Which multimorbidity clusters are associated with longer hospital stays in hypertensive patients?

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Abstract

Introduction: Hypertension (HT) is one of the world's most important health problems. This study aimed to identify and characterize multimorbidity clusters in hypertensive patients and to assess which characteristics were responsible for length of hospital stay (LOHS).
Material and methods: Data were obtained from 489 patients admitted to the cardiology department with HT as the main diagnosis. The Partitioning Around Medoids method was used to divide patients into 12 clusters. Dissimilarity between patients was measured using the Gower distance. The number of clusters was determined using the silhouette method.
Results: It was noted that myocardial infarction (MI) patients were significantly older than patients without comorbidities and patients from clusters 2, 3, 7, 8, and 10. In addition, patients with diabetes mellitus (DM) only and patients with DM, heart failure (HF), and obesity were significantly older than patients who were only obese. LOHS was significantly longer in patients with HF than in patients from clusters 1, 2, 5, 7, and 10; patients with chronic kidney disease (CKD) but without HF than in clusters 1, 5, and 7; patients with HF and obesity than in clusters 1 and 7; and patients with obesity and DM as well as patients with DM, HF, and often obesity than in patients without comorbidities.
Conclusions: The presence of additional health conditions impacts the duration of hospital stays for individuals with HT. The conditions HF, CKD, DM and obesity can lead to extended hospitalization. Patients' clinical profiles provided sufficient insights to predict the necessity for prolonged and more costly medical care.

Key words: hypertension, multimorbidity, clusters, hospitalization, conditions.

Introduction

In 2015, the number of people with arterial hypertension worldwide was estimated to be 1.13 billion, with over 150 million cases in Central and Eastern Europe. Globally, the overall prevalence of arterial hypertension among adults is 30–-45% [1–3]. Arterial hypertension also becomes

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more common with age, occurring in > 60% of individuals over 60 years old [4]. Due to the aging population, the adoption of a less active lifestyle, and the increase in average body weight, the global prevalence of arterial hypertension is expected to rise. It is estimated that the number of people with arterial hypertension will have increased by 15–20% by 2025, reaching approximately 1.5 billion [5]. Research indicates that up to two-thirds of patients with arterial hypertension have other co-existing medical conditions [6]. However, it is known that patients with multimorbidity are commonly excluded from large clinical studies or are underrepresented, which has limited the evidence on how to best manage elevated blood pressure (BP) in patients with additional co-existing conditions. An increase in the burden of comorbidities with hypertension is expected [7]. It is crucial to understand how the presence of co-existing conditions affects blood pressure trajectories and the management to enable the development of future policies and research [8]. In previous studies, associations were observed between specific co-existing conditions such as coronary heart disease, heart failure, depression, and dementia [9–11]. Multimorbidity, defined as the coexistence of two or more medical conditions in the same individual, is currently a common and unfortunately increasingly prevalent phenomenon [12, 13]. Patients with multimorbidity experience poorer health outcomes and also tend to more frequently utilize unplanned emergency hospital care [14]. Cluster analysis could lead to improved characterization of disease phenotypes and the exploration of possible subgroups within a well-characterized population of hypertensive patients [15]. Identifying clusters of conditions in hospitalized patients offers a pivotal chance to customize patient-centric care, leading to improved treatment outcomes and increased care efficiency [16].

Therefore, the aim of this study was to identify and characterize clusters of multimorbidity in a cohort of patients hospitalized at the Cardiology Department in the University Clinical Hospital in Wroclaw, Poland. Following characterization, the goal was to identify which clusters resulted in prolonged hospitalization.

Material and methods

Study design and setting

We performed a retrospective analysis of 489 medical records of patients who were admitted to the Clinical Cardiology Department of the University Clinical Hospital (Wroclaw, Poland) with hypertension (ICD10:I10) between January 2019 and June 2021. The Clinical Cardiology Department is recognized as a top-tier reference center, specializing in both conservative and invasive cardiological treatments.

