Information

Five-year disease-related risk of mortality in ambulatory frail older Japanese

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Objectives We investigated the 5-year disease-related mortality risk, including that associated with neoplasms, mental/behavioral/neurodevelopmental disorders, and diseases of the circulatory system and respiratory system,in ambulatory frail Japanese older adults.

Methods We retrospectively analyzed long-term care and health insurance claims data in this cohort study performed between April 2012 and March 2017. The primary outcome was mortality, and the secondary outcome was care-need level decline. Risk factors were determined based on the International Statistical Classification of Disease and Related Health Problems, 10th Revision codes, hospitalization, and institutionalization. The study included 1,239 ambulatory frail older adults newly certified as needing Support-Level care at baseline (April 2012–March 2013) across three Japanese municipalities.

Results Of the 1,239 participants, 454 (36.6%) died. Neoplasms (hazard ratio [HR] 2.69, 95% confidence interval [CI] 1.97–3.68) or respiratory system diseases (HR 1.62, 95%CI 1.26–2.08) were independently associated with mortality. Mental/behavioral/neurodevelopmental disorders (HR 1.39, 95%CI 1.17–1.66) or diseases of the respiratory system (HR 86, 95%CI 75–99) were independently associated with care-need level decline.

Conclusions This study suggests that neoplasms or respiratory system diseases were associated with a high mortality risk and that mental/behavioral/neurodevelopmental disorders were associated with care-need level decline among ambulatory frail older adults. Optimal disease management and effective long-term care are important to delay the onset of these events in older adults certified as needing Support-Level care.

Key words：care-need level decline, frail, ICD-10, mortality, older adults

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I. INTRODUCTION

Frailty is a state of increased vulnerability following a stressor, with the risk of adverse outcomes[1] including disability[2] or mortality[2,3]. Numerous studies conducted in western countries have shown that transitions to states of greater frailty were more common than transitions to states of lesser or no frailty[4~6].

However, a meta-analysis indicated that the frailty prevalence in older Japanese adults was lower than that in other counties[7,8]. The transition in frail older Japanese might be unique because the Japanese government implemented health and welfare policies in recent decades, as the front-runner of super-aging societies[9]. Japan, with 27.7% of its total national adult population aged ≥65 years in 2017[10], has the highest life expectancy (male＝81.09, female＝87.26 years old in 2018) in the world[11]. Japan has public-based care insurance programs for older adults, managed by local municipal governments. A public long-term care insurance (LTCI) program has been operating since 2000[12]. Additionally, Japan achieved universal coverage in health insurance for Japanese citizens in 1961, and the Late Elders' Health Insurance Program was established in 2008 as health insurance for all older adults aged ≥75 years[13].

The Japanese government has been attempting to

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implement new benefits in the LTCI program (called "KAIGO YOBO-NICHIJYO SEIKATSU SHIEN JIGYO" in Japanese) to target ambulatory frail older adults certified at the two lowest of seven care-need levels (Support Levels 1 or 2, called "YOSHIEN 1 or 2" in Japanese) to prevent them from developing disability or dependency[14]. The new benefits in the LTCI program mainly focus on preventing functional decline, including assisting with household chores or locomotion, physical exercise, training to prevent cognitive decline, and education for oral health and nutrition, but excluding disease management.

The risks of mortality or dependency of ambulatory frail older Japanese have rarely been clarified[15], particularly the disease-related risk of mortality has not been investigated sufficiently, although several recent cohort studies with sufficient sample sizes have reported risk of mortality[16~18] and care-need level decline[19~21] in the general older Japanese population. Recently, a seven-year large cohort study in the United States[22] suggested that heart disease, cancer, respiratory conditions, and dementia could be risk factors for mortality in frail older adults. The progress to death or functional decline of ambulatory frail older adults might differ from that of general older adults who might include people falling suddenly into disabled status or death from vigorous status, and disease-related risk factors in ambulatory frail older Japanese need to be clarified.

