Quadricep Muscle Ultrasound Imaging and Deep Learning

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English Abstract

Background

Aging and frailty add dimensions of complexity to the management of cardiovascular diseases. As the world population ages, accurately assessing frailty and vulnerability in older patients is becoming increasingly important. Sarcopenia is a component of the frailty syndrome that can be assessed through a variety of methods. Assessment of frailty and sarcopenia is often not feasible in very ill patients who may be bed bound and cannot carry out physical tasks. Musculoskeletal ultrasound imaging is proving to be useful in the identification of sarcopenia, a marker of frailty. Quadricep muscle thickness (QMT), an indicator of sarcopenia, can be measured from ultrasound images of the thigh. Currently, there is limited research surrounding the ability of muscle ultrasound images to provide valuable diagnostic information for frailty or for machine learning (ML) models to measure QMT.

Objectives

The primary goal of this study was therefore to develop ML models capable of predicting QMT based on provided quadricep ultrasound phased array images as input variables. The secondary goal was to confirm the relationships between QMT and handgrip strength (HGS), lean body mass (LBM), phase angle (PA), clinical frailty scale (CFS) score.

Methods

This study was a retrospective single-center cross-sectional cohort study conducted at the Jewish General Hospital. The study population consisted of adult inpatients and outpatients undergoing a transthoracic echocardiogram. Ultrasound images of the thigh served as the primary input (independent) variable for the ML models we developed. Ultrasound image collection was performed by trained sonographers at the Jewish General Hospital echocardiography laboratory. The images were retrospectively annotated to delineate the femur and the top of the quadricep muscle. Five different measures of frailty were used as the output (dependent) variables; HGS, CFS, LBM, bio impedance PA, and QMT. For the first experiment, single variable linear regression ML models were trained using the ultrasound images as input variables and the five different frailty measures as output variables. 5-fold cross validation was used to test the performance of the model and mean absolute error (MAE) was measured to determine the model accuracy. For the second experiment a segmentation model was trained to identify a region of interest on the ultrasound images. This region of interest was then used to train a new linear regression model to predict QMT values.

Results

The final cohort consisted of 486 patients with a mean age of 66 $\pm$ 14 years and was 57% female. Increasing QMT was positively associated with HGS, LBM, PA, while negatively associate with CFS.

The ML model using ultrasound images as inputs predicted QMT values with a MAE of 0.4478 ± 0.033 cm. The ML model that used ultrasound images overlaid with predicted binary masks from

the segmentation model predicted QMT with a MAE of 0.355 ± 0.021 cm. The ML model that used ultrasound images overlaid with ground truth binary masks predicted QMT with a MAE of 0.3210 ± 0.013 cm.

Conclusion

From these results it may be assumed that increased QMT could be used as a surrogate marker of these four different frailty measures. The models we have developed can provide a QMT value from a provided ultrasound image. This QMT value can further be used to determine the sarcopenic condition of the patient.

French Abstract

Introduction

La fragilité ajoute de la complexité au traitement des maladies cardiovasculaires. À mesure que la population mondiale vieillit, il devient de plus en plus important d'évaluer avec précision la fragilité et la vulnérabilité des patients âgés. La sarcopénie est une composante du syndrome de la fragilité qui peut être évaluée par diverses méthodes. L'évaluation de la fragilité et de la sarcopénie n'est souvent pas possible chez les patients très malades qui sont alités et incapables d'effectuer des tâches physiques. L'échographie musculosquelettique s'avère utile dans l'identification de la sarcopénie, un marqueur de fragilité. L'épaisseur du muscle quadriceps (EMQ) - un indicateur de sarcopénie - peut être mesurée à partir d'images échographiques de la cuisse. Actuellement, il existe peu de recherches sur la capacité des images échographiques musculaires à fournir des informations afin de diagnostiquer la fragilité.

Objectifs

L'objectif principal de cette étude était de développer des modèles d'apprentissages automatiques (MAA) capables de prédire l'EMQ sur la base d'images quadriceps échographiques de réseau phasé. L'objectif secondaire était de confirmer les liens entre l'EMQ et la force de la poignée (FP), la masse corporelle maigre (MCM), l'angle de phase (AP), et l'échelle clinique de fragilité (ECF).

Méthodes

Cette étude rétrospective a été effectuée sur une cohorte transversale monocentrique menée à l'Hôpital général juif. La population étudiée était composée de patients adultes hospitalisés et de patients externes subissant une échocardiographie transthoracique. Les images échographiques de

la cuisse ont servi de variable indépendante principale pour les MAA que nous avons développés. La collecte des images échographiques a été effectuée par des échographistes formés au laboratoire d'échocardiographie de l'Hôpital général juif. Les images ont ensuite été annotées pour délimiter le fémur et le haut du muscle quadriceps. Cinq mesures différentes de la fragilité ont été utilisées comme variables dépendantes ; la FP, le score sur l'ECF, la MCM, l'AP de la bioimpédance et l'EMQ. Pour la première expérience, des MAA à régression linéaire à variable unique ont été formés en utilisant les images échographiques comme variables indépendantes et les cinq mesures de fragilité différentes comme variables dépendantes. Une validation croisée à 5 fois a été utilisée pour tester les performances du modèle et l'erreur absolue moyenne (EAM) a été mesurée pour déterminer la précision du modèle. Pour la deuxième expérience, un modèle de segmentation a été formé pour identifier une région d'intérêt sur les images échographiques. Cette région d'intérêt a ensuite été utilisée pour former un nouveau modèle de régression linéaire afin de prédire les valeurs d'EMQ.

Résultats

La cohorte finale était composée de 486 patients avec un âge moyen de 66 ans ± 14 ans et était composée à 57 % de femmes. L'augmentation de l'EMQ était positivement associée à la force de la poignée, la masse corporelle maigre et l'angle de phase, mais négativement associée à la CFS. Le MAA utilisant des images échographiques comme variable indépendante prédit les valeurs de l'EMQ avec une EAM de 0.4478 ± 0.033 cm. Le MAA qui utilisait des images échographiques superposées avec des masques binaires prédits à partir du modèle de segmentation prédisait l'EMQ avec une EAM de 0.355 ± 0.021 cm. Le MAA qui utilisait des images échographiques superposées

avec des masques binaires de données de vérification prédisait l'EMQ avec une EAM de 0.3210 ± 0.013 cm.

Conclusion

À partir de ces résultats, on peut supposer que l'augmentation de la masse musculaire du quadriceps pourrait être utilisée comme marqueur de substitution pour ces quatre différentes mesures de fragilité. Les modèles que nous avons développés peuvent fournir une valeur d'EMQ à partir d'une image échographique donnée. Cette valeur de l'EMQ peut en outre être utilisée pour déterminer l'état sarcopénique du patient.

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Contribution of Authors

Jeremy Obrand

MSc candidate. Jeremy has conducted an extensive literature review and has taken the lead for the Quadricep Ultrasound Imaging study which includes data collection, data pre-processing and chart reviews. Jeremy assisted with data analysis and AI model design. Jeremy was responsible for writing the manuscript. Jeremy designed and initiated a new, prospective study (not discussed in this thesis) to supplement his current research. Attended weekly research team meetings and presented findings to the MSc Thesis Committee.

Bahareh Behboodi

Research Collaborator. Bahareh was responsible for writing the code used to develop and train the machine learning models. Bahareh was an integral part of this study and continues to collaborate on new prospective studies.

Dr. Jonathan Afilalo

Thesis supervisor. Dr. Afilalo provided continuous support on development of study design and how to carry out research in a new field for myself. He consistently provided me with feedback and spent time teaching me how to efficiently carry out statistical analysis.

Dr. Hassan Rivaz

Member of thesis committee. Attended committee meetings and weekly meetings related to the progression of the study. Provided insight with respect to the AI section of the study.

Dr. Ian Shrier

Member of thesis committee. Attended committee meetings and provided feedback on the study design.

Dr. Sonia Del Rincon

Academic Advisor. Attended committee meetings and provided feedback on the study design. Was very supportive during the submission process.

CHAPTER 1: THESIS INTRODUCTION

The diseases and medical conditions that accompany aging become more important with each passing year. The average age and life expectancy of the general population is growing, meaning that older individuals represent an increasingly larger proportion of society[1]. Aging is a process that poses numerous obstacles to clinicians and the health care system. Cardiovascular medicine is especially susceptible to the clinical complexities of identifying, evaluating, and treating older individuals.

The process of aging, while inevitable, is not identical from person to person. Interpersonal differences in aging can be explained by the differences between chronological age and biological age. While chronological age is simply a measure of years gone by, biological age or physiological age is characterized by progressive damage to cells and tissues that are tightly linked to epigenetic changes[2]. Age is a potent risk factor for cardiovascular disease (CVD), yet the risks associated with age refer to the consequences of biological age. Using an individual's chronological age for risk stratification is therefore not sufficient.

Frailty is best characterized as a syndrome with various symptoms that are often observed together. Frailty is an age associated ailment that is described by the physiological changes observed in aging and physical and cognitive decline[3]. Individuals identified as frail are at increased risk for major adverse health outcomes including hospitalization and mortality[4]. The physiological basis of frailty necessarily indicates that biological age rather than chronological age should be used. Assessment of frailty and biological age, however, remains relatively underexplored and no gold standard exists to identify vulnerable individuals[5].

The physical decline observed in the frailty syndrome is often characterized by a loss of muscle mass, quality, and strength. Decreases in muscle mass and strength is known as sarcopenia and has emerged as an effective indicator of frailty[6]. Sarcopenia represents the functional and physical aspect of frailty which remains a multi-system syndrome[6]. Assessing sarcopenia in a clinical setting could therefore provide valuable insight as to the frail state of older individuals. Sarcopenia deals specifically with muscle mass and function. Various tests such as handgrip strength (HGS) have been validated as good indicators of muscle strength and sarcopenia[7].

Additionally, imaging modalities have made their way to the forefront to characterize muscle mass and composition. Measuring quadricep muscle thickness (QMT) with ultrasound imaging has emerged as a promising tool for quantifying a patient's sarcopenic condition[8]. Muscle quality has also been shown to be a negative predictor of mobility and functional capacity in older adults[9]. Increased proportions of intramuscular adipose tissue (IMAT) is seen in frail individuals compared to non-frail age and body mass index (BMI) matched individuals[9]. QMT and strength are proving to be valuable measures of sarcopenia and frailty but should be supplemented with quadricep muscle quality (QMQ) assessment.

The objectives of this thesis were to perform a literature review on the current landscape of the evaluation of frailty in cardiovascular patients and to subsequently conduct a retrospective cross-sectional cohort study to train artificial intelligence (AI) models to determine QMT measurements from provided ultrasound images. Additionally, QMT was assessed as a frailty marker in comparison to different validated measures of frailty.

CHAPTER 2: LITERATURE REVIEW

Physiology of Age: Chronological age vs Biological Age

Across the world, populations are aging at unprecedented rates, meaning older adults compose a much larger proportion of society. Adults over the age of 60 are expected to account for 21.1% of the world population by 2050[10]. In 2019 adults over the age of 65 represented 17.5% of the Canadian population but accounted for over 45% of national health expenditure according to the Canadian Institute for Health Information (Figure 1). Additionally, once humans pass the threshold of 50 years of age an exponential increase in the burden of chronic conditions is observed[11]. The appropriate care and management of older patient groups poses many challenges for clinicians. An increased efficiency of identifying age-related vulnerability begins with understanding the physiology of aging.

When identifying and evaluating individuals in a medical setting, chronological age has often been used as a marker of vulnerability. This measure falls short due to the simple reason that individuals age at different rates. While chronological age counts the number of years that have passed since birth, biological age addresses the physiological changes that occur over an individual's lifetime. Biological age has been measured using numerous biomarkers that reflect physiological changes related to the aging process[12]. These biomarkers can be biochemical such as quantification of C-reactive protein (CRP), or functional such as the forced expiratory volume (FEV), or even circulatory such as blood pressure measurements[12]. These biomarkers, reflecting biological age, were demonstrated to have significantly better predictive value for mortality than chronological age[12]. To further demonstrate that aging is not a uniform process but rather an

individual process, researchers at Duke University established that age-related physiological changes occur in humans as early as 30 years of age[11]. Furthermore, these changes occur at different rates in different people[11]. Evaluating chronological age relies on the basis that physiological deterioration occurs in individuals over time. Multi system decline due to age can manifest itself in several ways; changes in body composition, energy imbalance, signaling network deficiencies, and neurodegeneration[13].

