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Survival of elderly outpatients: effects of frailty, multimorbidity and disability

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Abstract *This study aims to analyze the impact of frailty, multimorbidity and disability on the survival of elderly people attended in a geriatric outpatient facility, and identify the clinical risk factors associated with death. It is a longitudinal study, with 133 elderly people initially evaluated in relation to frailty, multimorbidity (simultaneous presence of three or more chronic diseases) and disability in Daily Life Activities. The Kaplan Meier method was used to analyze survival time, and the Cox regression was used for association of the clinical factors with death. In follow-up over six years, 21.2% of the participants died, survival being lowest among those who were fragile ($p < 0.05$). The variables frailty (HR = 2.26; CI95%: 1.03–4.93) and Chronic Renal Insufficiency (HR = 3.00; CI95%: 1.20–7.47) were the factors of highest risk for death in the multivariate analysis. Frailty had a negative effect on the survival of these patients, but no statistically significant association was found in relation to multimorbidity or disability. Tracking of vulnerabilities in the outpatient geriatric service is important, due to the significant number of elderly people with geriatric syndromes that use this type of service, and the taking of decisions on directions for care of these individuals.*

Key words *Survival analysis, Frail elderly person, Chronic disease, Comorbidity*

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Introduction

Frailty is a multidimensional syndrome characterized by physical, psychological and social vulnerability and stressors[1], neuroendocrine dysregulation and susceptibility to unfavorable outcomes, particularly reduction of survival time[2]. The literature shows that the syndrome is multifactorial and has proinflammatory characteristics. Specific conditions such as Chronic Renal Insufficiency (CRI) and cardiovascular diseases are also described as proinflammatory conditions associated with frailty in the elderly people[3,4].

Multimorbidity is a syndrome characterized by losses of physiological reserve and dysfunction of multiple systems of the organism (neurological, cardiovascular, urinary, endocrine, immunological and muscular-skeletal) over the years. Increasingly, studies on aging and the associated conditions of health analyze the simultaneity of illnesses in relation to adverse outcomes in health, including death. Co-existence of morbidities is considered to be an independent risk for death[5].

Disability, associated with frailty and multimorbidity, means difficulty in carrying out daily tasks that are indispensable to living in society, and is associated with mortality among the elderly population. Evaluation of the functional capacity of the elderly person is important as a prognostic factor in various contexts of healthcare (primary healthcare and tertiary-level complexity)[6].

Fried et al.[7] presented the biological phenotype of frailty, finding that the syndrome, although it can be superimposed on multimorbidity and disability, is separate from those two other conditions. Indeed, it is known that frailty[8], multiple chronic diseases[5] and disability[9], evaluated in isolation in elderly people resident in the community are predictors for negative events over time.

Particularly in relation to frailty, the operational model proposed by Linda Fried and collaborators shows association between the syndrome and mortality, in elderly people attended in low-complexity healthcare in the community[10]. In another context, among institutionalized elderly people, the phenotype model has also been validated, showing association between the syndrome and negative outcomes such as falls, hospitalization and seeking emergency care[11].

However, the impact of frailty on the survival of elderly people in service of tertiary-level complexity, through isolated investigation and with superimposition on multimorbidity or disability, is still little known. The characterization of the predictors of mortality in this specific population will provide evidences as to whether the care strategies are appropriate to the change in life expectancy.

Thus, this study aims to analyze the impact of fragility, multimorbidity and disability on the survival of elderly people attended in outpatient Geriatric service, and also to identify the clinical risk factors for the outcome of death in this context of healthcare.

Methods

This was a longitudinal study of clinical, health and survival information of 133 elderly patients of both sexes attended in the Geriatric Outpatient Facility of the Hospital de Clínicas of Campinas State University (Unicamp), Campinas, São Paulo State, Brazil, with an initial assessment in the period from October 2008 to September 2010.

