Keio University

CODING-BASED FRAILTY AND CLINICAL OUTCOMES IN COMMUNITY SETTINGS: A COHORT STUDY

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Abstract

Frailty is an age-related cumulative decline in multiple physiological systems, and is associated with poor outcomes. To date, several algorithms have been developed to identify frail people from large-scale health-care data. However, the international validity of these tools and the association between coding-based frailty and clinical outcomes among older people with common diseases have been insufficiently studied.

In this study, I examine the applicability of these frailty measurement algorithms to municipal government administrative claims data in Japan and assessed whether coding-based frailty is associated with poor outcomes. In Chapter 2, I measure frailty using two coding-based algorithms and examine the association between frailty and mortality or long-term care. In Chapter 3, I assess whether coding-based frailty is associated with the clinical outcomes of patients with atrial fibrillation.

The results show that coding-based frailty algorithms are applicable to Japanese administrative claims data and that coding-based frailty is associated with both long-term care service utilization and mortality in community settings. This study also indicates that the association between frailty and clinical outcomes should be considered in older people at the initiation of treatment. The findings of this thesis should contribute to the international measurement of coding-based frailty. Coding-based frailty may have utility in future research when the study of frail patients in experimental settings is not feasible.

Contents

List of Figures

Supplemental Figures

List of Tables

Supplemental Tables

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Related Publications

Chapter 2

This chapter includes a pre-copyedited, author-produced version of an article that has been accepted for publication in the journal *Age and Ageing* following peer review. The article, titled “Assessment of coding-based frailty algorithms for long-term outcome prediction among older people in community settings: a cohort study from the Shizuoka Kokuho Database” is authored by Nishimura S, Kumamaru H, Shoji S, Nakatani E, Yamamoto H, Ichihara N, Miyachi Y, Sandhu AT, Heidenreich PA, Yamauchi K, Watanabe M, Miyata H, and Kohsaka S. The version of record is available online at: https://doi.org/10.1093/ageing/afac009.

Chapter 3

This chapter contains the pre-peer reviewed version of an article titled "Frailty and subsequent adverse outcomes in older patients with atrial fibrillation treated with oral anticoagulants: the Shizuoka Study," authored by S. Nishimura, H. Kumamaru, S. Shoji, E. Nakatani, H. Yamamoto, N. Ichihara, Y. Miyachi, A.T. Sandhu, H. Miyata, and S. Kohsaka. The article has been submitted to the journal *Research and Practice of Thrombosis Haemostasis* for review.

Peer-reviewed conference presentations (poster)

Nishimura S, Kumamaru H, Shoji S, Nakatani E, Yamamoto H, Ichihara N, Miyachi Y, Miyata H, Kohsaka S. ASSOCIATION OF FRAILTY WITH LONG-TERM STROKE AND BLEEDING RISK IN OLDER PATIENTS WITH NON-VALVULAR ATRIAL FIBRILLATION: THE SHIZUOKA STUDY. J Am Coll Cardiol [Internet]. 2022 Mar;79(9):1139.

Abbreviations

AF	Atrial fibrillation
AUC	Area under the receiver operating characteristic curves
BID	Bis in die
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
DOAC	Direct oral anticoagulant
eFI	Electronic frailty index
HFRS	Hospital Frailty Risk Score
HR	Hazard ratio
ICD-10	International Classification of Diseases 10th version
IQR	Interquartile range
LSEMCS	Late-Stage Medical Care System
LTC	Long-term care
MI	Myocardial infarction
NHI	National Health Insurance
NSAIDs	Non-steroidal anti-inflammatory drugs
OAC	Oral anticoagulants
QD	Quaque die
RCT	Randomized controlled trial
SAS	Sleep apnea syndrome
SD	Standard deviation
SKDB	Shizuoka Kokuho Database
TIA	Transient ischemic attack
UK	United Kingdom
VTE	Venous thromboembolism

Chapter 1. Introduction

Frailty is a syndrome involving the increased vulnerability of multiple physiological systems, and it develops with age.[1–3] The frailty of older people is sometimes considered as important as chronological age in clinical practice.[1,4,5] Because frailty is associated with poor outcomes,[3,6–9] it has become a crucial public health issue in ageing populations.

The identification of frailty requires optimal instruments. To date, more than 60 frailty-measuring instruments have been utilized in studies of risk assessment of outcomes, methodologies, clinical decision-making, and more.[10] The recent increase in the secondary use of large-scale health-care data, such as electronic health records and administrative claims data, has been significant, and the methodologies for using these data have been investigated. Validated tools for the measurement of frailty based on large-scale health-care data emerged after the 2010s.[11,12] However, their international validity has been understudied because health-care systems differ among countries and regions.

Frailty is highly prevalent in older adults, and is estimated to affect 12%–23% of adults aged ≥60 years.[13] Clinical trials of pharmacotherapies usually exclude older patients with high-risk characteristics, including comorbidities and frailty.[14] Therefore, the association between frailty and clinical outcomes is generally unclear in terms of the pharmacotherapies used for common diseases in older people, although the balance between the benefits and risks of medications should be considered for frail patients.

Aims

In this thesis, I examine the applicability of coding-based algorithms for measuring frailty to administrative claims data in Japan and the associations between coding-based frailty and clinical outcomes. In Chapter 2, the applicability of coding-based frailty algorithms is reported. In Chapter 3, the association between frailty and clinical outcomes in patients with atrial fibrillation is reported.

Objectives

In Chapter 2, I first examine two frailty algorithms developed in the United Kingdom by applying these frailty measurement methods to an administrative claims database in Japan, the Shizuoka Kokuho Database (SKDB). I then investigate the association between coding-based frailty and mortality or the use of long-term care. In Chapter 3, I assess whether coding-based frailty at the initiation of oral anticoagulant therapies is associated with subsequent bleeding and embolic outcomes among patients with atrial fibrillation, which is common in older people.

Frailty models

Two models are commonly used for the assessment[10]: the phenotype model[15] and the cumulative deficit model.[3] The phenotype model was established by Fried and colleagues (2001) based on five indicators (unintentional weight loss, weak grip strength, self-reported exhaustion, slowness, and low physical activity).[1,15,16] To develop this model, data were obtained from a prospective, observational study in the United States (Cardiovascular Health Study). People with three or more of these indicators are considered frail, and those with 1–2 are considered 'pre-frail'. Those with no indicators are considered 'not frail' or 'robust'.[1,15] The cumulative deficit model (Frailty Index) was established by Rockwood and colleagues (2005) by using the Canadian Study of Health and Aging, a prospective cohort study. The Frailty Index includes 92 age-related deficits (e.g., symptoms, functional impairments, signs, and disabilities).[1,3] The frailty score is calculated as a ratio, with the number of deficits as the numerator and the total deficits as the denominator. These two models of frailty have been used by researchers to validate the outcomes of frailty algorithms based on routinely collected health-care data.

Coding-based algorithms to measure frailty

Algorithms used to measure frailty based on routinely collected electronic health records or administrative data have been developed and validated using the frailty models described above. To date, several frailty algorithms have been developed to analyse data on diagnoses, drug dispensation, and/or health service utilization among populations in specific settings (e.g., outpatient, and inpatient populations).[12,17–23] Some of these algorithms have been based on a specific country's medical system, and cannot be converted to Japanese claims data. In contrast, the electronic frailty index (eFI)[19] and the Hospital Frailty Risk Score (HFRS)[23] mainly use disease diagnoses or health status as the algorithm items, and are potentially compatible with Japanese health systems. They also allow internationally comparable analyses.

Electronic frailty index (eFI)

The eFI was developed by Clegg and colleagues (2016) based on the cumulative deficit model of frailty.[19] The index measures the proportion of 36 equally weighted deficits present in an individual, captured with the Clinical Terms Version 3 Read codes in routinely collected primary-care data in the UK[19,24] (Supplemental Table 1-1).

Hospital Frailty Risk Score (HFRS)

The HFRS was developed by Gilbert and colleagues (2018) from 109 ICD-10 codes to identify patients with high-risk conditions using routinely collected secondary-care hospital administrative data in the UK.[23,24] Each ICD-10 code is given a weight of 0.1–7.1, corresponding to the strength of its association with being in the frail subgroup (Supplemental Table 1-2).

Health-care utilization data in Japan

Health insurance

In Japan, all residents are covered by health insurance under Universal Health Coverage[25], the universal health insurance system.[26] All patients (except those on welfare) are enrolled in common health and payment systems. There are two main types of health insurance plans for residents aged <75 years: employment-based plans and community-based plans (i.e., the national health insurance [NHI] system). Whereas employment-based plans are provided to company employees and their families, community-based plans are schemes for people who are not enrolled in an employment-based plan. All residents aged ≥75 years are covered by the late-stage medical care system (LSEMCS) for the elderly, a community-based plan (Figure 1-1). Administrative claims data are issued by health-care providers, such as hospitals, clinics, and pharmacies, and are billed to insurers. Data are routinely collected not only by health-care providers, but also by the claims review, reimbursement organizations, and insurers. The administrative claims database, which was constructed by reimbursement organizations and insurers, offers relatively high traceability in terms of its ability to follow-up patients beyond the medical institutions, unless an enrolee removes his/her plan. This allows studies to follow up data over long periods for outcome.

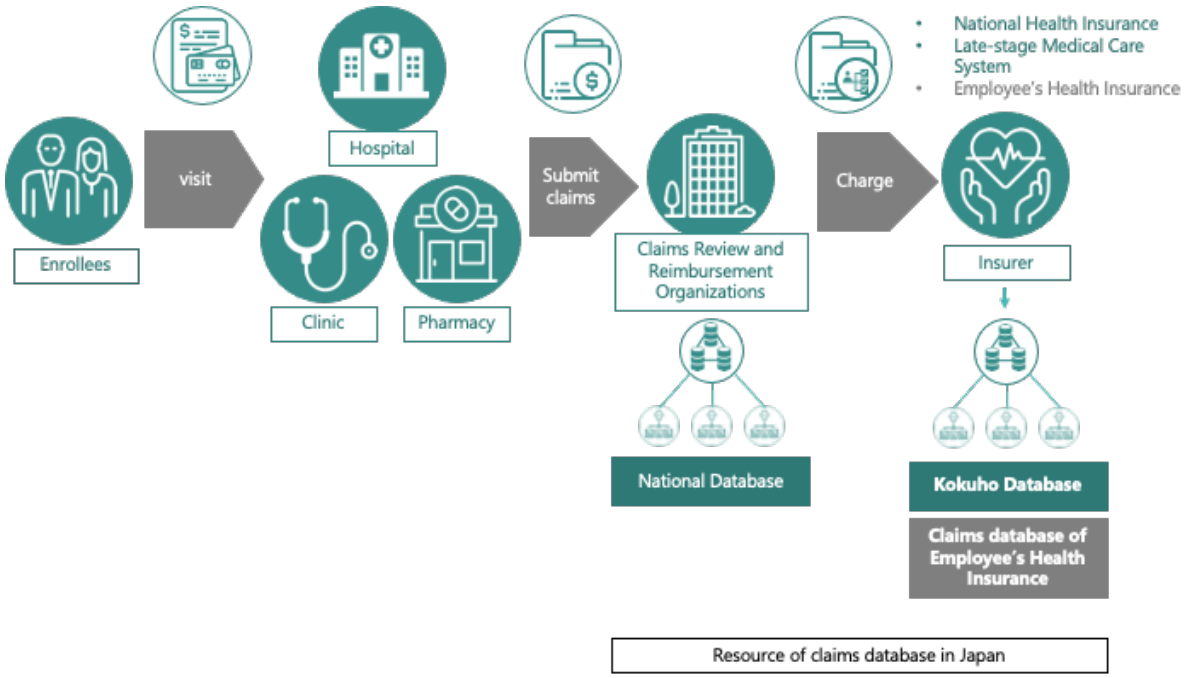


Figure 1-1 Sources of the administrative claims database in Japan

Figure was constructed with icons provided by Flaticon (https://www.flaticon.com).

Long-term care insurance

Japanese long-term care (LTC) insurance is a national system that promotes self-independence, in which municipal governments are the insurers. Based on a preliminary assessment and a doctor's opinion, the committee, which includes medical and welfare professionals, allocates the level of care required by each individual. The services covered include both institutional and in-home care. In-home care services include health-care (e.g., rehabilitation visits) and welfare services (e.g., home help services and day care for the elderly).[26,27]

Shizuoka Kokuho Database (SKDB)

The Shizuoka Kokuho Database (SKDB)[28] is the first large-scale municipal government health insurance database linked to long-term care insurance claims in Japan, and incorporates the claims of more than 2 million enrolees. The SKDB includes a subscriber list and monthly claims data for national health insurance, the late-stage medical care system, and long-term care insurance. Health insurance claims contain the disease code (ICD-10 code and Japanese disease code), the code for the procedure performed, medication, and device use (Figure 1-2). The data have been collected since April 2012. The data coverage of residents is ≤ 30% among people aged ≤60 years, but ≥70% among those aged ≥75 years.

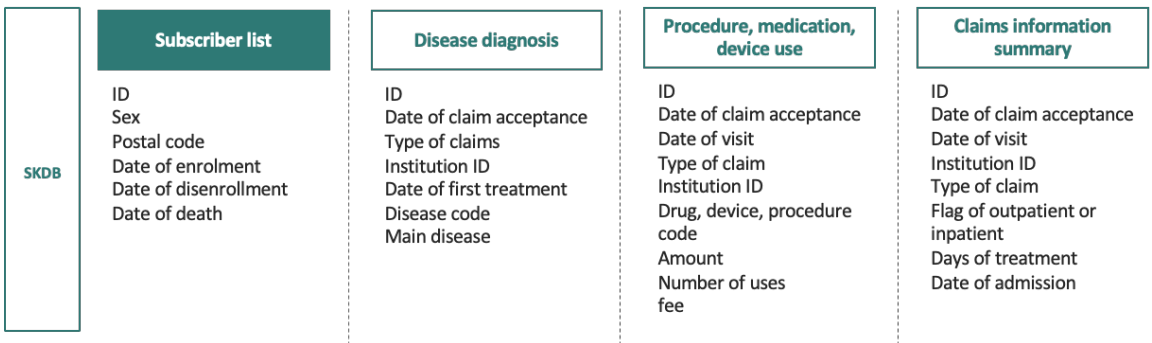


Figure 1-2 Contents of the Shizuoka Kokuho Database (health insurance claims)

Supplementary data

Chapter 1

Supplemental Table 1-1 The deficits included in electronic frailty index (Clegg et al., 2016)

Activity limitation	Ischaemic heart disease
Anaemia and haematinic deficiency	Memory and cognitive problems
Arthritis	Mobility and transfer problems
Atrial fibrillation	Osteoporosis
Cerebrovascular disease	Parkinsonism and tremor
Chronic kidney disease	Peptic ulcer
Diabetes	Peripheral vascular disease
Dizziness	Polypharmacy
Dyspnoea	Requirement for care
Falls	Respiratory disease
Foot problems	Skin ulcer
Fragility fracture	Sleep disturbance
Hearing impairment	Social vulnerability
Heart failure	Thyroid disease
Heart valve disease	Urinary incontinence
Housebound	Urinary system disease
Hypertension	Visual impairment
Hypotension/syncope	Weight loss and anorexia

Supplemental Table 1-2 ICD-10 codes in the Hospital Frailty Risk Score (Gilbert et al., 2018)

ICD- 10 code	ICD-10 name	Score
F00	Dementia in Alzheimer's disease	7.1
G81	Hemiplegia	4.4
G30	Alzheimer's disease	4
I69	Sequelae of cerebrovascular disease (secondary codes)	3.7
R29	Other symptoms and signs involving the nervous and musculoskeletal systems (R29・6 Tendency to fall)	3.6
N39	Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	3.2
F05	Delirium	3.2
W19	Unspecified fall	3.2
S00	Superficial injury of head	3.2
R31	Unspecified haematuria	3
B96	Other bacterial agents as the cause of diseases classified to other chapters (secondary code)	2.9
R41	Other symptoms and signs involving cognitive functions and awareness	2.7
R26	Abnormalities of gait and mobility	2.6
I67	Other cerebrovascular diseases	2.6
R56	Convulsions	2.6
R40	Somnolence	2.5
T83	Complications of genitourinary prosthetic devices	2.4
S06	Intracranial injury	2.4
S42	Fracture of shoulder and upper arm	2.3
E87	Other disorders of fluid	2.3
M25	Other joint disorders	2.3
E86	Volume depletion	2.3
R54	Senility	2.2
Z50	Care involving use of rehabilitation procedures	2.1
F03	Unspecified dementia	2.1
W18	Other fall on same level	2.1
Z75	Problems related to medical facilities and other health care	2
F01	Vascular dementia	2
S80	Superficial injury of lower leg	2
L03	Cellulitis	2
H54	Blindness and low vision	1.9
E53	Deficiency of other B group vitamins	1.9
Z60	Problems related to social environment	1.8
G20	Parkinson's disease	1.8
R55	Syncope and collapse	1.8
S22	Fracture of rib(s)	1.8
K59	Other functional intestinal disorders	1.8
N17	Acute renal failure	1.8
L89	Decubitus ulcer	1.7

ICD- 10 code	ICD-10 name	Score
Z22	Carrier of infectious disease	1.7
B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters	1.7
L97	Ulcer of lower limb	1.6
R44	Other symptoms and signs involving general sensations and perceptions	1.6
K26	Duodenal ulcer	1.6
I95	Hypotension	1.6
N19	Unspecified renal failure	1.6
A41	Other septicaemia	1.6
Z87	Personal history of other diseases and conditions	1.5
J96	Respiratory failure	1.5
X59	Exposure to unspecified factor	1.5
M19	Other arthrosis	1.5
G40	Epilepsy	1.5
M81	Osteoporosis without pathological fracture	1.4
S72	Fracture of femur	1.4
S32	Fracture of lumbar spine and pelvis	1.4
E16	Other disorders of pancreatic internal secretion	1.4
R94	Abnormal results of function studies	1.4
N18	Chronic renal failure	1.4
R33	Retention of urine	1.3
R69	Unknown and unspecified causes of morbidity	1.3
N28	Other disorders of kidney and ureter	1.3
R32	Unspecified urinary incontinence	1.2
G31	Other degenerative diseases of nervous system	1.2
Y95	Nosocomial condition	1.2
S09	Other and unspecified injuries of head	1.2
R45	Symptoms and signs involving emotional state	1.2
G45	Transient cerebral ischaemic attacks and related syndromes	1.2
Z74	Problems related to care-provider dependency	1.1
M79	Other soft tissue disorders	1.1
W06	Fall involving bed	1.1
S01	Open wound of head	1.1
A04	Other bacterial intestinal infections	1.1
A09	Diarrhoea and gastroenteritis of presumed infectious origin	1.1
J18	Pneumonia	1.1
J69	Pneumonitis due to solids and liquids	1
R47	Speech disturbances	1
E55	Vitamin D deficiency	1
Z93	Artificial opening status	1
R02	Gangrene	1
R63	Symptoms and signs concerning food and fluid intake	0.9
H91	Other hearing loss	0.9

ICD- 10 code	ICD-10 name	Score
W10	Fall on and from stairs and steps	0.9
W01	Fall on same level from slipping	0.9
E05	Thyrotoxicosis [hyperthyroidism]	0.9
M41	Scoliosis	0.9
R13	Dysphagia	0.8
Z99	Dependence on enabling machines and devices	0.8
U80	Agent resistant to penicillin and related antibiotics	0.8
M80	Osteoporosis with pathological fracture	0.8
K92	Other diseases of digestive system	0.8
I63	Cerebral Infarction	0.8
N20	Calculus of kidney and ureter	0.7
F10	Mental and behavioural disorders due to use of alcohol	0.7
Y84	Other medical procedures as the cause of abnormal reaction of the patient	0.7
R00	Abnormalities of heart beat	0.7
J22	Unspecified acute lower respiratory infection	0.7
Z73	Problems related to life-management difficulty	0.6
R79	Other abnormal findings of blood chemistry	0.6
Z91	Personal history of risk-factors	0.5
S51	Open wound of forearm	0.5
F32	Depressive episode	0.5
M48	Spinal stenosis (secondary code only)	0.5
E83	Disorders of mineral metabolism	0.4
M15	Polyarthrosis	0.4
D64	Other anaemias	0.4
L08	Other local infections of skin and subcutaneous tissue	0.4
R11	Nausea and vomiting	0.3
K52	Other noninfective gastroenteritis and colitis	0.3
R50	Fever of unknown origin	0.1

Chapter 2. Assessment of Coding-Based Frailty for Long-term Outcome Prediction

Summary

Background: Frailty is associated with increased risk of poor clinical outcomes, such as the requirement of long-term care or mortality. We investigated whether the Electronic Frailty Index (eFI) and Hospital Frailty Risk Score (HFRS) can be applicable in the Japanese health-care system and evaluated their associations with long-term outcomes.

Methods: We conducted a cohort study using a regional government administrative health-care and long-term care claims database in Japan 2014–2018. Plan enrolees aged ≥50 years were included. We applied the two algorithms to the cohort and assessed the scores' distributions alongside enrolees' 4-year mortality and initiation of government-supported long-term care (LTC). Using Cox regression and Fine–Gray models, we evaluated the association between frailty scores and outcomes as well as the models' discriminatory ability.

