

## The role of superb microvascular imaging in detecting low-grade inflammation among adults and those with chronic kidney disease: A preliminary study

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**Background/aim:** Pathophysiologic changes associated with chronic inflammation occur with aging and more prominently in patients with chronic kidney disease (CKD), and an association between chronic inflammation and muscle wasting has been identified. The microcirculation is extremely sensitive to the inflammatory process and actively participates in it. In a healthy adult, angiogenesis is a strictly controlled and rare occurrence. However, aberrant angiogenesis and the development of new tiny blood vessels are known in chronic inflammatory diseases. Superb microvascular imaging (SMI) is a noninvasive technique that can evaluate tiny vessels with low blood flow and provide quantitative data. Our goal was to detect increased blood flow secondary to low-grade chronic inflammation in micro-circulation in the rectus femoris (RF) muscle using SMI.

**Materials and methods:** This cross-sectional study involved 30 patients with CKD, 30 adults without CKD or other chronic illnesses, and 32 young healthy volunteers. This study was conducted in our university hospital between March and December 2021. The RF cross-sectional area (CSA) was measured, and vascular index (VI) values were obtained using SMI. All three groups' RF-CSA and VI values were compared.

**Results:** Although there was no statistically significant difference in RF-CSAs between the groups, the VI values of all three groups were statistically different ( $p < 0.001$ ). The median (min–max) VI values were 0.90 (0.60–1.30), 0.50 (0.20–1.0), and 0.30 (0.10–0.50) for the CKD, adult control, and young healthy groups, respectively. The VI significantly differentiated patients with CKD from all other patients and the adult control group. When a cutoff value of 6.5 was used for the VI in detecting increased blood supply in RF muscle in patients with CKD, the accuracy, positive predictive value, and negative predictive value were 93.5%, 85.3%, and 98.3%, respectively.

**Conclusion:** SMI can detect increased blood supply caused by low-grade inflammation in the RF muscle.

**Keywords:** Inflammation, superb microvascular imaging, adult, chronic kidney disease, muscle wasting disease

### 1. Introduction

Muscle wasting diseases (MWD), such as sarcopenia, are currently a hot research topic, due to increased awareness of the increasing prevalence of such conditions based on population aging [1,2]. Rosenberg coined the term sarcopenia in 1989 to define the reduction of skeletal muscle mass and strength with age [3]. Chronic kidney disease (CKD) causes an energy imbalance due to decreased protein intake and accelerated catabolism. As a result, sarcopenia may occur in patients with CKD during young adulthood [4,5]. Studies have shown that low muscle strength resulting from sarcopenia is associated with impaired clinical outcomes, diminished life quality, increased hospitalization, and increased mortality [4]. Several chronic diseases are associated with muscle mass loss among older adults, and whether this is due to aging or disease is unknown [6]. On the other hand, inflammation is a common

feature of chronic disease (with or without aging), and inflammation is frequently associated with hyperemia [7–9]. Inflammation is also associated with an increase in blood vessel proliferation [10].

Ultrasound (US) has been a reliable tool for determining muscle mass and quality by measuring the cross-sectional area (CSA), thickness, and volume of muscle [11]. Ultrasonographic elastography and contrast-enhanced US can detect muscle stiffness and changes in microvascular structure caused by sarcopenia; however, data are still limited [12,13]. US is commonly used in musculoskeletal (MSK) disorders due to advantages such as low cost and easy accessibility. However, there is no standardized threshold value for US measurements used to quantify muscle mass and quality, which significantly limits its applicability in sarcopenia [1]. It is well known that the capacity of Doppler US (DUS) to identify pathologic flow

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within MSK soft tissue indicates the presence of local active inflammation [14]. However, conventional DUS techniques have technical limitations in imaging small blood vessels due to exogenous Doppler signals caused by clutter such as surrounding tissue motion. Accordingly, wall filters should be used to eliminate clutter and motion distortions from conventional DUS imaging. This leads to reduced visualization of small blood vessels with slower blood flow that is approximately equivalent to the speed of tissue movement [15]. These limitations have been resolved by advanced flow detection imaging technology.

