Multimorbidity clusters among long-term breast cancer survivors in Spain: Results of the SURBCAN Study

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Keywords: Multimorbidity, breast cancer, survival, cluster analysis, electronic health records.

List of abbreviations

- BCS: breast cancer survivors
- IARC: International Agency for Research on Cancer
- NICE: National Institute for Health and Care Excellence
- NHS: National Health System
- SURBCAN: Survival Breast Cancer
- EHR: electronic health records
- ICD-9: International Classification of Diseases version 9
- ICD-10: International Classification of Diseases version 10
- ICPC-2: International Classification of Primary Care version 2
- CD: chronic diseases
- CCS: Clinical Classifications software
- AHRQ: Agency for Healthcare Research and Quality from the United States
- CCS-CD: codes that CCS reported as chronic diseases
- SD: standard deviation
- HCA: hierarchical cluster analysis
- O/E ratios: Observed/Expected ratios
- aHR: adjusted hazard ratio
- CI: confidence interval
- aRR: adjusted relative risk
- MSK: musculoskeletal

Article category: Research article – Cancer epidemiology

Novelty and Impact

We performed a cluster analysis in a cohort of long-term breast cancer survivors from Spain. Five multimorbidity clusters were identified by means of diagnosed chronic diseases recorded in the electronic health records. Their impact on mortality and health services use differed among the multimorbidity clusters. These results identify sub-groups of long-term breast cancer survivors with specific needs and mortality risks and indicate the need for greater focus on multimorbidity in clinical practice.

Abstract

The disease management of long-term breast cancer survivors (BCS) is hampered by the scarce knowledge of multimorbidity patterns. The aim of this study was to identify multimorbidity clusters among long-term BCS and assess their impact on mortality and health services use. We conducted a retrospective study using the electronic health records of 6512 BCS from Spain surviving at least 5 years. Clinical Classification software was used to classify chronic diagnoses, and multimorbidity clusters were identified by means of hierarchical cluster analysis. Observed/expected ratios were used to identify associated comorbidities. Adjusted Cox regression and negative binomial models were fitted to estimate the probability of use of primary care and hospital-based services according to the identified clusters. Five multimorbidity clusters were identified: C1-Unspecific (29.9%), C2-Metabolic and degenerative (28.3%), C3-Anxiety and fractures (9.7%), C4-Musculoskeletal and cardiovascular (9.6%), C5-Thyroid disorders (5.3%) plus the group of BCS without comorbidities (17.3%). All clusters except C5-Thyroid disorders were associated with higher mortality compared with BCS without comorbidities, the highest risk being in C4 (HR=1.88, 95%CI 1.68-2.33). Compared with BCS without comorbidity, women in cluster C3 showed the highest health services use both for primary care (RR=2.01, 95%CI: 1.90-2.12) and for hospital-based services (RR=2.75, 95%CI: 2.60-2.92). BCS in C4-Muskuloskeletal and cardiovascular showed the highest risk of mortality, while BCS in C3-Anxiety and fractures had the highest risk of health services use versus BCS without comorbidity. These results help to identify sub-groups of long-term BCS with specific needs and mortality risks and to guide BCS clinical practice regarding multimorbidity.

1. INTRODUCTION

Advances in the diagnosis and treatment of breast cancer along with improvements in population-based screening programs have contributed to increased breast cancer survival. Currently, the relative survival rate for breast cancer is around 90% at 5 years from diagnosis and 83% at 10 years [1,2]. This translates into a higher number of long-term breast cancer survivors (BCS) at risk of developing both chronic comorbidities due to cancer treatment and aging. Therefore, long-term BCS deserve special attention from health services as there is increasing recognition that the presence of comorbidities contributes to the severity of the disease. International organizations such as the International Agency for Research on Cancer (IARC), the National Institute for Health and Care Excellence (NICE) and the Spanish National Health System (NHS) have recently stated the need for a better understanding of the long-term needs of cancer survivors, and have recommended the study of multimorbidity among these patients and adapting cancer care to the chronic health model framework [3-5].

Recent studies have examined comorbidities and multimorbidity in long-term BCS. Multimorbidity, understood as the co-occurrence of two or more chronic conditions [6], is estimated to affect more than half of all BCS [7,8]. Some of the most prevalent breast cancer-associated comorbidities are hypertension, arthritis, and mental health disorders, among others [8-10]. Comorbidities not only affect symptom burden and health status but have also been associated with higher mortality and greater health services use, especially primary care [10,11]. Indeed, the presence of multimorbidity among long-term BCS challenges health providers and puts pressure on health systems, which struggle to provide comprehensive assessment of multimorbidity and coordinated care plans [12,13].

Despite this, most studies on BCS still focus on individual comorbidities instead of considering the relationships among them. These relationships are essential to understand which groups of comorbidities cause a higher disease burden and mortality or lead to increased health care seeking. In studies in the general population, this question has been studied using diverse methodological approaches [6,11,13,14]. One of the approaches used for grouping diseases is cluster analysis, which identifies multimorbidity patterns based on the similarities between diseases [14,15].

A better understanding of long-term BCS multimorbidity clusters may help to improve disease management, which could enhance quality of life and healthy aging through appropriate treatment and intervention in individual patients. To the best of our knowledge, it is currently unknown whether and to what extent multimorbidity clusters are present among long-term BCS and it remains unclear whether BCS with different comorbidity profiles differ in health status and other relevant outcomes.

