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Long-term prognostic significance of sarcopenia in acute ischemic stroke

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Abstract

Because sarcopenia is widely distributed in patients with acute ischemic stroke (AIS) and has not attracted enough attention, this study aims to explore the relationship between sarcopenia defined by temporal muscle thickness (TMT) and physical function and prognosis of patients with AIS. A total of 265 hospitalized nonsurgical AIS patients from 2015 to 2018, with an age range of 28 ~ 92, were analyzed retrospectively. The median value of TMT was used as the risk classification index of sarcopenia. The main results were the relationship between sarcopenia and Essen Stroke Risk Score, National Institutes of Health Stroke Scale, modified Rankin Score, water swallow test, venous thromboembolism assessment of medical inpatients, activities of daily living assessed by Barthel Index, and the relationship between TMT and final survival outcome. The mean TMT of men in the study cohort was higher than that of women. The measured values of TMT among different researchers had good consistency (intraclass correlation coefficient, 0.980; $P < .001$). After adjusting for confounding variables, logistic regression showed that sarcopenia was associated with Essen Stroke Risk Score (odds ratio, 1.89; $P < .05$) and Barthel Index (odds ratio, 1.67; $P < .05$). Kaplan-Meier analysis showed that the survival time of low TMT group was significantly lower than that of high TMT group (36 vs 49 months; $P < .001$). Multivariate Cox regression showed that there was causal correlation between sarcopenia and patient death (hazard ratio, 3.54; 95% confidence interval, 1.46–8.58; $P < .01$). As a potential comprehensive index, thickness of temporal muscle can be included in baseline evaluation to show the physical status, stroke recurrence, and survival prognosis of AIS patients.

Abbreviations: ADL = activities of daily living, AIS = acute ischemic stroke, ESRS = essen stroke risk score, Hb = hemoglobin, INR = international normalized ratio, NIHSS = National Institutes of Health Stroke Scale, NRS = nutrition risk screening, ROC = receiver operating characteristic, SMI = skeletal muscle index, TG = triacylglycerol, TMT = temporal muscle thickness, VTE = venous thromboembolism.

Keywords: prognosis, sarcopenia, stroke.

1. Introduction

As an age-related progressive syndrome of systemic skeletal muscle atrophy and dysfunction, sarcopenia was first proposed by Irwin Rosenber to describe the process of skeletal muscle loss in the elderly.[1] With the deepening of research, it is gradually found that sarcopenia can occur and progress through a variety of pathogenesis, such as forced braking, dysphagia, sympathetic overactivation, inflammatory response, and muscle denervation, especially closely related to some consumptive diseases.[2] Although the etiology of this secondary sarcopenia is not clear, in the process of the disease, it will not only become a part of the disease and jointly affect the survival and prognosis of patients, but also the complex clinical situation of patients will accelerate the loss rate of skeletal muscle and lead to the vicious cycle of body component loss.

According to the China cardiovascular health and disease report (2019), China accounts for 1/3 of the deaths of cerebrovascular diseases in the world, second only to malignant tumors and heart diseases. The prevalence of stroke will continue to increase in the next 20 years. As the main cause of adult disability rate, it causes varying degrees of disability of 15% of the world's population.[3,4] However, the traditional understanding is mostly limited to brain tissue injury itself; few studies have explored the relationship between body composition and stroke disease status or prognosis, and there is a lack of attention to the changes of tissue structure and basic metabolism of the main effector organ (skeletal muscle).

Recent studies have found that the temporal muscle, as an emerging useful index, is closely related to the survival outcome and prognosis of some brain tumor diseases and nervous system diseases, such as glioblastoma,[5] brain metastasis,[6] and some major postoperative complications.[7] However, so far, no study has explored the correlation between temporal muscle thickness (TMT) and the prognosis of patients with acute ischemic stroke (AIS). Therefore, this study defined TMT as a diagnostic index

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of sarcopenia, tried to retrospectively analyze whether the quantified skeletal muscle is related to poor functional status or the degree of nerve injury, and prospectively explored the relationship between TMT and final survival outcome.

