Skeletal Muscle Area Is an Independent Predictor for Mortality in Elderly Patients With ANCA Associated Vasculitis

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Abstract

Objectives This study aims to investigate the relationship between baseline skeletal muscle area and infections or death in elderly AAV patients with renal involvement.

Results A total of 57 AAV patients with renal involvement older than 65 years from a single center in China were enrolled. The mean age was 72.4 ± 5.6 years. The baseline BVAS score was 17.04 ± 4.40 , and eGFR was $18.64 (7.63, 33.79)$ ml/min $\times$ 1.73m². Skeletal muscle area was calculated on CT at the third lumbar vertebra level. The mean muscle area was 102.68 ± 24.41 cm². After a median follow-up of 555 days, 29 patients experienced 36 episodes of severe infections. The median time to infection was 30 (15, 63) days. Ten patients died of infection, and two of fatal bleeding. The median time to death was 59 (26, 77) days. The muscle area correlates with age and BMI. Univariate Logistic regression showed that age (OR 1.11, P=0.044), muscle area (OR 0.97, P=0.008) and hsCRP (OR 1.01, P=0.017) were predictors of severe infection. In the multivariate Cox regression, muscle area (HR 0.97, P=0.022) independently predicted one-year mortality.

Conclusion Elderly AAV patients have a high rate of infection and death during the first year following induction. Muscle area measured at L3 vertebrae level on non-contrast-enhanced CT is an independent predictor of 1-year infection and mortality.

Background

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is an important cause of rapid progressive glomerular nephritis in elder patients [1]. The peak incidence is in those aged 65–74 years [2]. Despite aggressive treatment with glucocorticoid and immunosuppressants, the mortality of AAV patients remains high in this group of patients. The first-year-mortality was 37% in patients older than 65 years, and close to 50% in those older than 80 years [3]. Infection is still the leading cause of death during the first year following induction therapy [4].

Skeletal muscle mass decrease with aging, which makes frailty a pervasive problem among elderly patients. The prevalence of sarcopenia in hospitalized patients older than 65 years is as high as 40%[5]. Patients with less muscle mass have consistently been shown with worse clinical outcomes[6]. However, quantifying skeletal muscle mass in elderly patients with a debilitating disease such as AAV is not an easy task and has not been done routinely. Anthropometric measures are prone to error [7] and the fluctuating fluid status may limit some imaging modalities[8]. Recently computed tomography (CT) scan provides a practical measurement of muscle mass in hospitalized patients. The muscle area at the third lumbar vertebra (L3) level on non-contrast-enhanced CT associates well with whole-body skeletal muscle volume [9]. This method has been used to estimate the muscle mass in patients with cancer, heart failure, chronic kidney disease (CKD), and in ICU patients, and muscle mass has been shown to correlate with mortality [10]. However, the relationship between muscle area and severe infection or death in patients with vasculitis is still not clear.

In the present study, we aim to identify the relationship between muscle area as measured at L3 vertebra level on non-contrast-enhanced CT in elderly AAV patients with clinical outcomes of infection and death.

Methods

Patient Selection

We performed a single-center retrospective study at Peking Union Medical College Hospital, a tertiary care hospital in Beijing, China. Consecutive patients aged 65 or older, diagnosed with AAV and renal involvement, with a CT scan done in PUMCH within 10 days of admission from June 2014 to June 2019, were included.

The diagnosis of AAV with renal involvement was made according to the following criteria. A positive serology for ANCA (indirect immunofluorescence, or an antigen-specific immunoassay for MPO-ANCA or PR3-ANCA), a rapidly elevated serum creatinine, or the presence of hematuria (≥ 10 red blood cells per high power field, or red cell casts) with or without proteinuria (>0.5 g/24 h). Detailed patient selection and flowchart was shown in Figure 1. The time of diagnosis was defined as the date of the first ANCA-positive assay. The study protocol was approved by the ethics committee of PUMCH. All methods were carried out in accordance with relevant guidelines and regulations.

