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The association between cardiovascular risk factors and major cardiovascular diseases decreases with increasing frailty levels in geriatric outpatients

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ABSTRACT

Background: Frailty marks a process of increasing dysregulation of physiological systems which increases the risk of adverse health outcomes. This study examines the hypothesis that the association between multiple cardiovascular risk factors (CVRF) and cardiovascular diseases (CVD) becomes stronger with increasing frailty severity. **Methods:** Cross-sectional analysis of 339 older adults (55.2% women; aged 75.2 ± 9.1 years) from an outpatient geriatric clinic from a middle-income country. The frailty index (FI) was calculated as the proportion of 30 possible health deficits. We assessed hypertension, diabetes, obesity, dyslipidemia, sedentarism and smoking as CVRF (determinants) and myocardial infarction, stroke, heart failure as CVD. Poisson regression models adjusted for age, sex, and education was applied to estimate the association between frailty as well as CVRF (independent variables) with CVD (dependent variable).

Results: Of the 339 patients, 18.3% were frail ($FI \geq 0.25$) and 32.7% had at least one CVD. Both frailty and CVRF were significantly associated with CVD (PR = 1.03, 95% CI 1.01 to 1.05; $p = 0.001$, and PR = 1.46, 95% 1.24 to 1.71; $p < 0.001$, respectively) adjusted for covariates. The strength of the association between CVRF and CVD decreased with increasing frailty levels, as indicated by a significant interaction term of frailty and CVRF ($p < 0.001$).

Conclusion: Frailty and CVRF are both associated with CVD, but the impact of CVRF decreases in the presence of frailty. When confirmed in longitudinal studies, randomized controlled trials or causal inference methods like Mendelian randomization should be applied to assess whether a shift from traditional CVRF to frailty would improve cardiovascular outcome in the oldest old.

1. Introduction

Cardiovascular diseases (CVD) are the most common cause of mortality in the world (WHO, 2019; Afilalo et al., 2014). According to the WHO, about 17.9 million people die annually from these conditions, which correspond to 31% of all deaths. In addition to these alarming

mortality rates, CVD can also lead to loss of basic and instrumental activities of daily living (WHO, 2019). The main risk factors for CVD are related to lifestyle (sedentary lifestyle, smoking, and obesity) and chronic health conditions (hypertension, dyslipidemia, and diabetes) (Afilalo et al., 2014; Heiskanen et al., 2021). Despite their increase prevalence in the younger population in recent years, CVD generally

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present in later life (Heiskanen et al., 2021).

Previous studies have shown that frailty, a state of decreased homeostatic reserve capacity and resistance to stressors due to cumulative declines in multiple physiological systems (Dent et al., 2019), is more prevalent among older people with CVD (Afilalo et al., 2014; Frisoli et al., 2015; Veronese et al., 2017). Studies in both developed and developing countries consistently show that frailty is associated with CVD (Frisoli et al., 2015; Veronese et al., 2017), increases the incidence of CVD (Veronese et al., 2017) and is associated with a 3-fold increase in mortality among cardiovascular patients (Frisoli et al., 2015). Most studies were based on the frailty phenotype (Veronese, 2020), which contrasts with the Frailty Index (FI) based on the accumulation of deficits model, by its categorical classification of frailty (Hoogendijk et al., 2019). The FI, defined as the proportion of health deficits present in a person, gives severity estimate of frailty as a marker of biological aging (Rockwood and Howlett, 2019). Furthermore, the relationship between frailty and cardiovascular risk factors (CVRF) on their combined risk of CVD is largely unknown. Theoretically, frailty might consist in an independent risk factor for CVD or as a mediating mechanism by which CVRF result in CVD. Finally, as frailty defines a state of physiological impairment of an organic system, cardiovascular events could be a result of accumulated CVRF and loss of vascular homeostatic reserve. Thus, frailty could potentially moderate the relation between CVRF and cardiovascular outcomes.

Based on the frailty model that minor stressors could have major health consequence due to less resilience of the physiological systems, this study examines the hypothesis that the association between CVRF and CVD significantly increases in the presence of frailty among geriatric outpatients from a middle-income country.

