







Association Between Changes in Frailty Index and Clinical Outcomes: An Observational Cohort Study

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Purpose: Although the association between a single assessment of frailty index (FI) and clinical outcomes has been revealed in prior studies, there is a lack of knowledge about the prognostic value of FI at different time points and the changes in repeated measurements of FI. Hence, we sought to determine the clinically meaningful changes in FI and reveal the association with the changes and a composite outcome of mortality and institutionalization.

Participants and Methods: This study was based on a longitudinal study of the Pyeongchang Rural Area cohort that included people aged 65 years or older, ambulatory and living at home. Individuals were divided into the worsened group (changes in FI \geq 0.03 during 2 years) and the stable group (changes in FI $<$ 0.03 during 2 years). The incidence of a composite outcome was compared between the two groups and the relationship was adjusted for age, sex, baseline FI, and follow-up FI.

Results: Of the 953 participants, 403 (42.3%) and 550 (57.7%) were included in the worsened group and the stable group, respectively. The worsened group had a significantly higher risk of the composite outcome than the stable group (HR, 2.37 [95% CI, 1.54–3.67]; $p < 0.001$). Although the higher risk remained significant after adjusting for age, sex, and baseline FI, the statistical significance disappeared after adjusting for follow-up FI ($p = 0.614$). The aggravation of FI in the worsened group was predominantly due to aggravation of FI domains, such as activities in daily living, cognitive function and mood, and mobility rather than comorbidity burden.

Conclusion: Aggravation of FI was associated with a composite outcome regardless of baseline FI, and the association was significantly reflected in the follow-up measurement of FI. The worsening FI was mainly attributable to functional geriatric domains.

Keywords: frailty index, changes in frailty index, mortality, geriatric domains

Introduction

Frailty, a common geriatric condition closely related to human aging, has been attracting interest in research and public healthcare in accordance with the global increase in the older population. Defined as a state of decreased physiological reserve and increased vulnerability to possible intrinsic or extrinsic stressors,^{1,2} studies have shown that frailty is associated with health-related outcomes in older people, including falls, functional decline, institutionalization, and mortality.^{1,3,4} A community-based study reported that frailty is observed in 10–15% of people aged 65 or older,⁵ with cross-sectional association with multimorbidity and disabilities, giving frailty the state of a core geriatric syndrome.^{6–8}

Frailty is not a static state, and longitudinal studies have reported on its dynamic changes.^{9–14} An established concept of the frailty cycle regarding pathophysiological mechanisms underlying the development of frailty (eg, chronic inflammation, undernutrition, decreased physical activity, and progression of organ pathologies with chronic diseases) is supported by both basic and clinical studies.^{3,15–17} As a result of this vicious cycle, disability and frailty worsen, and breaking this cycle with programs such as multicomponent geriatric intervention has been regarded as the key point in preventing the progression of frailty.^{18–20}

The frailty index (FI) has been recognized as one of the most effective methods for operationalizing frailty. The FI, based on the proportion of health deficits across symptoms, signs, diseases, disabilities, or laboratory findings, can be calculated according to the number of deficits divided by the total number of examined deficits.²¹ The relationship between a single assessment of FI and clinical outcomes has been demonstrated in many studies.^{22–25}

Worsening of FI, through reflecting the dynamic feature and serial assessment of frailty, has become an important surrogate marker for mortality.^{24,26} Also, some studies demonstrated different frailty trajectories and their impact on clinical outcomes according to baseline frailty status¹⁰ and age at death.²⁷ However, no study to date has focused on investigating the prognostic values of baseline FI, follow-up FI, and the changes in mortality and institutionalization due to functional impairment.

This study aimed to determine the clinically meaningful absolute changes in FI and identify the associations of changes in FI with a composite outcome of mortality and institutionalization in a rural community-based prospective cohort study in South Korea. Furthermore, we compared the deficit changes according to four domains of FI.

Participants and Methods

Study Population and Design

This longitudinal observational study was based on the Aging Study of Pyeongchang Rural Area (ASPRA), a prospective cohort study in Pyeongchang County, Gangwon Province, Korea.²⁸ The ASPRA was initially designed to study the natural course and clinical impact of frailty and geriatric syndromes in community-dwelling adults, and to develop geriatric multicomponent intervention schemes that are feasible in rural, resource-limited settings in Korea, the details of the ASPRA study have been published elsewhere.¹⁹

The inclusion criteria for the ASPRA were as follows: 1) aged 65 years or older, 2) registered in the National Healthcare Service, 3) ambulatory with or without an assistive device, 4) living at home at the time of the assessment, and 5) able to provide informed consent. The exclusion criteria were as follows: 1) living in a nursing home, 2) hospitalized, or 3) bed-ridden and receiving nursing-home level care at home.

