The relationship between albumin levels and the presence and progression of frailty in low to middle-income countries

An analysis of the International Mobility in Aging Study (IMIAS)

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Abstract

Introduction: frailty is a geriatric syndrome with multiple causes and contributing factors, which increases vulnerability to various health outcomes like disability and death. Low albumin is considered to be a potential indicator of frailty; however, the evidence is controversial. This study seeks to relate low albumin to the presence and progression of frailty in older adults in low and middle-income countries.

Design and analysis: this was a longitudinal observational study using data from the International Mobility in Aging Study (IMIAS). Data was analyzed from 837 adults 65 to 74 years of age from Tirana (Albania), Natal (Brazil) and Manizales (Colombia), who were followed from 2012 to 2016. The analysis included sociodemographic, anthropometric, physical health, mental health and mobility variables

Results: a multivariate logistic regression analysis showed that hypoalbuminemia (<4 gr/dL) (RR= 2.51, p= 0.021), poor grip strength (RR= 2.67, p= 0.001), a score < 8 on the Short Physical Performance Battery (SPPB) (RR= 4.641, p= 0.000) and a mobility disability (RR= 2.89, p=0.004) were independently related to a higher risk of developing frailty in four years.

Conclusions: low albumin in older adults is an independent risk factor for the developing frailty. This information is relevant and could contribute to predicting and treating frailty in older adults which could, in turn, prevent complications and lower the medical costs related to its care. **(Acta Med Colomb 2025; 50. DOI: https://doi.org/10.36104/amc.2025.3306).**

Keywords: *frailty, albumin, risk factor, older person*.

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Introduction

Frailty is defined as age-related progressive reduction of physiological reserves that confers extreme vulnerability to stress factors and increases the risk of a variety of adverse health outcomes (1) like a higher susceptibility to falls, injuries, functional limitations, dependency, disability and death in older people (2). Frailty is considered reversible in its initial stages; therefore, it can be treated and prevented (3).

Population aging due to increased life expectancy and lower birth rates will lead to an increase in age-related diseases and disability, generating multiple personal, social and economic consequences (4). This phenomenon is not limited to high-income countries, as life expectancy is steadily increasing in low and middle-income countries (5). In these countries, where healthcare resources are limited, the lack of equipment, qualified personnel or adequate and validated assessment techniques may make it difficult to perform tests and provide treatment (6, 7).

The literature describes two main conceptual models for frailty (1). The most frequently used is the model proposed by Fried et al. (8), that establishes frailty as a phenotype with five interrelated components: loss of strength, decreased walking speed, self-perceived weakness and fatigue, and unintentional weight loss (8). The second most disseminated model is the frailty index proposed by Rockwood et al. (9), focusing on frailty as an accumulation of deficits at different levels, through a set of clinical conditions and diseases.

The lack of a single operative definition and the complex underlying pathophysiology make it challenging to develop biomarkers for this condition, as these ambiguities directly affect the precision, sensitivity and specificity of the currently proposed biomarkers (10). More than 40 biomarkers have been investigated, including inflammatory, hematological,

immunological, cellular senescence, genetic and epigenetic markers (10,11). However, biomarkers able to distinguish between the changes related to frailty itself and those that can be attributed to comorbid diseases have still not been identified (12). Furthermore, most of these biomarkers are considered biological markers of aging, and therefore their abnormalities could be related to the aging process itself, regardless of the presence of frailty (10).

Low albumin levels have been related to multiple health outcomes in older people, like malnutrition, postoperative complications, infections, prolonged hospitalizations, functional dependency, disability, sarcopenia, frailty and death (13-18). However, the relationship between albumin and frailty is still a matter of debate (10, 19-21). Its relationship to various common comorbidities in older people, like liver diseases, nephrotic syndrome and acute malnutrition, make it difficult to use as an independent marker of frailty (10), as these factors could interfere with its interpretation and limit its reliability as a biomarker in this context.

Despite the growing number of studies on frailty biomarkers, most studies evaluating low albumin levels have a cross-sectional design and wide variability in the available evidence (10, 12), which restricts their interpretation and application in clinical practice. The objective of this study was to analyze the relationship between albumin levels and the presence and progression of frailty in older people in different epidemiological contexts in low to middle-income countries.

