January 2022

Musculoskeletal Outcomes Among Older Adults Following Hospitalization For Covid-19: A Pilot Study

Clara Ming Hei Wong
claramhwong@gmail.com

Musculoskeletal Outcomes among Older Adults following Hospitalization for COVID-19: A Pilot Study

Clara Wong

May 2022

Master of Public Health, Chronic Disease Epidemiology

Primary Mentor: Dr. Evelyn Hsieh

Secondary Mentor: Dr. Alexandra Hajduk

ABSTRACT

Background

Older individuals are at high risk for musculoskeletal impairment following hospitalization due to decreased neuromuscular function and bone mineral density (BMD) arising from illness itself, and external factors such as immobilization and changes in nutritional status. To address the knowledge gap regarding the longitudinal impact of COVID-19 on musculoskeletal outcomes, this thesis aimed to study the relationship between COVID-19 severity and physical functional, incidence of falls and fractures in older adults. Secondarily, in a subset of patients we examined the relationship between COVID-19 severity and osteoporosis- and sarcopenia-related measures.

Methods

This study analyzed data from the VALIANT study and VALIANT MSK Sub-study. The VALIANT study included individuals who were over 60 years old and were hospitalized due to COVID-19 in the Yale New Haven Hospital System (YNHHS) from July 2020-July 2021. Virtual interviews were performed at the time of hospitalization, and 1, 3, and 6-months post-hospitalization and measured a range of sociodemographic, clinical and general health-related characteristics, physical function domains relevant to musculoskeletal health and mobility, and incident falls and fractures. Patients who consented to be re-contacted were invited to participate in the VALIANT MSK Sub-study and presented for an in-patient visit which included a survey, serum sample collection, a dual-energy x-ray absorptiometry test, the short physical performance battery and grip strength assessment. Descriptive statistics were used to evaluate primary and secondary outcomes, stratified by COVID-19 severity as defined by SOFA score, inpatient level

of care, and inflammatory markers (high-sensitivity C-reactive protein and interleukin-6) at baseline and 6 months.

Results

Among 341 participants enrolled in the VALIANT parent study, the median age was 70.0 years (IQR 12) , with 49% female, and 72.5% White individuals while among the 62 participants in the VALIANT MSK Sub-Study, the median age was 67.0 years (IQR 10), with 49% females, and 64.2% White individuals. In the VALIANT cohort, when physical function status at 6 months was stratified by COVID-19 severity, multiple domains emerged as being significantly different. A higher proportion of patients who had a higher SOFA score (≥3) reported being unable to independently bathe (9.2% vs 2.4%, p<0.001), get in and out of a chair (5.8% vs 1.7%, p=0.017), use the toilet (3.8% vs 0.3%, p=0.006), shop (20.1% vs 11.6%, p=0.011), or walk flight of stairs (15.4% vs 8.2%, p=0.016). A significantly higher proportion of VALIANT participants with high inpatient hsCRP levels during hospitalization (≥97 mg/L) were unable to independently do housework (31.7% vs 21.1%, p= 0.013), shop (33.1% vs 19.7%, p=0.043), walk a quarter mile (28.5% vs 24.2%, p=0.009) and walk flights of stairs (37.0% vs 15.9%. p= 0.0114). In the VALIANT MSK Sub-study, a similar general trend was observed with a higher proportion of patients with SOFA scores ≥3 or hsCRP≥97 mg/L reporting that they were unable to independently perform certain physical function tasks.

At baseline, 101/339 (29.8%) VALIANT participants reported a fall in the past year before COVID-19 compared with 15/62 (24.2%) of VALIANT MSK Sub-Study participants. At 6 months, 24.3% of VALIANT participants reported having an incident fall since COVID infection compared with 19.4% of VALIANT MSK participants. When participants of both groups were categorized based on COVID severity no significant differences were seen in the

proportion of new falls in the 6 months. Seven participants overall reported having a fracture following COVID-19 hospitalization.

Among the VALIANT MSK participants, 3 participants (5.2%) had osteoporosis and 22 participants (37.9%) had osteopenia. Mean femoral neck (FN) BMD was lower among patients with hsCRP ≥97 (0.79 vs 0.21, $p<0.001$). Five participants (8.1%) met criteria for probable sarcopenia. No participants met criteria for sarcopenia or severe sarcopenia. When examining individual sarcopenia assessment components, there was no statistically significant difference when categorized based on COVID severity.

Conclusions

Our study shows that a greater proportion of older adults presenting with severe COVID-19 as defined by SOFA, inpatient level of care, or high hsCRP and high IL-6 had worse physical functional status and lower FN BMD at six months. Further multivariable analyses should explore whether these associations remain when adjusted for key musculoskeletal health-related covariates, and how baseline status is associated with outcomes at 6 months. Attention to the rehabilitation needs of patients following COVID-19 hospitalization is important, as well as consideration for osteoporosis and sarcopenia screening for those with more severe disease.

ACKNOWLEDGEMENTS

Musculoskeletal sub-study team:

1. Dr. Evelyn Hsieh, MD, PhD
   Assistant Professor of Medicine, Section of Rheumatology, Allergy and Immunology, Yale School of Medicine

2. Dr. Diego Cabrera, MD
   Research Affiliate, Section of Rheumatology, Allergy and Immunology, Yale School of Medicine

VALIANT team

1. Andrew Cohen, MD, DPhill
   Assistant Professor of Internal Medicine (Geriatrics), Yale School of Medicine

2. Lauren Ferrante, MD, MHS
   Assistant Professor of Medicine (Pulmonary), Yale School of Medicine

3. Alexandra Hajduk, PhD, MPH
   Associate Research Scientist, Yale School of Medicine

4. Mary Geda BSN, MSN, RN
   Associate Director, Program on Aging, Yale School of Medicine

5. Gail McAvay, PhD
   Research Scientist in Medicine (Geriatrics), Yale School of Medicine

6. Sumon Chattodpadhyay
   Programmer Analyst

7. Sandra Capelli
   Research Associate, Yale School of Medicine

8. Kizzy Hernandez-Bigos
   Research Associate, Yale School of Medicine

9. Amy Shelton
   Research Associate Internal Medicine (Geriatrics); Navigator, Program on Aging, Yale School of Medicine

10. Andrea Benjamin

Clinical Research Nurse, Internal Medicine (Geriatric), Yale School of Medicine

HRU/CSRU Yale Bone Center team

1. Karl Insogna, MD, FACP
   Center Director

2. Lynda Knaggs, RN
   HRU manager – Yale Center for Clinical Investigation (YCCI)

3. Carmen Galarza
   HRU coordinator – Yale Center for Clinical Investigation (YCCI)

4. *Mikhail Smolgovsky, MS*
   Research Associate – Yale Center for Clinical Investigation (YCCI)

5. Gina Petrosino
   DXA technician, Clinical Assistant Internal Medicine Endocrinology

6. *Lorraine Cole*
   DXA technician, Clinical Assistant Internal Medicine Endocrinology

MML team

1. Christine Simpson
   Research Associate Internal Medicine Endocrinology

2. Anna Maria Santoro, MS
   Research Assistant

TABLE OF CONTENTS

List of Tables

INTRODUCTION

Older individuals are at high risk for fracture in the months following hospitalization due to decreased neuromuscular function and bone mineral density (BMD) arising from illness, immobilization, and changes in nutritional status.[1] This risk may be compounded among patients hospitalized with severe or critical coronavirus disease 2019 (COVID-19), which is characterized by hyperinflammation.[2] Concurrently, from the macroscopic perspective of functional recovery, inpatient and post-discharge rehabilitation services are relatively restricted for patients with COVID-19, and access to caregivers at home and healthcare providers may be limited. All these factors create a perfect storm for prolonged disability, and increased falls and fractures among older patients hospitalized with COVID-19.

