論文題目

胸部大動脈術後患者における術後筋力低下の関連因子：後ろ向きコホート研究

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リハビリテーション療法学専攻

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CONTENTS

Abstract

Objective: Aortic surgery is often performed in elderly patients, and these patients have a high risk of postsurgical muscle weakness. To reinforce purposeful postsurgical rehabilitation, we aimed to investigate the factors associated with postsurgical muscle weakness in patients who underwent thoracic aortic surgery.

Methods: This retrospective cohort study analyzed data of consecutive patients who underwent elective thoracic aortic surgery with cardiopulmonary bypass, and whose knee extensor isometric muscle strength (KEIS) were measured pre- and postoperatively at University Hospital between January 2012 and December 2018. The primary outcome was percent change in KEIS (% change in KEIS). Multivariate linear regression analysis was used to identify independent risk factors for % change in KEIS.

Results: Overall, 218 patients were included and % change in KEIS was -9.2 (interquartile range: -23.4, 5.7) %. Multivariate linear regression analysis showed that mechanical ventilation time, days from initial sitting to 100 m walking, and the number of exercises in the rehabilitation room were associated with % change in KEIS.

Conclusions: This study may serve as a reference to stratify patients with thoracic aortic surgery at risk of postsurgical muscle weakness and may be helpful in planning preventive or alternative interventions. Further studies are needed to examine the

causality of factors associated with postsurgical muscle weakness and preventive or alternative interventions in these patients.

要旨

目的：大動脈手術の対象者は高齢者が多く，これらの対象者では術後筋力低下のリスクが高い。合目的的な術後リハビリテーション（リハ）を強化するため，本研究は胸部大動脈手術患者における術後下肢筋力低下の関連因子を調査することを目的とした。

方法：本後ろ向きコホート研究では，2012年1月から2018年12月に大学病院にて人工心肺を用いて胸部大動脈手術を受けた連続症例のうち，術前および術後の膝伸展筋力（下肢筋力）を測定した者のデータを解析した。主要アウトカムは下肢筋力変化率とした。多変量線形回帰分析を用いてKEIS変化率の独立したリスク因子を調査した。

結果：研究対象者は218名で，全体の下肢筋力変化率は-9.2% （四分位範囲 -23.4, 5.7）であった。多変量線形回帰分析の結果，下肢筋力変化率の有意な関連因子は，人工呼吸器管理時間，初回離床から100m歩行到達までの日数，運動療法室での運動回数であった。

結語：本研究は，胸部大動脈手術患者における術後筋力低下のリスクを層別化し，予防的または代替的な介入を計画する際の参考になると考えられる。胸部大動脈手術患者における術後筋力低下の関連因子の因果関係，および予防的または代替的な介入の検討については，今後のさらなる研究が必要である。

1. Introduction

The number of patients with aortic diseases, including diseases of the thoracic aorta, is on the increase as the society ages. In Japan, according to the annual surveys of the Japanese Association for Thoracic Surgery, thoracic aortic surgery was performed on 20,746 patients in 2017, which was more than a fivefold increase over the past 20 years (Shimizu et al, 2020). Although the pathogenesis and etiology of aortic diseases have not been established, the involvement of inflammation in the weakening of the aortic wall, arteriosclerosis, hypertension, and genetics have been reported. Since chronic inflammation is an established factor that is involved in the mechanism of development of atherosclerosis (Palinski and Tsimikas, 2002), coronary risk factors and chronic inflammation are two major characteristics of patients with aortic diseases.

Thoracic aortic surgery is one of the most difficult surgeries because the method of extracorporeal circulation differs depending on the surgical site; furthermore, systemic organ protection using hypothermia, aortic clamp, and retrograde or antegrade cerebral perfusion for brain protection are often employed. Although over 50% of descending aortic surgery has been changed to minimally invasive surgery using stent grafts, conventional thoracotomy, which induces massive postsurgical inflammation, is still the main procedure1 for 80 to 90% of surgeries involving replacement of aortic root, ascending aorta, and aortic arch (Shimizu et al, 2013). Cardiopulmonary bypass, which is essential for organ protection and is often used in thoracic aortic surgery, is also known to induce coagulation activity and inflammatory reactions due to changes in hemodynamics and contact with foreign bodies (McGuinness, Bouchier-Hayes and Redmond, 2008). These surgery-induced inflammation can be a trigger for postsurgical muscle proteolysis, and patients who undergo aortic surgery may consequently develop complications due to postsurgical muscle weakness including respiratory muscles (Smetana, Lawrence and Cornell, 2006).

In addition to the surgical invasiveness, various risk factors responsible for accelerating muscle weakness during the acute phase of critical illness and surgery include female sex, multiorgan system failure, hyperglycemia, certain medications, long duration of mechanical ventilation, inactivity, and malnutrition (Kress and Hall, 2014). It is widely known that disuse due to immobility is also a contributing factor to the decline in skeletal muscle function. Presurgical grip strength, body mass index, hemoglobin levels, and cardiopulmonary bypass time were reported as predictors of postsurgical muscle proteolysis in patients after cardiac surgery (Iida et al, 2016). Postsurgical muscle weakness and muscle loss result in a reduction in the ability to stand and walk, easy fatigability and low quality of life (van Venrooij et al, 2012; Zargar-Shoshtari and Hill, 2009; Bautmans et al, 2010). As noted above, patients undergoing thoracic aortic surgery are mostly elderly adults, who are increased catabolic status and decreased physiological reserve (Roubenoff, 2003). In view of these factors, patients undergoing aortic surgery can be at risk for postsurgical muscle weakness. However, there are few reports on physical function in patients undergoing thoracic aortic surgery. Clinical approaches for the prevention of postsurgical muscle weakness have not progressed because the factors associated with postsurgical muscle weakness are not clear in this population. Therefore, in this research, we aimed to retrospectively investigate the factors associated with postsurgical muscle weakness in patients undergoing thoracic aortic surgery.

