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Neurological complications of breast cancer: study protocol of a prospective cohort study

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ABSTRACT

Introduction: The improvement in breast cancer survival rates, along with the expected overdiagnosis and overtreatment associated with breast cancer screening, requires a comprehensive assessment of its burden. Neurological complications can have a devastating impact on these patients; neuropathic pain and chemotherapy-induced peripheral neuropathy are among the most frequently reported. This project aims to understand the burden of neurological complications of breast cancer treatment in Northern Portugal, and their role as mediator of the impact of the treatment in different dimensions of the patients' quality of life.

Methods and analysis: A prospective cohort study was designed to include 500 patients with breast cancer, to be followed for 3 years. The patients were recruited at the Portuguese Oncology Institute of Porto and evaluations were planned at different stages: pretreatment, after surgery, after chemotherapy (whenever applicable) and at 1 and 3 years after enrolment. Patients diagnosed with neuropathic pain or chemotherapy-induced peripheral neuropathy (subcohorts), were also evaluated at the moment of confirmation of clinical diagnosis of the neurological complication and 6 months later. In each of the follow-up periods, a neurological examination has been performed by a neurologist. Data were collected on sociodemographic and clinical characteristics, quality of life, sleep quality, and anxiety and depression. Between January and December 2012, we recruited and conducted the baseline evaluation of 506 participants. The end of the follow-up period is scheduled for December 2015.

Ethics and dissemination: The study protocol was approved by the Ethics Committee of the Portuguese Oncology Institute of Porto and all patients provided written informed consent. All study procedures were developed in order to assure data protection and confidentiality. Results from this project will be disseminated in international peer-reviewed journals and presented in relevant conferences.

Strengths and limitations of this study

- This protocol describes an ongoing prospective cohort study with baseline evaluation already performed.
- The study was approved by the ethics committee of the hospital where the patients were recruited.
- The results of this study will be submitted for publication in international peer-reviewed journals.
- The expected results may contribute to a better understanding of the burden of neurological complications of breast cancer treatment and their role as mediators of the impact of the treatment in different dimensions of the patients' quality of life.

INTRODUCTION

Breast cancer is the most frequent form of cancer and an important cause of cancer death among women, with an estimated 1.7 million new cases and half a million deaths worldwide.[1] Despite upward trends in incidence rates, due to an increasing exposure to risk factors and widespread use of mammography screening,[2] mortality has been declining in most affluent settings,[3] reflecting improvements in access to earlier diagnosis and effective treatments.[4 5] In Northern Portugal, the number of cases is expected to be nearly 50% higher in 2020,[6] assuming the most recent trends remain, and mortality rates have been declining since the 1990s in several regions.[7]

The improvement in breast cancer survival,[8] along with the expected overdiagnosis and overtreatment associated with breast cancer screening,[9] requires a comprehensive assessment of the burden of cancer, accounting for disability and losses in quality of life (QoL) due to the disease, treatment and sequelae.[10] Although health-related QoL in women with breast cancer has been addressed in several studies,[11–13] little attention has been dedicated to understanding the role of specific physical and psychological adverse effects of cancer management[14–17] in different dimensions of the patients' QoL.

Neurological complications of breast cancer treatment, including cognitive impairment, chemotherapy-induced peripheral neuropathy (CIPN), neuropathic pain (NP), encephalopathy and stroke,[18 19] may cause symptoms more disabling than the cancer itself[18]; CIPN and NP are among the most frequently reported.[18 20 21]

CIPN is a dose-limiting side effect of many chemotherapeutic agents that may lead to dose reduction and/or discontinuation of treatment.[22] The incidence of CIPN depends on chemotherapy regimens,[22] but the role of conditions such as diabetes or alcohol consumption have seldom been addressed.[23–25] Chronic NP is estimated to affect over a third of treated patients,[20 21] especially younger ones.[26–29] Despite some studies addressing the relationship between quality of sleep,[30 31] anxiety and depression[32] and the occurrence of pain, there is little information on the impact of these factors, specifically in NP. Moreover, data on type of surgery[26 29] and radiotherapy[28 29 33] as risk factors for NP are conflicting.

Although QoL is known to be impaired by pain,[34 35] to our knowledge no previous studies addressed the role of NP or CIPN as mediators of the effect of breast cancer treatment in different dimensions of QoL.

The burden of neurological complications in women with breast cancer, including NP and CIPN, remains poorly understood, namely regarding their aetiology, frequency and impact on patients' QoL. Prospective studies providing a comprehensive characterisation of these frequent side effects, and a methodologically sound assessment of their determinants and associations with specific dimensions of QoL, may contribute to a more accurate characterisation of the burden associated with breast cancer in different settings, as well as help to develop strategies to minimise the impact of these conditions during treatment.

This project aims to understand the burden of neurological complications of breast cancer treatment and their role as mediators of the impact of the treatment in different dimensions of the patients' QoL in Northern Portugal. The main specific objectives are as follows:

1. To estimate the incidence of neurological complications during the first 3 years after the diagnosis of breast cancer, and to characterise the clinical features and management of NP and CIPN.
2. To quantify the relationship between factors such as type of treatment, depression, anxiety and sleep disturbance or diabetes and alcohol consumption and the occurrence of NP and CIPN;
3. To assess the role of NP and CIPN as determinants of the variation in different dimensions of the patients' QoL.

METHODS AND ANALYSIS

Study design

This prospective cohort study was designed to evaluate a cohort of 500 women with incident breast cancer (main cohort) and subcohorts of patients diagnosed with NP (NP subcohort) and CIPN (CIPN subcohort), during a 3-year follow-up period (figure 1).

The study comprises the evaluation of all participants at baseline (before any treatment), 2 weeks after surgery, 3 weeks after chemotherapy (if applicable) and at 1 and 3 years after enrolment. In addition, the subcohorts of patients are evaluated at the moment of confirmation of clinical diagnosis of the neurological complication and 6-months after the diagnosis of the side effect (figure 1), in order to evaluate the chronicity of such conditions. The evaluations are performed by trained interviewers or clinicians, as applicable.

Selection of participants

Women admitted to the Breast Clinic of the Portuguese Institute of Oncology of Porto (IPO-Porto) suspected of having an incident breast cancer were potentially eligible. In 2012, we invited those who were proposed for surgery, either as primary treatment or after neoadjuvant therapy, aged 18 years or older, with histologically confirmed breast cancer diagnosed in the previous 3 months, not treated with chemotherapy and/or radiotherapy for other primary cancer, not having received any treatment for breast cancer before, not submitted to a previous breast surgery and capable of understanding the purposes of the study and willing to collaborate. We excluded those expected to receive cancer treatments other than surgery, if applicable, outside IPO-Porto.

We evaluated the cognitive function of each patient who accepted the invitation to participate, using the Montreal Cognitive Assessment.[36] Those scoring less than 17, or less than 16 for women over 65 years old,[37] were excluded from further evaluation.

Study questionnaires

Table 1 depicts the questionnaires used to evaluate the participants at baseline and at different stages of follow-up, and table 2 describes the instruments validated for the Portuguese population, which were used to assess cognitive function,[36 38] QoL,[39–42] quality of sleep,[43 44] anxiety and depression,[45 46] NP,[47 48] pain severity[48 49] and pain-related disability.[48 50]

Neurological evaluation

Newly occurring cases of neurological complications are identified through referral by any member of the clinical team, or during the systematic neurological evaluations described in table 1. Prevalent cases identified at the time of the scheduled evaluations are assigned an estimated date of onset based on information provided by the patients.

The systematic neurological evaluation, performed by a neurologist, comprises the assessment of cognitive functions, cranial nerves, muscular strength, sensitive function, reflexes, Babinski signal and evaluation of gait and coordination.

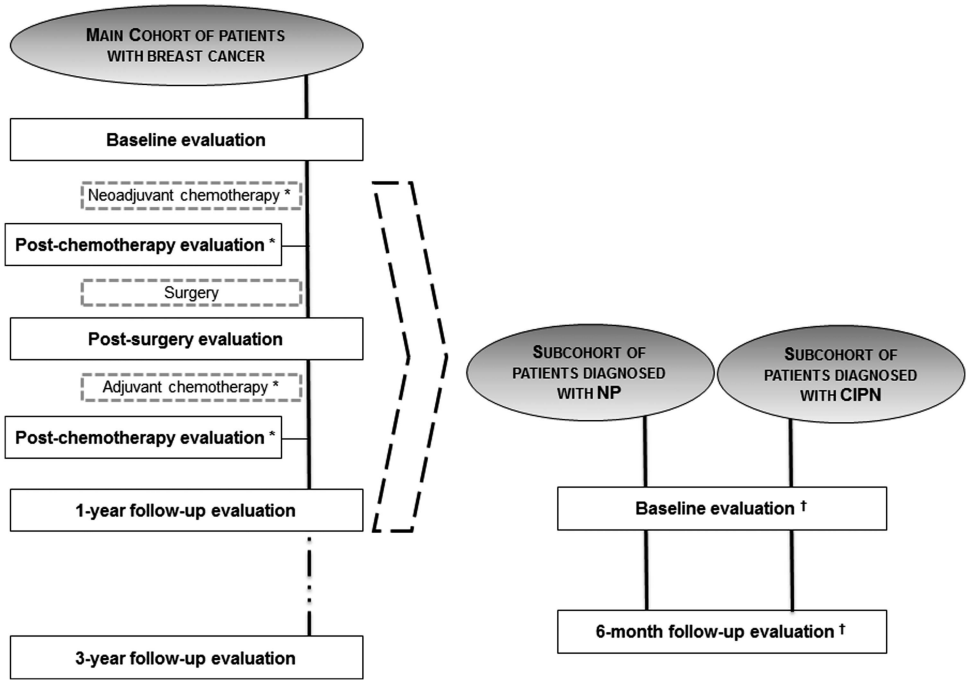

Figure 1 Study design and timing of baseline and follow-up evaluations in the main cohort and neuropathic pain and chemotherapy-induced peripheral neuropathy subcohorts. CIPN, chemotherapy-induced peripheral neuropathy; NP, neuropathic pain. *Not all patients are eligible for chemotherapy; †In addition to the evaluations that are performed for the main cohort.