We therefore aimed to firstly identify and describe multimorbidity clusters in a cohort of long-term BCS using hierarchical cluster analysis. A secondary objective was to assess the impact of these clusters on mortality and health services use.

2. MATERIALS AND METHODS

2.1. **Design, setting and study population**

The Survival Breast CANcer Cohort (SURBCAN) study is a retrospective cohort that includes long-term BCS from five Spanish areas within the Spanish NHS. This system provides universal coverage, financed mainly by tax revenue. Three of the five areas correspond to teaching hospitals: Hospital del Mar (Barcelona), serving 350,000 patients, Hospital Costa del Sol (Malaga), serving 387,000 patients, and Hospital 12 de Octubre (Madrid) covering a population of 432,000 people. The two remaining areas are the Autonomous Community of Navarre (population of 661,000 people) and the area covered by the EpiChron cohort (Aragon), which includes 1,253,292 individuals from Aragon. A detailed protocol has previously been published [16].

Long-term BCS are those women who survive at least 5 years since the primary breast cancer diagnosis [1,2]. All women ≥18 years old with a diagnosis of incident breast cancer between 2000 and 2006 and a survival period of at least 5 years after diagnosis were identified in each participating area and were followed-up from 2012 to 2016. Women were identified by means of cancer registries. To ensure a minimum 5-year survival period at baseline, all included women had to be alive at the beginning of the follow-up period. Long-term BCS were only included in the subsequent analysis if they had at least one contact recorded in their primary care electronic health records (EHR). All personal data were anonymized and no written informed consent was deemed necessary for this study. This project was approved by the Clinical Research Ethics Committee of each participating area.

2.2. **Variables, data sources and selection of diseases**

Clinical, tumor and sociodemographic data were retrieved from both primary care and hospital EHR as well as from tumor registries. Depending on each participating area, diagnoses were coded in the EHR using the International Classification of Diseases version 9 (ICD-9), the International Classification of Diseases version 10 (ICD-10) [17] and the International Classification of Primary Care version 2(ICPC-2)[18]. For this study, we selected all active diagnoses at the first contact with health services during the follow-up period (2012 to 2016), except for R codes (symptoms, signs, and abnormal clinical and laboratory findings, not elsewhere classified) and Z codes (factors influencing health status and contact with health services).

The main study variables were:

1) Long-term BCS characteristics at the beginning of follow-up: age (in years), survival time (5-10 years and > 10 years, Charlson index (0-1 or ≥2), active chronic diseases (CD) within the EHR (1 if present after 5 years of cancer survival and 0 if absent) and presence of multimorbidity (1 if present and 0 if absent).

To facilitate information management and cluster analysis, diagnoses were recoded using the Clinical Classifications software (CCS). CCS is a tool for classifying ICD-9 and ICD-10 diagnoses and procedures into a manageable number of 290 clinically meaningful categories developed by the Agency for Healthcare Research and Quality (AHRQ) from the United States [19]. For the purpose of the analysis, we only included in the cluster analysis

the codes reported by the CCS as CD (CCS-CD), which yielded 268 blocks. To complement the multimorbidity cluster analysis, we also assessed the presence of multimorbidity according to CCS-CD codes (1 if present and 0 if absent), the mean number of CCS-CD (continuous) and the Charlson index. The Charlson index was calculated using all the ICD-9, ICD-10 and ICPC-2 diagnoses reported in the EHR at the beginning of follow-up. Multimorbidity was defined by the presence of two or more CCS-CD and the baseline breast cancer diagnosis was excluded to calculate multimorbidity and the mean number of CCS-CD [6]. Women with no CD from the CCS list as well as those BCS with no diagnoses recorded in primary care EHR other than the breast cancer diagnose were considered as CCS-CD free BCS.

2) Breast cancer diagnosis characteristics: tumor behavior (in situ or invasive tumor) and breast cancer surgery (1 if surgery was performed and 0 if no surgery was performed). Data on tumor characteristics and treatment were not available for the EpiChron cohort.

3) Health services use: annual visits to primary care and hospital-based services per woman-year (continuous variable).

4) Long-term BCS characteristics at the end of follow-up: vital status (1 if exitus and 0 if alive).

2.3. **Statistical analysis**

Descriptive data are reported as frequencies (percentage) for categorical variables and as means (standard deviation, SD) and medians for continuous variables. We selected CCS-CD with a prevalence ≥2% in the total BCS sample to avoid statistical noise and therefore spurious findings in the cluster results. For the purpose of this study, baseline breast cancer diagnoses (ICD-9: C50; ICD-10: 174, 175, V10.3; ICPC-2: X76, Y78) were not included in the cluster analysis as it was an inclusion criterion [20]. Multimorbidity clusters were identified using hierarchical cluster analysis to retrieve non-random associations between CCS-CD in individuals. Hierarchical cluster analysis (HCA) is the major statistical method for finding homogeneous groups of cases based on the measured characteristics. The HCA endpoint is a set of clusters where each cluster is distinct from the others and the objects within each cluster are broadly similar. HCA starts by treating each observation as a separate cluster. Then, it identifies clusters that are closest together and afterwards, it combines the clusters sequentially, reducing the number of clusters at each step. In this study, we used the Ward method as the grouping technique and the Euclidean squared distance as an interval measure to estimate the distance between two clusters. [21].

