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2017

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RENAL DYSFUNCTION AND HEART FAILURE - CARDIORENAL SYNDROME: A Retrospective Study at Charlotte Maxeke Johannesburg Academic Hospital

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A Research report submitted to the Faculty of Health Sciences, Department of Internal Medicine, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the Degree of Master of Medicine in the Division of Cardiology.

DECLARATION

This research report is my own work and is submitted as part of my Degree of Master of Medicine. It has not previously been submitted to any institution or authority.

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Don Zachariah

ABSTRACT

RENAL DYSFUNCTION WITH HEART FAILURE: CARDIORENAL SYNDROME

A Retrospective study at Charlotte Maxeke Johannesburg Academic Hospital

INTRODUCTION

The field of medicine has been challenged by the dual epidemic of heart failure and renal insufficiency. There is an increasing need to identify these patients at an early stage so as to delay progression to renal damage. Furthermore there is a lack of local data assessing the relationship between heart failure and renal dysfunction.

AIMS

- To identify the prevalence of renal dysfunction in patients attending the heart failure clinic at Charlotte Maxeke Johannesburg Academic hospital (Cardiorenal syndrome Type II)
- To evaluate the relationship between severity of heart failure and severity of renal dysfunction
- To compare heart failure with reduced ejection fraction (HFREF) variables between patients with and without renal dysfunction.

METHODOLOGY

This study is a single center retrospective study of patients attending Charlotte Maxeke Johannesburg Academic Hospital Heart Failure Clinic. Heart failure patients included in this study were those with an ejection fraction < 50% as this is an accepted definition for HFREF. Patients with HFREF were analyzed specifically for the following; presence of renal dysfunction, Ejection Fraction (EF), Systolic Blood Pressure (SBP), Diastolic Blood

Pressure (DBP), Haemoglobin (HB), New York Heart Association (NYHA) functional class, furosemide dose , six minute walk test (6MWT) and Minnesota Living with Heart Failure Questionnaire (MLFQ) score .

Presence of renal dysfunction was identified based on the glomerular filtration rate (eGFR) value of less than 60ml/min/1.73m^2 as this is the threshold eGFR below which complications of renal impairment appear. The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) abbreviated formula:

(186.3 X serum creatinine) $^{-1.154}$ x (age) $^{-0.203}$ x (0.742 if female) x (1.212 if African)

The control group consisted of patients attending the clinic who did not have renal dysfunction.

RESULTS

A total 242 files were reviewed. Forty-two files were excluded from the study due to lack of adequate study data recorded in the file. Data was collected and entered into a database, which was analyzed using the Statistics/Data Analysis Program (STATA) Version 10.0.

The mean age of the study group was 53.3 years (SD± 15.05) with the youngest subject being 21 years old and the oldest subject aged 85 years. The mean SBP was 119mmHg and the mean DBP was 75mmHg.

The mean eGFR was 72.01 ml/min/1.73m^2. The overall prevalence of low eGFR (<60ml/min/1.73m^2) in the sample population was 34.5 %. The prevalence in female and male patients with a low eGFR was 35% and 33.6% respectively.

Analysis of MLFQ, 6MWT, DBP and age yielded a positive correlation with eGFR, which was statically significant ($p<0.05$). An insignificant correlation was obtained comparing eGFR with SBP ($p=0.07$), EF ($p=0.69$) and HB ($p=0.79$).

The Analysis of Variance Test (ANOVA), showed a significant correlation between eGFR values across the different NYHA functional classes (p 0.012). Thus it was found that the higher the NYHA class (clinically worse) was associated with worse renal function. The mean eGFR for NYHA I was 77.05 ml/min/1.73m^2, for NYHA II was 70.61 ml/min/1.73m^2, for NYHA III was 64.13 ml/min/1.73m^2 and NYHA IV was 50.02 ml/min/1.73m^2.

DISCUSSION

The overall prevalence of low eGFR (<60ml/min/1.73m^2) in this study was 34.5%, a finding consistent with international trials. The majority of patients in this study were in NYHA functional class I or II, thereby highlighting the fact that renal dysfunction is common in heart failure patients and starts early.

Statistically significant values were also obtained between eGFR and 6MWT, MLFQ, furosemide dose, age and DBP. The patients with higher 6MWT have better effort tolerance, thereby classifying their heart failure as milder. This in effect confirms that higher eGFR patients have higher effort tolerance. Higher MLFQ scores and higher furosemide doses are inversely correlated to eGFR. The more subjective symptoms you have, and the higher doses of furosemide you need, is a reflection of the severity of the heart failure. With regards to age, there is a normal physiological decline in eGFR with increasing age.

In this study a statistically significant negative correlation between eGFR and NYHA was found. Thus a higher NYHA class is associated with worse renal function. This suggests that the clinically more advanced the patient, the poorer the renal function.

Also, the prevalence of low eGFR (<60ml/min/1.73m^2) within each NYHA class, as expected, increased with increasing NYHA class. It was 27% for NYHA I, 38% for NYHA II, 40% for III, while class IV had 80% of low eGFR prevalence

CONCLUSION

The findings of this study confirm that the cardio-renal syndrome is common in a local cohort of heart failure patients. The study also suggests that renal dysfunction starts in the early stages of heart failure (NYHA I/II) and becomes more prevalent in patients with more advanced stages of heart failure. These findings highlight the need to treat heart failure patients early after presentation and more appropriately if we are to decrease complications such as renal dysfunction, thereby improving morbidity and mortality.

PREFACE

The Research Committee on Human Subjects, University of the Witwatersrand, approved this study.

Ethics Clearance Certificate No: M140254

ACKNOWLEDGEMENTS

To my supervisor Professor P. Manga, thank you for your effortless support and guidance. You are a true inspiration.

LIST OF ABBREVIATIONS

µg/L : micrograms per liter

g/dl : grams per deciliter

mg : milligrams

6MWT : Six minute walk test

ACE : Angiotensin Converting Enzyme

ACE-I : Angiotensin Converting Enzyme Inhibitor

ADHF : Acute Decompensated Heart Failure

ANOVA : Analysis of Variance Test

ARB : Angiotensin Receptor Blocker

CCF : Congestive Heart Failure

CKD : Chronic Kidney Disease

DBP : Diastolic Blood Pressure

EF : Ejection Fraction

eGFR : Estimated Glomerular Filtration Rate

HB : Haemoglobin

HF : Heart Failure

HFREF : Heart Failure with Reduced Ejection Fraction

HFPEF : Heart Failure with Preserved Ejection Fraction

MLFQ : Minnesota living With Heart Failure Questionnaire

MRA : Mineralocorticoid Receptor Blocker

N : Total Number

No. : Number

NYHA : New York Heart Association

SBP : Systolic Blood Pressure

SNS : Sympathetic Nervous System

SD : Standard Deviation

STATA : Statistics/ Data Analysis Program

WHO : World Health Organization

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Chapter 1: LITERATURE REVIEW

1.1 Background

Heart failure remains the main cause of hospitalization in patients aged more than 65 years.[1] Chronic Heart Failure (CHF) is a challenging condition to treat as the quality of life is severely affected. Despite great advances in the medical and device therapy of CHF secondary to left ventricular systolic dysfunction, life expectancy remains reduced with a significant impact on quality of life .The latter is a reflection not just of the poor exercise reserve but also of the co-morbidities that are associated with CHF such as renal dysfunction, anaemia, arrhythmias and sleep apnea. The coexistence of renal dysfunction and heart failure in the same patient is referred to as " Cardio-renal Syndrome" and this has an extremely poor prognosis.[2]

Definitions

Cardio-renal syndrome (CRS)

There is no single definition that describes CRS. The term CRS has generally been reserved for the decline of renal function in the setting of advanced heart failure. Several definitions have been proposed for worsening renal function and these include a 26.5umol/l increase in serum creatinine from baseline, an increase in serum creatinine above a threshold of 221umol/l, a 25% increase in creatinine from baseline, or a combination of these factors.[3, 4]

Ronco et al.[5] recently provided a more detailed classification of chronic renal failure in cardiac patients as follows:

Type 1- Acute Heart Failure resulting in acute kidney injury

Type 2- CHF causing progressive kidney disease

Type 3- Abrupt primary worsening of kidney function causing acute cardiac dysfunction, which manifests as HF (Reno-cardiac Syndrome)

Type 4 - Primary chronic kidney disease contributing to cardiac dysfunction

Type 5 - Systemic disorders causing both cardiac and renal dysfunction

Heart failure

The main terminology used to describe heart failure is based on the left ventricular ejection fraction (EF). Heart failure is now classified into:

{a} Heart failure with preserved EF (HFPEF)

{b} Heart failure with reduced ejection fraction (HFREF)

A normal EF is regarded as an EF above 50%. Severity of heart failure is graded using the New York Heart Association (NYHA) classification:

- NYHA I - no limitation to the physical activity.
- NYHA II - some limitation to the physical activity.
- NYHA III - marked limitation to physical activity.
- NYHA IV – inability to carry out any physical activity without discomfort.

