

Impact of Frailty on Major Adverse Cardiovascular Events in Chronic Obstructive Pulmonary Disease

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Purpose: Chronic obstructive pulmonary disease (COPD) is associated with frailty and leads to poor outcomes. The relationship between COPD and cardiovascular events is well established. However, the impact of frailty on cardiovascular events in COPD patients remains unknown. We aimed to evaluate the long-term association between frailty, assessed using the hospital frailty risk score (HFRS), and major adverse cardiovascular events (MACE) in COPD patients.

Patients and Methods: We recruited Japanese patients with COPD between 2013 and 2023 from Sado-Himawari Net, a regional electronic health record system in Sado City, Niigata Prefecture, Japan. MACE were defined as a composite of acute coronary syndrome, heart failure, and stroke. We classified the participants into four frailty categories according to HFRS: no-frailty with HFRS=0, low with HFRS >0 and <5, intermediate with HFRS ≥5 and <15, and high with HFRS ≥15. We used a Cox regression model adjusted for age, sex, inhaled treatments, and comorbidities to evaluate the hazard ratio (HR) for MACE.

Results: We recruited 1527 patients with COPD. In multivariable analysis, COPD was associated with MACE as follows: no-frailty versus low HFRS (HR, 1.47 [95% confidence interval, 1.01–2.14], $p < 0.05$), intermediate HFRS (HR 2.00 [1.34–2.97], $p < 0.001$), and high HFRS (HR 2.62 [1.50–4.59], $p < 0.001$). Similar relationships were observed even after adjusting for the severity of airflow limitation and COPD exacerbation.

Conclusion: Frailty was independently associated with MACE in COPD patients during the 10-year follow-up period. Frailty assessment supports the identification of patients with COPD at risk of MACE.

Keywords: chronic obstructive pulmonary disease, electronic health record, frailty, healthy longevity, major adverse cardiovascular events

Introduction

The elderly population has been rapidly expanding in Japan, which has the most aging society in the world.¹ The ageing of populations leading to an increase in the prevalence of frailty. Frailty is a geriatric syndrome that can be vulnerable to stressors due to a decline in multiple organ function.² Frailty is highly associated with chronic obstructive pulmonary disease (COPD).^{3,4} The prevalence of frailty is 32.1% in patients with COPD.⁵ Frailty leads to poor health outcomes in COPD, such as disability, hospitalization, and death.^{6–8}

The high prevalence of multimorbidity in COPD, including diabetes, cardiovascular diseases, chronic kidney disease, osteoporosis, and sarcopenia, is a key component of frailty in patients with COPD.⁹ Recently, a concept of syndemic, the occurrence of chronic disease clusters including COPD with shared risk factors (eg, ageing, smoking, and inactivity) and biological interactions, has been proposed to manage COPD with a multidisciplinary approach in the context of multimorbidity, moving away from considering COPD as just a single chronic respiratory disease.¹⁰

COPD is closely related to cardiovascular diseases as part of the complex interaction between multimorbid diseases. Compared with the general population, patients with COPD have a higher risk of developing major adverse cardiovascular events (MACE), including acute coronary syndrome (ACS), heart failure (HF), and stroke.^{11,12} The underlying mechanisms between COPD and MACE are hyperinflation of the lungs, endothelial dysfunction, hypoxemia, sympathetic hyperactivity, hypercoagulability, and systemic inflammation.^{13–17} MACE is a leading cause of mortality in COPD.¹⁸ Nonetheless, cardiovascular diseases are often undiagnosed and undertreated in patients with COPD, leading to worse outcomes.¹⁹

The identification of patients with COPD at risk for MACE is a cornerstone for reducing cardiovascular events and achieving healthy longevity in patients with COPD. Previous studies have demonstrated that frailty is a risk factor for poor prognosis in patients with cardiovascular disease.^{20,21} However, the impact of frailty on MACE in patients with COPD remains unknown. In this multicenter, longitudinal, and population-based study, we aimed to evaluate the long-term association between frailty and MACE in patients with COPD using routinely collected clinical data from Sado-Himawari Net, a regional electronic health record (EHR) system in Sado City, Niigata Prefecture, Japan.