From October 2014 to December 2018, 1338 individuals underwent baseline geriatric examinations in the ASPRA, and had variables to allow for FI calculation. Among these, we excluded 385 individuals who had missing variables for FI calculation at 2 years from baseline examination (reasons for exclusion are provided in detail in [Table S1](#)). The 953 remaining individuals were included in the final analysis ([Figure 1](#)).

The Institutional Review Board (IRB) of Asan Medical Center (Seoul, Korea) approved the protocol for this study (IRB number: 2015–0673), and all participants or their proxies had provided written informed consent before enrollment in the ASPRA cohort. The study was conducted per the approved study protocol, complying with the ethical rules for human experimentation stated in the Declaration of Helsinki.

Frailty Index

For quantitative evaluation of frailty burden, we built a 34-item FI based on the concept of deficit accumulation and established methods.^{29–31} The 34 items ([Table S2](#)) were categorized into four domains: ADL (activities in daily living), cognitive function and mood, comorbidity, and mobility. The FI was calculated as the cumulative deficit of the 34 items, with the total score ranging from 0 to 1. We defined participants with $FI \geq 0.25$ as frail and those with $FI < 0.25$ as non-frail.^{32,33}

Geriatric Parameters

Trained nurses annually performed a comprehensive geriatric assessment to evaluate the functional status and common geriatric conditions. Disability status was evaluated by asking the participants seven questions on ADL (bathing, continence, dressing, eating, toileting, transferring, and face and hands washing) and 10 questions on instrumental activities of daily living (IADL; food preparation, household chores, going out a short distance, grooming, handling finances, laundry, managing own medications, shopping, transportation, and using a telephone).³⁴ We also assessed multimorbidity, defined as having two or more of the 11 physician-diagnosed illnesses, including angina, arthritis,

