Clinical Impact of Measures for Frailty Severity in Poor-Risk Patients Undergoing Revascularization for Chronic Limb-Threatening Ischemia

Mitsuyoshi Takahara[1], Osamu Iida[2], Yoshimitsu Soga[3], Nobuyoshi Azuma[4] and Shinsuke Nanto[5]
on behalf of the PRIORITY investigators

[1]Department of Diabetes Care Medicine, and Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan
[2]Cardiovascular Center, Kansai Rosai Hospital, Hyogo, Japan
[3]Department of Cardiology, Kokura Memorial Hospital, Fukuoka, Japan
[4]Department of Vascular Surgery, Asahikawa Medical University, Hokkaido, Japan
[5]Department of Cardiology, Nishinomiya Municipal Central Hospital, Hyogo, Japan.

Aim: This study aimed to demonstrate the clinical impact of various frailty-related aspects in poor-risk patients undergoing revascularization for chronic limb-threatening ischemia (CLTI).

Methods: We analyzed a clinical database of a prospective multicenter observational study. A total of 562 CLTI patients who required assistance for their daily lives and were candidates for revascularization were included. We examined various measures of frailty severity, including activities of daily living (ADL)/mobility, physical performance, nutritional status, cognitive function, and cardiac function at baseline (before revascularization). Data on inflammatory markers at baseline and ADL/mobility before CLTI onset were also collected.

Results: The patients were aged 77 ± 10 years, 65% were non-ambulatory, and 38% were categorized as mild dementia or severer. The correlation coefficients between the frailty measures ranged from 0.00 to 0.91. The random forest analysis for one-year mortality risk showed that these frailty-related measures, as well as age and inflammatory markers, had a relatively high variable importance compared with comorbidities and limb severity.

Conclusion: The correlations between measures of frailty severity were not always strong but rather widely varied in CLTI patients who required assistance for their daily lives and were candidates for revascularization. Measures of frailty severity, as well as age and inflammatory markers, had a relatively large predictive impact on one-year mortality risk compared with comorbidities and limb severity in the population.

Introduction

Prognosis of chronic limb-threatening ischemia (CLTI) is generally poor, and frailty, commonly seen in CLTI patients, is associated with a poorer prognosis in the population[1-4]. For frail CLTI patients, primary amputation may be indicated[1, 5]; however, the treatment will further impair their activities of daily living (ADL), not only deteriorating their frailty severity but also increasing their family's burden of care. From such viewpoints, some CLTI patients requiring assistance for their daily lives will be candidates for limb salvage by revascularization in clinical practice.

Clinical guidelines suggest the importance of assessing frailty in CLTI patients who are candidates for revascularization[1]. However, frailty refers to various medical aspects of vulnerability, and it remained unclear to what extent the individual aspects

Address for correspondence: Osamu Iida, Cardiovascular Center, Kansai Rosai Hospital, 3-1-69 Inabaso, Amagasaki, Hyogo 660-8511, Japan
E-mail: iida.osa@gmail.com

would be correlated with one another, and whether they would be strongly associated with the mortality risk. The aim of this study was to assess clinical impact of preoperative measures of frailty severity in a poor-risk CLTI population undergoing revascularization.

Methods

The current study analyzed a clinical database of the Poor-Risk patients wIth and withOut RevascularIzation TherapY for critical limb ischemia (PRIORITY) registry[6], a prospective multicenter study. The details of this registry were described elsewhere[6]. In brief, this prospective multicenter observational study conducted in Japan registered 662 CLTI patients who required assistance for their daily lives because of their disability in ADL and/or impairment of cognitive function, between January 2014 and April 2015. Revascularization was either planned or not planned at registration. The study participants were followed-up for one year. The primary endpoint was one-year overall survival. The study was performed according to the Declaration of Helsinki and was approved by the ethics committee of each institution registering study subjects. Written informed consent was obtained from each participant or from his/her family as needed. Of the 662 registered participants, 562 were scheduled for revascularization, whereas the remaining 100 participants were not. The current study analyzed the 562 patients who were scheduled to undergo revascularization. Of these, 551 patients (98%) underwent revascularization (surgical reconstruction in 30 patients and endovascular therapy alone in 521). Scheduled revascularization was not performed (i.e., cancelled) in the remaining 11 patients (2%), because of their deteriorated general conditions after registration[6].

