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Original Research

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Longitudinal Association between Late-Life Depression (LLD) and Frailty: Findings from a Prospective Cohort Study (MiMiCS-FRAIL)

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Abstract

OBJECTIVES: The aim of the present study was to investigate whether late-life depression (LLD) is associated with incident frailty over time.

DESIGN: Prospective cohort study, one-year follow-up.

SETTING: Geriatric outpatient clinic, Southwestern of Brazil.

PARTICIPANTS: 181 follow-up participants aged 60 years or over.

MEASUREMENTS: Depressive disorders were classified as Major Depressive disorder (MDD) or Subthreshold Depression (STD) according to DSM-5 criteria. Depressive symptoms were assessed with validated versions of 15-item Geriatric Depression Scale (GDS-15) and 9-item Patient Health Questionnaire (PHQ-9). We performed binary logistic regressions to estimate the odds ratio (OR) for frailty in LLD adjusting for multiple confounders. Participants who were frail at baseline were excluded from the analyses according to measures of frailty (FRAIL questionnaire and 36-item Frailty Index, FI-36). We also estimated the risk ratio or relative risk (RR) and the risk difference (RD) for incident frailty.

RESULTS: We observed a 2 to 4-fold increased risk for incident frailty among participants with LLD. The presence of a depressive disorder was significantly associated with the onset of frailty (adjusted OR for FRAIL and FI-36: 3.07 [95% CI = 1.03 – 9.17] and 3.76 [95% CI = 1.09 – 12.97], respectively. Notably, the risk for frailty due to LLD was significantly higher with the FI-36 compared to the FRAIL (RR: 3.03 versus 2.23). RD was of 17.3% and 12.7% with the FRAIL and the FI-36, respectively.

CONCLUSION: Our data support the association between LLD and incident frailty over one year among geriatric outpatients, reinforcing longitudinal evidence from population-based studies.

Key words: Depression, frailty, aged, morbidity, prognosis, geriatric psychiatry.

Introduction

Late-life depression (LLD) accounts for the most common mental illness among older adults in clinical practice (1, 2) with a pooled prevalence rate of 7.2% for a depressive disorder and 17.1% for clinically relevant depressive symptoms (3). Moreover, the prevalence of LLD tends to be higher in a medical setting among patients compared to community-dwelling older adults (4, 5). Clinically, LLD differs from depression in younger adults by having higher rates of recurrence, more somatic comorbidities, more cognitive and functional impairment, and finally by its association with frailty (6, 7).

Frailty is a geriatric syndrome defined as an increased state of organic vulnerability and loss of resistance to stressors due to a reduced reserve in several physiological systems (8). Frailty is mostly operationalized by meeting at least three out of five criteria of the physical phenotype or with a score above the cut-off of the Frailty Index (FI) a multidimensional measure reflecting the proportion of at least 30 potential health deficits (9). A recent systematic review and meta-analysis showed that the prevalence of physical frailty is 12% (95% CI = 11 - 13%) for frailty phenotype and up to 24% (95% CI = 22 - 26%) when based on the FI (10). The prevalence of frailty in low to middle income countries is higher compared to the more developed countries and is estimated at 17.4% (95% CI = 14.4 - 20.7%) (11).

LLD and frailty are associated with adverse health outcomes (12, 13). Both conditions predisposes to a worse quality of life, burden of other diseases, greater cognitive decline, and higher disability rates (14-17). Three to four out of ten older adults with depression are frail, which may contribute to the increased mortality rates found among depressed individuals (13, 18, 19). Two meta-analyses have found that LLD and frailty have a reciprocal association (18, 20). Nonetheless, studies included in these meta-analyses showed a high degree of heterogeneity (18, 20). This may be explained by the many operationalisation of frailty (in particular) which more or less overlap with the criteria for a depressive disorder (21, 22) as well as the use of self-report screening tests to evaluate LLD (20). Four longitudinal studies showed a four-fold incident frailty among depressed seniors (18). However, these studies involved community-dwelling older adults and included only physical dimensions of frailty.

