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Dysmobility Syndrome and Risk of Mortality for Community-Dwelling Middle-Aged and Older Adults: The Nexus of Aging and Body Composition

Wei-Ju Lee^{1,2,3}, Li-Kuo Liu^{1,4}, An-Chun Hwang^{1,2,4}, Li-Ning Peng^{1,2,4}, Ming-Hsien Lin^{1,4} & Liang-Kung Chen^{1,2,4}

Dysmobility syndrome is a newly proposed concept to comprehensively consider bone-muscle-adiposity as a whole to associate with mortality and other adverse outcomes in the older adults. Little was known in Asian populations since the body composition was highly related to ethnicity. The study aimed to evaluate the association between dysmobility syndrome and mortality and to explore the most optimal operational definition for dysmobility syndrome. The prevalence of dysmobility syndrome was 3.9–10.1% based on different operational definitions of adiposity and skeletal muscle index. Subjects with dysmobility syndrome were older, more often to be women, having higher adiposity, lower lean body mass and bone mineral density. Multivariate Cox proportional hazard model showed that dysmobility and pre-dysmobility syndrome had higher risk of mortality than the robust group (Hazard ratio (HR): 11.3, 95% confidence interval (CI): 1.2–109.1; and HR 8.7, 95% CI 1.1–67.3, respectively). Overall, the modified operational definition of dysmobility syndrome in Asian populations using FNIIH-adjusted skeletal muscle mass and waist circumference-defined adiposity may be the most optimal model for mortality prediction. Taking the nexus of body composition as a whole to evaluate the mortality risk of older adults is an important improvement beyond sarcopenia and osteoporosis.

Epidemiological studies have shown the interrelated associations between muscle strength, walking speed, sarcopenia, osteoporosis, body fat composition and mortality among older adults^{1–5}. In current definitions of sarcopenia or skeletal muscle dysfunction, it needs both muscle quality and quantity to identify older people at risk for mobility limitation, falls and mortality^{6–9}. Previous studies have disclosed that osteoporosis and sarcopenia eventually shared similar trends in the associations with adverse health outcomes among older adults^{8,10}. The interconnected relationship between bone and muscle with adverse outcomes led to the proposal of the bone-muscle unit as a whole to evaluate the effect of mobility to health¹¹. Moreover, Binkley, *et al.*, extended the concept from the bone-muscle unit to propose a new condition, i.e. dysmobility syndrome, which took the comprehensive consideration of bone, muscle and adiposity to early identify older people at risk¹².

Operationally, dysmobility syndrome was defined by a score-based approach, which was similar to the definition of metabolic syndrome. Although the definition of dysmobility syndrome has been proposed, it remained to be a big challenge when the measurement of skeletal muscle was still under debate. Eventually, weight or height-adjusted skeletal muscle index identified people with very different clinical characteristics that weight-adjusted muscle index-defined low muscle mass tended to be overweight and obese while height-adjusted muscle index-defined low muscle mass tended to lean¹³. A recent study identified substantial differences in the prevalence of dysmobility syndrome and associated falls by using proposed definitions of skeletal muscle mass by

¹Aging and Health Research Center, National Yang Ming University, Taipei City, Taiwan. ²Institute of Public Health, National Yang Ming University, Taipei City, Taiwan. ³Department of Family Medicine, Taipei Veterans General Hospital Yuanshan Branch, Yilan County, Taiwan. ⁴Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei City, Taiwan. Correspondence and requests for materials should be addressed to L.-K.C. (email: lkchen2@vghtpe.gov.tw)