Superb microvascular imaging (SMI) is a novel technology that can separate flow data from overlapping tissue movement distortions, retaining tiny slow-flowing vasculature with excellent clarity and detail. SMI analyzes clutter motion and employs a unique algorithm to determine and reduce tissue movement, expose genuine blood flow, and evaluate tiny vessels with blood flow at quite a low speed. SMI has been considered a novel method for assessing various MSK conditions, including lateral epicondylitis, arthritides, and carpal tunnel syndrome [16,17]. SMI can also obtain quantitative data known as the vascular index (VI). To the best of our knowledge, no study on low-grade inflammation in the rectus femoris (RF) muscle using SMI has yet been published.

Even though MWDs impose personal, social, and economic burdens if left untreated, early detection and initiation of necessary treatments are critical [6]. The goal of this study was to determine whether SMI could be used to detect low-grade muscle inflammation by finding increased blood supply in the RF muscle of adults and people with CKD.

**2. Materials and methods**

Following approval from the local ethics committee (2019/343), this cross-sectional study was conducted between March and December 2021. The study population

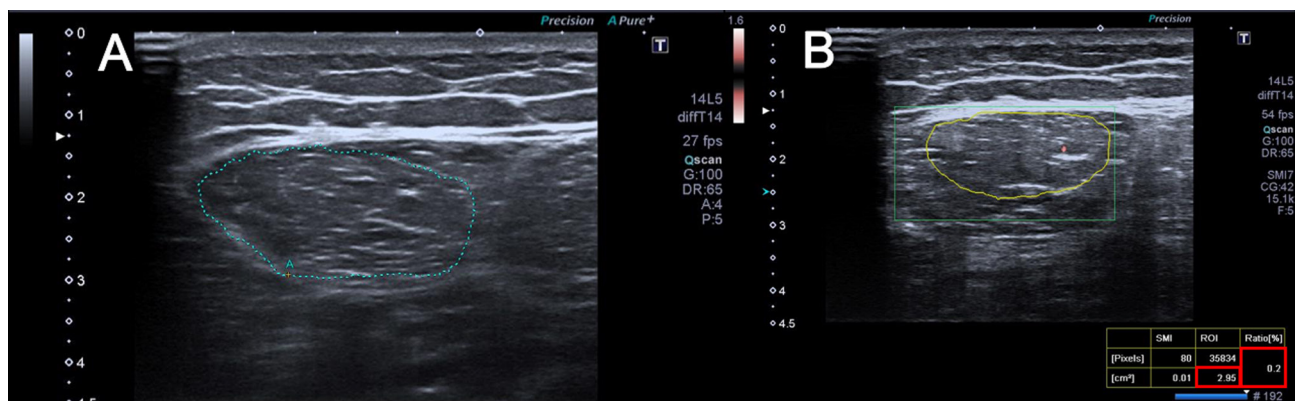
was selected from patients who presented to internal medicine and ultrasound outpatient clinics. The US examinations were performed after all patients had been informed about the examinations and the procedure and their written consent had been obtained. The patients were categorized into three groups for evaluation. The first group included patients with CKD on hemodialysis, the second group included adult patients without CKD, and the third group comprised young healthy volunteers.

All evaluations were performed by a single radiologist (N.S.) who had 6 years of SMI experience using a DUS device (Canon Medical Systems, Tokyo, Japan) with a high-frequency (14 MHz) linear array transducer. The transducer was positioned three-fifths of the distance between the anterior superior iliac spine and the superior patellar border, perpendicular to the thigh's long axis in its upper part [18]. This was the highest location of the thigh in all subjects at which the whole rectus femoris CSA (RF-CSA) could be demonstrated in a single field. Supine imaging was performed, with the resting leg supported in passive extension. To minimize underlying soft tissue diversion, excess contact gel was used.

