Psoas Muscle Area as a Measure for Sarcopenia and a Predictor of Poor Health Outcomes in Chronic Kidney Disease

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Abstract

Background: Sarcopenia often presents in parallel with chronic kidney disease (CKD), associated with a deconditioned state, chronic inflammation, and poor nutritional status. Psoas muscle area (PMA) measurements have been previously associated with mortality in CKD however, whether PMA can be useful in predicting other clinical outcomes such as hospitalizations, infections and other health events are less established.

Objective: The primary objective of this study is to report the association of PMA with hospitalizations, hemodialysis, mortality, and infections in patients with CKD.

Methods: A retrospective non-matched cohort study was conducted in a community nephrology clinic in Quebec, Canada, and included laboratory, radiological, and demographic data collected from April 1, 2015, until December 31, 2021. PMA was measured by two independent readers using the DICOM RADiant Viewer Software.

Main Findings: A total of 269 clinic charts were reviewed and included. Subjects had a median age of 74 years (IQR 31-92) with 58.3% reported as male. The prevalence of Grade 1 and 2, Grade 3, Grade 4 and Grade 5 CKD was 3%, 53%, 32%, and 10%. Median follow-up time was 1160 days (28-2516). Median measurement of PMA/height was 3.53 cm^2/m (0.5-8.73). Statistically significant concurrent relationships were documented between PMA and event-free time for dialysis and hospitalization. The adjusted HR for PMA < 2.66 cm^2/m are 0.39 (95% CI 0.16-0.94), p=0.0356. For hospital-free time, the adjusted HR for PMA quartiles showed a dose-dependent increase in effect size, with PMA about a 2-fold higher hazard risk ratio seen for a longer hospital admission-free period, (p=0.0273). The Cox hazard proportional multivariate analyses documented the concurrently negative relationships between PMA and length of survival and infection-free time, reaching a trend towards significance. For length of survival, PMA < 2.1 cm^2/m had an adjusted Hazard risk reduction of 82 % (HR 0.18 (95%CI 0.024-1.38)) and similarly for infection-free time until the first event, the adjusted HR for PMA < 2 cm^2/m are 0.38 (95% CI 0.17-1.0).

Conclusion: Our study demonstrated an overall association between increased health complication rates with increased comorbidity and decreased psoas muscle area. Further prospective studies are needed to identify methods for muscle mass sustainability.

Résumé

Contexte: La sarcopénie se présente souvent en parallèle avec l'insuffisance rénale chronique, souvent associée à un état de déconditionnement et inflammatoire, ainsi un mauvais statut nutritionnel. Les mesures de la zone musculaire du psoas montrent déjà des associations à la mortalité dans l'insuffisance rénale chronique, spécifiquement l'aire musculaire du psoas Cependant, l'utilité de ces mesures pour prévenir d'autres résultats cliniques est moins établie, tels que les taux d'hospitalisations, d'infections et d'autres événements de santé.

Objectif: L'objectif principal de cette étude est de rapporter l'association de l'aire musculaire du psoas avec les hospitalisations, l'hémodialyse, la mortalité et les infections chez les patients atteints de l'insuffisance rénale chronique.

Méthodologie : Une étude rétrospective a été menée dans une clinique de néphrologie communautaire au Québec, au Canada, et comprenait des données de laboratoire, radiologiques et démographiques, du 1^{e} avril 2015 à la fin du mois de décembre 2021. L'aire musculaire du psoas a été mesuré par deux lectrices indépendantes à l'aide du logiciel de visualisation DICOM RADiant.

Résultats : En tout 269 dossiers ont été examinés et inclus. Les participants avaient un âge médian de 74 ans (31-92) avec 58.3% étant des mâles. Les prévalences des insuffisances rénales chroniques de grade 1 et 2, de grade 3, de grade 4, et de grade 5 étaient de 3%, 53%, 32% et 10%, de façons respectives. La durée médiane de suivi était de 1160 jours (28-2516). La mesure médiane de l'aire musculaire du psoas ajusté par la taille était de 3.53 cm^2/m (0.5-8.73). Des relations concomitantes statiquement significatives ont été documentées entre aire musculaire du psoas et le temps sans événement pour la dialyse et l'hospitalisation. Le rapport de risque ajusté (RR) pour une aire musculaire du psoas moins de 2.66 cm^2/m était de 0.39 (IC à 95% 0.16-0.94, p=0.0356). Pour le temps sans hospitalisations, le RR ajusté pour les quartiles d'aire musculaire du psoas a montré une augmentation dose-dépendante de la taille de l'effet, avec un RR d'aire musculaire du psoas environ 2 fois plus élevé observé pour une période sans hospitalisations plus longue (p = 0.0273). Les analyses multivariées proportionnelles au risque de Cox ont documenté des relations simultanément négatives entre l'aire musculaire du psoas et la

durée de survie et le temps sans infection, atteignant une tendance à la signification. Pour la durée de survie, une aire musculaire du psoas moins de 2.1 cm^2/m avait une réduction du risque de risque ajustée de 82 % (RR 0.18 (IC à 95 % 0.024-1.38)) et de même pour le temps sans infection jusqu'au premier événement, le RR ajusté pour une aire musculaire du psoas moins de 2 cm^2/m = 0.38 (IC à 95 % 0.17-1.0).

Conclusion : Notre étude a démontré une association entre l'augmentation des taux de complications de santé avec une comorbidité accrue et une diminution de l'aire musculaire du psoas. D'autres études prospectives sont nécessaires pour identifier des méthodes efficaces pour maintenir la masse musculaire.

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Contribution of Authors

Song-ah Chai, BSc: Conception, performance, data collection, data analysis, manuscript preparation and review

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Abbreviations

AKI: acute kidney injury

ALM: appendicular lean mass

ASM: appendicular skeletal muscle

BIA: bioimpedance analysis

BMI: body mass index

CCI: Charlson Comorbidity Index

CD: Crohn's disease

CI: confidence interval

CLIP: chronic low-grade inflammatory profile

CKD: chronic kidney disease

CKD-EPI: CKD Epidemiology Collaboration

COPD: chronic obstructive pulmonary disease

CRP: C-reactive proteins

CT: computed tomography

DXA: dual X-ray absorptiometry

ESKD: end-stage kidney disease

ESRD: end-stage renal disease

EWGSOP: European Working Group on Sarcopenia in Older People

FNIH: Foundation for the National Institutes of Health

GFR: glomerular filtration rate

HDL-C: high-density lipoprotein cholesterol

HgbA1C: hemoglobin A1C

HR: hazard ratio

IBD: inflammatory bowel disease

IDA: iron deficiency anemia

IL-6: Interleukin-6

LVEF: left ventricular ejection fraction

MRI: magnetic resonance imaging

PMA: psoas muscle area

QoL: quality of life

RQ: respiratory quotient

SCWD: Society for Sarcopenia, Cachexia and Wasting Disorders

T2DM: type-2 diabetes mellitus

TSH : thyroid stiumulating hormone

UC: ulcerative colitis

UTI: urinary tract infection

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CHAPTER 1: LITERATURE REVIEW AND INTRODUCTION

Chronic Kidney Disease

Normal Kidney Function

The urinary system, also called the renal system, is the body's drainage network for removing waste and excessive fluid, usually eliminated in the form of urine (*The Urinary Tract & How it works*, 2023). It works to remove waste, regulate blood volume and pressure, and cellular and plasma electrolyte content, thereby maintaining proper fluid acid/base balance (Healthdirect Australia, n.d.). The urinary system has 6 distinct parts: Two kidneys receive blood from the systemic circulation and filter out the waste in the form of urea, which then passes through the ureters and accumulates in the bladder, and finally exits the body through the urethral passageway as urine (*The Urinary Tract & How it works*, 2023). Kidneys are known to be the primary organs of the urinary system, as they are the ones responsible for many important processes such as filtering out waste, releasing hormones to regulate blood pressure, and control the production of red blood cells (*Anatomy of the Urinary System*, 2019). They are bean-shaped organs located in the lumbar region of the spine, protected by the lower ribs, held in place by connective tissue (renal fascia), and surrounded by adipose tissue (perirenal fat), adding further protection (*Kidneys*, n.d.).

Normal renal function can be compromised by natural processes such as aging and disease. Normal renal function is estimated through equations such as the CKD Epidemiology Collaboration (CKD-EPI) (Levey et al., 2009), which calculates the glomerular filtration rate (GFR). For a healthy individual, a normal GFR ranges between 95 and 120 mL/min/1.73 m^2, depending on factors such as body size, sex and race (*Estimated Glomerular Filtration Rate,* 2023). Normal decline in renal function due to age is about 0.4 to 0.75 mL/min/year after the age of 40 (Imai et al., 2008; Lindeman et al., 1985). In the case of diseases with nephron mass loss, the urinary system's filtration units are unable to properly filter the blood and fluid content, leading to the unfortunate onset of a lifelong and oftentimes debilitating condition called chronic kidney disease (CKD). In many cases, the main driving causes of kidney disease would be a combination of the following: a progressive loss of nephrons and apoptosis of the cells that line various membranes

of the organ, which have a negative effect on glomeruli function, renal blood flow, and GFR (Glassock & Rule, 2016).

Chronic Kidney Disease

Chronic kidney disease, otherwise known as CKD, is a debilitating condition that affects individuals of all ages and ethnicities. It is a worldwide health problem with a prevalence ranging from 10 to 12 % in the general population in North America (Arora, 2013), and 23 to approximately 36% in the geriatric population (Zhang & Rothenbacher, 2008). An adult is considered to having CKD when they meet one of the following criteria: a GFR of less than 60 mL/min/1.73m^2, or a GFR greater than 60 mL/min/1.73m^2 with evidence of injury to the renal structure, for a duration equal or greater than 3 months. Examples of injury can include albuminuria, hematuria, and reoccurring acid/base and electrolyte disorders (National Kidney Foundation, 2002).

Table 1. CKD Grades (Estimated Glomerular Filtration Rate, 2023)

Grade	Estimated GFR	Kidney Function
1	90 ml/min/1.73m^2 or above	Normal function with possible renal damage
2	60-89 ml/min/1.73m^2	Mild loss of renal function
3a	45-59 ml/min/1.73m^2	Mild to moderate loss of renal function
3b	30-44 ml/min/1.73m^2	Moderate to severe loss of renal function
4	15-29 ml/min/1.73m^2	Severe loss of renal function
5	Less than 15 ml/min/1.73m^2	Renal failure

With the progression of CKD, a continuing decline in kidney function resulting from permanent loss of nephrons is observed (Grossman & Porth, 2014, p.1118). In conjunction, the combination of many mechanisms that are still unclear ultimately result in the progressive decline of the GFR. In CKD, as the kidney structure disintegrates from atrophic nephrons, the remaining nephrons try to compensate this loss by increasing its function to filter solute particles from the blood. Overtime, these nephrons stop functioning and get destroyed, eventually ending in kidney failure (Grossman & Porth, 2014, p.1118). The GFR is considered the best way to measure kidney function, usually estimated using the concentration of creatinine found in the blood. A healthy adult would present with a GFR of approximately 120 to 130 mL/min/1.73m^2, with small amounts

of blood protein (albumin) in the urine. However, a persistent increase in albumin content in the urine usually calls for a diagnosis of CKD and indicates early stages of renal disease. Other biomarkers of CKD can include abnormal urine sediments such as white blood cells, and abnormal scans (Grossman & Porth, 2014, pp.1118-1119). Other useful nutrients and ions that were unable to get reabsorbed into the circulation can also be found in a CKD urine sample.

Infections, Hospitalizations, and Mortality in CKD

It is currently known that infections are one of the leading causes of mortality in CKD populations, especially for those suffering from end-stage kidney disease (ESKD) (Canadian Institute for Health Information, 2005). It is also documented that, compared to non-CKD populations, patients suffering from renal disease show substantially higher incidences of urinary tract infections, respiratory tract infections as well as sepsis (Naqvi & Collins, 2006). Overall, renal patients are at higher disposition for infections and all-cause mortality for various reasons such as the presence of different comorbidities, advanced age, a compromised immune system as well as a decreased response to vaccinations (Dalrymple & Go, 2008). In a study aimed at delineating the association of CKD with infection-related death, Wang and colleagues (2011) found that lower estimated GFR is associated with higher mortality secondary to infection. More specifically, it was shown that in comparison to the reference group as those with an estimated GFR above 60 ml/min/1.73m^2, the Cox hazard proportional ratios for mortality were 1.36 (0.81-2.30) and 2.36 (1.04-5.38) for groups with an estimated GFR of 45 to 59.9 ml/min/1.73m^2 and an estimated GFR less than 45 ml/min/1.73m^2, respectively (Wang et al., 2011). Furthermore, it was also shown that individuals in later stages of renal disease are a 160% increased risk for genitourinary infection-related hospitalization (Dalrymple et al., 2012). The same study also showed those in advanced stage renal disease are at an increased risk for pulmonary-related hospitalizations to those with GFR equal to or greater than 90ml/min/1.73 m^2 (Dalrymple et al., 2012).

