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ORIGINAL ARTICLE

Individual and cumulative association of commonly used biomarkers on frailty: a cross-sectional analysis of the Mexican Health and Aging Study

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Abstract
Frailty has been recognized as a common condition in older adults, however, there is scarce information on the association between frailty and commonly used biomarkers. The aim of this study was to assess the individual and cumulative association of biomarkers with frailty status. This is a cross-sectional analysis of the 2012 wave of the Mexican Health and Aging Study. A sub-sample of 60-year or older adults with anthropometric measurements was analyzed. Frailty was defined with a 31-item frailty index and those considered frail had a score ≥ 0.21. Biomarkers were further categorized as normal/abnormal and tested both one by one and grouped (according to their usual cutoff values). Adjusted logistic models were performed. A total of 1128 older adults were analyzed and their mean age was 69.45 years and 51.24% of them were women. 26.7% ($n=301$) were categorized as frail. Individual biomarkers associated with frailty after adjusting for confounding were: hemoglobin [odds ratio (OR) 1.67, 95% confidence interval (CI) 1.13–2.46, $p=0.009$], glycated hemoglobin (OR 2.04, 95% CI 1.54–2.7, $p<0.001$) and vitamin D (OR 1.53, 95% CI 1.13–2.07, $p=0.005$). Those with ≥ 4 abnormal biomarkers had an independent association with frailty when compared to those without any abnormal biomarker (OR 2.64, 95% CI 1.3–5.25, $p=0.005$). Aside from the individual associations of specific biomarkers, our findings show that an incremental association of abnormal biomarkers increases the probability of frailty, accounting for the multidimensional nature of frailty and the possible interplay between components of the system that potentiate to give rise to a negative condition such as frailty.

Keywords Frail older adult · Geriatric epidemiology · Biomarkers · Aging

Introduction

Frailty has been recognized as a condition with multiple causality, characterized by an increase in the individual's vulnerability for developing adverse outcomes (e.g., disability, dependency, institutionalization and/or death) [1]. Adverse outcomes usually arise when the older adult is exposed to stressors [2], that in normal conditions would have no effect—or minimal—on the overall health status of the individual. The fact that frailty is a common condition in older adults and that this group of the population has an accelerated growth—in comparison to other age groups—increases the need for reliable information that helps to characterize it in different settings [3, 4], and in turn improves older adult care. In addition to narrowing the gap on the knowledge of frailty, it also helps in providing data on how commonly used biomarkers are part of some chronic diseases or even multimorbidity, closely related to the genesis of frailty. Having this in mind, older adults with abnormal biomarkers could be screened with readily available tools that include clinical features of the condition or may help to identify older adults that could benefit from a thorough geriatric assessment [5]. This is particularly true in those settings with scarce resources specialized for care of the older adults [6].

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In particular, biomarkers are substances that can be measured objectively in the body, reflecting underlying processes either of normal or abnormal physiology, and some of them are used commonly in the health care of older adults, as 'routine labs' (e.g., vitamin D, cholesterol, thyroid hormones and C-reactive protein) [7, 8]. There is evidence that these biomarkers have an association with frailty as a whole or with some of its components (i.e., physical performance, exhaustion, low physical activity, specific deficits, etc); in addition, some other conditions such as geriatric syndromes have been also associated to abnormal values of biomarkers (e.g., falls, late-life depressive symptoms, cognitive impairment, etc.). In particular, vitamin D has been associated with frailty [9], in different contexts and populations [10–14], and impacting the physical component of frailty through its effect in muscle strength. Moreover, different studies have shown that C-reactive protein (CRP) is associated with decreased gait speed and lower handgrip strength, along with overall lower physical function [15]. Finally, some evidence shows that high levels of thyroid-stimulating hormone (TSH) are associated with disability, cognitive dysfunction, osteoporosis and cardiovascular disease [16].

There is a complex interrelation of the physiologic systems that gives rise to frailty [17]. For example, some evidence points to the fact that a set of hormones have a stronger association with frailty when combined [18]. This goes in the same line on how the multi-causality of frailty could be better explained by synergic etiology rather than by the one-cause one-disease paradigm [19]. This has been shown by Rockwood et al., when composing a frailty index with biomarkers (i.e., addition of abnormal laboratory values), that had similar association as the conventional frailty index with adverse outcomes [8].

