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A RAZÃO NEUTRÓFILOS-LINFÓCITOS E AS CONCENTRAÇÕES DA PROTEÍNA C-REATIVA NÃO SÃO ASSOCIADAS COM A FORÇA, MASSA MUSCULAR E CAPACIDADE FUNCIONAL DE PACIENTES TRANSPLANTADOS RENAIS

NEUTROPHIL-LYMPHOCYTE RATIO AND C-REACTIVE PROTEIN LEVELS ARE NOT ASSOCIATED WITH STRENGTH, MUSCLE MASS, AND FUNCTIONAL CAPACITY IN KIDNEY TRANSPLANT PATIENTS

HEITOR OLIVEIRA SANTOS

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Dissertação apresentada ao Programa de Pós-Graduação em Ciências da Saúde da Faculdade de Medicina da Universidade Federal de Uberlândia, como requisito parcial para a obtenção do título de Mestre em Ciências da Saúde.

Área de concentração: Ciências da Saúde.

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Reuniu-se em web conferência pela plataforma Mconf-RNP, em conformidade com a PORTARIA Nº 36, DE 19 DE MARÇO DE 2020 da COORDENAÇÃO DE APERFEIÇOAMENTO DE PESSOAL DE NÍVEL SUPERIOR - CAPES, pela Universidade Federal de Uberlândia, a Banca Examinadora, designada pelo Colegiado do Programa de Pós-graduação em Ciências da Saúde, assim composta: Professores Doutores: João Felipe Mota (UFG), Geórgia das Graças Pena (UFU) e Erick Prado de Oliveira (UFU) orientador do candidato.

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“Uma pessoa inteligente aprende com os seus erros, uma pessoa sábia aprende com os erros dos outros”.

Augusto Cury

RESUMO

Introdução: Pouco se sabe sobre a associação da razão neutrófilos-linfócitos (RNL) e a proteína C-reativa (PCR) com os componentes da sarcopenia em pacientes transplantados renais (PTRs).

Objetivo: O objetivo deste estudo foi associar a RNL e a PCR com a força, massa muscular e capacidade funcional em PTRs.

Material e métodos: Foi realizado um estudo transversal (n = 108). A capacidade funcional foi avaliada pelo teste de velocidade de marcha de 4 metros e bateria de desempenho físico curto (SPPB), a força foi avaliada pela força de preensão manual e teste de sentar para levantar cinco vezes (5STS), a massa muscular esquelética apendicular (ASM) foi estimada por bioimpedância elétrica, e o índice da ASM (ASMI) foi calculado por ASM (kg)/altura (m^2). Foi utilizado o método de eletroquimioluminescência para analisar os níveis da PCR e o método citométrico XN-3000 Sysmex para obtenção dos valores do leucograma para cálculo da RNL.

Resultados: Não foram observadas associações significativas, tanto para as classificações RNL quanto para PCR na regressão linear simples e multivariada para os componentes da sarcopenia. Da mesma forma, no modelo de regressão linear multivariado ajustado para idade, sexo, circunferência da cintura, ingestão de proteína total, taxa de filtração glomerular, uso de calcineurina e inibidores de mTOR, tempo de transplante e ingestão de energia, os valores da NLR e CRP não foram associados com a força de preensão manual (β = 0,231 e 0,291, p = 0,389 e 0,577 para as classificações por NLR e CRP, respectivamente), 5STS (β = -0,114 e -0,202, p = 0,288 e 0,334 para as classificações por NLR e CRP, respectivamente), e ASM (β = -0,027 e 0,062, p = 0,813 e 0,788 para as classificações por NLR e CRP, respectivamente).

Conclusão: Os níveis da NLR e PCR não foram associados com os componentes da sarcopenia em PTRs.

Palavras-chave: Proteína C-reativa; sarcopenia; razão neutrófilos-linfócitos; inflamação; pacientes transplantados renais.

ABSTRACT

Introduction: Little is known about the association of neutrophil-lymphocyte ratio (NLR) and C-reactive protein (CRP) with the components of sarcopenia in kidney transplant patients (KTPs).

Objective: This study aimed to associate NLR and CRP with strength, muscle mass, and functional capacity in KTPs.

Material and methods: A cross-sectional study (n = 108) was performed. Functional capacity was assessed by the 4-meter gait speed test and short physical performance battery (SPPB), strength was evaluated by handgrip strength and five-times-sit-to-stand test (5STS), appendicular skeletal muscle mass (ASM) was estimated by bioelectrical impedance, and ASM index (ASMI) was calculated using the ASM (kg)/height (m^2). Electrochemiluminescence method was used for analyzing CRP levels and cytometric method XN-3000 Sysmex for obtaining leukogram values to calculate the NLR.

Results: No significant associations, both for the NLR and CRP classifications, were noted in the simple and multivariate linear regression for the sarcopenia components. Likewise, in the multivariate linear regression model adjusted for age, sex, waist circumference, total protein intake, glomerular filtration rate, use of calcineurin and mTOR inhibitors, transplant time, and energy intake, NLR and CRP levels were not associated with handgrip strength (β-values = 0.231 and 0.291, *p*-values = 0.389 and 0.577 for NLR and CRP classifications, respectively), 5STS (β-values = -0.114 and -0.202, *p*-values = 0.288 and 0.334 for NLR and CRP classifications, respectively), and ASM (β-values = -0.027 and 0.062, *p*-values = 0.813 and 0.788 for NLR and CRP classifications, respectively).

Conclusion: NLR and CRP levels were not associated with the components of sarcopenia in KTPs.

Keywords: C-reactive protein; sarcopenia; neutrophil-lymphocyte ratio; inflammation; kidney transplant patients.

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PCR	Proteína C-reativa
PTRs	Pacientes transplantados renais
RNL	Razão neutrófilos-linfócitos

Sumário

1. INTRODUÇÃO

A sarcopenia é uma condição clínica que permanece um desafio global (ABELLAN VAN KAN, 2009; SHAFIEE; KESHTKAR; SOLTANI; AHADI *et al.*, 2017), afetando a qualidade de vida de inúmeros pacientes e resultando em um mau prognóstico principalmente de pacientes que necessitam de acompanhamento médico frequente (CRUZ-JENTOFT, A. J.; BAHAT, G.; BAUER, J.; BOIRIE, Y. *et al.*, 2019; PAPADOPOULOU; TSINTAVIS; POTSAKI; PAPANDREOU, 2020). Os componentes da sarcopenia estão associados a níveis mais elevados de parâmetros inflamatórios séricos (BANO; TREVISAN; CARRARO; SOLMI *et al.*, 2017). Estes componentes são a força e a massa muscular, assim como a capacidade funcional, os quais são preditores de mortalidade e estão associados com a destruição (GARCIA-HERMOSO; CAVERO-REDONDO; RAMIREZ-VELEZ; RUIZ *et al.*, 2018; LI; XIA; ZHANG; GATHIRUA-MWANGI *et al.*, 2018). Concernente à inflamação, além de pior prognóstico de inúmeras doenças, a proteína C-reativa (PCR) e a relação neutrófilo-linfócito (NLR) são marcadores acessíveis e promissores na saúde muscular e, portanto, quando alterados, poderiam ser um dos desencadeadores da piora da força e a massa muscular, bem como baixa capacidade funcional, dada toda relação entre o aumento do status inflamatório com complicações metabólicas dos miócitos (COSTAMAGNA; COSTELLI; SAMPAOLESI; PENNA, 2015; DALLE; ROSSMEISLOVA; KOPPO, 2017).

A fisiopatologia de doenças renais é fortemente relacionada com a degradação muscular (PRICE; GOOCH; DONALDSON; ROBERTS-WILSON, 2010). Os pacientes transplantados renais (PTRs) são uma população que, infelizmente, não é tão estudada, enquanto existe constante demanda de atendimento ambulatorial em prol do manejo deles. Dada a relevância clínica do uso dos componentes da sarcopenia, a proposta da PCR e RNL como marcadores da saúde muscular, a relação entre a injúria renal e o catabolismo muscular, bem como a importância de buscar mais suportes para monitorar os PTRs, através de um estudo transversal objetivou-se verificar se os níveis de RNL e PCR estão ou não associados com os componentes da sarcopenia em PTRs. A fundamentação teórica a seguir fornece perspectivas que levaram a realização desta pesquisa.

2. FUNDAMENTAÇÃO TEÓRICA

2.1. O uso da força, massa muscular e capacidade funcional no diagnóstico da sarcopenia

A força, massa muscular e capacidade funcional são os componentes da sarcopenia, a qual é uma condição clínica que permanece um desafio global (ABELLAN VAN KAN, 2009; SHAFIEE; KESHTKAR; SOLTANI; AHADI *et al.*, 2017), afetando a qualidade de vida de inúmeros pacientes e resultando em um mau prognóstico dos pacientes hospitalizados (CRUZ-JENTOFT, A. J.; BAHAT, G.; BAUER, J.; BOIRIE, Y. *et al.*, 2019; PAPADOPOULOU; TSINTAVIS; POTSAKI; PAPANDREOU, 2020).