2. Methods

Study subjects

This was a retrospective cohort study. A total of 435 patients who underwent elective thoracic aortic surgery with cardiopulmonary bypass between January 2012 and December 2018, were consecutively surveyed. The eligibility criterion was: patients whose knee extensor isometric muscle strength (KEIS) was measured both preoperatively and on postoperative day 14. The exclusion criteria were presurgical cognitive impairment (Mini Mental State Examination score (Folstein, Folstein and McHugh, 1975) ≤17 points, 90 percentile of people aged 80 and older (Crum, Anthony, Bassett and Folstein, 1993)), patients with other intervention studies, postsurgical cerebrospinal disorders, staged thoracic endovascular aortic repair

(TEVAR) during hospitalization, and in-hospital death. Postsurgical cerebrospinal disorders were defined according to the criteria of the Japan Cardiovascular Surgery Database (JCVSD) (Japan Cardiovascular Surgery Database). The surgical day of staged TEVAR was not established and depended on the cases, affecting postsurgical progress of rehabilitation. Overall, 217 patients were excluded based on the exclusion criteria, and data for 218 patients were finally included in this study (Figure 1).

Primary outcome measure

The primary outcome was the percent change in KEIS (% change in KEIS). KEIS was measured preoperatively and on postsurgical day 14 using an isometric dynamometer (μTas F-1; ANIMA Corp, Tokyo, Japan) and was divided by body weight on the same day as the measurement. The patients sat on a bench with their hips and knees at flexed at 90°. The dynamometer was set in front of the distal shin and fixed to a bar of the bench. After one practice, the maximum KEIS was measured for five seconds twice on each side. The moment arm was measured from the lateral knee joint space to the top of the dynamometer belt. The greater peak torque per body weight value of the two measurements, on the right and the left, was obtained for analysis (Kitamura et al, 2019).

Other covariates

As other covariates of % change in KEIS, the demographic information, including smoking history, medical history, blood test, handgrip strength, surgical information, mechanical ventilation (MV) time, postsurgical rehabilitation progress, postsurgical complications, postsurgical nutrition, length of intensive care unit (ICU) stay, postsurgical hospital stay, and discharge to home or another hospital, were collected from the electronic medical records. The postsurgical rehabilitation progress was evaluated as follows: First, days from surgery to initial sitting was defined as the period from surgery to the first day of sitting on the edge of the bed. Similarly, we evaluated the days from initial sitting to 100 m walking and to the rehabilitation room for exercise. The fourth was the number of exercises in the rehabilitation room until postsurgical KEIS measurement was performed.

Handgrip strength was measured on the same day as the KEIS measurements. Handgrip, one of the markers for sarcopenia and frailty, which is also associated with length of hospital stay (Sultan, Hamilton and Ackland, 2012), was investigated to describe the characteristics of patients. The cutoff value of handgrip strength was < 28 kg for male and < 18 kg for female patients in this study (Chen et al, 2020). Handgrip strength was measured using a JAMAR digital dynamometer (Patterson Medical, Bolingbrook, USA) that was set at the second grip position. The patients sat on a bench with their elbows flexed set at 90°, and the wrist was in a neutral position. The maximum value measured twice on each hand, and the greater value was used (Kamiya et al, 2017). Obesity was evaluated using body mass index $\geq$ 25 kg/m^2 according to the Japanese definition (Examination Committee of Criteria for 'Obesity

Disease' in Japan; Japan Society for the Study of Obesity, 2002). MV time was defined according to the criteria of JCVSD (Japan Cardiovascular Surgery Database). If a patient needed repeated intubation and extubation, the total MV time was used. The maximum postsurgical blood glucose value was collected during the early morning blood tests on the first to third postsurgical days. Nutrition was investigated by computing the average daily dose of intravenous, enteral, and oral nutrition from postsurgical days 1-14. Among the postsurgical complications, pneumonia, acute kidney injury, and gastrointestinal complications were defined using the criteria of JCVSD (Japan Cardiovascular Surgery Database). Delirium was defined as those who were positive for Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) (Ely et al, 2001). CAM-ICU was assessed daily by nurses in the ICU every 4 hours. After ICU discharge, CAM-ICU was assessed by physical therapists from Monday to Saturday for patients with suspected delirium. Arrhythmias were defined as those that newly occurred postsurgicaly and required treatment. Dysphagia was defined as dysphagia diagnosed by swallowing evaluation or requiring swallowing therapy. It was reported that increased length of ICU stay was associated with skeletal muscle wasting (Puthucheary et al, 2013).

