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PREDICTIVE EFFECT OF MALNUTRITION ON LONG-TERM CLINICAL OUTCOMES AMONG OLDER MEN: A PROSPECTIVELY OBSERVATIONAL COHORT STUDY

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Abstract: *Objectives:* To determine whether nutritional status can predict 3-year cognitive and functional decline, as well as 4-year all-cause mortality in older adults. *Design:* Prospectively longitudinal cohort study. *Setting and participants:* The study recruited 354 men aged 65 years and older in the veteran's retirement community. *Measures:* Baseline nutritional status was evaluated using the Mini-Nutritional Assessment-Short Form (MNA-SF). Cognitive function and Activities of Daily Living (ADL) function were determined by the Mini-Mental State Examination (MMSE) and the Barthel Index, respectively. Three-year cognitive and functional decline were respectively defined as a >3 point decrease in the MMSE scores and lower ADL scores than at baseline. Univariate and multivariable logistic regression analyses were conducted to identify nutritional status as a risk factor in poor outcome. The Kaplan-Meier method and Cox proportional regression models were used to estimate the effect of malnutrition risk on the mortality. *Results:* According to MNS-SF, the prevalence of risk of malnutrition was 53.1% (188/354). Multivariate logistic regression found risk of malnutrition significantly associated with 3-year cognitive decline (Adjusted odds ratio [OR] 2.07, 95% Confidence Interval [CI] 1.05–4.08, P =0.036) and functional decline (Adjusted OR 1.83, 95% CI 1.01–3.34, P =0.047) compared with normal nutritional status. The hazard ratio (HR) for all-cause mortality was 1.8 times higher in residents at risk of malnutrition (Adjusted HR 1.82, 95% CI 1.19-2.79, P =0.006). *Conclusions:* Our results provide strong evidence that risk of malnutrition can predict not only cognitive and functional decline but also risk of all-cause mortality in older men living in a veteran retirement's community. Further longitudinal studies are needed to explore the causal relationship among nutrition, clinical outcomes, and the effect of an intervention for malnutrition.

Key words: Malnutrition, cognitive decline, functional decline, mortality, older adults.

Introduction

The world's population is aging and an estimated 2 billion people will be aged over 60 years by 2050 (1). Older adults tend to be more prone to nutritional deficiencies in addition to their accumulation of other comorbidities which exacerbate the problems of malnutrition. The prevalence of malnutrition is estimated at 4.8-35% among community-dwelling and home-bound older adults (2, 3) and 22–66.5% in acute hospitals, subacute units, and nursing homes (4-6). The estimated prevalence of malnutrition varies by settings and assessment tools, such as anthropometric measurement, laboratory tests, as well as nutritional questionnaires (7-9).

The multifactorial causes of malnutrition in older adults include old age, frailty, general health decline, loss of interest in life, impaired efficacy of swallowing, and institutionalization (10, 11); potential results include reduced body mass, poor wound healing, risk of infection, and organ failure (12, 13). Therefore, malnutrition is considered a risk factor for reduced physical function, delirium, higher hospital and readmission rates, and mortality, as well as the cause of significant economic burdens (14-17). Cross-sectional studies have proven the association of poor nutritional status with cognitive impairment and functional limitations, a relationship also shown to be multi-directional (18-20). Older adults at risk of malnutrition or with malnutrition are more likely to have cognitive impairment or functional limitations; likewise, older adults with cognitive impairment or functional limitation are also more likely to be at risk of malnutrition. Despite the importance of malnutrition, few studies have focused on the long-term effect of nutrition on cognition deterioration, with most focused on persons with dementia (21-23) or functional decline, particularly in hospitalized older adults (24, 25).

Currently, only a few studies have examined the longitudinally predictive effect of malnutrition on long-term cognitive decline, physical functional decline, and long-term mortality, particularly in community-dwelling older adults. The aim of our prospective observational cohort study is to investigate the effect of nutritional status on the three-year cognitive and functional decline and four-year all-cause mortality in older men in a veteran retirement home.

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Materials and Methods

Study Design and Participants

This prospectively observational study was initiated in 2013, and all subjects aged 65 and older were recruited from Gangshan Veterans Home, a veteran's retirement community in southern Taiwan (26). Although the Veterans Home has around 518 available beds, only about 400 residents usually live there. In total, we enrolled 408 residents who agreed to sign the informed consent. Of the 408 residents screened, two died within 50 days of enrollment and 52 were unable to complete the functional or cognitive evaluation were excluded from the study. After 3-year follow up until 2016, 271 of 354 participants were still alive and 43 were lost to follow up because they had moved. Of the 271 participants, 228 completed the functional evaluation and 203 completed the cognitive evaluation. The study was approved by the ethics committee of Kaohsiung Veterans General Hospital.