To our knowledge, there is no current information on the association of commonly used biomarkers and frailty in community-dwelling older adults. Therefore, the aim of the present study was to assess the individual and cumulative association of biomarkers with frailty status. We hypothesized that the association between frailty and serum markers would be stronger when added in comparison to any of the biomarkers alone.

Methods

Design and settings

This is a cross-sectional analysis of the third (2012) wave from the Mexican Health and Aging Study (MHAS), a prospective cohort conducted in Mexico since 2001. The aim and design of the MHAS are published elsewhere [20, 21]. In brief, there are four waves of this study (2001, 2003, 2012, and 2015) with a representative sample of community-dwelling Mexican older adults. A set of questionnaires (e.g., socio-demographic, health-related, cognitive performance, functional status, etc.) were applied head-to-head by standardized interviewers. Each wave included a sub-sample in which anthropometry and biomarkers were included. Regarding biomarkers, technical specificities for each of the biomarkers are available upon request.

For the purposes of this report, only 2012 data was analyzed. A total of 18,465 participants who were 50 years or older were assessed in this wave in which a sub-sample of 1128 individuals was included (with biomarkers and anthropometric measurements).

Measurements

Dependent variable

A frailty index (FI) constructed with standard procedures [22] was used to categorize older adults as frail or non-frail. The FI included 31 deficits from different domains: self-rated health, comorbidities, mental health and somatic symptoms (see Sect. 4 of the supplementary material). Each deficit was transformed into a score of 0 (deficit absent) to 1 (deficit present) with possible intermediate scores; afterwards all the scores were summed and divided by the total number of deficits (i.e., 31) for each participant. The final score ranged from zero (no deficits, lowest frailty score possible) to one (all deficits present, highest frailty score possible). A cutoff value of 0.21 or higher was used to define frailty, a value validated for Mexican older adults previously [23].

Independent variables

Biomarkers were obtained from a blood sample of peripheral venipuncture by trained personnel. Collected samples were centrifuged 30 min after the venipuncture at 2,500RPM for 15–20 min; serum was separated by this technique and preserved in 2 ml tubes under refrigeration (2–8 °C). These measurements were performed between October and November of 2012. Cutoff values to define abnormality were defined as follows: CRP $\geq$ 3 mg/dL, total cholesterol $\leq$ 200 mg/dL, high-density lipoprotein cholesterol (HDL-c) $\geq$ 40 mg/dL, thyroid-stimulating hormone (TSH) 0.45–4.12 mIU/mL, hemoglobin $\geq$ 13.5 g/dL for men and $\geq$ 12.0 g/dL for women, vitamin D $\geq$ 20 ng/ml and glycated hemoglobin $\leq$ 6.5%. In addition to individual biomarkers, a composite variable was constructed by adding abnormal biomarkers (ranging from 0 = no abnormal biomarkers to 4 or more abnormal biomarkers). These scores were then contrasted between frail and non-frail older adults (having as the reference group those without any abnormal biomarker).

Confounding

To further describe the study population, socio-demographic characteristics included, age, sex, marital status (married or not married), and years of education were included as well as body mass index (BMI). In addition, these variables were also used in the adjusted models to consider confounding.

Statistical analysis

Descriptive statistics were performed, quantitative variables are presented as means (± SD) and categorical variables as relative frequencies (percentage). Univariate analysis was performed to compare frail and non-frail participants in baseline demographics and biomarkers, using independent samples *t* test, and Chi square test for categorical variables. A multiple logistic regression model was fitted with frailty as the dependent variable, odds ratio (OR) with 95% confidence intervals (CI) were reported in unadjusted and adjusted (for age, sex, marital status, years in school and BMI) fashion. All analyses were performed with statistical package software STATA 14® (StataCorp 4905, Lakeway Drive, College Station, TX 77845 USA).

Ethical issues

The Institutional Review Boards or Ethics Committees of the University of Texas Medical Branch in the United States, the Instituto Nacional de Estadística y Geografía, the Instituto Nacional de Salud Pública and the Instituto Nacional de Geriatría in Mexico approved the study. All study subjects signed an informed consent form.

Results

From a total of 1128, 26.7% were categorized as frail ($n = 301$). Their mean age was 69.5 years (± SDS 7.8), and the frail older adults were significantly older ($p < 0.001$). Regarding years in school, frail older adults had significantly fewer completed years in school compared to those without frailty ($p < 0.001$). There is no difference between frail and non-frail people for BMI ($p < 0.05$). There was a significant higher proportion of abnormal and glycated hemoglobin, vitamin D levels and CRP in frail older adults (see Table 1).