Data analysis and sample size

We will compute cumulative incidence estimates and the corresponding 95% CIs for each of the neurological complications at 6, 12 and 36 months of follow-up. A sample of about 500 participants is needed to estimate cumulative incidences between 30 and 70% with a 95% CI up to 10% wide, or cumulative incidences near or under 30% with a 95% CI up to 8% wide. We will conduct descriptive analyses to characterise NP and CIPN regarding their clinical features and management among the patients included in the corresponding subcohorts.

To quantify the association between different factors and the occurrence of NP and CIPN, we will compute incidence rate ratios and 95% CI estimates, crude and adjusted for sociodemographic, clinical and QoL variables, using Poisson regression. A sample of approximately 500 women was estimated to be necessary, assuming a statistical power of 80%, a level of significance of 5% and: (1) one-third of the sample exposed to each of the risk factors evaluated (eg, mastectomy; anxiety and/or depression; poor sleep quality), an incidence rate of NP of at least 30/100 person-years in the first year and a relative risk estimate of at least 1.5; and (2) approximately half of the women submitted to chemotherapy, 10% of the sample exposed to each of the risk factors evaluated (eg, diabetes; high alcohol consumption), an incidence rate of CIPN of at least 20/100 person-years in the first year and a relative risk estimate of at least 2.

The association between NP and CIPN and the variation in QoL from baseline to 1-year evaluation and from 1-year to 3-year follow-up assessments will be quantified through crude and adjusted incidence rate ratios and 95% CI estimates, using Poisson regression. A sample of approximately 500 women was estimated to be necessary, assuming a statistical power of 80%, a level of significance of 5%, one-third of the sample with incident NP, an incidence rate of 25/100 person-years for moderate clinically meaningful worsening in QoL (decrease of at least 10 points in the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer (QLQ-C30) score[53]) and a relative risk estimate of at least 1.5. A sample of approximately 200 women was estimated to be necessary, assuming a statistical power of 80%, a level of significance of 5%, one-fifth of the sample with incident CIPN, an incidence rate of 25/100 person-years for moderate clinically meaningful worsening in QoL (decrease of at least 10 points in the QLQ-C30 score[53]) and a relative risk estimate of at least 2.

Training of the interviewers and use of standardised procedures for data collection is expected to contribute to a low proportion of missing data, and no imputation is being planned.

We estimate that the 3-year evaluation will be accomplished for at least 90% of the participants, taking into account the most recent survival data from Northern Portugal[54] and the fact that all women in our cohort were submitted to surgical treatment. The evaluations will be matched with routine appointments in the hospital, which is expected to contribute to minimise further loss to follow-up.

Table 1 Description of methods used for evaluation of participants at baseline and at different stages of follow-up

	Methods used for evaluation of participants									
Timing of evaluation	**Sociodemographic and clinical characteristics**	**Neurological evaluation**	**MoCA**	**HADS**	**PSQI**	**QLQ-BR23**	**QLQ-C30**	**BPI**	**DN4**	**PDI**
Main cohort of patients with breast cancer										
Baseline	✓*	✓	✓	✓	✓	✓	✓			
Postsurgery	✓†	✓								
Postchemotherapy	✓‡	✓								
1-year follow-up	✓§	✓	✓	✓	✓	✓	✓			
3-year follow-up	✓¶	✓	✓	✓	✓	✓	✓	✓**	✓**	✓**
Subcohort of patients diagnosed with NP††										
Baseline	✓‡‡	✓		✓	✓	✓	✓	✓	✓	✓
6-month follow-up	✓‡‡	✓		✓	✓	✓	✓	✓**	✓**	✓**
Subcohort of patients diagnosed with CIPN††										
Baseline	✓§§	✓				✓	✓			
6-month follow-up	✓§§	✓				✓	✓			

*Data is collected on sociodemographic (birth date, address, marital status, education, occupation and alcohol consumption) and clinical (medication used, history of previous neurological disease, diabetes, hypertension, thyroid pathology and oncological history) characteristics.
†Data is collected on type of surgery, cancer stage[51] and proposed treatment after surgery.
‡Data is collected on chemotherapy (drugs used, duration of treatment and total dose).
§Data is collected on radiotherapy (irradiated areas, total dose and duration of treatment) and hormonotherapy (drug), and other data is updated (marital status, cancer stage[51] and information regarding chemotherapy and radiotherapy).
¶Data is collected on smoking habits, fruits and vegetables consumption, and physical activity. Marital status, alcohol consumption and information regarding cancer stage and treatment are reviewed.
**Applicable only when NP is present at the moment of evaluation.
††In addition to the evaluations that are performed in the main cohort.
‡‡Data is collected concerning NP symptoms, aetiology, duration, localisation and pain management.
§§Data is collected regarding CIPN symptoms and chemotherapy details; CIPN is graded using Common Terminology Criteria for Adverse Events V.4.0[52] and Total Neuropathy score.[24]
BPI, Brief Pain Inventory[48 49]; CIPN, chemotherapy-induced peripheral neuropathy; DN4, Neuropathic Pain Questionnaire[47 48]; HADS, Hospital Anxiety and Depression Scale[45 46]; MoCA, The Montreal Cognitive Assessment[36 38]; NP, neuropathic pain; PDI, Pain Disability Index[48 50]; PSQI, Pittsburgh Sleep Quality Index[43 44]; QLQ-BR23, Breast cancer-specific module of the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer[39 40]; QLQ-C30, Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer.[39 41]

Table 2 Description of the instruments used for evaluation of the participants

Instruments	Description	Domains/subscales	Score
MoCA[36 38]	Test for the rapid screening of mild cognitive impairment—an intermediate clinical state between normal cognitive aging and dementia	Attention and concentration; executive functions; memory; language; visuoconstructional skills; calculations; orientation	Range: 0–30 Higher scores represent better cognitive performance
HADS[45 46]	Scale with 14 questions assessing anxiety and emotional distress among patients during the previous week	Depression; anxiety	Range (for each subscale): 0–21 Scores greater than or equal to 11 represent a case of anxiety or depression, as applicable
PSQI[43 44]	Index with 18 questions assessing sleep quality and disturbances during the previous month.	Subjective sleep quality; sleep latency; duration of sleep; habitual sleep efficiency; sleep disorders; use of medications for sleep; daytime dysfunction	Range: 0–21 Scores greater than 5 indicate poor sleep quality
QLQ-BR23[39 40]	Specific breast cancer scale with 23 questions assessing QoL in patients with breast cancer during the previous week and month	Functional scales: body image; sexual functioning; sexual enjoyment; future perspective Symptom scales/items: systemic therapy side effects; breast symptoms; arm symptoms; concern about hair loss	Range (scales and single-item): 0–100 Higher scores for a functional scale represent a healthy level of functioning. Higher scores for a symptom scale/item represent a higher level of symptomatology/ problems
QLQ-C30[39 41]	Scale with 30 questions assessing QoL in patients with cancer during the previous week	Global health status. Functional scales: physical functioning; role functioning; emotional functioning; cognitive functioning; social functioning. Symptom scales/items: fatigue; nausea and vomiting; pain; dyspnoea; insomnia; appetite loss; constipation; diarrhoea; financial difficulties	Range (scales and single-item): 0–100 Higher scores for the global health status and for a functional scale represent a healthy level of QoL and functioning, respectively. Higher scores for a symptom scale/item represents a higher level of symptomatology/ problems
BPI[48 49]	Questionnaire with 9 items used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning in the past 24 h	Severity of pain; impact of pain on daily function; location of pain; pain medications; amount of pain relief in the past 24 h or the past week	Range (for 'severity of pain' and 'pain interference'): 0–10 Higher scores for 'severity of pain' and 'pain interference' represent a higher level of pain severity and pain interference, respectively
DN4[47 48]	Test with 4 questions (10 items) for the screening of neuropathic pain	Not applicable	Range: 0–10 Scores greater than or equal to 4 are regarded as indicative of neuropathic pain
PDI[48 50]	Index with 7 items designed to assess pain-related disability, providing information that complements assessment of physical impairment	Family/home responsibilities; recreation; social activity; occupation; sexual behaviour; self-care; life-support activity	Range: 0–70 Higher scores represent greater disability due to pain

BPI, Brief Pain Inventory; CIPN, chemotherapy-induced peripheral neuropathy; DN4, Neuropathic Pain Questionnaire; HADS, Hospital Anxiety and Depression Scale; MOCA, The Montreal Cognitive Assessment; PDI, Pain Disability Index; PSQI, Pittsburgh Sleep Quality Index; QLQ-BR23, Breast cancer-specific module of the Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer; QLQ-C30, Quality of Life Questionnaire of the European Organization for Research and Treatment of Cancer; QoL, quality of life.