| | Total | Dysmobility status | | | |
|-----------------------------------------------------------------------|-------------|--------------------|-----------------|-------------|--------|
| | | Robust | Pre-dysmobility | Dysmobility | p |
| number | 1757 | 831(47.3) | 837(47.6) | 89(5.1) | |
| Age(years) | 63.8 ± 9.2 | 61.2 ± 8.1 | 65.2 ± 9.1 | 75.1 ± 8.5 | <0.001 |
| Men | 825(46.9) | 446(53.7) | 348(41.6) | 31(34.8) | <0.001 |
| Anthropometric measurements | | | | | |
| Height(cm) | 158.6 ± 8.0 | 160.3 ± 7.7 | 157.5 ± 7.8 | 152.5 ± 8.1 | <0.001 |
| Weight(Kg) | 62.6 ± 11.0 | 62.1 ± 9.2 | 63.6 ± 12.3 | 58.6 ± 11.5 | <0.001 |
| Body mass Index(kg/m ²) | 24.8 ± 3.6 | 24.1 ± 2.5 | 25.6 ± 4.2 | 25.3 ± 5.0 | <0.001 |
| Central obesity | 871(49.6) | 301(36.2) | 513(61.3) | 57(64.0) | <0.001 |
| Health behavior | | | | | |
| Smoke | | | | | 0.009 |
| never | 1233(70.2) | 568(68.4) | 599(71.6) | 66(74.2) | |
| current | 307(17.5) | 168(20.2) | 132(15.8) | 7(7.9) | |
| former | 217(12.4) | 95(11.4) | 106(12.7) | 16(18.0) | |
| Alcohol | | | | | <0.001 |
| never | 1036(59.0) | 445(53.6) | 527(63.0) | 64(71.9) | |
| current | 578(32.9) | 326(39.2) | 235(28.1) | 17(19.1) | |
| former | 143(8.1) | 60(7.2) | 75(9.0) | 8(9.0) | |
| Dual-energy X-ray absorptiometry | | | | | |
| Lean body mass(kg) | 41.7 ± 8.2 | 43.6 ± 8.3 | 40.4 ± 7.7 | 35.8 ± 6.9 | <0.001 |
| Appendicular skeletal muscle(kg) | 17.9 ± 4.1 | 19.1 ± 4.1 | 17.1 ± 3.8 | 14.7 ± 2.7 | <0.001 |
| Appendicular skeletal muscle/height ² (kg/m ²) | 7.0 ± 1.1 | 7.3 ± 1.1 | 6.8 ± 1.1 | 6.2 ± 0.8 | <0.001 |
| Appendicular skeletal muscle/BMI(m ²) | 0.7 ± 0.2 | 0.8 ± 0.2 | 0.7 ± 0.1 | 0.6 ± 0.1 | <0.001 |
| Total fat mass(kg) | 19.5 ± 7.0 | 17.2 ± 5.2 | 20.8 ± 7.9 | 21.7 ± 7.8 | <0.001 |
| Total fat percentage(%) | 31.6 ± 8.7 | 28.4 ± 7.3 | 34.3 ± 8.9 | 35.5 ± 9.6 | <0.001 |
| Lumbar bone marrow density | 1.0 ± 0.2 | 1.1 ± 0.2 | 1.0 ± 0.2 | 0.9 ± 0.2 | <0.001 |
| Hip bone marrow density | 0.8 ± 0.1 | 0.9 ± 0.1 | 0.8 ± 0.1 | 0.7 ± 0.1 | <0.001 |
| Physical performance | | | | | |
| Walking speed(m/s) | 1.5 ± 0.5 | 1.7 ± 0.5 | 1.4 ± 0.4 | 0.9 ± 0.4 | <0.001 |
| Handgrip strength(kg) | 28.1 ± 9.5 | 31.8 ± 8.8 | 25.6 ± 8.8 | 17.2 ± 5.8 | <0.001 |
| Function status | | | | | |
| Fall | 89(5.1) | 0(0.0) | 70(8.4) | 19(21.4) | <0.001 |
| The autonomy assessment scale | -0.2 ± 1.6 | 0.0 ± 0.3 | -0.2 ± 1.5 | -1.7 ± 5.4 | <0.001 |
| Charlson comorbidity index | 1.0 ± 1.3 | 0.8 ± 1.1 | 1.1 ± 1.3 | 1.9 ± 1.5 | <0.001 |

Table 1. Characteristics of participants of the I-Lan Longitudinal Aging Study. Numerical variables were expressed as mean ± standard deviation, categorized variables were expressed as number(%).

the European Working Group for Sarcopenia in Older People (EWGSOP), the International Working Group on Sarcopenia (IWGS) and the Foundation for the National Institutes of Health Sarcopenia Project (FNIH)¹⁴. These differences may be even more significant in Asia due to higher adiposity of Asian people than Caucasians, especially in women¹⁵. The FNIH criteria proposed using body mass index (BMI) for the adjustment of skeletal muscle index to harmonize the definition of muscle index⁷, which may result in bigger discrepancy in Asian populations.

Dysmobility syndrome proposed the comprehensive approach of bone-muscle-adiposity to health of older people, and the association between dysmobility syndrome and adverse health outcomes has been established in some studies¹². More research is needed to evaluate the impact of dysmobility syndrome on health of older people in different population with various characteristics. In particular, in Asia, the arbitrary score-based approach for definition of dysmobility syndrome deserves further investigation since the individual definition for adiposity and low muscle mass may differ from Western countries. Therefore, the main aim of this study intended to use a prospective population-based cohort to examine the association between dysmobility syndrome and mortality and to refine the operational definition of dysmobility syndrome through the outcome-based approach.