Definitions

CLTI was diagnosed if the patients had 1) chronic ischemic foot rest pain with an ankle pressure ＜50 mmHg, a toe blood pressure ＜30 mmHg, or a skin perfusion pressure ≤ 30 mmHg, 2) an ischemic foot ulcer or gangrene with an ankle pressure ＜70 mmHg, a toe blood pressure ＜50 mmHg, or a skin perfusion pressure ≤ 40 mmHg, or 3) ischemic foot rest pain, ulcer, or gangrene, with apparent critical ischemia indicated by other modalities.

The preoperative severity of frailty was assessed at baseline from various aspects, including ADL/mobility, physical performance, nutritional status, cognitive function, and cardiac function. ADL/mobility was measured using the modified Katz index of independence[7], ambulation, home-boundness, and the Life-Space Assessment (LSA)[8]. The modified Katz index counted the number of activities (bathing, dressing, toileting, transferring, continence, and feeding) performed independently, ranging from 0, total dependence, to 6, full independence. Ambulation was classified into the following 5 levels: "ambulatory without any use of equipment" (level 1), "ambulatory with the use of equipment" (level 2), "in a wheelchair without assistance (driving his/her wheelchair by him/herself)" (level 3), "in a wheelchair with assistance (pushed in a wheelchair)" (level 4), and "bed-ridden" (level 5). The levels of home-boundness were defined as "leaving home once or more per week" (level 1), "leaving the bedroom without assistance once or more per week" (level 2), "leaving the bedroom with assistance once or more per week" (level 3), and "leaving the bedroom less than once per week (regardless of assistance)" (level 4). The LSA scores ranged from 0 ("totally bed-bound") to 120 ("traveled out of town every day without assistance"). Physical performance was assessed according to 5-m gait speed and grip strength[9, 10]. Gait speed was categorized as ≤ 5 sec (level 4), 6 to 10 sec (level 3), 11 to 15 sec (level 2), and ＞15 sec (level 1), whereas grip strength was categorized as ＞30 kg in males and ＞20 kg in females (level 4), 25 to 30 kg in males and 17 to 20 kg in females (level 3), 16 to 24 kg in males and 11 to 16 kg in females (level 2), and ≤ 15 kg in males and ≤ 10 kg in females (level 1). Nutritional status was evaluated based on body mass index (BMI), hemoglobin level, serum albumin level, serum cholinesterase level, and total lymphocyte count (TLC)[11-14]. We also assessed the nutritional status using the geriatric nutritional risk index (GNRI)[15, 16] and the controlling nutritional status (CONUT) score[17]. In brief, the GNRI was calculated from serum albumin level and body weight relative to ideal body weight[15], whereas the CONUT score was calculated from serum albumin level, total cholesterol level, and TLC[17]. Cognitive function was evaluated according to the Global Deterioration Scale (GDS)[18], and ranged from stage 1 (no cognitive impairment) to stage 7 (late-stage dementia). Cardiac function was evaluated using ultrasonography-assessed left-ventricular ejection fraction (LVEF) and log-transformed circulating brain natriuretic peptide (BNP) levels. Health-related quality of life was quantified as health utility calculated from a validated Japanese version of EuroQol 5 Dimension (EQ-5D) in the original 3-level format, in which 0 indicated death and 1 indicated full health[19, 20]. We also included in the current analysis serum C-reactive protein (CRP) levels and absolute neutrophil count (ANC) as markers of systemic inflammation.

At the study registration, we collected data regarding ADL/mobility before the onset of CLTI, which were based on the medical records and the recollections of the patients and their family members. We also included these data in the current analysis.

Statistical Analyses

The data are presented as the mean ± standard deviation for continuous variables and as percentages for categorical variables, unless otherwise indicated. The correlations among the measures of frailty severity were assessed using the Spearman's method. Missing data were addressed by the multiple imputation by chained equations (MICE) method, using the R package *mice*. In the MICE procedure, we generated five imputed datasets and combined the estimates and standard errors based on the Rubin's rule. The association of baseline characteristics including the measures of frailty with the risk of one-year mortality was investigated by the Breiman's random forest for right-censored survival using the R package *randomForestSRC*. The predictive impact of respective variables was evaluated with the variable importance measure. All statistical analyses were performed using R version 3.6.0 (R Development Core Team, Vienna, Austria).

Results

The baseline characteristics of the study population are summarized in **Table 1**. Mean age was 77 ± 10 years; 65% were non-ambulatory, and 38% had GDS stage ≥ 4. Twenty-eight patients (5%) were lost to follow-up within one year, whereas the remaining patients (95%) either completed the one-year follow-up or died within one year. In total, 172 deaths were observed in the population, and the one-year overall survival rate of the study population was estimated to be 70.2% by the Kaplan-Meier method **(Fig. 1)**.

