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Heterogeneity in multimorbidity patterns and chronic disease association rules among middle-aged and older adults with cognitive impairment: A dual-cohort analysis of community and hospital real-world data

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Abstract

Objective

To compare chronic disease multimorbidity characteristics and association patterns in cognitively impaired middle-aged and older adults across community and clinical settings, and to provide evidence for stratified chronic disease management.

Methods

A dual-database parallel controlled design was adopted, uniformly referencing the 15 categories of chronic diseases from the China Health and Retirement Longitudinal Study (CHARLS) database. After homogenization of the two datasets, descriptive statistics, independent sample t-tests, and chi-square tests were used to compare baseline characteristics and comorbidity burden between the two groups. The Apriori association rule algorithm was employed to mine comorbidity association patterns and core disease clusters in both populations.

Results

This study included 796 community-dwelling older adults with physician-diagnosed memory disorders and 543 inpatients with confirmed cognitive disorders hospitalized from 2019 to 2025. Significant inter-group differences existed in sociodemographics, sleep quality and chronic disease counts. The community group showed left-skewed distribution: 32.91% had no somatic chronic conditions, mild-to-moderate multimorbidity dominated with a balanced middle-peaked pattern. The hospital group had a right-skewed distribution, with over 85% having three or more somatic chronic conditions. Association analysis identified 46 community rules forming an inflammation-related respiratory-digestive-joint-cardiac cluster. A total of 170 hospital rules indicated severe multisystem multimorbidity with renal, hepatic and pulmonary target organ damage, including 44 rules with 100% confidence.

Conclusion

Cognitively impaired populations exhibit prominent setting-specific multimorbidity heterogeneity. Early screening for inflammatory risks is essential for community residents, while hospitalized patients require standardized lipid management and targeted organ damage prevention.

1. Introduction

Cognitive impairment is a neurodegenerative disease with high prevalence among middle-aged and older adults. Due to its high prevalence, high disability rate, and heavy long-term care burden, it has become a major public health issue that seriously affects the health of the middle-aged and older population and constrains socioeconomic development(National Center For Neurological Disorders et al., 2024). As China's

population aging deepens and clinical diagnostic capabilities continue to improve, the size of the diagnosed cognitively impaired middle-aged and older adult population continues to expand(Chai, 2024; Wang et al., 2025). Exploring precise and effective prevention strategies and whole-course disease management has become a shared research focus in the fields of neurology and public health(Xijian and Song, 2025).

A large body of research indicates that somatic chronic conditions such as hypertension, diabetes, dyslipidemia, cardiovascular and cerebrovascular diseases are inextricably linked to the development of cognitive impairment. A study published in 2025 reported that 13% of diabetic patients aged 65–74 develop cognitive impairment, with the incidence rising to 24% in those over 75 years of age. The risk of dementia in patients with type 2 diabetes is 1.6 times that of the healthy population(LIN Yijia, 2025).

On the one hand, chronic-disease-mediated inflammation, cerebral small-vessel disease, oxidative stress, and insulin resistance may directly or indirectly injure neurons, expedite neurofunctional deterioration, and precipitate cognitive decline(Mogi et al., 2026). For instance, chronic cerebral hypoperfusion induces oxidative, inflammatory, and endoplasmic reticulum stress, ultimately resulting in vascular dementia(Zhen, 2024).

On the other hand, cognitive decline impairs patients' disease self-management abilities, leading to reduced medication adherence and disrupted lifestyle, which further exacerbates the disease and creates a vicious cycle. A multicenter cross-sectional study(Yao et al., 2025) covering 23,271 older adults across six regions in China found that hypertensive patients with comorbid cognitive impairment had worse treatment adherence and lower blood pressure control rates, suggesting that cognitive impairment may aggravate the disease through reduced medication adherence and lifestyle disruption, perpetuating the vicious cycle. Currently, most studies focus on the management of a single disease and cognitive function, or are confined to analyses within a single setting, lacking systematic comparisons of comorbidity characteristics across different settings.

Against this background, the present study employed a dual-database parallel comparative design that drew on the nationally representative community cohort of the China Health and Retirement Longitudinal Study (CHARLS) and single-center real-world inpatient clinical data. Targeting middle-aged and older adults aged 45 years and above with cognitive impairment, the present study implemented unified chronic-disease classification criteria and analytical approaches to systematically compare somatic chronic conditions multimorbidity burden, single-disease comorbidity stratification, and multiple-chronic-disease association rules between the two groups. This study sought to unpack differences and underlying mechanisms of multimorbidity patterns among cognitively impaired populations in community and clinical settings, and to generate an evidence-base for developing a stratified prevention-and-control system for community early screening and intervention and hospital-based comprehensive diagnosis and management.

2. Materials and Methods

2.1 Data Sources

2.1.1 Community Data Source

Community data were obtained from the 2020 wave of the China Health and Retirement Longitudinal Study (CHARLS) database(Zhao et al., 2014). CHARLS is a longitudinal survey of the Chinese middle-aged and older population conducted by the National School of Development at Peking University. The data cover more than 150 county-level units across 28 provinces in China, providing good population representativeness. The study employed a multistage stratified cluster sampling method to collect high-quality developmental data on households and individuals aged 45 and above in China, including basic information, income, employment, health status, and retirement. Somatic chronic conditions information was collected through self-reported physician-diagnosed medical history, encompassing 15 categories of common chronic diseases in middle-aged and older adults. This study used these 15 categories as the unified reference standard for chronic disease classification. Participants who self-reported a diagnosis of memory-related disease in CHARLS were selected as study subjects. Inclusion criteria: (1) age ≥ 45 years; (2) diagnosed with memory-related disease; (3) complete core variable information on chronic disease and sociodemographic characteristics. Elimination criteria: >20% missing variables. A total of 796 community participants were ultimately included.

