The depressed frail phenotype as a risk factor for mortality in older adults: A prospective cohort in Peru

Gabriel A.J. Vasquez-Góñi, Basilio M. Papuico-Romero, Diego Urrunaga-Pastor, Fernando M. Runzer-Colmenares, José F. Parodi

ABSTRACT

Introduction: Frailty and depression can coexist as depressed frail phenotype, useful for the comprehensive evaluation of older adults and prevention of adverse outcomes. The objective of this study was to evaluate the role of the depressed frail phenotype and its components as risk factors for mortality in older adults of the Centro Médico Naval (CEMENA) of Peru during 2010–2015.

Material and methods: We carried out a secondary data analysis of a prospective cohort that included older adults (60 years and older) treated in the Geriatrics service of CEMENA between the years 2010–2015. Frailty was defined as the presence of three or more Fried phenotype criteria and depression was determined using a Yesavage ultrashort scale score of three or more. The presence of both conditions was defined as depressed frail phenotype. In addition, sociodemographic characteristics, medical and personal history, and performance-based measures were included. We employed crude and adjusted Cox regression models to evaluate the association of interest and estimate Hazard Ratios (HR) with their respective 95% confidence intervals (95% CI).

Results: 946 older adults were included in the analysis, with a mean age of 78.0 ± 8.5 years. 559 (59.1%) were male, 148 (15.6%) were found to be frail, 231 (24.4%) had depressive symptoms, 105 (11.1%) had depressed frail phenotype, and 79 (8.3%) participants died during follow-up. The adjusted Cox regression analysis revealed that depressed frail phenotype (HR = 3.53; 95%CI: 2.07–6.00; p < 0.001) was a risk factor for mortality in older adults.

Conclusions: The depressed frail phenotype was associated with a higher risk of mortality in older adults. It is necessary to develop longitudinal studies that allow estimating this phenotype’s impact on mortality and evaluate interventions to improve quality of life and reduce the risk of adverse outcomes.

1. Introduction

Frailty is a condition defined by the presence of weakness, sedentary behavior, slow gait speed, exhaustion, and unintentional weight loss [1]. This syndrome is associated with a state of vulnerability that increases the risk of falls, disability, hospitalizations, morbidity and death [2, 3]. There are various definitions of frailty, but the most widely accepted is the frailty phenotype, which is the sum of conditions that lead to a dependent and vulnerable state, and the accumulation of deficit based on a pre-established disease that consumes physiological reserves and places older adults in a vulnerable state [4]. Nonetheless, according to the definition of frailty chosen, the prevalence may vary, being described as 13% worldwide and 21.7% in South America [5, 6]. Therefore, frailty represents a public health priority given the increase in the number of older adults in the latter region, and it is not the only relevant geriatric syndrome in South America.

Depression in older adults represents another relevant condition which has a prevalence ranging from 2.8% to 11.8% [7, 8, 9]. It is of note that the management of depression in older adults is challenging. This is due to possible underestimation of its presence in this population and the difficulties for treatment considering the high frequency of comorbidities and cognitive impairment [10]. Depression has also been associated with an increased risk of disability, hospitalizations, cognitive impairment, frailty and mortality, and thus, it must be diagnosed and treated in a timely manner [11, 12, 13]. Along this line, depression and frailty are two associated conditions, in which a deficit of dopaminergic function...
neurotransmitters affects physiological reserves, generating cognitive and motor impairment in older adults [14, 15].

Depression and frailty can present in different ways: they can coexist with an illness, be circumscribed in the clinical picture of a major illness, or they can occur bi- or unidirectionally [13, 16]. A systematic review evaluated the bidirectionality and unidirectionality between depression and frailty and revealed that an older adult with depression had three times the risk of frailty, while an older adult with frailty had approximately two times the risk of presenting depression [17] reinforcing the idea of unidirectionality between depression and frailty. However, it is more relevant to explore the impact that both conditions have on mortality of older adults.

Frailty and depression have been evaluated as predictors of disability [4], hospitalizations [4], and mortality [18, 19, 20] in older adults. Although both conditions can coexist as a syndrome called the depressed frail phenotype [14, 15], frailty follows a more orderly pathway to predict adverse outcomes; however, depression can also be affected by other comorbidities in older adults. Both conditions together can serve for the comprehensive evaluation of older adults in relation to adverse outcomes such as mortality [14, 15, 16, 20, 21]. Previous studies on this topic [15, 20, 22] reported non-conclusive results, and therefore, the objective of this study was to evaluate the role of the depressed frail phenotype and its components as predictors of mortality in older adults at the Centro Médico Naval of Peru from 2010-2015.

2. Materials and methods

2.1. Study design, population and sample

This study is a secondary analysis of a prospective cohort including 1891 older adults (60 years and over) from the Geriatrics Service of the Centro Médico Naval (CEMENA) “Cirujano Mayor Santiago Távara” recruited during the period from 2010-2015. The primary study evaluated the prevalence and factors associated with frailty in the study sample. The database is open access and can be downloaded from Figshare [23]. Participants with severe cognitive impairment, defined by a Mini-Mental State Examination (MMSE) score less than 17, were excluded [24]. Likewise, we excluded participants with a positive result in the clock test and those who did not have the variables of interest or did not agree to participate of the study.

Participants were enrolled annually until 2015, adding a new group of patients chosen by non-probability sampling each year until 2015. We did not perform an additional measurement to the baseline assessment in the participants, only mortality was assessed during follow-up. Of the 1,891 participants recruited, 577 were excluded for having an MMSE score less than 17 or having a positive result on the clock test and 368 for not having complete information for the variables of interest. Finally, we analyzed 946 participants. A statistical power of 100% was obtained, considering 946 participants and an odds ratio (OR) of 4.5 based on a previous study [22].

