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ORIGINAL ARTICLE

Frailty, multimorbidity patterns and mortality in institutionalized older adults in Italy

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Abstract

Background Little is known on how frailty influences clinical outcomes in persons with specific multimorbidity patterns.

Aims To investigate the interplay between multimorbidity and frailty in the association with mortality in older individuals living in nursing homes (NH).

Methods We considered 4,131 NH residents aged 60 years and over, assessed through the interRAI LTCF instrument between 2014 and 2018. Follow-up was until 2019. Considering four multimorbidity patterns identified via principal component analysis, subjects were stratified in tertiles (T) with respect to their loading values. Frailty Index (FI) considered 23 variables and a cut-off of 0.24 distinguished between high and low frailty levels. For each pattern, all possible combinations of tertiles and FI were evaluated. Their association (Hazard Ratio [HR] and 95% confidence interval) with mortality was tested in Cox regression models.

Results In the *heart diseases* and *dementia and sensory impairments* patterns, the hazard of death increases progressively with patterns expression and frailty severity (being HR T3 vs. T1 = 2.36 [2.01–2.78]; HR T3 vs. T1 = 2.12 [1.83–2.47], respectively). In *heart, respiratory and psychiatric diseases* and *diabetes, musculoskeletal and vascular diseases* patterns, frailty seems to have a stronger impact on mortality than patterns' expression.

Discussion Frailty increases mortality risk in all the patterns and provides additional prognostic information in NH residents with different multimorbidity patterns.

Conclusions These findings support the need to routinely assess frailty. Older people affected by specific groups of chronic diseases need a specific care approach and have high risk of negative health outcomes.

Keywords Multimorbidity patterns · Frailty · Nursing homes · Mortality · Older persons

Introduction

Multimorbidity, defined as the co-occurrence of two or more diseases in the same person, is a highly prevalent condition in older adults, especially in nursing home (NH) residents [1]. Multimorbidity has been associated with negative

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health outcomes, including hospitalization, faster functional decline, mortality, and more intense healthcare utilization [1]. However, the clinical picture of multimorbidity is characterized by a great heterogeneity, depending, in particular, on the specific combination of diseases occurring in the same individual [2]. Research studies have shown that specific chronic conditions tend to group together beyond chance due to common underlying risk factors or pathophysiological mechanisms [3]. Different multimorbidity patterns, characterized by the combination of cardiovascular, pulmonary, and neuropsychiatric diseases, have been defined [4]. These patterns are differentially associated with health outcomes, confirming that the effects of multimorbidity are strictly dependent on the underlying diseases combinations [5, 6].

Frailty is characterized by a progressive age-related decline in physiological systems, which confers extreme vulnerability to stressors and increases the risk of a range of adverse health-outcomes [7]. This condition is common in older adults, with a prevalence between 12 and 24% in community-dwelling individuals over 60 and up to 50% among NH residents [8, 9]. Presence of chronic diseases contributes substantially to the onset of frailty, and frailty may ease the development of chronic disease [10]. Almost 75% of frail individuals present with multimorbidity, but frailty is observed in less than 20% of individuals with multimorbidity, according to studies based on population-based cohorts [11]. It has been hypothesized that frailty can influence the management of chronic diseases and modulate the effect of multimorbidity on health outcomes [12]. In this context, guidelines focusing on multimorbidity suggest to use frailty instruments to identify persons at high risk of negative health outcomes and in need of specific care approaches [13, 14].

Although the interaction between multimorbidity and frailty has been already studied, little is known on the role that frailty may have on the clinical outcomes in people expressing specific patterns of multimorbidity. The aim of the present study is to evaluate the interplay between multimorbidity and frailty in the association with mortality in institutionalized older adults. This topic was studied in a sample of NH residents, since this represents a population with a high burden of multimorbidity and frailty and with an elevated mortality rate.

Methods

Study design and population

This observational and retrospective study was based on a sample of 4131 NH residents from the interRAI long-term care facility (LTCF) database of the Umbria Region, Italy, which collects information on all NH residents living in that geographical area. First ever assessment in the period from January 2014 to December 2018 was considered for the present study [15]. Participants were followed until death occurred before December 2019, or until the end of the maximum period of observation.