Fig. 2A illustrates the correlations among the measures of frailty severity. The intra-aspect absolute correlation coefficients among the ADL/mobility-related measures ranged from 0.70 to 0.89, and those among the nutritional parameters ranged from 0.12 to 0.91. The absolute correlation coefficient between the two measures of physical performance was 0.23, and that between the two cardiac parameters was 0.24. The coefficient between the two measures of systemic inflammation was 0.48. The inter-aspect correlation (e.g., between ADL/mobility and nutritional status) were not as strong; the absolute values of the correlation coefficients ranged from 0.00 to 0.59. ADL/mobility before CLTI onset generally presented

a weaker correlation with other measures of frailty at baseline (after CLTI onset) **(Fig. 2B)**. As shown in **Fig. 3**, the measures of frailty severity, as well as age and inflammatory markers, had a relatively large predictive impact on one-year mortality risk compared with comorbidities and limb severity. The factor with the largest variable importance measure was cholinesterase levels, followed by the Katz index at baseline, GDS, LVEF, age, BMI, the GNRI, grip strength, and CRP levels **(Fig. 3)**. Measures of ADL/mobility before CLTI onset did not always have a larger prognostic impact than those at baseline (i.e., after CLTI onset and before revascularization); the Katz index and ambulation before CLTI onset had a smaller variable importance measure than those at baseline, whereas the width of life space (LSA) and home-boundness after CLTI onset demonstrated a larger variable importance measure than those at baseline.

Discussion

The current study revealed the correlation among measures of frailty severity and their predictive impact on one-year mortality risk in CLTI patients who required assistance for their daily lives and were candidates for revascularization. The correlations were not always strong but rather widely varied. Measures of frailty severity, as well as age and inflammatory markers, had a relatively large predictive impact on one-year mortality risk compared with comorbidities and limb severity in the population.

Measures of frailty severity were not always strongly correlated with one another, suggesting that patients who were severe in one aspect of frailty were not always severe in another aspect of frailty. In other words, patients with a certain severity in one aspect of frailty could have considerable heterogeneity in another aspect. Our findings indicate that a poor-risk CLTI patients would be a highly heterogeneous population; measuring severity of frailty only with one index would overlook patients who are severe in another aspect of frailty.

The subsequent random forest analysis for survival demonstrated that frailty-related variables had a larger variable importance measure than comorbidities and limb severity. It would be worth taking into account these aspects of frailty severity in predicting mortality risk in the population. In contrast, some known prognostic factors including regular dialysis, cerebrovascular disease, coronary artery disease, tissue loss and infection[1] had a small, or no important influence on the mortality risk in this study. This might be because the population was

Table 1. Baseline characteristics of the study population

N	562	Cognitive impairment (GDS)	3.3 ± 2.0
Age (years)	77 ± 10	Gait speed	
Male sex	333 (59%)	1: >15 sec	48 (29%)
Receiving welfare	47 (8%)	2: 11-15 sec	27 (17%)
Diabetes mellitus	358 (64%)	3: 6-10 sec	60 (37%)
Regular dialysis	251 (45%)	4: ≤ 5 sec	28 (17%)
Cerebrovascular disease	190 (34%)	Grip strength	
Coronary artery disease	289 (51%)	1: ≤ 15 kg in males and ≤ 10 kg in females	138 (42%)
Aspirin use	374 (67%)	2: >15 kg in males and >10 kg in females	125 (38%)
Thienopyridine use	362 (64%)	3: >24 kg in males and >16 kg in females	39 (12%)
Cilostazol use	197 (35%)	4: >30 kg in males and >20 kg in females	27 (8%)
Anticoagulant use	135 (24%)	BMI (kg/m^2)	21.1 ± 3.7
Statin use	168 (30%)	Hemoglobin (g/dl)	11.1 ± 1.9
Health utility	0.460 ± 0.226	Total lymphocyte count (10^3/µl)	1.2 ± 0.6
ADL/mobility at baseline		Albumin (g/dl)	3.3 ± 0.6
Impaired ambulation		Cholinesterase (U/l)	205 ± 73
1: Ambulatory without any use of equipment	100 (18%)	GNRI	87 ± 11
2: Ambulatory with the use of equipment	98 (17%)	CONUT score	4.5 ± 2.7
3: In a wheelchair without assistance	68 (12%)	LVEF (%)	61 ± 12
4: In a wheelchair with assistance	192 (34%)	BNP (pg/mL)	165 (56 - 446)
5: Bed-ridden	104 (19%)	Absolute neutrophil count (10^3/µl)	4.9 (3.6 - 6.5)
Home-boundness		CRP (mg/dl)	1.17 (0.30-4.01)
1: Leave home once or more per week	184 (33%)	Tissue loss	472 (84%)
2: Leave the bedroom without assistance once or more per week	86 (15%)	Infection	167 (30%)
3: Leave the bedroom with assistance once or more per week	179 (32%)	Bilateral CLTI	170 (30%)
4: Leave the bedroom less than once per week	113 (20%)	Contralateral major amputation	32 (6%)
Independence in ADL (Katz index)	2.8 ± 2.4		
Width of life space (LSA)	19 ± 22		
ADL/mobility before CLTI onset			
Impaired ambulation			
1: Ambulatory without any use of equipment	216 (39%)		
2: Ambulatory with the use of equipment	126 (22%)		
3: In a wheelchair without assistance	40 (7%)		
4: In a wheelchair with assistance	116 (21%)		
5: Bed-ridden	63 (11%)		
Home-boundness			
1: Leave home once or more per week	311 (56%)		
2: Leave the bedroom without assistance once or more per week	48 (9%)		
3: Leave the bedroom with assistance once or more per week	135 (24%)		
4: Leave the bedroom less than once per week	65 (12%)		
Independence in ADL (Katz index)	3.9 ± 2.5		
Width of life space (LSA)	37 ± 33		

