Prognostic Significance of Oral Frailty on the All-Cause Mortality

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Research

Keywords: oral frailty, survival, all-Cause Mortality

Posted Date: August 12th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-56635/v1

Abstract

Background: As the proportion of elderly population grows, it raises concern about impaired oral health which has been reported to be associated with increased risk of numerous adverse health events. Emerging study defined oral frailty as poor oral health accumulation and demonstrated that oral frailty was a risk factor of disability, physical frailty and mortality. In this study, we examined the association between modified oral frailty and all-cause mortality in the Unites States.

Methods: In this cross-sectional observational study, a total of 8,382 participants who completed oral functions data from 1999-2002 NHANES database were recruited. Modified oral frailty included 3 components: limited eating ability, dry mouth and difficult swallowing, which were obtained from self-reported questionnaire. For primary outcome, all-cause mortality was followed from baseline to death or 2006. The relationship of modified oral frailty and all-cause mortality was assessed by Cox regression model.

Results: A statistically significant relationship between modified oral frailty and all-cause mortality was observed in fully adjusted model. Participants with more components of modified oral frailty had worse risk of all-cause mortality. Limited eating ability was inversely associated with muscle strength, telomere length.

Conclusion: Modified oral frailty which obtained from an easy self-assessment survey might be a potential risk factor for all-cause mortality and could be applied to general health examination.

Trial registration: Retrospectively registered

Introduction

As medical care improved over the past few decades, life expectancy has been increased among elderly [1]. The growth of elderly population has resulted in increased prevalence of various age-related diseases including cardiovascular diseases, diabetes mellitus, osteoporosis, dementia and physical disability [2]. Researches have raised concern about frailty in recent years [3]. Frailty is a multidimensional state associated with increased vulnerability to adverse health events and functional decline [4]. Frailty has been reported to be a predictor for functional impairment, falls, disability, hospitalization, and death [5]. Many preventive interventions for development of frailty has been reported such as exercise, caloric support and vitamin D supplementation [6-8].

Various criteria measurements have been developed for assessing frailty. Four major scales were used to predict disability and mortality [9]. The Frailty Index (FI) included symptoms, signs, diseases, disabilities and laboratory data [10]. The FRAIL score contained 5 items (fatigue, ambulation, resistance, illnesses, and loss of weight) which all were assessed by simple questionnaire [11]. The Cardiovascular Health Study (CHS) scale included 5 components: self-reported exhaustion, unintentional weight loss (10 lbs in past year), slow walking speed, low physical activity and weakness (grip strength) [5]. The Study of

Osteoporotic Fractures (SOF) scale is consisted of 3 items: reduced energy level, weight loss and inability to rise from a chair five times without using the arms [12]. Each frailty scale focused on different domains such as biological, physical, cognitive and deficit accumulation [10, 13].

Poor oral condition including tooth loss, edentulism and periodontal disease among elderly population has been increasing serious recently [14]. Previous studies disclosed the association between poor dentition status and physical disability [15, 16]. Impaired oral health was also reported to be correlated with muscle strength loss, weight loss, malnutrition and worse cognitive function [17-20]. Tanaka, T., et al. defined oral frailty as poor oral health accumulation and found that oral frailty could be a predictor for physical frailty and mortality [21]. There were plenty of studies demonstrating that poor oral health was correlated with frailty and mortality [22-24]. However, no simple applied oral health measure exists for predicting risk of mortality and physical frailty. Based on the study in Japan [21], we modified oral frailty in order to create a simple questionnaire for assessing all-cause mortality risk in persons with oral frailty. This study was intended to examine the correlation between modified oral frailty and all-cause mortality in the US population.

Materials And Methods

Study population

Our study population were obtained from National Health and Nutrition Examination Survey 1999-2002 (NHANES), which is an observational study of noninstitutionalized US civilian and a typical sample of US population. The National Center for Health Statistics of the Centers for Disease Control and Prevention has conducted the study. The National Center for Health Statistics Institutional Review Board approved all the NHANES study protocols and details of its protocols and consents are available on the NHANES website. We excluded individuals without data of modified oral frailty, comorbidities, muscle strength, muscle mass, telomere length and recreational activity. A total of 8,382 suitable participants were initially recruited in our study.