2. Methods

2.1. Study design, participants and procedures

The present study is a cross-sectional analysis of the baseline data of the first wave of the Multimorbidity and Mental health Cohort Study in Frailty and Aging (MiMiCS-FRAIL) study (Fig. 1). The MiMiCS-FRAIL cohort aims to explore the understanding of the bidirectional association between multimorbidity, frailty and depression within a geriatric outpatient environment (Aprahamian et al., 2020). The participants of this cohort study are eligible outpatients of a university-based interdisciplinary geriatrics program in the Southwestern of Brazil (city of Jundiaí, State of São Paulo). Eligible patients are: (1) all new referrals to the outpatient clinic from local general practitioners or through patient's

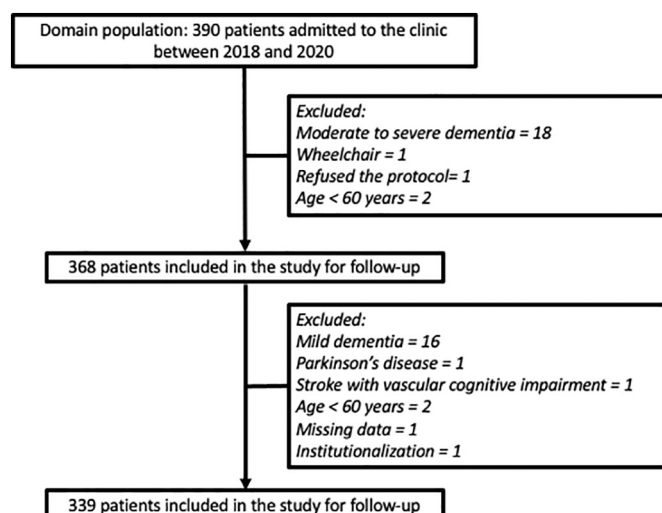


Fig. 1. Flow chart of included patients of the study.

direct access to the clinic; (2) aged 60 years or over; (3) with regular clinical follow-up with at least one visit every 12 months. Exclusion criteria are: (1) refusal to participate in the research; (2) dementia; (3) bipolar disorder; (4) psychotic disorder; (5) delirium or hospitalization in the last 30 days; (6) electroconvulsive therapy treatment; (7) wheelchair dependent; (8) severe sensory impairment; (9) severe motor impairment due to stroke or parkinsonism; (10) unstable clinical condition (e.g., decompensated heart failure, current infection); (11) terminal illness.

The recruitment for the MIMICS-FRAIL has started in January 2018 and is still ongoing. A multidisciplinary team of geriatricians, psychiatrists, and physical and nutritional therapists do an extensive clinical and psychiatric evaluation, and a comprehensive geriatric assessment is performed every 12 months. All patients receive a multi-axis diagnosis based in a multidisciplinary consensus meeting. The study is conducted in accordance with the ethical standards and procedures established by the Brazilian National Council of Health and all procedures were conducted following the precepts of research with humans established in the Helsinki Convention. The local ethical board approved this study under the protocol CAAE-12535218.5.0000.0065. All participants signed a written informed consent.

2.2. Measurements

2.2.1. Frailty

Frailty was evaluated using a FI. The FI accounts for the proportion of accumulated deficits derived from a count of symptoms, signs, laboratorial exams, conditions and disabilities across different health domains (ranging from 0 to 1). The index is calculated by the sum of present variables divided by total variables included. A previously validated electronic 36-item FI was used as a reference (Clegg et al., 2016). Eight items were removed from the original 36-item version due to their overlap with cardiovascular risks and outcomes variables (diabetes, hypertension, obesity, cerebrovascular disease, ischemic heart disease, atrial fibrillation, heart failure, and valvar heart disease) investigated in the present study. To ascertain the minimum requirement of 30 items of the FI (Rockwood and Howlett, 2019), two variables were included: sadness and chronic pain. The following 30 health deficits that composed the present FI are shown in Table 1. Disability was considered present when a patient needed any help with instrumental activities of daily living. Social vulnerability was considered present when a person answered positively on the question "Do you count with relatives or close friends to support you whenever you need them?" Frailty was defined as FI-30 of ≥ 0.25 (Rockwood and Howlett, 2019).