Evidence from clinical samples is scarce and most are cross-sectional involving either psychiatric outpatients (23, 24), renal transplant patients (25), geriatric inpatients (26) or are longitudinal studies in psychogeriatric clinics (19, 27, 28). Older adults referred to geriatric outpatient clinics are

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potentially more complex due to higher rates of multimorbidity, frailty and depression compared to community samples (29). The only longitudinal study in a sample with geriatric outpatients showed a 2.8 odds of incident frailty among depressed older adults treated with selective serotonin reuptake inhibitors monotherapy (30).

The present study has been designed to test whether depression is associated with an increase of frailty over time using the FI in addition to the self-report FRAIL questionnaire. The FI has a higher predictive ability of adverse events than other frailty measurements in both hospital and community settings (26, 31). Although the FI can be easily calculated based on data routinely collected in digital health records, it has been rarely used for assessing frailty in association with LLD and thus far only by cross-sectional analyses (32, 33). The aim of the present study was to investigate whether late-life depression (LLD) is associated with incident frailty.

Methods

Study design, participants and procedures

The Multimorbidity and Mental health Cohort Study in Frailty and Aging (MiMiCS-FRAIL) is an ongoing prospective cohort study aimed to investigate the interplay between LLD, frailty and inflammation started in January 2018 (34). Participants of the cohort are eligible outpatients of a university-based interdisciplinary geriatrics clinic in Southwestern of Brazil (city of Jundiaí, State of São Paulo). The present study included data from the first wave with a 1-year follow-up.

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

All included participants had a baseline assessment with a comprehensive geriatric assessment (CGA) protocol including a structured diagnostic interview, a complete physical and psychiatric evaluation and validated self-report questionnaires with a team of geriatricians, psychiatrists and physical therapists (32-34). Subsequently, patients are routinely followed-up every 12 months (at least) with the CGA.

Ethical considerations

The MiMiCS-FRAIL follows the ethical standards established by the Brazilian National Council of Health and is conducted in accordance with the human's rights and recommendations stipulated by the Helsinki Convention. Local and national ethical committee (University of São Paulo and Jundiai Medical School) approved this study. All participants signed an informed consent.

Measurements

Depression

LLD was initially evaluated by a geriatrician and posteriorly by a geriatric psychiatrist who confirmed the diagnosis of a depressive disorder following the mood section of the Structured Clinical Interview for DSM-5 disorders Clinical Version (SCID-5-CV). Depressive disorders were classified as either Major Depressive disorder (MDD) or Subthreshold Depression (STD) defined as «another specified depressive disorder» according to DSM-5 criteria (35). All participants were clinically evaluated for the exclusion of bipolar illness as well as to depression syndrome secondary to a medical condition by two geriatric psychiatry specialists. All diagnosis were confirmed in a consensus meeting of the clinical research team.

Validated versions of the 15-item Geriatric Depression Scale (GDS-15) (36) and the Patient Health Questionnaire (PHQ) 9-item version (37, 38) were used to measure depressive symptoms and depression severity (32, 33). Mild MDD corresponded to a score between 5 to 9 points, moderate from 10 to 14, moderately severe from 15 to 19, and severe from 20 to 27 points in PHQ-9 (6).

Frailty

Frailty was assessed in both baseline and follow-up according to two validated instruments, i.e. the FRAIL questionnaire (39-41) and the FI (42-44). The FRAIL questionnaire is a self-report screening questionnaire based on components of the Fried frailty phenotype (8) combined with the presence of multimorbidity in Frailty Index models (43). The FRAIL assesses the presence of fatigue, muscle resistance, ambulation, multimorbidity, and weight loss based on the following questions: (1) Fatigue: the answers "all the time" or "most of the time" to the question "How much of the time during the past 4 weeks did you feel tired?"; (2) Resistance: "yes" to the question "By yourself and not using aids, do you have any difficulty walking up 10 steps without resting?"; (3) Ambulation: "yes" to the question "By yourself and not using aids, do you have any difficulty walking several hundred yards?"; (4) Illness: presence of five or more illnesses out of 11; and (5) Loss of weight: respondents with a weight loss ≥ 5% of their total weight within one year. One point is given to an affirmative answer yielding a total score between 0 and 5; ≥ 3 points represents frailty.