Primeiramente, Cruz-Jentoft et al. determinaram a sarcopenia como uma situação médica adversa provinda da baixa quantidade de massa muscular junto com baixa força muscular e/ou baixo desempenho físico (CRUZ-JENTOFT; BAEYENS; BAUER; BOIRIE *et al.*, 2010). Nessa definição, a quantidade muscular foi considerada o principal preditor de sarcopenia (CRUZ-JENTOFT; BAEYENS; BAUER; BOIRIE *et al.*, 2010). Recentemente, no entanto, estes autores determinaram a força muscular como o principal preditor de sarcopenia em idosos (CRUZ-JENTOFT, ALFONSO J; BAHAT, GÜLISTAN; BAUER, JÜRGEN; BOIRIE, YVES *et al.*, 2019).

2.2. O manejo dos PTRs no Brasil

Apesar da ciência ser universal, é crucial destacar pontos específicos de cada país em prol de avaliar a validade interna, uma vez que existem grandes diferenças entre países desenvolvidos, em desenvolvimento e subdesenvolvidos na área da saúde (CAMERON; EWEN; ROSS-DEGNAN; BALL *et al.*, 2009). Os PTRs precisam de acompanhamento ambulatorial ao longo de suas vidas e, portanto, recursos e demandas diferem em todo o mundo (GLUSKIN; TZUKERT; MOR-YOSEF LEVI; GOTSMAN *et al.*, 2019; JOSEPHSON, 2011).

Ao avaliaram 69 países, Horvat et al. classificaram o Brasil como o país com o segundo maior número de doadores vivos de rim, atrás apenas dos Estados Unidos da América (HORVAT; SHARIFF; GARG; NETWORK, 2009). Tendo em mente este dado epidemiológico, algumas considerações internas e externas devem ser enfatizadas. Por exemplo, enquanto os transplantes no Brasil são realizados por um sistema único de saúde, oferecendo reembolso aos centros de transplante e favorecendo o acesso da população em geral, a necessidade constante de aumentar o número de doadores, o tempo

de isquemia fria dos rins causado por longas distâncias dos centros de transplante e outras divergências econômicas entre os estados e regiões brasileiras permanecem um desafio (DOS SANTOS; DA SILVA CARVALHO; PERES, 2019; MARTINS; FERREIRA; GONÇALVES; DE MARCO *et al.*, 2019).

Portanto, dado as limitações financeiras do Brasil voltadas ao tratamento do paciente que necessida do transplante renal, ou daqueles que já passaram pelo procedimento e estão sob acompanhamento médico, são de suma importância pesquisas que consideram custo-benefício e a aplicabilidade dos dados na prática clínica, fato que, a posteriori, pode até melhorar a gestão hospitalar. Além disso, indubitavelmente, novos conhecimentos científicos ainda são fundamentais no esforço de ampliar o arsenal clínico no manejo dos PTRs.

2.3. Vias fisiopatológicas da degradação muscular esquelética nos PTRs

A nível molecular, em pacientes com doença renal, várias vias metabólicas suportam uma interação entre as células musculares esqueléticas (isto é, os miócitos) com as células imunológicas, tais como os neutrófilos e linfócitos (GURAGAC; DEMIRER, 2016; TIDBALL, 2002). Em conjunto, este desequilíbrio entre as células musculares esqueléticas com as células imunológicas está associado com um aumento do estresse oxidativo, podendo clinicamente resultar na piora dos componentes da sarcopenia (GOMES; MARTINEZ; PAGAN; DAMATTO *et al.*, 2017). De maneira mais detalhada, a desregulação crônica na homeostase renal está ligada a um estado catabólico causado pela ativação da caspase-3, miostatina, sistema ubiquitina-proteassoma e lisossomos, cujo processo pode ser resultado da sinalização prejudicada da insulina, acidose metabólica, níveis elevados de angiotensina II, e processos outros inflamatórios relacionados (WANG; MITCH, 2014).

Além disso, o status persistentemente alto do estresse oxidativo é prejudicial à massa muscular, de modo que a taxa de filtração glomerular diminuída resulta no acúmulo de compostos urêmicos, por exemplo, indoxil sulfato, um metabólito oriundo da quebra de L-triptofano pela microbiota do cólon relacionado com o estresse oxidativo por meio do aumento da produção das espécies reativas de oxigênio (FUJII; NAKAI; FUKAGAWA, 2011; LEONG; SIRICH, 2016; SHIMIZU; BOLATI; ADIJIANG; ADELIBIEKE *et al.*, 2011; SHIMIZU; BOLATI; ADIJIANG; ENOMOTO *et al.*, 2010), as quais conhecidamente desencadeiam respostas inflamatórias (AOKI; TESHIMA;

KONDO; SAITO *et al.*, 2015; SUN; HSU; WU, 2013; WU; MEI; VLASSARA; STRIKER *et al.*, 2009).

Estas alterações afetam a via de sinalização da hematopoiese leucocitária na medula óssea, culminando em aumento da geração de granulócitos e baixa produção de linfócitos, assim, clinicamente repercutindo maiores valores de RNL (KING; GOODELL, 2011; PIETRAS, 2017). Em relação aos neutrófilos, a liberação das armadilhas extracelulares de neutrófilos produz espécies reativas de oxigênio, levando a um maior estado inflamatório e contribuindo para a desregulação metabólica renal e musculoesquelética (BRINKMANN; REICHARD; GOOSMANN; FAULER *et al.*, 2004; REMIJSEN; VANDEN BERGHE; WIRAWAN; ASSELBERGH *et al.*, 2011; ZAWROTNIAK; RAPALA-KOZIK, 2013).

2.4. PTRs e relação com componentes da sarcopenia

Recentemente, nosso grupo observou que cerca de 19% dos PTRs sob acompanhamento em um ambulatório específico de tratamento renal tinham sarcopenia (LIMIRIO; SANTOS; DOS REIS; DE OLIVEIRA, 2020). Além disso, alguns estudos transversais recentes demonstraram achados importantes quanto à prevalência de sarcopenia e mau prognóstico com base em seus componentes em PTRs (KOSOKU; UCHIDA; NISHIDE; KABEI *et al.*, 2020; MARTINS; FRANÇA; DIAS; RAYANNA DE OLIVEIRA *et al.*, 2020). Em um estudo, 11% de uma amostra composta por 210 PTRs tinha sarcopenia (KOSOKU; UCHIDA; NISHIDE; KABEI *et al.*, 2020), e 19% de 83 PTRs no outro estudo (MARTINS; FRANÇA; DIAS; RAYANNA DE OLIVEIRA *et al.*, 2020). Em relação à esta última investigação, entre os indivíduos sem sarcopenia, 18% tiveram diminuição da força de preensão manual e 40% da velocidade da marcha alterada, indicando que a avaliação individual dos componentes da sarcopenia tem sua importância (MARTINS; FRANÇA; DIAS; RAYANNA DE OLIVEIRA *et al.*, 2020).

Portanto, não apenas mudanças desfavoráveis na composição corporal pela diminuição da massa muscular, mas também, os profissionais da área da saúde que lidam com PTRs devem ter maior atenção com o comprometimento da capacidade funcional e a força desta população (GURALNIK; FERRUCCI; SIMONSICK; SALIVE *et al.*, 1995), que engloba desde o cuidado dietético e exercício físico à solicitação de marcadores bioquímicos complementares, como visto a seguir.

2.5. Uso da RNL como um possível marcador associado com os componentes da sarcopenia

As células do sistema imunológico, tais como neutrófilos e linfócitos, têm um papel bem conhecido em diversas estruturas e processos biológicos e, felizmente, são frequentemente analisadas na rotina clínica independentemente da renda do país (CHITTAWAR; DUTTA; QURESHI; SURANA *et al.*, 2017; GOMES; MORATO-CONCEICAO; GAMBATI; MACIEL-PEREIRA *et al.*, 2020; MARTINS; SILVEIRA; VIEGAS; BECK *et al.*, 2019; WU; ZOU; WANG; TAN *et al.*, 2019). Como mencionado no tópico 2.3, um aumento da contagem de neutrólfilos é nocivo à saúde muscular esquelética; concomitantemente, certa redução da contagem de linfócitos também pode afetar as fibras musculares, já que são células que produzem mediadores anti-inflamatórios. À vista disso, a RNL vem emergindo como um marcador clínico complementar de várias enfermidades, sendo-a também promissora na sarcopenia e, portanto, podendo ser associada com pior resultado dos componentes da sarcopenia (BORGES, T. C.; GOMES, T. L.; PICHARD, C.; LAVIANO, A. *et al.*, 2020).

Mais especificamente, além de ser um marcador prognóstico de sarcopenia, a RNL surgiu como um marcador complementar de câncer, bem como doenças cardiovasculares e renais (BORGES, T. C.; GOMES, T. L.; PICHARD, C.; LAVIANO, A. *et al.*, 2020; LIN; ZHANG; HUANG; CHEN *et al.*, 2018; MAINARDI; FERNANDES; PIMENTEL, 2020; SANTOS; IZIDORO, 2018; ZHAO; TAO; LIU, 2020). Em relação à esta última doença, maior atenção é imprescindível em prol de melhorar o manejo dos pacientes que sofrem dos distúrbios do rim, uma vez que existem diversos aspectos fisiopatológicos e desafios clínicos. Por exemplo, a doença renal crônica está ligada à inflamação de longo prazo, a qual afeta sistemicamente o corpo e, portanto, pode levar ao transplante renal (MIHAI; CODRICI; POPESCU; ENCIU *et al.*, 2018; TABRIZIANI; LIPKOWITZ; VUONG, 2018).