2.2. Variables

2.2.1. Dependent variable: Mortality

Mortality was defined as the death of older adults by all causes registered by the Epidemiology Office of CEMENA during the study period.

2.2.2. Exposure variables

2.2.2.1. Frailty. Exhaustion: this was defined using three questions from the Center for Epidemiological Studies depression scale (CES-D) [25]. These included: a) Do you feel full of energy? b) Do you feel that you cannot move on? c) Do you feel that everything you do is with effort? A positive answer to two or more questions was considered as exhaustion [1]. Weight Loss: assessed by the question “Have you recently lost weight such that your clothing has become looser?” A positive response defined the presence of weight loss [26]. Weakness: this was defined as grip strength less than 27 kg in male participants and less than 16 kg in women [27]. Sedentary behavior was defined using the Physical Activity Scale for the Elderly (PASE) as a score of less than 64 in men and less than 52 in women [26, 29]. Slow gait speed: this was evaluated as gait speed in four meters. Slow gait speed was considered as a speed less than 0.8 m/s or the impossibility to complete the test [27]. The highest time recorded in each participant was registered. Participants were considered frail when three or more criteria were present.

2.2.2.2. Depression. We employed the Yesavage ultra-short scale, which consists of five questions. A score of three or more was considered positive for depressive symptoms [30].

2.2.2.3. Depressed frail phenotype. The depressed frail phenotype was defined as the presence of both depression and frailty in the participants [22].

2.2.3. Other covariates

2.2.3.1. Söciodemographic characteristics. The following sociodemographic characteristics were collected: gender (male, female), age (60–70 years, 71–80 and ≥81), marital status (single, married/cohabitating, divorced/widower), educational level (<11 years or ≥11), living alone (no, yes).

2.2.3.2. Medical and personal history. We collected the following comorbidities from the medical records: type 2 diabetes mellitus (T2DM), chronic kidney disease, arterial insufficiency, heart failure, high blood pressure (HBP), chronic obstructive pulmonary disease (COPD), urinary incontinence, knee osteoarthritis, and overweight/obesity. Then, we created a variable that grouped the comorbidities in 0, 1, 2 and ≥3.

Likewise, a history of depression, tobacco consumption (no, yes), alcohol consumption (no, yes), hospitalizations in the last year (no, yes), falls in the last year (no, yes) and the number of medications prescribed were included.

2.2.3.3. Functional assessment. Social support was assessed using the Edinburgh frailty scale (no, yes) [28]. Disability to basic activities of daily living (BADL) was measured using the Barthel index, and participants with a score less than 100 were considered dependent [31]. In addition, cognitive impairment was assessed using the Montreal Cognitive Assessment (MoCA) [32].

2.3. Statistical analysis

We used the statistical package STATA v.14 for the analyses. The descriptive results of the qualitative variables were presented using relative and absolute frequencies, while the quantitative variables were described using measures of central tendency and dispersion. Pearson’s chi-square test was applied to compare the characteristics of the participants according to the exposure variables (frailty, depression, and depressed frail phenotype) and mortality. Likewise, differences between the numerical variables and the exposure and outcome variables were evaluated using the student’s t test or the Mann Whitney U test, according to the normal distribution of the numerical variable. Twelve Cox regression models (six crude and six adjusted) were carried out to evaluate the association between the depressed frail phenotype (and its components), with the incidence of mortality in the participants. The adjusted model included the following variables: sex, age, living alone, comorbidities, number of drugs prescribed, and falls in the last year.
These variables were chosen according to their association described in the literature [22]. The association measure reported was the hazard ratio (HR) with its respective 95% confidence interval (95%CI). Kaplan-Meier curves graphed the participants’ survival according to the presence of the depressed frail phenotype, and they were compared using the Log-rank test.

2.4. Ethical aspects

This study was approved by the ethics committee of the Universidad Científica del Sur (356-2020-PRE15) located in Lima, Peru. Since we analyzed a secondary database, we did not collect new information. Before entering the study, the participants provided signed informed consent.

3. Results

3.1. General characteristics of the sample and bivariate analysis according to the exposure variables

We included 946 older adults in the analysis with an average follow-up of 2.2 years. The mean age was 78.0 ± 8.5 and 559 (59.1%) were male. Likewise, 757 (80.0%) were married, 154 (16.3%) lived alone, 266 (28.1%) had three or more comorbidities, and 203 (21.5%) had a history of depression. Furthermore, 582 (61.5%) had functional dependence in BADL and only 90 (9.5%) did not have social support. Regarding the frailty components, 209 (22.1%) had exhaustion, 299 (31.6%) reported weight loss, and 274 (29.0%) had weakness, while 408 (43.1%) were sedentary and 101 (10.7%) had a slow gait speed. In total, 148 (15.6%) were found to be frail, 231 (24.4%) had depressive symptoms, 105 (11.1%) had the depressed frail phenotype and 79 (8.3%) participants died during follow-up (Table 1). The bivariate analysis between covariates and exposure variables is shown in Table 2.

3.2. Bivariate analysis according to mortality in the study sample

Mortality was found to be higher in patients with the depressed frail phenotype (53.2% vs. 46.8%; p < 0.001) compared to those who did not have this conditions. In addition, the incidence of mortality was higher in older adults with exhaustion (51.9% vs. 48.1%; p < 0.001), weight loss (43.0% vs. 57.0%; p = 0.022), weakness (62.0% vs. 26.0%; p < 0.001), sedentary behavior (78.5% vs. 39.9%; p < 0.001) and slow gait speed (11.4% vs. 10.6%; p = 0.830) compared to those who did not have these geriatric syndromes (Table 3).