- A previously validated 36-item Frailty Index (FI-36) was used (45). The FI-36 accounts for the proportion of accumulated deficits derived from a count of 36 symptoms, signs, laboratorial exams, conditions and disabilities across different health domains (ranging from 0 to 1). The index is achieved by the sum of present variables divided by

Table 1. Socio-demographic and clinical characteristics according to depression status (n=181)

Characteristics		Depression status			
		Non-depressed (n=92)	STD (n=43)	MDD (n=46)	P
Demographics:					
Age (years)	Mean (SD)	71.5 (9.1)	75.7 (7.9)	74.2 (9.3)	0.028
Female	n (%)	47 (51.1)	26 (60.5)	27 (58.7)	0.512
Education (years)	Mean (SD)	5.6 (4.5)	4.6 (4.5)	5.5 (4.8)	0.498
Clinical characteristics:					
BMI (kg/m2)	Mean (SD)	27.7 (4.5)	26.7 (4.3)	27.8 (5.7)	0.422
Cognitive functioning (10-CS)	Mean (SD)	7.3 (2.5)	6.7 (2.2)	6.1 (2.6)	0.021
Multimorbidity	n (%)	19 (20.7)	9 (20.9)	16 (34.8)	0.159
Polypharmacy	n (%)	53 (57.6)	31 (72.1)	34 (73.9)	0.092
Depression:					
Depressive symptoms (GDS-15)	Mean (SD)	2.6 (2.1)	5.6 (2.6)	7.3 (3.3)	<0.001
Severity of Depression (PHQ-9)	Mean (SD)	1.4 (1.4)	6.9 (1.4)	15.1 (4.1)	<0.001
Frailty:					
Screening (FRAIL)	n (%)	14 (15.2)	20 (46.5)	34 (73.9)	<0.001
Frailty Index (FI-36)	Mean (SD)	0.12 (0.07)	0.17 (0.06)	0.21 (0.09)	<0.001

Abbreviations: STD=subthreshold depression; MDD=major depressive disorder; SD=standard deviation; BMI=body mass index; 10-CS=10-point cognitive screening; GDS-15=Geriatric Depression Scale-15 item version; PHQ-9=Patient Health Questionnaire-9 item version; FRAIL=Scale of physical frailty; FI-36= Frailty Index-36 item; p=p-values calculated by ANOVA (in case mean (SD) are presented) or $\chi 2$ test (in case n (%) are presented). Bold values signifies $p < .05$

total variables included. The FI is a stronger predictor for adverse health outcome such as death than the presence of its individual components or multimorbidity (42, 46). The following 36 health deficits were included: anaemia, arthritis, cognitive impairment, visual impairment, diabetes, dyspnea, chronic renal disease, sleep disorder, peripheral vascular diseases, urinary tract disorders, thyroid disease, respiratory disease, cerebrovascular disease, ischemic heart disease, atrial fibrillation, fracture, hypertension, syncope, heart failure, urinary incontinence, disability, care dependency, osteoporosis, falls, parkinsonism and related disorders, loss of appetite or anorexia, polypharmacy, foot disorders, mobility problems, obesity, hearing loss, valvulopathy, dizziness, social vulnerability, pressure ulcers, peptic ulcers. Frailty was considered with a FI-36 of ≥ 0.25 (43, 44).

Covariates

Age, sex, years of education, body mass index, cognitive performance (according to the 10-Cognitive Screener test) (47), multimorbidity (≥ 2 chronic diseases), and polypharmacy (≥ 5 medications in current use) were included as covariates. These variables were chosen due to their previous association with both depression and frailty in the literature (9, 23, 48-50).