The Geriatric Outpatient Unit of HC Unicamp is a tertiary public health service, which attends, weekly, elderly people of 60 years of age or more, referred from outpatient facilities of the other medical specialties of that hospital and from the Basic Healthcare Units of the municipality of Campinas (São Paulo State) and the region.

The criteria for inclusion were: Elderly people using the Geriatric Outpatient Facility, in the age group 70-85 on initial evaluation, who agreed to participate in the study and signed the Free and Informed Consent Form. The criteria for exclusion were based on the criteria in the Cardiovascular Health Study (CHS), that is to say, elderly people with serious cognitive disabilities that prevented comprehension and carrying out of the tests, those with terminal conditions in palliative care, and those not in the specified age group[7].

Initially, the subjects were interviewed by the researchers responsible for the principal project, prior to the medical consultations scheduled for each participant. The primary data of the initial evaluation were obtained through a standardized evaluation sheet, comprising questionnaires related to demographic, socio-economic and health information.

The demographic variables collected were age, gender (male, female) and marital status (with or without partner). The socio-economic

variables analyzed were level of schooling (illiterate, 1-4 years, 5-8 years or >8 years of schooling), and individual monthly income (³ 2 times the minimum wage or < 2 times the minimum wage). The variables related to health condition were also investigated: number of morbidities diagnosed, and self-perception of health (good/very good, reasonable or bad/very bad).

Fragility was operationalized in accordance with the modified version[12], of the phenotype of frailty proposed by Linda Fried and collaborators[7]. In this adapted model, there are four components for identification of a frail elderly person, as follows:

a) Unintentional loss of weight: Measured by report from the participant. An unintentional loss of weight greater than 4.5 kg or 5% of body weight in the last 12 months, prior to the first evaluation, was considered.

b) Exhaustion: Evaluated on the basis of two self-reported questions on the Center for Epidemiologic Studies Depression Scale (CES-D):

– 7th question: "I felt that everything I did was an effort"; and

– 20th question: "I was unable to continue"[13,14].

For these questions there were four possibilities of response with respective scores from 0 to 3, reflecting the frequency with which the participant felt exhausted during the week, as follows: "rarely or never"= 0; "seldom" (1-2 days in the week) = 1; "sometimes" (3-4 days in the week) = 2; and "most of the time" = 3. Participants who scored '2' or '3' in any one of the two questions of the CES-D were classified as having exhaustion or fatigue and thus were included in the classification of frailty.

c) Slowness or reduction of speed of walking: Evaluated by the time in milliseconds spent walking 4.0 meters on a level surface, in three attempts, this being adapted from the recommendations of Guralnik et al.[15] and Nakano[16] adjusted for gender and Body Mass Index (BMI).

d) Muscular weakness: Strength of the dominant arm, measured by a Jamar® brand isokinetic dynamometer (Lafayette Instruments, Lafayette, Indiana, United States) and adjusted for gender and BMI. The participants made three attempts of manual pressure strength while seated, with the arm flexed at 90º in relation to the forearm, after a verbal command from the investigator to apply force to the handle in the said apparatus.

Participants classified as 'fragile' scored in three or more of the above-mentioned components. Those who were 'pre-fragile' scored one or two of these components, and the 'non-fragile' did not score in any of the four components of fragility[12].

The condition of multimorbidity was defined as the presence of three or more simultaneous chronic diseases of morbidities diagnosed and previously reported in electronic medical report files (stroke, congestive heart failure (CHF); coronary heart disease (CHD); cardiac arrhythmia; high blood pressure; dyslipidemia; chronic obstructive pulmonary disease (COPD); diabetes mellitus (DM); chronic renal insufficiency (CRI); Chagas disease; osteoporosis; osteoarthritis; depression; and hypothyroidism[17,18]. The variable multimorbidity was characterized in two modes: 'without multiple morbidity', to indicate individuals not suffering from multiple conditions, or 'with multiple morbidity' for those presenting multiple morbidity.