Assembling of the main cohort and subcohorts and 1-year follow-up

Figure 2 describes the assembling of the main cohort and the NP and CIPN subcohorts. During 2012, all patients admitted to the IPO-Porto with a potential diagnosis of breast cancer were evaluated (n=961) and those who were proposed for surgical treatment and met the eligibility criteria were invited to participate (n=588).

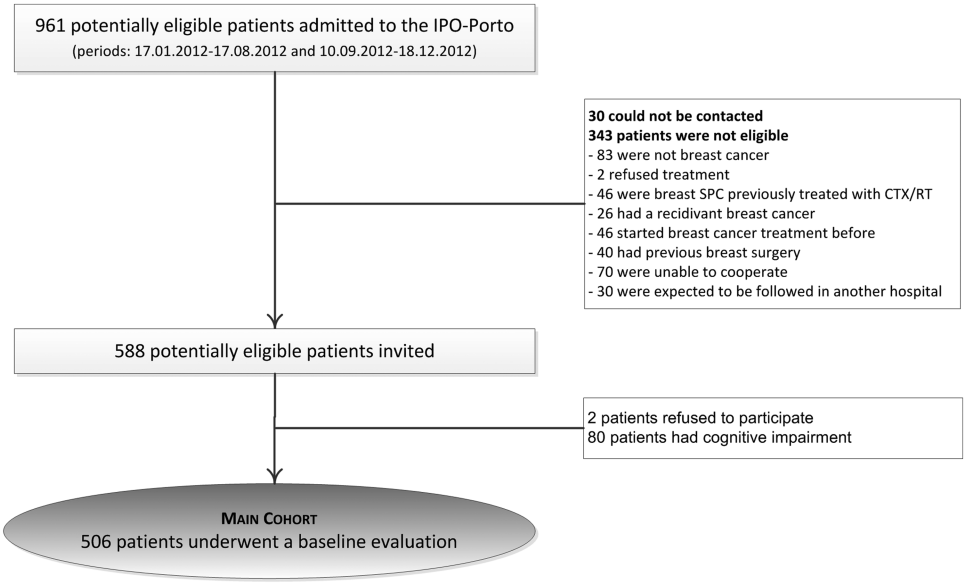

Figure 2 Flow chart describing the assembling of the main cohort and the neuropathic pain and chemotherapy-induced peripheral neuropathy subcohorts. CIPN, chemotherapy-induced peripheral neuropathy; CTX, chemotherapy; MoCA, The Montreal Cognitive Assessment; NP, neuropathic pain; RT, radiotherapy; SPC, second primary cancer.

Eighty patients with possible cognitive impairment were excluded and two refused to participate (no reason for refusing was specified). A total of 506 patients underwent a baseline evaluation before the first proposed treatment, constituting the main cohort. The subcohorts of NP and CIPN patients included those with a diagnosis of these conditions in the first year of follow-up.

The end of the follow-up period is scheduled for December 2015.

ETHICS AND DISSEMINATION

Written informed consent was obtained from all participants after the aims and procedures of the investigation had been fully explained by a member of the study group.

This is an observational investigation; as such we do not anticipate the occurrence of harmful effects related to participation in the study. To minimise the possible discomfort due to the need to go to the hospital for face-to-face evaluations or the duration of interviews, data collection procedures were designed to last no more than 60 min, and are scheduled to take place on the same day as other appointments in the hospital as part of regular clinical care.

All data regarding clinical aspects are collected by clinical members of the research team and privacy is assured. We guarantee data protection in accordance with Portuguese law. Participants were coded with a unique non-identifying number; the correspondence between this code and the personal identifiable information is stored in a file, to which only the principal investigator can have access. Only the research team has access to the database with anonymised data, saved on a password-protected secure computer.

The expected results may contribute to a better understanding of the burden of neurological complications of breast cancer treatment and their role as mediators of the impact of the treatment in different dimensions of the patients' QoL. The main findings of the study will be submitted for publication in international peer-reviewed journals and proposed for presentation at relevant international and national conferences. We will issue press releases to promote the dissemination of information relevant to the general population in the mass media. Moreover, this study will also contribute to the training of researchers through the production of master and doctoral theses.

Contributors NL and SP conceived and designed the study. SP and FF wrote the first version of the manuscript. NL, JC-L, TD and TS critically revised the manuscript for relevant intellectual content. All authors approved the final version for submission.

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Competing interests None.

Ethics approval Ethics Committee of the Portuguese Institute of Oncology of Porto (Ref. CES 406/011 and CES 99/014).