To characterize the identified clusters of multimorbidity that corresponded to each cluster of individuals, we calculated the frequency of CCS-CD in each cluster. The multimorbidity clusters to which each woman belonged were obtained by means of the presence of each CD (1 if present after 5 years of cancer survival and 0 if absent). We identified the diseases most frequently associated with a multimorbidity cluster using Observed/Expected ratios (O/E

ratios). O/E ratios were calculated by dividing the proportion of a given CCS-CD within a cluster by its prevalence in the overall BCS population. We considered a disease to be associated with a cluster when the O/E ratio was equal to or greater than 2 [22]. After applying these criteria, the research team interpreted and named the clusters. Descriptive statistics of sociodemographic data were compared using ANOVA and Pearson's chi-square test.

Adjusted Cox regression models were fitted to estimate the association between clusters and mortality and negative binomial regression models were used to estimate differences in health services use, by using the group of women without CCS-CD as the reference group. For mortality, Cox regression models showed adjusted hazard ratios (aHR) and 95% confidence intervals (CI) by age, survival time (5-10 years and > 10 years), tumor behavior, Charlson index and annual visits to primary care and hospital-based services. Negative binomial regression models provided adjusted relative risks (aRR) and 95% CI by age, vital status, tumor behavior and the Charlson index. Primary care and hospital visits included in these analyses were defined as the number of annual visits per woman per year during the follow-up (2012-2016). An additional sensitivity analysis was performed to further understand the time since diagnosis on BCS multimorbidity clusters. The significance level was set at α=0.05. Data analyses were performed using SPSS 23.

3. RESULTS

The SURBCAN cohort included a total of 6512 long-term BCS (Table 1). The mean age of the study participants at the beginning of follow-up was 66 years (SD 12.6). A total of 1590 (25.2%) of the included long-term BCS had survived more than 10 years since the primary breast cancer diagnosis. Out of 6512 long-term BCS included, 5387 (54.7%) had at least one CCS-CD reported in the EHR. As shown in Table 1, more than half had multimorbidity and the mean number of CCS-CD at the beginning of follow-up was 2.35 (SD 2.06). Invasive breast cancer was diagnosed in 87.3%, and breast surgery was performed in 96.9%. The median number of annual visits to primary care and hospital were 25.4 and 5.4, respectively. Over the follow-up period, there were 819 deaths (12.6%).

Table 2 shows the results of the HCA, which identified five clusters of individuals based on their underlying multimorbidity patterns. The prevalence of the 24 CCS-CD with ≥2% prevalence among all the BCS included is shown for each cluster as well as for the overall group of long-term BCS. A total of 469 BCS had miscellaneous CCS-CDs that individually did not exceed the ≥2% prevalence criterion and therefore we decided to merge them into a single category, named "BCS without CCS-CD comorbidities". Of the top 24 CCS-CD included, the most common was essential hypertension, found in 34.5% of BCS, followed by obesity and other nutritional and metabolic disorders (27.4%) and anxiety disorders (16.4%). Five clusters of long-term BCS were identified. The clusters were sorted in descending order by the number of individuals included. Using the prevalence of CCS-CD, O/E ratios (≥2 O/E ratios marked in bold in Table 2 and supplementary material 1) and after joint validation with the research team, we considered the five clusters as valid and named them as follows: *C1-Unspecific* was the most prevalent (n=1948; 29.9%), including 24.1% of miscellaneous disease, followed by *C2-Metabolic and degenerative*(n=1841;28.3%) with a 65.9% prevalence of essential hypertension, *C3-Anxiety and fractures* (n=633;9.7%), *C4-Musculoskeletal (MSK) and*

cardiovascular (n=623;9.6%) and *C5-Thyroid disorders* (n=342;5.3%).Women without CCS-CD represented 17.3% (n=1225) of the overall BCS. CCS-CD distribution and O/E ratios varied among clusters.

A descriptive analysis was carried out to characterize the identified clusters (Table 3). BCS in *C2-Metabolic and degenerative* were the oldest (mean age 70.0 years, SD 11.55) and those in *C3-Anxiety and fractures* were the youngest (mean age 63.0 years, SD 11.56) (p-value <0.0001). Multimorbidity was widely represented in all clusters, especially in *C4-MSK and cardiovascular*, in which multimorbidity was found in 93.4% of the women. In all groups, more than half of BCS had a Charlson index ≥2. Women within *C5-Thyroid disorders* had the highest mean number of annual visits to primary care (34.3 visits), while those in *C4-MSK and cardiovascular* showed the highest number of hospital admissions (7.5 per year). Nevertheless, analysis of the medians showed that *C1-Unspecific* was the cluster with the highest median number of annual primary care visits. This variation is attributed to the highest median number and wider range of the number of primary care visits among the included long-term BCS. The highest number of deaths was found in *C4-MSK and cardiovascular* (n=83, 13.3%) and the lowest in *C3-Anxiety and fractures* (n=35, 6.0%) (p-value <0.0001). BCS without CCS-CD comorbidities showed similar age (mean age=63.9 years, SD=14.4) and number of deaths (n=122, 11%) as the women with comorbidities.

The association between the multimorbidity clusters with both mortality and health services use was assessed through independent regression models (Table 4). Mortality was studied using a Cox regression model adjusted by age, survival time, tumor behavior, annual visits to primary and hospital care and the Charlson index, taking the group of women without CCS-CD comorbidities as the reference group for the cluster variable. All patterns except *C5-Thyroid disorders* (aHR 0.74 (95%CI: 0.31 - 0.96) showed statistically significant increased mortality compared with women without CCS-CD comorbidities, with *C4-MSK and cardiovascular* being the cluster showing the highest HR (aHR 1.88, 95%CI 1.68-2.33). Moreover, BCS diagnosed with an invasive tumor were more likely to die than those with an in situ tumor (aHR 2.72, 95%CI 1.49-3.78). Among BCS surviving 5-10 years, all multimorbidity clusters showed a higher mortality risk compared with BCS without CCS-CD comorbidities, but this association was not observed in the group of BCS surviving >10 years (Figure 1). However, BCS who had survived > 10 years showed a statistically significant lower mortality only in *C3 Anxiety and fracture* (aHR 0.80, 95%CI 0.10-0.97).