Material and Methods

Data Source

We used a routinely collected medical database from Sado-Himawari Net, an EHR system in Sado City, Niigata Prefecture, Japan. This regional EHR system was launched in April 2013 to facilitate cooperation between medical and long-term care resources and to effectively utilize the limited medical resources in the city. This EHR system covers the entire area of Sado across 81 facilities, including hospitals, medical clinics, dental clinics, pharmacies, nursing facilities, and health centers. This EHR system is based on common exchange protocols, such as Health Level Seven International (HL7) and Fast Healthcare Interoperability Resources (FHIR). The medical database includes information on age, sex, diseases, treatments, laboratory tests, and medical image data. All tables show consistent ID numbers for each patient across the tables. Data cleaning and pre-processing were conducted using Python package pandas (version 2.2.2). A total of 17,205 people living in Sado City participated in Sado-Himawari Net in March 2023. The geographical characteristics of Sado city, being on an isolated island (Sado island), lead to a small migration of people in this regional EHR system. Overall, healthcare in Sado City is covered within the regional EHR network system. Sado-Himawari Net continuously collects medical databases over time (every day) from 81 medical facilities across the entire area of this region (Sado city). These characteristics of this EHR system enable a continuous and longitudinal evaluation of clinical outcomes in a small population lost to follow-up in this cohort. We confirm that the data accessed complied with relevant data protection and privacy regulations.

Study Design and Participants

This was a retrospective multicenter longitudinal study. The study period was April 2013 to March 2023. A schematic representation of the study is illustrated in [Figure 1](#). Patients in Sado-Himawari Net database were recruited for this study. Patients with COPD were identified using the corresponding codes from the International Statistical Classification of Diseases and Related Health Problems, 10th revision (ICD-10), J42, J43, and J44 (any position). The eligibility criteria were patients with COPD diagnostic codes at least twice and subjects aged 40 years. The index date was defined as the earliest date of COPD diagnosis. The accuracy of these specific codes for COPD diagnosis was validated in previous reports, with a positive predictive value of 85.2–90.8% by COPD diagnostic codes alone.^{22–25} We obtained the occurrence of MACE and the time to first MACE. The end of the follow-up period was defined as follows: (i) the date of the first MACE for patients with MACE, (ii) March 2023 (the end of the study period) for patients without MACE, or (iii) the date of loss to follow-up from Sado-Himawari Net. Demographic data, such as age, sex, and inhaled treatments for COPD, were collected from the Sado-Himawari Net at baseline (within 1 year prior to the index date). Comorbidities were identified using corresponding ICD-10 codes ([Table S1](#)). Comorbidities included hypertension, diabetes, dyslipidemia, chronic kidney disease, sleep apnea syndrome, depression, sinusitis, and asthma. We evaluated COPD exacerbation during the follow-up period. COPD exacerbation was defined as dispensation claims for systemic

Study period: April 2013 - March 2023

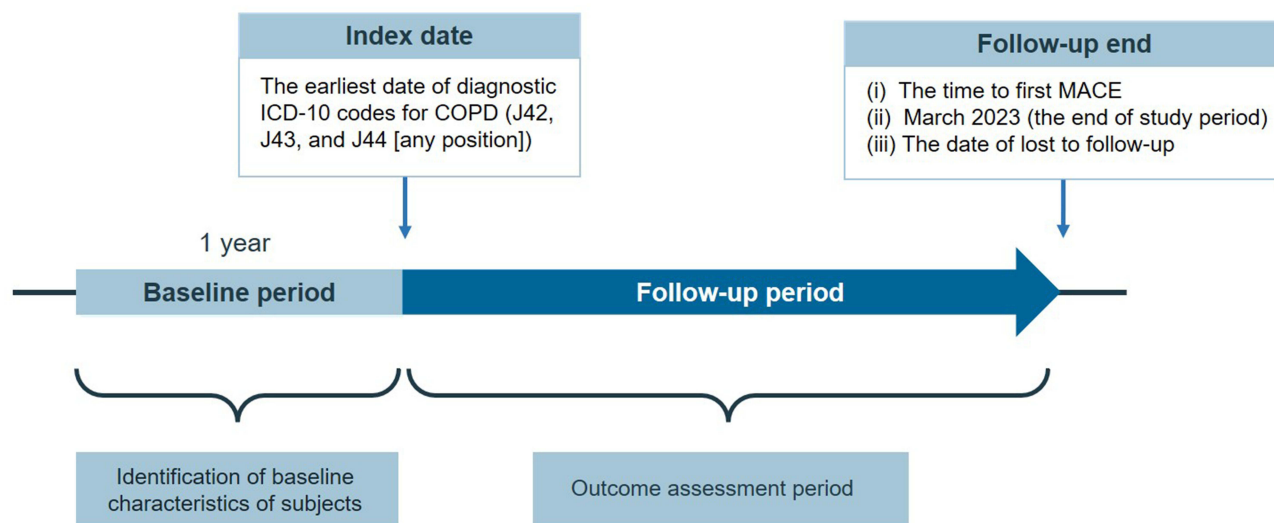


Figure 1 Study timeline. The index date was defined as the date of the earliest diagnostic code for COPD (ICD-10 codes: J42, J43, and 44). The end of follow-up was defined as the date of the first MACE occurrence, loss to follow-up, or March 31, 2023 (the end of the study period).