Postsurgical rehabilitation program

The postsurgical rehabilitation program was conducted according to the Guidelines for rehabilitation in patients with cardiovascular disease (JCS Joint Working Group, 2014). The doctors, nurses, and physical therapists mobilized the patients and progressed through the cardiac rehabilitation program if the patients were hemodynamically stable after the next day of surgery. The patients progressed to sitting, standing/stepping, walking in the room, and walking in the ward depending on their hemodynamic stability, oxygenation, and the subjective and objective symptoms of patients. The walking stages within the ward consisted of walking 50 m, 100 m, 200 m, and walking for 6-minutes, at a comfortable speed. The progression from one stage of rehabilitation to the next was determined by the patient's condition, rather than necessarily progressing from one stage to the next every day. Hence, some patients progressed two or more stages per day, and others stopped at the same stage for a few days. The progression of the program was stopped when the patients satisfied the criteria for terminating the rehabilitation program after large vessel surgery (JCS Joint Working Group, 2014). The postsurgical rehabilitation program at the ICU and the ward was conducted by physical therapists and nurses on weekdays and Saturdays, and by nurses on Sundays and on holidays for 20-60 minutes. Exercise in the rehabilitation room was initiated based on the progress of the early mobilization program and completion of 60 minutes of sitting tolerance. Since exercise in the rehabilitation room takes 40 to 60 minutes, only patients who could sit for more than 60 minutes were eligible for exercise in the rehabilitation room, taking into account the traveling time from the hospital ward. Exercise in the rehabilitation room was conducted for approximately 60 min on weekdays. In addition to aerobic exercise comprising mainly ergometer training, resistance training was conducted according to the muscle strength of the patients, and comprised squats and calf raises, knee extension/flexion, and hip abduction/adduction using equipment (HUR, Kokkola, Finland).

Statistical analysis

To extract factors associated with the rate of change in lower extremity muscle strength for the primary outcome, characteristics of the participants with and without % change in KEIS < 0% were compared using the Mann-Whitney U test, Student's t-test for the continuous variables, chi-square test, or Fisher's exact test for categorical variables. The Shapiro-Wilk test was used to analyze normality of the distribution for the continuous variables. Continuous variables were expressed as mean ± SD or median (IQR), depending on the normality of the data. We then performed univariate and multivariate linear regression analysis using % change in KEIS as the dependent variable. Presurgical KEIS was included as an independent variable using the forced-entry method. The other independent variables included in the forward selection were the factors that significantly related to % change in KEIS < 0% in the univariate analysis, taking into account the variance inflation factors and the medical reasons. We examined the residuals for the normality using the Shapiro-Wilk test, quantile-quantile plot, and histogram, and the Breusch-Pagan test was used to examine the heteroscedasticity (Breusch and Pagan, 1979). A P value of < 0.05, was considered statistically significant. SPSS version 27.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analyses.

3. Results

Characteristics of patients

The median age of the patients was 67 (IQR: 58, 73) years, and 27% of the patients were female. The most frequent comorbidity was hypertension (65%) followed by dyslipidemia (30%) and stroke (12%). Diabetes Mellitus was observed 11% of the patients. The presurgical KEIS was 1.20 (IQR: 0.96, 1.43) Nm/kg and grip strength was 35 ± 8 kgf for male and 20 (IQR: 17, 24) kgf for female (Table 1). The length of postsurgical hospital stay was 20 (IQR: 17, 26) days, and % change in KEIS was -9.2 (-23.4, 5.7) % (Table 2).

Comparison between the two groups (those with and without % change in KEIS < 0%) revealed that there was no significant difference in age or sex (Table 1). Compared to the % change in KEIS ≥ 0% group, the % change in KEIS < 0% group showed a significantly higher presurgical KEIS, longer surgical time and cardiopulmonary bypass time (Table 2). There was no significant difference in postoperative complications between the two groups. MV time, length of ICU stay, and postsurgical hospital stay were significantly longer in the % change in KEIS < 0% group than in the % change in KEIS ≥ 0% group. The progress of rehabilitation was significantly prolonged in the % change in KEIS < 0% group, and the number of exercises in the rehabilitation room was significantly less in these patients. The distribution of rehabilitation progress is shown in Figure 2.

Factors associated with % change in KEIS

A histogram of % change in KEIS was shown in Figure 3. In the multiple linear regression analysis adjusted for presurgical KEIS, MV time, days from initial sitting to 100 m walking, and the number of exercises in the rehabilitation room were found to be independently associated with the % change in KEIS (Table 3). The residuals of this model were not the heteroscedasticity ($P = 1.000$) or normally distributed ($P < 0.001$) (Figure 4).

4. Discussion

The findings from this study suggest that MV time, days from initial sitting to 100 m walking, and the number of exercises in the rehabilitation room were independent associated factors of % change in KEIS in patients underwent thoracic aortic surgery. To the best of our knowledge, this is the first study to demonstrate a decline in KEIS and its associated factors after thoracic aortic surgery. The findings of this study may provide a reference to stratifying patients at risk of postsurgical muscle weakness for planning preventive interventions.

In the present study, almost two-thirds of the patients had decline in KEIS, the median of % change in KEIS on postsurgical day 14 was -9.2%. In patients who underwent thoracic aortic surgery or cardiac surgery, no previous study has indicated the % change in KEIS on postsurgical day 14. In our other study that investigated % change in KEIS in elderly patients with diabetes mellitus who underwent cardiac surgery, the average value of % change in KEIS on postsurgical day 14 was -7.1% (unpublished data), which is comparable to this study. On day 7 after cardiac surgery, the % change in KEIS was reported to be -35 to -18% (Iida et al, 2016; Iwatsu et al, 2017). Based on the results of these reports and the findings of our study, including some unpublished data, % change in KEIS in postsurgical patients may depend on both the period after surgery and the characteristics of patients, such their age, presence of comorbidities, among others. The characteristics of patients who underwent total aortic arch replacement among 740 Japanese patients revealed that the mean age, prevalence of female, hypertension, dyslipidemia, diabetes mellitus, chronic lung disease and smoking were 70 years, 30, 79, 29, 13, 20, and 60%, respectively (Ikeno et al, 2020). In this study, the age and the prevalence of those factors were approximately equal to that report. In addition, the mean surgical time and cardiopulmonary bypass time were also similar to those in a previous study (Ikeno et al, 2020), suggesting the generalizability of the findings in this study.