The study aimed to identify the five-year disease-related risk of mortality, with respect to neoplasms, mental/behavioral/neurodevelopmental disorders, diseases of the circulatory system, and diseases of the respiratory system[22], which were classified by the International Statistical Classification of Disease and Related Health Problems, version 10 (ICD-10) codes, using records of hospitalization, and institutionalizations, in ambulatory frail older Japanese. The secondary outcome of the study was care-need level decline, as status changes in long-term care needs could also be predicted as changes related to mortality risk and the process of dying among older adults. The present study utilized both long-term care (LTC) and health insurance claims data, accumulated electronically by local governments. We also identified risk stratified by gender, as it is well-established that the prevalence of[23] and transition[24,25] in frailty differs by gender.

II. METHODS

1. Design and study settings

The study utilized a five-year retrospective cohort design and was conducted from April 2012 to March 2017 as part of the Southern Osaka Health and Aging (SOHA) study; data were collected from LTC and health care insurance claims of ambulatory frail older adults aged ≥65 years. The SOHA is still being implemented in three municipalities—Izumi, Izumiotsu, and Misaki—in the southern part of Osaka, Japan, and the study will collect data for a further five years.

The municipalities include residential or mountainous areas, which are located close to each other, and are around 50–60 km from downtown Osaka. The percentages of older adults in Izumi (20.0%) and Izumiotsu (21.3%) were slightly lower, but that in Misaki (31.8%) was higher than the national average of 24.1% at March 2013[26].

2. Study participants

We operationally defined ambulatory frail older adults as older adults who were certified as being in a Support Level of the LTCI program.

The LTCI reimburses expenses for home and/or facility care for older adults with LTC needs. First, older adults apply to their local government to have their care-needs assessed and scored by trained investigators using a standard comprehensive examination, which includes approximately 80 items. Based on a national standardized computer-aided system, applicants are assigned to one of seven levels of LTC need certifications, consisting of Support Level 1 (less frail) or 2 (frailer), or Care Levels 1 (less disabled) to 5 (most disabled). Older adults who are certified as being in a Support Level are ambulatory, which includes being able to walk and be independent in most activities of daily living, and not having serious cognitive functional decline, but having frailty and a little difficulty in instrumental activities of daily living[27]. Those who are certified as being in a Care Level are more severely disabled, have dementia or are chair- or bed-bound, and are eligible for admission to facilities offering continuous LTC[28].

The participants were all of the 1,658 older adult residents who were newly certified as Support Levels 1–2 in the LTCI program from April 2012 to March 2013 at the baseline, and consisted of 1,180 persons in Izumi, 363 persons in Izumiotsu, and 115 persons in Misaki, selected from each municipality record. The date on which the follow-up period ended was March 31, 2017. In the LTCI program, typically, the certifications renew every six months when applicants need continuous LTC; however, some older adults do not renew the certification if they do not want to. Out of 1,658 persons, 419 persons were certified only a single time at baseline and never applied for subsequent certification during the study period, which means that their values at baseline and follow-ups were the same and the Kaplan-Meier Curves and Cox proportional hazard regression could not be performed. Therefore, the number of persons analyzed was 1,239. We included study participants who were newly certified during the period but with histories of certifications before April 2012. We did not follow participants who moved out of the three municipalities (Figure 1).

3. Procedures

Data, which were composed of four datasets, includ-

ing LTC and health insurance claims, care-need comprehensive examinations assessed by trained investigators and resident registers, were collected from records accumulated electronically by each local government. LTC and health insurance claims datasets were recorded monthly. After unique numbers were assigned to each insured person to allow identification across these data, all data were anonymized to the researchers who analyzed them.

Health insurance claims data for participants who receive health care by public assistance because of low income were missing, as this data providing system is independent of the health insurance data.

The Nursing Research Ethical Committee of Osaka City University approved the study (no. 29-6-1, February 2, 2018). The study protocol was registered in the UMIN Clinical Trials Registry approved by the International Committee of Medical Journal Editors (no. UMINR000040040, December 12, 2018).

4. Measures

1) *Demographic characteristics of participants*

Characteristics of participants included age, gender, number of household members, and care-need level. Age, gender, and number of household members were collected from the resident register dataset. Dates for number of household members were April 1, 2012 for participants in Izumi and Misaki, and April 1, 2014 for those in Izumiotsu because Izumiotsu's register system was changed, so we were unable to collect the number of household members on April 1, 2012. Care-need level was collected from the care-need comprehensive examination dataset.