Clinical Data Collection

Clinical and laboratory data were obtained from hospital records. Demographics and history of major comorbidities (hypertension, coronary heart disease, diabetes mellitus, and pulmonary disease) along with the anthropometric measures were collected. The Birmingham Vasculitis Activity Score (BVAS) (version 3) was calculated by scoring symptoms in 9 organ systems (general, cutaneous, mucus membranes/eyes, ear nose and throat, chest, cardiovascular, abdominal, renal, and nervous system) using the information at the time of diagnosis. Baseline laboratory data including hemoglobin level, lymphocyte count, albumin level, serum creatinine level (for dialysis patient a pre-dialysis level was recorded), high sensitivity C reactive protein, immunoglobulin G level, 24-hour urine protein, hematuria, the type and level of ANCAs were also collected. The estimated GFR (eGFR) was calculated with the CKD-EPI equation[11].

The type, initial dosage, and duration of treatments for AAV including the use of steroids, cyclophosphamide (CYC), rituximab (RTX), other immunosuppressants, and plasmapheresis were recorded. Pulse steroid was defined as an intravenous dose of 250 mg per day or more. The first immunosuppressive agent used in addition to glucocorticoids defined the induction treatment.

All records of follow-up visits were reviewed, and all infectious episodes were recorded. Serious infection was defined as an infectious episode that required intravenous antibiotics or hospitalization. Diagnoses of infections were made according to clinical, radiological manifestations, and microorganism cultures.

Muscle area calculation

Skeletal muscle area was calculated from the first CT scan which was done within 10-days of admission. Non-contrast enhanced CT images with a 5-mm slice thickness were used. Scan parameters were 120 kV and approximately 147 mAs. All scans were made in the supine position. The transverse image at the L3 level most clearly displaying both vertebral transverse processes was selected. The selected image had to include all muscle at the level without any artifacts and the image had to be able to differentiate between muscle from surrounding tissues. Total muscle cross-sectional areas (cm²) were calculated with a previously published method using NIH ImageJ software. Muscles were quantified within a Hounsfield unit (HU) range of -29 to +150 HU [12].

Two individuals (Z.X.X, and Z.G.M.Y) were trained to correctly identify and quantify the lumbar vertebrae and the muscle areas. Each observer made three calculations and the mean value from the two observers' measurements was used as each patient's muscle area. Any patient identifier was erased from the CT scan so that the observers were blinded to patients' clinical survival status.

An example of an analyzed CT slice is shown in Figure 2, in which analyzed muscles were delineated.

Follow-up and endpoints

The inception time begins at the beginning of induction therapy. The last follow-up corresponded to the patient's death, up to 1-year follow-up, or the last visit before the end of the study (June 30th, 2019).

The primary outcome was time to death due to all causes during the 1-year follow-up, and the secondary outcome was the incidence of severe infections during the 1-year follow-up.

Statistical analysis

Baseline data were presented as mean $\pm$ SD for normally distributed data or as median (IQR 25 percentile, 75 percentile) for non-normally distributed data. Characteristics between patients with or without endpoint events were compared by Student's t-test or Mann-Whitney U-test for continuous data and Chi-square test or Fisher's exact test for categorical data.

Pearson and Spearman correlation coefficients were used to analyze the relationship between parametric variables and nonparametric variables. We used univariate and multivariate logistic regression to identify predictors of severe infection and the results were presented as odds ratio (OR) [95% confidence interval (CI)]. Univariate and multivariate Cox regressions were used to analyze the risk factors of death and presented as hazard ratio [HR] [95% confidence interval (CI)]. Variables with *P* values less than 0.1 in univariate analysis and factors reported in previous researches came into the multivariate analysis. We also used the Kaplan-Meier method to delineate the survival curve. All tests were two-tailed, and a *P* values of < 0.05 were considered significant. Confidence intervals (CIs) were calculated at the 95% level. Statistical analyses were performed using SPSS (24.0) software.

Results

The study population

Fifty-seven patients (47.4% male) with the age of 72.4 ± 5.6 years at diagnosis were included. The majority of the cohort tested positive for MPO-ANCA ($n = 49$, 85.9%), and four patients (7.0%) tested positive for PR3-ANCA. Two patients had nonspecific ANCA on immunofluorescence assay. Sixteen patients underwent renal biopsy and the results all supported the diagnosis of pauci-immune glomerulonephritis. The mean baseline BVAS score was 17.04 ± 4.40 . The mean baseline eGFR was $18.64 \text{ ml/min} \times 1.73 \text{ m}^2$ (7.63, 33.79). Ten patients needed dialysis at the time of diagnosis. The baseline demographics and clinical data were summarized in Table 1.

Table 1
Baseline Clinical characteristics of AVV patients.