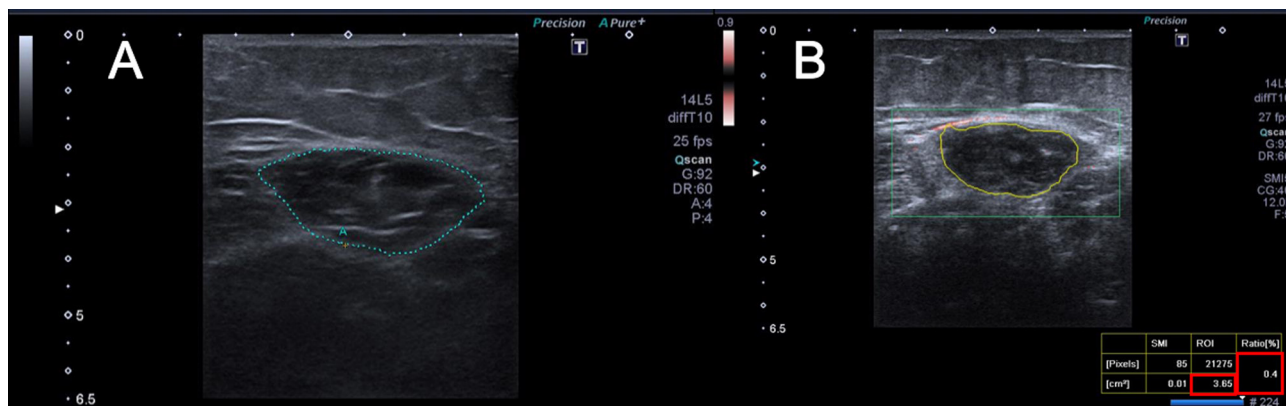
The internal echogenic line of the RF was manually outlined in a frozen image for RF-CSA calculation. The region of interest (ROI) was placed over the muscle to cover the entire muscle CSA, and quantitative data (VI values) were obtained through SMI examinations. Three measurements were retrieved and the average value was recorded (Figures 1A, 1B, 2A, 2B, 3A, and 3B). Images were obtained by selecting maximum Doppler gain and minimum pulse repetition frequency settings without allowing artifacts to occur because the vascular evaluation of the muscle is complex. All Doppler examinations in this study were performed using constant device parameters.

**2.1. Statistical analysis**

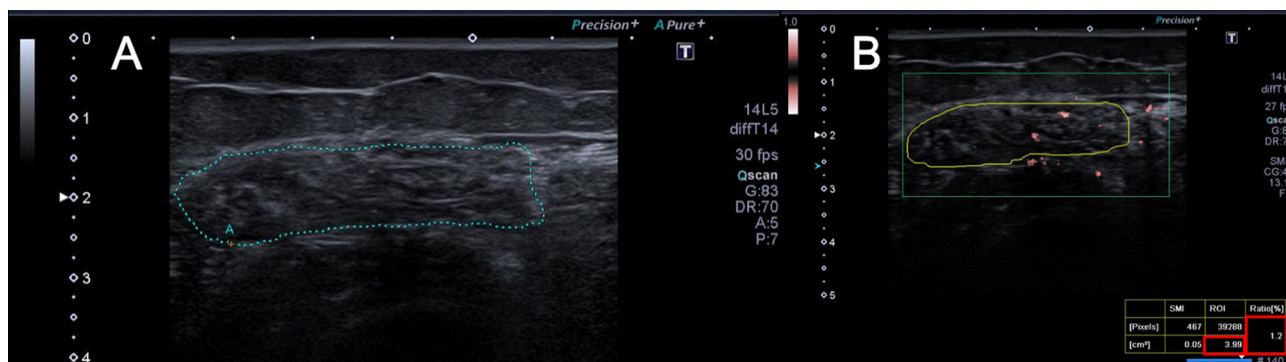
All procedures were conducted using the Statistical Package for the Social Sciences software (IBM SPSS Statistics



**Figure 1.** A 29-year-old healthy man. US (A) and SMI (B) images of the rectus femoris muscle are presented. The RF-CSA value is 2.95 cm<sup>2</sup>, and the VI value is 0.2.



**Figure 2.** A 62-year-old woman without CKD or any other chronic disease. US (A) and SMI (B) images show the rectus femoris muscle. The RF-CSA value is 3.65 cm<sup>2</sup>, and the VI value is 0.4.



**Figure 3.** A 58-year-old man with CKD is on hemodialysis. US (A) and SMI (B) images of the rectus femoris muscle are presented. The RF-CSA value is 3.99 cm<sup>2</sup>, and the VI value is 1.2.

21.0, IBM Corporation, Armonk, NY, USA). The Shapiro-Wilk test was used to determine whether the scale variable distributions were normal. Descriptive statistics are reported as the mean and standard deviation for continuous numerical variables. Categorical variables are represented by the number of patients and percentages. The Kruskal-Wallis test and one-way analysis of variance (ANOVA) were used to compare continuous numerical data, and chi-square tests were used to compare categorical variables. For pairwise comparison of data sets, Bonferroni and Mann-Whitney U test post-hoc tests were performed. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance. The optimal cut-off point was derived using the Youden index-if the area under the curve (AUC) was significant. DeLong's test was used to compare the differences in AUC values. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of diagnostic performance indicators were calculated. Differences were judged to be statistically significant at  $p < 0.05$ .