Renal dysfunction

In 2002 the Kidney Disease Outcomes Quality Initiative (KDOQI) classification was published to stage kidney disease based on the kidney function using the glomerular filtration rate (eGFR), irrespective of the diagnosis.

- Stage 1 - eGFR > 90 ml/min/1.73m^2
- Stage 2 - eGFR 60 – 89 ml/min/1.73m^2
- Stage 3 - eGFR 30 – 59 ml/min/1.73m^2
- Stage 4 - eGFR 15 – 29 ml/min/1.73m^2
- Stage 5 - eGFR < 15 ml/min/1.73m^2 (End stage kidney disease)

1.2 Prevalence of renal dysfunction in heart failure

Data from various sources demonstrate that approximately 20%- 40% of patients admitted to hospital for acute decompensated heart failure (ADHF) have associated renal dysfunction and end stage kidney disease.[6] Cowie et al[7] enrolled 248 patients with ADHF across eight European countries. The six-month follow-up showed that about a third of patients developed worsening renal function during their hospitalization.

Another study performed on 1004 patients admitted for a primary diagnosis of HF from 11 different hospitals, showed that worsening renal function developed in 27% of patients which happened within the first three days.[8] This large cohort study demonstrates that worsening renal failure occurs in HF patients and is in associated with adverse outcomes. In this study, association remained strong in old as well as young patients.

1.3 Renal Dysfunction and prognosis in heart failure

Heart failure is a dynamic syndrome that inhibits the ability of the heart to function as a pump to support physiological circulation. Heart failure and kidney function are closely interrelated in health and in disease. Renal function is commonly quantified by serum creatinine levels, or more precisely by estimated glomerular filtration rate (eGFR). Normal renal function is defined as eGFR values greater than 90ml/min/1.73m^2.

Even mildly decreased kidney function has shown to increase the mortality in heart failure patients. Hillege et al, showed a constant risk relationship of a 7 % increase in mortality for every 10ml/min decrease in eGFR.[9] Large heart failure international trials like SOLVD[10,11] have pointed out the degree of renal impairment in heart failure. These studies showed that renal dysfunction occurs early in CHF and will be discussed later.

A retrospective analysis in South Africa by Inglis et al[12], showed that out of the 163 black patients in the study group, only 12% had an eGFR < 60ml/min/1.73m^2. The prevalence in this study was much lower as compared to that found in the SOLVD trials. This could be explained by the average age of the South African cohort being much younger (48 years) and the likelihood of concomitant atherosclerotic disease being lower, as compared to the SOLVD cohort. No other local data assessing renal function in heart failure have been published.

Fonarow GC et al[13] found that the death rates doubled (9.4%) in patients with a serum creatinine level of 265umol/l or more. The Acute Decompensating Heart Failure National Registry (ADHERE) database which reported data over 100 000 patients with heart failure requiring hospitalization, showed the best predictor of outcome included both blood-urea & creatinine[14]. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT)[15], which included patients post myocardial infarction receiving good medical therapy, those with

eGFR lower than median had 1.5 times chance of adverse events such as death or myocardial infarction.

Despite the poor understanding of this complex disease entity, it is evident that coexistent renal dysfunction in the setting of heart failure worsens prognosis, irrespective of the degree of renal impairment.

1.4 Factors contributing to renal dysfunction in heart failure.

There are multiple risk factors for the increased incidence of CRS: older age, diabetes, uncontrolled HTN, anaemia, anti inflammatory drugs, diuretics, angiotensin converting enzyme inhibitors, prior myocardial infection, NYHA functional class, elevated cardiac troponins.

- Reduced renal perfusion is largely thought to be related to decreased cardiac output. However this is not always clinically evident. In the CORONA study[16], an international trial with over 5000 patients, 24% of the entrants had creatinine >130umol/l. The mean eGFR was < 60ml/min/1.73m2, indicating that majority of patients in CORONA would be classified as having at least Stage 3 chronic kidney disease. This is despite the fact that the mean arterial blood pressure was 129/76mmhg and 37% of the entrants were in NYHA FC I-II. This shows that depressed renal function does not appear to be characterized by a low output state as a significant number of these patients present with normal or elevated blood pressure.

- Impaired left ventricular function leads to hemodynamic derangements like low stroke volume and cardiac output, arterial under filling, elevated atrial and venous pressures. These hemodynamic changes trigger a variety of compensatory neuro-hormonal adaptations including activation of the sympathetic nervous system and the renin-

angiotensin-aldosterone system (RAAS) and increase in the release of vasopressin and endothelin-1, which promotes salt and water retention and systemic vasoconstriction. This adaptation contributes to the preservation of perfusion to the vital organs by maintenance of systemic pressure via arterial vasoconstriction in other circulations, including the renal circulation. However systemic constriction increases cardiac afterload, which reduces cardiac output, which further decreases renal perfusion. The most deleterious action of the RAAS in CRS is the activity of angiotensin II, which results in the formation of the reactive oxygen species.[17] Increased NADPH-oxidase activity, has been found in the hearts of patients with end stage HF. When the vicious cycle begins, it causes structural and functional irreparable damage to the heart and kidneys.

- Increased renal venous pressure by virtue of increased abdominal pressure or increased central venous pressure will decrease eGFR.[18]

- Venous congestion is shown to play a role in renal dysfunction in heart failure patients.[19]

- Right Ventricular (RV) dilatation and dysfunction can adversely affect the kidneys through RV dilatation, impairing left ventricular (LV) filling and therefore forward output (Reverse Bernheim phenomenon). [20]

- B-type natriuretic peptide (BNP) effects provide some beneficial effects. It inhibits RAAS, endothelin-1 and other such vasoconstrictors. As the name suggests, it promotes diuresis, enhances sodium excretion and may even increase eGFR.

- Renal dysfunction has been attributed to multiple factors coupled with pharmacological interventions that leads to renal sodium and water retention, which in turn leads to extracellular fluid expansion.[21]

- Excess SNS (sympathetic nervous stimulation) induces cardiac cell apoptosis, hypertrophy and focal myocardial necrosis.[22] It contributes to RAAS activation by directly stimulating renin release. SNS also induces inflammation by noradrenaline mediated cytokine production from the liver and the heart.[23, 24] Imbalance between the RAAS, SNS and inflammation provokes insult to the kidney.

- During a condition of ischemia/ reperfusion damage to the kidneys, hydrogen peroxide formation by the mono amino oxidase enzymes, induce a pro-apoptotic cascade in the proximal tubular cells [25] thereby leading to renal dysfunction.

- Cardio-renal-anaemia syndrome: The interaction between chronic heart failure, chronic kidney insufficiency and anaemia which is termed as the cardio-renal-anaemia syndrome. This syndrome causes a worsening of cardiac and renal function. Reduced cardiac output and renal blood flow worsen renal function. Reduced erythropoietin (EPO) production and reduced erythropoiesis causes anaemia. Anaemia exacerbates heart failure by increasing the heart rate and stroke volume.