	Total n = 57	Patient with infection (n = 29)	Patient without infection (n = 28)	P value
Demographics and muscle parameters				
Age, years	72.38 ± 5.55	73.91 ± 6.21	70.90 ± 4.44	0.037*
Male, n (%)	27 (47.3%)	13 (44.8%)	14 (50%)	0.700
BMI, kg/m ²	23.30 ± 3.86	23.84 ± 4.70	22.76 ± 2.77	0.298
Muscle area, cm ²	102.68 ± 24.41	94.55 ± 22.80	111.09 ± 23.49	0.009**
Comorbidities, n(%)				
Diabetes	14 (24.6%)	6 (20.7%)	8 (28.6%)	0.490
Pulmonary diseases [#]	17 (29.8%)	8 (27.6%)	9 (32.1%)	0.707
Hypertension	33 (57.9%)	9 (75.0%)	24 (53.3%)	0.177
Vasculitis Disease Activity				
BVAS	17 ± 4	17 ± 4	17 ± 5	0.440
Pulmonary vasculitis	35 (61.4%)	18 (62.1%)	17 (60.7%)	0.916
Baseline Lab results				
Lymphocyte, ×10 ⁹ /L	1.14 ± 0.48	1.07 ± 0.45	1.20 ± 0.51	0.357
Hemoglobin, g/L	95.4 ± 16.30	95.6 ± 16.1	95.3 ± 16.8	0.945
Scr, μmol/L	261.0 (149.5, 520.5)	310.0 (160.0, 526.5)	237.5 (134.3, 490.8)	0.793
eGFR, ml/min × 1.73 m ²	18.64 (8.31, 3.59)	12.49 (7.35, 31.82)	19.30 (7.87, 44.01)	0.221
Abbreviation: [#] COPD, chronic obstructive pulmonary disease and other pulmonary disease; BVAS, Birmingham Vasculitis Activity Score (version 3); BMI, Body Mass Index; Scr, Serum Creatinine; eGFR: Estimated Glomerular Filtration Rate; IgG, Immunoglobulin G; hsCRP, high-sensitivity C-reactive protein; MPO ANCA, Myeloperoxidase-antineutrophil Cytoplasmic Antibodies; GC, glucocorticoid; PE, Plasmapheresis.				
±: All ANCA titers were measured by antigen-specific immunoassay, 200 RU/mL is the upper limit of ANCA titer.				
* P value < 0.05				
** P value < 0.01				

	Total n = 57	Patient with infection (n = 29)	Patient without infection (n = 28)	P value
Albumin, g/L	33.1 ± 4.7	32.0 ± 4.9	34.7 ± 4.3	0.05*
Ig G, g/L	13.26 (10.74, 18.31)	13.26 (10.73, 15.50)	14.07 (10.75, 19.02)	0.269
hsCRP, mg/L	23.22 (2.11, 99.39)	46.55 (12.70, 134.40)	5.61 (1.57, 68.49)	0.018*
ANCA titer [±] , RU/mL	159.0 (87.0, 200.0)	159.0 (89.0, 200.0)	159.0 (86.0, 200.0)	0.822
Treatment				
Pulse GC, n (%)	21 (36.8%)	10 (34.5%)	11 (39.3%)	0.707
PE, n (%)	15 (26.3%)	9 (31.0%)	6 (21.4%)	0.410
Abbreviation: # COPD, chronic obstructive pulmonary disease and other pulmonary disease; BVAS, Birmingham Vasculitis Activity Score (version 3); BMI, Body Mass Index; Scr, Serum Creatinine; eGFR: Estimated Glomerular Filtration Rate; IgG, Immunoglobulin G; hsCRP, high-sensitivity C-reactive protein; MPO ANCA, Myeloperoxidase-antineutrophil Cytoplasmic Antibodies; GC, glucocorticoid; PE, Plasmapheresis.				
±: All ANCA titers were measured by antigen-specific immunoassay, 200 RU/mL is the upper limit of ANCA titer.				
* P value < 0.05				
** P value < 0.01				

Muscle Area

The muscle area at the third lumbar vertebrae level was $102.68 \pm 24.41 \text{ cm}^2$. Muscle area correlated with age ($r = -0.40$, $P = 0.002$) and BMI ($r = 0.39$, $P = 0.003$), while age and BMI were also correlated ($r = -0.34$, $P = 0.01$). The difference in muscle areas between males and females was significant with a mean muscle

area of $114.16 \pm 23.63 \text{ cm}^2$ for males and $92.34 \pm 20.40 \text{ cm}^2$ for females ($P < 0.0001$). There was no significant correlation between muscle area and other baseline characteristics, including whether having diabetes or pulmonary comorbidities, baseline serum albumin, creatinine, hemoglobin, and lymphocyte level. There was also no correlation between muscle area and dialysis status, whether receiving plasma apheresis or glucocorticoid pulse therapy (Supplementary table).