2.2.2. Cardiovascular risk factors

The independent variable consisted of the number of following CVRF present:

- Hypertension, defined as the average blood pressure $\geq 140/90$ mmHg measured twice at the dominant arm after a 5 minute rest (Unger et al., 2020).
- Diabetes mellitus, defined as at least two fasting glucose serum levels ≥ 126 mg and/or a glycated hemoglobin $\geq 6.5\%$ (ADA, 2021).
- Dyslipidemia, defined as a fasting LDL-cholesterol level ≥ 160 mg and/or an HDL-cholesterol level < 40 mg and/or triglycerides > 150 mg (Arnett et al., 2019).
- Obesity, defined as a body mass index (BMI) ≥ 30 kg/m².
- Sedentarism, operationalized as waking behavior characterized by an energy expenditure less than or equal to 1.5 metabolic equivalents, while in a sitting, reclining or lying posture (Owen et al., 2020).
- Currently smoking on a daily basis.

2.2.3. Cardiovascular diseases

Stroke, myocardial infarct, and heart failure (with ejection fraction

Table 1
Components of the 30-item frailty index.

Variable	Observations on deficit assignment
Diseases	
Anemia	Any kind of anemia
Arthritis	Osteoarthritis or rheumatologic disorders with arthritis
Chronic kidney disease	Calculated; With or without dialysis
Osteoporosis	Confirmed with densitometry
Parkinsonism (mild) and related disorders	Any movement disorder
Peptic ulcers	Recurrent or active ulcer
Peripheral vascular diseases	Venous or arterial disease
Respiratory disease	Asthma, COPD, pulmonary fibrosis, pneumonitis, bronchiectasis
Sleep disorder	Insomnia, parasomnias, obstructive apnea
Thyroid disease disorders	Hyperthyroidism or hypothyroidism
Urinary tract disorders	Chronic cystitis, obstructive disease
Symptoms	
Chronic pain	Referred by the patient; most of days
Dyspnea	Referred by the patient; most of days
Dizziness	Referred by the patient; most of days
Loss of appetite or anorexia	Referred by the patient; most of days
Sadness	Referred by the patient; most of days
Syncope	At least one episode in the last year
Geriatric syndromes	
Cognitive impairment	Memory of other cognitive complaints
Falls	Any fall in the last year
Fracture	Any fracture in the last year
Hearing loss	Referred by the patient or relative
Polypharmacy	Prescription check
Pressure ulcers	Referred by the patient or relative
Urinary incontinence	Any kind of incontinence
Visual impairment	Referred by the patient or relative
Social and function problems	
Care dependency	Disability for basic activities of daily living
Disability	Any degree of dependency for instrumental activities of daily living
Social vulnerability	Lack of a social network to support them when needed
Mobility problems	
Foot disorders	Deformities, step problems
Mobility problems	Necessity of help walking or use of orthosis

Note: COPD = chronic obstructive pulmonary disease; each variable if present corresponds to 1 point to be divided by 30 (variables) to generate the frailty index.

≤40%) were considered as major CVD. They were identified through clinical examination plus a gold standard biomarker (e.g., neuroimaging, troponin, ECG, coronary arteriography, or echocardiography). The dependent variable CVD consisted of the count of these events.

2.3. Confounders

Based on current literature (Hoogendijk et al., 2019), we included age, sex, and education as covariates.

2.4. Statistical analyses

Descriptive statistics (proportion or mean with standard deviation) were presented to characterize the sample. All continuous variables had a non-parametric distribution after histogram analysis and Kolmogorov-Smirnov test, except for age and body mass index (BMI). A comparison between patients with and without CVD was performed for the characterization of the sample using percentages for categorical variables and mean with standard deviation for continuous measures. Chi-square test and Mann-Whitney test (non-parametric variables) or Student's *t*-test (for age and BMI) were used to compare categorical and continuous variables, respectively. The Fisher test instead of chi-square test was used for groups with ≤5 individuals. Multiple Poisson regression models

adjusted for age, sex, and education were conducted to assess the association of CVRF and the FI (multiplied by 100 for better interpretation) with CVD. In the combined model, we first evaluated the interaction between CVRF and frailty in their association with CVD and will present stratified analysis (according to the presence of frailty) in case of significance. Goodness of fit was tested through verifying the assumption of a Poisson distribution of the dependent variable, a deviance variation (value/degree of freedom) between 0.9 and 1.1, Akaike Information Criterion (AIC) values, and the Omnibus test. *p*-Values lower than 5% were considered statistically significant. Data were analyzed using Statistical Package of the Social Sciences (SPSS), version 25.0.

3. Results

Among 339 participants, most participants were women (55.2%; *n* = 187), White (55.2%; *n* = 187) and had overweight or obesity (55.2%; *n* = 187). A total of 111 (32.7%) participants had at least 1 major CVD (22.4% had one, 7.5% had two, and 1.8% had three diseases). Overall, stroke was the most prevalent CVD (16.5%, *n* = 56), followed by heart failure (10.3%, *n* = 35) and myocardial infarction (9.1%, *n* = 31).