Statistical analysis

Descriptive statistics (proportion or mean with standard deviation) were presented to characterize the sample. All continuous variables showed a normal distribution based on the histogram and Shapiro-Wilk test. One-way ANOVA (continuous variables) or Chi-square test ($\chi 2$) (categorical variables) were applied to compare patients with either MDD, STD or no depression.

Of the follow-up participants, those who were frail at baseline and with missing data were excluded from the analyses, according to different definitions of frailty (the FRAIL questionnaire and the FI-36, respectively). Among non-frail participants at baseline, we performed binary logistic regressions to estimate the odds ratio (OR) for frailty (dependent variable) in participants with MDD or STD versus no-depression at baseline (independent variable). We also estimated the risk ratio or relative risk (RR) and the risk difference (RD) for incident frailty.

Goodness of fit was tested through Akaike Information Criterion (AIC) values, Hosmer-Lemeshow test and R2 (Cox-Snell). Multicollinearity problems were checked using the variance inflation factor. All regression models were adjusted for multiple confounders (described as covariates) and conducted for both the FRAIL questionnaire as well as the FI separately. P-values lower than 0.05 were considered statistically significant. Data were analysed using Statistical Package of the Social Sciences (SPSS), version 25.0.

Results

Characteristics of the sample

Of the 315 patients willing to participate at baseline, 134 met the exclusion criteria or lost to follow-up (see Figure 1), i.e.,

Figure 1. Flowchart of the samples (according to different definitions of frailty)

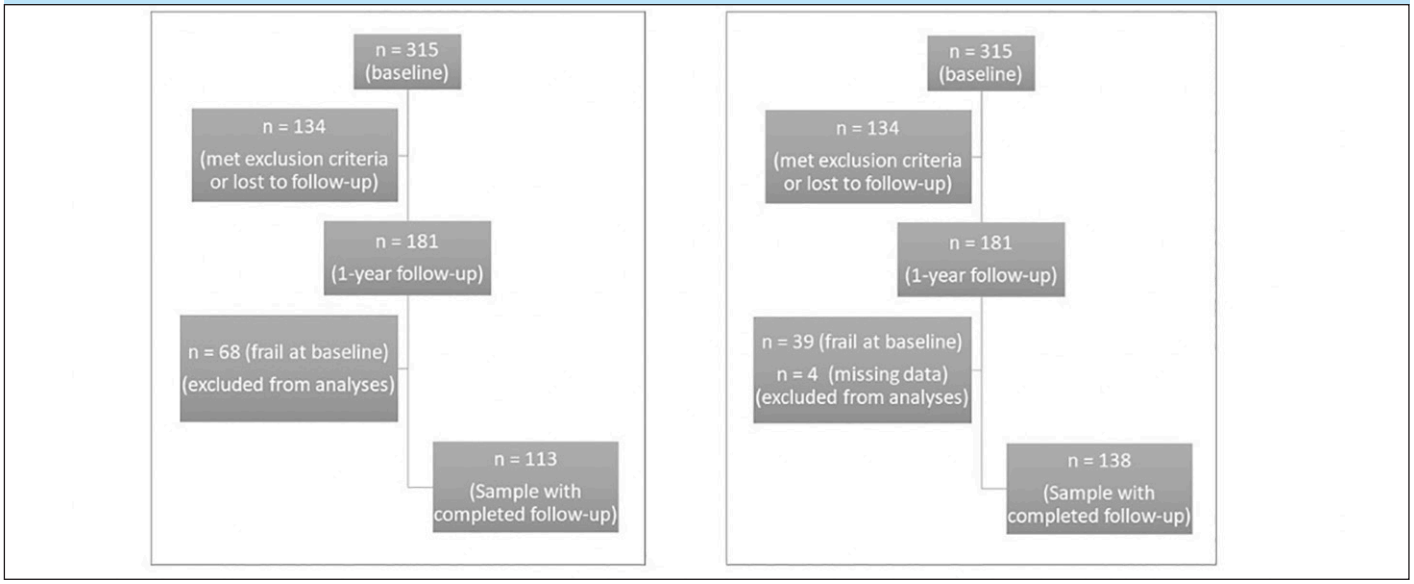
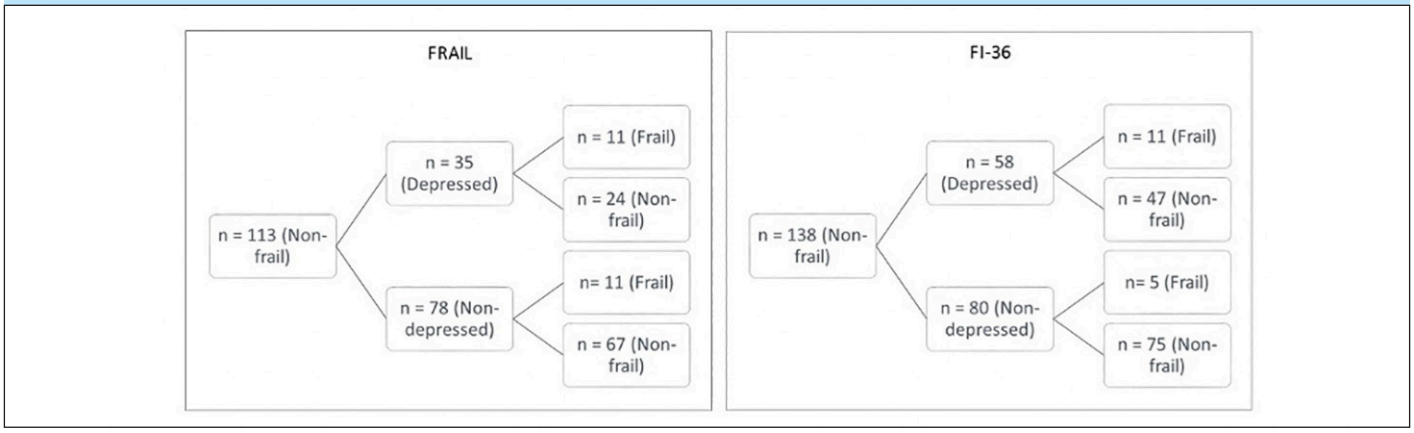