2. Materials and Methods

2.1. Research objects

The study cohort screened 342 nonsurgical AIS patients treated in the First Affiliated Hospital of Xinjiang Medical University from 2015 to 2018. Inclusion criteria include that the patients had clear diagnostic evidence of AIS from imaging and clinical records and brain Magnetic Resonance images and abdominal computer tomography images were obtained within 24 hours of admission. The exclusion criteria were as follows: missing data or unclear important level images; main complications: severe metabolic disorders such as chronic obstructive pulmonary disease, renal failure, liver failure, and human immunodeficiency virus infection; those who have serious disturbance of consciousness so that they are unable to conduct relevant clinical function evaluation; obvious muscle edema or severe asymmetric atrophy caused by craniotomy or other factors; and patients with incomplete teeth or severe dental diseases. After confirming that there was diagnostic evidence of AIS and clear follow-up results, 265 subjects were included in the study cohort. Because of the retrospective and anonymous nature of this study, written informed consent was waived by the medical ethics committee of the First Affiliated Hospital of Xinjiang Medical University.

2.2. Clinical variables

The general clinical data of patients before operation were collected, including age, gender, body mass index, D-dimer, prothrombin time, international normalized ratio, albumin, triglyceride (TG), total cholesterol, high-density lipoprotein, low-density lipoprotein, hemoglobin (Hb), and length of hospital stay, and whether concurrent atherosclerosis, hypertension, arrhythmia, pneumonia, and type 2 diabetes. At the same time, based on the 1-mm T_1 weighted image image collected by General Electric's 1.5T-magnetic resonance image scanner (reduce partial volume effect), the sylvian fissure and orbital roof are predefined as anatomical landmarks, and the largest cross-section of the temporal muscle under the same sequence of scanned images is tracked. Two researchers were under the condition of unknown clinical status of the patient, and Picture Archiving And Communication Systems software was used to perform 3 mean TMT measurements for each patient in the axial direction perpendicular to the long axis of temporal muscle: the sum of bilateral TMT measurements/2, so as to eliminate the impact from oral or partial dental diseases, although we have tried to avoid such patients when we included patients. Contrast enhanced images are considered available. After integrating all data and determining the median TMT, the stroke population was divided into sarcopenia group and nonsarcopenia group.

2.3. Clinical evaluation

Experienced neurologists with the following clinical scale assessment qualifications will perform relevant assessments on the admission of AIS patients with cognitive ability. These widely certified and widely used assessments include the following: the Essen Stroke Risk Score[8]: the highest score was 9 points, including age risk classification, hypertension, diabetes mellitus, myocardial infarction, past stroke history, frequency of smoking, peripheral arterial disease, and other cardiovascular diseases (excluding myocardial infarction and atrial fibrillation); National Institutes of Health Stroke Scale[9]: a standardized assessment with 15 items that can be used to measure the severity of stroke. The higher the number, the higher the severity. 0, no measured stroke symptoms; 1–4, minor stroke; 5–15, moderate stroke; 16–20, moderate-to-severe stroke; and 21–42, severe stroke; modified Rankin Scale[10]: a disability classification model readjusted from the original Rankin scale score, including 7 separate categories from grades 0–6, 0 (no symptoms), 1 (no significant disability), 2 (slight disability), 3 (moderate disability), 4 (moderately severe disability), 5 (severe disability), and 6 (expired); water swallow test[11]: an experimental method for evaluating swallowing ability, which is divided into grades 0–5. The patient sat upright and drank 30 mL of warm water to observe the required time and choking; venous thromboembolism (VTE) assessment[12]: a well-established model for assessing VTE risk by calculating independent individual risk factors, which incorporates multiple risk factors for VTE and stratifies patients for prevention by calculating a total score. An increased risk of VTE was defined as a cumulative score of at least 4; activities of daily living (ADL) are measured by Barthel index scale[13]: a scale that measures activity in patients' daily life pools, consisting of 10 independent activity behaviors with scores ranging from 0 to 100, and serves as a convenient model widely used by healthcare professionals. The higher the score, the greater the disability.

In addition, nurses performed the nutrition risk screening (2002)[14] within 48 hours after operation, to record the basic metabolic status: a nutrition screening tool recommended by the European Society for Clinical Nutrition and Metabolism guidelines. It includes 3 components: the nutritional score (body mass index, weight loss, and dietary intake), the disease severity score, and the age score (age >70 years). Patients are classified as having no or low risk when they have a total score <3 or as having a moderate or high risk when they have a total score ≥3.