2.1.2 Real-World Clinical Data

Clinical data were obtained from the electronic medical record system of a tertiary hospital for patients discharged between January 2019 and January 2025, using a retrospective case collection design. Study subjects were identified through discharge diagnosis keyword search. Keywords included: cognitive impairment, Alzheimer's disease, memory decline, cognitive decline, dementia, and other cognitive-related diagnoses. Inclusion criteria: (1) discharge diagnosis containing the above cognitive-related keywords; (2) age ≥ 45 years; (3) complete inpatient medical records with comprehensive discharge diagnosis information. Exclusion criterion: clinical death. Elimination criteria: >20% missing variables. A total of 543 real-world participants were ultimately included.

2.2 Variable Definitions and Outcome Measures

2.2.1 Baseline Variables

Baseline variables included sociodemographic characteristics such as age, sex, and marital status, as well as health-related indicators including sleep quality and the number of somatic chronic conditions.

2.2.2 Core Variables — Somatic chronic conditions

This study included 15 categories of common somatic chronic conditions.In addition to memory-related disease, these included: hypertension, diabetes, dyslipidemia, stroke, heart disease, chronic pulmonary disease, asthma, digestive system disease, kidney disease, liver disease, arthritis or rheumatic disease, malignant tumor, Parkinson's disease, and emotional or mental problems.

2.2.3 Outcome Measures

(1) Number of comorbidities: The total number of chronic diseases for each participant was calculated, and the distributional differences in overall comorbidity burden between the two groups were analyzed.

(2) Single-disease comorbidity stratification: For each somatic chronic conditions, using that disease as the index condition, the number of other chronic diseases concurrently present in the patient was counted, and the comorbidity burden stratification characteristics of single diseases were compared between the two groups.

(3) Multiple chronic disease association rules: The co-occurrence association patterns among the 15 chronic diseases were mined to identify high-frequency comorbidity combinations and strongly associated disease clusters.

2.3 Statistical Methods

2.3.1 Statistical and Visualization Methods

Descriptive statistics were used to analyze baseline characteristics and comorbidity distributions in the two groups. Continuous variables conforming to a normal distribution were expressed as mean ± standard deviation, and intergroup comparisons were performed using independent sample t-tests. Categorical variables were expressed as frequencies and percentages (n, %), and intergroup comparisons were performed using the chi-square (χ^2) test. The Apriori association rule algorithm was used to mine association rules for multiple chronic diseases in the two data sources. The minimum support was set at 0.01, and the minimum confidence at 0.5. Support, confidence, and lift were used as core evaluation metrics to quantitatively determine the strength and reliability of chronic disease comorbidity associations. All statistical analyses and visualizations were performed using R software (version 4.2.1). All statistical tests were two-sided, and a P-value < 0.05 was considered statistically significant.

2.3.2 Data Processing Principles

To ensure cross-database comparability, a unified chronic disease classification framework, variable coding rules, and missing value handling strategy were applied to both the community and hospital datasets. Missing values for continuous numeric variables such as age were imputed using the median. Missing values for categorical variables including marital status and sleep quality were imputed using the mode. Missing values for the 15 somatic chronic conditions variables were uniformly assigned a value of 0 to indicate absence of the corresponding disease. After missing value imputation, all variables were recoded and redefined, with the 15 somatic chronic conditions subjected to uniform binary coding.

A total of 2180 discharge diagnosis entries were extracted from the clinical dataset. Homologous diagnoses were merged with reference to the 15-category chronic disease classification standard for middle-aged and older adults from the CHARLS database. A total of 1140 diagnosis entries fell outside the scope of the CHARLS chronic disease framework and covered surgical history, electrolyte disturbances, gynecological and urological diseases and other conditions, and were excluded from statistical analyses of chronic diseases.

2.3.3 Statistical Evaluation Metrics

Three metrics were employed to evaluate the association rules: support, confidence, and lift.

Support indicates the proportion of study participants in whom a given disease combination occurs. Higher support values reflect more prevalent disease combinations.

Confidence represents the conditional probability that the consequent disease occurs when the antecedent disease is present. Higher confidence values indicate a more reliable rule.

Coverage indicates the proportion of study participants in whom the antecedent disease combination occurs, reflecting the scope of application of a given rule. Higher coverage values indicate that the antecedent combination is more common in the study population.

Lift reflects the extent to which the risk of the consequent disease is increased in the presence of the antecedent disease, calculated as the ratio of the observed confidence to the expected confidence under the assumption of independence. A lift value greater than 1 indicates a positive association between the antecedent and consequent diseases, with larger values denoting stronger association strength. A lift value equal to 1 suggests no association, whereas a value less than 1 implies a negative association.

2.4 Ethics Statement

The CHARLS database is a publicly accessible research database. All survey procedures were approved by the Ethics Review Committee of Peking University (approval number: IRB00001052-11015), and all participants provided informed consent. The hospital real-world data were derived from a retrospective medical record study, approved by the Zhuhai People's Hospital’s Medical Ethics Committee (approval number:2024 – 114). Due to the anonymized retrospective analysis of the study, informed consent from patients was waived. All personal identifying information was de-identified throughout the study, and patient privacy and data security were strictly protected. This study was performed in accordance with the Declaration of Helsinki.

3. Results

3.1 Baseline Characteristics and Overall Distribution of Chronic Disease Counts in the Two Groups

A total of 1,339 middle-aged and older adults with cognitive impairment aged 45 and above were ultimately included in this study, comprising 796 participants in the community group (CHARLS group) and 543 inpatients in the hospital group (Hospital group).

The CHARLS group had a mean age of 68.24 ± 9.41 years, with 45.9% (365 cases) male and 54.1% (431 cases) female; 24.1% (192 cases) lived alone, and 75.9% (604 cases) did not live alone. The community group had generally favorable self-rated health, with 58.7% (467 cases) reporting good sleep, 25.6% (204 cases) reporting poor sleep, and only 15.7% (125 cases) reporting fair sleep. The distribution of chronic disease counts in the CHARLS group was left-skewed: the proportion of participants with no somatic chronic conditions was the highest at 32.91% (262 cases), and the proportion gradually decreased as the number of diseases increased.