Treatment Strategies

CKD treatment often follows a risk factor modification treatment plan to slow the rate of nephron function loss. Examples include dietary changes, exercise, blood pressure control, smoking cessation, and glycemic control management. When necessary, usually if or when the

condition becomes progressive, physicians will advise on renal dialysis and/or renal transplant (Grossman & Porth, 2014, p.1124). At this point, the disease would have reached the later stages. In most cases, CKD patients will present with a plethora of comorbidities such as diabetes, hypertension, and cardiovascular disease. One comorbidity that is oftentimes overlooked by physicians is sarcopenia, a condition characterized by muscle mass loss.

Sarcopenia

Prevalence

Sarcopenia is a chronic, age-related condition that mainly presents as a decrease in muscle mass and quality, affecting around 10% of men and 10% of women in the general population (Shafiee et al., 2017). As sarcopenia becomes more widespread in aging populations, its prevalence can reach up to 22.6% in older adults (Bertschi et al., 2020). Furthermore, as sarcopenia becomes more and more a burden to society, morbidity and mortality rates, and medical care costs continue to rise. The increase in prevalence can be in part due to the natural decrease in muscle mass with time, specifically 3-8% per decade after the age of 60 (Volpi et al., 2004). A decrease in muscle mass comes accompanied with diminishing muscle strength and quality of life (QoL). Subsequently, the risk for falls and loss of physical independence increases, which has shown to increase hospitalization rates and mortality (Doherty, 2003). Age-related muscle mass loss tends to be mediated by age-related chronic low-grade inflammatory profile (CLIP), leading to catabolic reactions and changes to one's metabolic functions (Beyer et al., 2012; Marzetti et al., 2009). In CKD, additionally, one of the primary known causes of sarcopenia is chronic inflammation paired with poor nutritional status (Sato et al., 2016). As a result, a state of metabolic acidosis associates highly with protein wasting through mechanisms favouring protein breakdown and diminishing muscle protein synthesis (Sato et al., 2016). As far as identifying sarcopenia in CKD patients goes, there is no current consensus on sarcopenia prevalence in this population group, as there is no agreement on which operational criteria to apply during diagnosis in CKD (Sabatino et al., 2021). Hence, sarcopenia prevalence can range anywhere between 4 and 42%, depending on many factors such as the chosen cut-off values and disease stage (Chatzipetrou et al., 2022). In CKD populations, sarcopenia prevalence can also

range anywhere between 34.5 and 65.5% depending on the disease stage (Souza et al., 2017). Table 2 shows the wide range of sarcopenia prevalence within the CKD population, all dependent on operational definition, measurement tool, standardization method and disease classification.

Table 2. Reported Sarcopenia Prevalence Amongst CKD Populations

Author	Definition	Disease Grade	Method	Prevalence
Moreno-Gonzalez et al., 2020	EWGSOP2	n/a	BIA, handgrip, SPPB	9.6-13.9%
Jeong et al., 2019	AWGS	ESKD (ESRD)	BIA	2.8-9.5%
Souza et al., 2017	EWGSOP	CKD2-CKD5	DXA	11.9%
Kim et al., 2014	EWGSOP	ESKD (ESRD)	BIA, handgrip	33.7%
Foley et al., 2007	Janssen et al., 2000	n/a	BIA	4.5-27.2%

Risk Factors Associated with Sarcopenia

1. Age and Body Composition

With increasing prevalence with age, age also seemingly links to increased frailty and lowered physical activity levels (Therakomen et al., 2020). As age increases, the risk of sarcopenia development also increases via mechanisms previously mentioned. For individuals between 70-79 years old, the odds ratio is 6.87 (95% confidence interval (CI) 1.63–28.88) and for individuals 80 years old or older, the risk for sarcopenia doubles, with an odds ratio of 13.71 (95%CI 3.66–51.41) (Therakomen et al., 2020). Individuals diagnosed with sarcopenia will also experience alterations in body composition, a change often observed with increasing age. Overall, a higher body mass index (BMI) has been linked to a decrease in sarcopenia (Chen et al., 2020). Despite the protective factor of a higher BMI, it is important to keep monitoring for other markers such as fat to muscle ratio (Xu et al., 2020) because BMI has been shown to correlate with body fat content (Hervochon et al., 2017; Jeong et al., 2023), which can eventually lead to obesity. It is currently known that individuals with a BMI equal to or higher than 25 kg/m^2 are at a significantly higher risk for sarcopenia than individuals with BMI under 25 kg/m^2 (Lutski et al., 2020). Despite improving survival rates, a high BMI could be indicative of obesity, higher fat mass, which can link to higher inflammation and lower lean BMI (Honda et al., 2007). BMI in an obesity state is associated with higher inflammatory markers such c-reactive proteins (CRP) and Interleukin-6 (IL-6), which seems to be more prevalent in people with central obesity and low muscular strength

(Schrager et al. 2007; Cesari et al., 2005). Individuals in a state of obesity are known for being at a higher risk for sarcopenia than their non-obese counterparts after adjusting for age, background, insulin resistance and key biomarkers of inflammation and high fat content (Lutski et al., 2020). With the progression of sarcopenia, decreased physical activity levels would be a commonly observed behaviour, which would then decrease energy expenditure and increase risk of obesity. Obesity, higher BMI and age as well as higher visceral fat content would leave the stage to inflammation that could be detrimental to one's functional health and spiral into the vicious cycle of sarcopenia (Choi, 2016).

2. Sex

Sex has been proven to show inconsistent findings. There is evidence showing that sarcopenia is more prevalent among females than males in individuals under 70 years old, and that the opposite is true for individuals who are either 70 years or older (Kirchengast & Huber, 2009). More recent research showed that sarcopenia is more prevalent in males compared to females in Asia (Du et al., 2019), while some showed similar distributions (Tay et al., 2015). Hence, sex alone would not be sufficient to analyze risk for sarcopenia. Subfactors such as race, height, body composition, lifestyle and socioeconomic status would need to be further investigated. As a summary, research has clearly demonstrated that age seems to be a major precursor to many of the risk factors for sarcopenia which results in muscle loss (Cheng et al., 2021), and overall, a more significant effect size risk factor than sex.

3. Diabetes

Alongside age, diabetes also increases known risk factors. The diagnosis of diabetes compared to non-diabetics have a 50% increased risk for sarcopenia once adjusted for the aforementioned risk factors (Chung et al., 2021). Compared to their non-diabetic matches, individuals with type-2 diabetes mellitus (T2DM) are not only at a higher risk for low lean muscle, they also show decreased ability in physical performance (Lin et al., 2022). If poorly managed, chronic diabetes can lead to diabetic nephropathy, a common cause of CKD and ESKD (Huang et al., 2022). Diabetic nephropathy is known to affect around 31% of the general population, and 20% of the diabetic population (Çeliker et al., 2018). Similar to diabetic nephropathy, CKD is also considered a long-

term complication of diabetes, with approximately half of diabetic patients being affected by CKD (Thomas et al., 2015). Patients who have chronic diabetes and sarcopenia are known to be at a higher risk for severe diabetes diabetic kidney disease than those who do not present with sarcopenia (Huang et al., 2022). Unfortunately, diabetic nephropathy is highly correlated to lower muscle mass and poorer overall performance (Çeliker et al., 2018). In order to decrease occurrence of falls and autonomy loss from decreased muscle, people presenting with a diabetic profile should follow a comprehensive lifestyle modification management approach involving change in diet, exercise, smoking habits, and weight management. These modalities can be further potentiated using pharmacological therapies (de Boer et al., 2022). Also, oftentimes, people who have diabetes will also experience decreased kidney function. A special focus should be placed on the achievement or maintenance of proper glycemic control to delay the progression of diabetic kidney disease (Hahr & Molitch, 2015) and other microvascular disease complications.

4. Nutritional Status

With altered nutritional status, whether it is malabsorption, malnutrition, or inflammatory bowel disease (IBD), one can increase their risk for sarcopenia through the mediation of inflammatory pathways. Malabsorption can lead to many challenges such as intestinal insufficiency or even intestinal failure. Sarcopenia is known to affect approximately 70% of people with intestinal failure and around 35% of people with renal insufficiency (Skallerup et al., 2018). Malabsorption, when not treated in a timely fashion, can lead to the inability for the body to absorb and metabolize nutrients, known as malnutrition, further putting one at risk for sarcopenia (Sevastianos & Dourakis, 2016). Suppressed appetite due to chronic fatigue can lead to unintentional weight loss, a risk factor strongly associated with low muscle strength and low physical performance, both key markers of sarcopenia (Azzolino et al., 2020; Reijnierse et al., 2015). Nutrient deficiencies and metabolic imbalances stemming from either malabsorption or malnutrition can also be associated with IBD such as Crohn’s disease (CD) and ulcerative colitis (UC). Prevalence of sarcopenia in these populations can go as high as 45% among IBD cases with inflammation (Adams et al., 2017). Within this population group, low lean mass is a major factor. Unfortunately, sarcopenia in number of patients with IBD go undiagnosed (Bryant et al. 2015).

Despite the reported incidences of malnutrition-associated sarcopenia, malnutrition is a modifiable risk factor (Beaudart et al., 2019). However, it is important to note that overnutrition can be detrimental, to result in metabolic syndrome, which facilitates the development of sarcopenic obesity (Sevastianos and Dourakis, 2016).

Comorbidities Associated with Sarcopenia

1. Diabetes

T2DM is a common comorbidity with sarcopenia. Sarcopenia is known to affect approximately 15% of the diabetic population, while pre-sarcopenia affects approximately 14% of the diabetic population compared to 11% and 8% among healthy controls, respectively. (Wang et al., 2016; Chung et al., 2021). Also, people suffering from diabetes are approximately at a 1.5 fold increased risk for developing sarcopenia than their non-diabetic counterparts (Chung et al., 2021) as noted by the pooled OR = 1.518, 95% CI = 1.110 to 2.076, Z-value = 2.611, p = 0.009.

2. Chronic Lung disease

It is currently agreed upon that sarcopenia in patients with chronic obstructive pulmonary disease (COPD) is one of the relationships that is linked to adverse outcomes in this population group. In studies attempting to estimate the prevalence of sarcopenia in COPD patients, prevalence ranged from 24 to 39.6% (Costa et al., 2015; Limpawattana et al., 2017). Similar to CKD populations, COPD populations with sarcopenia show poor prognosis. Furthermore, lean body mass loss has shown to be associated with lower BMI (Costa et al., 2015). Patients with COPD have a 1.7 to 2-fold increased probability for sarcopenia compared to those without a COPD diagnosis (Borda et al., 2017; Tasar et al., 2015). Those with COPD also need to pay specific attention to their fat content, as they are 3 times more likely to present with sarcopenic obesity than those without COPD (Joppa et al., 2016). It has also been shown that overall, individuals with restrictive lung disease have a 2 to 3 fold increased risk of sarcopenia as well as sarcopenia with obesity than those without diagnosis. Thus, the risk of sarcopenia with and without obesity is increased with the presence of restrictive lung disease (Lee et al., 2019).

3. Cirrhosis

Sarcopenia is known to have a 24% increased risk to present with decompensated cirrhosis, once adjusted for factors such as age, sex, ethnicity and metabolic factors (Wijarnpreecha et al., 2019). The mechanisms resulting in sarcopenia among populations with pre-existing comorbidities are multifactorial. Some examples include the imbalance between protein synthesis and breakdown, decreased oral intake causing starvation which offsets homeostasis, and the role of insulin in the down regulation of protein catabolism and lipolysis (Dhaliwal & Armstrong, 2020). Other findings proposed that gluconeogenesis and fatty acid oxidation can lead to lower respiratory quotients (RQ) in patients with cirrhosis, which can possibly link to sarcopenia (Glass et al., 2013). They found that these patients have significantly lower RQ compared to healthy controls, which can be indicative of metabolic decompensation. Further along that line, psoas muscle area (PMA) has been shown to correlate highly with RQ (Glass et al., 2013).

4. Cancer

Cancer is associated with sarcopenia, especially in later stages of disease, with 35% of cancer patients at risk of sarcopenia (Barreto et al., 2021). The prevalence of sarcopenia in cancer cases range between 11 and 47%, depending on cancer type (Williams et al., 2021). Sarcopenia has not only been shown to relate to poor outcomes and exercise intolerance, it also shows significant association with fatigue in patients with cancer (Barreto et al., 2021). Research shows that patients at risk of sarcopenia have lower performance scores and are mostly hospitalized and sedentary. Furthermore, within the 35% at risk, 87% showed considerable fatigue levels (Barreto et al., 2021). In patients with lung cancer, progression-free survival is shown to decrease in patients with sarcopenia, with a lack of evidence on the effect of sarcopenia on overall survival (Go et al., 2016). In breast cancer, sarcopenia can affect approximately 16% of its patients, with up to 38% classified as obese among those who have sarcopenia (Villasenor et al., 2012). Colorectal cancer is also commonly linked to sarcopenia, with approximately 39% of colorectal cancer patients having sarcopenia (Lieffers et al., 2012). Prevalence will tend to increase with age and lower BMI. With cancer patients, sarcopenia can be associated with a higher rate of infection, length of hospital stay and critical need for rehabilitation care (Lieffers et al., 2012). Studies have

also demonstrated that cancer patients with an ECOG score of higher than 2 are at a significantly higher risk for developing sarcopenia (Zhang et al., 2015). Sarcopenia is also associated with increased risk of overall mortality (Villasenor et al., 2012), calling for urgency in new research and findings that will help reduce sarcopenia-related mortality in cancer patients.

