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Patterns of multimorbidity in medical inpatients: a multinational retrospective cohort study

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Abstract

Multimorbidity is frequent and represents a significant burden for patients and healthcare systems. However, there are limited data on the most common combinations of comorbidities in multimorbid patients. We aimed to describe and quantify the most common combinations of comorbidities in multimorbid medical inpatients. We used a large retrospective cohort of adults discharged from the medical department of 11 hospitals across 3 countries (USA, Switzerland, and Israel) between 2010 and 2011. Diseases were classified into acute versus chronic. Chronic diseases were grouped into clinically meaningful categories of comorbidities. We identified the most prevalent combinations of comorbidities and compared the observed and expected prevalence of the combinations. We assessed the distribution of acute and chronic diseases and the median number of body systems in relationship to the total number of diseases. Eighty-six percent ($n = 126{,}828/147{,}806$) of the patients were multimorbid (≥ 2 chronic diseases), with a median of five chronic diseases; 13% of the patients had ≥ 10 chronic diseases. Among the most frequent combinations of comorbidities, the most prevalent comorbidity was chronic heart disease. Other high prevalent comorbidities included mood disorders, arthropathy and arthritis, and esophageal disorders. The ratio of chronic versus acute diseases was approximately 2:1. Multimorbidity affected almost 90% of patients, with a median of five chronic diseases. Over 10% had ≥ 10 chronic diseases. This identification and quantification of frequent combinations of comorbidities among multimorbid medical inpatients may increase awareness of what should be taken into account when treating such patients, a growth in the need for special care considerations.

Keywords Multimorbidity · Patterns · Comorbidity · Chronic diseases

Abbreviations

CCI	Chronic Condition Indicator
CCS	Clinical Classification Software
CKD	Chronic kidney disease
HCUP	Healthcare Cost and Utilization Project
ICD	International Classification of Diseases

Introduction

With increasing life expectancy and improved healthcare, a higher proportion of adults develop multimorbidity, which is associated with adverse health outcomes, higher healthcare utilization, polypharmacy and worse quality of life [1–3]. Multimorbidity, most often defined as the presence of two or more chronic diseases, therefore represents a significant burden for healthcare systems and patients [4–7]. However, despite the importance of multimorbidity, little is known about the prevalence of the different chronic diseases and of their combinations in multimorbid hospitalized patients.

While interest has increased in studying non-random combinations of diseases [8], most data are derived from the ambulatory care settings [9–20]. We found only two studies assessing such combinations in inpatients [21, 22], but both studies included all diseases without distinguishing between

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acute and chronic diseases, although multimorbidity refers specifically to chronic diseases [1, 3].

Using standardized tools to classify and categorize the diseases [23, 24], the primary aim was to identify and quantify the most prevalent combinations of chronic diseases groups (comorbidities) in multimorbid medical inpatients. Our hypothesis was that besides well-known frequent combinations of comorbidities such as chronic heart disease and chronic kidney disease (CKD), other frequent combinations may be identified among medical multimorbid hospitalized patients. The secondary aim was to describe the relative proportions between acute and chronic diseases in multimorbid patients. Our hypothesis was that the chronic diseases represent the majority of all patient diseases.

Methods

Study design, setting and participants

We used a multicenter international retrospective cohort including all consecutive adults discharged alive from the medical department of ten academic and one non-academic (Christiana Care Health System) hospitals across three countries (seven in the USA, three in Switzerland and one in Israel) between 2010 and 2011 (Appendix A). Patients admitted to a surgical ward were not included. The US sites were part of a collaborative research on quality of care and the other institutions joined the group by interest and through networking. Only multimorbid patients were included in all the analyses, i.e. those with two or more chronic diseases based on the most common definition of multimorbidity [2, 25]. The presence of an acute disease in addition to the two or more chronic diseases was not an exclusion criterium. To limit inclusion of observation stays, we further restricted the cohort to patients with a hospital length of stay of at least 1 day. Moreover, as the initial data were collected to study hospital readmissions, only patients discharged home or to a nursing home were included.

The Institutional Review Board of each participating site reviewed the study and determined it to be non-human subjects research, as it involved secondary analysis of anonymized data.

Study variables and diseases categorization

All data were extracted from electronic medical records and included demographic, admission, hospitalization and discharge information, as well as International Classification of Diseases (ICD) diagnosis codes available at discharge (ICD-9 codes for the USA and Israel, ICD-10 codes for Switzerland).

We assessed multimorbidity according to the following aspects, as detailed below: (1) acute and chronic diseases; (2) categories of chronic diseases, defined as comorbidities; (3) body systems affected; (4) comorbidity indices.

Acute and chronic diseases

To differentiate between ICD codes for acute and chronic diseases, we used the Chronic Condition Indicator (CCI) developed by the Healthcare Cost and Utilization Project (HCUP), a Federal–State–Industry partnership sponsored by the Agency for Healthcare Research and Quality [23]. This tool defines a chronic disease as a condition lasting at least 12 months and meeting at least one of the following criteria: (a) it places limitations on self-care, independent living, and social interactions or (b) it results in the need for ongoing intervention with medical products, services and special equipment. The use of the CCI had the following advantages: (1) standardized classification method that warranties a homogeneous analysis through a large database; (2) open source and ease of use that allow reproducibility; (3) development based on several peer-reviewed journal articles [26–28].

