Sarcopenia assessed by quantity and quality of skeletal muscle is a prognostic factor for patients undergoing cardiac surgery

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Abstract (200 words)

Purpose: Sarcopenia was assessed as a prognostic factor for patients undergoing cardiac surgery by evaluating the quantity and quality of skeletal muscle.

Methods: Sarcopenia was assessed by perioperative abdominal computed tomography scan using total psoas muscle index (TPI) and intra-muscular adipose tissue content (IMAC). Patients were classified into high (HT, n = 143) and low (LT, n = 63) TPI groups, and low (LI, n=122) and high IMAC groups (HI, n=84)

Results: There were significantly more complications in the LT and HI groups compared to the HT and LI groups. (HT 15.4% vs LT 30.2%, P=0.014) (LI 11.5% vs HI 31.1%, P<0.001). There were more respiratory complications in the LT group (HT 0% vs LT 6.3%, P=0.002) and more surgical site infections in the HI group (LI 0.8% vs HI 7.1%, P=0.014). Multivariable analysis showed that low TPI and high IMAC significantly predict more major complications (OR 2.375; 95% CI 1.152-5.783; P = 0.036, OR 3.973; 95% CI 1.737-9.088; P = 0.001). Low TPI and high IMAC further increase the odds ratio. (ratio 6.356; 95% CI 1 2.424-16.660; P <0.001).

Conclusions: Sarcopenia is a risk factor for complications. The quantity and quality of muscle must be assessed to predict operative outcomes.

Clinical Trial Registration Number: UMIN000027077

Introduction

Sarcopenia is defined as progressive loss of skeletal muscle mass, strength, and power, and is regarded as a key component of frailty[1, 2]. It is caused by a variety of factors such as aging, cancer, bone fracture, chronic liver disease and malnutrition. It is derived physical disorders, a decline in the quality of life, and linked to a greater risk for adverse events such as death and illness [3]. It has been reported to be associated with postoperative outcomes, mortality or morbidity and prolonged hospitalization after abdominal surgery [4-7]. Recently similar associations have been described for patients undergoing cardiovascular surgery [2, 8-14].

There are various criteria for diagnosing sarcopenia and there is no single accepted standard. The European Working Group on Sarcopenia in Older People has reported several criteria including both muscle strength and mass. Therefore, hand grip test, gate speed and measurement of muscle mass using dual-energy X-ray absorption are necessary for diagnosis [3]. However, in patients who will undergo cardiac surgery, many patients with New York Heart Association Class III to IV heart failure and unstable angina are included, and these functional evaluations may not be performed accurately. The measurement of skeletal muscle mass is not currently included in preoperative screening. This can lead to errors in evaluating patients for frailty and sarcopenia.

Therefore, we have evaluated sarcopenia by measuring the iliopsoas muscle using computed tomography (CT) scan as a simple and convenient method. CT scan has been reported by some groups using it to define sarcopenia.

In addition to evaluating quantity of muscle, we also examined the quality of muscle. It has been reported that muscle fibers become thinner and lower density with aging[15], and it is also expected that the performance will also be different in the same quantity of muscle even in the state where the density of the muscle fibers is high. [15] We selected the intramuscular adipose content [16] as an indicator of quality of skeletal muscle which can be evaluated using CT scan. The intramuscular adipose tissue content (IMAC) is defined as the CT scan determined value of skeletal muscle divided by that of percutaneous adipose tissue [17]. A higher IMAC indicates a predominance of skeletal muscle over adipose tissue and was shown to predict operative outcomes in patients with hepatic cancer and liver transplantation[16, 18]. The effect on outcomes in cardiac surgery has not been investigated.

This study was undertaken to evaluate the impact of sarcopenia assessed by Total Psoas Muscle Index (TPI) and IMAC on outcomes after elective cardiac surgery in patients with heart failure or angina.

Patients and Methods

Patients

Patients in this study underwent cardiac surgery from March 2015 through February 2018, at Dokkyo Medical Hospital. Most patients underwent CT scan of the abdomen or thorax for screening or to determine indications for surgery. Of these, 206 patients evaluated by CT scan were classified into sarcopenia and non-sarcopenia groups based on TPI and IMAC. Patients scheduled to undergo cardiac surgery, were evaluated for frailty with a questionnaire and physical performance tests in the preoperative period.