Results: Among 827,744 enrolees, 42.8% were categorized by eFI as fit, 31.2% mild, 17.5% moderate, and 8.5% severe. For HFRS, 73.0% were low, 24.3% intermediate, and 2.7% high risk. Thirty-five of 36 predictors for eFI, and 92 of 109 codes originally used for HFRS were available in the Japanese system. Relative to the lowest frailty group, the highest frailty group had hazard ratios (95% CI) of 2.09 (1.98-2.21) for mortality and 2.45 (2.28-2.63) for LTC for eFI; those for HFRS were 3.79 (3.56–4.03) and 3.31 (2.87–3.82), respectively. The area under the receiver operating characteristics curves for the unadjusted model at 48 months were 0.68 for death and 0.68 for LTC for eFI, and 0.73 and 0.70, respectively, for HFRS.

Interpretation: The frailty algorithms were applicable to the Japanese system, and could

contribute to the identifications of enrolees at risk of long-term mortality or LTC use.

Introduction

Frailty is an age-related accumulation of physiological debilities, resulting in vulnerability, especially when triggered by clinical events. Previous studies have demonstrated that frail subjects have an increased risk of poor clinical outcomes, such as the requirement of long-term care or mortality.[1,11] With increasing life expectancy, the number of frail older people has increased substantially[29,30] and has become a major issue.[31] The guideline published by the International Conference of Frailty and Sarcopenia Research (ICFSR) task force strongly recommends that older people (aged ≥65 years) be screened with suitable frailty instruments.[32] Identification of frailty can be used to direct older persons towards appropriate interventions, and assist them in the maintenance of a healthy and independent lifestyle.

To facilitate the early identification of frail individuals in community settings and subsequent intervention, a validated screening tool, ideally associated with long-term outcomes and the use of healthcare resources, is required. Large-scale healthcare data (e.g., administrative claims data and electronic health records) currently provide information on patients' clinical encounters, diagnoses, and resource use. These data are increasingly used in clinical research, and provide evidence to facilitate clinical and policy decisions, complementing the evidence from clinical trials. To date, several algorithms have been developed to identify and measure frailty using these data, including the Electronic Frailty Index (eFI) [19] and the Hospital Frailty Risk Score (HFRS).[23]

HFRS has been used and largely validated in acute-care settings,[33–35] whereas eFI has been widely used in general practice in England [36] and converted to other diagnostic codes.[37,38] However, the international validity of these instruments and their association with long-term outcomes have been insufficiently studied. Therefore, we aimed to assess whether the eFI and HFRS, originally developed in the UK, can be implemented in the Japanese healthcare system. We also evaluated the association between frailty measured using these

algorithms with long-term outcomes (i.e., mortality and the initiation for government-supported long-term care [LTC]).

Methods

Study design and data source

We conducted a cohort study using the Shizuoka Kokuho Database (SKDB), an administrative claims database of enrolees in the municipal government health insurance program in Shizuoka Prefecture, Japan.[28] The SKDB contains health insurance claims data (e.g., monthly claims for patients' diagnoses, procedures, and medications) and LTC insurance claims data. Among residents aged <75 years, 22.3% are enrolled in National Health Insurance (NHI) and all residents ≥75 are enrolled in the Late-Stage Medical Care System (LSEMCS). All residents aged ≥65 years or those aged 40–64 with severe illness defined by the government (e.g., advanced cancer, rheumatic disease, amyotrophic lateral sclerosis, cerebrovascular disease) are eligible for LTC insurance. Japanese LTC insurance is a national system that aims to promote self-independence, where municipal governments are the insurers. Based on a preliminary assessment and a doctor's opinion, the committee, which includes medical and welfare professionals, allocates the level of care required by each individual. The covered services include both institutional and in-home care. In-home care services include healthcare (e.g., rehabilitation visits) and welfare services (e.g., home help services and day-care for the elderly).[26,39]

We accessed all data on procedures and diagnoses involved in health insurance (NHI and LSEMCS) claims and the use of LTC insurance for all beneficiaries during April 2012–September 2018. The study was approved by the Institutional Review Board of Shizuoka General Hospital (Shizuoka, Japan) [SGHIRB #2020004].

Participants

We selected insurance enrolees aged ≥50 years on April 1st, 2014, from the database. We included enrolees aged ≥50 years to compare the frailty score distributions among those aged 50–64 years with those who were older. We designated April 2014 as the 'index month',

and the preceding 12-month period as the 'look-back period'. We excluded any subjects who were ineligible for the health plan during the 24-month period preceding the index month to limit the target cohort to subjects with complete diagnostic records during the look-back period. We also excluded participants who had no recorded diagnosis during the look-back period. The assessment of frailty score distribution and its relationship with age was conducted using this full cohort. To reduce the required computation time, we conducted a time-to-event analysis in a randomly sampled 10% sub-set of the full analytical cohort. We sampled the enrolees using a simple random sampling method without replacement in SAS (PROC SURVEYSELECT). A longitudinal assessment of LTC service use was conducted among those from the sub-set of enrolees with no record of LTC service use during the look-back period and who were aged ≥65 years in April 2014 (LTC assessment cohort) (Figure 2-1). We deleted those aged <65 years because the requirement for the receipt of LTC services differed between participants aged 50–64 and ≥65 years.

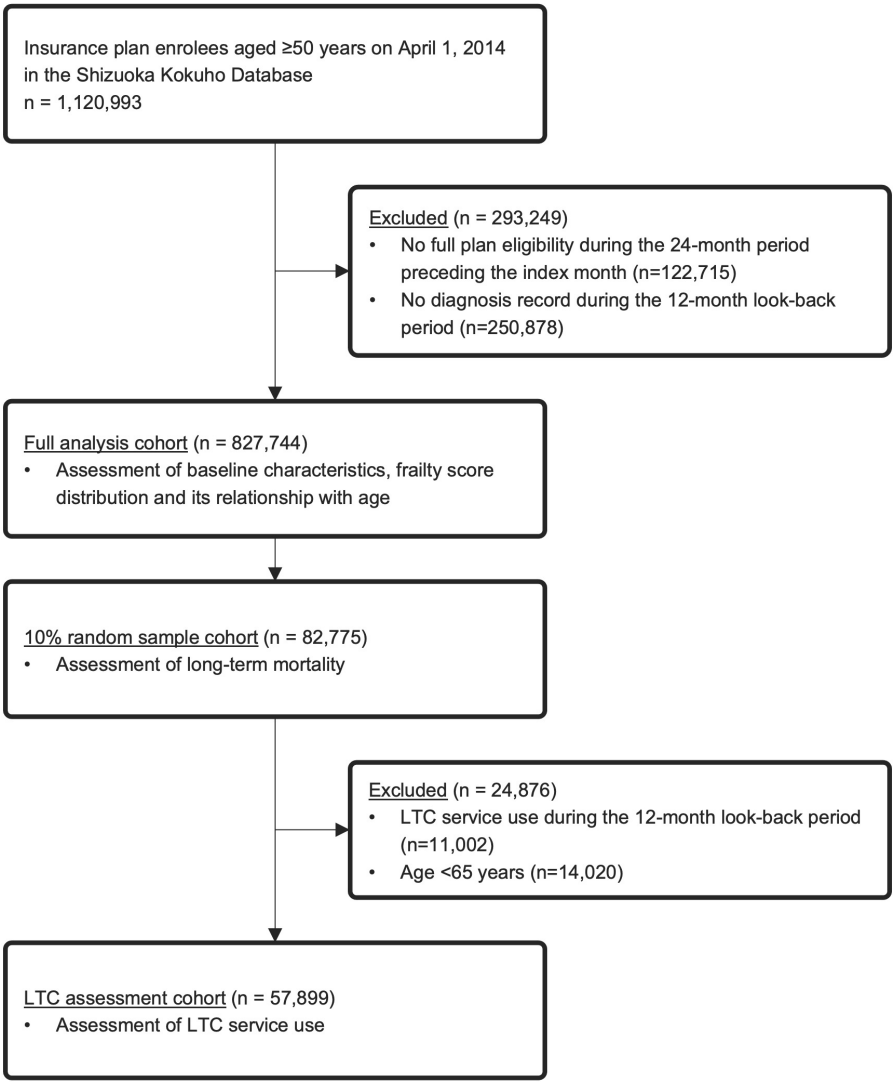


Figure 2-1 A flow diagram of the enrolment of the study cohort.

LTC, long-term care

Member characteristics

Sex and age data were extracted from the subscriber list, with data on each patient's diagnosis, medications, and LTC service use during the 12-month look-back period obtained from the claims data. Diagnosis codes were extracted with the Japanese electronic claims codes, which are linked to the corresponding International Classification of Diseases 10th version (ICD-10) codes.[40]

Frailty measurements

For each patient, we calculated eFI and HFRS based on the ICD-10 codes that were recorded in the inpatient and outpatient claims during the 12-month look-back period. For eFI calculation, we used the converted ICD-10 list of deficits based on previous studies (Supplemental Table 2-1).[41,42] We defined 'polypharmacy' as the prescription of ≥5 drugs over ≥6 months during the look-back period.[43] We then grouped the members into categories, using the cut-off points described in the original studies:[19,23] fit (0–0.12), mild frailty (>0.12–0.24), moderate frailty (>0.24–0.36), and severe frailty (>0.36) for eFI; low (<5), intermediate (5–15), and high (>15) risk for HFRS.

Outcomes

The main outcomes of interest were all-cause mortality and the use of government-supported LTC, which—accounting for death as a competing event—was assessed among those beneficiaries with no LTC service-use records from the look-back period.

Statistical analysis

We tabulated the baseline characteristics of the plan enrolees. We assessed the distributions of the two frailty scores and assessed their categorization. Each diagnosis code and polypharmacy's prevalence was evaluated. Spearman's correlation coefficient was used to

assess the relationship between age and the continuous frailty scores.

We censored participants at the time when their insurance plan enrolment terminated or on September 30th 2018, whichever came first (maximum follow-up period of 53 months). We estimated overall survival for each frailty category using Kaplan–Meier survival curves and compared them using the log-rank test. We constructed Cox proportional hazard models (with/without adjustment for age and sex) to determine the association between frailty score categories and mortality. We evaluated LTC initiation using cumulative incidence functions with Gray's test and Fine–Gray's subdistribution hazard models, with/without adjustment for age and sex. The discrimination was assessed from the time-dependent area under the receiver operating characteristic curves (AUC) using inverse probability weighting [44] for eFI and HFRS for outcomes at 12, 24, 36, and 48 months. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). R software version 3.5 (R Foundation for Statistical Computing, Vienna, Austria) was used to estimate the AUCs of the models with competing risks [45,46].

Results

Participant characteristics

Among the 827,744 insurance enrolees, the mean (SD) age was 74.2 (10.4) years and 59.4% were female. Participants were followed up for a median (IQRs) of 4.4 (4.4–4.4) years. The median (IQRs) frailty measure was 0.14 (0.09–0.26) for eFI and 2.2 (0–5.3) for HFRS (Table 2-1).

Table 2-1 Baseline characteristics

Characteristics		
N =	827,744	
Age (years), mean (SD)	74.2	(10.4)
Age group, N (%)		
50–64	140,774	(17)
65–74	309,771	(37.4)
75–84	228,628	(27.6)
≥85	148,571	(17.9)
Female, N (%)	491,497	(59.4)
Previous LTC service use, N (%)	109,511	(13.2)
LTC level, N (%)		
Support level	21,465	(2.6)
Care level 1–3	63,597	(7.7)
Care level 4–5	24,449	(3)
Number of medications, median (IQR)	13	(6–22)
eFI score, mean (SD)	0.17	(0.12)
HFRS score, mean (SD)	3.6	(4.3)
eFI frailty category, N (%)		
Fit	354,023	(42.8)
Mild	258,549	(31.2)
Moderate	145,091	(17.5)
Severe	70,081	(8.5)
HFRS frailty category, N (%)		
Low	604,211	(73.0)
Intermediate	201,359	(24.3)
High	22,174	(2.7)

SD, standard deviation; IQR, interquartile range; eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score; LTC, long-term care

The distribution of each score was heavily right-skewed, with maximum scores of 0.86 and 51.4, respectively (Figure 2-2). Of the study population, 354,023 (42.8%) were categorized by eFI as fit, 258,549 (31.2%) as mildly frail, 145,091 (17.5%) as moderately frail, and 70,081 (8.5%) as severely frail. Most participants were categorized by HFRS as low risk (604,211 [73.0%]), followed by intermediate (201,359 [24.3%]) and high (22,174 [2.7%]) risk. Among those aged <65 years (n=140,774), frail patients were less frequently observed compared to the older patients, with the 2,610 (1.9%) patients categorized as severely frail using eFI and the 707 (0.5%) patients categorized as high risk using HFRS. Upon limiting the enrolees to those included in the original eFI study (i.e., aged ≥65 years), 255,668 (37.2%) were categorized as fit, 227,520 (33.1%) as mildly frail, 136,311 (19.8%) as moderately frail, and 67,471 (9.8%) as severely frail. Among the participants aged ≥75 years with ≥1 admission record, the proportions of patients in the intermediate and high-risk groups based on HFRS were 54.1% and 16.7%, respectively (Supplemental Table 2-2).

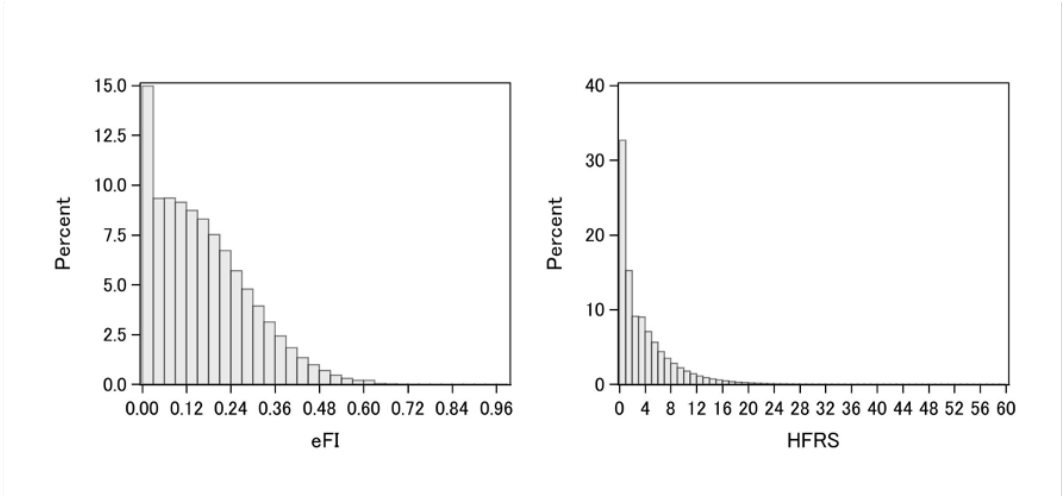


Figure 2-2 Histograms of frailty measures derived from healthcare claims data

eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score

Prevalence of predictors and relationships with age

We derived both HFRS and eFI using Japanese electronic claim codes linked to the corresponding ICD-10 codes. Supplemental Table 2-3 and Supplemental Table 2-4 list the variables and corresponding codes used for these measurements, together with their prevalence in the cohort. For HFRS, codes corresponding to 92 of the 109 ICD-10 diagnostic codes were available (the list of unavailable codes are shown in Table 2-2). The prevalence of each variable in the HFRS increased with age. Among the highly weighted diagnostic codes, Alzheimer's disease and the sequelae of cerebrovascular disease were markedly more prevalent in people aged ≥85 years (15.2% and 12.9%, respectively) than in those aged 50–64 years (0.2% and 1.9%, respectively) (Supplemental Table 2-3). For eFI, which consists of 36 variables, 35 were identified in the Japanese coding system, the exception being the code for "falls". Similar to the HFRS variables, many of the deficits had a much higher prevalence in people aged ≥85 years than in those aged 50–64 years (Supplemental Table 2-4). The prevalence of polypharmacy, cardiovascular diseases, and osteoporosis was highest among people aged ≥85 years. The proportion of subjects classified as severely frail increased with age: from 5.6% among 50–64-year-olds to 37.9% among those aged ≥85 years for eFI, and from 8.9% to 49.4%, respectively, for HFRS (Figure 2-3). Spearman's correlation coefficients between two frailty scores and age were 0.43 (95% CI 0.427–0.439) for eFI and 0.42 (95% CI 0.415–0.427) for HFRS.

Table 2-2 List of unobserved ICD-10 codes used in the Hospital Frailty Risk Score among Japanese claims system

Score	ICD10 code	ICD-10 name
7.1	F00	Dementia in Alzheimer's disease
3.2	W19	Unspecified fall
2.9	B96	Other bacterial agents as the cause of diseases classified to other chapters (secondary code)
2.1	Z50	Care involving use of rehabilitation procedures
2.1	W18	Other fall on same level
2	Z75	Problems related to medical facilities and other health care
1.8	Z60	Problems related to social environment
1.7	B95	Streptococcus and staphylococcus as the cause of diseases classified to other chapters
1.5	Z87	Personal history of other diseases and conditions
1.5	X59	Exposure to unspecified factor
1.2	Y95	Nosocomial condition
1.1	Z74	Problems related to care-provider dependency
1.1	W06	Fall involving bed
0.9	W10	Fall on and from stairs and steps
0.9	W01	Fall on same level from slipping, tripping and stumbling
0.8	U80	Agent resistant to penicillin and related antibiotics
0.7	Y84	Other medical procedures as the cause of abnormal reaction of the patient

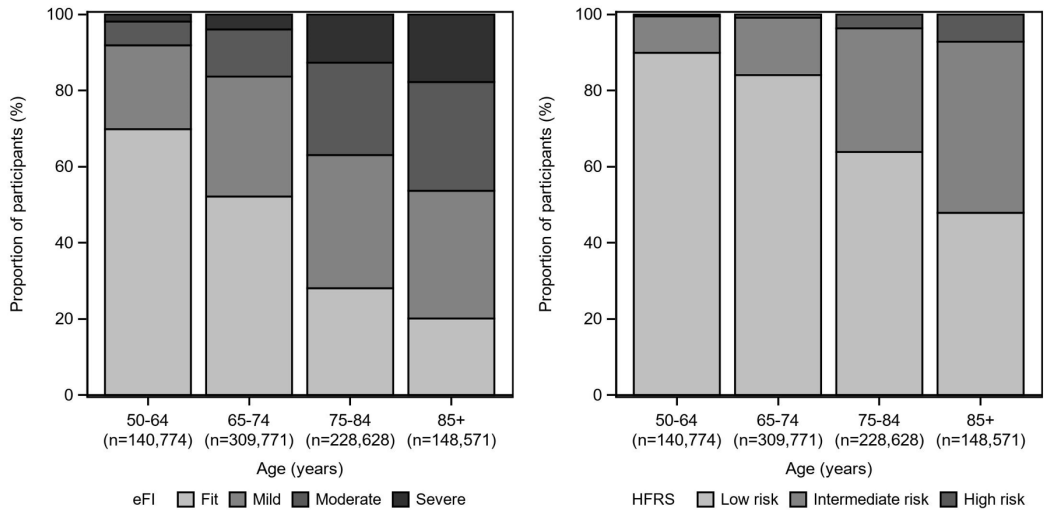


Figure 2-3 Proportions of frailty measures derived from healthcare claims data by age.

eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score

Risk of mortality and use of LTC service

Among a 10% random sample of participants (n=82,775), all-cause mortality per 100 person-year was 3.9. The survival rate at 48 months decreased with increasing severity of the frailty category, from 92.8% (95% CI, 92.5%–93.0%) in the fit group to 66.6% (95% CI, 65.5%–67.7%) in the severely frail group according to eFI categories, and from 91.4% (95% CI, 91.2%–91.6%) in the low-risk group to 45.6% (95% CI, 43.5%–47.6%) in the high-risk group according to HFRS category (Figure 2-4).