É fundamental enfatizar que a base de evidências ainda carece de uniformidade tanto para o diagnóstico de sarcopenia quanto para seus componentes. Tang et al. mostraram que a RNL foi levemente associada com a massa muscular apendicular e a força de preensão manual, mas não com sarcopenia, em idosos chineses (TANG; XIE; TAN; HU *et al.*, 2020). Por outro lado, valores mais elevados de RNL foram positivamente associados a um risco aumentado de sarcopenia em indivíduos mais velhos, conforme observado por Öztürk et al. (ÖZTÜRK; KUL; TÜRKBEYLER; SAYıNER *et*

al., 2018); também, valores mais elevados de RNL foram associados com maior risco de sarcopenia em pacientes com câncer na pesquisa de Borges et al. (BORGES, THAÍS C; GOMES, TATYANNE LN; PICHARD, CLAUDE; LAVIANO, ALESSANDRO *et al.*, 2020). Com relação aos componentes da sarcopenia, Borges et al. encontraram correlação negativa entre RNL e velocidade de marcha ($r = -0,48$, $p = 0,0001$), bem como entre RNL e força de preensão manual ($r = -0,29$, $p = 0,002$) através de um estudo transversal composto por 123 pacientes com câncer hospitalizados sob quimioterapia e/ou procedimento cirúrgico (BORGES, THAÍS C; GOMES, TATYANNE LN; PICHARD, CLAUDE; LAVIANO, ALESSANDRO *et al.*, 2020).

2.6. Uso da PCR como um possível marcador associado componentes da sarcopenia

Um status inflamatório elevado associado com altas concentrações do fator de necrose tumoral-alfa e da interleucina-6 desencadeia a produção da PCR, cuja proteína tem um impacto sistêmico através de danos nas estruturas vasculares, que por sua vez é uma matriz da gênese das complicações renais e cardiometabólicas (CESARI; PENNINX; NEWMAN; KRITCHEVSKY *et al.*, 2003; GIOVANNINI; ONDER; LIPEROTI; RUSSO *et al.*, 2011; LAINAMPETCH; PANPRATHIP; PHOSAT; CHUMPATHAT *et al.*, 2019). A inflamação sistêmica de baixo grau mediada pela PCR está associada ao aumento do estresse oxidativo in vivo, resultando em menor biodisponibilidade sistêmica do óxido nítrico, fato que pode contribuir para a sarcopenia em virtude de menor entrega de nutrientes e hormônios circulantes ao músculo esquelético (FICHTLSCHERER; BREUER; SCHACHINGER; DIMMELER *et al.*, 2004). Além disso, a senescência por si está relacionada com o aumento da cascata pró-inflamatória da PCR (TANG; FUNG; XU; LAN, 2017).

Em relação aos níveis circulantes da PCR, estudos longitudinais mostram associação de altas concentrações da PCR com baixa capacidade física em indivíduos mais velhos (PENNINX; KRITCHEVSKY; NEWMAN; NICKLAS *et al.*, 2004; SCHAAP; PLUIJM; DEEG; VISSER, 2006), enquanto uma meta-análise de estudos transversais demonstrou que pacientes com sarcopenia tinham níveis significativamente mais elevados da PCR quando comparados com aqueles sem sarcopenia, ou seja, grupos controle (BANO; TREVISAN; CARRARO; SOLMI *et al.*, 2017). Contudo, persiste o debate quanto à associação entre os níveis de PCR e idosos sem doenças ou distúrbios

renais. Em um estudo envolvendo 335 pacientes japoneses com idade média de 65 anos, o índice da musculatura esquelética apendicular e a força de preensão manual, mas não a velocidade de marcha, foram negativamente associados com os níveis de PCR (HIDA; IMAGAMA; ANDO; KOBAYASHI *et al.*, 2018). No *English Longitudinal Study of Aging*, um estudo de idosos residentes com idade média também de 65 anos, composto por 1.926 homens e 2.260 mulheres, após ajustes para idade, tabagismo, atividade física, educação, doenças inflamatórias e todas as outras doenças biológicas fatores, níveis elevados da CRP foram associados com menor força de preensão manual e pior desempenho do teste sentar e levantar em mulheres, cujo apenas este teste foi significativo para os homens (SOUSA; ZUNZUNEGUI; LI; PHILLIPS *et al.*, 2016).

2.7. Possível combinação do uso da PCR e RNL e relação com os componentes da sarcopenia em PTRs

Conforme referencial teórico posto, a RNL e a CRP como marcadores clínicos são frutíferos em prol de maior fornecimento para o manejo rotineiro de diversas doenças. Embora haja algumas disparidades à luz do estado inflamatório, tanto a PCR quanto a RNL podem ser considerados marcadores para indicar desfechos clínicos desfavoráveis (YANG; LIU; TAO; LI, 2020). Mais especificamente, a PCR é um marcador bem conhecido do processo inflamatório agudo causado por infecções agudas e inflamação crônica de baixo grau quando medida por meio do ensaio de alta sensibilidade (DINH; KASPERSEN; MIKKELSEN; PEDERSEN *et al.*, 2019; KUSHNER; SAMOLS; MAGREY, 2010; ROSVALL; ENGSTROM; JANZON; BERGLUND *et al.*, 2007), ao passo que a RNL é um marcador de baixo custo e eficaz que pode ser rotineiramente utilizado no monitoramento da inflamação sistêmica utilizando as contagens absolutas de neutrófilos e linfócitos de um hemograma completo (GUTHRIE; CHARLES; ROXBURGH; HORGAN *et al.*, 2013; IMTIAZ; SHAFIQUE; MIRZA; AYOOB *et al.*, 2012; USLU; KUCUK; SAHIN; UGAN *et al.*, 2015). Diante do uso destes marcadores em situações clínicas típicas, é fundamental maior compreensão diante à associação deles com os componentes da sarcopenia para elucidar os mecanismos relacionados à perda muscular em PTRs, uma vez que apenas algumas pesquisas exploraram esta temática (KOSOKU; UCHIDA; NISHIDE; KABEI *et al.*, 2020; MARTINS; FRANÇA; DIAS; RAYANNA DE OLIVEIRA *et al.*, 2020).

Existe uma considerável base mecanicista que respalda a importância deste cenário. À medida que maior contagem de neutrófilos em proporção aos linfócitos induz o aumento do estresse oxidativo e fatores inflamatórios associados, níveis mais elevados de citocinas pró-inflamatórias são frequentemente observados em pacientes com sarcopenia, tanto que as concentrações de interleucina-6 e fator de necrose tumoral-alfa estão fortemente associadas com pior resultado dos componentes da sarcopenia, particularmente, menor massa e força muscular (VISSER; PAHOR; TAAFFE; GOODPASTER *et al.*, 2002). Desencadeada pelo fator de necrose tumoral-alfa e a interleucina-6, a PCR é uma proteína produzida pelo fígado que combate a inflamação típica (SPROSTON; ASHWORTH, 2018) e, de fato, merece mais cogitação como um biomarcador tradicional com interações plausíveis entre o estado do músculo esquelético e a inflamação (PEPYS; HIRSCHFIELD, 2003; WAHLIN-LARSSON; WILKINSON; STRANDBERG; HOSFORD-DONOVAN *et al.*, 2017).

Por fim, vale a pena destacar que os PTRs estão mais propensos a indicadores desfavoráveis de estresse oxidativo e inflamação mesmo em condições pós-transplante (NAFAR; SAHRAEI; SALAMZADEH; SAMAVAT *et al.*, 2011). Em relação aos dados clínicos, as concentrações séricas de fator de necrose fator de necrose tumoral-alfa e interleucina-6 foram associadas com maior mortalidade em PTRs com enxerto funcionante (MOLNAR; NAGY; REMPORT; TAPOLYAI *et al.*, 2017), enquanto as concentrações de interleucina-6 e PCR também são associadas com eventos cardiovasculares primários e mortalidade por todas as causas nesta população (ABEDINI; HOLME; MARZ; WEIHRAUCH *et al.*, 2009).

3. OBJETIVOS

O objetivo da pesquisa foi verificar se os níveis de RNL e CRP estão associados com os componentes da sarcopenia (ou seja, força, massa muscular e capacidade funcional) em PRTs

4. ARTIGO

APRESENTAÇÃO:

Formato alternativo, adaptado conforme o estilo da revista *Clinical Nutrition*

TÍTULO:

NEUTROPHIL-LYMPHOCYTE RATIO AND C-REACTIVE PROTEIN LEVELS ARE NOT ASSOCIATED WITH STRENGTH, MUSCLE MASS, AND FUNCTIONAL CAPACITY IN KIDNEY TRANSPLANT PATIENTS

Neutrophil-lymphocyte ratio and C-reactive protein levels are not associated with strength, muscle mass, and functional capacity in kidney transplant patients

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Highlights

- NLR was not associated with the components of sarcopenia in KTPs.
- There was no association between CRP levels and the components of sarcopenia in KTPs.
- These parameters may be unnecessary as surrogate sarcopenia risk markers for KTPs.

Summary

Background & aims: Little is known about the association of neutrophil-lymphocyte ratio (NLR) and C-reactive protein (CRP) with the components of sarcopenia in kidney transplant patients (KTPs). This study aimed to associate these inflammatory markers with strength, muscle mass, and functional capacity.