Results

Table 1 summarized the characteristics of the whole study participants and compared differences by various status of dysmobility syndrome. In this study, the youngest participant was 50 years old and the oldest was 92. Among 89 (5.1%) participants with dysmobility syndrome, women were more predominant (6.5% versus 3.8%,

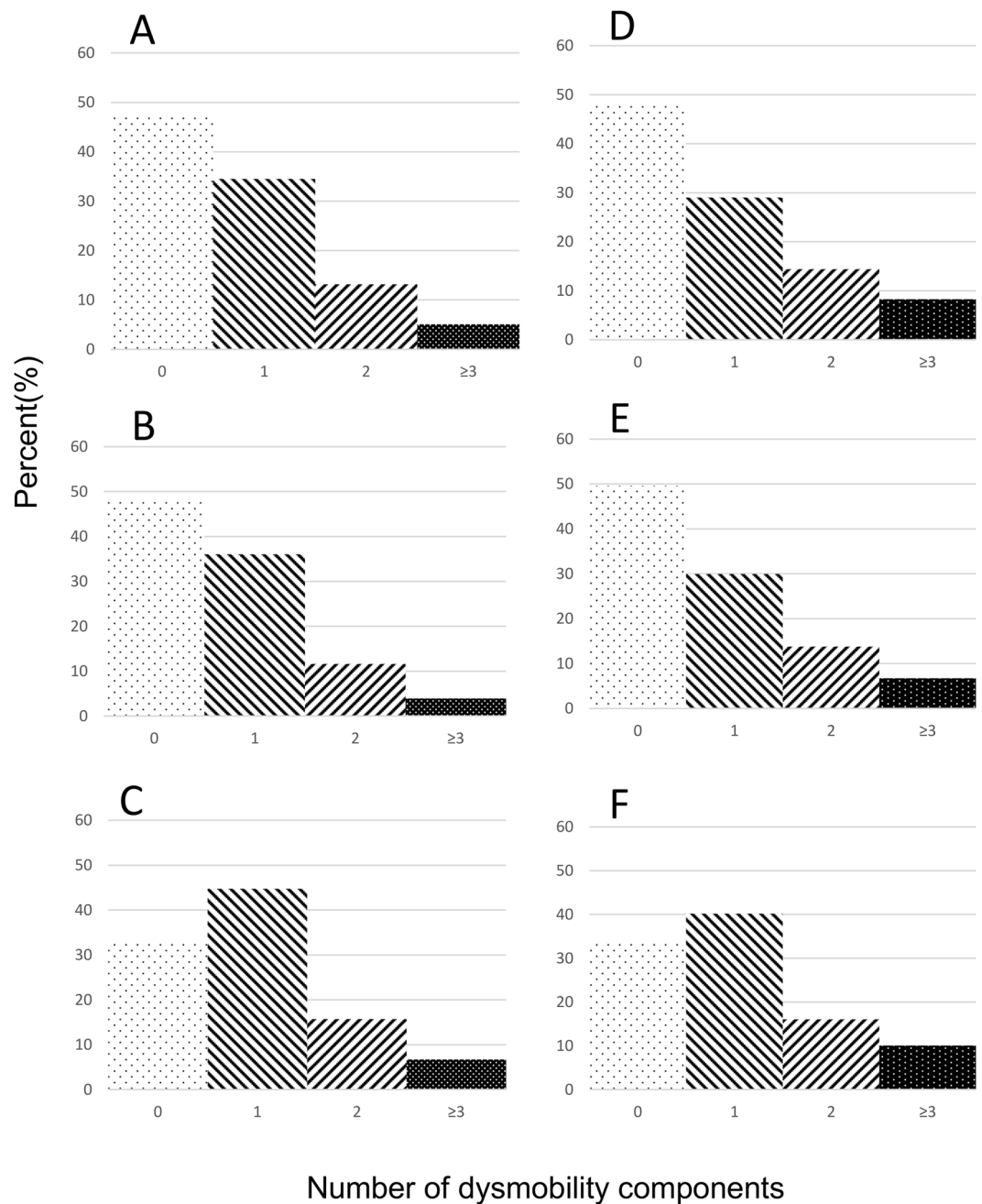


Figure 1. Distribution of dysmobility components by various muscle and fat definitions. Distribution of dysmobility syndrome by (A) original definition; (B) obesity determined by body mass index (C) obesity determined by central obesity (D) BMI adjusted muscle index (E) BMI adjusted muscle index plus obesity determined by BMI (F) BMI adjusted muscle index plus obesity determined by central obesity.

$p < 0.001$). During the median follow-up of 2.6 years, 18 participants died (3.7 per 1000 person-years at risk). Among all determinants of dysmobility syndrome, distribution of dysmobility components were right skewed (Fig. 1). The number of components for dysmobility syndrome significantly increased with advancing age (p for trend < 0.001) (Fig. 2).

Cox proportion hazard model for mortality prediction. Pre-dysmobility, dysmobility and low muscle strength were all significantly associated with mortality in age and sex adjusted and fully adjusted Cox regression analysis (Table 2). Table 2 also provided the estimated prevalence and hazard ratio for mortality of each component of dysmobility syndrome. Adiposity was most common condition (28.9%), followed by low hand-grip strength and osteoporosis. Among these conditions, only muscle strength and FNIIH-defined sarcopenia (BMI-adjusted muscle index) were significantly associated with mortality.