Treatments

All patients received glucocorticoid therapy. The regimen usually consists of 40 to $80 \text{ mg} \cdot \text{d}^{-1}$ intravenous methylprednisolone for a week and subsequent oral methylprednisolone or prednisone at an initial dosage of $0.80 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{d}^{-1}$ with tapering. Most patient received cyclophosphamide (CYC) for induction therapy ($n = 52, 91.1\%$). CYC was administered either by intravenous infusion of 0.4 to 0.6 g every week or an oral dose of 0.05 g to $0.1 \text{ g} \cdot \text{d}^{-1}$. Two patients were treated with Rituximab given as 500 mg and 1000 mg once.

Twenty-one patients (36.8%) with rapidly progressive renal failure and/or severe vasculitis involving other systems received three intravenous pulses of methylprednisolone ($0.25\text{--}1 \text{ g/day}$) before the induction therapy.

Fifteen patients (26.3%) with severe disease underwent plasma exchanges. Maintenance therapy was with oral cyclophosphamide in most patients (96.6%) during follow-up.

Risk Factors For Infection And Death

After a median follow-up of 555.0 ($125.5, 970.5$) days, twenty-nine patients experienced thirty-six episodes of serious infections, and ten infections resulted in ICU admission. The median time to the first infection was 26.5 (IQR: $10.5, 60.0$) days from induction therapy. Pneumonia ($n = 29$) and CMV viremia ($n = 7$) were most common infections.

We split the cohort into patients with and without severe infections and compared the demographic characteristics, muscle areas, comorbidities, disease severity, and baseline laboratory results between groups (Results shown in Table 1). Patients with infections were older with a mean age of 73.9 years compared to a mean of 70.9 years in those without infections ($P < 0.05$) and have a lower muscle area ($94.55 \pm 22.80 \text{ cm}^2$ verse $111.09 \pm 23.49 \text{ cm}^2$, $P < 0.05$). However, the BMIs between these two groups were not significantly different. Other parameters compared shown that patients with severe infections had higher hsCRP ($P < 0.05$) level at baseline and a trend toward lower albumin levels ($P = 0.05$).

In univariable logistic regression analysis, only increased age (OR = 1.11 , CI 1.00 to 1.23 , $P = 0.04$) decreased skeletal muscle area (OR = 0.98 , CI 0.94 to 0.99 , $P = 0.008$) and increased baseline hsCRP level (OR = 1.01 , CI 1.00 to 1.02 , $P = 0.017$) predicted serious infections during one year follow up. The other

non-significant variables were BMI, BVAS score, eGFR at the onset of disease, diabetes, pulmonary comorbidities, vasculitis affecting the respiratory system, glucocorticoid pulse therapy, and baseline nutritional markers. Multiple logistic regression models didn't find a significant relationship between muscle area, BVAS, baseline hsCRP, nor eGFR with severe infection (see Table 2).

Table 2
Univariate and multiple Logistic regression analysis of risk factors for serious infections