Methods: A cross-sectional study (n = 108) was performed. Functional capacity was assessed by the 4-meter gait speed test and short physical performance battery (SPPB), strength was evaluated by handgrip strength and five-times-sit-to-stand test (5STS), appendicular skeletal muscle mass (ASM) was estimated by bioelectrical impedance, and ASM index (ASMI) was calculated using the ASM (kg)/height (m^2). Electrochemiluminescence method was used for analyzing CRP levels and cytometric method XN-3000 Sysmex for obtaining leukogram values to calculate the NLR.

Results: No significant associations, both for the NLR and CRP classifications, were noted in the simple and multivariate linear regression for the sarcopenia components. Likewise, in the multivariate linear regression model adjusted for age, sex, waist circumference, total protein intake, glomerular filtration rate, use of calcineurin and mTOR inhibitors, transplant time, and energy intake, NLR and CRP levels were not associated with handgrip strength (β-values = 0.231 and 0.291, *p*-values = 0.389 and 0.577 for NLR and CRP classifications, respectively), 5STS (β-values = -0.114 and -0.202, *p*-values = 0.288 and 0.334 for NLR and CRP classifications, respectively), and ASM (β-values = -0.027 and 0.062, *p*-values = 0.813 and 0.788 for NLR and CRP classifications, respectively).

Conclusion: NLR and CRP levels were not associated with the components of sarcopenia in KTPs.

Keywords: C-reactive protein; sarcopenia; neutrophil-lymphocyte ratio; inflammation; kidney transplant patients.

1. Introduction

The components of sarcopenia, i.e., low amount of muscle mass, low strength, and low physical performance are associated with higher levels of serum inflammatory parameters [1] in virtue of the crosstalk between the skeletal muscle and inflammatory cells [2]. While musculoskeletal is partially regenerated by inflammation, chronic inflammation or high generation of inflammatory mediators entails a dysfunction and loss of skeletal muscle [2, 3]. Among the cells of the immune system, neutrophils and lymphocytes have a well-known role in many biological structures and processes and, fortunately, are often analyzed in clinical routine regardless of the country's income [4-7]. Interestingly, the neutrophil-lymphocyte ratio (NLR) has emerged as a prognostic marker of sarcopenia and many ailments, e.g., cancers, cardiovascular and kidney diseases [8-12]. Regarding the latter, further attention is imperative insofar as there are different pathophysiological aspects. For instance, chronic kidney disease is linked to long-term inflammation that systemically affects the body and, thus, can lead to renal transplantation [13, 14].

It is worthwhile to note that KTPs are prone to unfavorable indicators of oxidative stress and inflammation even in post-transplant conditions [15]. Regarding clinical data, serum tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) concentrations were independently associated to death with a functioning graft in KTPs [16], with IL-6 and CRP concentrations being independently associated with major cardiovascular events and all-cause mortality in this population as well [17]. Accordingly, higher cytokine levels are often observed in both elderly and renal patients with sarcopenia, and IL-6 and TNF-α have sharply associated with the components of sarcopenia, particularly lower muscle mass

and lower muscle strength [18-20]. Triggered by TNF-α and IL-6, CRP is a protein produced by the liver that recognizably fights against typical inflammation [21], deserving further cogitation as a traditional biomarker with plausible interactions between the status of skeletal muscle and inflammation [22, 23].

Although some disparities in light of the inflammatory status, both CRP and NLR can be considered as markers for indicating poor clinical outcomes [24]. More specifically, the CRP is a well-understood marker of acute inflammatory process caused by acute infections and chronic low-grade inflammation when measured via high-sensitivity assay [25-27], while NLR has been evoked as a routinely available and cost-effective measure of systemic inflammation derived from the absolute neutrophil and absolute lymphocyte counts of a full blood count [28-30]. In the face of the use of these markers in ubiquitous clinical situations, a more detailed understanding of their association with the components of sarcopenia are pivotal in order to elucidate underlying mechanisms related to muscle wasting in KTPs, given that only a handful of research has explored this subject matter [31, 32]. Thus, the purpose of this study was to ascertain whether or not NLR and CRP levels are associated with the components of sarcopenia in KTPs.

2. Methods

2.1. Subjects

A cross-sectional study was conducted at the Hospital of the Federal University of Uberlandia (Minas Gerais, Brazil), where an ambulatory care clinic for chronic kidney disease is located. Inclusion criteria were individuals aged ≥ 18 years with at least three months of kidney transplantation and able to answer

the questions and complete physical tests. Exclusion criteria were kidney graft rejection and/or failure and KTPs undergoing dialysis. Of a total of 360 patients seen at the outpatient clinic of kidney disease, 108 volunteers were selected for the study (**Figure 1**). This research was approved by the Federal University of Uberlandia Research Ethics Committees (protocol number: 1688246); all participants signed a consent form.

[Insert figure 1 here]

2.2. Anthropometric Assessment

Body weight was measured on a portable digital scale (Líder®) and height on a vertical mobile stadiometer (Welmy®). Afterward, body mass index was calculated using measures of body weight and height. Waist circumference was measured with a inelastic tape (Cescorf®) positioned at the midpoint between the last rib and the iliac crest [33]. The average from the three measurements was used.

2.3. Dietary Assessment

Dietary assessment was performed using 24-h dietary recalls on two different occasions: a face-to-face interview and a phone call (4 to 10 days after the first dietary recall) [34]. A trained and registered dietitian interviewed each volunteer using the 5-step multiple-pass method [35]. Collected data were

analyzed and calculated using the Nutrition Data System for Research (NDS-R©), software version 2014.

2.4. Physical Activity Level

The short version of the International Physical Activity Questionnaires (IPAQ) was used to assess the physical activity level [36]. Such a questionnaire is approved for the Brazilian population and affords information regarding the duration, frequency, and intensity of physical activities performed in the last week.

2.5. Body Composition

Bioelectrical impedance (Biodynamics® 450, Seattle, WA, USA) analysis with a frequency of 50 kHz was used to evaluate body composition. Subjects were instructed to avoid the intake of caffeine and alcoholic beverages in order not to alter the hydration status, as well as to avoid physical exercises and intense physical activities on the eve of the exam. Patients were evaluated after a 12-h overnight fast, requested to empty their urinary bladder 30 minutes before the exam and instructed to remain in the supine position for five minutes to ensure the balance of body fluids. HeartBeat (HeartBeat, Biotronik Comercial *Médica* Ltd., *São Paulo*, Brazil) electrodes were positioned on the right side of the body on the wrist, hand, ankle, and foot after each site was sterilized with alcohol. Values between 69% and 75% of total body water per lean mass were deemed acceptable [37]. The bioelectrical impedance analysis was performed outside the menstrual period for women of reproductive age. Raw bioelectrical impedance data were used to estimate body fat, fat-free mass, and total body water. Appendicular skeletal muscle mass (ASM) was calculated according to the revised European consensus on sarcopenia [38], using Sergi et al.' equation [39].

An anthropometric prediction equation for appendicular skeletal muscle mass index (ASMI) was used, comprising the ASM (kg)/height (m^2) [38].

2.6. Strength and Functional Capacity

Handgrip strength (HGS) and the five-times-sit-to-stand test (5STS) were performed to assess muscle strength [38]. HGS was measured three times by the use of the dominant hand on a Jamar® hydraulic dynamometer. Each subject was seated with the arm in neutral rotation and the elbow flexed at 90° so that the dynamometer was squeezed with maximum power and, thus, considering the highest value. Concerning the 5STS, the patient was instructed to sit and get up from the chair five times as fast as possible, and this test time was recorded [38, 40].

Functional capacity was evaluated using the short physical performance battery (SPPB) and the 4-meter gait speed test. SPPB included the standing balance test, 4-meter gait speed, and the 5STS. Each test had a maximum of 4 points, totalizing 12 points at the end of the test [41]. The standing balance test evaluates whether the patient can stand in three positions for ten seconds with the feet together, semi-tandem position and, tandem. The 4-m gait test consists of 1 m for the acceleration zone, 4 m of walking at the usual walking speed used in daily activities, and 1 m for the deceleration zone. The gait speed test was repeated without rest, and the attempt made in the shortest time was used to calculate the speed in meters per second [42]. All subjects received a voice command from the examiner to start the test.

2.7. Blood Sample Analysis

Blood samples were collected after a 12-h overnight fast on the same day that bioelectrical impedance was performed. Electrochemiluminescence method was employed to analyze the plasma levels of CRP (normal range: 0.3 mg/dL or 3 mg/L) [43], creatinine, urea, glucose, triglycerides, and total cholesterol and lipoprotein fractions. Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald equation [44]. Glomerular filtration rate was estimated by the chronic kidney disease epidemiology collaboration (CKD-EPI) equation [45]. Enzymatic colorimetric method was used to assess serum uric acid levels. The XN-3000 Sysmex cytometric method was used to obtain the leukogram values (normal range: 4,000-11,000 cell/mm^3). NLR and was calculated by dividing the absolute neutrophil count by the lymphocyte count.