3.3. Depressed frail phenotype as a predictor of mortality in older adults

In the adjusted Cox regression analysis, the depressed frail phenotype (aHR = 3.53; 95%CI: 2.07–6.00; p < 0.001) was found to be a predictor of mortality in older adults. In relation to the frailty components, we found that

| Table 1. Descriptive analysis of the study variables (n = 946). |
|---------------------|------|-----|
| Variables           | n    | %   |
| Sex                 |      |     |
| Female              | 387  | 40.9|
| Male                | 559  | 59.1|
| Age                 |      |     |
| 60–70 years old     | 159  | 16.8|
| 71–80 years old     | 448  | 47.4|
| ≥81 years old       | 339  | 35.8|
| Marital status      |      |     |
| Single              | 31   | 3.3 |
| Married/Cohabitating| 757  | 80.0|
| Divorced/Widower    | 158  | 16.7|
| Educational level   |      |     |
| ≤11 years           | 197  | 20.8|
| >11 years           | 749  | 79.2|
| Living alone        |      |     |
| No                  | 792  | 83.7|
| Yes                 | 154  | 16.3|
| Comorbidities       |      |     |
| 0                   | 77   | 8.1 |
| 1                   | 309  | 32.7|
| 2                   | 294  | 31.1|
| ≥3                  | 266  | 28.1|
| History of depression|     |    |
| No                  | 743  | 78.5|
| Yes                 | 203  | 21.5|
| BMI³                |      |     |
| 26.2 ± 5.4⁴        |      |     |
| History of tobacco consumption |     |    |
| No                  | 258  | 27.3|
| Yes                 | 688  | 72.7|
| History of alcohol consumption |     |    |
| No                  | 523  | 55.3|
| Yes                 | 423  | 44.7|
| Functional dependance in BADL² |     |    |
| No                  | 364  | 38.5|
| Yes                 | 582  | 61.5|
| Hospitalizations in the last year |     |    |
| No                  | 450  | 47.6|
| Yes                 | 496  | 52.4|
| Number of drugs prescribed |     |    |
| 3 (2–5)⁵           |      |     |
| Social support      |      |     |
| No                  | 90   | 9.5 |
| Yes                 | 856  | 90.5|
| MoCA³               |      |     |
| 27 (23–28)⁵         |      |     |
| Exhaustion          |      |     |
| No                  | 737  | 77.9|
| Yes                 | 209  | 22.1|
| Weight loss         |      |     |
| No                  | 647  | 68.4|
| Yes                 | 299  | 31.6|
| Weakness            |      |     |
| No                  | 672  | 71.0|
| Yes                 | 274  | 29.0|
| Sedentary behavior  |      |     |
| No                  | 538  | 56.9|
| Yes                 | 408  | 43.1|
| Slow gait speed     |      |     |
| No                  | 845  | 89.3|
| Yes                 | 101  | 10.7|

1 Body mass index.
2 Basic activities of daily life.
3 Montreal Cognitive Assessment.
4 Mean ± standard deviation.
5 Median (p25–p75).
Table 2. Descriptive and bivariate analyses based on the exposure variables (n = 946).

| Variables                      | Depressed frail phenotype |          | Frailty |          | P value | Depressive symptoms |          |
|-------------------------------|--------------------------|----------|---------|----------|---------|---------------------|---------|
|                               | No 88.9% (n = 841)       | Yes 11.1% (n = 105) |
| Sex                           | Female 359 (42.7)        | 28 (26.7) |
|                               | Male 482 (57.3)          | 77 (73.3) |
| Age (years)                   | 77.6 ± 8.44             | 81.1 ± 8.54 |
| 60–70 years old               | 151 (18.0) 8.7 (7.6)    | 147 (18.4) 12 (8.1) |
| 71–80 years old               | 405 (48.2) 43 (41.0)    | 384 (48.1) 64 (43.2) |
| >81 years old                 | 285 (33.8) 54 (51.4)    | 267 (33.5) 72 (48.6) |
| Marital status                | 0.094                   | 0.649    | 0.458   |
| Single                        | 29 (3.4) 2 (1.9)        | 28 (3.5) 3 (2.0) |
| Married/Cohabiting            | 679 (80.7) 78 (74.3)    | 637 (79.8) 120 (81.1) |
| Divorced/Widower              | 133 (15.8) 25 (23.8)    | 133 (16.7) 25 (16.9) |
| Educational level             | 0.094                   | 0.649    | 0.458   |
| ≤11 years old                 | 170 (20.2) 27 (25.7)    | 147 (18.4) 50 (33.8) |
| >11 years old                 | 671 (79.8) 78 (74.3)    | 651 (81.6) 98 (66.2) |
| Living alone                  | 0.047                   | 0.086    | 0.623   |
| No                            | 697 (82.9) 95 (90.5)    | 661 (82.8) 131 (88.5) |
| Yes                           | 144 (17.1) 10 (9.5)     | 137 (17.2) 17 (11.5) |
| Comorbidities                 | 0.579                   | 0.727    | 0.358   |
| No                            | 2 (1–3) 0.597           | 2 (1–3) 0.727 |
| 1                             | 69 (8.2) 8 (7.6)        | 66 (8.3) 11 (7.4) |
| 2                             | 275 (32.7) 34 (32.4)    | 259 (32.4) 50 (33.8) |
| ≥3                            | 236 (28.1) 30 (28.6)    | 224 (28.1) 42 (28.4) |
| History of depression         | 0.031                   | 0.033    | 0.510   |
| No                            | 652 (77.5) 91 (86.7)    | 617 (77.3) 126 (85.1) |
| Yes                           | 189 (22.5) 14 (13.3)    | 181 (22.7) 22 (14.9) |
| BMI1                          | 26.2 ± 5.34             | 26.5 ± 5.94 |
| History of tobacco consumption| <0.001                  | <0.001   | 0.497   |
| No                            | 212 (25.2) 46 (43.8)    | 183 (22.9) 75 (50.7) |
| Yes                           | 629 (74.8) 59 (56.2)    | 615 (77.1) 73 (49.3) |
| History of alcohol consumption| 0.526                   | 0.021    | 0.338   |
| No                            | 468 (55.6) 55 (52.4)    | 454 (56.9) 69 (46.6) |
| Yes                           | 373 (44.4) 50 (47.6)    | 344 (43.1) 79 (53.4) |
| Functional dependence in BADL2| 0.580                   | 0.574    | 0.059   |
| No                            | 321 (38.2) 43 (41.0)    | 304 (38.1) 60 (40.5) |
| Yes                           | 502 (61.8) 62 (59.0)    | 494 (61.9) 88 (59.5) |
| Hospitalizations in the last year| 0.844                  | 0.519    | 0.662   |
| No                            | 401 (47.7) 49 (46.7)    | 376 (47.1) 74 (50.0) |
| Yes                           | 440 (52.3) 56 (53.3)    | 422 (52.9) 74 (50.0) |
| Number of drugs prescribed    | <0.001                  | <0.001   | <0.001  |
| No                            | 3 (2–4) 7 (6–8)         | 3 (2–4) 7 (5–8) |
| Yes                           | 37 (4.4) 42 (40.0)      | 37 (4.6) 41 (27.7) |
| Social support                | <0.001                  | <0.001   | 0.435   |
| No                            | 69 (8.2) 21 (20.0)      | 51 (6.4) 39 (26.4) |
| Yes                           | 772 (91.8) 84 (80.0)    | 747 (93.6) 109 (73.6) |
| MoCA3                         | 27 (24–29) 19 (17–20)   | 27 (25–29) 20 (19–22) |
| Falls in the last year        | 0.787                   | 0.713    | 0.825   |
| No                            | 317 (37.7) 41 (39.0)    | 300 (37.6) 58 (39.2) |
| Yes                           | 524 (62.3) 64 (61.0)    | 498 (62.4) 90 (60.8) |
| Mortality                     | <0.001                  | <0.001   | <0.001  |
| No                            | 804 (95.6) 63 (60.0)    | 761 (95.4) 106 (71.6) |
| Yes                           | 37 (4.4) 42 (40.0)      | 37 (4.6) 41 (27.7) |