Comorbidities

Because more than 14,000 ICD codes would make the analysis difficult to interpret in a clinically meaningful way, we grouped the different ICD codes into comorbidities using the Clinical Classification Software (CCS) from HCUP, which collapses all ICD codes into 285 mutually exclusive categories [24]. Because we were interested in patterns of comorbidities related to multimorbidity, only chronic diseases were categorized. For this purpose, we thus excluded ICD codes for acute diseases as well as CCS categories for risk factors for diseases, complications of diseases, screening strategies and symptoms, as previously done, because they do not refer to specific diseases [22]. For clinical relevance, we further merged some comorbidities together (Appendix B). For example, we grouped together all chronic heart diseases, including cardiac dysrhythmias, coronary heart disease, non-hypertensive congestive heart failure and heart valve disorder. The different hospitals collected ICD codes which were then categorized by the first author using the above-mentioned tools.

Body systems affected

We further classified all diseases into 18 body system categories using the CCI: (1) infectious and parasitic diseases; (2) neoplasms; (3) endocrine, nutritional and metabolic diseases, and immunity disorders; (4) diseases of blood and blood-forming organs; (5) mental disorders; (6)

diseases of the nervous system and sense organs; (7) diseases of the circulatory system; (8) diseases of the respiratory system; (9) diseases of the digestive system; (10) diseases of the genitourinary system; (11) complications of pregnancy, childbirth, and the puerperium; (12) diseases of the skin and subcutaneous tissue; (13) diseases of the musculoskeletal system; (14) congenital anomalies; (15) certain conditions originating in the perinatal period; (16) symptoms, signs, and ill-defined conditions; (17) injury and poisoning; (18) factors influencing health status and contact with health services.

Comorbidity indices

We calculated the Deyo–Charlson Comorbidity Index and the Elixhauser-Van Walraven Comorbidity Index based on enhanced ICD-9-CM and ICD-10 codes (Table A1) [26, 29–32].

Statistical analyses

We presented baseline characteristics as proportions for categorical variables and median with interquartile range (IQR) for continuous variables. We described the prevalence of multimorbidity, the number of patients with ≥ 10 chronic diseases and the median number of body systems affected. For our primary aim, we first selected the main comorbidities showing a prevalence of more than 10% and then identified the most prevalent comorbidities combined with each of them. We presented the observed frequencies for each combination and compared them with the frequency that would have been expected if the two comorbidities were independent, calculated by multiplying the respective frequencies of each of the two comorbidities in the whole cohort. The resulting ratio of the observed/expected frequencies thus gives an indication on how dependent the two comorbidities are from each other. The combinations of comorbidities were not exclusive, so that patients with more than two comorbidities were counted in each combination of comorbidities that they presented. For example, a patient with chronic heart disease, CKD and thyroid disorders was counted in the three following combinations: (1) chronic heart disease + CKD, (2) chronic heart disease + thyroid disorders, and (3) CKD + thyroid disorders.

For our secondary aim, we used a two *y*-axis bar/line plot to display the distribution of acute and chronic diseases and the median number of body systems affected in relationship to the total number of diseases.

All analyses were performed using STATA 15.1 (StataCorp LP, College Station, TX, USA) or R version 3.4.4 (R Project for Statistical Computing).

Results

General description of multimorbidity

Overall, 126,828 (86%) of the 147,806 medical inpatients were multimorbid and included for analysis. Median age was 64 years (IQR 52, 76) with 52% ($n = 65{,}631$) men (Table 1). The median number of total diseases (acute or chronic) was ten (IQR 6, 14), with a median number of five (IQR 3, 8) chronic diseases and four (IQR 2, 5) body systems affected. We found that 16,024 (13%) of the patients had ≥ 10 chronic diseases. We found ten comorbidities (groups of chronic comorbidities) with a prevalence of more than 10% (Table 1).

Most prevalent combinations of comorbidities

The most prevalent combinations of comorbidities are presented in Table 2. The overall most prevalent combination was chronic heart disease with CKD (12%, $n = 15{,}050$). Among patients with chronic heart disease, 25% had CKD, while among those with CKD, 68% had chronic heart disease. Chronic heart disease was the most frequent comorbidity found in all of these combinations, with a prevalence ranging from 27% among patients with solid malignancy to 68% among those with CKD. Other frequent comorbidities included mood disorders, arthropathy and arthritis, esophageal disorders (including gastro-esophageal reflux), chronic obstructive pulmonary diseases and bronchiectasis, and thyroid disorders.

Observed frequency was substantially higher than expected frequency for the following combinations: chronic heart disease with CKD; chronic heart disease with pulmonary heart disease; CKD with peripheral and visceral atherosclerosis; CKD with nephritis, nephrosis, renal sclerosis; mood disorders with substance-related disorders; chronic obstructive pulmonary disease and bronchiectasis with pulmonary heart disease; substance-related disorders with esophageal disorders; substance-related disorders with liver disease. On the opposite, observed frequency was substantially lower than expected frequency for the following combinations: chronic heart disease with solid malignancy; solid malignancy with substance-related disorders.