Study population

We analyzed all patients who met the inclusion criteria: age ≥18 years and diagnosis of hypertension (ICD10:I10) at the time of admission. Data collected included patient identifiable and demographic details, episode management details, and general clinical information. Clinical information recorded as the main diagnosis and up to five other significant diagnoses was coded using the World Health Organization's International Classification of Diseases (ICD-10). The comorbidities included in the study were derived from the final diagnoses recorded in the patients' medical records. Finally, the medical records of 489 patients were examined. We investigated data such as age, sex, hypertension grade, and body mass index (BMI, kg/m^2), length of hospital stay (LOHS); comorbidities including heart failure (HF), diabetes mellitus (DM), chronic kidney disease (CKD), obesity (BMI > 30 kg/m^2), history of cerebral stroke (CS), and myocardial infarction (MI); results of blood tests including low-density lipoprotein (LDL), triglycerides (TG), high-density lipoprotein (HDL), total cholesterol (TC), albumins, transferrin, lymphocytes, procalcitonin, potassium (K), sodium (NaCl), hemoglobin A_{1c} (HbA_{1c}), and high-sensitivity C-reactive protein (hsCRP). All parameters were measured at the time of admission to the cardiology department. A nurse collected blood for laboratory tests. The specific tests required by the patient were determined by the admitting physician in the cardiology department. These tests were carried out at the hospital's laboratory (using the Alinity C, Abbott) according to Good Laboratory Practice guidelines.

Defining clusters of conditions and multimorbidity

Before conducting the analysis, we outlined the anticipated clusters that would be identified. The compositions of conditions found in the resulting patient groups were clinically examined by members of the study team (IU, BU, MW, MCZ). These condition clusters within each patient group were determined based on a combination of clinical review and evaluation of the most prevalent conditions in each patient group, and then identified and labeled according to the condition with the highest prevalence. Multimorbidity was defined as having recorded diagnoses of≥ 2 chronic conditions [17].

Statistical analysis

For comparing qualitative variable values between groups, the χ^2 test (with Yates' correction

for 2x2 tables) or Fisher's exact test was applied in cases in which expected counts were low in the tables. Quantitative variable values between two groups were compared using the Mann-Whitney test. Clustering was achieved through the Partitioning Around Medoids (PAM) method. Distances between observations were measured using the Gower metric. The optimal number of clusters was determined using the silhouette method. For comparing qualitative variable values within clusters, the χ^2 test (with Yates' correction for 2x2 tables) or Fisher's exact test was used when low expected counts occurred in the tables. Quantitative variable values within clusters were compared using the Kruskal-Wallis test. Upon detecting statistically significant differences, post-hoc analysis was conducted using Dunn's test to identify clusters showing statistically significant variance. The significance level adopted for analysis was 0.05. The analysis was performed using R software, version 4.1.3.

Results

Characteristics of group

Table I shows the characteristics of the group. A division into 2 groups was used: patients with < 2 comorbidities and patients with 2 or more comorbidities. In total, 163 patients (81 women, 82 men; mean age: 63.93 ±11.49) had multiple conditions (≥ 2 comorbidities). Patient profiles for each group were described by age, gender, laboratory test results, and hypertension grade. LDL, HDL, and TC were significantly higher in the group with < 2 comorbidities, whereas TG, hsCRP, K, and HbA_{1c} were significantly higher in the group with ≥ 2 comorbidities.

Table II indicates the patients' comorbidities. The largest percentage of patients had the comorbidities of obesity and diabetes.

Multimorbidity clusters

The cluster analysis of disease occurrence identified twelve groups of patients and describes the prevalence of all comorbidities in each patient group.