TREATMENT OF RENAL DYSFUNCTION IN HEART FAILURE

Patients with co-existing CHF and chronic kidney disease are especially challenging to treat. As mentioned earlier, there are studies linking renal dysfunction and adverse clinical outcomes in HF patients. It is important to note that heart failure treatments also negatively impact the glomerular filtration rate during treatment, which can denote a worse prognosis.[26]

On the other hand, some treatments of heart failure that are thought to decrease eGFR through intra-renal mechanisms reduce rates of mortality and morbidity.[27] Due to the complex nature of treatment, earlier intervention, more frequent monitoring and timely referral are important.

I will briefly review the general approaches currently available and some specific interventions currently proposed or under investigation, with a focus on the concept that heart failure is a progressive condition and that interventions should be guided by disease stage, patient clinical presentation and presence of co-morbidities.

- MAINTAINING EUVOLEMIA. In hypovolemia, GFR can be reduced by the reduction of effective plasma volume and renal hypoperfusion. In contrast, hypervolemic patients may have impaired renal function because of renal venous congestion, reduced renal perfusion pressure or renal compression. Therefore, intense and sudden variations in the plasma volume of patients with decompensated heart failure should be strongly avoided.

- SALT RESTRICTION. There is a paucity of data on the effect of restriction of salt intake in HF patients. Various guidelines advocate salt restriction based on the rationale that salt restriction improves BP control (a major risk factor in HF) and hence improve heart failure management. A registry in Sweden with over 60 000 patients, showed that a low sodium DASH diet reduces the long term rate of incident HF and thereby decreasing concomitant renal disease[38].

- ANGIOTENSIN CONVERTING ENZYME INHIBITORS (ACE-i) and angiotensin receptor blockers (ARB) can decrease filtration pressure within the glomerulus by inducing systemic hypotension and predominant vasodilation of the glomerular efferent arteriole. This manifests as a decrease in eGFR. The safety and efficacy of accepting 'modest' changes in glomerular filtration rate have been shown previously, [54] by illustrating that an acute increase in creatinine of up to 30% that stabilized within the first 2 months of ACE-i therapy was noted to have preservation of renal function in the longer term. Testani et al, [27] demonstrated that not only eGFR itself but also the factors that drive the change in eGFR predict clinical outcomes. Within the SOLVD trial,[11] early reduction in eGFR was associated with increased mortality within the placebo group as opposed to the group on enalapril. It is important to note that this trial excluded patients with creatine levels above 177umol/L as there is no evidence for safety above these levels.

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- BETA BLOCKERS: The influence of beta-blockers on renal function is much less understood. A small study suggested that initiation of beta-blocker therapy was associated with preserved renal function in heart failure patients with a lower baseline GFR but not in those with a higher baseline GFR, although these results are yet to be confirmed.[28]

- STATINS: Data from studies in patients with chronic kidney disease suggest that statins may preserve renal function.[29] In the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study,[30] the effect of atorvastatin administered at a dose 10 to 80 mg/day on renal function was studied. At the end of the study, creatinine clearance had worsened by 12% in the atorvastatin group and 4.9% in the "usual care" group. Additionally, a meta-analysis of 13 prospective trials that evaluated the effect of statins on renal function showed that treatment with statins reduced the decline in GFR with a possible trend towards proteinuria reduction.[31] Even though statins may have a positive influence on renal function of patients with heart failure, its effect on overall prognosis has not yet been thoroughly studied.

- RENAL DENERVATION: Hyperactivation of the SNS is involved in the pathophysiology of hypertension, renal insufficiency and heart failure. Devices have been developed for ablation of the renal sympathetic nerves by radiofrequency-emitting catheter that are inserted percutaneously through the femoral artery and then advanced to the renal artery. Renal function as assessed by serum creatinine, eGFR and cystatin C concentrations were not remarkably changed from baseline. There are ongoing trials are investigating the safety and efficacy of renal denervation in patients with CHF, and its application as a preventive measure for renal dysfunction remains speculative.[32]

- LOW DOSE DOPAMINE: IN ADHF, the infusion of low-dose dopamine has been shown to induce renal vasodilation and natriuresis mediated by "the stimulation of the dopamine alpha-1 and alpha-2 receptors in the proximal tubule, the thick ascending loop of Henle and the cortical collecting ducts".[33] In a meta-analysis of 61 trials that had patients at risk for acute renal failure to receive low-dose dopamine or placebo, dopamine was associated with a 24% increase in urine output, 4% relative decrease in serum creatinine

level and 6% relative increase in measured creatinine clearance.[34] In patients with systolic heart failure, low-dose dopamine has also been demonstrated to increase renal blood flow and GFR. In a clinical trial of patients with acute decompensated heart failure, the combination of infused low-dose furosemide and low-dose dopamine was found to be as effective as a high-dose furosemide infusion in terms of the clinical and diuretic response. Furthermore this combination was associated with a significantly lower rate of worsening renal function, suggesting a reno-protective effect in this patient population.[35]

- DIURETICS: Concerns regarding diuretic use involve ototoxicity, hypocalcaemia and diuretic-induced hypovolemia. These conditions become particularly important in the setting of ADHF because of the presence of hypotension, right ventricular failure and elevated intra-abdominal pressure as well as use of high diuretic doses. Thus, a reno-protective strategy could potentially be derived from the continuous infusion of smaller doses of a diuretic. However one recent clinical trial has shown that there is no significant difference in renal function when furosemide was given by bolus or by continuous infusion.[53]

In conclusion, the role of beta-blockers, angiotensin converting enzyme inhibitors (ACE-i), angiotensin receptor blocker (ARB) and mineralocorticoid receptor antagonist (MRA) are well established in CHF. There is increasing body of evidence to show both renal and cardiac benefits of ACE-I and ARB therapy blocker in CKD. However, a lot more focus needs be placed on clarifying the pathways through which agents influence renal function and the effects thereof on overall prognosis.

Chapter 2: STUDY DETAILS

2.1 Aims and Objectives

- To define the prevalence of co-morbid renal dysfunction in patients attending the heart failure clinic at Charlotte Maxeke Johannesburg Academic Hospital.
- To evaluate the relationship between the severity of heart failure and severity of renal dysfunction.
- To compare HFREF variables between patients with and without renal dysfunction.
- To determine the etiology of heart failure in patients attending the heart failure clinic at Charlotte Maxeke Johannesburg Academic Hospital.

2.2 Study Design and Methodology

The study is a single center retrospective study of patients attending the Charlotte Maxeke Johannesburg Academic Hospital Heart Failure Clinic. The patient files were analyzed specifically for presence of renal dysfunction, ejection fraction, blood pressure, NYHA functional class, furosemide dose, six-minute walk test duration and The Minnesota Living with Heart Failure Questionnaire score.

Heart failure patients included in the study are those with Ejection Fraction < 50% as this is the inclusion requirement for patients to be at followed up at the Heart failure Clinic at Charlotte Maxeke Academic Hospital.

The presence of probable renal dysfunction in this study was defined as a threshold of <60ml/min/1.73m^2, as this is the threshold below which complications of renal impairment appear[18].

The eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) abbreviated formula, which is:

(186.3 x serum creatinine) $^{-1.154}$ x (age)$^{-0.203}$ x (0.742 if female) x (1.212 if African)

The control group consisted of participants attending the clinic who did not have renal dysfunction.

The two groups were compared using:

- Six minute walk test
- Participant's symptom scores; using the Minnesota Living with Heart Failure Questionnaire (MLHFQ - Appendix I).
- Ejection Fraction
- Blood Pressure
- eGFR
- Dose of Furosemide
- ACE inhibitor use
- New York Heart Association (NYHA) functional class

2.2.1 Objective Assessment Measures

A] The Minnesota Living with Heart Failure Questionnaire (MLHFQ)

The MLFQ consists of 21 questions, which measure the effects of heart failure and its treatment on an individual's quality of life. The MLHFQ incorporates key physical, emotional, social and psychological dimensions of quality of life. The answer for each

question is assigned a numerical score from 0 to 5. The total score may vary from 0 – 105, with lower scores reflecting fewer heart failure symptoms and improved quality of life. The questionnaire has been validated[57] and is the questionnaire being used at the heart failure clinic at Charlotte Maxeke Johannesburg Academic Hospital.