Proportions of acute and chronic diseases

Chronic diseases represented 64% of all ICD diagnosis codes in patients with multimorbidity. The percentage of chronic versus acute diseases initially decreased as the total number of diseases increased from 100% chronic diseases in patients with two total diseases (by definition) to 71% in

Table 1 Baseline characteristics

Characteristics	Multimorbid cohort ($n = 126{,}828$)
Age, years, median (IQR)	64 (52, 76)
Men, *n* (%)	65,631 (52)
Country	
United States, *n* (%)	82,937 (65)
Switzerland, *n* (%)	33,871 (27)
Israel, *n* (%)	10,020 (8)
Description of multimorbidity	
Number of acute and chronic diseases, median (IQR)	10 (6, 14)
Number of chronic diseases, median (IQR)	5 (3, 8)
Number of body systems affected, median (IQR)	4 (2, 5)
Deyo–Charlson Comorbidity Index, median (IQR)[a]	2 (1, 3)
Elixhauser-Van Walraven Comorbidity Index, median (IQR)[b]	6 (1, 12)
Most prevalent comorbidities (prevalence ≥ 10%)	
Chronic heart disease, *n* (%)	60,298 (48)
Chronic kidney disease, *n* (%)	22,210 (18)
Mood disorders, *n* (%)	18,932 (15)
Arthropathy and arthritis, *n* (%)	18,348 (15)
Solid malignancy, *n* (%)	18,045 (14)
Esophageal disorders, *n* (%)	17,864 (14)
Other nervous system disorders, *n* (%)	16,349 (13)
Chronic obstructive pulmonary disease and bronchiectasis, *n* (%)	14,696 (12)
Thyroid disorders, *n* (%)	14,640 (12)
Substance-related disorders, *n* (%)	12,863 (10)
Hospitalization characteristics	
Length of stay, days, median (IQR)	5 (3, 8)
Number of admissions in the past year	0 (0, 2)

[a]Score range: 0 to 33 points

[b]Score range: − 19 to 89 points

those with five diseases (Fig. 1). The percentages of chronic and acute diseases remained relatively stable as the number of diseases further increased, with chronic diseases representing 64–73% of all diseases. The median number of body systems affected increased proportionally with the number of diseases and was about half the total number of diseases.

Discussion

In this large multinational study, we identified and quantified the most common combinations of comorbidities in multimorbid medical inpatients. Multimorbidity affected the great majority of patients, with a median of five chronic diseases per patient. The most common combination of comorbidities was, as expected, chronic heart disease and CKD. Mood disorders, arthropathy and arthritis, and esophageal disorders appeared to be very frequent comorbidities in combination with the most prevalent main comorbidities. Many combinations were observed more frequently than expected. In patients with more than five total diseases, chronic diseases represented two-thirds of the diseases. This study provides new insight on chronic comorbidities among multimorbid medical inpatients, a group of patients so far not well-studied.

General description of multimorbidity

The few previous studies in hospital settings reported a prevalence of multimorbidity of 63–99% [22, 33, 34]. This wide range can be mostly explained by different age distributions and/or the definition of multimorbidity, as only 23% of the patients were ≥ 65 years in the study with the lowest prevalence [22], while the study with the highest prevalence included only patients aged ≥ 65 years [33]. The 86% prevalence in our population with a median age of 64 years is consistent with those findings and provides a more precise estimate among a general population of medical inpatients.

Table 2 Observed and expected frequencies of the most prevalent combinations of comorbidities in multimorbid patients ($n = 126{,}828$)