5. End-Stage Cardiac Disease

In individuals with end-stage cardiac disease such as heart failure, sarcopenia is known to be a main cause in exercise intolerance and ventilatory insufficiency (Suzuki et al., 2018). It can not only lead to poor outcomes, but also be a culprit in longer hospital stay in this population group (Martone et al., 2017). Exercise intolerance can be also explained by reduced left ventricular ejection fraction (LVEF) and overall reduced appendicular skeletal muscle (ASM) mass in this population. Alongside reduced heart function, there have been significant findings correlating ASM mass and limited physical functioning (Fulster et al., 2013).

Defining Sarcopenia

As sarcopenia research continues to advance, the need to properly define the term is also becoming more crucial. Properly defining the term would allow for physicians to better diagnose their patients, it would also help researchers and academics better guide and conduct clinical trials. The term dates all the way back to the late 20th century, originally pinned by Irwin Rosenburg to define "paucity of flesh", referring specifically to age-related skeletal muscle loss (Rosenburg, 1989). Even though this may have seemed like a simple concept, there have been many ways to describe sarcopenia after noticing the coexistence of at least one chronic disease in 92% of aging populations (Moorthi & Avin, 2017). The term "sarcopenia" was gradually revised by health organizations and adapted to include any loss of muscle tissue and function, whether it was from aging, disease, low protein intake and/or physical inactivity (Moorthi & Avin, 2017).

One of the first organizations to propose a definition and guideline for sarcopenia was the EWGSOP (European Working Group on Sarcopenia in Older People) in 2010 (Yang et al., 2019; Schaap et al., 2018). Its guidelines are amongst the most widely used, with 3484 citations, including 2597 original articles in the Web of Science database (Yang et al., 2019). EWGSOP defined sarcopenia as low skeletal muscle mass and strength (for example handgrip strength),

and/or low physical performance (such as gait speed). EWGSOP-defined sarcopenia has been related to several adverse clinical outcomes, such as falls, fractures, physical performance, frailty and disability, poor QoL, and even death (Yang et al., 2019). EWGSOP later reviewed their original definition for sarcopenia and released an updated version, otherwise known as the EWGSOP2. According to the EWGSOP2, sarcopenia is only based on low skeletal muscle mass and strength, whereas physical performance like gait speed is no longer a component of sarcopenia. Instead, it can be used to classify disease severity. Cut off points have also been altered. A prospective observational study conducted by Yang and colleagues aimed at further investigating the differences. Results showed higher sensitivity in EWGSOP2 than its counterpart. The updated definition also showed higher performance for predicting falls or hospitalizations (Yang et al., 2019).

In 2014, the FNIH (Foundation for the National Institutes of Health) Sarcopenia Project suggested a new set of criteria and cut-off scores for low muscle mass and low grip strength based on empirical data from a large pooled dataset of older adults (Schaap et al., 2018). This time, they decided to adjust appendicular lean mass (ALM) and grip strength for body mass index to decrease sources of error (Studenski et al. 2014). A study by Schaap and colleagues (2018) decided to further investigate sarcopenia defined by the EWGSOP and the FNIH. In this study, 2 sarcopenia definitions used by FNIH were used: First, a disease characterized by low lean mass and low grip strength. Second, low lean mass, low muscle strength and slow gait speed. This study aimed at investigating the link between sarcopenia and the incidence of recurrent falls and fractures. It also aimed at clarifying the association between the components of EWGSOP and FNIH definitions for sarcopenia and the incidence of recurrent falls and fractures. In the end, there were no significant associations between groups. The study also concluded that lower cut-off values suggested by the FNIH might be too strict, thus overestimating sarcopenia prevalence (Schaap et al., 2018).

Although age is known to be a common factor in the onset of sarcopenia, the SCWD (Society for Sarcopenia, Cachexia and Wasting Disorders) argue that aging is not necessarily a prerequisite. For example, individuals with diabetes mellitus have an accelerated loss in muscle

mass and strength, eventually leading to sarcopenia diagnosis at a much younger age (Cederholm & Morley, 2015).

Despite their differences, sarcopenia defined by the EWGSOP, the SCWD and the FNIH have all been validated cross-sectionally and longitudinally, making them valid definitions in a clinical setting (Cederholm & Morley, 2015). It is important to note that the presence of multiple definitions for sarcopenia supports the argument that sarcopenia is difficult to be defined using one single definition given the multi-faceted nature of the disease. As previously mentioned, this is also known to contribute to the wide prevalence range.

As seen above, over time, other fitness components have been added to the original definition of sarcopenia which only addressed decreased muscle size. As researchers tried to better understand and better quantify sarcopenia, hand grip strength and gait speed have been added to more recent takes on defining sarcopenia. There could be many reasons for this decision to add new elements. While the essence of sarcopenia is a decrease in muscle mass, a decrease in muscle mass would also decrease muscle function as a result. Hence, adding new components to its diagnosis would allow for a more comprehensive understanding of muscle tissue. Hand grip strength could be useful in assessing muscle fibers recruitment, especially that of fast-twitch type IIa fibers (Tanganelli et al., 2021). The use of gait speed would allow assessment of sarcopenia that affects functional fitness and muscle function and endurance despite decreased muscle size (Kim et al., 2016; White et al., 2013).

The potential limitations of the addition of physical functionality components in a definition of sarcopenia include the decrease in the physical activity performance of the subject from a wide variety of causes such arthritis, carpal tunnel syndrome, cerebrovascular disease, peripheral neuropathy, and similar comorbidities. These definitions do not include the component of fat distribution, subcutaneous or visceral, particularly when fatty infiltration of muscle is not appreciated. Also, the different causes of sarcopenia are not taken into consideration in the description of the recognized definitions. The cut-off values for sarcopenia definitions may also vary according to the chronic disease and degree of inflammation.

As demonstrated by the literature, many efforts have been made by researchers to solidify the definition of sarcopenia. Yet, there is still a lack of clarity on what corresponds to the true meaning for sarcopenia. Given that many definitions and diagnosis criteria are widely available to help clinicians and healthcare professionals better understand sarcopenia, there has also been a lot of debate around not only the large prevalence of the disease, but also its effect on health complications.

Infections, Hospitalizations and Mortality associated with Sarcopenia

An important observation that clinicians and researchers made over time is the increased incidence rate for infections and mortality, as well as more frequent hospitalizations and longer hospital stays in individuals presenting with sarcopenia. For instance, individuals with sarcopenia are more likely to encounter postoperative complications such as wound infections compared to their non-sarcopenic counterparts (Miller et al., 2019), further burdening the patient's QoL as well as the healthcare system. With each additional recognized sarcopenia-related risk factor, the risk of the development of infections proportionally rises. Overall, patients with sarcopenia are at an increased risk for infections by 49.6%, and individuals with sarcopenic obesity are at an increased risk by 42.4% (Zhang et al., 2022). The risk for respiratory infections is increased by 56 and 57.4% for individuals with sarcopenia and those with sarcopenic obesity, respectively (Zhang et al., 2022). Common infections include that of respiratory nature, urinary tract infection (UTI) and soft tissue infection. Patients with infections also show significantly higher content of inflammatory markers, associated with higher risk for infection overall (Zhang et al., 2022). Sarcopenic patients are also at a relatively higher risk for nosocomial infections, oftentimes resulting in long-term effects such as dysphagia, a decrease in autonomy, and an increased dependence on medical devices (Cosquéric et al., 2006). Furthermore, a retrospective study showed higher incidences of pneumonia in sarcopenics versus non-sarcopenics (Altuna-Venegas et al., 2019), in line with other findings in support of increased respiratory infections among sarcopenic individuals (Zhang et al., 2022).

There is currently a consensus that people with sarcopenia are more likely to be admitted in hospital in comparison to their non-sarcopenic counterparts, which is also shown that the

likelihood is further increased with age (Giglio et al., 2018; Zhang et al., 2018; Olesen et al., 2019; Sousa et al., 2016). Furthermore, it is also known that patients with sarcopenia not only tend to be older and present longer hospital stays than those without sarcopenia, they also show lower probability of discharge than individuals with no sarcopenia (Sousa et al., 2016). Oftentimes, a decrease in QoL and physical function level are 2 phenomena observed with an increase in hospitalization in adults with muscle loss (Olesen et al., 2019). Although sarcopenia has been shown to be useful to predict the likelihood for hospitalization, it is not a strong predictor for length of hospital stay (Zhao et al., 2019). In the case of older adults who are already hospitalized, identification of progressive sarcopenia can be useful to predict readmission to hospital (Zhao et al., 2019).

Upon consideration of these findings, many research advances have been made to investigate whether sarcopenia can be used as a prediction tool for mortality in various populations. Overall, it is shown that sarcopenia poses higher all-cause mortality risk in older females, independent of risk factors such as obesity (Batsis et al., 2014). But as previously mentioned earlier in the literature review, sex would be considered a sufficient factor given the presence of inconsistent findings in various databases. Muscle mass loss also can be used as a prediction tool for mortality, especially in geriatric populations and in individuals, who present with risk factors and comorbidities related to sarcopenia, such as obesity and metabolic syndromes (Filippin et al., 2015). There are also other literatures available that studied the relationship between mortality and sarcopenia, but overall findings are consistent that support the strong statistically significant association between sarcopenia and mortality, regardless of the study population, operational definition, and follow time (Xu et al., 2021). These results should trigger the development of an action plan to implement efficient screening tools and preventative interventions to reduce early mortality. To mitigate these outcomes, physicians and academics have made many attempts to try to find a way to simple, user-friendly measure and quantify sarcopenia, which will be discussed in subsequent parts of this thesis.

PMA as a Potential Marker for Sarcopenia

Researchers have begun to examine ways to measure sarcopenia to better the QoL of patients affected by this debilitating condition. The current literature approves of many different methods of measurement for lean muscle mass, but two commonly used and often preferred means are dual X-ray absorptiometry (DXA) and bioimpedance analysis (BIA) (Yanishi et al., 2018). Although both are widely used across the medical field, DXA is preferred over BIA, as the latter tends to overestimate muscle compared to the former (Lee et al., 2018; Buckinx et al., 2015). However, it is important to note that skeletal muscle mass could be measured by either BIA or DXA without any statistically significant difference between the two, deeming both methods accurate in measuring the presence of sarcopenia. Also, both have been shown to correlate highly with muscle mass. In the case of a large-scale study, the use of BIA may be favoured over DXA from a standpoint of cost, user-friendliness, and possible exposure to radiation, which could all be concerns for geriatric populations (Wang et al., 2016). Considering these findings, DXA would be considered the current gold standard way of marking sarcopenia, however in the case of equipment shortage, BIA could also be used as an alternative without statistically significant compromise in the data if proper standardization methods are applied. There is also other research emerging further investigating other measurement tools, such as using 3D ultrasound techniques, also shown to measure sarcopenia in geriatric populations, another potential for patient follow-up and prognosis (Huet et al., 2023). As researchers continue to evaluate current methods and discover new measurement tools for muscle loss, there could be potential for a new gold standard, one that could be safer and more accessible across the world.

One method that has been suggested to quantify total skeletal muscle quantity is by using surrogate measures such as using the cross-sectional area of the psoas muscle. The psoas is a long fusiform-shaped muscle that lines each side of the spine, ending on the pelvic bone and the femur (Figure 1). This muscle group is known to be a major contributor in the flexion of the hip joint and plays an important role in connecting the upper body to the lower body. The muscle can move through an intricate innervation system involving the spinal nerves, specifically the anterior rami at the lumbar spine (L1-L4), and in part the femoral nerve (Siccardi et al., 2022).

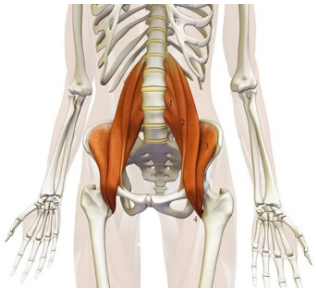

***Figure 1**. The psoas muscle group (Muraski, 2015)*[1]

There is literature supporting the use of the cross-sectional area of the psoas muscle as a measure for monitoring sarcopenia (See Table 3). Using PMA is not a new practice, as it is found in various studies to estimate skeletal muscle mass (Morrell et al., 2016; Celentano et al., 2020; Miller et al., 2019; Krell et al., 2013). Three common radiographic methods used to measure PMA are magnetic resonance imaging (MRI), computed tomography (CT), and DXA. With extensive research involving psoas muscle imaging, 3 main morphologies were identified: globular (Figure 2), triangular (Figure 3), and elongated (Figure 4). Its role in clarifying clinical outcomes in various population groups make PMA a widely accepted surrogate to estimate overall lean body mass (Morrell et al., 2016; Celentano et al., 2020). The psoas muscle has not only shown its use in predicting post-operative complications such as morbidities and mortality (Drudi et al., 2016; Hawkins et al., 2018), it has also proven to positively correlate with weight and BMI (Jones et al., 2014; Drudi et al., 2016). Given its capability of predicting negative health outcomes and in estimating whole lean body mass, PMA could see use in identifying high risk subsets in patients with sarcopenia who would be able to benefit from preop and postop intervention plans to increase overall muscle function (Drudi et al., 2016).