B] The six-minute walk test

The six-minute walk test was originally designed to test exercise tolerance in chronic respiratory or cardiac disease. Recently it has been used as a performance-based measure that assesses the functional exercise capacity. The six-minute walk test (6MWT) measures the maximum distance in meters that an individual is able to walk in six minutes, without supplementary oxygen, on a hard and flat surface. The test is simple to perform, requires inexpensive equipment, is safe and is fairly reproducible provided it is well standardized. The individual can walk at his or her own pace, resting intermittently if necessary for a total of six minutes. The 6MWT can be used to detect changes following therapeutic interventions and predict hospitalization and mortality. A lower score (reflecting less distance covered in 6 minutes) shows a worse functional assessment. The normal distance in healthy adults ranges from 400m to 700m. Walking less than 300 m during the 6MWT is shown to be a prognostic marker of cardiac death in patients with mild-to-moderate heart failure. [21]

C] Ejection fraction (EF)

Ejection Fraction represents the volumetric fraction of the blood that is pumped out of the ventricle with each cardiac cycle. Imaging via echocardiography allows meaningful mathematical expression of defining EF. In a healthy 70kg individual the typical EF is between 50-65%. Damage to the myocardium from whatever cause will result in a fall in

the contractile function of the heart and thus there will be a concomitant fall in EF. By definition HFREF the ejection fraction is less than 50%.

D] Blood Pressure

Blood Pressure is determined by the amount of blood pumped by the heart as well as taking into account the resistance to blood flow in the arteries. The more blood the heart pumps and the narrower the arteries, the higher the Blood Pressure.

E] Estimated GFR

According to the National Kidney Foundation practice guidelines, glomerular filtration is the best measurement to assess renal function. eGFR is a marker of the amount of the glomerular filtrate formed each minute in the nephrons of both kidneys which is measured by the rate of clearance of creatinine. The presence of kidney disease will lower the eGFR. There are five stages of chronic kidney disease as stated earlier.

F] Furosemide

Furosemide is used in patients with congestive cardiac failure to enhance urinary sodium excretion, thereby maintaining euvolemia and improving heart failure symptoms. The dosage of Furosemide required to minimize symptoms can be used as an indicator of the severity of heart failure.

G] ACE inhibitors

ACEi block the conversion of angiotensin I to angiotensin II, thereby lowering arteriolar resistance. The effects of this can lead to lower resistance in blood vessels in the kidneys which leads to improved natriuresis. Further advantages include its ability to decrease

plasma norepinephrine levels, thus breaking the deleterious circle of sympathetic and renin angiotensin system activation, and thereby causing the downward spiral in cardiac function in congestive heart failure.

H] The New York Heart Association (NYHA) classification

NYHA classification grades the severity of heart failure symptoms into four functional classes; NYHA I being mild heart failure symptoms and NYHA IV being severe. It is widely used in clinical practice and research as it provides a standardization of the severity of HF and response to treatment.

2.2.2 Inclusion Criteria

Patients diagnosed with systolic heart failure, HFREF, (EF < 50%), attending the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital.

2.2.3 Exclusion Criteria:

- Incomplete or missing data recorded in files.
- Co-morbid respiratory disease.

2.2.4 Limitations of the study

English is often not the first language of our patient group. Therefore the Minnesota Living with Heart Failure Questionnaire (MLHFQ) may not be accurately completed. Disadvantages of a retrospective analysis such as poor record keeping are unavoidable.

2.2.5 Strengths of this study include:

A highly experienced heart failure study team, headed by two senior cardiologists, that has been consistent for many years reviewed all the patients. The blood results are obtained from the same laboratory (National Health Laboratory Service – NHLS).

2.2.6 Statistical analysis

Data was collected and entered into a database using Microsoft Office Excel 2011. The data was analyzed using the Statistics/Data Analysis Program (STATA) Version 10.0.

A] Prevalence

Prevalence was calculated using the number of renal dysfunction patients divided by the total number of patients included in the study – the ratio was multiplied by 100 and expressed as a percentage.

B] MLFQ, 6MWT, Furosemide Dose, SBP, DBP, Haemoglobin with eGFR correlation

The relationship between the variables listed above, were analyzed using the pairwise correlation statistical test.

C] NYHA and eGFR

The relationship between NYHA functional class and eGFR concentration was assessed using the Analysis of Variance test (ANOVA).

CHAPTER 3: RESULTS

A total 242 files were reviewed from the Heart Failure Clinic at Charlotte Maxeke Johannesburg Academic Hospital. Forty-two files were excluded from the study due to lack of study data recorded in the file.

3.1 DEMOGRAPHICS

3.1.1 Patient Demographics

The study group comprised of 104 (52%) males and 96 (48%) females. The mean age of the study group was 53.1 years. The youngest subject was aged 21 years old and the oldest subject was aged 85 years old. The mean age for males was 57.09 and the mean age of females was 48.71.

NUMBER	
total number of patients	**200**
GENDER	
Males	**104**
Females	**96**
AGE	
Range	**21 - 85**
Mean +/- SD	**53.06**

Median	**55.5**
Male mean +/- SD	**57.08**
Female mean +/- SD	**48.70**
SD of age	**15.13**

Table 1: Patient demographics

3.1.2 eGFR

The mean eGFR recorded was 72.01ml/min/1.73m^2. The mean eGFR in male subjects was 72.30ml/min/1.73m^2 and in female subjects was mean 71.70ml/min/1.73m^2. The overall prevalence of low eGFR (< 60ml/min/1.73m^2) in the sample population was 34.5%. The male prevalence for low eGFR was found to be 17.5%(35 males) and in females 17% (34 females).

	eGFR <60
Female	**34**
Male	**35**
Total	**69**
Percentage	**34.5%**

Table 2: Sex prevalence of low eGFR

3.1.3 New York Heart Association Class

There were 85 patients with NYHA class I, 85 patients with class II, 25 patients with class III and 5 patients with class IV.

NYHA I	85 (42.5%)
NYHA II	85 (42.5%)

NYHA III	25 (12.5%)
NYHA IV	5 (2.5%

Table 3: Patients Percentage in NYHA class

Based on the 69 patients that had low eGFR (<60ml/min/1.73m^2), 23 patients were in NYHA class I, 32patients were in NYHA class II, 10 patients were in class III and the remaining 4patients were in class IV. Majority of the patients in the study belonged to NYHA class I and II. The prevalence of low eGFR within each class is tabulated as follows:

Prevalence of low eGFR (<60%) within each NYHA class	
NYHA I	**23 (27%)**
NYHA II	**32 (38%)**
NYHA III	**10 (40%)**
NYHA IV	**4 (80%)**

Table 4: Prevalance of low eGFR in different NYHA class

3.1.4 Haemoglobin

The mean Hb in the study population was 13.19g/dl . The overall prevalence of anaemia in the sample population was 19.5 % (39 patients) with male and female prevalence of 21.1% and 17.7% respectively.

	Number	**Percentage**
Anemic Males	22	21.1%
Anemic Females	17	17.7%
Total Anemic patients	39	19.5%

Table 5: Prevelance of Anaemia

3.5 Analysis of Minnesota Score/ Six-minute walk test/ Ejection Fraction/ Systolic Blood Pressure/ Diastolic Blood Pressure / Furosemide dose

The mean Minnesota Score was 35.62 (SD ±26.66) and the median was 28. Evaluation of the 6MWT found a mean of 383.25 meters (SD ± 98.3) and a median of 400 meters. The mean furosemide dose was 61.60mg (SD ± 48.74) and the median was 118.