Combination of comorbidities	Observed number, *n* (%)[a]	Observed overall prevalence, %[b]	Expected prevalence, %[c]	Observed/expected ratio
Chronic heart disease ($n = 60{,}298$), combined with				
Chronic kidney disease	15,050 (25)	11.8	8.3	1.4
Arthropathy and arthritis	9284 (15)	7.3	6.9	1.1
Chronic obstructive pulmonary diseases and bronchiectasis	9069 (15)	7.2	5.5	1.3
Esophageal disorders	8156 (14)	6.4	6.7	1.0
Thyroid disorders	7927 (13)	6.3	5.5	1.1
Mood disorders	7322 (12)	5.8	7.1	0.8
Other nervous system disorders	6926 (12)	5.5	6.1	0.9
Pulmonary heart disease	5863 (10)	4.6	2.8	1.6
Solid malignancy	4940 (8)	3.9	6.7	0.6
Peripheral and visceral atherosclerosis	4400 (7)	3.5	2.3	1.5
Chronic kidney disease ($n = 22{,}210$), combined with				
Chronic heart disease	15,050 (68)	11.8	8.3	1.4
Arthropathy and arthritis	4294 (19)	3.4	2.5	1.4
Other nervous system disorders	3332 (15)	2.6	2.3	1.1
Chronic obstructive pulmonary diseases and bronchiectasis	3212 (15)	2.5	2.0	1.3
Thyroid disorders	3125 (14)	2.5	2.0	1.1
Esophageal disorders	3039 (14)	2.4	2.5	1.0
Mood disorders	2754 (12)	2.2	2.6	0.8
Pulmonary heart disease	2373 (11)	1.9	1.0	1.9
Peripheral and visceral atherosclerosis	2155 (10)	1.7	0.8	2.1
Nephritis, nephrosis, renal sclerosis	2118 (10)	1.7	0.5	3.4
Mood disorders ($n = 18{,}932$), combined with				
Chronic heart disease	7322 (39)	5.8	7.1	0.8
Esophageal disorders	4058 (21)	3.2	2.1	1.5
Other nervous system disorders	3929 (21)	3.1	1.9	1.6
Substance-related disorders	3497 (19)	2.8	1.5	1.9
Arthropathy and arthritis	3147 (17)	2.5	2.2	1.1
Thyroid disorders	2909 (15)	2.3	1.7	1.4
Chronic kidney disease	2754 (15)	2.2	2.6	0.8
Chronic obstructive pulmonary diseases and bronchiectasis	2571 (14)	2.0	1.7	1.2
Solid malignancy	1888 (10)	1.5	2.1	0.7
Asthma	1861 (10)	1.5	1.0	1.5
Arthropathy and arthritis ($n = 18{,}348$), combined with				
Chronic heart disease	9284 (51)	7.3	6.9	1.1
Chronic kidney disease	4294 (23)	3.4	2.5	1.4
Esophageal disorders	3839 (21)	3.1	2.0	1.6
Mood disorders	3147 (17)	2.5	2.2	1.1
Other nervous system disorders	3122 (17)	2.5	1.9	1.3
Thyroid disorders	2798 (15)	2.2	1.7	1.3
Chronic obstructive pulmonary diseases and bronchiectasis	2288 (13)	1.8	1.7	1.0
Chronic ulcer of skin	1662 (9)	1.3	0.8	1.6
Asthma	1572 (9)	1.2	0.9	1.3
Osteoporosis	1290 (7)	1.1	0.6	1.8
Solid malignancy ($n = 18{,}045$), combined with				
Chronic heart disease	4940 (27)	3.9	6.7	0.6
Other nervous system disorders	2586 (16)	2.0	1.8	1.1
Esophageal disorders	2212 (12)	1.7	2.0	0.9

Table 2 (continued)

Combination of comorbidities	Observed number, *n* (%)[a]	Observed overall prevalence, %[b]	Expected prevalence, %[c]	Observed/expected ratio
Mood disorders	1888 (11)	1.5	2.1	0.7
Chronic obstructive pulmonary diseases and bronchiectasis	1864 (10)	1.3	1.6	0.9
Thyroid disorders	1651 (9)	1.3	1.6	0.8
Chronic kidney disease	1618 (9)	1.3	2.5	0.5
Arthropathy and arthritis	1415 (8)	1.1	2.1	0.5
Diseases of white blood cells	1328 (7)	1.0	0.8	1.3
Substance-related disorders	1050 (6)	0.8	1.4	0.6
Esophageal disorders ($n=17,864$), combined with				
Chronic heart disease	8156 (46)	6.4	6.7	1.0
Mood disorders	4058 (23)	3.2	2.1	1.5
Arthropathy and arthritis	3829 (22)	3.1	2.0	1.6
Chronic kidney disease	3039 (17)	2.4	2.5	1.0
Other nervous system disorders	3004 (17)	2.4	1.8	1.3
Thyroid disorders	2768 (16)	2.2	1.6	1.4
Chronic obstructive pulmonary disease and bronchiectasis	2652 (15)	2.1	1.6	1.3
Solid malignancy	2212 (12)	1.7	2.0	0.9
Asthma	1941 (11)	1.5	0.9	1.7
Substance-related disorders	1916 (11)	1.5	1.4	1.1
Other nervous system disorders ($n=16,349$), combined with				
Chronic heart disease	6926 (42)	5.5	6.1	0.9
Mood disorders	3929 (24)	3.1	1.9	1.6
Chronic kidney disease	3332 (21)	2.6	2.3	1.1
Arthropathy and arthritis	3122 (19)	2.5	1.9	1.3
Esophageal disorders	3004 (18)	2.4	1.8	1.3
Thyroid disorders	2059 (13)	1.6	1.5	1.1
Chronic obstructive pulmonary disease and bronchiectasis	2008 (12)	1.6	1.5	1.1
Substance-related disorders	1971 (12)	1.6	1.3	1.2
Chronic ulcer of skin	1622 (10)	1.3	0.7	1.9
Asthma	1243 (8)	1.0	0.7	1.4
Chronic obstructive pulmonary disease and bronchiectasis ($n=14,696$), combined with				
Chronic heart disease	9069 (62)	7.2	5.5	1.3
Chronic kidney disease	3212 (22)	2.5	2.0	1.3
Esophageal disorders	2652 (18)	2.1	1.6	1.3
Mood disorders	2571 (18)	2.0	1.7	1.2
Arthropathy and arthritis	2288 (16)	1.8	1.7	1.1
Substance-related disorders	2089 (14)	1.7	1.2	1.4
Other nervous system disorders	2008 (14)	1.6	1.5	1.1
Thyroid disorders	1967 (13)	1.6	1.5	1.1
Solid malignancy	1864 (13)	1.5	1.6	0.9
Pulmonary heart disease	1833 (13)	1.5	0.7	2.1
Thyroid disorders ($n=14,640$), combined with				
Chronic heart disease	7927 (54)	6.3	5.5	1.1
Chronic kidney disease	3125 (21)	2.5	2.0	1.3
Mood disorders	2909 (20)	2.3	1.7	1.4
Arthropathy and arthritis	2798 (19)	2.2	1.7	1.3
Esophageal disorders	2768 (19)	2.2	1.6	1.4
Other nervous system disorders	2059 (14)	1.6	1.5	1.1
Chronic obstructive pulmonary disease and bronchiectasis	1967 (13)	1.6	1.5	1.1

