Temporal muscle thickness predicts mortality in prevalent hemodialysis patients

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SUMMARY

OBJECTIVE: Ultrasonographic temporal muscle thickness measurement has recently emerged as a promising method of nutritional assessment in various conditions; hence, we aimed to determine the relationship between temporal muscle thickness and mortality in prevalent hemodialysis patients.
METHODS: Adult patients who were on a regular in-center hemodialysis program for ≥3 months were included, and patients with severe nonrenal organ failure or any recent significant disease inception were excluded. Baseline demographic; clinical, laboratory, and anthropometric data, including malnutrition inflammation score; and outcomes data were collected using a standardized form.
RESULTS: A total of 60 patients (32 males, diabetes prevalence: 26.6%) who met the eligibility criteria participated in the study, with a mean follow-up of 33.3±11.5 months, a median age of 66.5 (interquartile range 52.7–74) years, time on hemodialysis of 36 months, and a body mass index of 25.9 kg/m². Infections and cardiovascular events were the most common causes of overall mortality that occurred in 41.6% of the patients. Temporal muscle thickness was significantly lower in nonsurvivors (8.8 vs. 10.6 mm, p<0.001). Multivariate Cox regression analysis involving age, albumin, spKt/V, and malnutrition inflammation score revealed that temporal muscle thickness was a significant predictor of mortality (hazard ratio=0.740, p=0.035). Receiver operating characteristic curve analysis has shown 68% of sensitivity and 81.8% of specificity for a cutoff value of 9.4 mm (p<0.001). Temporal muscle thickness was weakly or mildly correlated with hemodialysis vintage, body mass index, albumin, and malnutrition inflammation score and moderately correlated with age (r=−0.536, p<0.001).
CONCLUSION: Ultrasonographic temporal muscle thickness has been found as a significant predictor of mortality in prevalent hemodialysis patients. Temporal muscle thickness could be a novel marker of nutritional status and predictor of mortality; hence, further studies are warranted.
KEYWORDS: Temporal muscle. Malnutrition. Hemodialysis. Mortality.

INTRODUCTION

Chronic kidney disease (CKD) is a common disease, with an estimated prevalence of above 800 million across the world[1]. The multidimensional costs of CKD are also very high, and according to a recent study, CKD resulted in 35.8 million disability-adjusted life-years in 2017[2]. The burden of CKD becomes even greater in patients with advanced stages of CKD, as the uremic milieu constitutes a unique environment, with multiple consequences, such as CKD, mineral bone disease, cardiovascular disease, and nutritional deterioration[3]. The course and status of nutrition are quintessential components of the evaluation and treatment of patients with advanced stages of CKD, and yet they are often overlooked in daily practice. The laborious nature of longitudinal follow-up of the components of nutritional status on top of busy routines could partially explain the reason for that.

A nomenclature and a set of diagnostic criteria for protein energy wasting (PEW) were proposed on behalf of the International Society for Renal Nutrition and Metabolism (ISRNM) in 2008, based on four categories, namely, biochemical parameters, body mass, muscle mass, and dietary intake[4]. A multidomain semiquantitative scale of malnutrition inflammation score (MIS) has been used in multiple studies to predict morbidity and mortality in maintenance hemodialysis (HD) patients[5,6]. Subjective global assessment and French PEW score were also proposed, but rather than using thresholds for any parameter, there is a general agreement to consider the longitudinal course of the nutritional components for the diagnosis and treatment.

Temporal muscle thickness (TMT) measured by ultrasonography has recently been proposed to correlate with nutritional status and changes in TMT to correlate with recent energy adequacy

in elderly patients[7,8]. Nutritional deterioration and sarcopenia, in particular, are common in both geriatrics and HD patients, while the underlying metabolic abnormalities are not identical; for example, muscle protein degradation and resting energy expenditure are increased only in HD patients, whereas insulin resistance and inflammation are increased and muscle protein synthesis is decreased in both patient groups[9]. We aimed to investigate the role of TMT in predicting malnutrition in prevalent HD patients.

METHODS

Study design and ethics committee approval: This is a single-center, prospective, observational study. Data were collected within 6 months between December 2018 and May 2019. Written informed consent was obtained from the patients, which included a detailed explanation of the objectives of the study and the methods to be used. An ethics committee approval was obtained from our hospital (decision number 159, dated November 14, 2018).

Inclusion and exclusion criteria: Patients over the age of 18 years who had been regularly receiving chronic HD treatment for at least 3 months due to end-stage renal failure in our hospital were included in this study. Those who were temporarily on dialysis due to acute kidney injury (AKI), those with a history of hospitalization and surgery within the past 3 months, and those with infectious disease, end-stage liver disease, malignancy, or malabsorption syndrome were excluded from the study.