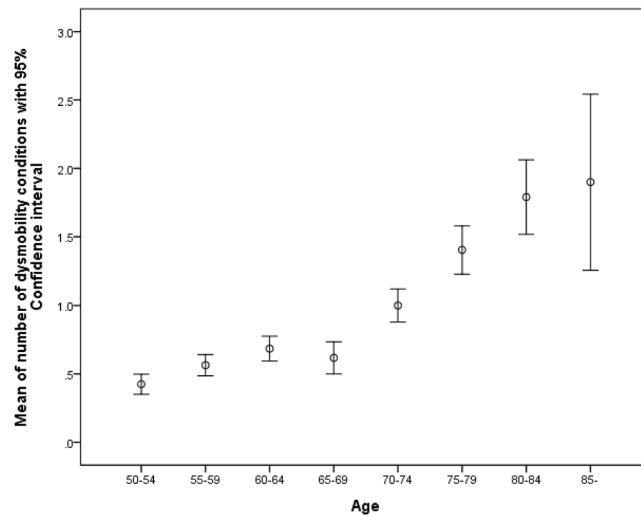


Figure 2. Mean of numbers of dysmobility conditions with 95% confidence interval versus age.

| Characteristic | n(%) | death(rate) | Age and sex adjusted | | Full adjusted model | | |
|-------------------------------|-----------|-------------|----------------------|---------------|---------------------|---------------|--------------|
| | | | HR(95% CI) | p | HR(95% CI) | p | |
| Dysmobility | | | | | | | |
| Robust | 831(47.3) | 1(0.1) | 1 | | 1 | | |
| Pre-dysmobility | 837(47.6) | 13(1.6) | 8.5(1.1–65.8) | 0.040 | 8.7(1.1–67.3) | 0.038 | |
| Dysmobility | 89(5.1) | 4(4.5) | 11.1(1.1–107.7) | 0.038 | 11.3(1.2–109.1) | 0.037 | |
| Dysmobility components | | | | | | | |
| High adiposity | | | | | | | |
| Prevalence ranking | | | | | | | |
| Fat percentage | 507(28.9) | 6(1.2) | 1.2(0.5–3.2) | 0.703 | 1.4(0.5–3.8) | 0.526 | |
| BMI | 413(23.5) | 2(0.5) | 0.5(0.1–2.0) | 0.299 | 0.5(0.1–2.2) | 0.350 | |
| Central obesity | 871(49.6) | 12(1.4) | 1 | 1.7(0.6–4.7) | 0.297 | 2.0(0.7–5.6) | 0.207 |
| Low muscle mass | | | | | | | |
| ASM/height ² | 193(11.0) | 3(1.6) | 1.0(0.3–3.4) | 0.9571 | 1.0(0.3–3.6) | 0.983 | |
| ASM/BMI | 330(18.8) | 7(2.1) | 2 | 1.5(0.6–3.9) | 0.420 | 1.7(0.7–4.7) | 0.265 |
| Weak handgrip strength | 297(16.9) | 12(4.0) | 3 | 5.1(1.7–14.9) | 0.003 | 5.4(1.8–16.3) | 0.003 |
| Slow walking speed | 57(3.2) | 4(7.0) | 6 | 2.1(0.6–7.1) | 0.248 | 2.3(0.6–8.9) | 0.212 |
| Osteoporosis | 209(11.9) | 6(2.9) | 4 | 2.0(0.7–5.8) | 0.201 | 1.9(0.6–5.8) | 0.285 |
| Fall | 89(5.1) | 1(1.1) | 5 | 0.7(0.1–5.3) | 0.737 | 0.7(0.1–5.3) | 0.705 |

Table 2. Prevalence and risk of mortality of dysmobility component conditions in the I-Lan Longitudinal Aging Study ASM, appendicular skeletal muscle; BMI, body mass index; bold type indicated statistical significance; Full model was adjusted by age, sex, the autonomy assessment scale, Charlson comorbidity index, smoke and alcohol consumption.

Discrimination between different definitions. Table 3 showed the effectiveness of mortality prediction of dysmobility syndrome by different definitions. In this study, we compared skeletal muscle index defined by different operational criteria. Both original dysmobility syndrome defined by Binkley, *et al.* and dysmobility syndrome using BMI-adjusted muscle index were associated with mortality. However, using the definition of dysmobility syndrome modified by BMI-adjusted muscle index eventually identified a higher prevalence of dysmobility syndrome. Major contributive components change and distribution of 6 components by different definitions were presented in Fig. 3.