2.4. Statistical analysis

All clinical data were entered into excel in a unified format and statistically analyzed by IBM Statistical Product Service Solutions statistics 21.0 software (SPSS, Inc., Chicago, IL, USA). Intraclass correlation coefficient was used to measure the repeatability of measurement results among different researchers. After the data passed the test of parallel lines, logistic regression was used to analyze the odds ratio (OR) between TMT and relevant clinical evaluation. To determine the relationship between TMT and the risk of patient death, receiver operating characteristic curve and the Youden method were used. Kaplan-Meier curve was used to calculate the survival curve, and the log-rank test was used to investigate the difference in survival time between the 2 groups. Multivariate Cox regression model was used to analyze the causal relationship between TMT and death risk, as well as other clinical variables that may affect survival outcomes. The 2-sided test level $a = 0.05$, P values <.05 were considered statistically significant.

3. Results

3.1. Comparison of clinical data

This study consisted of 265 patients (166 male and 99 female) who were diagnosed with AIS by imaging, and they were between 28 and 92 years old. Compared with nonsarcopenia, the age of sarcopenia group is higher ($P < .001$), and the biochemical indexes such as albumin ($P < .05$), TG ($P < .05$), and Hb ($P < .001$) remain at a low level. The number of AIS patients with sarcopenia complicated with atherosclerosis ($P < .05$), pulmonary infection ($P < .05$), and hypertension ($P < .05$) is more (Table 1).

Table 1

Comparison of general clinical data between sarcopenia and nonsarcopenia.

Independent variable	Sarcopenia (n = 131)	Nonsarcopenia (n = 134)	*P*
Gender, male/female	75/56	91/43	.073
Age, mean ± SD			
≤50	10	31	.000
50–60	32	49	
60–70	33	32	
70–80	30	18	
≥80	26	4	
BMI, median (IQR)	25[21-28]	25[22-28]	.669
LOS, median (IQR)	8[6-14]	7[6-10]	.370
Laboratory indicators			
D-dimer, median (IQR)	132[67-268]	108[58-257]	.137
PT, median (IQR)	11.5[11.5-11.7]	11.5[11.5-11.8]	.658
INR, median (IQR)	1.01[0.96-1.07]	1.01[0.97-1.06]	.916
Albumin, g/L, mean ± SD	41.46 ± 4.35	42.71 ± 3.94	.014
TG, mmol/L, median (IQR)	1.23[0.96-1.65]	1.39[1.11-1.94]	.019
TC, mmol/L, mean ± SD	3.86 ± 1.15	3.81 ± 0.93	.704
HDL, mmol/L, median (IQR)	1.01[0.87-1.19]	0.96[0.84-1.12]	.053
LDL, mmol/L, mean ± SD	2.61 ± 0.93	2.52 ± 0.83	.411
Hb, g/L, mean ± SD	135.07 ± 18.41	142.01 ± 16.15	.001
Coexisting diseases			
Atherosclerosis	58	42	.030
Hypertension	110	99	.044
Arrhythmia	35	28	.266
Lung infection	21	10	.030
Type 2 diabetes	50	38	.090

BMI = body mass index, Hb = hemoglobin, HDL = high-density lipoprotein, INR = international normalized ratio, IQR = interquartile range, LDL = low-density lipoprotein, LOS = length of stay, PT = prothrombin time, SD = standard deviation, TC = total cholesterol, TG = triglyceride.

Table 2

Comparison of clinical evaluation between sarcopenia and nonsarcopenia before treatment.

Independent variable	Sarcopenia (n = 131)	Nonsarcopenia (n = 134)	*P*
NRS 2002 (IQR)	1 (0–1)	0 (0–1)	0.001
Water swallow test ≥ 3	14	19	0.389
ESRS ≥ 3	73	39	0.000
NIHSS ≥ 5	36	32	0.502
VTE ≥ 4	23	15	0.139
Barthel index			
Self-care	20	45	.002
Mild	38	40	
Moderate	46	24	
Severe	20	17	
Extremely serious	7	8	
mRS			
0	3	13	.040
1	46	57	
2	31	20	
3	11	13	
4	36	26	
5	4	5	

BMI = body mass index, Hb = hemoglobin, HDL = high-density lipoprotein, INR = international normalized ratio, IQR = interquartile range, LDL = low-density lipoprotein, LOS = length of stay, PT = prothrombin time, SD = standard deviation, TC = total cholesterol, TG = triglyceride.

Table 3.

Logistic regression results of sarcopenia and preoperative clinical evaluation.