At the cellular level, the process of aging can in part be explained through the mechanisms of cellular senescence. Cellular senescence describes the permanent halting of the cell cycle and cellular proliferation, demonstrating that cells stop replicating over time[14]. Many age-related deficiencies have been tightly linked to cellular senescence, making it a focal point of current research[15]. Age related cellular senescence has been characterized by the progressive damage and changes that occurs to cells after undergoing many rounds of cellular division. Every time a cell divides, its telomeres are shortened. As cells continuously divide, telomeres continuously become shorter until they trigger senescence via the p53 molecule leading to downstream signalling to halt the cell cycle[14]. Telomere attrition throughout a cells lifespan can ultimately result in the loss of coding DNA sequences. These senescent cells with truncated chromosomes tend to acquire inflammatory phenotypes. The senescence associated secretory phenotype (SASP) is characterized by the release of numerous proinflammatory cytokines[1]. The concept of 'inflammaging' deals with these SASP cells and their role in chronic inflammation in older individuals[1]. Additionally, chronic inflammation has been demonstrated to be closely linked to the aging process and age associated-multimorbidity[16]. These aging cells seem to create problematic microenvironments leading to various diseases. SASP cells drive the progression of atherosclerosis and are even found in higher quantities in areas of the brain where neurodegeneration is observed[17, 18].

Cellular senescence plays a significant role in the process of aging and helps in part to explain the cellular basis of age-related diseases. Chronological age fails to take these cellular changes that occur at different rates in different individuals into consideration, making measurements of biological age seemingly more favorable in terms of risk stratification.

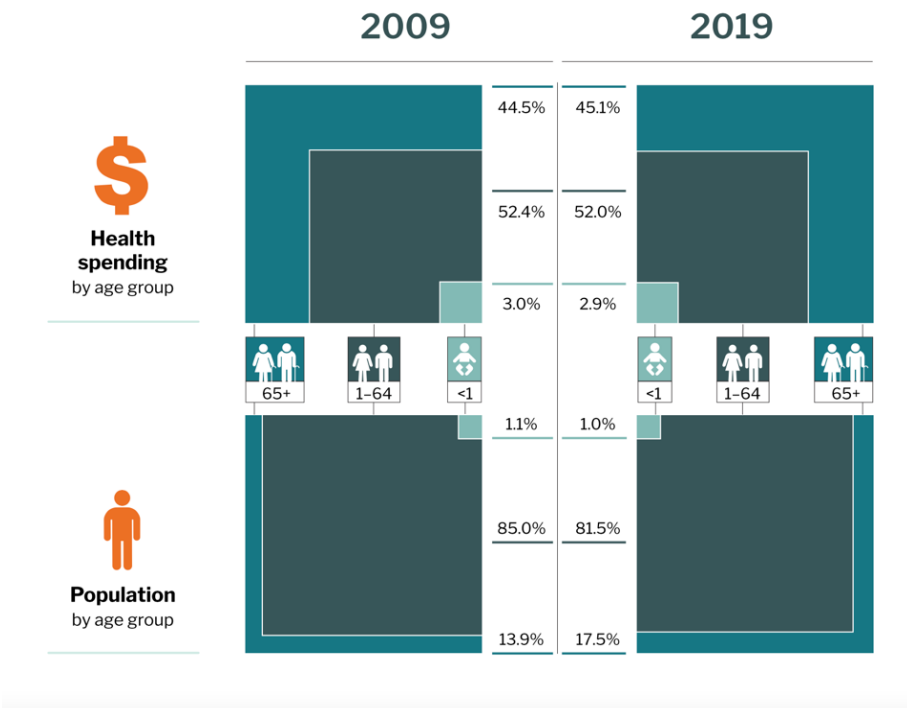

Figure 1

Defining Frailty

Frailty is a clinical syndrome that represents a manifestation of older biological age. The frailty syndrome is multidimensional and characterized by an increased state of vulnerability to stressors[5]. More specifically, this increased vulnerability to environmental and physiological stressors leads to increased susceptibility to negative health-related outcomes[5]. This age-related

syndrome can additionally be described by functional decreases of physiological systems and a decrease in physiological reserve[19]. As the definition of frailty has progressed over the years, decline in cognitive function in individuals has become an important facet in the frailty phenotype[3]. An estimated 40-50% of adults over the age of 80 are thought to meet the definition of frailty[20]. As was briefly touched upon in the discussion of biological aging, frailty cannot be described by one mechanism alone but rather is the result of a combination of multiple age-related processes. Cellular senescence, chronic inflammation, hormonal dysregulation, oxidative stress and epigenetic changes are just a few examples of the numerous physiological processes that interact to cause the frail phenotype (figure 2)[21]. In the clinical setting, for many years there has been no strict protocol to identify frailty. Clinicians have seemingly relied on the presence of the following age-related changes to identify frail individuals:[22]

1. Generalized weakness
2. Poor endurance
3. Weight loss or malnourishment
4. Reduced activity
5. Unsteady gait and risk of falling

Frailty has become an important focus of research across numerous medical disciplines, due to the information the frailty syndrome may provide with regards to risk of mortality, morbidity, and disability. Individuals who are identified as frail are often at heightened risk of adverse outcomes. Hospitalized older adults who are identified as frail have been shown to be at increased risk of in-hospital mortality than their robust counter parts[23]. Frailty and the associated

risks are not exclusive to hospital settings; frail older community-dwelling adults have been shown to be at increased risk of future disability[24]. Slowness and weight loss, commonly seen signs of frailty, are strongly associated with incident disability in community-dwelling elders[24]. This concept is important because increased disability results in increased dependency, reductions in quality of life, and increased resource use. Disability is a commonly discussed potential outcome in older populations, but it also serves as an important risk factor[22]. It is important to note that frailty, disability, and comorbidity are three distinct concepts. The interplay between these three entities often leads to the use of these terms interchangeably when in fact they refer to distinct processes.

While frailty is seen as the clinical manifestation of aging, it is important to note that the progression of the frailty syndrome is thought to be modifiable. Nutritional, physical, and cognitive intervention are currently being explored as to their impact on the progression of frailty. Intervention at these levels is proving to delay the progression of the frailty syndrome and in certain cases even reverse this seemingly unidirectional process[25].

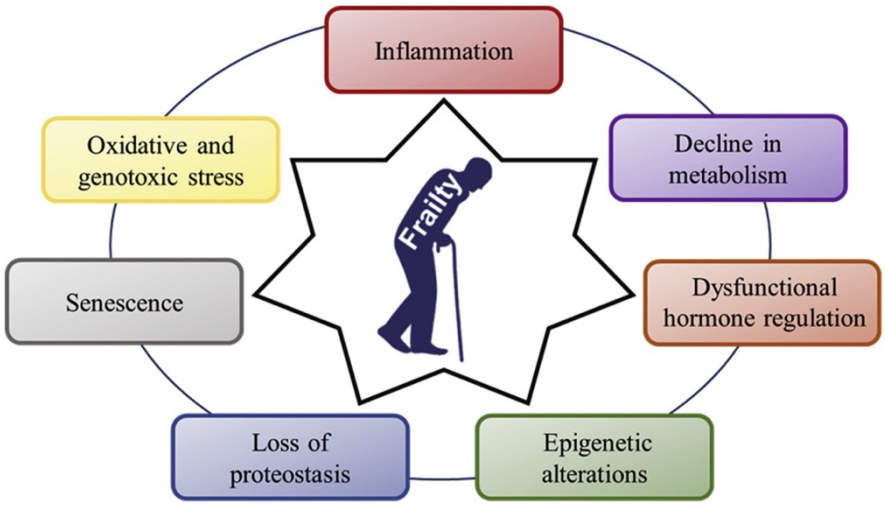

Figure 2[21] : The various physiological mechanisms that lead to the frailty syndrome.

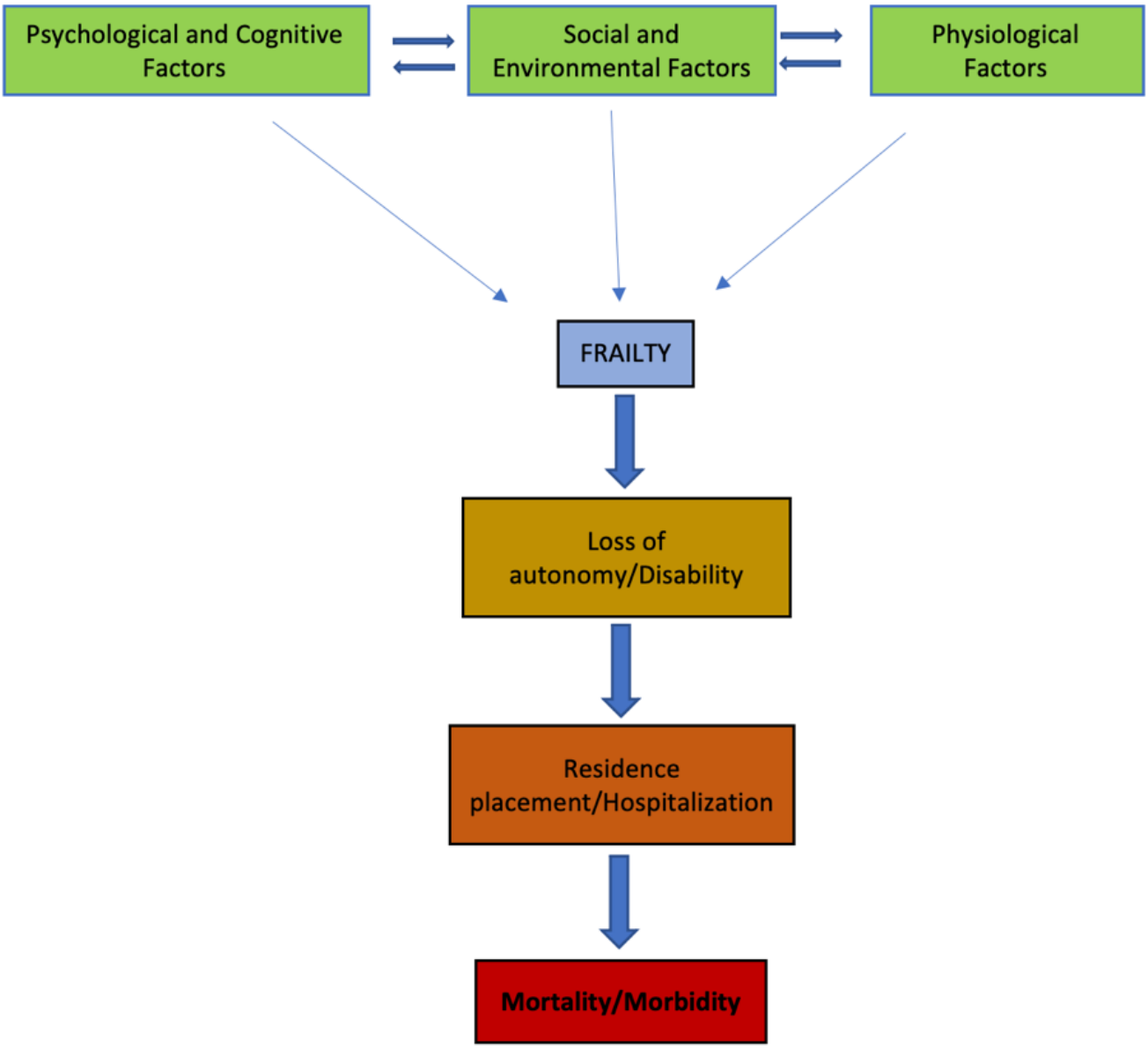

Figure 3: The interaction between numerous psychological, cognitive, social, environmental, and physiological factors can contribute to the frailty syndrome. Increasing frailty is accompanied by losses in autonomy which could lead to hospitalization or placement in homes. Frailty subsequently predisposes individuals to increased mortality and morbidity.