The Hospital group had a mean age of 70.02 ± 8.98 years, with 35.0% (190 cases) male and 65.0% (353 cases) female; 15.8% (86 cases) lived alone, and 84.2% (457 cases) did not live alone. The hospital group was dominated by abnormal sleep patterns, with 66.5% (361 cases) reporting fair sleep, 20.3% (110 cases) reporting poor sleep, and only 13.3% (72 cases) reporting good sleep. The distribution of chronic disease counts in the two groups showed completely opposite trends. The hospital group's distribution was right-skewed: only 1.1% (6 cases) had no chronic diseases, 4.4% (24 cases) had one disease, and 9.6% (52 cases) had two diseases; patients with three or more chronic diseases constituted the absolute majority, with over 85% of patients having three or more somatic chronic conditions. The differences in sociodemographic characteristics, sleep quality, and the number of somatic chronic conditions between the two groups were all statistically significant (all $P < 0.01$). Detailed data are presented in Table 1.

Table 1
Baseline Characteristics in the Two Groups

Groups		**CHARLS(n = 796)**	**Hospital(n = 543)**	**t/χ^2**	***P***
Age		68.24 ± 9.41	70.02 ± 8.98	3.470	<0.01
Gender	Male	365(45.9)	190(35.0)	15.697	<0.01
	Female	431(54.1)	353(65.0)		
Marital status	Living alone	192(24.1)	86(15.8)	13.461	<0.01
	Not living alone	604(75.9)	457(84.2)		
Sleep quality	Poor	204(25.6)	110(20.3)	398.640	<0.01
	Fair	125(15.7)	361(66.5)		
	Good	467(58.7)	72(13.3)		
Number of comorbidities	0	262(32.91)	6(1.1)	640.215	<0.01
	1	228(28.64)	24(4.4)		
	2	154(19.35)	52(9.6)		
	3	83(10.43)	96(17.1)		
	4	33(4.15)	131(24.1)		
	5	17(2.14)	99(18.2)		
	6	9(1.13)	73(13.4)		
	≥ 7	10(12.56)	62(11.4)		

3.2 Stratified Distribution Characteristics of Single-Disease Comorbidity for Somatic Chronic Conditions

Excluding memory-related diseases, 14 categories of common somatic chronic conditions were stratified into four comorbidity levels, namely with only the index disease, with one other chronic disease, with two other chronic diseases, and with three or more other chronic diseases. The distribution characteristics of the two groups are presented in Fig. 1, with Fig. 1A corresponding to the CHARLS group and Fig. 1B to the hospital group.

3.2.1 Stratified Single-Disease Comorbidity Characteristics in the CHARLS group

The four-level comorbidity structure of each disease in the CHARLS group was relatively balanced, with no obvious tendency toward high-burden clustering, and mild-to-moderate comorbidity accounted for the majority.

Proportion of patients with only the index disease

The overall range was 12.77%–31.25%. Malignant tumour (31.25%) and Parkinson's disease (30.99%) had the highest single-disease proportions. Emotional or mental problems, liver disease, arthritis, dyslipidaemia, stroke, and heart disease all had single-disease proportions in the 20%–23% range. Hypertension and diabetes had identical single-disease proportions (17.98%). Asthma had the lowest single-disease proportion (12.77%).

Proportion of patients with one other chronic disease

The overall range was 18.75%–33.77%. Dyslipidaemia had the highest proportion (33.77%), followed by stroke, liver disease, emotional or mental problems, and hypertension, all in the 28%–31% range. Malignant tumour had the lowest proportion (18.75%).

Proportion of patients with two other chronic diseases

The overall range was 6.25%–26.44%. Chronic pulmonary disease (26.44%) and kidney disease (26.09%) had the highest proportions, followed by digestive system disease and heart disease, both around 24%. Malignant tumour had the lowest proportion (6.25%).

Proportion of patients with three or more other chronic diseases

The overall range was 23.94%–44.68%. Asthma (44.68%) and malignant tumor (43.75%) had the highest proportions, followed by diabetes and digestive system disease, both exceeding 34%. Parkinson’s disease had the lowest proportion (23.94%).

3.2.2 Single-Disease Comorbidity Characteristics in the Hospital Group

In the hospital group, the comorbidity stratification for each disease type was highly skewed, with patients heavily concentrated at the level of having three or more other chronic diseases, and the proportions of

single-disease and mild comorbidity were extremely low.

Proportion of patients with only the index disease

The overall range was 0%–13.79%, with the vast majority of disease types below 4%. Malignant tumour had the highest single-disease proportion (13.79%), followed by arthritis or rheumatic disease (6.67%). Dyslipidaemia (2.26%), liver disease (0.75%), kidney disease (2.75%), and stroke (0.2%) all had single-disease proportions below 3%. Asthma had no cases of single-disease presentation.

Proportion of patients with one or two other chronic diseases

The overall level was low. The proportion with one other chronic disease was mostly in the 3%–10% range, and the proportion with two other chronic diseases was mostly in the 7%–18% range. Dyslipidaemia had the relatively highest mild-to-moderate comorbidity proportion, totalling 26.55%.

Proportion of patients with three or more other chronic diseases

All disease types had proportions exceeding 70%, making this the predominant phenotype. Arthritis or rheumatic disease (93.33%) and kidney disease (92.66%) had the highest proportions, followed by chronic pulmonary disease, liver disease, diabetes, and hypertension, all exceeding 85%. Even the lowest proportions, namely dyslipidaemia (71.19%) and malignant tumour (75.86%), were significantly higher than the corresponding levels in the community group.

3.2.3 Comparison of Comorbidity Stratification Between Groups

Regarding comorbidity-stratified distribution magnitudes, for each index somatic disease, the proportion of hospital patients with three or more other chronic diseases was generally 2–3-fold higher than that of community participants, whereas the proportion of patients with only the index disease was only one-fifth to one-tenth of the community level. Inter-group discrepancies were comparatively modest for malignant tumour and arthritis or rheumatic disease.

In terms of distribution patterns, the community group showed an approximately balanced mid-peaked comorbidity profile dominated by mild-to-moderate burden. In contrast, hospital patients exhibited a severe-comorbidity-skewed distribution, with patients having three or more chronic conditions constituting the overwhelming majority.