Table 3. Studies Using Cross-Sectional PMA to Quantify Sarcopenia Prevalence

Author	Population	Method	Prevalence
Okada et al., 2021	Intensive Care Unit Patients	CT Scan	33%
Nishimura et al., 2020	Geriatrics	CT Scan	25%
Harada et al., 2017	Nephrology Outpatients	CT Scan	41%

1 See Muraski (2015). Reprinted with permission. See Appendix A.

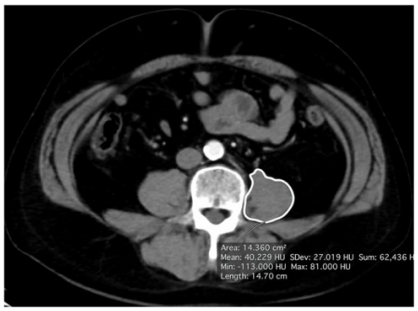

Figure 2. *A globular-shaped psoas muscle pair observed in male patients (Noguchi et al., 2020)*[2]

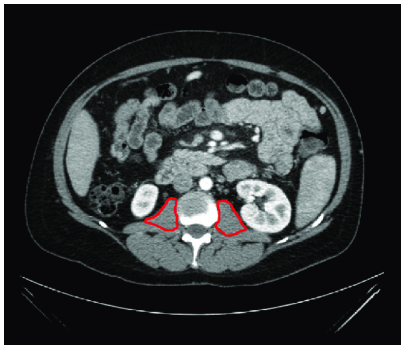

Figure 3. *A triangular psoas muscle pair observed in post-liver transplant patients (Graham et al., 2020)*[3]

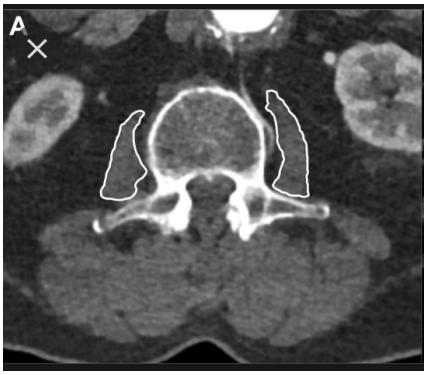

Figure 4. *An elongated psoas muscle pair observed in patients who have undergone a fenestrated and branched endovascular aortic repair (Kärkkäinen et al., 2020)*[4].

2 Reprinted from Noguchi et al. (2020). Licensed under Creative Commons.

3 Reprinted from Graham et al. (2020). Licensed under Creative Commons.

4 Reprinted from Journal of Vascular Surgery, Volume 73, Kärkkäinen, J. M., Oderich, G. S., Tenorio, E. R., Pather, K., Oksala, N., Macedo, T. A., Vrtiska, T. J., Mees, B., & Jacobs, M. R., soas muscle area and

As research on the effects of sarcopenia on patients with CKD is relatively new, more studies must be conducted to fully understand the impact sarcopenia has on wellbeing.

Understanding Sarcopenia-Related Health Outcomes in CKD Populations

Sarcopenia is an age-related condition and that is often ignored until it causes significant damage to the body, giving rise to many negative side-effects and worsening the state of any existing comorbidities. One of these comorbidities is CKD, where prevalence for sarcopenia can reach up to 65.5% (Souza et al., 2017). Also, one key aspect of CKD is that the pathology poses higher risk for health complications and mortality amongst affected population groups (National Kidney Foundation, 2002). Despite its high prevalence, this population lacks data on sarcopenia-related poor health outcomes, which is highly likely to play a factor in increased hospital stays, mortality, and medical care costs. It is also crucial to note that, in comparison to the CKD population, general and geriatric populations have a widely available database of information on infection, hospitalization and mortality rates that are related to sarcopenia.

Furthermore, it is known that infections are known to contribute to various health complications in CKD populations, stressing the need to clarify this relationship. Overall, CKD patients present with higher hospital admissions and longer stays for infections of respiratory nature and sepsis versus their healthier counterparts (Dalrymple & Go, 2008; Wang et al., 2011). It is also currently known that exposure to infectious disease is independently associated with an increased risk for all-cause mortality, which is further increased in advanced CKD (Chang et al., 2020). A possible explanation for high hospitalizations could be caused by the infections, which are more likely to occur with the presence of risk factors like age, hypoalbuminuria, immunosuppressive therapies and poor nutritional status (Dalrymple & Go, 2008). Literature stresses that infection is a major but often overlooked complication of CKD, and that more research is needed to better communicate the immense burden infections can cause in CKD populations (Ishigami & Matsushita, 2019). Bacteremia is the second leading cause of death in patients with advanced CKD/ESKD. Researchers found that blood infection tends to increase with

attenuation are highly predictive of complications and mortality after complex endovascular aortic repair, Issue 4, Pages 1178-1188.e1. Copyright (2023), with permission from Elsevier. See Appendix B.

lower estimated GFR. However, the independent interactions of sex and metabolic status with estimated GFR were shown to non-significant (James et al., 2008). The increased risk of blood infections with CKD could be explained that diseases of urologic nature as well as other factors such as nutritional status, chronic inflammation, and metabolic condition (James et al., 2008).

The research presented in this thesis will attempt to fill this gap by attempting to associate sarcopenia with negative outcomes in CKD populations such as hospital admissions, mortality, and infections. This will not only open the door to many possible improvements in CKD patient care, but also to other chronic populations with sarcopenia as a comorbidity. It will allow health professionals to predict risks of mortality in patients showing signs of muscle loss, thus allowing for early diagnosis and treatment, and better recovery via a precise and tailored action plan for each patient. Preventing rapid deterioration of the body will also be achieved by educating CKD patients or any at-risk populations of these findings and on ways to delay the onset or progression of disease.

In summary, given the high morbidity and mortality incidences, there is an urgent need to clarify the relationship between sarcopenia and poor health outcomes in CKD, a lifelong pathology presenting with an abnormally high prevalence of muscle loss.

Research Question and Hypothesis

As it is known that infection rates are high in populations with CKD, its link to sarcopenia has not been clearly stated (Chou et al., 2014). Specifically, there is very limited literature on whether sarcopenia known as decreased muscle mass can be associated with risks of infections, hospitalizations, and mortality in populations with kidney disease. By quantifying sarcopenia using height-adjusted PMA, and by presenting rates of infection, hospitalization and mortality classified by BMI quartiles and disease grade, it is our goal to clarify the relationship between PMA and undesired health outcomes in adults with CKD. The primary objective of this study is to investigate whether PMA is associated with negative health outcomes by presenting the crude and adjusted rates of mortality, infection, dialysis and hospitalizations in our sample according to height-adjusted psoas muscle area quartiles. The independent variable will be sarcopenia, the main exposure, which will be quantified using height-adjusted PMA classified by quartiles. Our

main variables of interest are the rates of infections, hospitalizations, dialysis and mortality in our sample, which will help us develop a Cox-Hazard proportional ratio model for each outcome. Other variables of interest include demographic, anthropometric and laboratory data. The secondary objective of this study is to determine the reliability of using the PMA as a surrogate measure for sarcopenia.

Based on what is currently available in the literature, we hypothesize that sarcopenia would not only increase in prevalence with disease progression, but also that decreased PMA will be associated with a higher risk of developing complications. The findings stemming from this study could suggest a model for a user-friendly screening tool for physicians, allowing for overall higher patient care standards.

CHAPTER 2: METHODOLOGY

Research Method

The study's research method followed a retrospective model as it was our goal to evaluate links in existing data by looking at the events that occurred over time since admission to the renal clinic in relation to our exposure variable, sarcopenia. There are several published studies using a similar model in order to bridge the gap between exposure and outcome as we are in this study (Zakaria et al., 2020; Bankar et al., 2021). The first cited research evaluates whether sarcopenia/frailty can predict survival and morbidity in its sample group by identifying sarcopenia/frailty using a surrogate measure (Zakaria et al., 2020). Likewise, another study followed a retrospective cohort study with 14 years of follow-up to associate frailty with poor health outcomes, where it was found that frailty measured using the Frailty Index was found to associate with worsening health outcomes (Bankar et al., 2021). Both studies clearly demonstrated the usefulness of retrospective studies in predicting survival and other morbidities. Literature also further validates the retrospective model as long as recruitment criteria are clearly defined, and that sample size is sufficient (Copas & Farewell, 2001).

Variable Collection

Demographic data (age, sex, race) was collected for the purpose of describing the participants in the study. In studies like ours, it would be important to present the demographic findings in a clear way for the reader to evaluate whether the sample pool is representative of our population of interest, that of CKD (Lee & Schuele, 2010). In the case that the representation is accurate, findings stemming from our study could potentially be used as a general model in treating patients suffering from CKD. However, in the opposite case, it would be very difficult to generalize the findings to the target population. Alongside demographics, other important components such as laboratory and radiology data, and comorbidities, which will all be further discussed in the following paragraphs.

Laboratory Data

Various laboratory data variables were collected from the patient charts in the clinic to get further insight into the patient's health status such as any deficiencies, infections, or other morbidities (Table 4). All blood samples were collected on the first visit at the nephrology clinic.

Table 4. Laboratory Variables

Laboratory Variable
Estimated Glomerular Filtration Rate
Hemoglobin
Serum Sodium
Serum Potassium
Serum Bicarbonate
Blood Urea Nitrogen
Serum Albumin
Hemoglobin A1C
Thyroid Stimulating Hormone
Blood Cholesterol
Corrected Calcium Albumin
Ionized Calcium
Serum Phosphate
C-Reactive Proteins
Ferritin

1. Estimated GFR

As mentioned in the previous chapter, CKD is diagnosed and classified using the GFR, which is the rate at which the glomeruli filter the blood and produces the filtrate. Given the challenges of directly measuring the filtration rate of the kidneys, it is recommended to estimate the GFR in accordance with the CKD-EPI formula (Levey & Stevens, 2010; Inker et al., 2021).

2. Hemoglobin

Hemoglobin levels is indicative of anemia status in CKD patients. Anemia is known to cause immense burden on the CKD population, with prevalences starting at approximately 11 to 13% and increasing depending on age and disease stage (Hanna et al., 2021).

3. Serum Sodium

In patients with renal deficiencies, impaired filtration channels can result in electrolyte disorders such as dysnatremias (hyper- and hyponatremia), marked by abnormal serum sodium concentrations. Dysnatremia is usually presented as serum sodium concentrations below 135 mmol/L or above 145 mmol/L (Arzhan et al., 2021).

4. Serum Potassium

Serum potassium is also an important biomarker in patients with CKD. Potassium imbalance (hyper- and hypokalemia- is a condition often noted in patients suffering from CKD. Hypokalemia is defined as serum potassium levels below 3.5 mmol/L and hyperkalemia is presented as serum potassium levels >5.0 mmol/L. In CKD, these conditions have shown to be indicative of negative health outcomes such as mortality (Nakhoul et al., 2015; Furuland et al., 2018). Oftentimes, potassium imbalances present with little to no warning sign before sudden health events, stressing the importance of constant monitoring (Kraft et al., 2005).

5. Serum Bicarbonate

Bicarbonate is a "base" substance that helps regulate the body's pH level. In the body, serum bicarbonate, a form of carbon dioxide dissolved the blood, is used as a marker for metabolic acidosis, a condition in which the kidneys are unable rid the excess acid resulting in lower serum bicarbonate relative to acid levels (*Facts about Metabolic Acidosis and Chronic Kidney Disease*, n.d.). A persistent progression in disease with worsening of metabolic acidosis could lead to comorbidity, and all-cause mortality (Fukasawa et al., 2022).

6. Blood Urea Nitrogen

Urea nitrogen is a waste product resulting from protein metabolism that is normally ridden of the body when the renal system functions properly. When kidney function is impaired, urea nitrogen is unable to be properly filtered out, which can result in abnormal levels of blood urea nitrogen (Dossetor, 1966; Seki et al., 2019). Blood urea nitrogen levels have been shown to, deeming it a risk factor for renal disease independently from estimated GFR, suggested in potentially predicting renal outcomes (Seki et al., 2019). It is also a marker of protein intake and malnutrition (Benabe et al., 1998).

