This chapter explores the correlations that have been found between these variables, offering a discussion of their independencies and effects regarding the research framework.

The aim of this study was to determine an association of the renal ultrasound features (grey scale and Doppler ultrasound) of adults with clinical and biochemical variant evidence of renal dysfunction. One hundred (n = 100) participants were included in this study which included 42 males and 52 females with ages ranging from 18 to 90 years. All participants who were referred from a nephrology clinic diagnosed with renal dysfunction by biochemical markers, had an ultrasound examination.

5.2 Demographic data

5.2.1 Association between age and a raised renal restive index (RRI)

In the observed cases, participants with renal dysfunction, regardless of their age, consistently had increased RRI values on the ultrasound examinations. Older participants (60-89 years) who are often linked with age-related physiological changes and younger participants (18-29 years) showed increased RRI values on their ultrasound examinations. There were two values obtained from the Spearman's correlation between age and RRI (r-r interval): -0.040 (right kidney) and -0.074 (left kidney).This implied that the relationship between RRI and age was weakly negative and monotonic. It was noted that there was no statistically significant correlation between age and a raised RRI. This finding implies that the presence of an elevated RRI is a distinctive trait seen across a broad spectrum of participants with renal dysfunction rather than being restricted to a particular age group.

In a study conducted by Theertha et al. (2023), raised RRI values are consistently observed in older and younger participants presenting with renal dysfunction, highlighting the importance of this parameter as a marker of changed renal blood flow dynamics in participants, independent of age.

5.2.2 Clinical indications and biochemical markers

Participants in this study were referred by a nephrologist and presented with renal dysfunction according to their clinical symptoms and biochemical markers. Specific biochemical markers, clinical symptoms and underlying disorders seen in these participants served as the basis for the referral by the nephrologist.

The clinical justifications for performing an ultrasound assessment in this study were outlined as shown in Figure 4.3 of Chapter 4. Among these, 50% of the participants had a known history of chronic kidney disease (CKD), making ultrasound imaging necessary. Additionally, 20% of those referred had a history of acute kidney injury (AKI), 10% had diabetes mellitus (DM) in the past, 10% had just received a diagnosis of renal dysfunction, and the final 10% had a clinical history of nephropathy. All of these individuals had an elevated RRI on ultrasound examination.

5.3 Association of participants' RRI with clinical and biochemical variant evidence of renal dysfunction

The participants in this study presented with renal dysfunction as indicated by their abnormal biochemical markers. The RRI of all participants in this study presenting with renal dysfunction was found to have a raised RRI > 0.7 on the ultrasound examination as shown in Figure 4.7. As the RRI increased, the eGFR slightly decreased; hence the correlation (r-values of -0.104 and -0.102) indicated a weak negative relationship between the RRI and eGFR for the right and left kidney, respectively.

Renal dysfunction typically occurs when there is mutual changes in biochemical markers. Elevated urea and creatinine levels indicate renal dysfunction, whereas reduced levels of GFR values are also indicative of renal dysfunction. An increase in the renal RRI was observed in both scenarios — higher urea and creatinine levels and lower GFR levels. As a result, there was a weak positive association between RRI and the biochemical indicators urea and creatinine and a weak negative correlation between RRI and GFR. This indicates that these metrics are interdependent when it comes to evaluating renal function.

In a study conducted by Provenzano et al. (2020) which included non-dialysis patients that were diagnosed with CKD based on the GFR less than the normal 60mL/min/1.73m2, revealed that the RRI was raised in patients with CKD, diabetes mellitus and cardiovascular disease, regardless of the level of the GFR. The co-morbidities of the patients in the study of Provenzano et al. (2020) were not present. Our cohort in this study produced similar results to the study of Provenzano et al (2020) i.e. regardless of eGFR levels in patients with renal dysfunction, RRI was raised. Similarly in a study conducted by Hanamura et al (2012) in which 202 patients underwent an ultrasound examination demonstrated that RRI increased

as the stage of CKD increased. From this study it was concluded that in patients with CKD, a raised RRI is considered to be a marker of renal function, renal prognosis and histological damage and furthermore a possible indication for steroids.