Data collection

Residents' evaluations were carried out using the multidimensional assessment instrument interRAI LTCF, which includes over 250 items (i.e., socio-demographic factors, physical and cognitive functions, clinical data). The instrument is currently used in several Italian regions and in over 35 countries globally for administrative and clinical purposes, allowing the creation of databases that can be useful for evaluating and comparing the characteristics of NH residents across different countries, languages and cultures [16]. Health professionals are trained to use different information sources (direct observation; interviews with the person under care, their family and friends, or formal service providers) and to review clinical records, both medical and nursing. Almost all of the InterRAI LTCF items were proven to meet high-reliability standards, with a substantial proportion of items showing excellent reliability [17].

Frailty

Frailty assessment was based on the calculation of Frailty Index (FI) [18]. Considering a set of potential deficits (i.e., signs, symptoms, diseases, functional status, physical performance indicators), the FI is based on the ratio between the number of deficits of the subject and the total number of potential deficits considered. In this study, the methodology by Zucchelli et al., based on the selection of deficits using an optimization algorithm, has been implemented. A detailed description of the functioning of the optimization algorithm (i.e., the genetic algorithm) is available elsewhere. Shortly, the genetic algorithm proposes near-optimal solutions to problems that cannot be solved analytically (such as finding the best combination of deficits for the creation of frailty index with several deficits available for inclusion). The algorithm starts by creating random combinations of features and, iteratively, evaluates their performance and recombines those combinations showing better performances. The algorithm stops after a certain number of iterations or when the variability among combinations is low (i.e., a single combination is showing a performance that largely outperform the others). In our study, the genetic algorithm was run on a random subsample of the data (i.e., training subsample—80%) and it was set to maximise the discriminative ability of the FI in the prediction of mortality in the whole dataset and in age (i.e., younger and older than 85 years old) and sex

(i.e., male and females) subgroups. The aim was to create a FI whose performance was stable across several different strata of the population [19]. The performance of the proposed FI (AUROC = 0.737) was evaluated in the remaining 20% of the dataset to evaluate the presence of overfitting (AUROC = 0.722). List of the final 23 deficits included in the FI calculation is shown in Online Resource 1. The index ranges from 0 (fit) to 1 (severe frailty); according to prior reports, residents were considered with high level of frail if they had a FI ≥ 0.25 [20, 21].

Chronic diseases

The presence of 57 chronic diseases was investigated among participating residents, in keeping with a methodology previously validated and modified to compile with the information available in the InterRAI- LTCF data collection form [22]. Both diseases prespecified in the interRAI form and those identified by means of their ICD-9 codes in the interRAI form, in addition to the prespecified ones, were analysed. From our previous experience with similar studies, we focused on conditions having a prevalence greater than 2%, in order to avoid some statistical noise introduced after considering diseases with a very low prevalence. Therefore, the analysis considered the 22 most common conditions [3, 5].

Covariates

Demographic variables included age and sex. Characteristics of the participants were measured using the multi-item summary scales embedded in the interRAI LTCF; for all these scales, lower numbers represent less impairment. The Activities of Daily Living (ADL) Hierarchy scale was used to measure functional status, varying from 0 (no impairment) to 6 (total dependence) [23]. Cognitive status was assessed using the Cognitive Performance Scale (CPS), with its scores ranging from 0 (intact) to 6 (very severe impairment) [24]. The MDS Depression Rating scale was used to evaluate the presence of depressive symptoms and a score ≥ 3 (out of 7) was used to diagnose depression [25].