Osteoporosis is characterized by low bone mass and microarchitectural deterioration of bone tissue.[3] Osteoporosis is a risk factor for fracture and is the most common metabolic bone disorder.[4] It is a major public health issue as there are typically no symptoms in the early stages of bone loss; with the first visible sign of the disease being a fracture. [4]Bone tissue is constantly lost by resorption and rebuilt by formation.[4] Bone loss occurs when the rate of resorption is higher than rate of formation.[3] As people age the creation of new bone tissue cannot keep up with the loss of old bone tissue; bone mass is lost faster than it is created.[3]Around 10 million individuals over age 50 in the US has osteoporosis of the hip and 33.6 million individuals over age 50 are at risk of osteoporosis with low bone density known as osteopenia.[5]As the U.S. population ages, the prevalence of osteoporosis and low bone mass is expected to increase. [5]

Sarcopenia is also a major cause of functional decline and mortality in older adults.[6] Decline of functional ability with age is a direct results of muscle weakness, loss of muscle force due to decline skeletal muscle mass.[6] In older adults aged 65-70, the prevalence of sarcopenia may be as high as 24%.[6] Older adults with sarcopenia on admission are 5 times more likely to have higher hospital costs than older adults without sarcopenia.[7] Sarcopenia increases risk of falls and fractures and is also associated with a wide range of comorbidities including cardiac disease, respiratory disease, and cognitive impairment, all of which leads to mobility disorder and loss of independence contributing towards lower quality of life.[8]

There has been a growing interest in common pathways of sarcopenia and osteoporosis such as hormonal pathways, immune inflammatory pathways and cross talk between skeletal muscles and bone cells through molecule interactions. In osteoimmunology studies, it has been suggested that systemic inflammation is linked to bone loss through proinflammatory cytokines such as interleukin 6 which can stimulate bone resorption[10] Interleukin 6 is also suggested to play a crucial role in the hyperinflammatory state characterized in patients with severe COVID-19.[11] To address this gap in knowledge of COVID on musculoskeletal outcomes, this thesis aimed to study the relationship between COVID severity and musculoskeletal health by functional status and incidence of falls and fractures in a cohort of patients over 60 years of age who were admitted to the Yale New Haven Hospital System (YNNHS) with COVID-19, and also identify sociodemographic, clinical and COVID-19-related risk factors that may impact this relationship. We hypothesized that more severe COVID-19 infection will be associated with worse musculoskeletal outcomes including greater likelihood of decline in functional status, and higher incidence of falls and fractures at 6 months.

METHODS

Study Design and Ethics Approvals

We performed a prospective longitudinal study of older adults hospitalized with COVID-19 at Yale New Haven Health System (YNHHS). This thesis utilized two data sets: the VALIANT (COVID-19 in Older Adults: A Longitudinal Assessment) study and VALIANT MSK (COVID-19 in Older Adults: A Longitudinal Assessment Musculoskeletal outcomes**)** sub-study. The research protocol for the parent study and sub-study were reviewed and approved by Yale University Institutional Review Board (IRES IRB). Due to the COVID-19 pandemic, a safety work plan was also submitted and approved by Yale University Environmental Health & Safety through the Human Research Study office. Verbal consent (VALIANT) and written consent (Sub-study) were obtained from patients prior to any interviews or in-person visit procedures were conducted.

Sample

VALIANT study

Recruited patients for the VALIANT study (HIC #2000028175) included individuals who are over 60 years old and were hospitalized due to COVID-19 and admitted into the YNHHS from July 2020-July 2021. Details of the parent study and baseline participant characteristics have recently been submitted for publication. In brief, patients were contacted by research personnel via YNHHS Insight video monitors. Patients completed a baseline interview, 1-month, 3-month and 6-month interviews. Interviews were conducted remotely (by phone or by video) and participants answered questions regarding their sociodemographic characteristics, baseline

health, COVID-related factors, and measures related to functional status and healthcare received since hospitalization for COVID-19.

Inclusion criteria: age >= 60 years old, hospitalized or recently hospitalized with COVID at YNHHS, have not opted out of research

Exclusion criteria: unable to provide informed consent and no proxy available, requested research opt-out, planned discharge to hospice/advance directive of "comfort measures only", long term residents of extended-care facilities, deceased, advanced dementia

VALIANT MSK sub-study

A subgroup of participants from VALIANT were invited to participate in a follow up study focused on musculoskeletal outcomes (HIC #2000030426) at 6-9 months post-infection. Patients were recruited from July 2020 to July 2021. Willing participants had an in-person hospital visit at 6-9months post-infection. This in-person study visit included a blood draw, a brief self-administered risk factor survey, DXA scan (bone mineral density and body composition assessments) and physical assessments (SPPB and grip strength).

Inclusion criteria: completed VALIANT study 6-month interview, agree to be contacted for related studies, primary residence in Connecticut

Exclusion criteria: opt out of being contacted for related studies, unable to physically come to the study site or perform study activities (e.g., wheelchair bound)

Measures

The primary study aim was to evaluate the association between baseline severity of COVID-19 with musculoskeletal outcomes at 6 months, including physical function (including decline from baseline), functional expectations at 6 months, and incident falls and fracture in patients enrolled in the VALIANT study. In a subset of participants enrolled in the VALIANT MSK sub-study, we explored the association of baseline severity of COVID-19 with secondary exploratory outcomes including bone mineral density (BMD)/osteoporosis and sarcopenia at 6-9 months post-hospitalization.

Exposures

Data regarding exposures was collected through a survey administered by study staff, and through medical chart review. COVID severity during hospitalization was evaluated using three approaches: highest level of care (floors vs. stepdown unit/intensive care unit), Sequential Organ Failure Assessment score (SOFA scores, <3 vs. ≥ 3) evaluating the six major organ function, and levels of inflammatory markers including high sensitivity C-reactive protein (65.5 vs. 97) and IL-6 (37 vs. 80) if available.

Data was also collected regarding baseline sociodemographic characteristics (age, sex, race, place/type of residence), baseline clinical characteristics (body mass index, smoking/alcohol use status, comorbidities and medications, general baseline health status, hearing/vision impairment), COVID-19 related factors (duration of hospitalization, treatments for COVID-19, rehabilitation services during and after hospitalization, other home care services required after hospitalization).

Primary Outcomes

Primary outcomes were measured as part of the VALIANT parent study. Physical function was measured via 9 survey items regarding disability in activities of daily living associated with

mobility/musculoskeletal function (Ability to bathe, get in and out of chair, use the toilet, do housework, shop, walk in your house, walk a quarter mile, require a device to walk a quarter mile and ability walking flight of stairs. Answer choices are No need help, Need help and unable to) Use of assistive devices are also considered (cane, walker, wheelchair and other device. Self-reported falls and fracture history at baseline, and new falls and fractures since COVID-19 hospitalization at 6 months was used to determine incidence of each.

Secondary Outcomes

Secondary measures were measured during VALIANT MSK Substudy activities, including a brief survey regarding fracture risk factors (sociodemographic, smoking and alcohol history and history of falls), SARC-F score[8] and dietary calcium intake assessment.