Theertha et al. (2023) conducted a cross-sectional comparison study which included 114 patients (58 with diabetes and 56 without). Each participant with chronic kidney disease (CKD) had undergone a histological examination and was sent for an abdominal ultrasound examination. The findings demonstrated a strong relationship between the renal resistive index (RRI) and estimated glomerular filtration rate (eGFR) ($p = 0.001$), as well as serum creatinine ($p = 0.001$). RRI, however, did not correlate with urine albumin excretion, systolic blood pressure or patient age. In CKD patients, a significant negative connection between RRI and eGFR was noted, suggesting that RRI gradually rose from the lower to the higher stages of CKD.

Patients with CKD who were tracked for at least two years in three nephrology clinics between 2006 and 2019 were examined in a retrospective study done by Kharsa et al. (2023). A total of 192 patients made up the study population where 124 patients demonstrated a RRI of ≥ 0.7. There was a significant negative association between the baseline eGFR and RRI ($p < 0.001$; Spearman correlation coefficient = -0.521). However, in contrast in our study, no statistically significant association was found between RRI and eGFR, only a weak negative correlation.

In the study conducted by Kawai et al. (2011), it was concluded that the lower the eGFR, the higher the RRI, an indirectly proportional relationship was noted between eGFR and a raised RRI, and that the RRI significantly correlates with organ damage. Furthermore, the authors stated that from this observation the RRI might be a very useful tool to evaluate the pathogenesis of renal damage and predict prognosis.

Hanamura et al. (2012) investigated the RRI using Doppler ultrasound in 202 patients with chronic kidney disease (CKD) in order to assess the value of RI as a non-invasive marker of renal histological damage and a prognostic indicator. According to the study, RI increased as the stages of CKD advanced. It was associated with renal histological alterations such as glomerulosclerosis, arteriolosclerosis and tubule-interstitial damage, as well as age, systolic blood pressure and estimated glomerular filtration rate (eGFR). This study assessed the multiple uses of the resistive index in individuals with chronic kidney disease (CKD) as determined by Doppler ultrasound. It showed that RI was the most accurate ultrasound index for CKD stages which supported the findings of our study.

In another research study, 30 patients with non-surgical parenchymal renal disease and blood creatinine levels > 1.4 mg/dL were chosen during routine visits for a cross-sectional study to determine whether the RRI and serum creatinine levels were significantly correlated

(Ghafoori & Shiva, 2007). Thirty (30) participants with serum creatinine levels less than 1.4 mg/dL made up the comparison group. Grey scale ultrasound was used to evaluate the participants' kidneys for hydronephrosis, bilateral symmetry, the presence of stones and any lesions or masses. The resistive index (RI) in 10 interlobar arteries was then determined using colour Doppler ultrasound (five in each kidney). The case group's mean ± SD serum creatinine level was 6.5 ± 0.6 mg/dL, while the control group's level was 1.0 ± 0.3 mg/dL. For the case group, the mean RI was 78.0% ± 1.9%, while for the control group it was 59.3% ± 0.8% ($p < 0.001$). There was a significant correlation between serum creatinine level and RRI ($r = 0.68$, $p < 0.001$). The study found that Doppler ultrasound-based RI measurement was a good indicator of renal function in renal parenchymal disease. As the RRI increased, there was a slight increase in the urea levels, namely a correlation of 0.0073 and 0.0010 for the right and left kidneys, respectively. It indicated a weak positive relationship between RRI and urea levels.

In our research study, all participants with elevated RRIs on ultrasound were found to have urea levels ranging from 7.2 to 29.7. Urea nitrogen concentrations in adult human blood should range from 2.1 to 7.1 mmol/L. Similar to this finding, during the ultrasound examination, patients with various creatinine levels ranging from 113 to 1 022 were also found to have higher RRIs, since the normal range for creatinine in men is 61.9 to 114.9 µmol/L and the normal range for women is 53 to 97.2 µmol/L.

In a study by Gopalakrishnan et al. (2019), the aim was to evaluate renal ultrasound characteristics using grey scale ultrasound, renal vascular resistance using Doppler and to correlate with biochemical parameters such as total cholesterol, triglycerides, urine albumin, blood urea nitrogen and fasting blood sugar (FBS) in patients with diabetic renal disease. The study findings indicated that renal echogenicity and renal resistant index values exhibited a positive correlation with blood urea nitrogen and serum creatinine, and that correlation was found to be statistically significant.