Abbreviations: COPD, chronic obstructive pulmonary disease; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. MACE, major adverse cardiovascular event.

corticosteroids within 14 days. This study was approved by the ethics review committee of Yamaguchi University Hospital (approval number:2022–023). This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was registered in the UMIN Clinical Trials Registry (UMIN000048551). Informed consent was waived by the ethics committee because of the retrospective nature of the study.

Frailty Risk Assessment

In the present study, we evaluated the hospital frailty risk score (HFRS) by using hospital administrative data at baseline as a measure of frailty risk. We calculated the HFRS for individual participants according to the methods described by Gilbert et al.²⁶ HFRS is a frailty assessment tool using 109 ICD-10 diagnostic codes from a health administrative database. Briefly, each ICD-10 code was assigned a score, and HFRS was calculated as the sum of scores for ICD-10 codes that the subjects had received during the hospital visits. The HFRS is a well-validated risk score for frailty that is associated with hospitalization, length of hospitalization, disability, and death. The frailty scores were classified into four categories: no-frailty with HFRS=0, low with HFRS >0 and <5, intermediate with HFRS ≥5 and <15, and high with HFRS ≥15, as previously defined.²⁶ No ICD-10 codes for calculating HFRS were included in the specific codes for the definition of individual MACE.

Outcome Measurements

The time to the first MACE was evaluated. MACE were defined as ACS, HF, or stroke occurrence after the index date. We selected ACS, HF, and stroke because these three were the most utilized MACE endpoints.²⁷ In all participants, we defined individual MACE (ie, ACS, HF, and stroke) by a combination of both ICD-10 codes and medications that were specific to the respective MACE, as previously described.^{28–30} ACS was defined as ICD-10 codes I20, I21, I22, I23, and I24 (codes for acute myocardial infarction and unstable angina) with antiplatelet agents. We defined HF using ICD-10 codes I50, I11.0, I13.0, and I13.2 (diagnostic codes for HF) for diuretics and/or cardiotonic drugs. Stroke was defined as ICD-10 codes I63 and I64 (specific codes for cerebral infarction occurrence) with medications for stroke (brain-protective drugs, antiplatelet agents, and/or anticoagulant drugs). The definitions of individual MACE (ACS, HF, and stroke) are detailed in [Table S2](#).

Statistical Analysis

In this study, we describe the numerical variables using the mean and standard deviation for each value. The incidence of MACE for each frailty category (ie, no-frailty, low, intermediate, and high) was calculated in patients with COPD using the Kaplan–Meier method, and differences were compared using the Log rank test with Python package lifelines (version 0.29.0). We applied a multivariate Cox proportional hazard model to evaluate whether these frailty categories were independently associated with MACE, with adjustment for confounding factors such as age, sex, comorbidities (hypertension, diabetes, dyslipidemia, chronic kidney disease, sleep apnea syndrome, depression, sinusitis, and asthma), and inhaled treatments for COPD (ie, inhaled corticosteroids, long-acting β_2 agonists, and/or long-acting muscarinic antagonists). We calculated hazard ratios (HR) and corresponding 95% confidence intervals (CIs) for the time to first MACE in the frailty categories (ie, no-frailty, low, intermediate, and high) using the Cox proportional hazard model. Patients were censored if they experienced any MACE or were lost to follow-up. Statistical analyses were performed using the SciPy package (version 1.7.3) in Python. All statistical tests were two-sided, and statistical significance was set at $p < 0.05$.

Sensitivity Analysis

We performed two sensitivity analyses to confirm the potential association between frailty and MACE in COPD patients. First, we performed a sensitivity analysis excluding patients who experienced COPD exacerbations during the observational period to verify whether the association between frailty and MACE was independent of COPD exacerbations. Second, we performed a sensitivity analysis to adjust for airflow limitation severity (ie, Global Initiative for Chronic Obstructive Lung Disease [GOLD] grade 1–4) in addition to age, sex, inhaled treatments, and comorbidities in subjects who underwent spirometry.

Results

Patients' Demographics

A total of 1527 patients with COPD were enrolled from Sado-Himawari Net (Figure 2). The mean age was 79.2 years old (SD 10.0) and 691 patients (45.3%) were female (Table 1). The proportion of male was higher in patients with COPD with MACE than in those without MACE. The number (proportions) of patients in each frailty category (no-frailty, low, intermediate, and high) were 230 (15.1%), 702 (46.0%), 519 (34.0%), and 76 (5.0%), respectively (Table 2). Participants with a higher frailty risk were older than those with a lower frailty risk.