1 Body mass index.
2 Basic activities of daily life.
3 Montreal Cognitive Assessment.
4 Mean ± standard deviation.
5 Median (p25–p75).
Table 3. Descriptive and bivariate analyses of the study variables based on all-cause mortality (n = 946).

| Variables                        | Mortality | P value |
|----------------------------------|-----------|---------|
|                                 | No 91.7% (n = 867) | Yes 8.3% (n = 79) | |
| Depressed frail syndrome          |            | <0.001  |
| No                               | 804 (92.7) | 37 (46.8) |
| Yes                              | 63 (7.3)  | 42 (53.2) |
| Frailty                          |            | <0.001  |
| No                               | 761 (87.8) | 37 (46.8) |
| Yes                              | 106 (12.2) | 42 (53.2) |
| Depressive symptoms              |            | <0.001  |
| No                               | 715 (82.5) | 0 (0)    |
| Yes                              | 152 (17.5) | 79 (100) |
| Sex                              |            | 0.204    |
| Female                           | 360 (41.5) | 27 (34.2) |
| Male                             | 507 (58.5) | 52 (65.8) |
| Age                              |            | 0.008    |
| 60–70 years old                  | 154 (17.8) | 5 (6.3)  |
| >71 years old                    | 409 (47.2) | 39 (49.4) |
| Marital status                   |            | 0.023    |
| Single                           | 28 (3.2)   | 3 (3.8)  |
| Married/Cohabiting               | 689 (79.5) | 68 (86.1) |
| Divorced/Widower                 | 150 (17.3) | 8 (10.1) |
| Educational level                |            | 0.062    |
| <11 years                        | 187 (21.6) | 10 (12.7) |
| >11 years                        | 680 (78.4) | 69 (87.3) |
| Living alone                     |            | 0.023    |
| No                               | 733 (84.5) | 59 (74.7) |
| Yes                              | 134 (15.5) | 20 (25.3) |
| Comorbidities                    |            | 0.323    |
| 2 (1–3)                          | 2 (1–2)    | 3 (2–4)  |
| 0                                | 71 (8.2)   | 6 (7.6)  |
| 1                                | 281 (32.4) | 28 (35.4) |
| 2                                | 265 (30.6) | 29 (36.7) |
| >3                               | 250 (28.8) | 16 (20.3) |
| History of depression            |            | 0.989    |
| No                               | 681 (78.6) | 62 (78.5) |
| Yes                              | 186 (21.4) | 17 (21.5) |
| BMI                              |            | 0.846    |
| 26.2 ± 5.2                      | 26.1 ± 6.9 |
| History of tobacco consumption   |            | 0.046    |
| No                               | 244 (28.1) | 14 (17.7) |
| Yes                              | 623 (71.9) | 65 (82.3) |
| History of alcohol consumption   |            | 0.432    |
| No                               | 476 (54.9) | 47 (59.5) |
| Yes                              | 391 (45.1) | 32 (40.5) |
| Functional dependency in BADL    |            | <0.001   |
| No                               | 308 (35.5) | 56 (70.9) |
| Yes                              | 559 (64.5) | 23 (29.1) |
| Hospitalizations in the last year|            | 0.544    |
| No                               | 415 (47.9) | 35 (44.3) |
| Yes                              | 452 (52.1) | 44 (55.7) |
| Number of prescribed drugs       |            | <0.001   |
| 3 (2–4)                          | 8 (7–8)    |
| Social support                   |            | 0.159    |
| No                               | 86 (9.9)   | 4 (5.1)  |
| Yes                              | 781 (90.1) | 75 (94.9) |
| MoCA                            |            | <0.001   |
| 27 (24–28)                       | 20 (18–20) |
| Exhaustion                       |            | <0.001   |
| No                               | 699 (80.6) | 38 (48.1) |
| Yes                              | 168 (19.4) | 41 (51.9) |
| Weight loss                      |            | 0.022    |
| No                               | 602 (69.4) | 45 (57.0) |
| Yes                              | 265 (30.6) | 34 (43.0) |

