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Multimorbidity patterns of chronic conditions and geriatric syndromes in older patients from the MoPIM multicentre cohort study.

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3 1 **MULTIMORBIDITY PATTERNS OF CHRONIC CONDITIONS AND GERIATRIC**
4 **SYNDROMES IN OLDER PATIENTS FROM THE MoPIM MULTICENTRE**
5 **2**
6 **3**
7 **COHORT STUDY.**

8
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3 31 **ABSTRACT**
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6 32 **Objectives:** To estimate the frequency of chronic conditions and geriatric
7
8 33 syndromes in older patients admitted to hospital because of an exacerbation of
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10 34 their chronic conditions, and to identify multimorbidity clusters in these patients.
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14 35 **Design:** Multicentre, prospective cohort study.
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17 36 **Setting:** Internal medicine or geriatric services of five general teaching hospitals
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19 37 in Spain.
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22 38 **Participants:** 740 patients aged 65 and older, hospitalized because of an
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24 39 exacerbation of their chronic conditions between September 2016 and December
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26 40 2018.
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30 41 **Primary and secondary outcome measures:** Active chronic conditions and
31
32 42 geriatric syndromes (including risk factors) of the patient, a score about clinical
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34 43 management of chronic conditions during admission, and destination at
35
36 44 discharge were collected, among other variables. Multimorbidity patterns were
37
38 45 identified using fuzzy c-means cluster analysis, taking into account the clinical
39
40 46 management score. Prevalence, observed/expected ratio and exclusivity of each
41
42 47 chronic condition and geriatric syndrome were calculated for each cluster, and
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44 48 the final solution was approved after clinical revision and discussion among the
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46 49 research team.
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49
50 50 **Results:** 740 patients were included (mean age 84.12 years, SD 7.01; 53.24%
51
52 51 female). Almost all patients had two or more chronic conditions (98.65%; 95%CI
53
54 52 98.23-99.07), the most frequent were hypertension (81.49%, 95%CI 78.53-84.12)
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56 53 and heart failure (59.86%, 95%CI 56.29-63.34). The most prevalent geriatric
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3 54 syndrome was polypharmacy (79.86%, 95%CI 76.82-82.60). Four statistically
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5 55 and clinically significant multimorbidity clusters were identified: osteoarticular,
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7 56 psychogeriatric, cardiorespiratory and minor chronic disease. Patient level
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9 57 variables such as sex, Barthel Index, number of chronic conditions or geriatric
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11 58 syndromes, chronic disease exacerbation 3 months prior to admission or
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13 59 destination at discharge differed between clusters.
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17
18 **Conclusions:** In older patients admitted to hospital because of the exacerbation
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20 61 of chronic health problems, it is possible to define multimorbidity clusters using
21
22 62 soft clustering techniques. These clusters are clinically relevant and could be the
23
24 63 basis to reorganize healthcare circuits or processes to tackle the increasing
25
26 64 number of older, multimorbid patients.
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31 65 **Trial registration number** NCT02830425, 12th July 2016
32
33

34 66 **Keywords:** Multimorbidity, patterns, soft clustering, older, chronic conditions,
35
36 67 geriatric syndromes.
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39 68 **Strengths and limitations of this study**

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41
42 69 - The multimorbidity analysis in this study has been developed from a
43
44 70 patient-centred point of view, considering a wide range of long-term
45
46 71 conditions that may require healthcare in older people.
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48 72 - To the best of our knowledge, this is the first published study of
49
50 73 multimorbidity clusters in older patients to include chronic diseases
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52 74 weighted by a clinical management score and geriatric syndromes.
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54 75 - Soft clustering is an innovative, methodologically robust technique that can
55
56 76 lead to reliable results in the field of multimorbidity analysis.
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3 77 - The list of chronic conditions and geriatric syndromes used in this study is
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5 78 comprehensive but not standardized, thus hindering comparability with
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7 79 other studies.
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10 **BACKGROUND**

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14 81 According to the most recent Eurostat baseline population projections, old-age
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16 82 dependency ratio (population 65y and over divided by population 15-64y) is about
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18 83 32% in the European Union (EU) and it is expected to reach 52% in 2050,
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21 84 meaning that the EU's population will continue to grow older[1]. Together with
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23 85 the fact that chronic conditions (CC) are the main cause of disability and mortality
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25 86 in Europe, this implies that the coexistence of two or more chronic health
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27 87 conditions, which constitutes the classic definition of multimorbidity, is becoming
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30 88 increasingly common[2].
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34 89 Multimorbidity is therefore turning into an important challenge for the health
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36 90 system because of the expanding proportion of older people with multiple CC and
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38 91 treatments as well as the difficulties associated with their clinical
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40 92 management[3,4]. Most clinical practice guidelines are focused on single
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42 93 diseases, with limited recommendations for multimorbid patients[5], and, in
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44 94 addition, randomized clinical trials often exclude older patients with
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46 95 multimorbidity[6]. Despite the importance of multimorbidity in clinical practice,
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48 96 different methodological approaches are still under debate and there is no gold
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50 97 standard, which makes it difficult to compare different estimations around the
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52 98 world[7–9].
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57 99 One of the novel, increasingly widespread definitions of multimorbidity considers
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59 100 the non-spurious association of certain CC by sharing pathophysiological

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3 101 mechanisms, giving rise to disease association patterns or clusters[10]. Other
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5 102 clinically relevant situations such as geriatric syndromes (GS) may also be
6
7 103 considered in the definition of these patterns, since they might have a great
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9 104 impact on the health-related quality of life and clinical management of old
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11 105 patients[11]. In fact, the purpose of multimorbidity characterization (i.e., predicting
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13 106 outcomes or use of health services, improving quality of care, organizing
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15 107 healthcare services, etc.), will have an influence on its definition. From a patient-
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17 108 centred point of view, a global consideration of all conditions that may require
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19 109 healthcare attention is necessary, even if they are not the reason for
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21 110 hospitalization. Along these lines, some countries have explicitly recommended
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23 111 to acknowledge all long-term conditions for optimising care of adult patients by
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25 112 reducing, for example, possible inappropriate treatments, multiple healthcare
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27 113 appointments or poor health-related quality of life[12–14].
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34 114 During the past decade, there has been an increasing amount of publications that
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36 115 consider multimorbidity[15], but few have focused on multimorbidity patterns in
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38 116 older patients and even fewer take into account GS[16]. For this reason, we
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40 117 launched a multicentre study in 2016 with multiple aims related to multimorbidity,
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42 118 appropriateness of chronic treatments and adverse drug reactions in older
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44 119 patients[17]. The objectives of the present analyses were to estimate the
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46 120 frequency of CC and GS in older patients admitted to hospital because of an
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48 121 exacerbation of their CC, and to identify possible multimorbidity patterns in these
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50 122 patients.
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55 123 **METHODS**

56 124 **Design and setting**

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3 125 A multicentre, prospective cohort study including older patients hospitalized at
4
5 126 the internal medicine or geriatric services at five general teaching hospitals in
6
7 127 three different regions of Spain between September 2016 and December 2018
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9 128 was designed. The detailed protocol was previously published[17].
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13 129 For the purposes of the study, older patients (≥ 65 years old) admitted as a result
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15 130 of the exacerbation of their chronic pathology were included. Patients referred to
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17 131 home hospitalization, admitted because of an acute process not related to any
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19 132 chronic disease, or with a fatal outcome expected at the time of admission were
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21 133 not included.
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26 134 No written informed consent was deemed necessary for this study.
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29 135 **Data acquisition and variables**

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32 136 The following sociodemographic and clinical data was retrieved by the clinical
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34 137 team responsible for the patient: patient's code, date of birth, sex, functional
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36 138 status just before entering the hospital (Barthel index)[18], household (alone, with
37
38 139 relatives or other people, in a nursing home), existence of any contact with
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40 140 healthcare services (primary care, emergencies, hospital admission, outpatient
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42 141 care, home care) in the 3 months prior to hospitalization due to exacerbation of
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44 142 any chronic disease, and destination at discharge from the present episode of
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46 143 hospitalization (home, transfer to another hospital, transfer to a nursing home,
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48 144 *exitus*).
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54 145 Active CC of the patient at arrival to hospital, including some risk factors, were
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56 146 collected (see Supplemental Table 1). For this purpose, the physicians of the
57
58 147 project defined, on a consensual basis, a limited list of 64 CC, coming from the
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3 148 114 groups defined by Salisbury and colleagues[19] and including the 19
4
5 149 categories of the Charlson Index[20]. Following the same criteria as Salisbury, a
6
7 150 condition was considered to be chronic when it lasted for at least 6 months,
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9 151 including past conditions that require ongoing disease or risk management,
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11 152 important conditions with a significant risk of recurrence, or past conditions that
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13 153 have continuing implications for patient management[19]. Drug-related conditions
14
15 154 of this list refer to poor management of medication related to a chronic disease
16
17 155 that has clinical implications in that hospitalization (such as any drug intolerance
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19 156 or an excess drug poisoning).

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24 157 Additionally, for each of the CC, it was also recorded if they had required clinical
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26 158 management (both at admission and during hospitalization) by assigning a
27
28 159 (subjective) correlative score (CM=1, 2, 3...) to each one, according to their
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30 160 clinical importance during the attention process. Thus, CC that did not have any
31
32 161 significance during hospitalization, although recorded, had a score equal to zero.

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37 162 Specific GS and risk factors (acute confusional syndrome/delirium, chronic pain,
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39 163 cognitive/intellectual impairment, constipation, depression or anxiety, dysphagia,
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41 164 frailty, immobility, incontinence (urinary/faecal), instability/falls, malnutrition,
42
43 165 polypharmacy, pressure ulcers, sensorial deficit, sleep disorders/insomnia) were
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45 166 also recorded. Two of the departments systematically apply a recently developed
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47 167 scale for frailty [21], while the others consider clinical judgement (although based
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49 168 on the same variables).

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54 169 In order to address potential sources of bias, a pilot study was conducted with
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56 170 the first 10 admissions per centre to validate the data collection process and
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58 171 identify problems that could arise. After that, proper changes were made in the
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3 172 protocol and questionnaire. All available information sources were consulted in
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5 173 order to register CC and GS, and the defined list was not closed. Nonetheless,
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7 174 the registration of CC and GS was based on clinical criteria.
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10 175 **Sampling and analysis**

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14 176 A consecutive sample of 740 patients meeting the inclusion criteria were
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16 177 included, proportionally distributed to the annual volume of hospitalizations of the
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18 178 medicine and/or geriatric services of each centre. The estimated sample of 800
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20 179 patients (see protocol[17]) could not be reached due to organizational reasons in
21
22 180 one of the participating centres.
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26 181 For the purposes of the analyses, some CC were grouped according to clinical
27
28 182 criteria: Hemiplegia was included in cerebrovascular disease; metastatic solid
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30 183 tumour, leukaemia, lymphoma and any malignancy were grouped into
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32 184 'neoplasia'; hepatitis B and C were included in mild liver disease, and both
33
34 185 congestive and non-congestive heart failure were grouped into 'heart failure'.
35
36 186 Other diseases were finally excluded of the analyses considering that they have
37
38 187 no impact on acute healthcare (cataract, dermatitis, diverticular disease of the
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40 188 colon, glaucoma, haemorrhoids, other vascular diseases and prostatic benign
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42 189 hypertrophy). In the end, 51 CC and 15 GS were analysed.
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48 190 The updated Charlson Comorbidity Index[22], age adjusted, was computed and
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50 191 categorized according to tertiles distribution.
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53 192 Descriptive statistics were performed to assess patient clinical and
54
55 193 sociodemographic characteristics and to obtain overall prevalence estimates of
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57 194 CC and GS, stratified by sex. Multimorbidity was firstly defined as the presence
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3 195 of two or more CC. Cumulative number of CC and GS per patient were computed,
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5 196 respectively.

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8 197 *Multimorbidity patterns*

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11 198 CC or GS with a prevalence <2% were excluded to avoid statistical noise and
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13 199 therefore spurious findings in the cluster solutions, leaving a list of 40 CC and 15
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15 200 GS. In order to take into account if a CC had required clinical management (CM),
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17 201 a ratio variable (R) was computed as follows:

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22 202 If $CC=0$ & $CM=0 \rightarrow R=0$

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25 203 If $CC=1$ & $CM=m \rightarrow R=1/m$; $\max(m) = \max(\text{value}(CM)) = 8$;

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27
28 204 If $CC=1$ & $CM=0 \rightarrow R=0.1$

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31 205 All patients were included, without regard to having multimorbidity, so as to obtain
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33 206 clusters that were more representative. Data for the analysis comprised the ratio
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35 207 (R) and syndrome (GS) variables.

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39 208 Multimorbidity patterns were identified using the fuzzy c-means cluster analysis
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41 209 algorithm, which belongs to the family of *soft* clustering algorithms. The algorithm
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43 210 estimates c cluster centres (similar to k -means) but with fuzziness so that
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45 211 individuals may belong to more than one pattern. Through this technique, we
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47 212 obtained clusters of individuals and a membership matrix, which indicates the
48
49 213 degree of participation of each subject in each cluster.

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53 214 As a first step, and similarly to Violán *et. al.*[23], the PCAmix algorithm for
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55 215 categorical (GS) and continuous data (R) was implemented to reduce and
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57 216 transform the dataset to all continuous data[24]. To decide the number of retained
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3 217 dimensions, the Karlis-Saporta-Spinaki rule was used[25]. Then, a soft clustering
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5 218 algorithm was applied to fuzzily distribute the population into a set of clusters,
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7 219 corresponding to the different multimorbidity patterns. We computed three
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9 220 validation indices to obtain the optimal number of clusters (K) and the optimal
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11 221 value of the fuzziness parameter (m): the partition coefficient whose optimal
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13 222 choice for coefficient is at the maximum, and the Xie-Beni and the partition
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15 223 entropy validation indices, whose optimal indices are at the minimum[26].
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17 224 Considering the stochastic nature of the clusters, and the requirement of stable
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19 225 multimorbidity clusters, 100 independent clustering repetitions were applied to
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21 226 obtain the stable final solution.
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27 227 To characterize the multimorbidity patterns corresponding to each cluster of
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29 228 individuals, the prevalence of CC and GS in each cluster was calculated.
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31 229 Observed/expected (O/E) ratios were calculated by dividing the prevalence of a
32
33 230 given disease within a cluster by its prevalence in the overall population. The
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35 231 exclusivity of CC and GS, defined as the fraction of patients with the disease in
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37 232 the cluster over the total number of patients with the disease, was also calculated.
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41 233 A disease or a syndrome was considered to be relevant in a given cluster of
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43 234 individuals when its O/E ratio was >1 and its exclusivity was $>25\%$ [27–29]. The
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45 235 statistical significant final solution ranged from 4 to 8 clusters. After clinical
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47 236 revision and discussion among the research team, 4 different clusters were
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49 237 considered to make clinical sense according to the objective of the clustering.
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52 238 There is currently no consensus in the literature on the criteria used to select the
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54 239 number of clusters or the O/E ratio cut-off point due to, in part, the novelty of the
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56 240 analysis.
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241 Finally, sociodemographic and clinical variables were described for all patients
 242 assigned to each cluster. Analyses were performed using R 3.6.0 and SPSS 22.

243 Patient and Public Involvement

244 Since this was an observational study with variables and outcomes related to the
 245 healthcare process, this research was developed without patient involvement.
 246 Patients were not invited to comment on the study design and were not consulted
 247 to develop patient relevant outcomes or interpret the results.

248 RESULTS

249 740 patients aged 65 years or older were included, with a mean age of 84.12
 250 years (SD 7.01), a 53.24% of females and a mean Barthel Index of 65.07 (median
 251 75). Sociodemographic and clinical variables are summarised in Table 1. Almost
 252 all patients had two or more CC (98.65%; 95%CI 98.23-99.07), with a median of
 253 8 CC and 6 GS per patient. Nearly 70% had consulted a health care service in
 254 the 3 months prior to hospitalization due to chronic disease exacerbation.

255 Table 1. Sociodemographic and clinical variables of the studied cohort.

Sociodemographic and clinical variables		N	%	95% CI
Age	< 70	33	4.46	3.19 - 6.20
	70-74	48	6.49	4.93 - 8.50
	75-79	82	11.08	9.02 - 13.55
	80-84	181	24.46	21.50 - 27.68
	85-89	232	31.35	28.11 - 34.78
	90-94	134	18.11	15.50 - 21.05
	>= 95	30	4.05	2.85 - 5.73
Sex	Female	394	53.24	49.64 - 56.81
	Male	346	46.76	43.19 - 50.36
Barthel index	< 20	90	12.16	10.00 - 14.71
	20-35	76	10.27	8.28 - 12.67
	40-55	124	16.76	14.24 - 19.62
	60-95	294	39.73	36.27 - 43.30
	100	156	21.08	18.30 - 24.17
Age adjusted, updated Charlson	2-5	148	20.00	17.28 - 23.03

Sociodemographic and clinical variables		N	%	95% CI
Comorbidity Index	6-8	411	55.54	51.94 - 59.08
	9-14	181	24.46	21.50 - 27.68
Household	With relatives/other people	523	70.68	67.30 - 73.84
	Nursing home	95	12.84	10.62 - 15.44
	Alone	122	16.49	13.99 - 19.33
Chronic disease exacerbation 3 months prior to admission	No	225	30.41	27.20 - 33.81
	Yes (total)	515	69.59	66.19 - 72.80
	Primary care	342	46.22	42.65 - 49.82
	Emergencies	263	35.54	32.17 - 39.06
	Hospital admission	193	26.08	23.05 - 29.36
	Outpatient care	8	1.08	0.55 - 2.12
Destination at discharge	Home	468	63.24	59.71 - 66.64
	Nursing home	105	14.19	11.86 - 16.89
	Another hospital	101	13.65	11.36 - 16.31
	Exitus	66	8.92	7.07 - 11.19
Multimorbidity	No	10	1.35	1.35 - 1.36
	Yes	730	98.65	98.23 - 99.07

256 CI = Confidence interval

257 Figure 1 shows the distribution of the number of CC by age groups. The most
 258 frequent CC were hypertension (81.49%, 95%CI 78.53-84.12) and heart failure
 259 (59.86%, 95%CI 56.29-63.34) (see Supplemental Table 2). Heart failure was also
 260 the main cause of hospitalization (30.7% of patients had CM score=1), followed
 261 by COPD (20.7%) (Supplemental Table 3).