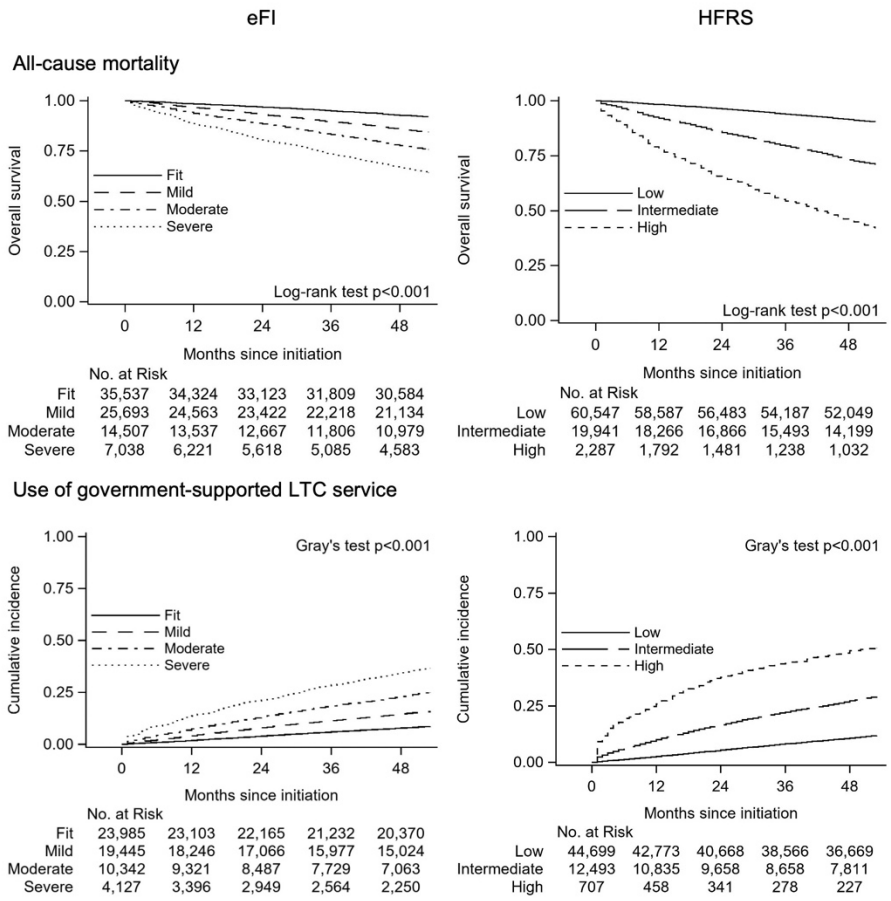


Figure 2-4 Kaplan–Meier survival curves for mortality and cumulative incidence functions of long-term care service use for up to 53 months according to frailty.

eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score

The hazard of death increased alongside the severity of frailty, with/without adjustment for age/sex: adjusted hazard ratio (HR) 2.09 (95% CI 1.98–2.21) for severely frail subjects relative

to fit subjects according to eFI, and HR 3.79 (95% CI 3.56–4.03) for high-risk subjects relative to low-risk subjects according to HFRS (Table 2-3).

Table 2-3 Results of Cox proportional hazard model regression for mortality and Fine–Gray proportional subdistribution hazard model regression for use of government-supported long-term care services among participants who used no long-term care services

		eFI							HFRS					
		No of events (*)		Unadjusted		Adjusted†			No of events (*)		Unadjusted		Adjusted†	
Outcome				HR (95% CI) ¶		HR (95% CI)¶					HR (95% CI)¶		HR (95% CI)¶	
Mortality‡		12,580	(3.9)						12,580	(3.9)				
	Fit	2,714	(1.9)	1	-	1	-	Low	5,573	(2.3)	1	–	1	–
	Mild	3,920	(3.8)	2.05	(1.95–2.15)	1.22	(1.16–1.28)	Intermediate	5,695	(7.8)	3.45	(3.33–3.58)	1.87	(1.80–1.95)
	Moderate	3,460	(6.3)	3.35	(3.19–3.53)	1.52	(1.45–1.60)	High	1,312	(20.1)	8.99	(8.47–9.55)	3.79	(3.56–4.03)
	Severe	2,486	(10.1)	5.43	(5.14–5.73)	2.09	(1.98–2.21)							
Use of LTC services§		9,264	(3.9)						9,264	(3.9)				
	Fit	2,073	(2.1)	1	–	1	–	Low	5,284	(2.8)	1	–	1	–
	Mild	3,100	(3.9)	1.9	(1.80–2.01)	1.3	(1.23–1.38)	Intermediate	3,623	(7.4)	2.74	(2.63–2.86)	1.75	(1.67–1.83)
	Moderate	2,584	(6.2)	3.14	(2.97–3.33)	1.7	(1.60–1.80)	High	357	(15.2)	5.99	(5.32–6.74)	3.31	(2.87–3.82)
	Severe	1,507	(9.5)	5.03	(4.71–5.38)	2.45	(2.28–2.63)							

eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score; HR, hazard ratio; CI, confidence interval; LTC, long-term care

*Event rate per 100 person years †Adjusted for age and sex. ‡n=82,775 §n=57,899; 24,876 participants aged ≤65 years or those with the records of the use of LTC service during the look-back period were excluded. ¶Hazard ratios for the use of LTC service were estimated using Fine–Gray's subdistribution hazard models.

In participants aged ≥65 years with no previous LTC service use (n=57,899), the event rate of the LTC service initiation was 3.9 per 100 person-years. We observed a similar relationship between frailty severity and the 48-month cumulative incidence of LTC service use: from 7.9% (95% CI 7.5%–8.2%) in the fit group to 34.5% (95% CI 33.0%–35.9%) in the severely frail group for eFI, and from 10.8% (95% CI 10.5%–11.0%) in the low-risk group to 49.4% (95% CI 45.6%–53.0%) in the high-risk group for HFRS (Figure 2-4). We observed an increase in the incidence of LTC service initiation with increasing frailty severity; even after adjusting for age and sex. The subdistribution hazard ratio (sHR) for the severely frail compared with fit was 2.45 (95% CI 2.28–2.63) on eFI, and the adjusted sHR for high risk compared with low risk subjects was 3.31 (95% CI 2.87–3.82) on HFRS (Table 2-3). Supplemental Figure 2-1 and Supplemental Figure 2-2 show the Kaplan–Meier survival curves and cumulative incidence functions stratified by age group, respectively. Mortality and incidence of LTC service use increased with age. Separation of the curves was most pronounced in the 75–84-year age group. Depicted separation was also more pronounced across the HFRS than eFI categories.

Model discrimination

The two algorithms discriminated the participants well at each time point. The AUC for mortality on HFRS (base model: 0.77 at 12 months, 0.73 at 48 months) was slightly superior to that on eFI (0.70 and 0.68, respectively). Among people aged ≥65 years with no history of LTC service use during the look-back period, the AUCs for LTC service use outcome at 12 and 48 months were 0.71 and 0.68, respectively, for eFI, and 0.75 and 0.70, respectively, for HFRS (Table 2-4). After adjustment for age and sex, the 48-month AUC for LTC service use was similar for eFI (48-month AUCs: mortality = 0.82, LTC service use = 0.84) and HFRS (0.84 and 0.85, respectively).

Table 2-4 Time-dependent AUC estimates for mortality and government-supported long-term care service use.

Outcome		AUC							
		12 months		24 months		36 months		48 months	
		Base model	+ Age, sex	Base model	+ Age, sex	Base model	+ Age, sex	Base model	+ Age, sex
Mortality*									
	eFI	0.70	0.81	0.69	0.82	0.68	0.82	0.68	0.82
	HFRS	0.77	0.83	0.75	0.83	0.73	0.83	0.73	0.84
Use of LTC services†									
	eFI	0.71	0.82	0.68	0.83	0.68	0.84	0.68	0.84
	HFRS	0.75	0.84	0.72	0.84	0.70	0.84	0.70	0.85

AUC, area under the curve; eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score; LTC, long-term care

*n=82,775

†n=57,899; 24,876 participants aged ≤65 years or those with the records of the use of LTC service during the look-back period were excluded.

Chapter discussion

We applied two frailty scores, eFI and HFRS, to a Japanese health systems database. Although several diagnostic codes in the algorithms were unavailable in the Japanese coding system, the application of these algorithms resulted in frailty score distributions with good variation, similar to those reported in the original cohorts in the UK.[19] Frailty scores were strongly associated with the incidences of death and LTC service use, and showed acceptable discriminatory power (AUC >0.68), supporting their transferability to the Japanese systems. The HFRS better discriminated the outcomes than the eFI at each time point.

The observed right-skewed distributions were similar to those reported in the original and other externally validated studies.[19,23,47] eFI was developed within an ambulatory population. eFI scores in our cohort were higher (fit, 43%; mild frailty, 31%; moderate frailty, 18%; severe frailty, 9%) than in the original study (fit, 50%; mild frailty, 35%; moderate frailty, 12%; severe frailty, 3%). Several deficits (e.g., cerebrovascular disease, diabetes mellitus, heart failure, and peptic ulcer) were more prevalent in our cohort than in the original. The HFRSs in our cohort were lower (low risk, 73%; intermediate risk, 24%; high risk, 3%) than those in a previous study constructed with a 1-year look-back window (low risk, 41%; intermediate risk, 37%; high risk, 22%).[48] This is probably attributable to the inclusion in our cohort of health-plan enrolees without admission records. Upon restricting the participants to those aged ≥75years with a history of ≥1 admissions, the prevalence of frailty became more similar to the previous study, and most patients were in the intermediate risk category. Fewer participants were classified as low or high risk than in the previous study. This could be partly explained by our use of diagnostic records from both inpatient and outpatient claims.

Among the 36 deficits used in the algorithm to capture the original eFI using ICD-10 codes, one deficit, “fall”, was missing from the Japanese claims codes. Among the 109 codes

used to define HFRS in the original study, 17 were missing. “Fall”, which is included in both eFI and HFRS, is one of the key factors used to measure frailty, given its high prevalence and strong association with frailty.[49,50] Missing such a component from the algorithm to capture frailty possibly distorted the assessment of frailty relative to the originally intended concept. However, several diagnostic codes included in score measurements are strongly associated with falls. In our study, codes for fragility fractures within the HFRS and eFI, such as fractures of the proximal humerus (included as part of ICD 10 code S42; fracture of shoulder and upper arm), distal radius (included as part of S52; fracture of forearm), and femoral neck and trochanteric fracture (included as part of S72; fracture of femur), were observed. These codes may have acted as proxies for “falls” in our study, reducing the impact of missingness.

The long-term prognoses of frail patients have been evaluated with the eFI.[19,51] HFRS is commonly used in studies evaluating clinical outcomes during hospitalization or after discharge,[33,35,52] but the association with long-term outcomes is less studied. In our assessment, the discrimination of the HFRS model was better than that of the eFI model at each time point, supporting its potential utility in studies of long-term outcomes. At the same time, both frailty scores were associated with both outcomes in our study, even after stratification by age group. This supports the notion that these frailty scores identify frailty-specific conditions, independent of age.

The two frailty scores were clearly associated with mortality and LTC initiation, which is consistent with past prospective studies using clinically measured frailty scores.[53–55] The relationship between frailty and LTC resource utilization is especially important in the context of LTC-insurance-system sustainability in aging societies. In prior analyses, the need for help from others was considered as a proxy for frailty.[56–58] Another study developed a frailty score from healthcare claims data using activities of daily living dependency as an outcome.[59] Our study adds support to the longitudinal association between frailty and LTC requirement. The assessment of how frailty among older people increases the need for LTC services in the target population may help us to estimate resource needs in the near future.

Strengths of this study includes the application of two validated frailty scores to a comprehensive population in Japanese health system. This is the first study obtained two frailty scores from primary care data along with secondary care, while the scores developed using primary- or secondary- care data alone in original study. Our study using health insurance claims data linking with long-term care insurance claims adds the value for population-based geriatric assessment. Notably, claims of Late-Stage Medical Care System for the elderly, which covered all residents aged ≥75 years, allow us to assess long-term association between frailty algorithms and poor outcomes (i.e., long-term care service initiation and mortality). Future work of development of the algorithms having accuracy for predicting outcomes at individual-level are recommended.

This study had noteworthy limitations. First, the frailty scores of the participants admitted to geriatric health service facilities may have been underestimated because the payment for medical services (e.g., drugs prescribed for long-term disease management by the attached medical institution) is not covered by health insurance but by LTC insurance.[60] Second, the date (day-level) of dispensation or device use is unknown in the Shizuoka Kokuho Database (SKDB) as well as the date of disease diagnosed. Third, the applicability of the algorithms to administrative claims data in this study does not ensure its transferability to other databases. Forth, although we evaluated applicability of frailty algorithms, validity of frailty scores to traditional measurement tools (frailty phenotype or frailty index) was not examined in Japan. Additional studies of validation for physical frailty scale are required.

Supplementary data

Chapter 2

Supplemental Table 2-1 List of deficits evaluated using the Electronic Frailty Index and corresponding ICD 10 codes/definitions recorded in the claims database.

No.	eFI	ICD 10 code/definition
1	Activity limitation	R26, S78, S88, S98, T13.6, Y83, Z99.3, G11, G81, G82, G83, M62
2	Anaemia and haematinic deficiency	D50, D51, D52, D53, D64
3	Arthritis	M05, M06, M07, M09, M10, M11, M12, M13, M15, M16, M17, M18, M19, M31.5, M32, M33, M34, M35, M36
4	Atrial fibrillation	I44, I48, I49
5	Cerebrovascular disease	G45, G46, I6, H34
6	Chronic kidney disease	I12, I13, N01, N03, N05, N07, N08, N18, N19, N25, I77
7	Diabetes	E10.9, E11.9, E12.9, E13.9, E14.9
8	Dizziness	I95, R55, R42, E86, H81, H82, H83
9	Dyspnoea	R06
10	Falls	Not available
11	Foot problems	B353, G575, G576, L60, M201, M202, M203, M204, M205, M206, M213, M214, M215, M216, M722, M766, M773, M775, S90, S91, S92, S93, S94, S96, S97, S99, Q66
12	Fragility fracture	M484, S22, S32, S33, S42, S43, S62, S72, S73, M485, M800, M808, M843, M847, S02, S12, S52, S82, S92
13	Hearing impairment	H833, H90, H91, G960, H60, H61, H62, H71, H73, H74, H92, H93
14	Heart failure	I11, I13, I26.0, I27, I42, I43, I50, I51, I09.9, I255
15	Heart valve disease	I05, I06, I07, I08, I34, I35, I36, I37, I390, I391, I392, I393, I394, A520, I091, I098, I38, Q230, Q231, Q232, Q233
16	Housebound	R40, Z50, Z74, Z75.5
17	Hypertension	I10, I11, I12, I13, H350
18	Hypotension/syncope	I95, R55, R42, E86
19	Ischaemic heart disease	I20, I21, I22, I23, I24, I25
20	Memory and cognitive problems	F00, F01, F02, F03, F04, F05, F06.7, G30, G31, R41, R54, F2, F3, F41, R44, R45
21	Mobility and transfer problems	R26, S78, S88, S98, T136, G11, G81, G82, G83, M62
22	Osteoporosis	M80, M81, M82
23	Parkinsonism and tremor	G122, G20, G21, G22, G23, G25, G26, G32, G35, R25
24	Peptic ulcer	K21, K25, K26, K27, K28, K29, R12
25	Peripheral vascular disease	I65, I70, I71, I72, I73, I771, K551, K558, K559, R02, Z958, Z959, I790, I792, Z958
26	Polypharmacy	≥5 drugs prescriptions for a total of ≥6 months during the baseline period
27	Requirement for care	R40
28	Respiratory disease	J45, J46, J40, J41, J42, J43, J44, J47, J60, J61, J62, J63, J64, J65, J67, J684, J70, J13, J14, J15, J16, J18, J22, J20, J90, J961, J980
29	Skin ulcer	I83, I98, L03, L08, L89, L97, L984
30	Sleep disturbance	G47, F51
31	Social vulnerability	F1, R460, R468, Z59, Z60, Z63, Z73

No.	eFI	ICD 10 code/definition
32	Thyroid disease	E00, E01, E03, E04, E05, E06, E079, E890, R946
33	Urinary incontinence	N31, N393, N394, R15, R32, Z466
34	Urinary system disease	N30, N34, N39.0, N39.8, N39.9, R31, R33, T835
35	Visual impairment	H25, H28, H35, H40, H43, H53, H54
36	Weight loss and anorexia	E41, E43, E44, E46, E53, E55, E66, E83, E87, R53, R628, R63, R64, F500, F501, F508, F509

Supplemental Table 2-2 Frequencies of eFI and HFRS categories within study population (n=827,744) and those with ≥1 admission in the preceding year (n=10,375) by age groups.

Study population		Age (years)			
	All	50–64	65–74	75–84	≥85
N =	827,744	140,774	309,771	228,628	148,571
Female	491,497 (59.4)	78,707 (55.9)	173,439 (56.0)	137,417 (60.1)	101,934 (68.6)
eFI category:					
Fit	354,023 (42.8)	98,355 (69.9)	161,597 (52.2)	64,184 (28.1)	29,887 (20.1)
Mild	258,549 (31.2)	31,029 (22.0)	97,644 (31.5)	80,018 (35.0)	49,858 (33.6)
Moderate	145,091 (17.5)	8,780 (6.2)	38,379 (12.4)	55,465 (24.3)	42,467 (28.6)
Severe	70,081 (8.5)	2,610 (1.9)	12,151 (3.9)	28,961 (12.7)	26,359 (17.7)
HFRS category:					
Low risk	604,211 (73.0)	126,610 (89.9)	260,416 (84.1)	146,039 (63.9)	71,146 (47.9)
Intermediate risk	201,359 (24.3)	13,457 (9.6)	46,810 (15.1)	74,291 (32.5)	66,801 (45.0)
High risk	22,174 (2.7)	707 (0.5)	2,545 (0.8)	8,298 (3.6)	10,624 (7.2)
≥1 admission in the preceding year		Age (years)			
	All	50–64	65–74	75–84	≥85
N =	10,375	1,146	3,391	3,160	2,678
Female	5,331 (51.4)	493 (43.0)	1,503 (44.3)	1,612 (51.0)	1,723 (64.3)
eFI category:					
Fit	1,643 (15.8)	363 (31.7)	757 (22.3)	308 (9.7)	215 (8.0)
Mild	3,040 (29.3)	414 (36.1)	1,204 (35.5)	844 (26.7)	578 (21.6)
Moderate	3,047 (29.4)	247 (21.6)	910 (26.8)	1,005 (31.8)	885 (33.0)
Severe	2,645 (25.5)	122 (10.6)	520 (15.3)	1,003 (31.7)	1,000 (37.3)
HFRS category:					
Low risk	4,320 (41.6)	685 (59.8)	1,926 (56.8)	1,155 (36.6)	554 (20.7)
Intermediate risk	4,863 (46.9)	416 (36.3)	1,291 (38.1)	1,594 (50.4)	1,562 (58.3)
High risk	1,192 (11.5)	45 (3.9)	174 (5.1)	411 (13.0)	562 (21.0)

Values are numbers (percentages). eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score

Supplemental Table 2-3 List of ICD-10 codes contained in HFRS and numbers of participants (%) with the codes in the cohort according to age-group.

No.	Score	ICD10 code	description	All N = 827,744 N (%)	50–64 years N = 140,774 N (%)	65–74 years N = 309,771 N (%)	75–84 years N = 228,628 N (%)	≥85 years N = 148,571 N (%)
1	4.4	G81	Hemiplegia	7,292 (0.9)	852 (0.6)	2,013 (0.6)	2,495 (1.1)	1,932 (1.3)
2	4.0	G30	Alzheimer's disease	42,386 (5.1)	345 (0.2)	3,178 (1.0)	16,258 (7.1)	22,605 (15.2)
3	3.7	I69	Sequelae of cerebrovascular disease (secondary codes)	53,251 (6.4)	2,721 (1.9)	11,378 (3.7)	19,966 (8.7)	19,186 (12.9)
4	3.6	R29	Other symptoms and signs involving the nervous and musculoskeletal systems (R29・6 Tendency to fall)	1,849 (0.2)	207 (0.1)	489 (0.2)	632 (0.3)	521 (0.4)
6	3.2	N39	Other disorders of urinary system (includes urinary tract infection and urinary incontinence)	43,871 (5.3)	4,409 (3.1)	12,417 (4.0)	14,543 (6.4)	12,502 (8.4)
7	3.2	S00	Superficial injury of head	12,259 (1.5)	1,027 (0.7)	2,913 (0.9)	4,084 (1.8)	4,235 (2.9)
5	3.2	F05	Delirium	4,999 (0.6)	127 (0.1)	524 (0.2)	1,646 (0.7)	2,702 (1.8)
8	3.0	R31	Unspecified haematuria	25,466 (3.1)	2,899 (2.1)	9,376 (3.0)	8,306 (3.6)	4,885 (3.3)
9	2.7	R41	Other symptoms and signs involving cognitive functions and awareness	1,979 (0.2)	105 (0.1)	453 (0.1)	883 (0.4)	538 (0.4)
10	2.6	I67	Other cerebrovascular diseases	27,438 (3.3)	2,639 (1.9)	8,999 (2.9)	9,743 (4.3)	6,057 (4.1)
11	2.6	R26	Abnormalities of gait and mobility	6,448 (0.8)	331 (0.2)	1,234 (0.4)	2,534 (1.1)	2,349 (1.6)
12	2.6	R56	Convulsions	1,492 (0.2)	249 (0.2)	479 (0.2)	454 (0.2)	310 (0.2)
13	2.5	R40	Somnolence	6,960 (0.8)	529 (0.4)	1,402 (0.5)	2,368 (1.0)	2,661 (1.8)
14	2.4	S06	Intracranial injury	9,202 (1.1)	683 (0.5)	2,085 (0.7)	3,187 (1.4)	3,247 (2.2)
15	2.4	T83	Complications of genitourinary prosthetic devices	6 (0.0)	1 (0.0)	3 (0.0)	1 (0.0)	1 (0.0)
16	2.3	E86	Volume depletion	68,774 (8.3)	7,685 (5.5)	18,182 (5.9)	22,289 (9.7)	20,618 (13.9)
17	2.3	E87	Other disorders of fluid	30,408 (3.7)	3,065 (2.2)	7,478 (2.4)	10,212 (4.5)	9,653 (6.5)
18	2.3	M25	Other joint disorders	32,165 (3.9)	4,034 (2.9)	10,068 (3.3)	10,732 (4.7)	7,331 (4.9)
19	2.3	S42	Fracture of shoulder and upper arm	4,730 (0.6)	415 (0.3)	1,102 (0.4)	1,580 (0.7)	1,633 (1.1)
20	2.2	R54	Senility	250 (0.0)	(0.0)	6 (0.0)	35 (0.0)	209 (0.1)