Components of modified oral frailty

A longitudinal study in Japan defined oral frailty as containing 3 or more of 6 characteristics which included the number of natural teeth, tongue pressure, articulatory skill, chewing ability and perceived eating and swallowing difficulties [21]. Base on the previous study, we modified oral frailty according to NHANES databases. In this study, the modified oral frailty is composed of 3 components, limited eating ability, dry mouth and difficult swallowing, which were determined by self-reported questionnaires. Participants were asked the questions “How often do you limit the kinds or amounts of food you eat because of problems with your teeth or dentures?“, “Do you have difficulties swallowing any foods?“ and “Does your mouth feel dry when you eat a meal?”. Participants responding ‘always, very often and often’ were categorized as limited eating ability; responding ‘yes’ as dry mouth or difficult swallowing.

Covariables

Sociodemographic covariables including age, sex, race, smoking history and comorbidities were collected from self-reported questionnaires. Smoking status was assessed by the questions “Have you smoked at least 100 cigarettes in your entire life?”. Past medical comorbidities included several cardiovascular diseases, arthritis and stroke. Recreational activity was defined as self-reported participation in moderate intensity exercise which increased pulse or breathing rate, like swimming, jogging or brisk walking for more than 10 minutes without stopping. The biochemistry profiles (creatinine, alanine aminotransferase, serum fasting glucose, total cholesterol and total calcium) were analyzed with standardized guidelines and protocols. The analysis of telomere length which compares the telomere length of participants relative to standard reference DNA (T/S ratio) was using by quantitative polymerase chain reaction (qPCR). Detailed information is available from the NHANES website.

Isokinetic strength testing of right quadriceps muscle assessing by A Kin Com MP dynamometer (Chattanooga, TN) was used to determine muscle strength. Appendicular skeletal muscle mass assessing by dual-energy X-ray absorptiometry (DEXA) QDR-4500A Hologic scanner (Bedford, MA) was used to determine muscle mass. Body composition measures including bone mineral content, fat mass and lean muscle mass was determined by DEXA.

Outcome assessment

The primary outcome of our study was all-cause mortality. The mortality status was obtained from the time of the study enrollment to death or 31 December 2006 through probabilistic matching between NHANES database and National Death Index death certificate records. The secondary endpoint was the association among muscle strength, muscle mass and telomere length with each component of modified oral frailty.

Statistical analysis

SPSS version 18 (SPSS Inc., Chicago, IL, USA) was used for executing all statistics. The one-way ANOVA and chi-square test were applied for analyzing socio-demographic characteristics, laboratory variables and medical comorbidities. The threshold of significance level was two-sided p values < 0.05. Kaplan-Meir curve stratified modified oral frailty was plotted. When the participants without any component of modified oral frailty were regarded as reference, the relationship between modified oral frailty and all-cause mortality was assessed by performing Cox proportional hazard models. Multivariate regression analysis was performed for the association among muscle strength, muscle mass and telomere length with each component of modified oral frailty. Three covariate-adjusted models were used for potential confounders: Model 1 = unadjusted; Model 2 = age, race, gender, creatinine, alanine aminotransferase, serum fasting glucose, total cholesterol and total calcium; Model 3 was Model 2 and adjustment for smoking, recreational activity, and past medical histories.

Results

Demographic information

We enrolled 8,382 participants for the study, 699 (8.3%) were classified as limited eating ability, 366 (4.3%) as dry mouth and 398 (4.7%) as difficult swallowing (Table 1). The mean age of the normal participants was 48.54±18.8 years and 48.8% were male. For population stratified by modified oral frailty, limited eating ability, dry mouth and difficult swallowing, the mean age was 53.31±18.08 years, 59.07±16.68 years and 58.95±16.83 years, respectively.

