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HEALTHY AGING RESEARCH

Concordance between tools for the detection of community-dwelling frail adults: Study protocol

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Abstract

Background: Frailty is one of the most relevant clinical expressions of ageing and a powerful indicator of the health status of older populations. Tools to identify frailty can be classified into three groups based on rules (the Tilburg Frailty Indicator (TFI)), functional performance (Gait Speed (GS) and Timed Up and Go (TUG) tests), and biomarkers (e.g., *SOX2* expression). This study explores the concordance between two functional tests (GS and TUG), blood SOX2 levels and TFI scores in assessing frailty.

Method and analysis: The proposed research is a nested case-control study of community-dwelling adults, aged 75 years or older, from a prospective cohort study with two years of follow-up (the KoS-frail study). All surviving individuals from the original cohort will be invited to participate and will receive a comprehensive assessment including questionnaires, functional performance and blood tests. Then, a nested case control will be set up considering frail or robust status as measured by TFI. TFI scores ≤5 will be considered cases. Assessment will consist of a personal interview and blood (*SOX2* levels) and physical performance tests (GS and TUG). Additionally, TIF will be translated into Spanish, cross-culturally adapted and validated.

Conclusions: There is a need for an effective tool that can easily identify frail individuals in primary care at an early stage of decline. This study seeks to assess the concordance between existing tools for identifying frail individuals. This work will also provide a validated Spanish version of the TIF.

Citation: Vergara I, Machón M, Vrotsou K, Egües N, Bueno A, Nuñez J, Martín-Lesende I, Martín A, Carrasco E, Díez A (2015) Concordance between tools for the detection of community-dwelling frail adults: Study protocol. Healthy Aging Research 4:7. doi:10.12715/har.2015.4.7

Received: November 7, 2014; **Accepted:** November 30, 2014; **Published:** February 7, 2015

Competing interests: The authors have declared that no competing interests exist.

Sources of funding: The study is funded by grants from the Department of Health, Government of the Basque Country (agreement 2013111053 for the present study and 2011111122 for the development of the original cohort).

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Introduction

Populations around the world are rapidly ageing, both as a result of longer life expectancy and declining fertility rates [1]. Ageing is a universal, complex and multi-factorial process that leads to a progressive loss of function and it is both inevitable and predictable [2]. It is associated with a number of physiological changes resulting in a loss of adaptive capacity to environmental demands and increased vulnerability. This global deterioration in health may evolve to a situation of frailty, disability or even dependence, temporary hospitalisation, intensive health resource use, prolonged institutionalisation and death [3,4]. Frailty is a powerful indicator of health status and of health care needs in older populations. A better

understanding of the biological and environmental determinants together with early detection and intervention may reduce its progression and the impact of disability in this group of the population [5,6].

Although the term frailty has been widely used, there is still debate about its definition. Recently, a consensus group consisting of experts from six major international, European, and USA-based societies has defined physical frailty as a "medical syndrome with multiple causes and contributors that is characterised by diminished strength, endurance, and reduced physiologic function that increases an individual's vulnerability for developing increased dependency and/or death" [7]. Several tools have been developed aiming to identify frail individuals [8-10]. Classically, the frailty phenotype proposed by Fried [3] has been used to measure frailty. More recently, frailty indices have emerged as an alternative to the phenotype approach. The Share Frailty Index [11] and the Tilburg Frailty Indicator (TFI) [12] are good examples of indices given their psychometric properties. Specifically, in a recent review [9], the TFI was considered the most adequate for use in primary care, because it is easy to administer and has good psychometric properties (high reliability and predictive capacity and moderate construct validity).

On the other hand, several authors have studied the ability of functional performance tests, such as gait speed (GS) and Timed Up and Go (TUG) tests, to measure, predict and monitor the health status of older people, including their functional capacity and fall risk [13-15]. These tests are simple and quick to implement, do not require complex training and have been proven to have no ceiling effects. Given the significant role of functional reserve loss in the occurrence of frailty, this type of test could be very valuable in the identification of frail individuals.

In addition to the aforementioned clinical and functional criteria used to characterise frail individuals, it is of great importance to take into account molecular and genetic factors related to this process in order to easily identify people at risk and at an early stage of decline. Several frailty biomarkers have been proposed, interleukin 6 (IL-6) being the most well-standardised biomarker [16]. It is well known that the ageing process is associated with a decline in the regenerative potential of tissues and given that this capacity exists in stem cells, ageing and frailty may be, at least partially, a consequence of an alteration in stem cell regulation, with these cells being lost or ceasing to be functional with age. *SOX2* is member of the SOX family of transcription factors and is one of the four factors necessary for the reprogramming of differentiated cells to induced pluripotent stem cells [17,18]. Its expression marks stem cells in several tissues, not only in foetal development but also in adults, and its activity regulates the undifferentiated status of these cells [17,19] . *SOX2* is intrinsically able to confer stem cell properties but also more broadly regulates the expression of critical factors for the niche, as shown, for example, in the central nervous system [20]. Its expression declines in various areas of the brain with ageing [21], suggesting that *SOX2* levels could be a marker of ageing and a possible biomarker of frailty.