Independent variable	OR (95% CI)	*P*
ESRS ≥ 3	1.89 (1.08–3.33)	.027
VTE ≥ 4	1.44 (0.68–3.07)	.342
Water swallow test ≥ 3	0.79 (0.36–1.73)	.548
Barthel index	1.67 (1.05–2.67)	.030
mRS	1.30 (0.81–2.08)	.272
NIHSS	1.50 (0.88–2.54)	.132

CI = confidence interval, ESRS = Essen Stroke Risk Score, mRS = modified Rankin Score, NIHSS = National Institutes of Health Stroke Scale, OR = odds ratio, VTE = venous thromboembolism assessment.

3.2. Correlation between TMT and clinical evaluation

The TMT values of the study cohort ranged from 1.4 to 11.6 mm. The average TMT of men was 0.58 mm, which was significantly higher than that of women ($P < .05$). The intraclass correlation coefficient of the average TMT data measured by the 2 researchers is 0.980 ($P < .001$), which indicates that there is a high degree of consistency between the measurement results of different researchers.

After analyzing the baseline data of 265 AIS patients within 48 hours of admission, we found that the sarcopenia group was more likely to have a risk of malnutrition ($P < .01$), stroke recurrence ($P < .001$), worse ADL ($P < .01$), and poor neurological status ($P < .05$) (Table 2). In order to explore the relationship between TMT and patients' clinical status, water swallow test ≥3 was defined as the presence of swallowing dysfunction, Essen Stroke Risk Score ≥3 was defined as the greater risk of stroke recurrence, and VTE ≥4 was defined as having a risk of VTE. After adjusting for mixed variables such as age, albumin, TG, and Hb, the logistic regression model showed that sarcopenia was a risk factor for the recurrence of AIS patients (OR, 1.89; $P < .05$), which was also an important reason for the decline of ADL (OR, 1.67; $P < .05$) (Table 3).

3.3. Correlation between TMT and survival outcome

According to the results of area under curve analysis, TMT was significantly related to mortality (area under curve, 0.83; 95% confidence interval, 0.76–0.90; $P < .001$) (Fig. 1). Multivariate Cox regression model showed that low TMT was an important risk factor related to the prognosis of AIS patients and the risk ratio (hazard ratio, 3.54; 95% confidence interval, 1.46–8.58) (Table 4). This means that compared with normal TMT, people with low TMT will face nearly 3 times the risk of death. The log-rank test of Kaplan-Meier analysis showed that the survival time of patients above the median TMT (49 months) was significantly longer than ($\chi^2 = 17.677$, $P < .001$) that of patients below the median TMT (36 months) (Fig. 2). In addition, we found significant differences ($\chi^2 = 9.354$, $P < .01$) in median survival time between male (45 months) and female (39 months).

4. Discussion

In recent years, abnormal atrophy of skeletal muscle has been considered as a disease (International Classification of Diseases-10-clinical modification, M62.84) and a powerful predictor of the prognosis of some chronic diseases (such as chronic obstructive pulmonary disease and heart failure) and tumor patients. However, existing studies have pointed out that this progressive syndrome accounts for almost half of the stroke population, but the study of stroke-related sarcopenia is less than that of simple sarcopenia. The skeletal muscle index (SMI) of the third lumbar segment (L_3), which is closely related to the whole body skeletal muscle mass, is usually used as the gold standard for the diagnosis of sarcopenia.[15,16] The main reason why functional indicators (such as 6-minute walking test and maximum voluntary grip strength) are difficult to function is impaired neurological function. AIS patients are often accompanied by varying degrees of physical disability, loss of consciousness, and cognitive impairment. Considering the actual situation of patients with intracerebral hemorrhage and AIS, functional

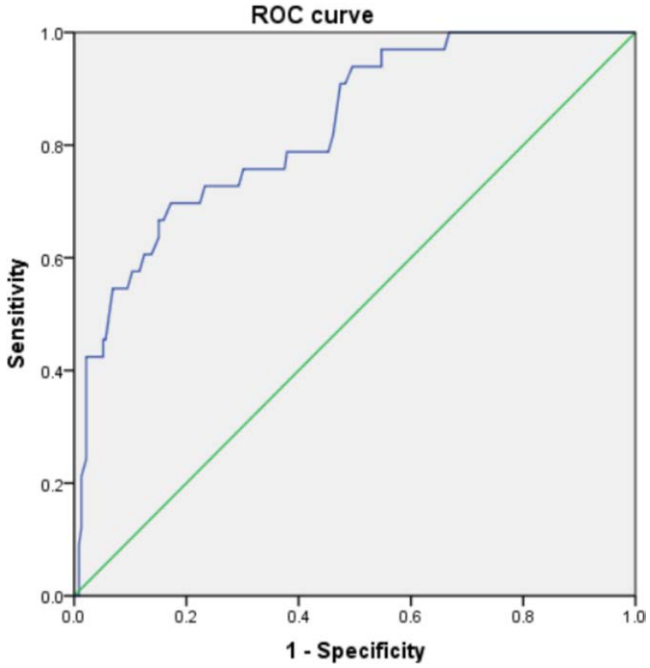

Figure 1. Correlation between TMT and patient death. ROC = receiver operating characteristic, TMT = temporal muscle thickness.