Statistical analysis

Principal component analysis was used to determine the multimorbidity patterns, with the aim to reduce the observed variables into a smaller set of composite variables, each indicating a different pattern of multimorbidity. Since the variables were dichotomous, a correlation matrix with tetrachoric correlations was used and the optimal number of components was determined with the "elbow" method [26, 27]. Considering the scree plot of the eigenvalues of the correlation matrix, the elbow corresponds to the distinct break of the curve; it is recommended to retain the components above this break, as they contribute most to the explanation of the variance. Component loadings (range − 1/ + 1) were used to determine how the diseases related to the identified components, with a high component loading indicating that a disease was well represented by the considered component. The components were then named in accordance with the diseases that most characterized them [5]. Four patterns of multimorbidity were identified: *heart diseases* (including ischemic heart disease, heart failure, arrythmia and atrial fibrillation); *dementia and sensory impairments* (dementia, hearing and visual impairment); *heart, respiratory and psychiatric diseases* (ischemic heart disease, chronic obstructive pulmonary disease, heart failure, neurotic stress related disease and depression); and *diabetes, musculoskeletal and vascular diseases* (cerebrovascular diseases, diabetes, hypertension and musculoskeletal disease). For each component, participants were stratified in tertiles with respect to their loading values. From the lowest to the highest tertile, the subject's expression of the multimorbidity pattern associated with the specific component increased. For each pattern, the possible combinations of tertiles and FI were evaluated: the first combination considered subjects with low expression of the multimorbidity pattern and low FI, while the last combination considered subjects with high expression of the multimorbidity pattern and high FI. Cox proportional hazards regression models were used to estimate adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) of mortality for the levels of FI in each tertile, with the combination of first tertile and low FI used as the reference category. Cox regression models were adjusted for sex, age and total number of diseases. In the analyses, a P value of < 0.05 was considered as statistically significant. The proportional hazards assumption of the Cox models was tested using both the Schoenfeld residual test and graphical assessment; the models did not meet the hazard proportionality assumption. However, this did not invalidate our results [28, 29]. Statistical analyses were performed using the software Stata version 16.0 (Stata Corporation, College Station, TX, USA).

Ethical approval

The project received approval form the Ethical Committee of the Università Cattolica del Sacro Cuore in Rome.

Results

Characteristics of the sample at baseline are shown in Table 1. The 4131 participants had a mean age of 84.4 years (± 8) and 2902 (70%) were females. Participants were observed for a mean follow-up of 2.2 years and up to 5 years. Individuals with high frailty index were more likely to be female (71.3%) and presented a mean number

Table 1 Characteristic of the study population at baseline, in the whole sample and by Frailty Index

	All, $N=4131$	Low frailty index, $N=1889$	High frailty index $N=2242$
Age (mean, SD)	84.2 (8.4)	83.2 (8.9)	85.1 (7.9)
Female	2902 (70.2)	1304 (69.0)	1598 (71.3)
Male	1229 (29.8)	585 (31.0)	644 (28.7)
Dementia	2549 (61.7)	1024 (54.2)	1525 (68.0)
Parkinson's disease	346 (8.4)	139 (7.4)	207 (9.2)
Cerebrovascular disease	940 (22.8)	289 (15.3)	651 (29.0)
Ischemic heart disease	1563 (37.8)	483 (25.6)	1080 (48.2)
COPD[a]	824 (19.9)	209 (11.2)	615 (27.4)
Heart failure	742 (17.9)	169 (9.0)	573 (25.6)
Neurotic stress-related disease	1239 (29.9)	589 (31.2)	650 (29.0)
Depression	1288 (31.2)	617 (32.7)	671 (29.9)
Schizophrenia	201 (4.9)	137 (7.3)	64 (2.9)
Cancer	363 (8.8)	114 (6.0)	249 (11.1)
Diabetes	916 (22.2)	406 (21.5)	510 (22.8)
Arrythmia	162 (3.9)	42 (2.2)	120 (5.4)
Atrial fibrillation	160 (3.9)	41 (2.2)	119 (5.3)
Visual impairment	1217 (29.5)	402 (21.3)	815 (36.4)
Hearing impairment	1108 (26.8)	339 (18.0)	769 (34.3)
Hip fracture	228 (5.5)	49 (2.6)	179 (8.0)
Hypertension	692 (16.8)	349 (18.5)	343 (15.3)
Osteoarthritis	114 (2.8)	67 (3.6)	47 (2.1)
Other MSK[b] diseases	231 (5.6)	95 (5.0)	136 (6.1)
Other neurologic diseases	100 (2.4)	39 (2.1)	61 (2.7)
Thyroid disease	98 (2.4)	48 (2.5)	50 (2.2)
Skin ulcer	1072 (25.9)	182 (9.6)	890 (39.7)
Mean number of diseases	3.9 (1.9)	3.9 (1.9)	4.6 (1.9)
Deaths	2034 (49.2)	742 (39.3)	1292 (57.6)