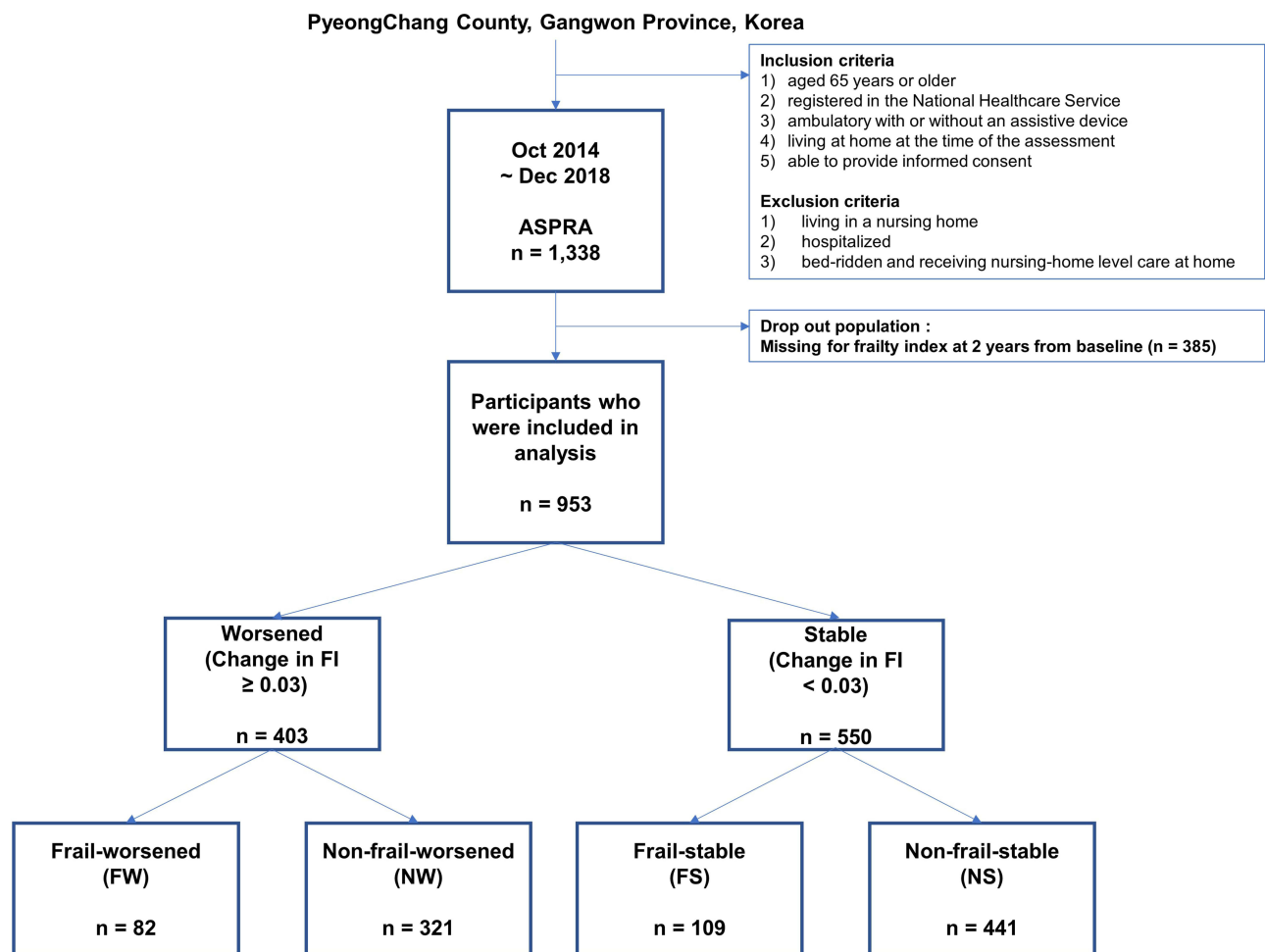


Figure 1 Study population flow chart.

Abbreviations: ASPRA, Aging Study of Pyeongchang Rural Area; FI, frailty index.

asthma, cancer, chronic lung disease, congestive heart failure, diabetes, heart attack, hypertension, kidney disease, and stroke. We measured the dominant grip strength using a handgrip dynamometer (T.K.K 5401 Grip-D, Takei, Tokyo, Japan), and proceeded with an analysis of the best of the two measurements. Depression was defined according to the Korean version of the Center for Epidemiological Studies Depression (CES-D) scale greater than 20 points.³⁵ Polypharmacy was defined as taking five or more prescription medications daily. We evaluated cognitive function through the use of the Korean version of the Mini-Mental State Examination (MMSE) and defined cognitive dysfunction as MMSE score of <24 .³⁶

Clinically Meaningful Changes in FI

In line with a previous study,⁹ we defined changes in FI of 0.03 or more as clinically meaningful changes. Accordingly, we categorized the study individuals into two groups by absolute changes in FI during 2 years: worsened group (increase in FI ≥ 0.03) and stable group, which included both stationary (change in FI < 0.03) and improved groups (decrease in FI ≥ 0.03). Then, each group was further divided into two subgroups according to baseline FI: the frail-worsened (FW) group, which was frail (FI ≥ 0.25) at baseline and worsened; the non-frail-worsened (NW) group, which was non-frail (FI < 0.25) at baseline and worsened; the frail-stable (FS) group, which was frail at baseline and remained stable; and the non-frail-stable (NS) group, which was non-frail at baseline and remained stable. The cutoff value (≥ 0.25) for the FI was determined following a previous study.^{25,37} This cutoff effectively predicted the risk of death and institutionalization well in the same cohort.³⁰

Outcome Assessment

We used the composite outcome of death and institutionalization due to functional impairment to assess composite outcome-free survival for clinical outcome evaluation through phone interviews with the participants or their family members every 3 months. Death was additionally captured from records of the Community Health Post network system. For this analysis, we used composite outcome data captured up to August 2020.

Statistical Analysis

Statistical analysis was performed using the R Statistical Software (version 3.6.3; R Foundation for Statistical Computing, Vienna, Austria). Independent *t*-tests and the Chi-squared test were used to evaluate the continuous and categorical variables of the participants' characteristics, respectively. The estimated mortality of the worsened and stable groups was calculated with Kaplan–Meier estimators, and a Log rank test was used for between-group comparisons. Another Kaplan–Meier analysis was performed to compare the FW, NW, FS, and NS groups.