As shown by the multivariate logistic regression adjusted models (Table 2), frail older adults who had lower levels of hemoglobin had 1.67 times the risk of being frail ($p < 0.05$) compared with people with higher levels and lower levels

Table 1 General description of the sample by frailty status

	Total ($n = 1128$)	Frail ($n = 301$ [26.68%])	Non-frail ($n = 827$ [73.32%])	*p* value
Age, mean (SD)	69.45 (7.77)	71.93 (9.26)	68.54 (6.94)	< 0.001
Women, *n* (%)	578 (51.24)	204 (35.29)	374 (64.71)	< 0.001
Married, *n* (%)	654 (57.98)	143 (21.87)	511 (78.13)	< 0.001
Years in school, mean (SD)	4.5 (4.26)	3.03 (3.32)	5.11 (4.43)	< 0.001
Body mass index, mean (SD)	28.41 (5.3)	28.89 (6.12)	28.24 (4.96)	0.068
Hemoglobin, *n* (%)	173 (14.6)	99 (57.2)	74 (42.7)	0.015
Glycated hemoglobin, *n* (%)	467 (39.5)	267 (57.1)	200 (42.8)	< 0.001
Total cholesterol, *n* (%)	167 (14.7)	77 (46.1)	90 (53.8)	0.366
HDL cholesterol, *n* (%)	538 (47.6)	270 (50.1)	268 (49.8)	0.586
Thyroid-stimulating hormone, *n* (%)	204 (17.2)	109 (53.4)	95 (46.5)	0.133
Vitamin D, *n* (%)	416 (36.8)	236 (56.7)	180 (43.2)	< 0.001
C-reactive protein, *n* (%)	478 (40.4)	271 (56.7)	207 (43.3)	< 0.001
Number of abnormal biomarkers				
0	86 (7.62)	14 (16.28)	72 (83.72)	< 0.001
1	229 (20.3)	192 (83.84)	37 (16.16)	
2	368 (32.62)	85 (28.24)	283 (76.9)	
3	275 (24.38)	92 (33.45)	183 (66.55)	
≥ 4	170 (15.07)	73 (42.94)	97(57.06)	

Frailty was considered present in those older adults with a frailty index score ≥ 0.21

Cutoff values to define abnormality were defined as follows: C-reactive protein (CRP) 3 mg/dL, total cholesterol < 200 mg/dL, high-density lipoprotein cholesterol [HDL-c] ≥ 40 mg/dL, thyroid-stimulating hormone (TSH) 0.45–4.12 mIU/mL, hemoglobin ≥ 13.5 g/dL for men and ≥ 12.0 g/dL for women, vitamin D ≥ 20 ng/ml and glycated hemoglobin ≤ 6.5%

Table 2 Multivariate logistic regression for frailty, individual abnormal biomarkers and number of abnormal biomarkers

	Unadjusted OR (95% CI)	*p* value	Adjusted OR (95% CI)[a]	*p* value
Hemoglobin	1.42 (1.01–2.03)	0.049	1.67 (1.13–2.46)	0.009
Glycated hemoglobin	1.88 (1.44–2.44)	< 0.001	2.04 (1.54–2.7)	< 0.001
Total cholesterol	1.01 (0.7–1.47)	0.934	1.04 (0.7–1.55)	0.822
HDL cholesterol	0.88 (0.68–1.15)	0.377	0.87 (0.65–1.16)	0.347
Thyroid-stimulating hormone	1.33 (0.92–1.93)	0.129	1.19 (0.8–1.7)	0.375
Vitamin D	1.7 (1.3–2.22)	< 0.001	1.53 (1.13–2.07)	0.005
C-reactive protein	1.7 (1.36–2.17)	< 0.001	1.4 (1.08–1.81)	0.01
Number of abnormal biomarkers				
None	Reference			
1	0.9 (0.5–1.94)	0.979	0.8 (0.39–1.61)	0.53
2	1.54 (0.82–2.87)	0.17	1.24 (0.65–2.39)	0.503
3	2.58 (1.38–4.82)	0.003	2.02 (1.04–3.8)	0.035
4 or more	3.87 (2.02–7.39)	< 0.001	2.64 (1.3–5.25)	0.005