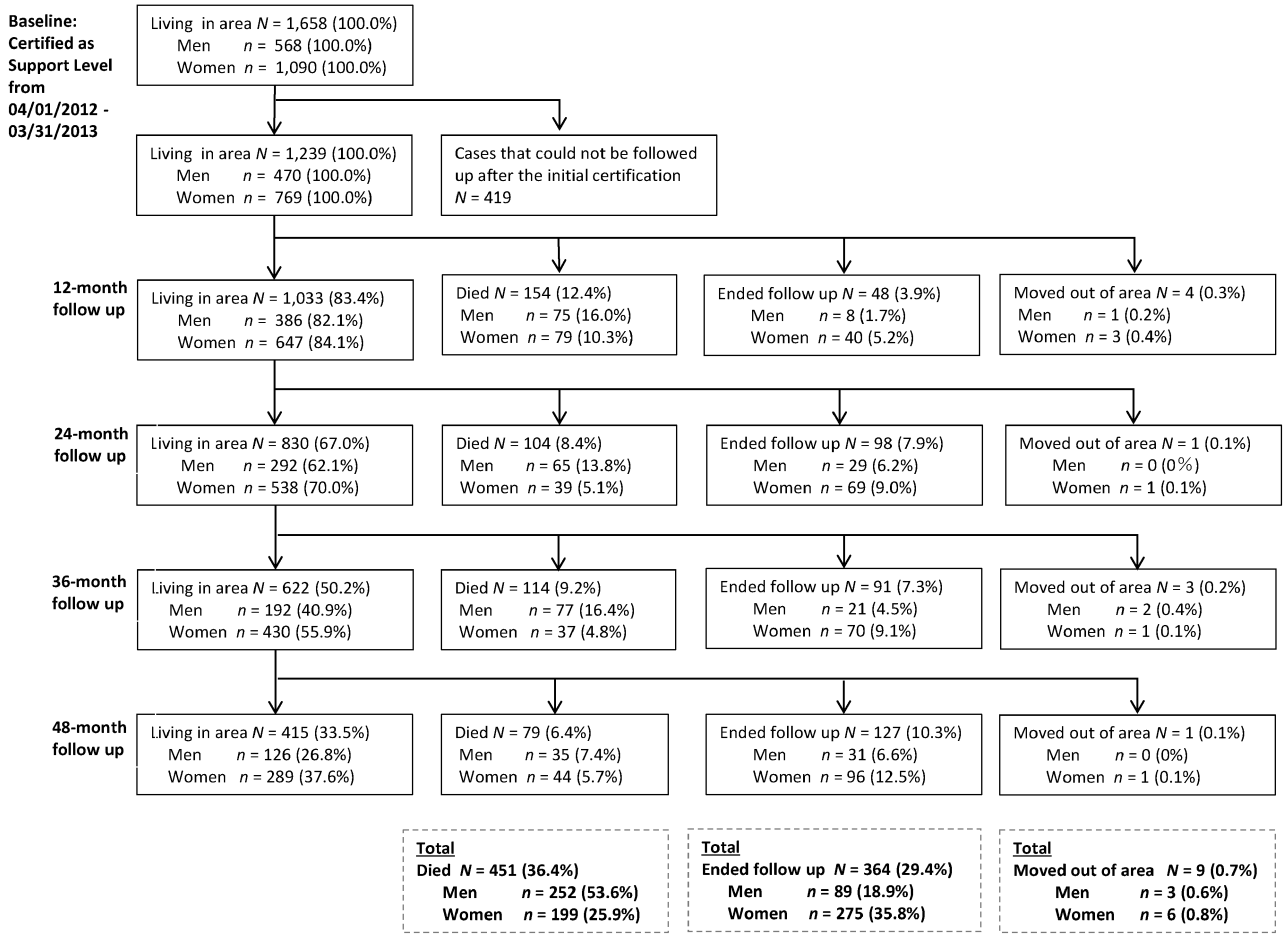
2) *Outcomes*

The primary outcome of the present study was mortality, and the secondary outcome was care-need level decline. Date of death was obtained from the resident register dataset. Seven categories (Support Levels 1–2 or Care Levels 1–5) of care-need level were collected from the care-need assessment dataset. Care-need level decline was defined as individuals who moved into Care Level 1 or lower from Support Level 1 or 2 at baseline[28].