Multivariable Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence interval (CI) between the worsened group and the stable group after adjusting for age, sex, FI measured at baseline and 2 years from baseline. We stratified the participants into four groups for the sensitivity analysis based on baseline FI according to cutoff values of 0.1, 0.2, and 0.3. We compared the Kaplan–Meier curves of the worsened and stable groups for each stratum. Furthermore, we stratified the participants into four strata based on FI after 2 years from baseline and compared the worsened group with the stable group in each stratum.

To determine the aggravated FI domain, the changes in the deficit over 2 years were calculated for each domain among the FW, NW, FS, and NS groups.

Results

Baseline Characteristics

Of the 953 participants, 403 (42.3%) were included in the worsened group and 550 (57.7%) were included in the stable group. As shown in Table 1, participants in the worsened group were significantly more likely to be female, older, with shorter education years, weaker grip strength, and more cognitive dysfunction than those in the stable group. Baseline FI did not significantly differ between the two groups (*P* = 0.87). The average change in FI was 0.02 and 0.11 in the stable and worsened groups, respectively.

Table 1 Baseline Characteristics of Study Population According to Changes in the Frailty Index During 2 Years

Characteristics	Worsened Group (n = 403)	Stable Group (n = 550)	P-value
Age	75.1 ± 6.2	73.0 ± 5.2	<0.001
Female	251 (62.3)	286 (52.0)	0.002
Baseline FI	0.16 ± 0.11	0.16 ± 0.12	0.87
FI at 2 years from baseline	0.27 ± 0.14	0.14 ± 0.11	<0.001
Education years	4.3 ± 2.7	5.5 ± 3.5	<0.001
Low income	36 (8.9)	31 (5.6)	0.07
Multimorbidity	163 (40.4)	207 (59.6)	0.42
Dominant grip strength	21.2 ± 8.9	23.7 ± 10.0	<0.001
ADL disability	40 (9.9)	67 (12.2)	0.32
IADL disability	113 (28.0)	175 (31.8)	0.24
Depression	38 (9.5)	43 (7.8)	0.45
Cognitive dysfunction	129 (32.1)	127 (23.1)	0.003
Polypharmacy	101 (25.1)	111 (20.2)	0.09
History of falling in the previous year	0.21 ± 0.90	0.27 ± 0.92	0.27

Note: Data are mean ± standard deviation or n (%).

Abbreviations: ADL, activity of daily living; FI, frailty index; IADL, instrumental activity of daily living; SD, standard deviation.

A total of 385 individuals were excluded from the analysis due to the lack of FI measurement at 2 years from baseline. The comparison of baseline demographic characteristics between the study population and the excluded individuals is shown in [Table S3](#). Compared with the study population, the excluded group was older, had a higher baseline FI and higher proportions of individuals with ADL disability, IADL disability, depression, and cognitive dysfunction.

Incidence of Composite Outcome and Changes in FI During 2 Years

At a mean follow-up duration of 56.9 (SD 9.6) months, 35 (3.7%) participants had died and 54 (5.7%) had been institutionalized because of functional impairment. As shown in [Figure 2A](#), survival of participants without composite outcome (mortality and institutionalization by functional decline) was significantly higher in the stable group than in the worsened group (Log rank test $P < 0.0001$).

We categorized the participants into four groups (FW, NW, FS, and NS) according to the baseline FI and changes in FI ([Figure 2B](#)). The average change in the FI was 0.13, 0.11, -0.05 , and -0.01 in the FW, NW, FS, and NS groups, respectively. Group FW had the worst prognosis, while individuals in the NS group had the best prognosis. There was no significant difference between the composite outcome-free survival of Group NW and Group FS (Log rank test $P = 0.4$).

Impact of Baseline FI and Changes of FI on the Composite Outcome

A Cox regression analysis was performed to adjust for age, sex, and FI at baseline and after 2 years ([Table 2](#)). In the unadjusted model, the worsened group had a significantly higher risk of composite outcome compared with the stable group (HR, 2.37 [95% CI, 1.54–3.67]; $P < 0.001$). The higher risk of the worsened group for the composite outcome remained statistically significant after adjusting for age and sex (model 2) or age, sex, and baseline (model 3). However, after these adjustments for age, sex, and FI after 2 years from baseline, the risk of composite outcome did not differ significantly between the two groups (HR, 1.13 [95% CI, 0.70–1.84]; $P = 0.61$), suggesting that changes in FI over time significantly contributed to the composite outcome.