7. Serum Albumin

Serum albumin levels are another marker that should be closely monitored as it can be a sign a kidney damage. Albumin is an essential protein that helps the body perform many of its regulatory functions (*What is albuminuria?*, 2022) . In CKD, high levels of albumin protein are

excreted into the urine, resulting in a sufficient decline in serum albumin levels has been shown to closely relate to poor prognosis and overall decrease in organ function, independent of albuminuria (Cheng et al., 2023; Lang et al., 2018).

8. Hemoglobin A1C

Hemoglobin A1C (HgbA1C) levels are used to assess glycemia levels in patients with CKD. Normally, higher HgbA1C levels are strongly associated with more severe cases of CKD after adjusting for traditional risk factors, as well as subsequent cardiovascular events (Hernandez et al., 2013). When HgbA1C is evaluated in the context of sarcopenia, it is reported that higher levels of HgbA1C are associated with lower muscle mass (Qiao et al., 2021). Although HgbA1C levels are important to monitor, it may not be enough to predict poor renal prognosis as someone enters later stages of the disease and/or if they present with coexisting syndromes such as diabetes due to possible inaccurate interpretations (Kang et al., 2015; Copur et al. 2020). In these cases, other supporting laboratory findings would be necessary for better prognosis and treatment plan.

9. Thyroid Stimulating Hormone

An imbalance in thyroid stimulating hormone (TSH) levels could be suggestive of impaired thyroid function. Hypothyroidism has been linked to a worsened estimated GFR, suggesting a link between a lack in TSH and a progression in disease state (Iqbal et al., 2022). Literature also supports that an overt increase in TSH can also put someone at risk for CKD (Chuang et al., 2016). This is because thyroid function and CKD status are closely related. More specifically, lower TSH levels are associated with lower GFR and renal blood flow, whereas higher TSH levels are associated with higher GFR and renal blood flow. Hence, it is inevitable that thyroid dysfunction can pose negative effects on vital renal structure and physiological processes, ultimately diminishing urinary concentrating ability (Basu & Mohapatra, 2012). In relation to sarcopenia, the link between thyroid and muscle mass is complex, but research has found that TSH has a U-curve association with sarcopenia (Szlejf et al., 2020).

10. Blood Cholesterol

Patients with CKD generally present with a poor lipid profile. A poor lipid profile, represented by an overall high triglyceride content and lower high-density lipoprotein cholesterol (HDL-C) content, has been shown to be omnipresent in patients affected by CKD, especially predominant in later stages of the disease (Weldegiorgis & Woodward, 2022). This bi-directional relationship could be explained by an interplay between inflammation, plaque formation and cardiovascular disease. Also, it is also understood that a decrease in HDL-C levels can decrease glucose metabolism, elevating one's risk for diabetes (Weldegiorgis & Woodward, 2022). Although a lower HDL-C content (<30 mg/dL) has been shown to associate with an increased risk for renal damage, research also claims that overtly high serum levels (>or= 60 mg/dL) could increase risk for ESKD in CKD patients, highlighting the U-shaped association between HDL-C levels and ESKD development (Nam et al., 2019).

11. Calcium and Serum Phosphate Levels

Calcium is a crucial mineral in the body as it holds important functions in the optimal functioning of the nervous, musculoskeletal, and cardiovascular systems. Normally, calcium is absorbed into the blood with the help of activated vitamin D before being delivered to the many systems in the body (*Kidney Failure Risk Factor: Serum Calcium*, 2020). Unfortunately, in CKD, the kidneys are unable to absorb calcium in the blood because of the inability to make active vitamin D, usually indicative of calcium-related disorders (*Kidney Failure Risk Factor: Serum Calcium*,2020; Hu et al., 2022). Hence, measuring serum calcium levels would deem useful in identifying calcium disorders in CKD patients (*Kidney Failure Risk Factor: Serum Calcium*,2020 ; Baird, 2011; Minisola et al., 2021; Slomp et al., 2003). Alongside calcium levels, serum phosphate content could also contribute to mineral deficiency in CKD. In CKD, the kidneys are unable to rid the excess phosphorous from the circulation, which contributes to a state of hyperphosphatemia (Fourtounas, 2011). An excess in serum phosphate can further contribute to vascular calcification via osteoblastic transcription activity in the blood vessels, making it an indispensable cardiovascular risk factor (Mathew et al., 2008). The current recommendation is that serum phosphate levels should be situated between 0.87 and 1.78 mmol/L depending on CKD

progression (Fourtounas, 2011; Hruska et al., 2009; Mathew et al., 2008). In summary, poor calcium and serum phosphate profiles could lead severe mineral deficiency, possibly ending in bone disorders and overall weakness (Hu et al., 2022).

12. C-Reactive Proteins

CRPs are inflammatory markers indicative of infection that is often studied in CKD risk and progression (Gao et al., 2020, Tonelli et al., 2005). Chronic inflammation and exposure to CRP is a known factor to contribute to an increased risk for developing CKD (Gao et al., 2020). Research has also shown that higher baseline levels of CRP are associated with an accelerated decline in kidney function and concomitantly lead to kidney failure if not treated (Tonelli et al., 2005), or in worse cases, mortality (Menon et al., 2005).

13. Ferritin

Ferritin is a blood protein that contains iron (Worwood, 1990), making it an important marker for iron status among the CKD population. Ferritin helps regulate the metabolism and availability of iron for erythropoiesis, a process by which new red blood cells are produced (Ueda & Takasawa, 2018). Iron insufficiency resulting from abnormal ferritin levels can lead to iron deficiency anemia (IDA). IDA can either be absolute or functional. Absolute iron deficiency present with low iron stores and a serum ferritin concentration = or < 100 ng/mL in predialysis patients. In functional iron deficiency, however, iron stores are adequate, but there is an insufficient amount of iron available for erythropoiesis, which would present as elevated ferritin levels (Gafter-Gvili et al., 2019). The independent effects of ferritin on CKD progression not clearly establish given that it can also be influenced by inflammation, hence it is recommended that both factors are considered for prognosis of a patient with CKD (Ueda & Takasawa, 2018).

Psoas Muscle Area Measurement

Several ways to estimate whole-body skeletal muscle mass are available. One of the methods is by measuring a specific region of the body and using it as a surrogate measure. It has been shown that PMA is a widely accepted surrogate to estimate overall lean body mass (Morrell et al., 2016; Celentano et al., 2020) given its accuracy and user-friendliness (Jones et al., 2014).

PMA measurements tend to be user-friendly in that they are non-invasive, do not require any extensive training, and that the scans are routinely requested in the clinic and, thus, usually widely available. PMA measurements have been widely used to quantify muscle mass and define sarcopenia for ease of assessment. PMA has also been evaluated and applied in a population undergoing hemodialysis (Ito et al., 2021; Yajima et al., 2022; Yamaguchi et al., 2021). Total PMA, when compared to cross-sectional area measured the lumbar vertebral level, show high degree of correlation (Jones et al., 2014; Zannoni et al., 2020). Despite this, there is variation in the psoas muscle parameters based on factors like age, sex, race, and total body surface area (Baracos, 2017), which can create discrepancies in measurements and cut-off values. In order to adjust for body size, PMA measurements have been standardized by height in our study.

Assessing sarcopenia indirectly with the psoas muscle has not only shown its use in predicting post-operative complications (Drudi et al., 2016; Hawkins et al., 2018), it has also proven to positively correlate with weight and BMI (Jones et al., 2014; Drudi et al., 2016). Given its capability of predicting negative health outcomes and in estimating whole body mass, PMA could see use in identifying high risk subsets in patients with sarcopenia who would be able to benefit from preoperative and postoperative intervention plans to increase overall physical function (Drudi et al., 2016). Furthermore, we are also seeing many studies supporting the use of PMA as a surrogate measure for sarcopenia and frailty in various chronic populations (Derstine et al., 2017; Okada et al., 2021; Bahat et al., 2021; Nishimura et al., 2020; Ito et al., 2021; Morrell et al., 2016; Harada et al., 2017).

In the clinic, PMA was measured using the Dicom RADiant Viewer Software visualizing software and hand-tracing tool. A cross-sectional area of the abdomen at the lumbar spine was retrieved for all patients. The right and left psoas muscles were identified and were traced using the cursor. Both observers each took turns and completed all the measurements. Afterwards, their measurements (right and left) were averaged, and another average was calculated from both observers' right and left PMA average. Each observer's average was averaged once again and divided by the height for each patient to account for body size.

Outcome Collection

Over the course of the study, outcomes collected included the following: infections, dialysis history, transplants, hospitalizations, transfers, loss to follow-up and death. The frequency of infections and hospitalizations were reported as dates until the end of study date. The point at which the study ended included the occurrence of any of the following events: patient transfer, loss to follow up, dialysis and/or death.

Hospitalization

Hospitalization was confirmed in the occasion that the patient has been admitted to the emergency for a duration equal to or longer than 72 hours. This was validated by consulting the patient's medical records and charts and through identification of 3 blood tests on 3 consecutive days.

Infection

1. Pneumonia

The presence of pneumonia was confirmed by identifying 2 of the 3 following criteria: a positive chest X-ray diagnosis written in the medical report by the radiology department, an elevated white blood cell count, and either a product cough with antibiotic use or admission to hospital. Chest X-rays were provided by the on-site radiologist and visualized on the McKesson Laboratories Software. The measurement done was time to first infection. A cut-off of 10 infections was applied.

2. Urinary Tract Infection

An occurrence of a UTI was confirmed when a positive urine culture was accompanied by either antibiotics or hospital admission. Documentation of urinary tract infection was cut off at a total of 10 UTIs, which was selected arbitrarily. The outcome measure was time to first infection.

3. Bacteremia

Bacteremia status was confirmed in the event where at least 2 positive blood cultures were identified when consulting the medical charts. Subsequently, patients also had to be admitted to the hospital for the event to be considered valid.

Transplant and Dialysis Histories

Transplant and dialysis histories were confirmed by consulting patient charts and the clinical database system. Transplant was confirmed by consulting the patient's medical records and double-checked with the on-site nephrologist. For dialysis, serum creatinine levels were monitored on the database system. Normally, dialysis was confirmed by identifying drastic changes in estimated GFR and serum creatinine levels, and by consulting the on-site nephrologist for further validation.

Transfer and Loss to Follow-up

Patient transfer status was confirmed consulting the clinic database, the government registry or, in rare cases, by contacting the patient's family members for follow-up purposes. Loss to follow-up status was confirmed in a similar manner. However, the loss to follow-up was also validated through laboratory testing which indicated patient was alive but did not follow-up on the regular scheduled visits.

Mortality

Mortality was confirmed in various ways due to the lack of information for some patients. As these subjects were regularly followed for three to four times a year, mortality was confirmed when no further blood tests were performed and documented in the hospital database system. Mortality status was also confirmed if there was documentation in the clinical charts. If no information was available from patient charts or clinical database, the government portal was consulted by the on-site nephrologist. In very few cases, where patients relocated to another country, the family members were contacted for follow-up purposes and asked about patient status.

Statistical Analyses

Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc.). Significance levels were set at a p value of 0.05 and all continuous variables from the univariate analyses were presented either as means and standard deviations, or as medians and ranges. A statistical significance with a p value between 0.05 and 0.10 was indicative of a trend. Univariate analyses were performed on all variables and exposure variables and cumulative outcome rates were computed. Kruskal-Wallis tests were performed on several groups for comparison and statistical similarities for health outcomes. Psoas muscle area measurements were adjusted by height and categorized into quartiles, and by using the Spearman Correlation, interobserver reading reliability was evaluated. For ease of analysis, the Charlson Comorbidity Index (CCI) was applied and its relationship with PMA was evaluated using a general linear regression model. Any statistically significant variables from the bivariate analyses were included in the multivariate models. Time to event analyses were presented using Cox Hazard proportional models evaluating relationships using PMA as the exposure variable. Outcomes of time to first infection, time to first hospitalization, time to first dialysis, and mortality were analyzed.

CHAPTER 3: MANUSCRIPT

Psoas Muscle Area as a Measure for Sarcopenia and a Predictor of Health Outcomes in Chronic Kidney Disease

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Abstract

Background: Sarcopenia often presents in parallel with chronic kidney disease (CKD), associated with a deconditioned state, chronic inflammatory state, and poor nutritional status. Psoas muscle area (PMA) measurements have been previously associated with mortality in CKD however, whether these measurements can be useful in predicting other clinical outcomes such as hospitalizations, infections and other health events are less established. **Objective:** The primary objective of this study is to report the association of PMA with hospitalizations, hemodialysis, mortality, and infections in patients with CKD. **Methods:** A retrospective non-matched cohort study was conducted in a community nephrology clinic in Quebec, Canada, and included laboratory, radiological, and demographic data collected from April 1, 2015, until December 30, 2021. PMA was measured by two independent readers using the Dicom RADiant Viewer Software. **Main Findings:** 269 clinic charts were reviewed and included. Subjects had a median age of 74 years (IQR 31-92) with 58.3% reported as male (156/269). The prevalence of Grade 1 and 2, Grade 3, Grade 4 and Grade 5 CKD was 3%, 53%, 32%, and 10%. Median follow-up time was 1160 days (28-2516). Median measurement of PMA/height was 3.53 cm^2/m (0.5-8.73). Statistically significant concurrent relationships were documented between PMA and evneent-free time for dialysis and hospitalization. The adjusted hazard ratio (HR) for PMA < 2.66 cm^2/m are 0.39 (95% CI 0.16-0.94), p=0.0356. For hospital-free time, the adjusted HR for PMA quartiles showed a dose-dependent increase in effect size, with PMA about a 2-fold higher hazard risk ratio seen for a longer hospital-free period, (p=0.0273). The Cox hazard proportional multivariate analyses documented the concurrently negative relationships between PMA and length of survival and infection-free time, reaching a trend towards significance. For length of survival, PMA < 2.1 cm^2/m had an adjusted Hazard risk reduction of 82 % (HR 0.18 (95%CI 0.024-1.38)) and similarly for infection-free time until the first event, the adjusted HR for PMA < 2 cm^2/m are 0.38 (95% CI 0.17-1.0). **Conclusion:** Our study demonstrated an overall association between increased health complication rates with increased comorbidity and decreased PMA. Further prospective studies are needed to identify methods for muscle mass sustainability.