### 3. Results

In total, 92 patients (aged 17–93 years; 43 males, 49 females) were enrolled in this study, 30 of whom had CKD, 30 were adults without CKD or another chronic disease, and 32 were young healthy volunteers. There was no difference between the groups in terms of sex, body mass index, and RF-CSA ( $p > 0.05$ ). The demographic features of the study population are presented in Table 1.

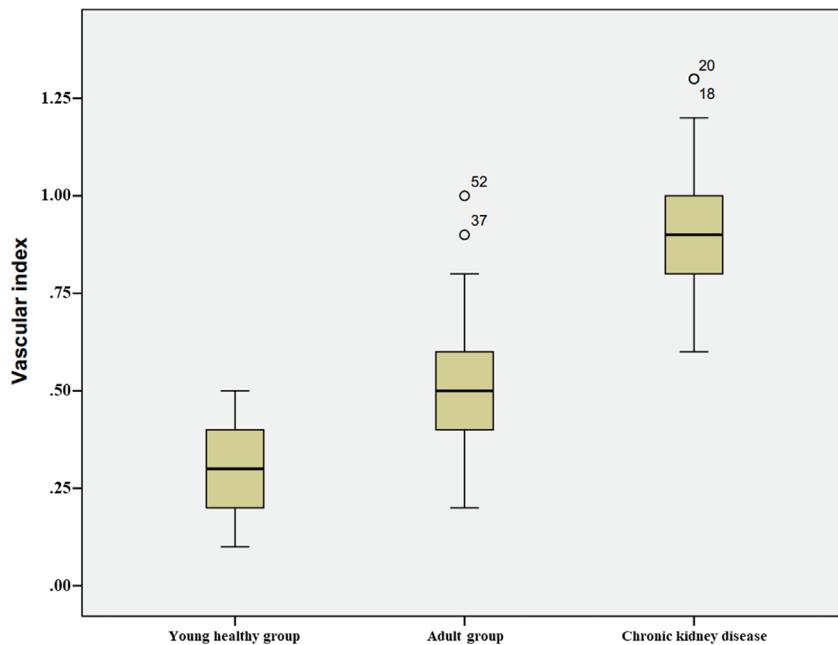
The median (min-max) VI values were 0.90 (0.60–1.30), 0.50 (0.20–1.0), and 0.30 (0.10–0.50) for the CKD, adult control, and young healthy groups, respectively. The patients with CKD had the highest VI, and there was a statistically significant difference between the groups ( $p < 0.001$ ) (Figure 4). When patients with CKD were evaluated in subgroups according to the presence or absence of additional disease, no significant difference was found between the groups in VI ( $p > 0.05$ ).

ROC analysis revealed that RF muscle VI  $\geq 6.5$  could distinguish CKD from all groups, the CKD from the adult group without CKD, and adult patients from young

**Table 1.** Clinical characteristics and ultrasound findings of patients and healthy volunteers.

	Chronic kidney disease (n = 30)	Adult control group (n = 30)	Young healthy group (n = 32)	p-value
<b>Gender *</b>				0.578
Male	15 (50)	14 (47)	15 (47)	
Female	15 (50)	16 (53)	17 (53)	
<b>Age (years) **</b>	60.17 ± 17.44 <sup>b</sup>	54.73 ± 9.09 <sup>c</sup>	30.22 ± 5.31 <sup>b,c</sup>	<b>&lt;0.001</b>
<b>Duration of the disease (years)</b>	4.3 ± 2.97	-		-
<b>Additional disease</b>				
with	8 (26.7)	-		-
without	22 (73.3)	-		-
<b>BMI (kg/m<sup>2</sup>) **</b>	26.33 ± 5.58	26.32 ± 3.32	24.87 ± 2.99	0.273
<b>Muscle area (cm<sup>2</sup>) **</b>	4.45 ± 1.67	4.76 ± 1.18	4.99 ± 1.37	0.331
<b>VI ***</b>	0.90 (0.60–1.30) <sup>a,b</sup>	0.50 (0.20–0.10) <sup>a,c</sup>	0.30 (0.10–0.50) <sup>b,c</sup>	<b>&lt;0.001</b>

\* Chi-square tests, data are presented as counts, with percentages in brackets; \*\* One-Way ANOVA test, data are presented as mean ± standard deviation; \*\*\* Kruskal-Wallis test, data are presented as median (min-max); bold values indicated that statistically significant (p < 0.05); a: Chronic kidney disease vs. adult control group (p < 0.001), b: Chronic kidney disease vs. young healthy group (p < 0.001), c: Adult control group vs. young healthy group (p < 0.001). BMI: Body mass index; VI: Vascular index.