Data are expressed as mean ± standard deviation, median (interquartile range), or number (percentage). All data were values at baseline (i.e., after CLTI onset and before revascularization), except for measures of ADL/mobility, whose values were both at baseline and before CLTI onset. Data were missing on impaired ambulation before CLTI onset in 1 patients (0.2%), home-boundness before CLTI onset in 3 patients (1%), the Katz index before CLTI onset in 2 patients (0.4%), the width of life space (LSA) before CLTI onset in 3 patients (1%), health utility in 125 patients (22%), gait speed in 399 patients (71%), grip strength in 233 patients (41%), BMI in 8 patients (1%), total lymphocyte count in 15 patients (3%), serum albumin level in 10 patients (2%), cholinesterase level in 114 patients (20%), the GNRI in 17 patients (3%), the CONUT score in 36 patients (6%), LVEF in 58 patients (10%), BNP in 104 patients (19%), absolute neutrophil count in 19 patients (3%), and CRP in 1 patients (0.2%).
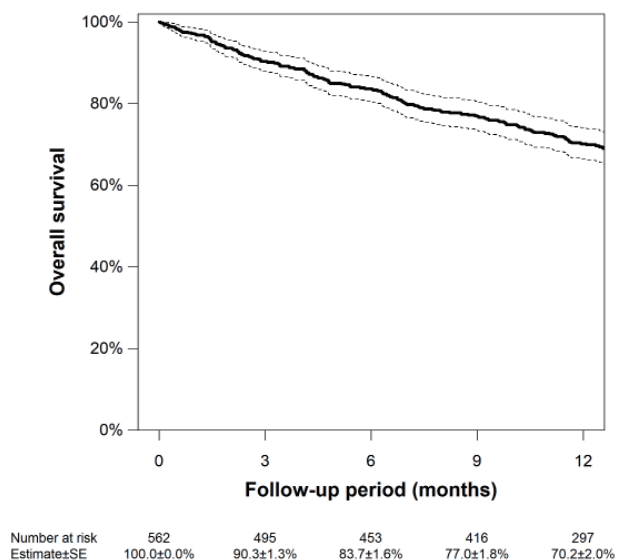
Fig. 1. Kaplan-Meier estimate of overall survival