Functionality was evaluated by the Katz Index[19], to measure disabilities in Daily Life Activities (DLA), as follows: dressing oneself; taking a shower; feeding oneself; using the bathroom; lying down in and getting up from bed; control of urination and evacuation. Disability was categorized as 'without deficit' for those with no functional loss and 'with deficit' for those that had one or more functional losses in DLA.

Follow-up period for the study was the period between the date of initial evaluation and the date of telephone contact, which was made only once with each subject or person responsible to verify whether the subject was still alive. Monitoring was finalized in October 2014, so that the longest completed follow-up period was six years after the initial evaluations in 2008. The survival time, in days, was defined as the period between the date of the initial evaluation and the date of death[20].

All the analyses were carried out using the statistics program SPSS®, version 22.0. The study sample was described according to frequencies, for the category variables (gender, marital status, level of schooling, income, multimorbidity, disability in DLA, classification as frail, and deaths), with the respective absolute frequencies (n) and percentages (%) and descriptive analyses, using average and standard deviation, of the numerical variables (age, number of simultaneous chronic morbidities, and DLA preserved).

The survival curves were obtained by the non-parametric *Kaplan-Meier* method[20]. For this, participants were divided into analyses according to presence of failure, disability and multimorbidity for characterization of the differences of survival time within each condition (Log

Rank test). Data which did not present the event of interest (death) were censored at the closing of the study, that is to say those people who remained alive until the telephone contact. The censored cases were introduced into the analyses to estimate the probability of survival of all the participants in the survey[20].

For analysis of the Hazard Ratio for the outcome *death*, the univariate and multivariate Cox regression was used. Chronic diseases diagnosed; Multimorbidity; DLA deficit; and frailty were included as variables in the univariate regression analysis. Subsequently, for the multivariate analysis there were selected only variables that had $p < 0.20$ in the univariate analysis. Finally, the result of the final multivariate regression model was obtained using the *stepwise forward* method for selection of variables in the equation, with the clinical predictors that presented $p < 0.05$ and a confidence interval of 95%. The level of significance adopted for all the statistical tests was $p < 0.05$.

This study was approved by the Research Ethics Committee of the Medical Sciences Faculty of Unicamp, as an addendum to the principal project "investigation of anemia, frailty and vitamin B12 deficiency as risk factors for falls in elderly people".

Results

The average age of the subjects was 78.09 ± 5.34 years, with 26.3% male and 73.7% female. By socio-economic breakdown, 45.4% had studied from one to four years, and 39.2% were illiterate. A majority (73.6%) had monthly individual income less than two times the minimum wage and reported not having a partner (60.3%). In the frailty variable, 56.1% were classified as pre-frail; 28.8% as frail and 15.2% as non-frail. The prevalence of multimorbidity was 66.2%, and average number of simultaneous chronic diseases was 3.22 ± 1.78. The most prevalent chronic diseases were: High blood pressure (66.2%), Congestive Heart Failure (29.3%) and DM (21.1%). In terms of disability, 22.7% had some DLA deficit, and the average number of DLAs preserved was 5.52 ± 1.16. A majority of frail individuals were female (78.9%). Some subjects had superimposition of frailty and multimorbidity (19.7%), and some had frailty and loss of DLA functionality (10.6%). Of the total of all participants, 28 (21.2%) died and 104 (78.8%) remained alive.

Figures 1 and 2 show the results of survival analysis by the Kaplan Meier method[20] in terms of frailty, multimorbidity and disability. The frail individuals had a higher probability of survival than the pre-frail and the non-frail ($p = 0.008$) (Figure 1B). In the stratification of frailty with disability or multimorbidity, the frail individuals had the shortest survival time, independently of whether or not they also had disability ($p = 0.04$) (Figure 2A) and/or presence of multiple chronic diseases ($p = 0.002$) (Figure 2B).