3) *Candidate risk factors*

To identify the risk of mortality and care-need level decline, candidate risk factors included disease group identified by ICD-10 codes[29], hospitalizations, and institutionalization. Because the hospitalization and institutionalization could have occurred because of disease, we included them as the candidate risk factors of the primary outcome. However, care-need level decline could occur in advance of institutionalization, and we did not include institutionalization as a secon-

Figure 1 Flow of study participants.



dary outcome.

The occurrence of hospitalizations and ICD-10 codes were obtained from the health insurance claims dataset. We utilized four diseases categories, including neoplasms, mental/behavioral/neurodevelopmental disorders, diseases of the circulatory system, and diseases of the respiratory system[22] from the major disease categories of ICD-10, which could be considered risk factors of mortality among older frail adults. For example, individuals diagnosed with both "essential hypertension" and "subsequent myocardial infarction" in the same month were counted as having two categories of diseases of "the circulatory system."

The occurrence of institutionalization was collected from the LTCI claims dataset. Institutionalization was defined as using services in three types of facilities: nursing homes for the elderly (called *Tokuyo* in Japanese), rehabilitation facilities (*Roken*), or hospitals for the elderly (*Ryoyogata*) under the LTCI program.

4) *Adjusted variables*

Adjusted variables in the Cox regression models included gender, age, number of household members, municipalities, history of certification in the LTCI program, and home-based service utilization.

History of certification in the LTCI program before baseline and home-based service utilization by participants were recorded as they could be related to risk. Home-based service utilization from the LTCI claims dataset was categorized in eight groups including home aid, visiting nursing, visiting bathing, visiting rehabilitation, adult daycare, outpatient rehabilitation, respite stay, and providing assistive devices.

5. Statistical analysis

All statistical analyses were performed using R version 3.5.1 (http://www.rproject.org), with a two-sided *P*-value less than .05 indicating statistical significance. Baseline characteristics of participants were presented as frequencies and percentages for categorical variables. Since normality of age was met, age was summarized with means and standard deviations (*SD*). All variables except age and municipalities were dichotomous.

For the primary analysis, to assess the relationships between primary outcome and candidate risk factors. Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using multivariable Cox proportional hazard models, including time-varying covariates and baseline factors. We provided the time-varying Cox models for evaluating hospitalization, institutionalizations, and each ICD-10 code, respectively, and each variable was treated as a time-dependent variable. Each model was adjusted for gender, age, numbers of household members, municipalities, and history of certification in the LTCI program and home-based services utilization including home aid, visiting-nursing, -bathing, or -rehabilitation, adult-day care, outpatient rehabilitation, respite stay, and providing assistive devices.

For the secondary analysis, the relationships between the secondary outcome and risk factors were also confirmed using multivariable cox proportional hazard analysis after adjusting for confounding factors.

Subgroup analyses by gender were also performed. Kaplan-Meier curves for mortality and care-need level decline are reported by gender.

III. RESULTS

1. Demographic characteristics of participants at baseline

The flow of study participants is shown in Figure 1. There were 470 men (37.9%) and 769 women (62.1%), for a total of 1,239 (100.0%) participants who were registered as living in the area at baseline. The total number of participants who died during the period was 451 (36.4%), including 252 (53.6%) of 470 (100.0%) men and 199 (25.9%) of 769 (100.0%) women; additionally, 9 (0.7%) participants moved out of the area. The participants were registered sequentially in fiscal year 2012 at baseline, and a total of 364 participants were reached at follow up; these are identified in Figure 1, which shows when participants ended their follow ups. Thus, the number of participants who were living in the area and followed up on was 415 (33.5%) at the 48-month follow up.

Demographic characteristics of participants at baseline are shown in Table 1. In all participants, the mean age was 79.0 years old (SD 6.8), and 32.0% (n =396) were living alone. The proportion of participants receiving public assistance from the sample of all participants was 7.8%.