Hemodialysis: High-flux HD was applied to the patients by using biocompatible HD membranes with a dialysate containing standard bicarbonate and 140 mEq/l sodium. While blood flow rates varied between 300 and 350 ml/min, the dialysate flow rate was kept constant at 500 ml/min. To calculate the given dialysis dose (urea reduction ratio [URR] and spKt/V), the post-dialysis plasma urea levels of the same dialysis session were measured by the Daugirdas method.

Data collection: The first evaluation, including demographic, anthropometric, and biochemical data, was performed for all patients in December 2018. Demographic data, laboratory parameters, and dialysis adequacy measurements (URR and spKt/V) were obtained retrospectively by examining the patient files. Anthropometric measurements were calculated by examining the patients 15–30 min after the end of the mid-week HD session. Triceps skinfold thickness (TST) was measured at the back of the arm, from the midpoint between the olecranon and the acromion, with the arms released from the side, by applying standard pressure by clamping the skin with the Saehan Skinfold Caliper. After fasting overnight, predialysis (before the mid-week session) venous blood samples were taken from all subjects in the morning. MIS is a reliable scoring

system that has been used to predict malnutrition-related events and/or serious clinical outcomes. Scoring is done by looking at nutritional history, physical examination, body mass index (BMI), and laboratory data. It consists of 4 parts and 10 questions. Each question is given a score between 0 (normal) and 3 (severe malnutrition). Scoring is done between 0 (normal) and 30 (severe malnutrition). High score reflects the severity of malnutrition and inflammation. It has been proven that high MIS scores are predictors of morbidity and mortality in these patients[5,6]. A Toshiba (Toshiba Medical Systems Company, Ōtawara, Japan), Aplio 500 device (USA), and a 12-MHz linear probe were used for TMT measurement. The linear transducer was placed in the temporal fossa perpendicular to the muscle plane with gentle pressure, approximately 2 cm below the upper part of the lateral edge of the eyelid bilaterally. The thickness of the middle part of the temporal muscle was measured. During the collection of ultrasonographic images, three measurements were recorded for each muscle. The average of three measurements for the right and left sides was taken as the final data[7].

Statistical analysis

The SPSS 20.0 software (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The suitability of the variables for normal distribution was examined using the Kolmogorov-Smirnov and the Shapiro-Wilk tests. Since the data did not fit the normal distribution, descriptive statistics were presented as median (interquartile range [IQR]: 25–75%), frequency distribution, and percentage. The chi-square and Fisher's exact tests were used to evaluate categorical variables. The Mann-Whitney U test was used for comparing the two independent groups. The relationship between the variables was evaluated using the Spearman's correlation test. The diagnostic decision-making feature of TMT (median) in predicting mortality was evaluated by receiver operating characteristic (ROC) curve analysis. A multivariate Cox regression model was created for the analysis of independent variables associated with all-cause mortality. The Kaplan-Meier survival analysis was used for detecting the mean survival time of all patients and TMT (median) cutoff groups. The statistical significance level was accepted as $p < 0.05$.

RESULTS

The demographic data and laboratory analysis results of the 60 patients (male/female: 32/28) are shown in Table 1. Of the total, 16 (26.6%) patients were diabetic. The median (IQR) age and HD vintage of all patients were 66.5 (52.7–74) years and 36 (15.7–95.2) months, respectively. The vascular access types of the patients were as follows: 37 with an arteriovenous

(AV) fistula, 21 with a tunneled central venous catheter, and 2 with an AV graft. The median (IQR) MIS and TMT values of all patients were 8.5 (6–10.2) and 9.7 (8.7–10.9) mm, respectively. Notably, 25 (41.6%) patients died during the follow-up period (33.3±11.5 months). Causes of death were as follows: 14 (56%) infections (8 COVID-19, 5 sepsis, and 1 infective endocarditis), 5 (20%) ischemic heart diseases, 4 (16%) cerebrovascular accidents, and 2 (8%) complications of HD insufficiency such as hyperkalemia and hypervolemia.

When compared to survived patients, the nonsurvivor group was significantly older (60 vs. 73 years, p=0.008), had lower serum albumin (3.8 vs. 3.7 g/l, p=0.002), higher MIS (8 vs. 10, p=0.001), and lower TMT median values (10.6 vs. 8.8 mm, p<0.001). However, there were no significant differences between the two groups regarding gender, HD vintage and adequacy, frequency of patients with diabetes and/or catheters, anthropometric measurements, and laboratory parameters, except serum albumin (Table 1).