262 There were some differences in CC between sexes, with females having more
 263 frequently heart failure, degenerative arthropathy, obesity, hip fracture, thyroid
 264 disease, asthma, osteoporosis, vertigo and non-schizophrenic mental disorders.
 265 Males, in turn, had more frequently COPD, gout, neoplasia, peripheral
 266 arteriopathy and ulcerative disease.

267 The most prevalent GS was polypharmacy (79.86%, 95%CI 76.82-82.60),
 268 followed by frailty (61.76%, 95%CI 58.20-65.19). Females had a significantly
 269 higher number of GS compared to males (Wilcoxon rank sum test, $p < 0.001$), as

270 well as a higher prevalence of depression/anxiety, chronic pain, constipation,
271 frailty, urinary/faecal incontinence and immobility.

272 Four statistically and clinically significant multimorbidity clusters or patterns were
273 identified in our study population. For all clusters, CC and GS with an
274 observed/expected ratio >1 and exclusivity >25% are represented in Figure 2
275 (see also Supplemental Table 4). Sociodemographic and clinical characteristics
276 of patients in each cluster are described in Table 2.

277 Table 2. Sociodemographic and clinical variables of the multimorbidity clusters.

		Osteoarticular	Psycho-geriatric	Minor chronic conditions	Cardio-respiratory
Number of patients included, n (%)		132 (17.8)	153 (20.7)	179 (24.2)	276 (37.3)
Age at admission (y, mean \pm SD)		84.03 \pm 6.48	84.51 \pm 7.25	83.94 \pm 7.19	84.06 \pm 7.03
Sex, n (%)	Male	34 (25.7)	66 (42.8)	99 (55.5)	147 (53.4)
	Female	98 (74.3)	87 (57.2)	80 (44.5)	129 (46.6)
Barthel Index (mean \pm SD)		63.06 \pm 24.78	47.62 \pm 34.94	64.96 \pm 33.56	75.76 \pm 27.52
Total n° chronic conditions (mean \pm SD)		11.5 \pm 3.64	7.68 \pm 3.19	8.86 \pm 3.08	7.59 \pm 2.61
Total n° geriatric syndromes / risk factors (mean \pm SD)		7.76 \pm 2.07	8.16 \pm 2.82	6.4 \pm 3.32	4.42 \pm 2
Charlson Comorbidity Index, n (%)	2-5	26 (19.9)	24 (15.6)	37 (20.4)	61 (22.2)
	6-8	73 (55.1)	89 (58.5)	96 (53.8)	153 (55.3)
	9-14	33 (25.0)	40 (25.9)	46 (25.7)	62 (22.6)
Household, n (%)	With relatives / other people	91 (68.7)	103 (67.2)	133 (74.5)	196 (71.1)
	Nursing home	16 (11.8)	28 (18.4)	23 (12.8)	28 (10.3)
	Alone	26 (19.5)	22 (14.3)	23 (12.7)	52 (18.7)
Chronic disease exacerbation 3 months prior to the index admission, n (%)	No	24 (18.3)	46 (30.1)	48 (27.0)	106 (38.5)
	Yes (total)	108 (81.7)	107 (69.9)	130 (73.0)	170 (61.5)
	Primary care	83 (62.7)	66 (43.3)	92 (51.6)	101 (36.5)
	Emergencies	71 (53.6)	40 (26.2)	69 (38.5)	83 (30.2)
	Hospital admission	49 (37.1)	46 (30.1)	47 (26.1)	51 (18.6)
	Outpatient care	1 (0.7)	0 (0.3)	3 (1.4)	4 (1.4)
Destination at discharge, n (%)	Home	86 (65.3)	83 (54.0)	111 (62.0)	188 (68.1)
	Nursing home	15 (11.1)	33 (21.3)	26 (14.5)	32 (11.5)
	Another hospital	15 (11.3)	17 (11.3)	26 (14.7)	42 (15.3)
	Exitus	16 (12.3)	20 (13.3)	16 (8.8)	14 (4.9)

278 SD = standard deviation.

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3 279 The first cluster, named *osteoarticular*, included 132 patients (17.8%) having
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5 280 osteoporosis, fractures, inflammatory osteoarticular disease, chronic pain and
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7 281 degenerative arthropathy. Moreover, vertigo, sleep apnoea, asthma,
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10 282 depression/anxiety and sleep disorders were also over-represented. This cluster
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12 283 included patients with the highest number of both CC and GS. About three
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14 284 quarters were female, and most of them (82%) accessed healthcare services 3
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17 285 months prior to this admission.

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20 286 Cluster 2, called *psychogeriatric*, had 152 patients (20.7%) and included mostly
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22 287 GS: pressure ulcers, immobility, malnutrition, cognitive impairment, dementia,
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24 288 incontinence and frailty. Patients in this group had a mean Barthel index lower
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27 289 than 50 and a high number of GS. Furthermore, nearly 20% of them were living
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29 290 in a nursing home and in-hospital mortality was about 13%.

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32 291 Cluster 3, named *minor chronic disease*, had 179 (24.2%) patients, and
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34 292 represents a group of patients with a variety of conditions, such as hypertension,
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36 293 dyslipidaemia, anaemia, gout, chronic renal insufficiency, polypharmacy, non-
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38 294 ischaemic heart disease, and diverse GS. O/E ratios were close to 1 in most
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41 295 cases.

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44 296 Finally, cluster 4, called *cardiorespiratory*, included 276 (37.3%) patients. The
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46 297 over-represented diagnoses were COPD, heart failure and cardiac arrhythmia,
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48 298 although the O/E ratios were very low. In this cluster, with the lowest number of
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51 299 CC and GS, and a Barthel index greater than 75, nearly 40% had no healthcare
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53 300 consultation for a chronic disease exacerbation in the previous 3 months. This
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56 301 group had the lowest in-hospital mortality (5%).

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59 302 **DISCUSSION**
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3 303 The present study aimed to identify multimorbidity patterns in patients aged 65
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5 304 and above admitted to hospital because of an exacerbation of CC. The soft
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7 305 clustering technique used, together with clinical criteria, was able to identify 4
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9 306 different multimorbidity patterns, named osteoarticular, psychogeriatric, cardio-
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11 307 respiratory and minor chronic disease, in a patient-centred approach taking into
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13 308 account the importance of each disease in hospital management. Remarkably,
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15 309 high chronic multimorbidity was found in all patients, regardless of the cluster. To
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17 310 the best of our knowledge, this is the only study published to date that has
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19 311 analysed multimorbidity patterns taking into account both CC (with their weight
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21 312 during clinical management) and GS in this type of patients. Hence, these
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23 313 identified patterns allow us to take a further step towards understanding the
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25 314 patients' current or future healthcare needs.

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31 315 All clusters contain groups of conditions that make sense and are mostly
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33 316 pathophysiologically related. From the clinical point of view, these clusters
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35 317 resemble patient profiles that are intuitively perceived. Moreover, some
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37 318 descriptive variables such as sex, Barthel index, mean number of CC or GS,
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39 319 chronic pathology exacerbations in previous months, or hospital mortality, are
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41 320 distributed in such a way that they may reinforce the distinction of these groups.

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46 321 Coexistence of CC and GS was observed in all clusters except for the
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48 322 cardiorespiratory, reinforcing the need to consider other clinically relevant
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50 323 situations rather than only CC. In particular, the exclusivity and prevalence of GS
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52 324 such as immobility, malnutrition, cognitive impairment or dementia were
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54 325 considerable in the psychogeriatric cluster.

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3 326 Interestingly, highly prevalent CC, such as heart failure and COPD, which also
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5 327 frequently involve clinical management, only showed remarkable exclusivity and
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7 328 O/E ratio in the cardiorespiratory pattern and were not over-represented
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10 329 elsewhere. This highlights the fact that even though some CC may not be over-
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12 330 represented in a cluster, they can have a high prevalence and therefore need to
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14 331 be properly addressed too.

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18 332 With respect to the osteoarticular cluster, it displayed a pattern of female
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20 333 predominance, with many CC and GS, high healthcare needs in recent months
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22 334 due to their chronic pathology, and high in-hospital mortality. Thus, this profile
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24 335 would identify a group of patients with a high probability of decompensation and
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26 336 death.

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30 337 Finally, the so-called minor chronic diseases cluster was not very well defined. It
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32 338 included some risk factors (hypertension, dyslipidaemia, polypharmacy) as well
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34 339 as some CC and GS. Thus, it would be possible that it does not represent a real
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36 340 cluster but either the set of cases that did not belong anywhere else.

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40 341 It should be noted that the type of analysis, the purpose for designing these
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42 342 patterns and also their interpretation could all lead to different results or
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44 343 conclusions. For instance, our aim in defining multimorbidity patterns in this
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46 344 cohort was to identify profiles of patients with similar needs and even a similar
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48 345 short-term prognosis at that time. For this reason, the importance of their
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50 346 pathologies in the course of hospitalization was taken into account. Hence, the
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52 347 ones that tend to have a minimal impact on clinical management, such as risk
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54 348 factors like hypertension or dyslipidaemia did not have a leading role in the
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56 349 patterns.
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350 Comparison with other studies

351 Given the type of patients under study and the methodological approach to
352 identify multimorbidity patterns, there are few publications to directly compare our
353 results to. Clerencia-Sierra and colleagues[16] analysed multimorbidity patterns
354 in hospitalized older patients. Their methodological and analytical approach was
355 slightly different, and they did not take into account the weight of the diseases
356 during the hospitalization process; however, they found a similar percentage of
357 multimorbidity (99.7%) and 4 patterns that partially coincide with those of our
358 study: cardiovascular, induced-dependency, falls, and osteoarticular.

359 Furthermore, several authors have published data on patterns identified from
360 primary care electronic records in different age groups, with lists of non-
361 comparable chronic problems and using different techniques (cluster analysis,
362 exploratory factor analysis or latent class analysis)[16,28–33]. These results
363 would not be directly comparable with our study, but all of them highlight the
364 ability to identify association patterns of chronic diseases.

365 Strengths and limitations

366 The strengths of this study are the prospective design, ensuring data quality by
367 thorough record keeping, the ascertainment of all CC and GS of the patient, as
368 well as the use of a novel clustering technique. Soft clustering is a
369 methodologically robust technique less susceptible to outliers in the data, choice
370 of distance measure and the inclusion of inappropriate or irrelevant variables[23].
371 Besides, our approach focuses on the patient instead of the pathologies, using a
372 comprehensive list of conditions that includes both CC and GS, and determining
373 a probability of belonging to each cluster. Additionally, we have taken into account

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3 374 the relative importance of the different CC in the clinical management of the
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5 375 patient during hospitalization, thus providing a better picture of the possible
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7 376 complexity and needs during hospitalization.
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11 377 Furthermore, our work is not only limited to the identification of possible patterns.
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13 378 We have validated them, in some way, by analysing some of the patients'
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15 379 variables such as sex, number of CC, previous contacts with the health system,
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17 380 hospital mortality or need for a nursing home.
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21 381 Nonetheless, our study presents some limitations that need to be considered.
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23 382 Firstly, the identification of chronic pathologies does not exclusively follow a
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25 383 validated list of codes but either an adaptation of different ones, a fact that could
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27 384 hinder comparability with other studies on multimorbidity. Secondly, as this study
28
29 385 is not longitudinal, the chronology in which CC or GS appear cannot be analysed.
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31 386 It is possible for a patient to evolve from one pattern to another throughout life,
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33 387 as some authors have already pointed out[34], and therefore, the results only
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35 388 show the present situation. However, given the purpose of the defined patterns,
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37 389 this would not in itself be a limitation.
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42 390 The clinical conditions severity or other possible aggravating factors have neither
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44 391 been taken into account. Nevertheless, the registration of a variable that takes
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46 392 into account the relevance of each CC during the care process acts, in some way,
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48 393 as an indirect indicator of complexity when dealing with patients admitted
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50 394 because of decompensation.
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54 395 Clinical implications

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57 396 These patterns are not a picture of the community but of older patients in geriatric
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59 397 or internal medicine departments, which are generally in more need of health
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3 398 services and more complex clinical management. However, not all of these
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5 399 patients have the same requirements. In fact, one in five patients (the
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7 400 psychogeriatric cluster) caused a great burden to both the patient and their
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9 401 relatives while the patients in the most frequent cluster (cardiorespiratory), with
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11 402 lower dependency and less GS, seemed to have better immediate outcome.
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14 403 Therefore, it is possible that the therapeutic objectives should be different in these
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16 404 patients. More importantly, the ability to distinguish patients more objectively than
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18 405 with the mere clinical impression may allow the design of better processes,
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20 406 services or alternatives to conventional hospitalization. In addition, some patterns
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22 407 may include patients with an increased risk of potentially inappropriate
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24 408 prescription or adverse drug reactions. These aspects will be the object of future
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26 409 analyses.

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31 410 Finally, the development of clinical practice guidelines according to these
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33 411 patterns needs to be considered, although it may be difficult given the magnitude
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35 412 of the diseases comprised in each pattern [4,13]

36 37 38 39 413 **Conclusions**

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42 414 In conclusion, in older patients admitted to hospital because of the exacerbation
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44 415 of chronic health problems, it is possible to define multimorbidity clusters or
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46 416 patterns using appropriate statistical techniques. These patterns make clinical
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48 417 sense and could be the basis to reorganize circuits, processes or healthcare
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50 418 models to tackle the increasing number of older, multimorbid patients.