Table 1 presents the univariate and multivariate Cox regression for the variables considered in this study. In the multiple analysis the independent clinical factors associated with risk of death were CRI and frailty (Table 1).

Discussion

The principal result of this study showed that the frail individuals attended in the Geriatric Outpatient Unit had the lowest survival time. Also, frailty and CRI were variables associated with higher risk of the outcome death.

The prevalence of frailty, multimorbidity and disabilities increases with advancing age. In the data from FIBRA (*Rede de Estudos sobre Fragilidade em Idosos Brasileiros* – the Study Network on Frailty in Brazilian Elderly People)[21] and SABE (*Saúde, Bem-Estar e Envelhecimento* – Health, Well-being and Aging)[22], the percentage of frail elderly people aged over 65, and over, was 9.1% and 8.0%, respectively. Other population studies[23,24] show that 50% of the elderly population in the same age group have multiple chronic diseases, and 20% have disabilities. However, surveys carried out with elderly people attended in the outpatient context show even higher values, of 18% for frailty[25], 66.2% for multimorbidity[26] and 46.3% for disability in DLAs[27]. In our study, it is probable that the high prevalence of frail individuals (28.8%) has an association with the high indices observed for high blood pressure, CCI and DM. The literature emphasizes that inflammatory diseases such as high blood pressure, CRI, cardiovascular diseases and DM are associated with the development of the frailty syndrome in the elderly person, by the mechanism of activation of the proinflammatory pathways in the organism over the long term. Release of the biomarkers Interleukin- 6 (IL-6) and C-reactive Protein (CRP) in the organism influences metabolic and homeostatic dysregulation, causing a predisposition to frailty[28].

The relationship of each one of the three independent variables with survival time, in isola-