Table 3 (continued)

| Variables                        | Mortality | P value |
|----------------------------------|-----------|---------|
|                                 | No 91.7% (n = 867) | Yes 8.3% (n = 79) | |
| Weakness                         |            | <0.001   |
| No                               | 642 (74.0) | 30 (38.0) |
| Yes                              | 225 (26.0) | 49 (62.0) |
| Sedentary behavior               |            | <0.001   |
| No                               | 521 (60.1) | 17 (21.5) |
| Yes                              | 346 (39.9) | 62 (78.5) |
| Slow gait speed                  |            | 0.830    |
| No                               | 775 (89.4) | 70 (88.6) |
| Yes                              | 92 (10.6)  | 9 (11.4)  |
| Falls in the last year           |            | 0.153    |
| No                               | 334 (38.5) | 24 (30.4) |
| Yes                              | 533 (61.5) | 55 (69.6) |

1. Body mass index.
2. Basic activities of daily life.
3. Montreal Cognitive Assessment.
4. Mean ± standard deviation.
5. Median (p25–p75).

participants with exhaustion and depression (aHR = 1.99; 95%CI: 1.17–3.40; p = 0.011), weight loss and depression (aHR = 2.10; 95%CI: 1.24–3.55; p = 0.006), weakness and depression (aHR = 4.11; 95%CI: 2.31–7.34; p < 0.001), sedentary behavior and depression (aHR = 6.00; 95%CI: 3.33–10.84; p < 0.001) and slow gait speed and depression (aHR = 3.12; 95%CI: 1.54–6.30; p = 0.002) (Table 4) had a higher risk of death. Likewise, we found a greater risk of mortality in the depressed frail phenotype group according to the Kaplan-Meier curve (p < 0.001) (Figure 1).

4. Discussion

4.1. Main findings

To our knowledge, this is the first study evaluating this association in older Latin American adults, for which we consider our findings to be novel and of great utility for the identification of vulnerable groups at higher risk of mortality. Thus, it would be relevant to prioritize screening for depression and frailty, as well as the coexistence of both geriatric syndromes in comprehensive geriatric evaluations.

4.2. Comparison with previous studies

In this study we found that the prevalence of depression, frailty, and the depressed frail phenotype was 24.4%, 15.6%, and 11.1%, respectively. The prevalence of frailty and depression is lower than that reported in previous studies carried out in Spain and Denmark [15, 22]. However, it is higher than what was reported in an Australian study [20]. It should be noted that no previous study has reported the prevalence of depressed frail phenotype. Likewise, a systematic review found a prevalence of frailty in older South American adults of 21.7%, being higher than that reported in our study [6]. On the other hand, it was lower than the prevalence of frailty of 13% found in a systematic review using the Fried phenotype [5].

We found an association between the depressed frail phenotype and mortality in older adults in Peru. This finding to similar to the results of previous studies carried out in Australia [20], Denmark [15] and Spain [22]. However, only two of these studies estimated an association measure [15, 22], and all three were carried out in high-income countries. Only one study evaluated the impact of depression on each frailty component [15], and the follow-up time in this study was shorter compared to the previous studies [15, 20, 22]. It should be noted that we employed the Fried phenotype to evaluate frailty, while in previous
studies this variable was measured with instruments based on deficit accumulation, which are not the most widely accepted [33, 34]. We evaluated the risk of mortality according to each component of the depressed frail phenotype, determining that sedentary behavior, weakness and slow gait speed were the components with the highest risk, which differs from a previous study [15]. To our knowledge, this is the first study to evaluate the impact of depressed frail phenotype on the mortality of older adults in Latin America, providing novel data on the impact of this condition on the population of our region.

We found that older adults with depressed frail phenotype and who died were older, had a greater number of prescribed drugs, and a higher frequency of disability. Previous studies are consistent with our findings, where increasing age was associated with a higher risk of frailty and mortality [35]. Likewise, a study carried out in Spanish older adults found that disability, and polypharmacy were risk factors for mortality, independently of depressed frail phenotype [22]. In addition, depression has been described as a risk factor for disability and mortality in older adults [36], therefore it is necessary to prevent it.

### 4.3. Interpretation of results

The depressed frail phenotype is a condition that generates a high risk of mortality in older adults. Frailty is characterized by a deficit of homeostasis in relation to an adverse event in older adults, which, added to depression, can increase the risk of mortality [13, 14, 37]. The pathophysiology of the depressed frail phenotype as a predictor of mortality is based on the chronic inflammatory state that is usually present in older adults and is associated with frailty and depression. This inflammatory state affects the dopaminergic system and the basal ganglia of older adults, which together with comorbidities such as type 2 diabetes mellitus, metabolic syndrome and low level of physical activity, increases the risk of adverse events. Other theories to explain the development of this syndrome are mitochondrial and dopaminergic dysfunction, hormonal dysregulation of the hypothalamic pituitary adrenal axis, and accelerated cellular aging [14]. Similarly, vascular involvement can produce depressive symptoms and alterations in physical and cognitive performance [38, 39].