Figure 2. Flowchart of prospective samples



59 participants dropped out (withdraw of consent due to fear of COVID-19), 49 were too ill to participate (32 hospitalization in the last 30 days; 10 dementia cases, 3 severe motor impairment due to stoke; 2 terminal illness; 1 severe sensory impairment; 1 wheelchair dependent) and 26 deceased. The mean age of the 181 participants was 73.2 years, and 55.2% were women. Furthermore, 46/181 (25.4%) participants had major depressive disorder (MDD) and 43/181 (23.8%) subthreshold depression. Table 1 presents follow-up characteristics, stratified by depression status.

Prospective associations between depression and frailty at one-year follow-up

Of the 181 follow-up participants, 113 were non-frail at baseline according to the FRAIL questionnaire. Figure 2 shows the proportion of frail and non-frail within the depressed group compared to non-depressed one. The incidence rate of frailty in the depressed group versus non-depressed was (11/35) 31.4% versus (11/78) 14.1%, respectively ($\chi 2 = 4.62$, df = 1, p = 0.031). Therefore, the RD was 17.3% and the RR was 2.23 [95% CI: 1.07 – 4.64].

Of the 181 follow-up participants, 138 were non-frail at baseline regarding FI-36 (see Figure 2). The incidence rate of frailty in the depressed group versus non-depressed was (11/58) 19% versus (5/80) 6.3%, respectively ($\chi 2 = 5.30$, df = 1, p = 0.021). Furthermore, the RD was 12.7% and the RR was 3.03 [95% CI = 1.11 – 8.26].