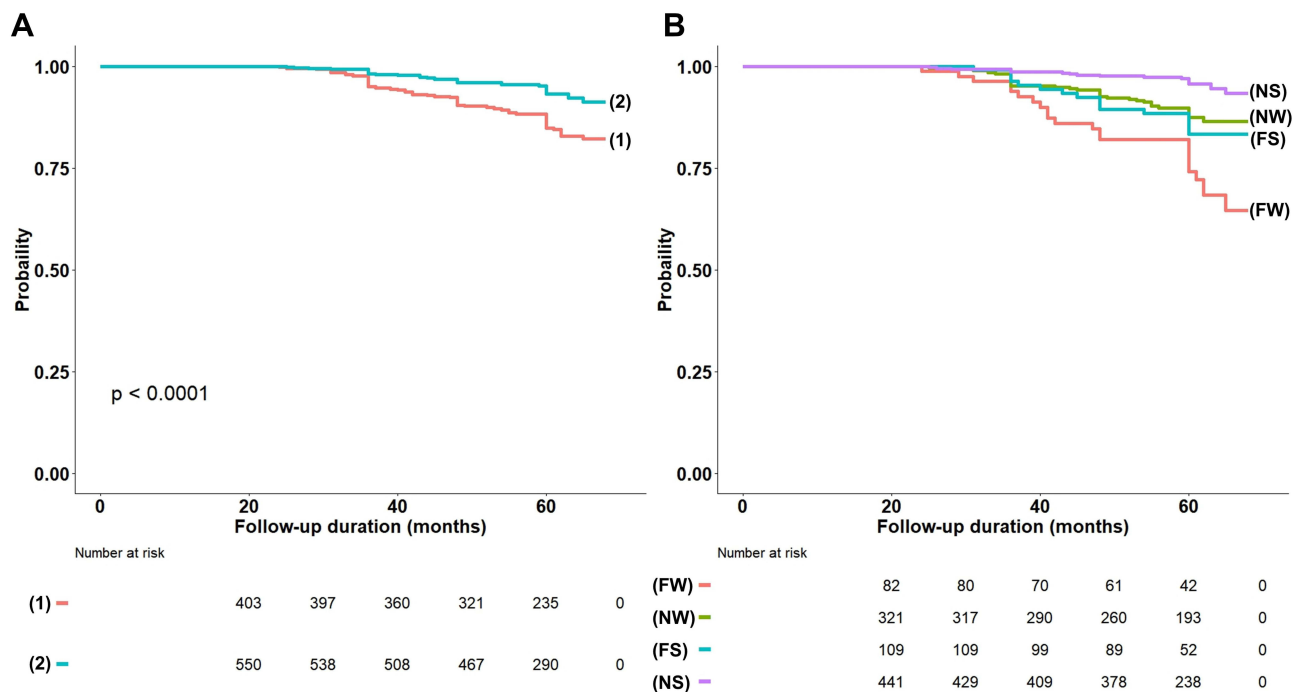


Figure 2 Kaplan–Meier curves for the probability of composite outcome-free survival according to baseline frailty index and changes in frailty index. **(A)** Worsened group (group 1) vs stable group (group 2). **(B)** FW (frail at baseline and worsened) vs FS (frail at baseline and stable) vs NW (non-frail at baseline and worsened) vs NS (non-frail at baseline and stable) Kaplan–Meier curves of the groups categorized based on baseline FI and changes in the FI during 2 years.

Table 2 Cox Proportional Hazard Analysis for the Risk of the Composite Outcome

Model	HR*	95% CI	P-value
Model 1 (unadjusted)	2.37	1.54–3.67	<0.001
Model 2 (adjusted for age and sex)	1.64	1.04–2.57	0.032
Model 3 (adjusted for age, sex, baseline FI)	1.87	1.19–2.95	0.007
Model 4 (adjusted for age, sex, follow-up FI)	1.13	0.70–1.84	0.614

Notes: *Hazard ratio was calculated for the worsened group, with the stable group as a reference.

Abbreviations: CI, confidence interval; FI, frailty index; HR, hazard ratio.

We divided the participants into four categories according to baseline FI, and 358 (37.6%), 299 (31.4%), 193 (20.3%), and 103 (10.8%) had a baseline FI of <0.1, 0.1–0.2, 0.2–0.3, and ≥ 0.3 , respectively. Kaplan–Meier analysis showed that in each category, the worsened group had worse outcomes than the stable group (Log rank test $P < 0.001$, $P = 0.052$, 0.16, and 0.10, respectively; [Figure 3A](#)).