51 52 53 54 419 **List of abbreviations**

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58 420 CC: chronic condition
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3 421 GS: geriatric syndrome
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6 422 CM: clinical management
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9 423 O/E: observed/expected
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12 424 COPD: chronic obstructive pulmonary disease
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15 425 **Figure captions**
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18 426 Figure 1. Distribution of the number of chronic conditions (excluding the following
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20 427 risk factors: hypertension, dyslipidaemia, obesity, osteoporosis and drug-related
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22 428 conditions) in relation to age groups.
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26 429 Figure 2. Observed/Expected (O/E) ratio and prevalence of chronic conditions
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28 430 and geriatric syndromes/risk factors per multimorbidity cluster. Conditions with
29
30 431 exclusivity >25% and O/E ratios >1 in each cluster are represented. Conditions
31
32 432 are ordered by O/E ratio and from cluster 1 to 4. *COPD: Chronic Obstructive*
33
34 433 *Pulmonary Disease*
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38
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53
54 440 **Competing interests**
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56
57 441 The authors declare that they have no competing interests.
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3 442 **Data sharing statement**
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6 443 The datasets used and/or analysed during the current study are available from
7
8 444 the corresponding author upon reasonable request.
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11 445 **Authors' contributions**
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14 446 MB conceived and supervised the study, discussed the results, wrote the first
15
16 447 version of the manuscript. SH, RJ, EdJ, RE and CM participated in patient
17
18 448 inclusion, data collection and discussion of the results and revised the
19
20 449 manuscript. AR executed the analysis and interpretation of multimorbidity
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22 450 clusters. CV collaborated in the execution of the analyses and in the interpretation
23
24 451 of the multimorbidity patterns. ML participated in the statistical and graphical
25
26 452 analysis of the results, in the discussion of the results and the revision of several
27
28 453 manuscript versions. PR collaborated in the questionnaires' design, patient
29
30 454 inclusion, data collection and discussion of results and revised the manuscript.
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32 455 All authors read and approved the final manuscript.
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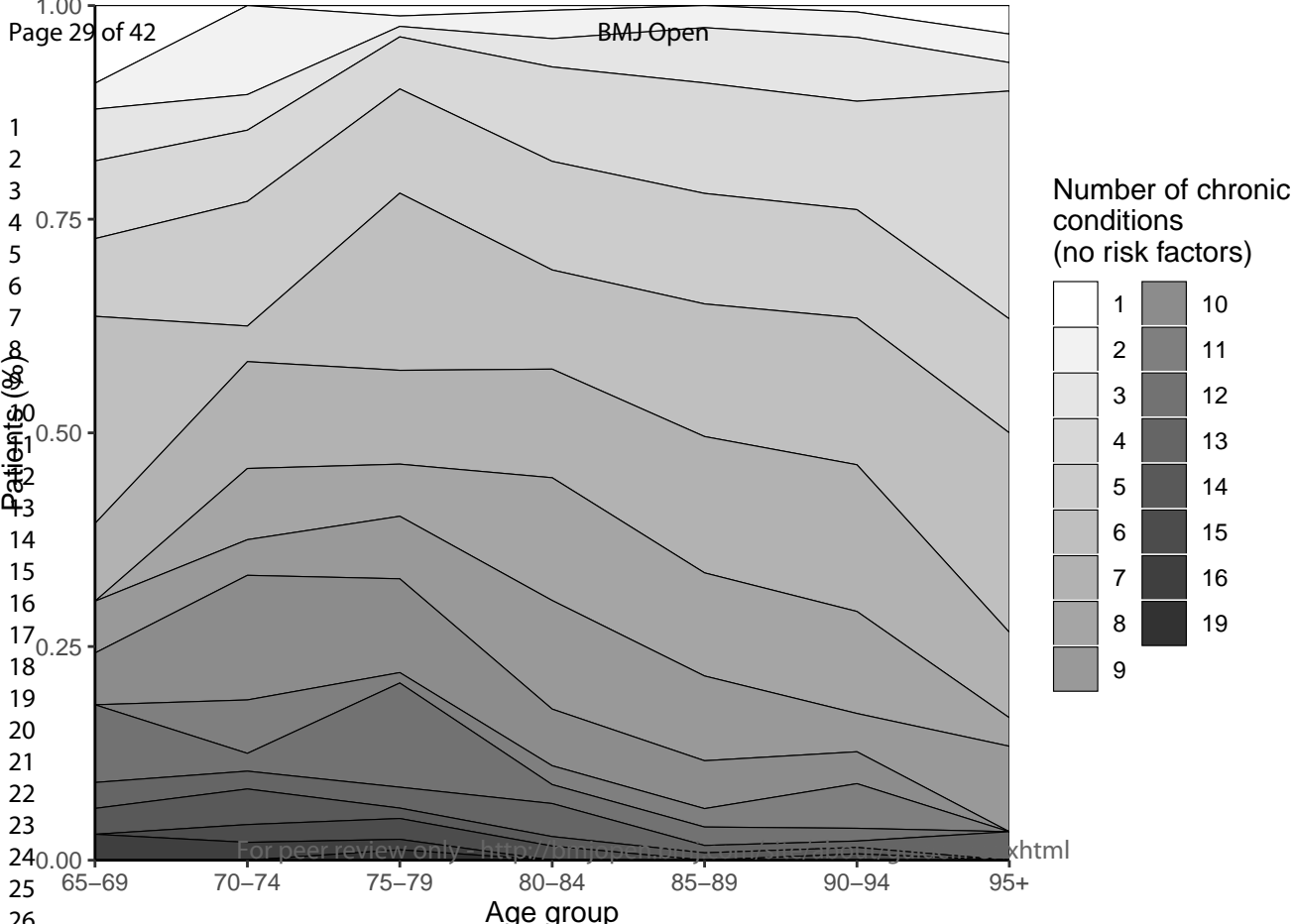
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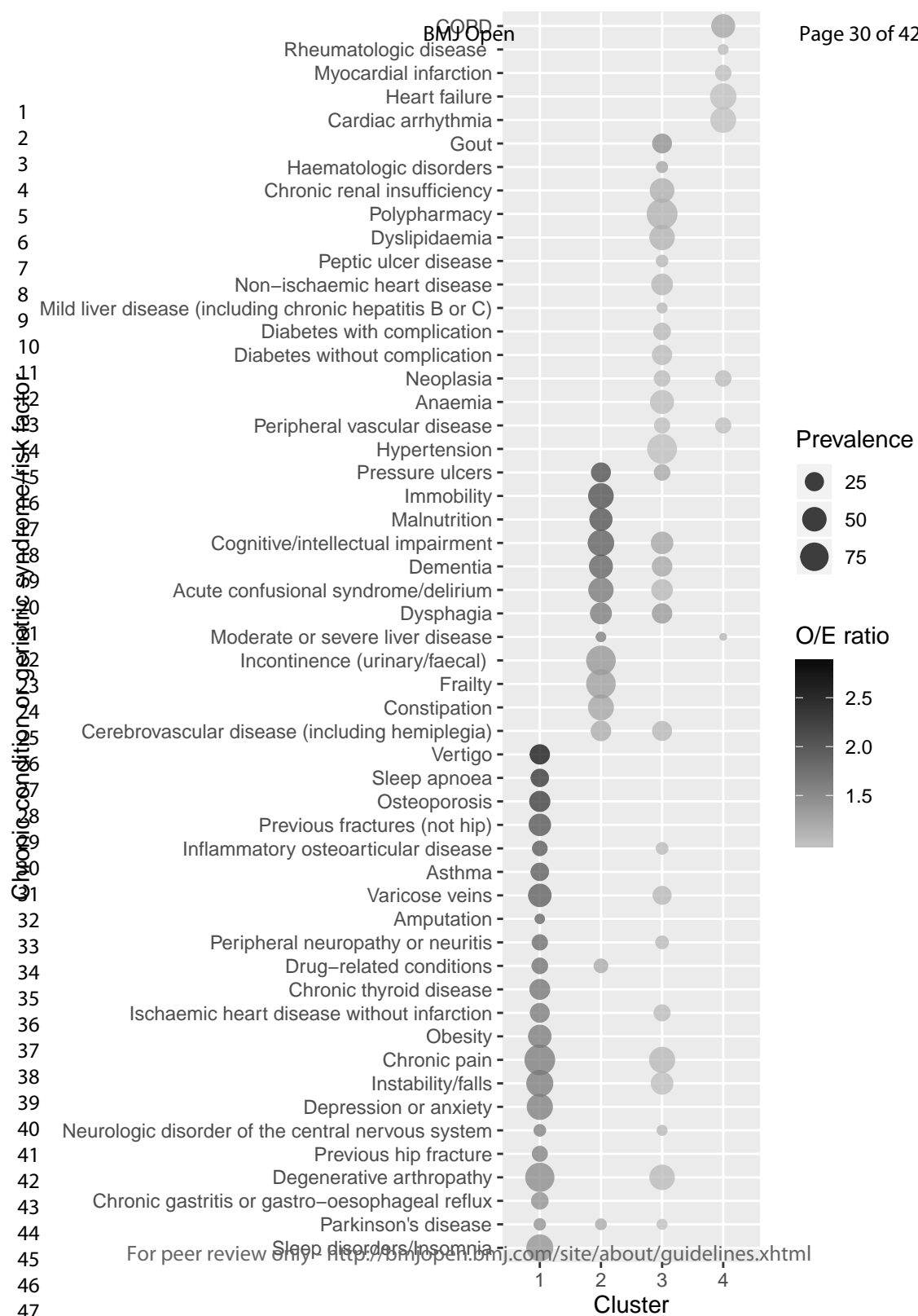
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Supplemental Table 1. Chronic conditions and geriatric syndromes recorded.

Chronic conditions	Geriatric syndromes and risk factors
<i>Charlson Index</i>	
1. AIDS/HIV	Acute confusional syndrome/delirium
2. Any malignancy (excluding skin)	Chronic pain
3. Cerebrovascular disease	Cognitive/Intellectual impairment
4. Chronic obstructive pulmonary disease	Constipation
5. Congestive heart failure	Depression or Anxiety
6. Dementia	Dysphagia
7. Diabetes with complication	Frailty
8. Diabetes without complication	Immobility
9. Hemiplegia	Incontinence (Urinary/faecal)
10. Leukaemia	Instability/falls
11. Lymphoma	Malnutrition
12. Metastatic solid tumour	Polypharmacy
13. Mild liver disease	Pressure ulcers
14. Moderate or severe liver disease	Sensorial deficit
15. Moderate or severe renal disease	Sleep disorders/Insomnia
16. Myocardial infarction	
17. Peptic ulcer disease	
18. Peripheral vascular disease	
19. Rheumatologic disease	
<i>Other conditions</i>	
20. Amputation	
21. Anaemia	
22. Asthma	
23. Cardiac arrhythmia	
24. Cataract	
25. Chronic hepatitis (B or C)	
26. Chronic pancreatic disease	
27. Degenerative arthropathy	
28. Dermatitis or eczema	

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- 1 29. Diverticular disease of the colon
 - 2 30. Drug-related conditions
 - 3 31. Dyslipidaemia (risk factor)
 - 4 32. Fibromyalgia
 - 5 33. Gallstones (previous hepatic colic)
 - 6 34. Chronic gastritis or gastro-oesophageal
 - 7 reflux
 - 8 35. Glaucoma
 - 9 36. Gout
 - 10 37. Haemorrhoids
 - 11 38. Haematologic disorders (myelodysplastic
 - 12 syndrome, gammopathy, polycythaemia)
 - 13 39. Hypertension (risk factor)
 - 14 40. Inflammatory osteoarticular disease
 - 15 41. Irritable bowel syndrome
 - 16 42. Ischaemic heart disease without infarction
 - 17 43. Migraine
 - 18 44. Neurologic disorder of the central nervous
 - 19 system
 - 20 45. Non-congestive heart failure
 - 21 46. Non-ischaemic heart disease
 - 22 (miocardiopathy, valvulopathy)
 - 23 47. Non-schizophrenic mental disorders
 - 24 (excluding depression and anxiety)
 - 25 48. Obesity (risk factor)
 - 26 49. Osteoporosis (risk factor)
 - 27 50. Other neurological pathologies (essential
 - 28 tremor)
 - 29 51. Other vascular diseases (ischaemia,
 - 30 aneurism)
 - 31 52. Parkinson's disease
 - 32 53. Peripheral neuropathy or neuritis
 - 33 54. Post-traumatic stress disorder
 - 34 55. Previous fractures (not hip)
 - 35 56. Previous hip fracture
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- 1 57. Prostatic benign hypertrophy
 - 2 58. Schizophrenia
 - 3 59. Sleep apnoea
 - 4 60. Chronic thyroid disease
 - 5 61. Tuberculosis
 - 6 62. Urinary tract stones (nephritic colic)
 - 7 63. Varicose veins of lower extremities
 - 8 64. Vertigo
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Supplemental Table 2. Prevalence rates of chronic conditions and geriatric syndromes / risk factors in the study population by sex, separately listed in decreasing order of total prevalence rate.

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
CHRONIC CONDITIONS									
Risk factors									
Hypertension	330	83.76	79.79 - 87.07	273	78.90	74.30 - 82.87	603	81.49	78.53 - 84.12
Dyslipidaemia	189	47.97	43.08 - 52.90	171	49.42	44.19 - 54.67	360	48.65	45.06 - 52.25
Obesity	127	32.23	27.81 - 37.00	66	19.08	15.28 - 23.55	193	26.08	23.05 - 29.36
Osteoporosis	82	20.81	17.09 - 25.09	21	6.07	4.00 - 9.10	103	13.92	11.61 - 16.60
Drug-related conditions	44	11.17	8.42 - 14.66	23	6.65	4.47 - 9.78	67	9.05	7.19 - 11.34
Chronic Diseases									
Heart failure	255	64.72	59.88 - 69.28	188	54.34	49.07 - 59.51	443	59.86	56.29 - 63.34
Cardiac arrhythmia	216	54.82	49.89 - 59.67	207	59.83	54.58 - 64.86	423	57.16	53.57 - 60.68
Degenerative arthropathy	228	57.87	52.94 - 62.64	157	45.38	40.21 - 50.64	385	52.03	48.43 - 55.61
Anaemia	182	46.19	41.33 - 51.13	152	43.93	38.80 - 49.20	334	45.14	41.58 - 48.74
Moderate or severe renal disease	164	41.62	36.86 - 46.55	156	45.09	39.93 - 50.35	320	43.24	39.72 - 46.84
Chronic obstructive pulmonary disease (COPD)	90	22.84	18.97 - 27.24	183	52.89	47.63 - 58.09	273	36.89	33.49 - 40.43
Non-ischaemic heart disease	125	31.73	27.33 - 36.48	113	32.66	27.93 - 37.77	238	32.16	28.90 - 35.61
Diabetes without complication	101	25.63	21.57 - 30.17	100	28.90	24.38 - 33.89	201	27.16	24.08 - 30.48
Cerebrovascular disease (including hemiplegia)	95	24.11	20.15 - 28.57	93	26.88	22.48 - 31.78	188	25.41	22.40 - 28.66
Dementia	103	26.14	22.05 - 30.70	76	21.97	17.92 - 26.62	179	24.19	21.24 - 27.40
Varicose veins of lower extremities	98	24.87	20.86 - 29.37	66	19.08	15.28 - 23.55	164	22.16	19.32 - 25.29
Previous fracture (not hip)	87	22.08	18.27 - 26.44	52	15.03	11.65 - 19.18	139	18.78	16.13 - 21.76
Gout	57	14.47	11.34 - 18.28	80	23.12	18.99 - 27.84	137	18.51	15.88 - 21.47
Chronic thyroid disease	93	23.60	19.68 - 28.04	42	12.14	9.11 - 16.00	135	18.24	15.63 - 21.19
Diabetes with complication	70	17.77	14.31 - 21.85	63	18.21	14.50 - 22.62	133	17.97	15.37 - 20.90
Ischaemic heart disease without infarction	58	14.72	11.56 - 18.56	62	17.92	14.24 - 22.31	120	16.22	13.74 - 19.05
Myocardial infarction	47	11.93	9.09 - 15.50	64	18.50	14.76 - 22.93	111	15.00	12.61 - 17.75
Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	29	7.36	5.17 - 10.37	82	23.70	19.52 - 28.45	111	15.00	12.61 - 17.75
Peripheral vascular disease	31	7.87	5.60 - 10.95	74	21.39	17.39 - 26.01	105	14.19	11.86 - 16.89
Chronic gastritis or gastro-oesophageal reflux	55	13.96	10.88 - 17.73	42	12.14	9.11 - 16.00	97	13.11	10.87 - 15.73

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
Asthma	74	18.78	15.23 - 22.93	8	2.31	1.18 - 4.50	82	11.08	9.02 - 13.55
Gallstones	39	9.90	7.33 - 13.25	40	11.56	8.61 - 15.36	79	10.68	8.65 - 13.11
Vertigo	54	13.71	10.66 - 17.45	23	6.65	4.47 - 9.78	77	10.41	8.41 - 12.81
Previous hip fracture	52	13.20	10.21 - 16.90	15	4.34	2.64 - 7.03	67	9.05	7.19 - 11.34
Sleep apnoea	34	8.63	6.24 - 11.82	32	9.25	6.63 - 12.76	66	8.92	7.07 - 11.19
Peripheral neuropathy or neuritis	27	6.85	4.75 - 9.79	34	9.83	7.12 - 13.42	61	8.24	6.47 - 10.45
Inflammatory osteoarticular disease	26	6.60	4.54 - 9.49	23	6.65	4.47 - 9.78	49	6.62	5.04 - 8.65
Peptic ulcer disease	11	2.79	1.57 - 4.93	35	10.12	7.36 - 13.74	46	6.22	4.69 - 8.19
Haematologic disorders	14	3.55	2.13 - 5.88	22	6.36	4.24 - 9.44	36	4.86	3.53 - 6.66
Parkinson disease	15	3.81	2.32 - 6.19	19	5.49	3.54 - 8.42	34	4.59	3.31 - 6.35
Rheumatologic disease	22	5.58	3.72 - 8.31	10	2.89	1.58 - 5.24	32	4.32	3.08 - 6.04
Mild liver disease (including chronic hepatitis B or C)	12	3.05	1.75 - 5.25	20	5.78	3.77 - 8.76	32	4.32	3.08 - 6.04
Neurologic disorder of the CNS	11	2.79	1.57 - 4.93	21	6.07	4.00 - 9.10	32	4.32	3.08 - 6.04
Moderate or severe liver disease	9	2.28	1.21 - 4.28	10	2.89	1.58 - 5.24	19	2.57	1.65 - 3.98
Amputation	4	1.02	0.40 - 2.58	12	3.47	1.99 - 5.96	16	2.16	1.34 - 3.48
Urinary tract stones	9	2.28	1.21 - 4.28	5	1.45	0.62 - 3.34	14	1.89	1.13 - 3.15
Non-schizophrenic mental disorders	11	2.79	1.57 - 4.93	1	0.29	0.01 - 1.62	12	1.62	0.93 - 2.81
Irritable bowel syndrome	7	1.78	0.86 - 3.62	4	1.16	0.45 - 2.93	11	1.49	0.83 - 2.64
Chronic pancreatic disease	4	1.02	0.40 - 2.58	6	1.73	0.80 - 3.73	10	1.35	0.74 - 2.47
Tuberculosis	5	1.27	0.54 - 2.94	4	1.16	0.45 - 2.93	9	1.22	0.64 - 2.30
Other neurological pathologies	3	0.76	0.26 - 2.21	6	1.73	0.80 - 3.73	9	1.22	0.64 - 2.30
Fibromyalgia	6	1.52	0.70 - 3.28	2	0.58	0.16 - 2.08	8	1.08	0.55 - 2.12
Migraine	4	1.02	0.40 - 2.58	0	0.00	0.00 - 1.10	4	0.54	0.21 - 1.38
Schizophrenia	1	0.25	0.01 - 1.42	2	0.58	0.16 - 2.08	3	0.41	0.14 - 1.19
Post-traumatic stress disorder	1	0.25	0.01 - 1.42	2	0.58	0.16 - 2.08	3	0.41	0.14 - 1.19
AIDS/HIV	0	0.00	0.00 - 0.00	0	0.00	0.00 - 0.00	0	0.00	0.00 - 0.00
GERIATRIC SYNDROMES AND RISK FACTORS									
Polypharmacy	310	78.68	74.37 - 82.44	281	81.21	76.76 - 84.98	591	79.86	76.82 - 82.60
Frailty	269	68.27	63.52 - 72.67	188	54.34	49.07 - 59.51	457	61.76	58.20 - 65.19
Incontinence (Urinary/faecal)	273	69.29	64.57 - 73.64	157	45.38	40.21 - 50.64	430	58.11	54.52 - 61.61
Chronic pain	231	58.63	53.71 - 63.39	171	49.42	44.19 - 54.67	402	54.32	50.72 - 57.88
Constipation	201	51.02	46.09 - 55.92	139	40.17	35.14 - 45.42	340	45.95	42.39 - 49.55

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
Sleep disorders/Insomnia	189	47.97	43.08 - 52.90	144	41.62	36.54 - 46.88	333	45.00	41.45 - 48.60
Sensorial deficit	169	42.89	38.10 - 47.83	145	41.91	36.83 - 47.17	314	42.43	38.92 - 46.02
Instability/falls	158	40.10	35.38 - 45.01	128	36.99	32.08 - 42.20	286	38.65	35.21 - 42.21
Depression or anxiety	193	48.98	44.08 - 53.91	75	21.68	17.66 - 26.32	268	36.22	32.83 - 39.74
Acute confusional syndrome / delirium	118	29.95	25.64 - 34.65	117	33.82	29.03 - 38.95	235	31.76	28.50 - 35.20
Cognitive/Intellectual impairment	133	33.76	29.26 - 38.56	96	27.75	23.29 - 32.69	229	30.95	27.72 - 34.37
Immobility	114	28.93	24.68 - 33.60	78	22.54	18.46 - 27.23	192	25.95	22.92 - 29.22
Dysphagia	78	19.80	16.16 - 24.01	81	23.41	19.26 - 28.15	159	21.49	18.68 - 24.59
Malnutrition	76	19.29	15.70 - 23.47	71	20.52	16.60 - 25.09	147	19.86	17.15 - 22.89
Pressure ulcers	57	14.47	11.34 - 18.28	38	10.98	8.11 - 14.72	95	12.84	10.62 - 15.44

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Supplemental Table 3. Weight as an indicator of importance on clinical management assigned to each chronic condition. Weight values range from 0 to 8, where 0 means no clinical management was required and 1 to 8 indicate clinical management from main cause of hospitalization (1) to chronic condition requiring the least medical attention (8). Chronic conditions are displayed in alphabetical order.