Table 1. Demographic and laboratory data of all patients and groups.

	All patients (n=60)	Survivors (n=35)	Nonsurvivors (n=25)	p-value
Demographics				
Age (years)	66.5 (52.7–74)	60 (44–70.5)	73 (56–77.5)	**0.008**
Gender (male/female)	32/28	20/15	12/13	0.484
HD vintage (months)	36 (15.7–95.2)	24 (14.5–89.5)	48 (20–100.5)	0.342
Diabetes mellitus, n (%)	16 (26.6)	7 (20)	9 (36)	0.169
HD adequacy and access				
spKt/V	1.4 (1.2–1.6)	1.40 (1.3–1.6)	1.30 (1.2–1.4)	0.052
Catheter, n (%)	21 (35)	9 (25.7)	12 (48)	0.074
Anthropometry				
Dry weight (kg)	71.2 (59.2–80.5)	77 (62–80.2)	66.5 (57.7–82.2)	0.475
Body mass index (kg/m²)	25.9 (22.7–29.2)	26.3 (23.2–29.9)	25.4 (21–28.7)	0.419
Triceps skinfold thickness (mm)	16 (13–18)	16 (14–18)	14 (12–18)	0.135
Laboratory				
Predialysis urea (mg/dL)	128.5 (105.7–151)	131 (108.5–150.5)	122 (100.5–157)	0.795
Predialysis creatinine (mg/dL)	7.4 (5.6–8.9)	7.5 (6.3–9.1)	6.6 (4.7–8.7)	0.063
Hemoglobin (g/dL)	10.9 (9.8–11.9)	10.7 (9.8–12)	11.2 (9.9–11.8)	0.832
Uric acid (mmol/L)	6.2 (5.3–6.6)	6.3 (5.4–7)	5.6 (5.2–6.5)	0.203
Sodium (mmol/L)	138 (136–140)	138 (137–140)	137 (135–139.5)	0.423
Potassium (mEq/L)	4.8 (4.3–5.4)	4.8 (4.3–5.2)	5.1 (4.2–5.4)	0.519
Calcium (mg/dL)	9 (8.7–9.5)	9.1 (8.8–9.4)	9 (8.6–9.5)	0.741
Phosphorus (mg/dL)	5.1 (4–6.5)	5 (4–6.6)	5.2 (3.9–6.3)	0.820
Intact PTH (pg/mL)	468 (231–648)	478 (226–626)	460 (198–742)	0.894
Ferritin (ng/mL)	307 (164–493)	319 (200–486)	217 (143–530)	0.428
Total cholesterol (mmol/L)	162 (145–206)	164 (147–210)	162 (141–194)	0.300
LDL (mmol/L)	93 (81–119)	95 (83–132)	90 (68.5–107)	0.179
Triglyceride (mmol/L)	116 (87–177.7)	128 (87–179)	110 (86–173)	0.499
Hs-CRP (mg/dL)	0.5 (0.1–2)	0.5 (0.1–1.9)	1.3 (0.1–2.2)	0.504
Albumin (g/L)	3.8 (3.4–3.9)	3.8 (3.6–4)	3.7 (3.2–3.8)	**0.002**
MIS	8.5 (6–10.2)	8 (5.5–9)	10 (8–12)	**0.001**
TMT-median (mm)	9.7 (8.7–10.9)	10.6 (9.5–11.4)	8.8 (8.5–10)	**<0.001**

Data were presented as median and interquartile range (25–75%). Statistically significant (p<0.05) values were marked in bold.
HD: hemodialysis; spKt/V: single-pool Kt/V; PTH: parathormone; LDL: low-density lipoprotein; Hs-CRP: high-sensitivity C-reactive protein; MIS: malnutrition inflammation score; TMT: temporal muscle thickness.

In correlation analysis (Table 2), we found statistically significantly negative correlations between TMT (median) values and age (r=−0.536, p<0.001), HD vintage (r=−0.328, p=0.012), and MIS (r=−0.330, p=0.010). Significantly positive correlation was present between TMT (median) values and dry weight (r=0.396, p=0.002), BMI (r=0.335, p=0.009), TST (r=0.314, p=0.014), predialysis serum uric acid (r=0.368, p=0.004), and albumin (r=0.286, p=0.027).

The multivariate Cox regression model was created for the analysis of independent variables associated with all-cause mortality (Table 3). Low TMT (median) (p=0.035), low serum albumin (p=0.010), and high MIS (p=0.037) were found to be independent predictors of mortality.