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

REFERENCES

1. Ferlay J, Soerjomataram I, Ervik M, *et al*. *GLOBOCAN 2012 v1.0, Cancer incidence and mortality worldwide: IARC cancerbase No. 11*. Lyon, France: International Agency for Research on Cancer, 2013. http://globocan.iarc.fr/ (accessed 16 Jul 2014).
2. Althuis MD, Dozier JM, Anderson WF, *et al*. Global trends in breast cancer incidence and mortality 1973–1997. *Int J Epidemiol* 2005;34:405–12.
3. Amaro J, Severo M, Vilela S, *et al*. Patterns of breast cancer mortality trends in Europe. *Breast* 2013;22:244–53.
4. Clarke M, Collins R, Darby S, *et al*. Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;366:2087–106.
5. Jatoi I, Miller AB. Why is breast-cancer mortality declining? *Lancet Oncol* 2003;4:251–54.
6. RORENO. *Projeções da incidência de cancro na Região Norte—2013, 2015 e 2020*. Porto: Instituto Português de Oncologia do Porto, 2013.
7. Bastos J, Barros H, Lunet N. [Breast cancer mortality trend in Portugal (1955–2002)]. *Acta Med Port* 2007;20:139–44.
8. Verdecchia A, Guzzinati S, Francisci S, *et al*. Survival trends in European cancer patients diagnosed from 1988 to 1999. *Eur J Cancer* 2009;45:1042–66.
9. Independent UK Panel on Breast Cancer Screening. The benefits and harms of breast cancer screening: an independent review. *Lancet* 2012;380:1778–86.
10. Soerjomataram I, Lortet-Tieulent J, Parkin DM, *et al*. Global burden of cancer in 2008: a systematic analysis of disability-adjusted life-years in 12 world regions. *Lancet* 2012;380:1840–50.
11. Howard-Anderson J, Ganz PA, Bower JE, *et al*. Quality of life, fertility concerns, and behavioral health outcomes in younger breast cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104:386–405.
12. Lemieux J, Goodwin PJ, Bordeleau LJ, *et al*. Quality-of-life measurement in randomized clinical trials in breast cancer: an updated systematic review (2001–2009). *J Natl Cancer Inst* 2011;103:178–231.
13. Montazeri A. Health-related quality of life in breast cancer patients: a bibliographic review of the literature from 1974 to 2007. *J Exp Clin Cancer Res* 2008;27:32.
14. Burstein HJ, Griggs JJ. Adjuvant hormonal therapy for early-stage breast cancer. *Surg Oncol Clin N Am* 2010;19:639–47.
15. Rocco N, Rispoli C, Pagano G, *et al*. Breast cancer surgery in elderly patients: postoperative complications and survival. *BMC Surg* 2013;13(Suppl 2):S25.
16. Pierce SM, Recht A, Lingos TI, *et al*. Long-term radiation complications following conservative surgery (CS) and radiation therapy (RT) in patients with early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1992;23:915–23.
17. Azim HA Jr, de Azambuja E, Colozza M, *et al*. Long-term toxic effects of adjuvant chemotherapy in breast cancer. *Ann Oncol* 2011;22:1939–47.
18. Khasraw M, Posner JB. Neurological complications of systemic cancer. *Lancet Neurol* 2010;9:1214–27.
19. Giglio P, Gilbert MR. Neurologic complications of cancer and its treatment. *Curr Oncol Rep* 2010;12:50–9.
20. Jung BF, Ahrendt GM, Oaklander AL, *et al*. Neuropathic pain following breast cancer surgery: proposed classification and research update. *Pain* 2003;104:1–13.
21. Jung BF, Herrmann D, Griggs J, *et al*. Neuropathic pain associated with non-surgical treatment of breast cancer. *Pain* 2005;118:10–14.
22. Miltenburg NC, Boogerd W. Chemotherapy-induced neuropathy: a comprehensive survey. *Cancer Treat Rev* 2014;40:872–82.
23. Brouwers EE, Huitema AD, Boogerd W, *et al*. Persistent neuropathy after treatment with cisplatin and oxaliplatin. *Acta Oncol* 2009;48:832–41.
24. Smith EM, Beck SL, Cohen J. The total neuropathy score: a tool for measuring chemotherapy-induced peripheral neuropathy. *Oncol Nurs Forum* 2008;35:96–102.
25. Vincenzi B, Frezza AM, Schiavon G, *et al*. Identification of clinical predictive factors of oxaliplatin-induced chronic peripheral neuropathy in colorectal cancer patients treated with adjuvant Folfox IV. *Support Care Cancer* 2013;21:1313–19.
26. Bokhari FN, McMillan DE, McClement S, *et al*. Pilot study of a survey to identify the prevalence of and risk factors for chronic neuropathic pain following breast cancer surgery. *Oncol Nurs Forum* 2012;39:E141–9.
27. Vilholm OJ, Cold S, Rasmussen L, *et al*. The postmastectomy pain syndrome: an epidemiological study on the prevalence of chronic pain after surgery for breast cancer. *Br J Cancer* 2008;99:604–10.
28. Peuckmann V, Ekholm O, Rasmussen NK, *et al*. Chronic pain and other sequelae in long-term breast cancer survivors: nationwide survey in Denmark. *Eur J Pain* 2009;13:478–85.
29. Gulluoglu BM, Cingi A, Cakir T, *et al*. Factors related to post-treatment chronic pain in breast cancer survivors: the interference of pain with life functions. *Int J Fertil Womens Med* 2006;51:75–82.
30. Edwards RR, Almeida DM, Klick B, *et al*. Duration of sleep contributes to next-day pain report in the general population. *Pain* 2008;137:202–7.
31. Raymond I, Nielsen TA, Lavigne G, *et al*. Quality of sleep and its daily relationship to pain intensity in hospitalized adult burn patients. *Pain* 2001;92:381–8.
32. Phyomaung PP, Dubowitz J, Cicuttini FM, *et al*. Are depression, anxiety and poor mental health risk factors for knee pain? A systematic review. *BMC Musculoskelet Disord* 2014;15:10.
33. Jensen MP, Chang HY, Lai YH, *et al*. Pain in long-term breast cancer survivors: frequency, severity, and impact. *Pain Med* 2010;11:1099–106.
34. Caffo O, Amichetti M, Ferro A, *et al*. Pain and quality of life after surgery for breast cancer. *Breast Cancer Res Treat* 2003;80:39–48.
35. Palesh OG, Collie K, Batiuchok D, *et al*. A longitudinal study of depression, pain, and stress as predictors of sleep disturbance among women with metastatic breast cancer. *Biol Psychol* 2007;75:37–44.
36. Nasreddine ZS, Phillips NA, Bedirian V, *et al*. The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695–9.
37. Freitas S, Simoes MR, Alves L, *et al*. Montreal cognitive assessment (MoCA): normative study for the Portuguese population. *J Clin Exp Neuropsychol* 2011;33:989–96.
38. Freitas S, Simões MR, Martins C, *et al*. Estudos de adaptação do montreal cognitive assessment (MoCA) para a população portuguesa. *Avaliação Psicológica* 2010;9:345–57.
39. Aaronson NK, Ahmedzai S, Bergman B, *et al*. The European organization for research and treatment of cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. *J Natl Cancer Inst* 1993;85:365–76.
40. Sprangers MA, Groenvold M, Arraras JI, *et al*. The European organization for research and treatment of cancer breast cancer-specific quality-of-life questionnaire module: first results from a three-country field study. *J Clin Oncol* 1996;14:2756–68.
41. Pais-Ribeiro J, Pinto C, Santos C. Validation study of the Portuguese version of the QLC-C30-V.3. *Psicologia, Saúde Doenças* 2008;9:89–102.
42. Dewolf L, Koller M, Velikova G, *et al*. *EORTC quality of life group translation procedure*. 3rd edn. Brussels: EORTC Quality of Life Group Publication, 2009.
43. Buysse DJ, Reynolds CF III, Monk TH, *et al*. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;28:193–213.
44. Marques D, Gomes AA, Meiavia A, *et al*. Reliability and initial validation of the Pittsburgh Sleep Quality Index, European Portuguese version: a preliminary study in a sample of higher education students. *Sleep Med*. 2013;14,(Suppl 1):e140.
45. Pais-Ribeiro J, Silva I, Ferreira T, *et al*. Validation study of a Portuguese version of the hospital anxiety and depression scale. *Psychol Health Med* 2007;12:225–35.
46. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand* 1983;67:361–70.
47. Bouhassira D, Attal N, Alchaar H, *et al*. Comparison of pain syndromes associated with nervous or somatic lesions and development of a new neuropathic pain diagnostic questionnaire (DN4). *Pain* 2005;114:29–36.
48. Azevedo LF, Pereira AC, Dias C, *et al*. [Translation, cultural adaptation and multicentric validation study of chronic pain screening and impact assessment instruments]. *Dor* 2007;15:6–56.
49. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. *Ann Acad Med Singapore* 1994;23:129–38.
50. Pollard CA. Preliminary validity study of the pain disability index. *Percept Mot Skills* 1984;59:974.
51. Edge SB, Byrd DR, Compton CC, *et al*. *AJCC cancer staging manual*. 7th edn. New York: Springer; 2010.
52. CTCAE. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 4.0. DCTD, NCI, NIH, DHHS, 2010. http://ctep.cancer.gov/ (accessed 1 Jan 2012).
53. Osoba D, Rodrigues G, Myles J, *et al*. Interpreting the significance of changes in health-related quality-of-life scores. *J Clin Oncol* 1998;16:139–44.
54. RORENO. Análise de Sobrevivência, Principais Cancros da Região Norte, *2000/2001*. Porto: Registo Oncológico Regional do Norte, 2010.

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Functional and cognitive impairment prevention through early physical activity for geriatric hospitalized patients: study protocol for a randomized controlled trial

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Abstract

Background: Frail older adults have reduced functional and physiological reserves, rendering them more vulnerable to the effects of hospitalization, which frequently results in failure to recover from the pre-hospitalization functional loss, new disability or even continued functional decline. Alternative care models with an emphasis on multidisciplinary and continuing care units are currently being developed. Their main objective, other than the recovery of the condition that caused admission, is the prevention of functional decline. Many studies on functional decline have discussed the available evidence regarding the effectiveness of acute geriatric units. Despite the theoretical support for the idea that mobility improvement in the hospitalized patient carries multiple benefits, this idea has not been fully translated into clinical practice.

Methods/design: This study is a randomized clinical trial conducted in the Department of Geriatrics of a tertiary public hospital with 35 beds allocated. Hospitalized patients who meet the inclusion criteria will be randomly assigned to the intervention or control group. The intervention will consist of a multicomponent exercise training programme, which will be composed of supervised progressive resistance exercise training, balance-training, and walking for 5–7 consecutive days. During the training period, patients will be trained in 20 min sessions twice a day (morning and evening).

Discussion: Functional and cognitive impairment after and during acute hospitalization in older adults is a major determinant of the later need for health resources. If our hypothesis is correct and shows that a multicomponent, individualized and progressive exercise programme provides effective therapy for improving the functional capacity of acute elderly patients hospitalized for medical pathology versus conventional care, a change of the current system of hospitalization of elderly patients with medical conditions may be justified.

Trial registration: ClinicalTrials.gov Identifier: NCT02300896 (Date of registration 19 November 2014)

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Background

Frail older adults have reduced functional and physiological reserves, rendering them more vulnerable to the effects of hospitalization, which frequently results in failure to recover from the pre-hospitalization functional loss [1], new disability [2], or even continued functional decline [3]. Furthermore, consequences arise at multiple levels including cognitive impairment, longer hospital stays and institutionalization, poor mood, delirium, deconditioning, aspirations, pressure ulcers, falls, decreased caloric intake, social isolation, poor quality of life, increased use of health-related resources, disability and death [3–16].