2.8. Statistical analysis

The individuals were characterized according to the NLR and CRP tertiles. One-way analysis of variance (ANOVA) with Tukey post hoc test was performed to compare the discrepancy between the mean of likely pairs. Non-parametric data were obtained from the Kruskal–Wallis test. Data were described as mean and standard deviation or median, minimum, and maximum. Chi-squared (χ^2) test was used to compare data in percentages, i.e., categorical variables.

Simple linear regression analysis was carried out as a statistical model to associate the NLR and CRP levels with the components of sarcopenia, i.e., HGS, ASM, ASMI, gait speed, SPPB, and the 5STS, followed by the Multivariate linear regression model adjusted for age, sex, waist circumference (cm), total protein intake (g/kg/d), glomerular filtration rate (ml/min/173m^2), use of calcineurin inhibitor and mTOR inhibitors; transplant time (months) and energy intake (kcal).

As independent variables, both NLR and CRP were added to that statistical model along with confounding variables in order to appraise the prediction of the variances for the parameters of sarcopenia, which were the dependent variables. Age, sex, waist circumference (cm), total protein intake g/kg/d, glomerular filtration rate (ml/min/173m^2), calcineurin inhibitor, mTOR inhibitors, transplant time (months), and daily energy intake (kcal) were the confounding variables added to the statistical model. Analyses were performed according to ≥ 50 and <50 years old as well. Stata 14 (StataCorp, College Station, TX, USA) was the statistical software used. *P*-values ≤ 0.05 were considered significant.

3. Results

There was no difference between tertiles within both NLR and CRP groups for demographic data (age and sex), comorbidities, alcohol intake, smoking, physical activity level, determinants of sarcopenia, and use of drugs. Conversely, individuals within the 1st tertile of NLR, when compared to the 3rd tertile, had a lower pretransplant body weight (p = 0.028).) Subjects within the 1st tertile of CRP, in turn, when compared to the 3rd tertile had a lower current body mass index (p = 0.042), waist circumference (p = 0.049), fat mass in kilograms (p = 0.030) and in percentage (p = 0.032) while having increased fat mass in percentage (p = 0.049) **(Table 1)**.

Regarding transplant data, individuals within the 1st tertile of the NLR classification, when compared to the 3rd tertile, had a lower dialysis time (p = 0.006) while the transplant time was higher in the 1st tertile when compared to the other tertiles (p = 0.001). In addition, there was a statistical difference between

peritoneal dialysis (p = 0.002) and type of donor (p = 0.004), i.e., living and cadaveric donation. In the dietetic data for CRP classification, energy intake was lower in the 3rd tertile when compared to the other tertiles (p = 0.048), and the consumption of monounsaturated fats was lower in the 1st tertile than in the 2nd and 3rd tertiles (p = 0.016). In contrast, no significant differences were detected between the tertiles for NLR classification **(Table 1)**.

Pertaining to biochemical parameters, triglyceride (p = 0.044) and very-low-density lipoprotein cholesterol (p = 0.033) levels were different between the tertiles of NLR, and CRP levels diverged from the tertiles categorized for CRP (p < 0.001). In the analyses of complete blood count, neutrophils and mature neutrophils had intragroup differences for both tertiles of NLR and CRP classifications (p < 0.001 for both neutrophils and mature neutrophils in the NLR classification; p = 0.006 and 0.011 for neutrophils and mature neutrophils in the CRP classification, respectively), whereas lymphocytes, NLR and platelet-lymphocytes ratio differed between groups only for classification by NLR (p < 0.001 for all variables) **(Table 1)**.

[Insert Table 1 here]

No significant differences, neither NLR nor CRP classifications, were noted in analyses of simple and multivariate linear regression in relation to the determinants of sarcopenia (**Table 2**).

[Insert Table 2 here]

Discussion

Viewed collectively, this research does not support an association between NLR and CRP with the components of sarcopenia in KTPs. Correspondingly, employing simple and multivariate linear regression, we did not find significant differences for either classification for NLR or CRP levels with strength, muscle mass, and functional capacity.

KTPs need ambulatory monitoring throughout their lives [46, 47] and, undoubtedly, new scientific insights are still fundamental in the effort to expand the understanding of this population that, beyond well-established problems treated with pharmacological agents, can suffer from sarcopenia [48]. Not only unfavorable shifts in body composition by decreasing the muscle mass but also impairment in functional capacity and strength is a worldwide concern that may generally affect the clinical population and elderly subjects at the same time, thus involving KTPs [49]. Interestingly, working on that same population, our group recently observed that approximately 19% of KTPs who attended an outpatient clinic suffered from sarcopenia [48]. In addition, a couple of recent cross-sectional studies have demonstrated important findings as to the prevalence of sarcopenia and poor prognosis based on its components in KTPs [31, 32]. In one study, 11% of a sample consisting of 210 KTPs had sarcopenia [31], and 19% of 83 KTPs in the other [32]. Regarding the latter, among individuals without sarcopenia, 18% had a decrease in HGS and 40% in altered gait speed, hence indicating that an individual evaluation of sarcopenia components should be taken into consideration as well [32].

At the molecular level, in patients with kidney disease, various mechanisms sustain the crosstalk signaling mechanisms related to the

musculoskeletal and immune cells used in the NLR, which collectively may entail a poor outcome of sarcopenia components. For instance, chronic dysregulation in renal homeostasis is linked with a catabolic status caused by activation of the caspase-3, myostatin, ubiquitin-proteasome system, and lysosomes, which may be resulted from hindered insulin signaling, metabolic acidosis, raised angiotensin II levels, and related inflammatory processes [50]. In addition, persistently high status of oxidative stress is harmful to muscle mass, and diminished glomerular filtration rate results in the accumulation of uremic compounds, e.g., indoxyl sulfate, a metabolite from the breakdown of L-tryptophan by colon microbes, induces oxidative stress through reactive oxygen species [51-54] and then triggering inflammatory responses [55-57]. These changes affect the signaling pathway of leukocyte hematopoiesis in the bone marrow, culminating in increased granulocyte generation and low lymphocyte production, clinically therefore leading to higher NLR values [58, 59]. With regard to neutrophils, their release of neutrophil extracellular traps produces reactive oxygen species, leading to a higher inflammatory status and contributing to metabolic dysregulation in the kidney and musculoskeletal [60-62].

Against all unfavorable biological rationale of muscle wasting caused by the higher production of neutrophils per a low production of lymphocytes in patients with kidney disorders, herein, we observed a non-significant association between NLR and the components of sarcopenia. Nevertheless, it is crucial to emphasize that the evidence base is bereft of uniformity pertaining to both diagnoses of sarcopenia and its components. Tang et al. showed that NLR was slightly associated with ASM and HGS, but not with sarcopenia, in elderly Chinese [63]. In contrast, high values of NLR were positively associated with an

increased risk of sarcopenia in older individuals, as noted by Öztürk et al. [64], and were associated with the risk of sarcopenia in cancer patients in the Borges et al.' research [65]. With regard to sarcopenia components, Borges et al. found a negative correlation between NLR and gait speed ($r = -0.48$, $p = 0.0001$), as well as between NLR and HGS ($r = -0.29$, $p = 0.002$), through their cross-sectional study composed of 123 hospitalized cancer patients undergoing chemotherapy and/or surgery [65]. Given that hospitalized cancer patients suffer from severe acute inflammation and are prone to controlled inflammation in the long-term follow-up [66, 67], we believe that this population is more sensitive to changes in the components of sarcopenia compared with the KTPs in our study, who were not in a sufficient inflammatory state to be directly associated with the components of sarcopenia, perhaps because they already undergo extensive muscle wasting induced by hemodialysis.

Concerning CRP levels, longitudinal studies have shown associations of high levels of CRP with low physical capacity in older individuals [68, 69], and a meta-analysis of cross-sectional studies demonstrated that patients with sarcopenia had significantly higher levels of CRP when compared to those without sarcopenia—i.e. control groups [1]. In the present study, we did not observe significant association regarding the CRP levels and components of sarcopenia KTPs, while debate persists as to this association among older individuals without kidney diseases or disorders. In a study involving 335 community-dwelling people (mean age, 65 years) from Japan, the ASMI and HGS, but not gait speed, were negatively associated with CRP levels [70]. In the *English Longitudinal Study of Ageing*, a study of community-dwelling older adults (mean age, 65 years) consisting of 1,926 men and 2,260 women, after

adjustments for age, smoking, physical activity, education, inflammatory diseases, and all other biological factors, elevated CRP levels were associated with poorer HGS and chair stand performance in women but only chair stand performance in men [71]. In the *International Mobility in Aging Study* (IMIAS), a longitudinal and multicenter study that tested a total of 1,371 patients (aged 65–74) for CRP from Canada, Colombia, and Brazil, CRP was significantly associated with low HGS and poor physical performance in bivariate analyses, but HGS association with CRP disappeared after adjustment by socioeconomic factors and health behaviors [72].