Table 2 (continued)

Combination of comorbidities	Observed number, *n* (%)[a]	Observed overall prevalence, %[b]	Expected prevalence, %[c]	Observed/expected ratio
Solid malignancy	1651 (11)	1.3	1.6	0.8
Dementia	1271 (9)	1.0	0.7	1.4
Pulmonary heart disease	1191 (8)	0.9	0.7	1.3
Substance-related disorders ($n=12,863$), combined with				
Chronic heart disease	4367 (34)	3.4	4.8	0.7
Mood disorders	3497 (27)	2.8	1.5	1.9
Chronic obstructive pulmonary diseases and bronchiectasis	2089 (16)	1.7	1.2	1.2
Other nervous system disorders	1971 (15)	1.6	1.3	1.2
Esophageal disorders	1916 (15)	1.5	1.4	1.1
Liver disease	1668 (13)	1.3	0.5	2.6
Chronic ulcer of skin	1331 (10)	1.1	0.6	1.8
Chronic kidney disease	1299 (10)	1.0	1.8	0.6
Arthropathy and arthritis	1275 (10)	1.0	1.5	0.7
Solid malignancy	1050 (8)	0.8	1.4	0.6

The combinations of comorbidities were not exclusive, so that patients with more than two comorbidities were counted in each combination of comorbidities that they presented.

[a]Among the patients with the main comorbidity

[b]Among the whole multimorbid cohort ($n=126,828$)

[c]Calculated by multiplying the observed frequencies of each of the two comorbidities among the whole multimorbid cohort ($n=126,828$)

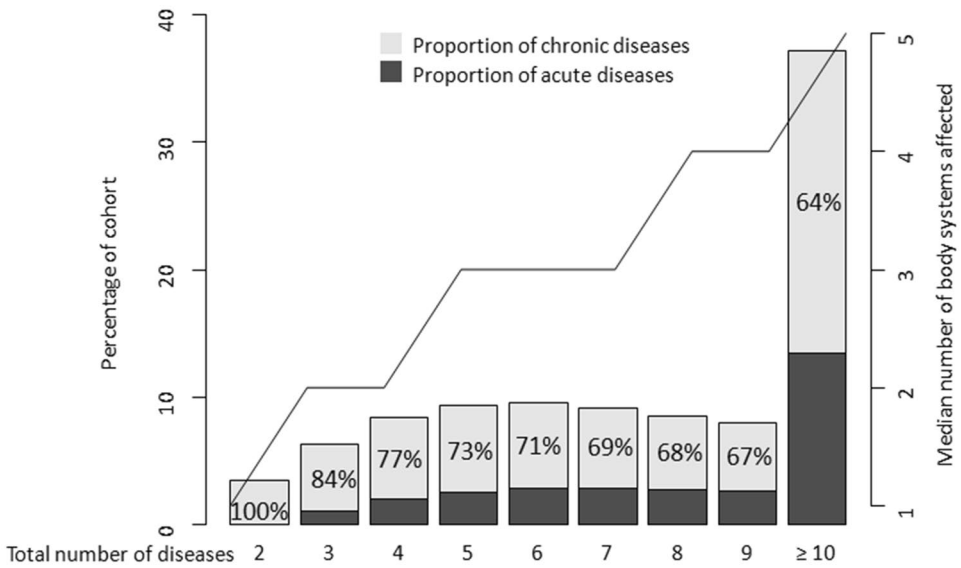

Fig. 1 Proportions of acute versus chronic diseases in multimorbid patients ($n=126,828$). Percentages displayed in the grey bars are the percentages of chronic diseases for each particular total number of diseases. The line represents the number of body systems affected

Unlike previous studies that most often assessed multimorbidity either as a simple count of diseases or as a weighted index, we used both measures, allowing us to compare them. Median Deyo–Charlson Comorbidity Index and Elixhauser-Van Walraven Comorbidity Index were rather low (two and six, respectively), despite the median number of chronic diseases of five. Although these indices are broadly used in research settings to assess and weight multimorbidity or to adjust for it in analyses, they were initially developed to predict mortality and not to measure multimorbidity. The low values we found for these indices in our cohort underline their low sensitivity to detect multimorbidity [35], suggesting that they may not be very accurate to define multimorbidity or weight its severity, most likely because they only include a limited number of conditions. However, further research should compare the ability of these scores and of other measurements of multimorbidity to predict health outcomes or costs.