Dotted lines indicate 95% confidence intervals. SE, standard error.
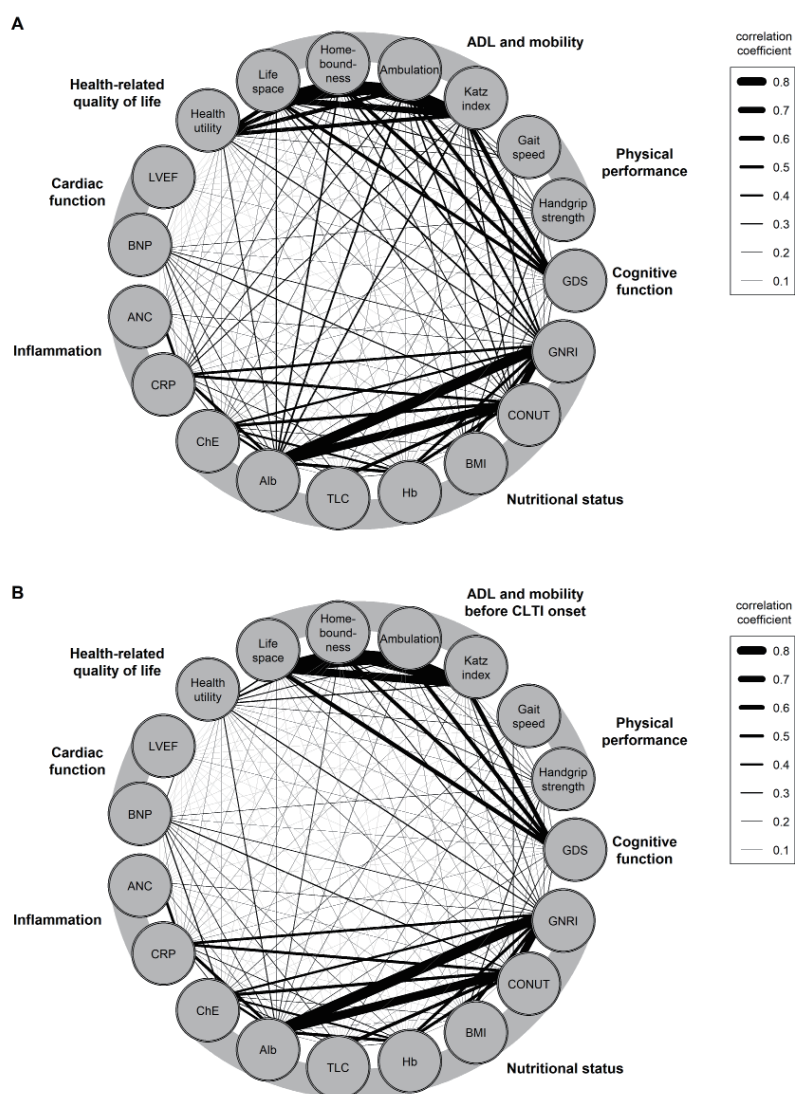

Fig. 2. Correlations among the frailty-related parameters

The data are Spearman's correlation coefficients. Black lines indicate $P<0.05$, whereas gray lines indicate $P>0.05$. Panel B is the same as Panel A, except for the measures of ADL/mobility, which were the values before CLTI onset in Panel B, whereas they were those at baseline (i.e., after CLTI onset and before revascularization) in Panel A. The correlation coefficient between the measure before CLTI onset and that at baseline was 0.76 for the Katz index, 0.72 for ambulation, 0.71 for home-boundness, and 0.70 for the width of life space, respectively. Alb, albumin; ANC, absolute neutrophil count; BMI, body mass index; BNP, brain natriuretic peptide; ChE, cholinesterase; CONUT, controlling nutritional status score; CRP, C-reactive protein; GNRI, geriatric nutritional risk index; the LVEF, left ventricular ejection fraction; GDS, the Global Deterioration Scale; Hb, hemoglobin; TLC, total lymphocyte count.
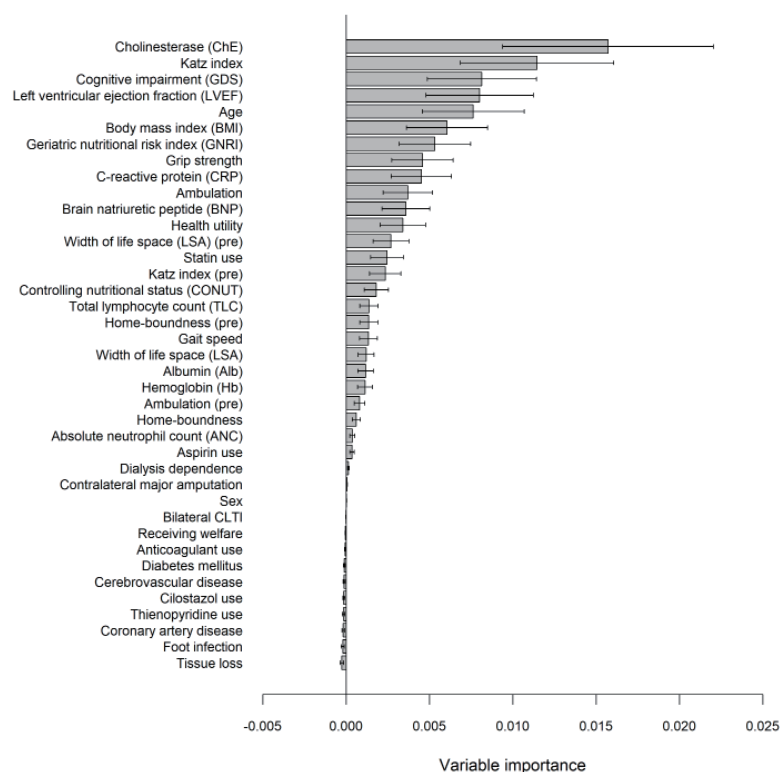
225