**Figure 4.** VI values of young, healthy volunteers, adult patients without CKD or another chronic disease, and CKD patients on hemodialysis. The values of all three groups are significantly different from each other.

healthy individuals with 93.5%, 90.0%, and 74.2% accuracy, respectively (Table 2) (Figures 5A, 5B, and 5C). Moreover, VI demonstrated excellent diagnostic performance in detecting increased blood supply in RF muscle in patients with CKD.

**4. Discussion**

This study has four major findings. First, we found a significant increase in VI values without a decrease in RF-CSA values in patients with CKD. Second, we demonstrated increased vascularity for the adult patient group and patients with CKD by quantifying VI using SMI with objective numerical data. Third, the increase in VI values for patients with CKD was markedly higher than for the adult group. Fourth, we found cut-off values that could be used to detect low-grade inflammation in the RF muscle among patients with CKD and adults using SMI.

When weak muscular strength is detected, MWDs (such as sarcopenia) are likely. A reduced amount or quality of muscle confirms a sarcopenia diagnosis. Sarcopenia is considered severe when there is a combination of reduced muscular strength, low muscle quantity or quality, and poor physical performance. With an increasing need to analyze muscles and diagnose sarcopenia in its early phases, high-resolution imaging is anticipated to be used more frequently in the future, first in research investigations, then in clinical practice [6].

In a recent study to evaluate the anatomic architectural features of the RF muscle in healthy older adults, the mean value of RF-CSA was determined as 4.6 cm<sup>2</sup> [19]. In another study comparing healthy and older patients affected by chronic obstructive pulmonary disease, RF-CSA was measured as 4.63 cm<sup>2</sup> and 3.48 cm<sup>2</sup>, respectively [20]. In studies conducted with patients with chronic

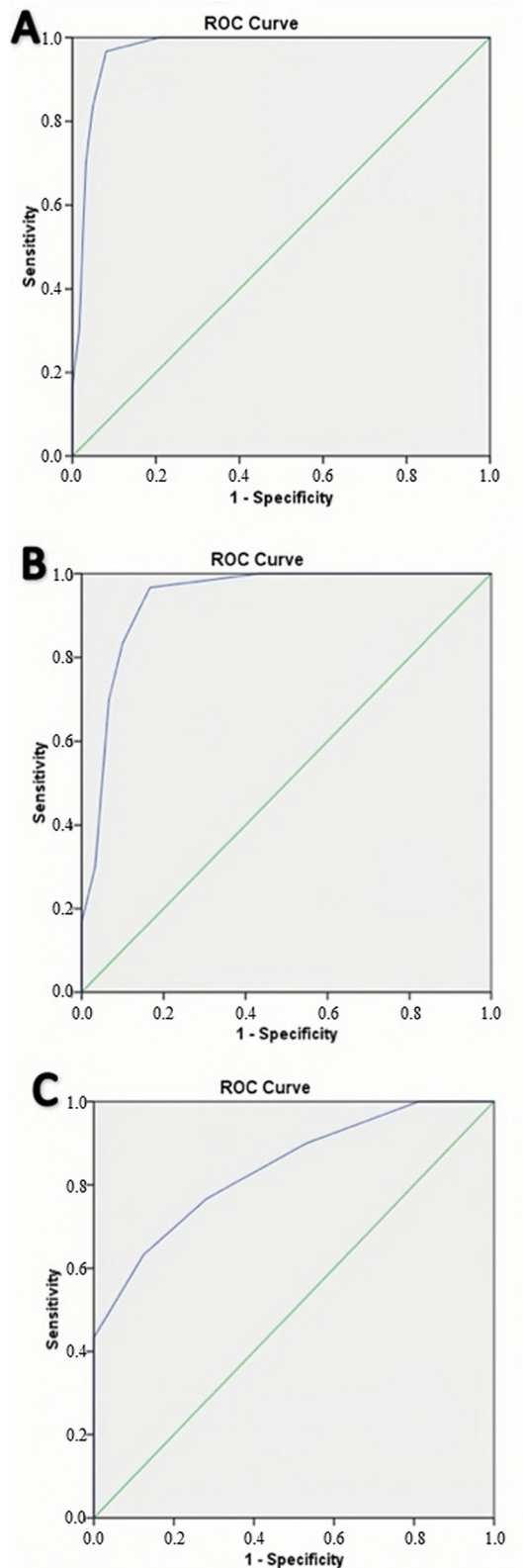
diseases or hospitalized patients, bioelectrical impedance analysis (BIA) was also evaluated and patients with low BIA values were compared with those with normal values. It has been reported that patients with low BIA values have significantly lower RF-CSA values than other groups [21–23]. Although not statistically significant, RF-CSA values were highest in the healthy young group and lowest in the CKD group in this study, consistent with the literature. We did not use BIA in our study; however, the difference between healthy young people and the other groups was not statistically significant, and all RF-CSA values were similar to healthy groups in the literature. These findings show there is an increase in blood supply in the RF muscle during the period before significant muscle mass loss occurs. We believe this is critical in terms of the effort to obtain quantitative data and cut-off values for the period preceding muscle mass loss, which is also highlighted in the literature [1,3].