Frailty and Sarcopenia

The physical decline observed in the frailty syndrome is often characterized by a loss of muscle mass, quality, and strength. Age-accompanied decreases in muscle mass and strength are known as sarcopenia and has emerged as an indicator of frailty. The components of the frailty phenotype that were described by Fried et al. serve as markers of sarcopenia[22]. Weight loss, exhaustion, weakness, slow walking speed, and low physical activity, are all markers of either decreased muscle mass or function. When looked at independently of frailty, sarcopenia and poor functional performance also serve as robust predictors of poor health-related outcomes and disability[26].

While frailty and sarcopenia are not synonymous concepts, most older adults who are identified as frail are also sarcopenic[27]. The concurrence of both these syndromes is important because evaluation of frailty by clinicians is often based on characteristics of sarcopenia[28]. The *European Working Group on Sarcopenia in Older People* (EWGSOP) defined Sarcopenia as a

> "…syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life and death."

The definition changed the way sarcopenia was evaluated by incorporating reduced muscular function and strength in the presence of loss of mass[29]. The evaluation of functional capacity for sarcopenia broadened the physical characteristics of the syndrome. Sarcopenic obesity has become an important concept where obese individuals may still suffer from decreased muscle mass and function while maintaining a high total body mass. Older obese individuals who are also

sarcopenic have been shown to be at higher risk for poor health-related outcomes than their non-sarcopenic counterparts[28]. The paradoxical nature of sarcopenic obesity makes it harder to assess and diagnose, yet the inflammatory processes related to obesity further enhances muscle degradation, causing these individuals to be at higher risk for negative outcomes[30].

Several factors contribute to the onset and progression of severity of sarcopenia in older adults. Genetic factors have been attributed to interpersonal differences for sarcopenia notably allelic differences for specific enzymes, loss of motor neurons and changes in motor unit organisation[31, 32, 33]. The most pervasive cause of sarcopenia, however, is muscle disuse and inactivity[28]. During exercise, anti-inflammatory mediators known as myokines are released that help maintain muscle mass[34]. When exercise is stopped for extended periods of time and sedentary habits are adopted, increased levels of pro-inflammatory mediators are observed[35]. Age-related decreases in physical activity leads to increased inflammation and subsequent muscle degradation, this decrease in muscle quality and strength reinforces sedentarism further exacerbating the sarcopenia and frailty syndromes. The cyclical relationship between sarcopenia and exercise is an important target for intervention. Additionally, as muscles degrade, increased adipose deposits within skeletal muscle are observed[36]. This is known as intramuscular adipose tissue (IMAT) and results in decreased functional capacity of the muscle as well as increased inflammation[36]. IMAT can potentially serve as a surrogate marker of frailty and sarcopenia in the future. Frail individuals tend to have higher proportions of IMAT than their non-frail BMI matched counterparts[9]. Muscle size and thickness have often been parameters assessed for sarcopenia and frailty, but muscle quality needs to be taken into consideration as well. Deposits of adipose tissue within skeletal muscle, such as the quadriceps have been shown to be more strongly related to decreases in autonomy of older adults than decreases in muscle mass alone[37].

Cardiovascular Disease and Frailty

Commonalities Between Frailty and CVD

Many of the physiological and lifestyle factors that exacerbate the frailty syndrome are the same factors that lead to increased risk of cardiovascular disease (CVD). Age and age-related physiological changes sit at the top of the list for risk factors in CVD[38]. The co-occurrence of frailty and CVD in older patients is becoming increasingly prevalent as the population continues to age. A meta-analysis conducted by Afilalo et al. looked at nine studies consisting of 54, 250 elderly patients and found that in patients with coronary artery disease (CAD) or heart failure (HF), 50-54% of these patients were also frail[39]. Interestingly this does not clarify the directionality of this relationship. Frail patients are more at risk of developing CVD and patients with CVD are also more at risk for developing the frailty syndrome[40]. In patients with CVD, however, the presence of clinical frailty increases the risk for mortality and disability.[39]

When previously defining frailty in this literature review, the concept of inflammageing, discussing chronic inflammation in older adults, was closely linked to the frailty phenotype. Chronic inflammation in CVD has been a widely investigated area of research. Oxidative stress caused by aging, obesity, diabetes, and other metabolic disorders are conducive to a plethora of different forms of CVD[41]. The inflammatory mediators that result in sarcopenia and increased frailty also damage endothelial cells, leading to vascular damage and remodeling[1]. Age associated inflammation also leads to increased atherosclerosis and insulin resistance, potent factors in the development of CVD[1]. Much like in frailty, multi-system dysfunction is common in patients with CVD, highlighting the synergistic relationship between the two[40].

Frailty as a Risk Factor

Across numerous studies, frailty has been associated with poor survival in a "dose-responsive" manner[42]. Presence of an increased number of components of the frailty syndrome leads to increased rates of mortality[42]. In CVD specifically, the risk of mortality doubles in frail older adults, even when adjusting for age and comorbid conditions[43]. The role of frailty in CVD has been demonstrated from the subclinical level to HF and cardiac surgery.

Preceding clinical CVD, subclinical manifestations of CVD take place. Individuals who are identified as frail tend to have increased symptoms of underlying CVD[44]. Additionally, the reverse trend has been observed in a study from University College London, where carotid intima-media thickening (CIMT) was measured as a marker of subclinical CVD[45]. In this study by McKechnie et al., the presence of subclinical CVD was strongly associated with incident frailty[45]. Interestingly, other studies have shown that individuals with slow gait, a sign of frailty as described by Fried, were more likely to have CIMT and other subclinical markers of CVD[46]. Frailty is prevalent in CVD even before the symptoms manifest themselves in acute clinical settings.

The bi-directional relationship between frailty and CVD is emphasized in the case of HF. As discussed, frailty is a multi-system syndrome in which individuals are more vulnerable to decompensation. In the context of HF, frail patients are more predisposed to increased frequency of hospitalization and complication[43]. Additionally, frailty predisposes cardiac patients to increased myocardial injury in response to cardiac exacerbations, thereby predisposing frail individuals to developing clinical HF[43]. Numerous studies have demonstrated a strong association between frailty in HF and poor clinical outcomes[47]. It is important to note that patient reported quality of life is also worsened in HF patients who manifest the frail phenotype[47]. The multi system

degeneration that occurs in HF and frailty also demonstrates an overlapping of physiological pathways. Hormonal dysregulation, chronic inflammation and increased muscle catabolism are consequences of both ailments, and therefore the interaction of both HF and frailty leaves patients in a heightened state of vulnerability[48]. Frailty and HF are intertwined to the extent that almost 50% of HF patients are also frail[49]. It is therefore becoming of increasing importance to understand how the identification and intervention of frailty in HF patients may provide benefit for patient centered outcomes.

In the context of CAD and percutaneous coronary intervention (PCI), frailty further complicates risk assessment and outcomes. Numerous studies have demonstrated that frail patients undergoing PCI have a higher risk of mortality and morbidity following the procedure[43]. Frailty has been shown to significantly increase the rate of 18-month and 3-year mortality in patients following PCI[50]. Additionally, reductions in quality of life are also more pronounced in frail patients post PCI[50, 51]. The increased risk of adverse outcomes post-PCI in the presence of frailty highlights the importance of proper frailty evaluation.

Frailty as a risk factor becomes increasingly important when evaluating heavily invasive procedures such as cardiac surgery. The decreased physiological reserve and resilience that defines the frailty syndrome is important to consider in the context of the extreme physiological stressor that is cardiac surgery. The procedure itself is taxing on multiple physiological systems, but the recovery period when a patient is bed bound is a major contributor to decline in patient condition. Frail patients who undergo invasive cardiac procedures have increased rates of mortality and increased length of hospital stay[43]. In a study performed by Afilalo et al. at the Jewish General Hospital in Montreal, gait speed was shown to be a powerful predictor of mortality and morbidity in older cardiac surgery patients[52]. The benefits and potential risks need to be evaluated in the

case of frail, older cardiac surgery patients to determine if an invasive procedure will truly lead to an increased quality of life or reduced risk of death. Transcatheter aortic valve replacement (TAVR) is a procedure that was developed in response to the frailty dilemma in cardiac surgery. Frail, elderly patients make up the majority of individuals who undergo TAVR, yet frail patients are still at increased risk for mortality following the procedure[43]. Frailty serves as a potent predictor of risk in cardiac patients from a subclinical level up to an acute level. Proper evaluation of the frailty syndrome is therefore something that needs to be taken into consideration in the clinical setting.

Evaluation of Frailty in Older Adults

There are currently various tools and models for frailty assessment in use. Evaluation methods are based on the two differing models of frailty: the frailty phenotype and the accumulation of deficits model. The frailty phenotype considers the following five clinical features: weakness, slow gait, weight loss, exhaustion and low physical activity[22]. The accumulated deficits model of frailty focuses on comorbid conditions in addition to cognitive, psychological and social factors[53].

The Frailty Phenotype Model

When assessing the frailty phenotype, physical function and sarcopenia are evaluated using various tests. The Fried scale and the Short Physical Performance Battery (SPPB) remain the two most used tools for evaluation of the frailty phenotype[54]. The Fried scale assesses the five clinical

features of the frailty phenotype outlined above. If three or more of the clinical features are present in a patient, the individual is diagnosed as frail according to the Fried scale[55].

To evaluate the dimensions of the Fried scale, specific tests and questions are used. Weakness is generally measured using a handheld dynamometer to determine hand grip strength (HGS). Specific sex and BMI stratified cut-offs are used to determine if a patient's HGS is deemed as frail or robust[55]. Unintentional weight loss is determined if the patient has lost 10 or more pounds in the previous 12 months not due to exercise or dieting[55]. Slow gait speed is measured using variations of the four- or five-meter walk tests. Sex and height stratified cut-offs are used for gait speed measures. Self-reported exhaustion is evaluated based on the following two questions taken from the Centre for Epidemiological Studies Depression scale (CES-D): (1) "How often in the last week did you feel like everything you did was an effort," (2) "How often in the last week did you feel like you could not get going"[55]. If patients state they felt they could not get going or required effort for all their daily activities at least three days in the last week, they would be considered frail[55]. Low physical activity considers the frequency with which patients exercise during the week; sex stratified cut-offs measured in energy expenditure per week (kcal) are used to classify patients as frail or robust[55].

The SPPB scale specifically addresses physical performance measures and does not address exhaustion or fatigue. The SPPB scale uses the chair rise test, gait speed, and tandem balance to measure the frailty phenotype[56]. Each test is given a score from 1-4 based on specific cut-offs resulting in a maximum possible score of 12 and a minimum possible score of 0. A score of 5 or less on the SPPB scale is indicative of frailty[56]. Gait speed in the case of SPPB is measured in the same way as the Fried scale. The chair rise test asks patients to stand and sit down five times as quickly as possible while not using their hands, this is a timed test[56]. The tandem balance test

asks patients to stand with their feet touching side by side, in a semi tandem position or in a full tandem position. Patients must be able to stand in all three positions for 10 seconds each to score full points[56].

These two ways of measuring the frailty phenotype are important ways of determining risk due to the relationship of frailty and various health related outcomes. In nursing home residents, the Fried scale was shown to be a powerful predictor of all cause mortality[57]. Similar results were seen in pre-operative patients, the Fried scale was an effective tool to predict post procedural mortality and various patient centered outcomes[58]. Interestingly across many studies, the Fried scale falls under criticism for its feasibility. While a few of the assessed domains are simple, it is not always easy to evaluate gait speed in the case of severely frail patients in an acute setting[59]. Gait speed serves as a marker of sarcopenia and physical functioning but cannot be assessed in bed bound patients. Frailty as defined by the SPPB criteria has been associated with increased risk of disability, prolonged length of stay and all-cause mortality in hospitalized patients[60]. The SPPB scale is thought to be an effective tool for risk prediction and frailty diagnosis in older patients[59]. As with the Fried scale, the same problems in terms of feasibility arise with the SPPB scale. All three assessed domains require a patient to be mobile and fall short in the case of severely frail individuals who are restricted in their ability to move independently.