Variable	Unadjusted OR [95%CI]	P value	Adjusted§ OR [95% CI]	P value
Age	1.11 [1.00 to 1.23]	0.044*		
Male	0.70 [0.25 to 1.99]	0.503		
Muscle area	0.97 [0.94 to 0.99]	0.008**	0.98 [0.97 to 1.01]	0.169
BMI	1.05 [0.91 to 1.21]	0.480		
Diabetes	0.72 [0.21 to 2.42]	0.590		
Pulmonary comorbidities	0.63 [0.20 to 1.99]	0.633		
BVAS	1.05 [0.93 to 1.19]	0.397	1.04 [0.95 to 1.14]	0.439
Pulmonary Vasculitis	0.94 [0.32 to 2.74]	0.916		
Dialysis at baseline	0.64 [0.16 to 2.56]	0.527		
ANCA titer	1.00 [0.99 to 1.01]	0.954		
eGFR	0.98 [0.96 to 1.02]	0.306	0.98 [0.96 to 1.00]	0.089
Lymphocyte	0.71 [0.23 to 2.19]	0.555		
Immunoglobulin G level	0.96 [0.86 to 1.08]	0.511		
Albumin	0.89 [0.79 to 1.01]	0.899		
Hemoglobin	1.01 [0.97 to 1.04]	0.722		
hsCRP	1.01 [1.00 to 1.02]	0.017*	1.01 [0.99 to 1.01]	0.099
Plasmapheresis	1.82 [0.55 to 6.01]	0.329		
Methylprednisolone Pulse	0.91 [0.31 to 2.67]	0.862		
Abbreviations: BMI body mass index, BVAS Birmingham Vasculitis Activity Score (version 3), ANCA Antineutrophil Cytoplasmic Antibodies, eGFR estimated glomerular filtration rate, hsCRP high sensitivity C-Reactive Protein				
§ Variables included in multiple Logistic regression model: muscle area, BVAS, eGFR and hsCRP level				
* P value < 0.05				

A total of twelve death occurred in our cohort, with a mortality rate of 21.1% for the first year. Ten patients died of infection, one died of gastrointestinal bleeding and one died of a ruptured aortic aneurysm. The median time to death was 59 (IQR 26.3, 75.0) days from diagnosis. The Kaplan-Meier survival plot was shown in Fig. 3. Except for the muscle area ($P = 0.008$), there are no significant differences in the clinical markers between the dead and survived patients. Patients who died within the first year had a trend toward older age ($P = 0.051$) and higher baseline hsCRP ($P = 0.075$).

In univariable Cox regression, age (HR = 1.14, CI 1.03 to 1.26, $P = 0.014$), skeletal muscle area (HR = 0.96, CI 0.94 to 0.99, $P = 0.016$), and undergoing plasmapheresis (HR = 3.43, CI 1.10 to 10.65, $P = 0.03$) significantly predicted 1-year mortality. In multiple Cox regression model because that muscle area correlates with age (see supplementary table) and our end events are limited we constructed the model with muscle area, BVAS and the status of plasmapheresis. Multiple Cox regression models indicated that muscle area (HR = 0.96, CI 0.94 to 0.98, $P = 0.02$) was an independent predictor of death, when adjusted by BVAS, and whether undergoing plasmapheresis (See Table 3).

Table 3
Predictors of 1 year mortality in univariable and multiple Cox regression analysis

Variable	Unadjusted HR [95%CI]	P value	Adjusted§ HR [95% CI]	P value
Age	1.14 [1.03 to 1.26]	0.014*		
Male	0.71 [0.23 to 2.23]	0.556		
Muscle area	0.96 [0.94 to 0.99]	0.016*	0.96 [0.94 to 0.98]	0.02*
BMI	0.97 [0.83 to 1.15]	0.751		
Diabetes	1.49 [0.45 to 4.95]	0.515		
Pulmonary comorbidities	0.21 [0.03 to 1.59]	0.130		
BVAS	1.07 [0.94 to 1.23]	0.309	1.12 [0.97 to 1.29]	0.11
Pulmonary Vasculitis	1.00 [0.32 to 3.17]	0.990		
Dialysis at baseline	0.42 [0.06 to 3.27]	0.410		
ANCA titer	1.00 [0.99 to 1.01]	0.590		
eGFR	0.99 [0.95 to 1.03]	0.639		
Lymphocyte	0.71 [0.19 to 2.76]	0.628		
IgG level	0.99 [0.87 to 1.13]	0.931		
Albumin	0.98 [0.89 to 1.11]	0.833		
Hemoglobin	0.99 [0.95 to 1.02]	0.444		
hsCRP	1.06 [0.99 to 1.01]	0.140		
Plasmapheresis	3.43 [1.10 to 10.65]	0.03*	2.87 [0.89 to 9.23]	0.077
Methylprednisolone Pulse	0.83 [0.25 to 2.75]	0.758		
Abbreviations: BMI body mass index, BVAS Birmingham Vasculitis Activity Score (version 3), ANCA Antineutrophil Cytoplasmic Antibodies, eGFR estimated glomerular filtration rate, hsCRP high sensitivity C-Reactive Protein				
§ Variables included in multiple Cox regression model: muscle area, BVAS score and whether receiving plasmapheresis treatment				
* P value < 0.05				
** P value < 0.01				

Discussion

In this retrospective cohort study, we reported the clinical characteristics, risk factors of infections, and prognosis in elderly patients with AAV. To our knowledge, this is the first study to examine the muscle area in elderly AAV patients and showed that muscle area is an independent predictor for both infection and death.