All participants also underwent a comprehensive DXA scan performed by trained DXA technicians at the Yale Bone Center. DXA includes bone and body composition scans yielding bone mineral density and regional body composition. Dual X-ray absorptiometry (DXA) is the preferred diagnostic tool to measure bone mineral density (BMD) measurements of the femoral neck, total hip and lumbar spine.[3] These measurements are used in the diagnosis of osteoporosis and prediction of fracture risk.[3] For this study, we will measure the bone mineral density (g/cm^2) as well as the T-score, which is generated by comparing the BMD of the individual to the mean BMD of a young healthy standard reference population.[3] This score is used to classify patients as having normal BMD, osteopenia or osteoporosis.[3]

Sarcopenia is often under-diagnosed and undertreated due to the complexity of measuring muscle mass and muscle quality. [8] The proposed study utilizes the sarcopenia definition updated in 2019 by the European Working Group on Sarcopenia in Older People (EWGSOP).[8] This

definition combines the SARC-F screening tool, and Short Physical Performance Battery (SPPB) to assess for and determine severity of sarcopenia. SARC-F is a simple and rapid questionnaire consists of 5 questions on strength, assistance in walking, rise from a chair, climb stairs, and falls. SPPB is a short physical assessment consist of a balance test, a 4-meter gait speed test, and a chair stand test.[9] For this study, we further used DXA total body lean tissue mass measurements as a confirmation of muscle quantity and quality. [8]

Lastly, we performed the SPPB physical assessment and upper extremity handgrip test using a Jamar hydraulic hand dynamometer. These tests are well-established measurements for lower and upper extremity physical function assessment that are feasible in clinical care settings and are associated with short-term mortality, disability, hospitalization among other outcomes.[8]

Fasting blood samples were also collected from each study participant and stored for future analyses of bone turnover and bone metabolism biomarkers.

Data Analysis

All analyses were performed using SAS (SAS 9.4 TS1M7 MBCD3170), and followed best practices for analyzing and accounting for limitations of observational data.

At the outset of data analysis, all variables were examined linearly using descriptive techniques. Stratified analyses of the primary and secondary outcomes were carried out for patients based upon the exposure groups (SOFA score, hospital ward, and inflammatory markers) dichotomized as described above. T-tests were applied for continuous variables, Wilcoxon rank sum tests for ordered/non-normally distributed variables, and chi-squared tests for non-ordered categorical variables. All statistical tests were two-tailed with a significance level set at alpha (α) < 0.05.

Key baseline covariates related to the outcomes of interest (e.g., known/suspected risk factors for bone fracture based on the literature such as age, sex, tobacco use, medications associated with bone loss, duration of immobilization/hospitalization) will be examined in univariate analyses and those that reach a significance level of $p<0.2$ will be considered for inclusion in future multivariable models.

RESULTS

Baseline characteristics of study participants

Sociodemographic Characteristics

A total of 341 participants were enrolled in the VALIANT parent study, and of those, 62 participants subsequently participated in the VALIANT MSK Sub-Study. Baseline characteristics of study participants are shown in **Table 1**.

The median age of participants in VALIANT was older than that of participants in VALIANT MSK [(70 vs. 67 years ($p<0.001$)]. Other characteristics were statistically similar between the two groups. Women comprised 49% of the participants in both groups. Most patients in both the parent study and sub-Study were White with 219 participants (72.5%) in VALIANT and 34 participants (64.2%) VALIANT MSK. Black participants comprised 26.5% of the overall VALIANT cohort, and 34% of those who enrolled in VALIANT MSK. Less than 2% of participants in both groups were Asian.

Participants' living situation at baseline was similar between those in the overall VALIANT sample and those who participated in the Sub-study. The majority of patients lived at home with others at baseline (70.5% and 64.5%, respectively), approximately one-third lived at home alone, and fewer participants reported living in a short-term rehabilitation or assisted living facility at

baseline. None of the patients enrolled in the VALIANT MSK Sub-study lived in an assisted living facility at baseline.

Health-Related Characteristics

Approximately three quarters of patients in both groups rated their general health as good, very good, or excellent prior to being hospitalized with COVID-19. More individuals enrolled in the VALIANT study reported never smoking compared with those in the VALIANT MSK Sub-Study [146 (47.6%) vs. 19 (35.2%) participants, p=0.096]. Alcohol use data was only available for sub-study participants, and on 2 (3.5%) participants reported consuming more than 3 units of alcohol per day.

The median BMI was at 30.0 (IQR 9.1) kg/m^2 for participants in VALIANT and 30.5 (IQR 9.1) among those who enrolled in the sub-study. Participants in VALIANT had a median comorbidity count of 3 (IQR 3) those in VALIANT MSK has a median comorbidity count of 2 (IQR 2). Those enrolled in the sub-study had lower rates of chronic kidney disease, end stage renal disease, cardiovascular disease, heart failure, and cancer, and higher rates of myocardial infarction, immunocompromised status (history of autoimmune disease, HIV, or solid organ transplant) and liver disease. However, these differences were not statistically different. In both groups, over 75% of patients had hypertension and approximately 45% of participants suffered from diabetes.

Factors Related to COVID-19 Hospitalization

Participants in the MSK Sub-Study had a similar median duration of COVID hospitalization [7 (IQR 6) days] compared to those in the overall VALIANT study [8 (IQR 6) days]. Data were available for four medications or medication classes related to each participant's COVID-19

hospitalization, including dexamethasone, remdesivir, tocilizumab. Participants in the VALIANT MSK sub-study participants were more likely to receive remdesivir compared to those who were not enrolled in the sub-study (87% v. 68.9%, p=0.0037). Rates of treatment with dexamethasone (74.2% vs 62.7%) and Tocilizumab (27.4% vs 18.3%) were also higher among patients enrolled in the sub-study, although these did not reach statistical significance.

COVID-19 Severity

Table 1 shows the measures related to COVID-19 severity. The median inpatient SOFA score was 3 for both groups. In terms of required level of care, the majority of the participants were admitted into the general hospital floors [272 participants (80.0%) in VALIANT and 46 participants (74.2%) in VALIANT MSK]. There were 29 participants (8.5%) in VALANT who received care in the SDU compared to 10 participants (16.1%) in the sub-study. Similar proportions of participants required intensive care [40 participants (11.7%) in VALIANT and 6 (10.0%) in VALIANT MSK, p=0.057]. When looking at inpatient markers of inflammation, the median IL-6 level was 20.6 pg/ml for participants in VALIANT and 48.9 pg/ml for those in the VALIANT MSK Sub-study (p=0.4353), whereas median hsCRP levels were 90.1mg/L and 118.8 mg/L for participants in the parent study versus sub-study, respectively (p=0.6581).

Musculoskeletal Outcomes

<u>Physical Function</u>

Baseline physical function status differed in certain domains between the overall cohort of VALIANT participants and those enrolled in the MSK sub-study (**Table 2**). Specifically, in the overall cohort, a higher proportion of participants reported being unable to independently use the toilet (5.6% vs 0.0%, p=0.034, do housework (30.4% vs 13.0%, p=0.004), shop (28% vs 10.0%, p=0.0014) and walk up a flight of stairs (24.3% vs 10.0%, p=0.011).

Overall baseline physical function status and 6 months physical function status are relatively similar. There were 38.0% of participants at 6 months who are unable to independently walk a quarter mile as compared to 32.5% of participants at baseline. On the other hand, there were 4.1% participants who are unable to independently use the toilet as compared to 5.6% of participants at baseline. Similar trends were observed in the VALIANT MSK sub-study. Overall baseline physical function status and 6 months physical function status are similar.