Values are presented as absolute number and column percentage (%)

[a]COPD chronic obstructive pulmonary disease

[b]MSK musculoskeletal

of diseases of 4.6 (± 1.9) vs. 3.9 (± 1.9). Only neurotic stress-related disease, depression, schizophrenia, hypertension, and osteoarthritis were more common in residents with a lower level of frailty. Overall mortality was higher in residents with a high level of frailty (57.6% vs. 39.3%). The distribution of the study population in the tertiles of the multimorbidity patterns stratified by level of frailty are reported in Online Resource 2. Figure 1 shows the hazard ratios for mortality across combinations of frailty levels and tertiles of each pattern, where higher tertiles identified residents with greater expression of that specific multimorbidity pattern. The reference category are the participants with low level of frailty and with little expression of the multimorbidity pattern. For the *heart diseases* and *dementia and sensory impairments* patterns, we observed that frailty and pathologies have an additive effect on mortality. In particular in *heart diseases*, the risk of mortality progressively increases with the increasing expression of the multimorbidity pattern, both in those with low frailty (HR 1.24, 95% CI 1.06–1.47; HR 1.41, 95% CI 1.15–1.73), and in those with a high level of frailty (HR 1.74, 95% CI 1.46–2.07; HR 2.01, 95% CI 1.73–2.33; HR 2.36, 95% CI 2.01–2.78). For the *dementia and sensory impairments* pattern, a significant estimate in those with a low level of frailty is observed only for the last tertile (1.37, 95% CI 1.14–1.64), while in the high level of frailty group the risk progressively increases with the increasing expression of the pattern (HR 1.70, 95% CI 1.44–2.01; HR 1.92 95% CI 1.64–2.25; HR 2.12, 95% CI 1.83–2.47). For the *heart, respiratory and psychiatric diseases* and *diabetes, musculoskeletal and vascular diseases* patterns, significant estimates are observed only with a high level of frailty. In particular, the *heart, respiratory and psychiatric diseases* pattern showed a decreasing trend (HR 1.81, 95%