The association between the MV time and % change in KEIS was consistent with those of a previous study in postsurgical patients. MV time, along with surgical time, is an inducer of postsurgical inflammation (Ranieri et al, 1999) and increased inflammation has been shown to be an associated with muscle proteolysis and postsurgical muscle weakness (Iida et al, 2016; Iida, Yamada, Nishida and Nakamura, 2010). Prolonged MV is a risk factor for the generalized muscle weakness, the so-called ICU-acquired weakness (Kress and Hall, 2014). Similar findings have reported in critically ill patients in whom skeletal muscle wasting occurs early and rapidly after prolonged MV (Puthucheary et al, 2013). Prolonged MV invokes the dose of the sedative medications, a powerful inducer for muscle weakness, and these medications could last for several hours to days after their administration was stopped. It has also been reported that the prolonged MV is associated with increased length of ICU and hospital stay, and long-term prognosis (Bailey et al, 2011; Cox et al, 2007; LaPar et al, 2013; Saleh et al, 2012). Therefore, the MV time can be regarded as a notable risk factor for postsurgical muscle weakness.

In this study, the days from initial sitting to 100 m walking was selected as a correlation of % change in KEIS, suggesting the possibility of early initiation and progression of walking as a preventive measure for postsurgical muscle weakness. In our hospital, the achievement of 100 m walking leads to permission for the patients to walk to the toilet, and to increase activity within the ward. A previous study has reported that the delayed achievement of 100 m walking after cardiac surgery was associated with decreased in-hospital step counts before discharge (Takahashi et al, 2015), supporting the association between 100 m walking and patients' physical activity. Another report found that early activity on postsurgical days 1-5 positively correlated with exercise tolerance on postsurgical day 6 in cardiac surgery patients (Mungovan et al, 2017). Taken together, these findings suggest that greater postsurgical physical activity may lead to improved physical function. Delayed walking in patients with aortic surgery may be due to advanced age, low activities of daily living (ADL), postsurgical complications such as stroke, and systemic conditions such as impaired oxygenation, arrhythmia, and low output syndrome, or agitation (Taya et al, 2008). In this study, the most frequent postsurgical complication was arrhythmia (30%), followed by delirium (15%). In patients with heart valve surgery, postsurgical atrial fibrillation was an independent predictor of delayed postsurgical walking, and delayed walking was reported as a significant associated factor for decreased postsurgical lower extremity function in the group with postsurgical atrial fibrillation (Kato et al, 2019). Neuromuscular electrical stimulation (NMES) may be helpful in these cases of postsurgical complications, as NMES is beneficial for KEIS at discharge (Sumin et al, 2020). However, there is a possibility that the patients with delayed 100 m walking were already suffering from muscle weakness caused by surgery-induced inflammation or postsurgical complications; the results of this study should be carefully interpreted with a possibility of reverse causality.

Another factor related to % change in KEIS was the number of exercises in the rehabilitation room, suggesting that exercising more often may reduce the degree of extremity muscle weakness. Exercise after thoracic aortic surgery is strongly recommended to improve ADL and exercise tolerance (JCS Joint Working Group, 2021). In a randomized controlled trial, improved exercise tolerance in combination with early walking and exercise has been reported in cardiac surgery patients (Zanini et al, 2019). Results of the present study in patients who underwent thoracic aortic surgery support the previous studies. According to the postsurgical rehabilitation program in our hospital, the initiation of exercise training at the rehabilitation room in this study indicated the sitting tolerance of 60 minutes and stable respiratory/circulatory condition during 200 m or 6-minute walking. Therefore, the number of days between the achievement of 100 m walking and starting exercise training in the rehabilitation room, varied depending on the patients' condition. If the patient's presurgical low ADL results in a delayed walking and reduced the number of exercises in the rehabilitation room, it is suggested that the patient switch to exercising in the rehabilitation room as soon as sitting tolerance is achieved. If the number of exercises is limited due to overlap with an examination, it may be necessary to coordinate as much as possible in advance. Exercise cannot be implemented in patients of unstable systemic conditions such as arrhythmias or oxygenation, and tailored interventions to prevent postsurgical muscle weakness, such as NMES described above, may be factored in (Sumin et al, 2020). Due to the observational design of the study, the reverse causality may also need to be cautioned. However, the duration of exercise training in the rehabilitation room was negatively associated with muscle weakness in the multivariate analysis adjusted for the days to achieve 100 m walking. This suggested that an increased amount of exercise training during the post-acute phase may help to prevent muscle weakness.

Contrary to our expectations, postsurgical delirium was not associated with % change in KEIS. Delirium after cardiac surgery has been associated with postsurgical clinical outcomes, including declined functional status, cognitive dysfunction, hospital readmissions, and mortality (Brown, 2014). The incidence of delirium after cardiac surgery is 26-52% (Brown, 2014); the incidence in this study was 15%. This low incidence rate of delirium may be explained by the exclusion of emergency cases or those with postsurgical cerebral infarction. In addition, the prevalence of delirium after ICU discharge was likely to be underestimated since CAM-ICU assessment in the ward was continued only for patients with suspected delirium. These may be the reasons for the low influence of delirium on muscle weakness in this study.

In this study, univariate analysis was performed by grouping the patients by the % change in KEIS < 0% in order to examine factors to be entered into the multivariate analysis. Since minimal clinically important difference is not clear on KEIS and no previous studies are available to our knowledge, we used the % change in KEIS < 0%, which represents the presence or absence of muscle weakness of lower extremity. We also considered not only the univariate results but also the variance inflation factors and medical reasons in selecting the independent variables for the multivariate linear regression analysis, and therefore we believe that there were no obvious errors in the selection of the independent variables.