Baseline Demographic Data and Comprehensive Geriatric Assessment

The demographic data, including age, educational level, marital status, and body mass index (BMI), was collected by well-trained research nurses through an in-person interview. We also performed a comprehensive geriatric assessment, including self-reported visual and hearing impairments, comorbidities (as evaluated by the Charlson's Comorbidity Index [CCI], which consists of 19 categories of weighted comorbidities) (27), polypharmacy (defined as currently using more than five concurrent prescription drugs for over 2 weeks), the symptoms of depression (using the 15-item Chinese Geriatric Depression Scale, GDS-15) (28), cognitive function, and activities of daily living (ADLs). The Chinese version of the Mini-Mental State Examination (MMSE) is a widely-used instrument for evaluating cognitive function (29, 30), and scores less than 24 indicate impaired cognitive impairment (31). We used Barthel Index to evaluate the ADLs. This index uses 10 variables to describe ADLs and mobility; its total ADL score ranges from 0 to 100 (32).

The Mini Nutritional Assessment-Short Form (MNA-SF) is a valid and sensitive rapid nutritional screening for older adults. The six questions of the MNA-SF address food intake, weight loss, mobility, psychological stress or acute disease, presence of dementia or depression, and BMI. When height or weight cannot be assessed, an alternate scoring for BMI includes the measurement of calf circumference. The MNA-SF has a maximum score of 14; a score of <11 suggests a risk of malnutrition and a score >12 is normal (33).

Outcomes and Follow Up

Cognitive decline after 3-year follow up was defined as a decrease of 3 points or more in follow-up MMSE scores relative to baseline scores (34). Functional decline after three years was defined as a lower ADL score at follow up than at baseline (35). Subjects' survival dynamics were continuously supported by the staff of Gangshan Veterans Home and the medical record showed 222 residents still alive on December 31, 2017. Time to death was calculated from the date at baseline to the date of death. Mortality was compared between the normal group and those at risk of malnutrition.

Statistical Analysis

Continuous variables were expressed as the mean ± standard deviation and categorical data were expressed as numbers (percentages). Continuous variables were compared by Student's t-test. Categorical data were compared using the Chi square test or Fisher's Exact test, as appropriate. Univariate analyses were conducted to examine the relationship between nutritional status and cognitive as well as functional decline. Multivariate logistic regression models were created to evaluate whether risk of malnutrition is an independent predictor of cognitive and functional decline at the three-year follow up. Age, CCI, polypharmacy, hearing impairment, baseline cognitive status, baseline ADL, and baseline GDS-15 were included as covariates in multivariate logistic regression analysis (34, 36, 37).

The Kaplan-Meier method was used to estimate survival curves between groups at risk of malnutrition or not using the log-rank test. Cox proportional regression models estimated the effect of nutritional status on the risk of death after adjusting for potential confounders. Crude and adjusted hazard ratios (HR) and 95% confidence intervals (CI) were estimated from these models. For all tests, a p value < 0.05 (two-tailed) was considered statistical significant. SPSS for Windows version 21.0 was used for all analyses (IBM Corp., Armonk, NY).

Results

Clinical Characteristics of the Study Population

Overall, 354 residents were enrolled in the study (mean age 85.40±5.63 years). Table 1 summarizes the sociodemographic, functional, and clinical characteristics of the normal and risk of malnutrition groups. Risk of malnutrition as assessed by MNA-SF was observed in 188 residents (53.1%) and 166 residents (46.9%) had normal nutritional status. The mean age was 86.1±5.3 years in the risk of malnutrition group and 84.6±5.9 years in the normal group (P=0.010). The MNA-SF scores were 8.7±2.3 and 13.2±0.9 (P<0.001) in the risk of malnutrition and normal groups, respectively, and those residents with risk of malnutrition had lower BMI (22.1±4.1 in the risk of malnutrition group and 25.0±2.8 in the normal group, P<0.001).