PARAMETER	RESULTS
Minnesota score	
Mean ±SD	**35.62 (SD ±26.66)**
Median	**28**
6 Minute Walk Test (meters)	
Mean ±SD	**383.25 (SD ± 98.3)**
Median	**400**
Ejection fraction	
Mean	**27.76**
Median	**26.50**
SBP	
Mean	**119.12**
Median	**118**
DBP	

PARAMETER	RESULTS
Mean	**75.91**
Median	**75**
Furosemide dose (mg)	
Mean ± SD	**61.60 (SD ± 48.74)**
Median	**118**

Table 6: Mean/Median valves of Minnesota score, six-minute walk test, Ejection fraction, Systolic Blood Pressure, Diastolic Blood Pressure, Furosemide dose.

3.3 Pairwise correlation of variables with estimated GFR

	n	R value	P value
MLFQ	196	-0.179	0.012
6MWT	183	0.222	0.003
Furosemide	161	-0.218	0.006
SBP	200	0.127	0.072
DBP	200	0.156	0.027
EF	200	0.028	0.698
HB	200	-0.019	0.794
AGE	200	-0.422	0.000

Table 7: Pairwise correlation with regards to eGFR

The study found that the MLFQ, 6MW, Furosemide, DBP and Age were significantly correlated to eGFR. On the other hand SBP, EF and HB did not show any correlation to eGFR. The graphs for the individual correlations are shown below.

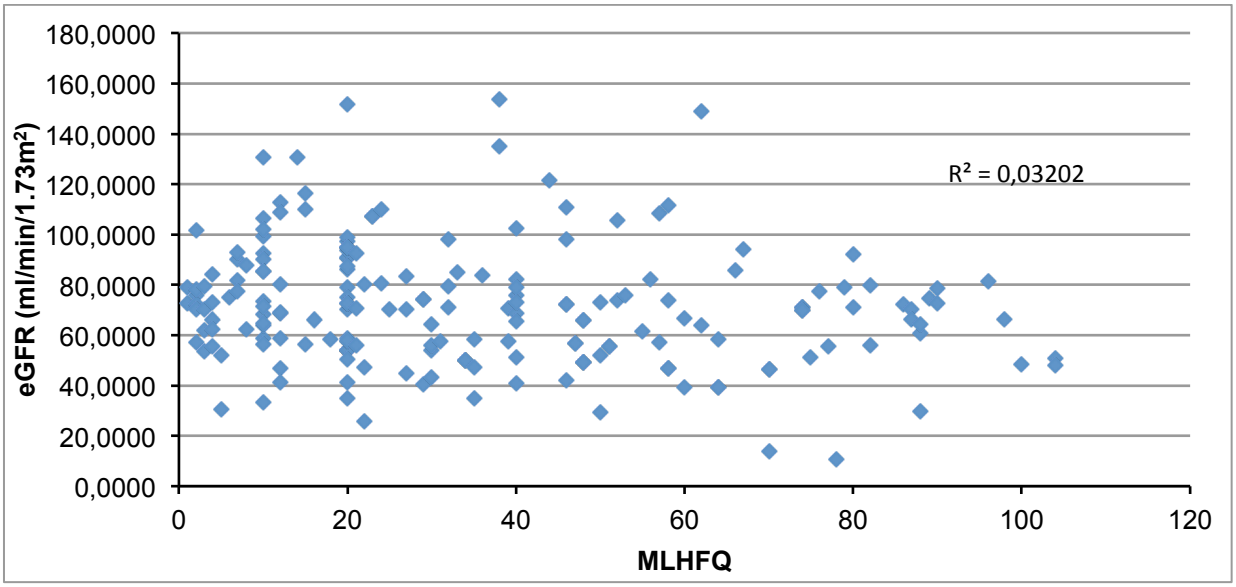


Figure 1: Correlation between eGFR and Minnesota Living with Heart Failure Questionnaire