Our cohort demonstrated a wide range of renal function scores with individuals, all of whom had increased RRIs on ultrasound examinations. This observation emphasises the lack of a clear link between particular renal characteristics and the development of an elevated RRI. This intricate link highlights how renal dysfunction is multifaceted and manifests in altered blood flow dynamics, as shown by the higher RRI in ultrasound examinations.

5.3.1 Association between kidney size and participants presenting with renal dysfunction

The independent variables used to determine renal dysfunction were biochemical markers GFR-MDRD, GFR EPI, urea and creatinine. A GLzdM was used to determine whether there was a statistically significant association between kidney size and biochemical markers GFR-

MDRD, GFR EPI, urea and creatinine. Other independent variables such as gender and age were also included in the Type III Wald Chi-square analysis.

In our research study, gender could have had a significant impact on kidney size, as the relationship between kidney size and gender was deemed statistically significant at the 0.01 level ($p < 0.05$). The Type III Wald Chi-square test for the predictor “creatinine” suggested that there was a statistically significant association between kidney size and creatinine with a p-value < 0.001. In terms of age, the relationship between kidney size and age was not statistically significant ($p = 0.799$). The biochemical markers GFR-MDRD, GFR EPI and urea were not linked to kidney size in this investigation, with p-values of 0.242, 0.319 and 0.649, respectively, when their levels indicated renal dysfunction.

Kaptein and Kaptein (2017) describe renal ultrasound features such as kidney sizes that are short in length to indicate CKD, while kidney sizes that are normal or increased in length may occur in AKI due to nephritis or in CKD due to diabetes mellitus or an infiltrative cause. In our research study, all participants ($n = 100$) presented with renal dysfunction. However, as noted in Figure 4.4, 92% of the participants demonstrated kidney sizes that were within the normal range (9-12 cm), 3% of the participants had kidneys that were small in size (< 9 cm) and the remaining 5% of participants showed an increase in kidney size (> 12 cm). Results from our research study showed that there was no statistical significance between kidney size and renal dysfunction.

The absence of statistical significance does not imply the absence of an association; rather, it indicates that there is insufficient evidence to conclude that certain variables have a significant impact on kidney size, based on the available data and the selected significance level. In contrast, Makusidi et al. (2014) highlight how important kidney size is to a full understanding of renal disorders. Their research highlights the importance of renal length for prognosis prediction, as well as diagnosis and treatment of renal illnesses.

The importance of renal length as a crucial metric in assessing renal function is further reinforced by the considerable association between renal volume and length and glomerular filtration rate (GFR) that has been amply proven. The complicated connection between renal morphology and renal function is highlighted by this association, giving clinicians important information that can help with the exact diagnosis, efficient treatment and long-term prognosis of a variety of renal illnesses. Such knowledge is essential for creating tailored therapeutic strategies that are informed, thereby improving patient outcomes.

The findings from our cohort highlight the need to conduct further research on the association between kidney size and patients presenting with renal dysfunction. There was only one longitudinal measurement included in this cohort. Volumetric measurements of kidney dimensions should be included in future research. Further investigations should examine the relevance of kidney size variations, in particular when using kidney volume

measurements in patients presenting with renal dysfunction. This method can clarify the possible diagnostic and prognostic value of kidney volume measurements in the context of renal pathology.

5.3.2 Kidney size, kidney echogenicity and renal cortical thickness in participants with renal dysfunction

Most participants in this study who presented with renal dysfunction demonstrated normal kidney cortical thickness (99%) and normal kidney sizes (92%) on their ultrasound examinations. Regarding kidney echogenicity, 31% of the participants showed normal echogenicity, whereas 69% showed increased echogenicity (hyperechoic in comparison to the liver and spleen) of the kidneys.