Fig. 3. Impact of baseline characteristics on one-year mortality risk

Data are variable importance measures for random forest and 95% confidence intervals. A suffix of "(pre)" indicates the data before CLTI onset, whereas the others were at baseline (i.e., after CLTI onset and before revascularization).

limited to patients requiring assistance for their daily lives. Whereas a patient with one of the comorbidities was likely vulnerable, one free from the comorbidity would be also vulnerable due to other comorbidities. Consequently, both patients were similarly vulnerable, and the comorbidity would fail to discriminate the mortality risk.

Among nutrition-related markers, cholinesterase levels presented the largest variable importance measure for survival. Whilst malnutrition is a well-known predictor for mortality risk in many other populations[21-24], the markers and components of the scores are often influenced by other clinical manifestations. Albumin levels might be altered by renal dysfunction, infection and inflammatory status[25, 26]. TLC can be also affected by infection[14]. Hemoglobin levels can be affected by various etiologies including renal dysfunction and impaired hematopoiesis. Furthermore, BMI and body weight relative to ideal body weight (calculated from height) can be underestimated in amputees (who are light in weight due to limb loss), whereas it can be overestimated in edematous patients with cardiac and/or renal dysfunction, and osteoporotic patients with height loss due to spinal compression fractures. Total

cholesterol levels, a component of the CONUT score, could be modified by anti-hyperlipidemic treatment[27]. In poor-risk CLTI patients, for whom these clinical conditions would be likely relevant, these nutritional markers and scores might be inferior in reflecting their true general nutritional status. On the other hand, cholinesterase levels might be less affected by these conditions and, therefore, could work as a more useful marker[28].

We also found that inflammatory markers, especially CRP levels, were correlated with manifestations of frailty, especially nutritional markers, and with the mortality risk. Recent studies demonstrated that malnutrition correlates to inflammation and leads to develop atherosclerosis, and this concept is called as the malnutrition-inflammation-atherosclerosis syndrome[29]. Our findings would indicate this vicious circle in the population.

Another prognostic factor with the largest variable importance was the Katz index. On the other hand, the other ADL/mobility-related measures had a smaller variable importance measure, which might come from their main reliance on ambulatory status. Ambulatory status is directly affected by lower limb

ischemia, and therefore will be variable after revascularization. The mortality risk would be incurred by postoperative general disability in ADL, which might be more closely correlated to other preoperative aspects of ADL than ambulation. The Katz index reflects not only ambulation but also these other aspects of ADL and might be superior in this respect. The predictive superiority of grip strength to gait speed could be also explained from this respect; gait speed can be largely dependent on ambulatory ability. Measures of ADL/mobility before CLTI onset did not always have a larger prognostic impact than those at baseline, which might be partially because the data were subject to the recall bias.

There are several study limitations. First, the PRIORITY registry collected one-year data, and it remained unknown whether the observed effects were sustained over a longer follow-up period. Second, data on some other inflammatory markers, e.g., interleukins and tumor necrosis factor alpha, which would potentially have some clinical impact on their frailty and prognosis, were not available. Third, data on ADL/mobility before CLTI onset would be subject to the recall bias. Fourth, the current findings were not externally validated. Furthermore, the PRIORITY registry was conducted in Japan. Although frailty in Japan might not be so different than that in other countries, there are likely some differences in terms of health care systems, culture, and brief, which could affect indication for revascularization versus major amputation toward frail CLTI. Future studies will be needed to validate the current findings.

Conclusion

We demonstrated the correlation among measures of frailty severity and their predictive impact on one-year mortality risk in CLTI patients who required assistance for their daily lives and were candidates for revascularization. The correlations were not always strong but rather widely varied. Measures of frailty severity, as well as age and inflammatory markers, had a relatively large predictive impact on one-year mortality risk compared with comorbidities and limb severity in the population.

Acknowledgements and Notice of Grand Support

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest regarding this manuscript.