Analysis of the association of multimorbidity clusters with health services use showed that the five comorbidity patterns were statistically associated with an increased use of both primary care and hospital-based services compared with women without CCS-CD comorbidities. BCS in *C3-Anxiety and fractures* were the most likely to contact both primary care (aRR 2.01, 95%CI 1.90-2.12) and the hospital (aRR 2.75, 95%CI 2.60-2.92). BCS with a diagnosis of an invasive tumor had a 20% greater probability of seeking primary care than BCS diagnosed with an in situ tumor (aRR 1.20, 95%CI 1.15-1.28), while no excess risk was observed for hospital-based services (aRR 1.04, 95%CI 0.99-1.08). BCS who died during follow-up as well as those with a Charlson index ≥2 were more likely to use hospital-based services (aRR 1.12, 95%CI 1.08-1.17 and aRR 1.23, 95%CI 1.18-1.26, respectively).

4. DISCUSSION

In this study, we describe multimorbidity clusters among long-term BCS. To the best of our knowledge, this is the first analysis to use cluster analysis to study multimorbidity among long-term BCS. Three main findings emerged from the results. First, five clusters of long-term BCS were identified within the BCS group showing CCS-CD comorbidities, accounting for 83.7% of the cohort. Two of the clusters covered 58.2% of all long-term BCS, namely *C1-Unspecific* (29.9%) and *C2-Metabolic and degenerative* (28.3%), with hypertension being the most frequent CD in the latter and in the overall group of long-term BCS. Second, all BCS in multimorbidity clusters except the C5-*Thyroid disorders* cluster showed higher mortality than BCS without CCS-CD, with the highest mortality being in *C4-MSK and cardiovascular*. Third, *C3-Anxiety and fractures* had the highest probability of use of both primary and hospital care, although women in the five clusters showed a higher probability of visiting both primary care and hospital-based services than the group of long-term BCS without CCS-CD comorbidities.

The results of this study show a similar prevalence of multimorbidity and CD to other works carried out among BCS. More than half of the long-term BCS had multimorbidity and the most frequent CDs within our sample were essential hypertension, obesity and other nutritional, endocrine and metabolic disorders, as well as anxiety disorders. Although there are no other studies focusing on multimorbidity cluster analysis among long-term BCS in the Spanish context, studies conducted in the United States [23], Canada [8] and Europe [24,25] have also reported hypertension and anxiety disorders as being some of the most frequent comorbidities among this group of women. The prevalence of multimorbidity among BCS has been reported to be around 40% in the UK [25] and 50% in Canada [8]. Within the Spanish context, anxiety disorders and obesity were found to be highly prevalent in this group of women in a study conducted in southern Spain [26], but that study had no data on hypertension. The main differences with our study in terms of the frequency of comorbidities could be due to our exhaustive study of all the CD among long-term BCS, and not only the most prevalent or relevant CDs, which are also diagnoses validated in the EHR by a physician and are not self-reported by patients as was the case in other previous studies.

The clusters obtained in this study seem to be consistent with other cluster analyses that included the general population with a similar age and context to our own [6,14,27]. As in the current study, other studies have also reported that the cluster with unspecific diseases, which also includes relatively younger women with a lower disease burden and less multimorbidity, is usually the most frequent [6,11,14,28,29]. This cluster seems to represent those long-term BCS with no severe complications of their baseline comorbidities. Indeed, other studies agree that younger women are less likely to be diagnosed with multiple diseases [28,30]. However, further analysis of the CCS-CD prevalence and O/E ratios within *C1-Unspecific* reveals that BCS within this cluster had cardiovascular risk factors, such as hypertension and dyslipidemia, which deserve special attention to prevent worsening of the health status of these women. Nevertheless, this cluster is the one most replicated in the overall literature of studies using the general population or specific diseases [14,28].

Another interesting finding was the multimorbidity associated with diabetes, gathered in *C2-Metabolic and degenerative* cluster. The results show that C2 mainly presents as an

involvement of the vascular system by means of diabetes, hypertension, glaucoma, cardiac dysrhythmias and sense organ disorders. This could indicate worsening of health status and complications through the presence of several diseases of the same system in the same cluster [14,31]. Metabolic involvement among BCS has been previously described. On the one hand, metabolic syndrome has been shown to be associated with an increased risk of breast cancer [32,33] and, on the other hand, chemotherapy treatment has also been associated with diabetes due to estrogen suppression [34]. These findings could explain the increased risk of primary care use in C2 compared to other clusters due to CD such as hypertension or diabetes that contribute to highlight the need for intensive follow-up to control these diseases, which is usually done by primary care professionals.

The same effect occurred within C4-*MSK and cardiovascular*, showing involvement mainly of the MSK and cardiovascular system. The increased risk of developing comorbidities related to these systems, such as osteoporosis or cardiac dysrhythmias, has been widely described as late effects of breast cancer treatment [35,36]. This may be because the treatment with trastuzumab and anthracyclines has been associated with the presence of cardiac events, while radiotherapy has been associated with ischemic heart disease [35,37]. In addition, aromatase inhibitor treatment can lead to osteoporosis among long-term BCS [38,39]. It would be of interest to assess such associations within our sample through information about specific treatments in future research.