Traditional risk factors for functional decline secondary to hospitalization are usually associated with comorbidities, malnutrition, depression, age, severity of illness and cognitive status [17–19]. However, the current model of care for hospitalized older adults plays an important role as a risk factor for in-hospital functional deterioration and has only recently begun to be evaluated [4, 20]. In-hospital mobility seems to be directly related to post-hospitalization functional outcomes [4, 20] and is one of the strongest predictors of functional decline. Hospitalized elderly patients are often bedridden; some studies show that more than 83 % of these patients are bedridden versus 4 % who are permitted to stand or walk [21, 22]. In older adults hospitalized for nondisabling conditions, in-hospital risk factors such as low mobility account for immediate and 1-month post-hospitalization functional declines [23]. Furthermore, illnesses and injuries that lead to hospitalization increase the likelihood of transitioning from non-frail to pre-frail, frail, or greater frailty states. Moreover, increasing evidence has shown that many older individuals have the capacity to recover from frailty and pre-frailty, although the likelihood of attaining a less frail state is lower. This probability can be reduced by approximately 50 % for each intervening hospitalization [24]. The figures regarding functional decline during hospital admission are heterogeneous and vary from 38-80 % depending on the study [10, 20, 25–27]. In a study conducted in our department [28], secondary functional impairment on admission was noted in 80 % of the patients susceptible to such impairment, persisting at discharge in 30 % of the patients.

Muscle strength and aerobic capacity decrease rapidly as a result of immobilization. After only ten days of rest, a healthy elderly person can lose 12–14 % of their VO_{2max} and muscle strength in the lower extremities [29]. In addition, skeletal muscle power decreases more rapidly than muscle strength with advancing age [30] and is also strongly associated with functional outcomes and functional capacity in elderly individuals at risk of disability [31, 32]. At the muscular level, reduced muscle use is associated with myofibrillar protein loss, muscle atrophy, and impaired control of the recruitment of motoneurons; at the clinical level, reduced muscle use is associated with decreased coordination, muscle strength, power output, aerobic capacity, balance, and exercise tolerance [5]. The consequences usually extend over time, and may produce long-term effects [30].

Alternative care models for an emphasis on multidisciplinary and continuing care units are currently being developed. Their main objective, other than the recovery of the condition that caused admission [32], is the prevention of functional decline. Many studies on functional decline have discussed the available evidence regarding the effectiveness of acute geriatric units [33, 34]. Despite the theoretical support for the idea that mobility improvement in the hospitalized patient carries multiple benefits, this idea has not been fully translated into clinical practice, and some studies have found paradoxical results [35]. The new models include exercise as an essential part of conventional treatment, at least when the patients are discharged to their homes [36]. Simple and basic procedures such as increasing the walking duration by 12 min or daily slow walking can reduce the average hospital stay [37]. In all of these circumstances, a comprehensive geriatric assessment of this type of patient should also consider the close link between the functional and cognitive situations, in addition to the previous theoretical concepts [38].

Exercise and early rehabilitation programmes are among the mechanisms by which functional and cognitive decline is prevented during hospitalization. Although risk factors associated with hospitalization and functional decline after discharge have been intensively studied, few randomized clinical trials have examined the potential benefits of conducting standard exercise programmes for hospitalized acute elderly medical patients. Nevertheless, the theoretical framework allows us to grasp the scope of possible improvement that exists for this population sector when such interventions are applied properly and selectively. The benefits of exercise have been clinically, biologically and even economically confirmed [39, 40], making exercise part of the therapeutic arsenal at our disposal. Multicomponent programs, and especially resistance exercise that includes muscle power training, are currently the most relevant interventions to slow down disability and other adverse outcomes, but these programmes have not been tested in acute geriatric patients. Moreover, to be effective, exercise has to be prescribed with a progressive individualized plan, similar to other medical treatments [31]. Some prospective studies have previously shown that hospitalization of older adults in a suitable environment can reduce disability and enhance the recovery of compromised activities during and after the acute event, which is contrary to some theories that highlight only the negative aspects or removal from the living environment [41].

The Cochrane reviews regarding exercise for acutely hospitalized elderly medical patients included only seven randomized controlled trials and two controlled clinical trials out of 3138 potentially relevant articles; the effect of exercise on measures of functional outcome was uncertain, and no effects of intervention on adverse events were found. A small reduction in the stay and total hospital costs (silver-level evidence) was found [42]. However, very few studies have explored the feasibility of conducting exercise programmes for hospitalized acute elderly patients [43]. Furthermore, evidence is lacking to determine which types of hospitalized elderly patients would benefit more from each programme and whether each programme is viable.

Study design and setting

This study is a randomized clinical trial conducted in the Department of Geriatrics of a tertiary public hospital with 35 beds allocated. Hospitalized patients who meet the inclusion criteria will be randomly assigned to the intervention or control group. Patient recruitment will begin within the first 48 h of admission to the ward, and these patients will be identified through a list of patients admitted to the hospital and assigned to the Department of Geriatrics. The study flow diagram is shown in Fig. 1. After signing an informed consent form, the subjects will be randomly assigned (as explained below) to either the intervention or control group. The researcher who decides whether the patient is assigned to the intervention or control group will not be the attending physician. Patients or their relatives (if the patient has cognitive impairment) will be informed of the random inclusion in one group, but will not be informed as to which they belong. The data for both the intervention group and the control group will be obtained at four different times: the initial visit during the acute hospitalization, at discharge, and at one and three months after discharge from the outpatient clinic. Time of measurement of the different variables is shown in Table 1. The protocol employs relevant standard protocol items for clinical trials according to the SPIRIT 2013 statement [44] and follows the CONSORT statement [45] for transparent reporting. The trial is registered at ClinicalTrials.gov, identifier NCT02300896.

Adverse events, including muscle pain, fatigue, and general aches and pains will be recorded by the training and testing staff and by self-report during the study period. We will also record the number of falls during the study and for one year prior to admission.

This study has been approved by the Navarra Clinical Research Ethics Committee (Pyto 23/2014).

Study participants and eligibility criteria

Individuals over 75 years of age admitted to the Department of Geriatrics of the Complejo Hospitalario de Navarra between March 2015 and March 2017.

The inclusion criteria are:

- Age: 75 years or older.
- Able to ambulate with or without personal/technical assistance.
- Barthel Index ≥60
- Able to communicate.
- Informed consent: Must be capable and willing to provide consent.

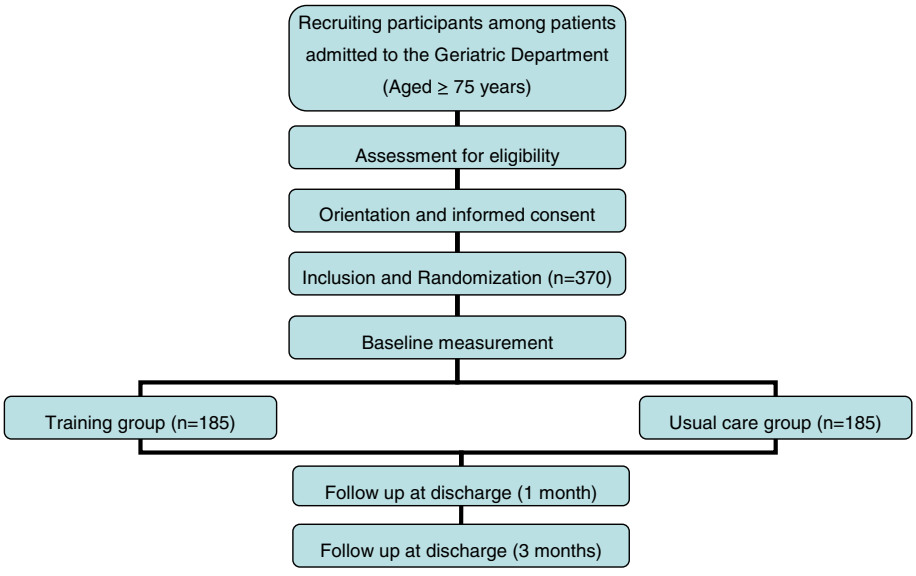

Fig. 1 Flow diagram of the study protocol

Table 1 Time of measurement of the different variables on the participants of the study

Measurement	T1 Baseline	T2 After training or control period	T3 1-month	T4 3-months
Categorical scale of pain	X	X	X	X
Barthel Index	X	X	X	X
Geriatric depression Scale of Yasavage	X	X	X	X
Mini-Mental State Examination (MMSE)	X	X	X	X
Short Physical Performance Battery (SPPB)	X	X	X	X
Gait Velocity Test (GVT)	X	X	X	X
Dual-task (verbal and counting GVT)	X	X	X	X
Maximal isometric force of handgrip, knee extension and hip flexion	X	X	X	X
1RM (Leg press, Chest press and Knee extension)	X	X	X	X
Muscle power at 50 % 1RM in Leg press	X	X	X	X
Confusion Assessment Method (CAM)	X	X	X	X
Quality of Life (EQ-5D)	X	X	X	X
Geriatrics syndromes	X	X	X	X
Isaacs set test	X	X	X	X
Trail Making Test (TMT)	X	X	X	X
Laboratory parameters	X			
Diseases considered grouped by ACG of Salisbury and CIE-10 codes	X			
Cumulative Illness Rating Scale for Geriatrics (CIRS-G)	X			
Zarit Scale	X			
Falls	X	X	X	X
Mini Nutritional Assessment (MNA)	X			

The exclusion criteria are:

–Duration of hospitalization < 6 days.
–Any factor precluding performance of the physical training programme or testing procedures as determined by the attending physician. These factors include, but are not limited to the following:
- Terminal illness.
- Myocardial infarction in the past 3 months.
- Unstable cardiovascular disease or other medical condition.
- Upper or lower extremity fracture in the past 3 months.
- Severe dementia (GDS 7).
- Unwillingness to either complete the study requirements or to be randomized into the control or intervention group.