In the VALIANT cohort, when physical function status at 6 months was stratified by COVID-19 severity, multiple domains emerged as being significantly different. A higher proportion of patients who had a higher SOFA score (≥3) reported being unable to independently bathe (9.2% vs 2.4%, p<0.001), get in and out of a chair (5.8% vs 1.7%, p=0.017), use the toilet (3.8% vs 0.3%, p=0.006), shop (20.1% vs 11.6%, p=0.011), or walk flight of stairs (15.4% vs 8.2%, p=0.016). No significant differences were observed in physical function domains based upon inpatient level of care received. A significantly higher proportion of VALIANT participants with high inpatient hsCRP levels during hospitalization (≥97 mg/L) were unable to independently do housework (31.7% vs 21.1%, p= 0.013), shop (33.1% vs 19.7%, p=0.043), walk a quarter mile (28.5% vs 24.2%, p=0.009) and walk flights of stairs (37.0% vs 15.9%. p= 0.0114). When stratified analyses were performed based upon inpatient IL-6 levels, the proportion of patients

who noted difficulty with physical function was higher across several domains among those with higher IL-6 levels (≥37), however none of these differences were statistically significant.

Among patients enrolled in the VALIANT MSK Sub-study, a similar general trend was observed with a higher proportion of patients with SOFA scores ≥3 or hsCRP≥97 mg/L reporting that they were unable to independently perform certain physical function tasks, however none of these were statistically significant and, in several domains, it was not possible to performed stratified analyses due to the low total number of patients reporting difficulty in that domain.

Use of Assistive Devices

At baseline, the 16.5% of participants in VALIANT reported using a cane, 17.7% used a walker, and 5.6% used a wheelchair. A similar proportion of participants reported using canes (15.7%) and walkers (18.0%) at 6 months, however the proportion of patients using wheelchairs increased to 8.2% although this was not statistically significant.

In the overall cohort of patients in VALIANT, patients with a SOFA score ≥3 were more likely to report use of a walker (12.6% v. 5.4%, p=0.006) and wheelchair (6.1% vs. 2.0%, p=0.023) at 6 months compared with those with a SOFA score <3. When stratified by inpatient level of care, those who received step down or ICU-level care were less likely to report using a cane at 6 months (0.68% vs. 15%, p=0.017). When stratifying based upon inpatient inflammatory marker levels, a higher proportion of VALIANT participants who had low hsCRP level reported using a cane at 6 months (10.5 vs 5.3, p=0.045) and there was a general trend of higher use of assistive devices among participants with inpatient Il6 levels <37 ng/mL, including use of canes (12.6% vs 4.9%) and walkers (15.5% vs 5.8%). However, these differences were not statistically significant.

Among participants who enrolled in the VALIANT MSK Sub-Study, the proportion of patients using a cane remained unchanged from baseline to six months (16.1%), however use of other assistive devices (walker, wheelchair, or other device) increased slightly, although this change did not reach statistical significance. When stratified by COVID-19 severity, no significant differences were seen based upon SOFA Score category. Among patients who were treated in the SDU/ICU, there was a lower proportion of participants using a cane at 6 months (12.9% vs 3.2%, p=0.65). Finally, a higher proportion of patients with hsCRP <97 mg/L and IL-6 level <37 pg/mL reported using a cane compared to patients with higher inpatient inflammatory marker levels. Participants with Il-6 levels <37 pg/mL also reported high rates of using a walker (11.1% vs 6.7%) or a wheelchair (4.4% vs 0.0%), although as with the overall VALIANT cohort, these differences were not statistically different.

Falls and Fractures

At baseline, 101/339 (29.8%) VALIANT participants reported a fall in the past year before COVID-19 compared with 15/62 (24.2%) of VALIANT MSK Sub-Study participants. At 6 months, 24.3% of VALIANT participants reported having an incident fall since COVID infection compared with 19.4% of VALIANT MSK participants.

When participants were categorized based on SOFA scores no significant differences were seen in the proportion of new falls in the 6 months after COVID-19 hospitalization among the VALIANT participants (11.3% vs 13.1%) or VALIANT MSK participants (8.1% vs 11.3%). A higher proportion of participants who received care on the general medical floors reported a fall as compared to the SDU/ICU in both VALIANT (21.0% vs 3.4%, p-value=0.60) and VALIANT MSK Sub-Study participants (14.5% vs 4.9%, p-value=0.94). Similarly, when categorized by inpatient hsCRP or Il-6 levels, a higher proportion of participants reported falling since COVID-

19 hospitalization in the low hsCRP group (14.1% vs 10.6% in VALIANT and 11.9% vs 8.5% in VALIANT MSK) and low Il-6 group (18.6 vs 6.4% in VALIANT and 15.6% vs 2.2% in VALIANT MSK). However, these differences did not reach statistical significance.

No data were collected regarding fracture history at baseline, however 7 participants (2.4%) reported a fracture after hospitalization for COVID-19 in the VALIANT cohort, compared with 1 participant (1.6%) within the VALIANT MSK sub-study (p=0.55). The number of fractures reported was not sufficient to detect statistically significant differences between COVID-19 severity groups.

Osteoporosis and Fracture Risk

Table 3 demonstrates osteoporosis and Sarcopenia-Related Outcomes at 6 Months in the VALIANT MSK Substudy, Overall and by Severity Categories (N=62). Out of the 62 VALIANT MSK participants, 3 participants (5.2%) had osteoporosis, 22 participants (37.9%) had osteopenia and 37 participants (63.8%) had normal BMD. When stratified by SOFA score, level or care, or inpatient inflammatory marker levels, no significant differences were seen between the two groups. However, among these, a greater proportion of participants with Il-6 levels ≥37 pg/mL met criteria for osteopenia compared with those with Il-6 values <37 (40.0% vs 30.0%).

The mean of lumbar spine (LS) BMD among participants in the MSK Sub-Study was 1.15±0.23 g/cm^2, mean total hip (TH) BMD was 0.98±0.21 g/cm^2, and mean femoral neck (FN) BMD was 0.82±0.19 g/cm^2. Mean LS BMD and TH BMD levels remained relatively similar when stratified by SOFA score, level of care and inflammatory marker levels. However, mean FN BMD was lower among patients with hsCRP ≥97 (0.79 vs 0.21, p<0.001).

The mean of FRAX score for 10-year risk of major osteoporotic fracture was 6.94±5.1 and mean FRAX score for10-year risk of hip fracture was 1.31±1.8. No significant differences were observed between patients when stratified by inpatient SOFA scores, level of care or inflammatory marker levels.

Sarcopenia

Among patients in the VALIANT MSK Sub-Study, five participants (8.1%) met criteria for probable sarcopenia. No participants met criteria for sarcopenia or severe sarcopenia. Four of the participants with probable sarcopenia had a SOFA score of 3.

When examining individual sarcopenia assessment components, 21(33.9%) participants had a SARC-F score >4, and 13(21.0%) had altered grip strength, 27(43.5%) had altered SPPB and 4(6.5%) had altered ASMI. Among participants with SARC-F scores >4, statistical differences were not seen by COVID-19 severity category.

Among patients with altered grip strength, no significant differences were seen by COVID-19 severity category. A higher proportion of altered grip strength participants in floor level care (10/47, 27.9% vs 3/16, 18.8%). There is a relatively similar proportion of altered grip strength participants in both hsCRP level groups and il6 level groups.

There is a higher proportion of altered SPPB participants in the SOFA 3 and above group (17/37, 45.9% vs 10/25, 38.5%). There is also a higher proportion of altered SPPB participants in the floor level of care group (20/46, 55.6% vs 7/17, 43.8%). hsCRP and il6 levels has relatively similar proportion of altered SPPB participants within each groups. There is relatively similar proportion of altered ASMI participants within the SOFA score, level of care, hsCRP and il6 categories.