Clinical Outcomes

Table 3 shows cumulative proportions of occurring any MACE and individual MACE (ie, ACS, HF, and stroke) in all subjects and subjects in each frailty category: no frailty, low, intermediate, and high. A total of 363 (23.8%) patients with COPD experienced MACE during the 10-year follow-up. The number (proportion) of subjects with ACS, HF, and stroke occurrence were 113 (7.4%), 155 (10.2%), and 195 (12.8%), respectively (Table 3). The higher HFRS groups (eg high with $\text{HFRS} \geq 15$ points) showed a more frequent occurrence of any MACE.

The Association Between Frailty and Risk of MACE Occurrence

The severity of frailty, as evaluated by the HFRS, was significantly associated with an increased risk of a composite of MACE occurrence in patients with COPD. Figure 3 shows the cumulative incidence curve of any MACE in the subjects during the 10-year follow-up period. Patients with COPD and a higher HFRS score showed a higher proportion of MACE (log-rank $p < 0.001$). In the Cox proportional hazard model adjusted for age, sex, inhaled treatments, and comorbidities, frailty categories were significantly associated with MACE occurrence as follows: no-frailty versus low HFRS (HR 1.47 [95% confidence interval, 1.01–2.14], $p < 0.05$), intermediate HFRS (HR 2.00 [1.34–2.97], $p < 0.001$), and high HFRS (HR 2.62 [1.50–4.59], $p < 0.001$) (Table 4).

Sensitivity Analysis

The association between frailty and MACE in patients with COPD was generally consistent with the sensitivity analysis.

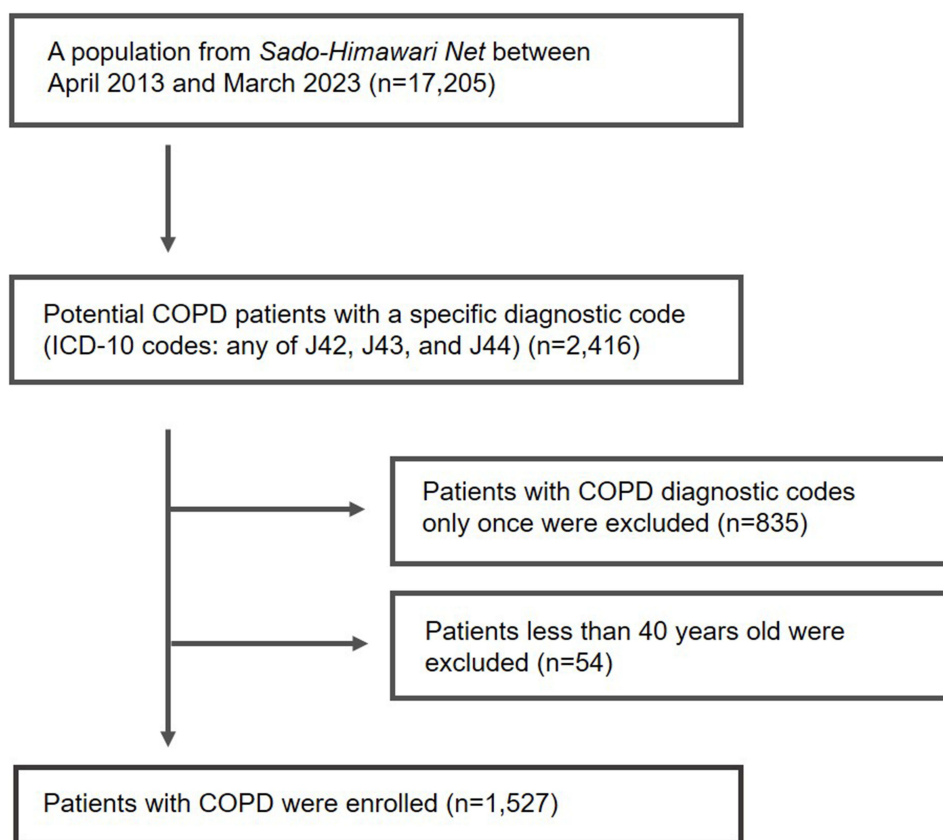


Figure 2 Flow diagram of the inclusion/exclusion of COPD participants in this study. For the analysis of the present study, a total of 1527 patients with COPD were enrolled.

Abbreviations: COPD, chronic obstructive pulmonary disease; ICD-10, International Statistical Classification of Diseases and Related Health Problems, Tenth Revision.

Even when including only patients without COPD exacerbations during the follow-up period ($n=1339$), COPD patients with a higher HFRS category had a higher incidence of MACE ([Figure S1](#)). In the multivariable analysis adjusted for age, sex, inhaled treatments, and comorbidities in this sub-population, the association between frailty and MACE remained statistically significant as follows: no-frailty versus low HFRS (HR 1.49 [1.01–2.18], $p<0.05$); intermediate HFRS (HR 1.98 [1.32–2.98], $p<0.005$), and high HFRS (HR 2.48 [1.39–4.42], $p<0.005$), respectively ([Table S3](#)).