Chronic conditions	Weight 0		Weight 1		Weight 2		Weight 3		Weight 4		Weight 5		Weight 6		Weight 7		Weight 8	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
AIDS/HIV	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Amputation	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Anaemia	596	80.54	28	3.78	46	6.22	40	5.41	19	2.57	8	1.08	3	0.41	0	0	0	0
Asthma	704	95.14	30	4.05	3	0.41	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Rheumatologic disease	729	98.51	5	0.68	3	0.41	3	0.41	0	0	0	0	0	0	0	0	0	0
Cardiac arrhythmia	595	80.41	35	4.73	69	9.32	28	3.78	10	1.35	3	0.41	0	0	0	0	0	0
Cerebrovascular disease (including hemiplegia)	703	95	28	3.78	3	0.41	3	0.41	2	0.27	1	0.14	0	0	0	0	0	0
Chronic gastritis or gastro-oesophageal reflux	733	99.05	4	0.54	1	0.14	1	0.14	1	0.14	0	0	0	0	0	0	0	0
Chronic pancreatic disease	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Chronic obstructive pulmonary disease (COPD)	554	74.86	153	20.68	19	2.57	8	1.08	5	0.68	0	0	1	0.14	0	0	0	0
Chronic thyroid disease	722	97.57	2	0.27	1	0.14	4	0.54	7	0.95	3	0.41	1	0.14	0	0	0	0
Degenerative arthropathy	718	97.03	3	0.41	7	0.95	4	0.54	4	0.54	3	0.41	1	0.14	0	0	0	0
Dementia	687	92.84	32	4.32	14	1.89	4	0.54	3	0.41	0	0	0	0	0	0	0	0
Diabetes with complication	710	95.95	9	1.22	7	0.95	5	0.68	4	0.54	2	0.27	3	0.41	0	0	0	0
Diabetes without complication	698	94.32	11	1.49	5	0.68	13	1.76	8	1.08	2	0.27	1	0.14	2	0.27	0	0
Drug-related conditions	722	97.57	5	0.68	3	0.41	3	0.41	4	0.54	1	0.14	1	0.14	1	0.14	0	0
Dyslipidaemia	735	99.32	0	0	0	0	0	0	4	0.54	1	0.14	0	0	0	0	0	0
Fibromyalgia	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Gallstones	730	98.65	6	0.81	3	0.41	1	0.14	0	0	0	0	0	0	0	0	0	0
Gout	737	99.59	0	0	0	0	2	0.27	0	0	1	0.14	0	0	0	0	0	0
Haematologic disorders	730	98.65	2	0.27	5	0.68	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Heart failure	410	55.41	227	30.68	85	11.49	13	1.76	4	0.54	0	0	1	0.14	0	0	0	0
Hypertension	698	94.32	10	1.35	14	1.89	12	1.62	4	0.54	2	0.27	0	0	0	0	0	0
Inflammatory osteoarticular disease	727	98.24	8	1.08	1	0.14	1	0.14	1	0.14	1	0.14	1	0.14	0	0	0	0
Irritable bowel syndrome	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ischaemic heart disease without infarction	714	96.49	10	1.35	14	1.89	1	0.14	0	0	1	0.14	0	0	0	0	0	0

1	Migraine	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	Mild liver disease (including chronic hepatitis B or C)	733	99.05	5	0.68	0	0	1	0.14	0	0	0	0	0	0	1	0.14
3	Moderate or severe liver disease	724	97.84	12	1.62	2	0.27	1	0.14	0	0	1	0.14	0	0	0	0
4	Moderate or severe renal disease	552	74.59	39	5.27	77	10.41	44	5.95	23	3.11	4	0.54	1	0.14	0	0
5	Myocardial infarction	716	96.76	20	2.7	3	0.41	1	0.14	0	0	0	0	0	0	0	0
6	Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	724	97.84	5	0.68	7	0.95	1	0.14	1	0.14	2	0.27	0	0	0	0
7	Neurologic disorder of the CNS	736	99.46	2	0.27	2	0.27	0	0	0	0	0	0	0	0	0	0
8	Non-ischaemic heart disease	695	93.92	15	2.03	16	2.16	12	1.62	0	0	2	0.27	0	0	0	0
9	Non-schizophrenic mental disorders	732	98.92	2	0.27	2	0.27	1	0.14	2	0.27	1	0.14	0	0	0	0
10	Obesity	737	99.59	0	0	1	0.14	2	0.27	0	0	0	0	0	0	0	0
11	Osteoporosis	730	98.65	2	0.27	3	0.41	2	0.27	2	0.27	0	0	1	0.14	0	0
12	Other neurological pathologies	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	Parkinson's disease	737	99.59	3	0.41	0	0	0	0	0	0	0	0	0	0	0	0
14	Peptic ulcer disease	737	99.59	2	0.27	1	0.14	0	0	0	0	0	0	0	0	0	0
15	Peripheral neuropathy or neuritis	737	99.59	1	0.14	1	0.14	1	0.14	0	0	0	0	0	0	0	0
16	Peripheral vascular disease	728	98.38	9	1.22	1	0.14	1	0.14	0	0	0	0	1	0.14	0	0
17	Post-traumatic stress disorder	739	99.86	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
18	Previous fracture (not hip)	730	98.65	5	0.68	2	0.27	2	0.27	1	0.14	0	0	0	0	0	0
19	Previous hip fracture	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	Schizophrenia	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	Sleep apnoea	716	96.76	5	0.68	9	1.22	5	0.68	1	0.14	4	0.54	0	0	0	0
22	Tuberculosis	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	Urinary tract stones	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	Varicose veins of lower extremities	725	97.97	1	0.14	6	0.81	2	0.27	4	0.54	2	0.27	0	0	0	0
25	Vertigo	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Supplemental table 4. Prevalence, Observed/Expected (O/E) ratios and exclusivity of chronic conditions and geriatric syndromes / risk factors per multimorbidity cluster. Conditions with prevalence >2% were included. O/E ratios were calculated by dividing the prevalence of a disease within the cluster by its prevalence in the overall population. Exclusivity was calculated by dividing the number of patients with the disease in the cluster by the total number of participants with the disease. Conditions are ordered by decreasing O/E ratio of cluster 1.

	Cluster 1			Cluster 2			Cluster 3			Cluster 4		
	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)
Vertigo	29.58	2.84	50.67	9.52	0.91	18.92	6.85	0.66	15.90	4.05	0.39	14.52
Sleep apnoea	22.11	2.48	44.19	5.82	0.65	13.50	8.12	0.91	21.99	4.85	0.54	20.33
Osteoporosis	33.39	2.40	42.76	9.95	0.71	14.79	9.44	0.68	16.38	9.72	0.70	26.07
Previous fracture (not hip)	39.67	2.11	37.65	17.87	0.95	19.68	15.16	0.81	19.49	11.66	0.62	23.19
Inflammatory osteoarticular disease	13.61	2.06	36.65	2.78	0.42	8.69	7.21	1.09	26.31	5.03	0.76	28.36
Asthma	22.50	2.03	36.19	9.37	0.85	17.49	7.77	0.70	16.94	8.72	0.79	29.37
Varicose veins of lower extremities	44.58	2.01	35.86	15.2	0.69	14.19	24.37	1.10	26.56	13.89	0.63	23.40
Amputation	4.190	1.94	34.56	1.72	0.8	16.45	2.00	0.92	22.30	1.55	0.71	26.69
Peripheral neuropathy or neuritis	15.37	1.86	33.23	6.00	0.73	15.06	9.03	1.10	26.46	5.58	0.68	25.26
Drug-related conditions	16.31	1.80	32.12	11.23	1.24	25.66	7.41	0.82	19.76	5.45	0.60	22.46
Chronic thyroid disease	32.14	1.76	31.40	13.73	0.75	15.57	16.06	0.88	21.26	15.52	0.85	31.77
Ischaemic heart disease without infarction	27.75	1.71	30.5	10.85	0.67	13.84	17.59	1.08	26.20	12.79	0.79	29.46
Obesity	44.29	1.70	30.27	19.14	0.73	15.18	25.15	0.96	23.28	21.84	0.84	31.27
Chronic pain	91.68	1.69	30.09	50.3	0.93	19.15	59.72	1.10	26.55	35.23	0.65	24.22
Instability/falls	65.05	1.68	30.00	36.74	0.95	19.66	40.06	1.04	25.03	26.19	0.68	25.30
Depression or Anxiety	60.05	1.66	29.56	35.49	0.98	20.27	30.57	0.84	20.38	28.89	0.80	29.79
Neurologic disorder of the CNS	7.10	1.64	29.28	4.92	1.14	23.54	4.78	1.11	26.72	2.37	0.55	20.47
Previous hip fracture	14.76	1.63	29.06	9.23	1.02	21.08	6.20	0.69	16.55	8.08	0.89	33.31
Degenerative arthropathy	80.19	1.54	27.48	48.11	0.92	19.13	56.15	1.08	26.06	38.08	0.73	27.34
Chronic gastritis or gastro-oesophageal reflux	19.39	1.48	26.37	9.09	0.69	14.35	12.6	0.96	23.22	12.66	0.97	36.07
Parkinson's disease	6.72	1.46	26.07	5.73	1.25	25.78	4.77	1.04	25.08	2.84	0.62	23.06
Sleep disorders/Insomnia	64.93	1.44	25.72	51.57	1.15	23.70	42.58	0.95	22.85	33.41	0.74	27.73
Moderate or severe renal disease	59.30	1.37	24.44	29.11	0.67	13.92	51.19	1.18	28.59	38.27	0.88	33.05
Non-ischaemic heart disease	43.07	1.34	23.87	23.15	0.72	14.89	36.01	1.12	27.04	29.46	0.92	34.20

1	Myocardial infarction	19.88	1.33	23.63	10.00	0.67	13.79	14.68	0.98	23.64	15.64	1.04	38.94
2	Dyslipidaemia	64.28	1.32	23.55	35.21	0.72	14.97	55.63	1.14	27.62	44.11	0.91	33.86
3	Frailty	81.11	1.31	23.41	82.71	1.34	27.70	55.05	0.89	21.53	45.26	0.73	27.36
4	Anaemia	59.26	1.31	23.40	42.23	0.94	19.35	47.71	1.06	25.53	38.34	0.85	31.72
5	Gallstones	13.87	1.30	23.16	10.6	0.99	20.54	9.66	0.90	21.85	9.85	0.92	34.46
6	Haematologic disorders	6.24	1.28	22.88	2.80	0.58	11.91	6.24	1.28	30.99	4.46	0.92	34.22
7	Constipation	57.53	1.25	22.32	58.53	1.27	26.35	36.80	0.80	19.34	39.36	0.86	31.99
8	Incontinence (Urinary/faecal)	72.26	1.24	22.17	82.95	1.43	29.52	54.73	0.94	22.75	39.78	0.68	25.56
9	Gout	22.86	1.23	22.01	9.85	0.53	11.01	27.66	1.49	36.08	15.32	0.83	30.90
10	Diabetes with complication	21.71	1.21	21.53	14.68	0.82	16.89	19.79	1.10	26.59	16.84	0.94	34.99
11	Polypharmacy	96.12	1.20	21.45	64.75	0.81	16.77	92.87	1.16	28.08	72.07	0.90	33.70
12	Rheumatologic disease	5.08	1.17	20.93	4.16	0.96	19.91	3.34	0.77	18.66	4.69	1.08	40.50
13	Dysphagia	24.83	1.16	20.60	36.49	1.70	35.13	29.98	1.40	33.70	6.09	0.28	10.58
14	Cerebrovascular disease (including hemiplegia)	29.02	1.14	20.36	30.75	1.21	25.04	28.38	1.12	26.98	18.79	0.74	27.62
15	Acute confusional syndrome/delirium	36.00	1.13	20.21	54.77	1.72	35.67	35.27	1.11	26.82	14.71	0.46	17.30
16	Heart failure	66.53	1.11	19.81	57.88	0.97	20.00	54.09	0.90	21.82	61.52	1.03	38.37
17	Peripheral vascular disease	15.71	1.11	19.74	10.69	0.75	15.58	14.98	1.06	25.50	14.89	1.05	39.17
18	Hypertension	89.07	1.09	19.48	78.13	0.96	19.83	84.73	1.04	25.11	77.62	0.95	35.57
19	Cardiac arrhythmia	61.85	1.08	19.29	52.03	0.91	18.82	56.49	0.99	23.87	58.20	1.02	38.02
20	Peptic ulcer disease	6.70	1.08	19.22	5.00	0.80	16.64	6.97	1.12	27.09	6.17	0.99	37.05
21	Sensorial deficit	39.51	0.93	16.60	44.27	1.04	21.58	43.84	1.03	24.95	41.89	0.99	36.87
22	Immobility	23.10	0.89	15.87	56.49	2.18	45.03	26.23	1.01	24.41	10.21	0.39	14.69
23	Moderate or severe liver disease	2.23	0.87	15.46	4.33	1.69	34.91	0.69	0.27	6.51	2.96	1.15	43.11
24	Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	12.74	0.85	15.15	13.39	0.89	18.46	16.19	1.08	26.07	16.20	1.08	40.32
25	Chronic obstructive pulmonary disease (COPD)	29.97	0.81	14.48	27.29	0.74	15.30	34.75	0.94	22.75	46.90	1.27	47.47
26	Mild liver disease (including chronic hepatitis B or C)	3.41	0.79	14.04	4.69	1.08	22.41	4.81	1.11	26.84	4.25	0.98	36.70
27	Cognitive/Intellectual impairment	23.44	0.76	13.50	62.07	2.01	41.48	39.53	1.28	30.85	11.74	0.38	14.17
28	Diabetes without complication	20.64	0.76	13.54	30.98	1.14	23.59	29.45	1.08	26.18	26.69	0.98	36.69
29	Pressure ulcers	7.44	0.58	10.33	28.11	2.19	45.28	16.20	1.26	30.48	4.78	0.37	13.90
30	Dementia	12.34	0.51	9.10	47.13	1.95	40.30	30.43	1.26	30.38	13.10	0.54	20.23
31	Malnutrition	8.69	0.44	7.80	42.75	2.15	44.50	13.57	0.68	16.50	16.60	0.84	31.20

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
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11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	15-16
14				
15	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
18				
19				
20	Generalisability	21	Discuss the generalisability (external validity) of the study results	17
21				
22	Other information			
23	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20
24				
25				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.

BMJ Open

Multimorbidity patterns of chronic conditions and geriatric syndromes in older patients from the MoPIM multicentre cohort study.