Consistent with findings in our study, Sidappa et al. (2013) found that, on ultrasound, kidney echogenicity and its grading correlated more strongly with serum creatinine in patients with CKD when compared to parameters such as kidney size and cortical thickness. These findings suggested that kidney echogenicity was a potential clinically significant diagnostic marker in patients with CKD. In another cross-sectional study by Bwemelo et al. (2019) comprising 145 patients diagnosed with CKD using the National Kidney Foundation's standards, the findings demonstrated a significant association between renal echogenicity and renal function, with a p-value < 0.001 and a large correlation coefficient of $r^2 = 0.622$. Furthermore, the positive likelihood ratio ($+11.6$; $p < 0.001$) confirmed kidney echogenicity diagnostic value in CKD patients in correlation with GFR. These findings highlighted the potential of renal echogenicity as a useful diagnostic tool for evaluating renal function.

In the study by Hanamura and colleagues (2012), with the aim to assess the value of the RRI as a predictive factor and non-invasive predictor of renal histological damage carried out on 202 patients with CKD, the study demonstrated that the RRI measured was the best marker of CKD and showed good correlations with renal function and histological damage scores.

5.4 Limitations of the study

This study had limitations related to various factors and challenges.

It was challenging to accurately determine the renal resistive index (RRI), especially in older patients and those with increased body mass indices (BMIs). As explained by Brahee et al. (2013) the position of adipose tissue becomes problematic when imaging the abdomen with ultrasound particularly when it is thickest over the area of interest, as fat may attenuate with ultrasound beam and reduce the quality of the image.

Assessment and sampling of intrarenal arteries in kidneys displaying morphological or atrophic alterations posed significant challenges. In kidneys with atrophic changes, the

arteries may be smaller and more difficult to visualise, making sampling of these arteries challenging and almost impossible.

Additionally, patients often had trouble holding their breath during long periods of time during the ultrasound exams, most likely due to the condition of the patients who find it difficult to breathe.

Clinical situations, including cardiac arrhythmias and cerebrovascular accidents (CVAs), confounded the measurement of RRI. Moreover, assessment and sampling of intrarenal arteries in kidneys displaying morphological or atrophic alterations posed significant challenges. Sveceny et al. (2022) explain that renal microcirculation is evaluated by the RRI in response to various diseases. Furthermore, a number of hemodynamic renal and extrarenal variables affect the measurement of RRI. The most significant extrarenal values are found in arterial vascular compliance, cardiac function and systolic and diastolic blood pressure. The most significant renal factors are capillary wedge pressure, interstitial pressure and venous pressure.

5.5 Conclusion

In conclusion, in tour cohort of participants presenting with renal dysfunction according to biochemical markers it was noted that irrespective of age, there was a raised RRI noted on their ultrasound examinations. Despite the different clinical indications, participants demonstrated a raised RRI on ultrasound. Using biomarkers to confirm renal dysfunction, all participants presenting with renal dysfunction demonstrated on ultrasound a raised RRI indicating a consistent relationship between renal dysfunction and a raised RRI. The raised RRI was a common trait amongst all these participants. It highlighted the potential use of RRI as a ultrasound marker for renal dysfunction in this population. This study demonstrated a significant association between the RRI and the clinical and biochemical markers of renal dysfunction in these participants. This study's findings also offer convincing evidence of the intricate interactions between renal dysfunction, renal resistive index (RRI), and numerous morphological and textural features of the kidneys in the cohort under study. The relationship between the Renal Resistive Index (RRI) and the clinical and biochemical markers of renal dysfunction in adult participants is highlighted in this cohort.

The objectives of this study were met as a comprehensive analysis of the renal ultrasound findings and their association with biochemical markers of renal dysfunction was provided. Grey scale imaging and Doppler ultrasound were utilized to evaluate the renal morphology and vascular dynamics.

These results highlight how crucial it is to combine biochemical testing with grey scale and Doppler ultrasound imaging in order to improve the early identification of renal dysfunction.

The study advances clinical guidelines for renal assessment and improves diagnostic accuracy by demonstrating the usefulness of ultrasound imaging modalities.
Further investigation in this field is expected to increase knowledge of renal pathophysiology, and to open the door to more specialized diagnostic and treatment strategies for renal illnesses in South Africa.

5.6 Recommendations for future studies

This study demonstrated a significant association between the renal resistive indices and biochemical evidence of renal dysfunction. Future studies with a larger diverse cohort of patients are needed to confirm these findings and determine whether renal ultrasound examinations should be part of the early treatment pathway in patients' presenting with renal dysfunction.