Table 2 shows the characteristics of the participants according to the presence of any CVD. Male sex, being married, hypertension, and dyslipidemia were more frequent among participants with at least one major CVD. The prevalence of frailty was 18.7% (Table 1), with no significant difference according to the presence of any CVD. However, mean FI was significantly higher among participants with cardiovascular events (*p* = 0.036).

The CVRF as well as the FI were significantly associated with CVD when adjusted for age, sex, and education (CVRF: PR = 1.46 [95% CI: 1.24–1.71], *p* < 0.001, Chi² Likelihood Ratio = 40.65, *df* = 4, *p* < 0.001; frailty: PR = 1.03 [95% CI: 1.01–1.05], *p* = 0.001, Chi² Likelihood Ratio = 29.82, *df* = 4, *p* < 0.001). When combined into one model, we identified an interaction between the number of CVRF and the FI (PR = 1.01 [95% CI: 1.00–1.03], *p* < 0.001). Stratified analyses showed that the association between CVRF and CVD was significantly weakened in the presence of frailty (CVRF in frail patients: PR = 1.37 [95% CI:

Table 2

Participants' characteristics according to the presence of major cardiovascular diseases (CVD).

	Total <i>n</i> = 339 (100%)	No CVD <i>n</i> = 228 (67.3%)	≥1 CVD <i>n</i> = 111 (32.7%)	<i>p</i> [#]
Age, mean (SD)	75.2 ± 9.1	74.8 ± 9.3	76.8 ± 8.6	0.197
Male sex, <i>n</i> (%)	152 (44.8)	84 (36.6)	68 (61.3)	<0.001
Non-white ethnicity, <i>n</i> (%)	81 (23.9)	50 (21.9)	31 (27.9)	0.230
Currently married, <i>n</i> (%)	191 (56.3)	115 (50.4)	76 (68.5)	0.002
Income ^a , <i>n</i> (%)	51 (15)	37 (16.2)	14 (12.6)	0.380
Physical activity, <i>n</i> (%)	283 (83.5)	191 (81.6)	92 (87.6)	0.169
Smoking, <i>n</i> (%)	15 (4.4)	11 (4.7)	4 (3.8)	0.481
Hypertension, <i>n</i> (%)	243 (71.7)	148 (64.9)	95 (85.6)	<0.001
Diabetes, <i>n</i> (%)	127 (37.5)	78 (34.2)	49 (44.1)	0.076
Dyslipidemia, <i>n</i> (%)	64 (18.9)	36 (15.8)	28 (25.2)	0.037
Obesity, <i>n</i> (%)	78 (23.0)	53 (23.2)	25 (22.5)	0.882
BMI, mean (SD)*	26.7 (5.1)	26.7 (5.4)	26.9 (4.4)	0.657
Frailty index, mean (SD)	0.16 (0.09)	0.15 (0.09)	0.17 (0.01)	0.036
Frailty, <i>n</i> (%)	62 (18.7)	39 (16.7)	23 (21.9)	0.249

Abbreviations: BMI, body mass index; all categorical analysis used chi-square test except for smoking (Fisher test).

^a < US\$ 500/month.

* *t*-Test.

[#] Mann-Whitney.

0.94–1.99], $p = 0.102$; CVRF in non-frail patients: PR = 1.45, [95% CI: 1.21–1.75], $p < 0.001$) (Fig. 2).

4. Discussion

In this cross-sectional study, we found that among geriatric outpatients both CVRF and frailty were associated with CVD. In contrast to our hypothesis, the association between CVRFs and CVD did not increase but even decreased with increasing levels of frailty. Although cross-sectional results, this might imply that in the oldest old prevention of cardiovascular outcomes could benefit from targeting traditional CVRFs to also targeting frailty. This hypothesis might be tested in future clinical trials.