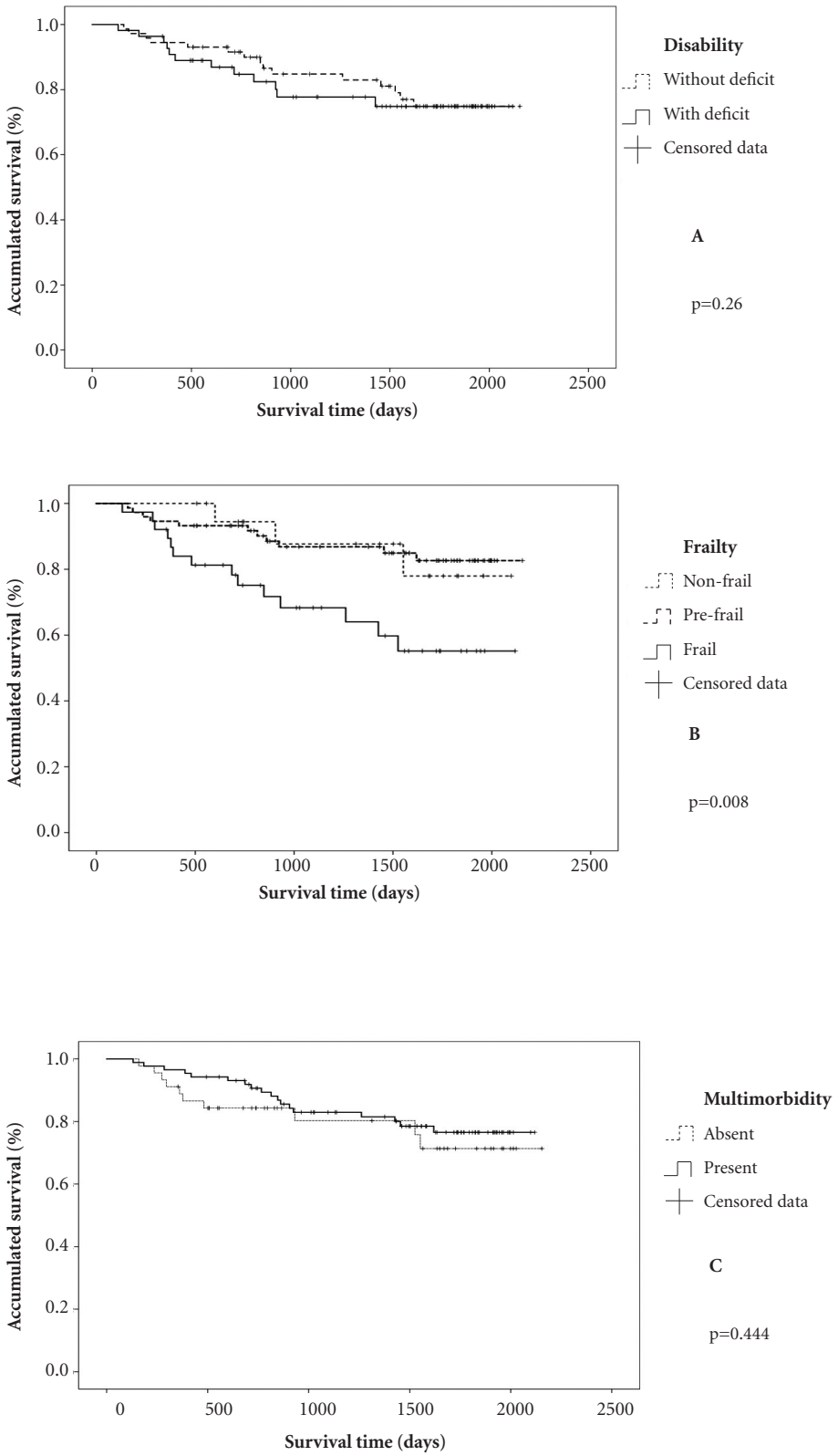

Figure 1. Survival curves of elderly people attended in Geriatric Outpatient facility (*Hospital das Clínicas* [HC] of Unicamp, Brazil), in 2008 – 2010, by disability in DLA (A), multi-morbidity (B) and frailty (C).