2. Kaplan-Meier Curves for mortality and care-need level decline by gender

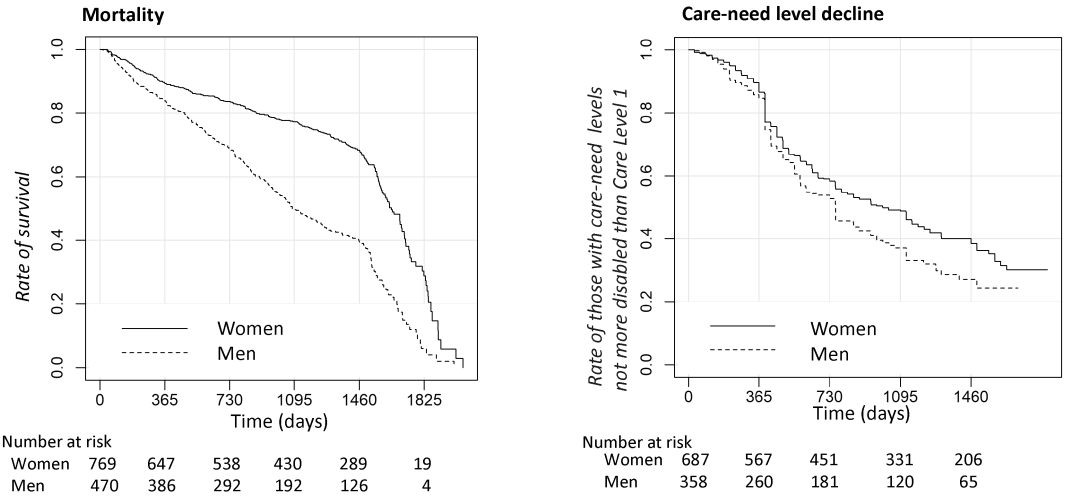
Kaplan-Meier Curves for mortality according to gender were described and showed that men were

Table 1 Demographic characteristics of participants

Age	Mean (*SD*)	79.0(6.8)
Gender	Men, *n* (%)	470(37.9)
	Women, *n* (%)	769(62.1)
Number of household members at baseline	Alone, *n* (%)	396(32.0)
	Two people, *n* (%)	503(40.6)
	Three people, *n* (%)	144(11.6)
	More than four people, *n* (%)	155(12.5)
Care-need level at baseline	Support Level 1: mildly disabled, *n* (%)	733(59.2)
	Support Level 2: severely disabled, *n* (%)	506(40.8)

Note. N=1,239; *SD*, standard deviation.

Figure 2 Kaplan-Meier Curves for mortality and care-need level decline according to gender in subjects (N=1,658).



Care-need level decline was defined as older adults with care-need levels more severely disabled than Support Level 2 in the Long-Term Care Insurance program.

In the care-need level of the system, there are 7 categories: Support Level 1 (less frail) or 2 (more frail) and Care Level 1 (less disabled) to 5 (more disabled).

Table 2 Adjusted risk of mortality in subjects (N=1,239)

Factors[a] associated with mortality	All (N=1,239)		Men (N=470)		Women (N=769)	
	Crude HR (95%CI)	Adjusted HR[b] (95%CI)	Crude HR (95%CI)	Adjusted HR[b] (95%CI)	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
Hospitalizations[c]	3.35 (2.61–4.29)***	2.47 (1.82–3.37)***	3.38 (2.46–4.65)***	2.37 (1.58–3.57)***	3.20 (2.19–4.70)***	2.61 (1.63–4.18)***
Institutionalizations[c]	1.95 (1.36–2.8)***	1.00 (.58–1.73)	2.48 (1.44–4.28)**	1.00 (.43–2.31)	1.94 (1.19–3.14)**	.97 (.43–2.22)
Neoplasms	3.06 (2.39–3.91)***	2.69 (1.97–3.68)***	2.07 (1.49–2.86)***	1.09 (1.27–2.84)***	3.48 (2.37–5.10)***	4.47 (2.86–6.98)***
Mental/behavioral/ neurodevelopm ental disorders	1.06 (.8–1.41)	1.01 (.72–1.40)	.91 (.68–1.22)	1.10 (.62–1.97)	.86 (.56–1.32)	.83 (.47–1.48)
Diseases of the circulatory system	.93 (.72–1.20)	.76 (.57–1.01)	.90 (.64–1.26)	.83 (.55–1.23)	.92 (.64–1.33)	.71 (.46–1.09)
Diseases of the respiratory system	1.60 (1.30–1.97)***	1.62 (1.26–2.08)***	1.96 (1.47–2.60)***	1.80 (1.26–2.58)***	1.08 (.78–1.50)	1.2 (.81–1.78)

HR=Hazard Ratio　95%CI=95% Confidence Interval

* P<.05; ** P<.01; *** P<.001

[a] The individual explanatory variables were hospitalizations, institutionalizations, and ICD-10 codes including neoplasms, mental/behavioral/neurodevelopmental disorders, diseases of the circulatory system, and diseases of the respiratory system.