Inflammation is the body’s natural defense reaction to foreign pathogens or damage, and it functions to heal tissue and preserve homeostasis. Age-related inflammation is low-grade and ongoing, with increasing proinflammatory cytokines and C-reactive protein levels and a decrease in antiinflammatory cytokines. However, it is asymptomatic with different degrees of pathophysiologic alterations. With age, this alteration in the immune system is known as inflamm-aging or chronic inflammation. It has also been defined as a feature of “immunosenescence” [7]. Chronic inflammation impairs the aging body in various ways (for example, insulin irregularity, hormonal and epigenetic changes, endothelial malfunction, and microvascular alterations). These problems may cause sarcopenia by rendering muscles weaker, speeding up cellular metabolism, and making it harder to keep track of energy. Furthermore,

**Table 2.** Diagnostic performance of vascular index (VI) values to distinguish chronic kidney disease (CKD) patients from adult patients and healthy volunteers.

	<b>CKD vs. all control group</b>	<b>CKD vs. adult patients group</b>	<b>Adult patients vs. young healthy group</b>
<b>AUC (95% CI)</b>	0.970 (0.938–1.000)	0.939 (0.875–1.000)	0.839 (0.742–0.936)
<b>p-value</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
<b>Cut-off</b>	>0.65	>0.65	>0.35
<b>Sensitivity</b>	96.7 (82.2–99.9)	96.7 (82.8–99.9)	76.7 (57.7–90.1)
<b>Specificity</b>	91.9 (82.2–97.3)	83.3 (65.3–94.4)	71.9 (53.3–86.3)
<b>PPV</b>	85.3 (71.4–93.1)	85.3 (72.2–92.8)	71.9 (58.7–82.2)
<b>NPV</b>	98.3 (89.2–99.8)	96.2 (78.3–99.4)	76.7 (62.4–86.7)
<b>Accuracy</b>	93.5 (86.3–97.6)	90.0 (79.5–96.2)	74.2 (61.5–84.5)

AUC: Area under the curve; 95% CI: 95% confidence interval; bold values indicated that statistically significant (p < .05); PPV: Positive predictive value; NPV: Negative predictive value.



**Figure 5.** ROC curves with AUC for differentiating CKD patients from adult patients and healthy volunteers. CKD vs. all control group B (A), CKD vs. adult patients group C (B), adult patients group vs. young, healthy group (C).

the association between chronic inflammation and muscle wasting has been defined as the influence of the homeostatic equilibrium between protein synthesis and catabolism at the muscular level. Besides, impaired immune homeostasis can contribute to the sarcopenia cascade during the chronic inflammatory state by directly causing the loss of regeneration potential of muscle stem cells [7,24].