References

1) Conte MS, Bradbury AW, Kolh P, White JV, Dick F, Fitridge R, Mills JL, Ricco JB, Suresh KR, Murad MH, Aboyans V, Aksoy M, Alexandrescu VA, Armstrong D, Azuma N, Belch J, Bergoeing M, Bjorck M, Chakfe N, Cheng S, Dawson J, Debus ES, Dueck A, Duval S, Eckstein HH, Ferraresi R, Gambhir R, Garguilo M, Geraghty P, Goode S, Gray B, Guo W, Gupta PC, Hinchliffe R, Jetty P, Komori K, Lavery L, Liang W, Lookstein R, Menard M, Misra S, Miyata T, Moneta G, Munoa Prado JA, Munoz A, Paolini JE, Patel M, Pomposelli F, Powell R, Robless P, Rogers L, Schanzer A, Schneider P, Taylor S, De Ceniga MV, Veller M, Vermassen F, Wang J, Wang S, Gvg Writing Group for the Joint Guidelines of the Society for Vascular Surgery ESfVS and World Federation of Vascular S: Global Vascular Guidelines on the Management of Chronic Limb-Threatening Ischemia. Eur J Vasc Endovasc Surg, 2019; 58: S1-S109 e133

2) Hata Y, Iida O, Asai M, Masuda M, Okamoto S, Ishihara T, Nanto K, Kanda T, Tsujumura T, Okuno S, Matsuda Y, Takahara M and Mano T: Risk Stratification for 2-Year Mortality in Patients with Chronic Limb-Threatening Ischemia Undergoing Endovascular Therapy. J Atheroscler Thromb, 2021; 28: 477-482

3) Iida O, Takahara M, Soga Y, Kodama A, Terashi H, Azuma N, on behalf of the SPINACH investigators: The Association of Preoperative Characteristics with Reintervention Risk in Patients Undergoing Revascularization for Chronic Limb-Threatening Ischemia. J Atheroscler Thromb, 2021; 28: 52-65

4) Takahara M, Iida O, Soga Y, Kodama A, Terashi H, Azuma N, on behalf of the SPINACH study investigators: Current and Past Obesity in Japanese Patients with Critical Limb Ischemia Undergoing Revascularization. J Atheroscler Thromb, 2021; 28: 44-51

5) Aboyans V, Ricco JB, Bartelink MEL, Bjorck M, Brodmann M, Cohnert T, Collet JP, Czerny M, De Carlo M, Debus S, Espinola-Klein C, Kahan T, Kownator S, Mazzolai L, Naylor AR, Roffi M, Rother J, Sprynger M, Tendera M, Tepe G, Venermo M, Vlachopoulos C, Desormais I, Document R, Widimsky P, Kolh P, Agewall S, Bueno H, Coca A, De Borst GJ, Delgado V, Dick F, Erol C, Ferrini M, Kakkos S, Katus HA, Knuuti J, Lindholt J, Mattle H, Pieniazek P, Piepoli MF, Scheinert

D, Sievert H, Simpson I, Sulzenko J, Tamargo J, Tokgozoglu L, Torbicki A, Tsakountakis N, Tunon J, de Ceniga MV, Windecker S and Zamorano JL: Editor's Choice - 2017 ESC Guidelines on the Diagnosis and Treatment of Peripheral Arterial Diseases, in collaboration with the European Society for Vascular Surgery (ESVS). Eur J Vasc Endovasc Surg, 2018; 55: 305-368

6) Iida O, Takahara M, Soga Y, Azuma N, Nanto S and Uematsu M: Prognostic Impact of Revascularization in Poor-Risk Patients With Critical Limb Ischemia: The PRIORITY Registry (Poor-Risk Patients With and Without Revascularization Therapy for Critical Limb Ischemia). JACC Cardiovasc Interv, 2017; 10: 1147-1157

7) Wallace M and Shelkey M: Monitoring functional status in hospitalized older adults. Am J Nurs, 2008; 108: 64-71; quiz 71-62

8) Peel C, Sawyer Baker P, Roth DL, Brown CJ, Brodner EV and Allman RM: Assessing mobility in older adults: the UAB Study of Aging Life-Space Assessment. Phys Ther, 2005; 85: 1008-1119

9) Afilalo J, Karunananthan S, Eisenberg MJ, Alexander KP and Bergman H: Role of frailty in patients with cardiovascular disease. Am J Cardiol, 2009; 103: 1616-1621

10) Chen LK, Liu LK, Woo J, Assantachai P, Auyeung TW, Bahyah KS, Chou MY, Chen LY, Hsu PS, Krairit O, Lee JS, Lee WJ, Lee Y, Liang CK, Limpawattana P, Lin CS, Peng LN, Satake S, Suzuki T, Won CW, Wu CH, Wu SN, Zhang T, Zeng P, Akishita M and Arai H: Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. J Am Med Dir Assoc, 2014; 15: 95-101