Method

This was a longitudinal observational study using data from IMIAS, a longitudinal, prospective, multi-center population cohort study conducted in five cities (Tirana, Albania; Natal, Brazil; Manizales, Colombia; Kingston, Canada; and San Jacinto, Canada). The main objective of IMIAS was to understand the differences in mobility disability in older adults from different settings with different social, cultural, and socioeconomic aspects, as well as healthcare systems.

The study began in 2012 with a representative sample from each site, stratified by sex, recruiting 200 men and 200 women per city, for a total of 2,002 older adults aged 65 to 74 years. A summary of the study and the cohort details are extensively described in another document (22).

The inclusion criterion was to be registered in the database during the data gathering years 2012, 2014 and 2016. The exclusion criterion used in IMIAS was severe cognitive decline, established by a Leganes test equal to or greater than four, as these individuals were considered unable to answer the questionnaire and carry out the physical function tests, as well as freely consent to participate. In our analysis, we excluded 512 participants without follow up throughout the four years, and 141 participants without albumin measurement in 2012.

Our study analyzed data from a total of 837 men and women from Albania, Natal and Manizales. Sociodemographic, anthropometric, physical health, mental health and mobility variables were included. The Strengthening The Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed in preparing and presenting this study. (23).

Frailty was measured using the frailty phenotype based on a modified version of Fried et al.'s (8) original criteria. This model includes five physical components: involuntary weight loss, weakness, slow walking speed, exhaustion and low physical activity. Participants with three or more of these components were classified as frail, those with one or two components as pre-frail, and those with no components as not frail.

In this study, albumin values were operationalized as a dichotomous variable. Albumin was defined as normal when it was equal to or greater than 4 g/dL, and low when it was less than 4 g/dL, based on the literature that has associated these levels with frailty. The selection of this cut-off point is described in the statistical analysis and results sections.

Different variables were included based on the literature review of their importance and relationship to frailty. The sociodemographic and anthropometric data were represented by age, sex, study site, educational level, income, body mass index and weight. Physical health data included the presence of chronic illnesses (hypertension, diabetes, cancer, chronic pulmonary disease, heart disease, cerebrovascular disease, osteoarthritis and osteoporosis), self-reported health, polypharmacy, eyesight deterioration, the Short Physical Performance Battery (SPPB) and mobility disability (Nagi questions). In addition, mental health was represented by the presence of depression (CES-D).

Statistical analysis

A descriptive analysis (frequencies, distribution, medians and standard deviation) was performed, and the prevalence and incidence of frailty was calculated in the different follow-up waves. The normality of the variables was measured with the Kolmogorov-Smirnov test. After this, differences in 2012 albumin levels were sought between the groups (frail and not frail) using the Mann-Whitney U test, as the distribution was not normal.

To identify the best cut-off point for low albumin, we analyzed different cut-off points in the literature relating albumin and frailty using Chi square. With albumin as a dichotomous variable, a longitudinal bivariate analysis was done through logistic regression, as there was a categorical dependent variable. Finally, a multivariate logistic regression model was built adjusting for multiple confounding variables, and the Cox & Snell and Nagelkerke R squares were applied.

All statistical analyses were done using the R statistical package with Jamovi.

Ethical considerations

The IMIAS study was approved by the ethics committee at each study site and the research ethics committees at Univer-

sidad Federal de Rio Grande do Norte (Brazil), the Albanian Public Health Institute (Albania) and Universidad de Caldas (Colombia). The researchers responsible for the databases gave their endorsement and consent for these analyses.

Likewise, the data are labeled and coded with assignment codes to prevent participant identification.

Results

The specific characteristics by frailty status in 2012 are presented in Table 1. Frailty was more frequent in women and people with a higher burden of comorbidities. Participants classified as frail had more falls and a greater tendency toward polypharmacy and reported worse self-perceived health. They also had lower scores on the SPPB, less grip strength and lower levels of hemoglobin.

The prevalence of frailty was 5.5% in 2012, increasing to 9.1% in 2014, and was 8.9% in 2016. The incidence of frailty from 2012 - 2014 was 33.45 cases per 1,000 persons/year, with a reduction in 2012 - 2016 of 29.25 cases per 1,000 persons/year (Figures 1 and 2).