Sensitivity analysis. A sensitivity analysis was conducted by excluding all participants died within one year after baseline interview. In the fully adjusted Cox proportional hazard model, subjects with dysmobility and pre-dysmobility syndrome had higher risk of mortality (HR 9.93 and 6.09; 95% CI 1.01–97.62 and 0.77–48.42, respectively) than robust ones. Moreover, FNIH-defined sarcopenia (HR 3.68, 95% CI 1.10–12.3) and low handgrip strength (HR:5.00, 95% CI 1.50–16.71) were both significantly associated with risk of mortality.

| Definition of dysmobility syndrome | Prevalence n(%) | Age and sex adjusted HR(95% CI) | Harrell's R ² | AIC | BIC |
|---------------------------------------------------------------------|-----------------|---------------------------------|--------------------------|-------|-------|
| Original version (Binkley) | | | reference | 224.3 | 227.9 |
| Obesity as BMI ≥ 27 kg/m ² | | | | | |
| Robust | 851(48.4) | 1 | 0.012 | 226.9 | 230.4 |
| Pre-dysmobility | 837(47.6) | 4.7(1.0–21.0) | | | |
| Dysmobility | 69(3.9) | 4.6(0.7–30.8) | | | |
| Obesity as central obesity | | | | | |
| Robust | 577(32.8) | 1 | 0.017 | 228.1 | 231.6 |
| Pre-dysmobility | 1062(60.4) | 4.2(0.5–33.2) | | | |
| Dysmobility | 118(6.7) | 8.3(0.9–80.1) | | | |
| BMI-adjusted muscle index and high body fat percentage | | | | | |
| Robust | 849(48.3) | 1 | –0.005 | 223.2 | 226.8 |
| Pre-dysmobility | 763(43.4) | 7.5(1.0–59.2) | | | |
| Dysmobility | 145(8.3) | 14.0(1.6–123.1) | | | |
| BMI-adjusted muscle index and obesity as BMI ≥ 27 kg/m ² | | | | | |
| Robust | 871(49.6) | 1 | 0.013 | 227.2 | 230.8 |
| Pre-dysmobility | 768(43.7) | 4.0(0.9–18.3) | | | |
| Dysmobility | 118(6.7) | 5.6(1.0–31.7) | | | |
| BMI-adjusted muscle index and obesity as central obesity | | | | | |
| Robust | 592(33.7) | 1 | 0.004 | 225.2 | 228.7 |
| Pre-dysmobility | 988(56.2) | 3.3(0.4–26.8) | | | |
| Dysmobility | 177(10.1) | 10.2(1.2–90.9) | | | |

Table 3. Prevalence and risk of mortality by various definitions of dysmobility syndrome. HR, Hazard ratio; CI, confidence interval; AIC, Akaike Information Criterion; BIC, Bayesian information criterion; BMI, body mass index.

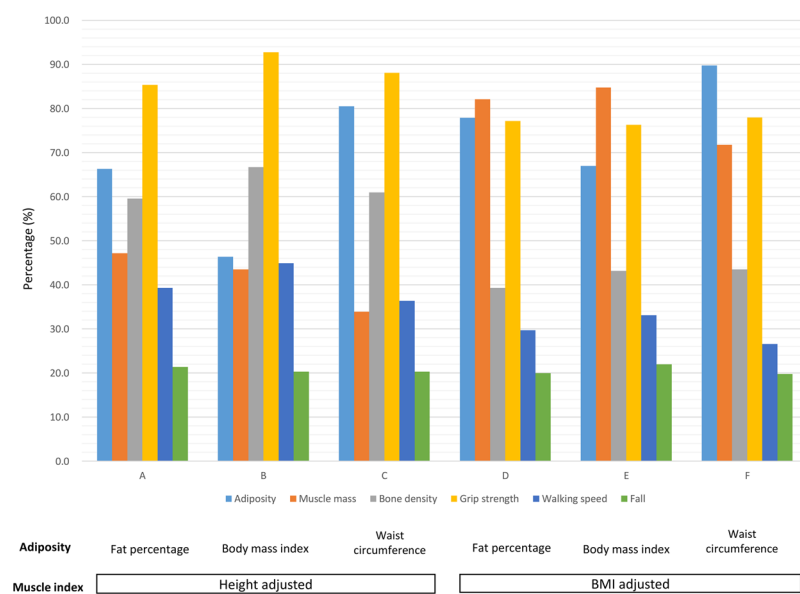


Figure 3. Distributions of dysmobility conditions by six different definitions of dysmobility syndrome.

In the arbitrary score-based approach for definition of dysmobility syndrome, Table 4 summarized the comparison of prediction for mortality risk between different criteria other than 3 of 6 components and results showed the 3 of 6 components showed the better predictive power.