- Cluster 1: Patients without comorbidities;
- Cluster 2: Patients solely with obesity;
- Cluster 3: Patients with obesity and DM;
- Cluster 4: Patients with HF and CKD;
- Cluster 5: Patients solely with diabetes;
- Cluster 6: Patients solely with MI;
- Cluster 7: Patients with obesity and CS and, in nearly half the cases, also with DM;
- Cluster 8: Patients with CKD and other diseases but (unlike cluster 4) without heart failure;
- Cluster 9: Patients with obesity and MI;
- Cluster 10: Patients solely with CS;
- Cluster 11: Patients solely with heart failure and obesity;
- Cluster 12: Patients with diabetes and heart failure and (very often, though not always) with obesity (Table III).

Patients in cluster 6 were significantly older than patients in clusters 1, 2, 3, 7, 8, and 10. Patients in clusters 5 and 12 were significantly older than patients in cluster 2 (Table IV).

The LOHS in each cluster was then compared (Table V). Longer hospitalization occurred for the following:

- Patients in cluster 4, as compared to patients in clusters 1, 2, 5, 7, and 10;
- Patients in cluster 8, as compared to patients in clusters 1, 5, and 7;
- Patients in cluster 11, as compared to patients in clusters 1 and 7;
- Patients in clusters 3 and 12, as compared to patients in cluster 1.

Discussion

Based on the Global Burden of Diseases, Injuries, and Risk Factors Study 2019, which includes mortality and DALYs (disability-adjusted life years) assessments for 87 risk factors and combinations of risk factors at global and regional levels, it can be determined that between the years 1990 and 2019, the worldwide prevalence of hypertensive heart disease (HHD) increased by 138%. The prevalence of HHD may continue to rise, because some people with hypertension around the world are being overlooked and may not be receiving appropriate care [18]. Identifying clusters of conditions in hospitalized patients serves as the initial step in recognizing opportunities for tailoring patient-centered care to those with unmet needs. The subsequent vital step comprises assessing the clinical outcomes of patients in each cluster, understanding the reasons for poor outcomes among specific clusters, and mapping the prevalent healthcare pathways for patients within each distinct cluster. Hence there is a lack of extensive data on the most frequent clusters of conditions, although it is widely recognized that multimorbidity presents in various forms, resulting in a diverse array of combinations of conditions. Some of these conditions might share commonalities in their origin and treatment requirements; this is termed concordant multimorbidity. For example, diseases such as coronary heart disease and cerebrovascular disease, which have a shared etiology, such as high blood pressure, tend to coexist frequently. In contrast, discordant multimorbidity involves conditions that seem unrelated or demand different approaches in management [19]. Multimorbidity can encompass a wide array of condition combinations. Evidence suggests that specific conditions tend to cluster

Table I. Characteristics of patients divided into groups of < 2 and ≥ 2 comorbidities