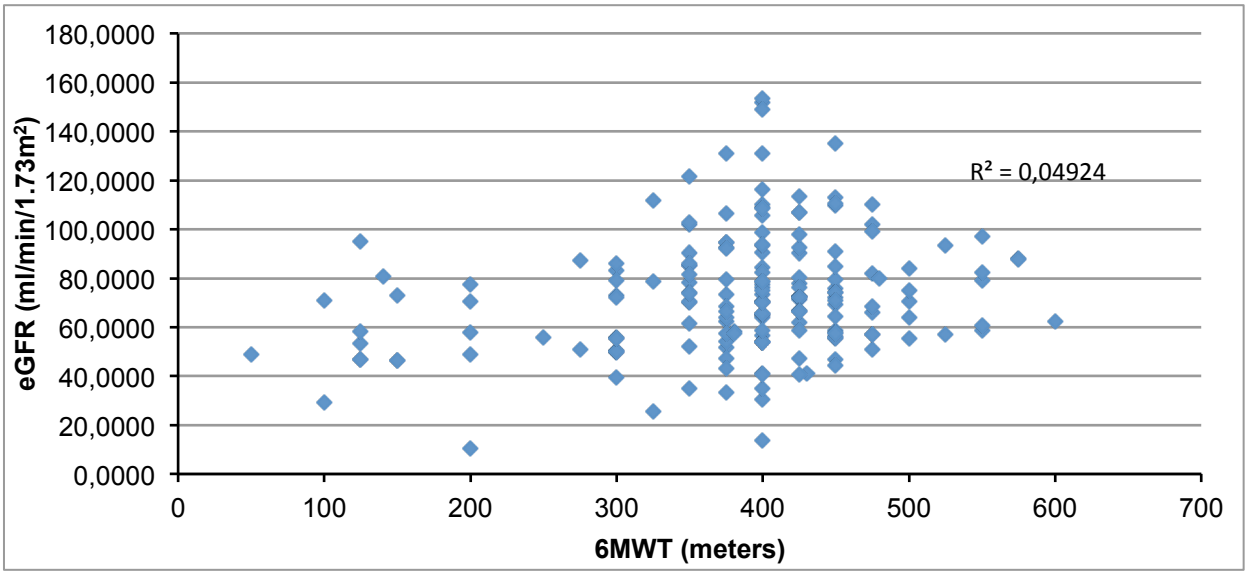


Figure 2: Correlation between eGFR and six-minute walk test

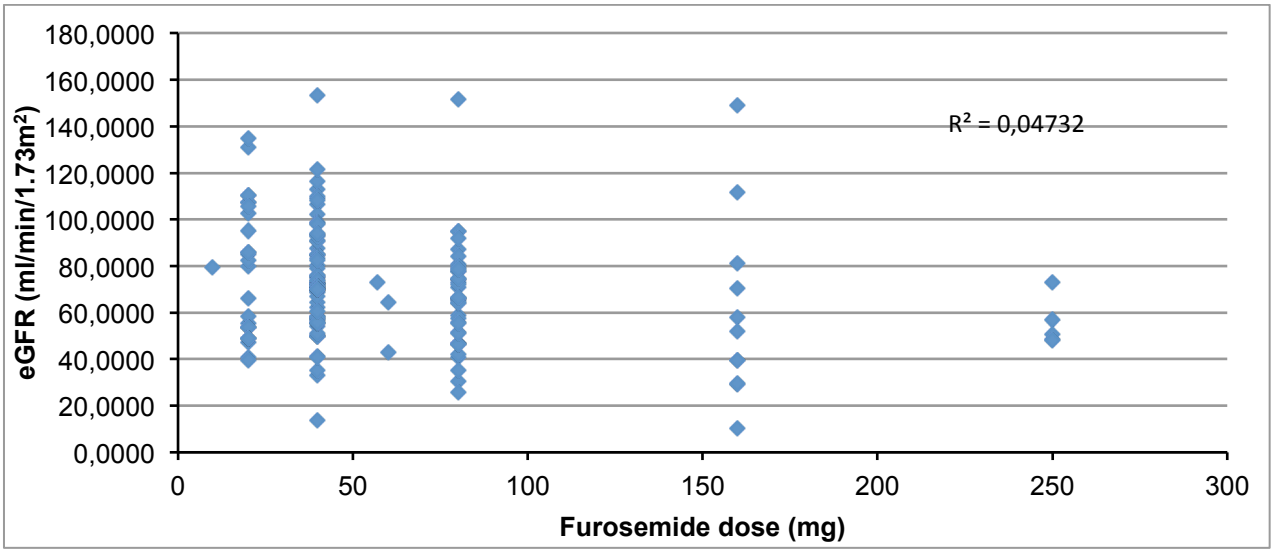


Figure 3: Correlation between eGFR and Furosemide dose

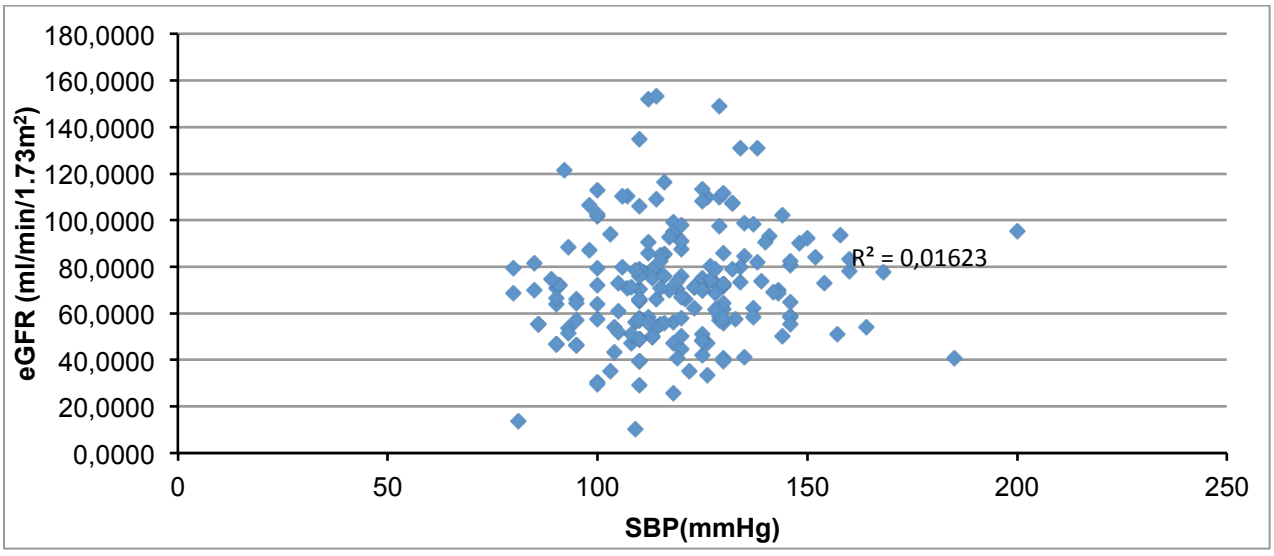


Figure 4: Correlation between eGFR and Systolic Blood Pressure

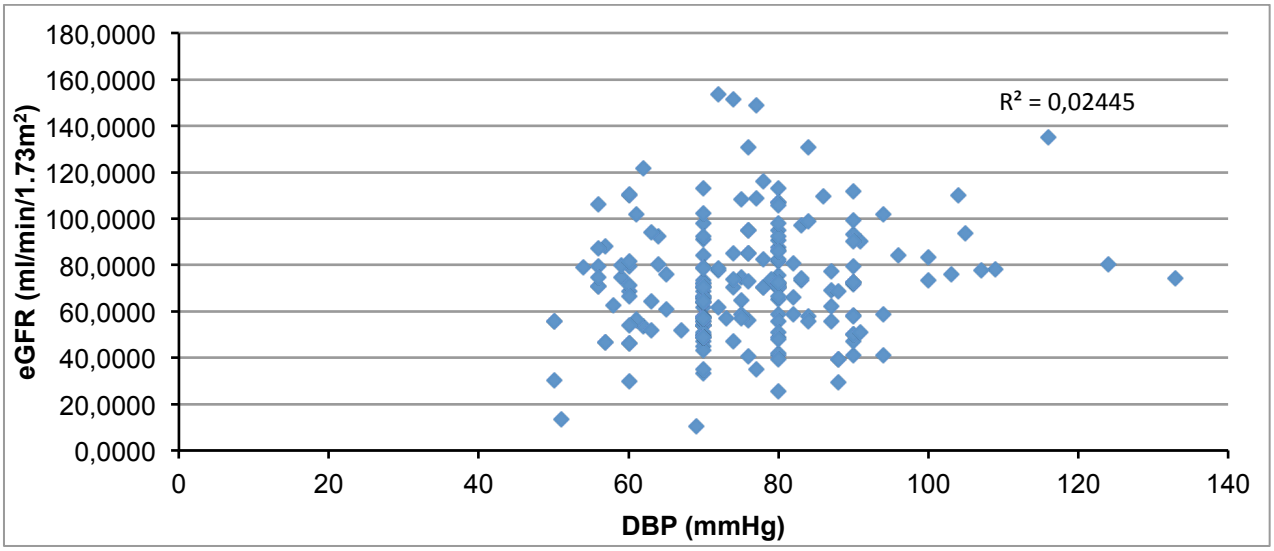


Figure 5: Correlation between eGFR and Diastolic Blood Pressure

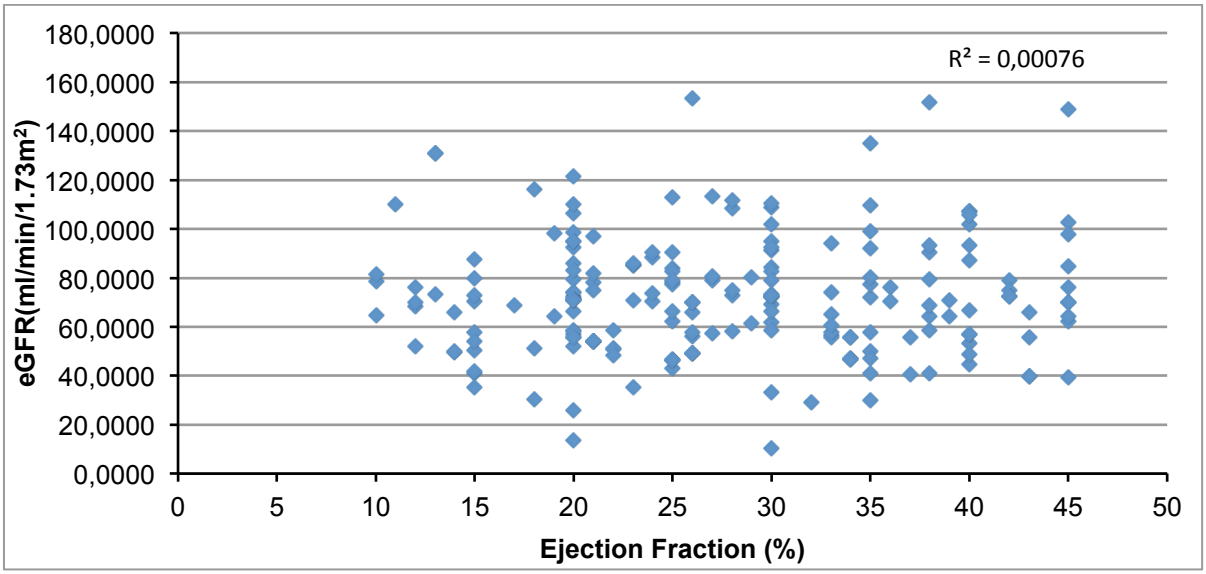


Figure 6: Correlation between eGFR and Ejection Fraction

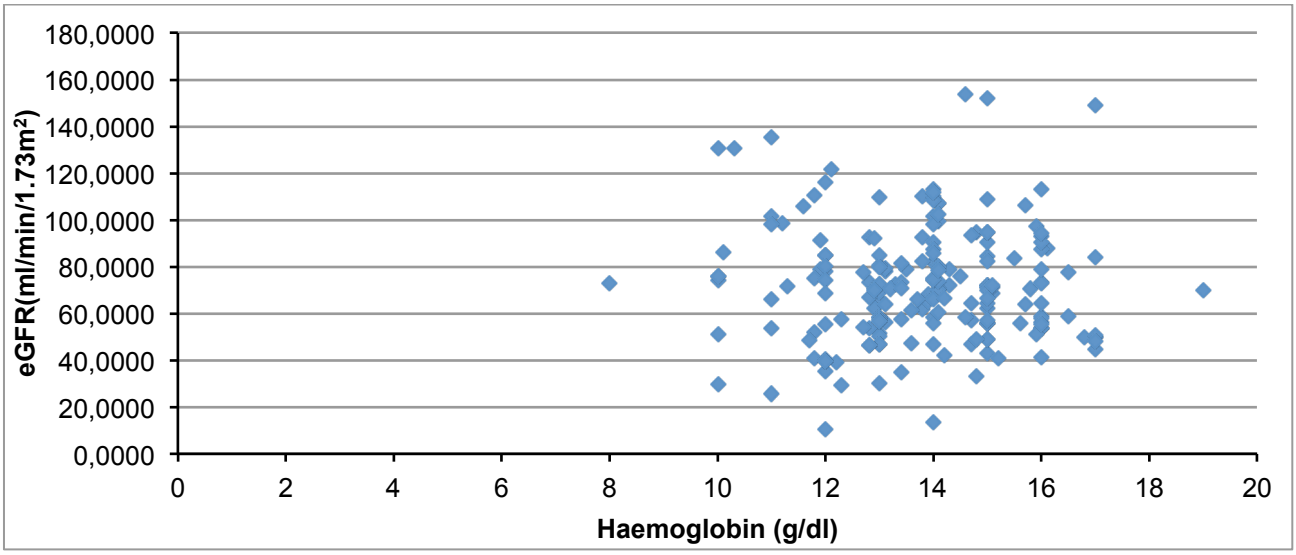


Figure 7: Correlation between eGFR and Haemoglobin

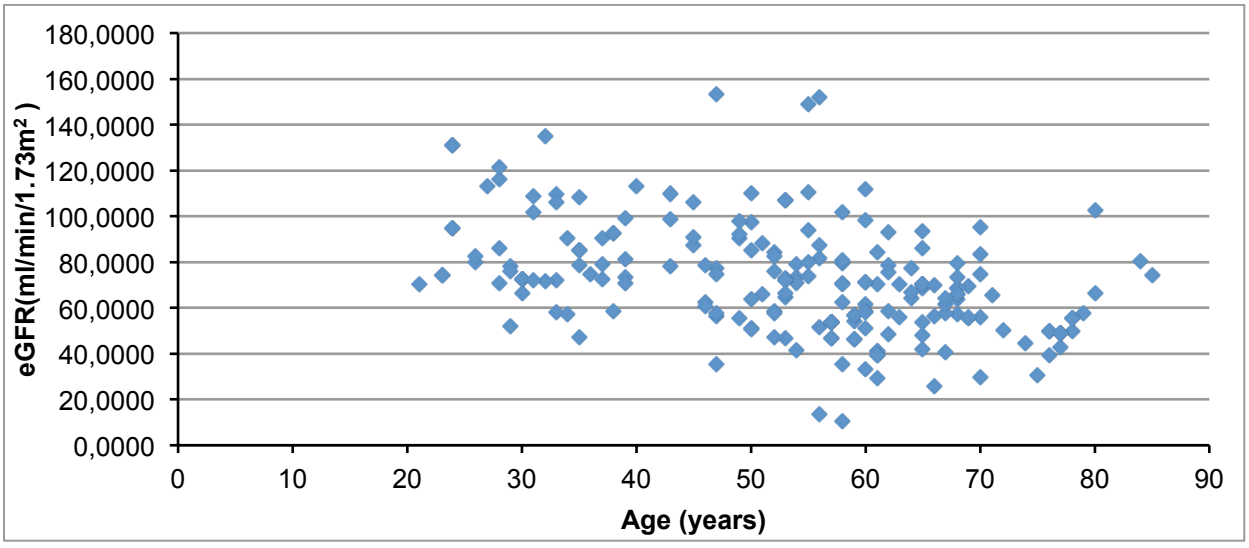


Figure 8: Correlation between eGFR and Age

3.4 ANOVA Analysis of NYHA with eGFR (ml/min/1.73m^2)

The Analysis of Variance Test (ANOVA) was conducted to assess if there was a difference in eGFR values by NYHA functional class. Of interest is that this study showed that the mean eGFR was significantly lower with higher NYHA class ($p < 0.012$).

	Descriptives		
	eGFR		
NYHA	**NUMBER OF PATIENTS**	**MEAN**	**STD.DEVIATION**
I	85	77.05	22.94
II	85	70.61	24.06
III	25	64.13	25.39
IV	5	50.02	15.25
TOTAL	200	72.02	24.09

Table 8: ANOVA analysis with eGFR

CHAPTER 4: DISCUSSION

4.1 Demographics

The study was conducted on a sample of 200 patients (n=200). Of this, 48% were females and 52% were males. The mean age of the study patients was 53.3 years. The mean ages for males was 57.4 years and for females was 48.8 years. The mean age in this study is a decade younger than other published data. [8,9]

4.2 Prevalence of low eGFR

The overall prevalence of low eGFR (<60mL/min/1.73m^2) was 34.5%. There was not much difference between male and female prevalence (50.7% vs 49.3%).