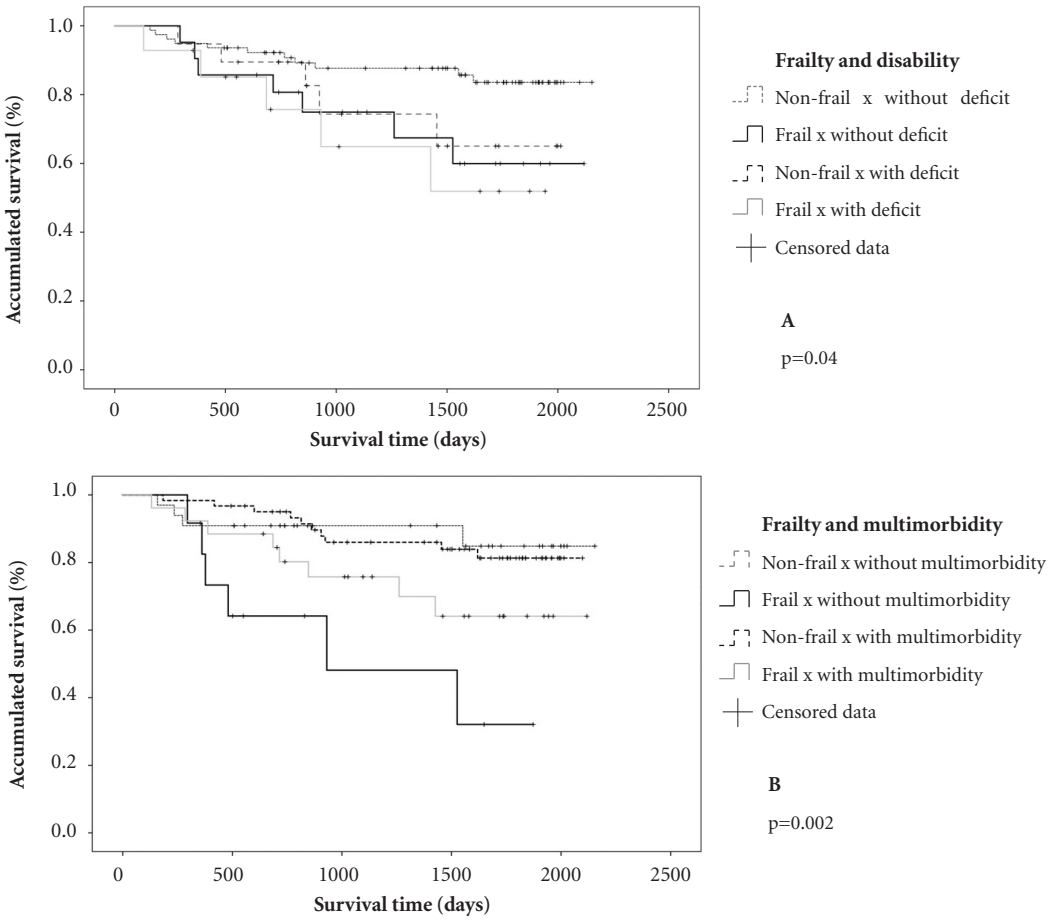

Figure 2. Survival curves of elderly people attended in Geriatric Outpatient facility (*Hospital das Clínicas* [HC] of Unicamp, Brazil), in 2008 – 2010, by stratification of disability in DLA (A) and multimorbidity (B).

tion, is evidenced through the surveys on elderly people resident in the community[29-31]. The original study of the phenotype of frailty presented the syndrome in its biological context and differentiated it from disability and multimorbidity, in a group of elderly people resident in the community. However, the authors analyzed the survival time only as a function of the classification of frailty (non-frail, pre-frail and frail)[7] and there is a scarcity of studies that incorporates frailty, multimorbidity and loss of functionalities simultaneously in analyzes of survival time, so as to characteristic a profile of greater risk.

Although all these geriatric syndromes have an impact on mortality, our studies showed that, in these elderly people with healthcare of higher complexity, it was only frailty that was statistically associated with reduction of survival time. The stratification of the groups in accordance with superimposition with multimorbidity or disability showed that the introduction of the variable *frailty* in the models produced statistically significant differences, since fragile elderly people with or without multiple simultaneous chronic diseases and disabilities in DLA had lower survival time. These findings corroborated the importance of frailty as a predictor of lower survival time, independently of the functional status and number of simultaneous chronic diseases.

These results are in accordance with the literature, since frailty is an independent predictor of survival time in elderly people attended in outpatient facilities after cardiovascular surgery[32] and sufferers from CRI[33], that is to say, in patients of

Table 1. Clinical risk factors for death in elderly people attended in Geriatric Outpatient facilities (*HC* of Unicamp, Brazil) in 2008 and 2010.

Variables	Univariate analysis			Multivariate analysis		
	*HR	**CI (95%)	*p*	*HR	**CI (95%)	*p*
Coronary heart disease	1.60	0.64-3.95	0.308			
Congestive heart failure	*2.49*	*1.19-5.23*	*0.016*			
Heart arrhythmia	2.33	0.80-6.74	0.118			
Chagas disease	1.19	0.48-2.96	0.694			
Arterial disease	1.34	0.57-3.17	0.495			
Cardiopathy	*2.39*	*1.12-5.12*	*0.024*			
Stroke	1.84	0.55-6.12	0.316			
High blood presure	0.87	0.39-1.94	0.748			
Pre-existing disease or injury	1.13	0.51-2.50	0.758			
Diabete mellitus	0.90	0.36-2.23	0.832			
Chronic renal insuffiency	*2.39*	*0.97-5.90*	*0.058*	*3.00*	*1.20-7.47*	*0.018*
COPD	2.94	0.88-9.77	0.077			
Depression	1.28	0.38-4.24	0.685			
Rheumatism	0.49	0.21-1.13	0.097			
Multimorbidity (≥3 NTCDs)	0.73	0.34-1.60	0.445			
Disabilities (DLA)	1.17	0.55-2.52	0.672			
Frailty	*3.06*	*1.45-6.43*	*0.003*	*2.26*	*1.03-4.93*	*0.040*