The magnitude of inter-group disparities varied markedly across diseases. The largest gaps in comorbidity burden occurred for Parkinson’s disease and kidney disease, suggesting their comorbidity load increases substantially with disease progression. Malignant tumours showed the smallest difference, indicating its association with cognitive impairment is less affected by cumulative comorbidity effects.

3.3 Multiple Chronic Disease Association Rule Analysis

3.3.1 Multiple Chronic Disease Association Rule in the CHARLS Group

A total of 46 chronic disease association rules were mined in the CHARLS group. The top 20 strong association rules were selected by lift ranking (Table 2), exhibiting an overall profile of high lift and low support. For the top 20 rules, support ranged from 0.01 to 0.03, confidence from 0.50 to 0.89, and lift from 3.06 to 8.87. Over 80% were triple or higher-order combinations, suggesting that strongly associated multimorbidity patterns in the community population were predominantly multi-disease clusters. Based on disease attributes and association strength, the top 20 rules were categorized into three clusters.

Table 2
Multiple Chronic Disease Association Rule in the CHARLS Group(top20 by lift)

No.	Antecedent (LHS)	Consequent (RHS)	Count	Support	Confidence	Coverage	Lift	Sample Rank
1	Chronic Pulmonary Disease, Digestive System Disease, Heart Disease	Asthma	6	0.01	0.75	0.02	8.87	32
2	Asthma, Digestive System Disease, Heart Disease	Chronic Pulmonary Disease	6	0.01	0.75	0.02	4.69	33
3	Asthma, Chronic Pulmonary Disease, Heart Disease	Digestive System Disease	6	0.01	0.86	0.01	4.51	34
4	Dyslipidemia, Heart Disease, Hypertension	Diabetes	8	0.02	0.73	0.02	4.45	17
5	Diabetes, Dyslipidemia, Heart Disease	Hypertension	8	0.02	0.67	0.02	4.08	18
6	Chronic Pulmonary Disease, Stroke	Digestive System Disease	6	0.01	0.75	0.02	3.95	35
7	Asthma, Chronic Pulmonary Disease, Digestive System Disease	Heart Disease	6	0.01	0.75	0.02	3.91	36
8	Digestive System Disease, Dyslipidemia, Kidney Disease	Chronic Pulmonary Disease	6	0.01	0.60	0.02	3.76	37

No.	Antecedent (LHS)	Consequent (RHS)	Count	Support	Confidence	Coverage	Lift	Sample Rank
9	Asthma, Dyslipidemia	Chronic Pulmonary Disease	6	0.01	0.55	0.02	3.41	38
10	Arthritis or Rheumatic Disease, Chronic Pulmonary Disease	Digestive System Disease	9	0.02	0.64	0.03	3.39	12
11	Asthma, Dyslipidemia	Digestive System Disease	7	0.01	0.64	0.02	3.35	26
12	Digestive System Disease, Heart Disease	Arthritis or Rheumatic Disease	14	0.03	0.58	0.05	3.34	2
13	Hypertension, Kidney Disease	Heart Disease	7	0.01	0.64	0.02	3.32	27
14	Digestive System Disease, Dyslipidemia	Chronic Pulmonary Disease	13	0.02	0.50	0.05	3.13	5
15	Digestive System Disease, Stroke	Chronic Pulmonary Disease	6	0.01	0.50	0.02	3.13	39
16	Diabetes, Heart Disease, Hypertension	Dyslipidemia	8	0.02	0.89	0.02	3.11	19
17	Arthritis or Rheumatic Disease, Heart Disease	Digestive System Disease	14	0.03	0.58	0.05	3.07	3
18	Arthritis or Rheumatic Disease, Hypertension	Digestive System Disease	7	0.01	0.58	0.02	3.07	28
19	Diabetes, Heart Disease	Hypertension	9	0.02	0.50	0.03	3.06	13
20	Dyslipidemia, Emotional or	Diabetes	7	0.01	0.50	0.03	3.06	29

No.	Antecedent (LHS)	Consequent (RHS)	Count	Support	Confidence	Coverage	Lift	Sample Rank
	Mental Problem							

The digestive–respiratory–cardiac cluster was the strongest multimorbidity combination in the community. Among patients with concurrent chronic lung disease, digestive system disease, and heart disease, 75% also had asthma, with a disease risk 8.87 times that of the general population (Rule 1, lift = 8.87). Digestive, respiratory, and cardiac diseases served as mutual high-risk factors for one another (Rules 2 and 3). Respiratory diseases demonstrated widespread inflammation-mediated multimorbidity effects with digestive, osteoarticular, and cardiovascular diseases (Rules 6 and 10).

The metabolic syndrome cluster centered on hypertension, dyslipidemia, heart disease, and diabetes, representing the classic metabolic syndrome combination, with lift of 3.06–4.45. Rule 4 indicated that among patients with concurrent dyslipidemia, heart disease, and hypertension, 73% also had diabetes. Rule 5 showed that among patients with concurrent diabetes, dyslipidemia, and heart disease, 67% also had hypertension. Rule 16 demonstrated that among patients with concurrent diabetes, heart disease, and hypertension, 89% also had dyslipidemia. These rules also indicate that clustering of cardiovascular and cerebrovascular metabolic diseases was already evident in the community cognitively impaired population.

The osteoarticular–digestive–cardiovascular and cerebrovascular cluster centered on arthritis or rheumatic disease, digestive system disease, heart disease, and hypertension, with lift of 3.07–3.34. Rules 12 and 17 were the two rules with the largest sample sizes in this cluster, suggesting that a common disease mechanism, such as chronic inflammation, may exist between degenerative osteoarticular disease and digestive and cardiovascular diseases, which may in turn contribute to memory decline in middle-aged and older adults.

In addition to the three common chronic disease clusters described above, scattered rules were also identified, including hypertension plus kidney disease leading to heart disease (Rule 13, lift = 3.32), and dyslipidemia plus emotional or mental problems leading to diabetes (Rule 20, lift = 3.06). These suggest that kidney disease and mental health issues may have potential synergistic effects with metabolic diseases in community-dwelling middle-aged and older cognitively impaired patients, though these have not yet formed stable clusters.