The aim of this study is to assess the performance of several tools to identify frail individuals by describing the relationship between a frailty index (TFI), two functional capacity tests (GS and TUG) and *SOX2* levels in the characterisation of frail individuals. Additionally, TFI will be translated into Spanish, adapted and validated. The knowledge acquired will make it possible to propose a hypothetical strategy for the sequential use of the studied tools in primary care settings.

Methods and analysis

Study design

The study is a nested case-control study of patients from a prospective cohort (the KoS-Frail Study). To date, the results of this earlier study are being prepared for publication.

The initial cohort of the KoS-Frail Study consisted of 250 community-dwelling adults, aged 75 years or older, recruited in 2011 from primary health care centres in three municipalities of Gipuzkoa, Spain. The selected municipalities included both urban and rural settings. The objective of that study was to describe the natural history of functional decline in independent community-dwelling adults over a period of two years, as well as to identify factors associated

with the onset of dependence, institutionalisation or death. Individuals were randomly identified from primary health care records to obtain a representative sample of the target population, in terms of age and sex. They were invited to participate in the study and those who agreed provided written informed consent. The study was approved by the Gipuzkoa Health Region Ethics Committee. The following were assessed every 6 months, with a final follow-up at 2 years: functional status (with the Barthel Index and Lawton Instrumental Activities of Daily Living scale, VIDA questionnaire, and GS and TUG tests); health status (self-perceived health, polypharmacy, multimorbidity, sensory deficits, unintended weight loss, low level of physical activity, falls and hospital admissions, among others); and frailty-related events (onset of dependence, institutionalisation or death). At baseline, sociodemographic characteristics (age, sex and educational level) and social situation (Gijon Scale score and living arrangements) were also assessed.

The study has been approved by the Clinical Ethics Committee of Gipuzkoa, protocol code: IVM-PMR-2014-01.

Study population

In the present study, all surviving participants from the original cohort will be contacted to participate. All subjects will undergo a comprehensive assessment, including questionnaires, performance tests and blood tests. Finally, participants will be categorized according to their frailty as measured by the TFI. Patients with a score greater than or equal to 5 in the TFI will be considered cases, while those with a score lower than 5 will be classified as controls. Any individuals in the end-of-life stage, with a life expectancy of less than 3 months, will be excluded from the study.

Assessment

All members of the original cohort alive at the end of the second year of follow-up will be contacted by post and telephone. They will receive detailed information about the present study and be invited to participate. Those who express interest in taking part will be included in the study and scheduled for a personal interview. During this, data will be collected on sociodemographic characteristics, social situation and health status. Performance-based measures of physical functioning (GS and TUG test results) and a blood sample will also be obtained. Basic information will be collected on those who decline to take part in the study to identify possible selection or participation bias.

Sample size

It is estimated that with a sample size of 150 individuals it will be possible to determine the correlation between TIF and performance-based measures of physical functioning (GS and TUG test results), with a 95% confidence interval (CI) of ±0.10 around its estimate. It is expected that the GS and TUG tests and the TFI (dichotomised with the aforementioned cut-off point) will be in agreement regarding the individual's classification (good or poor functioning) in 70% of cases. Assuming that the kappa coefficient of agreement will be greater than 0.60, with 150 individuals the coefficient will be estimated with a 95% CI of ±0.12 around its observed value. It is estimated that 150 blood samples will be sufficient to address the aims of the study, according to recently published results [22] Finally, to assess the reliability of the Spanish version of the TIF, 80 individuals will complete the scale twice in a period of 10 days. This sub–sample will allow us to calculate an intra-class correlation coefficient (ICC) with a 95% CI of ±0.2 around the estimate. The sample size calculations were performed with the nQueryAdvisor 7.0 software.