Similarly, in the subgroup of patients with spirometry ($n=514$), COPD patients with a higher HFRS category had a higher incidence of MACE ([Figure S2](#)). The association between HFRS and MACE was consistent even after adjusting for the severity of airflow limitation in the COPD subpopulation who underwent spirometry ($n=514$). After adjusting for the severity of airflow limitation by GOLD classification (ie GOLD 1–4) in addition to age, sex, inhaled treatments, and comorbidities, the association between frailty categories and MACE occurrences remained statistically significant as follows: no-frailty versus low HFRS (HR 1.31 [0.76–2.26], $p=0.33$), intermediate HFRS (HR 2.08 [1.17–3.68], $p<0.05$), and high HFRS (HR 3.37 [1.35–8.43], $p<0.05$), respectively ([Table S4](#)).

Discussion

Utilizing routinely collected clinical data from the EHR system during the 10-year follow-up, we demonstrated that frailty, assessed using HFRS, was associated with a higher proportion of MACE (a composite of ACS, HF, or stroke) in Japanese patients with COPD. Frailty was independently associated with MACE in patients with COPD, even after adjustment for age, sex, comorbidities, inhaled treatments, COPD exacerbations, and severity of airflow limitation, although these results might not be generalized to patients in the other countries.

Table 1 Baseline Characteristics of COPD Patients with and without MACE During the Follow-up Term

Variables	All of COPD Patients n=1527	With MACE n=363	Without MACE n=1164
Age (yr), mean±SD	79.2±10.0	81.2±7.8	78.6±10.5
Gender (Female/male), n	691/836	152/211	539/625
Comorbidities			
Hypertension, n (%)	723 (47.3)	165 (45.5)	558 (47.9)
Chronic kidney disease, n (%)	93 (6.0)	33 (9.1)	60 (5.2)
Dyslipidaemia, n (%)	582 (38.1)	163 (44.9)	419 (36.0)
Diabetes, n (%)	463 (30.3)	126 (34.7)	337 (29.0)
Asthma, n (%)	531 (34.8)	129 (35.5)	402 (34.5)
Sinusitis, n (%)	201 (13.2)	41 (11.3)	160 (13.7)
Sleep apnea syndrome, n (%)	603 (39.5)	156 (43.0)	447 (38.4)
Depression, n (%)	287 (18.8)	81 (22.3)	206 (17.7)
Inhalation treatments			
ICS, n (%)	273 (17.9)	62 (17.1)	211 (18.1)
LABA, n (%)	344 (22.5)	80 (22.0)	264 (22.7)
LAMA, n (%)	201 (13.2)	51 (14.0)	150 (12.9)
Frailty assessment			
HFRS (points), mean±SD	5.0±5.0	5.9±5.4	4.8±4.8
No frailty (HFRS=0), n (%)	230 (15.1)	35 (9.6)	195 (16.8)
Low (HFRS >0 and <5), n (%)	702 (46.0)	156 (43.0)	546 (46.9)
Intermediate (HFRS ≥5 and <15), n (%)	519 (34.0)	148 (40.8)	371 (31.9)
High (HFRS≥15), n (%)	76 (5.0)	24 (6.6)	52 (4.5)

Notes: Numbers in the table indicate either the mean±SD or percentage.

Abbreviations: MACE, major adverse cardiovascular events; COPD, chronic obstructive pulmonary disease; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; HFRS, hospital frailty risk score.

From the results of the sensitivity analysis, we found that frailty was an independent risk factor for MACE in patients with COPD, even after controlling for the effects of COPD exacerbations and airflow limitation severity. COPD exacerbations were highly associated with an increased risk of MACE in previous studies from Japan and other countries.^{31–35} Nonetheless, even after excluding subjects who experienced COPD exacerbations during the follow-up period, the association between frailty and MACE in patients with COPD remained significant in the present study. The severity of airflow limitation has also been associated with MACE in previous reports.^{36–38} In contrast, even after adjustment for the severity of airflow limitation defined by the GOLD classification (ie, GOLD 1–4) in a sub-population of COPD patients with spirometry, a higher HFRS category was associated with a risk of developing MACE.