3.3.2 Multiple Chronic Disease Association Rule in the Hospital Group

Using the same algorithm, a total of 170 chronic disease association rules were mined in the hospital group. The top 20 disease association rules by lift are presented in Table 3. Unlike the CHARLS group, the hospital group's association rules were characterized by low support and high lift. In terms of rule structure, the antecedents were predominantly underlying chronic diseases such as heart disease, stroke, and liver disease, while the consequents were concentrated on three types of target organ damage, namely kidney disease, liver disease, and chronic pulmonary disease, exhibiting a pattern of multiple underlying system diseases accumulating toward end-stage target organ damage. All top 20 rules involved triple or higher-order

combinations, with quadruple combinations predominating. Support ranged from 0.01 to 0.12, confidence from 0.60 to 0.86, and lift from 3.00 to 3.89. The number of cases corresponding to each individual rule ranged from 6 to 12, indicating that these strongly associated combinations constituted a relatively small proportion of all hospitalized patients and represented a severe, multisystem-involved high-risk subgroup. Based on the disease attributes and pathological mechanisms of the consequents, the hospital strong association rules were categorized into three multimorbidity clusters.

Table 3
Multiple Chronic Disease Association Rule in the Hospital Group(top20 by lift)

No.	Antecedent (LHS)	Consequent (RHS)	Count	Support	Confidence	Coverage	Lift	Sample Rank
1	Heart Disease, Hypertension, Liver Disease, Stroke	Kidney Disease	7	0.01	0.78	0.02	3.89	105
2	Chronic Pulmonary Disease, Heart Disease, Liver Disease, Stroke	Kidney Disease	6	0.01	0.75	0.01	3.75	136
3	Hypertension, Kidney Disease, Parkinson's Disease	Liver Disease	6	0.01	0.86	0.01	3.43	137
4	Kidney Disease, Parkinson's Disease, Stroke	Liver Disease	6	0.01	0.86	0.01	3.43	138
5	Dyslipidemia, Heart Disease, Liver Disease, Stroke	Kidney Disease	12	0.02	0.67	0.03	3.33	61
6	Digestive System Disease, Heart Disease, Kidney Disease, Stroke	Chronic Pulmonary Disease	7	0.01	0.78	0.02	3.33	106
7	Digestive System Disease, Heart Disease, Hypertension, Liver Disease	Chronic Pulmonary Disease	7	0.01	0.78	0.02	3.33	107
8	Liver Disease, Parkinson's Disease, Stroke	Kidney Disease	6	0.01	0.67	0.02	3.33	139

No.	Antecedent (LHS)	Consequent (RHS)	Count	Support	Confidence	Coverage	Lift	Sample Rank
9	Digestive System Disease, Heart Disease, Kidney Disease, Liver Disease	Chronic Pulmonary Disease	6	0.01	0.75	0.01	3.21	140
10	Digestive System Disease, Heart Disease, Liver Disease, Stroke	Chronic Pulmonary Disease	6	0.01	0.75	0.01	3.21	141
11	Chronic Pulmonary Disease, Digestive System Disease, Heart Disease, Stroke	Kidney Disease	7	0.01	0.64	0.02	3.18	108
12	Heart Disease, Liver Disease, Stroke	Kidney Disease	12	0.02	0.63	0.04	3.16	62
13	Chronic Pulmonary Disease, Digestive System Disease, Dyslipidemia, Heart Disease, Liver Disease	Kidney Disease	6	0.01	0.60	0.02	3.00	142
14	Chronic Pulmonary Disease, Heart Disease, Liver Disease, Stroke	Digestive System Disease	6	0.01	0.75	0.01	2.91	143
15	Diabetes, Heart Disease, Liver Disease	Chronic Pulmonary Disease	7	0.01	0.64	0.02	2.73	109
16	Chronic Pulmonary Disease, Diabetes, Dyslipidemia, Kidney Disease	Digestive System Disease	7	0.01	0.70	0.02	2.72	110

No.	Antecedent (LHS)	Consequent (RHS)	Count	Support	Confidence	Coverage	Lift	Sample Rank
17	Chronic Pulmonary Disease, Hypertension, Liver Disease, Stroke	Diabetes	6	0.01	0.75	0.01	2.70	144
18	Chronic Pulmonary Disease, Kidney Disease, Liver Disease	Digestive System Disease	11	0.02	0.69	0.03	2.67	69
19	Chronic Pulmonary Disease, Diabetes, Digestive System Disease	Liver Disease	8	0.01	0.67	0.02	2.67	94
20	Hypertension, Liver Disease, Parkinson's Disease	Diabetes	11	0.02	0.73	0.03	2.64	70

The multisystem disease with secondary kidney damage cluster contained the association rules with the highest lift. Antecedents covered multisystem diseases involving the heart, brain, liver, respiratory system, and digestive system, while consequents were uniformly kidney disease, indicating that the kidney is the most vulnerable common target organ following accumulation of multiple chronic diseases. Rule 1, heart disease plus hypertension plus liver disease plus stroke leading to kidney disease, had the highest lift of 3.89, indicating that among patients with concurrent heart, brain, liver, and hypertensive diseases, 78% also had kidney damage, with a risk 3.89 times that of general hospitalized patients. Rule 12 showed that among patients with concurrent heart, brain, and liver diseases, 63% had kidney damage. When dyslipidemia was also present, 67% had kidney damage (Rule 5). When respiratory disease was also present, 75% had kidney damage (Rule 2). These findings suggest that coexistence of heart, brain, and liver diseases constitutes the core underlying combination for kidney damage, with risk progressively increasing when dyslipidemia, lung disease, or digestive disease is superimposed.

The Parkinson's disease with renal or cerebrovascular disease and secondary liver damage cluster represents a multimorbidity pattern unique to neurodegenerative diseases. Although it contained only two rules, Rules 3 and 4, both had lift of 3.43 and confidence of 0.86, making them the highest-confidence rules among all rules. These results suggest that when Parkinson's disease patients also have kidney disease or cerebrovascular disease, 86% also have abnormal liver function. This combination did not form a strong association in the community population and is a characteristic multimorbidity manifestation in hospitalized Parkinson's patients with cognitive impairment.