Résumé

Contexte: La sarcopénie se présente souvent en parallèle avec l'insuffisance rénale chronique (IRC), souvent associée à un état de déconditionnement et inflammatoire, ainsi un mauvais statut nutritionnel. Les mesures de la zone musculaire du psoas montrent déjà des associations à la mortalité dans l'IRC, spécifiquement l'aire musculaire du psoas (AMP). Cependant, l'utilité de ces mesures pour prévenir d'autres résultats cliniques est moins établie, tels que les taux d'hospitalisations, d'infections et d'autres événements de santé.

Objectif: L'objectif principal de cette étude est de rapporter l'association de l'AMP avec les hospitalisations, l'hémodialyse, la mortalité et les infections chez les patients atteints de l'IRC.

Méthodologie : Une étude rétrospective a été menée dans une clinique de néphrologie communautaire au Québec, au Canada, et comprenait des données de laboratoire, radiologiques et démographiques, du 1^{e} avril 2015 à la fin du mois de décembre 2021. L'AMP a été mesuré par deux lectrices indépendantes à l'aide du logiciel de visualisation DICOM RADiant.

Résultats : 269 dossiers ont été examinés et inclus. Les participants avaient un âge médian de 74 ans (EI 31-92) avec 58.3% étant des mâles (156/269). Les prévalences des IRC de grade 1 et 2, de grade 3, de grade 4, et de grade 5 étaient de 3%, 53%, 32% et 10%, façons respectives. La durée médiane de suivi était de 1160 jours (28-2516). La mesure médiane de l'AMP ajusté par la taille était de 3.53 cm^2/m (0.5-8.73). Des relations concomitantes statiquement significatives ont été documentées entre AMP et le temps sans événement pour la dialyse et l'hospitalisation. Le rapport de risque ajusté (RR) pour une AMP moins de 2.66 cm^2/m était de 0.39 (IC à 95% 0.16-0.94, p=0.0356). Pour le temps sans hospitalisations, le RR ajusté pour les quartiles d'AMP a montré une augmentation dose-dépendante de la taille de l'effet, avec un RR de PMA environ 2 fois plus élevé observé pour une période sans hospitalisations plus longue (p = 0.0273). Les analyses multivariées proportionnelles au risque de Cox ont documenté des relations simultanément négatives entre l'AMP et la durée de survie et le temps sans infection, atteignant une tendance à la signification. Pour la durée de survie, un AMP moins de 2,1 cm^2/m avait une réduction du risque de risque ajustée de 82 % (RR=0.18 (IC à 95 % 0.024-1.38)) et de même pour

le temps sans infection jusqu'au premier événement, le RR ajusté pour un AMP moins de 2 cm^2/m = 0.38 (IC à 95 % 0.17-1.0).

Conclusion : Notre étude a démontré une association entre l'augmentation des taux de complications de santé avec une comorbidité accrue et une diminution de l'AMP. D'autres études prospectives sont nécessaires pour identifier des méthodes efficaces pour maintenir la masse musculaire.

Introduction

Sarcopenia is an age-related disease characterized by muscle and function loss as well as a physical marker of frailty affecting 10% of males and 10% of females in the general population (Shafiee et al., 2017) and up to 22.6% in populations around the age of 84 years (Bertschi et al., 2020). Unfortunately, sarcopenia is known to drive mortality rates and high medical care costs, causing immense burden to society. Sarcopenia is also known to have an abnormally high presence in a subset of individuals where this debilitating condition is linked to chronic inflammation along with poor nutritional status (Cobo et al.,2018): chronic kidney disease (CKD). Sarcopenia has a prevalence of 34.5% in earlier CKD stages/grades and can go up to 65.5% in later stages/grades (Souza et al., 2017). One of the complications often seen in CKD is metabolic acidosis, which is often linked to protein muscle wasting through the means of protein-degrading mechanisms overpowering those responsible for protein synthesis (Sato et al., 2016). The study describes uremic toxin indoxyl sulfate which stimulates an antioxidant response and mitochondrial dysfunction (Sato et al., 2016). There are currently many ways to measure sarcopenia, out of which an indirect measurement such as psoas muscle area has been used in the literature. Studies have shown that low psoas muscle area can be used as a marker of sarcopenia and frailty in various clinical populations (Nishimura et al.,2020), as well as those with CKD (Yang et al., 2022). There is also a general consensus that infection and frailty have a bidirectional relationship. Frailty is known to be a predictor of healthcare associated infections, and vice versa (Consentino et al., 2021; Vetrano et al., 2021).

Despite sarcopenia being highly prevalent in CKD, it is also known to affect a wide range of other chronic medical diseases. One widespread metabolic disease that commonly presents with sarcopenia is Type-2 diabetes mellitus (T2DM), where it is known that roughly 15% of the population with diabetes mellitus is affected by muscle loss and frailty (Wang et al., 2016; Chung et al., 2021). Studies also show that people suffering from diabetes are at a 50% increased risk for presence of sarcopenia than their healthy counterparts (OR=1.518, 95% CI:1.110-2.076, p=0.009) (Chung et al., 2021). Similarly in other comorbidities, sarcopenia is also widely prevalent in chronic lung disease. It is currently agreed upon that sarcopenia in chronic obstructive pulmonary disease (COPD) is one of the relationships that is linked to adverse outcomes. Prevalence of

sarcopenia ranged from 24 to 39.6% with these two studies but the severity of COPD showed proportional increase in the sarcopenia prevalence. (Costa et al., 2015; Limpawattana et al., 2017). Like patients with T2DM, those with COPD are also 3-fold more likely to have sarcopenic obesity than their healthy counterparts (OR=3.3, 95% CI:2.0-5.4, p<0.001) (Joppa et al., 2016). Patients with interstitial lung disease have a prevalence of frailty between 12 to 50 % (Guler & Ryerson, 2020). Other chronic diseases are also known to be associated with frailty such as cancer, cirrhosis, and cardiomyopathy (Wijarnpreecha et al., 2019; Barreto et al., 2021; Suzuki et al., 2018).

With a growing number of health incidences in a population where sarcopenia is highly prevalent, it is important to develop and evaluate a user-friendly marker of sarcopenia to better quantify the risk of poor health outcomes such as infections, hospitalizations and mortality rates among CKD patients (Dalrymple & Go, 2008; Hemmelgarn et al., 2010; James et al., 2008).

The primary objective of this study is to report the association of PMA with negative health outcomes (hospitalizations, hemodialysis, mortality and infection) in patients with CKD. By quantifying sarcopenia prevalence using height-adjusted PMA measurements, and by presenting rates of infection, hospitalization and mortality based on PMA and body mass index (BMI) quartiles, this study intends on further investigating the relationship between PMA and the aforementioned health outcomes in adults with CKD. A secondary objective of this study is to determine the reliability of using the psoas muscle area as a surrogate measure for sarcopenia.

The objectives were met in a retrospective non-matched cohort study, consisting of 269 patient datafiles from the web-based PAC's database in a nephrology clinic of a community hospital in Pointe-Claire, Quebec. Data included laboratory and radiological results, and demographics from April 1, 2015, until December 31, 2021. Furthermore, PMA was measured by two independent readers using the Dicom RADiant Viewer Software.

Methods

The study protocol was granted research ethics approval from the St. Mary's Hospital Research Ethics Board, meeting the criteria for the Helsinki declaration.

Data was collected from the charts of a nephrology clinic in Pointe-Claire, Quebec. In the clinic, there are 5 physicians, all nephrologists, each attending to around 250 patients. However, for the purpose of this study, only one physician's data was collected. In a random sampling pool, 269 medical charts from the community hospital nephrology clinic were identified and included. Prior to this, 1000 original charts were present, out of which 358 met the inclusion criteria. Finally, 269 presented with computed tomography (CT) scans and met the inclusion criteria. All data sets were collected and entered into an electronic Excel database. For samples to be considered valid for the study, the inclusion criteria were to be met: at least 18 years old, estimated GFR readings equal or under 90 mL/min/1.73m^2 and a patient in the renal clinic for at least 6 months. Patients who met at least one of the exclusion criteria were not included in the study: presence of acute kidney injury (AKI), life expectancy of no more than 6 months, undergoing any acute surgery or chemotherapy or admitted in hospital frequently and resulting in AKI.

Variables collected from the charts included patient profiles, psoas anthropometrics, renal diagnosis, any comorbidities and/or risk factors, baseline estimated GFR, laboratory and radiology results from April 1st 2015, until December 2021. Estimated glomerular filtration rate was calculated using the CKD Epidemiology Collaboration (CKD-EPI) formula (Levey & Stevens, 2010). The laboratory data variables were collected from patient charts and help better understand patient health status such as any deficiencies, infections, or other morbidities. Laboratory variables included the following: estimated GFR, hemoglobin, serum sodium and potassium, serum bicarbonate, blood urea nitrogen, serum albumin, hemoglobin A1C, TSH, uric acid, blood cholesterol, calcium corrected for albumin, ionized calcium, serum phosphate, CRP, and ferritin.

Outcomes that were identified included infections (blood, pneumonia, urine), transplants, hospitalization occurrences, dialysis history, date of transfer, loss to follow-up and death. Urinary tract infection (UTI) was defined as a positive urine bacterial culture and use of antibiotics or admission to hospital. Pneumonia was defined as two of the three following findings: positive diagnosis from chest x-ray scans, elevated white cell count, and productive cough with antibiotic use or admission to hospital. Bacteremia was defined as two or more aerobic or anaerobic bottles of positive bacterial culture and requiring admission to hospital. Hospitalization was defined as

the date when the patient was admitted to the emergency department for more than 72 hours. Lastly, mortality was defined as documentation from the clinic charts and no further blood tests in the database system. Data on mortality were first taken from hospital laboratory PACS reports. In the case of any missing information, we would confirm it using written hospital laboratory results.

The main exposure variable was a marker of sarcopenia, which was determined using psoas muscle area as a surrogate measure for whole body lean mass. Psoas muscle area was measured manually using a digital software on patient routine CT scans. Right and left psoas muscle areas and perimeters along with respective averages were calculated for each reader. Inter-reader values were also calculated. Lastly, each average psoas muscle area (factoring both readers) was adjusted by height by dividing each measurement with the patient's height squared in meters.

Statistical analyses were performed on SAS 9.4 Statistical Analysis Software. All prevalence data was estimated as a percentage with 95% confidence intervals using binomial proportions. Continuous variables were summarized as medians, ranges, means and standard deviations. Psoas muscle measurements height adjusted were categorized by quartiles. Interobserver readings were assessed using Spearman correlation coefficient. The cumulative crude rates were calculated for the psoas muscle quartiles. A linear regression model was applied to assess the relationships between the Charlson Comorbidity Index (CCI) and PMA measurements, with BMI individually. The CCI is a widely used analysis tool in clinical research that help predict long-term mortality in different population subgroups (Charlson et al., 2022). One of the main clinimetric properties of the CCI is that of incremental validity, where adding this index to other measures better predicts mortality-related outcomes (Charlson et al., 2022). The effect size and statistical significance for PMA measurements adjusted by height in percentiles were explored for 5^{th}, 7.5^{th}, 10^{th}, 25^{th}, 33^{rd}, 50^{th}, 55^{th}, 60^{th}, 66^{th}, 75^{th}, 95^{th} percentiles. Due to the largest effect size and statistical significance, the relationships between psoas muscle measurements by percentile and time free of events (infection, hospitalization, dialysis and mortality) were utilized to apply unconditional and adjusted Cox Hazard Proportional

models. Variables found statistically significant in the bivariate analyses were included in the final multivariate models.