DISCUSSION

To our knowledge this is the first study to longitudinally evaluate musculoskeletal outcomes after COVID-19 hospitalization among older adults, and to study the impact of severity of COVID-19 on these outcomes. In the VALIANT cohort, when physical function status at six months was stratified by COVID-19 severity, multiple domains emerged as being significantly different. We observed a higher proportion of patients who had a higher SOFA score reported being unable to independently bathe, get in and out of a chair, use the toilet, shop and walk up a flight of stairs. There was also a significantly higher proportion of participants with high hsCRP levels during their hospitalization who were unable to independently do housework, shop, walk a quarter mile and walk up a flight of stairs at six months. Interestingly, when stratified analyses were performed based on inpatient level of care received, no significant differences were observed. Although differences did not reach statistical significance, among those with high IL-6 levels, there was a general trend of higher proportions of patients with physical function limitations across several domains.

Much of COVID-19 literature has focused on the biology, and acute clinical manifestations and outcomes of the virus, and intermediate-term aftereffects such as long covid (or post-acute sequelae of COVID-19), defined by symptoms persisting four to twelve weeks post infection.[12] Moreover, COVID-19 also disproportionally affects older adults. Huang and colleagues, carried out a large cohort study in Wuhan, China describing 6-month health consequences of 2469 hospitalized adult patients with COVID-19 based on disease severity.[13] However, their study was more focused on severe cases of COVID, pulmonary function and treatment-related aftermath of COVID-19 hospitalized patients and less on general long-term consequences. Furthermore, there was no mention of bone and muscle health. The present study

focuses uniquely on 6-month health consequences of patients over the age of 60 years hospitalized for COVID-19, and also looks specifically at their bone and muscle health outcomes in relation COVID-19 severity.

According to the NIH COVID treatment guidelines, COVID severity is classified into asymptomatic, mild, moderate, severe, and critical based on clinical assessment or imaging of oxygen saturation. There have also been presented studies at 2021 FDA Science Forum conducted recently by Center for Drug Evaluation and Research that have looked at respiratory support as a measurement for COVID severity (supplemental oxygen, non-invasive ventilation, or invasive mechanical ventilation). Although these are all valid measurements, they focus on one major organ system – the respiratory system and do not consider other potential important complications, which may be particularly important in older adults, our population of interest. We therefore chose to define severity using three different perspective, including a clinical measure of multi-organ function, the SOFA score, level of care received as a reflection of overall intensity of medical and nursing services required during hospitalization, and levels of serum inflammatory markers, hsCRP and IL-6 which may reflect the degree of hyperinflammation due to COVID-19.

SOFA scores have been used in the intensive care unit to predict clinical outcomes of patients with multiple organ failure. [14] It has been suggested that SOFA scores could be used to evaluate COVID-19 severity and potentially mortality risk, and have been linked to lower physical function in this population. This measure is based on the evaluation of 6 major organ functions: circulation, respiration, hepatic, renal, central nervous system and coagulation functions, and each organ is given a score between 0-4. [14] It is considered an easy-to-use systematic tool during hospitalization yet there have also been studies that suggest that due to use

of mechanical ventilation on critical ill patients with COVID pneumonia SOFA score is not a good presentation of patient status. [14] The findings from our study are consistent in that greater proportions of patients with higher SOFA scores were found to have limitations in multiple physical function domains relevant to musculoskeletal health, and to report use of walkers or wheelchairs at six months.

Contrary to what we expected, care on the general medical floors was related to more reported falls in the six months following hospitalization as compared to patients the SDU/ICU in both the VALIANT and VALIANT MSK Sub-study participants. Inpatient level of care (Floor vs SDU/ICU) reflects both medical treatment and nursing related factors including the ratio of nurses to patients and hence would provide valuable insight into overall hospital stay but also severity of COVID symptoms. It is possible more falls were observed in patients who received care on the general medical floors due to earlier and more unsupervised attempts at mobility, or less attention to physical therapy or home care needs post-discharge.

We observed a general trend of patients having physical function difficulty across several physical function domains in the group of patients with high hsCRP or high IL-6 levels, although the differences for IL-6 did not reach statistical significance. HsCRP is a commonly used biomarker for general inflammation [15] and has been shown in the literature to be positively correlated with myocardial injury in critical cases of COVID.[15] Interleukin 6 (IL-6) is suggested to contribute toward the proinflammatory cytokine storm in more severe COVID-cases and has also been associated with poor outcomes in COVID-19. [16] Particularly relevant for our study, systemic inflammation is known to be linked to bone loss due to increased activation of osteoclasts, which are responsible for bone resorption. [16]

One of the major findings in this study is that mean FN BMD was shown to be lower among patients with hsCRP ≥97 mg/L. To date, osteoporosis risk in the setting of COVID-19 has mostly been analyzed from the lens of bone loss from immobility due to COVID-19 containment. [17] Although osteoporosis is considered a treatable and preventable condition, it is suggested that alterations in mobility and physical activity leads to acute changes in body composition described as osteosarcopenic obesity which promotes oxidative stress and proinflammatory cytokines [17]. It has been suggested that there is considerable musculoskeletal dysfunction in some patients with COVID-19, however, few studies have actually measured bone and muscle health after COVID-19 infection. This is the first COVID cohort study specifically looking at musculoskeletal outcomes after 6 months hospitalization. At the beginning of the COVID pandemic, multiple papers described clinical manifestation of SARS 2003 in order to raise awareness regarding potential manifestations that may be seen with COVID-19. [18] They suggested certain musculoskeletal consequences and mechanisms which may aid our understanding of the current COVID-19 infection. [18] For example, skeletal muscle, synovium, and cortical bone are potential sites of direct SARS-CoV-2 infection. [18]This may potentially compound the other potential sociodemographic and clinical risks for bone and muscle impairment in our population of interest, such as older age, history of falls and general health.

The present study did not find statistically significant differences in rates of sarcopenia-related measures in our study, although this may be related to the modest size of our sample. There have been limited studies on sarcopenia and COVID-19, with only one review that we are aware of focused on acute sarcopenia and its impact on muscle degradation in COVID-19, especially for older adults. Acute sarcopenia refers to the acute loss of muscle mass and function

associated with hospitalization. We utilized the definition developed by European Working Group on Sarcopenia in Older people (EWGSOP2) and performed physical assessment with VALIANT MSK participants based on this definition. It is suggested that the combination of multiple environmental factors such as decreased nutrition, increased physical inactivity and acute hospitalization may intensify acute sarcopenia for patients with COVID-19. [19] Some prior studies have focused on the relationship between acute sarcopenia and hospitalization, but have not previously studied COVID-19 related hospitalization. Similar to our hypothesis, these studies have found patients' underlying comorbidities, inflammation, nutritional status and physical function status to be factors associated with sarcopenia outcomes.

Contrary to what we expected, a higher proportion of participants who received care on the general medical floors reported a fall as compared to the SDU/ICU in both VALIANT and VALIANT MSK Sub-study participants. However, these differences did not reach statistical significance. Furthermore there were not enough fracture events in our cohort to draw conclusions regarding the relationship between COVID-19 hospitalization, COVID-19 severity, and fractures. Future larger studies are needed explore both falls and fracture outcomes further.