Our cohort consists of elderly patients with a fairly high BVAS score at baseline. In our study, the 1-year mortality rate was high at 21.1% which was comparable with a survival rate of 72–88% in previous cohorts [3, 13, 14]. The rate of serious infection was also high with half the patients experiencing at least one episode of serious infection during 1 year follow up which was higher than previously reported by Yang et al. in another Chinese cohort [15]. This may be explained by the older age and higher baseline BVAS score of our cohort. Most deaths were due to serious infections. Both death and infection rates were the highest during the first 6 months starting from induction therapy and was in line with previous studies [16].

In the present study, we focused on the impact muscle mass at baseline have on infections and prognosis. Many factors relating to patient, disease severity, or treatment strategy had been identified as risk factors for infections and mortality in previous studies of AAV patients. In most studies, age has consistently been identified as a strong predictor of worse outcomes [3, 13, 15]. The human body undergoes many changes with aging. An important change is the loss of muscle mass and muscle function which is predictive of adverse health outcomes, such as longer hospital admission, poorer quality of life, and mortality [17]. When superimposed on other chronic medical conditions, such as cancer, heart failure, chronic obstructive pulmonary disease or chronic kidney disease, elderly patients with lower muscle mass have worse outcomes. For acutely ill patients, higher muscle mass on CT scan was also associated with better survival [10].

But to date, there have been no studies focusing on quantifying muscle mass in AAV patients nor the relationship between muscle reserve and clinically important outcomes. One reason for this may be a lack of an appropriate evaluating method for muscle mass in critically ill patients with excessive water load. This is the first study to use muscle area at L3 on non-contrast CT to quantify muscle. This method has been shown to have a good correlation with modalities such as dual-energy X-ray absorptiometry (DXA) [9] while providing more details on specific muscles, adipose tissues, and organs. The results of the present study suggest that

baseline skeletal muscle area on CT scan correlates with BMI but was a more powerful prognostic marker. This showed that using CT done routinely can be a practical way to obtain muscle areas and can provides additional prognostic information to complement traditional risk factors.

The results of our study showed that muscle area is related to infection and is an independent predictor for death. Muscle reserve is important in fighting infections. Studies have shown that skeletal muscle mass is a predictor of mortality in ICU patients and patients with aspiration pneumonia [18]. A decrease in muscle mass and strength especially in swallowing related muscles may affect the prognosis of pneumonia in older patients [19]. The majority of infections in our study were pneumonia and the most

deaths were due to infections. It may be postulated that muscle area affects the prognosis of infections through influencing older patients' ability to clear pathogens and recover from infections. Moreover, the Skeletal muscle has been shown to be a major immunoregulatory organ and produces a range of soluble factors, which have anti-inflammatory and immunoprotective effects[20]. These myokines may help regulate the body's defense against infections especially in autoinflammatory diseases. The underlying mechanisms linking low muscle area to worse outcome especially in systemic inflammatory diseases need to be addressed by more basic and clinical researches.

The cut-off values for muscle area on CT scan have been proposed for various diseased populations which were often based on optimal stratification for survival [21]. Due to a lack of data on patients with glomerulonephritis and rheumatic diseases. It was not possible to compare our results with a similar population. There haven't been any population-wide studies to establish a distribution of muscle area to allow for the calculation of Z score. However, values have been reported for a healthy Caucasian population of 20 to 82 years of age and the lower five percentile was 134.0 cm² for males and 89.2 cm² for females [22]. Fifty-six percent (female n = 12, male n = 20) of our cohort had low skeletal muscle at baseline according to this cut off value. The survival curve of patients with high and low muscle area separates though not reaching a statistically significant level by log-rank test (P = 0.19) as shown in supplement Fig. 1. The result indicates a cross of these survival curves with the patient of less muscle having a worse survival after the first 2 months. This may indicate that baseline skeletal muscle is a better marker of muscle reserve and have more predictive values for survival after the acute phase of the disease. Larger sample size and longer follow-up are needed to verify this. However, we have to be cautious in interpreting this cut-off value because it is made for the Caucasian population and may not reflect the muscle area changes in the Asian population.