Research Findings

A total of 269 patient files were included in this study, where 42% were female and 58% were male along with 30.5% who either were first or second-generation immigrants. The study group was mostly of Caucasian race. The median body mass index was 28.0 (14.8-53.2), 45.7% had a diagnosis of diabetes mellitus, 75.5% were hypertensive and 33% had cardiovascular disease (Table 5). Baseline laboratory data showed a median estimated GFR of 33.0 (9-79) mL/min/1.73m^2, respectively of Grade 3 CKD (Table 6). The cumulative crude urinary tract infection rate and pneumonia rate was 5.7 per person- months and 1.5 per person-months (Table 7). Patients were followed for a median 1160 days (28-2516) (Table 8). The cumulative crude event rates for hospitalization, dialysis and mortality were 10.2, 33.3, and 3 person-months, respectively (Table 7). Statistical significance levels were calculated using 95% confidence intervals.

Table 5. Patients Baseline Characteristics

Demographics	**n**	**Median/Proportion**	**Range/Ratio**
Age (years)	269	74	31 – 92
Sex	269		
Female		42	113
Male		58	156
Race	269		
Arab		9.3	25
Asian		15.6	42
Black		5.02	14
Caucasian		68.0	183
Hispanic		1.9	5
First or second-generation immigrant	269	30.5	82
Clinical			
Body mass index	267		
Class 1 less than 18.5 (kg/m^2)		1.9	5
Class 2 18.5-24.9 (kg/m^2)		26.6	71
Class 3 25-29.9 (kg/m^2)		34.5	92
Class 4 greater than 30 (kg/m^2)		37	99
Weight (kg)	269	79	43.0 – 171.0
Height (m)	269	1.68	1.45– 1.96

Systolic blood pressure (mmHg)	229	143	88 – 239
Diastolic blood pressure (mmHg)	229	75	40 – 102
Body mass index (kg/m^2)	269	28.0	14.8-53.2
Charlson Comorbidity Score	269	7	2-13
Chronic Kidney Disease	269		
Grade 2		3	8
Grade 3		52.8	142
Grade 4		34.6	93
Grade 5		9.6	26
Renal diagnosis	269		
Cardiorenal		4.1	11
Diabetes mellitus		30.1	81
Glomerular disease		15.0	40
Renovascular		27.9	75
Other		23.04	62
Medical Records Diagnosis			
Coronary artery disease	269	33.1	89
Diabetes Mellitus	269	45.7	123
Hypertension	269	75.5	203
Congestive heart failure	269	21.2	57
Chronic Obstructive Pulmonary Disease	269	20	54
Obstructive sleep apnea	269	6.32	17
Hypothyroidism	269	14.9	40
Dementia	269	3.72	10
Pacemaker	269	5.58	15
Atrial fibrillation	269	14.1	38
Gout	269	16.4	44
Gastroesophageal reflux disease	269	11.5	31
Peripheral vascular disease	269	16	43
Cerebrovascular disease	269	10.4	28
Cirrhosis	269	2.2	6
Cancer	269	31	84
Deep venous thrombosis	269	3.4	9
Dyslipidemia	269	47.2	127
Autoimmune	269	14.9	40

Table 6. Baseline Laboratory Data

	n	Median/Proportion	Range/Ratio
Estimated GFR(mL/min/1.73 m^2)	269	33.0	9.0 – 79.0
Hemoglobin (g/L)	267	122	76 – 172
Serum Sodium (mmol/L)	269	139	127 – 148
Serum Potassium (mmol/L)	269	4.5	2.6 – 6.0
Serum Bicarbonate (mmol/L)	232	25	14 – 33
Blood urea nitrogen (mmol/L)	252	11.5	3.2 – 42.8

Serum Albumin (g/L)	263	38	19- 47
Hemoglobin A1c (%)	251	6	4.4– 14.70
TSH (mIU/L)	230	1.83	0.06 – 109.50
Uric Acid (umol/L)	255	391	172 – 879
Total cholesterol (mmol/L)	243	4.4	1.74 – 8.6
HDL cholesterol (mmol/L)	239	1.13	0.54 – 2.44
LDL cholesterol (mmol/L)	239	2.1	0.02 – 5.9
Calcium Corrected for Albumin (mmol/L)	203	2.4	1.2 – 2.8
Ionized Calcium (mmol/L)	50	1.255	1.13 – 1.54
Serum Phosphate (mmol/L)	261	1.2	0.63 – 2.26
C reactive protein (mg/L)	215	5.8	1.6 – 145.0
Ferritin (ug/L)	251	74.0	3-1022.0

Table 7. Crude Rates Categorized in Height-Adjusted Psoas Muscle Area Quartiles

Person-Month Rate	Overall	Q1	Q2	Q3	Q4
Death	3	0.3	1.8	0.3	0.6
Dialysis	33.3	30.6	0.3	1.8	0.6
Urinary tract infection	5.7	1.2	1.8	1.8	0.6
Pneumonia	1.5	0.6	0.3	0	0.6
Hospitalizations	10.2	2.1	2.7	4.2	1.2

Table 8. Time to follow-up and Proportion of Events

Variable	N	Median/Proportion	Range/Ratio
Time of follow-up (days)	269	1160	28-2516
Transfer	269	23.4	63
Dialysis	268	19.3	51
Mortality	269	12.3	33

Baseline characteristics and baseline laboratory data were organized by PMA quartiles, showing statistically significant associations with age, sex, body composition, the presence of sleep apnea, hypothyroidism, hemoglobin levels, serum albumin content, high-density lipoprotein cholesterol, albumin-corrected calcium, and serum phosphate ($p<0.05$) (Table 9,10). Crude person-month rates have been categorized in height-adjusted PMA quartiles, showing varying non-statistically significant trends for each outcome (Table 11). The PMA quartiles are defined as the value of the PMA with height adjusted at 0 to 25th percentile, 25th to 50th percentile, 50th to 75th percentile and greater than 75th percentile. The same system would

be applied for BMI quartiles. The overall interobserver correlation of psoas muscle area measurements approximated 0.7 (Table 13).

Table 9. Baseline Characteristics categorized by height-adjusted psoas muscle area quartiles

	Q1	**Q 2**	**Q3**	**Q4**	**P-value**
Demographics	Median/Proportion	Median/Proportion	Median/Proportion	Median/Proportion	
Age (years)	79 (52-92)	75.5 (41-92)	70.5 (37-92)	69 (31-91)	**<0.0001**
Sex					**<0.0001**
Female	81 (55)	53 (35)	28 (19)	6 (4)	
Male	19 (13)	47 (31)	72 (49)	94 (63)	
Race					0.4871
Arab	7.4 (5)	4.6 (3)	12 (8)	13.4 (9)	
Asian	22 (15)	15 (10)	12 (8)	13.4 (9)	
Black	3 (2)	3 (2)	3 (2)	12 (8)	
Caucasian	66 (45)	77 (51)	72 (49)	57 (38)	
Hispanic	1.5 (1)	0 (0)	57 (38)	4.5 (3)	
Clinical					
Charlson Comorbidity	8 (3-13)	7 (2-13)	7 (2-12)	7 (3-12)	**0.0336**
Body mass index	25.4 (15.8-48.8)	27 (19-50)	28 (18-53)	30 (15-52)	**0.0005**
Class 1 < 18.5 (kg/m^2)	3 (2)	43 (29)	29 (20)	25 (17)	**0.0003**
Class 2 18.5-24.9	0 (0)	32 (21)	38 (25)	30 (20)	
Class 3 25-29.9 (kg/m^2)	1.5 (1)	21 (14)	38 (26)	40 (27)	
Class 4 > 30 (kg/m^2)	3 (2)	11 (7)	32 (21)	54 (35)	
Weight (kg)	70.9 (43-121)	74 (53-125)	83 (47.5-171)	87 (47-136)	**<0.0001**
Height (m)	1.6 (1.5-2)	1.7 (1.5-1.9)	1.7 (1.4-1.9)	1.7 (1.5-1.9)	**<0.0001**
CKD					
CKD 2	1.5 (1)	4.6 (3)	3 (2)	3 (2)	0.6823
CKD 3	62 (42)	41 (27)	50 (34)	58 (39)	
CKD 4	28 (19)	47 (31)	37 (25)	27 (18)	
CKD 5	9 (6)	7.6 (5)	27 (18)	12 (8)	
Renal diagnosis					0.9825
Cardiorenal	3 (2)	4.6 (3)	4.4 (3)	4.5 (3)	
Diabetes mellitus	29 (20)	29 (19)	25 (17)	25 (17)	
Glomerular disease	19 (13)	14 (9)	19 (13)	19 (13)	
Renovascular	35 (24)	26 (17)	22 (15)	28 (19)	
Other	14 (9)	27 (18)	29 (20)	22 (15)	
Medical Records					
Coronary artery disease	41 (28)	38 (25)	28 (19)	25 (17)	0.1518
Diabetes Mellitus	41 (28)	45 (30)	43 (29)	54 (36)	0.4664
Hypertension	82 (56)	73 (48)	73.5 (50)	73 (49)	0.5058
Congestive heart failure	26.5 (18)	22.7 (15)	21 (14)	15 (10)	0.4222
Cerebrovascular disease	10 (7)	12 (8)	6 (4)	13.4 (9)	0.5029
Peripheral vascular	15 (10)	21 (14)	12 (8)	16 (11)	0.5072

Chronic Obstructive	26 (18)	18 (12)	24 (16)	12(8)	0.1625
Obstructive sleep apnea	4.4 (3)	1.5 (1)	6 (4)	13.4 (9)	**0.0335**
Hypothyroidism	29 (20)	7.6 (5)	10.3 (7)	12 (8)	**0.0013**
Dementia	4.4 (3)	6 (4)	3 (2)	1.5 (1)	0.5444
Pacemaker	7.4 (5)	6.1 (4)	5.9 (4)	3 (2)	0.7294
Atrial fibrillation	21 (14)	13.6 (9)	16 (11)	6 (4)	0.1005
Gout	13 (9)	15 (10)	15 (10)	22 (15)	0.4822
Gastroesophageal reflux	7.4 (5)	9.1 (6)	13 (9)	16.4 (11)	0.3476
Cancer	28 (19)	30 (20)	40 (27)	27 (18)	0.3581

Table 10. Baseline Laboratory Data Categorized by Height-Adjusted Psoas Muscle Area Quartiles

	Q1	**Q2**	**Q3**	**Q4**	**P-value**
Estimated GFR (mL/min/1.73 m^2)	34 (10-66)	29 (10-79)	30.5 (10-73)	37 (9-63)	0.2248
Hemoglobin (g/L)	113 (77-156)	120.5 (85-159)	124 (82-167)	132 (76-172)	**0.0002**
Serum Sodium (mmol/L)	139 (130-145)	138.5 (127-145)	139 (132-145)	139 (133-148)	0.7500
Serum Potassium (mmol/L)	4.5 (2.6-6)	4.6 (3.6-5.6)	4.5 (3.4-5.9)	4.5 (3-5.8)	0.5461
Serum Bicarbonate (mmol/L)	25 (18-33)	25 (14-31)	25 (16-31)	25 (18-30)	0.7062
Blood urea nitrogen (mmol/L)	10.7 (5-33.3)	12.1 (3.6-37)	12.1 (3.2-32)	10.9 (3.4-42.8)	0.2821
Serum Albumin (g/L)	37.5 (21-44)	38 (24-46)	36.5 (19-47)	40 (27-45)	**0.0094**
Hemoglobin A1c (%)	5.9 (4.4-10)	5.8 (4.4-10.2)	6 (5.2-15.7)	5.8 (4.6-10.5)	0.7411
TSH (mIU/L)	4 (0.4-13)	2.8 (0.6-109.5)	1.8 (0.2-12.1)	1.7 (0.06-12)	0.0490
Uric Acid (umol/L)	377.5 (201-	386 (202-707)	398 (240-879)	411 (172-690)	0.0878
Total cholesterol (mmol/L)	4.3 (2.4-8.1)	3.9 (1.9-6.2)	4.1 (1.7-7.2)	4.2 (2.3-8.6)	0.4530
HDL cholesterol (mmol/L)	1.3 (0.6-2.0)	1.2 (0.5-2.4)	1.0 (0.6-2.3)	1.0 (0.6-2.4)	**0.0015**
LDL cholesterol (mmol/L)	2.2 (0.6-5.6)	2 (0.02-4.5)	2 (0.6-4.5)	2.3 (0.4-5.6)	0.3880
Calcium Corrected for Albumin (mmol/L) Ionized Calcium (mmol/L)	2.4 (1.3-2.8)	2.4 (2-2.7)	2.4 (2.2-2.7)	2.4 (1.2-2.8)	**0.0400**
Serum Phosphate (mmol/L)	1.3 (0.8-1.9)	1.2 (0.7-2.3)	1.3 (0.7-2.3)	1.1 (0.6-1.8)	**0.0120**
C reactive protein (mg/L)	6.2 (1.9-145)	5.6 (1.6-122)	6.2 (1.6-32)	5.5 (4-99.5)	0.4217
Ferritin (ug/L)	71 (3-393)	57 (7-924)	90 (5-743)	94 (9-1022)	0.0932

Table 11. Time to Follow-up and Proportion of Events Categorized By Psoas Muscle Area Quartiles

	Q1 Median (range)	Q2 Median (range)	Q3 Median (range)	Q4 Median (range)	P-value
Time of follow up	1266 (1-2516)	1245 (28-2327)	1159 (28-2352)	1191 (76-2393)	0.3845
Transfer	22 (15)	17 (11)	29 (20)	25 (17)	0.3561
Dialysis	18 (12)	14 (9)	25 (17)	19.4 (13)	0.4123
Mortality	13 (9)	20 (13)	10 (7)	6 (4)	0.1052

Table 12. Median Psoas Muscle Area Measurements Categorized by Psoas Muscle Area Quartiles

	Q1 Median (range)	Q2 Median (range)	Q3 Median (range)	Q4 Median (range)	P-value
Average Psoas Muscle	3.5 (0.9-4.9)	4.9 (4.3-6.6)	6.6 (5.1-8.3)	8.8 (7.3-14.9)	**<0.0001**
Average Psoas Muscle	2.1 (0.5-2.7)	3 (2.7-3.5)	3.8 (3.5-4.5)	5.1 (4.5-8.73)	**<0.0001**

Table 13. Spearman Correlation of Interobserver Psoas Muscle Measurements

	Non-Adjusted Average Psoas Muscle	Height-Adjusted Average Psoas Muscle
BMI 1	0.90	0.28
BMI 2	0.75	0.72
BMI 3	0.70	0.66
BMI 4	0.74	0.70
Female	0.71	0.71
Non-diabetic	0.65	0.63
Diabetic	0.51	0.47
Male	0.72	0.74
Non-diabetic	0.72	0.73
Diabetic	0.47	0.50

The unadjusted and adjusted Cox Hazard Ratio for survival is indicated in Table 14 (n=221). The Cox Hazard Proportional model was adjusted for diastolic blood pressure, congestive heart failure, thyroid stimulating hormone, baseline estimated GFR and serum albumin contents. According to this model, individuals with a PMA of less than 2.1 cm^2/m have an adjusted hazard ratio (HR) risk reduction of survival of 82%, with p=0.0997, indicative of a trend.