Randomization and blinding

The study participants will be randomized (www.randomizer.org) into an intervention group and a control group. Participants will be explicitly informed and reminded not to discuss their randomization assignment with the assessment staff. The assessment staff will be blinded to the participant randomization assignment, as well as to the main study design and to what changes we expect to occur in the study outcomes in either group.

It will not be possible to conceal the group assignment from the staff involved in the training of the intervention group.

Patients or their families (if the patient has cognitive impairment) will be informed of the random inclusion in one group, but will not be informed as to which group they belong.

Statistics and sample size

The required simple size to detect a difference of 15 % in the frequency of patients that get at discharge a functional improvement greater than 10 points in Barthel Index is 161 patients in each group. Assuming a loss of 15 % of patients in the follow-up, we fixed a final sample size of 185 patients per group.

In an initial descriptive analysis, for qualitative variables we will calculate frequencies and confidence intervals, and for continuous variables, statistics of central tendency and dispersion such as means, standard error and confidence intervals or median and interquartile range. In order to assess the extent of the therapeutic effect, we will compute for every patient the difference between final and initial level of the outcome variables. Normality of continuous variables will be checked graphically and through K-M and Shapiro-Wilk tests, and their differences between groups by means of parametric tests (T-Tests, ANOVA) or non-parametric tests (Mann–Whitney U, Kruskal- Wallis). A Bonferroni post-hoc test will be used to evaluate statically significant ($p < 0.05$) group and time differences. Associations between clinical and biomechanical tests will be reported by their correlation

coefficient (r value), level of significance (p value), and the amount of variance explained (r2 value). Values of r will be used to indicate small (r = 0.10), medium (r = 0.30), and large (r = 0.50) size correlations (i.e., effect size). Finally, the relationship between qualitative variables will be assessed through χ^2 and Fisher exact tests. The level of statistical significance will be 0.05. Data will be analyzed with SPSS package 21.0

Detailed description

Usual care group (control)

Participants randomly assigned to the usual care group will receive normal hospital care, which includes physical rehabilitation when needed.

Intervention group (training)

The intervention will consist of a multicomponent exercise training programme [46], which will be composed of supervised progressive resistance exercise training, balance-training, and walking for 5–7 consecutive days. During the training period, patients will be trained in 20 min sessions twice a day (morning and evening).

The supervised multicomponent exercise training programme will be comprised of upper and lower body strengthening exercises, tailored to the individual's functional capacity, using weight machines and aiming for 2–3 sets of 8–10 repetitions at an intensity of 30–60 % of 1RM (Matrix, Johnson Health Tech, Ibérica, S.L. Torrejón de Ardoz, Madrid, Spain) combined with balance and gait retraining exercises that progressed in difficulty and functional exercises, such as rises from a chair. The second part of the session will consist of functional exercises such as knee extension and flexion, hip abduction, balance movements, and daily walking in the hospital. A minimum of 2 days elapsed between consecutive training sessions. The resistance exercises focused on the major upper and lower limb muscles. Each resistance training session will include 2 exercises for the leg extensor muscles (bilateral leg extension and bilateral knee extension muscles) and 1 exercise for upper limbs (seated bench press). During the progressive resistance training, instruction will be provided to the participants to perform the exercises at a high velocity of motion. However, care will be taken to ensure that exercises were executed with correct form. In each session, subjects will perform a specific warm-up with one set of very light loads for the upper and lower body. Balance and gait retraining exercises that progressed in difficulty will be also implemented: semi-tandem foot standing, line walking, stepping practice, walking with small obstacles, proprioceptive exercises on unstable surfaces (foam pads sequence), and altering the base of support and weight transfer from one leg to the other. One experienced physical trainer will carefully supervise all training sessions. The training sessions will last for approximately 40 min. The approximate duration of each part of the training will be: 5 min of warm-up, 10 min balance and gait retraining, 15 min of resistance training, and five minutes of stretching (cool-down). The training protocol is shown in Table 2. Participants and their family members will be carefully familiarized with the training procedures in advance.

Outcome measures

Primary outcome

The primary outcome measure is the change in functional and cognitive status during the study period. The functional capacity of patients will be evaluated by the Short Physical Performance Battery (SPPB) [47], which evaluates, balance, gait ability, and leg strength using a single tool. The total score will range from 0 (worst) to 12 points (best). The SSPB test has been shown to be a valid instrument for screening frailty and predicting

Table 2 Intervention group exercises

	Exercise	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6*	Day 7*
Morning	Rises from a chair	1×5	1×10	2×10	3×10	3×8	3×8	3×8
	Leg press	1RM + 1×10 (30 % 1RM)	2×10 (30 % 1RM)	3×10 (40 % 1RM)	3×10 (50 % 1RM)	3×8 (60 % 1RM)	3×8 (60 % 1RM)	3×8 (60 % 1RM)
	Chet press	1RM + 1×10 (30 % 1RM)	2×10 (30 % 1RM)	3×10 (40 % 1RM)	3×10 (50 % 1RM)	3×8 (60 % 1RM)	3×8 (60 % 1RM)	3×8 (60 % 1RM)
	Leg extension	1RM + 1×10 (30 % 1RM)	2×10 (30 % 1RM)	3×10 (40 % 1RM)	3×10 (50 % 1RM)	3×8 (60 % 1RM)	3×8 (60 % 1RM)	3×8 (60 % 1RM)
Afternoon	Leg extension (0,5 – 1,0 Kg)		2×10	2×10	2×10	2×10	2×10	2×10
	Leg flexion (0,5 – 1,0 Kg)		2×10	2×10	2×10	2×10	2×10	2×10
	Hip abduction (0,5 – 1,0 Kg)		2×10	2×10	2×10	2×10	2×10	2×10
	Hand grip ball		2×10	2×10	2×10	2×10	2×10	2×10

*In case that the patient is still hospitalized

disability, institutionalization, and mortality. A total score of less than 10 indicates frailty and a high risk of disability and falls. One-point change in the score has clinical relevance [48, 49]. Loss of handgrip of the dominant hand is a useful tool for the measurement of functional capacity. It is a strong predictor of disability, morbidity, and mortality as well as one of the components of Fried's frail phenotype. Furthermore, the functional status of patients will also be assessed before measurements with the Barthel Index, an international and validated tool of disability. The scores range from 0 (severe functional dependence) to 100 (functional independence) [50]. Gait ability will be assessed using the 6-metre gait velocity test (GVT). Starting and ending limits will be marked on the floor with tapelines for a total distance of 8 m. Participants will be instructed to walk in their self-selected usual pace for two attempts. The results of both trials will be averaged to obtain a single value. The first and last metre, considered the warm-up and the deceleration phases, respectively, will not be included in the calculations of the gait assessment. Dual task conditions (gait evaluation during the simultaneous performance of a cognitive motor action) have recently been recognized as a sensitive assessment method for interactions between cognition, gait, falls and frailty. Changes of gait parameters (i.e., gait velocity and gait variability) while performing a dual task test (dual task cost) could be early predictors of falls risk (50) and useful tools for functional evaluations in frail elderly patients. Exercise can modify dual task cost and consequently fall risk and functional capacity (31). The dual-task paradigm [51] will be used in the 6-m habitual gait velocity test (GVT). Two trials will be performed to assess the gait velocity while performing a verbal or counting task (verbal GVT and counting GVT, respectively). During the verbal dual-task condition (verbal GVT), we will measure the gait velocity while participants are naming animals aloud. During the arithmetic dual-task condition (counting GVT), we will assess the gait velocity while participants are counting backward aloud from 100 by ones. The cognitive score will be measured by counting the number of animals named (dual-task with verbal performance) or determining how many numbers were counted backward (dual-task with arithmetic performance). Isometric upper (right hand grip) and lower limb (right knee extensors and hip flexors) muscle strength will be measured using a manual dynamometer. Maximal dynamic strength will be assessed using the 1RM test in the bilateral leg press, knee extension and bench press exercises using exercise machines (Exercycle, S.L., BH Group, Vitoria, Spain). In the first assessment, the subjects will warm up with specific movements for the exercise test. Each subject's maximal load will be determined in no more than five attempts, with a 3-min recovery period between attempts. After determination of the 1RM values, the subjects will perform ten repetitions at maximal velocity at intensities of 50 % of 1RM to determine the maximum power (w) and the loss of power during the ten repetitions in the leg press machine. The power will be recorded by connecting a velocity transducer to the weight plates (T-Force System, Ergotech, Murcia, Spain). During all neuromuscular performance tests, a strong verbal encouragement will be given to each subject to motivate them to perform each test action as optimally and rapidly as possible. Qualified fitness specialists will individually monitor and carefully supervise all training sessions and provide instruction and encouragement during all sessions. Distribution of the training sessions throughout the day should minimize cumulative fatigue and help to maintain adherence. Adherence to the exercise intervention programme will be documented in a daily register of sessions. Changes in cognitive-affective status after the intervention will be measured using the Mini Mental State Examination, Yesavage GDS and Trail Making Test (Table 3).