No.	Score	ICD10 code/description		All N = 827,744 N (%)	50–64 years N = 140,774 N (%)	65–74 years N = 309,771 N (%)	75–84 years N = 228,628 N (%)	≥85 years N = 148,571 N (%)
21	2.1	F03	Unspecified dementia	18,450 (2.2)	286 (0.2)	1,585 (0.5)	6,024 (2.6)	10,555 (7.1)
22	2.0	F01	Vascular dementia	769 (0.1)	18 (0.0)	83 (0.0)	303 (0.1)	365 (0.2)
23	2.0	L03	Cellulitis	19,634 (2.4)	2,961 (2.1)	6,126 (2.0)	5,777 (2.5)	4,770 (3.2)
24	2.0	S80	Superficial injury of lower leg	4,330 (0.5)	517 (0.4)	1,159 (0.4)	1,464 (0.6)	1,190 (0.8)
25	1.9	E53	Deficiency of other B group vitamins	12,991 (1.6)	1,610 (1.1)	3,965 (1.3)	4,503 (2.0)	2,913 (2.0)
26	1.9	H54	Blindness and low vision	653 (0.1)	83 (0.1)	172 (0.1)	210 (0.1)	188 (0.1)
27	1.8	G20	Parkinson’s disease	14,224 (1.7)	1,674 (1.2)	3,182 (1.0)	5,435 (2.4)	3,933 (2.6)
28	1.8	K59	Other functional intestinal disorders	251,473 (30.4)	21,255 (15.1)	62,610 (20.2)	89,326 (39.1)	78,282 (52.7)
29	1.8	N17	Acute renal failure	1,981 (0.2)	204 (0.1)	484 (0.2)	659 (0.3)	634 (0.4)
30	1.8	R55	Syncope and collapse	1,925 (0.2)	133 (0.1)	441 (0.1)	710 (0.3)	641 (0.4)
31	1.8	S22	Fracture of rib(s)	21,085 (2.5)	1,412 (1.0)	4,564 (1.5)	7,851 (3.4)	7,258 (4.9)
32	1.7	L89	Decubitus ulcer	10,227 (1.2)	438 (0.3)	947 (0.3)	2,828 (1.2)	6,014 (4.0)
33	1.7	Z22	Carrier of infectious disease	584 (0.1)	100 (0.1)	255 (0.1)	164 (0.1)	65 (0.0)
34	1.6	A41	Other septicaemia	9,574 (1.2)	898 (0.6)	2,336 (0.8)	3,147 (1.4)	3,193 (2.1)
35	1.6	I95	Hypotension	7,092 (0.9)	1,096 (0.8)	2,003 (0.6)	2,365 (1.0)	1,628 (1.1)
36	1.6	K26	Duodenal ulcer	13,247 (1.6)	2,048 (1.5)	5,381 (1.7)	3,897 (1.7)	1,921 (1.3)
37	1.6	L97	Ulcer of lower limb	1,056 (0.1)	131 (0.1)	241 (0.1)	341 (0.1)	343 (0.2)
38	1.6	N19	Unspecified renal failure	22,804 (2.8)	2,473 (1.8)	5,668 (1.8)	7,765 (3.4)	6,898 (4.6)
39	1.6	R44	Other symptoms and signs involving general sensations and perceptions	1,468 (0.2)	272 (0.2)	558 (0.2)	424 (0.2)	214 (0.1)
40	1.5	G40	Epilepsy	21,446 (2.6)	4,993 (3.5)	6,645 (2.1)	6,101 (2.7)	3,707 (2.5)
41	1.5	J96	Respiratory failure	28,476 (3.4)	2,592 (1.8)	6,736 (2.2)	9,572 (4.2)	9,576 (6.4)
42	1.5	M19	Other arthrosis	40,716 (4.9)	3,896 (2.8)	12,056 (3.9)	14,696 (6.4)	10,068 (6.8)
43	1.4	E16	Other disorders of pancreatic internal secretion	4,259 (0.5)	503 (0.4)	1,306 (0.4)	1,450 (0.6)	1,000 (0.7)
44	1.4	M81	Osteoporosis without pathological fracture	170,324 (20.6)	10,013 (7.1)	46,893 (15.1)	65,025 (28.4)	48,393 (32.6)

No.	Score	ICD10 code	description	All N = 827,744 N (%)	50–64 years N = 140,774 N (%)	65–74 years N = 309,771 N (%)	75–84 years N = 228,628 N (%)	≥85 years N = 148,571 N (%)
45	1.4	N18	Chronic renal failure	28,414 (3.4)	2,930 (2.1)	7,317 (2.4)	9,800 (4.3)	8,367 (5.6)
46	1.4	R94	Abnormal results of function studies	4,588 (0.6)	683 (0.5)	1,691 (0.5)	1,394 (0.6)	820 (0.6)
47	1.4	S32	Fracture of lumbar spine and pelvis	23,690 (2.9)	800 (0.6)	3,868 (1.2)	9,402 (4.1)	9,620 (6.5)
48	1.4	S72	Fracture of femur	14,837 (1.8)	488 (0.3)	1,561 (0.5)	4,689 (2.1)	8,099 (5.5)
49	1.3	N28	Other disorders of kidney and ureter	61,620 (7.4)	6,256 (4.4)	19,757 (6.4)	20,949 (9.2)	14,658 (9.9)
50	1.3	R33	Retention of urine	8,130 (1.0)	466 (0.3)	1,749 (0.6)	2,818 (1.2)	3,097 (2.1)
51	1.3	R69	Unknown and unspecified causes of morbidity	1 (0.0)	(0.0)	1 (0.0)	(0.0)	(0.0)
52	1.2	G31	Other degenerative diseases of nervous system	2,272 (0.3)	193 (0.1)	498 (0.2)	864 (0.4)	717 (0.5)
53	1.2	G45	Transient cerebral ischaemic attacks and related syndromes	13,709 (1.7)	921 (0.7)	3,718 (1.2)	5,202 (2.3)	3,868 (2.6)
54	1.2	R32	Unspecified urinary incontinence	2,193 (0.3)	143 (0.1)	543 (0.2)	852 (0.4)	655 (0.4)
55	1.2	R45	Symptoms and signs involving emotional state	1,616 (0.2)	189 (0.1)	351 (0.1)	492 (0.2)	584 (0.4)
56	1.2	S09	Other and unspecified injuries of head	5,548 (0.7)	454 (0.3)	1,389 (0.4)	1,837 (0.8)	1,868 (1.3)
57	1.1	A04	Other bacterial intestinal infections	4,124 (0.5)	594 (0.4)	1,262 (0.4)	1,194 (0.5)	1,074 (0.7)
58	1.1	A09	Diarrhoea and gastroenteritis of presumed infectious origin	93,159 (11.3)	15,540 (11.0)	31,591 (10.2)	27,091 (11.8)	18,937 (12.7)
59	1.1	J18	Pneumonia	63,512 (7.7)	6,331 (4.5)	16,624 (5.4)	19,615 (8.6)	20,942 (14.1)
60	1.1	M79	Other soft tissue disorders	66,405 (8.0)	7,364 (5.2)	20,837 (6.7)	23,347 (10.2)	14,857 (10.0)
61	1.1	S01	Open wound of head	6,416 (0.8)	626 (0.4)	1,460 (0.5)	2,097 (0.9)	2,233 (1.5)
62	1.0	E55	Vitamin D deficiency	342 (0.0)	34 (0.0)	116 (0.0)	126 (0.1)	66 (0.0)
63	1.0	J69	Pneumonitis due to solids and liquids	6,828 (0.8)	254 (0.2)	743 (0.2)	2,021 (0.9)	3,810 (2.6)
64	1.0	R02	Gangrene	819 (0.1)	108 (0.1)	209 (0.1)	278 (0.1)	224 (0.2)
65	1.0	R47	Speech disturbances	4,546 (0.5)	535 (0.4)	1,369 (0.4)	1,492 (0.7)	1,150 (0.8)
66	1.0	Z93	Artificial opening status	4,093 (0.5)	416 (0.3)	977 (0.3)	1,299 (0.6)	1,401 (0.9)
67	0.9	E05	Thyrotoxicosis [hyperthyroidism]	25,724 (3.1)	4,930 (3.5)	9,914 (3.2)	7,198 (3.1)	3,682 (2.5)

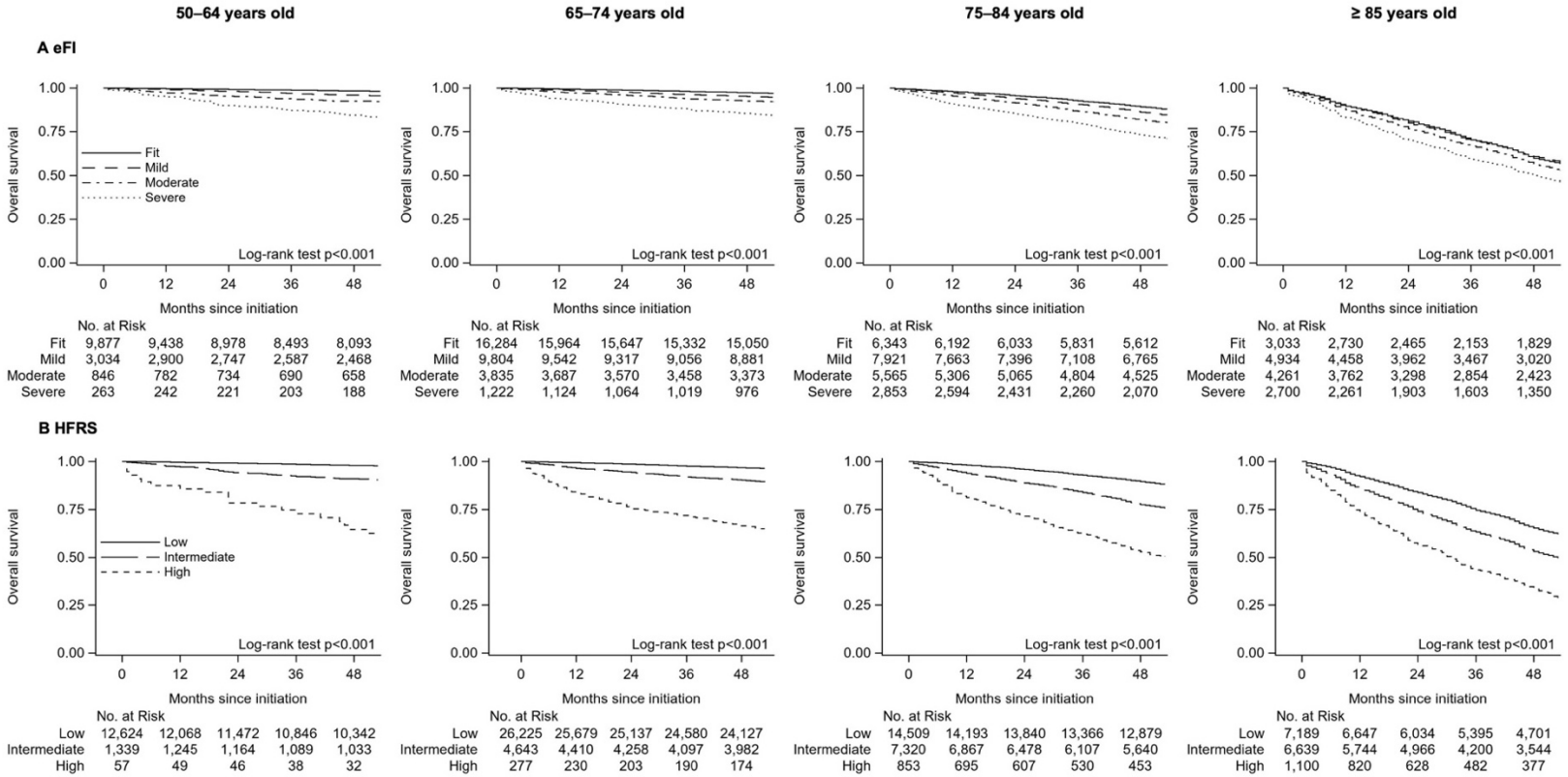
No.	Score	ICD10 code	description	All N = 827,744 N (%)	50–64 years N = 140,774 N (%)	65–74 years N = 309,771 N (%)	75–84 years N = 228,628 N (%)	≥85 years N = 148,571 N (%)
68	0.9	H91	Other hearing loss	17,130 (2.1)	2,038 (1.4)	6,064 (2.0)	5,835 (2.6)	3,193 (2.1)
69	0.9	M41	Scoliosis	3,523 (0.4)	332 (0.2)	1,113 (0.4)	1,366 (0.6)	712 (0.5)
70	0.9	R63	Symptoms and signs concerning food and fluid intake	21,729 (2.6)	1,952 (1.4)	5,240 (1.7)	7,513 (3.3)	7,024 (4.7)
71	0.8	I63	Cerebral Infarction	120,357 (14.5)	7,584 (5.4)	32,555 (10.5)	45,394 (19.9)	34,824 (23.4)
72	0.8	K92	Other diseases of digestive system	22,919 (2.8)	2,425 (1.7)	7,351 (2.4)	7,690 (3.4)	5,453 (3.7)
73	0.8	M80	Osteoporosis with pathological fracture	1,951 (0.2)	75 (0.1)	392 (0.1)	788 (0.3)	696 (0.5)
74	0.8	R13	Dysphagia	9,800 (1.2)	570 (0.4)	1,589 (0.5)	3,235 (1.4)	4,406 (3.0)
75	0.8	Z99	Dependence on enabling machines and devices	57 (0.0)	4 (0.0)	22 (0.0)	16 (0.0)	15 (0.0)
76	0.7	F10	Mental and behavioural disorders due to use of alcohol	1,523 (0.2)	444 (0.3)	644 (0.2)	323 (0.1)	112 (0.1)
77	0.7	J22	Unspecified acute lower respiratory infection	258 (0.0)	13 (0.0)	30 (0.0)	86 (0.0)	129 (0.1)
78	0.7	N20	Calculus of kidney and ureter	26,725 (3.2)	4,871 (3.5)	10,854 (3.5)	7,517 (3.3)	3,483 (2.3)
79	0.7	R00	Abnormalities of heart beat	20,071 (2.4)	2,113 (1.5)	6,315 (2.0)	6,941 (3.0)	4,702 (3.2)
80	0.6	R79	Other abnormal findings of blood chemistry	1,107 (0.1)	152 (0.1)	403 (0.1)	346 (0.2)	206 (0.1)
81	0.5	F32	Depressive episode	50,870 (6.1)	7,535 (5.4)	15,344 (5.0)	16,466 (7.2)	11,525 (7.8)
82	0.5	M48	Spinal stenosis (secondary code only)	82,225 (9.9)	5,355 (3.8)	23,690 (7.6)	33,415 (14.6)	19,765 (13.3)
83	0.5	S51	Open wound of forearm	1,199 (0.1)	77 (0.1)	223 (0.1)	358 (0.2)	541 (0.4)
84	0.5	Z91	Personal history of risk-factors	14 (0.0)	8 (0.0)	4 (0.0)	1 (0.0)	1 (0.0)
85	0.4	D64	Other anaemias	61,211 (7.4)	6,417 (4.6)	17,636 (5.7)	20,334 (8.9)	16,824 (11.3)
86	0.4	E83	Disorders of mineral metabolism	13,230 (1.6)	1,963 (1.4)	3,998 (1.3)	4,393 (1.9)	2,876 (1.9)
87	0.4	L08	Other local infections of skin and subcutaneous tissue	17,688 (2.1)	2,821 (2.0)	5,580 (1.8)	5,044 (2.2)	4,243 (2.9)
88	0.4	M15	Polyarthrosis	2,695 (0.3)	601 (0.4)	1,078 (0.3)	727 (0.3)	289 (0.2)
89	0.3	K52	Other noninfective gastroenteritis and colitis	11,450 (1.4)	1,167 (0.8)	3,135 (1.0)	4,011 (1.8)	3,137 (2.1)
90	0.3	R11	Nausea and vomiting	39,874 (4.8)	6,231 (4.4)	13,332 (4.3)	12,392 (5.4)	7,919 (5.3)

No.	Score	ICD10 code/description		All N = 827,744 N (%)	50–64 years N = 140,774 N (%)	65–74 years N = 309,771 N (%)	75–84 years N = 228,628 N (%)	≥85 years N = 148,571 N (%)
91	0.1	R50	Fever of unknown origin	12,736 (1.5)	1,978 (1.4)	3,397 (1.1)	3,526 (1.5)	3,835 (2.6)

Supplemental Table 2-4 List of deficits included in eFI and numbers of participants (%) with each deficit according to age-group.

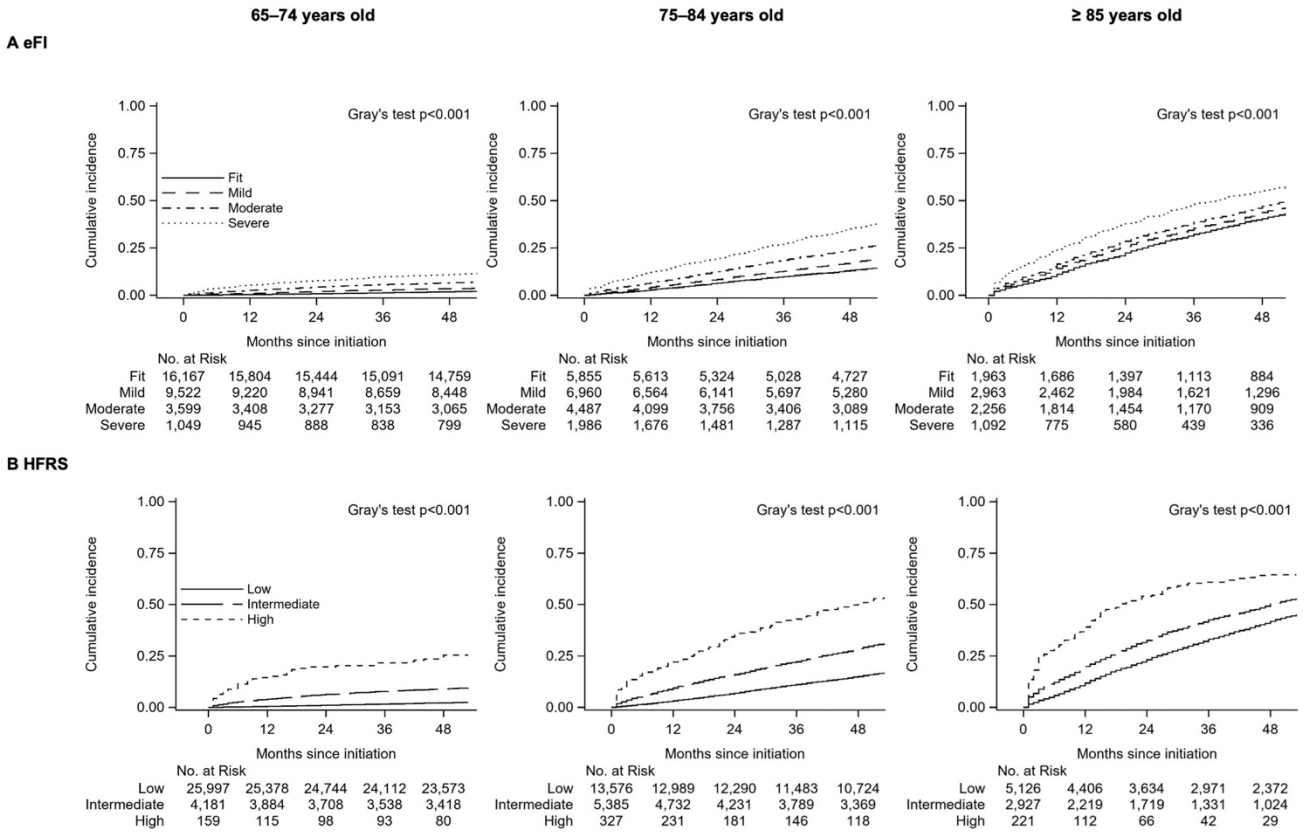
	Deficit	Overall N = 827,744 N (%)	50–64 years N = 140,774 N (%)	65–74 years N = 309,771 N (%)	75–84 years N = 228,628 N (%)	≥85 years N=148,571 N (%)
1	Activity limitation	53,225 (6.4)	5,195 (3.7)	14,048 (4.5)	17,847 (7.8)	16,135 (10.9)
2	Anaemia and haematinic deficiency	139,033 (16.8)	15,427 (11.0)	37,672 (12.2)	46,550 (20.4)	39,384 (26.5)
3	Arthritis	252,311 (30.5)	28,786 (20.4)	80,812 (26.1)	85,931 (37.6)	56,782 (38.2)
4	Atrial fibrillation	128,666 (15.5)	10,272 (7.3)	38,100 (12.3)	45,651 (20.0)	34,643 (23.3)
5	Cerebrovascular disease	216,607 (26.2)	16,696 (11.9)	62,518 (20.2)	77,707 (34.0)	59,686 (40.2)
6	Chronic kidney disease	57,718 (7.0)	6,119 (4.3)	17,014 (5.5)	19,425 (8.5)	15,160 (10.2)
7	Diabetes	380,329 (45.9)	49,380 (35.1)	140,308 (45.3)	120,001 (52.5)	70,640 (47.5)
8	Dizziness	155,399 (18.8)	17,640 (12.5)	46,852 (15.1)	52,489 (23.0)	38,418 (25.9)
9	Dyspnoea	8,195 (1.0)	884 (0.6)	2,222 (0.7)	2,663 (1.2)	2,426 (1.6)
11	Foot problems	67,472 (8.2)	9,452 (6.7)	23,599 (7.6)	19,912 (8.7)	14,509 (9.8)
12	Fragility fracture	71,864 (8.7)	5,522 (3.9)	16,020 (5.2)	25,102 (11.0)	25,220 (17.0)
13	Hearing impairment	81,373 (9.8)	10,743 (7.6)	29,373 (9.5)	26,115 (11.4)	15,142 (10.2)
14	Heart failure	190,246 (23.0)	14,384 (10.2)	49,168 (15.9)	65,680 (28.7)	61,014 (41.1)
15	Heart valve disease	58,036 (7.0)	4,435 (3.2)	16,658 (5.4)	21,126 (9.2)	15,817 (10.6)
16	Housebound	6,960 (0.8)	529 (0.4)	1,402 (0.5)	2,368 (1.0)	2,661 (1.8)
17	Hypertension	500,635 (60.5)	54,755 (38.9)	172,600 (55.7)	161,799 (70.8)	111,481 (75.0)
18	Hypotension/syncope	134,872 (16.3)	15,026 (10.7)	39,661 (12.8)	45,680 (20.0)	34,505 (23.2)
19	Ischaemic heart disease	170,741 (20.6)	14,586 (10.4)	51,336 (16.6)	59,571 (26.1)	45,248 (30.5)
20	Memory and cognitive problems	148,839 (18.0)	18,793 (13.3)	36,012 (11.6)	47,556 (20.8)	46,478 (31.3)
21	Mobility and transfer problems	53,225 (6.4)	5,195 (3.7)	14,048 (4.5)	17,847 (7.8)	16,135 (10.9)
22	Osteoporosis	171,111 (20.7)	10,054 (7.1)	47,081 (15.2)	65,299 (28.6)	48,677 (32.8)
23	Parkinsonism and tremor	52,106 (6.3)	7,096 (5.0)	14,619 (4.7)	19,164 (8.4)	11,227 (7.6)
24	Peptic ulcer	446,850 (54.0)	59,406 (42.2)	155,248 (50.1)	140,354 (61.4)	91,842 (61.8)
25	Peripheral vascular disease	142,739 (17.2)	13,021 (9.2)	48,320 (15.6)	50,987 (22.3)	30,411 (20.5)
26	Polypharmacy	356,656 (43.1)	30,576 (21.7)	101,581 (32.8)	130,026 (56.9)	94,473 (63.6)
27	Requirement for care	6,960 (0.8)	529 (0.4)	1,402 (0.5)	2,368 (1.0)	2,661 (1.8)