Parameter		Group		*P*-value
		< 2 comorbidities (*N* = 326)	**≥ 2 comorbidities (*N* = 163)**	
Age [years]	Mean ± SD	62.24 ±12.96	63.93 ±11.49	0.17
	Median	63	66	
	Quartiles	55–71	57–71	
TG [mg/dl]	Mean ± SD	124.09 ±62.47	145.05 ±72.16	< 0.001*
	Median	110	127	
	Quartiles	80–147	100–162.5	
LDL [mg/dl]	Mean ± SD	135.38 ±53.83	125.4 5±59.4	0.013*
	Median	135	113	
	Quartiles	93.5–169	83–156	
HDL [mg/dl]	Mean ± SD	54.91 ±14.46	50.58 ±13.22	0.001*
	Median	54	49	
	Quartiles	46–63	41–57	
TC [mg/dl]	Mean ± SD	195.19 ±50.48	183.85 ±52.87	0.008*
	Median	191	177.5	
	Quartiles	159–231	145.25–210	
hsCRP [mg/l]	Mean ± SD	6.23 ±23.89	9.96 ±27.18	< 0.001*
	Median	1.75	2.92	
	Quartiles	0.89–3.38	1.31–7.35	
Albumin [g/dl]	Mean ± SD	3.5 ±1.02	3.54 ±0.48	0.951
	Median	3.65	3.55	
	Quartiles	2.77–4.43	3.35–3.73	
Transferrin [g/l]	Mean ± SD	2.5 ±0.6	2.23 ±0.75	0.306
	Median	2.34	2.08	
	Quartiles	2.09–2.76	1.86–2.77	
Lymphocytes [%]	Mean ± SD	26.03 ±8.31	23.03 ±8.45	0.123
	Median	25.9	25	
	Quartiles	20.4–31.05	17.82–26.92	
Procalcitonin [ng/ml]	Mean ± SD	2.93 ±11.13	1.24 ±3.88	0.624
	Median	0.04	0.05	
	Quartiles	0.02–0.21	0.03–0.32	
K [mmol/l]	Mean ± SD	4.21 ±0.45	4.39 ±0.61	0.002*
	Median	4.19	4.28	
	Quartiles	3.94–4.42	4.02–4.63	
Na [mmol/l]	Mean ± SD	140.06 ±2.83	139.67 ±2.84	0.151
	Median	140	140	
	Quartiles	139–142	138–141	
HbA_{1c} (%)	Mean ± SD	5.81 ±0.64	6.51 ±1.27	< 0.001*
	Median	5.7	6.1	
	Quartiles	5.5–6	5.7–6.75	
Sex	Female	178 (54.60%)	81 (49.69%)	0.353
	Male	148 (45.40%)	82 (50.31%)	
Hypertension grade	1	71 (21.78%)	27 (16.56%)	0.227
	2	170 (52.15%)	85 (52.15%)	
	3	52 (15.95%)	34 (20.86%)	
	Unknown	33 (10.12%)	17 (10.43%)	

*p: Mann-Whitney test for quantitative variables, χ^2 or Fisher's exact test for qualitative variables: low-density lipoprotein (LDL), triglycerides (TG), high-density lipoprotein (HDL), total cholesterol (TC), albumins, transferrin, lymphocytes, procalcitonin, potassium, sodium, hemoglobin A1c, high-sensitivity C-reactive protein (hsCRP). *Statistically significant (p < 0.05).*

together more frequently than others. These clusters can exhibit either a concordant or discordant nature in their presentation, as shown in the present study [20–23].

Our study findings were not unexpected. Among hypertensive patients, various comorbidities were evident, with prevalent conditions including diabetes (28%), obesity (37%), and heart failure (14%). The research identified 12 different clusters, including obesity only, diabetes with obesity, heart failure with chronic kidney disease, and myocardial infarction. Age discrepancies were observed; notably, MI patients were considerably older than those without comorbidities or those from clusters 2, 3, 7, 8, and 10. Patients with diabetes, with heart failure, and with obesity were notably older than those classified solely as obese. Importantly, the Qian *et al.* study concluded that worldwide, the most significant percentage increase in deaths and DALYs attributable to risk due to HHD were consistent with high BMI. The most significant increase in the risk-attributable death rate standardized by age for HHD was found in men with high BMI [18]. The LOHS also significantly differed, with extended durations for patients with specific conditions, compared to patients without comorbidities, including heart failure; chronic kidney disease without heart failure; heart failure and obesity; obesity with diabetes; and diabetes with heart failure, often in association with obesity. Relevantly, patients with diabetes, MI, heart failure, and obesity were significantly older than patients from other clusters, which complies with other findings [16]. The majority of the heightened burden of comorbidity is predominantly associated with concordant cardiometabolic conditions, including hypertension, diabetes, and obesity, which are recognized to co-occur in the general population [24].

Study limitations: While our study has yielded valuable insights into the clusters of comorbidities in hypertensive patients and factors influencing the LOHS, it is imperative to acknowledge inherent limitations that warrant consideration. The utilization of electronic health records introduces certain constraints, notably its reliance on documented diagnoses. This limitation implies that cases that remain undiagnosed or individuals lacking contact with healthcare services may not be represented within our dataset, potentially resulting in an underestimation of actual prevalence rates within the broader population. Furthermore, the absence of critical clinical parameters such as serum uric acid (SUA) or diabetes duration, coupled with incomplete patient medical histories and the exclusion of markers associated with hypertension-induced organ damage, emphasizes the necessity for prudence when interpreting our findings. The incorporation of missing data and a comprehensive discussion addressing these limitations are imperative steps towards attaining a more nuanced understanding of the study's outcomes and their wider implications.