To our knowledge, this is the first study to demonstrate a long-term association between frailty assessed by HFRS and the risk of developing MACE in patients with COPD, although HFRS is not a physical frailty assessment tool like Fried phenotype which can be prevented by rehabilitation and nutrition. Previous studies have shown that frailty is associated

Table 2 Baseline Characteristics of Patients with COPD Stratified by Frailty Categories

Variables	No Frailty n=230	Low n=702	Intermediate n=519	High n=76
Age (yr), mean±SD	74.4±9.6	77.8±10.2	82.4±8.7	84.7±7.7
Gender (Female/male), n	102/128	303/399	243/276	43/33
Comorbidities				
Hypertension, n (%)	135 (58.7)	375 (53.4)	192 (37.0)	21 (27.6)
Chronic kidney disease, n (%)	1 (0.4)	24 (3.4)	57 (11.0)	11 (14.5)
Dyslipidaemia, n (%)	78 (33.9)	278 (39.6)	201 (38.7)	25 (32.9)
Diabetes, n (%)	48 (20.8)	236 (33.6)	160 (30.8)	19 (25.0)
Asthma, n (%)	88 (38.3)	228 (32.5)	188 (36.2)	27 (35.5)
Sinusitis, n (%)	34 (14.8)	110 (15.7)	52 (10.0)	5 (6.6)
Sleep apnea syndrome, n (%)	53 (23.0)	254 (36.2)	248 (47.8)	48 (63.2)
Depression, n (%)	18 (7.8)	113 (16.1)	131 (25.2)	25 (32.9)
Inhalation treatments				
ICS, n (%)	58 (24.8)	138 (19.7)	73 (14.1)	5 (6.6)
LABA, n (%)	74 (31.3)	171 (24.4)	93 (17.9)	8 (10.5)
LAMA, n (%)	45 (19.6)	98 (14.0)	53 (10.2)	5 (6.6)
HFRS (points), mean±SD	0.0±0.0	2.6±1.2	8.4±2.7	19.4±4.1

Notes: Numbers in the table indicate either the mean±SD or percentage.

Abbreviations: ICS, inhaled corticosteroids; LABA, long-acting β_2 agonist; LAMA, long-acting muscarinic antagonist; HFRS, hospital frailty risk score.

Table 3 The Proportion of Major Adverse Cardiovascular Events Stratified by Frailty Categories During the 10-Year Follow-up

Variables	No Frailty n=230	Low n=702	Intermediate n=519	High n=76
Any MACE, n (%)	35 (15.2)	156 (22.2)	148 (28.5)	24 (31.6)
ACS, n (%)	12 (5.2)	52 (7.4)	42 (8.1)	7 (9.2)
HF, n (%)	11 (4.8)	70 (10.0)	61 (11.8)	13 (17.1)
Stroke, n (%)	16 (7.0)	79 (11.3)	86 (16.6)	14 (18.4)

Abbreviations: MACE, major adverse cardiovascular event; ACS, acute coronary syndrome; HF, heart failure.

with worse outcomes in patients with pre-existing cardiovascular diseases. Previous study demonstrated that physical frailty measured by Fried phenotype was associated with a poor prognosis in patients with preexisting cardiovascular diseases.²⁰ Another previous prospective study showed that a multi-domain frailty (physical, social, and cognitive domain) was a prognostic factor of cardiovascular outcomes in patients with chronic heart failure.²¹ The frailty assessed by HFRS was related to poor prognosis following stroke and transient ischemic attack.³⁹ The results of the present study