Table 14. Proportional Cox Hazard Ratio For Time to Death

	model	HR adjusted	95% CI	P-value	HR unadjusted	95% CI	P-value
PMA < 2.1 cm^2/m	A	0.18	0.02-1.38	0.0997	0.7	0.21-2.28	0.5503
PMA < 2.1 cm^2/m	B	0.16	0.02-1.21	0.0762	0.7	0.21-2.28	0.5503

Proportional Cox Hazard Ratio created for time to death associated with psoas muscle areas less than 2.1 cm^2/m, adjusted for diastolic blood pressure, congestive heart failure, thyroid stimulating hormone, baseline eGFR and serum albumin in model A (N=221). In model B, the hazard ratio is adjusted for Charlson comorbidity index, thyroid stimulating hormone levels, baseline estimated glomerular filtration rate, serum albumin and diastolic blood pressure (n =227).

Table 15 shows the Cox HR for dialysis event- free time (n=242) adjusted for diastolic blood pressure, CCI, thyroid stimulating hormone, baseline estimated GFR and serum albumin. Findings indicate that for groups in the first quartile compared to individuals with PMA greater than 2.66 cm^2/m, the dialysis event-free period is reduced by 61% and results showed a statistically significant association (p=0.0356).

Table 15. Proportional Cox Hazard Ratio for Event-Free Time for Dialysis

	HR adjusted	95% CI	P-value	HR unadjusted	95% CI	P-value
PMA< 2.66 cm^2/m	0.39	0.16-0.938	0.0356	0.73	0.37-1.43	0.3573

Proportional Cox Hazard Ratio generated for event-free time for dialysis associated with psoas Muscle areas less than 2.66 cm^2/m, adjusted for Charlson comorbidity index, baseline estimated glomerular filtration rate, systolic blood pressure and urine albumin/creatinine ratio (n=242).

Table 16 shows the adjusted and unadjusted Cox HR for infection-free time (n=246) adjusted for baseline eGFR, baseline hemoglobin A1C, serum albumin and CCI. According to this model, individuals with a PMA of less than 2 cm^2/m have an adjusted HR risk reduction of infection free period of 62%, with a trend toward significance.

Table 16. Proportional Cox Hazard Ratio model for Event-Free time for Infection

	HR adjusted	95% CI	P-value	HR unadjusted	95% CI	P-value
PMA< 2.0 cm^2/m	0.38	0.14-1.0	0.0613	0.46	0.17-1.26	0.1298

Proportional Cox Hazard Ratio model generated for event-free time for infection associated with psoas muscle areas less than 2.0 cm^2/m, adjusted for baseline estimated glomerular filtration level, Charleson comorbidity index, serum albumin and hemoglobin A1c (N=246).

Table 17. Proportional Cox Hazard Ratio model for the Event-Free time for Hospitalization

	HR adjusted	95% CI	P-value	HR unadjusted	95% CI	P-value
Q1	1.01	0.74-2.2	0.9814	1.73	0.83-3.62	0.1416
Q2	1.16	0.54-2.5	0.7075	2.11	1.03-4.32	**0.0423**
Q3	2.24	1.09-4.56	0.0273	2.86	1.42-5.75	**0.0032**
Q4				Referent		

Proportional Cox Hazard Ratio model created for the event-free time for hospitalization according to psoas muscle area quartiles, adjusted for baseline chronic kidney disease grade, serum albumin, Charleson comorbidity index, hemoglobin level and hemoglobin A1 level (n=240).

Discussion

Findings stemming from this study are showing consistency with literature-known dialysis and mortality associations with psoas muscle size and good psoas muscle interobserver assessment. Studies of similar nature assessed interobserver reliability, showing an acceptable coefficient of 0.965 (Thurston et al., 2018). Current literature also suggests other studies that applied similar principles to evaluate the association between sarcopenia and poor health outcomes in clinical populations (Okamura et al., 2019; Zuckerman et al., 2017; Paknikar et al., 2016; Hawkins et al., 2018; Hsu et al., 2019).

Different methods have been applied to measure muscle mass such as handgrip, mid-arm muscle circumference, and appendicular fat free mass to assess sarcopenia and its relationship with infections and mortality (Giglio et al.,2018; Pereira et al., 2015; Wilkinson et al., 2021). PMA muscle measurement is most convenient and user-friendly for application in a population with chronic disease and frequent health care encounters given that it requires little to no effort on their behalf. Our study in contrast contributes to the literature through the demonstration of the association of psoas muscle size to hospitalization and dialysis initiation.

It is key to note that there are several constituents of frailty including muscle mass, muscle strength, cognitive function, motor function and psychological health. As an independent risk factor for UTI, the component of frailty most likely contributes to the risk is mobility (Chao et al., 2021). Multiple factors associated with frailty can place a person at risk for infection including immunological, anatomical (such bladder retention) and comorbid conditions such as diabetes mellitus and cerebrovascular disease (Song & Abraham, 2008). It's also important to note that

recurrent infections have shown to lead patients into a state of malnutrition, which can ultimately lead to frailty (Carlsson et al., 2013). Carlsson et al. (2013) describes an elderly that develops malnutrition following a urinary tract event within the year prior. The bidirectional relationship between frailty and infection is exemplified by the studies stated before, those that develop infections are more likely to be frail and yet others develop malnutrition after an infection. (Chao et al., 2021; Carlsson et al., 2013). Hence, early recognition of frailty and intervention are both key for maintain quality of life (QoL). Balance and resistance training are examples of interventions that contribute to building muscle, thereby improving proprioception and mobility, and reducing fall risk. Increasing protein intake for reversing frail state would also be key to address such cases. Frailty has also shown susceptibility to pneumonia and hospitalization by 2-fold (Iwai-Saito et al., 2021).

There is again a bidirectional relationship between frailty, a condition closely linked to sarcopenia, and pulmonary infections because serious lower respiratory tract infections have shown to result in malnutrition and frailty (Park et al., 2021). The components of frailty with the highest risk for pneumonia are physical activity, nutritional status, and depressive symptoms (Iwai-Saito et al., 2021). Vaccinations against influenza could potentially reduce the risk of pneumonia occurrence and associated mortality, but further studies would be needed to confirm this (Kwong et al., 2018; Ma et al., 2021).

Findings from our study could see applications in modern patient care. Firstly, the use of PMA from routine scans could provide a relatively quick and effective screening tool for physicians and could pose a benefit for follow-up assessments, if necessary, in order to record patients' stability or disease improvement. Our findings also highlight the necessity of strength training to preserve or even increase muscle mass (Balakrishnan et al., 2010; Noor et al., 2021). It also adds to the importance of dietary supplementation, which could help fuel interventions aimed at improving sarcopenia-related outcomes such as preventing or even slowing down any forms of diseases worsened by muscle loss and subsequent deconditioning (Hirai et al., 2016; Noor et al., 2021). The association between low lean muscle mass and increased infections would also urge healthcare professionals to look out for other risk factors for infections such as muscle loss to

minimize morbidity and mortality among their patients. With this new user-friendly tool, early interventions could be put into place with community services to minimize hospitalizations.

There are three types of study limitations evident in the observational data presented. First, given the retrospective nature of this cohort study, the selection bias of the study population from one community hospital clinic may not have external generalizability. Only patients who had completed a CT scan of the abdomen within a relatively short period were included in the study, which implies subject adherence. Thus, non-adherent patients may have not been included. Second, exposure to measurement bias is also obvious from this study due to the discrepancy in muscle size, body habitus and morphology. The manual outline measurement is still more accurate than the elliptoid measurement method used in other studies, as the elliptoid method was an overestimate in the psoas muscle area measurement. Lastly, the outcome measurement for mortality may underestimate the events since the data was taken from the hospital laboratory testing rather than the provincial death registry.

CHAPTER 4: CONCLUSION AND SUMMARY

Overall, there is a clearer understanding of sarcopenia and its effects in aging and chronic populations. However, there is an underrepresentation of this in the CKD population, a subgroup where protein wasting and poor nutritional status is widespread, and where infections largely contribute to increasing mortality rates. There is also a lack of standardized methods to measure sarcopenia in at-risk populations, making it difficult to monitor. The lack of sarcopenia research in CKD patients could be a contributing factor to the lack in awareness and agreement on operational criteria for sarcopenia diagnosis and prevalence in this population group. By suggesting a surrogate measure for sarcopenia from routine CT scans, this study demonstrated the association of whole-body skeletal muscle mass with adverse health outcomes such as hospitalizations, dialysis, infections, and mortality in CKD populations.

One of the principal strengths of this study is the suggestion of a possible use for routine scans as an objective predictor tool for health complications. This sort of tool could facilitate early interventions in clinical settings, which could further reduce morbidity and mortality rates in various chronic population groups. This would allow physicians better screen their patients and classify them by risk, allowing hospital staff to perform a better triage when handling large numbers of patients. More specifically, the study justifies the use of a ser friendly tool for early recognition of a marker of sarcopenia below average or median size of the psoas muscle group. Another strength of this study is the solidification of the literature on the possible health complications that are related to muscle loss, emphasizing the importance of interventions aimed at preserving and increasing muscle mass and quality. The study also confirms good interobserver correlation of the psoas muscle. Moving forward, interventions would include protein supplementation and physical activity to maintain or augment muscle mass in CKD patients. Overall, the study underlies the utility of a retrospective model to evaluate chronic disease state and the role of muscle mass measurement in clinical care and applications in patient prognosis.

The study presents with a few limitations. Given the retrospective nature of the research, a convenience sampling method was used, creating a selection bias in the study population. Hence, findings stemming from the research may lack external generalizability. Second, factors such as muscle quality and morphology were not adjusted for by the PMA measuring tool, which could have either overestimated or underestimated the measurement. Lastly, the outcome

measurement for mortality showed a lack in consistency, which could have underestimated the occurrence of this event. The data was originally taken from the hospital laboratory PACS reports at first, and then confirmed with the written hospital laboratory results if information was missing. It was expected that all deaths would be reported in the hospital charts or clinic charts, but unfortunately were not, which resulted in a possible underestimation of in-hospital mortality events.

If the research project had to be redone, the data collection phase would have been done differently: Given that data collection period was longer due to the large volume of raw data, in retrospect, using a more consistent formatting during the raw data collection would have allowed for a more efficient data cleaning process.

In conclusion, future studies would be needed to develop the application of a marker of sarcopenia as a predictor of poor health outcomes and explore its causality in various population groups. Topics would include temporal relations such as muscle size variation over time with muscle CT scans, and exercise and nutrition interventions over a predetermined period. Other suggestions could also include physicians raising awareness on sarcopenia and educating patients presenting with risk factors on ways to better their lifestyle to delay disease onset.

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APPENDIX A. PERMISSION TO REPRINT FIGURE 1

Permission

Erika Muraski <erika@setptusa.com>
Wed 5/10/2023 11:48 AM

To: Song-ah Chai <song-ah.chai@mail.mcgill.ca>

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Thank you for your e-mail. Please feel free to use Psoas Muscle Figure from artile entitled "The Psoas Muscle . . . What and Where Is That" for your graduate thesis.

Thanks
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