A potential cycle of the depressed frail phenotype has also been described, in which depression unidirectionally causes weight loss and a reduction in physical activity, generating sarcopenia, decreased metabolic rate and strength, and greater exhaustion in older adults due to a deficiency in adenosine triphosphate production [14, 40, 41]. Taking this into account, the probability of falls increases, with the subsequent loss of immobilization. Eventually body strength decreases, creating a cycle. Immobilized older adult suffer from slow gait speed and perform less physical activity, leading to depression, thus forming a vicious circle [1]. This is consistent with our findings, in which the most important components of the depressed frail phenotype were sedentary behavior, weakness and slow gait speed.

### Table 4. Cox regression models to evaluate the association between the depressed frail phenotype and the risk of mortality in the study sample.

|                  | Crude          | Adjusted       |
|------------------|----------------|----------------|
| **Depressed frail phenotype** |                |                |
| No               | Reference      | Reference      |
| Yes             | 10.88          | 3.53           |
| 95%CI            | 6.99-16.94     | 2.07-6.00      |
| P value          | <0.001         | <0.001         |
| **Depressed frail phenotype components** |                |                |
| Exhaustion + depression |                |                |
| No               | Reference      | Reference      |
| Yes             | 9.38           | 1.99           |
| 95%CI            | 6.03-14.61     | 1.17-3.40      |
| P value          | <0.001         | 0.011          |
| Weight loss + depression |                |                |
| No               | Reference      | Reference      |
| Yes             | 8.51           | 2.10           |
| 95%CI            | 5.44-13.30     | 1.24-3.55      |
| P value          | <0.001         | 0.006          |
| Weakness + depression |                |                |
| No               | Reference      | Reference      |
| Yes             | 11.90          | 4.11           |
| 95%CI            | 7.54-18.76     | 2.31-7.34      |
| P value          | <0.001         | <0.001         |
| Sedentary behavior + depression |                |                |
| No               | Reference      | Reference      |
| Yes             | 19.60          | 6.00           |
| 95%CI            | 11.43-33.62    | 3.33-10.84     |
| P value          | <0.001         | <0.001         |
| Slow gait speed + depression |                |                |
| No               | Reference      | Reference      |
| Yes             | 4.46           | 3.12           |
| 95%CI            | 2.23-8.94      | 1.54-6.30      |
| P value          | <0.001         | 0.002          |

HR: hazard ratio; aHR: adjusted hazard ratio; CI: confidence interval.

1 Adjusted for: sex, age, living alone, comorbidities, number of prescribed drugs and falls in the last year.

---

**Figure 1.** Kaplan-Meier survival curves according to the depressed frail phenotype.
We must mention that both syndromes are independent of each other, but they can simultaneously coexist in older adults. Another possibility is that one acts as a cause for the other, which is why it is relevant to carry out more longitudinal studies to verify this hypothesis and determine triggering conditions. Finally, depression and frailty can manifest in different ways, when in fact they are part of the same disorder.

4.4. Relevance in clinical practice

The increase in the prevalence of frailty, depression, and the depressed frail phenotype indicates the relevant need to consider certain aspects of clinical practice and the management of older adults. While treatment with antidepressants has shown to improve the management of depression [42], this therapy may not be applicable in frail people, who have a higher risk of adverse outcomes [43]. On the other hand, nutritional interventions and exercise aimed at improving muscle strength in the lower extremities, gait speed and preventing future falls, have shown good results [44, 45]. Nonetheless, the depressed population is not usually included in these programs [46, 47, 48], even though they would provide a greater impact to combat sedentary behavior and exhaustion. There are still gaps in relation to the usefulness of pharmacological and non-pharmacological interventions to improve the quality of life of older adults with the depressed frail phenotype, as well as to avoid a greater impact of depression in frail individuals, and vice versa. Nonetheless, the use of antidepressants could have serious adverse effects in frail and comorbid populations, such as an increased risk of hyponatremia, bleeding, vision disturbances, memory loss, delirium, and falls [49, 50]. This situation highlights the need for more intervention studies including patients with the depressed frail phenotype due to the high risk of mortality.

Various non-pharmacological interventions are available for the prevention and treatment of depression in older adults, such as exercise, cognitive behavioral therapy (CBT), behavioral activation, problem-solving therapy, and bright-light therapy [51]. The positive effect of CBT on depressive symptoms in older adults has been described in previous systematic reviews and meta-analyses [51, 52, 53, 54, 55]. However, more studies are needed to evaluate the safety and efficacy of these interventions even in older adults with depressed frail phenotype.

4.5. Strengths and limitations

Our study has some limitations: 1) The population consisted of retired marines and their families, who share certain characteristics that may vary compared to the general population of older adults in Peru and may therefore not be representative. 2) We analyzed a secondary database, in which relevant variables for this study could not be measured or included, such as the use of antidepressants and other comorbidities. 3) Depression was not evaluated using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition; however, we employed a screening scale with adequate diagnostic performance which has been widely used in previous studies [22, 50]; 4) We did not perform annual measurements to record the appearance of new comorbidities, the occurrence of falls and hospitalizations, which could be relevant for the incidence of mortality; 5) The follow-up time to assess mortality may not be sufficient in certain cohort groups. Despite the limitations described, this is the first study in Latin America to evaluate the depressed frail phenotype as a predictor of mortality in older adults and our results provide relevant information to understand this phenomenon.

5. Conclusions

We found that the depressed frail phenotype and its components were risk factors for mortality in older adults. Sedentary behavior, weakness, and slow gait speed had the greatest impact on mortality, for which interventions in these components should be prioritized. It is necessary to develop more longitudinal studies that allow estimating the impact of this syndrome on mortality and evaluate interventions to improve quality of life and reduce the risk of adverse outcomes.