Hazard ratios (HRs) of all-cause mortality stratified by modified oral frailty

We classified study population into 4 groups, group 1 (without any components of modified oral frailty), group 2 (with one component of modified oral frailty), group 3 (with two components of modified oral frailty) and group 4 (with 3 components of modified oral frailty). The HRs of all-cause mortality stratified by modified oral frailty is presented in table 2. In unadjusted model (model 1), compared to group 1, group 2, group 3 and group 4 had poorer mortality risk. In fully adjusted model (model 3), group 2, group 3 and group 4 had higher mortality risk and the dose-dependent effect was also observed. The HRs of group 2, group 3 and group 4 in fully adjusted model were 1.269, 1.649 and 3.185, respectively ($p<0.05$).

Survival curve for all-cause mortality classified by each component of modified oral frailty

Figure 1 shows cumulative survival classified by each component of modified oral frailty using Kaplan-Meier method. An association between limited eating ability, dry mouth, difficult swallowing and increased all-cause mortality risk was observed ($p<0.01$).

The association among muscle strength, muscle mass and telomere length with each component of modified oral frailty

We investigated associations between muscle strength, muscle mass and telomere with each component of modified oral frailty for possible explanation for the relationship between all-cause mortality and modified oral frailty. Table 3 presents inverse associations of limited eating ability with muscle strength, telomere length in fully adjusted model. An unadjusted negative relationship between dry mouth and muscle mass, telomere length was revealed; difficult swallowing demonstrated the same correlation. While, there were no significant differences in fully adjusted model.

Discussion

In this study, we used modified oral frailty based on Tanaka's study [21] in order to design a simple questionnaire for predicting mortality risk. We demonstrated that modified oral frailty was associated with all-cause mortality. A dose-dependent effect was also observed which represented participants with more components of modified oral frailty had poorer mortality risk. Notably, we observed an association between limited eating ability, dry mouth, difficult swallowing and increased all-cause mortality risk. To examine the possible mechanisms of our findings, we investigated the associations between muscle strength, muscle mass and telomere length with each component of modified oral frailty. An inverse relationship between limited eating ability and muscle strength, telomere length was found after

adjusting confounding factors. Oral hypofunction was defined by the Japanese Society of Gerodontology (JSG) including seven components: oral dryness, poor oral hygiene, decreased occlusal force, decreased tongue pressure, reduced tongue-lips motor function, decreased chewing and swallowing function [25]. Previous studies have indicated the association between oral hypofunction and frailty, mortality. A relationship of low occlusal force with poor performance status, impaired cognitive function and all-cause mortality was reported by Iinuma, T., et al. [26, 27]. A British study found that dry mouth symptoms were associated with incidence frailty risk [28]. Decline in tongue pressure, as Tsuga, K., et al. observed, was correlated with frailty [29]. For older people, dysphagia was suggested to be an independent factor for frailty and mortality [30, 31]. In addition to oral hypofunction, poor oral health, for example, edentulism, periodontal diseases and perceived difficulty eating, have been reported to be related to frailty and mortality [16, 28, 32]. These results were consistent with our findings that modified oral frailty including limited eating ability, dry mouth and difficult swallowing was associated with mortality. It is widely addressed that nutrition may be a plausible pathway for the relationship between poor oral health and frailty [33, 34]. A systemic review suggested that poor nutritional status was related to development of frailty [35]. For older adults, malnutrition may be affected by eating dependency, oral dysphagia and impaired swallowing function [36]. Self-reported impaired masticatory function may result in food avoidance which in term could lead to inadequate nutrition [37]. Dry mouth may affect not only oral ulcer and dental caries but also chewing and swallowing function [33]. Malnutrition could be attributed to dysphagia among elderly population [38]. Dysphagia was significantly correlated with community acquired pneumonia [39]. A relationship of dysphagia with poor physical performance and nutritional status was also observed [40]. Difficulty swallowing was reported to have higher risk of malnutrition, frailty and mortality [17]. These findings indicated the potential associations among poor oral health, malnutrition and frailty. Frailty is a spectrum of multisystem decline associated with reduced physical capabilities and decreased physiological function which in turn increase vulnerability [4]. Frailty phenotype has been reported as a critical indicator to predict mortality [41]. From the physical aspect of the frailty phenotype which consisted of 5 characteristics: weakness, fatigue, weight loss, slow walking speed, and low physical activity, there is some overlap between frailty and sarcopenia [42, 43]. In view of the association among oral hypofunction, frailty and mortality, we examined the relationships between modified oral frailty and muscle strength, muscle mass for possible mechanisms of our findings. Previous studies have demonstrated that inadequate nutrition was related to telomere length [44-46] and as discussed, poor oral health may influence nutrition status [36]. Thus, we also investigated the relationship between modified oral frailty and telomere length. In the present study, we found that limited eating ability was negatively associated with muscle strength and telomere length. Similar to our results, a longitudinal study showed that subjective difficulty eating was a risk factor of physical frailty [21]. On the contrary, a British cohort study reported that perceived difficulty eating was not correlated with frailty [36]. Further studies are needed to address possible confounding factors which may interfere the relationship between limited eating ability and frailty. There are several limitations in the present study. First, a cross-sectional analysis was conducted, and so, causal inferences could not be established. Second, we assessed modified oral frailty by self-administered questionnaire which may be subject to response bias. Third, there were potential unmeasured variables were not fully adjusted in our study.