The Accumulated Deficits Model

The accumulation of comorbid conditions, various health deficits, cognitive decline and other psychological and social factors are considered in the accumulated deficits model of frailty. The two methods of measuring frailty under this model are the Frailty Index (FI) and the Clinical Frailty Scale (CFS).

The frailty index is a value calculated based on all the accumulated symptoms, signs, functional impairments, diseases, radiographic, electrocardiographic or laboratory abnormalities that a patient displays[61]. The FI is calculated as a quotient of all the deficits present relative to all possible deficits considered[62]. The FI has also been shown to be a strong predictor of mortality across the literature[62]. The CFS is a scale from 1-9 where clinicians attribute a score to patients based on comorbidity, functional capacity, and cognitive ability; a higher score indicates increased frailty and vulnerability[63]. The CFS is a judgement-based evaluation tool that allows clinicians to interpret information how they see fit. Despite the seemingly subjective nature of the CFS, many studies across cultures and languages have demonstrated high reliability and validity of this clinical frailty measure[64, 65, 66, 67]. The use of FI and CFS demonstrate similar predictive capabilities with respect to mortality as the Fried and SPPB scales. The Fried and SPPB scales may be better at determining functional capacity due to the physical nature of the assessments, but there is a trade-off with reduced feasibility in relation to FI and CFS.

Ultrasound and Sarcopenia

Sarcopenia is described by decreases in muscle strength, mass, and quality. Muscle strength can be measured using a variety of physical tests, making it the most commonly assessed dimension of sarcopenia. Muscle mass can be measured using different scales and body scans, ranging from simple Body Mass Index (BMI) calculations to more complex devices such as Bio-electrical Impedance Analysis (BIA) scales that utilize micro currents of electricity to measure body composition. Muscle quality remains the dimension of sarcopenia that is less assessed, yet as discussed above, it may provide powerful prognostic information.

Different imaging modalities can provide insight into the enigma of muscle quality in older patients. Ultrasound is safe in terms of limited radiation and portable versions of ultrasound probes are starting to be increasingly present in clinical settings. The safety and feasibility of ultrasound make it a particularly interesting avenue of exploration from a frailty and sarcopenia standpoint.

Skeletal muscle ultrasound imaging can be used to quantify muscle mass by visualizing the muscle and subsequently measuring muscle thickness[68]. Ultrasound is also capable of investigating muscle quality. Fat infiltration and intramuscular fibrous tissue can be analyzed on skeletal muscle ultrasound images providing insight into the functional capacity of the muscle[68].

Echo intensity (EI) demonstrates changes in tissue. More fat or fibrous tissue makes a muscle appear whiter and increases the mean pixel intensity (brightness) of the muscle[68]. Specific contractile components of skeletal muscle appear darker or more hypoechogenic while the whiter regions are hyperechogenic. When measuring mean pixel intensity to determine the EI of skeletal muscle, lower values correspond to darker, less echogenic areas which are thought to correspond to higher muscle quality[69]. Higher values of EI are thought to correspond with decreased muscle

quality and potential muscle disease[70]. Research around this is still limited, yet certain studies are showing a negative relationship between EI and muscle strength and function. This relationship highlights the potential for muscle quality to be used as a surrogate marker for muscle strength and sarcopenia[70].

Differences in muscle quality and EI are important when considering two muscles of the same cross-sectional area but differing EI. While both muscles may be the same size, the functional capacity of the muscle with hyperechogenic regions may have reduced functional capacity and could meet the criteria for frailty diagnosis. Individuals with high values of skeletal muscle EI have been found to have lower locomotive function than individuals with lower EI values[71]. Changes in muscle composition and EI relative to aging are especially important in the context of frailty and sarcopenia. In numerous studies of healthy subjects, individuals over the age of 60 were found to have increased EI relative to their younger counter parts across numerous major muscle groups, indicating reduced muscle quality[72]. Additionally, research has shown that frailty as measured by the Fried scale was associated with higher EI values of the quadriceps[73]. EI is still being validated as a marker of sarcopenia but could prove to be an effective and feasible diagnostic tool in clinical settings.

It is important to note that several factors can influence the EI of a muscle, such as hydration and glycogen levels[69]. Increased EI has been seen in conjunction with exercise and therefore adds confusion to the research indicating that high values of EI corresponds to lower quality muscles[74]. Ultimately, EI and ultrasound as a diagnostic tool for frailty and sarcopenia is a promising avenue for future frailty research, but increased investigation will be necessary to determine its role in a clinical setting.

Conclusion and Study Motivation

This literature review sought to determine the current landscape of frailty evaluation and assessment. No gold standard for frailty evaluation exists. Current methods such as the Fried scale and the SPPB are effective at determining frailty in patients who are somewhat mobile but falls short for extremely frail patients who may be bed bound. Imaging modalities are becoming increasingly prevalent in frailty research. Ultrasound imaging can be easily done at bedside and probes are becoming increasingly portable.

Little research has assessed the ability of ultrasound images to determine a patient's frail condition. This hole in current research has inspired our investigation of the ability of ultrasound images of the thigh muscle to provide information on sarcopenia and frailty. Artificial intelligence (AI) in medicine is changing the way patients are evaluated and diagnosed; this has influenced our development of machine learning models to help measure thigh muscle size and quality to eventually try and improve current methods of frailty evaluation.

CHAPTER 3: MANUSCRIPT TO BE SUBMITTED

Quadricep Muscle Ultrasound Imaging: A Machine Learning Approach to Frailty Assessments

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Disclosures

None.

English Abstract

Background

Aging and frailty add dimensions of complexity to the management of cardiovascular diseases. As the world population ages, accurately assessing frailty and vulnerability in older patients is becoming increasingly important. Sarcopenia is a component of the frailty syndrome that can be assessed through a variety of methods. Assessment of frailty and sarcopenia is often not feasible in very ill patients who may be bed bound and cannot carry out physical tasks. Musculoskeletal ultrasound imaging is proving to be useful in the identification of sarcopenia, a marker of frailty. Quadricep muscle thickness (QMT), an indicator of sarcopenia, can be measured from ultrasound images of the thigh. Currently, there is limited research surrounding the ability of muscle ultrasound images to provide valuable diagnostic information for frailty or for machine learning (ML) models to measure QMT.

Objectives

The primary goal of this study was therefore to develop ML models capable of predicting QMT based on provided quadricep ultrasound phased array images as input variables. The secondary goal was to confirm the relationships between QMT and handgrip strength (HGS), lean body mass (LBM), phase angle (PA), clinical frailty scale (CFS) score.

Methods

This study was a retrospective single-center cross-sectional cohort study conducted at the Jewish General Hospital. The study population consisted of adult inpatients and outpatients undergoing a transthoracic echocardiogram. Ultrasound images of the thigh served as the primary input (independent) variable for the ML models we developed. Ultrasound image collection was performed by trained sonographers at the Jewish General Hospital echocardiography laboratory. The images were subsequently annotated to delineate the femur and the top of the quadricep muscle. Five different measures of frailty were used as the output (dependent) variables; HGS, CFS, LBM, bio impedance PA, and QMT. For the first experiment, single variable linear regression ML models were trained using the ultrasound images as input variables and the five different frailty measures as output variables. 5-fold cross validation was used to test the performance of the model and mean absolute error (MAE) was measured to determine the model accuracy. For the second experiment a segmentation model was trained to identify a region of interest on the ultrasound images. This region of interest was then used to train a new linear regression model to predict QMT values.

Results

The final cohort consisted of 486 patients with a mean age of 66 $\pm$ 14 years and was 57% female. Increasing QMT was positively associated with HGS, LBM, PA, while negatively associate with CFS.

The ML model using ultrasound images as inputs predicted QMT values with a MAE of 0.4478 ± 0.033 cm. The ML model that used ultrasound images overlaid with predicted binary masks from

the segmentation model predicted QMT with a MAE of 0.355 ± 0.021 cm. The ML model that used ultrasound images overlaid with ground truth binary masks predicted QMT with a MAE of 0.3210 ± 0.013 cm.

Conclusion

From these results it may be assumed that increased QMT could be used as a surrogate marker of these four different frailty measures. The models we have developed can provide a QMT value from a provided ultrasound image. This QMT value can further be used to determine the sarcopenic condition of the patient.

INTRODUCTION

The world population is ageing at a rapid rate such that approximately 16% of the world population is expected to be over the age of 65 by the year 2050[1]. This trend of increasingly older adults translates to increasingly older patients. For adults 65 years of age and older, cardiovascular disease is the leading cause of disability[2]. Older patients remain the demographic most at risk for adverse outcomes following a cardiovascular event or diagnosis[3]. Additionally, older patients are at higher risk for mortality and morbidity following cardiac surgery[4].

A patient's level of vulnerability can be described by their level of frailty. Frailty is a geriatric syndrome and is described by decreased physiological reserve and ability to cope with physiological stressors, such as cardiac surgery or hospitalization[5]. Frailty has been used as a measure of biological age which is a more accurate risk predictor than chronological age[6]. Certain biomarkers have been increasingly used as surrogate markers of frailty and have been subject to investigation.

Sarcopenia has been a validated marker of frailty; evaluating methods to measure decreased muscle strength, quality and size has therefore been a focal point of frailty related studies[7]. Hand grip strength (HGS), clinical frailty scale (CFS) scores, and various body composition measures have been evaluated and validated as screening tools for sarcopenia and frailty[8].

Measuring HGS, CFS, lean body mass (LBM) and phase angle (PA) while promising, are perhaps not feasible measurements to take in all patient populations such as those in ICU or bedbound patients. Various imaging modalities have shown preliminary success in highlighting sarcopenic phenotypes. The use of ultrasound and assessing light intensity in images has been

shown to be good indicators of sarcopenia. Muscle thickness and quality are important characteristics that can be evaluated in ultrasound images, yet no studies have developed machine learning artificial intelligence models that can predict QMT from a provided ultrasound image. The primary goal of this study was therefore to develop ML models capable of predicting QMT based on provided quadricep ultrasound phased array images as input variables. The secondary goal was to confirm the relationships between QMT and HGS, LBM, PA, CFS.

METHODS

Study Design

This study was a retrospective single-center cross-sectional cohort study conducted at the Jewish General Hospital. Data collection began in January 2019 and was finished in December of 2019.

Study Population

The study population consisted of adult inpatients and outpatients undergoing a transthoracic echocardiogram (TTE) at the Jewish General Hospital. Exclusion criteria were: (1) pregnant women, (2) patients with cardiovascular implantable devices (pacemaker or defibrillators) as bio-impedance (BIA) could not be used, (3) patients who did not consent to being weighed using BIA, (4) patients who could not verbally consent.

Ultrasound Image Acquisition and Preparation

Ultrasound images served as the primary input variable for the ML model we developed. Ultrasound image collection was performed by trained sonographers at the Jewish General Hospital echocardiography laboratory. Sonographers performed routine clinically indicated TTE exams. Additionally, sonographers were asked to acquire an additional, non-standard image of the anterior mid-thigh. All images were acquired using a phased array cardiac ultrasound probe.

The ultrasound images of the thighs from patients were stored in the hospital data-base and were accessible through the *ViewPoint 6* and *EchoPac* software. The anterior thigh images were loaded, and all annotations made by the sonographers had to be removed such that no labels remained. The images were exported and analyzed on the DICOM viewing software, *Osirix.* For each quadricep image, we delineated the upper border of the femur using nine equally spaced points such that the fifth point was positioned centrally on the upper margin of the bone. These points represented coordinates on the ultrasound image to be used for thickness measurements and as reference points for our machine learning model. Similarly, we used five points to delineate the approximate superior limit of the quadricep muscle. The third point in this series of five points was positioned centrally on the upper margin of the muscle; this central point was roughly aligned with the central point of the femur. The thickness of the muscle was calculated by measuring the distance between the central points on the femur and the upper limit of the quadricep. The two distinct sets of points for each image were stored as Java Script files (JSON) to be used as reference coordinates in the development of the AI model.