At best, our research was carried out in KTPs, whose population is less investigated when compared to older individuals with preserved renal function. In addition, to the best of our knowledge, we believe that CRP values, even the highest tertiles, could be not biologically impactful to affect the musculoskeletal to an extent that is translated into impaired components of sarcopenia. Given the as-yet-unrecognized association between high levels of CRP, beyond borderline (e.g. > 3 mg/dL), and the components of sarcopenia, we encourage further investigation in this regard. Thus, it is fundamental to review mechanistic pathways so that our previous hypothesis—i.e., an inverse association between CRP levels and the components of sarcopenia in KTPs—can be streamlined to future research. Along those nuanced lines, elevated status of TNF-α and IL-6 caused by the systemic inflammation triggers the CRP production, whose protein affects vascular structures, a cornerstone of kidney and cardiometabolic complications [73-75]. Low-grade systemic inflammation mediated by CRP is associated with increased oxidative stress in vivo, leading to impaired systemic bioavailability of nitric oxide, which might contribute to sarcopenia in virtue of less

nutrient and hormonal delivery to the muscle [76]. Moreover, senescence in itself is related to the increase in the pro-inflammatory cascade of CRP [77], while older people represent a considerable proportion of KTPs [78].

Indeed, this study provides further underpinnings for the global population inserted in the circles of kidney transplantation. Importantly, Horvat et al. evaluated 69 countries and found Brazil as the second largest number of living donors, behind only the USA [79]. Bearing this in mind, some intra- and inter-country considerations ought to be emphasized. For instance, while transplants in Brazil are performed by a unified health system, offering reimbursement to transplant centers and favoring access for the general population, the constant need to increase the number of donors, cold ischemia time caused by long distances from transplant centers, and others economic divergences among Brazilian states and regions remains a challenge [80, 81].

The present work has some methodological limitations. The cross-sectional fashion of this research does not translate a causal interaction between NLR and CRP levels with sarcopenia development. ASMI was evaluated by bioelectrical impedance using the Sergi et al.' equation [39], whose formula is not endorsed for KTPs. Nevertheless, it should be noted that, thus far, there is no approved equation to estimate muscle mass for KTP [82]. Hence, the use of Sergi et al.' equation is a convenient and pragmatic way of assessing ASMI in real-world intervention, as supported by the revised European consensus on definition and diagnosis of sarcopenia [38]. In addition, the absence of defined cutoff points for the NLR and the diagnosis of sarcopenia in KTPs ought to be pointed out as limitations. Lastly, it is worthwhile mentioning that we did not investigate the entire

CRP pathway, thus we encourage the design of future insights working on the whole cascade of CRP/pro-inflammatory cytokines axis for KTPs.

Despite the aforementioned caveats, concrete strengths are noteworthy, given that not only unfavorable shifts in body composition by decreasing the muscle mass but also impairment in functional capacity is a worldwide concern that may generally affect the clinical population and elderly subjects at the same time, thereby involving KTPs [49]. The intention of analyzing the interaction between NLR and the components of sarcopenia is a novelty particularly taking into account the KTPs. Apart from NLR, the use of CRP as a cost-effective marker is fruitful in terms of providing further practical knowledge of diseases. Notwithstanding the neutral results, this study is able to furnish the literature with straightforward information that must be propagated in order to minimize the unnecessary use of surrogate markers in the management of sarcopenia.

Conclusion

NLR and CRP levels were not associated with the components of sarcopenia, i.e., strength, muscle mass, and functional capacity, in KTPs. Despite the physiological and pathophysiological rationales regarding CRP, neutrophils, and lymphocytes, as well as their relevance as feasible tools in a plethora of medical settings, these markers may be unsuitable when embarking on the diagnosis of sarcopenia and the nexus with its components, specifically in KTPs. To avoid untrustworthy information due to borderline to moderately elevated levels of clinical biomarkers, of note, further investigation focusing on a higher inflammatory state, represented by highest means and/or ordered distribution of

CRP and NLR values, is imperative to draw a firm conclusion with respect to the association of these markers and the components of sarcopenia in KTPs.

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Conflicts of Interest

The authors declare no conflict of interest.

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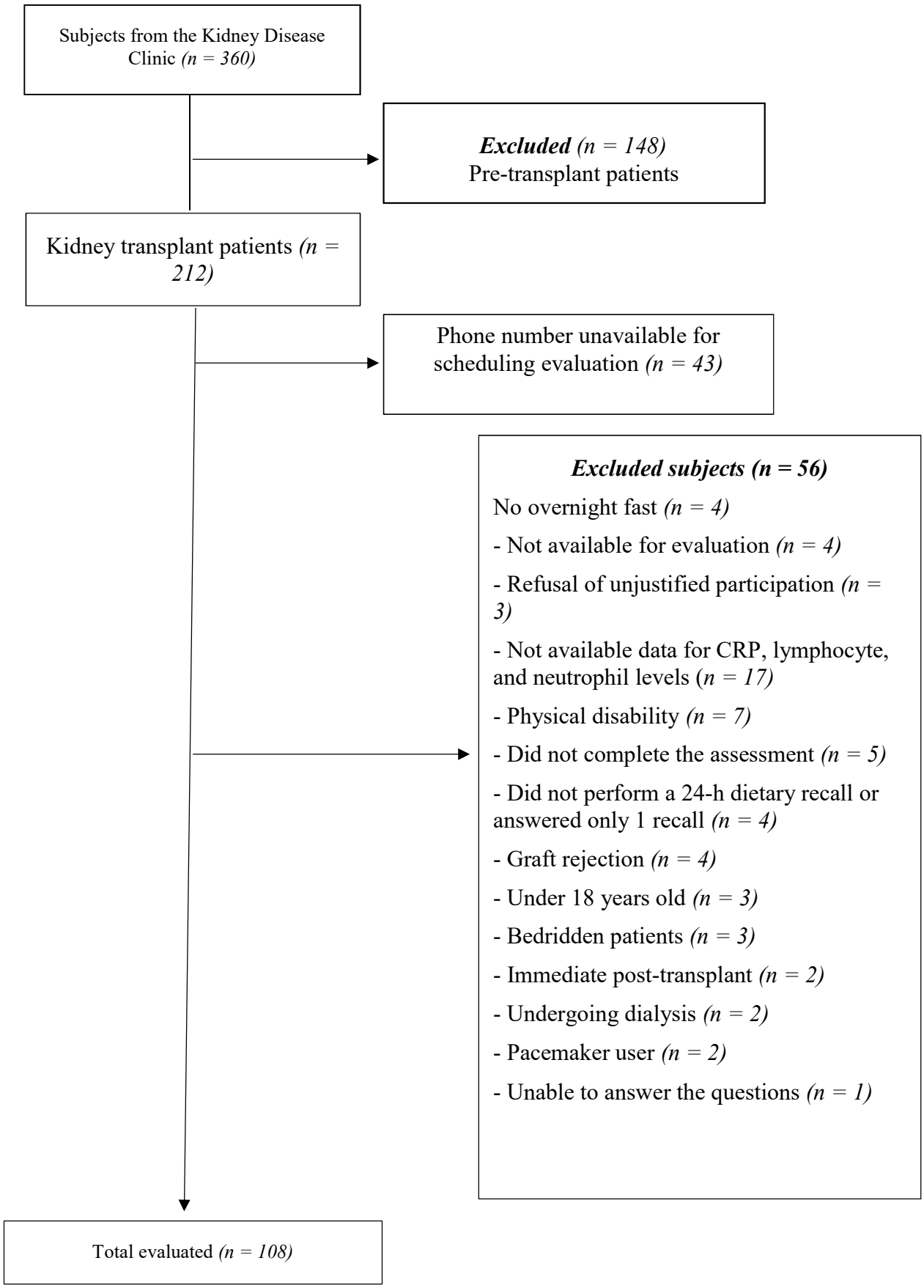

Figure 1. Flowchart of the subjects evaluated.

Table 1. Demographic characteristics, components of sarcopenia, biomarkers, drugs, and dietary data, according to tertiles of NLR and CRP.

Variables	NLR				CRP			
	1st tertile (n = 36)	2nd tertile (n = 36)	3rd tertile (n = 36)	*p*-value	1st tertile (n = 36)	2nd tertile (n = 37)	3rd tertile (n = 35)	*p*-value
Demographic data								
Age (years)	47.5 ± 11.6	46.5 ± 12.5	50.6 ± 11.9	0.312	48.2 ± 12.4	46.2 ± 10.6	50.3 ± 13.0	0.354
Sex, n (%)								
Male	22 (61.1)	29 (80.6)	23 (63.9)	0.158	25 (69.4)	28 (75.7)	21 (60.0)	0.355
Female	14 (38.9)	7 (19.4)	13 (36.1)		11 (30.6)	9 (24.3)	14 (40.0)	
Comorbidities								
Diabetes, n (%)	11 (30.6)	11 (30.6)	5 (13.9)	0.169	8 (22.2)	9 (24.3)	10 (28.6)	0.821
Hypertension, n (%)	30 (83.3)	29 (80.6)	26 (72.2)	0.488	28 (72.2)	28 (83.8)	25 (80.0)	0.471
Alcohol intake								
Consumer, n (%)	13 (36.1)	11 (30.6)	11 (30.6)	0.844	11 (30.6)	12 (32.4)	12 (34.3)	0.945
Non-consumer, n (%)	23 (63.9)	25 (69.4)	25 (69.4)		25 (69.4)	25 (67.6)	23 (65.7)	
Smoking								
Non-user, n (%)	0 (0.0)	4 (11.1)	1 (2.8)	0.065	2 (5.6)	2 (5.4)	1 (2.9)	0.831
User, n (%)	36 (100)	32 (88.9)	35 (97.2)		34 (94.4)	35 (94.6)	34 (97.1)	
Physical activity level								
Weekly physical activity (minutes)	215.4 ± 233.4	164.0 ± 174.0	176.7 ± 179.6	0.518	183.9 ± 177.8	180.5 ± 182.8	192.0 ± 232.3	0.969
Sarcopenia Components								
Handgrip strength (kg)	17.7 ± 8.0	20.3 ± 10.2	17.8 ± 9.7	0.426	19.7 ± 10.2	19.4 ± 8.5	16.6 ± 9.2	0.300
Gait speed (m/sec)	1.07 ± 0.20	1.11 ± 0.19	1.11 ± 0.27	0.674	1.13 ± 0.06	1.12 ± 0.26	1.05 ± 0.22	0.324
5STS, sec	11.1 (7.9–17.3)	11.5 (7.5–25.2)	10.9 (8.4–18.1)	0.305	11.0 (8.3–21.4)	11.2 (7.5–16.1)	11.1 (7.9–25.2)	0.998
Sarcopenia prevalence (n, %)								
No sarcopenia	10 (27.8)	9 (25.0)	8 (22.2)	0.809	10 (27.8)	10 (27.0)	7 (20.0)	0.756
Probable sarcopenia	20 (55.6)	18 (50.0)	20 (55.6)		20 (55.6)	18 (48.7)	20 (57.1)	
Sarcopenia	16.7	25.0	19.4		6 (16.7)	9 (24.3)	7 (20.0)	
Severe sarcopenia	0	0	2.8		0	0	2.9	
Anthropometric characteristics								
Current body weight (kg)	72.7 ± 16.5	69.5 ± 14.4	69.2 ± 12.8	0.528	66.1 ± 14.3	72.4 ± 14.8	77.9 ± 14.2	0.091
Height (m)	1.61 ± 0.08	1.65 ± 0.07	1.63 ± 0.10	0.210	1.64 ± 0.10	1.63 ± 0.09	1.63 ± 0.08	0.791