In the ROC curve analysis (Figure 1), we found that the optimal cutoff value of TMT (median) for predicting death was 9.4 mm (p<0.01, AUC 0.782, 95%CI 0.663–0.901). The sensitivity and specificity of this cutoff value were 68% and 81.8%, respectively. Positive and negative predictive values were 0.48 and 0.91, respectively, positive and negative likelihood ratios were 3.74 and 0.39, respectively, while the diagnostic odds ratio was 8.70 (95%CI 2.13–35.21).

Table 2. Bivariate correlation analysis of temporal muscle thickness (median) with demographic, anthropometric, and laboratory variables.

TMT (median)	Correlation coefficient (r)	p-value
Age	-0.536	**<0.001**
HD vintage	-0.328	**0.012**
Dry weight	0.396	**0.002**
BMI	0.335	**0.009**
TST	0.314	**0.014**
Uric acid	0.368	**0.004**
Albumin	0.286	**0.027**
MIS	-0.330	**0.010**

TMT: temporal muscle thickness; HD: hemodialysis; BMI: body mass index; TST: triceps skinfold thickness; MIS: malnutrition inflammation score. Bold characters indicate statistically significant results.

Table 3. Multivariate cox regression model created for the analysis of independent variables associated with all-cause mortality.

Predictors of mortality	p-value	Hazard ratio	95%CI	
			Lower	Upper
Age (years)	0.641	1.009	0.972	1.047
TMT (median)	**0.035**	0.740	0.559	0.980
spKt/V	0.176	0.250	0.033	1.862
Albumin	**0.010**	0.214	0.066	0.694
MIS	**0.037**	1.180	1.010	1.380

TMT: temporal muscle thickness; spKt/V: single-pool Kt/V; MIS: malnutrition inflammation score. Bold characters indicate statistically significant results.

The overall mortality rate and mean survival time of all patients were 41.6% and 33.6±1.45 months, respectively. Out of 60 patients, 24 patients had TMT (median) under the cutoff value (≤9.4 mm), while 36 patients had TMT (median) above the cutoff value (>9.4 mm). The mortality rate was significantly higher in TMT (median) ≤9.4 mm group compared to the TMT (median) >9.4 mm group [70.8% (17/24) vs. 22.2% (8/36), respectively, p (log-rank) <0.001]. Likewise, as compared to TMT (median) >9.4 mm, the mean survival time of the patients with TMT (median) ≤9.4 mm was found significantly lower [37.4±1.34 vs. 27.9±2.65 months, respectively, p (log-rank) <0.001] during the follow-up period. Figure 2 illustrates the Kaplan-Meier patient survival curve according to the TMT (median) cutoff value.
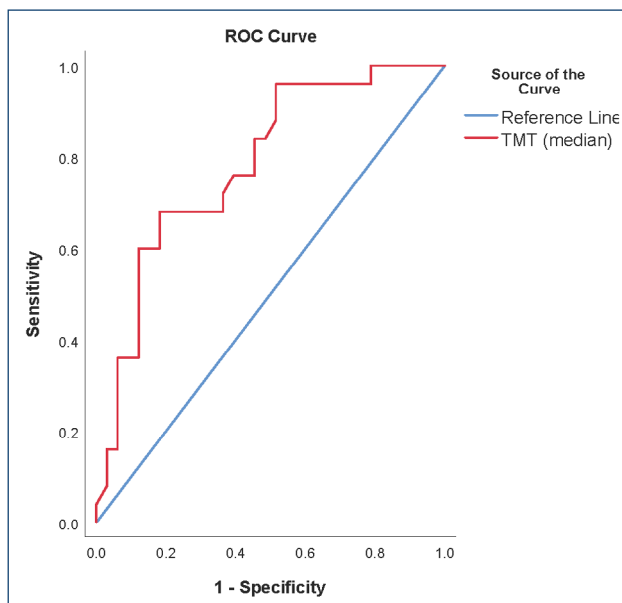

Figure 1. Receiver operating characteristic (ROC) analysis of the relationship temporal muscle thickness (median) and mortality.
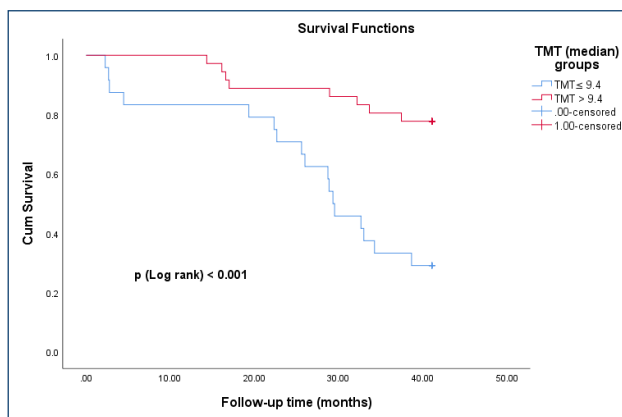

Figure 2. Kaplan-Meier patient survival curve according to temporal muscle thickness (median) groups.