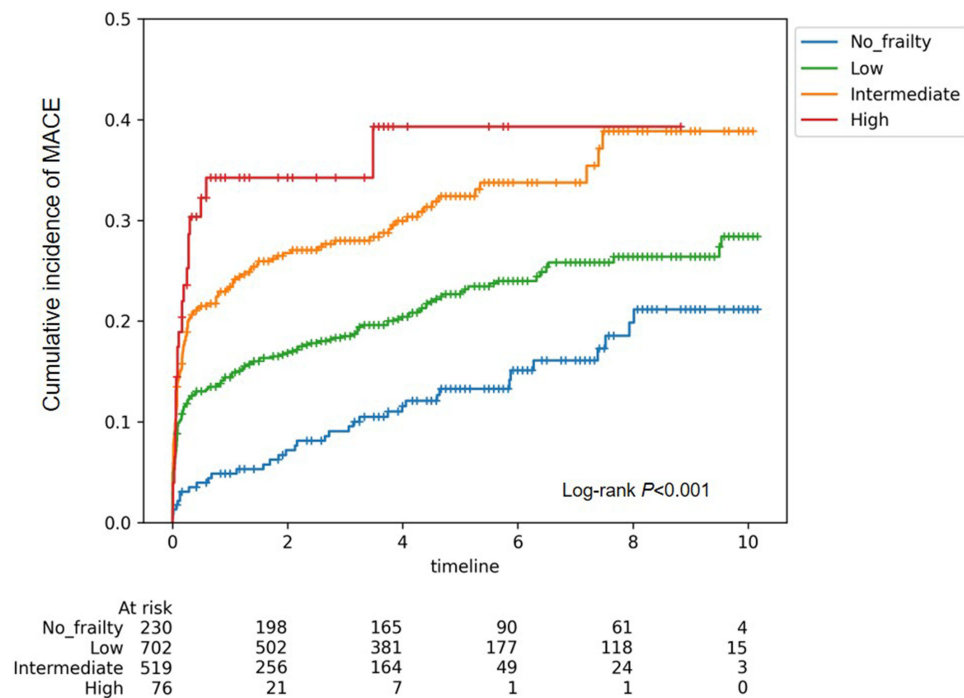


Figure 3 The Kaplan–Meier curves show cumulative incidence of MACE (any of acute coronary syndrome, heart failure, and stroke) in COPD patients in four frailty categories: No-frailty, HFRS=0 (blue line); low, HFRS >0 and <5 (green line); intermediate, HFRS \geq 5 and <15 (Orange line); high, HFRS \geq 15 (red line).

Abbreviations: MACE, major adverse cardiovascular events; COPD, chronic obstructive pulmonary disease; HFRS, hospital frailty risk score.

are in line with these previous reports. Taken together with the results of our study, these findings reinforce an association between frailty and MACE. The underlying pathophysiological mechanisms linking frailty and MACE are believed to be subclinical atherosclerosis due to oxidative stress, endothelial senescence, and systemic inflammation.^{40–42} Furthermore, our study is the first to focus on this association in patients with COPD, while these previous reports showed an association in patients with pre-existing cardiovascular diseases. COPD patients with frailty showed an increased level of senescence-associated secretory phenotype proteins such as interleukine-6 and growth differentiation factor-15,^{43,44} which potentially aggravate the association between MACE and COPD. These complicated and mutual interactions between the three conditions (frailty, MACE, and COPD) may be a plausible underlying mechanism linking frailty with COPD and MACE in the present study.

Table 4 Cox Multivariate Proportional Hazard Ratio for MACE in Patients with COPD (n=1527)

HFRS	HR (95% CI)	P Value
No-frailty	1 (reference)	-
Low	1.47 (1.01–2.14)	<0.05
Intermediate	2.00 (1.34–2.97)	<0.001
High	2.62 (1.50–4.59)	<0.001

Notes: Adjusted for age, sex, comorbidities, and inhaled treatment (inhaled corticosteroids, long-acting β_2 agonists, and/or long-acting muscarinic antagonists).

Abbreviations: MACE, major adverse cardiovascular events; COPD, chronic obstructive pulmonary disease; HFRS, hospital frailty risk score; HR, hazard ratio; CI, confidence interval.

The association between frailty and MACE in COPD provides an opportunity to stratify the cardiopulmonary risk in patients with COPD. The coexistence of COPD and cardiovascular diseases is frequently observed. The coexistence of these two diseases is related to worse outcomes than those of either disease alone. However, cardiovascular diseases are often underdiagnosed and undertreated in COPD patients. Notably, a previous study reported that 70% of COPD patients were underdiagnosed with coronary artery disease identified by electrocardiography.¹⁹ Given the association between frailty and MACE in COPD in this study, a frailty assessment supports the identification of COPD patients with cardiopulmonary risk. Physical frailty assessment tools, such as Fried phenotypes, remain the gold standard for evaluating physical frailty status. However, it is difficult to implement these physical frailty assessments in routine clinical practice, owing to limitations in human resources, time, and space in medical facilities. In contrast, utilizing a readily available frailty screening tool such as HFRS and a patient-reported outcome measurement will help to easily detect COPD patients with frailty.^{26,45} Consequently, in COPD patients with frailty, early screening with exercise electrocardiograms and/or cardio-echograms may aid early detection of subclinical cardiovascular risk and personalized intervention to mitigate cardiovascular risk. Further prospective studies are required to verify whether early multi-discipline approaches for COPD patients with frailty will reduce the incidence of MACE and ultimately improve longevity in this population.

As part of the complicated relationship between frailty and multimorbidity conditions, we focused on the association between frailty and MACE in patients with COPD. It is not clear how frailty results in adverse outcomes, including disability, hospitalization, and mortality in patients with COPD. Numerous factors such as environmental factors, social factors, genetic factors, and comorbidities might be synergistically and mutually involved in COPD patients with frailty and their accelerated ageing.⁴⁶ Our results may provide insights into understanding these complicated mechanisms in terms of cardiopulmonary relationships. The relationship between frailty and MACE in this study might explain the worse health outcomes (eg, disability, hospitalization, and mortality) in patients with both COPD and frailty. Further comprehensive approaches across multiple organs are required to understand the complex mechanisms of frailty progression in COPD patients. Tian et al showed that biological aging processes are driven by the multiple organ system network of participants in the UK biobank cohort,⁴⁷ which can be a clue for understanding the complicated mechanisms of frailty progression.