Compared with the normal group, residents at risk of malnutrition had higher CCI scores (1.70±1.82 vs. 1.02±1.30, P<0.001) and higher rates of polypharmacy (70.7% vs. 56.6%, P=0.006) and hearing impairment (87.8% vs. 77.7%, P=0.012). In addition, the residents at risk of malnutrition were more likely to be cognitively impaired than those in the normal group

Table 1
Demographic characteristics of 354 participants with or without risk of malnutrition

Characteristics	Total (N=354)	Normal (N=166, 46.9%)	Risk of malnutrition (N=188, 53.1%)	P value
Age (years) †	85.4±5.6	84.6±5.9	86.1±5.3	0.010
Educational level ‡				0.135
No formal education	60 (16.9%)	33 (19.9%)	27 (14.4%)	
Primary school	193 (54.5%)	84 (50.6%)	109 (58%)	
Secondary school	84 (23.7%)	44 (26.5%)	40 (21.3%)	
College/university	17 (4.8%)	5 (3.0%)	12 (6.4%)	
Marital status				0.401
Single	136 (38.4%)	68 (41.0%)	68 (36.2%)	
Married	8 (2.3%)	5 (3.0%)	3 (1.6%)	
Widowed/Divorced	210 (59.3%)	93 (56.0%)	117 (62.2%)	
MNA-SF	10.8±2.9	13.2±0.9	8.7±2.3	<0.001
Body mass index (kg/m2)	23.5±3.8	25.0±2.8	22.1±4.1	<0.001
CCI	1.38±1.63	1.02±1.30	1.70±1.82	<0.001
Hearing impairment	294 (83.1%)	129 (77.7%)	165 (87.8%)	0.012
Visual impairment	315 (89.0%)	144 (86.7%)	171 (91.0%)	0.207
Polypharmacy	227 (64.1%)	94 (56.6%)	133 (70.7%)	0.006
Cognitive function				<0.001
Intact (MMSE ≥24)	139 (39.3%)	84 (50.6%)	55 (29.3%)	
Cognitive impairment (MMSE <24)	215 (60.7%)	82 (49.4%)	133 (70.7%)	
ADL scores	79.7±25.9	92.3±13.3	68.6±29.1	<0.001
GDS-15 scores	3.75±3.32	2.48±2.56	4.92±3.51	<0.001

MNS-SF: mini nutritional status-short form; CCI: Charlson comorbidity index score; MMSE: mini-mental state examination; ADL: activities of daily living; GDS-15: geriatric depression scale.

(70.7% vs 49.4%, P<0.001). Residents at risk of malnutrition also had lower ADL scores (68.6±29.1 vs. 92.3±13.3, P<0.001) and presented with more depressive symptoms (GDS scores 4.92±3.51 vs. 2.48±2.56, P<0.001).

Table 2
Independently predictive effect of malnutrition on 3-year follow-up cognitive and functional decline

	Cognitive Decline		Functional Decline	
	OR (95% CI)	P value	OR (95% CI)	P value
Risk of malnutrition				
Unadjusted	2.15 (1.09-4.22)	0.027	2.20 (1.24-3.91)	0.007
Adjusted	2.07 (1.05-4.08)	0.036	1.83(1.01-3.34)	0.047

Adjusted for covariates of age, Charlson comorbidity index score, baseline cognitive status, baseline ADL scores, GDS-15, polypharmacy, hearing impairment. ADL: activities of daily living; OR: odds ratio; CI: confidence interval; GDS-15: geriatric depression scale.

Predictive Effect of Risk of Malnutrition on 3-year Cognitive and Functional Decline

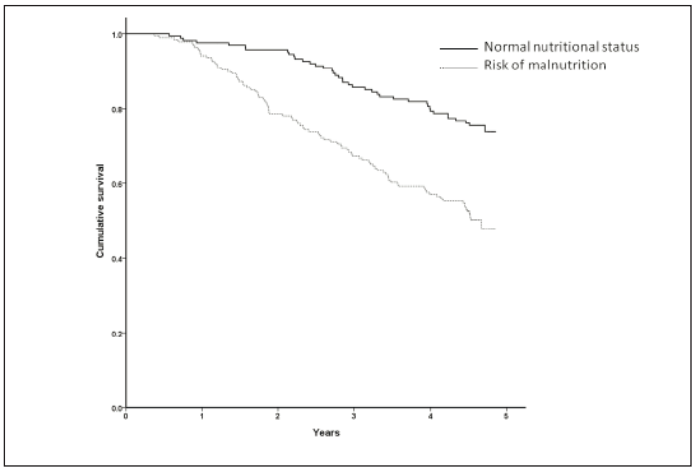
Univariate logistic regression showed that risk of malnutrition was significantly associated with three-year cognitive decline (OR 2.15, 95% CI 1.09–4.22, P=0.027) and functional decline (OR 2.20, 95% CI 1.24–3.91, P=0.007) (Table 2). In the multivariate logistic regression model, risk of malnutrition was also an independent risk factor for 3-year follow-up cognitive decline (adjusted OR 2.07, 95% CI 1.05–4.08, P=0.036) and functional decline (adjusted OR 1.83, 95% CI 1.01–3.34, P=0.047) after adjusting for all covariates. Baseline cognitive status was also a significant predictor of three-year functional decline after adjusting for all covariates (adjusted OR 2.61, 95% CI 1.38–4.92, P=0.003, not shown in the tables).