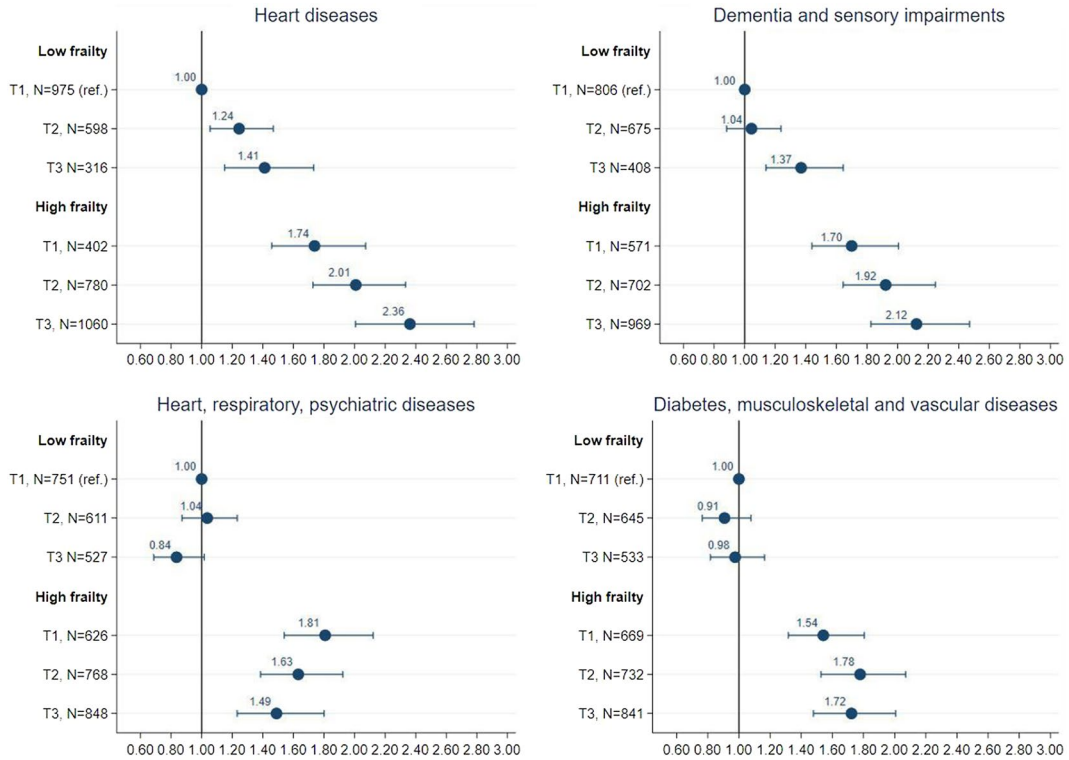

Fig. 1 Hazard ratios of multimorbidity patterns stratified by Frailty Index. Higher tertiles (T = tertile) identify residents with greater expression of the specific multimorbidity pattern. Estimates adjusted for age, sex, number of diseases

CI 1.54–2.12; HR 1.63, 95% CI 1.38–1.92, HR 1.49, 95% CI 1.23–1.80).

Discussion

The present study examines the interplay between frailty and multimorbidity patterns in institutionalized older adults and it shows that frailty increases mortality risk in all the disease patterns examined. In the *heart diseases* and *dementia and sensory impairments* patterns the risk of death increases progressively with patterns expression and frailty severity, suggesting a dose–response effect of diseases and frailty in shaping the prognosis. At the opposite, in the *heart, respiratory and psychiatric* and in the *diabetes, musculoskeletal and vascular diseases* patterns, frailty seems to have a stronger impact on mortality than pattern expression. To the best of our knowledge, this is the first study assessing the interaction between multimorbidity patterns and frailty on mortality in institutionalized older adults.

Overall, these findings indicate the importance of frailty in determining prognosis and support the need to assess frailty in persons with multimorbidity in order to identify those with the highest mortality risk, beyond disease patterns. Frailty is a multidimensional condition that provides in-depth information that goes beyond what captured by a standard clinical assessment, and that can be seen as a measure of accelerated biological aging [7]. Furthermore, frailty is a condition that may influence disease management and modify the effect of disease treatments on clinical outcomes [30]. Considering the high prevalence of functional and cognitive deficits, frail patients have a reduced ability to adhere to prescribed pharmacological and non-pharmacological treatments and an increased risk of treatment-related adverse events [12]. In line with these concepts is the observation that pharmacological treatment differs according to the level of frailty and frail residents receive fewer pharmacological treatments and in particular a lower number of preventive treatments (i.e., bisphosphonates, vitamin D, and acetylsalicylic acid) than non-frail patients [31]. This may be due to the fact that frailty is associated with reduced life expectancy and therefore use of preventive treatments may be unrewarding in this population. To note, the NICE guidelines on multimorbidity underline the need of assessing frailty in order to identify people who may benefit from an approach to care that takes account of multimorbidity, suggesting that frailty is a key condition that should influence the approach to the care of chronic conditions [13]. This concept was also pointed out by the recently published Italian guidelines on multimorbidity and polypharmacy [14].