DISCUSSIONS

Mortality rates are unacceptably high in patients with end-stage renal disease receiving chronic HD. The presence of PEW is a modifiable risk factor that is associated with mortality[10]. There is evidence in the recent literature that a decrease in temporal muscle mass may be a strong predictor of malnutrition and mortality in various conditions[11,12]. To the best of our knowledge, for the first time in HD patients, we have shown that the TMT measured by ultrasonography could predict moderate-to-severe malnutrition and all-cause mortality.

The preference to study TMT as a surrogate measure of nutrition and muscle mass may be twofold logical: first, the temporal muscle is a striated muscle and has a strong correlation with calf circumference, and second, the temporal muscle is an important masticatory muscle that could reflect the exercise of chewing and hence dental health and nutritional intake[13,14]. In addition, the measures of TMT have a low tendency to be affected by exercise or rest versus clench[15].

Reports on the prevalence of PEW in dialysis patients vary largely, but in a recent meta-analysis that included 90 studies from 34 countries, the IQR for PEW prevalence was found to be 28–54%[16]. In this study, mild, moderate, and severe malnutrition was found in 31.7, 36.7, and 31.7% of the patients, respectively. Strict criteria, older age, high rates of catheter use, and single-center bias may account for the high prevalence of malnutrition. The overall mortality during a mean follow-up of 33 months was 46%, and the main causes of mortality were infections and cardiovascular diseases. These figures are comparable with the large analyses of HD patients[17]. An ROC analysis for TMT to predict mortality have shown an AUC of 0.782 with moderate sensitivity (68%) and specificity (81.8%), but notably these findings were comparable with those of MIS and all-cause mortality analysis. In contrast to MIS, however, TMT is relatively more practical to perform, which could improve the attendance of nutritional status surveillance and treatment of HD patients. Furthermore, TMT and MIS have independently predicted mortality as shown in the multivariate Cox regression analysis; hence, a combination of TMT and MIS may further improve the predictive power of the singular use of each test.

Another important finding from this study was that TMT was weakly correlated with more conventional nutritional indicators, notably serum albumin, MIS, and BMI. The interpretation of these data does not seem straightforward, but at least this is roughly similar to the results of a previous study of the elderly reported by Hasegawa et al.[7] These data suggest that TMT has a discriminative validity. A large anthropometric study aimed at determining the normal ranges of TMT in healthy individuals and a method of correction according to body surface area or height, etc. to generate more comparable data that could arguably provide more refined results.

There are several limitations of this study. The sample size is small, and the study was conducted at a single HD center. The ultrasonography of TMT was performed by one experienced radiologist who was unaware of the patients' clinical data; this fact bypasses the interobserver inconsistency, whereas intraobserver consistency was not tested. The normal ranges of TMT were not determined in healthy controls, a cutoff value was identified based on ROC analysis, and the follow-up was relatively short. The measurement of TMT was done at the beginning of the study and follow-up measurements were not done; hence, the data rely solely on the initial measurements. However, to prevent an observer-related systematic error, we preferred the arithmetic average of six measurements (three on the right side and three on the left side) for each patient. Notably, even though our study population was relatively small, the statistical analysis has shown a significant relationship between TMT and mortality, which is contrary to what we were more likely to find out (a wide range of CI for TMT in a small sample size should reduce the power of the study). We believe that such a finding suggests that the TMT may truly be a strong predictor of adverse outcomes and its variability across patients could be high. For both reasons, the characteristics and value of TMT in patient monitoring for nutritional status and clinical outcomes merit further studies. The utilization of widely recognized MIS and anthropometric parameters simultaneously in this study strengthens the validity of the results.

CONCLUSION

As a method for evaluating the nutritional status and outcomes of prevalent HD patients, TMT measurement by ultrasonography has shown promising results in predicting all-cause mortality. The correlation of TMT with other parameters, such as BMI, serum albumin, MIS, HD vintage, and TST, was rather weak, which raises the possibility that TMT could be a new independent marker of nutritional status. Further studies on larger HD patients with longer follow-up and the inclusion of healthy individuals are needed to validate the results of this study.

AUTHORS' CONTRIBUTIONS

EK: Conceptualization, data curation, and formal analysis. **TŞ:** Writing – original draft and writing – review & editing. **SD:** Data curation and writing – review & editing. **MB:** Conceptualization and data curation.

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