In conclusion, the presence of additional health conditions impacts the duration of hospital stays for individuals with hypertension. Conditions such as HF, CKD, DM, and obesity can lead to extended hospitalization among hypertensive patients. Patients' clinical profiles provided sufficient insights to predict the need for prolonged and more costly medical care.

Table II. Comorbidities

Comorbidities	*n*	%*
HF	68	13.91
DM	138	28.22
CKD	67	13.70
CS	65	13.29
MI	38	7.77%
Obesity	181	37.01

HF – heart failure, DM – diabetes mellitus, CKD – chronic kidney disease, CS – cerebral stroke, MI – myocardial infarction.

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Table III. Occurrence of diseases divided into clusters

Comorbidities	Cluster 1 (*N* = 157)	Cluster 2 (*N* = 76)	Cluster 3 (*N* = 41)	Cluster 4 (*N* = 32)	Cluster 5 (*N* = 43)	Cluster 6 (*N* = 12)	Cluster 7 (*N* = 17)	Cluster 8 (*N* = 32)	Cluster 9 (*N* = 16)	Cluster 10 (*N* = 32)	Cluster 11 (*N* = 11)	Cluster 12 (*N* = 20)
HF	0.0%	0.0%	0.0%	100.0%	0.0%	0.0%	0.0%	0.0%	6.2%	12.5%	100.0%	100.0%
DM	0.0%	0.0%	100.0%	25.0%	100.0%	8.3%	41.2%	31.2%	18.8%	15.6%	0.0%	100.0%
CKD	0.0%	0.0%	7.3%	84.4%	0.0%	0.0%	11.8%	100.0%	12.5%	0.0%	0.0%	5.0%
CS	0.0%	0.0%	0.0%	15.6%	0.0%	0.0%	100.0%	18.8%	0.0%	100.0%	0.0%	25.0%
MI	0.0%	0.0%	0.0%	15.6%	0.0%	100.0%	0.0%	6.2%	100.0%	6.2%	0.0%	5.0%
Obesity	0.0%	100.0%	100.0%	12.5%	0.0%	0.0%	100.0%	12.5%	100.0%	0.0%	100.0%	60.0%

HF – heart failure, DM – diabetes mellitus, CKD – chronic kidney disease, CS – cerebral stroke, MI – myocardial infarction.