Most prevalent combinations of comorbidities

A novel approach of our study to assess combinations of comorbidities was to group chronic diseases expected to cluster together and to exclude acute diseases, risk factors, complications, screening strategies and symptoms, with the aim to focus on the chronic diseases contributing to multimorbidity. This allowed us to identify combinations of comorbidities in a more clinically meaningful way. For example, CKD, mood disorders, arthropathy and arthritis, esophageal disorders, chronic obstructive pulmonary disease and bronchiectasis, and thyroid disorders were frequently found in the combinations of comorbidities. Furthermore, some combinations were found more frequently than expected, which could be because one predisposes to the other, the two have common risk factors, or treatment for one causes the other. For example, some were more common for obvious pathophysiologic reasons like chronic heart disease with CKD or because of a common precursor like smoking for the combination of chronic heart disease with chronic obstructive pulmonary disease and bronchiectasis. But there were some unexpected combinations and some cases where the combination was less common than would have been expected, such as chronic heart disease with solid malignancy, which highlights that these two comorbidities are more independent from each other and therefore reflects more a fortuitously combination due to the high prevalence of both comorbidities.

Although we cannot make conclusions about causality from this analysis, unmasking those combinations of comorbidities offers a better understanding of the patterns of multimorbidity and could help to better target interventions to improve outcomes of multimorbid patients. For example, the fact that almost one-fourth of patients with arthropathy and arthritis also had CKD outlines the importance of avoiding NSAIDs as painkillers among patients with arthropathy and arthritis. Similarly, as 12% of patients with chronic heart disease also have thyroid disorders, healthcare providers should try to avoid prescribing amiodarone to patients with chronic heart disease or monitor the thyroid function. Quantifying the frequency of the most prevalent combination of comorbidities of chronic heart disease and CKD is also noteworthy, as they have been shown to be associated with worse outcomes such as inhospital death [21, 36].

These findings are difficult to compare with the few previous studies conducted in inpatients because of differences in data sources and multimorbidity assessment [21, 33, 34, 37]. Those studies indeed either used a different categorization system or included acute and chronic diseases, as well as symptoms and risk factors. They thus described a high prevalence of cardiovascular risk factors, heart diseases and particular symptoms, and of combinations between chronic heart diseases and cardiovascular risk factors.

Proportions of acute and chronic diseases

In patients with more than five total diseases, the proportions of chronic versus acute diseases remained quite stable with about two-thirds as chronic diseases. We could have expected an exponential increase of the percentage of acute diseases, as patients with more chronic diseases may be more severely ill, which was not the case. This suggests that the number of additional acute diseases is proportional to the number of chronic diseases in patients with more than five diseases, possibly corresponding to the number of chronic diseases susceptible to decompensation. The number of body systems affected was about half the number of diseases, suggesting that some body systems include more diseases, with a median of two diseases per body system affected. To our knowledge, this is the first study that assessed the distribution of acute and chronic diseases and of body systems affected in multimorbid patients.

Clinical implications

This study highlights the high prevalence of different combinations of comorbidities and therefore the importance of being able to gather all the necessary skills to treat patients in their whole and not only one disease at a time. This may contrast with the recent increase in medical ultra-specialization and the opening of competence centers (e.g. chronic heart disease center). Although those centers frequently care for multimorbid patients, they still often apply disease-specific guidelines that may not be appropriate for multimorbid patients, as the latter are rarely included in trials used to develop these guidelines [38]. Our description of the different patterns of multimorbidity may increase awareness of what should be taken into account when treating such patients. Furthermore, it outlines the necessity to develop specific guidelines for multimorbid patients, and reveals which most prevalent combinations of comorbidities they should focus on in priority.

Limitations and strengths

Our study has several limitations. First, as for any study using electronic medical records, diagnoses are subject to coding quality and therefore we cannot exclude underreporting of some diseases. However, on the other hand, using ICD codes allowed us to assess a broad range of diseases, unlike most previous studies [1, 5, 39–41]. Second, although we used an objective tool to classify the diseases, we further grouped some categories and excluded ICD codes referring to risk factors, complications, screening strategies and symptoms; while it was performed to unmask less expected associations, it may, however, have brought some subjectivity and prevented some comparison with previous studies.

Third, we performed crude analyses, because we were interested in multimorbidity independently of other factors, we thus cannot conclude on any subgroup difference, e.g. according to gender or age. Fourth, we cannot exclude differences in coding across the hospitals from different countries and healthcare systems, which may have brought some heterogeneity; however, such variability may turn out to increase results generalizability, given that it makes them applicable to a higher number of different settings. Fifth, although we restricted the cohort to patients with a length of stay of at least 1 day, we cannot completely exclude the inclusion of some patients admitted for observation stay only, and who may present different patterns of comorbidities than those admitted for inpatient care. Sixth, because the cohort was initially built to study readmissions, we included only patients discharged home, so that our results may not be generalized to patients who were discharged to another hospital or to a nursing home as well as to patients who died during hospital stay. Finally, some combinations may have been observed only because of the high frequency of each comorbidity. However, this study did not have the pretention to uncover causal associations, but only observed frequencies.