Table 1. A total of 837 patients (2012).

Variable	Frail (46)	Not frail (791)	P value
Age (years)	70.07+/-2.70	69.15+/-2.97	0.040*
Sex, female, n (%)	31 (67.4)	403 (50.9)	0.021*
Comorbidity (> or equal to 2) (%)	39 (84.8)	445 (56.3)	0.000*
Chronic conditions, n (%)			
Hypertension	7 (15.2)	85 (10.7)	0.069
Diabetes mellitus	13 (28.3)	164 (20.7)	0.047*
Cancer	1 (2.2)	26 (3.3)	0.864
Pulmonary disease	11 (23.9)	82 (10.4)	0.017*
Heart disease	16 (34.8)	172 (21.7)	0.051
Stroke	9 (19.6)	26 (3.3)	0.000*
Osteoarthritis	27 (58.7)	307 (38.8)	0.027*
Osteoporosis	20 (43.5)	145 (18.3)	0.000*
Polypharmacy (>= 5 medications) (%)	43 (69.4)	506 (39.3)	0.000*
History of falls (%)	29 (46.8)	337 (26.2)	0.000*
SPPB >=8 (%)	23 (37.1)	1,186 (92.2)	0.000*
Good - very good self-reported health, n (%)	9 (14.5)	776 (60.5)	0.000*
Grip strength, kg/f [IQR]	16 [12]	27 [15]	0.000*
CRP, mg/L [IQR]	2.9 [6.1]	2[3.6]	0.075
IL-6, pg/ml [IQR]	2.9 [6.1]	2 [2.4]	0.072
Hgb, g/L [IQR]	129 [25.1]	139 [24]	0.001*
BMI ($kg*m^{-2}$) [IQR]	27.3 [6.05]	27.2 [2.8]	0.678
HbA1c, % [IQR]	6.15 [1.12]	5.85 [0.77]	0.185

*Notes: * statistically significant p, 283 participants with no reported CRP, 330 participants with no reported IL 6, [IQR] = Interquartile range, SPPB: Short Physical Performance Battery.*

In 2012, the median albumin for frail participants was 4.45 gr/dL and 4.6 g/dL for non-frail participants, with a statistically significant difference (p = 0.043). The relationship between low albumin and frailty according to different cut-off points established in the 2012 data is summarized in Table 2. There were statistically significant differences for values under 3.8 gr/dL (p= 0.033) and under 4 gr/dL (p=0.001).

In the longitudinal bivariate analysis between low albumin in 2012 and frailty in 2014 and 2016, the relative risk (RR) was calculated with both cut-off points, as shown in Table 3. After four years, the RR was 2.64 (p=0.027 95% CI 1.115-6.256) for albumin lower than 3.8 gr/dL and 3.145 (p= 0.000 95% CI 1.679-5.891) for albumin below 4 gr/dL. No longitudinal relationship was found after two years for either case.

The multivariate logistic regression analysis showed that low albumin (< 4 gr/dL; RR= 2.51, p= 0.021), low grip strength (RR= 2.67, p= 0.001), an SPPB < 8 points (RR= 4.641, p= 0.000) and a mobility disability status (RR= 2.89, p=0.004), were independently associated with

