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Authors

Hu, Ashley
Prosper, Ashley
Ruchalski, Kathleen
et al.

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Transplant & Mechanical Support: Short Report

Sarcopenia Predicts Outcomes After Lung Transplantation in Older Lung Transplant Candidates

Ashley Hu, MD,[1] Ashley Prosper, MD,[1] Kathleen Ruchalski, MD,[1] Christian Fulinara, BA,[2] Alina Huynh, BA,[2] David Sayah, MD, PhD,[3] Stephen S. Weigt, MD,[3] Jonathan Singer, MD,[4] Abbas Ardehali, MD,[5] Reshma Biniwale, MD,[5] Deena Goldwater, MD, PhD,[6] and Joanna Schaenman, MD, PhD[2]

ABSTRACT

BACKGROUND As lung transplantation (LT) expands to older recipients, objective approaches to evaluate the aging are needed to optimize posttransplantation outcomes. Frailty assessment and sarcopenia have shown promise as tools for predicting clinical outcomes.

METHODS Patients older than 55 years undergoing evaluation for LT were enrolled in an institutional review board–approved study. Sarcopenia was measured on pretransplantation chest computed tomography images, measuring cross-sectional area and average attenuation of the pectoralis major muscle at 1 slice above the aortic arch. Frailty was measured using the Fried frailty phenotype (FFP) and Short Performance Physical Battery (SPPB).

RESULTS The study evaluated 84 patients with results of computed tomography of the chest available for review; 63% were classified as frail or prefrail by SPPB and 53% were frail by FFP. Sex-corrected sarcopenia was associated with frailty by FFP ($P = .004$) or SPPB ($P = .044$). Sarcopenia, measured by area or average attenuation, was significantly associated with length of stay after transplantation ($P = .017$ and $P = .022$, respectively), with a median 12 days for those with higher muscle mass compared with 21 days for those with lower muscle mass. Total time in the hospital in the first year after transplantation was also associated with sarcopenia by area ($P = .090$) or average attenuation ($P = .046$).

CONCLUSIONS A multifaceted approach to the evaluation of older patients can improve risk stratification, optimizing organ allocation to improve LT outcomes.

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An aging population has contributed to older lung transplant recipients, compounded by the prevalence of idiopathic pulmonary fibrosis (IPF).[1] IPF and other diseases of the aging lung are associated with cellular senescence, important in the pathogenesis of aging.[2] Older patients who undergo transplantation experience increased rates of death and infection.

Previous studies have found that frailty is linked with worse outcomes, including an increased risk of early posttransplantation rehospitalization and death.[3] Various frailty measures have been applied in transplantation; however, there is no consensus on how to measure frailty. Two commonly used methods are the Fried frailty phenotype (FFP) and the Short Performance Physical Battery (SPPB) tests.[3]

Sarcopenia encompasses both the function and the physicality of muscle.[4] Physicality of muscle can be assessed by measuring the quality and quantity of muscle. This can be done with imaging, such as with

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[1]Department of Radiology, David Geffen School of Medicine at UCLA, Los Angeles, California; [2]Division of Infectious Diseases, David Geffen School of Medicine at UCLA, Los Angeles, California; [3]Division of Pulmonary Medicine, Department of Medicine, David Geffen School of Medicine at UCLA, Los Angeles, California; [4]Division of Pulmonary, Critical Care, Allergy and Sleep Medicine, UCSF, San Francisco, California; [5]Department of Cardiothoracic Surgery, David Geffen School of Medicine at UCLA, Los Angeles, California; and [6]Division of Geriatrics, David Geffen School of Medicine at UCLA, Los Angeles, California

Address correspondence to Dr Schaenman, Division of Infectious Diseases, David Geffen School of Medicine at UCLA, 108333 Le Conte Ave, Los Angeles, CA 90925; email: jschaenman@mednet.ucla.edu.

computed tomography (CT), magnetic resonance imaging, or dual-energy X-ray absorptiometry, validated approaches for sarcopenia determination.[5] In this study, we use CT as the imaging modality for assessment as it is available in patients undergoing evaluation for lung transplantation (LT).

Quality and quantity of muscle are represented on CT imaging as the average muscle attenuation and cross-sectional area (CSA), respectively. Fewer studies evaluate the impact of sarcopenia on LT, with focus on psoas and paraspinal muscles,[6,7] and some come to conflicting conclusions.[8,9] Whereas there is general acceptance of measuring muscle area at the L3 vertebral body,[10] there is no established standard in the chest. Our approach uses the easily identifiable pectoralis major muscle.