Declarations

Author contribution statement

Gabriel A.J. Vasquez-Goitì, Basilio M. Papuico-Romero: Conceived and designed the analysis; Wrote the paper.

Diego Urrunaga-Pastor: Conceived and designed the analysis; Analyzed and interpreted the data; Wrote the paper.

Fernando M. Runzer-Colmenares: Conceived and designed the analysis; Analyzed and interpreted the data; Contributed analysis tools or data; Wrote the paper.

Jose F. Parodi: Analyzed and interpreted the data; Contributed analysis tools or data; Wrote the paper.

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

The authors do not have permission to share data.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

Acknowledgements

We acknowledge the staff of the Centro de Investigación del Envejecimiento – Faculty of Medicine from the Universidad de San Martín de Porres, Perú, and the staff of the Geriatrics Service of the Centro Médico Naval del Perú for the logistical support provided. In addition, we want to thank the Universidad Científica del Sur for the financial support in the payment of the article processing charge.

References

[1] L.P. Fried, C.M. Tangen, J. Walston, A.B. Newman, C. Hirsch, J. Gottdiener, et al., Frailty in older adults: evidence for a phenotype. J. Gerontol. Ser. A. Biol. Sci. Med. Sci. 56 (3) (2001) 146–157.

[2] G. Kojima, Frailty as a predictor of future falls among community-dwelling older people: a systematic review and meta-analysis, J. Am. Med. Dir. Assoc. [Internet] 16 (12) (2015) 1027–1033.

[3] A.L.L. Cunha, N. Veronese, S. de Melo Borges, N.A. Ricci, Frailty as a predictor of adverse outcomes in hospitalized older adults: a systematic review and meta-analysis, Ageing Res. Rev. [Internet] 56 (September) (2019) 100960.

[4] D. Bickford, R.T. Morin, C. Woodworth, E. Verduzco, M. Khan, E. Burns, et al., The relationship of frailty and disability with suicidal ideation in late life depression, Aging Ment. Health (2019) 1–6.

[5] R. O’Cosimh, D. Sezgin, M.R. O’Donovan, D. William Molloy, A. Clegg, K. Rockwood, et al., Prevalence of frailty in 62 countries across the world: a systematic review and meta-analysis of population-level studies, Age Ageing 50 (1) (2021) 96–104.

[6] H.J. Coelho-Junior, E. Marzetti, A. Picca, R. Calvani, M. Cesari, M.G. Uchida, Prevalence of prefrailty and frailty in South America: a systematic review of observational studies, J. Frailt. Aging 9 (4) (2020) 197–213.

[7] R.D. de Sousa, A.M. Rodrigues, M.J. Gregório, J.D.C. Branco, M.J. Gouveia, H. Canhão, et al., Anxiety and depression in the Portuguese older adults: prevalence and associated factors, Front. Med. 4 (NOV) (2017) 1–12.

[8] L. Sjöberg, B. Karlsson, A.R. Atti, I. Skoog, L. Fratiglioni, H.X. Wang, Prevalence of depression: comparisons of different depression definitions in population-based samples of older adults, J. Affect. Disord. [Internet] 221 (2017) 123–131.
M. Guerra, C.P. Ferri, A.L. Sosa, A. Salas, C. Gaona, V. Gonzales, et al., Late-life depression in Peru, Mexico and Venezuela: the 10/66 population-based study, Br. J. Psychiatry 195 (6) (2019) 510–515.

A.M. Gum, B. King-Kallimanis, R. Kohn, Prevalence of mood, anxiety, and substance-abuse disorders for older Americans in the national comorbidity survey-replication, Am. J. Geriatr. Psychiatr. [Internet] 17 (9) (2009) 769–781.

D. Kong, P. Solomon, X.Q. Dong, Depressive symptoms and onset of functional disability over 2 years: a prospective cohort study, J. Am. Geriatr. Soc. 67 (9) (2019) S538–S544.

D. Gallagher, A. Kiss, K. Lancot, N. Herrmann, Depression and risk of Alzheimer Dementia: a longitudinal analysis to determine predictors of increased risk among older adults with depression, Am. J. Geriatr. Psychiatr. [Internet] 26 (8) (2018) 819–827.

J.G. Ruiz, M. Rodríguez-Suárez, F. Tang, R. Aparicio-Ugarriza, J. Ferri-Guerra, N.Y. Mohammed, et al., Depression but not frailty contributed to a higher risk for all-cause hospitalizations in male older veterans, Int. J. Geriatr. Psychiatr. 35 (1) (2020) 37–44.

P.J. Brown, B.R. Rutherford, K. Yaffe, J.M. Tandler, J.L. Ray, E. Pott, et al., The depressed frail phenotype: the clinical manifestation of increased biological aging, in: American Journal of Geriatric Psychiatry, 24, Elsevier B.V., 2016, pp. 1084–1094.

P.J. Brown, S.P. Roose, R. Fioo, X. Liu, T. Rantanen, J.R. Sue, et al., Frailty and depression in older adults: a high-risk clinical population, Am. J. Geriatr. Psychiatr. 22 (11) (2014) 1083–1095.

J. Sy, C.E. McCulloch, K.L. Johansen, Depressive symptoms, frailty, and mortality among dialysis patients, Hemodial. Int. 23 (2) (2019 Apr) 239–246.

S. van den Berg, C. Wiersema, J.M. Hegeman, R.H.S. van den Brink, J.D. Linkous, J.C. Kvedar, The American telemedicine association, J. Telemed. Telecare 11 (7) (2005) 376–378.

H.T. Nguyen, S.A. Black, L.A. Ray, D.V. Espino, K.S. Markides, Predictors of decline among dialysis patients, Hemodial. Int. 22 (11) (2014) 1083–1095.