Mortality risk of dysmobility syndrome was examined in the group aged 50–69 and the group aged 70 and over according to previous study.¹⁶ In the age and sex adjusted Cox proportional model, mortality risk for dysmobility were significant in the group aged 50–69 (HR 45.0, 95% 2.7–746.9) but the association was insignificant in the group aged 70 and over.

| Dysmobility syndrome defined by different numbers of conditions | Prevalence n(%) | Age and sex adjusted HR(95% CI) | AIC | BIC |
|-----------------------------------------------------------------|-----------------|---------------------------------|---------|---------|
| 0 vs. 1 vs. ≥ 2 | | | | |
| Robust | 831(47.3) | 1 | 224.137 | 227.698 |
| Pre-dysmobility | 606(34.5) | 7.7(0.9–62.6) | | |
| Dysmobility | 320(18.2) | 10.5(1.3–87.4) | | |
| 0 vs. 1–2 vs. ≥ 3 | | | | |
| Robust | 831(47.3) | 1 | 224.301 | 227.863 |
| Pre-dysmobility | 837(47.6) | 8.5(1.1–65.8) | | |
| Dysmobility | 89(5.1) | 11.1(1.1–107.7) | | |
| 0 vs. 1–3 vs. ≥ 4 | | | | |
| Robust | 831(47.3) | 1 | 224.457 | 228.019 |
| Pre-dysmobility | 909(51.7) | 8.8(1.1–67.3) | | |
| Dysmobility | 17(1.0) | 10.6(0.6–183.7) | | |

Table 4. Prevalence and mortality risk by different selected numbers of dysmobility components. AIC, Akaike Information Criterion; BIC, Bayesian information criterion.

Discussion

Dysmobility syndrome was significantly associated with the risk of mortality among middle-aged and older adults, and the results remained robust after excluding subjects who died within the first 12 months of study. A dose-response effect between robust/predysmobility/dysmobility syndrome and mortality was observed. Moreover, using BMI-adjusted skeletal muscle index and waist circumference-defined obesity as the components for definition of dysmobility syndrome had highest AIC and BIC, which indicated better power for mortality prediction.

Due to the complexity of health in older people, researchers were keen to develop a comprehensive model to predict adverse outcomes of older people through a cluster of risk factors. In the clinical practice, sarcopenia, balance and other related factors were involved in the FRAX model to improve prediction for fragility fractures^{17,18}. Morley, *et al.*, suggested to emphasize the mobility domains to sarcopenia as sarcopenia with limited mobility¹⁹. Binkley, *et al.*, proposed the concept of dysmobility syndrome to capture sarcopenia, osteoporosis, mobility and balance simultaneously, which showed significant associations for the risk of falls, fractures, and even mortality of dysmobility syndrome¹². Several cross-sectional studies have demonstrated the associations between previous fractures and dysmobility syndrome^{14,20} and results from the current study supported that dysmobility syndrome significantly predicted mortality among middle-aged and older Taiwanese.

Hill, *et al.*, indicated the need to refine the arbitrary cut-off points of dysmobility syndrome and suggested differences of anthropometric measures between Asian people and the Caucasian²¹. There were considerable debates about instruments for measurements of adiposity and muscle mass^{7,13,22}, and results of this study suggested using waist circumference-defined adiposity and BMI-adjusted muscle index to define dysmobility syndrome in Asian populations. Among selection of muscle indices, FNIH-defined sarcopenia was significantly associated with mortality but height-adjusted muscle indices failed to reach statistical significance. Similar results were found in our previous studies that BMI-adjusted strength was more superior to handgrip strength *per se* in predicting cardiovascular risk²³. Although adiposity ranked the highest prevalence among six components of dysmobility syndrome, muscle strength was the most powerful predictor for mortality, which was consistent with the result from a national representative population-based study⁵. However, a study of 558 older men living in the retirement community showed that walking speed but not handgrip strength predicted all-cause mortality²⁴, which may imply that handgrip strength may be a better mortality predictor among the otherwise healthy community-dwelling older adults. Nevertheless, dysmobility syndrome tried to capture adiposity-muscle-bone, strength, and performance in a score-based comprehensive approach.

Reported prevalence of dysmobility syndrome from Western countries was around 22–34%^{12,14,16}, but a Korean study of 6,070 women with the mean age 74.1 years showed that only 43 subjects were positive for dysmobility syndrome²⁵. Results from this current study showed that the prevalence of dysmobility syndrome ranged between 3.9–10.1% by using different operational definitions for muscle indices and adiposity. Prevalence of dysmobility syndrome by using BMI-adjusted muscle index (6.7–10.1%) were higher than that by using height-adjusted muscle index (3.9–6.7%). Those of dysmobility syndrome identified by BMI-adjusted muscle index were more likely to have higher adiposity and low muscle mass, and that defined by height-adjusted muscle index were more likely to be slowness or weakness. The prevalence of dysmobility syndrome in this study was similar to that from the National Health and Nutrition Examination Survey (NHANES) 1999–2002 if adiposity was determined by waist circumference. The risk of dysmobility syndrome has been reported higher in older adults aged 50–69 than those aged 70 and over¹⁶.