[b] Adjusted for gender, age, numbers of household members, municipalities, care-need levels, history of certification in the LTCI program, and homebased services utilization including home aid, visiting-nursing, -bathing, or -rehabilitation, adult-day care, outpatient rehabilitation, respite stay, and providing assistive devices.

[c] yes vs. no=1 vs. 0

more likely to die (Figure 2). Those for care-need level decline according to gender were described and showed that care-need levels of men were more likely to decline (Figure 2).

3. Adjusted risk of mortality

The adjusted hazard ratio of mortality by time-varying Cox proportional hazards regression is shown in Table 2. Hospitalizations (adjusted HR=2.47,

Table 3 Adjusted risk of care-need level decline in subjects (N=1,239)

Factors[a] associated with mortality	All (N=1,239)		Men (N=470)		Women (N=769)	
	Crude HR (95%CI)	Adjusted HR[b] (95%CI)	Crude HR (95%CI)	Adjusted HR[b] (95%CI)	Crude HR (95%CI)	Adjusted HR[b] (95%CI)
Hospitalizations[c]	1.27 (1.13–1.42)***	1.18 (1.05–1.33)**	1.26 (1.06–1.50)**	1.24 (1.05–1.47)**	1.27 (1.10–1.46)**	1.15 (.99–1.34)
Neoplasms	0.88 (.70–1.12)	.87 (.70–1.09)	0.77 (.55–1.08)	.86 (.63–1.18)	.96 (.69–1.33)	.93 (.68–1.26)
Mental, behavioral/ neurodevelopmental disorders	1.35 (1.12–1.61)**	1.39 (1.17–1.66)**	1.14 (.83–1.57)	1.20 (.89–1.63)	1.45 (1.17–1.80)**	1.52 (1.24–1.87)***
Diseases of the circulatory system	1.07 (.90–1.28)	.95 (.80–1.13)	1.05 (.77–1.43)	.89 (.67–1.20)	1.07 (.86–1.33)	.99 (.81–1.22)
Diseases of the respiratory system	.87 (.75–1.01)	.86 (.75–.99)*	.98 (.77–1.25)	.89 (.72–1.10)	.80 (.66–.97)*	.82 (.69–.99)*

HR = Hazard Ratio 95%CI = 95% Confidence Interval
* P<.05; ** P<.01; *** P<.0001

[a] The individual explanatory variables were hospitalizations and ICD-10 codes including neoplasms, mental/behavioral/ neurodevelopmental disorders, diseases of the circulatory system, and diseases of the respiratory system.

[b] Adjusted for gender, age, numbers of household members, municipalities, history of certification in the LTCI program, and home-based services utilization including home aid, visiting-nursing, -bathing, or -rehabilitation, adult-day care, outpatient rehabilitation, respite stay, and providing assistive devices.

[c] yes vs. no = 1 vs. 0

[d] Care-need level decline was defined as older adults with care-need levels more severely disabled than Support Level 2 in the LTCI program.

95%CI = 1.82–3.37) were associated with mortality under adjustment for confounders. Participants with neoplasms (adjusted HR = 2.69, 95%CI = 1.97–3.69) or diseases of the respiratory system (HR = 1.62, 95% CI = 1.26–2.08) were more likely to die compared to those not having each type of disease.

In the subgroup analyses, men with diseases of the respiratory system (adjusted HR = 1.80, 95%CI = 1.26–2.58) or neoplasms (adjusted HR = 1.09, 95% CI = 1.27–2.84) had higher mortality. Women with neoplasms (adjusted HR = 4.47, 95%CI = 2.86–6.98) were more likely to die.

The variance inflation factors (VIF) for all explanatory variables in the models were less than three, which indicated that no significant multicollinearity was observed for all analyses.

4. Adjusted risk of care-need level

The adjusted hazard ratio of care-need level decline by time-varying Cox proportional hazards regression is shown in Table 3. Hospitalizations (adjusted HR = 1.18, 95%CI = 1.05–1.33) were associated with care-need level decline. Care-need level of participants with mental/behavioral/neurodevelopmental disorders (adjusted HR = 1.08, 95%CI = 1.02–1.14) was more likely to decline than in those not having each type of disease. However, in participants with diseases of the respiratory system (adjusted HR = .86, 95%CI = .75–.99), it was less likely to decline.