Secondary Outcome Measures:

- Quality of life: EuroQol Scale
- Delirium: Confusion Assessment Method
- Mortality: Number of days alive after admission to the hospital
- Use of health resources: New admissions to the hospital, admission to nursing homes, and visits to the general practitioner
- Falls

Discussion

Functional and cognitive impairment after and during acute hospitalization in older adults is a major determinant of the later need for health resources. If our hypothesis is correct and shows that a multicomponent, individualized and progressive exercise programme provides effective therapy for improving the functional capacity of acute elderly patients hospitalized for medical pathology versus conventional care, a change of the current system of hospitalization of elderly patients with medical conditions may be justified. While the current system does not promote the execution of a scheduled exercise routine during the hospitalization period, if we can modify the current guidelines, it is likely that patients will present lower levels of functional and cognitive impairment after the hospitalization period, experience a better quality of life, produce lower consumption of healthcare resources (less readmissions and lower institutionalization), and finally, exhibit reduced mortality.

This trial is also relevant because exercise interventions in elderly patients have usually been performed in

Table 3 Collected variables

1. Baseline measurements: Outcomes measures will be collected on the test day written in an information sheet.	
1.1. Individual characteristics:	
Demographic variables	Information regarding the age and the gender of the patients will be collected.
Functional status	Reflects the ability of the patient for performing activities of daily living, as well as the capacity to relate with others and participating in society. It will be measured with the Barthel Index.
Functional capacity	SPPB, Gait velocity, Handgrip, dual tests.
Cognitive function	Highlights cognitive impairments that might interfere with self-care and independence in elderly patients. In the present study, we will use the Mini Mental State Examination, and the Trail Making Test as executive function parameters, as well as the Confusion Assessment method for delirium evaluation, and the Geriatric depression Scale of Yesavage as an indicator of psychosocial status.
Caregiver burden	Will be measured through Zarit scale.
Nutritional status	Indicates malnutrition risk in elderly patients. In addition to the weight and height data, information related to factors that increase the risk of malnutrition will be collected. These will be measured via MNA test.
Quality of Life	Evaluates the individual's social well being, due to its easiness in administration, validity and reliability, the EuroQol-5D is one of the questionnaires with largest diffusion and validity.
Geriatrics syndromes	Characterised by the simultaneous presence of illnesses, clinical and functional conditions that can usually lead to incapacity. The specific presence of immobility, incontinence, constipation, pressure ulcers, cognitive impairment, delirium, depressive tendencies, falls, insomnia, visual impairments, hearing impairments, malnutrition, dysphagia, and pain.
Comorbidity	Will be measured by means of Cumulative Illness Rating Scale-Geriatrics (CIRS-G).
1.2. Intervention-measurements	
Upper and lower strength	Maximal isometric force of knee extension, handgrip and hip flexion.
Dynamic muscle power on variable resistance exercise machine.	Will be measured through a T-force system device, connected to the variable resistance machine, so it is able to assess the velocity and power of every single lift.
Kinematic variables of human movement.	Gait patterns of the patients will be recorded by a triaxial accelerometer while performing the GVT. This small device traces acceleration force, speed and angular position data in the three planes.
2. Follow-up: Institutionalization, survival, functional impairment, quality of life, health care resources use (e.g. GP visits emergencies, hospital admission, medicine consumption).	

participants in the community, institutions or hospitalized for rehabilitation purposes. Frequently, older patients with multiple comorbidities are routinely excluded due to acute medical conditions. To date, few randomized clinical trials have been conducted and normally these trials use heterogeneous interventions (sometimes poorly explained), while our study allows the extrapolation of results through a well-defined methodology applied to other areas. The introduction of an exercise programme in hospitalized elderly patients as well as being viable and likely producing no increase in costs, could have a significant impact on both the short and long term by improving health care and functional parameters. Moreover, if our results are as expected, a possible new targeted and therapeutic tool during hospitalization for these complex patients could be developed and implemented in hospitals everywhere. We believe that, as with other medical treatments, the programme should be planned, individualized and monitored.

Another innovative aspect of our study compared with the few clinical trials published so far is the utilization of an interdisciplinary team that manages not only the clinical aspects but also the physiotherapy and engineering kinematics. Furthermore, in the case that the means used for experimental quantification of the power and muscle strength kinematic variables are feasible, it raises the possibility of incorporating commonly used means and patenting both the systematic interventions and the mechanisms of quantification

Trial status

The trial commenced recruitment on March 5, 2015 and is currently open for recruitment. Recruitment will cease when 370 participants have been randomized. It is anticipated this target will be reached by March 2017.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

The protocol was developed by NM, AC, FZ, NS, JA, ML, MG, NF and MI. KC provided advice on the statistical analysis. NM, AC, FZ, NS, ML and MI prepared the initial manuscript. All authors reviewed the final manuscript prior to submission. All authors read and approved the final manuscript.