	Deficit	Overall N = 827,744 N (%)	50–64 years N = 140,774 N (%)	65–74 years N = 309,771 N (%)	75–84 years N = 228,628 N (%)	≥85 years N=148,571 N (%)
28	Respiratory disease	296,158 (35.8)	43,931 (31.2)	101,177 (32.7)	86,952 (38.0)	64,098 (43.1)
29	Skin ulcer	60,068 (7.3)	7,854 (5.6)	17,137 (5.5)	17,734 (7.8)	17,343 (11.7)
30	Sleep disturbance	212,043 (25.6)	23,962 (17.0)	65,990 (21.3)	72,298 (31.6)	49,793 (33.5)
31	Social vulnerability	3,562 (0.4)	1,027 (0.7)	1,638 (0.5)	652 (0.3)	245 (0.2)
32	Thyroid disease	86,782 (10.5)	13,649 (9.7)	30,878 (10.0)	26,430 (11.6)	15,825 (10.7)
33	Urinary incontinence	31,231 (3.8)	2,074 (1.5)	7,405 (2.4)	11,841 (5.2)	9,911 (6.7)
34	Urinary system disease	118,283 (14.3)	13,888 (9.9)	38,284 (12.4)	38,441 (16.8)	27,670 (18.6)
35	Visual impairment	216,959 (26.2)	22,517 (16.0)	77,858 (25.1)	74,436 (32.6)	42,148 (28.4)
36	Weight loss and anorexia	79,906 (9.7)	9,170 (6.5)	21,961 (7.1)	26,799 (11.7)	21,976 (14.8)



Supplemental Figure 2-1 Kaplan–Meier survival curves for mortality for up to 53 months by age group.

eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score



Supplemental Figure 2-2 Cumulative incidence functions of long-term care service use for up to 53 months by age group.

eFI, Electronic Frailty Index; HFRS, Hospital Frailty Risk Score

Chapter 3. Association between Coding-based Frailty and Clinical Outcomes

Summary

Background: In older patients with atrial fibrillation (AF), frailty is frequently prevalent. However, the prognostic value of frailty for adverse events after initiation of oral anticoagulants (OACs) is unclear. We assessed whether frailty at the time of OAC initiation is associated with subsequent bleeding or embolic events.

Design and Settings: Community-based cohort study using an universal administrative claims database incorporating primary and hospital care records in Shizuoka, Japan.

Methods: We extracted patients aged ≥65 years with non-valvular AF who initiated OAC between 2012-2018**.** Frailty was assessed using the electronic frailty index (eFI). The association between frailty and bleeding event, as well as ischemic stroke/transient ischemic attack (TIA) were evaluated using Fine–Gray and restricted cubic spline model.

Results: Among 12,585 AF patients, 7.8% were categorized as fit, 31.5% as mildly frail, 34.8% as moderately frail, and 25.9% as severely frail. The risk of bleeding was associated with a higher eFI (adjusted subdistribution hazard ratio [95% confidence interval] versus fit, mild frailty: 1.15 [1.02–1.30]; moderate frailty: 1.42 [1.24–1.61]; severe frailty: 1.86 [1.61–2.15]), while the association was weaker for ischemic stroke/TIA. The spline models demonstrated that the relative hazard for bleeding increased steeply with increasing eFI.

Interpretation: Patients with frailty who initiate OAC therapy have a higher risk of bleeding, highlighting the importance of discussing this increased risk with AF patients who have frailty and assessing frailty at the time of OAC initiation.

Introduction

Atrial fibrillation (AF) is associated with a substantial risk of systemic embolic events,[61,62] and the risk is particularly high in older AF patient.[62,63] Oral anticoagulants (OACs) have been shown to reduce the embolic complication rate, and their use is strongly supported in the international clinical practice guidelines.[64,65] However, they remain under-used in clinical practice, particularly for frail patients,[66–68] despite the recommendations to use OAC regardless of the frailty status.[69,70]

The efficacy of OACs is assumed to be achieved at the expense of an increased risk of bleeding. Frailty is an age-related cumulative decline in physiological systems and is known to be associated with higher risk of falls, fractures, gastrointestinal bleeding, and cerebral trauma, frequently precludes initiation of OAC.[1,71] However, the precise association between frailty and subsequent embolic or bleeding events among AF patients treated with OACs in the community population is unknown. Previous studies that evaluated the association of frailty with outcomes in AF patients on OACs were predominantly small-scale studies or their assessments were not made in community settings.[72–74] Furthermore, there are gaps between knowledge from RCTs and real-world clinical practice,[75] since RCTs often include patients with fewer chronic medical conditions, less frailty, and lower risk for adverse outcomes than the real-world population.

We therefore investigated the association between frailty and clinical outcomes among AF patients treated with OAC in a large community-based cohort derived from administrative claims data, incorporating primary and hospital care records, in Japan.

Methods

Study design and data source

We conducted a cohort study using the Shizuoka Kokuho Database (SKDB) between April 2012 and September 2018.[28] The SKDB is an administrative claims database of beneficiaries in the municipal government insurance program (national health insurance and late-stage medical care system for the elderly) in Shizuoka Prefecture, Japan. All data in the SKDB were anonymized. Among all residents aged <75 years, 22.3% are enrolled in the national health insurance (e.g., self-employed and unemployed), and all residents aged ≥75 years old are enrolled in the late-stage medical care system for the elderly. We utilized basic information (i.e., age, sex, date of death) and health insurance claims (e.g., monthly claims for patients' diagnoses, procedures, laboratory tests ordered, drugs dispensed, and dates of hospital admissions) from the SKDB. This study was approved by the Ethnic Committee of Shizuoka Graduate University of Public Health (Shizuoka, Japan) (#SGUPH_2021_001_006).

Study population and follow-up

We selected patients with non-valvular AF who initiated OAC therapy (warfarin or direct oral anticoagulants [DOACs]: apixaban, dabigatran, edoxaban, or rivaroxaban) between April 2013 and March 2018. We designated the month of dispensation of the first OAC as the 'index month'. We included patients aged ≥65 years who had initiated OAC monotherapy in an outpatient setting and had at least one record of AF diagnosis (International Classification of Diseases (ICD)-10 code I48x but not the disease code for valvular AF or AF after surgery) in the preceding 12 months. We excluded patients who had been continuously enrolled in an insurance plan for <12 months (baseline period) before OAC initiation, or with alternate potential indications for OAC therapy besides non-valvular AF based on prior diagnoses of the following conditions: venous thromboembolism, rheumatic mitral valve disease,

intracardiac thrombosis, mechanical or bioprosthetic heart valve, mitral valve repair, or valvular AF (Supplemental Table 3-1). The follow-up of outcomes started in the index month (first OAC prescription). Each patient was censored at the occurrence of the outcome of interest, death, the end of enrolment in the plan, or the end of the study period (September 2018), whichever came first (Figure 3-1). Embolic or bleeding events were not competing risks for each outcome of interest. For example, if bleeding occurred before an embolic event, the patient was not censored at the time of bleeding but at the time of the embolic event.

Patient characteristics

Information on the demographics (i.e., sex, age) of each patient was extracted from the insurance subscriber list. We assessed the patients' baseline comorbidities and previous medication use using the recorded diagnoses and the dispensation claims during the 12 months preceding the index month and in the index month (Supplemental Table 3-2 and Supplemental Table 3-3). We also collected data on the daily dose of DOAC in the index month among patients initiating DOAC therapy. Drug dosing was classified as reduced dose (apixaban, 2.5 mg BID; dabigatran, 110 mg BID; edoxaban, 30 mg QD; rivaroxaban; 10 mg QD) or standard dose (apixaban, 5 mg BID; dabigatran, 150 mg BID; edoxaban, 60 mg QD; rivaroxaban, 15 mg QD). The approved dose of rivaroxaban in Japan was 10 mg once daily for patients with a creatinine clearance rate of 15 to 49 ml/min or 15 mg once daily for patients with a creatinine clearance rate of ≥50 ml/min, based on pharmacokinetic modeling data and the results of the J-ROCKET AF trial.[76] Dose data on patients initiated with neither the standard nor the reduced dose were treated as missing.

We assessed the risk scores for bleeding and thromboembolism using the HAS-BLED scores and CHA_2DS_2-VASc scores, respectively, based on the diagnosis claims recorded in the index month and the preceding 12 months (Supplemental Table 3-4 and Supplemental Table 3-5). The labile international normalized ratio, a component of the HAS-BLED score, was excluded from the calculation because this datum was unavailable in

SKDB.

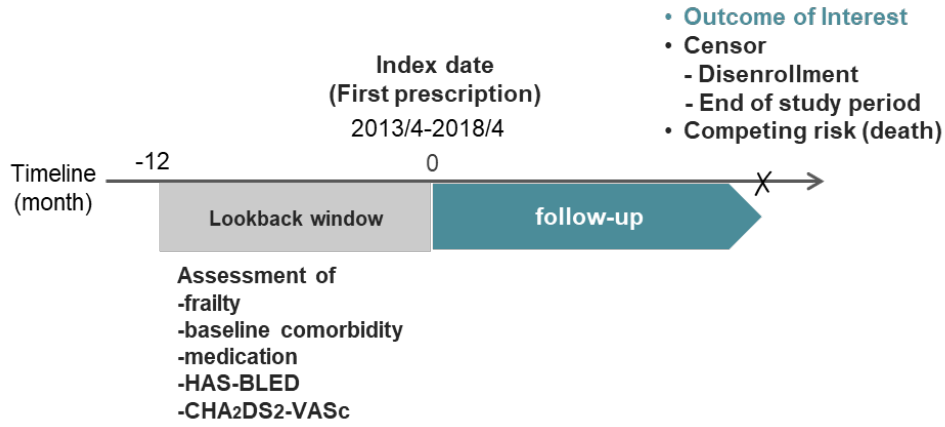


Figure 3-1 Study design timeline

Frailty assessment

We evaluated the patient's frailty using the electronic Frailty Index (eFI).[19] The eFI is a coding-based algorithm based on the cumulative deficit model as the theoretical framework. This algorithm was developed from electronic health records in the United Kingdom. The cumulative deficit model is an accumulation of age-related deficits: signs, symptoms, diseases, disabilities and polypharmacy. The eFI was validated for the relevant outcomes (e.g,, mortality, nursing home admission and frailty phenotype). Because one of the 36 variables included in the index (i.e., falls) is not available in the Japanese claims coding system, we calculated the score based on 35 variables using the records of diagnoses, according to the ICD-10 codes, and the dispensation records for the previous 12 months and the index month (Supplemental Table 3-6).[77] The eFI is used to categorize patients into four groups: fit (eFI score of 0–0.12), mildly frail (> 0.12–0.24), moderately frail (> 0.24–0.36), and severely frail (> 0.36).[19]

Outcomes

The outcomes of interest were bleeding events and embolic events defined using the diagnostic codes. The primary bleeding outcome was a composite outcome of major

bleeding and minor bleeding. Major bleeding was defined as events including intracranial bleeding, gastrointestinal bleeding, or bleeding with shock, in an inpatient setting. Minor bleeding was defined as other bleeding events that not classified as major bleeding, recorded in an inpatient or an outpatient setting (Supplemental Table 3-7). The embolic outcome was a secondary outcome, including ischemic stroke and transient ischemic attack (TIA), diagnosed in an inpatient setting. Major bleeding was also assessed as the secondary outcome.

Statistical analysis

To describe patients' characteristics and the prevalence of the 35 deficits evaluated to calculate eFI, continuous variables are presented as medians and interquartile ranges (IQRs), and categorical variables as numbers and percentages. There were no missing data except for data on the dose category. To assess the associations between the bleeding and thromboembolism risk scores and frailty, we tabulated and displayed the HAS-BLED and CHA_2DS_2-VASc scores according to the eFI groups. Spearman's correlation coefficients of two risk scores with eFI were also estimated. We compared the frequencies of the deficits used to calculate eFI across the categories of both these scores (HAS-BLED and CHA_2DS_2-VASc). We assessed the percentage of DOAC patients who initiated treatment with a reduced-dose regimen according to the eFI groups.

We evaluated the outcomes using cumulative incidence functions for up to 64 months and compared the curves across eFI categories with Gray's test. Death was considered a competing risk. We evaluated the association between frailty and outcomes using univariable and multivariable Fine–Gray subdistribution hazard models, after adjustment for the following covariates : sex, baseline comorbidities (cancer, chronic kidney disease, chronic obstructive pulmonary disease, depression, diabetes mellitus, heart failure, hypertension, liver disease, peptic ulcer, peripheral arterial disease, previous admission for myocardial infarction, previous admission for bleeding, previous admission for stroke,

rheumatoid arthritis, and sleep apnoea syndrome) and the use of medications (antihypertensive drugs, antidiabetic drugs, nitrates, statins, non-steroidal anti-inflammatory drugs [NSAIDs], antiarrhythmic drugs, antiplatelet drugs, other lipid-lowering drugs, antidepressants, and antacids). Because our intention was to investigate whether coding-based frailty is associated with outcomes, age was not included in the adjusted model in the main analysis. However, an adjustment for age was made in a supplementary analysis. We also conducted an analysis adjusting for sex, comorbidities (cancer, chronic obstructive pulmonary disease, depression, liver disease, previous admission for bleeding, previous admission for stroke, rheumatoid arthritis, and sleep apnoea syndrome), and medication use (statins, NSAIDs, other lipid-lowering drugs, and antidepressants) with the exception of eFI components that were not related to stroke.

To depict the associations between eFI as a continuous variable and the outcomes, we constructed restricted cubic spline models with four knots at the quintile points, adjusted for sex, baseline comorbidities, and the use of medications. We used an eFI score of 0.12, which is the threshold between fit and mild frailty, as the reference point. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

A total of 12,585 patients with previously diagnosed AF initiating OAC therapy (median [IQRs] age, 80 [72–85] years; 45.4% female) were identified (Figure 3-2). 980 (7.8%) were categorized as fit, 3967 (31.5%) as mildly frail, 4385 (34.8%) as moderately frail, and 3253 (25.9%) as severely frail (Table 3-1). Of these patients, 17.8% were prescribed warfarin, 23.6% apixaban, 10.0% dabigatran, 15.1% edoxaban, and 33.5% rivaroxaban. Apixaban was more frequently prescribed for the severely frail (27.8%) than for those with lower eFI scores. Compared with patients who are fit, patients with severe frailty were more likely to have a

high bleeding risk (HAS-BLED ≥ 3: fit 36.7% vs severely frail 95.3%) or high thromboembolism risk (CHA_2DS_2-VASc ≥ 4: fit 35.0% vs severely frail 98.9%) (Figure 3-3). CHA_2DS_2-VASc score has a stronger correlation with eFI score (Spearman's $\rho = 0.63$, 95% CI 0.62-0.64) than HAS-BLED score (Spearman's $\rho = 0.54$; 95% CI, 0.53-0.55).

Table 3-1 Baseline characteristics of 12,585 OAC initiators among patients with atrial fibrillation

		eFI categories			
	Total (n=12,585)	Fit (n=980)	Mild (n=3967)	Moderate (n=4385)	Severe (n=3253)
Follow-up, months	31 (17,47)	35 (20,49)	33 (18,48)	32 (17,47)	28 (15,43)
Age, years	80 (72, 85)	72 (69, 81)	74 (70, 83)	81 (7, 86)	83 (78, 87)
Age, groups					
- 65–74, n (%)	4799 (38.1)	619 (63.2)	2025 (51.1)	1484 (33.8)	671 (20.6)
- 75–84, n (%)	4222 (33.6)	227 (23.2)	1170 (29.5)	1580 (36.0)	1245 (38.3)
- ≥85, n (%)	3564 (28.3)	134 (13.7)	772 (19.5)	1321 (30.1)	1337 (41.1)
Sex					
- Male, n (%)	6872 (54.6)	678 (69.2)	2509 (63.3)	2307 (52.6)	1378 (42.4)
- Female, n (%)	5713 (45.4)	302 (30.8)	1458 (36.8)	2078 (47.4)	1875 (57.6)
Type of OAC					
- Warfarin, n (%)	2245 (17.8)	189 (19.3)	709 (17.9)	745 (17.0)	602 (18.5)
- Apixaban, n (%)	2974 (23.6)	172 (17.6)	849 (21.4)	1050 (24.0)	903 (27.8)
- Dabigatran, n (%)	1258 (10.0)	126 (12.9)	400 (10.1)	449 (10.2)	283 (8.7)
- Edoxaban, n (%)	1895 (15.1)	142 (14.5)	566 (14.3)	667 (15.2)	520 (16.0)
- Rivaroxaban, n (%)	4213 (33.5)	351 (35.8)	1443 (36.4)	1474 (33.6)	945 (29.1)
Baseline comorbidities					
Cancer, n (%)	4531 (36.0)	189 (19.3)	1109 (28.0)	1608 (36.7)	1625 (50.0)
Chronic kidney disease, n (%)	726 (5.8)	8 (0.8)	81 (2.0)	228 (5.2)	409 (12.6)
COPD, n (%)	1524 (12.1)	27 (2.8)	265 (6.7)	575 (13.1)	657 (20.2)
Depression, n (%)	737 (5.9)	2 (0.2)	68 (1.7)	216 (4.9)	451 (13.9)
Diabetes mellitus, n (%)	8654 (68.8)	269 (27.5)	2399 (60.5)	3252 (74.2)	2734 (84.1)
Heart failure, n (%)	8498 (67.5)	263 (26.8)	2246 (56.6)	3211 (73.2)	2778 (85.4)
Hypertension, n (%)	10304 (81.9)	580 (59.2)	2997 (75.6)	3735 (85.2)	2992 (92.0)
Liver disease, n (%)	3776 (30.0)	150 (15.3)	947 (23.9)	1419 (32.4)	1260 (38.7)
Peptic ulcer, n (%)	2977 (23.7)	46 (4.7)	554 (14.0)	1077 (24.6)	1300 (40.0)
Peripheral arterial disease, n (%)	2362 (18.8)	16 (1.6)	354 (8.9)	886 (20.2)	1106 (34.0)
Previous admission for MI, n (%)	74 (0.6)	1 (0.1)	5 (0.1)	17 (0.4)	51 (1.6)
Previous admission for bleeding, n (%)	259 (2.1)	0 (0.0)	28 (0.7)	100 (2.3)	131 (4.0)
Previous admission for stroke, n (%)	315 (2.5)	5 (0.5)	48 (1.2)	87 (2.0)	175 (5.4)
Rheumatoid arthritis, n (%)	613 (4.9)	10 (1.0)	88 (2.2)	195 (4.5)	320 (9.8)
SAS, n (%)	186 (1.5)	2 (0.2)	32 (0.8)	61 (1.4)	91 (2.8)
Medication use					
Antihypertensives, n (%)	9770 (77.6)	575 (58.7)	2908 (73.3)	3530 (80.5)	2757 (84.8)
Anti-diabetic drugs, n (%)	1881 (15.0)	68 (6.9)	524 (13.2)	710 (16.2)	579 (17.8)
Nitrates, n (%)	1352 (10.7)	15 (1.5)	223 (5.6)	486 (11.1)	628 (19.3)
Statins, n (%)	3512 (27.9)	139 (14.2)	930 (23.4)	1347 (30.7)	1096 (33.7)
NSAIDs, n (%)	5390 (42.8)	205 (20.9)	1327 (33.5)	1920 (43.8)	1938 (59.6)
Anti-arrhythmic drugs, n (%)	2797 (22.2)	222 (22.7)	826 (20.8)	964 (22.0)	785 (24.1)
Anti-platelet drugs, n (%)	3510 (27.9)	75 (7.7)	776 (19.6)	1309 (29.9)	1350 (41.5)
Other lipid-lowering drugs, n (%)	741 (5.9)	35 (3.6)	191 (4.8)	294 (6.7)	221 (6.8)
Antidepressants, n (%)	1136 (9.0)	11 (1.1)	163 (4.1)	396 (9.0)	566 (17.4)
Antacid, n (%)	5613 (44.6)	110 (11.2)	1153 (29.1)	2130 (48.6)	2220 (68.2)
HAS-BLED	3 (3,4)	2 (2,3)	3 (2,4)	4 (3,4)	4 (4,5)
CHA_2DS_2-VASc	5 (4,6)	3 (2,4)	4 (4,5)	6 (5,6)	7 (6,8)

Values are medians (Q25, Q75) for continuous variables; numbers and percentages for categorical variables.
OAC=oral anticoagulant; eFI=Electronic Frailty Index; COPD=chronic obstructive pulmonary disease; MI=myocardial infarction; SAS=sleep apnea syndrome; NSAIDs=Non-steroidal anti-inflammatory drugs;
CHA_2DS_2-VASc=congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, stroke, valvular disease, age 65-74; HAS-BLED=age>65 years, hypertension, abnormal renal and liver function, prior stroke, bleeding history or predisposition, drugs/alcohol concomitantly, and labile international normalized ratio.