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3 1 **MULTIMORBIDITY PATTERNS OF CHRONIC CONDITIONS AND GERIATRIC**
4 **SYNDROMES IN OLDER PATIENTS FROM THE MoPIM MULTICENTRE**
5 **2**
6 **3**
7 **COHORT STUDY.**

8
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10
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1
2
3 31 **ABSTRACT**
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6 32 **Objectives:** To estimate the frequency of chronic conditions and geriatric
7
8 33 syndromes in older patients admitted to hospital because of an exacerbation of
9
10 34 their chronic conditions, and to identify multimorbidity clusters in these patients.
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14 35 **Design:** Multicentre, prospective cohort study.
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17 36 **Setting:** Internal medicine or geriatric services of five general teaching hospitals
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19 37 in Spain.
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22 38 **Participants:** 740 patients aged 65 and older, hospitalized because of an
23
24 39 exacerbation of their chronic conditions between September 2016 and December
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26 40 2018.
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30 41 **Primary and secondary outcome measures:** Active chronic conditions and
31
32 42 geriatric syndromes (including risk factors) of the patient, a score about clinical
33
34 43 management of chronic conditions during admission, and destination at
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36 44 discharge were collected, among other variables. Multimorbidity patterns were
37
38 45 identified using fuzzy c-means cluster analysis, taking into account the clinical
39
40 46 management score. Prevalence, observed/expected ratio and exclusivity of each
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42 47 chronic condition and geriatric syndrome were calculated for each cluster, and
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44 48 the final solution was approved after clinical revision and discussion among the
45
46 49 research team.
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50 50 **Results:** 740 patients were included (mean age 84.12 years, SD 7.01; 53.24%
51
52 51 female). Almost all patients had two or more chronic conditions (98.65%; 95%CI
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54 52 98.23-99.07), the most frequent were hypertension (81.49%, 95%CI 78.53-84.12)
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56 53 and heart failure (59.86%, 95%CI 56.29-63.34). The most prevalent geriatric
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3 54 syndrome was polypharmacy (79.86%, 95%CI 76.82-82.60). Four statistically
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5 55 and clinically significant multimorbidity clusters were identified: osteoarticular,
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7 56 psychogeriatric, cardiorespiratory and minor chronic disease. Patient level
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9 57 variables such as sex, Barthel Index, number of chronic conditions or geriatric
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11 58 syndromes, chronic disease exacerbation 3 months prior to admission or
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13 59 destination at discharge differed between clusters.
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18 **Conclusions:** In older patients admitted to hospital because of the exacerbation
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20 61 of chronic health problems, it is possible to define multimorbidity clusters using
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22 62 soft clustering techniques. These clusters are clinically relevant and could be the
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24 63 basis to reorganize healthcare circuits or processes to tackle the increasing
25
26 64 number of older, multimorbid patients.
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30 **Trial registration number** NCT02830425, 12th July 2016
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34 **Keywords:** Multimorbidity, patterns, soft clustering, older, chronic conditions,
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36 67 geriatric syndromes.
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39 **Strengths and limitations of this study**

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- 42 69 - The multimorbidity analysis in this study has been developed considering
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44 70 a wide range of long-term conditions that may require healthcare in older
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46 71 people.
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48 72 - To the best of our knowledge, this is the first published study of
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50 73 multimorbidity clusters in older patients to include chronic diseases
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52 74 weighted by a clinical management score and geriatric syndromes.
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54 75 - Soft clustering is an innovative, methodologically robust technique that can
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56 76 lead to reliable results in the field of multimorbidity analysis.
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3 77 - The list of chronic conditions and geriatric syndromes used in this study is
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5 78 comprehensive but not standardized, thus hindering comparability with
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8 79 other studies.
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10 80 **BACKGROUND**

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14 81 According to the most recent Eurostat baseline population projections, old-age
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16 82 dependency ratio (population 65y and over divided by population 15-64y) is about
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18 83 32% in the European Union (EU) and it is expected to reach 52% in 2050,
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21 84 meaning that the EU's population will continue to grow older[1]. Together with
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23 85 the fact that chronic conditions (CC) are the main cause of disability and mortality
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25 86 in Europe, this implies that the coexistence of two or more chronic health
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27 87 conditions, which constitutes the classic definition of multimorbidity, is becoming
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30 88 increasingly common[2].
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33 89 Multimorbidity is therefore turning into an important challenge for the health
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35 90 system because of the expanding proportion of older people with multiple CC and
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37 91 treatments as well as the difficulties associated with their clinical
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39 92 management[3,4]. Most clinical practice guidelines are focused on single
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41 93 diseases, with limited recommendations for multimorbid patients[5], and, in
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43 94 addition, randomized clinical trials often exclude older patients with
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45 95 multimorbidity[6]. Despite the importance of multimorbidity in clinical practice,
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47 96 different criteria about which conditions should be considered and how to
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49 97 aggregate them are still under debate, which makes it difficult to compare
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51 98 different estimations around the world[7–9].
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57 99 One of the novel, increasingly widespread definitions of multimorbidity considers
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59 100 the non-spurious association of certain CC by sharing pathophysiological

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3 101 mechanisms, giving rise to disease association patterns[10]. In order to identify
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5 102 those patterns, different statistical methodologies have been explored. Among
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7 103 these techniques, soft clustering allows to focus on patients rather than
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9 104 diagnoses and is a useful method when there is a high overlap of diagnoses
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11 105 between patients, as it enables patients to belong to more than one multimorbidity
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13 106 pattern with a certain probability[11]
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18 107 Besides CC, other clinically relevant situations such as geriatric syndromes (GS)
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20 108 may also be considered in the definition of these patterns, since they might have
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22 109 a great impact on the health-related quality of life and clinical management of old
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24 110 patients[12]. In fact, the purpose of multimorbidity characterization (i.e., predicting
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26 111 outcomes or use of health services, improving quality of care, organizing
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28 112 healthcare services, etc.), will have an influence on its definition. In order to have
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30 113 an accurate picture of the morbidity of each patient, a global consideration of all
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32 114 conditions that may require healthcare attention is necessary, even if they are not
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34 115 the reason for hospitalization. Along these lines, some countries have explicitly
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36 116 recommended to acknowledge all long-term conditions for optimising care of
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38 117 adult patients by reducing, for example, possible inappropriate treatments,
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40 118 multiple healthcare appointments or poor health-related quality of life[13–15].
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46 119 During the past decade, there has been an increasing amount of publications that
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48 120 consider multimorbidity[16], but few have focused on multimorbidity patterns in
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50 121 older patients and even fewer take into account GS[17]. For this reason, we
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52 122 launched a multicentre study in 2016 with multiple aims related to multimorbidity,
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54 123 appropriateness of chronic treatments and adverse drug reactions in older
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56 124 patients[18]. The objectives of the present analyses were to estimate the
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58 125 frequency of CC and GS in older patients admitted to hospital because of an
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3 126 exacerbation of their CC, and to identify possible multimorbidity patterns in these
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5 127 patients.

8 128 **METHODS**

10 129 **Design and setting**

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15 130 A multicentre, prospective cohort study including older patients hospitalized at
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17 131 the internal medicine or geriatric services at five general teaching hospitals in
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19 132 three different regions of Spain between September 2016 and December 2018
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22 133 was designed. The detailed protocol was previously published[18].

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25 134 For the purposes of the study, older patients (≥ 65 years old) admitted as a result
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27 135 of the exacerbation of their chronic pathology were included. Patients referred to
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29 136 home hospitalization, admitted because of an acute process not related to any
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31 137 chronic disease, or with a fatal outcome expected at the time of admission were
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34 138 not included.

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38 139 No written informed consent was deemed necessary for this study.

39 40 41 140 **Data acquisition and variables**

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44 141 The following sociodemographic and clinical data was retrieved by the clinical
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46 142 team responsible for the patient: patient's code, date of birth, sex, functional
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48 143 status just before entering the hospital (Barthel index)[19], household (alone, with
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50 144 relatives or other people, in a nursing home), existence of any contact with
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52 145 healthcare services (primary care, emergencies, hospital admission, outpatient
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54 146 care, home care) in the 3 months prior to hospitalization due to exacerbation of
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57 147 any chronic disease, and destination at discharge from the present episode of
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3 148 hospitalization (home, transfer to another hospital, transfer to a nursing home,
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5 149 *exitus*).

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8
9 150 Active CC of the patient at arrival to hospital, including some risk factors, were
10
11 151 collected (see Supplemental Table 1). For this purpose, the physicians of the
12
13 152 project defined, on a consensual basis, a limited list of 64 CC, coming from the
14
15 153 114 groups defined by Salisbury and colleagues[20] and including the 19
16
17 154 categories of the Charlson Index[21]. Following the same criteria as Salisbury, a
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19 155 condition was considered to be chronic when it lasted for at least 6 months,
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21 156 including past conditions that require ongoing disease or risk management,
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23 157 important conditions with a significant risk of recurrence, or past conditions that
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25 158 have continuing implications for patient management[20]. Drug-related conditions
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27 159 of this list refer to poor management of medication related to a chronic disease
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29 160 that has clinical implications in that hospitalization (such as any drug intolerance
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31 161 or an excess drug poisoning).

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37 162 Additionally, for each of the CC, it was also recorded if they had required clinical
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39 163 management (both at admission and during hospitalization) by assigning a
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41 164 (subjective) correlative score (CM=1, 2, 3...) to each one, according to their
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43 165 clinical importance during the attention process. Thus, CC that did not have any
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45 166 significance during hospitalization, although recorded, had a score equal to zero.
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48 167 This correlative score was later used to compute a ratio to reflect the weight of
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50 168 each CC in each patient in the index hospitalization.

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54 169 Specific GS and risk factors (acute confusional syndrome/delirium, chronic pain,
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56 170 cognitive/intellectual impairment, constipation, depression or anxiety, dysphagia,
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58 171 frailty, immobility, incontinence (urinary/faecal), instability/falls, malnutrition,
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3 172 polypharmacy, pressure ulcers, sensorial deficit, sleep disorders/insomnia) were
4
5 173 also recorded. Two of the departments systematically apply a recently developed
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7 174 scale for frailty [22], while the others consider clinical judgement (although based
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9 175 on the same variables).

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13 176 In order to address potential sources of bias, a pilot study was conducted with
14
15 177 the first 10 admissions per centre to validate the data collection process and
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17 178 identify problems that could arise. After that, proper changes were made in the
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19 179 protocol and questionnaire. All available information sources were consulted in
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21 180 order to register CC and GS, and the defined list was not closed. Nonetheless,
22
23 181 the registration of CC and GS was based on clinical criteria.

24 25 26 27 28 182 **Sampling and analysis**

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31 183 A consecutive sample of 740 patients meeting the inclusion criteria were
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33 184 included, proportionally distributed to the annual volume of hospitalizations of the
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35 185 medicine and/or geriatric services of each centre. The estimated sample of 800
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37 186 patients (see protocol[18]) could not be reached due to organizational reasons in
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39 187 one of the participating centres.

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43 188 For the purposes of the analyses, some CC were grouped according to clinical
44
45 189 criteria: Hemiplegia was included in cerebrovascular disease; metastatic solid
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47 190 tumour, leukaemia, lymphoma and any malignancy were grouped into
48
49 191 'neoplasia'; hepatitis B and C were included in mild liver disease, and both
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51 192 congestive and non-congestive heart failure were grouped into 'heart failure'.
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53 193 Other diseases were finally excluded of the analyses considering that they have
54
55 194 no impact on acute healthcare (cataract, dermatitis, diverticular disease of the
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3 195 colon, glaucoma, haemorrhoids, other vascular diseases and prostatic benign
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5 196 hypertrophy). In the end, 51 CC and 15 GS were analysed.
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9 197 The updated Charlson Comorbidity Index[23], age adjusted, was computed and
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11 198 categorized according to tertiles distribution.
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13
14 199 Descriptive statistics were performed to assess patient clinical and
15
16 200 sociodemographic characteristics and to obtain overall prevalence estimates of
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18 201 CC and GS, stratified by sex. Multimorbidity was firstly defined as the presence
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20 202 of two or more CC. Cumulative number of CC and GS per patient were computed,
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22 203 respectively.
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24 25 26 204 *Multimorbidity patterns* 27

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29 205 CC or GS with a prevalence <2% were excluded to avoid statistical noise and
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31 206 therefore spurious findings in the cluster solutions, leaving a list of 40 CC and 15
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33 207 GS. In order to take into account if a CC had required clinical management (CM),
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35 208 a ratio variable (R) was computed as follows:
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39 209 If $CC=0$ & $CM=0 \rightarrow R=0$
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42 210 If $CC=1$ & $CM=m \rightarrow R=1/m$; $\max(m) = \max \text{value}(CM) = 8$;
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46 211 If $CC=1$ & $CM=0 \rightarrow R=0.1$
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49 212 Multimorbidity patterns were identified using the fuzzy c-means cluster analysis
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51 213 algorithm, which belongs to the family of *soft* clustering algorithms. The algorithm
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53 214 estimates c cluster centres (similar to k -means) but with fuzziness so that
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55 215 individuals may belong to more than one pattern. Through this technique, we
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3 216 obtained clusters of individuals and a membership matrix, which indicates the
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5 217 degree of participation of each subject in each cluster.
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8 218 As a first step, and similarly to Violán *et. al.*[24], the PCAmix algorithm for
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10 219 categorical and continuous data (GS and R variables respectively) was
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12 220 implemented to reduce and transform the dataset to all continuous data[25]. To
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14 221 decide the number of retained dimensions, the Karlis-Saporta-Spinaki rule was
15
16 222 used[26]. Then, a soft clustering algorithm was applied to fuzzily distribute the
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18 223 population into a set of clusters, corresponding to the different multimorbidity
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20 224 patterns. We computed three validation indices to obtain the optimal number of
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22 225 clusters (K) and the optimal value of the fuzziness parameter (m): the partition
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24 226 coefficient whose optimal choice for coefficient is at the maximum, and the Xie-
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26 227 Beni and the partition entropy validation indices, whose optimal indices are at the
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28 228 minimum[27]. Considering the stochastic nature of the clusters, and the
29
30 229 requirement of stable multimorbidity clusters, 100 independent clustering
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32 230 repetitions were applied to obtain the stable final solution.
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39 231 To describe each identified cluster of individuals, the prevalence of CC and GS
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41 232 in each one was calculated. Observed/expected (O/E) ratios were calculated by
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43 233 dividing the prevalence of a given disease within a cluster by its prevalence in the
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45 234 overall population. The exclusivity of CC and GS, defined as the fraction of
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47 235 patients with the disease in the cluster over the total number of patients with the
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49 236 disease, was also calculated. A CC or a GS was considered to be relevant in a
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51 237 given cluster of individuals when its O/E ratio was >1 and its exclusivity was
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53 238 $>25\%$ [28–30]. The statistical significant final solution ranged from 4 to 8 clusters.
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57 239 After clinical revision and discussion among the research team, 4 different
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59 240 clusters were considered to be consistent with the clinical observations as well
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241 as the objective of the clustering. There is currently no consensus in the literature
 242 on the criteria used to select the number of clusters or the O/E ratio cut-off point
 243 due to, in part, the novelty of the analysis.

244 Finally, sociodemographic and clinical variables were described for all patients
 245 assigned to each cluster. Analyses were performed using R 3.6.0 and SPSS 22.

246 Patient and Public Involvement

247 Since this was an observational study with variables and outcomes related to the
 248 healthcare process, this research was developed without patient involvement.
 249 Patients were not invited to comment on the study design and were not consulted
 250 to develop patient relevant outcomes or interpret the results.

251 RESULTS

252 740 patients aged 65 years or older were included, with a mean age of 84.12
 253 years (SD 7.01), a 53.24% of females and a mean Barthel Index of 65.07 (median
 254 75). Sociodemographic and clinical variables are summarised in Table 1. Almost
 255 all patients had two or more CC (98.65%; 95%CI 98.23-99.07), with a median of
 256 8 CC and 6 GS per patient. Nearly 70% had consulted a health care service in
 257 the 3 months prior to hospitalization due to chronic disease exacerbation.

258 Table 1. Sociodemographic and clinical variables of the studied cohort.

Sociodemographic and clinical variables	N	%	95% CI	
Age	< 70	33	4.46	3.19 - 6.20
	70-74	48	6.49	4.93 - 8.50
	75-79	82	11.08	9.02 - 13.55
	80-84	181	24.46	21.50 - 27.68
	85-89	232	31.35	28.11 - 34.78
	90-94	134	18.11	15.50 - 21.05
Sex	>= 95	30	4.05	2.85 - 5.73
	Female	394	53.24	49.64 - 56.81

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Sociodemographic and clinical variables		N	%	95% CI
	Male	346	46.76	43.19 - 50.36
Barthel index	< 20	90	12.16	10.00 - 14.71
	20-35	76	10.27	8.28 - 12.67
	40-55	124	16.76	14.24 - 19.62
	60-95	294	39.73	36.27 - 43.30
	100	156	21.08	18.30 - 24.17
Age adjusted, updated Charlson Comorbidity Index	2-5	148	20.00	17.28 - 23.03
	6-8	411	55.54	51.94 - 59.08
	9-14	181	24.46	21.50 - 27.68
Household	With relatives/other people	523	70.68	67.30 - 73.84
	Nursing home	95	12.84	10.62 - 15.44
	Alone	122	16.49	13.99 - 19.33
Chronic disease exacerbation 3 months prior to admission	No	225	30.41	27.20 - 33.81
	Yes (total)	515	69.59	66.19 - 72.80
	Primary care	342	46.22	42.65 - 49.82
	Emergencies	263	35.54	32.17 - 39.06
	Hospital admission	193	26.08	23.05 - 29.36
	Outpatient care	8	1.08	0.55 - 2.12
Conditions requiring clinical management (CM)	Home care	14	1.89	1.13 - 3.15
	1	302	40.81	37.36 - 44.39
	2	216	29.19	26.03 - 32.57
	3	106	14.32	11.98 - 17.03
	4	72	9.73	7.80 - 12.08
	5	28	3.78	2.63 - 5.41
	6	13	1.76	1.03 - 2.98
	7	2	0.27	0.07 - 0.98
Destination at discharge	8	1	0.14	0.007 - 0.76
	Home	468	63.24	59.71 - 66.64
	Nursing home	105	14.19	11.86 - 16.89
	Another hospital	101	13.65	11.36 - 16.31
Multimorbidity	Exitus	66	8.92	7.07 - 11.19
	No	10	1.35	1.35 - 1.36
	Yes	730	98.65	98.23 - 99.07

259 CI = Confidence interval

260 Figure 1 shows the distribution of the number of CC by age groups. The most
 261 frequent CC were hypertension (81.49%, 95%CI 78.53-84.12) and heart failure
 262 (59.86%, 95%CI 56.29-63.34) (see Supplemental Table 2). Heart failure was also
 263 the main cause of hospitalization (30.7% of patients had CM score=1), followed
 264 by COPD (20.7%) (Supplemental Table 3).