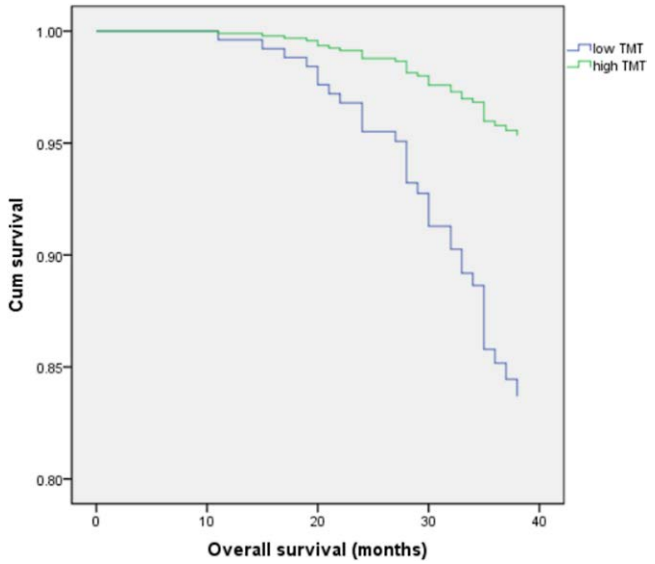

Figure 2. Survival time curves of low TMT and high TMT. TMT = temporal muscle thickness.

Table 4.

Multivariate Cox regression between TMT and various clinical variables

Independent variable	HR (95% CI)	*P*
Gender	0.47 (0.22–1.01)	.052
Age	1.25 (0.85–1.84)	.265
BMI	1.04 (0.94–1.15)	.442
D-dimer	1.00 (1.00–1.00)	.133
PT	0.26 (0.05–1.24)	.091
INR	0.53 (0.02–15.54)	.712
Albumin	0.96 (0.86–1.07)	.485
TG	1.76 (0.83–3.75)	.141
TC	0.47 (0.14–1.66)	.243
HDL	4.01 (0.72–23.51)	.113
LDL	2.39 (0.59–9.77)	.225
Hb	0.99 (0.96–1.01)	.374
NRS	0.89 (0.56–1.41)	.626
Sarcopenia (TMT)	3.54 (1.46–8.58)	.005

CI = confidence interval, Hb = hemoglobin, HDL = high-density lipoprotein, HR = Hazard ratio, INR = international normalized ratio, LDL = low-density lipoprotein, NRS = nutrition risk screening, PT = prothrombin time, TC = total cholesterol, TG = triglyceride, TMT = temporal muscle thickness.

examination, dual-energy X-ray absorption, and bioelectrical impedance analysis, which are very vulnerable to liquid components, may not cover all AIS patients safely and conveniently.

It should be noted that patients with central nervous system diseases rarely have computer tomography and Magnetic Resonance examinations at the L_3, and standard body composition image postprocessing operations are less. Compared with increasing the medical burden of patients and the clinical work of doctors, the emerging index TMT of sarcopenia used in our study may have more clinical value, Moreover, Leitner et al[17] found that TMT was closely related to cross sectional area and SMI indicators of L3 level. The pathological atrophy of temporal muscle can be used as a reliable parameter for nutritional status evaluation, which has basically formed a professional consensus.[18] And many research results also pointed out that TMT has high consistency in measurement results, making it widely used, and can be a substitute indicator of L3-SMI, because the overall quantification of body composition requires nearly half an hour, not to mention time-consuming training on dissection and use of third-party software. According to the above, compared with the professional training of superficial ultrasound detection and complex and time-consuming image postprocessing operation, TMT may be more convenient in clinical application.