Table IV. Patient characteristics by cluster

Parameter		Cluster													*P*-value
		Cluster 1 (*N* = 157)	**Cluster 2 (*N* = 76)**	**Cluster 3 (*N* = 41)**	**Cluster 4 (*N* = 32)**	**Cluster 5 (*N* = 43)**	**Cluster 6 (*N* = 12)**	**Cluster 7 (*N* = 17)**	**Cluster 8 (*N* = 32)**	**Cluster 9 (*N* = 16)**	**Cluster 10 (*N* = 32)**	**Cluster 11 (*N* = 11)**	**Cluster 12 (*N* = 20)**	**Total (*N* = 489)**	
Age [years]	Mean ± SD	61.62 ±14.05	60.22 ±11.79	63.2 ±10.34	63.91 ±13.88	66.3 ±11.66	71.58 ±11.56	60.82 ±11.41	63.12 ±13.34	63.69 ±10.65	62.44 ±10.39	63.82 ±7.97	67.1 ±9.3	62.81 ±12.5	$p = 0.046$*
	Median	63	60	66	66.5	67	74.5	65	64	65	65	62	66	64	
	Quartiles	55–72	54–66.25	57–71	58.25–71.5	61.5–72	69–80	54–69	56.5–71	58.5–69	59.75–70	58.5–69.5	61.5–73.75	56–71	5, 12 > 2 6 > 3, 10, 7, 8, 1, 2
Sex	Female	89 (56.69%)	43 (56.58%)	14 (34.15%)	15 (46.88%)	22 (51.16%)	9 (75.00%)	12 (70.59%)	14 (43.75%)	8 (50.00%)	15 (46.88%)	8 (72.73%)	10 (50.00%)	259 (52.97%)	$p = 0.16$
	Male	68 (43.31%)	33 (43.42%)	27 (65.85%)	17 (53.12%)	21 (48.84%)	3 (25.00%)	5 (29.41%)	18 (56.25%)	8 (50.00%)	17 (53.12%)	3 (27.27%)	10 (50.00%)	230 (47.03%)	
HT grade	1	35 (22.29%)	13 (17.11%)	7 (17.07%)	4 (12.50%)	11 (25.58%)	1 (8.33%)	2 (11.76%)	7 (21.88%)	5 (31.25%)	7 (21.88%)	3 (27.27%)	3 (15.00%)	98 (20.04%)	$p = 0.375$
	2	83 (52.87%)	45 (59.21%)	18 (43.90%)	18 (56.25%)	23 (53.49%)	5 (41.67%)	13 (76.47%)	18 (56.25%)	5 (31.25%)	11 (34.38%)	7 (63.64%)	9 (45.00%)	255 (52.15%)	
	3	24 (15.29%)	12 (15.79%)	11 (26.83%)	5 (15.62%)	7 (16.28%)	1 (8.33%)	1 (5.88%)	5 (15.62%)	6 (37.50%)	8 (25.00%)	0 (0.00%)	6 (30.00%)	86 (17.59%)	
	Unknown	15 (9.55%)	6 (7.89%)	5 (12.20%)	5 (15.62%)	2 (4.65%)	5 (41.67%)	1 (5.88%)	2 (6.25%)	0 (0.00%)	6 (18.75%)	1 (9.09%)	2 (10.00%)	50 (10.22%)	

*p: Kruskal–Wallis test + post-hoc analysis (Dunn's test) for quantitative variables, χ^2 or Fisher's exact test for qualitative variables. *Statistically significant ($p < 0.05$), HT – hypertension.*

Table V. Comparison of length of hospitalization across clusters

LOHS [days]	Cluster												*P*-value
	Cluster 1 (*N* = 157)	**Cluster 2 (*N* = 76)**	**Cluster 3 (*N* = 41)**	**Cluster 4 (*N* = 32)**	**Cluster 5 (*N* = 43)**	**Cluster 6 (*N* = 12)**	**Cluster 7 (*N* = 17)**	**Cluster 8 (*N* = 32)**	**Cluster 9 (*N* = 16)**	**Cluster 10 (*N* = 32)**	**Cluster 11 (*N* = 11)**	**Cluster 12 (*N* = 20)**	
Mean ±SD	2.76 ±2.42	3.08 ±1.96	3.9 ±3.23	4.97 ±3.99	2.65 ±1.77	4 ±3.36	2.71 ±2.76	4.16 ±3.32	3.62 ±2.42	3.41 ±2.59	3.91 ±1.92	3.55 ±1.93	< 0.001
Median	2	3	3	4	3	3	1	3	3	3	4	3.5	
Quartiles	1–3	1–4	1–5	3–7	1–3	1.75–4.25	1–3	2–5	1.75–5	1–5	3–5	2–5	4 > 1 0, 2, 5, 1, 7; 8 > 5,1, 7; 11 > 1, 7; 12, 3 > 1

p: Kruskal–Wallis test + post-hoc analysis (Dunn's test). LOHS – length of hospital stay.

Ethical approval

The study was approved by the Bioethics Committee of Wroclaw Medical University, protocol no. KB-205/2021.

Conflict of interest

The authors declare no conflict of interest.

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