* HR= Hazard ratio. ** CI (95%) = Confidence interval for hazard ratio. Statistical significance p <0.05.

high risk for mortality. Interestingly, frailty and CRI were clinical factors of higher risk for death in the sample studied. These results are in line with the literature, since the risk of death among fragile elderly people is five times higher than in the non-fragile[29]. CRI is also a clinical condition associated with mortality in elderly people: specifically among those in their 80s, the renal function is reduced by half and the risk of death is three times greater in relation to those without the condition[34].

Pugh et al.[35], noted in a three-year follow-up study that frailty and CRI had risk ratios for death of 1.18 (CI95%: 1.05–1.33) and 1.35(CI95%:1.16–1.57), respectively, being variables associated independently with death in 283 elderly people in outpatient healthcare, with an average age of 70 years. Stronger associations were observed in a prior study[36] of elderly people (n=10256) aged 60 and over, attended in a service of tertiary complexity. In the final multiple regression model, frailty (HR = 2.00; CI95%:1.5-2.7) and CRI (HR = 3.00; CI95%:2.2–4.1) were independent variables associated with death.

Care of elderly people in services of tertiary complexity limits access to the service to those with more serious health conditions, compared to those that live in the community and use primary healthcare[37]. The elderly patients attended in outpatient facilities have a higher number of comorbidities, multimorbidity, disability and mortality[38]. The finding that disability and multimorbidity were not predictors of lower survival time is an indication of the clinical importance of frailty and its implication in susceptibility to the outcome death in this specific group of elderly people with more clinical complexity. Another possible hypothesis to explain these findings is that these individuals are in a better situation of control of their illnesses due to the fact that they are linked to the specialized service, but these suggestions cannot be analyzed, because the work was not designed with this objective.

This study did not analyze the therapeutic support in relation to the different conditions, that is to say, frailty, multimorbidity and disability, and this could be one of the explanations for the differences in the survival time outcomes. Further studies should be directed toward answering these questions in relation to elderly people attended in outpatient facilities. Another limitation is the small size of the sample, and thus the results of this study cannot be generalized to larger populations of elderly people.

However, this study does provide one important piece of information about the implication of these syndromes in the survival of elderly people in service of tertiary complexity. The follow-up period for these patients was over a period of six years, which is an appropriate follow-up for analysis of the outcomes of interest. Another positive aspect is that studies[23,39,40] show association of multimorbidity with survival generically, however, they do not analyze the impact of specific diseases on the subjects.

Conclusion

Frailty was a predictor of lower survival time in elderly people attended in geriatric service, within a follow-up period of six years. The validity of the phenotype model proposed by Fried and colleagues in the year 2001 in prediction of the outcome death in elderly people with a profile of need for high complexity assistance was verified. This is important for the identification of risks between specific groups of elderly people, for the purpose of helping professionals in directing prevention and treatment of conditions that lead to early death. The results show the importance of systemic evaluation of frailty in Comprehensive Geriatric Assessment for detection of individuals who have a higher degree of vulnerability for negative outcomes.

Collaborations

DEC Leme participated in the design and design, analysis and interpretation of the data and writing of the article. RP Thomaz participated in the project design, data collection and review of the article. FSA Borim participated in the analysis and interpretation of data and critical review relevant intellectual content. SL Brenelli participated in the preparation of the project and final revision of the article. DV Oliveira participated in the final review of the article to be published. A Fattori participated in designing and designing, analyzing and interpreting the data, writing the article and critically reviewing the intellectual content.

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