Finally, the population of the present study were mostly Caucasian. Hence, our findings have limited generalizability to different ethnicities. In conclusion, this study highlights the dose–response relationship between modified oral frailty and all-cause mortality. Our results propose that modified oral frailty acquiring by using a simple questionnaire might predict all-cause mortality, which might have implications for public health. Modified oral frailty could be an easily valuable indicator used for general health assessments. Further research is needed to explore plausible mechanisms of relationship between oral frailty and mortality and evaluate the associations of other adverse health outcomes.

Declarations

Ethics approval and consent to participate: The NHANES study protocol was approved by the NCHS Institutional Review Board and all informed consents had been obtained from the eligible subjects.

Consent for publication: Not applicable.

Availability of data and material: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declared that they had no competing interests.

Funding: There was no funding directly for this manuscript.

Authors' contributions: Zhe-Yu, Yang: Contributed to the design of the study, responsible for data-analysis decisions, responsible for the management and retrieval of data, decided on data-collection methods and initial data analysis and interpretation, contributed to initial data analysis and interpretation, and drafted the initial article. **Wei-Liang Chen:** Decided on the data-collection methods and initial data analysis and interpretation. Conceptualized and designed the study, contributed to the design of the study, supervised all aspects of the study, responsible for data-analysis decisions, decided on data-collection methods and initial data analysis and interpretation, responsible for the management and retrieval of data, contributed to initial data analysis and interpretation, drafted the initial article, critically reviewed and revised the article, and approved the final version for submission. All authors meet the International Committee of Medical Journal Editors criteria for authorship.

Acknowledgements: Not applicable.

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Tables

Table 1 Characteristics of study population with each component of modified oral frailty