11) Shetty PS and James WP: Body mass index. A measure of chronic energy deficiency in adults. FAO Food Nutr Pap, 1994; 56: 1-57

12) Waterlow JC: Enzyme changes in malnutrition. J Clin Pathol Suppl (Assoc Clin Pathol), 1970; 4: 75-79

13) Zhang Z, Pereira SL, Luo M and Matheson EM: Evaluation of Blood Biomarkers Associated with Risk of Malnutrition in Older Adults: A Systematic Review and Meta-Analysis. Nutrients, 2017; 9: pii: E829. doi: 810.3390/nu9080829

14) Omran ML and Morley JE: Assessment of protein energy malnutrition in older persons, Part II: Laboratory evaluation. Nutrition, 2000; 16: 131-140

15) Bouillanne O, Morineau G, Dupont C, Coulombel I, Vincent JP, Nicolis I, Benazeth S, Cynober L and Aussel C: Geriatric Nutritional Risk Index: a new index for evaluating at-risk elderly medical patients. Am J Clin Nutr, 2005; 82: 777-783

16) Matsuo Y, Kumakura H, Kanai H, Iwasaki T and Ichikawa S: The Geriatric Nutritional Risk Index Predicts Long-Term Survival and Cardiovascular or Limb Events in Peripheral Arterial Disease. J Atheroscler Thromb, 2020; 27: 134-143

17) Ignacio de Ulibarri J, Gonzalez-Madrono A, de Villar NG, Gonzalez P, Gonzalez B, Mancha A, Rodriguez F and Fernandez G: CONUT: a tool for controlling nutritional status. First validation in a hospital population. Nutr Hosp, 2005; 20: 38-45

18) Reisberg B, Ferris SH, de Leon MJ and Crook T: The Global Deterioration Scale for assessment of primary degenerative dementia. Am J Psychiatry, 1982; 139: 1136-1139

19) EuroQol G: EuroQol--a new facility for the measurement of health-related quality of life. Health Policy, 1990; 16: 199-208

20) Tsuchiya A, Ikeda S, Ikegami N, Nishimura S, Sakai I, Fukuda T, Hamashima C, Hisashige A and Tamura M: Estimating an EQ-5D population value set: the case of Japan. Health Econ, 2002; 11: 341-353

21) Cereda E, Pedrolli C, Zagami A, Vanotti A, Piffer S, Opizzi A, Rondanelli M and Caccialanza R: Nutritional screening and mortality in newly institutionalised elderly: a comparison between the geriatric nutritional risk index and the mini nutritional assessment. Clin Nutr, 2011; 30: 793-798

22) Cereda E, Pedrolli C, Zagami A, Vanotti A, Piffer S, Opizzi A, Rondanelli M and Caccialanza R: Body mass index and mortality in institutionalized elderly. J Am Med Dir Assoc, 2011; 12: 174-178

23) Rice AL, Sacco L, Hyder A and Black RE: Malnutrition as an underlying cause of childhood deaths associated with infectious diseases in developing countries. Bull World Health Organ, 2000; 78: 1207-1221

24) Maruyama K, Nakagawa N, Koyama S, Maruyama JI and Hasebe N: Malnutrition Increases the Incidence of Death, Cardiovascular Events, and Infections in Patients with Stroke after Rehabilitation. J Stroke Cerebrovasc Dis, 2017; 2018: 716-723

25) Kaysen GA, Kirkpatrick WG and Couser WG: Albumin homeostasis in the nephrotic rat: nutritional considerations. Am J Physiol, 1984; 247: F192-202

26) Don BR and Kaysen G: Serum albumin: relationship to inflammation and nutrition. Semin Dial, 2004; 17: 432-437

27) Sato Y, Uzui H, Morishita T, Fukuoka Y, Hasegawa K, Ikeda H, Tama N, Ishida K, Miyazaki S and Tada H: Effects of PCSK9 Inhibitor on Favorable Limb Outcomes in Patients with Chronic Limb-Threatening Ischemia. J Atheroscler Thromb, 2021; 28: 754-765

28) Sato T, Yamauchi H, Suzuki S, Yoshihisa A, Yamaki T, Sugimoto K, Kunii H, Nakazato K, Suzuki H, Saitoh S and Takeishi Y: Serum cholinesterase is an important prognostic factor in chronic heart failure. Heart Vessels, 2015; 30: 204-210

29) Stenvinkel P, Heimburger O, Lindholm B, Kaysen GA and Bergstrom J: Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). Nephrol Dial Transplant, 2000; 15: 953-960