Large heart failure international trials including SOLVD Prevention (SOLVD-P) and SOLVD Treatment (SOLVD-T) have pointed out the degree of renal impairment in heart failure. Interestingly, 21% of the patients in the SOLVD-P trial had eGFR <60ml/min/1.73m^2. This figure is all the more remarkable, as the patients in this trial were New York Heart Association (NYHA) functional class I-II (mild heart failure). In the SOLVD-T Trial, 35% of the patients had eGFR <60ml/min/1.73^2 and the majority of these patients were NYHA Class II. Our study shows similar suggestions, as 85% of our cohort was NYHA I/II.

A local, South African study, conducted by Inglis et al[12] in 2007 showed that only 12% (out of a study group of 163 black African patients) had an eGFR <60ml/min/1.73m^2. This number is significantly lower than Western values and could be explained by the average age of their South African study cohort being younger (48 years). The mean age of the patient group included in this study was higher at 53.3 years and thus the likelihood of atherothrombotic disease being higher, thereby contributing to comparative prevalence's to international studies. Also, their cohort involved fewer patients (163 black patients) who were newly diagnosed heart failure patients. Our study involved various races and most of

our patients had established heart failure that were chronic attendees to the heart failure clinic.

4.3 eGFR and New York Heart Association Class

One-way analysis of variance (ANOVA) was conducted to assess whether there was a difference in the eGFR by NYHA level. There is sufficient evidence to suggest that individuals with different NYHA levels have different eGFR scores. The mean eGFR decreases with increasing NYHA class. The p value was 0.012, which can conclude that individuals with different NYHA have different eGFR scores. The results indicate that patients in NYHA class I have eGFR scores that are significantly higher that NYHA II (p value=0.008), NYHA III (p value=0.002) and NYHA IV (p value=0.001). This means that there is an inverse relationship between eGFR and NHYA levels.

The difference in average eGFR by NYHA levels is illustrated below.