Using BMI-adjusted rather than height-adjusted muscle indices identify more individuals with dysmobility syndrome, who tend to have higher adiposity and lower muscle mass but less likely to be weakness and slowness. Among three significant predictive models of six different definitions, highest predictive ability for mortality was that with adiposity of waist circumference-based and muscle mass of BMI-adjusted index. It is possible due to obesity-related health risk related to central distributed adiposity rather than total fat amount²⁶. However, further

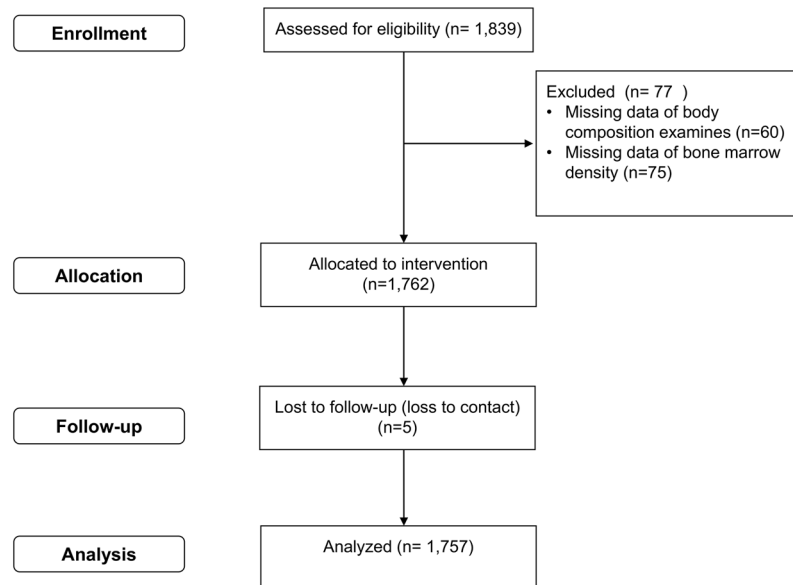


Figure 4. Participants derived from I-Lan Longitudinal Aging Study.

investigations are needed to examine the effectiveness of the model for hip fracture prediction or other geriatric conditions.

Despite all efforts went into this study, there were still some limitations. First, in this study, history of falls was defined as previous fall within the past three months instead of last year in the original definition of dysmobility syndrome, which may underestimate the prevalence of dysmobility syndrome. Second, participants of the study cohort were living in rural region and otherwise healthy, which may also underestimate the impact of dysmobility syndrome on mortality. Third, sex-specific analysis was not done due to limited sizes of sample. However, the interaction between sex and dysmobility were insignificant. Nevertheless, this study not only described the epidemiology and association with mortality in Asian populations, but also clarify the most optimal modifications in the operational definitions of dysmobility syndrome.

Conclusion

Dysmobility syndrome was significantly associated with mortality among community-dwelling middle-aged and older adults in Taiwan. Using waist circumference and BMI-adjusted muscle index were the most appropriate modified model for mortality prediction. Further intervention study is needed to evaluate the reversibility of dysmobility syndrome and mortality reduction.

Methods

Participants and study design. The I-Lan Longitudinal Aging Study (ILAS) was a prospective population-based cohort study, which aimed to investigate the association between sarcopenia, frailty and cognitive function of middle-aged and older adults in Taiwan. ILAS design, participant's recruitment, and data collection have been reported elsewhere in detail²⁷. Briefly, inhabitants aged 50 years and over in Yuanshan Township of I-Lan County in Taiwan were randomly selected from the household registrations of the county government and were invited through mail, postcard or telephone by research nurses. The inclusion criteria of ILAS were inhabitant aged 50 years of age or over living in Yuanshan Township presently and had no recent plan to move their residence. The exclusion criteria were (1) participants who could not communicate with research nurses, (2) those with limited life expectancy due to major illness (3) current residents in long-term facilities, and (4) those who were unable to complete evaluations due to poor function. Overall, 1,839 participants received face-to-face interviews by the research staff, and 1,779 of them received subsequent body composition tests and physical examinations. Among them, 77 participants were excluded for analysis due to data incompleteness. Survival status was documented and timed to the nearest month through telephone survey every three months until Jun 2015 and 5 participants were lost to follow-up. Overall, data of 1703 were obtained for analysis in this study (Fig. 4).

Ethics statement and data availability. The observational design and reporting format follow STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines²⁸. A written informed consent was obtained from every participant. The institutional review board of the National Yang Ming University approved the study protocol. The design and procedures of the study were carried out in accordance with the principles of the Declaration of Helsinki. The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Muscle strength and physical performance. In this study, muscle strength was measured by using handgrip strength (Smedley's Dynamo Meter; TTM, Tokyo, Japan). For every participant, the best measurement of three trials and allowed one pre-test trial at an upright standing position with straight down-side arms. The best

performance was taken for analysis and those with muscle strength lower than 26 kg in men and 18 kg in women were referred as low muscle strength⁹. Gait speed were determined by a timed 6-meter walk and participants were instructed at usual paces with a static start without deceleration throughout a 6 m straight line at a more than 8 m length examine room. Those walked slower than 0.8 meter/second were defined as slow walking speed^{8,9}.