This study seeks to add further understanding of sarcopenia by correlating it to frailty and clinical outcomes to identify risk for post-LT morbidity and mortality.

IN SHORT

- In a single-center cohort of older candidates for lung transplantation, we demonstrated that sarcopenia, as determined by radiographic assessment of the pectoral muscle on chest computed tomography, was distinct from age of the patient and physical frailty.
- Increased muscle area and attenuation were significantly associated with successful transplantation, postoperative length of stay, and total hospital time in the first year after transplantation.
- Sarcopenia assessment is a useful tool for lung transplant candidacy.

PATIENTS AND METHODS

This study was approved by the local institutional review board. Informed consent was obtained from patients older than 55 years who were being evaluated for LT at our center. FFP and SPPB were measured during outpatient clinic visits for evaluation of LT candidacy.

To evaluate sarcopenia, CSA and average attenuation of the bilateral pectoralis major muscles were obtained using OsiriX software on pretransplantation axial chest CT images at 1 slice above the aortic arch. A manual region of interest was drawn around each pectoralis major muscle bilaterally to determine CSA. From this region of interest, contour was defined by segmenting out the regions containing the prespecified Hounsfield unit range of −29 to 150 HU, as previously defined to represent soft tissue density (Figure 1). The 2 sides were averaged to obtain a final value. Values were independently verified by 2 blinded thoracic subspecialty-trained radiologists.

Statistical analysis was performed with JMP Pro 13 software (SAS Institute). Nonparametric analysis was performed for numeric variables and Pearson for categorical variables. Linear regression was used to compare numeric values. Competing risks analysis was not applied to the study of readmission, given that deaths occurred significantly later after readmission. P value $< .05$ was considered statistically significant.

RESULTS

CHARACTERISTICS OF THE PATIENTS. A total of 86 patients were consented for the study between the years 2017 and 2020 (Supplemental Figure). Two patients did not have CT images of the chest available for review, leaving a total of 84 patients. Patients ranged in age from 57 to 73 years and most commonly had restrictive lung disease (67.9%) due to IPF (Table 1); 10.7% died on the waiting list, and 63 patients (75%) underwent transplantation during the period of evaluation (Table 2). The age range of patients receiving a transplant was similar to that of the total cohort (60-73 years). The median length of stay (LOS) after transplantation was 14.5 days (interquartile range, 10-24 days). On lung biopsy, 25.0% of patients had rejection, primarily A1 (n = 7) followed by A2 (n = 4), and 2 patients each had A3 or B1R.

RESULTS OF FRAILTY AND SARCOPENIA ANALYSES. Frailty as measured by SPPB and FFP was determined as described before, with a median of 9 and 3, respectively (Supplemental Table 1). A linear regression of frailty score by age yielded an R^2 of 0.004 with a P value of .553 for SPPB and an R^2 of 0.005 with a P value of .539 for FFP, demonstrating no correlation between frailty and age.

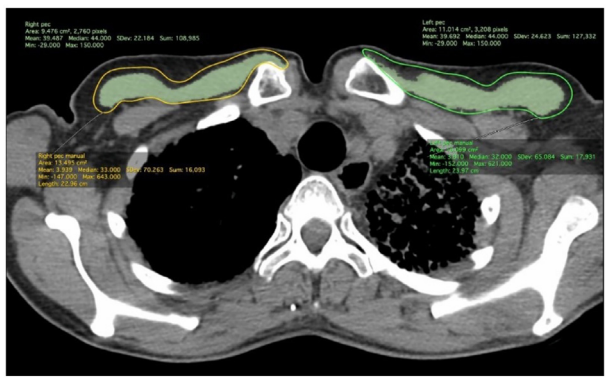

FIGURE 1 Study example. A region of interest is plotted around each pectoralis muscle. Hounsfield unit parameters of −29 to 150 HU are specified; the software highlights pixels that meet the criteria.

TABLE 1 Distribution of Demographic Characteristics

Demographic Characteristic (N = 86)	% or Median (Range)
Age, y	66 (57-73)
Female sex	40.5
Race/ethnicity	
Non-Hispanic white	76.2
Hispanic	14.3
Other	9.5
Diagnosis group[a]	
A	26.2
B	6.0
C	0.0
D	67.9
Lung allocation score	33 (28-78)
Body mass index, kg/m^2	25.7 (15.6-36.0)

[a]Diagnosis groups: A, obstructive lung disease (eg, emphysema); B, pulmonary vascular disease (eg, primary pulmonary hypertension); C, cystic fibrosis or immunodeficiency disorder; D, restrictive lung disease (eg, idiopathic pulmonary fibrosis).