This study had several limitations. This cohort study was limited to a single health system in the U.S. and therefore results cannot be generalized to a wider population. The sample size was relatively small, especially when observing clinical outcomes such as falls or fractures. As this is an observational study, this study is more susceptible to selection bias and confounding. Importantly, the next steps for analysis will use multivariable regression to evaluate the relationship between COVID-19 severity and musculoskeletal outcomes adjusted for key covariates (e.g., age, BMI, smoking history, and other bone-health related factors) . In addition, we acknowledge that an added limitation to both the VALIANT and VALIANT MSK study was

the logistical barriers to participating in research during the COVID-19 pandemic, which meant that patients with the most severe disease or greatest amount of disability may not have been able to or willing to participate. Finally, as COVID-19 is relatively new and research is constantly expanding in this field, the inflammatory marker cut offs we selected based on the currently available literature is extrapolated from studies that were not focused specifically on musculoskeletal outcomes. Therefore, future analyses will also seek to evaluate the most appropriate thresholds for identifying patients at increased risk for poor musculoskeletal outcomes. We hope that this study has shared some insights on COVID-19 severity and musculoskeletal outcomes. Future studies should aim to further confirm and elucidate our findings in larger cohorts, and help identify potential areas for prevention and intervention in order to optimize the musculoskeletal health of older persons after COVID-19 infection.

References

(1) Gardner RL, Harris F, Vittinghoff E, Cummings SR. The Risk of Fracture Following Hospitalization in Older Women and Men. *Arch Intern Med.* 2008;168(15):1671–1677. doi:10.1001/archinte.168.15.1671

(2) Severe Outcomes Among Patients with Coronavirus Disease 2019 (COVID-19) — United States, February 12–March 16, 2020. MMWR Morb Mortal Wkly Rep 2020;69:343-346. DOI: http://dx.doi.org/10.15585/mmwr.mm6912e2external icon.

(3) Sözen T, Özışık L, Başaran NÇ. An overview and management of osteoporosis. *Eur J Rheumatol*. 2017;4(1):46-56. doi:10.5152/eurjrheum.2016.048

(4) NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. *JAMA*. 2001;285(6):785-795. doi:10.1001/jama.285.6.785

(5)Office of the Surgeon General (US). Bone Health and Osteoporosis: A Report of the Surgeon General. Rockville (MD): Office of the Surgeon General (US); 2004. 4, The Frequency of Bone Disease. Available from: https://www.ncbi.nlm.nih.gov/books/NBK45515/

(6) Santilli V, Bernetti A, Mangone M, Paoloni M. Clinical definition of sarcopenia. *Clin Cases Miner Bone Metab*. 2014;11(3):177-180.

(7) Antunes AC, Araújo DA, Veríssimo MT, Amaral TF. Sarcopenia and hospitalisation costs in older adults: a cross-sectional study. *Nutr Diet*. 2017;74(1):46-50. doi:10.1111/1747-0080.12287

(8) Alfonso J Cruz-Jentoft, Gülistan Bahat, Jürgen Bauer, Yves Boirie, Olivier Bruyère, Tommy Cederholm, Cyrus Cooper, Francesco Landi, Yves Rolland, Avan Aihie Sayer, Stéphane M Schneider, Cornel C Sieber, Eva Topinkova, Maurits Vandewoude, Marjolein Visser, Mauro Zamboni, Writing Group for the European Working Group on Sarcopenia in Older People 2 (EWGSOP2), and the Extended Group for EWGSOP2, Sarcopenia: revised European consensus on definition and diagnosis, *Age and Ageing*, Volume 48, Issue 1, January 2019, Pages 16–31, https://doi.org/10.1093/ageing/afy169

(9) Bahat, G., Yilmaz, O., Oren, M.M. *et al.* Cross-cultural adaptation and validation of the SARC-F to assess sarcopenia: methodological report from European Union Geriatric Medicine Society Sarcopenia Special Interest Group. *Eur Geriatr Med* **9,** 23–28 (2018). https://doi.org/10.1007/s41999-017-0003-5

(10) F. Coury, O. Peyruchaud, and I. Machuca-Gayet, "Osteoimmunology of Bone Loss in Inflammatory Rheumatic Diseases," Frontiers in Immunology, vol. 10, Apr. 2019.

(11) Vatansever HS, Becer E. Relationship between IL-6 and COVID-19: to be considered during treatment. Future Virol. (2020) 15:817–22. 10.2217/fvl-2020-0168

(12) Cortinovis M, Perico N, Remuzzi G. Long-term follow-up of recovered patients with COVID-19. *Lancet*. 2021;397(10270):173-175. doi:10.1016/S0140-6736(21)00039-8

(13) Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet*. 2021;397(10270):220-232. doi:10.1016/S0140-6736(20)32656-8
(14) Raschke RA, Agarwal S, Rangan P, Heise CW, Curry SC. Discriminant Accuracy of the SOFA Score for Determining the Probable Mortality of Patients With COVID-19 Pneumonia Requiring Mechanical Ventilation. *JAMA*. 2021;325(14):1469–1470. doi:10.1001/jama.2021.1545
(15) Guo T, Fan Y, Chen M, et al. Cardiovascular Implications of Fatal Outcomes of Patients With Coronavirus Disease 2019 (COVID-19). *JAMA Cardiol*. 2020;5(7):811–818. doi:10.1001/jamacardio.2020.1017
(16) Vatansever HS, Becer E, Vatansever HS, Becer E. Relationship between IL-6 and COVID 19: to be considered during treatment. Future Virol. 2020;15:817–22. https://doi.org/10.2217/fvl-2020-0168
(17) Lim MA, Kurniawan AA. Dreadful Consequences of Sarcopenia and Osteoporosis due to COVID-19 Containment. *Geriatric Orthopaedic Surgery & Rehabilitation*. January 2021. doi:10.1177/2151459321992746
(18)Disser NP, De Micheli AJ, Schonk MM, et al. Musculoskeletal Consequences of COVID-19. *J Bone Joint Surg Am*. 2020;102(14):1197-1204. doi:10.2106/JBJS.20.00847
(19) Cruz-Jentoft AJ, Bahat G, Bauer J, et al. Sarcopenia: revised European consensus on definition and diagnosis [published correction appears in Age Ageing. 2019 Jul 1;48(4):601]. *Age Ageing*. 2019;48(1):16-31. doi:10.1093/ageing/afy169