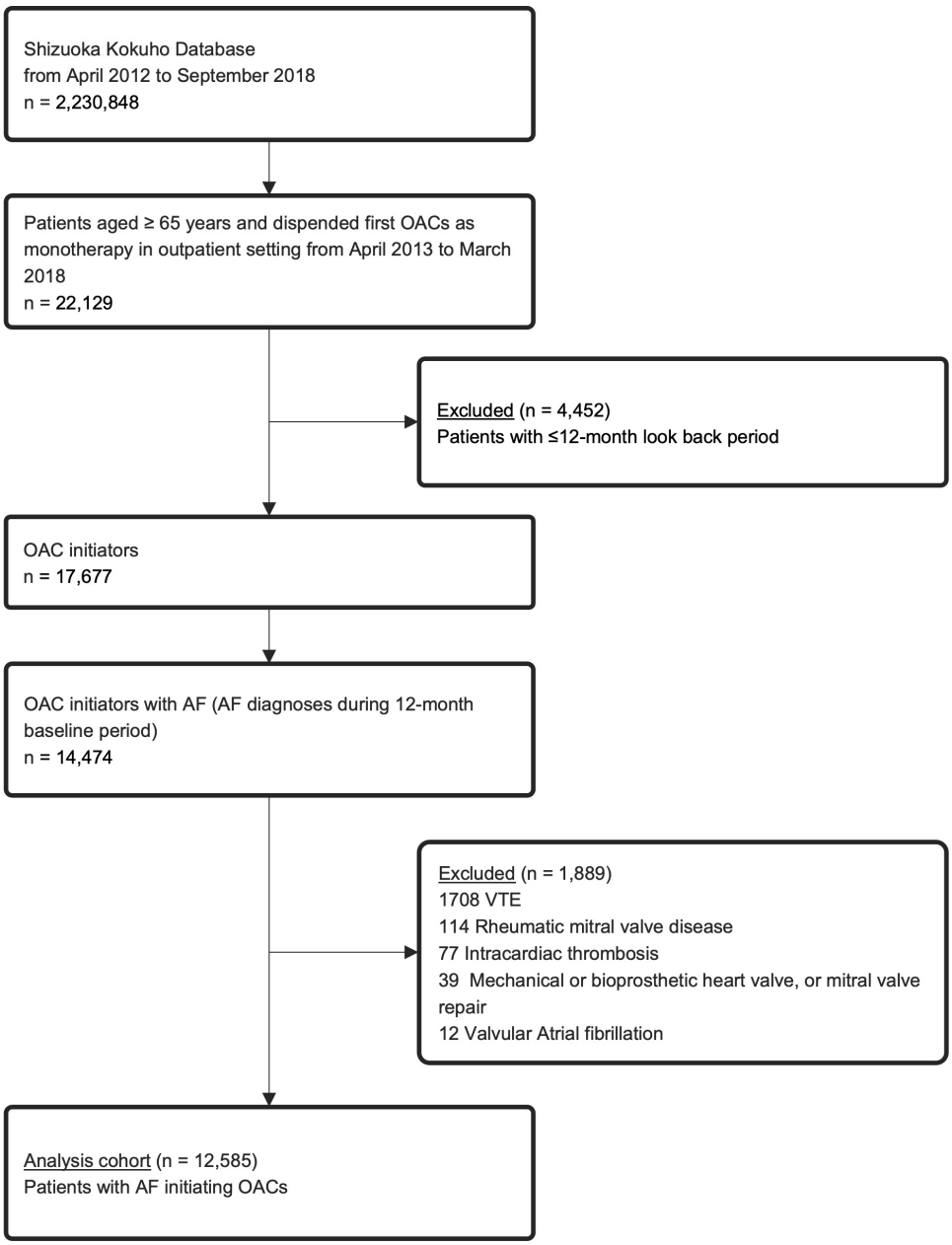


Figure 3-2 Cohort flow chart

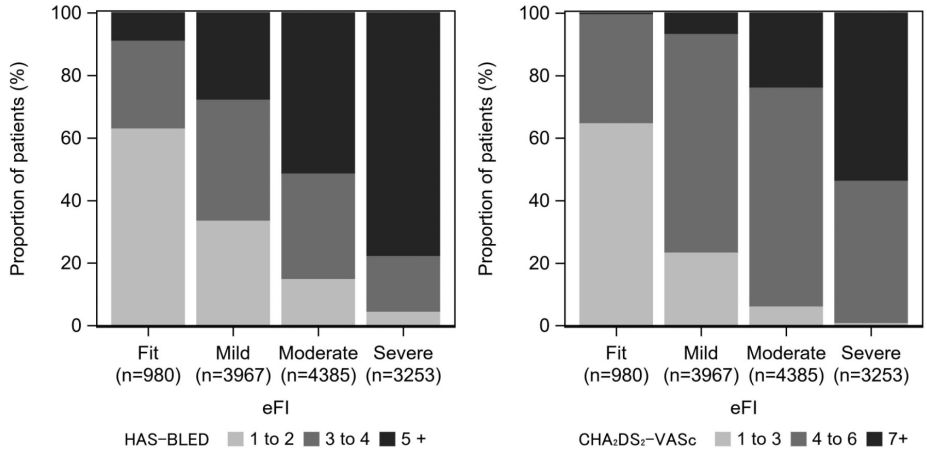


Figure 3-3 HAS-BLED and CHA2DS2-VASc scores by eFI categories

The frequency of each deficit used to calculate eFI was higher among those in the severely frail category (Supplemental Table 3-8). The prevalence of each of the 35 deficits used to calculate eFI, not only those included in the bleeding and stroke risk scores (e.g., hypertension, diabetes mellitus, and cerebrovascular disease) but also frailty-specific deficits (e.g., activity limitation, fragility fracture, weight loss, and anorexia) was more prevalent in patients with higher risk scores (Supplemental Figure 3-1 and Supplemental Figure 3-2). Patients in the higher eFI categories were more likely to receive reduced-dose DOACs than fit patients (Figure 3-4).

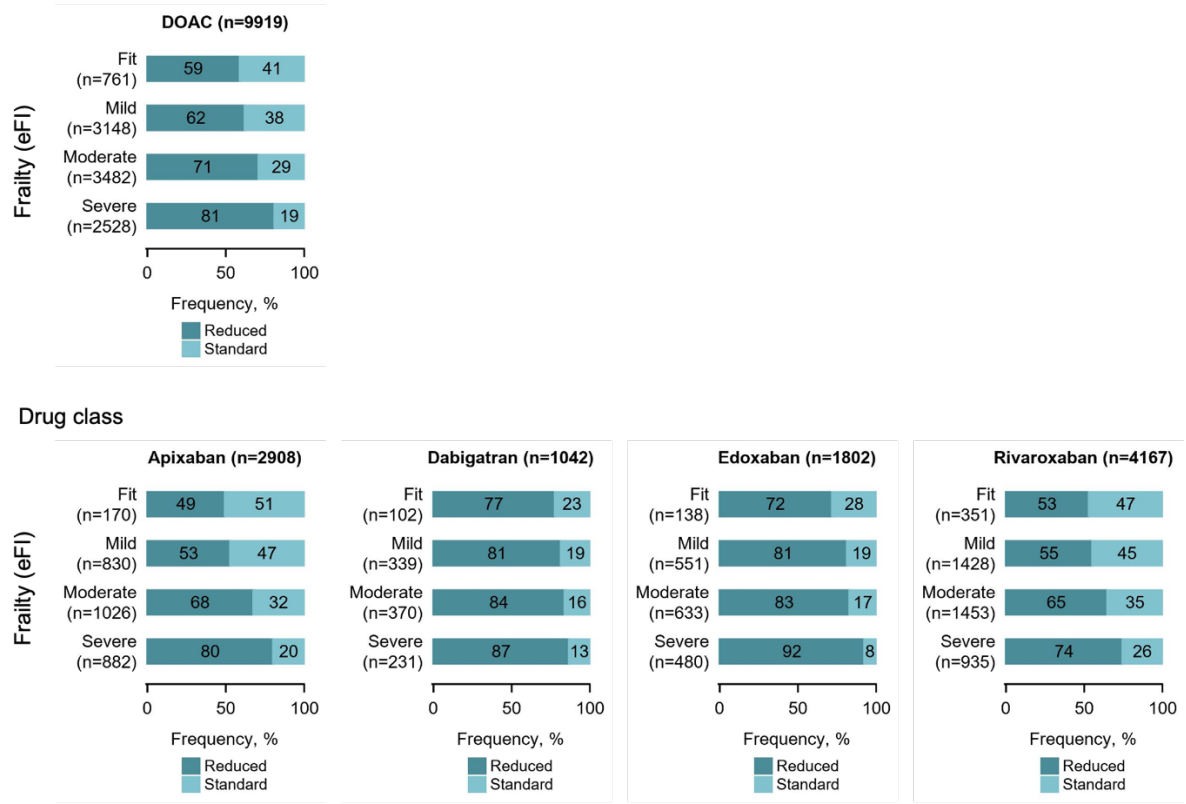


Figure 3-4 Associations between frailty and DOAC dose

Incidence of clinical outcomes

During follow-up (median 31 months, 25th–75th percentiles 17–47 months), 5, 226 bleeding events and 493 ischemic stroke/TIA events occurred, giving annual event rates of 15.5 and 1.5 per 100 patient-years, respectively (Table 3-2). The event rate was 1.2 per 100 patient-years for major bleeding. The overall 5-year cumulative incidence was 53.1% (95% confidence interval [CI] 51.6%–54.5%) for bleeding, 5.7% (4.9%–6.5%) for ischemic stroke/TIA, and 5.1% (4.4%–5.8%) for major bleeding (Supplemental Figure 3-3).

The annual event rates among patients who were fit and severely frail were 11.2 and 21.0 per 100 patient-years for bleeding, respectively; 1.0 and 1.7 per 100 patient-years for ischemic stroke/TIA, respectively; and 0.7 and 1.5 per 100 patient-years for major bleeding, respectively (Table 3-2). Figure 3-5 shows the cumulative incidence functions for the primary and secondary bleeding outcomes compared across the frailty categories. The cumulative

incidence curves for the frailty categories were substantially separated for the bleeding end points, but minimally different for ischemic stroke/TIA. For major bleeding, the cumulative incidence curves for the moderately and severely frail patients differed only slightly, but differed considerably from the curve for fit patients.

Table 3-2 Summary of clinical outcomes and their association with frailty

Outcome	Events (n)	Event rate[a] (95% CI)	Unadjusted sHR (95% CI)	Adjusted[b] sHR (95% CI)
Ischaemic stroke/TIA				
Total	493	1.5 (1.3–1.6)	-	-
Fit	28	1.0 (0.7–1.4)	Ref	Ref
Mild	155	1.4 (1.2–1.6)	1.40 (0.94–2.09)	1.27 (0.83–1.94)
Moderate	175	1.5 (1.3–1.7)	1.43 (0.96–2.13)	1.25 (0.80–1.97)
Severe	135	1.7 (1.4–2.0)	1.55 (1.03–2.32)	1.26 (0.77–2.06)
Bleeding				
Total	5226	15.5 (15.1–15.9)	-	-
Fit	318	11.2 (10.1–12.6)	Ref	Ref
Mild	1414	12.8 (12.1–13.5)	1.15 (1.02–1.30)	1.15 (1.02–1.30)
Moderate	1826	15.4 (14.7–16.1)	1.44 (1.28–1.62)	1.42 (1.24–1.61)
Severe	1668	21.0 (20.0–22.1)	1.98 (1.76–2.23)	1.86 (1.61–2.15)
Major bleeding				
Total	419	1.2 (1.1–1.4)	-	-
Fit	21	0.7 (0.5–1.1)	Ref	Ref
Mild	114	1.0 (0.9–1.2)	1.37 (0.86–2.18)	1.30 (0.81–2.09)
Moderate	161	1.4 (1.2–1.6)	1.76 (1.12–2.77)	1.61 (0.98–2.63)
Severe	123	1.6 (1.3–1.8)	1.87 (1.18–2.97)	1.61 (0.93–2.80)
Competing event (all-cause death)				
Total	2027	6.0 (5.8–6.3)	-	-
Fit	94	3.3 (2.7–4.1)	-	-
Mild	453	4.1 (3.7–4.5)	-	-
Moderate	711	6.0 (5.6–6.4)	-	-
Severe	769	9.7 (9.0–10.4)	-	-

TIA=transient ischaemic attack. sHR=subdistribution hazard ratio
[a]Event rate per 100 patient-years.
[b]Models adjusted for sex, medical history, and medications.

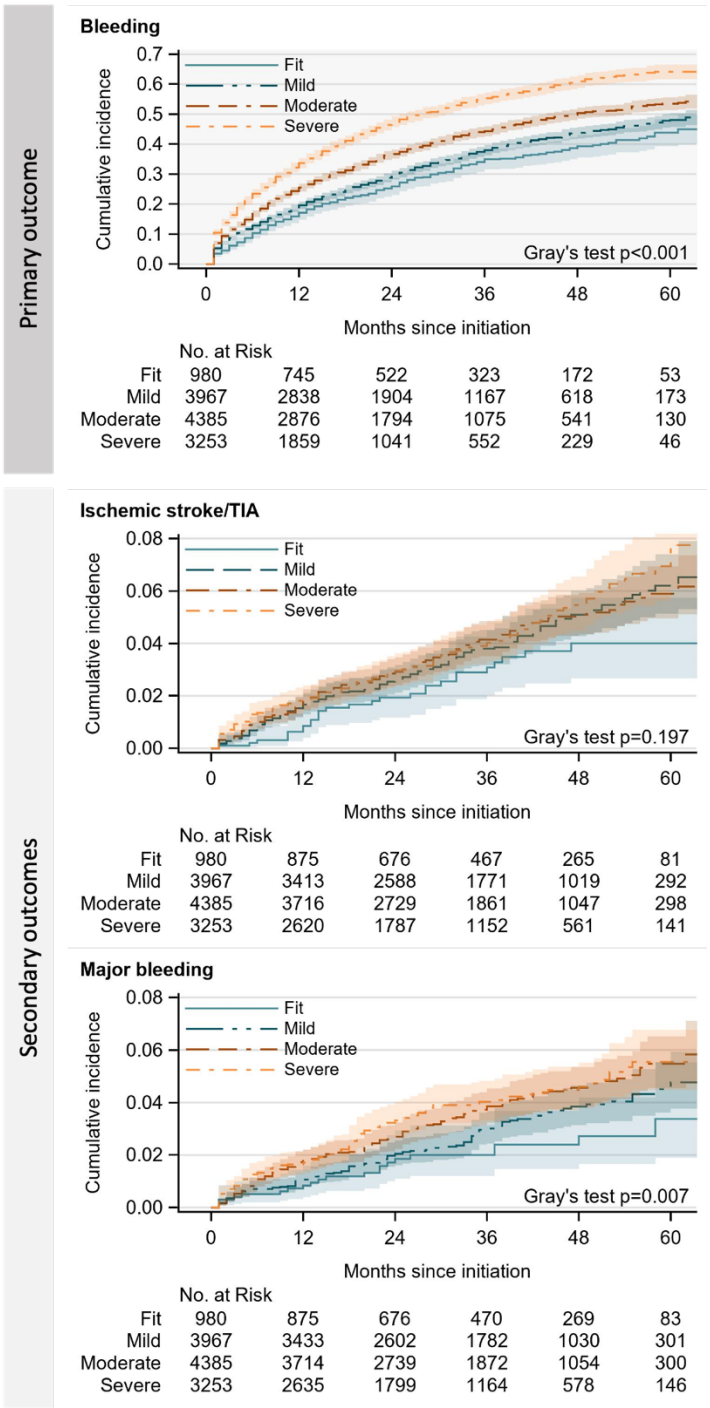


Figure 3-5 Cumulative incidence of outcomes stratified by eFI categories

Note: Shaded bands indicated 95% confidence intervals.

Associations between frailty and clinical outcomes

After adjustment for sex, baseline comorbidities, and medications, the risk of bleeding was associated with an increased eFI score with adjusted subdistribution hazard ratios (sHRs) of 1.15 (95% CI, 1.02–1.30) in mild frailty; 1.42 (1.24–1.61) in moderate frailty; and 1.86 (1.61–2.15) in severe frailty compared with fit patients. On the other hand, the association of frailty was weaker for ischaemic stroke/TIA (adjusted sHR [95% CI] comparing fit, mild frailty: 1.27 [0.83–1.94]; moderate frailty: 1.25 [0.80–1.97]; and severe frailty: 1.26 [0.77–2.06]) (Table 3-2). For the secondary bleeding outcome, we observed an upward trend in the sHR with increased eFI severity (adjusted sHR: mild frailty, 1.30 [0.81–2.09]; moderate frailty, 1.61 [0.98–2.63]; severe frailty, 1.61 [0.93–2.80]). An adjusted model, including age, showed similar results, except for major bleeding (Table 3-3). When not adjusting age and indicators of eFI, frailty was associated with ischemic stroke/TIA. (Table 3-4) The spline curves were consistent with these results: patients with lower eFI scores had a lower relative subdistribution hazard for bleeding, and the relative subdistribution hazard increased steeply with increasing eFI (Figure 3-6).