Considering the high infection rate and mortality rate, it is prudent to weight the risk of infection when deciding on treatment strategies. Recent findings from a randomized trial show that a dose reduced glucocorticoid was noninferior as maintenance therapy[23]. Therefore, identifying risk factors of infections and death to personalize the intensity of treatment and to identify patients who might benefit more from modified treatment regimens is of great clinical importance. Skeletal muscle area may be valuable in this sense. We can stratify patients by this parameter and adapt the intensity of treatment accordingly.

There are limitations to this study. First, this was a retrospective study from a single center therefore may not be representative of all vasculitis patients. Second, due to the sample size, there were not enough endpoint events to accommodate the analysis of more predictors and the impact muscle area may have on long term survival. Third, this study only focused on muscle area but not muscle quality or function. The evolving definition of sarcopenia relies more on the functional decline of muscle as opposed to a mere change in muscle mass. More investigations are needed in the area of muscle quantity and quality in patients with systemic inflammatory diseases.

Conclusions

Elderly patients with AAV have a high rate of infection and death during the first year following immunosuppressive treatment. Muscle area as measured at the L3 vertebrae level on non-contrast-enhanced CT is an independent predictor of 1-year mortality in elderly AAV patients.

List Of Abbreviations

ANCA: Anti-neutrophil cytoplasmic antibody

AAV: Anti-neutrophil cytoplasmic antibody-associated vasculitis

CKD: chronic kidney disease

BVAS: Birmingham Vasculitis Activity Score

CYC: cyclophosphamide

DXA: dual-energy X-ray absorptiometry

Declarations

Ethics approval and consent to participate: The research is approved by the ethics committee of Peking Union Medical College Hospital. All methods were carried out in accordance with relevant guidelines and regulations and informed consent for collecting clinical and laboratory information were obtained from all subjects or their legally authorized representatives.

Consent for publication: Not applicable.

Availability of data and materials: The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors have no conflicts of interest to declare.

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Authors' contributions

XX. Z.; Designed and performed data collection and analysis of this study and drafted the manuscript.
P.X.; Co-Designed the study. JY.L. and GMY.Z.; Collected clinical and CT data.

H.S.; Supervised CT data collection. LM.C.; Approved of the study design and manuscript.

XM.L. and Q.Y.; Supervised the research.

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References

1. Zhu P, Zhou FD, Zhao MH: **The renal histopathology spectrum of elderly patients with kidney diseases: a study of 430 patients in a single Chinese center.** *Medicine (Baltimore)* 2014, **93**:e226.
2. Watts RA, Lane SE, Bentham G, Scott DG: **Epidemiology of systemic vasculitis: a ten-year study in the United Kingdom.** *Arthritis Rheum* 2000, **43**:414–419.
3. Bomback AS, Appel GB, Radhakrishnan J, Shirazian S, Herlitz LC, Stokes B, D'Agati VD, Markowitz GS: **ANCA-associated glomerulonephritis in the very elderly.** *Kidney Int* 2011, **79**:757–764.
4. Flossmann O, Berden A, de Groot K, Hagen C, Harper L, Heijl C, Hoggund P, Jayne D, Luqmani R, Mahr A, et al: **Long-term patient survival in ANCA-associated vasculitis.** *Ann Rheum Dis* 2011, **70**:488–494.
5. Sousa AS, Guerra RS, Fonseca I, Pichel F, Amaral TF: **Sarcopenia among hospitalized patients - A cross-sectional study.** *Clin Nutr* 2015, **34**:1239–1244.
6. Landi F, Camprubi-Robles M, Bear DE, Cederholm T, Malafarina V, Welch AA, Cruz-Jentoft AJ: **Muscle loss: The new malnutrition challenge in clinical practice.** *Clin Nutr* 2019, **38**:2113–2120.
7. Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, Martin FC, Michel JP, Rolland Y, Schneider SM, et al: **Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People.** *Age Ageing* 2010, **39**:412–423.
8. Buckinx F, Landi F, Cesari M, Fielding RA, Visser M, Engelke K, Maggi S, Dennison E, Al-Daghri NM, Allepaerts S, et al: **Pitfalls in the measurement of muscle mass: a need for a reference standard.** *J Cachexia Sarcopenia Muscle* 2018, **9**:269–278.
9. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE: **A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care.** *Appl Physiol Nutr Metab* 2008, **33**:997–1006.
10. Prado CM, Purcell SA, Alish C, Pereira SL, Deutz NE, Heyland DK, Goodpaster BH, Tappenden KA, Heymsfield SB: **Implications of low muscle mass across the continuum of care: a narrative review.** *Ann Med* 2018, **50**:675–693.
11. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al: **A new equation to estimate glomerular filtration rate.** *Ann Intern Med* 2009, **150**:604–612.