Current BMI (kg/m²)	27.6 ± 5.8	25.4 ± 5.2	25.9 ± 4.7	0.174	24.5 ± 5.3 [a]	26.9 ± 4.9 [ab]	27.5 ± 5.4 [b]	**0.042**
Pretransplant body weight (kg)	55.1 ± 12.8 [a]	60.9 ± 10.6 [ab]	62.9 ± 13.3 [b]	**0.028**	57.6 ± 12.3	58.7 ± 12.9	62.5 ± 12.5	0.252
Pretransplant BMI (kg/m²) †	21.4 (16.9–30.4)	22.9 (13.1–33.2)	22.8 (17.1–34.6)	0.330	20.1 (15.6–30.4)	22.7 (13.1–29.3)	22.8 (17.1–34.6)	0.566
Waist circumference (cm)	96.8 ± 16.1	93.1 ± 14.7	92.8 ± 13.3	0.447	89.6 ± 15.2 [a]	95.2 ± 13.8 [ab]	98.0 ± 14.2 [b]	**0.049**
Calf circumference (cm)	34.6 ± 3.5	33.8 ± 4.1	34.6 ± 3.5	0.518	33.8 ± 3.3	34.8 ± 3.6	34.5 ± 4.2	0.472
Body composition								
Appendicular skeletal muscle mass (kg) †	18.0 (13.0–25.4)	19.3 (13.9–25.4)	19.2 (11.5–25.4)	0.676	19.2 (13.0–23.5)	19.1 (11.5–25.4)	19.4 (12.5–25.4)	0.721
Appendicular skeletal muscle mass index (kg/m²)	7.2 ± 1.1	7.2 ± 0.9	6.9 ± 0.8	0.219	7.0 ± 0.8	7.2 ± 1.0	7.0 ± 1.1	0.419
Lean mass (kg)	50.4 ± 9.9	51.3 ± 10.1	49.8 ± 8.5	0.805	48.9 ± 9.8	52.3 ± 9.9	50.3 ± 8.6	0.311
Fat mass (kg)	22.3 ± 10.0	18.20 ± 7.1	19.4 ± 7.8	0.109	17.3 ± 8.3 [a]	20.1 ± 8.1 [ab]	22.5 ± 8.5 [b]	**0.030**
Fat mass (%)	29.7 ± 8.6	25.6 ± 7.0	27.5 ± 7.9	0.09	25.4 ± 8.1 [a]	27.2 ± 8.0 [ab]	30.3 ± 7.2 [b]	**0.032**
Transplant data								
Dialysis time (months)	35.5 ± 34.3 [a]	56.3 ± 38.5 [ab]	67.5 ± 51.6 [b]	**0.006**	45.0 ± 40.9	57.7 ± 47.7	56.6 ± 42.5	0.397
Dialysis time, n (%)								
Peritoneal dialysis	16.7*	0*	0*	**0.002**	8.3	8.1	0.0	0.279
Hemodialysis	80.6	94.4	83.3		86.1	86.5	85.7	
Peritoneal dialysis and Hemodialysis	2.8	5.6	16.7		5.6	86.1	8.3	
Transplant time (month)	135.0 ± 87.6 [a]	84.5 ± 76.7 [b]	70.7 ± 61.7 [b]	**0.001**	105.2 ± 83.6	82.8 ± 82.8	102.7 ± 74.3	0.429
Number of Transplants, n (%)								
1º transplant	97.2	86.1	91.7	0.234	97.22	94.59	82.86	0.066
>1 transplant	2.8	13.9	8.3		2.78	5.41	17.14	
Type of donor, n (%)								
Living donation	22 (61.1)	10 (27.8)	10 (27.8)	**0.004**	18 (50.0)	12 (32.4)	12 (34.3)	0.243
Cadaveric donation	14 (38.9)	26 (72.2)	26 (72.2)		18 (50.0)	25 (67.6)	23 (65.7)	

Drugs								
Tacrolimus (mg/d) †	0 (0–9)	2 (0–16)	2 (0–10)	0.717	0 (0–16)	2 (0–15)	2 (0–6)	0.883
Cyclosporine (mg/d) †	0 (0–150)	0 (0–125)	0 (0–200)	0.837	0 (0–150)	0 (0–125)	0 (0–200)	0.535
Azathioprine (mg/d) †	0 (0–100)	0 (0–50)	0 (0–100)	0.370	0 (0–100)	0 (0–50)	0 (0–100)	0.517
Mycophenolate Sodium (mg/d) †	0 (0–1440)	0 (0–1440)	360(0–1440)	0.129	0 (0–1440)	0 (0–1440)	0 (0–1440)	0.621
Mycophenolate Mofetil (mg/d) †	0 (0–2000)	0 (0–2000)	0 (0–2000)	0.877	0 (0–2000)	0 (0–200)	0 (0–200)	0.738
Everolimus (mg/d) †	0 (0–1.5)	0 (0–1)	0 (0–2)	0.939	0 (0–1.5)	0 (0–1.5)	0 (0–2)	0.786
Sirolimus (mg/d) †	0 (0–2)	0 (0–2)	0 (0–0)	0.920	0 (0–2)	0 (0–2)	0 (0–2)	0.999
Loop diuretics (mg/d) †	0 (0–80)	0 (0–80)	0 (0–80)	0.740	0 (0–80)	0 (0–80)	0 (0–80)	0.569
Thiazide diuretics (mg/d) †	0 (0–50)	0 (0–25)	0 (0–50)	0.972	0 (0–0)	0 (0–50)	0 (0–50)	0.834
Prednisone (mg/d) †	5 (0–20)	7.5 (0–10)	5 (0–20)	0.246	5 (0–20)	5 (0–20)	5 (0–10)	0.933
Calcineurin inhibitors, n (%)	14 (38.9)	12 (33.3)	11 (30.6)	0.750	15 (41.7)	11 (29.7)	11 (31.4)	0.512
Cell proliferation inhibitor, n (%) †	5 (13.9)	6 (16.7)	4 (11.1)	0.793	5 (13.9)	5 (13.5)	5 (14.3)	0.996
mTOR inhibitors, n (%) †	29 (80.6)	29 (80.6)	30 (83.3)	0.940	31 (86.1)	30 (81.8)	27 (77.1)	0.621
Corticoids, n (%)	34 (94.4)	35 (97.2)	33 (91.7)	0.589	35 (97.2)	34 (91.9)	33 (94.3)	0.609
Biochemical parameters								
Uric acid (mg/dL) †	6.20 (3.1–11.5)	6.3 (3.5–11.3)	6.6 (3.7–13.4)	0.770	6.2 (3.1–13.4)	6.4 (4.4–11.5)	6.3 (3.5–12.5)	0.498
Urea (mg/dL) †	40.85 (20.7–115.8)	45.2 (15.0–141.2)	49.8 (26.7–156.5)	0.062	40.8 (17.2–156.5)	43.7 (15–102.5)	47.0 (26.8–104.3)	0.324
Creatinine (mg/dL) †	1.3 (0.7–6.9)	1.37 (0.7–6.1)	1.36 (0.8–8.7)	0.312	1.31 (0.7–8.7)	1.37 (0.81–6.13)	1.32 (0.68 – 3.43)	0.707
GFR (ml/min/1.73m²)	61.1 ± 19.3	57.5 ± 23.3	51.7 ± 22.0	0.183	56.3 ± 25.8	60.4 ± 18.6	53.5 ± 20.2	0.400
Blood glucose (mg/dL) †	91.9 (75–212)	96.0 (71–407)	90.3 (70–183)	0.601	91.0 (70–162)	91.9 (71–212)	98.0 (71–407)	0.623
CRP (mg/dL)	0.27 (0.03–11.68–)	0.20 (0.03–2.48)	0.43 (0.03–7.39)	0.316	0.05 (0.03–0.16)	0.29 (0.17–0.45)	1.08 (0.52–11.68)	**< 0.001**
Total cholesterol (mg/dL)	191.8 ± 47.6	187.9 ± 39.0	188.3 ± 43.2	0.918	186.4 ± 36.8	185.8 ± 46.7	196.2 ± 45.3	0.529
LDL-C (mg/dL) †	107.0 (36.0–239.0)	101.5 (62.0–166.0)	102.0 (57.0–196.0)	0.964	105.5 (64.0–239.0)	98.0 (26.0–210.0)	107.0 (39.0–196.,)	0.408