In addition to delineating the superior margins of the bone and muscle, we resized the ultrasound images to 700x1000 pixels such they would all be uniform. We then cropped the images using various cropping sizes to focus on regions of interest (ROI) of varying size. The size of the

ROIs were determined as a function of the percentage of the total thickness of the muscle in each image. In addition to uncropped images, three different ROI dimensions were evaluated. 40%, 60% and 80 % of the muscle thickness were used as the dimensions of the square ROIs. Multiple machine learning models were subsequently trained using either uncropped images or one of the three discussed cropped ultrasounds. The rationale behind cropping the images was to minimize the presence of artifacts from the software or during image acquisition; this would allow the model to evaluate the muscle tissue only within the specified region.

Covariates

In addition to ultrasound images, age and sex were recorded. Weight and height were measured as part of the normal routine of the TTE exam. Heart Failure (HF) status was also recorded.

Deep Learning Model Frailty Outputs

Five different markers of frailty were used as output (dependent) variables. As such, different models were trained to predict each of the five different outputs based on the provided inputs (ultrasound image). Concurrently with TTE examination, a Clinical Frailty Scale (CFS) score was recorded, handgrip strength (HGS) was assessed, and patients were weighed on a bioimpedance scale (BIA) to yield phase angle (PA) and lean body mass measurements (LBM). QMT was measured retrospectively.

The Clinical Frailty Scale (CFS) rates patients based on the evaluation of the patient's symptoms, level of mobility and disabilities in activities of daily living (ADL) and instrumental

activities of daily living (IADL). Patients are scored on a scale from 1-9; a lower score indicates robustness while a higher score indicates increased frailty and vulnerability.

HGS was measured by trained interviewers with a Jamar hydraulic handheld dynamometer that was adjusted to the patient's hand size. Patients were seated with their elbow bent at 90 degrees and pressed against the side of their body. Patients were asked to squeeze the dynamometer once with each hand and a third time with the strongest hand and the results to the nearest kilogram were recorded. The highest of the three measurements was used in the study.

At the time of TTE examination patients were weighed using BIA. Electrodes connected to the BIA scale were placed on each hand and each foot. Patients were asked to sit with their arms spread out to the side so that there was no contact between their torso and arms. The BIA measured the resistance of imperceptible electrical currents passed through the body. Measured resistance values are used to compute the Total Body Water (TBW) as well as intracellular body water (ICW) and extracellular body water (ECW). Additionally, the measurements can be used to calculate PA and lean body mass (LBM). We used PA and LBM as additional frailty markers in the ML model. PA values of frailty were measured on a continuous scale.

Machine Learning Approach

Experiment 1: Single Variable Linear Regression Model

Multiple different linear regression (LR) ML models were trained with one input variable and one output variable each. For the first five LR models the uncropped ultrasound image was used as an input. Model 1 was trained using HGS as the output variable. Model 2 was trained using LBM as the output variable. Model 3 was trained using PA as the output variable. Model 4 was trained using CFS as the output variable. Model 5 was trained using QMT as the output variable.

The models were validated using 5-fold cross validation. The accuracy of the model was measured by calculating the mean absolute error (MAE).

Experiment 2: Segmentation Model

The second experiment required the sequential training of two models: a segmentation model and an LR model. The predicted output of the segmentation model was used as the input for the second LR model assessing QMT.

A segmentation model was trained to produce binary masks that contained a region of interest from a provided ultrasound image. The segmentation model was trained using ground truth (GT) binary masks that were generated from the annotated ultrasound images. The lateral points of the annotations were used to delineate the mask border. The inputs to the segmentation model were the ultrasound images containing no annotations. The outputs were the predicted masks using the plain ultrasound images.

A LR model was then trained using a combination of the plain ultrasound images and the output of the segmentation model. The predicted masks from the segmentation model were overlaid on their corresponding ultrasound images, providing a cropped ROI. This cropped ultrasound image was then provided as the input to the LR model to predict muscle thickness. The model was validated using 5-fold cross validation and accuracy was measured by MAE.

Additionally, a LR model was trained using the GT segmentation masks and ultrasound images. The GT masks were overlaid on their corresponding images and this ROI was provided as an input to the model to subsequently predict QMT.

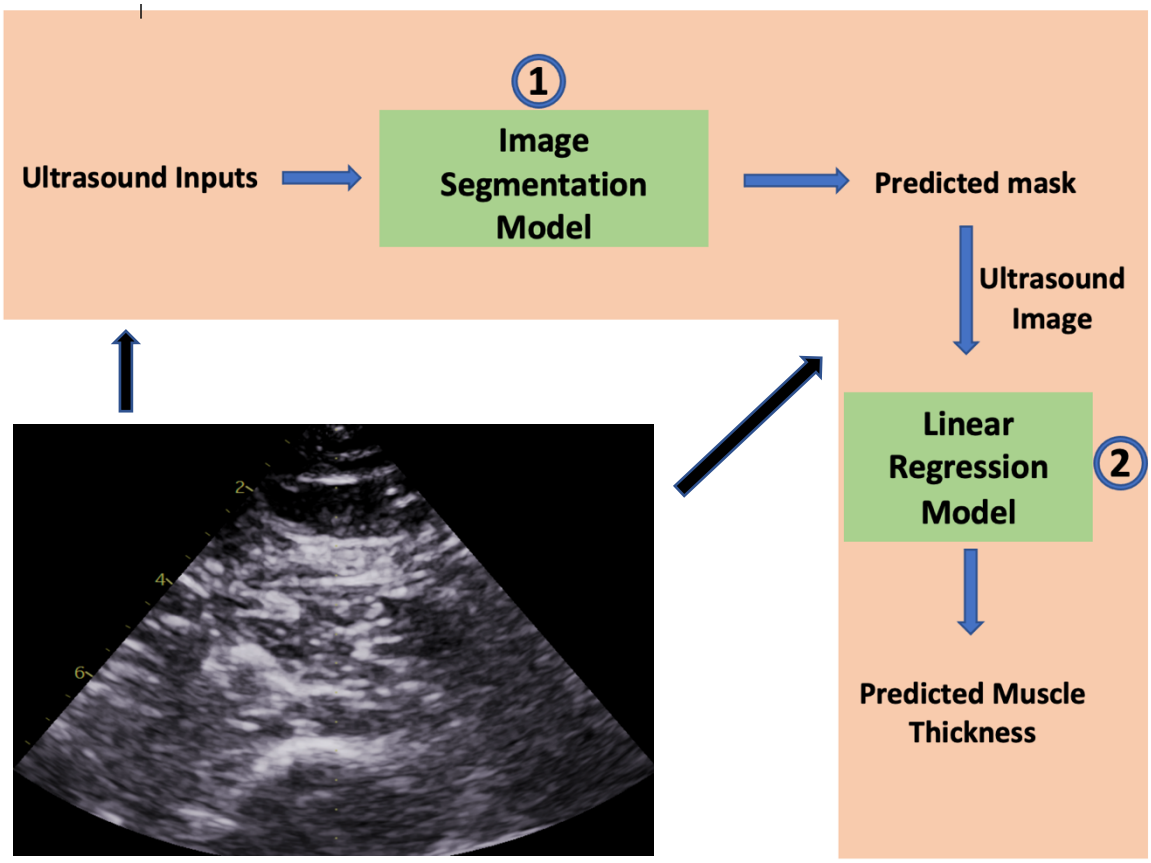

Figure 1: Methodology of *experiment 2.* The first step was to train the segmentation model. Using the outputs of the segmentation model, we trained the LR model to predict muscle thickness.

RESULTS

Baseline Characteristics

The final cohort consisted of 486 patients. 549 patients were recruited and consented to the study. 63 patients were excluded from the study due to missing data or poor ultrasound image quality. The study cohort had a mean age of 66 ± 14 years and was 57% female. The mean values for the frailty measures across the study cohort were as follows: the mean BMI was 28.9 ± 6, the mean CFS was 3 ± 1, the mean HGS was 26.1kg ± 11.4kg, the mean LBM was 48.2kg ± 10.9kg, the mean PA was 4.9° ± 1.0°, and the mean QMT was 3.33cm ± 1.08cm.

The mean BMI values were very similar across male and female patients across all age groups with the lowest BMI of 28.3 in female patients over the age of 70, and the highest BMI of 29.4 in female patients under the age 70. HGS, a strong predictor of frailty, was 24% lower in male patients over the age of 70 compared to their younger counterparts. HGS in older female patients was lower by 21% compared to their younger counterparts. The same trends with respect to age and sex were observed for LBM and PA. Baseline characteristics are further outlined in Table 1.

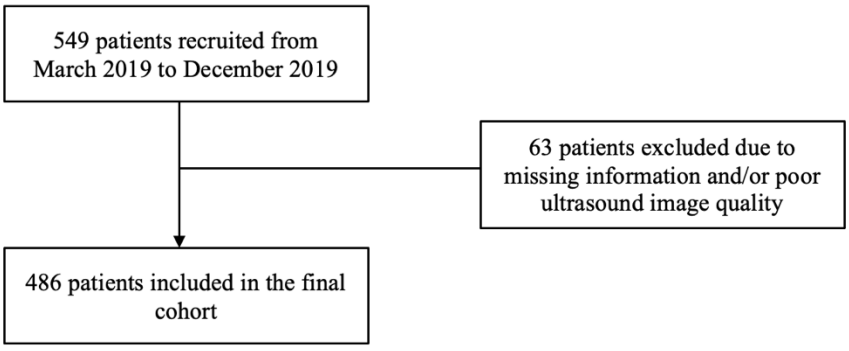

Figure 2: Flow Diagram.

Table 1: Baseline characteristics by sex and age.

	N	Age (Mean)	BMI	CFS	HGS (kg)	Weight (kg)	LBM (kg)	PA (∘)	QT (mm)
Female < 70 Years	156	56.2	29.4	2.7	22.1	75.3	43.9	5	36.2
Male < 70 Years	108	55.5	29.2	2.6	38.7	87.4	60.1	5.9	34.3
Female ≥ 70 Years	122	78.3	28.3	3.4	17.5	68.7	39.7	4.2	31.33
Male ≥ 70 Years	100	78.8	28.7	3.3	29.3	80.5	52.4	4.5	29.2

Quadricep Thickness

The validated frailty measures of HGS, CFS, LBM and PA were all compared to QMT. A positive relationship was observed between QMT and HGS, LBM, PA. Figures 3-5 demonstrate the scatter plots of these relationships. A negative relationship was observed between QMT and CFS; lower CFS values indicate increased robustness. As QMT decreased, CFS and frailty was observed to slightly increase (Figure 6).