Our study also has several strengths. First, we used several methods to assess multimorbidity. In particular, we differentiated acute from chronic diseases, since the number of diseases in the definition of multimorbidity includes only chronic diseases and not acute diseases. Second, we used standardized tools to classify ICD codes, allowing a more objective evaluation than self-reported diagnoses which were used in up to 75% of previous reports [1]. Third, unlike most studies on multimorbidity in hospital settings that included only elderly patients [7, 21, 33], we included adults aged 18 years or older, allowing us to study an unusually young inpatient population, and to underline that multimorbidity prevalence is already high in such patients, probably because multimorbidity often already develops before the age of 65 years. Finally, the large and multinational sample increases the generalizability of the results.

Conclusions

The great majority of medical inpatients were multimorbid with a median number of five chronic diseases per multimorbid patient. In this study, we identified and quantified several interesting common combinations of comorbidities besides the frequent well-known combination of chronic heart disease with chronic kidney disease. Furthermore, we found that among patients with more than five diseases, about two-thirds of the diseases were chronic. This large multinational study offers an innovative insight into the patterns of multimorbidity in medical inpatients. Our findings may increase the awareness of healthcare providers on the patterns of multimorbidity and highlight the importance to develop appropriate guidelines for the high number of patients who cumulate common comorbidities.

Author contributions CEA and JD designed the study, directed its analysis, including quality assurance and control, interpreted the data and drafted the article. NF and AL designed the study's analytic strategy and performed the statistical analyses. JLS, PM-V, JS, ADA, EZ, SK, EEV, ER, JM and GSF contributed to data collection. JLS contributed to major revisions of the manuscript. All authors critically reviewed the manuscript and agreed for submission.

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Data availability All data generated or analysed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Statement of human and animal rights The Institutional Review Board of each participating site reviewed the study and determined it to be non-human subjects research, as it involved secondary analysis of anonymized data.

Informed consent Not applicable.

References

1. Diederichs C, Berger K, Bartels DB (2011) The measurement of multiple chronic diseases—a systematic review on existing multimorbidity indices. J Gerontol Ser A Biol Sci Med Sci 66(3):301–311
2. Johnston MC, Crilly M, Black C, Prescott GJ, Mercer SW (2018) Defining and measuring multimorbidity: a systematic review of systematic reviews. Eur J Pub Health 29:1–7
3. van den Akker M, Buntinx F, Knottnerus JA (1996) Comorbidity or multimorbidity. Eur J Gen Pract 2(2):65–70
4. Vogeli C, Shields AE, Lee TA, Gibson TB, Marder WD, Weiss KB et al (2007) Multiple chronic conditions: prevalence, health consequences, and implications for quality, care management, and costs. J Gen Intern Med 22(Suppl 3):391–395
5. Bahler C, Huber CA, Brungger B, Reich O (2015) Multimorbidity, health care utilization and costs in an elderly community-dwelling population: a claims data based observational study. BMC Health Serv Res 15:23
6. Hopman P, Heins MJ, Korevaar JC, Rijken M, Schellevis FG (2016) Health care utilization of patients with multiple chronic diseases in the Netherlands: differences and underlying factors. Eur J Intern Med 35:44–50
7. Centers for Medicare and Medicaids Services (2012) Chronic conditions among medicare beneficiaries C, 2012 edn. Baltimore,