265 There were some differences in CC between sexes, with females having more
 266 frequently heart failure, degenerative arthropathy, obesity, hip fracture, thyroid
 267 disease, asthma, osteoporosis, vertigo and non-schizophrenic mental disorders.
 268 Males, in turn, had more frequently COPD, gout, neoplasia, peripheral
 269 arteriopathy and ulcerative disease.

270 The most prevalent GS was polypharmacy (79.86%, 95%CI 76.82-82.60),
 271 followed by frailty (61.76%, 95%CI 58.20-65.19). Females had a significantly
 272 higher number of GS compared to males (Wilcoxon rank sum test, $p < 0.001$), as
 273 well as a higher prevalence of depression/anxiety, chronic pain, constipation,
 274 frailty, urinary/faecal incontinence and immobility.

275 Four statistically and clinically significant multimorbidity clusters or patterns were
 276 identified in our study population. For all clusters, CC and GS with an
 277 observed/expected ratio >1 and exclusivity $>25\%$ are represented in Figure 2
 278 (see also Supplemental Table 4 for all CC and GS). Sociodemographic and
 279 clinical characteristics of patients in each cluster are described in Table 2.

280 Table 2. Sociodemographic and clinical variables of the multimorbidity clusters.

		Osteoarticular	Psycho-geriatric	Minor chronic conditions	Cardio-respiratory
Number of patients included, n (%)		132 (17.8)	153 (20.7)	179 (24.2)	276 (37.3)
Age at admission (y, mean \pm SD)		84.03 \pm 6.48	84.51 \pm 7.25	83.94 \pm 7.19	84.06 \pm 7.03
Sex, n (%)	Male	34 (25.7)	66 (42.8)	99 (55.5)	147 (53.4)
	Female	98 (74.3)	87 (57.2)	80 (44.5)	129 (46.6)
Barthel Index (mean \pm SD)		63.06 \pm 24.78	47.62 \pm 34.94	64.96 \pm 33.56	75.76 \pm 27.52
Total n° chronic conditions (mean \pm SD)		11.5 \pm 3.64	7.68 \pm 3.19	8.86 \pm 3.08	7.59 \pm 2.61
Total n° geriatric syndromes / risk factors (mean \pm SD)		7.76 \pm 2.07	8.16 \pm 2.82	6.4 \pm 3.32	4.42 \pm 2
Charlson Comorbidity Index, n (%)	2-5	26 (19.9)	24 (15.6)	37 (20.4)	61 (22.2)
	6-8	73 (55.1)	89 (58.5)	96 (53.8)	153 (55.3)
	9-14	33 (25.0)	40 (25.9)	46 (25.7)	62 (22.6)
Household, n (%)	With relatives / other people	91 (68.7)	103 (67.2)	133 (74.5)	196 (71.1)

		Osteoarticular	Psycho-geriatric	Minor chronic conditions	Cardio-respiratory
	Nursing home	16 (11.8)	28 (18.4)	23 (12.8)	28 (10.3)
	Alone	26 (19.5)	22 (14.3)	23 (12.7)	52 (18.7)
Chronic disease exacerbation 3 months prior to the index admission, n (%)	No	24 (18.3)	46 (30.1)	48 (27.0)	106 (38.5)
	Yes (total)	108 (81.7)	107 (69.9)	130 (73.0)	170 (61.5)
	Primary care	83 (62.7)	66 (43.3)	92 (51.6)	101 (36.5)
	Emergencies	71 (53.6)	40 (26.2)	69 (38.5)	83 (30.2)
	Hospital admission	49 (37.1)	46 (30.1)	47 (26.1)	51 (18.6)
	Outpatient care	1 (0.7)	0 (0.3)	3 (1.4)	4 (1.4)
	Home care	2 (1.5)	2 (1.1)	3 (1.8)	7 (2.6)
Destination at discharge, n (%)	Home	86 (65.3)	83 (54.0)	111 (62.0)	188 (68.1)
	Nursing home	15 (11.1)	33 (21.3)	26 (14.5)	32 (11.5)
	Another hospital	15 (11.3)	17 (11.3)	26 (14.7)	42 (15.3)
	Exitus	16 (12.3)	20 (13.3)	16 (8.8)	14 (4.9)

281 SD = standard deviation.

282 The first cluster, named *osteoarticular*, included 132 patients (17.8%) having
 283 osteoporosis, fractures, inflammatory osteoarticular disease, chronic pain and
 284 degenerative arthropathy. Moreover, vertigo, sleep apnoea, asthma,
 285 depression/anxiety and sleep disorders were also over-represented. This cluster
 286 included patients with the highest number of both CC and GS. About three
 287 quarters were female, and most of them (82%) accessed healthcare services 3
 288 months prior to this admission.

289 Cluster 2, called *psychogeriatric*, had 152 patients (20.7%) and included mostly
 290 GS: pressure ulcers, immobility, malnutrition, cognitive impairment, dementia,
 291 incontinence and frailty. Patients in this group had a mean Barthel index lower
 292 than 50 and a high number of GS. Furthermore, nearly 20% of them were living
 293 in a nursing home and in-hospital mortality was about 13%.

294 Cluster 3, named *minor chronic disease*, had 179 (24.2%) patients, and
 295 represents a group of patients with a variety of conditions, such as hypertension,
 296 dyslipidaemia, anaemia, gout, chronic renal insufficiency, polypharmacy, non-

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3 297 ischaemic heart disease, and diverse GS. O/E ratios were close to 1 in most
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5 298 cases.
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9 299 Finally, cluster 4, called *cardiorespiratory*, included 276 (37.3%) patients. The
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11 300 over-represented diagnoses were COPD, heart failure and cardiac arrhythmia,
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13 301 although the O/E ratios were very low. In this cluster, with the lowest number of
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15 302 CC and GS, and a Barthel index greater than 75, nearly 40% had no healthcare
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17 303 consultation for a chronic disease exacerbation in the previous 3 months. This
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19 304 group had the lowest in-hospital mortality (5%).
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23 305 **DISCUSSION**

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26 306 The present study aimed to identify multimorbidity patterns in patients aged 65
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28 307 and above admitted to hospital because of an exacerbation of CC. The soft
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30 308 clustering technique used, together with clinical criteria, was able to identify 4
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32 309 different multimorbidity patterns, named osteoarticular, psychogeriatric, cardio-
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34 310 respiratory and minor chronic disease, in a patient-centred approach taking into
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36 311 account the importance of each disease in hospital management. Remarkably,
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38 312 high chronic multimorbidity was found in all patients, regardless of the cluster. To
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40 313 the best of our knowledge, this is the only study published to date that has
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42 314 analysed multimorbidity patterns taking into account both CC (with their weight
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44 315 during clinical management) and GS in this type of patients. Hence, these
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46 316 identified patterns allow us to take a further step towards understanding the
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48 317 patients' current or future healthcare needs.
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55 318 Two very important aspects of multimorbidity patterns analysis are the purpose
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57 319 for designing such patterns and the target population, which clearly condition the
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59 320 obtained results or conclusions. For instance, our aim in defining multimorbidity
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3 321 patterns in this cohort was to identify profiles of patients with similar clinical needs
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5 322 during the index hospitalization and even a similar short-term prognosis at that
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7 323 time. For this reason, the importance of their pathologies in the course of
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9 324 hospitalization was also taken into account. Hence, the ones that tend to have a
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11 325 minimal impact on clinical management, such as risk factors like hypertension or
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13 326 dyslipidaemia did not have a leading role in the patterns.
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17 327 All clusters contain coherent groups of conditions that are mostly
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19 328 pathophysiologically related. From the clinical point of view, these clusters
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21 329 resemble patient profiles that are intuitively perceived. Moreover, some
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23 330 descriptive variables such as sex, Barthel index, mean number of CC or GS,
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25 331 chronic pathology exacerbations in previous months, or hospital mortality, are
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27 332 distributed in such a way that they may reinforce the distinction of these groups.
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32 333 Coexistence of CC and GS was observed in all clusters except for the
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34 334 cardiorespiratory, reinforcing the need to consider other clinically relevant
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36 335 situations rather than only CC. In particular, the exclusivity and prevalence of GS
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38 336 such as immobility, malnutrition, cognitive impairment or dementia were
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40 337 considerable in the psychogeriatric cluster.
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44 338 Interestingly, highly prevalent CC, such as heart failure and COPD, which also
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46 339 frequently involve clinical management, only showed remarkable exclusivity and
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48 340 O/E ratio in the cardiorespiratory pattern and were not over-represented
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50 341 elsewhere. This highlights the fact that even though some CC may not be over-
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52 342 represented in a cluster, they can have a high prevalence and therefore need to
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54 343 be properly addressed too.
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3 344 With respect to the osteoarticular cluster, it displayed a pattern of female
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5 345 predominance, with many CC and GS, high healthcare needs in recent months
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7 346 due to their chronic pathology, and high in-hospital mortality. Thus, this profile
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9 347 would identify a group of patients with a high probability of decompensation and
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11 348 death.

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15 349 Finally, the so-called minor chronic diseases cluster was not very well defined. It
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17 350 included some risk factors (hypertension, dyslipidaemia, polypharmacy) as well
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19 351 as some CC and GS. Thus, it would be possible that it does not represent a real
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21 352 cluster but either the set of cases that did not belong anywhere else.

22 23 24 25 353 Comparison with other studies

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28 354 Given the type of patients under study and the methodological approach to
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30 355 identify multimorbidity patterns, there are few publications to directly compare our
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32 356 results to. Clerencia-Sierra and colleagues[17] analysed multimorbidity patterns
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34 357 in hospitalized older patients. Their methodological and analytical approach was
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36 358 slightly different, and they did not take into account the weight of the diseases
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38 359 during the hospitalization process; however, they found a similar percentage of
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40 360 multimorbidity (99.7%) and 4 patterns that partially coincide with those of our
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42 361 study: cardiovascular, induced-dependency, falls, and osteoarticular.

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47 362 Furthermore, several authors have published data on patterns identified from
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49 363 primary care electronic records in different age groups, with lists of non-
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51 364 comparable chronic problems and using different techniques (cluster analysis,
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53 365 exploratory factor analysis or latent class analysis)[17,29–34]. These results
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55 366 would not be directly comparable with our study, but all of them highlight the
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57 367 ability to identify association patterns of chronic diseases.
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3 368 Strengths and limitations
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6 369 The strengths of this study are the prospective design, ensuring data quality by
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8 370 thorough record keeping, the ascertainment of all CC and GS of the patient, as
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10 371 well as the use of a novel clustering technique. Soft clustering is a
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12 372 methodologically robust technique less susceptible to outliers in the data, choice
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14 373 of distance measure and the inclusion of inappropriate or irrelevant variables[24].
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16 374 Besides, our approach focuses beyond organ diseases by incorporating GS, and
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18 375 using a comprehensive list retrieved by the clinical team. Additionally, we have
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20 376 taken into account the relative importance of the different CC in the clinical
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22 377 management of the patient during hospitalization, thus providing a better picture
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24 378 of the possible complexity and needs during hospitalization.
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30 379 Furthermore, our work is not only limited to the identification of possible patterns.
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32 380 We have validated them, in some way, by analysing some of the patients'
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34 381 variables such as sex, number of CC, previous contacts with the health system,
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36 382 hospital mortality or need for a nursing home.
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40 383 Nonetheless, our study presents some limitations that need to be considered.
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42 384 Firstly, the identification of chronic pathologies does not exclusively follow a
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44 385 validated list of codes but either an adaptation of different ones, a fact that could
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46 386 hinder comparability with other studies on multimorbidity. Secondly, as this study
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48 387 is not longitudinal, the chronology in which CC or GS appear cannot be analysed.
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50 388 It is possible for a patient to evolve from one pattern to another throughout life,
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52 389 as some authors have already pointed out[35], and therefore, the results only
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54 390 show the present situation. However, given the purpose of the defined patterns,
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56 391 this would not in itself be a limitation.
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3 392 From a clinical point of view, the lack of usage of standard scales or diagnostic
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5 393 criteria for determining all CC or GS could question the validity of this information.
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7 394 However, the study gathered the data as it was routinely registered in the different
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9 395 departments. Frailty should derive from a comprehensive assessment of the
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11 396 patient in a standardized way that still lacks of systematic implementation in the
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13 397 healthcare routine[36]. Nevertheless, our multimorbidity study wanted to go a little
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15 398 further, also considering GS (frailty included), an unusual fact in the bibliography
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17 399 on clusters of multimorbidity in older patients in spite of its importance for decision
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19 400 making in the clinical practice.

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24 401 The clinical conditions severity or other possible aggravating factors have neither
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26 402 been gathered. Nevertheless, the registration of a variable that takes into account
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28 403 the relevance of each CC during the care process acts, in some way, as a proxy
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30 404 of the importance of each disease in the index hospitalization when dealing with
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32 405 patients admitted because of decompensation. Considering the purpose of
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34 406 defining the patterns in the whole study, and not knowing useful precedents in
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36 407 the consulted bibliography, the assignment made by the medical professional
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38 408 who attended the patient was an easy, simple measure, and shared by all
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40 409 professionals at the time of writing the clinical course.

41 Clinical implications

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49 411 These patterns are not a picture of the community but of older patients in geriatric
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51 412 or internal medicine departments, which are generally in more need of health
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53 413 services and more complex clinical management. However, not all of these
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55 414 patients have the same requirements. In fact, one in five patients (the
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57 415 psychogeriatric cluster) caused a great burden to both the patient and their
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3 416 relatives while the patients in the most frequent cluster (cardiorespiratory), with
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5 417 lower dependency and less GS, seemed to have better immediate outcome.
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7 418 Therefore, it is possible that the therapeutic objectives should be different in these
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9 419 patients. More importantly, the ability to distinguish patients more objectively than
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11 420 with the mere clinical impression may allow the design of better processes,
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13 421 services or alternatives to conventional hospitalization. Indeed, the identification
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15 422 of multimorbidity patterns in subsets of the population in order to detect
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17 423 underlying factors, understand their burden on patients and develop preventive
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19 424 strategies is considered a research priority. Finally, the development of clinical
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21 425 practice guidelines according to these patterns needs to be considered, although
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23 426 it may be difficult given the magnitude of the diseases comprised in each pattern
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25 427 [4,14]. In addition, some patterns may include patients with an increased risk of
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27 428 potentially inappropriate prescription or adverse drug reactions. These aspects
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29 429 will be the object of future analyses.
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36 430 **Conclusions**

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39 431 In conclusion, in older patients admitted to hospital because of the exacerbation
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41 432 of chronic health problems, it is possible to define multimorbidity clusters or
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43 433 patterns using appropriate statistical techniques. These patterns seem clinically
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45 434 coherent and could be the basis to reorganize circuits, processes or healthcare
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47 435 models to tackle the increasing number of older, multimorbid patients.
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51 436 **List of abbreviations**

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54 437 CC: chronic condition

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57 438 GS: geriatric syndrome
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3 439 CM: clinical management
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6 440 O/E: observed/expected
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9 441 COPD: chronic obstructive pulmonary disease
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12 442 **Figure captions**

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15 443 Figure 1. Distribution of the number of chronic conditions (excluding the following
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17 444 risk factors: hypertension, dyslipidaemia, obesity, osteoporosis and drug-related
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19 445 conditions) in relation to age groups.
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23 446 Figure 2. Observed/Expected (O/E) ratio and prevalence of chronic conditions
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25 447 and geriatric syndromes/risk factors per multimorbidity cluster. Conditions with
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27 448 exclusivity >25% and O/E ratios >1 in each cluster are represented. Conditions
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29 449 are ordered by O/E ratio and from cluster 1 to 4. *COPD: Chronic Obstructive*
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32 450 *Pulmonary Disease*
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23
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30 470 **Authors' contributions**