Our study, which used an EHR system, has several strengths. First, the utilization of this regional EHR system enabled a longitudinal assessment of clinical outcomes with a small proportion of loss to follow-up for the following reasons: (i) the geographical characteristics of the EHR system (isolated island, Sado Island, with few migrations); (ii) the healthcare system in this region (completion of the overall healthcare within this regional EHR system); and (iii) continuity of medical database collection in this EHR system (Sado-Himawari Net continuously collects the medical database across 81 medical facilities every day). These characteristics of the EHR system are advantageous in evaluating the natural history of COPD. Second, the regional EHR system used in the present study, Sado-Himawari Net, consists of 81 medical facilities, reflecting a real-world clinical setting. This finding supports the generalizability of our results. Third, using the EHR system, frailty could be automatically evaluated by calculating the HFRS based on ICD-10 codes. Frailty assessment, such as the Fried frailty phenotype in routine clinical practice, is difficult to implement owing to time constraints and limited space and human resources in hospitals. By contrast, the EHR-based frailty assessment HFRS can be automatically obtained using routinely collected ICD-10 codes, which overcomes the challenge of assessing frailty in routine clinical practice. Fourth, owing to the longitudinal nature of Sado-Himawari Net, this EHR system continuously collects routine medical information over time, which enables the calculation of HFRS before the occurrence of MACEs. The time between HFRS calculation and MACE occurrence reinforces the longitudinal association between frailty and MACE in patients with COPD.

This study had several limitations need to be mentioned. First, the mean age of patients with COPD was 79.2 years old in the present study. This older demographic, compared to the broader COPD population, might have influenced the study outcomes. Second, we did not obtain cardiovascular risk factors such as smoking, alcohol history, and body mass index. Third, we used a health administrative database to diagnose diseases, which may lead to misclassification of diseases, including COPD, in the present study, as with all studies using EHR systems. A significant limitation of the present study is that subjects with COPD were recruited based on ICD-10 coding rather than spirometry-defined COPD.

Fourth, the rate of inhaled treatment was low in patients with COPD from Sado-Himawari Net, which may have affected our results. This may be because there were no pulmonologists in the medical facilities of the regional EHR system. Nonetheless, the rate of inhaled treatments in the present study was similar to that in previous studies of COPD using the EHR database.^{33,48} Fifthly, this study did not include participants without COPD, and did not completely demonstrate the direct interaction between COPD, frailty, and MACE. The further study including subjects without COPD will reinforce this relationship. Finally, we did not exclude patients with MACE prior to the index date, possibly leading to left censoring or truncation. This potential bias in the EHR database might have affected the estimation of HR for MACE in this study. The EHR database was not collected for the purpose of this study, and the results of studies using EHR systems should be interpreted with caution.

Conclusion

In conclusion, we verified the long-term impact of frailty on MACE in patients with COPD during a 10-year follow-up, even after adjustment for age, sex, comorbidities, inhaled treatments, COPD exacerbations, and airflow limitation severity. Frailty assessment may play an important role in the identification of COPD patients at risk of MACE, leading to personalized and early interventions using a multi-discipline approach (eg, pulmonologists and cardiologists). Prevention of frailty progression in COPD may ultimately reduce the cardiopulmonary risk toward healthy longevity.

Data Sharing Statement

Clinical data from Sado-Himawari Net were only available to the participating researchers because the participants of the present study did not agree that their data would be shared publicly.

Ethics Approval and Informed Consent

This study was approved by the ethics review committee of Yamaguchi University Hospital (approval number:2022-023). Informed consent was waived by the ethics committee because of the retrospective nature of the study.

Acknowledgments

We thank Mari Shimizu, Kuniaki Imai, Tetsuo Akita, and Hajime Yokota at Healthcare Relations Co., Ltd. and Kenji Sato at Sado General Hospital for providing the EHR database from Sado-Himawari Net. We also thank Nanami Shiosaki at Yamaguchi University for support in obtaining the EHR database.

Author Contributions

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

Funding

This work was funded by the AstraZeneca K.K. (Externally Sponsored Research Program [ESR-21-21503]). The funder of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Disclosure

KH received speaker fees from AstraZeneca, Kyorin Pharmaceutical, Novartis Pharma and Sanofi. KO received speaker fees from AstraZeneca, Boehringer Ingelheim and Sanofi. TH received speaker fees from AstraZeneca, Novartis Pharma and Sanofi. KM received speaker fees from AstraZeneca, Boehringer Ingelheim, GlaxoSmithKline, Kyorin Pharmaceutical, Novartis Pharma and Sanofi. The other authors have no conflicts of interest to declare related to our work.

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