R.M. Kok, C.F. Reynolds, Management of depression in older adults: a review, J. Gerontol. Geriatr. [Internet] 55 (3) (2012) 522–526.

A.K. Forsman, I. Schierenbeck, K. Wahlbeck, Psychosocial interventions for the treatment of older adults with depression: questionable benefits and considerations for frailty, BMC Geriatr. 19 (1) (2019) 1–11.

D.R. Petty, A. House, P. Knapp, T. Raynor, A. Zermansky, Prevalence, duration and indications for prescribing of antidepressants in primary care (3), Age Ageing 35 (5) (2006) 523–526.

A.J. Cruz-Jentoft, J.P. Baeyens, J.M. Bauer, Y. Boirie, T. Cederholm, F. Landi, et al., Frailty in older adults with depression and cognitive decline, Aging Ment. Health (2019) 1–23.

H.R. Bogner, K.H. Morales, C.F. Reynolds, M.S. Gary, M.L. Bruce, Course of depression and mortality among older primary care patients, Am. J. Geriatr. Psychiatr. 20 (10) (2012) 895–903.

D.L. Waters, R.N. Baumgartner, P.J. Garry, B. Vellas, Advantages of dietary, exercise-related, and therapeutic interventions to prevent and treat sarcopenia in older adults: an update, Clin. Interv. Aging 5 (2010) 259–270.

S.Y. Lee, M.K. Franchetti, A. Imanbayev, J.J. Gallo, A.P. Spira, H.B. Lee, Non-pharmacological treatment for depression in older adults: a systematic review of the efficacy of psychotherapy interventions, Arch. Gerontol. Geriatr. [Internet] 55 (3) (2012) 522–526.

S.S. Simon, T.A. Cordas, C.M.C. Bottino, Cognitive behavioral therapies in older adults with depression and cognitive deficits: a systematic review, Int. J. Geriatr. Psychiatr. 30 (3) (2015) 223–233.

J. Apostolo, E. Bobrowicz-Campos, M. Rodrigues, I. Castro, D. Cardoso, The effectiveness of non-pharmacological interventions in older adults with depressive disorders: a systematic review, Int. J. Nurs. Stud. 58 (2016) 59–70.

U. Jonsson, G. Bertilsson, P. Allard, H. Gyllensvärd, A. Söderlund, A. Tham, et al., Psychological treatment of depression in people aged 65 years and over: a systematic review of efficacy, safety, and cost-effectiveness, PLoS One 11 (8) (2016) 1–20.

S.G. Aguilar-Nava, J.J. Mimenza-Alvarado, J.E. Aguilar-Esquível, S.G. Yeverino-Castro, T. Juez-Cedillo, S. Mejía-Arango, Motoric cognitive risk syndrome: prevalence and risk of cognitive impairment in a population study in the Mexican health and aging study 2012-2015, J. Nutr. Health Aging 23 (3) (2019) 227–231.

D.L. Waters, R.N. Baumgartner, P.J. Garry, B. Vellas, Antidepressant use and the prevention of all-cause hospitalizations in male older veterans, J. Am. Med. Dir. Assoc. 16 (4) (2015) 296–300.

J.D. Linkous, J.C. Kvedar, The American telemedicine association, J. Telemed. Telecare 11 (7) (2005) 376–378.

S.S. Simon, T.A. Cordas, C.M.C. Bottino, Cognitive behavioral therapies in older adults with depression and cognitive deficits: a systematic review, Int. J. Geriatr. Psychiatr. 30 (3) (2015) 223–233.

A.J. Cruz-Jentoft, J.P. Baeyens, J.M. Bauer, Y. Boirie, T. Cederholm, F. Landi, et al., Frailty in older adults with depression and cognitive decline, Aging Ment. Health (2019) 1–23.

P.J. Brown, B.R. Rutherford, K. Yaffe, J.M. Tandler, J.L. Ray, E. Pott, et al., The depressed frail phenotype: the clinical manifestation of increased biological aging, in: American Journal of Geriatric Psychiatry, 24, Elsevier B.V., 2016, pp. 1084–1094.

P.J. Brown, S.P. Roose, R. Fioo, X. Liu, T. Rantanen, J.R. Sue, et al., Frailty and depression in older adults: a high-risk clinical population, Am. J. Geriatr. Psychiatr. 22 (11) (2014) 1083–1095.

J.D. Linkous, J.C. Kvedar, The American telemedicine association, J. Telemed. Telecare 11 (7) (2005) 376–378.

R.F. Coen, K. McCarron, M. Casey, H. McNulty, E. Laird, A.M. Molloy, et al., The frontal assessment battery: normative performance in a large sample of older community-dwelling hospital outpatient or general practitioner attendees, J. Geriatr. Psychiatr. Neurol. 29 (6) (2016) 338–343.

G.A. van Kan, Y.M. Robbers, H. Bergman, J.E. Morley, S.B. Kritchevsky, B. Vellas, et al., The I.A.N.A Task Force on frailty assessment of older people in clinical practice, in: American Journal of Geriatric Psychiatry, 24, Elsevier B.V., 2016, pp. 1084–1094.

G.A. Van Den Berg, C. Wiersema, J.M. Hegeman, R.H.S. Van Den Brink, J.D. Linkous, J.C. Kvedar, The American telemedicine association, J. Telemed. Telecare 11 (7) (2005) 376–378.

H.R. Bogner, K.H. Morales, C.F. Reynolds, M.S. Gary, M.L. Bruce, Course of depression and mortality among older primary care patients, Am. J. Geriatr. Psychiatr. 20 (10) (2012) 895–903.

J.D. Linkous, J.C. Kvedar, The American telemedicine association, J. Telemed. Telecare 11 (7) (2005) 376–378.