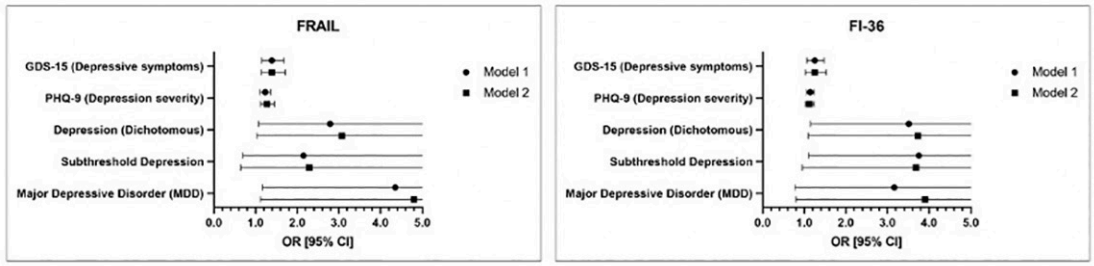
Table 2 shows the odds ratios for incident frailty in either patients with STD or MDD. Based on the FRAIL questionnaire, only MDD was significantly associated with the onset of frailty at follow-up in the fully adjusted analyses. Based on the FI-36, neither STD nor MDD was significantly associated with the onset of frailty at follow-up. Nonetheless, since the statistical power was rather low, we post-hoc tested whether the presence of any depressive disorder (either STD or MDD) was associated with the onset of frailty. This analyses showed that the presence of a depressive disorder was significantly associated with the onset of frailty as measured with the FRAIL questionnaire (unadjusted: OR=2.79 [95%CI = 1.07 – 7.27], p=0.036; adjusted: OR = 3.07 [95% CI = 1.03 – 9.17], p = 0.044) as well as with the FI-36 (unadjusted: OR = 3.51 [95%CI = 1.15 – 10.74], p = 0.028; adjusted: OR = 3.76 [95% CI = 1.09 –

Table 2. Prospective associations between baseline depression (independent variable) and different definitions of frailty at one-year follow-up (dependent variable) by logistic regression

	FRAIL (n=113)			FI-36 (n=138)		
	OR	95% CI	p	OR	95% CI	p
Depressive disorders (DSM-5):						
Model 1:						
Subthreshold depression (STD)	2.15	(0.69 – 6.64)	0.184	3.75	(1.10 – 12.79)	0.035
Major depressive disorder (MDD)	4.35	(1.17 – 16.17)	0.028	3.16	(0.77 – 12.91)	0.109
Model 2:*						
Subthreshold depression (STD)	2.29	(0.64 – 8.26)	0.204	3.68	(0.95 – 14.30)	0.060
Major depressive disorder (MDD)	4.80	(1.12 – 20.65)	0.035	3.90	(0.80 – 18.93)	0.091
Depressive symptoms:						
Model 1:						
Depression severity (PHQ–9)	1.23	(1.10 – 1.36)	<0.001	1.14	(1.05 – 1.24)	0.002
Depressive symptoms (GDS–15)	1.39	(1.15 – 1.68)	0.001	1.25	(1.06 – 1.47)	0.007
Model 2:*						
Depression severity (PHQ–9)	1.27	(1.12 – 1.45)	<0.001	1.12	(1.02 – 1.24)	0.023
Depressive symptoms (GDS–15)	1.39	(1.14 – 1.71)	0.001	1.25	(1.02 – 1.53)	0.031

Abbreviations: STD=subthreshold depression; MDD=major depressive disorder; GDS-15=Geriatric Depression Scale-15 item version; PHQ-9=Patient Health Questionnaire-9 item version; FRAIL=Scale of physical frailty; FI-36= Frailty Index-36 item; OR = odds ratio; 95% CI = 95% Confidence Interval; p = p-values; Bold values signifies p < .05; Model 1 = unadjusted model; Model 2 = fully adjusted model; * Adjusted for age, sex, education, BMI, cognition, multimorbidity and polypharmacy.