A recent meta-analysis shows that several cross-sectional and longitudinal studies have explored the association between frailty and cardiovascular disease (Veronese et al., 2017). These studies preclude the conclusion that frailty may be considered a CVRF based on its association with incident cardiovascular outcomes as well as cardiovascular mortality (Jiang et al., 2017; Li et al., 2019; Fan et al., 2020). Although this conclusion requires further exploration, but several factors must be point out for this argument. The FI is considered a measure of biological aging and it can outperform DNA methylation age and other biomarkers related to accelerated aging (Kim et al., 2017). The explanation of these associations is sought in shared pathophysiological mechanisms of frailty and CVD like deoxyribonucleic acid damage, shorter telomere length (Ashar et al., 2015; Zaslavsky et al., 2013), higher oxidative stress and inflammatory levels (Soysal et al., 2016; Uchmanowicz, 2020). In this meta-analysis (Veronese et al., 2017), however, 18 out of the 21 studies had assessed frailty according to the physical phenotype criteria. The use of the frailty phenotype among cardiovascular patients has recently been criticized being inferior to other frailty scales and different between males and females (Chung et al., 2021).

Multidimensional measures of frailty like the FI may consist an important risk factor for cardiovascular events as multiple conditions (e.g., dyslipidemia), diseases (e.g., diabetes) and lifestyle (e.g., sedentarism) are involved in the development of vascular pathology. To our knowledge, only three studies have explored the association between CVD and frailty using the FI (Wallace et al., 2014; Aguayo et al., 2018; Farooqi et al., 2020). These three studies, all identified a prospective association between the FI and subsequent cardiovascular events, despite some limitations. First, the FI includes many health deficits that largely overlap with traditional CVRF (e.g. elevated glucose levels). While we have excluded these health deficits in the FI applied in our study, these other studies did not (Aguayo et al., 2018). Secondly, two of these three studies (Wallace et al., 2014; Farooqi et al., 2020) used only 17 and 26 health deficits to construct their FI, while it has been argued that at least 30 health deficits should be considered to construct a valid FI (Searle et al., 2008). Finally, one of these studies included only participants of clinical trials (Farooqi et al., 2020), which constitute a highly selective sample. A very recent study without these flaws showed that a multidimensional prognostic index (MPI) to assess frailty was associated with several CVRF and predicted incident CVD among 4211 community-dwelling adults over an 8-year follow-up (Veronese et al., 2021).

For proper interpretation, however, significant limitations of our study should be taken into account, especially the fact that our cross-sectional design precludes causal interpretation. Our sample came from a single center in a middle-income country with lower educational level, which could compromise extrapolation of our findings. However, this is the first study from a naturalistic design cohort study from an outpatient clinic using a validated FI. Moreover, all CVRF and CVD were examined by more than one physician prospectively and using standard diagnostic procedures. Finally, potential limitations regarding the adjustment for covariates in our regression analysis should be addressed. Secondary variables are associated with frailty among older adults such

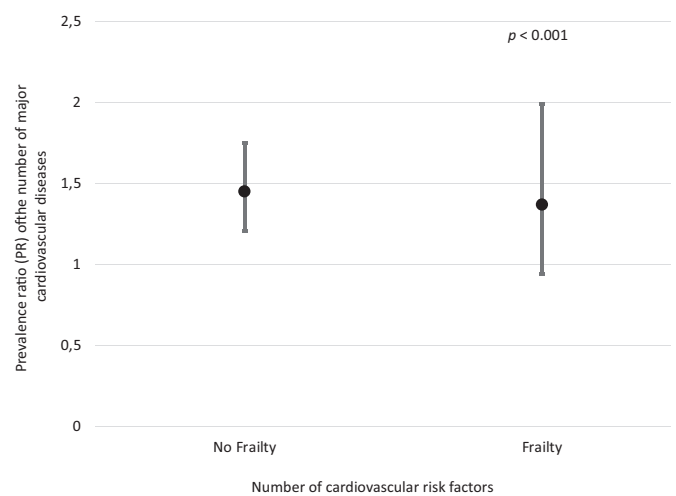


Fig. 2. Association between the number of cardiovascular risk factors and the number of major cardiovascular disease stratified by the frailty status.

as underweight, chronic renal disease, and lower socioeconomic status (Hoogendijk et al., 2019). A larger sample size would better support the adjustment for multiple variables.

To the best of our knowledge, our study is the first to explore the interaction between frailty severity by using a 30-item FI excluding CVRF items and traditional CVRF. Interestingly, we found the opposite of our initial hypothesis as in our finding the association between CVRF and CVD decreases with increasing frailty severity. However, these findings fit with accumulating evidence that the risk-benefit ratio of intensive treatment against CVRF among frail older adults (e.g., aggressive antihypertensive treatment) turns around due to increased risk on iatrogenic damage.

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