The last two clusters, C2 and C4, were characterized by cardiometabolic diseases, which are indicators of life expectancy. Both clusters included the oldest long-term BCS and those with highest Charlson index. *C4-MSK and cardiovascular* had the highest mortality risk and *C2-Metabolic and degenerative* showed a similar mortality risk to the other clusters. These differences in mortality risks among clusters can be explained by several factors. The Charlson index was originally created to predict mortality based on the presence of specific diseases. However, the excess mortality in C4 may be due to disease associations not included in the the index. In addition, not all cardiovascular and metabolic diseases carry the same mortality risk [40]. Nevertheless, long-term BCS are supposed to be monitored and screened for cardiovascular risk factors more often, which allows health professionals to prevent and anticipate cardiac events, reducing mortality [8]. Even so, cardiovascular diseases have been associated with higher mortality in other studies due to the hemodynamic disruptions caused by cardiovascular diseases, which agrees with the higher mortality found in *C4-MSK and cardiovascular* [40,41].

On the other hand, the cluster leading to the highest burden of primary care and hospital-based services use was *C3-Anxiety and fractures.* Other studies have also shown an increased use of primary care among woman with anxiety disorders [42,43]. This higher use is often explained by greater comorbid illnesses associated with anxiety. In addition, the increased use of hospital-based services can be explained by the burden of care of pathological fractures. Anxiety and pathological fractures are recognized consequences of cancer treatment [7-9]. Furthermore, there is evidence that antidepressants are associated with an increased risk of fractures [44], which could have contributed to the creation of this cluster mix and its relationship with health services use.

As for *C5-Thyroid disorders*, recent studies have reported an association between hypothyroidism and breast cancer, which has been attributed to radiotherapy [39]. Even so, C5 showed significantly lower mortality than the other clusters. Other studies have attributed this lower mortality among women in this cluster to the lower burden of disease associated with thyroid-related disorders [45].

In short, over 80% of long-term BCS had some comorbidity, which translated into higher healthcare utilization than BCS without comorbidities. Primary care professionals play a major role in the management of the late effects of breast cancer and non-cancer conditions to prevent the appearance of new comorbidities or an increase in multimorbidity [46]. Co-occurring diseases, compared with single diseases, have a greater effect on reduced survival and less multimorbidity allows better disease management [11,47]. Care coordination is therefore essential to ensure that long-term BCS receive adequate attention from all levels of care as well as to prevent worsening of their health status, the development of further comorbidities, and an increase in multimorbidity.

4.1. Strengths and limitations

This is one of the largest population-based studies of multimorbidity among long-term BCS to date (N=6512 long-term BCS; n=1590 >10-year survivors). Our data identify five clusters (apart from the group without CD) and relate them with the patterns of healthcare use and their risk of death. In addition, to measure comorbidities we used the CCS, a rarely used approach in multimorbidity research that provides a tool that classifies diseases in 290 easier to manage categories. CCS is a validated, relatively new approach and is available for researchers, which we consider a strength of this classification.

This study also has some limitations. Comparison with other studies was hampered by the lack of studies focusing on long-term BCS with similar methodology. Another limitation is the cross-sectional approach used to identify multimorbidity clusters, which makes it difficult to understand the order of appearance of the diseases, the transition of BCS between clusters, the occurrence of new clusters during the follow-up period or in the future, and the evaluation of causality. Last, we lacked information on more detailed tumor characteristics, treatment, diagnoses and other cluster determinants that would have allowed us to explore more deeply the relationship between cluster membership and mortality or health services use. Further analysis with a different methodology would be needed to provide a longitudinal cluster analysis assessment.

4.2 Implications for practice and conclusions

The results of this study indicate that multimorbidity among long-term BCS is highly frequent and widely heterogeneous. Furthermore, the five multimorbidity clusters have a different impact on mortality and healthcare services use. These results help to identify sub-groups of long-term BCS with specific needs and mortality risks and shed light on the need to shift BCS clinical practice away from healthcare focused on single diseases and to guide it toward multimorbidity. The care of multimorbidity is a challenge that institutions and health professionals must take into account to improve care delivery. Identifying profiles of BCS and their individual needs helps to achieve the objectives of patient-centered care as well as to