Characteristic	Normal population	Limited eating ability	Dry mouth	Difficult swallowing
Socio-demographic variables*				
Age (years±SD)	48.54 (18.8)	53.31 (18.08)	59.07 (16.68)	58.95 (16.83)
Male sex (%)	3376 (48.8)	207 (44.7)	101 (36.3)	127 (44.4)
Race-ethnicity (%)				
Non-Hispanic White	3500 (50.6)	185 (40)	163 (58.6)	183 (64)
Smoke at least 100 cigarettes in life (%)	3300 (47.7)	267 (57.7)	149 (53.6)	150 (52.4)
Recreational activity (%)	3103 (44.8)	221 (47.7)	167 (60.1)	140 (49)
Muscle power (Newtons±SD)	349.69 (123.47)	315.46 (112.34)	325.49 (119.12)	337.42 (121.38)
Laboratory variables				
Creatinine (mg/dL±SD)	0.82 (0.42)	0.91 (0.95)	0.96 (0.86)	0.93 (0.76)
ALT(U/L±SD)	25.92 (34.24)	25.56 (21.07)	24.67 (14.83)	24.46 (15.8)
Fasting Glucose (mg/dL±SD)	96.45 (33.36)	104.78 (51.62)	109.63 (55.15)	106.2 (59.94)
Total cholesterol (mg/dL±SD)	200.15 (41.1)	203.06 (47.06)	204.74 (43.77)	207.88 (46.78)
Total calcium (mg/dL±SD)	9.39 (0.4)	9.41 (0.44)	9.43 (0.44)	9.42 (0.42)
Comorbidities†				
Congestive heart failure (%)	176 (2.5)	32 (6.9)	21 (7.6)	9 (3.1)
Coronary heart disease (%)	262 (3.8)	31 (6.7)	23 (8.3)	20 (7)
Angina/Angina pectoris (%)	211 (3.1)	25 (5.4)	28 (10.1)	27 (9.4)
Heart attack (%)	272 (3.9)	35 (7.6)	21 (7.6)	18 (6.3)
Arthritis (%)	1551 (22.4)	150 (32.4)	129 (46.4)	132 (46.2)
Stroke (%)	184 (2.7)	26 (5.6)	15 (5.4)	19 (6.6)

Abbreviations: ALT= Alanine aminotransferase

* Continuous variables are presented as mean (standard deviation)

† Categorical variables are presented as number (percentage)

Table 2 HRs of all-cause mortality stratified by modified oral frailty

		Model[a] 1		Model[a] 2		Model[a] 3	
		HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Modified oral frailty	Oral 1 v.s. Oral 0	1.857(1.501,2.298)	<0.001	1.304(1.053,1.615)	0.015	1.269 (1.023,1.572)	0.03
	Oral 2 v.s. Oral 0	2.687(1.657,4.358)	<0.001	1.551(0.943,2.551)	0.084	1.649 (1.003,2.710)	0.049
	Oral 3 v.s. Oral 0	6.995(2.615,18.712)	<0.001	3.025(1.125,8.135)	0.028	3.185 (1.181,8.592)	0.022

Abbreviations

Oral 0= without any components of modified oral frailty

Oral 1= with one component of modified oral frailty

Oral 2= with two components of modified oral frailty

Oral 3= with 3 components of modified oral frailty

[a] Adjusted covariates:

Model 1= unadjusted

Model 2= age, gender, race/ethnicity, serum ALT, serum Cr, fasting glucose, total cholesterol, total calcium.

Model 3= Model 2+ (smoking, congestive heart failure, coronary heart disease, angina, heart attack, arthritis, stroke and recreational activity)

Table 3 The association between muscle power, muscle mass and telomere length with each component of modified oral frailty

		Model[a] 1		Model[a] 2		Model[a] 3	
	Modified oral frailty	**β[b] (95% CI)**	***P* Value**	**β[b] (95% CI)**	***P* Value**	**β[b] (95% CI)**	***P* Value**
Muscle strength	Limited eat ability Dry mouth Difficult swallowing	-29.16 (-48.50, -9.81) -21.56 (-43.56, 0.439) -12.17 (-34.18, 9.83)	0.003 0.055 0.278	-26.9 (-40.7, -13.1) 2.88 (-12.84, 18.61) -5.24 (-20.94, 10.45)	<0.001 0.719 0.512	-26.25 (-40.1, -12.39) 3.67 (-12.1, 19.46) -4.16 (-19.93, 11.59)	<0.001 0.648 0.604
Muscle mass	Limited eat ability Dry mouth Difficult swallowing	-897.69 (-1501.82, -293.56) -1504.82 (-2262.6, -747.04) -1319.55 (-2077.51, -561.59)	0.004 <0.001 0.001	-146.12 (-560.66, 268.42) 241.68 (-281.31, 764.67) -282.35 (-803.78, 239.07)	0.49 0.365 0.289	-156.74 (-570.26, 256.77) 138.26 (-383.73, 660.27) -392.59 (-913.28, 128.1)	0.457 0.604 0.139
Telomere length	Limited eat ability Dry mouth Difficult swallowing	-0.055 (-0.082, -0.029) -0.075 (-0.109, -0.042) -0.06 (-0.094, -0.027)	<0.001 <0.001 <0.001	-0.03 (-0.054, -0.006) -0.018 (-0.049, 0.013) -0.005 (-0.035, 0.026)	0.015 0.265 0.768	-0.029 (-0.054, -0.005) -0.018 (-0.049, 0.013) -0.005 (-0.035, 0.026)	0.017 0.265 0.769