Study limitations

Firstly, we must describe that this was a single-center, retrospective cohort study. Such retrospective analysis usually includes selection bias. However, as discussed above, the characteristics of our population were similar to those of other large population study on patients with aortic arch replacement (Ikeno et al, 2020), and generalization seems to be possible. Second, as a nature of cohort study, causal relationship could not be determined. Third, test-retest reliability of the KEIS was not confirmed for this study. However, the measurement protocol used in this study has reported to show good test-retest reliability (Kato M, Yamasaki H, Nakajima K, and Hiiragi Y, 2001), and the measurement for each patient was conducted by trained physical therapists. Finally, we could not deny the possibility of the existence of unregistered confounders of % change in KEIS, such as the dosage of sedatives or circulatory agonists and the level of postsurgical activity of patients. Nevertheless, our study still has clinically significant findings that will contribute to qualifying postsurgical rehabilitation practices in patients at high risk of postsurgical muscle weakness. Further studies are needed to examine the causal effect of the factors selected in this study on postsurgical muscle weakness in patients who underwent thoracic aortic surgery.

5. Conclusions

Based on the findings of this study, we hypothesized that % change in KEIS after thoracic aortic surgery was induced by MV time, days from initial sitting to 100 m walking, and the number of exercises in the rehabilitation room. This study may help the stratification of patients at risk of postsurgical muscle weakness and may be helpful in planning preventive or alternative interventions. Further studies are needed to examine the causality of factors associated with postsurgical muscle weakness and preventive or alternative interventions in these patients.

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8. Figures

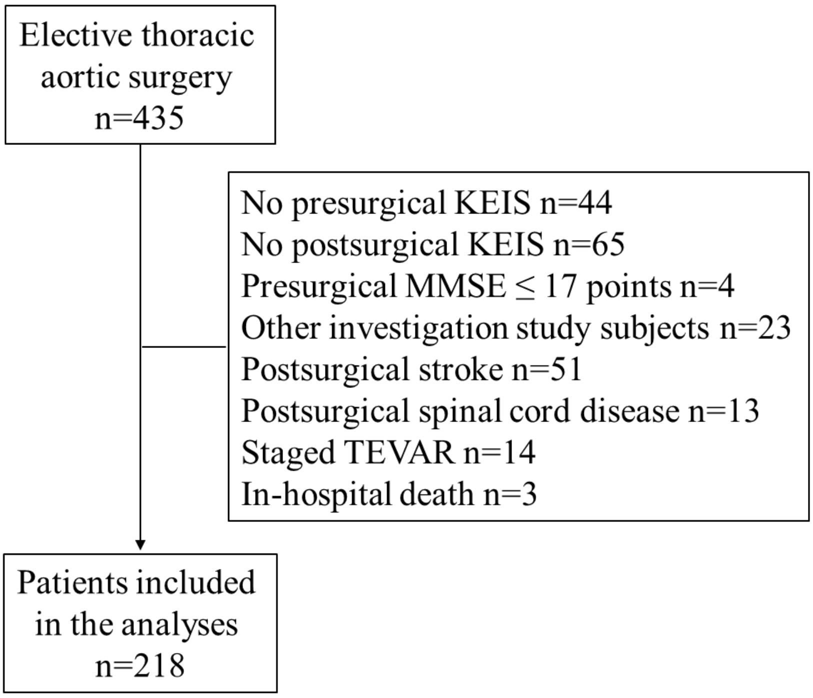

Figure 1. Flow diagram of study participants. Abbreviations: KEIS, knee extensor isometric muscle strength; MMSE, Mini Mental State Examination; TEVAR, Thoracic Endovascular Aortic Repair.