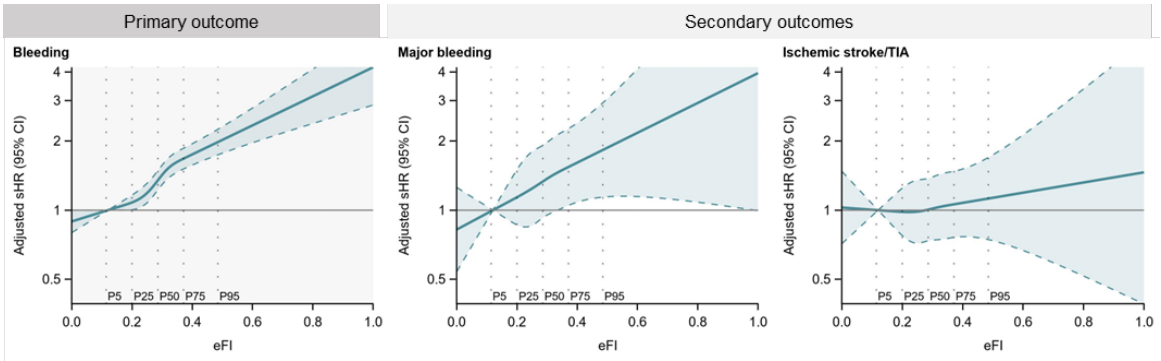


Figure 3-6 Associations between eFI and outcomes

Note: Model is adjusted for sex, medical history, and medications. Subdistribution hazard ratios with 95% confidence interval are plotted. An eFI score of 0.12 (cut-off score between fit and mild frailty) is the reference standard. Bleeding events are defined as any outpatient or inpatient bleeding event. The vertical dotted lines show thresholds for percentiles of eFI value. Abbreviations: eFI, electronic frailty index; TIA, transient ischaemic attack; DOAC, non-vitamin K oral anticoagulant; HR, hazard ratio; CI, confidence interval

Table 3-3 Association between frailty and outcomes after adjustment for age, sex, baseline comorbidities and medication use

Outcome	Adjusted[a] sHR (95% CI)
Ischemic stroke/TIA	
Fit	Ref
Mild	1.16 (0.76–1.77)
Moderate	1.01 (0.64–1.59)
Severe	0.95 (0.58–1.56)
Bleeding	
Fit	Ref
Mild	1.13 (1.00–1.28)
Moderate	1.36 (1.19–1.55)
Severe	1.75 (1.51–2.03)
Major bleeding	
Fit	Ref
Mild	1.17 (0.73–1.88)
Moderate	1.27 (0.77–2.10)
Severe	1.18 (0.67–2.07)

TIA=transient ischemic attack.
[a]Models adjusted for age, sex, medical history, and medications.

Table 3-4 Association between frailty and outcomes after adjustment for sex, baseline comorbidities and medication use with the exception of eFI components that were not related to stroke admission

Outcome	Adjusted[b] sHR (95% CI)
Ischemic stroke/TIA	
Fit	Ref
Mild	1.41 (0.94–2.12.)
Moderate	1.46 (0.97–2.19)
Severe	1.49 (0.97–2.30)
Bleeding	
Fit	Ref
Mild	1.12 (0.99–1.26)
Moderate	1.36 (1.21–1.53)
Severe	1.79 (1.58–2.03)
Major bleeding	
Fit	Ref
Mild	1.37 (0.86–2.20)
Moderate	1.76 (1.10–2.83)
Severe	1.83 (1.11–3.02)

TIA=transient ischaemic attack.
[a]Event rate per 100 patient-years.
[b]Models adjusted for sex, medical history, and medications, with the exception of eFI components that were not related to stroke admission.

Chapter discussion

In this contemporary population-based study of older AF patients aged ≥65 years who had initiated OAC therapy, the prevalence of frailty was common in the community setting, and 26% of the subjects were severely frail. We found a strong association between frailty and increased risk of bleeding. Our results suggest that the increased risk of bleeding in frail AF patients should be shared with these patients.

Overall, 26% of AF patients aged ≥65 years on OAC were severely frail, whereas 7.8% were fit. A systematic review reported that the prevalence of frailty among AF patients was 50.4%– 75.4%, depending on the age distribution of the target, and on how frailty was defined.[18] A self-reported frailty scale and other frailty indices were included among those definitions, but no frailty measure based on health-care data was reported. However, the distribution of eFI and the median age in our study were similar to those in a previous study that included AF patients in a primary care setting (median age, 80 years; severe frailty, 23%; fit, 10.5%).[71]

We identified a considerable association between frailty and an increased risk of bleeding. A higher risk of bleeding among frail AF patients has been a concern when initiating OAC,[78,79] and previous studies have reported a positive association between frailty and bleeding among AF patients. This association has been most evident in observational real-world studies.[71,72,79,80] Single-center studies form Italy[72] and Japan[79] and post hoc analysis from RCT[74] found that the frailty was associated with major bleeding defined by the International Society on Thrombosis and Hemostasis criteria. Whereas large-scale and community setting study was limited, a study from the United Kingdom using primary care records reported the association between frailty and gastrointestinal bleeding.[71] Although definitions of frailty and bleeding have variations, the result of the association between frailty and bleeding in the present study is consistent with those of previous studies. Several observational studies have reported that age is an independent predictor of stroke, but not of

bleeding among older AF patients.[81,82] Our observation of an association between frailty and bleeding indicates that frailty should be considered a bleeding risk, as great as or greater than chronological age. Although 'falls', which is also included as a predictor in eFI (but was not available in the present study), is a component of frailty, a prospective cohort study found that a high risk of falls was not associated with major bleeding.[83] Frailty, a cumulative decline in physiological systems, may contribute to bleeding rather than the high risk of fall itself.

Importantly, our study does not support the withholding or withdrawal of OAC initiation because of the high risk of bleeding. The updated ESC clinical practice guidelines (2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS))[65] states that "Frailty, comorbidities, and increased risk of falls do not outweigh the benefits of OAC given the small absolute risk of bleeding in anticoagulated elderly patients" because the net clinical benefit of OAC is considered to be much greater than any potential harm. However, to date, the precise relationship (or formal quantitative analysis) between frailty status and clinical outcome (bleeding and stroke) in patients with AF with an indication of OAC remains largely unclear.[84] There is uncertainty about the balance between the benefit (i.e., stroke prevention) and harm (i.e., bleeding events) among patients with frailty.

The crude incidence of a bleeding events is considerably high in frail patients and a large-scale study including AF patients with a broad range of clinical backgrounds is warranted. Recent small-scale RCT have shown that more bleeding events (i.e., major or clinically relevant nonmajor bleeding) occurred in frail patients than in non-frail patients (21.4% [42/185] vs 15.6% [53/289], respectively).[85] Because the safety and efficacy of OACs for very frail AF patients remain controversial, [24,25,29] our study suggests that trials are required to assess the safety and efficacy of withholding OACs after bleeding events in frail elderly patients. Moreover, frailty should be incorporated in risk assessment as a part of shared decision-making for OAC initiation.[28] The high bleeding risk in frail patients must be

recognized.

In the present study, we found that patients with moderate to severe frailty had a limited increase in the incidence of ischemic stroke/TIA compared with those who were not frail after OAC initiation. The association between frailty and stroke is controversial.[80,86] An unclear association between frailty and an increased risk of stroke among AF patients has predominantly been reported in studies conducted in primary care settings.[71,87] Other studies that have reported an association between frailty and stroke among AF patients were prospective cohort studies or post hoc analyses from RCTs.[74,88] In our study of AF patients aged ≥65 years (median age, 80 years), frailty was not strongly associated with ischemic stroke/TIA after adjustment for sex, comorbidities, and medication use. However, when not including indicators of eFI in the adjustments, frailty was found to be associated with ischemic stroke/TIA. This suggests that the association between frailty and stroke events may have been weakened by adjusting for comorbidities and concomitant medication use, which are also included in eFI.

In this study, which was based on a contemporary claims database, DOACs were more frequently prescribed (n = 10,340, 82%) than warfarin, and more frequently than in previous studies. [71,74,75,79,88,89] A recent meta-analysis of RCTs and an observational study showed that DOACs were preferable to warfarin in terms of a bleeding risk.[64,75,90] In the United States clinical practice guidelines[64], DOACs were strongly recommended as a first-line therapy in preference to warfarin among eligible patients.[64,65] The proportion of DOAC prescriptions has increased rapidly since the entry of DOACs onto the market in Japan, as well as in the United Kingdom and the United States.[91–94] The current prescription trends must be taken into consideration when interpreting our findings.

The strength of this study includes large sample size, population-based assessment in a community setting, and a relatively longer follow-up period than previous studies. To our knowledge, this study is the first study to report the impact of frailty in AF patients prescribed OAC using contemporary observational data. The present study described the

association with outcomes using categorical and continuous frailty scales, enable us to estimate the nonlinear relationship between frailty and risk of outcomes.

This study should be interpreted in the context of several limitations. First, the validity of disease codings in administrative claims databases has been has reported to have suboptimal accuracy. However, in a previous study, we found that the eFI calculated from Japanese claims accurately predicted mortality and the use of long-term care services. Second, we evaluated the association between frailty of AF patients initiating OAC treatment and outcomes, whereas most previous studies have described the associations between frailty and clinical outcomes among AF patients with or without OAC treatment. Therefore, patients with relatively more severe AF might have been included in this study (99.3% of patients had CHA_2DS_2-VASc scores ≥ 2) than in previous research. Third, we included specific disease codes based on our clinical knowledge of the events (stroke/TIA and bleeding). The codes selected for the outcome were reviewed by experts. However, the definitions have not been validated. These circumstances may have caused misclassification. In particular, clinical information on bleeding such as hemoglobin drop was not available in the claims data. Therefore, we could not define the bleeding events based on standardized criteria (e.g., criteria defined by the International Society on Thrombosis and Haemostasis).

Supplementary data

Chapter 3

Supplemental Table 3-1 List of diagnoses for exclusion

Excluded diagnoses	ICD 10 code/definition
Venous thromboembolism	I260, I269, I800, I801, I802, I803, I808, I809, I81, I820, I821, I822, I823, I828, I829, O223, O871, O882
Rheumatic mitral valve disease	I050, I051, I052, I058, I059
Intracardiac thrombosis	I513
Mechanical or bioprosthetic heart valve, or mitral valve repair	Z952, Z954
Valvular Atrial fibrillation	Disease code for valvular atrial fibrillation and atrial fibrillation after surgery I489

Supplemental Table 3-2 List of ICD-10 codes and definitions for baseline comorbidities

Comorbidity	International Classification of Diseases (ICD) codes
Cancer	Cxx
Chronic kidney disease	N181, N182, N183, N184, N185, N189
Chronic obstructive pulmonary disease	J42, J430, J431, J432, J439, J440, J441, J448, J449
Depression	F320, F321, F322, F323, F328, F329, F330, F331, F332, F333, F334, F339
Diabetes mellitus	E10, E100, E101, E102, E103, E104, E105, E106, E107, E109, E11, E110, E111, E113, E114, E115, E116, E117, E119, E13, E133, E131, E130, E134, E132, E137, E136, E139, E135, E14, E140, E141, E142, E143, E144, E145, E146, E149
Heart failure	I500, I501, I509
Hypertension	I10
Liver disease	K700, K701, K702, K703, K704, K709, K732, K739, K730, K738, K746, K741, K740, K743, K744, K745, K759, K750, K753, K754, K758, K752, K751, K768, K761, K769, K763, K765, K767, K764, K766, K760, K762
Peptic ulcer disease	K259, K257, K255, K253, K251, K250, K252, K254, K256, K269, K260, K262, K263, K261, K267, K264, K266, K265, K279, K277, K270, K284, K285, K289, K287
Peripheral arterial disease	I700, I701, I702, I7020, I7021, I708, I709, I739
Previous admission for myocardial infarction	I210, I211, I212, I213, I214, I219, I220, I221, I228, I229
Previous admission for bleeding	A162, A16, B30, D50, D62, D66, D68, D69, E07, E27, G36, G95, G96, H05, H11, H16, H20, H210, H31, H35, H40, H43, H44, H47, H60, H66, H73, H92, I21, I23, I31, I60, I61, I62, I63, I69, I78, I84, I85, I864, J04, J33, J90, J94, J95, K04, K0, K09, K12, K13, K14, K22, K25, K26, K27, K28, K29, K57, K62, K66, K76, K8, K92, L50, M25, N02, N28, N30, N32, N36, N42, N48, N50, N64, N83, N8, N89, N90, N92, N93, N939, N95, O71, O90, R04, R18, R19, R23, R31, R57, R58, S00, S01, S05, S06, S09, S10, S141, S24, S27, S30, S34, S36, S37, S39, S40, S50, S60, S70, S80, S90, T00, T06, T090, T09, T14, T79, T810, T81, T87, T90

Comorbidity	International Classification of Diseases (ICD) codes
Previous admission for stroke	I63, I630, I631, I632, I633, I634, I635, I636, I638, I639
Rheumatoid arthritis	M0690, M0691, M0692, M0693, M0694, M0695, M0696, M0697, M0698
Sleep apnoea syndrome	G473

Supplemental Table 3-3 List of WHO Anatomical Therapeutic Chemical (ATC) Classification codes for definitions of baseline medication use

Medication	WHO ATC Classification codes
Antihypertensive drugs	C07, C08, C09A, C09D
Antidiabetic drugs	A10
Nitrates	C01DA
Statins	C10AA
NSAIDs	M01A
Antiarrhythmic drugs	C01B
Antiplatelet drugs	B01AC04, B01AC22, B01AC05, B01AC06, B01AC07, B01AC23, B01AC24
Other lipid-lowering drugs	C10 (except for C10AA)
Antidepressants	N06
Antacid	A02BA, A02BC

Supplemental Table 3-4 List of ICD-10 codes and definitions for HAS-BLED risk factors

HAS-BLED risk factor	ICD-10 codes/definitions
Hypertension	I10, I119, I120, I129, I150, I151, I152, I158, I159
Abnormal renal/liver function	K702, K703, K704, K709, K730, K732, K738, K739, K740, K741, K743, K744, K745, K746, K750, K751, K752, K753, K754, K758, K759, K760, K761, K762, K763, K764, K765, K766, K767, K768, K769, N181, N182, N183, N184, N185, N189, N19, N26
Stroke	I60, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I61, I610, I611, I613, I614, I615, I616, I618, I619, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64, I740, I741, I742, I743, I744, I745, I748, I749, G459
Bleeding history or predisposition	D640, D641, D649, D648, D644, D643, D642, D551, D552, D550, D538, D510, D530, D560, D582, D518, D539, D580, D511, D564, D581, D520, D591, D532, D589, D571, D572, D573, D596, D594, D531, D561, D529, D588, D559, D599, D513, D569, D563, D500, D508, D528, D578, D509, D562, D512, D593, D519, D501, D570, D595, D592, D590, D521, D62, A162, A16, B30, D50, D62, D66, D68, D69, E07, E27, G36, G95, G96, H05, H11, H16, H20, H210, H31, H35, H40, H43, H44, H47, H60, H66, H73, H92, I21, I23, I31, I60, I61, I62, I63, I69, I78, I84, I85, I864, J04, J33, J90, J94, J95, K04, K0, K09, K12, K13, K14, K22, K25, K26, K27, K28, K29, K57, K62, K66, K76, K8, K92, L50, M25, N02, N28, N30, N32, N36, N42, N48, N50, N64, N83, N8, N89, N90, N92, N93, N939, N95, O71, O90, R04, R18, R19, R23, R31, R57, R58, S00, S01, S05, S06, S09, S10, S141, S24, S27, S30, S34, S36, S37, S39, S40, S50, S60, S70, S80, S90, T00, T06, T090, T09, T14, T79, T810, T81, T87, T90
Labile international normalized ratio	Not applicable
Elderly (≥65 years)	-
Drugs or excessive alcohol drinking	K700, K701, F102, F105, F106, F107, F100, F101, F103, F104, T513, T519, T512, T510, T511

Supplemental Table 3-5 List of ICD-10 codes and definitions for CHA2DS2-VASc risk factors

CHA2DS-VASc risk factor	ICD-10 codes/definitions
Congestive heart failure	I500, I501, I509, I110
Hypertension	I119, I120, I129, I150, I151, I152, I158, I159 Antihypertensive medications listed in Supplemental Table 3-3
Age ≥ 75 years	-
Diabetes mellitus	E10, E100, E101, E102, E103, E104, E105, E106, E107, E109, E11, E110, E111, E113, E114, E115, E116, E117, E119, E13, E130, E131, E132, E133, E134, E135, E136, E137, E139, E14, E140, E141, E142, E143, E144, E145, E146, E149 Anti-diabetic medications listed in Supplemental Table 3-3
Stroke/TIA/TE	I60, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I61, I610, I611, I613, I614, I615, I616, I618, I619, I630, I631, I632, I633, I634, I635, I636, I638, I639, I64, I740, I741, I742, I743, I744, I745, I748, I749, G459
Vascular disease	E105, E115, E135, E145, I210, I211, I212, I213, I214, I219, I220, I221, I228, I229, I420, I421, I422, I423, I424, I425, I426, I427, I428, I429, I700, I701, I702, I7020, I7021, I708, I709, I739
Age 65–74 years	-
Sex category (female)	-

Supplemental Table 3-6 List of ICD-10 codes and the definitions corresponding to variables in eFI

No.	eFI	ICD 10 code/definition
1	Activity limitation	R26, S78, S88, S98, T13.6, Y83, Z99.3, G11, G81, G82, G83, M62
2	Anaemia and haematinic deficiency	D50, D51, D52, D53, D64
3	Arthritis	M05, M06, M07, M09, M10, M11, M12, M13, M15, M16, M17, M18, M19, M31.5, M32, M33, M34, M35, M36
4	Atrial fibrillation	I44, I48, I49
5	Cerebrovascular disease	G45, G46, I6, H34
6	Chronic kidney disease	I12, I13, N01, N03, N05, N07, N08, N18, N19, N25, I77
7	Diabetes	E10.9, E11.9, E12.9, E13.9, E14.9
8	Dizziness	I95, R55, R42, E86, H81, H82, H83
9	Dyspnoea	R06
10	Falls	Not available
11	Foot problems	B353, G575, G576, L60, M201, M202, M203, M204, M205, M206, M213, M214, M215, M216, M722, M766, M773, M775, S90, S91, S92, S93, S94, S96, S97, S99, Q66
12	Fragility fracture	M484, S22, S32, S33, S42, S43, S62, S72, S73, M485, M800, M808, M843, M847, S02, S12, S52, S82, S92
13	Hearing impairment	H833, H90, H91, G960, H60, H61, H62, H71, H73, H74, H92, H93
14	Heart failure	I11, I13, I26.0, I27, I42, I43, I50, I51, I09.9, I255
15	Heart valve disease	I05, I06, I07, I08, I34, I35, I36, I37, I390, I391, I392, I393, I394, A520, I091, I098, I38, Q230, Q231, Q232, Q233
16	Housebound	R40, Z50, Z74, Z75.5
17	Hypertension	I10, I11, I12, I13, H350
18	Hypotension/syncope	I95, R55, R42, E86
19	Ischaemic heart disease	I20, I21, I22, I23, I24, I25
20	Memory and cognitive problems	F00, F01, F02, F03, F04, F05, F06.7, G30, G31, R41, R54, F2, F3, F41, R44, R45
21	Mobility and transfer problems	R26, S78, S88, S98, T136, G11, G81, G82, G83, M62
22	Osteoporosis	M80, M81, M82
23	Parkinsonism and tremor	G122, G20, G21, G22, G23, G25, G26, G32, G35, R25
24	Peptic ulcer	K21, K25, K26, K27, K28, K29, R12
25	Peripheral vascular disease	I65, I70, I71, I72, I73, I771, K551, K558, K559, R02, Z958, Z959, I790, I792, Z958
26	Polypharmacy	≥5 drugs prescriptions for a total of ≥6 months during the baseline period
27	Requirement for care	R40
28	Respiratory disease	J45, J46, J40, J41, J42, J43, J44, J47, J60, J61, J62, J63, J64, J65, J67, J684, J70, J13, J14, J15, J16, J18, J22, J20, J90, J961, J980
29	Skin ulcer	I83, I98, L03, L08, L89, L97, L984
30	Sleep disturbance	G47, F51
31	Social vulnerability	F1, R460, R468, Z59, Z60, Z63, Z73
32	Thyroid disease	E00, E01, E03, E04, E05, E06, E079, E890, R946
33	Urinary incontinence	N31, N393, N394, R15, R32, Z466

No.	eFI	ICD 10 code/definition
34	Urinary system disease	N30, N34, N39.0, N39.8, N39.9, R31, R33, T835
35	Visual impairment	H25, H28, H35, H40, H43, H53, H54
36	Weight loss and anorexia	E41, E43, E44, E46, E53, E55, E66, E83, E87, R53, R628, R63, R64, F500, F501, F508, F509