TABLE 2 Clinical Outcomes of Study Patients[a]

Clinical Outcomes (N = 84)	% or Median (Range)
Death on waiting list	10.7
Transplanted	75
Single-lung transplant	56.5
Length of stay, d	14.5 (4-177)
Readmission in first year	67.8
No. of readmissions	1 (0-7)
Total time in hospital in first year, d	24 (4-276)
Biopsy-proven rejection	25.0

[a]Two patients without computed tomography scans available for review were excluded from analysis.

Analysis of sarcopenia was performed by total average pectoralis muscle area over height squared (A/h^2) and muscle attenuation (Supplemental Table 1). As A/h^2 varied significantly by sex ($P < .001$; Supplemental Table 2), patients were divided into high vs low groups by sex. Sarcopenia was not associated with age by either area ($P = .784$) or average attenuation ($P = .090$). Frailty and sarcopenia were not correlated by area ($P = .133$ for FFP, $P = .187$ for SPPB) or attenuation ($P = .795$ for FFP, $P = .531$ for SPPB). When corrected for sex, sarcopenia as measured by total area was found to be associated with frailty assessment by both FFP ($P = .004$) and SPPB ($P = .044$).

CLINICAL OUTCOMES AND SARCOPENIA. Sarcopenia as measured by either A/h^2 or average attenuation was not associated with death on the waiting list ($P = .919$ and $P = .729$, respectively). Analysis by A/h^2 was not associated with transplantation ($P = .804$; Figure 2A). For sarcopenia by average attenuation, attenuation in patients who underwent transplantation was 36.1 compared with 29.6 in those who did not, although this did not reach statistical significance ($P = .176$; Figure 2B). Dividing patients into high-attenuation vs low-attenuation groups demonstrated a significant association between sarcopenia and not achieving transplantation ($P = .023$), with patients with increased muscle mass 5-fold more likely to undergo transplantation. This association was not seen by area ($P = .450$).

LOS demonstrated a significant association with sarcopenia as measured by A/h^2 ($P = .032$). When corrected by sex, there was also a significant association with sarcopenia by area and LOS ($P = .017$), with a median 12.5 days for higher compared with 17 days for lower area (Figure 2C). A significant association was also seen for attenuation and LOS ($P = .022$), with a median 12 days compared with 21 days for lower muscle mass (Figure 2D).

Neither readmission nor the number of readmissions in the first year was significantly associated with sarcopenia as measured by either A/h^2 ($P = .638$ and $P = .980$, respectively) or attenuation ($P = .501$ and $P = .699$, respectively).

Total time in the hospital for the first post-transplantation year was associated with A/h^2 ($P = .044$). Analysis of area by sex demonstrated a median of 19 total hospital days in the group with high muscle mass compared with 27 days in the group with low muscle mass ($P = .090$; Figure 2E). Evaluation of patients by attenuation demonstrated a median total hospital time of 18.5 days in the high-attenuation group vs 29 days in the low-attenuation group ($P = .046$; Figure 2F). Analysis of death after transplantation did not show association with area ($P = .243$) or attenuation ($P = .814$).

COMMENT

This study represents data from a simultaneous evaluation of frailty and sarcopenia in a cohort of LT candidates. We demonstrate how these conditions correlate with each other and investigate the association between sarcopenia and clinical outcomes, including total time in the hospital, using a novel approach for sarcopenia assessment in LT candidates. Given the increasing medical complexity of LT candidates, the ability to risk stratify by sarcopenia analysis in standard CT images is promising. This approach can target preoperative interventions, including nutrition optimization and rehabilitation. The lack of association between sarcopenia and age emphasizes the independence from chronologic age. Frailty is a separate entity from sarcopenia, and yet both syndromes have been associated with poor