In the multiorgan damage with chronic lung disease cluster, antecedents covered multisystem diseases involving the digestive system, heart, kidneys, liver, and brain (Rules 6 and 7), with lift of 3.21–3.33.These rules reflect the pathological pattern of cardiopulmonary interaction and digestive–respiratory synergistic damage under conditions of multiorgan dysfunction. Older patients with multiple systemic diseases often experience decreased swallowing function, prolonged bed rest, and reduced immunity, making them susceptible to chronic pulmonary infections and obstructive ventilatory dysfunction, ultimately forming a vicious cycle between chronic lung disease and multisystem damage.

In addition to the three common chronic disease clusters, 44 rules with 100% confidence were also identified in the hospital group. Among these, 39 rules had dyslipidaemia as the consequent, with antecedents encompassing two-to-five-disease combinations across the metabolic, cardiocerebrovascular, respiratory, digestive, and neurodegenerative systems. The lift values remained stable within the 1.09 to 1.92 range. This pattern suggests that dyslipidaemia serves as a common pathological basis among hospitalized cognitively impaired patients with multiple chronic diseases. Regardless of the primarily affected system, virtually all patients with two or more moderate-to-severe somatic chronic conditions also presented with dyslipidaemia.

4. Discussion

This study demonstrate significant differences in comorbidity burden and multimorbidity patterns between the two groups. The prevalence of multiple chronic diseases and the number of comorbidities were significantly higher in hospitalized cognitively impaired patients than in the community population, and the distributions of chronic disease counts in the two groups showed completely opposite skewness trends. The community population was characterized by the parallel coexistence of “respiratory–digestive–joint–cardiac” inflammation-related diseases, representing an early high-risk subgroup. In contrast, the hospital population exhibited greater depth of chronic disease accumulation and higher disease complexity overall.

4.1 Differences in Comorbidity Burden

The completely opposite distributional trends in chronic disease counts between the two groups may be primarily attributable to Berkson’s bias, also known as hospital admission rate bias. Inclusion of hospital samples inherently carries a disease-severity filtering effect. Patients enter the hospital-based care system only when somatic chronic conditions acutely worsen, complications develop, or cognitive impairment leads to substantial decline in activities of daily living that requires specialized care. This screening mechanism naturally excludes patients with single diseases, stable conditions, and mild cases without complications. It ultimately produces the extreme distribution where over 85 percent of patients have three or more chronic diseases. In contrast, the CHARLS community sample adopts population-based random sampling. The 32.91 percent proportion of participants free of somatic chronic conditions in the community group indirectly reflects population-level characteristics of populations in the early stage of cognitive impairment. And the community group may include both genuine early-stage patients with mild cognitive impairment and a substantial number of healthy older adults who mistakenly regard physiological memory decline as a disease. Differences between the two groups partly stem from disparities in participant sources and sampling approaches. Nevertheless, intrinsic pathological differences in the diseases themselves remain to be further verified.

In addition to admission-rate bias, fundamental discrepancies in cognitive-impairment diagnostic criteria between the two groups may constitute another core explanation for disparities in comorbidity burden. All hospital-sample patients carried discharge diagnoses that explicitly documented cognitive impairment, Alzheimer's disease, memory decline and related conditions. Diagnoses were confirmed by clinicians with support from imaging and neuropsychological assessments. These patients had generally reached the clinical disease stage and presented inherently higher rates of somatic-condition comorbidity. Community-source data relied on self-reported memory-related diseases recalled and reported by respondents, and standardized neuropsychological evaluation might not have been performed. Such enrollment approaches may cause some middle-aged and older adults to misclassify physiological memory decline and benign age-related forgetfulness as cognitive impairment. The dataset may also include individuals with moderate dementia who cannot accurately recall prior disease histories, as well as undiagnosed mild cases with stable disease status. Such misclassification introduces two sources of bias. It includes individuals with purely physiological memory decline who generally have few somatic chronic conditions, and it excludes some mild cases as well as patients with severe dementia who frequently suffer from multiple somatic chronic conditions. Jointly, these biases reduce the observed somatic chronic-condition burden in the community group and dilute comorbidity proportions among genuine community-dwelling patients with cognitive impairment.

Furthermore, the mean age of the hospital group was higher than that of the CHARLS group. Previous studies have shown that age acts both as a core risk factor for cognitive-impairment progression and as a predictor of chronic-disease accumulation(Di Carlo et al., 2000; Zhang et al., 2020; Dintica and Yaffe, 2022). Owing to different cognitive-assessment tools adopted by the hospital and CHARLS groups, the severity of cognitive impairment cannot be directly compared across populations. Nonetheless, multimorbidity patterns and age distribution imply that hospital-group participants may be trapped in a vicious cycle between somatic chronic conditions and cognitive impairment, producing explosive rises in comorbidity counts. By contrast, the community population contains numerous mild cases, which accounts for its comparatively lower comorbidity burden.

4.2 Differences in Multimorbidity Patterns

The two groups differed not only in the number of comorbidities but also in their core multiple chronic disease association rules

4.2.1 Multimorbidity Patterns of Community

The predominant multimorbidity patterns among community-dwelling participants were represented by an inflammation-related cluster involving respiratory, digestive, osteoarticular, and cardiovascular disorders, followed by a metabolic-syndrome-related cluster. The resulting association rules exhibited an overall profile of high lift and low support. According to the inflammaging theory, chronic disorders such as obesity, arthritis, and chronic obstructive pulmonary disease represent clinical manifestations of persistent systemic low-grade inflammation(Santoro et al., 2021; Chen et al., 2026). On the one hand, as systemic chronic inflammation increases, it may gradually involve the respiratory, digestive, osteoarticular, and cardiovascular systems, and may even give rise to the dispersed clustering of multi-system diseases. On the other hand,

sustained peripheral inflammation can cross the blood-brain barrier, activate central microglia and astrocytes, and trigger neuroinflammation. This neuroinflammatory response serves as a key driver of β-amyloid deposition and tau-protein hyperphosphorylation, which constitute the core pathological processes of Alzheimer's disease(Fronza et al., 2023; Kiraly et al., 2023).