Appendix

Table 1. Baseline Characteristics of Study Participants

Variable	¥ALIANT (N=341)	Participant in ¥ALIANT MSK Sub-Study	
		Yes (N=62)	No (N=279)
Age *Median (IQR)*	70 (12)	**67 (10.0)**	**71 (13.0)*****
Sex *n(%)*			
Male	166 (51)	32(51.6)	134 (48.0)
Female	175 (49)	30(48.4)	145 (52.0)
Race *n(%)*			
White	219 (72.5)	34 (64.2)	185 (74.3)
Black	80 (26.5)	18 (34.0)	62 (24.9)
Asian	3 (1.0)	1 (1.9)	2 (0.8)
Ethnicity *n(%)*			
Hispanic	47 (13.7)	10(16.1)	36 (12.9)
Non-Hispanic/other	294 (86.2)	52(83.9)	242 (86.7)
Baseline living situation *n(%)*			
At home alone	92 (27.1)	21 (33.9)	71 (25.6)
At home with others	239 (70.5)	40 (64.5)	199 (71.8)
Short term Rehab/Facility	5 (1.47)	1 (1.6)	4 (1.4)
Assisted living facility	3 (0.88)	0 (0.0)	3 (1.1)
Impairment *n(%)*			
Hearing	120 (35.5)	21 (33.9)	99 (35.9)
Vision	50 (14.9)	8 (13.1)	42 (15.3)
General Health *(Excellent, Very good and Good)*	235 (75.8)	191 (76.1)	44 (72.1)
Smoking status *n(%)*			
Current Smoker	25 (8.1)	4 (7.4)	31 (8.3)
Never Smoked	146 (47.6)	19 (35.2)	127 (50.2)
Prior Smoker	136 (44.3)	31 (57.4)	105 (41.5)
Alcohol use status *n(%)* N=57			
3 or more units/day	NA	2 (3.5)	NA
Less than 3 units/day	NA	55 (96.5)	NA
BMI *Median (IQR)*	30.0 (9.1)	30.5 (9.1)	29.8 (9.3)
Comorbidities *n(%)*			
Myocardial Infarction	22 (6.5)	5 (8.1)	17 (6.09)
Chronic Kidney Disease	82 (24.1)	11 (17.7)	71 (25.5)
End Stage Renal Disease	21 (6.2)	2 (3.2)	19 (6.8)
Lung Disease	128 (37.5)	23 (37.1)	105 (37.6)
Cardiovascular Disease	47 (13.8)	6 (9.7)	41 (14.7)
Diabetes	150 (44.0)	28 (45.2)	122 (43.7)
Heart Failure	83 (24.3)	11 (17.7)	72 (25.8)
Hypertension	266 (78.0)	49 (79.0)	217 (77.8)
Immunocompromised status¥	48 (14.1)	10 (16.1)	38 (13.6)
Liver Disease	47 (13.8)	12 (19.3)	35 (12.5)
Cancer	82 (24.1)	13 (20.1)	69 (24.7)
Comorbidity Score *Median(IQR)* (Range: 0-11)	3 (3)	2 (2)	3 (3)
Duration of Hospitalization *Median days (IQR)*	8 (6)	7 (6)	8 (6)
Inpatient SOFA Score *Median(IQR)*	3 (2)	3 (3)	3 (2)
Inpatient Level of Care *n(%)*			
Floor	272 (80.0)	46 (74.2)	226 (81.0)
Step Down Unit	29 (8.5)	10 (16.1)	19 (6.8)
Intensive Care Unit	40 (11.7)	6 (10.0)	34 (12.2)
Inpatient Markers of Inflammation *Median(IQR)*			
IL-6 (pg/ml)	20.6 (49.8) (n=240)	48.9 (42.8) (n=45)	21.4 (49.8) (n=195)
hsCRP (mg/L)	90.1 (126.0) (n=329)	118.8 (146.4) (n=59)	91.7 (123.6) (n=270)
COVID-19 Treatment Received *n(%)*			
Dexamethasone	221(64.8)	46 (74.2)	175 (62.7%)
Remdesivir	246(72.1)	**54 (87.1)**	**192 (68.8)****
Tocilizumab	68 (20.0)	17 (27.4)	51 (18.3)

*p<0.05; **p<0.01; *** p<0.001

¥ Autoimmune disease, HIV+, receipt of solid organ transplant

COVID-19: Coronavirus Disease 2019; SOFA: Sequenial organ failure assessment; SDU: Stepdown unit; ICU: Intensive care unit; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6

Table 2. Physical Function, Falls and Fractures at Baseline and 6 Months, Overall and by Inpatient Severity Categories, among VALIANT (n=341) and VALIANT MSK Substudy (n=62) Participants

	Baseline	6 Months								
			Inpatient SOFA Score		Inpatient Level of Care		Inpatient hsCRP Level		Inpatient Il-6 Level	
VALIANT PARTICIPANTS	Overall at Baseline (N=341) *	Overall (N=341) *	<3 (n=47)	≥3 (n=294)	Floors (n=272)	SDU/ICU (n=69)	<97 (n=58)	≥97 (n=283)	<37 (n=136)	≥37 (n=205)
***Needs Help With* or is *Unable to Perform* the Following Activities:**										
Bathing	35 (10.3)	34 (11.6)	7 (2.39)	**27 (9.2)*** **	27 (9.2)	7 (2.4)	16 (5.6)	134 (47.2)	14 (6.9)	117 (57.1)
Getting in and out of chair	22 (6.5)	22 (7.5)	5 (1.7)	**17(5.8)***	19 (6.5)	3 (1.02)	13 (4.6)	138 (48.4)	8 (3.9)	124 (60.2)
Using the toilet	**19 (5.6)***	12 (4.1)	1 (0.3)	**11 (3.8)****	10 (3.4)	2 (0.7)	6 (2.11)	145 (50.9)	4 (2.0)	128 (62.1)
Housework	**103 (30.4)****	97 (33.1)	41 (14.0)	56 (19.1)	81 (28.0)	16 (5.5)	60 (21.1)	**90 (31.7)***	51 (24.9)	80 (39.0)
Shopping	**95 (28.0)*****	93 (31.7)	34 (11.6)	**59 (20.1)***	76 (26.0)	17 (5.8)	56 (19.7)	**94 (33.1)***	51 (24.9)	80 (39.0)
Walking in your house	27 (8.0)	23 (7.8)	7 (2.4)	16 (5.4)	20 (6.8)	3 (1.0)	15 (5.3)	136 (47.7)	11 (5.3)	121 (58.8)
Walking a quarter mile	110 (32.5)	110 (38.0)	48 (16.6)	62 (21.4)	93 (32.1)	17 (5.9)	68 (24.2)	**80 (28.5)****	55 (27.0)	76 (37.3)
Uses a device to walk quarter mile	158 (87.3)	108 (85.7)	10 (8.0)	56 (44.4)	3 (2.4)	19 (15.1)	51 (41.1)	55 (44.4)	46 (52.9)	27 (31.0)
Flight of stairs	**82 (24.3)***	69 (23.6)	24 (8.2)	**45 (15.4)***	57 (19.5)	12 (4.1)	45 (15.9)	**105 (37.0)***	36 (17.6)	95 (46.3)
Use of Assistive Devices										
Use of cane	56 (16.5)	46 (15.7)	27 (9.2)	19 (6.5)	44 (15.0)	**2 (0.68)***	30 (10.5)	**15 (5.3)***	26 (12.6)	10 (4.9)
Use of walker	60 (17.7)	53 (18.0)	16 (5.4)	**37 (12.6)****	43 (14.6)	10 (3.4)	30 (10.5)	22 (7.7)	32 (15.5)	12 (5.8)
Use of wheelchair	19 (5.6)	24 (8.2)	6 (2.0)	**18 (6.1)***	20 (6.8)	4 (1.4)	15 (5.3)	8 (2.8)	12 (5.8)	4 (2.0)
Use of other device	1 (0.3)	9 (3.1)	2 (0.68)	7 (2.4)	5 (1.7)	**4 (1.4)***	5 (1.8)	4 (1.4)	3 (1.5)	3 (1.5)
Falls (in past year)since COVID-19)	101¥339 (29.8)	71 (24.3)	33 (11.3)	38 (13.1)	61 (21.0)	10 (3.4)	40 (14.1)	30 (10.6)	38 (18.6)	13 (6.4)
Fractures Since COVID-19	NA	7 (2.4)	3 (1.0)	4 (1.4)	7 (2.4)	0 (0.0)	6 (2.1)	1 (0.4)	5 (2.4)	1 (0.5)
	Overall	Overall	Inpatient SOFA Score		Inpatient Level of Care		Inpatient hsCRP Level		Inpatient Il-6 Level (n=45)	
VALIANT MSK SubStudy Participants	(n=62)	(n=62)	<3 (n=25)	≥3 (n=37)	Floors	SDU/ICU	<97 (n=31)	≥97 (n=28)	<37 (n=30)	≥37 (n=15)
***Needs Help With* or is *Unable to Perform* the Following Activities:**										
Bathing	3 (4.9)	4 (6.5)	1 (1.6)	3 (4.9)	3 (4.8)	1 (1.6)	1 (1.7)	31 (52.5)	2 (4.4)	1 (2.2)
Getting in and out of chair	2 (3.2)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	32 (54.3)	0 (0.0)	0 (0.0) ¥
Using the toilet	**0 (0.0)**	0 (0.0)	0 (0.0)	0 (0.0) ¥	0 (0.0)	0 (0.0) ¥	0 (0.0)	0 (0.0) ¥	0 (0.0)	0 (0.0) ¥
Housework	**8 (13.0)**	15 (24.2)	5 (8.1)	10 (16.1)	11 (17.7)	4 (6.5)	10 (17.0)	22 (37.3)	10 (22.2)	5 (11.1)
Shopping	**6 (10.0)**	13 (21.0)	4 (6.5)	9 (14.5)	9 (14.5)	4 (6.5)	8 (13.6)	24 (40.7)	8 (17.8)	5 (11.1)
Walking in your house	2 (3.2)	1 (1.6)	0 (0.0)	1 (1.6)	1 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)¥	0 (0.0)	0 (0.0) ¥
Walking a quarter mile	13 (21.0)	17 (27.4)	6 (9.7)	11 (17.7)	10 (16.1)	7 (11.3)	10 (17.0)	22 (37.3)	11 (24.4)	5 (11.1)
Uses a device to walk quarter mile	34 (87.2)	32 (94.1)	13 (38.2)	19 (55.9)	7 (20.6)	25 (73.5)	16 (48.5)	15 (45.5)	13 (62.0)	6 (28.6)
Flight of stairs	**6 (10.0)**	9 (14.5)	4 (6.5)	5 (8.1)	6 (10.0)	3 (4.9)	6 (10.2)	26 (44.1)	6 (13.3)	3 (6.7)
Use of Assistive Devices										
Use of cane	10 (16.1)	10 (16.1)	5 (8.1)	5 (8.1)	8 (12.9)	2 (3.2)	7 (11.9)	3 (5.1)	7 (15.6)	2 (4.4)
Use of walker	6 (9.7)	8 (12.9)	3 (4.8)	5 (8.1)	4 (6.5)	4 (6.5)	4 (6.8)	4 (6.8)	5 (11.1)	3 (6.7)
Use of wheelchair	1 (1.6)	2 (3.2)	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.6)	1 (1.7)	1 (1.7)	2 (4.4)	0 (0.0)
Use of other device	0 (0.0)	3 (4.9)	1 (1.6)	2 (3.2)	1 (1.6)	2 (3.3)	1 (1.7)	2 (3.5)	2 (4.6)	0 (0.0)
Falls (in past year)since COVID-19)	15 (24.2)	12 (19.4)	5 (8.1)	7 (11.3)	9 (14.5)	3 (4.9)	7 (11.9)	5 (8.5)	7 (15.6)	1 (2.2)
Fractures Since COVID-19	NA	1 (1.6)	1 (1.6)	0 (0.0)	1 (1.6)	0 (0.0)	0 (0.0)	1 (1.7)	0 (0.0)	0 (0.0) ¥