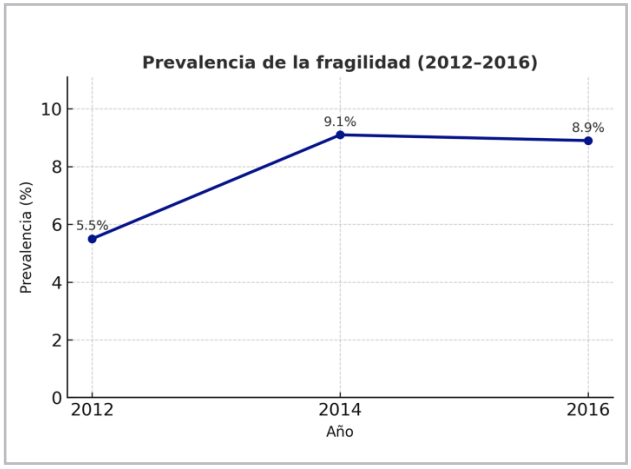

Figure 1. *Prevalence (%) of frailty in the IMIAS study (n=837).*

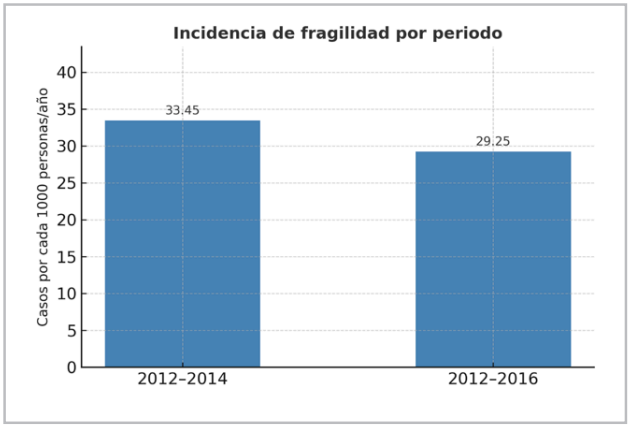

Figure 2. *Incidence of frailty in the IMIAS study.*

Table 2. *Low albumin and frailty according to the cut-off points in the literature (Chi square).*

Cut-off points							
< 3.5 gr/dL[1]	p= 0.690	S: 0%;	Sp: 99.0%	PPV: 0%	NPV: 91	LR+: 0	LR-: 1.01
< 3.8 gr/dL[2]	p= 0.033*	S: 9%	Sp: 96%	PPV: 19%	NPV: 92%	LR+: 2.25	LR-: 0.95
< 4,0 gr/dL[3]	p= 0.001*	S: 20%	Sp: 93%	PPV: 21%	NPV: 92	LR+: 2.86	LR-: 0.86

Notes: *[1]Forcillo J, et al (22) [2]Visser M, et al. (23) [3]Yanagita, I. et al. (16). S: sensitivity, Sp: specificity, PPV: Positive predictive value, NPV: Negative predictive value, LR +: Positive likelihood ratio, LR - : Negative likelihood ratio, *: statistically significant p.*

Tabla 3. *Análisis bivariado longitudinal.*

2012 – 2014				2012 -2016			
Punto de corte albúmina baja	**B (error estándar)**	**p**	**RR[1] (IC 95%)**	**Punto de corte albúmina baja**	**B (error estándar)**	**p**	**RR[1] (IC 95%)**
< 3.8 gr/dL	0.621 (0.132)	0.137	1.86(0.821-4.216)	< 3.8 gr/dL	0.971(0.440)	0.027*	2. 641(1.115-6.256)
< 4.0 gr/dL	0.245 (0.329)	0,457	0.457(0.671-2.433)	< 4.0 gr/dL	1.146(0.320)	0.000*	3.145(1.679-5.891)

Notas: **=p estadísticamente significativa, RR[1]= Riesgo relativo sin ajustar.*

a higher risk of developing frailty in the period from 2012 to 2016 (Table 4).

In addition, the Cox & Snell (0.140) and Nagelkerke (0.313) R squares were calculated, which indicated that this model could explain up to 31.3% of the onset of frailty over a four-year period.

Discussion

This study investigated the relationship between low albumin levels and the presence and progression of frailty in an international cohort of older adults. The results obtained indicate that, after adjusting for multiple variables, participants with albumin levels below 4 g/dL had a 2.5 times higher risk of frailty after four years of follow up than those with normal albumin levels. Within a risk model, low albumin, together with low grip strength, an SPPB <8 points and a mobility disability status can explain up to 31.3% of the onset of frailty over a four-year period in the IMIAS study participants.

Possible mechanisms and explanations of the findings

Inflammaging contributes to the pathogenesis of various age-related diseases like sarcopenia and frailty syndrome (24, 25). In this context of chronic inflammation, the liver responds by producing various acute phase reactants, while albumin synthesis reduces, making it a negative acute phase protein and an inflammatory marker (26). This relationship could explain the negative relationship found between albumin levels and frailty.