establish preventive activities according to their health status. Further studies aiming to understand environmental and lifestyle risk factors underlying these multimorbidity clusters are needed to create increasingly personalized care.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA. SEER Cancer Statistics Review, 1975-2015. National Cancer Institute. Bethesda. Available at: https://seer.cancer.gov/csr/1975_2015/. Accessed 21 Feb 2019.
2. Baeyens-Fernández JA, Molina-Portillo E, Pollán M, Rodríguez-Barranco M, Del Moral R, Arribas-Mir L, Sánchez-Cantalejo Ramírez E, Sánchez MJ. Trends in incidence, mortality and survival in women with breast cancer from 1985 to 2012 in Granada, Spain: a population-based study. BMC Cancer. 2018;18(1):781.
3. Global strategy and action plan on ageing and health. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. Available at: file:///Users/apple/Downloads/WHO-GSAP-2017%20(2).pdf. Accessed 10 November 2020.
4. Multimorbidity: clinical assessment and management (NG56). NICE guideline. National Institute for Health and Care Excellence (NICE). 2016. Available at: https://www.nice.org.uk/guidance/ng56. Accessed 10 November 2020.
5. Estrategia para el abordaje de la cronicidad en el Sistema Nacional de Salud. Informe de Evaluación y líneas prioritarias de actuación. Instituto de Salud Carlos III. 2019. Available at: file:///Users/apple/Downloads/Evaluacion_E._Cronicidad_Final%20(2).pdf. Accessed 10 November 2020.
6. Prados-Torres A, Poblador-Plou B, Calderón-Larrañaga A, Gimeno-Feliu LA, González-Rubio F, Poncel-Falcó A, Sicras-Mainar A, Alcalá-Nalvaiz JT. Multimorbidity patterns in primary care: interactions among chronic diseases using factor analysis. PLoS One. 2012;7(2):e32190.
7. Ess SM, Herrmann C, Bouchardy C, Neyroud I, Rapiti E, Konzelmann I, Bordoni A, Ortelli L, Rohrmann S, Frick H, Mousavi M, Thürlimann B. Impact of subtypes and comorbidities on breast cancer relapse and survival in population-based studies. Breast. 2018 Oct;41:151-158.
8. Ng HS, Vitry A, Koczwara B, Roder D, McBRide ML. Patterns of comorbidities in women with breast cancer: a Canadian population-based study. Cancer Causes Control. 2019; 30: 931–941.
9. Ong W, Schouwenburg M, Annelotte CM, Van Bommel A, Caleb Stowell C, Kim H. Allison, Benn KE, Browne JP, Cooter RD, Delaney GP, Duhoux FP, Ganz PA, Hancock P, Jagsi R, Knaul FM, Knip AM, Koppert LB, Kuerer HM, McLaughin S, Mureau MAM, Partridge AH, Reid DP, Sheeran L, Smith TJ, Stoutjesdijk M, Jeanne M, Peeters V, Wengström Y, Yip CH, Saunders C. A Standard Set of Value-Based Patient-Centered Outcomes for Breast Cancer. Jama Oncology. Published online December 26, 2016. Available at: [https://www.europadonna.org/wp-

content/uploads/A-Standard-Set-of-Value-Based-Patient-C...utcomes-Measurement-ICHOM-Initiative.pdf]. Accessed May 2019.

10. Heo J, Chun M, Oh YT, Noh OK, Kim L. Metabolic comorbidities and medical institution utilization among breast cancer survivors: a national population-based study. Korean J Intern Med. 2020;35(2):421-428.
11. Vetrano DL, Roso-Llorach A, Fernández S, Guisado-Clavero M, Violan C, Onder G, Fratiglioni L, Calderon-Larrañaga A, Marengoni A. Twelve-year clinical trajectories of multimorbidity in a population of older adults. Nat Commun. 2020;11(1):3223.
12. Whitty CJM, MacEwen C, Goddard A, Alderson D, Marshall M, Calderwood C, Atherton F, McBride M, Atherton J, Stokes-Lampard H, Reid W, Powis S, Marx C. Rising to the challenge of multimorbidity. BMJ. 2020;368:l6964.
13. Crabtree BF, Miller WL, Howard J, Rubinstein EB, Tsui J, Hudson SV, O'Malley D, Ferrante JM, Stange KC. Cancer Survivorship Care Roles for Primary Care Physicians. Ann Fam Med. 2020;18(3):202-209.
14. Violán, C., Roso-Llorach, A., Foguet-Boreu, Q, Guisado-Clavero, M, Pons-Vigues M, Pujol-Ribera E. Multimorbidity patterns with K-means nonhierarchical cluster analysis. BMC Fam Pract 19, 108 (2018).
15. Giannoula A, Gutierrez-Sacristán A, Bravo Á, Sanz F, Furlong LI. Identifying temporal patterns in patient disease trajectories using dynamic time warping: A population-based study. Sci Rep. 2018;8(1):4216.
16. Jansana A, Del Cura I, Prados-Torres A, Sanz Cuesta T, Poblador-Plou B, Gimeno Miguel A, Lanzuela M, Ibañez B, Tamayo I, Moreno-Iribas C, Padilla-Ruiz M, Redondo M, Comas M, Domingo L, Diaz-Holgado A, Salamanca FJ, Castells X, Sala M. Use of real-world data to study health services utilisation and comorbidities in long-term breast cancer survivors (the SURBCAN study): study protocol for a longitudinal population-based cohort study. BMJ Open. 2020;10(9):e040253.
17. World Health Organization: ICD-10 International Statistical Classification of Diseases and Related Health Problems 10th Revision Version for 2010. http://apps.who.int/classifications/apps/icd/icd10online/ . Accessed 17 Feb 2020.
18. Okkes IM, Becker HW, Bernstein RM, Lamberts H. The march 2002 update of the electronic version of ICPC-2. A step forward to the use of ICD-10 as a nomenclature and a terminology for ICPC-2. Family Practice. 2002; 19(5):543-6.
19. Agency for Healthcare Research and Quality. Healthcare Cost and utilization Project. https://www.hcup-us.ahrq.gov/. Accessed 17 Feb 2020.
20. Recalde M, Manzano-Salgado CB, Díaz Y, Garcia-Gil MDM, Marcos-Gragera R, Ribes-Puig J. Validation of cancer diagnoses in electronic health records: results from the Information System for Research in Primary Care (SIDIAP) in Northeast Spain. Clin Epidemiol. 2019;11:1015-1024.