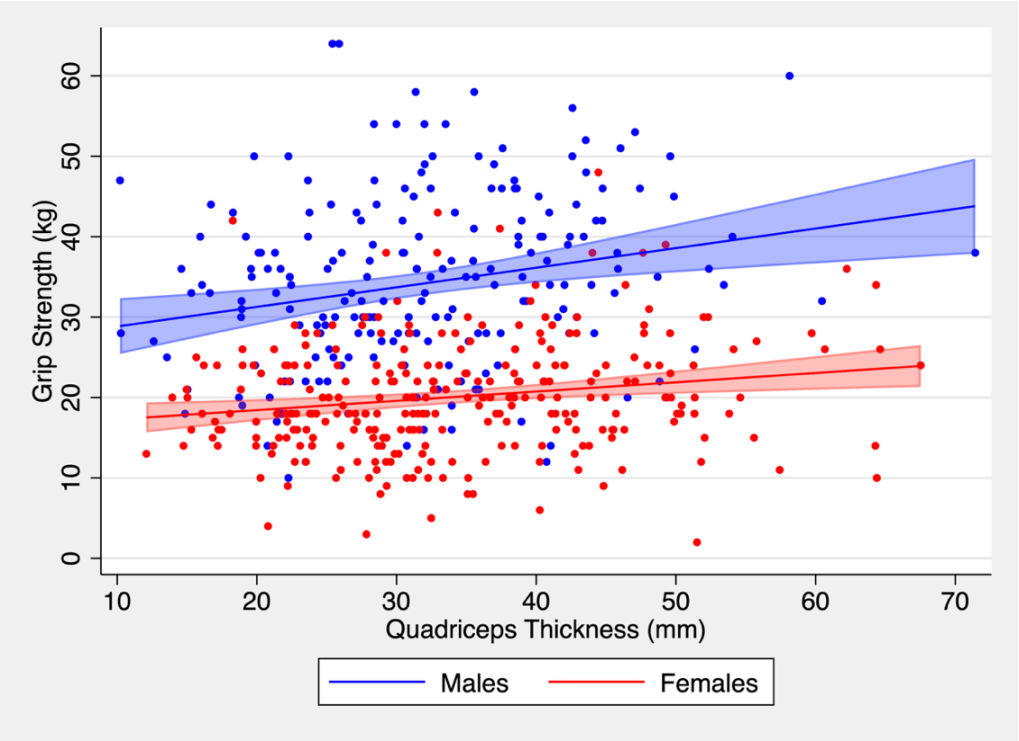

Figure 3: Scatter plot showing the linear relationship and 95% confidence intervals for Hand Grip Strength (kg) vs Quadricep muscle thickness (mm) for males and females.

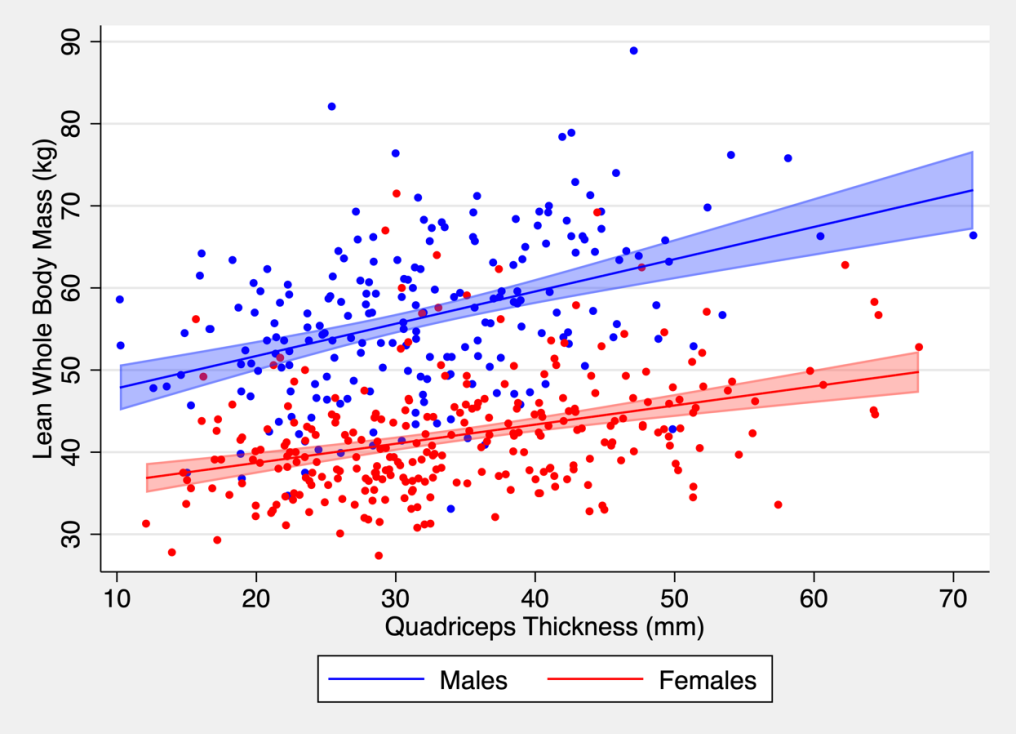

Figure 4: Scatter plot showing the linear relationship and 95% confidence intervals for Lean Whole Body Mass (kg) vs Quadricep muscle thickness (mm) for males and females.

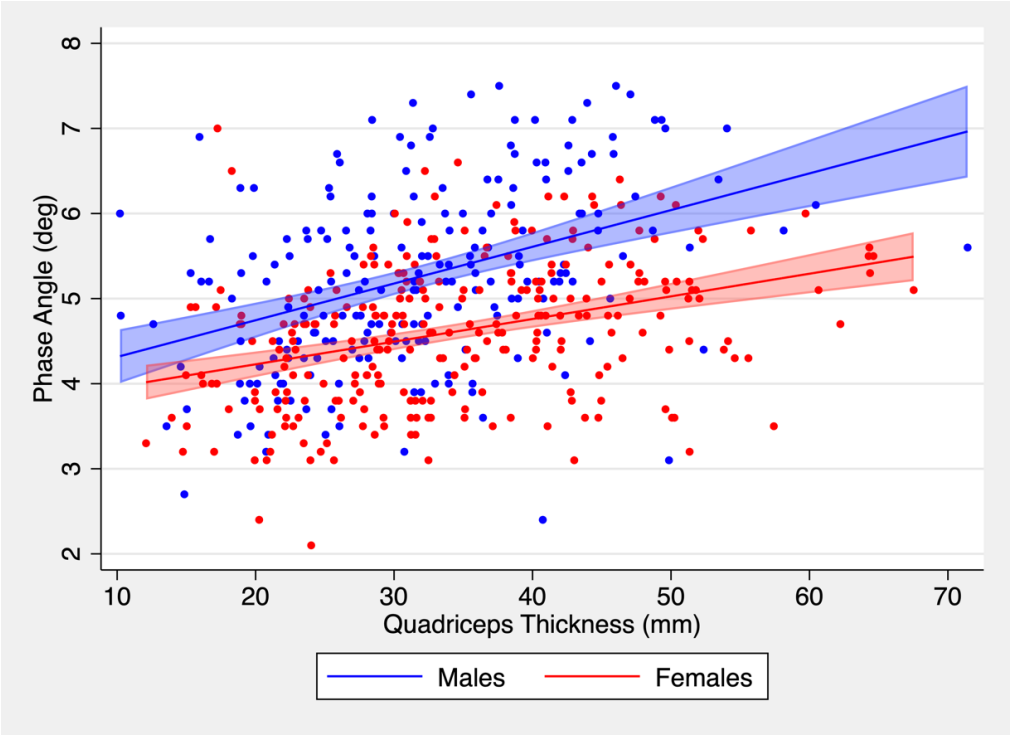

Figure 5: Scatter plot showing the linear relationship and 95% confidence intervals for Phase Angle (deg) vs Quadricep muscle thickness (mm) for males and females.

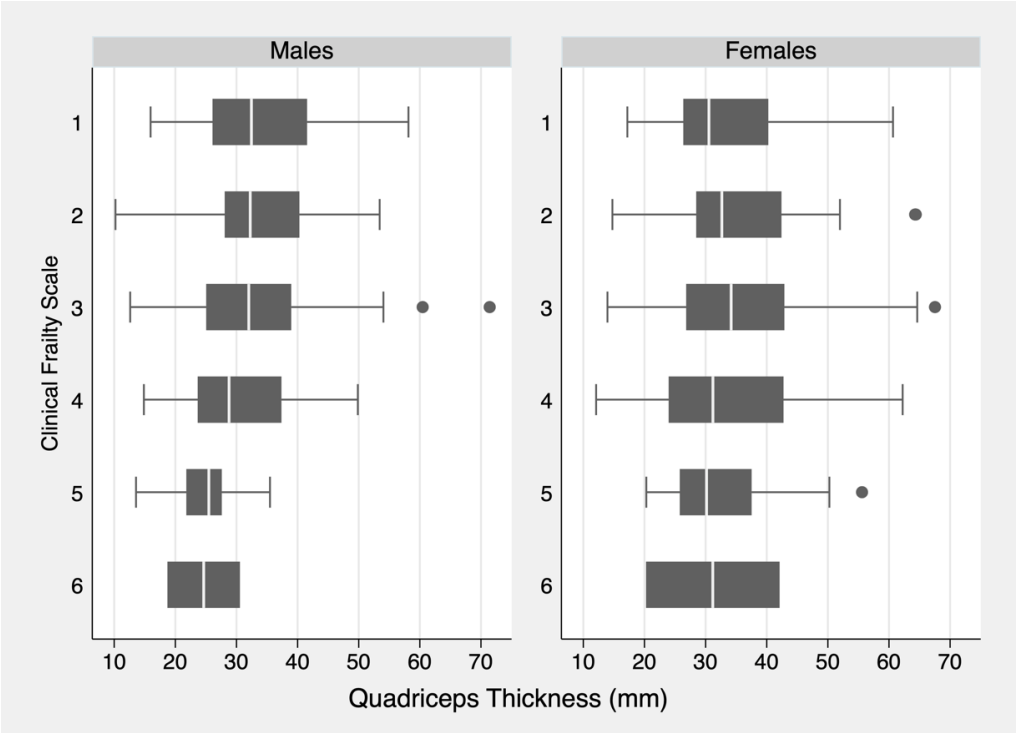

Figure 6: Box plots showing the relationship between the Clinical Frailty Scale and Quadricep muscle thickness (mm) for males and females.

Machine Learning Image Preprocessing

486 ultrasound images were preprocessed and removed of all annotations and edits that had been made by technicians (Figure 7). All 486 images were then annotated delineating the femur and the top of the quadricep muscle. 5 points were used for the top of the muscle while 9 points delineated the bone (Figure 7). Muscle thickness was also measured across all images.

a) b)

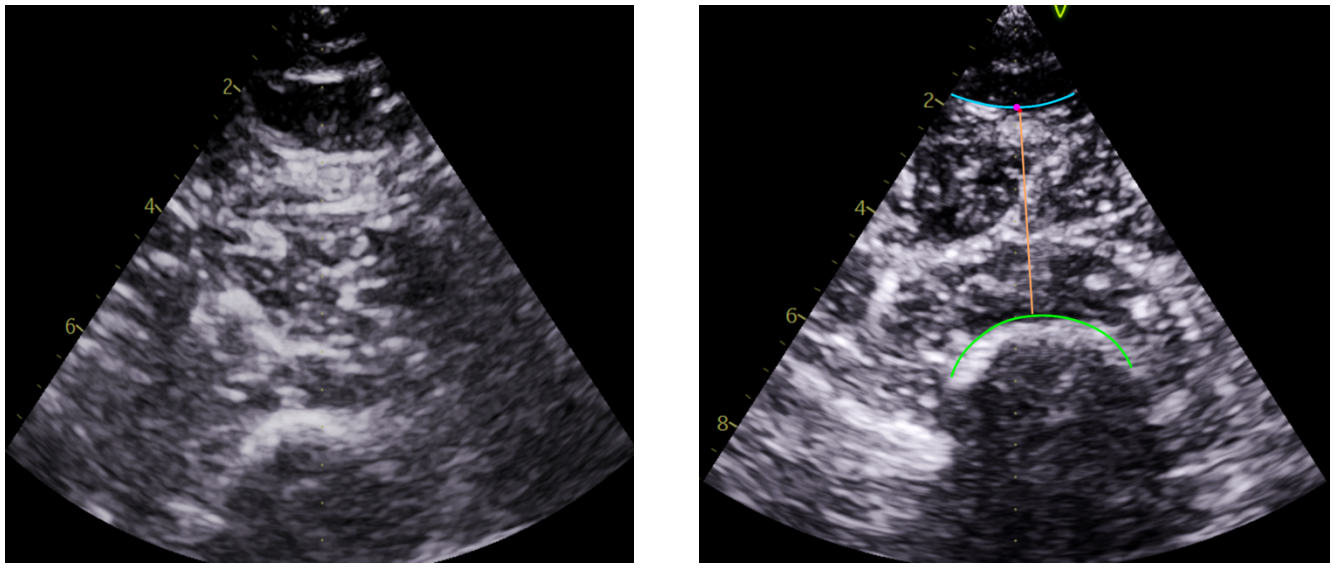

Figure 7: Sample ultrasound images of the quadricep **(a)** without annotation and **(b)** with annotations. The green line delineates the top of the femur, the blue line delineates the top of the quadricep muscle, and the orange line connects two points, providing a muscle thickness measurement.