Beyond chronic inflammatory pathways, metabolic disorders also contribute to cognitive impairment. Metabolic conditions including hypertension, diabetes, dyslipidaemia, and heart disease damage cerebrovascular endothelial function and promote atherosclerosis, thereby inducing cerebral small-vessel disease. The subsequent pathological manifestations, including white-matter hyperintensities, cerebral microbleeds, and lacunar infarcts, disrupt cerebral tissue integrity and haemodynamic homeostasis, and ultimately result in neuronal injury and cognitive decline(Patel and Edison, 2024). Furthermore, as a high-energy-consuming organ, the brain is particularly vulnerable to disrupted insulin signalling. Cerebral insulin resistance impairs neuronal energy metabolism, synaptic plasticity, and neurotransmitter release, and can directly drive Alzheimer’s-disease-related pathological changes. This observation has led some researchers to refer to Alzheimer’s disease as type 3 diabetes(Kciuk et al., 2024).

Notably, the high lift and low support profile of the association rules can be partly explained by sample composition. This statistical profile indicates that such disease combinations are not widespread within the community population and merely characterize a high-risk subgroup. This phenomenon may be partly explained by sample composition. The community sample contained some mild cases and healthy older adults with only subjective memory-related complaints; the inclusion of these individuals lowers population-level estimates of overall disease co-occurrence.

4.2.2 Multimorbidity Patterns of Hospital

The hospital cognitively impaired population exhibited coexistence of an baseline comorbidity subgroup and a severe subgroup, reflecting the overall features of deeper chronic disease accumulation and higher disease complexity among hospitalized patients.

On the one hand, 44 association rules with 100% confidence were identified in the hospital population, including 39 rules with dyslipidaemia as the consequent, 3 with hypertension, and 2 with cerebral infarction. The antecedents covered nearly all disease systems, including the metabolic, cardiovascular, cerebrovascular, respiratory, digestive, neurodegenerative, and malignant tumour systems. These rules indicate that when patients had two or more moderate-to-severe somatic chronic conditions, virtually all of them also presented with dyslipidaemia. This may be explained by the fact that dyslipidaemia is not only the initiating factor of atherosclerosis but also a common pathological basis for the development and progression of hypertension, diabetes, cardiovascular, cerebrovascular diseases, and kidney disease(Gao et al., 2022). Meanwhile, multisystem damage involving chronic inflammation, insulin resistance, and hepatic and renal dysfunction can in turn exacerbate lipid metabolism disorders(Gál et al., 2026), thereby forming a vicious cycle. Another possibility is that hospitalized patients routinely undergo comprehensive biochemical testing, which eliminates the underreporting commonly observed in community data. The relatively low lift values of these rules, ranging from 1.09 to 1.92, further suggest that dyslipidaemia is already highly prevalent among hospitalized patients with multiple chronic diseases, and that the association-enhancing effect of disease co-occurrence has been diluted by the high baseline prevalence. This further underscores

that lipid management should be regarded as a foundational intervention for the cognitively impaired population throughout the entire course of diagnosis and treatment, potentially slowing the progression of multisystem damage by controlling this common pathological basis of multiple diseases.

Rules with kidney disease as the consequent showed the highest lift of 3.89. When the core combination of heart, brain, and liver diseases was superimposed on different disease systems, the lift for kidney damage consistently exceeded 3, indicating that the kidney serves as a common target organ for multiple diseases. From a mechanistic perspective, the kidney, as one of the most richly perfused organs in the body, bears the core functions of drug metabolism and toxin clearance. When patients present with multisystem diseases, multiple mechanisms act together, including reduced cardiac output, decreased renal perfusion, toxin accumulation, and drug nephrotoxicity, which can significantly increase the risk of chronic kidney disease(Kaesler et al., 2020; Spicher et al., 2025; Guan et al., 2026). Once kidney damage occurs, it in turn aggravates fluid and sodium retention and toxin accumulation, further deteriorating cardiac and cerebral function, and thereby creating a vicious cycle of multi-organ damage. Kidney damage may therefore serve as a core early warning signal for poor prognosis in cognitively impaired hospitalized patients(Bugnicourt et al., 2013).

The concomitant liver damage observed when Parkinson's disease is combined with renal or cerebrovascular disease represents a unique comorbidity pattern among hospitalized patients with neurodegenerative diseases. The two related rules both had a confidence of 0.86 and a lift of 3.43, indicating that the proportion of abnormal liver function in Parkinson's disease patients with concomitant renal or cerebrovascular disease was significantly higher than that in the general hospitalized population. This may be related to the long disease course of Parkinson's disease, during which long-term administration of relevant medications increases the metabolic burden on the liver(Korczeniewska et al., 2025). Meanwhile, the autonomic nervous dysfunction accompanying Parkinson's disease indirectly affects hepatic blood flow regulation and metabolic function, and when combined with kidney damage and cerebrovascular disease, systemic metabolic disturbances are further aggravated, thereby increasing the risk of abnormal liver function(Brito et al., 2025; Yuanyuan et al., 2025).

A bidirectional interaction exists between chronic lung disease and multisystem damage. On the one hand, chronic lung disease can damage multiple organs, including the heart, brain, and kidney, through mechanisms such as hypoxaemia and systemic inflammatory responses(Zhu et al., 2024; Schmuziger et al., 2025). On the other hand, patients with moderate-to-severe cognitive impairment are prone to recurrent aspiration and hypostatic pneumonia because of decreased activity tolerance, prolonged bed rest, and impaired swallowing function, which ultimately progresses to chronic lung disease(Spandorfer et al., 2025). This bidirectional interaction establishes a stable comorbidity chain between chronic lung disease and multisystem damage, and forms significant and robust association rules in hospitalized patients.

Although the support values of the association rules in the hospital cognitively impaired population are relatively low, indicating a lower clinical incidence than other rules, these rules may represent the clinically most concerning severe conditions and may have guiding value for stratified management and prognostic assessment of hospitalized cognitively impaired patients.