21. Zhang Z, Murtagh F, Van Poucke S, Lin S, Lan P. Hierarchical cluster analysis in clinical research with heterogeneous study population: highlighting its visualization with R. Ann Transl Med. 2017 Feb;5(4):75.
22. Schäfer I, Kaduszkiewicz H, Wagner, HO, Schön G, Scherer M, Van den Bussche H. Reducing complexity: a visualisation of multimorbidity by combining disease clusters and triads. BMC Public Health.2014; 14:1285.
23. Roy S, Vallepu S, Barrios C, Hunter K. Comparison of Comorbid Conditions Between Cancer Survivors and Age-Matched Patients Without Cancer. J Clin Med Res. 2018;10(12):911-919.
24. Derks MGM, van de Velde CJH, Giardiello D, Seynaeve C, Putter H, Nortier JWR, Dirix LY, Bastiaannet E, Portielje JEA, Liefers GJ. Impact of Comorbidities and Age on Cause-Specific Mortality in Postmenopausal Patients with Breast Cancer. Oncologist. 2019;24(7):e467-e474.
25. Khan NF, Mant D, Carpenter L, Forman D, Rose PW. Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. Br J Cancer. 2011 Nov 8;105 Suppl 1(Suppl 1):S29-37.
26. Álvarez-Salvago F, Galiano-Castillo N, Arroyo-Morales M, Cruz-Fernández M, Lozano-Lozano M, Cantarero-Villanueva I. Health status among long-term breast cancer survivors suffering from higher levels of fatigue: a cross-sectional study. Support Care Cancer. 2018 Oct;26(10):3649-3658.
27. Guisado-Clavero M, Roso-Llorach A, López-Jimenez T, Pons-Vigués M, Foguet-Boreu Q, Muñoz MA, Violán C. Multimorbidity patterns in the elderly: a prospective cohort study with cluster analysis. BMC Geriatr. 2018;18(1):16.
28. Violán C, Fernández-Bertolín S, Guisado-Clavero M, Foguet-Boreu Q, Valderas JM, Vidal Manzano J, Roso-Llorach A, Cabrera-Bean M. Five-year trajectories of multimorbidity patterns in an elderly Mediterranean population using Hidden Markov Models. Sci Rep. 2020;10(1):16879.
29. Atella V, Piano Mortari A, Kopinska J, Belotti F, Lapi F, Cricelli C, Fontana L. Trends in age-related disease burden and healthcare utilization. Aging Cell. 2019;18(1):e12861.
30. Jindai K, Nielson CM, Vorderstrasse BA, Quiñones AR. Multimorbidity and Functional Limitations Among Adults 65 or Older, NHANES 2005-2012. Prev Chronic Dis. 2016;13:E151.
31. Hughes LD, McMurdo ME, Guthrie B. Guidelines for people not for diseases: the challenges of applying UK clinical guidelines to people with multimorbidity. Age Ageing. 2013;42(1):62-9.
32. Derks MGM, Blok EJ, Seynaeve C, Nortier JWR, Kranenbarg EM, Liefers GJ, Putter H, Kroep JR, Rea D, Hasenburg A, Markopoulos C, Paridaens R, Smeets JBE, Dirix LY, van de Velde CJH. Adjuvant tamoxifen and exemestane in women with postmenopausal early breast cancer (TEAM): 10-year follow-up of a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2017;18(9):1211-1220.

33. Esposito K, Chiodini P, Capuano A, Bellastella G, Maiorino MI, Rafaniello C, Giugliano D. Metabolic syndrome and postmenopausal breast cancer: systematic review and meta-analysis. Menopause. 2013;20(12):1301-9.
34. Rachner TD, Coleman R, Hadji P, Hofbauer LC. Bone health during endocrine therapy for cancer. Lancet Diabetes Endocrinol. 2018;6(11):901-910.
35. Bowles EJ, Wellman R, Feigelson HS, Onitilo AA, Freedman AN, Delate T, Allen LA, Nekhlyudov L, Goddard KA, Davis RL, Habel LA, Yood MU, McCarty C, Magid DJ, Wagner EH; Pharmacovigilance Study Team. Risk of heart failure in breast cancer patients after anthracycline and trastuzumab treatment: a retrospective cohort study. J Natl Cancer Inst. 2012;104(17):1293-305.
36. Gulati M, Mulvagh SL. The connection between the breast and heart in a woman: Breast cancer and cardiovascular disease. Clin Cardiol. 2018;41(2):253-257.
37. Yu AF, Jones LW. Breast cancer treatment-associated cardiovascular toxicity and effects of exercise countermeasures. Cardiooncology. 2016;2:1. doi: 10.1186/s40959-016-0011-5.
38. Ghazi M, Roux C. Hormonal deprivation therapy-induced osteoporosis in postmenopausal women with breast cancer. Best Pract Res Clin Rheumatol. 2009;23(6):805-11.
39. Molina JR, Barton DL, Loprinzi CL. Chemotherapy-induced ovarian failure: manifestations and management. Drug Saf. 2005;28(5):401-16.
40. Formiga F, Chivite D, Manito N, Casas S, Llopis F, Pujol R. Hospitalization due to acute heart failure. Role of the precipitating factors. Int J Cardiol. 2007;21;120(2):237-41.
41. Gimeno-Miguel A, Gracia Gutiérrez A, Poblador-Plou B, Coscollar-Santaliestra C, Pérez-Calvo JI, Divo MJ, Calderón-Larrañaga A, Prados-Torres A, Ruiz-Laiglesia FJ. Multimorbidity patterns in patients with heart failure: an observational Spanish study based on electronic health records. BMJ Open. 2019 Dec 23;9(12):e033174.
42. Gurmankin Levy A, Maselko J, Bauer M, Richman L, Kubzansky L. Why do people with an anxiety disorder utilize more nonmental health care than those without? Health Psychol. 2007 Sep;26(5):545-53.
43. Kujanpää T, Jokelainen J, Auvinen J, Timonen M. Generalised anxiety disorder symptoms and utilisation of health care services. A cross-sectional study from the "Northern Finland 1966 Birth Cohort". Scand J Prim Health Care. 2016 Jun;34(2):151-8.
44. Donnelly K, Bracchi R, Hewitt J, Routledge PA, Carter B. Benzodiazepines, Z-drugs and the risk of hip fracture: A systematic review and meta-analysis. PLoS One. 2017;12(4):e0174730.
45. Kanyilmaz G, Aktan M, Koc M, Demir H, Demir LS. Radiation-induced hypothyroidism in patients with breast cancer: a retrospective analysis of 243 cases. Med Dosim. 2017;42(3):190-196.
46. Rubin G, Berendsen A, Crawford SM, Dommett R, Earle C, Emery J, Fahey T, Grassi L, Grunfeld E, Gupta S, Hamilton W, Hiom S, Hunter D, Lyratzopoulos G, Macleod U, Mason R, Mitchell G, Neal RD, Peake M, Roland M, Seifert B, Sisler J, Sussman J, Taplin S, Vedsted P, Voruganti T, Walter F, Wardle J, Watson E, Weller D, Wender R, Whelan J, Whitlock J, Wilkinson C, de Wit N,