The low quality of skeletal muscle is usually due to the breaking of the balance of protein synthesis and decomposition, which mediates the rupture of mitochondrial energy supply chain and protein-energy malnutrition caused by low albumin. The lack of raw materials for the formation of skeletal muscle will not only affect the degree of functional recovery but also affect the expression of plasticity genes in the brain recovery mechanism after stroke.[19,20] Yoshimura et al[21] found that lower Hb was closely related to the severity of sarcopenia, recovery of physical function, and swallowing function in the rehabilitation cohort after stroke. The European Society for Parenteral and Enteral Nutrition[22] proposed a professional consensus that malnutrition is widely involved in the pathogenesis of nervous system diseases. These findings are consistent with our findings that baseline indicators such as albumin and Hb remain low in the sarcopenia cohort.

In addition, according to the report,[3] malnutrition also affects the survival results of more than 20% of stroke patients in China. This may be considering that some intensity of deliberate exercise will further aggravate the severity of functional disability after stroke. After more than 6 months of disease development, survivors will accumulate too much fat in muscles, which will lead to the disorder of tumor necrosis factor-α, interleukin-2,6, and high-sensitivity C-reactive protein. Furthermore, it not only indirectly increases mortality risk by accelerating skeletal muscle loss but also promotes the progression of atherosclerosis and hypertension, which may partly explain the high incidence of atherosclerosis and hypertension in our sarcopenia cohort. Similar mechanism was also found in the relationship between low skeletal muscle mass and patient infection.[23,24]

In addition, the consumption of skeletal muscle content will lead to a lack of energy and a feeling of general weakness, and the further fatigue reaction will directly reduce physical activity, good mental state, and physical recovery speed, forming an adverse cycle of reduced ADL and increasing risk of stroke recurrence.[25] A survey of the elderly in Chinese communities[26] also showed that sarcopenia accounted for a considerable proportion (25%) in the elderly cohort and was independently

associated with disability and poor ADL. Chen et al[27] found in the hip fracture cohort that sarcopenia significantly reduced ADL in patients with hip fracture, especially men. Our research also shows that low skeletal muscle mass can worsen ADL, and it is also an important risk factor for stroke recurrence.

At present, more and more studies have noticed the potential relationship between TMT and brain diseases. Furtner et al[6] gradually found that the prognostic value of TMT is not limited to metastatic melanoma patients, but also breast and lung cancer. The increase in millimeter TMT is associated with an increased risk of death of about 20%. The median survival time of our patients with high TMT (49 months) was significantly longer than that of patients with low TMT (36 months). Our findings that the median survival time of patients with high TMT (49 months) was significantly longer than that of patients with low TMT (36 months) were similar to the published conclusions. Steindl et al[7] reported that TMT values ranged from 3.75 to 15.75 mm in the nervous system disease cohort. Muglia et al[28] and Huq et al[29] reported that in the glioblastoma cohort, the average TMT value was 8.4 mm in the primary group and 9.55 mm in the recurrent group, but there were significant differences at the age level. These conclusions indicate that TMT values vary greatly in different diseases. Our study also shows that although the average TMT value of male patients (0.58 mm) is significantly higher than that of female patients (0.52 mm), the median survival time of female patients (39 months) is significantly lower than that of male patients (45 months). However, gender is not an important factor in the death of related patients, which means that the predictive effect of TMT on the prognosis of AIS patients has nothing to do with gender, which is mutually confirmed with the study by Huq et al.[29]

However, although the sample size of this study has certain statistical ability, but in addition to the survival time, the functional evaluation results are only limited to patients before treatment. Therefore, it is also necessary to conduct long-term and comprehensive dynamic research on patients in the context of large samples to expand the clinical application of our research results. Second, as an emerging indicator of AIS-related sarcopenia, TMT still lacks further gender investigation and efficacy analysis of comparing systemic muscle components. Finally, the study cannot determine the causal relationship between TMT and clinical functional results. Considering the prompt value of TMT to the real-time state of patients before and after treatment, high-quality randomized controlled trials to correct potential variables are also needed.

5. Conclusion

TMT has a certain suggestive value for the risk of recurrence and the changes of activities of daily life after stroke, and is an independent predictor of survival outcomes in patients with AIS. Whether it can be used as a valuable indicator that can comprehensively display physical status in the baseline examination of stroke needs to be verified in large-sample cohort studies.

Author contributions

Yu-Xuan Li contributed to the actual design of the research, the definition of search formulas, the acquisition of relevant data, and the writing of the original article. Wen-Wen Xia is responsible for the review of the included studies and extracted data and final results. Juan Hou contributed half of the data analysis and explanation, and finally determined the outline of the article. All authors have approved the final version.

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