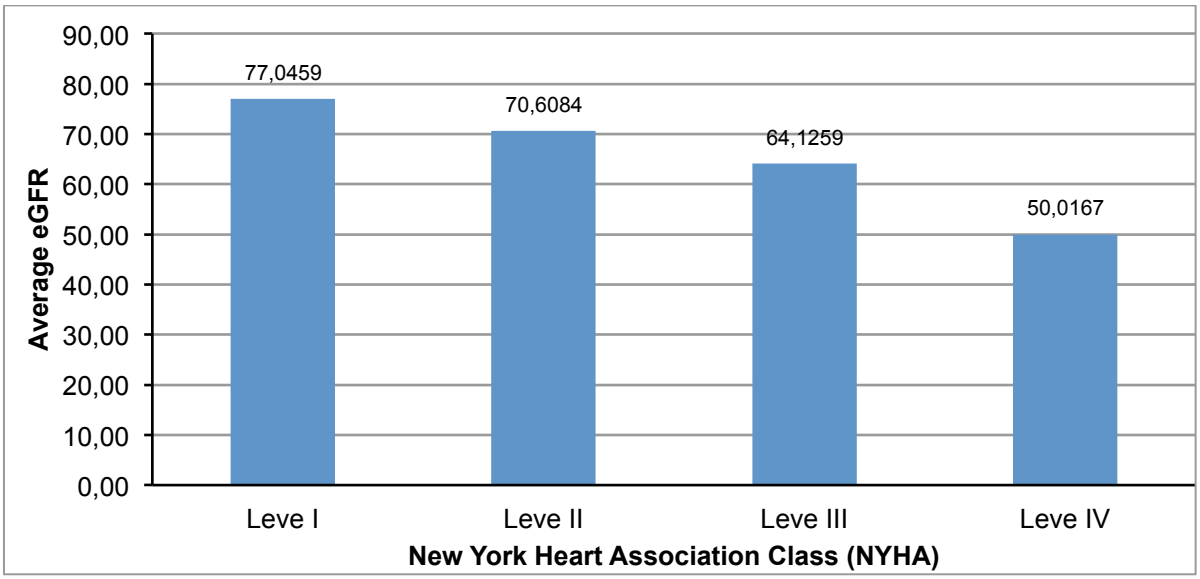


Figure 9: Correlation between eGFR and NYHA

This would follow intuitive thought that the worse the degree of failure, the worse the complications such as renal dysfunction. As alluded to earlier, there are various mechanisms for decreased renal function in heart failure patients. Interestingly, similar results to the CORONA study (referenced before) showed that reduced cardiac output is not the sole mechanism of reduced renal perfusion. As found in that study, a significant number of those patients presented with normal or elevated blood pressures. Our study

found similar results. SBP was 119mmHg (Minimum 80mmHg and Maximum 200mgHg, and mean DBP was 76mmHg (minimum 50mmHg and maximum of 133mgHg).

4.4 eGFR and Minnesota score:

As expected, a significant positive correlation was found between eGFR and the Minnesota score (p value= 0.012). It must come with no surprise that patients with a higher severity of heart failure have a poorer physical, emotional, social and psychological health. Poor kidney functions only aggravate the quality of life further. This is all very stressful - and it becomes difficult to cope with the physical effects of kidney failure.

4.5 eGFR and Six minute walk test

Significant correlation was noted between eGFR and the six-minute walk test (p value=0.003). The six-minute walk test accurately assesses the patient's effort tolerance. The results are a good indicator of the severity of heart failure based on the functional class.

Patients with renal dysfunction, like CKD, are mostly inactive and have reduced physical functioning and performance[36].

A recent study was done on a group of 83 patients with CKD[37] .The study patients had to partake in 150 minutes of moderate intensity exercise (per week) together with education about behavior and lifestyle changes. There was an 11 percent increase in their maximal aerobic capacity of those in the study group, while those in the control group had a 1 percent decline. Importantly, patients in the exercise group also showed improved heart function. However, larger studies with longer follow-ups are needed before we can be sure that this type of program is beneficial to renal dysfunction patients.

Resistance and aerobic exercise programs should be started at relatively low intensity thereby slowly increased as tolerated by symptoms so as to avoid injury and discontinuation of exercise.[36]

The risk of both musculoskeletal and cardiac types of adverse events is higher with the high intensity exercise than with sub maximal exercise[39].

4.6 eGFR and Furosemide dose

Patients with more severe heart disease require higher doses of furosemide and this explained the positive correlation between eGFR and furosemide (p value= 0.006).

The ability of furosemide to act at very low levels of GFR[55] encouraged its popularity in the therapy of renal edema and oliguria of chronic renal failure. Existing data also pointed that there was an increase in the renal circulation following furosemide[56]. It was also noted that furosemide shortens the evolution and reduces the number of dialysis hours. The recommended dose of furosemide is about 40 - 200 mg / day. However doses unto 4000 mg have been used before with no major toxic effects being noted[40]. Intravenous administration takes effect in a few minutes and thereafter remains active for unto 6 to 8 hours. It has also been found that there is no difference between administering IV bolus furosemide vs IV continuous infusion furosemide[53].

4.7 eGFR and Haemoglobin

Anaemia is not so prevalent in earlier stages of chronic kidney disease. A study has shown that patients with stage III renal disease have a rate of concurrent anaemia of 5.2%, as opposed to a worse rate of 44.1% in those with stage IV disease. [(42)]

Silverberg et al[43] described the "cardio-renal-anaemia syndrome," which refers to a vicious cycle where decreased kidney function leads to reduced erythropoietin production and, thence, anaemia.

The morbidity and mortality depend not only on the underlying etiology of the patient's anaemia but also the stage of the disease. The etiology of anaemia in advanced disease, tends to be multifactorial (eg. decreased red blood cell production due to lack of erythropoietin, increased red blood cell hemolysis [intravascular or extravascular], as well as more blood loss due to multiple veno-punctures for various investigations).

It has been shown that black patient together with an increased prevalence of anaemia have also a four fold increased risk of developing chronic kidney disease compared to white patients[44].

The CHOIR (Correction of Haemoglobin and Outcomes in Renal Insufficiency) trial[45], showed that a high haemoglobin target is associated with a increased risk of progression of CKD, which is apparently augmented by concurrent smoking.

Severe anaemia leads to a regulatory compensatory left ventricular hypertrophy (LVH). Such LVH will lead to precipitation of CHF, which will cause a decline in renal perfusion and thereby resulting in further kidney damage. Levin et al[46] estimated that for every 1g/dl decrease in HB concentration, there is a 6% risk of LVH in patients with chronic kidney disease.

4.8 eGFR and Age

There was a negative and significant correlation between the eGFR and age (p value= 0.00) which is consistent with international studies . Cross sectional studies have uniformly shown that the GFR declines steadily with age. It starts at age 30–40 years, with an increased rate of decline after age 65–70 years.[48]

In the original studies of Davies and Shock[49] the estimated decline in GFR was 0.96 ml/min/year or rather 10 ml/min/decade.

The decline in GFR is a result of a progressive changes in the vascular tree; " related to the effect of oxidative stress and telomere shortening, or perhaps linked to an action of angiotensin II".[50]

Among the 548 normal participants studied by Rowe et al[51] the creatinine clearance rate fell from 140 ml/min/1.73m^2 to about 97 ml/min/1.73m^2 from age 30 years to age 80 years.

In conclusion, GFR slowly declines with ageing as a normal "biological phenomenon linked to organ senescence".

4.9 eGFR and Diastolic Blood Pressure

On comparison of eGFR with the diastolic blood pressure, a statistically significant correlation was obtained (p value= 0.027). The relationship between blood pressure and the kidneys is complex and each is seen to adversely affect the other. There are other international studies that have yielded similar result. In the Renal Iohexol Clearance Study in Tromso 6 (RENIS T6)[52], 1593 subjects (aged 50-62 years) were studied and analysis of the association between blood pressure and e GFR were made. Importantly, patients with Diabetes, Chronic kidney disease or Cardiovascular disease were excluded. This study demonstrated that an increase in the diastolic blood pressure had a slightly reduced eGFR in the middle aged healthy cohort.

THE FUTURE

This study highlights the burden of renal dysfunction in heart failure patients. A prevalence of Cardio-Renal syndrome has been found to be as high as 34.5%. It points out the need for effective strategies in treating heart failure aggressively and thereby decrease the rate of renal dysfunction which holds a poorer prognosis. The limitations of this study are that it is a retrospective analysis and does not reflect any data on mortality/morbidity or prognosis. It also does not study the effect of specific therapy on cardiorenal syndrome.

Potential future studies at the heart failure clinic include:

- Study evaluating benefits pre and post specialist intervention.

- The effect of adding ACE-i to eGFR involving a prospective study in South Africa.

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