Machine Learning Models

1. The first ML model was the LR model using the unannotated ultrasound images. The LR model was successfully trained to provide QMT values for corresponding ultrasound images provided as inputs. The mean MAE for the 5-fold cross validation was 0.4478 ± 0.033cm. The MAE values for the test sets of each fold of the cross validation are listed in Table 2 under Model 1.

2. The second ML model used was trained using two steps. The QMT predictions were more accurate than in the single step single variable LR model. The first step comprised the segmentation model. The segmentation model was successfully trained using the GT binary masks created with the image annotations (Figure 8). The mean dice score for the segmentation model was 0.856 ± 0.013. The dice scores for each fold of the segmentation model are listed in Table 2. For LR Model 2, the predicted binary masks were then overlayed on the ultrasound images, providing the ROI for the QMT LR model (figure 8). The mean MAE for the LR model using the predicted masks was 0.355 ± 0.021cm. All the MAE values for each fold of the cross-validation for the LR model are listed in Table 2 under Model 2.

3. To further evaluate the performance of the model, an additional LR model was made using the GT binary masks overlaid on ultrasound images as input variables rather than the predicted binary masks from the segmentation model. This LR model performed slightly better with a mean MAE of 0.3210 ± 0.013cm. All the MAE values for each fold of the cross-validation for the LR model are listed in Table 2 under Model 3.

Table 2: Linear regression model mean absolute error (cm) and segmentation model dice score for each fold of 5-fold cross-validation for Model 1, 2, 3 and the Segmentation Model. The mean and the standard deviation of the MAE and DSC in these 5 test sets is provided.

Fold	LR Model 1 MAE	LR Model 2 MAE	LR Model 3 MAE	Segmentation Model DSC
1	0.4621	0.3357	0.3194	0.84
2	0.4926	0.3653	0.3372	0.87
3	0.4028	0.3613	0.3254	0.85
4	0.4372	0.33	0.3019	0.87
5	0.4443	0.3806	0.3211	0.85
Mean MAE	0.4478 ± 0.033	0.355 ± 0.021	0.3210 ± 0.013	
Mean DSC				0.86 ± 0.013

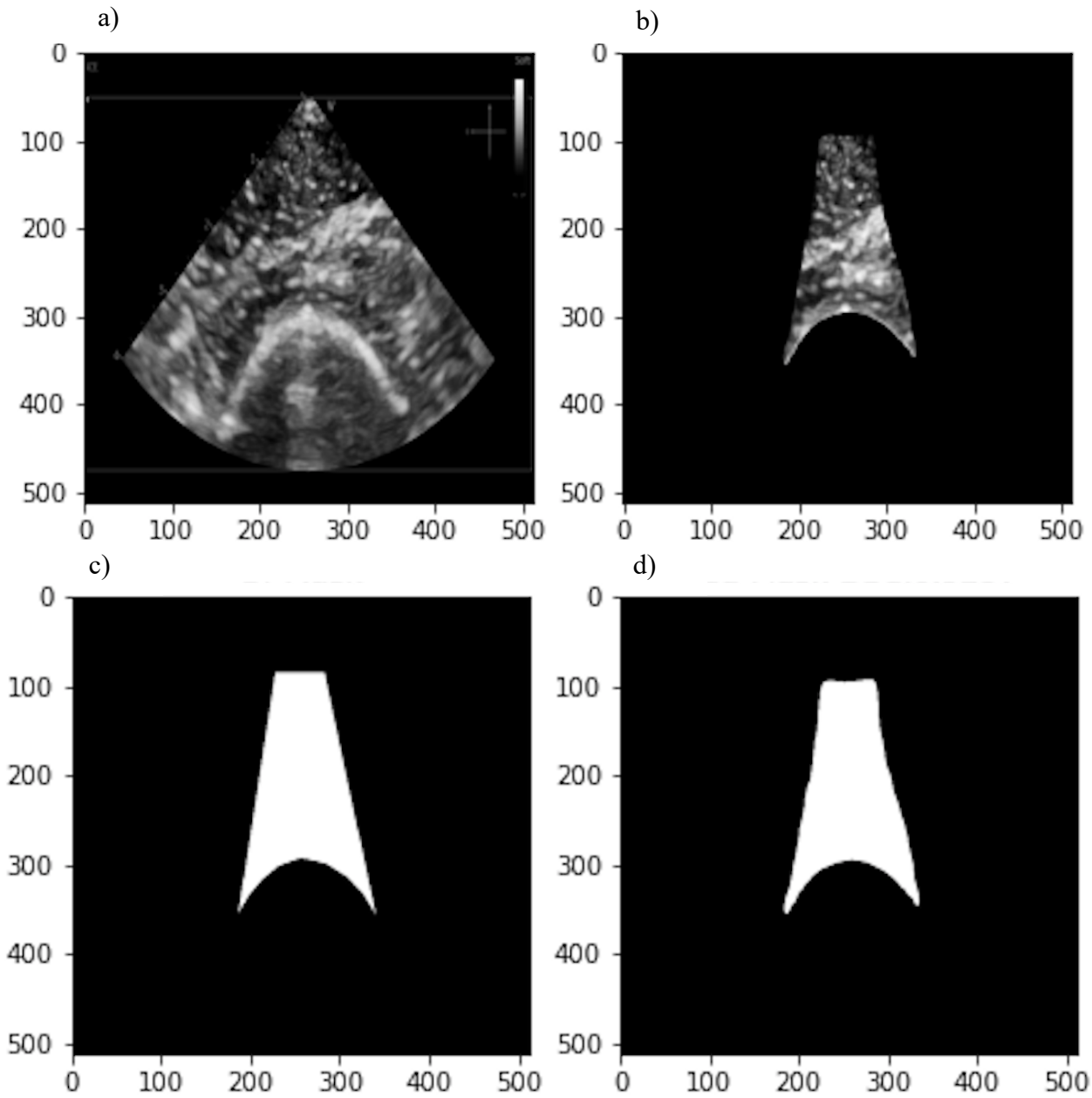

Figure 8: Sample ROI cropping beginning with (a) whole, unaltered ultrasound image. (c) Ground truth binary mask was made to train the segmentation model so that it could provide (d) a predicted binary mask as an output for a given ultrasound image. The predicted binary mask was then overlaid on the corresponding ultrasound image to create (b) a cropped ROI for the LR model to subsequently predict QMT.

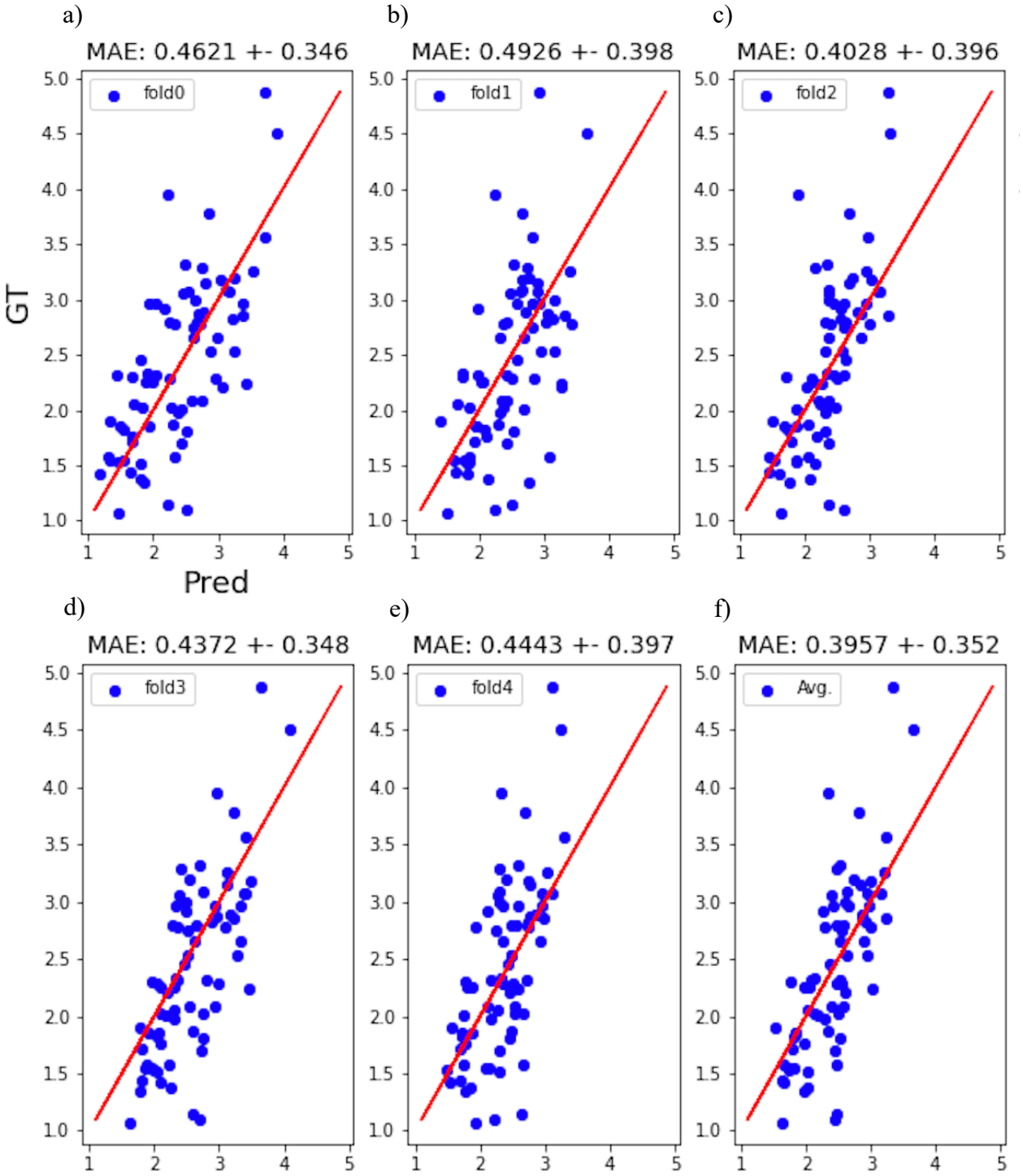

Figure 9: Scatter plots showing Ground Truth vs Predicted QMT values for LR Model 1 using whole ultrasound images as inputs. Each fold of the 5-fold cross validation is shown in addition to (f) the mean.