Figure 3. Odds ratios for frailty (according to the FRAIL and the FI-36)



12.97], p = 0.036). Both measures of depressive symptoms (measured by PHQ-9 and GDS-15) were also associated with a higher odds ratio for frailty according to the FRAIL and FI-36 (Table 2 and Figure 3).

Discussion

Main findings

In summary, this prospective cohort study found a 2 to 4-fold increased risk for incident frailty among non-frail participants with depression (mainly depressive disorders) compared to non-depressed patients. Regarding the hypothesis of this study, our data support the association between LLD and incident frailty over a one-year follow-up among geriatric outpatients. Findings were rather robust regarding the measurement of either frailty or depression.

The incidence rates of frailty in the depressed group were higher than the non-depressed one, and are in line with previous studies (30, 48, 49, 51, 52). The incidence of frailty varies depending on the population being assessed and the diagnostic criteria used. We demonstrated that both frailty measures are roughly similar with respect to the onset of frailty. Four studies found an incident frailty from 9% (30, 52) to 15% (48, 49) when compared to 19% in our sample with the FI. In the study conducted by Paulson and colleagues (51), the incidence of frailty was of 31.8%, a similar rate found in the current study (31.4%) with the FRAIL questionnaire.

A recent systematic review and meta-analysis demonstrated that the prospective relationship between depressive symptoms and incident frailty was robust (20). This review concluded that depressed older adults are 3 times more at risk to develop frailty than those without depression (20). In line with this study, we found a RR of 2 to 3 for incident frailty depending on the criteria used to define frailty. Notably, the risk for frailty due to depression was significantly higher when used FI compared to FRAIL (RR for FI and FRAIL: 3.03 and 2.23, respectively).

On the other hand, frailty and depression may share a common vulnerability to the same stressors, which could result in an overlap of both conditions (22, 18). Even though this hypothesis was recently confirmed (53), it contradicts

evidence-based literature review which has demonstrated a uni- or bi-directional associations between both constructs (18, 20, 21). For instance, a population-based cohort study, Rugao Longevity and Aging Study (RuLAS), showed that depressive symptoms (measured by the GDS-15) were related to the emergence of frailty over a 3-years follow-up (OR = 2.79 [95% CI = 1,09–7,10]), after adjusting for covariates (52). Chu and colleagues (54) also confirmed that frailty (measured by Fried frailty phenotype) was associated with depressive symptoms (measured by GDS) after longitudinal analyses (OR = 2.12, 95% CI = 1.17–3.83), considering the adjusted models. As previously mentioned (52, 54), the same cohort study investigated the relationship between depressive symptoms and frailty reciprocally, which reinforces the bidirectional association between both conditions.

However, the current study extends to the findings of these studies that depressive disorders (mainly MDD) also predicts the onset of frailty. The core symptoms of MDD according to the DSM-5 describe a specific depression syndrome (6) so adopting the diagnostic criteria for depression adds the credibility to the methodology used in this study. Depression screening instruments (i.e. GDS-15 and PHQ-9) do not immediately lead to a diagnosis but can accurately identify patients who are at risk. In addition, our findings can contribute with the assessment of depressive symptoms that seem to yield similar and good results (32, 33). These results could be explained by findings that depressive symptoms were associated with an increased risk for frailty (OR = 2.20, [95% CI = 1.88–2.57]) over 3-years follow-up (48). The same cohort study has shown that depression severity was a risk factor for frailty (severe symptoms, OR = 2.19 [95% CI = 1.86–2.59]; moderate symptoms, OR = 1.31 [95% CI = 1.14–1.50]) (49). Paulson and colleagues (51) found a 2.8-fold for the incident frailty, considering the profile of greater burden of cerebrovascular disease and more severity of depressive symptoms, among women with vascular depression.