Microcirculation is highly sensitive to inflammatory processes and plays an essential role in the inflammatory response. Throughout inflammation, all segments of the microvasculature, such as arterioles, capillaries, and venules, exhibit distinct physiologic alterations that aim to increase the transport of inflammatory cells. One of the most well-known effects of inflammation on microcirculation is an increase in the rate of blood vessel proliferation [10]. Although color DUS and power DUS are commonly used diagnostic tools for evaluating blood flow, they are insufficient for determining microcirculation [17,25]. Therefore, we used SMI, a unique Doppler examination, to assess microcirculation with the adults and patients with CKD in this study, which enabled us to analyze the microcirculatory blood flow in the RF muscles of patients in the study groups together with the differences between the groups.

According to the European Working Group on Sarcopenia in Elderly People, sarcopenia can be primary or secondary. The former is associated with aging, whereas the latter, which occurs in early adulthood, is related to other conditions, and may or may not be related to aging [4,26]. Secondary sarcopenia can occur as a result of nutritional causes such as malnourishment, malabsorption disorders, and anorexic drugs; reduced activity settings such as rest cure, zero-gravity environments, and sedentary lifestyle; and diseases, for example, severe organ failure, inflammatory conditions, and endocrine or malignant diseases. The main distinction between primary and secondary sarcopenia is that muscle loss in the secondary form is age-related. In addition, muscle mass loss also occurs consistently after the fourth decade of life. It also depends on conditions that accelerate protein breakdown and, as a result, is more severe and occurs more often than as a result of the natural aging process [4,26]. When comparing age-related and CKD-related sarcopenia, the most notable distinction is that protein breakdown is evident in CKD-related sarcopenia but may not be the case in age-related sarcopenia. It has also been reported that inflammation is more prominent in CKD-related than in age-related sarcopenia.

We recorded higher VI values in patients with CKD than in both adult and young individuals in our study, supporting the more inflammatory condition revealed by all of these mechanisms. By comparing the groups, we found data demonstrating that inflammation increased with age, and, as stated, increased considerably more among patients with CKD. Even though we came to this conclusion

without observing a decrease in muscle area in the adults and patients with CKD, we think that either treatment or physical activities that do not lead to muscle atrophy in patients with an increased blood supply in SMI will be important for preventing morbidity and death from sarcopenia in the future.

It seems sensible to investigate the possibility of regenerative therapeutic approaches for regulating the chronic inflammatory response to treat sarcopenia. Modulation of inflammatory signaling pathways is recognized as the primary therapeutic target, especially with some positive results in animal models, and is attractive for application in human trials [7]. The prominence of modulation of inflammation in treatment strategies also reveals the importance of early recognition of the inflammatory process. This study can also measure how well therapy works, and we hope it will be used as a model for future studies in this area.

As the world's population over 60 years is predicted to double in the next 30 years, the clinical and economic implications of sarcopenia are becoming a public health issue. The global frequency of sarcopenia is anticipated to increase from 50 million in 2010 to over 200 million by 2050 [1,26]. As a result, detecting sarcopenia early and implementing preventative interventions will save money in the long run by reducing treatment costs and labor losses. SMI, an imaging modality that does not require contrast material, does not include radiation and is easily accessible, will be able to predict sarcopenia among older patients and people with CKD. Therefore, SMI has recently been a popular way to evaluate MSK disorders, particularly inflammatory diseases. Even though US has been used to measure muscle mass in patients with sarcopenia and to assess the structure and elasticity of the muscle sonographically, there have been no studies with SMI evaluating the microvascular system and inflammation during the period before muscle mass loss begins.

There are several limitations to this study. The number of patients in this study was limited, and a larger sample size is needed to validate our results. We did not test for inflammatory indicators in the patients' serum. However, this may provide an important direction for future studies. We could not assess interobserver variability because a radiologist with SMI experience performed all the examinations. Although monochrome SMI can display more details about vascular architecture [25], we were unable to employ monochrome SMI because VI cannot be quantified using monochrome SMI in current US devices. The patients' muscular functioning, nutrition, and exercise status were not evaluated because this was a preliminary study, and they did not have a confirmed diagnosis of sarcopenia. The planned next steps for the investigation include involving people who have a clear diagnosis.

In conclusion, SMI can contribute to the detection of low-grade inflammation with quantitative data among adult patients, particularly those with CKD. Due to the constraints of current imaging methods in detecting sarcopenia and the efforts to obtain quantitative data and determine cut-offs, which are the most significant limitations in recent studies, we hope that our research will signifi-

cantly contribute to mitigating these limitations and lead to further studies in this area.

### Conflict of interest

The authors declare that there are no financial or other relations that could lead to a conflict of interest.

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