[a] Adjusted covariates:

Model 1= unadjusted

Model 2= age, gender, race/ethnicity, serum ALT, serum Cr, fasting glucose, total cholesterol, total calcium.

Model 3= Model 2+ (smoking, congestive heart failure, coronary heart disease, angina, heart attack, arthritis, stroke and recreational activity)

[b]β coefficient can be interpreted as the degree of association of muscle strength, muscle mass and telomere with each measurement of modified oral frailty

Figures

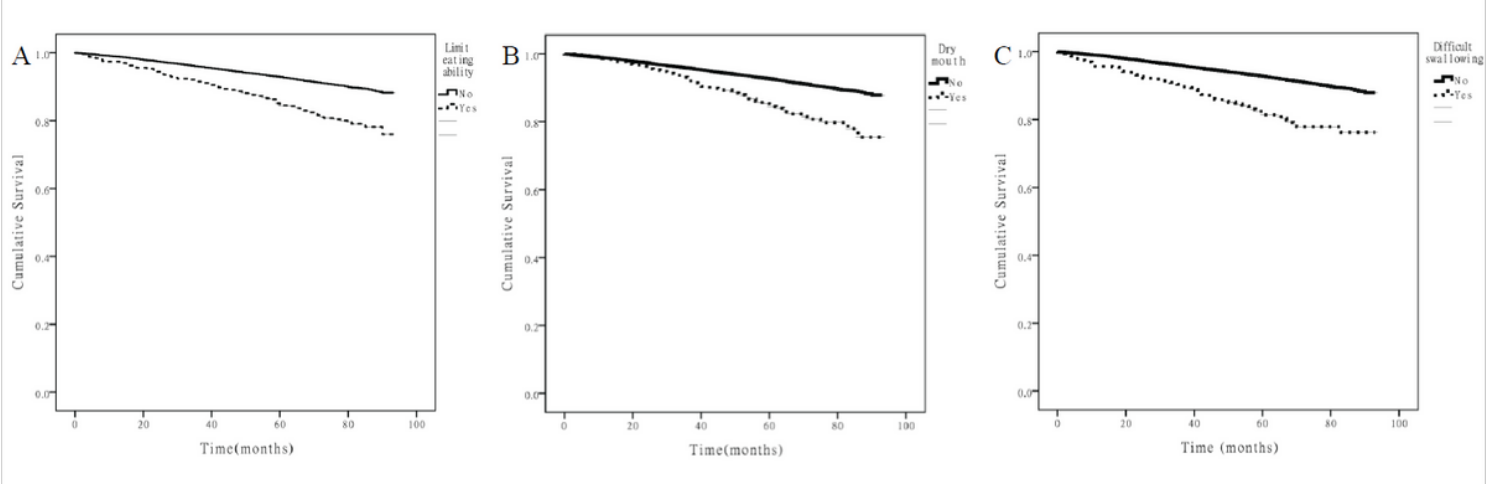

Figure 1

Kaplan-Meier (KM) curves showed cumulative survival probability of modified oral frailty: Limited eating ability (A), Dry mouth (B) and Difficult swallowing (C).