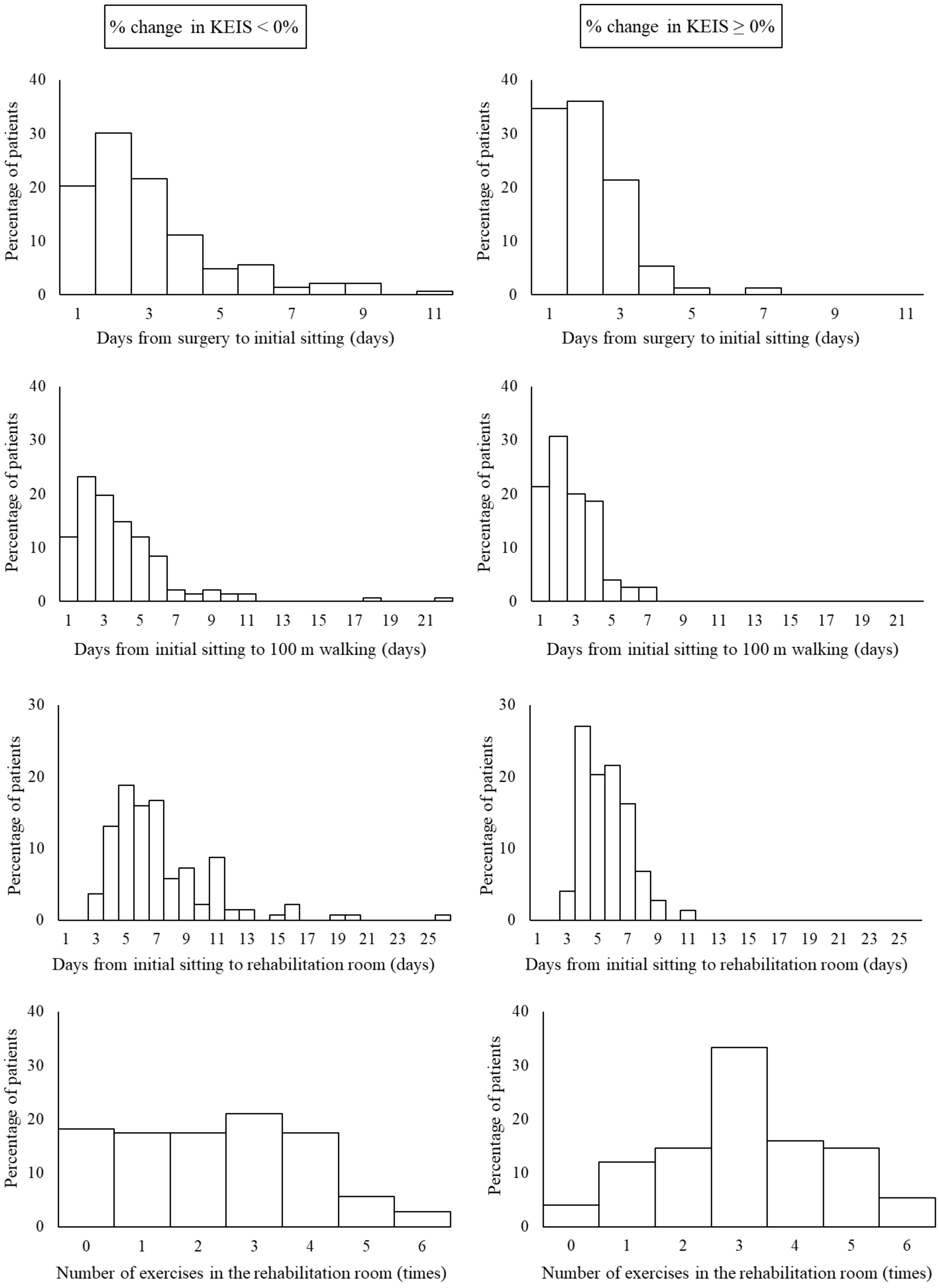

Figure 2. Histogram of rehabilitation progress.

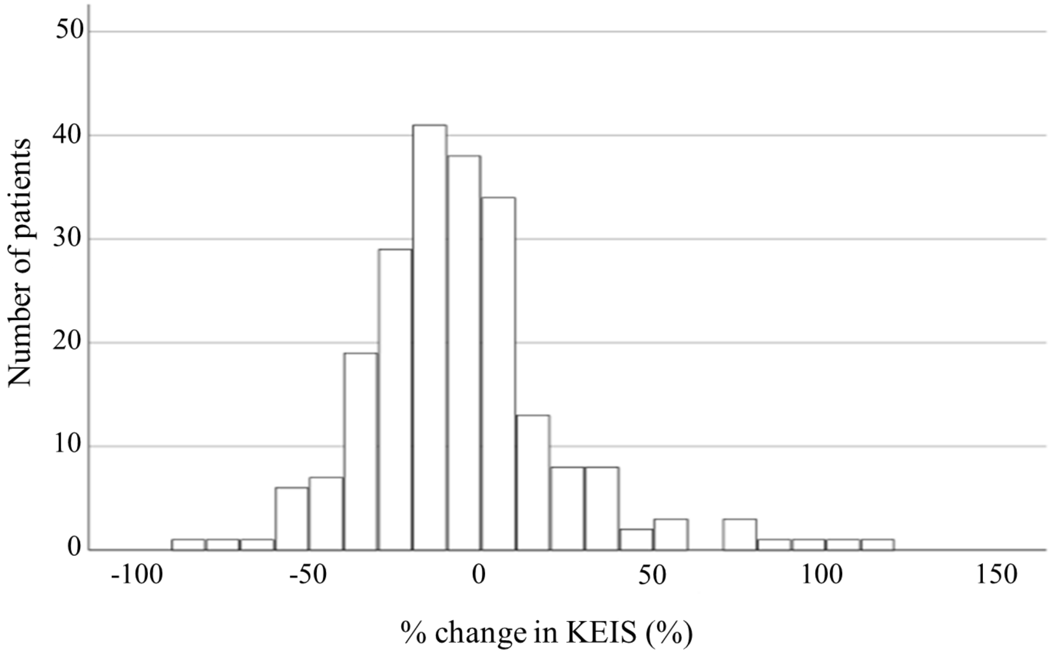

Figure 3. Distribution of the % change in KEIS. Median % change in KEIS was -9.2 (-23.4, 5.7) %. Abbreviations: KEIS, knee extensor isometric muscle strength.