In the subgroup analyses for men, there was no significant association between candidate risk factors and care-need level decline. In those for women, care-need levels of participants with mental/behavioral/neurodevelopmental disorders (adjusted HR = 1.52, 95% CI = 1.24–1.87) were more likely to decline than in those not having each type of disease, but in those with diseases of the respiratory system (adjusted HR = .82, 95%CI = .69–.99), it was less likely to decline.

IV. DISCUSSION

The present study was a longitudinal analysis of the five-year risk of mortality and care-need level decline in a municipality-representative population-based ambulatory frail older adult sample. Because of the separate management of LTC and health insurance by local governments, several high-maintenance collation works are necessary to identify personal data in each dataset, and few studies have analyzed both LTC and health insurance claims data[30,31]. However, a strength of the SOHA study is that it linked large electronic health insurance databases.

Results showed that ambulatory older men were more likely to die than women during the five years studied, suggesting that after being newly certified as Support Level 1 or 2, men died earlier than women, without prolonged disabled status or with rapid progression into disability[25].

The risk of mortality over five years was higher in acute or progressive diseases, including neoplasms (adjusted HR＝2.69) or diseases of the respiratory system (adjusted HR＝1.62), which suggests that acute diseases could exacerbate frailty and lead to death; these results were consistent with another study on frail older adults[22]. Regarding risk of mortality according to gender, neoplasms were a risk factor in either gender, but diseases of the respiratory system were a risk factor in men only, which was consistent with a previous report[24].

Risk of care-need level decline was associated with diseases of mental/behavioral/neurodevelopmental disorders, including dementia. Dementia caused irreversible functional decline in frail older adults, which is also consistent with a government report regarding risks for those in Care Levels 1–5[32]. Adjusted HR was 1.08 for mental/behavioral/neurodevelopmental disorders, which could be interpreted as fragile. The results suggested that mental/behavioral/neurodevelopmental disorders including dementia might affect care-need level decline in ambulatory frail older adults. Risks of care-need level decline in women were the same as those in all subjects, because men were more likely to die and most of the participants analyzed were women.

Hospitalization was associated with mortality and care-need level decline, because hospitalization[24,33] reduced the chance of recovery from having a frailer status and the results were consistent with other reports[24,33].

The results indicated that several internal chronic diseases were associated with mortality or care-need level decline. Although the present new benefits (KAIGO YOBO JIGYO) in ambulatory frail older Japanese mainly aim to prevent functional decline, including rehabilitation or cognitive function decline, the effects of managing symptoms of chronic or incurable diseases were underestimated[34]. Health care aimed at managing symptoms of chronic diseases, including nurses' consultations in primary care or home visiting settings, might be provided to older adults certified as Support Level by health care professions in collaboration with long-term care sections in local municipal government or agencies, which are mainly composed of social or welfare care professions.

The present study has several limitations. First, the ICD-10 was used to diagnose participants who visited clinics or were hospitalized in the current month. However, not all diseases that participants had could be entered in the analyses.

Second, a limited number of sociodemographic characteristics were considered because electronic data was used, and there might have been an association between present risk and social or family support.

Third, we used an operational definition of "ambulatory frail" as being Support Level in Japanese LTCI. Results should be interpreted carefully when applying them to other countries.

Fourth, a total of 415 participants (36.4%) were analyzed at the 48-month follow up in the present study, because 364 participants (29.4%) ended their follow ups. The characteristics of those participants should be investigated in further research.

Finally, we analyzed the ICD-10 categories in terms of single diseases, yet most frail older adults are multimorbid[34]. Thus, further analyses should be conducted that examine the association of multimorbidity and adverse events in frail older adults.

In conclusion, the results suggest that several diagnosed diseases were associated with mortality or care-need decline, and disease management related care could be provided to delay these events, in collaboration with LTC.

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The study protocol was registered in the UMIN Clinical Trials Registry approved by International Committee Medical Journal Editors (no. UMIN000035132, December 12, 2018).

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The authors have no conflicts of interest to declare.

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