We conducted this study of patients for whom function tests would not be able to correctly evaluate frailty. Therefore, study patients were limited to those who were to undergo coronary artery bypass grafting, valve replacement or repair, or a combination. Patients over age 75 years were enrolled. Exclusion criteria included: (1) emergent surgical procedures, because the mortality rate and the complication rate strongly correlate with preoperative circulatory dynamics, (2) patients undergoing cardiac surgery for infectious endocarditis. Since infection is strongly correlated with the postoperative state and length of stay is extended due to antibiotic treatment even though the postoperative course may be smooth, and (3) patients with uninterpretable or

missing CT scan data.

Imaging analysis

Frail patients who had a perioperative abdominal or thoracic CT scan were identified. The CT scans were analyzed to measure cross-sectional muscle area at the L3 vertebra. Frailty is evaluated by TPI calculated as bilateral psoas muscle area in mm^2 divided by height in m^2. (Fig 1A)

Patients were divided into two groups, a high TPI group (HT) and a low TPI group (LT) as non-sarcopenia and sarcopenia groups. IMAC was calculated as previously described [14, 16-18] using the IMAC region of interest (ROI) of the multifidus muscle (Hounsfield units)/ROI of subcutaneous fat (Hounsfield units). Subfascial muscular tissue in the multifidus muscle on the preoperative CT cross-sectional image at the umbilical level (Figure 1B). Trained observer (cardiothoracic surgeon) who is different from a person who collects the data, performed all measurements, TPI and IMAC.

Statistical Analysis

All continuous variables were expressed as the mean ± standard deviation. A comparison of the clinical characteristics of sarcopenia and non-sarcopenia was performed using Pearson's

chi-square test for categorical variables and the unpaired Student's t-test for continuous variables. P-values <0.05 were considered to be statistically significant. Analysis was performed using SPSS software (Version 25, Inc., Chicago, IL, USA) .We defined the cut off value of TPI, referred from the report of that Asian trauma patients who underwent CT scan examination as . [12]

Cut-off value for men: 689 mm^2 /m^2 TPI <689 mm^2 /m^2 →low TPI(LT),TPI >_ 689 mm^2 /m^2 →high TPI(HT). Cut-off value for women: TPI = 440 mm^2 /m^2 TPI<440mm^2/m^2 low TPI>_440cm^2=m^2 →high TPI. There is no previous research that measured the mean value of IMAC in normal Japanese people. Therefore, cut-off values were calculated from a receiver operating characteristics (ROC) curve. Multivariate analysis was performed with multiple logistic analysis.

Results

Patient Characteristics

Patients are divided into the sarcopenia group and the non-sarcopenia group based on TPI and IMAC. Patients evaluated by CT scan were classified into high TPI and low TPI groups, low IMAC and high IMAC groups. There is no difference in basic characteristics, preoperative heart failure status, or Euro score in the high and low TPI groups. (Table 1) The age was higher in the low TPI group, but there was no significant difference. There was no significant difference in preoperative nutritional indicators such as serum albumin or Geriatric Nutritional Risk Index, but it was lower in the low TPI group. Age was significantly higher in the high IMAC group. Body mass index was higher in the low IMAC group. (Table 2) The two sarcopenia indicators had different characteristics. The surgery procedure was mainly valve replacement and coronary artery bypass grafting and there was no difference between the two groups. Cardiopulmonary bypass times were similar in the two groups.

Early outcomes

ICU stay and hospital stay did not have a significant difference but was longer in the low TPI and high IMAC groups. In terms of postoperative complications, patients in low TPI group had higher risks of pneumonia compared with high TPI (LT: 4% vs HT:0 %, P=0.002). Otherwise patients in the high IMAC group had higher risks of SSI compared with low IMAC (HI: 6% vs LI: 1%, P=0.014). There were more patients in the low TPI group that could not discharged home and were transferred to a hospital (LT: 14.3% vs HT: 4.2%, P=0.01). Mortality rate was similar in the two groups. (Tables 3, 4)

Relationship between muscle area, mass and function

For patients who underwent cardiac surgery between August 2016 and February 2018, hand grip strength and gait speed did not correlate with TPI and IMAC (hand grip: TPI, R^2 = 0.136, P =0.174 IMAC, and gait speed: R^2 = 0.127, P =0.02) (Figures 3A-D). TPI and the Euro score ,TPI and IMAC were not correlated also.(Figure 4-5)

We defined major complication based on Japan Adult Cadiovascular Surgery database.