When we divided the participants based on the FI measured after 2 years, 273 (28.6%), 245 (25.7%), 267 (28.0%), and 168 (17.6%) had a FI of <0.1, 0.1–0.2, 0.2–0.3, and ≥ 0.3 , respectively. In the analysis of participants whose FI after 2 years from baseline was 0.1–0.2, 0.2–0.3, ≥ 0.3 , there was no significant association between the changes of FI ≥ 0.03 and the outcome (Log rank test $p = 0.59$, 0.74, and 0.93, respectively; [Figure 3B](#)), suggesting the importance of the up-to-date frailty status that combines both baseline FI and its changes over time in predicting outcome.

Changes in the Deficits by Four Major Domains of FI

The mean changes in the deficit of the FI in four major domains are shown in [Figure 4](#) and [Table S4](#). In groups FW, NW, FS, and NS, the mean changes in the ADL domain were 0.17, 0.11, -0.08 and -0.02 , respectively. The mean changes in the deficit of the mobility domain were 0.17, 0.14, -0.10 , and -0.03 , respectively, and those of the cognitive function and mood domain were 0.13, 0.14, -0.07 and -0.02 , respectively. The mean changes in the deficit of the comorbidity domain were 0.04, 0.05, 0.03 and 0.02, respectively. When groups FW and NW were compared, only the ADL domain showed a significant difference in the mean changes in the deficit (independent t -test $P = 0.009$).

Discussion

We identified an association between the worsening of FI of more than 0.03 during 2 years and an increased risk of mortality and institutionalization regardless of age, sex, and baseline FI. The prognostic impact of changes in FI was attenuated when adjusted by the FI measurement at 2 years after baseline. Changes in FI over 2 years were mainly driven by the geriatric functional domains of ADL, mobility, cognitive function and mood, rather than changes in the burden of comorbidity.

In our study, we stratified the participants according to the baseline FI and FI after 2 years. When stratified by baseline FI, participants with significantly increased FI had worse clinical outcomes than those in the other group; however, when individuals were stratified according to FI measured at 2 years from baseline, there were no significant differences in the incidence of composite outcome between the stable worsened groups. These findings underscore the prognostic importance of measuring FI at a time point encompassing individuals' prior aging trajectories, including recent changes.

A recent study that analyzed 5672 adults over the age of 65 with data from the National Health in Aging Trends Study showed that increments in FI were associated with mortality among pre-frail (FI, 0.15–0.24) and frail (FI ≥ 0.25) individuals, but not among robust (FI < 0.15) individuals.³⁸ Following this observation, we found that the aggravation of FI was associated with the composite outcome regardless of baseline FI. Worsening of FI adjusted by the baseline FI was related to mortality as well as the relationship between baseline FI and mortality. By further stratifying individuals according to FI after 2 years, we found that follow-up FI at 2 years after baseline was a better predictor of composite outcome than baseline FI.

Another study analyzing 909 individuals reported that the most recent FI was the dominant factor for predicting mortality among serial measurements of FI.³⁹ Our results add to this argument by demonstrating that the most recent FI