Furthermore, evidence suggests that low serum albumin is related to a higher risk of reduced muscle mass and strength in older people (27-29). This indicates that muscle

Table 4. *Multivariate analysis, logistic regression.*

Relationship between albumin < 4 gr/dL (2012) and frailty (2016)			
	B (standard error)	**p**	**RR (95% CI)**
Low albumin	0.920 (0.400)	0.021*	2.51 (1.14-5.491)
Grip strength	0.983 (0.306)	0.001*	2.672 (1.468-4.863)
SPPB	1.353 (0.342)	0.000*	4.641 (1.376-9.065)
Mobility disability (400 meters or a flight of stairs)	1.063 (0.374)	0.004*	2.894 (1.391-6.024)
Self-reported health	0.681 (0.408)	0.095	1.976 (0.888-4.398)
Sex	0.464 (0.329)	0.159	1.590 (0.834-3.032)
Polypharmacy	0.400 (0.322)	0.213	1.492 (0.794-2.803)
Comorbidity	-0.327 (0.362)	0.366	0.721 (0.355-1.465)
Visual impairment	-0.012 (0.352)	0.972	0.988 (0.496-1.968)
Depression	0.215 (0.320)	0.501	1.240 (0.663-2.321)
Walking speed	0.311 (0.337)	0.356	1.365 (0.705-2.640)
Level of education	-0.070 (0.061)	0.256	0.933 (0.827-1.052)
Income	0.485 (0.329)	0.140	1.624 (0.853-3.093)
Weight	-0.010 (0.013)	0.434	0.990 (0.966-1.015)

*Notes: *=statistically significant p, RR= relative risk.*

mass and function can deteriorate as a result of degraded protein synthesis caused by malnutrition (18). This process is another plausible mechanism behind the results, in which probable concurrent sarcopenia and a deficient nutritional status may create a vicious cycle favoring physical frailty (18, 30).

The risk model obtained from the multivariate analysis reflects the fact that physical function loss is a key sign of phenotypic frailty. Reduced grip strength, a low SPPB score and mobility disability showed a significant association with frailty, which could be directly related to sarcopenia, a key physiological component of physical frailty syndrome (19).

Despite being a complex model with multiple variables, it could only explain up to 31.3% of the onset of frailty over a four-year period, which highlights the multifactorial nature of frailty.

Comparison with other studies

The prevalence of frailty went from 5.5 to 8.9% over a period of four years, which is consistent with the results of other studies showing that prevalence increases with age (31). In a meta-analysis in low to middle-income countries in 2018, Siriwardhana DD, et al. (5) reported a wide range of frailty prevalence in older adults in the community, ranging from 3.9 to 51.4%, depending on the instrument used. A national study from the Health, Wellbeing and Aging project in Colombia (SABE Colombia, in Spanish) (32) reported higher levels, with a prevalence of 17.9%. At the local level, Gómez et al. (34) reported a prevalence of 12.1%, with similar findings, in which frailty was more common in women and in older people with a higher burden of comorbidity, polypharmacy, and lower performance on physical function tests (33).

The incidence of frailty was 33.45 cases per 1,000 people/year between 2012 and 2014, falling to 29.25 cases per 1,000 people/year between 2012 and 2016. These rates are lower than those reported in other studies with older people in the community. In the Longitudinal Study of Health and Retirement in China, Xu W et al. (34) reported an incidence of 60.6 cases per 1,000 people/year over a period of 2.1 years. In a retrospective population-based cohort study by Ganta N, et al. (35), the incidence rate (also over a four-year period) was much higher: 75.05 cases per 1,000 people/year. Likewise, in a systematic review with meta-analysis in 2019, Ofori-Asenso R, et al. found an incidence rate of 43.4 cases per 1,000 people/year, with a median follow-up of three years (36). This could be explained by the variability in frailty measurement instruments, as well as the inclusion criteria of the different studies. For IMIAS, the older adults at the beginning of the cohort had low levels of disability. This could also explain a lower baseline risk, compared to participants in other studies.