Supplemental Table 3-7 List of ICD-10 codes for outcomes

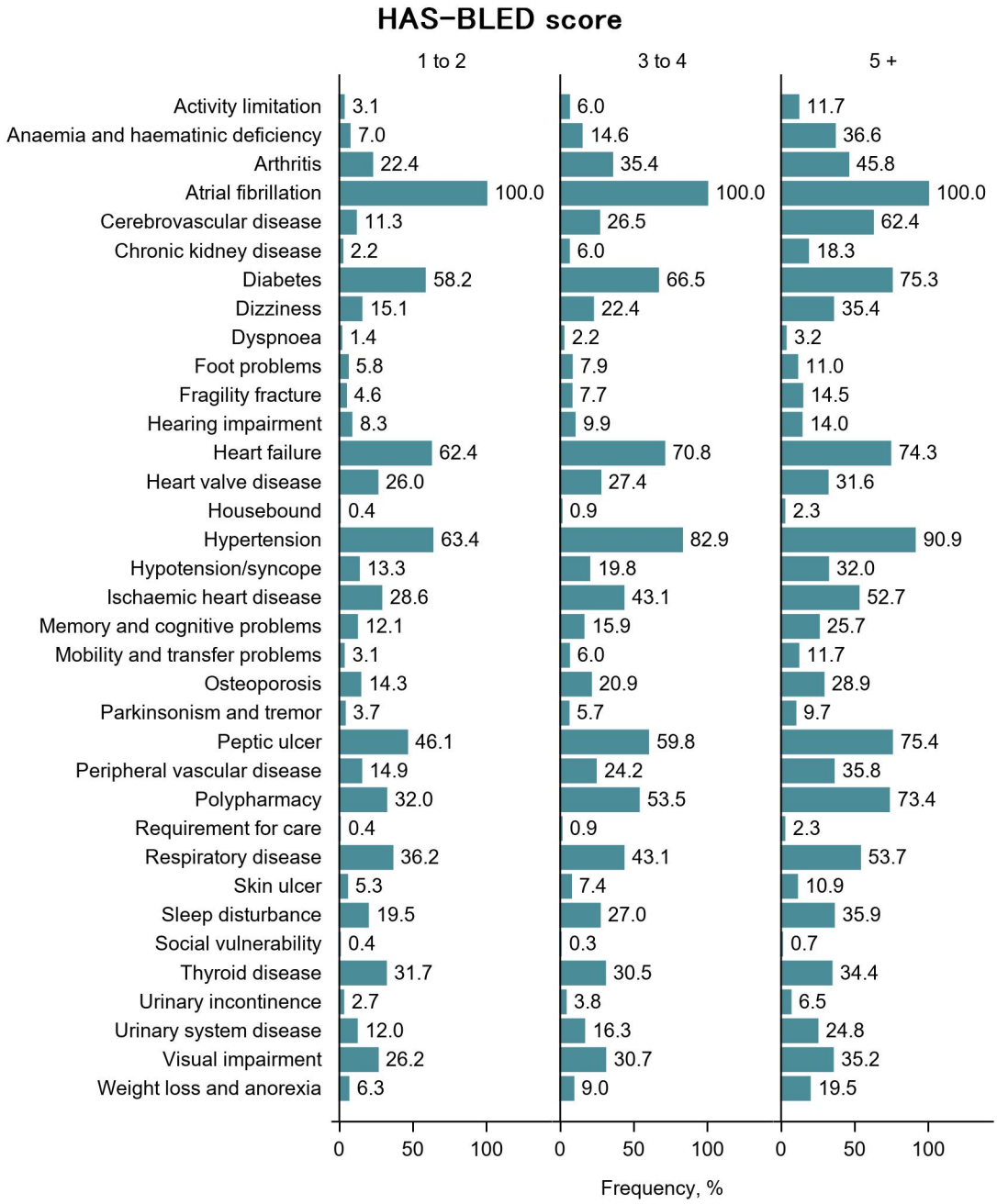
Outcomes	International Classification of Diseases (ICD) codes
Ischaemic stroke/TIA	
Ischaemic stroke	I633, I634, I635, I636, I638, I639, I64
TIA	G450, G451, G453, G454, G458, G459
Bleeding (major and minor)	A162, A165, B303, D500, D62, D66, D683, D698, D699, E078, E274, G361, G951, G968, H052, H113, H168, H208, H210, H313, H350, H356, H357, H405, H431, H448, H470, H603, H669, H738, H922, I213, I230, I312, I600, I601, I602, I603, I604, I605, I606, I607, I608, I609, I610, I611, I613, I614, I615, I618, I619, I620, I621, I629, I638, I690, I691, I780, I788, I850, I864, J041, J339, J90, J942, J950, K049, K068, K092, K121, K137, K148, K226, K228, K250, K252, K254, K256, K260, K262, K264, K266, K270, K284, K290, K571, K573, K625, K649, K661, K762, K768, K859, K920, K921, K922, L508, M2506, M2509, N029, N288, N300, N304, N309, N328, N368, N421, N488, N501, N645, N830, N831, N836, N837, N838, N898, N908, N921, N922, N923, N924, N930, N938, N939, N950, O717, O901, O902, R040, R041, R042, R048, R049, R18, R195, R233, R31, R571, R58, S000, S001, S002, S003, S004, S005, S007, S008, S013, S019, S050, S051, S063, S0630, S0631, S064, S0640, S0641, S065, S0650, S0651, S066, S0660, S0661, S068, S0680, S0681, S098, S100, S101, S141, S241, S271, S2710, S2711, S272, S2720, S2721, S278, S2780, S2781, S279, S2790, S2791, S301, S302, S341, S361, S3610, S3611, S3680, S369, S3690, S3691, S370, S3700, S3701, S3780, S390, S400, S408, S500, S501, S600, S601, S701, S800, S801, S902, T009, T060, T090, T093, T140, T144, T145, T146, T794, T810, T811, T876, T905
Major bleeding	
Intracranial bleeding	
Subarachnoid haemorrhage	I600, I601, I602, I603, I604, I605, I606, I607, I608, I609
Intracerebral haemorrhage	I610, I611, I613, I614, I615, I618, I619
Subdural haemorrhage (acute, nontraumatic)	I620
Nontraumatic extradural haemorrhage	I621
Intracranial haemorrhage (nontraumatic), unspecified	I629

Outcomes	International Classification of Diseases (ICD) codes
Other cerebral infarction	I638
Sequelae of cerebrovascular disease	I690, I691
Epidural haemorrhage	S064, S0640
Traumatic subdural haemorrhage	S065, S0650, S0651
Gastrointestinal bleeding/bleeding with shock	
Gastro-oesophageal laceration-haemorrhage syndrome	K226
Other specified diseases of oesophagus	K228
Gastric ulcer	K250, K252, K254
Duodenal ulcer	K260, K262, K264, K266
Acute haemorrhagic gastritis	K290
Diverticular disease of large intestine without perforation or abscess	K573
Gastrointestinal haemorrhage, unspecified	K922
Haemorrhagic shock	R571

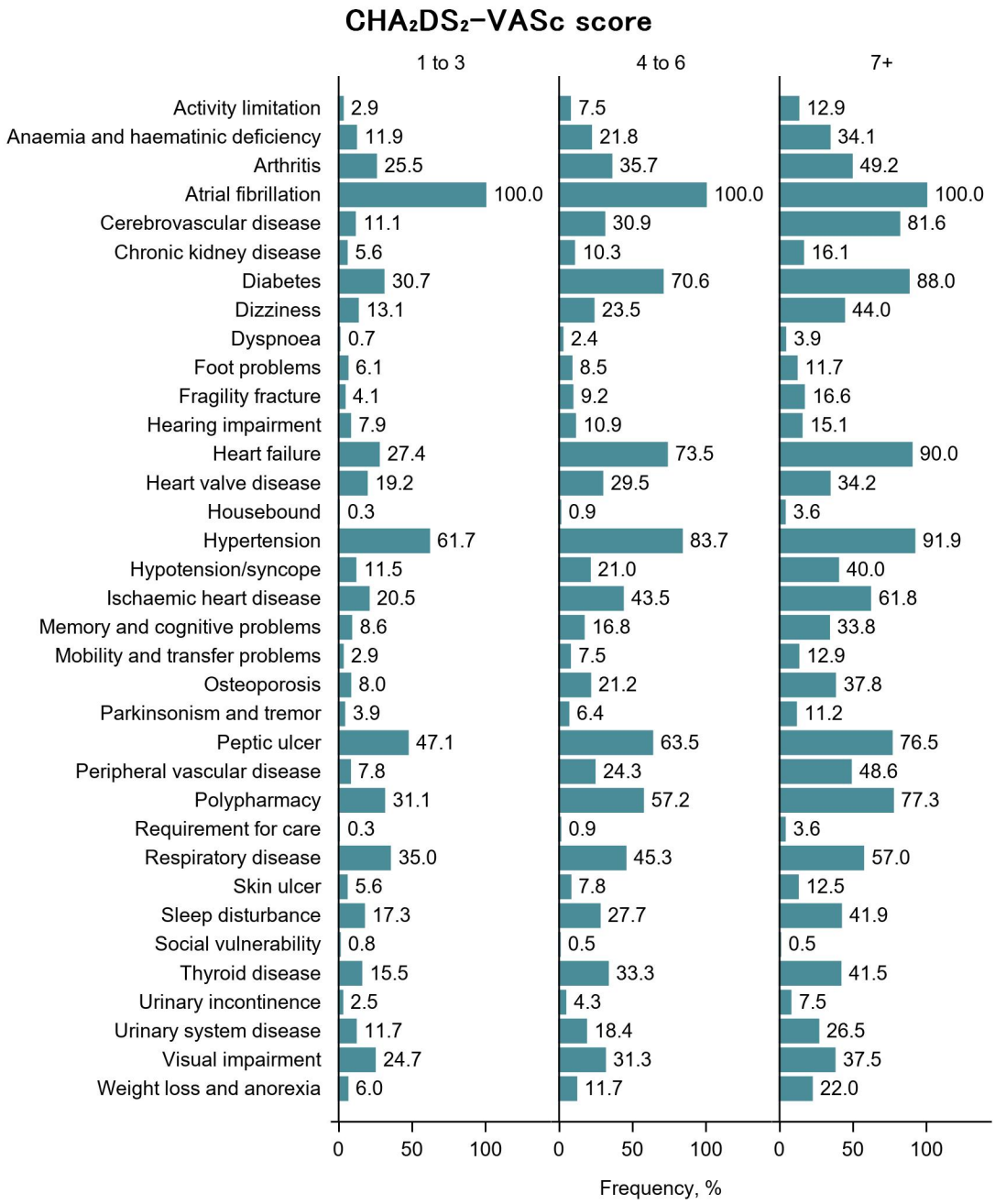
Supplemental Table 3-8 Prevalence of deficits in Electronic Frailty Index

	Total	eFI, category			
		Fit	Mild	Moderate	Severe
eFI (Deficits)	n=12585	n=980	n=3967	n=4385	n=3253
Activity limitation	1016 (8.1)	0 (0.0)	75 (1.9)	300 (6.8)	641 (19.7)
Anaemia and haematinic deficiency	2933 (23.3)	27 (2.8)	473 (11.9)	1016 (23.2)	1417 (43.6)
Arthritis	4708 (37.4)	82 (8.4)	901 (22.7)	1736 (39.6)	1989 (61.1)
Atrial fibrillation	12585 (100.0)	980 (100.0)	3967 (100.0)	4385 (100.0)	3253 (100.0)
Cerebrovascular disease	5047 (40.1)	78 (8.0)	928 (23.4)	1862 (42.5)	2179 (67.0)
Chronic kidney disease	1380 (11.0)	17 (1.7)	195 (4.9)	442 (10.1)	726 (22.3)
Diabetes	8662 (68.8)	270 (27.6)	2399 (60.5)	3255 (74.2)	2738 (84.2)
Dizziness	3387 (26.9)	11 (1.1)	336 (8.5)	1169 (26.7)	1871 (57.5)
Dyspnoea	313 (2.5)	1 (0.1)	36 (0.9)	100 (2.3)	176 (5.4)
Foot problems	1120 (8.9)	11 (1.1)	168 (4.2)	400 (9.1)	541 (16.6)
Fragility fracture	1285 (10.2)	13 (1.3)	136 (3.4)	402 (9.2)	734 (22.6)
Hearing impairment	1442 (11.5)	21 (2.1)	198 (5.0)	501 (11.4)	722 (22.2)
Heart failure	8882 (70.6)	279 (28.5)	2395 (60.4)	3355 (76.5)	2853 (87.7)
Heart valve disease	3661 (29.1)	80 (8.2)	862 (21.7)	1372 (31.3)	1347 (41.4)
Housebound	181 (1.4)	0 (0.0)	15 (0.4)	39 (0.9)	127 (3.9)
Hypertension	10365 (82.4)	582 (59.4)	3014 (76.0)	3767 (85.9)	3002 (92.3)
Hypotension/syncope	3036 (24.1)	8 (0.8)	282 (7.1)	1022 (23.3)	1724 (53.0)
Ischaemic heart disease	5592 (44.4)	62 (6.3)	1112 (28.0)	2181 (49.7)	2237 (68.8)
Memory and cognitive problems	2475 (19.7)	25 (2.6)	326 (8.2)	829 (18.9)	1295 (39.8)
Mobility and transfer problems	1016 (8.1)	0 (0.0)	75 (1.9)	300 (6.8)	641 (19.7)
Osteoporosis	2924 (23.2)	26 (2.7)	391 (9.9)	1031 (23.5)	1476 (45.4)
Parkinsonism and tremor	904 (7.2)	10 (1.0)	101 (2.5)	285 (6.5)	508 (15.6)
Peptic ulcer	8076 (64.2)	174 (17.8)	1853 (46.7)	3149 (71.8)	2900 (89.1)
Peripheral vascular disease	3479 (27.6)	23 (2.3)	524 (13.2)	1318 (30.1)	1614 (49.6)
Polypharmacy	7313 (58.1)	60 (6.1)	1353 (34.1)	2967 (67.7)	2933 (90.2)
Requirement for care	181 (1.4)	0 (0.0)	15 (0.4)	39 (0.9)	127 (3.9)
Respiratory disease	5860 (46.6)	135 (13.8)	1204 (30.4)	2248 (51.3)	2273 (69.9)
Skin ulcer	1079 (8.6)	6 (0.6)	171 (4.3)	334 (7.6)	568 (17.5)
Sleep disturbance	3718 (29.5)	39 (4.0)	561 (14.1)	1383 (31.5)	1735 (53.3)

	Total	eFI, category			
		Fit	Mild	Moderate	Severe
eFI (Deficits)	n=12585	n=980	n=3967	n=4385	n=3253
Social vulnerability	67 (0.5)	4 (0.4)	13 (0.3)	24 (0.5)	26 (0.8)
Thyroid disease	4102 (32.6)	56 (5.7)	991 (25.0)	1493 (34.0)	1562 (48.0)
Urinary incontinence	606 (4.8)	9 (0.9)	73 (1.8)	174 (4.0)	350 (10.8)
Urinary system disease	2435 (19.3)	36 (3.7)	406 (10.2)	831 (19.0)	1162 (35.7)
Visual impairment	4004 (31.8)	104 (10.6)	835 (21.0)	1472 (33.6)	1593 (49.0)
Weight loss and anorexia	1682 (13.4)	10 (1.0)	153 (3.9)	514 (11.7)	1005 (30.9)

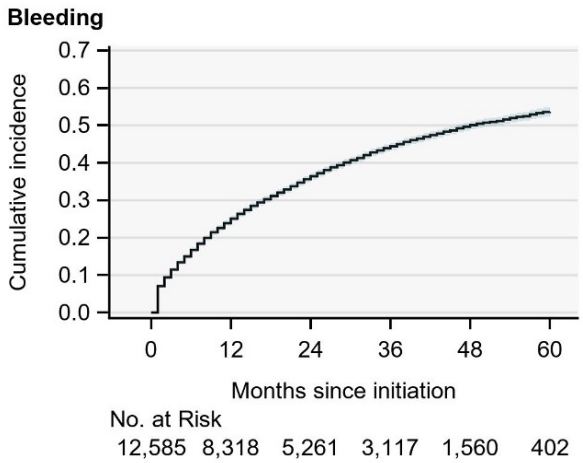


Supplemental Figure 3-1 Prevalence of deficits in eFI by HAS-BLED score group

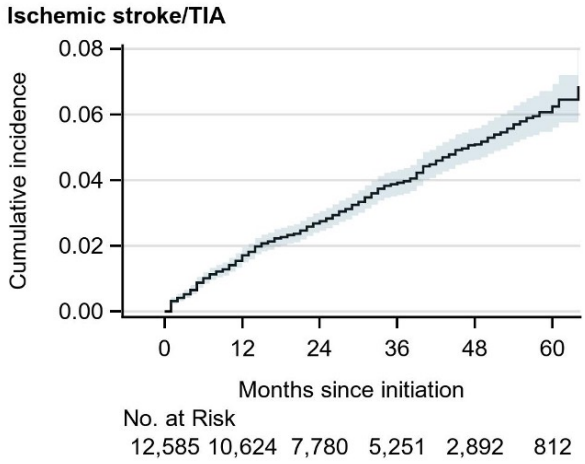


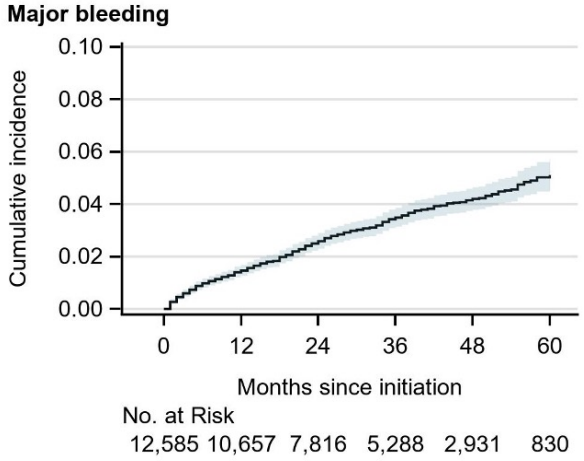
Supplemental Figure 3-2 Prevalence of deficits in eFI by CHA2DS2-VASc score group

Primary outcome



Secondary outcomes





Supplemental Figure 3-3 Cumulative incidence of outcomes by subgroup

Cumulative incidence curves with 95% confidence intervals are plotted.

Chapter 4. Discussion

In this thesis, I evaluated the applicability of coding-based algorithms to the measurement of frailty in a community setting using administrative claims data, and the association between coding-based frailty and clinical outcomes. I first focused on the algorithms used to measure frailty, eFI and HFRS, which were developed using large-scale health-care data, and examined their applicability to Japanese claims data. I then applied the frailty algorithms to a pharmacoepidemiology study and evaluated the associations between patients' frailty and their clinical outcomes.

Key findings

I applied the two frailty algorithms to a Japanese administrative claims database. In **Chapter 2**, the algorithms of the frailty tools were found to be applicable to Japanese health-care utilization data and had comparable score distribution to previous studies. The algorithms were also able to identify subjects at greater risk of death or more likely to use long-term care (LTC) services. In **Chapter 3**, coding-based frailty was associated with a higher risk of bleeding among frail patients with atrial fibrillation (AF) treated with oral anticoagulants (OACs). The results indicate that the association between frailty and the increased risk of bleeding among frail patients should be carefully considered at OAC initiation, and that coding-based frailty is a valuable tool in investigating common diseases in older adults.

Assessment of coding-based frailty for long-term outcome prediction

In **Chapter 2**, the discrimination of the two algorithms was moderate (AUC $\geq$ 0.68), and the two coding-based frailty indices were associated with the long-term outcome of death and with the use of long-term care services. When the frailty algorithms were applied to claims data collected from hospitals, clinics, and in- and outpatient settings, they predicted the long-term outcomes of patients well.

Another significant finding reported in this chapter was that the predictive ability

of eFI based on Read Codes for long-term outcomes showed little change when the Read Codes were converted to international disease classification codes (i.e., ICD-10 codes). The ability to predict long-term outcomes moderately well should expand the scope of studies of frailty in future research. The finding that the coding-based frailty index is associated with death and the use of LTC services (which is considered a proxy for frailty) is particularly important when evaluating the applicability of frailty algorithms.

Association between coding-based frailty and clinical outcomes

The clinical practice guidelines state that the net clinical benefit of using OAC outweighs the risk of bleeding, even in frail patients.[65] In **Chapter 3**, I demonstrated that coding-based frailty is associated with an increased risk of bleeding outcomes in frail patients with AF. This study suggests that the increased risk of bleeding should be discussed with these patients when physicians consider the initiation of OAC therapy.

This chapter evaluated the association between eFI and outcomes, taking into account comorbidities and medication use, but not including components of eFI except for stroke admission. Previous studies have used a similar type of frailty index (coding-based, constructed using the deficit accumulation approach) to examine the relationship between frailty[17,19,23] and outcomes, taking into account patient characteristics included in the frailty score indicators.[95–97] However, some studies that have examined the association between eFI and clinical outcomes have not considered comorbidities and medication use, which are included in indicators of the frailty index.[71,88] It is debatable whether adjustments for characteristics already included in the frailty index are appropriate. Further research is needed to determine the appropriateness of these adjustments.

Strengths and limitations

To my knowledge, this thesis is the first report of the association between coding-based frailty and long-term clinical outcomes in primary-care and inpatient settings. I measured

frailty with administrative claims data that are routinely collected on a nationwide scale in Japan and are recorded with uniform standards. This report of the applicability of the coding-based frailty index should contribute to future research in community settings in Japan and other regions. Another strength of the study is that the SKDB covers ≥70% of residents aged ≥75 years, so any demographic bias is relatively small in the older population.

There are limitations to studies that use administrative claims data. Several disease codes in Japan are not fully covered in the original ICD-10 codes. Similarly, several disease codes are insufficiently mapped to or from the ICD-10 classification. Further validation studies of the coding accuracy of disease diagnoses are required.

Future directions

Other recommendations for further research include the investigation of whether coding-based algorithms predict outcomes beyond the research scope, health systems, and countries/regions addressed, especially in terms of the diseases and medications closely associated with frailty. Such studies would contribute to the assessment of clinical outcomes among frail patients and to the shared decision-making processes in clinical encounters, in which frailty is considered as important or more important than chronological age.

Conclusion

The algorithms for frailty investigated here are applicable to Japanese administrative claims data. Coding-based frailty is associated with the utilization of long-term care and mortality in community settings, and risk of bleeding among patients with atrial fibrillation. The increased risk of adverse outcomes among frail patients should be considered in clinical practice and communicated to these patients. Coding-based frailty may have utility in future research when the study of frail patients in experimental settings is not feasible.

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