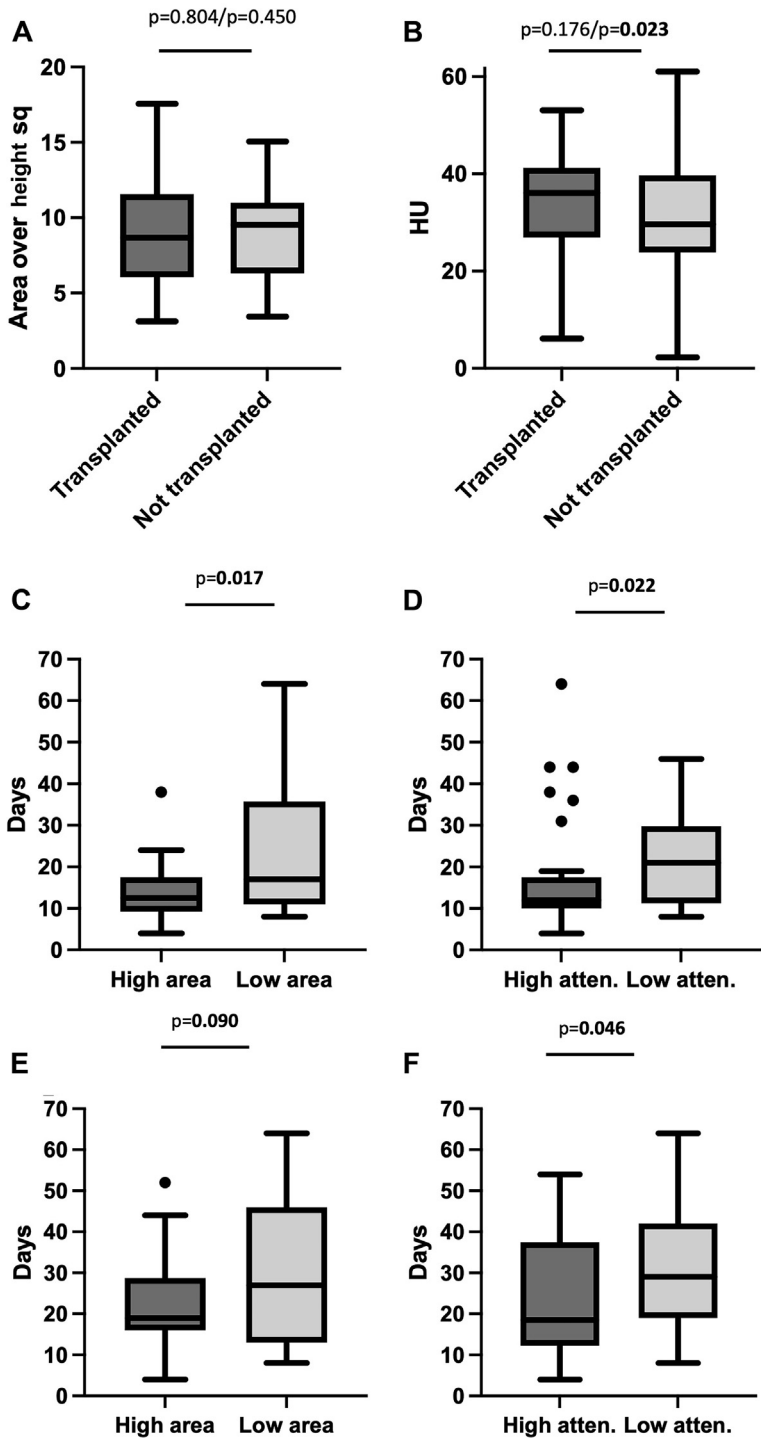

FIGURE 2 Association between sarcopenia and clinical outcomes. (A) Sarcopenia by area squared and transplant status. (B) Sarcopenia by attenuation and transplant status. (C) Sarcopenia by area and length of stay for the hospitalization after transplantation. (D) Sarcopenia by attenuation and length of stay. (E) Sarcopenia by area squared and total time in hospital (during the first year after transplantation). (F) Sarcopenia by attenuation and total time in hospital. Whiskers define Tukey distribution. *P* values for quantitative and categorical comparisons are shown. For area, categorical classes are by sex. *P* values < .05 are shown in bold.

clinical outcomes.[3] Our data demonstrated that frailty and sarcopenia are overlapping but not identical syndromes, with sex playing an important role.

Whereas there is no universally established protocol for measuring sarcopenia, CSA of L3 is widely used; however, not all LT patients have a CT image of the abdomen available for review. Studies of the chest have used measurements of all muscle CSA at the carina, T12, and L1 and selective measurement of the pectoralis muscle.[5,8,9] We chose to use the pectoralis muscle because it is easily identifiable and reproducible, with high intraoperator reliability. Limitations to using the CSA of the pectoralis muscle are due to variability of the position of the aortic arch. This study was limited as a small single-center study; it may not have been possible to account for all confounders. Future studies will explore whether predictive ability of sarcopenia differs by sex.

In conclusion, the goal of this work is to define the need for targeted interventions that may improve clinical outcomes, thus allowing the growing numbers of older patients to enjoy the benefits of transplantation.

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.atssr.2022.11.005] on http://www.annalsthoracicsurgery.org.

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Data are available on request. The data are not publicly available to protect privacy and confidentiality of research participants. Date of last institutional review board approval: May 12, 2022.

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DISCLOSURES

The authors have no conflicts of interest to disclose.

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