Zimmermann C. The expanding role of primary care in cancer control. Lancet Oncol. 2015 Sep;16(12):1231-72.

47. Ibarra-Castillo C, Guisado-Clavero M, Violan-Fors C, Pons-Vigués M, López-Jiménez T, Roso-Llorach A. Survival in relation to multimorbidity patterns in older adults in primary care in Barcelona, Spain (2010-2014): a longitudinal study based on electronic health records. J Epidemiol Community Health. 2018;72(3):185-192.

Declarations

Authors' contributions

MS, AJ, LD, MC, BP, APT, AG made substantial contributions to the design and conception of the study. AD, TS, IDC took responsibility for the data acquisition of the Madrid sub-cohort, BP, AG, ML for the Aragon sub-cohort, MP, MCM, CM, MR for the Costa del Sol sub-cohort, BI, IT, JG, JB, CM, RB for the Navarre sub-cohort and MS, AJ, JL, TDS, MC, LD, MA for the Hospital del Mar sub-cohort. AJ took responsibility for data analysis, interpretation and drafting the article.

MS, LD, MC, BP, APT, AG, IDC, BI, TDS, XC, MR, MR provided advice for the study design, critical interpretation of the study, and gave final approval of the version to be published. All of the authors have read and approved the manuscript.

Compliance with Ethical Standards:

Disclosure of potential conflicts of interest: None to declare

Ethics approval: This article does not contain any studies with human participants or animals performed by any of the authors. This project was accepted by the Clinical Research Ethics Committee of Parc de Salut Mar (nº2016/6835/I), Clinical Research Ethics Committee of Hospital Costa del Sol (002-Sept17-PI-Surcan), Clinical Research Ethics Committee of Navarrabiomed (Pyto2017/75), Clinical Research Ethics Committee of Idiap Jordi Gol (P17/222), Clinical Research Ethics Committee of Aragón (05/2017).

Informed consent: For this type of study formal consent is not required.

Data Availability Statement: Further details of the data analyzed in this work are available from the corresponding author on request.

Funding

This work was supported by Carlos III Health Institute [PI16/00244] and [PI19/00056] and by FEDER (European Regional Development Fund/European Social Fund), and by the Research Network on Health Services in Chronic Diseases [RD16/0001/0013].

Acknowledgments

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The authors acknowledge the dedication and support of the SURBCAN Study Group (alphabetical order): IMIM (Hospital del Mar Medical Research Institute), Barcelona: Mercè Abizanda, Xavier Castells, Mercè Comas, Laia Domingo, Talita Duarte, Anna Jansana, Javier Louro, Anna Renom, María Sala. Hospital Costa del Sol, University of Malaga: María del Carmen Martínez, Cristóbal Molina, María del Carmen Padilla, Maximino Redondo. Grupo EpiChron de Investigación en Enfermedades Crónicas, del Instituto Aragonés de Ciencias de la Salud, Aragón: Antonio Gimeno-Miguel Manuela Lanzuela, Beatriz Poblador-Plou, Alexandra Prados-Torres. Primary Care Research Unit. Gerencia de Atención Primaria, Hospital Universitario 12 de Octubre, Madrid: Ángel Alberquilla, Isabel del Cura, Antonio Díaz, Teresa Sanz, Guillermo Pérez, Ana María Muñoz, Francisco Javier Salamanca, Óscar Toldos. Grupo de investigación en servicios sanitarios y cronicidad de la Fundación Miguel Servet, Navarra: Javier Baquedano, Rossana Burgui, Javier Gorricho, Berta Ibáñez, Conchi Moreno, Ibai Tamayo.

Figure legends

Figure 1.

aHR: adjusted hazard ratio for age, tumor behavior, primary and hospital care contacts and Charlson index. CI: confidence interval. MSK: musculoskeletal.
Mortality was assessed through vital status at the end of follow-up (31st December 2016).
*BCS without comorbidities were defined as those BCS without CD from the Clinical Classification software list and those without any comorbidity reported in the EHR.