Table 3
Risk of malnutrition to predict all-cause mortality using Cox proportional hazards model analysis

Parameters	Unadjusted HR (95% CI)	P value	Adjusted HR (95% CI)	P value
Risk of malnutrition	2.51 (1.73-3.64)	<0.001	1.82 (1.19-2.79)	0.006
Age	1.06 (1.03-1.09)	<0.001	1.06 (1.03-1.09)	<0.001
CCI	1.19 (1.08-1.33)	0.001	1.15(1.03-1.30)	0.018
Baseline cognitive status	1.80 (1.24-2.63)	0.002	1.34 (0.88-2.03)	0.172
Baseline ADL scores	0.99 (0.98-1.00)	<0.001	1.00 (0.99-1.01)	0.978
GDS-15	1.09 (1.031.14)	0.001	1.04 (0.99-1.10)	0.158
Polypharmacy	1.33 (0.921.92)	0.135	1.02 (0.69-1.51)	0.922

HR: hazard ratio; CCI: Charlson comorbidity index score; ADL: activities of daily living; GDS-15: geriatric depression scale.

Figure 1
Kaplan-Meier survival analysis by nutritional status during the 4-year



Log rank test X2 =25.04, P<0.001

Predictive Effect of Risk of Malnutrition on All-Cause Mortality

All-cause mortality was tracked through the end of 2017. A total of 132 participants died, 92 in the risk of malnutrition group and 40 in the normal group at baseline. Kaplan-Meier analysis indicated a reduced survival probability associated with risk of malnutrition, as shown in Figure 1 (log-rank test X2=25.04, P<0.001). The crude HR for all-cause mortality was 2.51 times higher among residents at risk of malnutrition than in those without risk of malnutrition, as indicated in Table 3 (unadjusted HR: 2.51, 95% CI 1.73–3.64, P<0.001). After adjusting for all co-variables, risk of malnutrition, older age, and CCI were associated with a significantly higher risk of mortality (adjusted HR 1.82, 95% CI 1.19-2.79, P=0.006; adjusted HR 1.06, 95% CI 1.03-1.09, P <0.001; adjusted HR 1.15, 95% CI 1.03-1.30, P=0.018, respectively).

Discussion

The primary aim of this prospectively observational cohort study was to provide evidence of the association of risk of malnutrition with poor long-term clinical outcomes. We simultaneously assessed the 3-year follow-up cognitive and functional decline and 4-year all-cause mortality. The two major findings of this study are: (1) Risk of malnutrition was an independent predictor for 3-year cognitive and functional decline; and (2) Four-year all-cause mortality was significantly predicted by the risk of malnutrition among older men in a veteran retirement home.

Malnutrition in older adults is often underestimated or unaddressed because of the absence of a universally accepted definition and an appropriate tool. For example, MNA takes 10-15 minutes to administer (38, 39), but the MNA-SF takes less than 5 minutes. Both can predict risk of malnutrition in older adults (39, 40), and have been validated in different races, community-living, institutionalized or hospitalized, and even frail adults (40-42). The prevalence of risk of malnutrition based on the MNA-SF in this study was 53.1% among older men with an average age of 85 years. This higher prevalent than in community-dwelling older adults (35%, mean age 81 years) (3) or domiciliary care services individuals (43.2%, mean age 79 years) (43) may be due to the older age of our study subjects. We also found that our residents at risk of malnutrition had lower BMI, poorer ADL function, more comorbidities, more depressive symptoms, greater self-reported hearing impairment, more polypharmacy, and more cognitive impairment. This result was compatible with previous evidence that risk of malnutrition is associated with age, depression, cognitive impairment, multimorbidity, polypharmacy, impaired physical function, or a combination of these factors (10, 11, 18). An increased risk of malnutrition, associated with multiple declines, should increase the alertness to screen early for malnutrition using an applicable and fast tool, e.g., MNA-SF.