In the *heart diseases* and *dementia and sensory impairments* patterns frailty and patterns expression seem having an additive effect in determining prognosis. This finding suggests that these patterns of multimorbidity and frailty have two partially distinct constructs that influence the risk of death in a complementary way. As mentioned, frailty is a multidimensional construct that covers relevant non-clinical aspects that can influence prognosis, including physical function, cognition, social factors, geriatric syndromes. This joint effect of frailty and multimorbidity on prognosis was also shown in case of occurrence of acute diseases. In a recent study on COVID-19 patients, the occurrence of multimorbidity and frailty seems to have an additive effect on prognosis in older adults, suggesting that both these conditions should be considered in the decision-making process and clinical management of COVID-19 patients [32]. Expression of the *diabetes, musculoskeletal and vascular diseases* pattern does not seem to impact on survival, and high frailty index is associated with an increased risk of death independently of expression of this pattern. A possible explanation relates to the fact that this pattern covers a group of individuals with less severe multimorbidity. This hypothesis is in line with previous findings showing that individuals with a higher burden of cardiovascular risk factors, such as hypertension, diabetes, obesity, and dyslipidaemia, but still with a relatively low prevalence of cardiovascular and neuropsychiatric diseases have lower mortality rates [3]. Similarly, a lack of impact on mortality was shown for the heart, respiratory and psychiatric pattern in absence of severe frailty and the association between this pattern and mortality in individuals with severe frailty showed a non-significant negative dose–response effect. Such observations may have 2 different explanations. First, having a high loading factor for this pattern likely excludes the possibility of having high loading factors on other more lethal patterns. Second, a healthy survivor effect might be at play; survival until late life of individuals characterized by such a heterogeneous group of diseases might imply a lower severity of the diseases themselves. However, being the mean age of institutionalized older adults so high, this is questionable, because a healthy survivor effect might have an impact on all individuals.

This study has several strengths. First, we used a validated data collection instrument (i.e., interRAI) and a standardized methodology to identify multimorbidity patterns. Moreover, the longitudinal design with up to 5 years of observation, which allowed to capture both short- and long-term prognoses of NH residents. Finally, it explores the interplay between disease and frailty, which has been rarely performed in this clinical setting. The following limitations should also be considered. First, although the disease assessment was carried out by trained assessors, we cannot exclude the presence of some misclassification and detection bias in our analyses. Still, a good reliability of the diagnoses has been previously demonstrated in the interRAI environment [17]. Second, data on diseases severity, a factor which can strongly influence prognosis, was not collected. Third, the dimensionality reduction technique used in this study does not find a direct clinical applicability on the single patient, being a sample of individuals needed to be available to run the analysis. Similarly, the attribution of individuals to specific patterns of multimorbidity is based on a probabilistic principle, making hard to identify unique correspondences between individuals and disease patterns. However, this reflects the reality, where a number of different conditions generate an endless number of disease combinations, some of them explained by pathophysiological principles, and other stochastically generated. Fourth, in the present paper we adopted a definition of frailty that is based on an accumulation of deficits, which is operationalized by the calculation of a FI as proposed by Rockwood [18]. Therefore, our results are not generalizable to different frailty constructs and definitions (i.e., physical frailty). Also, although the proportional hazards assumption of the Cox models was not met in the analyses, this finding does not invalidate our results. Indeed, when the hazard ratio does not remain constant over time, the coefficient represents an "average" effect over the event times [28, 29]. Finally, these data were collected in a sample of NH residents in Italy and they could not be generalizable to other settings and countries.

Conclusions and implications

Our study suggests that frailty provides additional prognostic information in terms of mortality in NH residents with different multimorbidity patterns. This finding supports the routine assessment of frailty to help healthcare professionals in identifying older people affected by specific groups of chronic diseases that have high risk of negative health outcomes and need a specific approach to care.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40520-022-02269-8.

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Availability of data and material The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Code availability Not applicable.

Declarations

Conflict of interest authors of the manuscript declare they have no financial relationships in the previous three years with any organizations that might have an interest in influencing the submitted work and no other relationships or activities (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript. No author declares any conflict of interest.

Ethical approval The project received approval form the Ethical Committee of the Università Cattolica del Sacro Cuore in Rome.

Informed consent In accordance with the Italian legislation, the permission to use anonymized electronic healthcare records is granted for observational epidemiological research as the present one.

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