The median albumin in the frail group was 4.45 gr/dL, higher than the levels reported in other studies. Hubbard RE, et al. (37), reported a mean albumin of 3.95 gr/dL in frail participants; however, the study was done on hospitalized patients with high levels of dependency in activities of daily living, which explains the differences with our study, which was done in older people in the community. Similarly, Smit E et al. (38), reported a mean albumin of 3.98 gr/dL for the group of frail patients, in a study from the Third National Health And Nutrition Exam Survey (NHANES III) in the United States, which included older people in the community (38). This difference in albumin levels may be due to the initial characteristics of the IMIAS cohort in 2012, where the prevalence of frailty was low.

The relationship between albumin and frailty has been explored in various studies that have used different cut-off points to define low albumin (20, 39, 40). This is consistent with the scientific literature, as there is no consensus on a specific cut-off point (41). A level less than 3.5 g/dL is one of the most frequently reported thresholds (39, 40). Although this cut-off point is the most commonly used, our study showed no significant association with frailty in 2012, which could be explained by the elevated median albumin recorded in the participants.

Most of the studies that support our findings have a cross-sectional design, were performed in different population groups and used different methodologies to measure frailty (10,12). In a cross-sectional study of diabetic patients in Japan, Yanagita, I, et al. (20) showed that albumin levels < 4 gr/dL constituted a risk factor for frailty, with an OR of 5.79 ($p < 0.001$) (20). On the other hand, in a prospective cohort study in a general surgery unit for older adults, Abraham A et al. (42) showed that albumin levels <3.5 gr/dL had an almost four times higher likelihood of occurring in frail than non-frail patients (OR = 3.98, $p < 0.001$) (42).

The longitudinal relationship between albumin and frailty has been less explored, with few studies. In a cohort of patients with chronic kidney disease on hemodialysis - only 28% of whom were over age 65 - Kutner NG, et al. (43) found that, over a period of two years, higher serum albumin levels were associated with a lower likelihood of frailty (OR = 0.18, $p < 0.001$) (43).

The association between low grip strength, an SPPB <8 points, mobility disability and frailty has been widely documented (27). In a predictive study with a panel design, nested within IMIAS, Benjumea (44) confirmed that an SPPB <8 (OR 7.903), the inability to climb at least 10 stairsteps and/or walk 400 meters (OR 4.945) and low grip strength (OR 30.5) are significant predictors of progression to frailty (44).

However, despite these findings, albumin does not appear to be a reliable biomarker for frailty. The literature review presented has not shown a consistent relationship between albumin and frailty, and the R square (Cox & Snell and Nagelkerke) values were low in the models used for this analysis. This suggests that the model has a limited explanatory power for the phenomenon, and albumin only appears to be relevant when used together with other measures.

Strengths and limitations

This study has several strengths. First, it is a multicenter study nested within a longitudinal study of older adults in the community with initially low comorbidity. Standardized tools were used in all cities, which reduces variability in data collection. In addition, the inclusion of culturally diverse cities in low and middle-income countries adds a valuable dimension for analyzing the relationship between low albumin and frailty. Few studies have evaluated this relationship longitudinally, which confers an additional value to our findings.

The study's limitations include a secondary data analysis, and the samples not being representative of all older adults living in communities in Albania, Brazil and Colombia. Despite using validated scales for the variables of association, some of them are self-reported, and therefore the possibility of information bias cannot be totally ruled out. However, data analysis was done using values that showed statistical significance. A

Implications for clinical practice and research

This study increases the evidence regarding the longitudinal relationship between low albumin and frailty, which may have an impact on early interventions to prevent the progression of frailty in older people. There is a need for more longitudinal studies in different populations to allow the results to be generalized and compared. Furthermore, additional studies are needed to determine the best cut-off point for albumin associated with frailty, which could optimize its use as a clinical biomarker.

Conclusions

We found that low albumin in older people in the community is an independent risk factor for the onset of frailty. We emphasize the importance of the physical phenotype of frailty, which shows that it is a slow process that may be preceded by and linked to low albumin, strength reduction, impaired function and mobility disability.

The World Health Organization (WHO) has indicated that early frailty identification and intervention is a public health priority (21). The results of this study can contribute to identifying at-risk older adults, in whom prevention and early intervention strategies should be implemented. This, in turn, could reduce complications and lower healthcare costs in low and middle-income countries.

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