MD. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/Downloads/2012Chartbook.pdf
8. Prados-Torres A, Calderon-Larranaga A, Hancco-Saavedra J, Poblador-Plou B, van den Akker M (2014) Multimorbidity patterns: a systematic review. J Clin Epidemiol 67(3):254–266
9. Freund T, Kunz CU, Ose D, Szecsenyi J, Peters-Klimm F (2012) Patterns of multimorbidity in primary care patients at high risk of future hospitalization. Popul Health Manag 15(2):119–124
10. Garcia-Olmos L, Salvador CH, Alberquilla A, Lora D, Carmona M, Garcia-Sagredo P et al (2012) Comorbidity patterns in patients with chronic diseases in general practice. PLoS ONE 7(2):e32141
11. Cornell JPJ, Williams JW (2007) Multimorbidity clusters: clustering binary data from multimorbidity clusters: clustering binary data from a large administrative medical database. App Multivar Res 12(3):163e82
12. Goldstein G, Luther JF, Jacoby AM, Haas GL, Gordon AJ (2008) A Taxonomy of medical comorbidity for veterans who are homeless. J Health Care Poor Underserved 19(3):991–1005
13. John R, Kerby DS, Hennessy CH (2003) Patterns and impact of comorbidity and multimorbidity among community-resident American Indian elders. Gerontologist 43(5):649–660
14. Kirchberger I, Meisinger C, Heier M, Zimmermann AK, Thorand B, Autenrieth CS et al (2012) Patterns of multimorbidity in the aged population: results from the KORA-age study. PLoS ONE 7(1):30556
15. Newcomer SR, Steiner JF, Bayliss EA (2011) Identifying subgroups of complex patients with cluster analysis. Am J Manag Care 17(8):e324–e332
16. Prados-Torres A, Poblador-Plou B, Calderon-Larranaga A, Gimeno-Feliu LA, Gonzalez-Rubio F, Poncel-Falco A et al (2012) Multimorbidity patterns in primary care: interactions among chronic diseases using factor analysis. PLoS ONE 7(2):e32190
17. Marengoni A, Rizzuto D, Wang HX, Winblad B, Fratiglioni L (2009) Patterns of chronic multimorbidity in the elderly population. J Am Geriatr Soc 57(2):225–230
18. Schafer I, von Leitner EC, Schon G, Koller D, Hansen H, Kolonko T et al (2010) Multimorbidity patterns in the elderly: a new approach of disease clustering identifies complex interrelations between chronic conditions. PLoS ONE 5(12):e15941
19. van den Bussche H, Koller D, Kolonko T, Hansen H, Wegscheider K, Glaeske G et al (2011) Which chronic diseases and disease combinations are specific to multimorbidity in the elderly? Results of a claims data based cross-sectional study in Germany. BMC Public Health 11:101
20. Holden L, Scuffham PA, Hilton MF, Muspratt A, Ng SK, Whiteford HA (2011) Patterns of multimorbidity in working Australians. Popul Health Metr 9(1):15
21. Marengoni A, Bonometti F, Nobili A, Tettamanti M, Salerno F, Corrao S et al (2010) In-hospital death and adverse clinical events in elderly patients according to disease clustering: the REPOSI study. Rejuvenation Res 13(4):469–477
22. Wong A, Boshuizen HC, Schellevis FG, Kommer GJ, Polder JJ (2011) Longitudinal administrative data can be used to examine multimorbidity, provided false discoveries are controlled for. J Clin Epidemiol 64(10):1109–1117
23. Agency for Healthcare Research and Quality (AHRQ) (2018) Healthcare Cost and Utilization Project (HCUP). Chronic Condition Indicator (CCI) for ICD-9-CM. https://www.hcup-us.ahrq.gov/toolssoftware/chronic/chronic.jsp. Accessed 23 Jun 2018
24. Agency for Healthcare Research and Quality (AHRQ) (2018) Clinical Classifications Software (CCS) for ICD-9-CM. https://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed 23 Jun 2018
25. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M et al (2014) Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PLoS ONE 9(7):e102149
26. Elixhauser A, Steiner C, Harris DR, Coffey RM (1998) Comorbidity measures for use with administrative data. Med Care 36(1):8–27
27. Hwang W, Weller W, Ireys H, Anderson G (2001) Out-of-pocket medical spending for care of chronic conditions. Health Aff (Project Hope) 20(6):267–278
28. Perrin EC, Newacheck P, Pless IB, Drotar D, Gortmaker SL, Leventhal J et al (1993) Issues involved in the definition and classification of chronic health conditions. Pediatrics 91(4):787–793
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR (1987) A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 40(5):373–383
30. Deyo RA, Cherkin DC, Ciol MA (1992) Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 45(6):613–619
31. van Walraven C, Austin PC, Jennings A, Quan H, Forster AJ (2009) A modification of the Elixhauser comorbidity measures into a point system for hospital death using administrative data. Med Care 47(6):626–633
32. Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC et al (2005) Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 43(11):1130–1139
33. Clerencia-Sierra M, Calderon-Larranaga A, Martinez-Velilla N, Vergara-Mitxeltorena I, Aldaz-Herce P, Poblador-Plou B et al (2015) Multimorbidity patterns in hospitalized older patients: associations among chronic diseases and geriatric syndromes. PLoS ONE 10(7):e0132909
34. Friedman B, Jiang HJ, Elixhauser A, Segal A (2006) Hospital inpatient costs for adults with multiple chronic conditions. Med Care Res Rev MCRR 63(3):327–346
35. Schneider F, Kaplan V, Rodak R, Battegay E, Holzer B (2012) Prevalence of multimorbidity in medical inpatients. Swiss Med Wkly 142:w13533
36. van Deursen VM, Urso R, Laroche C, Damman K, Dahlstrom U, Tavazzi L et al (2014) Co-morbidities in patients with heart failure: an analysis of the European Heart Failure Pilot Survey. Eur J Heart Fail 16(1):103–111
37. Wong RY, Miller WC (2008) Adverse outcomes following hospitalization in acutely ill older patients. BMC Geriatr 8:10
38. Jadad AR, To MJ, Emara M, Jones J (2011) Consideration of multiple chronic diseases in randomized controlled trials. JAMA 306(24):2670–2672
39. Pati S, Swain S, Metsemakers J, Knottnerus JA, van den Akker M (2017) Pattern and severity of multimorbidity among patients attending primary care settings in Odisha, India. PLoS ONE 12(9):e0183966
40. Pati S, Swain S, Hussain MA, van den Akker M, Metsemakers J, Knottnerus JA et al (2015) Prevalence and outcomes of multimorbidity in South Asia: a systematic review. BMJ Open 5(10):e007235
41. Lochner KA, Cox CS (2013) Prevalence of multiple chronic conditions among Medicare beneficiaries, United States, 2010. Prev Chronic Dis 10:E61

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