Frailty was considered present in those older adults with a frailty index score ≥ 0.21

Cutoff values to define abnormality were defined as follows: C-reactive protein (CRP) 3 mg/dL, total cholesterol < 200 mg/dL, high-density lipoprotein cholesterol (HDL-c) ≥ 40 mg/dL, thyroid-stimulating hormone (TSH) 0.45–4.12 mIU/mL, hemoglobin ≥ 13.5 g/dL for men and ≥ 12.0 g/dL for women, vitamin D ≥ 20 ng/ml and glycated hemoglobin ≤ 6.5%

[a]Adjusted models for: age, sex, marital status, years in school and body mass index

of vitamin D indicates 1.53 times the risk of frailty in comparison with people who had higher concentrations. Moreover, older adults with higher levels of glycated hemoglobin have 2.04 times the risk of being frail. Regarding CRP, the adjusted model showed an OR of 1.4 (95% CI 1.08–1.81, $p = 0.01$). Although other parameters did not demonstrate statistical significance, trends are shown in the expected direction. Regarding the incremental association of the addition of abnormal biomarkers, as the number of altered parameters increases, the risk of frailty also increased, with the highest significance for ≥ 4 abnormal biomarkers (OR 2.64; 95% CI 1.3–5.25; $p < 0.05$), when compared to no abnormal biomarker.

Discussion

According to our results, there is an association between frailty and commonly used biomarkers individually—especially for those that have shown to be related to the physiopathology of frailty—and also an incremental association when adding abnormal biomarkers. Our results showed that hemoglobin and vitamin D are associated individually with frailty, results that are similar with those reported by Schoufour et al. where hemoglobin was inversely correlated with frailty in both the unadjusted and adjusted models ($p < 0.001$) and with those from Sanchis et al. where levels of vitamin D were lower in frail people in comparison with non-frail ($p < 0.05$) [24, 25]. In addition, an association has also been established between diabetes and frailty [26, 27], as in our study a higher level of glycated hemoglobin was also associated with frailty. Moreover, CRP as a marker of inflammatory status was also associated with frailty in our study, as already shown in a previous work [28].

When adding the number of abnormal biomarkers, the strength of association with frailty was higher; this finding is more in line with the proposed deficit accumulation path to frailty, that has also shown to be associated with adverse outcomes [29]. In this respect, it is known that the sum of altered biomarkers can be useful in identifying the individual risk of frailty (because the biomarkers make part of chronic diseases or multimorbidity that lead to frailty) [2, 8], functional decline [30] and disability [11]. Notwithstanding, Van Hemelrijck et. al. constructed a mortality score based on the number of abnormal biomarkers, and noted that those older adults who had more than three altered biomarkers were at significantly higher risk for 3- and 7-year mortality than those with one or two biomarkers ($p < 0.01$) [28], similar to our results, that showed an association with frailty when three or more abnormal biomarkers were present, but not with one or two. It is important to stress the fact that intervening in those conditions related to abnormal biomarkers or as a group, could finally impact on the development of frailty or its progression. For example, the supplementation of vitamin D has shown to improve muscle strength, this in turn would turn in a better physical status that could prevent frailty or even halt its progression.

Our study has a number of relevant limitations that should be considered to interpret the results appropriately. The first one is that from our data, no causal relationship could be inferred due to its cross-sectional nature. Future research should focus on the pathophysiological mechanisms

that underlie abnormal biomarkers and the impact of these alterations in trajectories of frailty and its adverse outcomes such as disability. Although a vast number of biomarkers had been reported to be linked with frailty and other conditions in older adults, in the Mexican context, those reported in the present work are the most used in the clinical asset, so that comparisons with other reports can be difficult to done. However, other biomarkers could have been studied that have been associated with frailty in other populations; in this work we were limited to those available in MHAS. One common problem when it comes to older adults is the use of cutoff values, the vast majority of these reference values come from younger population or not the same population of the manuscript; another approach could be based on the distribution of the biomarkers data, however, we decided using commonly used reference values to make the interpretation of the associations easier.

Specific biomarkers were associated with frailty, particularly those involved in the pathophysiology of this condition. In addition, a higher number of abnormal biomarkers was also associated with frailty irrespective of which was, pointing also to the deficit accumulation pathway to frailty.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in the present study were in accordance with the ethical standards of the National Geriatrics Institute research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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