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33 471 MB conceived and supervised the study, discussed the results, wrote the first
34
35 472 version of the manuscript. SH, RJ, MA, RE and GJN participated in patient
36
37 473 inclusion, data collection and discussion of the results and revised the
38
39 474 manuscript. AR executed the analysis and interpretation of multimorbidity
40
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42
43 476 of the multimorbidity patterns. ML participated in the statistical and graphical
44
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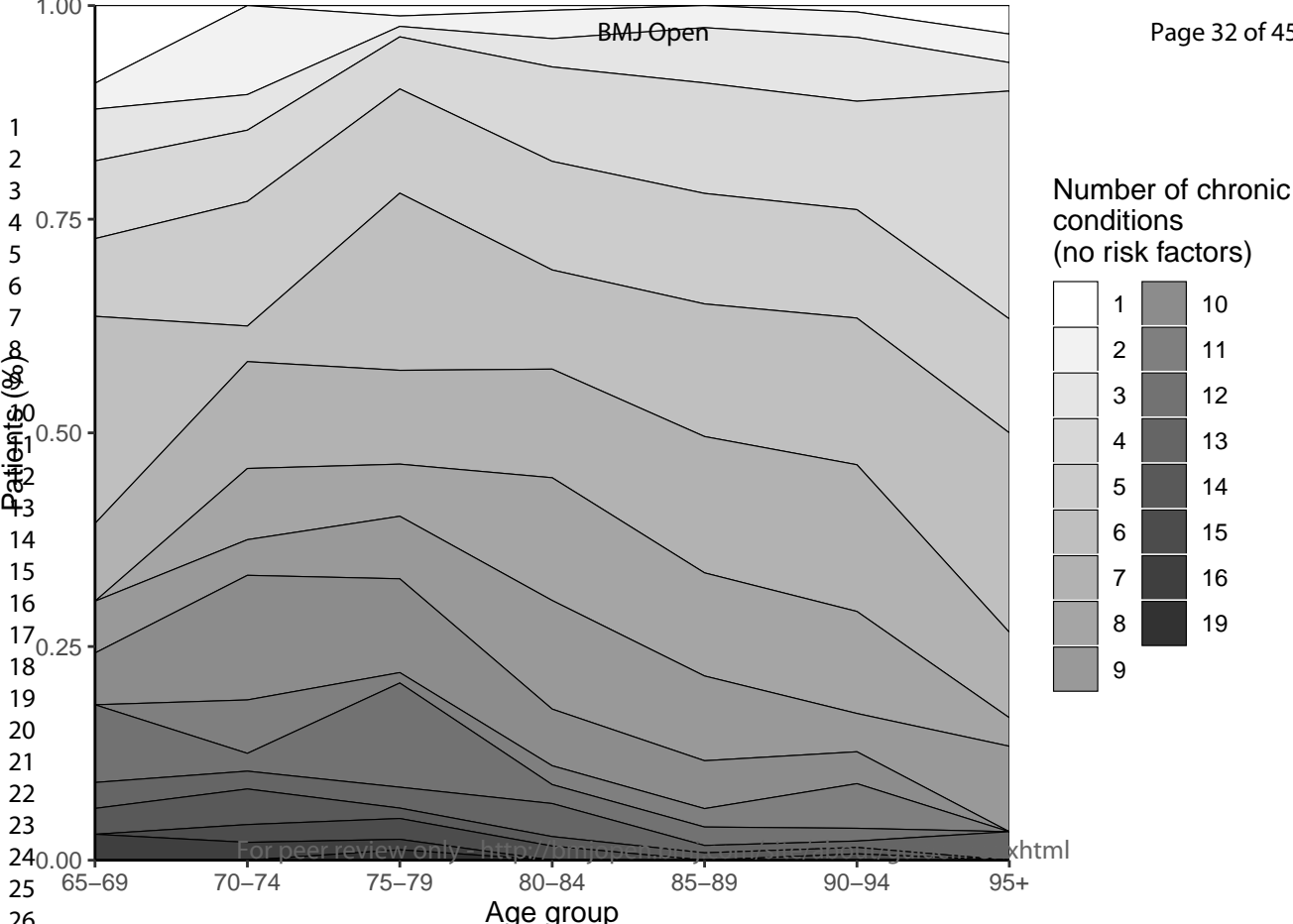
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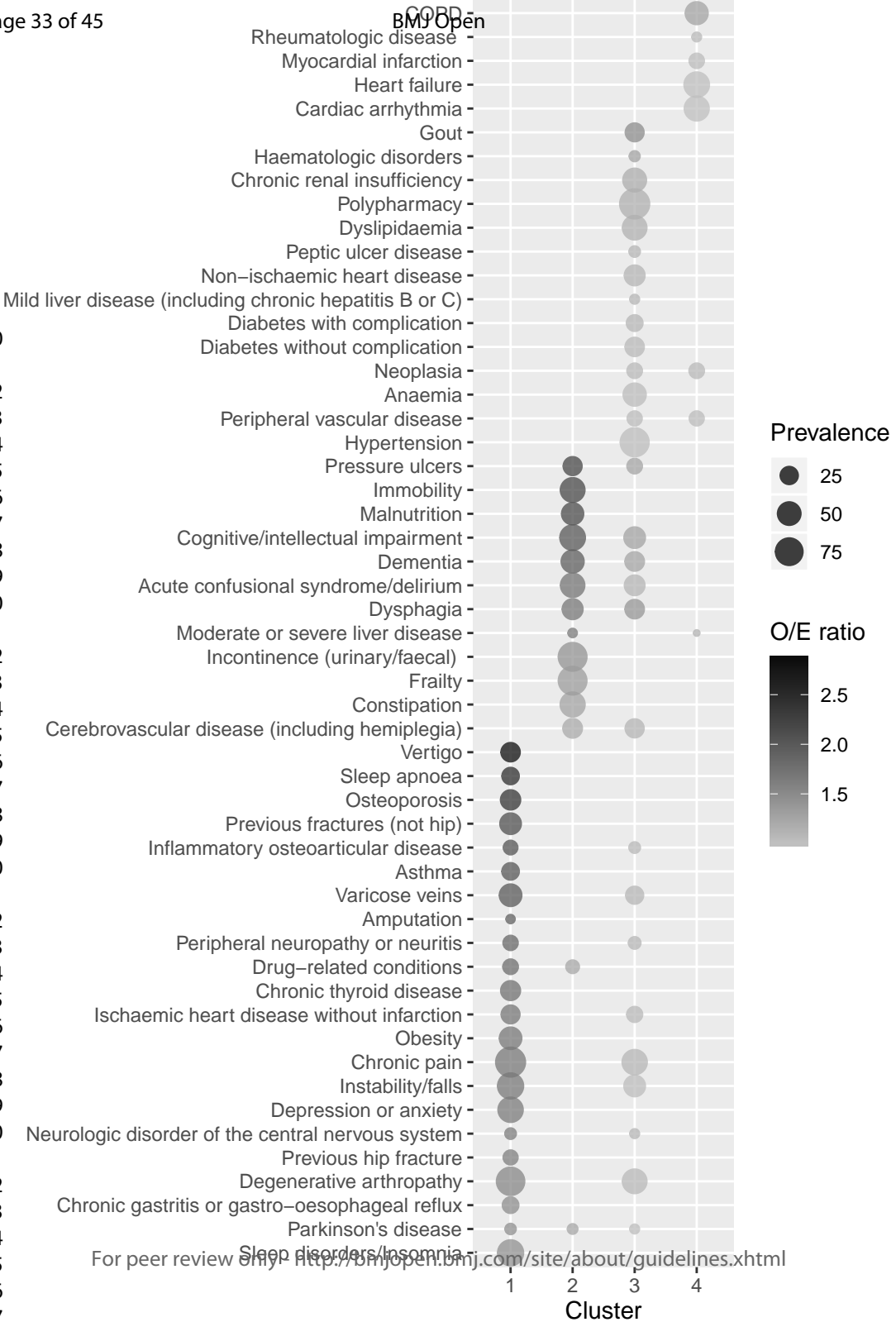
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Supplemental Table 1. Chronic conditions and geriatric syndromes recorded.

Chronic conditions	Geriatric syndromes and risk factors
<i>Charlson Index</i>	
1. AIDS/HIV	Acute confusional syndrome/delirium
2. Any malignancy (excluding skin)	Chronic pain
3. Cerebrovascular disease	Cognitive/Intellectual impairment
4. Chronic obstructive pulmonary disease	Constipation
5. Congestive heart failure	Depression or Anxiety
6. Dementia	Dysphagia
7. Diabetes with complication	Frailty
8. Diabetes without complication	Immobility
9. Hemiplegia	Incontinence (Urinary/faecal)
10. Leukaemia	Instability/falls
11. Lymphoma	Malnutrition
12. Metastatic solid tumour	Polypharmacy
13. Mild liver disease	Pressure ulcers
14. Moderate or severe liver disease	Sensorial deficit
15. Moderate or severe renal disease	Sleep disorders/Insomnia
16. Myocardial infarction	
17. Peptic ulcer disease	
18. Peripheral vascular disease	
19. Rheumatologic disease	
<i>Other conditions</i>	
20. Amputation	
21. Anaemia	
22. Asthma	
23. Cardiac arrhythmia	
24. Cataract	
25. Chronic hepatitis (B or C)	
26. Chronic pancreatic disease	
27. Degenerative arthropathy	
28. Dermatitis or eczema	

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- 1 29. Diverticular disease of the colon
 - 2 30. Drug-related conditions
 - 3 31. Dyslipidaemia (risk factor)
 - 4 32. Fibromyalgia
 - 5 33. Gallstones (previous hepatic colic)
 - 6 34. Chronic gastritis or gastro-oesophageal
 - 7 reflux
 - 8 35. Glaucoma
 - 9 36. Gout
 - 10 37. Haemorrhoids
 - 11 38. Haematologic disorders (myelodysplastic
 - 12 syndrome, gammopathy, polycythaemia)
 - 13 39. Hypertension (risk factor)
 - 14 40. Inflammatory osteoarticular disease
 - 15 41. Irritable bowel syndrome
 - 16 42. Ischaemic heart disease without infarction
 - 17 43. Migraine
 - 18 44. Neurologic disorder of the central nervous
 - 19 system
 - 20 45. Non-congestive heart failure
 - 21 46. Non-ischaemic heart disease
 - 22 (miocardiopathy, valvulopathy)
 - 23 47. Non-schizophrenic mental disorders
 - 24 (excluding depression and anxiety)
 - 25 48. Obesity (risk factor)
 - 26 49. Osteoporosis (risk factor)
 - 27 50. Other neurological pathologies (essential
 - 28 tremor)
 - 29 51. Other vascular diseases (ischaemia,
 - 30 aneurism)
 - 31 52. Parkinson's disease
 - 32 53. Peripheral neuropathy or neuritis
 - 33 54. Post-traumatic stress disorder
 - 34 55. Previous fractures (not hip)
 - 35 56. Previous hip fracture
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1 57. Prostatic benign hypertrophy

2 58. Schizophrenia

3 59. Sleep apnoea

4 60. Chronic thyroid disease

5 61. Tuberculosis

6 62. Urinary tract stones (nephritic colic)

7 63. Varicose veins of lower extremities

8 64. Vertigo

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Supplemental Table 2. Prevalence rates of chronic conditions and geriatric syndromes / risk factors in the study population by sex, separately listed in decreasing order of total prevalence rate.

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
CHRONIC CONDITIONS									
Risk factors									
Hypertension	330	83.76	79.79 - 87.07	273	78.90	74.30 - 82.87	603	81.49	78.53 - 84.12
Dyslipidaemia	189	47.97	43.08 - 52.90	171	49.42	44.19 - 54.67	360	48.65	45.06 - 52.25
Obesity	127	32.23	27.81 - 37.00	66	19.08	15.28 - 23.55	193	26.08	23.05 - 29.36
Osteoporosis	82	20.81	17.09 - 25.09	21	6.07	4.00 - 9.10	103	13.92	11.61 - 16.60
Drug-related conditions	44	11.17	8.42 - 14.66	23	6.65	4.47 - 9.78	67	9.05	7.19 - 11.34
Chronic Diseases									
Heart failure	255	64.72	59.88 - 69.28	188	54.34	49.07 - 59.51	443	59.86	56.29 - 63.34
Cardiac arrhythmia	216	54.82	49.89 - 59.67	207	59.83	54.58 - 64.86	423	57.16	53.57 - 60.68
Degenerative arthropathy	228	57.87	52.94 - 62.64	157	45.38	40.21 - 50.64	385	52.03	48.43 - 55.61
Anaemia	182	46.19	41.33 - 51.13	152	43.93	38.80 - 49.20	334	45.14	41.58 - 48.74
Moderate or severe renal disease	164	41.62	36.86 - 46.55	156	45.09	39.93 - 50.35	320	43.24	39.72 - 46.84
Chronic obstructive pulmonary disease (COPD)	90	22.84	18.97 - 27.24	183	52.89	47.63 - 58.09	273	36.89	33.49 - 40.43
Non-ischaemic heart disease	125	31.73	27.33 - 36.48	113	32.66	27.93 - 37.77	238	32.16	28.90 - 35.61
Diabetes without complication	101	25.63	21.57 - 30.17	100	28.90	24.38 - 33.89	201	27.16	24.08 - 30.48
Cerebrovascular disease (including hemiplegia)	95	24.11	20.15 - 28.57	93	26.88	22.48 - 31.78	188	25.41	22.40 - 28.66
Dementia	103	26.14	22.05 - 30.70	76	21.97	17.92 - 26.62	179	24.19	21.24 - 27.40
Varicose veins of lower extremities	98	24.87	20.86 - 29.37	66	19.08	15.28 - 23.55	164	22.16	19.32 - 25.29
Previous fracture (not hip)	87	22.08	18.27 - 26.44	52	15.03	11.65 - 19.18	139	18.78	16.13 - 21.76
Gout	57	14.47	11.34 - 18.28	80	23.12	18.99 - 27.84	137	18.51	15.88 - 21.47
Chronic thyroid disease	93	23.60	19.68 - 28.04	42	12.14	9.11 - 16.00	135	18.24	15.63 - 21.19
Diabetes with complication	70	17.77	14.31 - 21.85	63	18.21	14.50 - 22.62	133	17.97	15.37 - 20.90
Ischaemic heart disease without infarction	58	14.72	11.56 - 18.56	62	17.92	14.24 - 22.31	120	16.22	13.74 - 19.05
Myocardial infarction	47	11.93	9.09 - 15.50	64	18.50	14.76 - 22.93	111	15.00	12.61 - 17.75
Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	29	7.36	5.17 - 10.37	82	23.70	19.52 - 28.45	111	15.00	12.61 - 17.75
Peripheral vascular disease	31	7.87	5.60 - 10.95	74	21.39	17.39 - 26.01	105	14.19	11.86 - 16.89
Chronic gastritis or gastro-oesophageal reflux	55	13.96	10.88 - 17.73	42	12.14	9.11 - 16.00	97	13.11	10.87 - 15.73

	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
Asthma	74	18.78	15.23 - 22.93	8	2.31	1.18 - 4.50	82	11.08	9.02 - 13.55
Gallstones	39	9.90	7.33 - 13.25	40	11.56	8.61 - 15.36	79	10.68	8.65 - 13.11
Vertigo	54	13.71	10.66 - 17.45	23	6.65	4.47 - 9.78	77	10.41	8.41 - 12.81
Previous hip fracture	52	13.20	10.21 - 16.90	15	4.34	2.64 - 7.03	67	9.05	7.19 - 11.34
Sleep apnoea	34	8.63	6.24 - 11.82	32	9.25	6.63 - 12.76	66	8.92	7.07 - 11.19
Peripheral neuropathy or neuritis	27	6.85	4.75 - 9.79	34	9.83	7.12 - 13.42	61	8.24	6.47 - 10.45
Inflammatory osteoarticular disease	26	6.60	4.54 - 9.49	23	6.65	4.47 - 9.78	49	6.62	5.04 - 8.65
Peptic ulcer disease	11	2.79	1.57 - 4.93	35	10.12	7.36 - 13.74	46	6.22	4.69 - 8.19
Haematologic disorders	14	3.55	2.13 - 5.88	22	6.36	4.24 - 9.44	36	4.86	3.53 - 6.66
Parkinson disease	15	3.81	2.32 - 6.19	19	5.49	3.54 - 8.42	34	4.59	3.31 - 6.35
Rheumatologic disease	22	5.58	3.72 - 8.31	10	2.89	1.58 - 5.24	32	4.32	3.08 - 6.04
Mild liver disease (including chronic hepatitis B or C)	12	3.05	1.75 - 5.25	20	5.78	3.77 - 8.76	32	4.32	3.08 - 6.04
Neurologic disorder of the CNS	11	2.79	1.57 - 4.93	21	6.07	4.00 - 9.10	32	4.32	3.08 - 6.04
Moderate or severe liver disease	9	2.28	1.21 - 4.28	10	2.89	1.58 - 5.24	19	2.57	1.65 - 3.98
Amputation	4	1.02	0.40 - 2.58	12	3.47	1.99 - 5.96	16	2.16	1.34 - 3.48
Urinary tract stones	9	2.28	1.21 - 4.28	5	1.45	0.62 - 3.34	14	1.89	1.13 - 3.15
Non-schizophrenic mental disorders	11	2.79	1.57 - 4.93	1	0.29	0.01 - 1.62	12	1.62	0.93 - 2.81
Irritable bowel syndrome	7	1.78	0.86 - 3.62	4	1.16	0.45 - 2.93	11	1.49	0.83 - 2.64
Chronic pancreatic disease	4	1.02	0.40 - 2.58	6	1.73	0.80 - 3.73	10	1.35	0.74 - 2.47
Tuberculosis	5	1.27	0.54 - 2.94	4	1.16	0.45 - 2.93	9	1.22	0.64 - 2.30
Other neurological pathologies	3	0.76	0.26 - 2.21	6	1.73	0.80 - 3.73	9	1.22	0.64 - 2.30
Fibromyalgia	6	1.52	0.70 - 3.28	2	0.58	0.16 - 2.08	8	1.08	0.55 - 2.12
Migraine	4	1.02	0.40 - 2.58	0	0.00	0.00 - 1.10	4	0.54	0.21 - 1.38
Schizophrenia	1	0.25	0.01 - 1.42	2	0.58	0.16 - 2.08	3	0.41	0.14 - 1.19
Post-traumatic stress disorder	1	0.25	0.01 - 1.42	2	0.58	0.16 - 2.08	3	0.41	0.14 - 1.19
AIDS/HIV	0	0.00	0.00 - 0.00	0	0.00	0.00 - 0.00	0	0.00	0.00 - 0.00
GERIATRIC SYNDROMES AND RISK FACTORS									
Polypharmacy	310	78.68	74.37 - 82.44	281	81.21	76.76 - 84.98	591	79.86	76.82 - 82.60
Frailty	269	68.27	63.52 - 72.67	188	54.34	49.07 - 59.51	457	61.76	58.20 - 65.19
Incontinence (Urinary/faecal)	273	69.29	64.57 - 73.64	157	45.38	40.21 - 50.64	430	58.11	54.52 - 61.61
Chronic pain	231	58.63	53.71 - 63.39	171	49.42	44.19 - 54.67	402	54.32	50.72 - 57.88
Constipation	201	51.02	46.09 - 55.92	139	40.17	35.14 - 45.42	340	45.95	42.39 - 49.55

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	Female (394)			Male (346)			Total (740)		
	N	%	95% CI	N	%	95% CI	N	%	95%CI
Sleep disorders/Insomnia	189	47.97	43.08 - 52.90	144	41.62	36.54 - 46.88	333	45.00	41.45 - 48.60
Sensorial deficit	169	42.89	38.10 - 47.83	145	41.91	36.83 - 47.17	314	42.43	38.92 - 46.02
Instability/falls	158	40.10	35.38 - 45.01	128	36.99	32.08 - 42.20	286	38.65	35.21 - 42.21
Depression or anxiety	193	48.98	44.08 - 53.91	75	21.68	17.66 - 26.32	268	36.22	32.83 - 39.74
Acute confusional syndrome / delirium	118	29.95	25.64 - 34.65	117	33.82	29.03 - 38.95	235	31.76	28.50 - 35.20
Cognitive/Intellectual impairment	133	33.76	29.26 - 38.56	96	27.75	23.29 - 32.69	229	30.95	27.72 - 34.37
Immobility	114	28.93	24.68 - 33.60	78	22.54	18.46 - 27.23	192	25.95	22.92 - 29.22
Dysphagia	78	19.80	16.16 - 24.01	81	23.41	19.26 - 28.15	159	21.49	18.68 - 24.59
Malnutrition	76	19.29	15.70 - 23.47	71	20.52	16.60 - 25.09	147	19.86	17.15 - 22.89
Pressure ulcers	57	14.47	11.34 - 18.28	38	10.98	8.11 - 14.72	95	12.84	10.62 - 15.44

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Supplemental Table 3. Weight as an indicator of importance on clinical management assigned to each chronic condition. Weight values range from 0 to 8, where 0 means no clinical management was required and 1 to 8 indicate clinical management from main cause of hospitalization (1) to chronic condition requiring the least medical attention (8). Chronic conditions are displayed in alphabetical order.