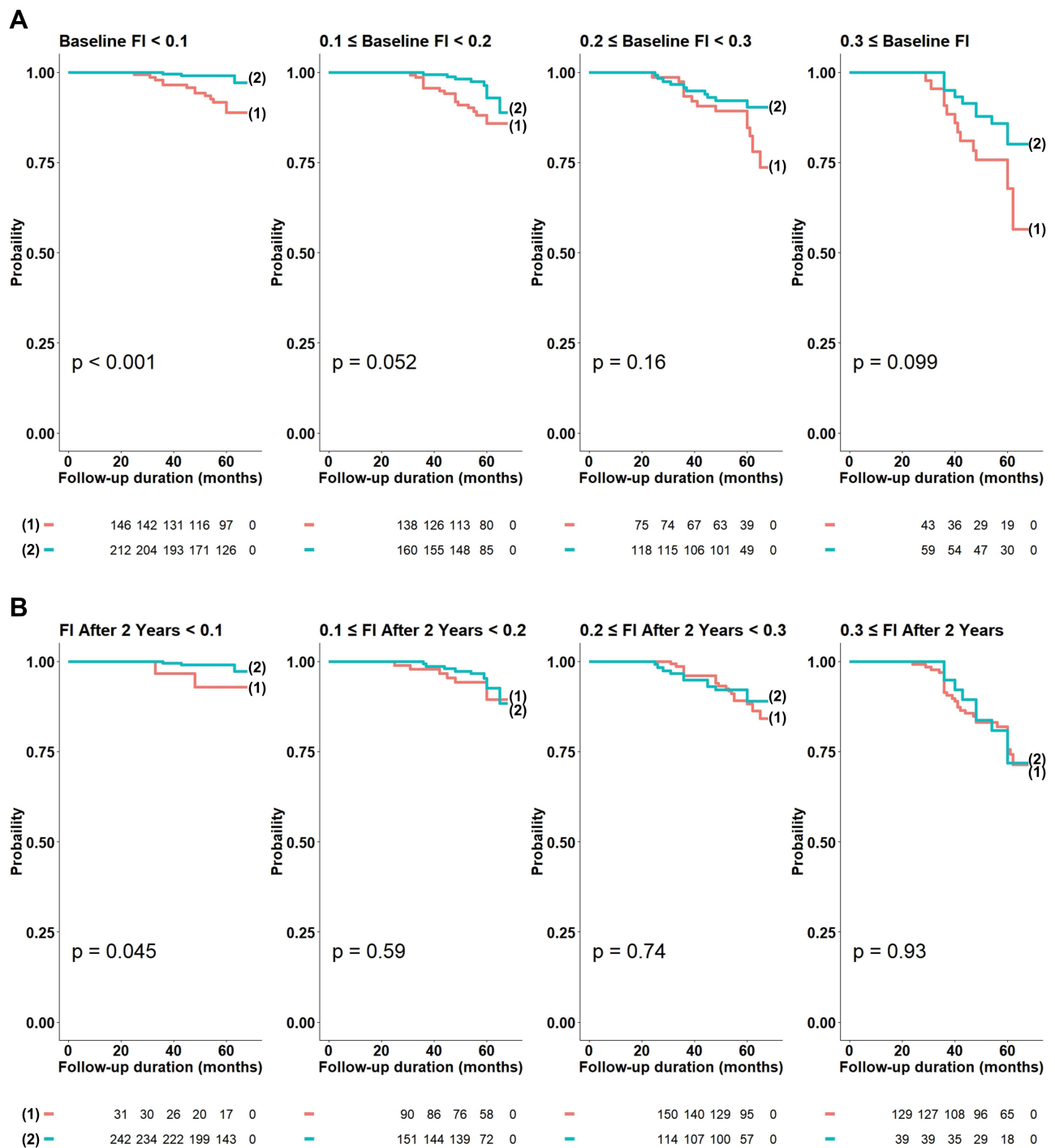


Figure 3 Kaplan–Meier curves for the probability of composite outcome-free survival stratified by baseline FI and follow-up FI (A) Worsened group (group 1) vs stable group (group 2) stratified by baseline FI. (B) Worsened group (group 1) vs stable group (group 2) stratified by follow-up FI at 2 years after baseline. **Abbreviation:** FI, frailty index.

can reflect the past trajectory of FI because the survival curves of patients in the same group according to the most recent FI were similar regardless of changes in FI (i.e., worsened vs. stable, Figure 3B), which is consistent with a recent study.²⁷ The survival outcomes were statistically different between the worsened and stable group among participants whose follow-up FI was <0.1. This difference may be attributed to incomplete matching of FI at 2 years after