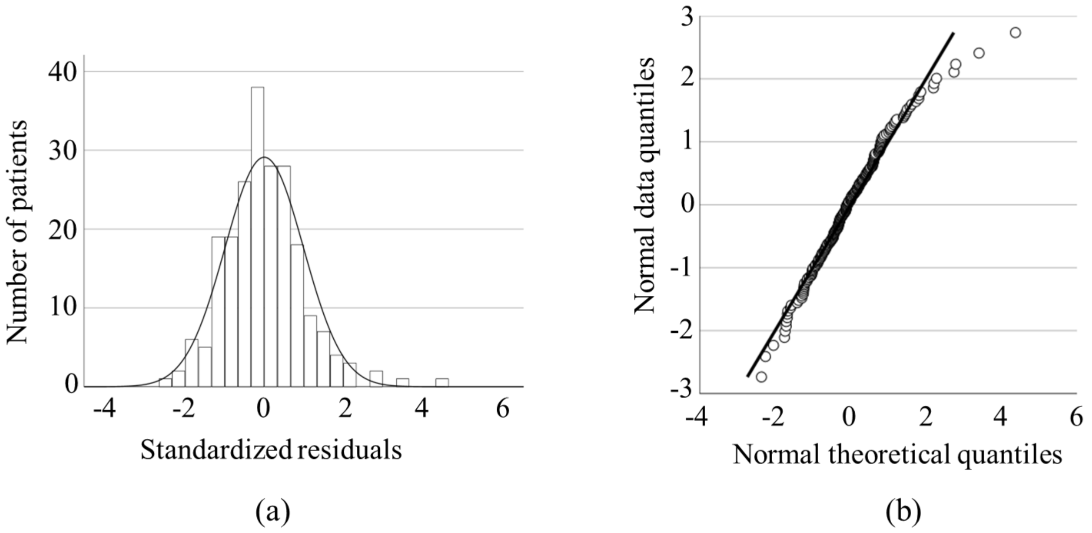

Figure 4. (a) Histogram of the standardized residuals from multiple linear regression analysis. (b) Quantile-quantile plot (QQ-plot) of the standardized residuals from multiple linear regression analysis. Histogram of the standardized residuals and QQ-plot also shows that the residuals of the multiple linear regression model were not normally distributed. Histogram of the standardized residuals would look like a bell-shape and QQ-plot would look like a straight line distribution. But the residuals of this model were not the normality with Shapiro-Wilk test ($P < 0.001$).

9. Tables

Table 1 Characteristics of patients

	Overall (n=218)	% change in KEIS < 0% (n=143)	% change in KEIS ≥ 0% (n=75)	*P* value
Age, yr	67 (58, 73)	67 (58, 73)	68 (56, 72)	0.863
< 65 years	83 (38)	40 (35)	43 (41)	
65-74 years	97 (45)	53 (47)	44 (42)	0.685
≥ 75 years	38 (17)	20 (18)	18 (17)	
Female	59 (27)	33 (23)	26 (35)	0.067
Weight, kg	63 ± 12	65 ± 12	58 ± 11	< 0.001
BMI, kg/m^2	23 ± 3	24 ± 3	22 ± 3	< 0.001
< 18.5 kg/m^2	14 (6)	4 (3)	10 (13)	
18.5-24.9 kg/m^2	145 (67)	91 (64)	54 (72)	< 0.001
≥ 25 kg/m^2	59 (27)	48 (34)	11 (15)	
Smoking history	145 (67)	81 (72)	64 (61)	0.094
Blood test				
Serum creatinine, mg/dL	0.87 (0.72, 1.07)	0.91 (0.76, 1.10)	0.84 (0.67, 0.95)	0.004
Hemoglobin, g/dL	12.6 ± 1.7	12.7 ± 1.6	12.5 ± 1.8	0.445
Serum albmin, g/dL	4.0 (3.8, 4.2)	4.0 (3.8, 4.2)	4.0 (3.8, 4.3)	0.257
CRP, mg/dL	0.13 (0.06, 0.42) (n=215)	0.12 (0.05, 0.41) (n=142)	0.15 (0.07, 0.44) (n=73)	0.340

Comorbidity				
Hypertension	142 (65)	95 (66)	47 (63)	0.579
Dyslipidemia	66 (30)	44 (31)	22 (29)	0.826
Diabetes mellitus	23 (11)	15 (11)	8 (11)	0.968
COPD	7 (3)	5 (4)	2 (3)	0.546
Stroke	25 (11)	13 (9)	12 (16)	0.128
Heart failure	18 (8)	12 (8)	6 (8)	0.921
Muscle strength				
Presurgical KEIS, Nm/kg	1.20 (0.96, 1.43)	1.27 (1.04, 1.52)	1.07 (0.70, 1.24)	< 0.001
Presurgical handgrip strength				
Male, kgf	35 ± 8 (n=158)	36 ± 7 (n=109)	34 ± 9 (n=49)	0.150
Female, kgf	20 (17, 24)	20 (19, 23)	20 (17, 26)	0.748
Handgrip strength, male < 28 kgf, female < 18 kgf	45 (21)	23 (16)	22 (29)	0.023

Abbreviations: KEIS, knee extensor isometric muscle strength; BMI, body mass index; CRP, C-reactive protein; COPD, chronic obstructive pulmonary disease. Values are mean ± SD for normal distribution, median (IQR) for non-normal distribution or n (%).

Table 2 Surgical and postsurgical data

	Overall (n=218)	% change in KEIS < 0% (n=143)	% change in KEIS ≥ 0% (n=75)	*P* value
Surgical data				
Replaced site				0.382
Aortic root, Ascending aorta	47 (22)	26 (18)	21 (28)	
Aortic arch	111 (51)	77 (54)	34 (45)	
Descending aorta	17 (8)	10 (70)	7 (9)	
Thoracoabdominal aorta	33 (15)	22 (15)	11 (15)	
Aortic arch + descending aorta	10 (5)	8 (6)	2 (3)	
Approach				0.413
Median incision	151 (69)	98 (69)	53 (71)	
Left thoracotomy	59 (27)	38 (27)	21 (28)	
L-shaped sternotomy	8 (4)	7 (5)	1 (1)	
Surgical time, hr	7.3 (6.1, 9.1)	7.8 (6.7, 9.7)	6.4 (5.7, 7.9)	< 0.001
Cardiopulmonary bypass time, hr	3.5 (2.7, 4.3)	3.8 (2.9, 4.5)	3.0 (2.6, 3.6)	<0 .001
Cardiopulmonary bypass time ≥ 5hr	30 (14)	25 (18)	5 (7)	0.028
Lowest body temperature, °C	25.7 (24.3, 31.7)	25.4 (24.3, 31.6)	26.5 (24.6, 31.7)	0.178
< 23.0 °C	25 (11)	16 (11)	8 (11)	0.614
23.0-28.9 °C	133 (56)	83 (58)	39 (52)	
≥ 29.0 °C	74 (33)	44 (31)	28 (37)	