Body composition and bone mineral density. Body fat mass, lean body mass and bone mineral density were measured by a whole body dual-energy X-ray absorptiometry (DXA) scan with a Lunar Prodigy instrument (GE Healthcare, Madison, WI, USA) in this study. Appendicular skeletal muscle mass (ASM) was calculated as the sum of the lean soft tissue mass of all four limbs. Height-adjusted muscle index and BMI-adjusted muscle index, calculated by appendicular skeletal muscle mass divided by height square (ASM/height², kg/m²) and BMI (ASM/BMI, m²) were used to determined low muscle mass, respectively⁷⁻⁹. For all participants, height-adjusted skeletal muscle index lower than 7 kg/m² and BMI-adjusted skeletal muscle mass index lower than 0.789 m² in men were considered as low muscle mass; height-adjusted skeletal muscle mass lower than 5.4 kg/m² and BMI-adjusted skeletal muscle mass < 0.512 m² in women were referred as low muscle mass^{7,9}. Osteoporosis was determined by the diagnostic criteria from the World Health Organization (WHO) and those with T-score of lumbar or hip bone mineral density (BMD) less than -2.5 were defined as osteoporosis²⁹.

Dysmobility syndrome. Original definition of dysmobility syndrome was proposed by Binkley, *et al.*¹², in which people had three or more of the following conditions were considered having dysmobility syndrome, i.e. high body fat, low muscle mass, osteoporosis, slow walking speed, weak muscle strength and fall in last three months. On the other hand, subjects with one or two conditions were categorized as pre-dysmobility in this study. Currently, six operative definitions of dysmobility syndrome had been reported by using different combinations of muscle index (height square adjusted and BMI adjusted) and various adiposity determinants (body percent fat > 30% in men and > 40% in women¹², BMI ≥ 27 kg/m²³⁰, waist circumference > 90 cm in men and > 80 cm in women³¹).

Other confounders. Selected variables that possibly influenced vital status of participants in the multivariate statistical analysis and not included in the dysmobility syndrome were listed in this section. Tobacco consumption was categorized into three classes as current smoker, ex-smoker who quitted in the past 6 months, and non-smoker. Alcohol consumption was categorized into three groups as current drinker, ex-drinker who quitted in the past 6 months and non-drinker. The autonomy assessment scale (SMAF), a 29-items scale ranging from 0 to 87 points, was used to describe the general functional status, which measured activities of daily living (ADL), instrumental activities of daily living (IADL), mental function, and communications³². The Charlson's Comorbidity Index (CCI), ranging from 1 to 6, was used describe the severity of underlying medical conditions³³.

Statistical analysis. In this study, numerical variables were expressed as mean ± standard deviation and categorical variables were expressed as proportions. Descriptive characteristics were compared by one-way ANOVA, chi-square analysis, or Fisher Exact test when appropriate. Cox proportional hazard regression model was used to explore the association between dysmobility status, individual component of dysmobility syndrome, sarcopenia and mortality. A test of assumption of proportionality indicated that no significant trend in hazards ratio with time ($p = 0.794$), which showed the assumption were not violated. Interaction between age, sex, SMAF, severity of disease, smoking, drinking and dysmobility syndrome were examined and showed no statistical significance. The mortality risk of dysmobility syndrome using different cutoff points of muscle index, walking speed, and adiposity compared to the results from the main analysis, which was conducted by comparison of Harrell's R², the Akaike Information Criterion (AIC) and the Bayesian information criterion (BIC)³⁴. Harrell's R² estimates the proportion of explained variance in the proportional hazard model and is used to compare the performance in mortality prediction of dysmobility syndrome defined by different measures³⁵. A secondary analysis was conducted to assess influence of the pre-existing illness on main results by excluding participants died within one year. In addition, impact of possible non-responder bias was examined by comparison between excluded and enrolled subjects. Although the excluded subjects were significantly older (66.9 versus 63.8 years), more likely to be current smokers (35.4% versus 17.5%) and more commonly to be men (63.1% versus 54.8%), however, they did not differ significantly from the 1757 participants in terms of gender, multimorbidity, drinking status, central obesity and mortality.

A two-sided p -value < 0.05 and 95% Confidence Intervals (CI) not spanning the null hypothesis values were considered statistically significant. All analyses were performed with the SAS statistical package, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

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Author Contributions

Lee W.J., Liu L.K., Hwang A.C. and Chen L.K. designed the study and Lee W.J. conducted the main statistical analysis and Lee W.J. and Chen L.K. wrote the main manuscript and Liu L.K., Hwang A.C., Peng L.N., Lin M.H. and Chen L.K. provided critical comments on results and discussion. All authors reviewed the manuscript.

Additional Information

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