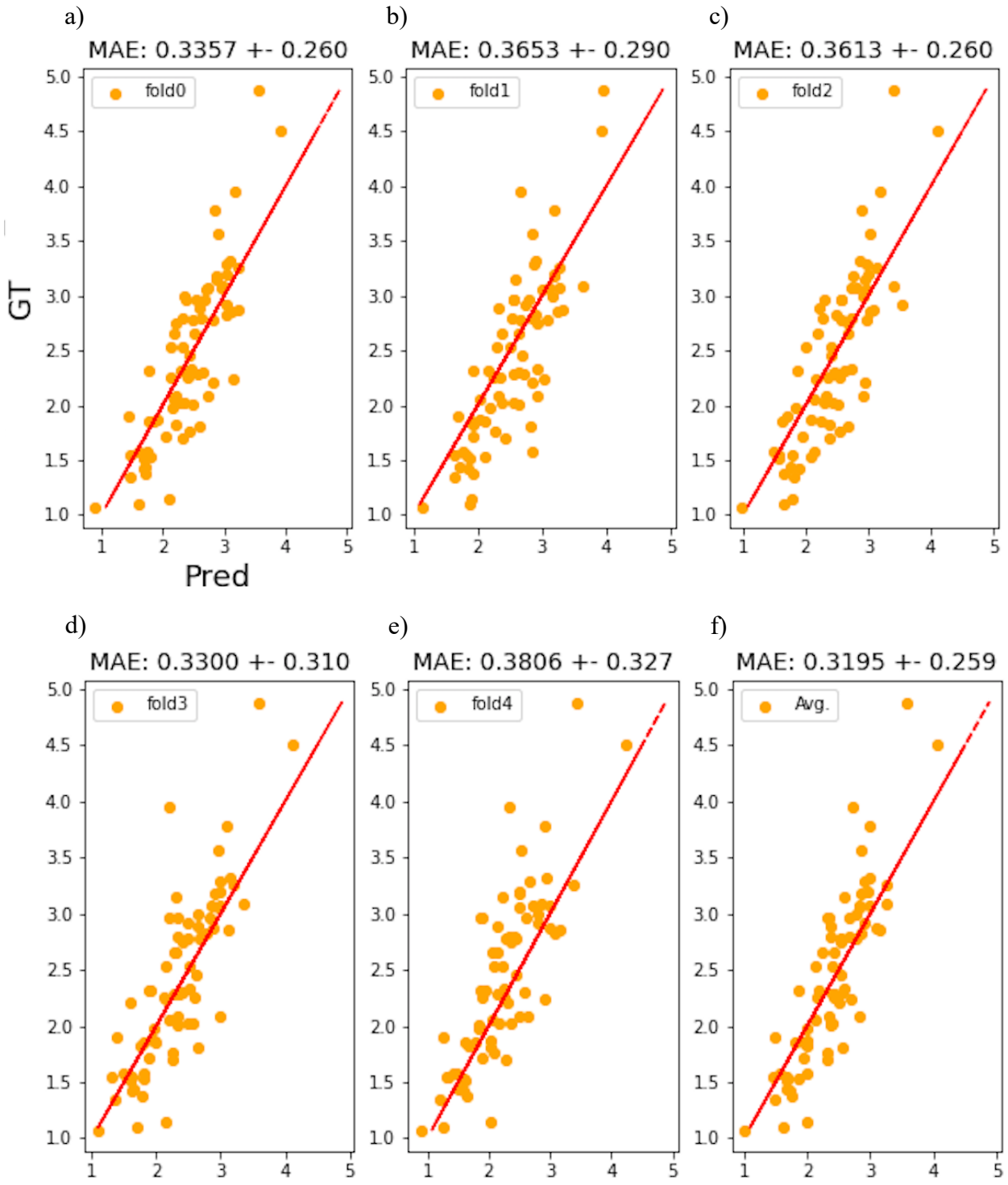

Figure 10: Scatter plots showing Ground Truth vs Predicted QMT values for LR Model 2 using ultrasound images overlaid with predicted binary masks from the segmentation model as inputs. Each fold of the 5-fold cross validation is shown in addition to (f) the mean.

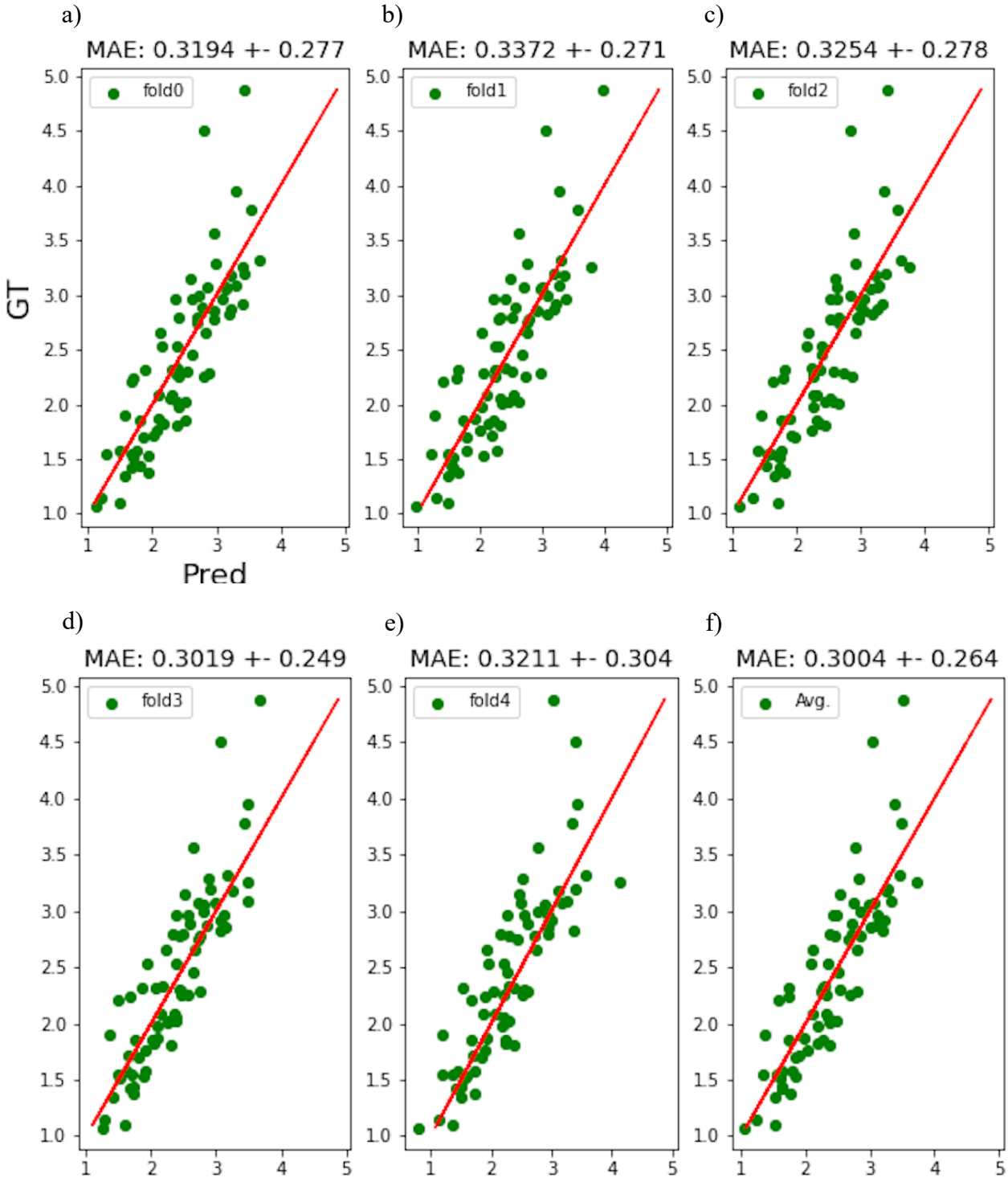

Figure 11: Scatter plots showing Ground Truth vs Predicted QMT values for LR Model 3 using ultrasound images overlaid with ground truth binary masks as inputs. Each fold of the 5-fold cross validation is shown in addition to (f) the mean.

CONCLUSION

This study primarily aimed to develop ML regression and segmentation models to predict QMT by using ultrasound images as input variables. Additionally, the study aimed to evaluate the relationship between QMT and four different frailty related variables. The findings indicate that QMT was positively associated with increased HGS, LBM and PA. QMT was also found to be negatively associated with CFS. From these results it may be assumed that increased quadricep muscle mass could be used as a surrogate marker for these four different frailty measures. This conclusion is an extension of the results of several studies in the literature that have demonstrated low muscle mass and sarcopenia as indicators of the frailty syndrome. Additionally, the machine learning models that were developed showed promising results. The models we have developed can provide a QMT value from a provided ultrasound image. This QMT value can further be used to determine the sarcopenic condition of the patient.

Several frailty assessments are available, such as the Fried scale, the short physical performance battery (SPPB), etc. yet no gold standard for evaluation exists. While many of these assessments are useful tests to determine a patient's functional capacity and by extension, frailty, these assessments can be long, and require a certain level of mobility. Bed bound patients and severely frail individuals cannot be accurately assessed using many of these methods. Ultrasound imaging can easily be performed at bedside and a QMT measurement could provide useful information to clinicians regarding the vulnerability of patients.

Despite the successful development of these ML models, the single variable LR models that were developed to predict HGS, LBM, PA and CFS from ultrasound input images could not accurately do so. There are certain limitations that should be addressed in future studies that seek

to develop similar ML models. The first was the image quality. All ultrasound images were acquired with a phased array cardiac probe; this probe is not meant for musculoskeletal image acquisition. Additionally, fewer than 500 images from patients were included in this study. This is a rather small sample size in the context of machine learning. Finally, physical strength was only measured using HGS and did not comprise a lower limb component.

Future research using thigh ultrasound images for frailty evaluation should incorporate the use of a linear array ultrasound probe, to ensure clear image quality. Lower extremity strength should also be measured such that all the elements of sarcopenia (muscle mass, strength, and quality) may be incorporated into future models.

QMT proves to be a promising screening tool in identifying frail individuals. The results demonstrate that QMT values can be accurately predicted from provided ultrasound images using LR and image segmentation ML models. The challenges posed by the frailty syndrome for clinicians is not only the management of the syndrome but also the detection of the condition. ML models using quadricep ultrasound images are an exciting avenue of frailty evaluation that should be further explored.

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CHAPTER 4: THESIS CONCLUSION

The global population is aging at a rapid rate. Age is an important risk factor for cardiovascular disease; efficiently identifying vulnerable, older individuals has become a focal point of cardiovascular research. Understanding the differences between biological age and chronological age helps to explain the individual differences in the aging process. The frailty syndrome deals with decreased physiological reserve and is associated with increased rates of mortality and morbidity. Despite this knowledge, no gold standard for frailty evaluation exists. Imaging modalities have been increasingly explored as a tool to identify sarcopenia in patients. Sarcopenia can act as a surrogate marker of frailty. Ultrasound images of the thigh muscle could therefore potentially provide important frailty diagnostic information.

The literature review on the frailty syndrome discussed the current understanding of the frailty syndrome, its relationship with cardiovascular diseases, and how we evaluate it. Although certain frailty assessments such as the Fried scale or the SPPB scale provide relevant insight into a patient's functional capacity, these assessments are not feasible in extremely frail individuals and only provide indirect assessments of sarcopenia. Extremely frail or bed-bound patients cannot be assessed in many cases due to their physical limitations. Previous research has been done to demonstrate that muscle size is associated with physical function and by extension robustness. Ultrasound images can be performed at bedside and can provide instantaneous information about muscle quality. Little work has been done however to demonstrate the relationships between quadricep muscle thickness and various frailty measures. Additionally, little research has made use of machine learning models to determine muscle thickness from provided ultrasound images.

According to the findings of the manuscript, HGS, LBM, and QMT all decline with age, while CFS increases. The results demonstrate that QMT is positively associated with HGS, LBM,

PA, while the inverse is observed with CFS. QMT needs to be further validated as a frailty marker but proves to be a useful marker of sarcopenia. The study most importantly demonstrated that machine learning models could accurately predict the QMT measurements from provided ultrasound images. This finding helps to lay the groundwork for future machine learning models targeting ultrasound imaging and frailty.

It is important to discuss the limitations of this study. The cohort size of 489 patients is quite small especially with respect to machine learning methodology. This both reduces the external validity of the study and is a potential reason for certain insignificant results in some of the linear regression machine learning models. Additionally, the patient population consisted mostly of outpatients and therefore did not include many severely frail patients. The patient population was not entirely representative of the full range of the frailty syndrome. Finally, the images were acquired with a phased array cardiac probe; this limited the quality of the musculoskeletal images that were used.

Going forward, a more comprehensive patient population should be analyzed; cardiac inpatients would be a good next step to include increasingly frail individuals. Additionally, a linear array probe should be used so that the image quality may increase and so that values such as mean pixel intensity can be easily and accurately measured. To our knowledge, ultrasound imaging has never been routinely used to assess patient frailty. The development of more robust predictive machine learning models using ultrasound images of the thigh should be a focus for frailty research. No gold standard exists for frailty evaluation and ultrasound imaging of the musculoskeletal system could prove to be an effective indicator of frailty and vulnerability in cardiac patients.

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