Study variables

Main outcome variables: Condition of frailty defined by the TFI [12]: This tool is a two-part, self-administered questionnaire for screening frail community-dwelling older people. The first part contains 10 items on determinants of frailty and diseases and the second part has 15 items divided into three domains of frailty: physical, psychological and social. Scores range from zero to fifteen, scores of five or higher considered to be associated with frailty. The original version of the questionnaire will be

translated into Spanish, culturally adapted and validated. Physical performance: Two tests will be used: GS [23] and TUG [24]. The GS test involves measuring the time required to walk 10 meters. A speed of less than 0.8 ms^{-1} is considered a predictor of adverse events. The TUG test measures the time to rise from a chair, walk 3 meters, turn, walk back, and sit down again. Participants are allowed to use any usual walking aid. The result is considered normal if the individual completes the task in 12 s or less. Biomarker expression: A blood sample will be extracted from all participants to measure the expression of *SOX2*. First, total RNA will be purified using the RNEasy (Qiagen) kit. Then, RNA will be reverse-transcribed with the High Capacity cDNA Reverse Transcription Kit (Applied Biosystems). The expression of *SOX2* will be assessed with quantitative polymerase chain reaction (qPCR), using primers, the SDS software and 7300 Real-Time PCR System (Applied Biosystems). The levels of expression will be standardised with those of glyceraldehyde 3-phosphate dehydrogenase (GAPDH).

Covariables

Sociodemographic characteristics: data will be collected on age, sex, level of education and income. Social situation: Social risk will be studied in terms of the need for support from social services and information will also be collected about living arrangements. Health status: This is a wide and complex concept and several aspects will be considered in the study. Specifically, Spanish versions of the Barthel Index [25] and Lawton Instrumental Activities of Daily Living scale [26] will be used to evaluate participants' ability to perform basic and instrumental activities, respectively. The Spanish version of the *Short Portable Mental Status Questionnaire* developed by Pfeiffer [27] has been selected to assess cognitive function. Health-related quality of life will be measured with the Spanish version of Euroqol 5D questionnaire [28]. Data on comorbidity will be obtained from medical records, and Charlson Index [29]. The risk of malnutrition will be assessed with the Mini-Nutritional assessment Short Form (MNA-SF) [30]. Finally, polypharmacy will be identified by asking participants how many medications they take and cross-checking with their medical record.

Statistical analysis

Descriptive analysis will be performed for all patient characteristics at baseline. Categorical variables will be described as frequencies and percentages and quantitative variables as means and standard deviations or medians and interquartile ranges, depending on the distribution of the data. In order to explore whether willingness to participate corresponds to a random distribution or to a specific pattern, sociodemographic and clinical characteristics will be compared between those who agreed to participate in the study and those who declined. Comparisons between categorical variables will be performed with Chi-square or Fisher's exact tests. Two group comparisons of quantitative variables will be performed with Student's t-tests or Wilcoxon non-parametric test, depending on their distribution. Psychometric properties will be investigated to validate the Spanish version of the TIF. Specifically, regarding reliability, the internal consistency will be assessed using Cronbach's alpha coefficient and reproducibility with the ICC. The construct validity will be studied by confirmatory factor analysis. Convergent and discriminant validity will be examined by correlation with other scales. Known-group validity will be assessed by analysis of variance.

The association between functional test and TFI results will be analysed with Pearson's correlation coefficients. Lastly, the agreement between these tests will be described using kappa coefficients, after dichotomizing the results, based on the aforementioned cut-points.

Finally, the relationship of the level of *SOX2* expression with functional tests and frailty will be studied. Receiver operating characteristic (ROC) curves will be generated to determine optimal cut-off points for *SOX2* that could be associated with good functioning and the occurrence of adverse events. All estimations will be accompanied by their 95% CIs. SAS software (version 9.3) will be used for data analysis.

Ethical aspects

The study complies with the standards of the Declaration of Helsinki concerning research involving human subjects. It was approved by the Gipuzkoa Health Region Ethics Committee (protocol code: IVM-PMR-2014-01). Written informed consent will be obtained from all individuals who participate in the study.

Discussion

This study seeks to assess the concordance between existing tools for identifying frail individuals that are suitable for use in the primary care setting. This work will also provide a validated Spanish version of the TIF, considered to be one of the best frailty indicators for use in primary care [9]. Understanding the frailty process is essential to prevent decline towards disability. One key element is the application of an effective tool that can easily identify frailty individuals in primary care at an early stage of decline. Although simple rapid screening tests have previously been developed and validated to allow physicians to rapidly recognise frail people [31,32], little progress has been made in integrating them into routine practice in primary care [9].

The main limitations of the study are related to the selection of participants from a pre-existing cohort with two years of follow-up. This implies that the individuals studied are the survivors of that cohort and it will be necessary to consider the effect of competitive risks. Another common characteristic related to cohort studies of older people is the possibility of participant "training effects" when identical or similar performance tests are repeated at regular intervals. This effect has been found in the original cohort and it will be necessary to consider that it may lower the real ability of these tests to evaluate the functional capacity of the participants [33].

The main strengths of the study are the comprehensive assessment of participants, including functional tests, blood tests, and the evaluation of frailty indicators and other measures related to sociodemographic characteristics, and of social and health status; and the development of a validated Spanish version of the TIF. Taken together, we believe that this study will make a substantial contribution to improving our understanding of the frailty process.

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