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References

1. Mudge AM, O'Rourke P, Denaro CP. Timing and risk factors for functional changes associated with medical hospitalization in older patients. J Gerontol A Biol Sci Med Sci. 2010;65(8):866–72. doi:10.1093/gerona/glq069.
2. Davydow DS, Hough CL, Levine DA, Langa KM, Iwashyna TJ. Functional disability, cognitive impairment, and depression after hospitalization for pneumonia. Am J Med. 2013;126(7):615–24. doi:10.1016/j.amjmed.2012.12.006. e5.
3. Boyd CM, Landefeld CS, Counsell SR, Palmer RM, Fortinsky RH, Kresevic D, et al. Recovery of activities of daily living in older adults after hospitalization for acute medical illness. J Am Geriatr Soc. 2008;56(12):2171–9. doi:10.1111/j.1532-5415.2008.02023.x.
4. Brown CJ, Friedkin RJ, Inouye SK. Prevalence and outcomes of low mobility in hospitalized older patients. J Am Geriatr Soc. 2004;52(8):1263–70. doi:10.1111/j.1532-5415.2004.52354.x.
5. Creditor MC. Hazards of hospitalization of the elderly. Ann Intern Med. 1993;118(3):219–23.
6. Allman RM, Goode PS, Patrick MM, Burst N, Bartolucci AA. Pressure ulcer risk factors among hospitalized patients with activity limitation. JAMA. 1995;273(11):865–70.
7. Gillick MR, Serrell NA, Gillick LS. Adverse consequences of hospitalization in the elderly. Soc Sci Med. 1982;16(10):1033–8.
8. Fortinsky RH, Covinsky KE, Palmer RM, Landefeld CS. Effects of functional status changes before and during hospitalization on nursing home admission of older adults. J Gerontol A Biol Sci Med Sci. 1999;54(10):M521–6.
9. Narain P, Rubenstein LZ, Wieland GD, Rosbrook B, Strome LS, Pietruszka F, et al. Predictors of immediate and 6-month outcomes in hospitalized elderly patients. The importance of functional status. J Am Geriatr Soc. 1988;36(9):775–83.
10. Hirsch CH, Sommers L, Olsen A, Mullen L, Winograd CH. The natural history of functional morbidity in hospitalized older patients. J Am Geriatr Soc. 1990;38(12):1296–303.
11. Inouye SK, Wagner DR, Acampora D, Horwitz RI, Cooney Jr LM, Hurst LD, et al. A predictive index for functional decline in hospitalized elderly medical patients. J Gen Intern Med. 1993;8(12):645–52.
12. Sager MA, Franke T, Inouye SK, Landefeld CS, Morgan TM, Rudberg MA, et al. Functional outcomes of acute medical illness and hospitalization in older persons. Arch Intern Med. 1996;156(6):645–52.
13. Rudberg MA, Sager MA, Zhang J. Risk factors for nursing home use after hospitalization for medical illness. J Gerontol A Biol Sci Med Sci. 1996;51(5):M189–94.
14. Covinsky KE, Justice AC, Rosenthal GE, Palmer RM, Landefeld CS. Measuring prognosis and case mix in hospitalized elders. The importance of functional status. J Gen Intern Med. 1997;12(4):203–8.
15. Lakhan P, Jones M, Wilson A, Courtney M, Hirdes J, Gray LC. A prospective cohort study of geriatric syndromes among older medical patients admitted to acute care hospitals. J Am Geriatr Soc. 2011;59(11):2001–8. doi:10.1111/j.1532-5415.2011.03663.x. Epub 2011 Oct 10.
16. Hannan EL, Magaziner J, Wang JJ, Eastwood EA, Silberzweig SB, Gilbert M, et al. Mortality and locomotion 6 months after hospitalization for hip fracture: risk factors and risk-adjusted hospital outcomes. JAMA. 2001;285(21):2736–42.
17. McCusker J, Kakuma R, Abrahamowicz M. Predictors of functional decline in hospitalized elderly patients: a systematic review. J Gerontol A Biol Sci Med Sci. 2002;57(9):M569–77.
18. Covinsky KE, Martin GE, Beyth RJ, Justice AC, Sehgal AR, Landefeld CS. The relationship between clinical assessments of nutritional status and adverse outcomes in older hospitalized medical patients. J Am Geriatr Soc. 1999;47(5):532–8.
19. Volpato S, Onder G, Cavalieri M, Guerra G, Sioulis F, Maraldi C, et al. Characteristics of nondisabled older patients developing new disability associated with medical illnesses and hospitalization. J Gen Intern Med. 2007;22(5):668–74. doi:10.1007/s11606-007-0152-1.
20. Zisberg A, Shadmi E, Sinoff G, Gur-Yaish N, Srulovici E, Admi H. Low mobility during hospitalization and functional decline in older adults. J Am Geriatr Soc. 2011;59(2):266–73. doi:10.1111/j.1532-5415.2010.03276.x.
21. Covinsky KE, Palmer RM, Fortinsky RH, Counsell SR, Stewart AL, Kresevic D, et al. Loss of independence in activities of daily living in older adults hospitalized with medical illnesses: increased vulnerability with age. J Am Geriatr Soc. 2003;51(4):451–8.
22. Brown CJ, Redden DT, Flood KL, Allman RM. The underrecognized epidemic of low mobility during hospitalization of older adults. J Am Geriatr Soc. 2009;57(9):1660–5. doi:10.1111/j.1532-5415.2009.02393.x.
23. Zisberg A, Shadmi E, Gur-Yaish N, Tonkikh O, Sinoff G. Hospital-associated functional decline: the role of hospitalization processes beyond individual risk factors. J Am Geriatr Soc. 2015;63(1):55–62. doi:10.1111/jgs.13193.
24. Gill TM, Gahbauer EA, Han L, Allore HG. The relationship between intervening hospitalizations and transitions between frailty states. J Gerontol A Biol Sci Med Sci. 2011;66(11):1238–43. doi:10.1093/gerona/glr142.
25. Warshaw GA, Moore JT, Friedman SW, Currie CT, Kennie DC, Kane WJ, et al. Functional disability in the hospitalized elderly. JAMA. 1982;248(7):847–50.
26. Lamont CT, Sampson S, Matthias R, Kane R. The outcome of hospitalization for acute illness in the elderly. J Am Geriatr Soc. 1983;31(5):282–8.
27. McVey LJ, Becker PM, Saltz CC, Feussner JR, Cohen HJ. Effect of a geriatric consultation team on functional status of elderly hospitalized patients. A randomized, controlled clinical trial. Ann Intern Med. 1989;110(1):79–84.
28. Martinez-Velilla N, Urbistondo-Lasa G, Veintemilla-Erice E, Cambra-Contin K. [Determining the hours hospitalised patients are bedridden due to their medical condition and functional impairment and secondary mortality]. Rev Esp Geriatr Gerontol. 2013;48(2):96. doi:10.1016/j.regg.2012.05.003.
29. Kortebein P, Symons TB, Ferrando A, Paddon-Jones D, Ronsen O, Protas E, et al. Functional impact of 10 days of bed rest in healthy older adults. J Gerontol A Biol Sci Med Sci. 2008;63(10):1076–81.
30. Izquierdo M, Aguado X, Gonzalez R, Lopez JL, Hakkinen K. Maximal and explosive force production capacity and balance performance in men of different ages. Eur J Appl Physiol Occup Physiol. 1999;79(3):260–7. doi:10.1007/s004210050504.
31. Casas Herrero A, Cadore EL, Martinez Velilla N, Izquierdo RM. Physical exercise in the frail elderly: an update. Rev Esp Geriatr Gerontol. 2015;50(2):74–81. doi:10.1016/j.regg.2014.07.003.
32. Casas-Herrero A, Cadore EL, Zambom-Ferraresi F, Idoate F, Millor N, Martinez-Ramirez A, et al. Functional capacity, muscle fat infiltration, power output, and cognitive impairment in institutionalized frail oldest old. Rejuvenation Res. 2013;16(5):396–403. doi:10.1089/rej.2013.1438.
33. Gutierrez Rodriguez J, Dominguez Rojas V, Solano Jaurrieta JJ. Functional deterioration secondary to hospitalization for an acute disease in the elderly. An analysis of its incidence and the associated risk factors. Rev Clin Esp. 1999;199(7):418–23.
34. Baztan JJ, Suarez-Garcia FM, Lopez-Arrieta J, Rodriguez-Manas L. Efficiency of acute geriatric units: a meta-analysis of controlled studies. Rev Esp Geriatr Gerontol. 2011;46(4):186–92. doi:10.1016/j.regg.2011.02.005.
35. Arora VM, Plein C, Chen S, Siddique J, Sachs GA, Meltzer DO. Relationship between quality of care and functional decline in hospitalized vulnerable elders. Med Care. 2009;47(8):895–901. doi:10.1097/MLR.0b013e3181a7e3ec.
36. Courtney MD, Edwards HE, Chang AM, Parker AW, Finlayson K, Bradbury C, et al. Improved functional ability and independence in activities of daily living for older adults at high risk of hospital readmission: a randomized controlled trial. J Eval Clin Pract. 2012;18(1):128–34. doi:10.1111/j.1365-2753.2010.01547.x.
37. Fisher SR, Kuo YF, Graham JE, Ottenbacher KJ, Ostir GV. Early ambulation and length of stay in older adults hospitalized for acute illness. Arch Intern Med. 2010;170(21):1942–3. doi:10.1001/archinternmed.2010.422.
38. Mudge AM, Giebel AJ, Cutler AJ. Exercising body and mind: an integrated approach to functional independence in hospitalized older people. J Am Geriatr Soc. 2008;56(4):630–5. doi:10.1111/j.1532-5415.2007.01607.x.

39. Baztan JJ, Galvez CP, Socorro A. Recovery of functional impairment after acute illness and mortality: one-year follow-up study. Gerontology. 2009;55(3):269–74. doi:10.1159/000193068.
40. de Morton NA, Keating JL, Jeffs K. The effect of exercise on outcomes for older acute medical inpatients compared with control or alternative treatments: a systematic review of randomized controlled trials. Clin Rehabil. 2007;21(1):3–16. doi:10.1177/0269215506071313.
41. Mercante O, Gagliardi C, Spazzafumo L, Gaspari A, David S, Cingolani D, et al. Loss of autonomy of hospitalized elderly patients: does hospitalization increase disability? Eur J Phys Rehabil Med. 2014;50(6):703–8.
42. de Morton NA, Keating JL, Jeffs K. Exercise for acutely hospitalised older medical patients. Cochrane Database Syst Rev. 2007;1:CD005955. doi:10.1002/14651858.CD005955.pub2.
43. Kosse NM, Dutmer AL, Dasenbrock L, Bauer JM, Lamoth CJC. Effectiveness and feasibility of early physical rehabilitation programs for geriatric hospitalized patients: a systematic review. BMC Geriatr. 2013;13:107. doi:10.1186/1471-2318-13-107.
44. Chan AW, Tetzlaff JM, Gotzsche PC, Altman DG, Mann H, Berlin JA, et al. SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials. BMJ. 2013;346:e7586. doi:10.1136/bmj.e7586.
45. Moher D, Schulz KF, Altman DG, Consort. The CONSORT statement: revised recommendations for improving the quality of reports of parallel group randomized trials. BMC Med Res Methodol. 2001;1:2.
46. Izquierdo M, Cadore EL. Muscle power training in the institutionalized frail: a new approach to counteracting functional declines and very late-life disability. Curr Med Res Opin. 2014;30(7):1385–90. doi:10.1185/03007995.2014.908175.
47. Guralnik JM, Simonsick EM, Ferrucci L, Glynn RJ, Berkman LF, Blazer DG, et al. A short physical performance battery assessing lower extremity function: association with self-reported disability and prediction of mortality and nursing home admission. J Gerontol. 1994;49(2):M85–94.
48. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995;332(9):556–61. doi:10.1056/NEJM199503023320902.
49. Guralnik JM, Ferrucci L, Pieper CF, Leveille SG, Markides KS, Ostir GV, et al. Lower extremity function and subsequent disability: consistency across studies, predictive models, and value of gait speed alone compared with the short physical performance battery. J Gerontol A Biol Sci Med Sci. 2000;55(4):M221–31.
50. Mahoney FI, Barthel DW. Functional Evaluation: The Barthel Index. Md State Med J. 1965;14:61–5.
51. Beauchet O, Annweiler C, Dubost V, Allali G, Kressig RW, Bridenbaugh S, et al. Stops walking when talking: a predictor of falls in older adults? Eur J Neurol. 2009;16(7):786–95. doi:10.1111/j.1468-1331.2009.02612.x.