HDL-C (mg/dL) †	47.0 (31.0–79.0)	44.6 (24.0–87.4)	48.0 (24.0–99.0)	0.389	47.0 (28.0–87.4)	43.20 (24.0–84.0)	48.0 (24.0–99.0)	0.772
Triglycerides (mg/dL) †	164.0 (65.7–497.1)	184.0 (68.0–473.0)	133.5 (43.0–715.0)	**0.044**	145.0 (64.0–363.0)	180.0 (74.0–497.1)	169.8 (43.0–715.0)	0.082
VLDL-C (mg/dL) †	32.5 (8.0–99.0)	36.5 (14.0–95.0)	28.0 (9.0–143.0)	**0.033**	29.0 (13.0–73.0)	35.0 (8.0-99.0)	33.5 (9.0–143.0)	0.092
Complete blood count								
Neutrophils (mm³) †	3,954 (555–7,683)	4,407 (2,663–9,362)	5,330 (2,747–70,869)	**< 0.001**	4,117 (2,376–8,740)	4,412 (555–70,869)	5,317 (1,064–51,688)	**0.006**
Lymphocytes (mm³)	2,826.5 ± 814.5 [a]	2,134 ± 655 [b]	1,567.6 ± 694.2 [c]	**< 0.001**	2,091 ± 787.7	228.7 ± 880.7	2,207.7 ± 995.9	0.778
Basophils (mm³) †	50.4 (16.6–112.5)	41.2 (72.0–174.0)	42.3 (16.0–75.6)	0.435	44.9 (7.2–112.5)	41.5 (16.6–174.0)	29.4 (16.0–71.0)	0.658
Band cells (mm³) †	204.0 (62.0–756.0)	140.0 (57.0–553.0)	234.0 (48.0–1380.0)	0.356	168.0 (62.0–1380.0)	216.0 (86.0–903.0)	187.5 (48.0–960.0)	0.398
Mature neutrophils (mm³) †	3,905 (555–7,683)	4,331 (2,460–9,362)	5,260 (2665–69,966)	**< 0.001**	4,112 (2,356–7,360)	4,290 (555–69,966)	5,254 (1,064–51,688)	**0.011**
Platelets (K/mm³)	241.8 ± 77.3	210.8 ± 52.3	223.9 ± 59.1	0.123	223.2 ± 67.2	222.1 ± 51.6	231.48 ± 74.49	0.799
NLR †	1.44 (0.29–1.84)	2.21 (1.87–2.53)	3.43 (2.53–20.34)	**< 0.001**	2.19 (0.80–7.60)	2.0 (0.8–20.3)	2.4 (0.3–18.7)	0.057
Dietetic data								
Energy (kcal)	1786.5 ± 561.0	1809.3 ± 632.1	1656.2 ± 568.5	0.494	1704.7 ± 621.0 [ab]	1933.7 ± 578.8 [a]	1604.5 ± 519.8 [b]	**0.048**
Carbohydrates (g)	211.9 ± 75.2	220.2 ± 82.5	207.3 ± 90.6	0.797	207.6 ± 84.4	235.8 ± 90.0	194.8 ± 67.3	0.095
Carbohydrates (%)	66.3 ± 64.8	58.6 ± 55.3	56.1 ± 38.7	0.707	66.0 ± 71.5	61.1 ± 52.8	53.8 ± 28.0	0.631
Sugar (g)	65.3 ± 43.0	58.1 ± 36.8	60.7 ± 51.4	0.784	60.1 ± 48.0	64.4 ± 42.1	59.5 ± 42.3	0.872
Fructose (g)	11.6 ± 10.0	9.9 ± 10.7	8.1 ± 8.4	0.304	8.8 ± 7.7	11.5 ± 12.2	9.2 ± 8.7	0.4394
Total protein (g)	91.4 ± 34.8	87.8 ± 43.3	79.2 ± 22.1	0.303	84.6 ± 34.3	93.7 ± 37.1	79.7 ± 31.4	0.217
Total protein (%)	26.8 ± 21.3	21.5 ± 12.4	21.5 ± 10.4	0.251	24.3 ± 16.1	23.3 ± 16.2	22.3 ± 14.7	0.862
Total protein (g/kg)	1.3 ± 0.6	1.4 ± 0.9	1.2 ± 0.42	0.548	1.4 ± 0.8	1.4 ± 0.6	1.1 ± 0.5	0.235

Animal protein (g)	67.5 ± 33.8	60.9 ± 41.1	55.2 ± 18.9	0.277	59.9 ± 32.0	66.3 ± 35.6	57.1 ± 30.2	0.476
Vegetal protein (g)	23.9 ± 8.7	27.0 ± 12.1	24.00 ± 9.7	0.359	24.7 ± 10.8	27.5 ± 11.1	22.6 ± 8.2	0.131
Total fats (g)	63.2 ± 27.5	63.6 ± 30.7	56.1 ± 20.1	0.410	59., ± 28.9	68.0 ± 26.5	55.6 ± 22.7	0.117
Total fats (%)	38.7 ± 27.2	33.4 ± 19.7	33.0 ± 19.7	0.494	35.7 ± 25.9	37.2 ± 26.2	32.1 ± 12.2	0.614
Monounsaturated fats (g)	21.7 ± 10.7	22.0 ± 11.7	18.7 ± 7.2	0.316	18.9 ± 9.1 [a]	24.6 ± 11.8 [b]	18.7 ± 7.9 [ac]	**0.016**
Polyunsaturated fats (g)	16.2 ± 7.4	16.7 ± 10.0	14.9 ± 6.1	0.589	15.8 ± 10.2	17.7 ± 6.6	14.2 ± 6.2	0.176
Cholesterol (mg)	276.2 ± 152.1	270.6 ± 180.8	282.4 ± 162.2	0.955	273.4 ± 184.6	288.9 ± 144.7	266.3 ± 164.6	0.837
Omega-3 (g)	1.8 ± 0.6	1.9 ± 1.2	1.6 ± 0.7	0.339	1.7 ± 1.1	2.0 ± 0.7	1.6 ± 0.8	0.221
Omega-6 (g)	14.0 ± 6.9	13.1 ± 5.7	13.6 ± 6.2	0.822	12.7 ± 6.9	14.7 ± 5.5	13.3 ± 6.2	0.382
Fiber (g)	13.2 ± 5.5	14.6 ± 8.3	12.9 ± 6.4	0.529	13.9 ± 7.9	13.9 ± 6.3	12.9 ± 6.2	0.770

BMI, body mass index; CRP, C-reactive protein; GFR, glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NLR, neutrophil-lymphocyte ratio; VLDL-C, very-low density lipoprotein cholesterol; 5STS, five-times-sit-to-stand test. [a b c:] Tukey's Test for Post-Hoc Analysis; * There was statistical significance but the test was not able to detect the difference between groups. † Non-parametric data obtained from the Kruskal–Wallis Test. ‡ handgrip strength + appendicular skeletal muscle mass (kg/m²) + gait speed. Data were described as mean and standard deviation or median, minimum, and maximum.

Table 2. Association of strength, muscle mass and functional capacity parameters with NLR and CRP levels using analyses of simple and multivariate linear regression

	NLR				CRP			
	Simple linear regression		Multivariate linear regression		Simple linear regression		Multivariate linear regression	
	β	*p*-value	β	*p*-value	β	*p*-value	β	*p*-value
Handgrip strength (kg)	0.057	0.075	0.231	0.389	-0.237	0.712	0.291	0.577
5STS (sec)	-0.076	0.460	-0.114	0.288	-0.046	0.821	-0.202	0.334
ASM (kg)	-0.130	0.273	-0.027	0.813	0.072	0.759	0.062	0.788
ASMI (kg/h²)	-0.058	0.075	-0.367	0.242	0.031	0.632	0.040	0.505
Gait speed (m/sec)	0.011	0.132	0.013	0.082	-0.004	0.773	0.004	0.769
SPPB	0.052	0.350	0.076	0.170	0.036	0.744	0.152	0.157

ASM, appendicular skeletal muscle mass; ASMI, appendicular skeletal muscle mass index; SPPB, short physical performance battery protocol; 5STS, five-times-sit-to-stand test. Multivariate linear regression model adjusted for age, sex, waist circumference (cm), total protein intake (g/kg/d), glomerular filtration rate (ml/min/173m^2), use of calcineurin inhibitor and mTOR inhibitors; transplant time (months) and energy intake (kcal).

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