The major complications is consisted in 7 subgroup (Operative, neurologic, pulmonary, infective, vascular, renal, others) and 31 item. [19] [20] It is based on The Society of Thoracic Surgeon

National data base. [21]

Univariate analysis revealed that sarcopenia, age, serum albumin, GNRI, CPB time, low TPI and high IMAC were significant risk factors for developing complications. Patients with both low TPI and high IMAC have an odds ratio is 2 to 3 times greater than those with only low TPI or high IMAC.

(OR, both low TPI and high IMAC: 6.356, low TPI: 3.284, high IMAC: 3.284)

Multivariate analysis demonstrated that cardiopulmonary bypass time (hazard ratio, 1.007; 95% confidence interval 1.002–1.013, P = 0.006), low TPI (hazard ratio, 2.581; 95% confidence interval 1.152–5.783, P = 0.036) and high IMAC (hazard ratio, 3.973; 95% confidence interval 1.737–9.088; P = 0.001) were significant risk predictors for the development of complications (Table 5).

Discussion

This study demonstrates that TPI and IMAC and cardiopulmonary bypass time are the independent predictors of major complication. In recent years, cardiac surgery has changed drastically because of the development of minimally invasive treatment. The development of catheter-based therapy for the treatment of aortic stenosis in patients at high risk has led to a focus on concepts of frailty in determining the optimal treatment for aortic stenosis in elderly patients [10, 22, 23]. In the near future, mitral valve lesions will also treated by catheter-based therapy, and the evaluation of frailty will be of greater importance [24-26].

In this study, cardiopulmonary bypass time and sarcopenia are significant risk factors for the development of complications. It has been reported previously that CPB time increase complication. CBP induce a systemic inflammatory response and cause lung injury, [27] and also renal dysfunction is major complication of CBP. [28]

Consideration of sarcopenia as a risk factor may lead to improved outcomes even in patients that do not have indications for catheter treatment. By using the results of CT scan analysis and functional tests to determine preoperative risk, a more appropriate technique will be selected, resulting in improved outcomes.

Sarcopenia assessment by the iliopsoas muscle area using CT scan is considered to be an established tool to diagnose sarcoenia. ~~It is reported that low TPI leads to differences in survival and rate of complications after liver transplantation surgery and in patients with cancer [4-7, 13]. It has been recently suggested that sarcopenia leads to increased hospital length of stay after cardiac surgery[13]. Sarcopenia assessed by TPI is an objective frailty assessment tool for predicting outcomes following either open or transcatheter aortic valve replacement [11]. Sarcopenia has also been associated with the development of complications and decreased overall survival after thoracic aortic surgery[12].~~

Zuckerman et al measured the cross-sectional lean muscle area at the L4 vertebra (psoas muscle area, lumbar muscle area) and the T4 vertebra (thoracic muscle area) in patients undergoing cardiac surgery. The associations of these three muscle areas with frailty markers and postoperative length of stay were investigated. They concluded that the psoas muscle area was the most highly associated indicator to predict length of stay [13]. The lumbar muscles better reflect muscle strength and mobility of the lower limbs compared to the lumbar and chest muscle groups. The lumbar muscles are the lumbar pillars, the legs of the hip joint and the flexor of the stabilizer.

Therefore, it plays a decisive role in walking, rising from a seated position, and maintaining balance[29].

Previous studies focused on skeletal muscle mass and suggested that not only the amount of muscle is important, but also the quality is important, and focused on muscle quality as a new sarcopenia evaluation index. We selected IMAC which is expresses “fattening” of the muscles. A decline in the quality of muscle correlates with muscle weakness and functional deterioration[30]. It also correlates with the severity of non-alcoholic steatohepatitis[17]. There are few reports of postoperative outcomes considering sarcopenia evaluation using IMAC, but some reports suggest a significant correlation between muscle mass and quality and prognosis in patients undergoing gastrointestinal surgery [16, 31, 32]. A high IMAC was an independent risk factor for skeletal muscle wasting in patients undergoing vascular surgery[14].