*p<0.05; **p<0.01; *** p<0.001; ¥ unable to perform stratified analyses due to size of groups

NA: Not avaialble; COVID-19: Coronavirus Disease 2019; SOFA: Sequenial organ failure assessment; SDU: Stepdown unit; ICU: Intensive care unit; hsCRP: high-sensitivity C-reactive protein; IL-6: interleukin-6

[a]numbers may not sum to 341 participants due to missing data

Table 3. Osteoporosis and Sarcopenia-Related Outcomes at 6 Months in the VALIANT MSK Substudy, Overall and by Severity Categories (N=62)

		Inpatient SOFA Score		Inpatient Level of Care		Inpatient hsCRP Level (N=59)		Inpatient Il-6 Level	
Outcome	**Total (N=62)**	<3 (n=25)	≥3 (n=37)	Floors (n=46)	SDU/ICU (n=16)	<97 (n=31)	≥97 (n=28)	<37 (n=30)	≥37 (n=15)
Osteoporosis Category *n(%)*									
Osteoporosis diagnosis	3 (5.2)	1 (4.0)	2 (5.4)	2 (4.3)	1 (6.3)	2 (6.5)	1 (3.6)	2 (6.7)	1 (6.7)
Osteopenia diagnosis	22 (37.9)	9 (36)	13 (35.1)	16 (34.7)	6 (37.5)	12 (38.7)	10 (35.7)	10 (30.0)	6 (40.0)
Normal	37 (63.8)	15 (60)	22 (59.4)	28 (60.9)	9 (56.3)	17 (54.8)	17 (60.7)	18 (60.0)	8 (53.3)
Bone Mineral Density *mean ±SD*									
Lumbar Spine n=62	1.15 (0.23)	1.14 (0.3)	1.16 (0.2)	1.16 (0.2)	1.13 (0.2)	1.15 (0.2)	1.15 (0.2)	1.16 (0.2)	1.14 (0.2)
Total Hip n=59	0.98 (0.21)	0.97 (0.2)	0.99 (0.2)	0.99 (0.2)	0.97 (0.2)	0.94 (0.2)	1.03 (0.2)	0.95 (0.2)	1.01 (0.3)
Femoral Neck n=59	0.82 (0.19)	0.81 (0.2)	0.83 (0.2)	0.82 (0.2)	0.81 (0.2)	**0.79 (0.2)**	**0.21 (0.2)*****	0.80 (0.2)	0.84 (0.2)
FRAX Score *mean±SD*									
Major Osteoporotic Fracture	6.94 (5.1)	7.43 (5.9)	6.59 (4.4)	7.09 (5.1)	6.51 (4.9)	7.79 (5.8)	5.97 (3.8)	6.24 (5.1)	7.65 (5.04)
Hip Fracture	1.31 (1.8)	0.97 (1.3)	1.56 (2.1)	1.35 (1.9)	1.17 (1.5)	1.53 (2.1)	1.05 (1.3)	1.13 (1.6)	1.48 (1.9)
Sarcopenia Category *n(%)*									
Probable Sarcopenia	5 (8.1)	1 (3.8)	4 (10.8)	4 (11.1)	1 (6.3)	2 (6.5)	3 (10.7)	3 (10)	2 (13.3)
Confirmed Sarcopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Severe Sarcopenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Components *n(%)*									
SARCF >4	21 (33.9)	8 (30.8)	13 (35.1)	16 (44.4)	5 (31.3)	12 (38.7)	9 (32.1)	12 (40)	9 (60)
Altered Grip Strength	13 (21.0)	5 (19.2)	8 (21.6)	10 (27.9)	3 (18.8)	4 (12.9)	9 (32.1)	6 (20)	7 (46.7)
Altered SPPB	27 (43.5)	10 (38.5)	17 (45.9)	20 (55.6)	7 (43.8)	15 (48.4)	12 (42.9)	15 (50)	12 (80.0)
Altered ASMI	4 (6.5)	2 (7.7)	2 (5.4)	3 (8.3)	1 (6.3)	3 (9.7)	1 (3.6)	3 (10)	1 (6.7)

*p<0.05; **p<0.01; *** p<0.001; ¥ unable to perform stratified analyses due to size of groups