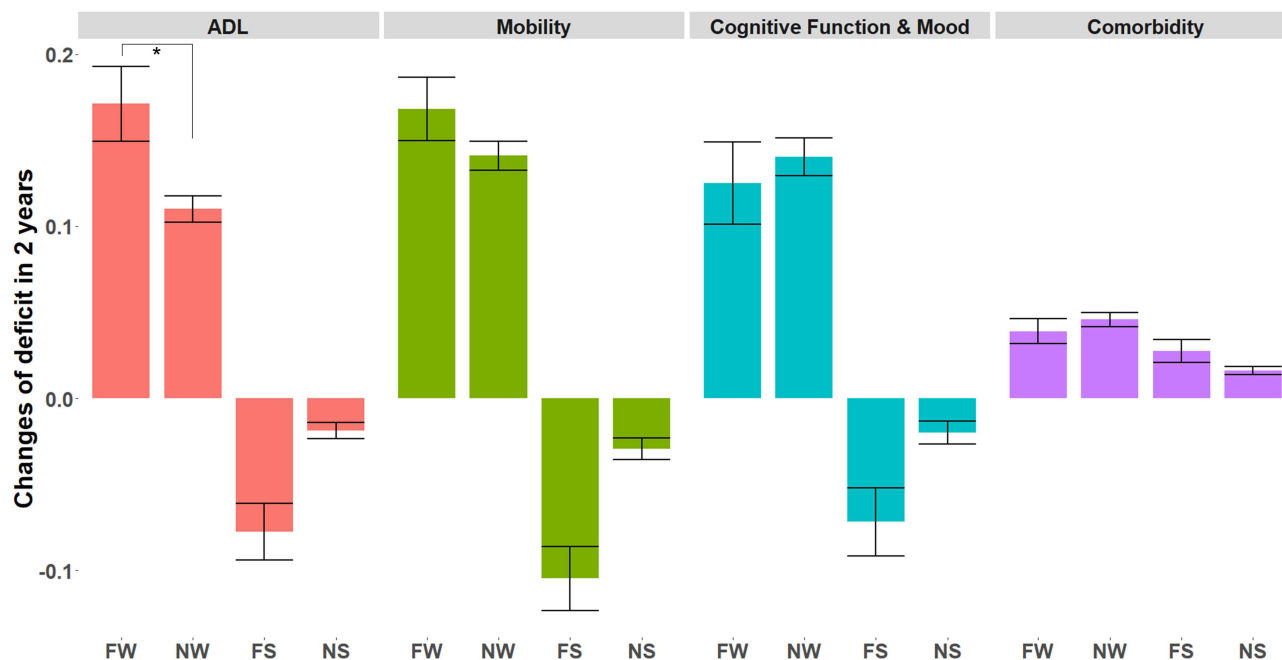


Figure 4 Changes of deficit in the four main domains of the frailty index. FW (frail at baseline and worsened) vs FS (frail at baseline and stable) vs NW (non-frail at baseline and worsened) vs NS (non-frail at baseline and stable).

Note: Error bar represents the standard error of the mean. * $p = 0.009$ (see [Table S4](#)).

stratification. As we categorized individuals according to aggravation, the mean FI after 2 years was significantly higher in the worsened group than in the stable group (0.08 vs 0.05; $P < 0.001$; data not shown).

As far as we know, this is the first study to divide FI changes according to functional domains. Individuals who experienced worsening FI over 2 years had an increasing burden of deficits throughout different geriatric domains. Furthermore, ADL impairment from FI changes was significantly more prominent in individuals with higher baseline FI. This observation supports the concept of the accumulation of deficits, from chronic disease to the development of mobility impairments and subsequent development of care needs due to impaired ADL.²⁵

This study has two main implications. Assessment of the risk of mortality and institutionalization is important to both clinicians and policymakers. This study highlights the prognostic value of repeated FI measurement in older adults in predicting the risk of mortality and institutionalization. Our results can guide the interpretation of FI at each time point. Furthermore, our observation suggests the potential value of enrolling vulnerable community-dwelling people in a well-designed, multicomponent geriatric intervention program that has shown efficacy in preventing composite outcome-free survival, as well as improving frailty status and physical performance.^{18,20,40}

This study has a few limitations. Since the population excluded due to missing FI value at 2 years was frailer, had more disability and cognitive decline compared with the study population, the association between changes in FI and the composite outcome might have been underestimated. Additionally, objective measurements of physical performance were omitted in our analysis because we did not perform a physical performance battery test in the first year of the ASPRA cohort. The calculated values of FI and mobility domain analysis might have been affected. Lastly, our results may have limited generalizability because the data were gathered from a single cohort from a rural area of Korea. Adaptation in individuals who are institutionalized or living in urban areas may therefore be challenging. Our observation should be validated in independent populations for broader generalizability.

Conclusion

Progression of frailty over time was associated with mortality and institutionalization regardless of the baseline frailty status. The association was considerably reflected in the follow-up FI at 2 years from baseline. The increases in deficit were largely due to the worsening of geriatric functional domains, rather than the increment of comorbidity burden.

Repeated assessment of the frailty status to delineate the aging trajectory may help clinicians and policymakers identify high-risk individuals and prepare for their functional decline.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Hee-Won Jung cofounded Dyphi Inc, a startup company developing sensor technologies on human movement and robotics. Otherwise, all authors declare that there are no potential conflicts of interest.

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