12. Gomez-Perez SL, Haus JM, Sheean P, Patel B, Mar W, Chaudhry V, McKeever L, Braunschweig C: **Measuring Abdominal Circumference and Skeletal Muscle From a Single Cross-Sectional Computed Tomography Image: A Step-by-Step Guide for Clinicians Using National Institutes of Health ImageJ.** *JPEN J Parenter Enteral Nutr* 2016, **40**:308–318.
13. Titeca-Beauport D, Francois A, Lobbedez T, Guerrot D, Launay D, Vrigneaud L, Daroux M, Lebas C, Bienvenu B, Hachulla E, et al: **Early predictors of one-year mortality in patients over 65 presenting with ANCA-associated renal vasculitis: a retrospective, multicentre study.** *BMC Nephrol* 2018, **19**:317.
14. Weiner M, Goh SM, Mohammad AJ, Hruskova Z, Tanna A, Bruchfeld A, Selga D, Chocova Z, Westman K, Eriksson P, et al: **Outcome and treatment of elderly patients with ANCA-associated vasculitis.** *Clin J Am Soc Nephrol* 2015, **10**:1128–1135.
15. Yang L, Xie H, Liu Z, Chen Y, Wang J, Zhang H, Ge Y, Hu W: **Risk factors for infectious complications of ANCA-associated vasculitis: a cohort study.** *BMC Nephrol* 2018, **19**:138.
16. McGregor JG, Negrete-Lopez R, Poulton CJ, Kidd JM, Katsanos SL, Goetz L, Hu Y, Nachman PH, Falk RJ, Hogan SL: **Adverse events and infectious burden, microbes and temporal outline from immunosuppressive therapy in antineutrophil cytoplasmic antibody-associated vasculitis with native renal function.** *Nephrol Dial Transplant* 2015, **30 Suppl 1**:i171-181.
17. Cruz-Jentoft AJ, Sayer AA: **Sarcopenia.** *Lancet* 2019, **393**:2636–2646.
18. Maeda K, Akagi J: **Muscle Mass Loss Is a Potential Predictor of 90-Day Mortality in Older Adults with Aspiration Pneumonia.** *J Am Geriatr Soc* 2017, **65**:e18-e22.
19. Okazaki T, Ebihara S, Mori T, Izumi S, Ebihara T: **Association between sarcopenia and pneumonia in older people.** *Geriatr Gerontol Int* 2020, **20**:7–13.
20. Pedersen BK, Febbraio MA: **Muscles, exercise and obesity: skeletal muscle as a secretory organ.** *Nat Rev Endocrinol* 2012, **8**:457–465.
21. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, Baracos VE: **Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study.** *Lancet Oncol* 2008, **9**:629–635.
22. van der Werf A, Langius JAE, de van der Schueren MAE, Nurmohamed SA, van der Pant K, Blauwhoff-Buskermolen S, Wierdsma NJ: **Percentiles for skeletal muscle index, area and radiation attenuation based on computed tomography imaging in a healthy Caucasian population.** *Eur J Clin Nutr* 2018, **72**:288–296.
23. Walsh M, Merkel PA, Peh CA, Szpirt WM, Puechal X, Fujimoto S, Hawley CM, Khalidi N, Flossmann O, Wald R, et al: **Plasma Exchange and Glucocorticoids in Severe ANCA-Associated Vasculitis.** *N Engl J Med* 2020, **382**:622–631.

Figures

Figure 1

Study Flowchart Showing the Selection of Eligible Patients

Figure 2

Steps of Measuring Muscle Area on Computed Tomography Scan a. The transverse image at the third lumbar vertebra level most clearly displaying both vertebral transverse processes was selected b. Outer perimeter of abdominal muscle is selected at threshold of -250 HU (Hounsfield unit) c. Changing the threshold to -29 to +150 HU to outline abdominal muscle and organs d. Inner perimeter of abdominal muscle is selected and the muscle area is calculated as the area inside threshold between outer and inner perimeters

Figure 3

Kaplan-Meier Curve of One Year Survival

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