Chronic conditions	Weight 0		Weight 1		Weight 2		Weight 3		Weight 4		Weight 5		Weight 6		Weight 7		Weight 8	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
AIDS/HIV	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Amputation	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Anaemia	596	80.54	28	3.78	46	6.22	40	5.41	19	2.57	8	1.08	3	0.41	0	0	0	0
Asthma	704	95.14	30	4.05	3	0.41	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Rheumatologic disease	729	98.51	5	0.68	3	0.41	3	0.41	0	0	0	0	0	0	0	0	0	0
Cardiac arrhythmia	595	80.41	35	4.73	69	9.32	28	3.78	10	1.35	3	0.41	0	0	0	0	0	0
Cerebrovascular disease (including hemiplegia)	703	95	28	3.78	3	0.41	3	0.41	2	0.27	1	0.14	0	0	0	0	0	0
Chronic gastritis or gastro-oesophageal reflux	733	99.05	4	0.54	1	0.14	1	0.14	1	0.14	0	0	0	0	0	0	0	0
Chronic pancreatic disease	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Chronic obstructive pulmonary disease (COPD)	554	74.86	153	20.68	19	2.57	8	1.08	5	0.68	0	0	1	0.14	0	0	0	0
Chronic thyroid disease	722	97.57	2	0.27	1	0.14	4	0.54	7	0.95	3	0.41	1	0.14	0	0	0	0
Degenerative arthropathy	718	97.03	3	0.41	7	0.95	4	0.54	4	0.54	3	0.41	1	0.14	0	0	0	0
Dementia	687	92.84	32	4.32	14	1.89	4	0.54	3	0.41	0	0	0	0	0	0	0	0
Diabetes with complication	710	95.95	9	1.22	7	0.95	5	0.68	4	0.54	2	0.27	3	0.41	0	0	0	0
Diabetes without complication	698	94.32	11	1.49	5	0.68	13	1.76	8	1.08	2	0.27	1	0.14	2	0.27	0	0
Drug-related conditions	722	97.57	5	0.68	3	0.41	3	0.41	4	0.54	1	0.14	1	0.14	1	0.14	0	0
Dyslipidaemia	735	99.32	0	0	0	0	0	0	4	0.54	1	0.14	0	0	0	0	0	0
Fibromyalgia	739	99.86	0	0	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
Gallstones	730	98.65	6	0.81	3	0.41	1	0.14	0	0	0	0	0	0	0	0	0	0
Gout	737	99.59	0	0	0	0	2	0.27	0	0	1	0.14	0	0	0	0	0	0
Haematologic disorders	730	98.65	2	0.27	5	0.68	2	0.27	1	0.14	0	0	0	0	0	0	0	0
Heart failure	410	55.41	227	30.68	85	11.49	13	1.76	4	0.54	0	0	1	0.14	0	0	0	0
Hypertension	698	94.32	10	1.35	14	1.89	12	1.62	4	0.54	2	0.27	0	0	0	0	0	0
Inflammatory osteoarticular disease	727	98.24	8	1.08	1	0.14	1	0.14	1	0.14	1	0.14	1	0.14	0	0	0	0
Irritable bowel syndrome	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Ischaemic heart disease without infarction	714	96.49	10	1.35	14	1.89	1	0.14	0	0	1	0.14	0	0	0	0	0	0

1	Migraine	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
2	Mild liver disease (including chronic hepatitis B or C)	733	99.05	5	0.68	0	0	1	0.14	0	0	0	0	0	0	1	0.14
3	Moderate or severe liver disease	724	97.84	12	1.62	2	0.27	1	0.14	0	0	1	0.14	0	0	0	0
4	Moderate or severe renal disease	552	74.59	39	5.27	77	10.41	44	5.95	23	3.11	4	0.54	1	0.14	0	0
5	Myocardial infarction	716	96.76	20	2.7	3	0.41	1	0.14	0	0	0	0	0	0	0	0
6	Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	724	97.84	5	0.68	7	0.95	1	0.14	1	0.14	2	0.27	0	0	0	0
7	Neurologic disorder of the CNS	736	99.46	2	0.27	2	0.27	0	0	0	0	0	0	0	0	0	0
8	Non-ischaemic heart disease	695	93.92	15	2.03	16	2.16	12	1.62	0	0	2	0.27	0	0	0	0
9	Non-schizophrenic mental disorders	732	98.92	2	0.27	2	0.27	1	0.14	2	0.27	1	0.14	0	0	0	0
10	Obesity	737	99.59	0	0	1	0.14	2	0.27	0	0	0	0	0	0	0	0
11	Osteoporosis	730	98.65	2	0.27	3	0.41	2	0.27	2	0.27	0	0	1	0.14	0	0
12	Other neurological pathologies	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
13	Parkinson's disease	737	99.59	3	0.41	0	0	0	0	0	0	0	0	0	0	0	0
14	Peptic ulcer disease	737	99.59	2	0.27	1	0.14	0	0	0	0	0	0	0	0	0	0
15	Peripheral neuropathy or neuritis	737	99.59	1	0.14	1	0.14	1	0.14	0	0	0	0	0	0	0	0
16	Peripheral vascular disease	728	98.38	9	1.22	1	0.14	1	0.14	0	0	0	0	1	0.14	0	0
17	Post-traumatic stress disorder	739	99.86	1	0.14	0	0	0	0	0	0	0	0	0	0	0	0
18	Previous fracture (not hip)	730	98.65	5	0.68	2	0.27	2	0.27	1	0.14	0	0	0	0	0	0
19	Previous hip fracture	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
20	Schizophrenia	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
21	Sleep apnoea	716	96.76	5	0.68	9	1.22	5	0.68	1	0.14	4	0.54	0	0	0	0
22	Tuberculosis	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
23	Urinary tract stones	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0
24	Varicose veins of lower extremities	725	97.97	1	0.14	6	0.81	2	0.27	4	0.54	2	0.27	0	0	0	0
25	Vertigo	740	100	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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Supplemental table 4. Prevalence, Observed/Expected (O/E) ratios and exclusivity of chronic conditions and geriatric syndromes / risk factors per multimorbidity cluster. Conditions with prevalence >2% were included. O/E ratios were calculated by dividing the prevalence of a disease within the cluster by its prevalence in the overall population. Exclusivity was calculated by dividing the number of patients with the disease in the cluster by the total number of participants with the disease. Conditions are ordered by decreasing O/E ratio of cluster 1.

	Cluster 1			Cluster 2			Cluster 3			Cluster 4		
	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)	Prevalence (%)	O/E ratio	Exclusivity (%)
Vertigo	29.58	2.84	50.67	9.52	0.91	18.92	6.85	0.66	15.90	4.05	0.39	14.52
Sleep apnoea	22.11	2.48	44.19	5.82	0.65	13.50	8.12	0.91	21.99	4.85	0.54	20.33
Osteoporosis	33.39	2.40	42.76	9.95	0.71	14.79	9.44	0.68	16.38	9.72	0.70	26.07
Previous fracture (not hip)	39.67	2.11	37.65	17.87	0.95	19.68	15.16	0.81	19.49	11.66	0.62	23.19
Inflammatory osteoarticular disease	13.61	2.06	36.65	2.78	0.42	8.69	7.21	1.09	26.31	5.03	0.76	28.36
Asthma	22.50	2.03	36.19	9.37	0.85	17.49	7.77	0.70	16.94	8.72	0.79	29.37
Varicose veins of lower extremities	44.58	2.01	35.86	15.2	0.69	14.19	24.37	1.10	26.56	13.89	0.63	23.40
Amputation	4.190	1.94	34.56	1.72	0.8	16.45	2.00	0.92	22.30	1.55	0.71	26.69
Peripheral neuropathy or neuritis	15.37	1.86	33.23	6.00	0.73	15.06	9.03	1.10	26.46	5.58	0.68	25.26
Drug-related conditions	16.31	1.80	32.12	11.23	1.24	25.66	7.41	0.82	19.76	5.45	0.60	22.46
Chronic thyroid disease	32.14	1.76	31.40	13.73	0.75	15.57	16.06	0.88	21.26	15.52	0.85	31.77
Ischaemic heart disease without infarction	27.75	1.71	30.5	10.85	0.67	13.84	17.59	1.08	26.20	12.79	0.79	29.46
Obesity	44.29	1.70	30.27	19.14	0.73	15.18	25.15	0.96	23.28	21.84	0.84	31.27
Chronic pain	91.68	1.69	30.09	50.3	0.93	19.15	59.72	1.10	26.55	35.23	0.65	24.22
Instability/falls	65.05	1.68	30.00	36.74	0.95	19.66	40.06	1.04	25.03	26.19	0.68	25.30
Depression or Anxiety	60.05	1.66	29.56	35.49	0.98	20.27	30.57	0.84	20.38	28.89	0.80	29.79
Neurologic disorder of the CNS	7.10	1.64	29.28	4.92	1.14	23.54	4.78	1.11	26.72	2.37	0.55	20.47
Previous hip fracture	14.76	1.63	29.06	9.23	1.02	21.08	6.20	0.69	16.55	8.08	0.89	33.31
Degenerative arthropathy	80.19	1.54	27.48	48.11	0.92	19.13	56.15	1.08	26.06	38.08	0.73	27.34
Chronic gastritis or gastro-oesophageal reflux	19.39	1.48	26.37	9.09	0.69	14.35	12.6	0.96	23.22	12.66	0.97	36.07
Parkinson's disease	6.72	1.46	26.07	5.73	1.25	25.78	4.77	1.04	25.08	2.84	0.62	23.06
Sleep disorders/Insomnia	64.93	1.44	25.72	51.57	1.15	23.70	42.58	0.95	22.85	33.41	0.74	27.73
Moderate or severe renal disease	59.30	1.37	24.44	29.11	0.67	13.92	51.19	1.18	28.59	38.27	0.88	33.05
Non-ischaemic heart disease	43.07	1.34	23.87	23.15	0.72	14.89	36.01	1.12	27.04	29.46	0.92	34.20

1	Myocardial infarction	19.88	1.33	23.63	10.00	0.67	13.79	14.68	0.98	23.64	15.64	1.04	38.94
2	Dyslipidaemia	64.28	1.32	23.55	35.21	0.72	14.97	55.63	1.14	27.62	44.11	0.91	33.86
3	Frailty	81.11	1.31	23.41	82.71	1.34	27.70	55.05	0.89	21.53	45.26	0.73	27.36
4	Anaemia	59.26	1.31	23.40	42.23	0.94	19.35	47.71	1.06	25.53	38.34	0.85	31.72
5	Gallstones	13.87	1.30	23.16	10.6	0.99	20.54	9.66	0.90	21.85	9.85	0.92	34.46
6	Haematologic disorders	6.24	1.28	22.88	2.80	0.58	11.91	6.24	1.28	30.99	4.46	0.92	34.22
7	Constipation	57.53	1.25	22.32	58.53	1.27	26.35	36.80	0.80	19.34	39.36	0.86	31.99
8	Incontinence (Urinary/faecal)	72.26	1.24	22.17	82.95	1.43	29.52	54.73	0.94	22.75	39.78	0.68	25.56
9	Gout	22.86	1.23	22.01	9.85	0.53	11.01	27.66	1.49	36.08	15.32	0.83	30.90
10	Diabetes with complication	21.71	1.21	21.53	14.68	0.82	16.89	19.79	1.10	26.59	16.84	0.94	34.99
11	Polypharmacy	96.12	1.20	21.45	64.75	0.81	16.77	92.87	1.16	28.08	72.07	0.90	33.70
12	Rheumatologic disease	5.08	1.17	20.93	4.16	0.96	19.91	3.34	0.77	18.66	4.69	1.08	40.50
13	Dysphagia	24.83	1.16	20.60	36.49	1.70	35.13	29.98	1.40	33.70	6.09	0.28	10.58
14	Cerebrovascular disease (including hemiplegia)	29.02	1.14	20.36	30.75	1.21	25.04	28.38	1.12	26.98	18.79	0.74	27.62
15	Acute confusional syndrome/delirium	36.00	1.13	20.21	54.77	1.72	35.67	35.27	1.11	26.82	14.71	0.46	17.30
16	Heart failure	66.53	1.11	19.81	57.88	0.97	20.00	54.09	0.90	21.82	61.52	1.03	38.37
17	Peripheral vascular disease	15.71	1.11	19.74	10.69	0.75	15.58	14.98	1.06	25.50	14.89	1.05	39.17
18	Hypertension	89.07	1.09	19.48	78.13	0.96	19.83	84.73	1.04	25.11	77.62	0.95	35.57
19	Cardiac arrhythmia	61.85	1.08	19.29	52.03	0.91	18.82	56.49	0.99	23.87	58.20	1.02	38.02
20	Peptic ulcer disease	6.70	1.08	19.22	5.00	0.80	16.64	6.97	1.12	27.09	6.17	0.99	37.05
21	Sensorial deficit	39.51	0.93	16.60	44.27	1.04	21.58	43.84	1.03	24.95	41.89	0.99	36.87
22	Immobility	23.10	0.89	15.87	56.49	2.18	45.03	26.23	1.01	24.41	10.21	0.39	14.69
23	Moderate or severe liver disease	2.23	0.87	15.46	4.33	1.69	34.91	0.69	0.27	6.51	2.96	1.15	43.11
24	Neoplasia (including leukaemia, lymphoma, metastatic solid tumour)	12.74	0.85	15.15	13.39	0.89	18.46	16.19	1.08	26.07	16.20	1.08	40.32
25	Chronic obstructive pulmonary disease (COPD)	29.97	0.81	14.48	27.29	0.74	15.30	34.75	0.94	22.75	46.90	1.27	47.47
26	Mild liver disease (including chronic hepatitis B or C)	3.41	0.79	14.04	4.69	1.08	22.41	4.81	1.11	26.84	4.25	0.98	36.70
27	Cognitive/Intellectual impairment	23.44	0.76	13.50	62.07	2.01	41.48	39.53	1.28	30.85	11.74	0.38	14.17
28	Diabetes without complication	20.64	0.76	13.54	30.98	1.14	23.59	29.45	1.08	26.18	26.69	0.98	36.69
29	Pressure ulcers	7.44	0.58	10.33	28.11	2.19	45.28	16.20	1.26	30.48	4.78	0.37	13.90
30	Dementia	12.34	0.51	9.10	47.13	1.95	40.30	30.43	1.26	30.38	13.10	0.54	20.23
31	Malnutrition	8.69	0.44	7.80	42.75	2.15	44.50	13.57	0.68	16.50	16.60	0.84	31.20

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STROBE Statement—Checklist of items that should be included in reports of *cohort studies*

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	1 2-3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-8
Bias	9	Describe any efforts to address potential sources of bias	7-8
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-11
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	8-11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	11
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	11-12
Outcome data	15*	Report numbers of outcome events or summary measures over time	12

1	Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-14
2			(b) Report category boundaries when continuous variables were categorized	
3			(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
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9	Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	-
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11	Discussion			
12				
13	Key results	18	Summarise key results with reference to study objectives	15-16
14				
15	Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17-18
16				
17	Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-19
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19				
20	Generalisability	21	Discuss the generalisability (external validity) of the study results	17
21				
22	Other information			
23	Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	20
24				
25				

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at <http://www.strobe-statement.org>.