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APPENDICES

Appendix A: Patient Informed Consent (English, Afrikaans, Zulu and Xhosa)

Study Title: *The significance of Renal Resistive Index as a non-invasive marker in renal dysfunction.*

Principal Investigator : Naazneen Ebrahim (MSc Radiography student)

Supervisors: Dr M Kemp (Principal Supervisor)

Ms F Isaacs (External Supervisor)

I, [.....NAME OF PATIENT] agrees to participate in the research study I have read and understand the information leaflet.

I also grant permission to extend to publication of the information in all media and languages worldwide. I will be free to withdraw from participation in the study at any time with no adverse consequences. My personal information will be kept confidential at all times

SIGNATURE OF PATIENT _____

SIGNATURE OF HEALTH PROFESSIONAL OBTAINING PERMISSION _____

DATE _____

For any queries please feel free to contact

Ms Naazneen Ebrahim (Researcher) on (011)488 4007. Dr Merlisa Kemp (Supervisor) on (021) 959 6538 KempMe@cput.ac.za

HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE

Secretary – Research Ethics Committee

Health and Wellness Sciences, Bellville Campus, CPUT.

Mr. Nomathemba “Thembi” Seth

sethn@cput.ac.za

Thank you.

Principal Investigator Naazneen Ebrahim

Phone: 021 959 6917

PASIËNTTOESTEMMINGSVORM (AFRIKAANS)

Studietitel: *The significance of Renal Resistive Index as a non-invasive marker in renal dysfunction*

Hoofnavorser: Naazneen Ebrahim (MSc Radiografie-student)

Studieleiers: Dr M Kemp (Hoofstudieleier)

Me F Isaacs (Eksterne studieleier)

Ek, ..., stem in om deel te neem aan die navorsingstudie waarvan ek in die inligtingsblad gelees het.

Ek gee ook toestemming vir die publikasie van die inligting in alle media en tale wêreldwyd.

Dit staan my vry om te eniger tyd aan die studie te onttrek sonder enige nadelige gevolge vir my.

My persoonlike inligting sal te alle tye vertroulik gehou word.

Pasiënt se handtekening _____

Gesondheidswerker se handtekening _____

Datum _____

Vir enige navrae kontak asseblief:

Me Naazneen Ebrahim (Navorser) by 011 488 4007 of Dr Merlisa Kemp (Studieleier) by 021 959 6538

E-posadres: KempMe@cput.ac.za

GESONDHEIDS- EN WELSTANDSWETENSKAPPE SE ETIEKKOMITEE

Sekretaresse – Navorsingsetiekkomitee

Gesondheids- en Welstandswetenskappe

Bellville-kampus, KSUT

Me. Nomathemba “Thembi” Seth

E-pos: sethn@cput.ac.za

Dankie.

Hoofnavorser Naazneen Ebrahim

Telefoon: 021 959 6917

IMVUME ENOLWAZI KWESIGULI (ZULU) IMVUME ENOLWAZI KWESIGULI (ZULU)

Study Title: The significance of Renal Resistive Index as a non-invasive marker in renal dysfunction.

Principal Investigator : Naazneen Ebrahim (MSc Radiography student)

Supervisors: Dr M Kemp (Principal Supervisor)

Ms F Isaacs (External Supervisor)

Mina [.....] Ngiyavuma ukubamba iqhaza ocwaningweni engifunde ngalo epheshaneni lolwazi.

Ngiphinde nginikeze imvume yokudlula ekushicililweni kolwazi kuyo yonke imithombo yezindaba nezilimi emhlabeni wonke.

Ngizokhululeka ukuthi ngihoxe ekubambeni iqhaza ocwaningweni nganoma yisiphi isikhathi ngaphandle kwemiphumela emibi.

Imininingwane yami yomuntu siqu izogcinwa iyimfihlo ngaso sonke isikhath

Isignesha yesiguli _____

Isignesha yochwepheshe bezempilo/ udokotela _____

Usuka _____

Nganoma yimiphi imibuzo ngicela ukhululeke ukuxhumana nomphathi wami. Ms Naazneen Ebrahim (Researcher) on (011)488 4007.