The lack of correlation between TPI and the Euro score suggests the opportunity for a unique risk assessment tool for patients undergoing cardiac surgery. TPI and IMAC were not correlated . Both TPI and IMAC showed sarcopenia status, but they are independent indicators.

IMAC does not correlate with TPI in the present study which is consistent with previous reports. Low TPI and high IMAC are risk factors for complications and an indicator of sarcopenia

with different properties[16, 31, 32]. Based on the above results, the routine application of early nutrition therapy and rehabilitation in patients with sarcopenia might improve postoperative outcomes but verifying this will require further clinical trials. In rehabilitation of the elderly, the diagnosis of sarcopenia, identification of its cause, and management are necessary. To synthesize muscles, ingesting essential amino acids for energy supplementation is effective [33].

The nutritional intervention added to resistance training during rehabilitation may improve skeletal muscle mass to improve the ability to perform activities of daily living. [34] In patients undergoing liver transplantation, perioperative nutritional therapy was demonstrated to significantly improve overall survival in patients with sarcopenia, but in patients without sarcopenia survival was not affected. In elderly perioperative patients with a diagnosis of sarcopenia, the determination of its cause and appropriate management are required.

Evaluation of a patient for sarcopenia using TPI and IMAC may provide guidance for understanding operative risk and selection of the most appropriate surgical procedure. Sarcopenia may also be a prognostic factor for the development of complications, especially respiratory complications and prolonged hospitalization stay. Identifying patients with sarcopenia may improve surgical outcomes by suggesting interventions such as perioperative rehabilitation and

improving nutritional status.

There are several acknowledged limitations in this study. The study population includes patients for elective surgery only, so mortality or morbidity may be lower than all patients undergoing cardiac surgery. This study is a single center retrospective study. A larger sample size may be needed to confirm these findings. We did not investigate other data about frailty scales, including the outcomes of quality of life. The study patients are all Asian, and it is not clear whether the same cut-off value could be used for other ethnic groups.

Conclusions

This study demonstrates the impact of sarcopenia on outcomes following elective cardiac surgery in the elderly. Sarcopenia is not a predictor of mortality following cardiac surgery, but the incidence of complications is higher in patients with sarcopenia. Sarcopenia should be recognized as a new risk factor in patients undergoing cardiac surgery. Psoas muscle area and intramuscular adipose tissue content are frailty assessment tools for patients undergoing cardiac surgery. It is important to consider both muscle mass and muscle quality to assess their impact on patients undergoing cardiac surgery.

Conflict of interest statement: Yuriko Kiriya and other co-authors have no conflict of interest.

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Figure Legends

Figure 1. Image analysis of Total Psoas Area Index (TPI) as an indicator of muscle quantity.

(A) Cross-sectional computed tomography (CT) scan images at the L3 level

(B) A CT scan image that with low TPI indicating sarcopenia.

(C) A CT scan image with high TPI indicating no sarcopenia.

Figure 2. Image analysis of intramuscular adipose tissue content (IMAC) as an indicator of muscle quality.

(A) Cross-sectional computed tomography (CT) scan images at the umbilical level.

(B) Four small circles were placed on subcutaneous fat away from major vessels. (C) The example of patient's CT image with high IMAC indicating sarcopenia.

(D) The example of patient's CT image with low IMAC indicates non sarcopenia.

Figure 3. The relationship of functional test and Total Psoas Area Index (TPI)

A) The relationship of Hand grip test and TPI

B) The relationship of Gate speed test and TPI

C) The relationship of Hand grip test and intramuscular adipose tissue content (IMAC)

D) The relationship of Gate speed test and IMAC

Figure 4

A) The relationship of Euro score and Total Psoas Area Index

B) The relationship of Euro score and intramuscular adipose tissue content

Figure 5. The relationship of Total Psoas Area Index and intramuscular adipose tissue contente, OR

Odds ratio, CI Confidence interval