Postsurgical data				
Mechanical ventilation time, hr	17 (9, 38)	19 (9, 44)	14 (8, 19)	< 0.001
ICU stay, d	3 (2, 4)	3 (2, 5)	2 (2, 3)	< 0.001
Postsurgical hospital stay, d	20 (17, 26)	22 (17, 26)	18 (16, 24)	0.001
Discharge to home	212 (97)	138 (97)	74 (99)	0.327
Postsurgical complications				
Pneumonia	11 (5)	10 (7)	1 (1)	0.061
Delirium	32 (15)	25 (18)	7 (9)	0.106
Arrhythmia	66 (30)	46 (32)	20 (27)	0.401
Deglutition disorder	13 (6)	10 (7)	3 (4)	0.287
Acute kidney injury	4 (2)	3 (2)	1 (1)	0.573
Gastro-intestinal complication	3 (1)	3 (2)	0 (0)	0.280
Neuromuscular blocking agents	2 (1)	2 (1)	0 (0)	0.429
Nutrition administration, kcal/d	1502 (1387, 1609)	1486 (1349, 1600)	1514 (1438, 1650)	0.091
Blood test				
Peak CRP, mg/dL	18.0 (13.9, 22.5)	18.2 (14.4, 23.8)	17.0 (13.9, 20.6)	0.090
Maximum blood glucose, mg/dL	149 (134, 166)	151 (135, 167)	147 (131, 166)	0.350
Maximum blood glucose ≥ 200 mg/dL	14 (6)	10 (7)	4 (5)	0.438
Muscle strength				
Postsurgical KEIS, Nm/kgf	1.12 ± 0.39	1.05 ± 0.36	1.24 ± 0.42	0.001
% change in KEIS, %	-9.2 (-23.4, 5.7)	-18.4 (-29.9, -9.5)	14.2 (5.3, 31.1)	< 0.001
Postsurgical handgrip strength				
Male, kgf	31 ± 8	31 ± 8	32 ± 8	0.357

Female, kgf	19 (17, 21)	19 (17, 20)	20 (17, 25)	0.194
% change in handgrip strength				
Male, %	-11.6 (-20.6, 2.8)	-14.8 (-22.0, -4.5)	-5.2 (-11.7, 1.0)	< 0.001
Female, %	-6.7 (-14.7, 0.5)	-10.5 (-20.6, 0.0)	-4.8 (-9.6, 1.8)	0.036
Rehabilitation progress				
Days from surgery to initial sitting, d	2 (1, 3)	2 (2, 4)	2 (1, 3)	< 0 .001
Days from initial sitting to 100 m walking, d	3 (2, 4) (n=217)	3 (2, 5) (n=142)	2 (2, 4) (n=75)	0.001
Days from initial sitting to rehabilitation room, d	6 (5, 7) (n=212)	6 (5, 9) (n=138)	5 (4, 7) (n=74)	< 0.001
Number of exercises in the rehabilitation room, times	3 (1, 4)	2 (1, 4)	3 (2, 4)	0.001

Abbreviations: KEIS, knee extensor isometric muscle strength; ICU, intensive care unit; CRP, C-reactive protein. Values are mean ± SD for normal distribution, median (IQR) for non-normal distribution or n (%).

Table 3 Linear regression analysis for % change in KEIS

	Univariate linear regression analysis				Multivariate linear regression analysis			
	Standardized regression coefficient (β)	Partial regression coefficient	95% CI	*P* value	Standardized regression coefficient (β)	Partial regression coefficient	95% CI	*P* value
Age (increment by 5 yr)	-0.032	-0.336	-1.761, 1.089	0.642				
BMI <18.5 kg/m^2	0.149	17.567	1.861, 33.272	0.029				
18.5–24.9 kg/m^2		(Reference)						
≥ 25 kg/m^2	-0.115	-7.492	-16.157, 1.174	0.090				
Surgical time (increment by 1 hr)	-0.275	-3.611	-5.306, -1.916	< 0.001				
Mechanical ventilation time (increment by 1 hr)	-0.409	-0.301	-0.391, -0.211	< 0.001	-0.283	-0.209	-0.297, -0.122	< 0.001
ICU stay (increment by 1 d)	-0.432	-5.442	-6.966, -3.917	< 0.001				
Delirium	-0.160	-13.036	-23.836,	0.018				

			-2.235					
Nutrition administration (increment by 100 kcal/d)	0.143	2.118	0.157, 4.079	0.034				
Peak CRP (increment by 1 mg/dL)	-0.191	-4.157	-7.024, -1.289	0.005				
Maximum blood glucose (increment by 10mg/dL)	-0.125	-1.167	-2.413, -0.079	0.066				
Days from surgery to initial sitting (increment by 1 d)	-0.376	-6.108	-8.127, -4.089	< 0.001				
Days from initial sitting to 100 m walking (increment by 1 d)	-0.314	-3.547	-4.987, -2.107	< 0.001	-0.213	-2.407	-3.833, -0.981	0.001
Number of exercises in the rehabilitation room (increment by 1 time)	0.296	5.235	2.965, 7.504	< 0.001	0.124	2.192	0.000, 4.384	0.04998

Abbreviations: KEIS, knee extensor isometric muscle strength; BMI, body mass index; ICU, intensive care unit; CRP, C-reactive protein. Adjusted $R^2 = 0.385$. Variables entered into multivariate analysis using the forward selection method were listed in the table. Multivariate analysis was adjusted for presurgical KEIS entered by the forced-entry method.