Due to a lack of relevant data, the current study provides limited information on potential underlying factors and biological plausibility. Some previous studies assessed the pathophysiology and causation of frailty in depressed older adults. A cross-sectional study from the NESDO evaluated the association between physical frailty and low-grade inflammation in LLD assessing three inflammatory markers, namely, C-reactive protein (CRP), interleukin-6 (IL-6) and neutrophil gelatinase-associated lipocalin (NGAL) (55). Among the most relevant findings, frailty or severity of depressive symptoms were not associated with higher levels of inflammatory markers. In addition, the findings of the Health Aging and Body Composition Study (HABCS) reinforces these analyses due to lack of evidence between inflammation, depression, slow gait and mortality (56). Inflammation, depression and slow gait define a phenotype at risk of death. Trajectories of inflammation had an independent effect on mortality after accounting for covariates and the effect of trajectories of slow gait on mortality depended on depression status (56). Arts and colleagues (57) investigated the association between leucocyte telomere length (LTL) as molecular marker of aging and the frailty phenotype and whether these associations would be moderated by the presence of a depressive disorder. LTL was related to frailty but with a really small effect on LLD (57). Arts and colleagues (19) showed that frailty and aging related biomarkers (especially CRP and vitamin D) predicts mortality among depressed older patients. Therefore, there is a lack of validity of these results mainly in longitudinal studies that could confirm the pathogenesis and the causation of frailty in LLD.

Strengths and limitations

To our knowledge, this is the first prospective study to examine LLD and frailty (assessed with the FI and a CGA) in a geriatric outpatient clinic. Thus, this is clinically relevant because depressed geriatric outpatients have an increased risk of becoming frail. In addition, the prevalence of frailty in Brazil is higher in those individuals recruited from health care services when compared to community ones (30% versus 22%, respectively) (58).

Second, the current study focused on the changes in the FI, because of its robust flexibility and wide reproducibility that does not depend on which deficits are chosen (44). It is crucial to emphasize that both frailty measures were roughly similar regarding the onset of frailty. The FRAIL is a really feasible screening instrument and highly relevant in clinical practice (40). Therefore, the FRAIL questionnaire was used as a measure of comparison with the changes in the FI in order to infer whether our findings would be consistent.

Third, our analyses were based on DSM-5 criteria, in order to distinguish MDD from STD instead of considering only depressive symptoms. STD is generally also seen as an important depressive syndrome in late life (59). Most previous studies have only assessed self-report depressive symptoms in the association with frailty phenotype and this may be confounded with the presence of frailty (18, 20).

Finally, the assessment and control of confounders were performed by stratifying the study sample and using fully-adjusted statistical analyses on the association between LLD and frailty. This could explain one possible direction of this association and internally validate our predictive model. Therefore, our main findings represent as not being a result by chance neither of a potential measurement or confounding biases.

Limitations of the current study should be also considered. We are unable to generalize completely our findings to other groups because our patients presented lower levels of schooling and worse cognitive functioning when compared to general population. In addition, our sample size could have resulted in underpowered analyses (some participants dropped out due to fear of COVID-19) and a larger sample might find results more robust. Other studies could replicate and validate these findings to other clinical settings with different based-population samples.

Conclusions and implications

According to the hypothesis of this study, it has been confirmed that depressive disorders predicts the changes in frailty. For instance, a depressed older adult becomes increasingly sedentary and socially isolated, resulting in a greater odds of developing physical symptoms of frailty such as weakness, exhaustion and slow gait. Thus, screening for both LLD and frailty is crucial in order to reduce the burden of these clinical conditions and adverse health outcomes in older adults.

Future research should be directed to successful treatment of LLD in frail seniors because of the potential capacity for psychosocial interventions to improve physical-health outcomes. Prince and colleagues (60) have already highlighted: "no health without mental health". As a result, this approach could lead to an increased behavioral and social activation, thereby improving the levels of physical and social activity in these individuals, and, thus, reducing the risk of the onset and progression of frailty. Finally, further studies should address the underlying mechanisms in the relationship between LLD and frailty.

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Ethical standards: This study was conducted according to the ethical guidelines of research with human beings, approved by the local Ethics Committee.

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