Good nutrition contributes to healthy brain development, which may protect against the onset of dementia and slow cognitive decline. Accumulating evidence has shown that, while some individual nutrients may protect brain health, the total dietary pattern and general nutritional status also play an important role in cognitive decline (44, 45). Poor nutritional status may precede or accompany dementia onset and progression (22). One study found that one in seven older adults with newly-diagnosed Alzheimer's Disease were at risk of malnutrition (46). In our study, risk of malnutrition was associated with not only cognitive impairment but also 3-year cognitive decline. A few studies have demonstrated similar findings, but they enrolled only participants with dementia (21-23). They showed, in those in the community or long-term care facilities, a strong correlation between malnutrition and cognitive deterioration as well as functional decline, institutionalization, hospitalization and death, after follow up ranging from six months to six years. Malnutrition is

considered as a modifiable risk factor for cognitive decline or incident dementia. Nutrition intervention has also been included as part of a multidomain intervention to prevent cognitive decline in some large-scale population-based trials, although the clinical effect of nutrition intervention in the multidomain intervention could not be totally clarified (47-49).

In addition to cognitive deterioration, functional decline in older adults reduces quality of life. Nutritional status has been shown to influence the onset and course of disability (50). Malnutrition is significantly associated with geriatric conditions in dependent older adults, and is key in the pathogenesis of sarcopenia and frailty, which lead to subsequent functional decline (51-53). We also found malnutrition significantly associated with functional deterioration. Furthermore, baseline cognitive status was also an important predictor of 3-year functional decline, a result also supported by a study of community-dwelling older adults in Italy (35). Cognitive impairment may lead to an erosion of the physical skills needed to maintain functional independence and leave the older adult less resistant to acute stressors, often accelerating functional dependence (54). The effects of nutrition, aging brain, and cognitive deficit on functional decline may be linked by complex pathways.

Risk of malnutrition was also closely related to long-term mortality. Most studies, focused on hospital patients, found that older adults with malnutrition have significantly higher risk for complications and mortality (55-57). Our residents in a retirement community also had a significant association between risk of malnutrition and 4-year all-cause mortality. This association remained significant after controlling for relevant variables, including baseline characteristics, functional status, and comorbidities. Our study provides a warning that risk of malnutrition should be identified early and interventions begun, to prevent early death. Chen et al. enrolled male residents living in a similar retirement community, but in different Veterans homes, and used the Minimum Data Set (MDS) to define malnutrition (58). They found that malnutrition was highly predictive of 18-month crude mortality after adjusting for age and BMI, but the effect disappeared after adding CCI as a covariate. Compared with our study, their lower prevalence of malnutrition, only 6.1% of all study residents, may be due to the use of the stricter MDS-based definition of malnutrition, e.g., "parenteral or enteral nutrition support" and "presence of pressure ulcers." Both items are less common the physical fit, and therefore not useful in this setting. However, residents identified by these items should be more frail and at greater risk of further disability; indeed, malnutrition independently tripled the risk for functional decline in this study (58). Another study by Shakersain surveyed 3,041 participants aged over 60 years (mostly living at home) in the Swedish National Study on Aging and Care; they also found significantly shorter survival for subjects with risk of malnutrition or malnutrition, based on the MNA-SF (59). The survival effect was further associated with nutritional status in combination with abnormalities in hemoglobin and albumin.

Despite our research effort, there were several limitations in the present study. First, the participants were all retired male veterans. Thus, they were similar in diet as well as living conditions. This homogeneity may limit the extrapolation of the study results to general populations. Second, the residents did not undergo a clinical assessment for dementia and we cannot determine the cause of cognitive decline. Third, only 76.3% of residents (270/354) were investigated after the 3-year follow-up and only 57.3% of residents (203/354) completed the subsequent cognitive assessment. The lower follow-up rate for cognitive change may potentially bias the study results. However, the lost to follow up residents included those who died and may potentially skew toward the more frail or a higher percentage with malnutrition. Thus, our results may underestimate the predictive effect of malnutrition on clinical outcomes. Four, the definition of cognitive decline in a community-based population is inconsistent, and the efficacy of our definition for cognitive decline should be re-evaluated in the future. Fifth, this is a prospective observational cohort design. The intervention effect for malnutrition remain unclear, even though malnutrition is an independently predictor of clinical outcomes.

From a preventive point of view, the effects of nutrition in long-term cognitive, functional and survival prognosis have become more and more important. Our results provide strong evidence that risk of malnutrition can predict not only cognitive and functional decline but also risk of all-cause mortality in older men living in a veteran retirement's community. Further longitudinal studies are needed to explore the causal relationship among nutrition, the development of cognitive and functional decline, and the effect on clinical outcomes after an intervention for malnutrition.

Disclosure statement: All authors declare no conflicts of interest for this study.

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Ethical Standards: The prospectively observational study was approved by the ethics committee of Kaohsiung Veterans General Hospital. The study was waived the requirement for patient consent. (VGHKS14-CT7-19).

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