Dr Merlisa Kemp (Supervisor) on (021) 959 6538

KempMe@cput.ac.za

HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE

Secretary – Research Ethics Committee

Health and Wellness Sciences

Bellville Campus, CPUT

Mr Nomathemba: sethn@cput.ac.za

Ngiyabonga Principal Investigator Naazneen Ebrahim

Phone: 021 959 6917

IMVUME ENOLWAZI NGESIGULANA (XHOSA)

Study Title: *The significance of Renal Resistive Index as a non-invasive marker in renal dysfunction*.

Principal Investigator : Naazneen Ebrahim (MSc Radiography student)

Supervisors: Dr M Kemp (Principal Supervisor)

Ms F Isaacs (External Supervisor)

Mna, [.....] Ngiyavuma ukuthatha inxaxheba kuphononongo lophando endifunde ngalo kwiphetshana lolwazi.

Ndikwanika imvume yokwandisa ulwazi kuwo onke amajelo eendaba neelwimi kwihlabathi liphela.

Ndiza kukhululeka ukuba ndirhoxe ekuthatheni inxaxheba kuphononongo nangaliphi na ixesha ngaphandle kweziphumo ezibi.

Ulwazi lwam lobuqu luya kugcinwa luyimfihlo ngamaxesha onke

Utyikityo lwesigulane _____

Utyikityo lwengcali yezempilo/ ugqhirha _____

Umhla _____

Ngayo nayiphi na imibuzo nceda uqhagamshelane nomphathi wam

For any queries please feel free to contact

Ms Naazneen Ebrahim (Researcher) on (011)488 4007. Dr Merlisa Kemp (Supervisor) on (021) 959 6538. KempMe@cput.ac.za

HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE

Secretary – Research Ethics Committee

Health and Wellness Sciences

Bellville Campus, CPUT

MrNomathemba “Thembi” Seth sethn@cput.ac.za

Enkosi

Principal Investigator Naazneen Ebrahim

Phone: 021 959 6917

Appendix B: Written permission from HOD of tertiary hospital in Johannesburg, Gauteng

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOPITAL

Enquiries: Ms. FM Mahlobo
Telephone: (011 488 4007)
Email: Florence.mahlobo@gauteng.gov.za
Alt email: fmmahlobo@gmail.com
Ultrasound Department
CMJAH
20 September 2022

To: Whom It May Concern
Dear Sir/Madam

Re: Research for Ms. Naazneen Ebrahim on …….
The ultrasound department will be able to assist Ms. Naazneen Ebrahim on the research subject above.
Ultrasound Management will ensure that service delivery is not compromised during the research study.

Mahlobo 20 September 2022

Ms. FM Mahlobo Date
AD Ultrasound

Appendix C: Ethical Approval

HEALTH AND WELLNESS SCIENCES RESEARCH ETHICS COMMITTEE (HWS-REC)

Registration Number NHREC: REC- 230408-014

P.O. Box 1906 • Bellville 7535 South Africa Symphony Road Bellville 7535

Tel: +27 21 959 6917

Email: sethn@cput.ac.za

Faculty of Health and Wellness Sciences Dear Ms Naazneen Ebrahim

10 November 2022

REC Approval Reference No: CPUT/HWS-REC 2022/H23

Re: APPLICATION TO THE HWS-REC FOR ETHICS CLEARANCE

Approval was granted by the Health and Wellness Sciences-REC to **Ms**. **Naazneen Ebrahim** for ethical clearance. This approval is for research activities related to research for **Ms. Naazneen Ebrahim** at Cape Peninsula University of Technology.

TITLE: The significance of Renal Resistive Index (RI) as a non-invasive marker in renal dysfunction

Supervisor: Dr Merlisa Kemp and Ms Ferial Isaacs

Comment: **Approval will not extend beyond 11 November 2023.** An extension should be applied for 6 weeks before this expiry date should data collection and use/analysis of data, information and/or samples for this study continue beyond this date.

The investigator(s) should understand the ethical conditions under which they are authorized to carry out this study and they should be compliant to these conditions. It is required that the investigator(s) complete an **annual progress report** that should be submitted to the HWS-REC in December of that particular year, for the HWS-REC to be kept informed of the progress and of any problems you may have encountered.

Kind Regards

Ms Carolynn Lackay

Chairperson – Research Ethics Committee Faculty of Health and Wellness Sciences