Taken together, the differences in chronic disease burden and multimorbidity patterns between the community and hospital cognitively impaired populations result from the combined effects of multiple factors, including sampling frame bias, heterogeneity in diagnostic criteria, natural disease progression, pathophysiological mechanisms, and measurement methodology.

5. Clinical and Public Health Implications

The community population contains a large number of mild cases, representing a critical intervention window for delaying cognitive decline. Simplified neuropsychological scales could improve the accuracy of identifying high-risk individuals, avoiding both over-intervention and missed diagnosis. Current community-based chronic disease management in China mostly focuses on risk factor control for hypertension, dyslipidaemia and diabetes. However, the present study identified an early inflammation-related multimorbidity cluster involving respiratory, digestive and osteoarticular disorders with stronger association strength among community-dwelling participants. The risk of cognitive decline attributable to this cluster has been substantially under-recognized. Anti-inflammation-oriented lifestyle interventions, rather than management targeting merely blood pressure and glucose, may therefore be implemented to help slow the progression of cognitive impairment.

Hospitalized cognitively impaired patients exhibit an extremely high prevalence of multimorbidity, which places higher demands on specialized hospital-based diagnosis and treatment models. First, lipid management should be implemented as a foundational intervention during hospitalization. Second, early targeted screening for renal and cerebrovascular function should be performed. Meanwhile, a multidisciplinary collaboration mechanism should be actively established. Nephrotoxic drugs ought to be avoided and risks related to polypharmacy should be highlighted to reduce or interrupt the vicious cycle of multi-organ damage. For patients with Parkinson's disease and concurrent cognitive impairment, attention should be paid to alterations in glucose metabolism and liver function to identify occult multimorbidity-related damage, optimize medication regimens, and minimize adverse drug reactions.

6. Conclusion

Based on the CHARLS public cohort database and real-world clinical data, this study conducted a systematic comparative analysis of chronic disease multimorbidity characteristics and association rules among middle-aged and older adults aged 45 years and above with cognitive impairment. The results showed that the cognitively impaired population exhibited significant clustering of chronic disease coexistence. Hypertension, diabetes, stroke, and dyslipidaemia were the core coexisting diseases, and these somatic chronic conditions may represent important factors influencing the progression of cognitive impairment in middle-aged and older adults. The CHARLS community sample and the clinical real-world sample showed marked heterogeneity in the distribution of chronic disease coexistence, the structure of multimorbidity combinations, and association rules. The community population was predominantly characterized by insidious, mild-to-moderate multimorbidity, whereas the hospitalized clinical population exhibited a highly concentrated pattern of severe multimorbidity. Clinical management should develop stratified intervention strategies tailored to different settings. At the community level, priority should be given to screening and

intervention for cognitive function and early inflammation-related risk factors. At the hospital level, comprehensive management of metabolic, vascular, and target-organ damage should be emphasized.

7. Limitations and Research Directions

The sources and classification of chronic disease information in this study were heterogeneous. Community chronic disease data were primarily based on self-report and susceptible to recall bias. Hospital data were processed through disease category merging for unified inter-group comparison, which inevitably omitted detailed information regarding disease subtypes, severity, and complications. Furthermore, several conditions beyond the established 15-disease classification framework were excluded from statistical analyses, which may have underestimated the actual multimorbidity burden among hospitalized patients. Baseline characteristics were unbalanced between the community and hospital groups. Key confounding factors, including disease severity, medication status, lifestyle behaviors, and social support, were not fully adjusted for in the analysis. These limitations may partially account for the observed differences in multimorbidity patterns between the two populations. In addition, the current cross-sectional design can only reveal correlational relationships between chronic multimorbidity and cognitive impairment. It cannot determine the temporal sequence or causal direction of disease progression, nor can it distinguish whether multimorbidity accelerates cognitive decline or whether cognitive deterioration exacerbates poor chronic disease management. Future longitudinal cohort studies are warranted to clarify the predictive value of inflammation-related clusters, metabolic–vascular clusters, and high-risk renal damage subgroups for cognitive deterioration and adverse clinical outcomes, and to further verify potential causal relationships and disease progression trajectories. Targeted community and hospital interventions can be developed and validated via randomized controlled trials based on the distinct multimorbidity subgroups identified in this study, supporting stratified multimorbidity management for cognitively impaired populations.

Abbreviations

China Health and Retirement Longitudinal Study(CHARLS)

Declarations

Ethics approval and consent to participate: The CHARLS database is a publicly accessible research database. All survey procedures were approved by the Ethics Review Committee of Peking University (approval number: IRB00001052-11015), and all participants provided informed consent at the time of original data collection. The hospital real-world data were derived from a retrospective medical record study, approved by the Medical Ethics Committee of Zhuhai People's Hospital (approval number: 2024-114). The ethics committee waived the requirement for patient informed consent for this anonymized retrospective analysis. All personal identifying information was de-identified throughout the study, patient privacy and data security were strictly protected, and this study was performed in accordance with the Declaration of Helsinki.

Consent for publication: Not applicable. No individual identifiable data, images, videos or case reports of any participants are included in this manuscript.

Availability of data and materials: The community dataset analysed in this study was obtained from the publicly available China Health and Retirement Longitudinal Study (CHARLS), which can be accessed by registered researchers via the official CHARLS website. The clinical dataset from the tertiary hospital is not publicly available due to patient privacy protection and institutional data governance restrictions. De-identified, cleaned and processed clinical data that support the findings of this study are available from the corresponding author upon reasonable request and after official institutional approval. All data processing methods are available within the manuscript.

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Authors' contributions: M.Z. and L.Y. performed data curation, drafted the main manuscript text, and prepared all tables. J.L.P. and X.X.X. conducted data curation and statistical analysis. Y.T.L. verified and checked all research data. Y.T. designed the research and supervised the overall study framework. J.W.P. provided methodological guidance for statistical analysis. J.H.Z. revised and polished the manuscript language. H.Y.W. conceived the study, coordinated research resources, and reviewed the final manuscript. All authors have read and approved the final submitted version of the manuscript.

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Figures

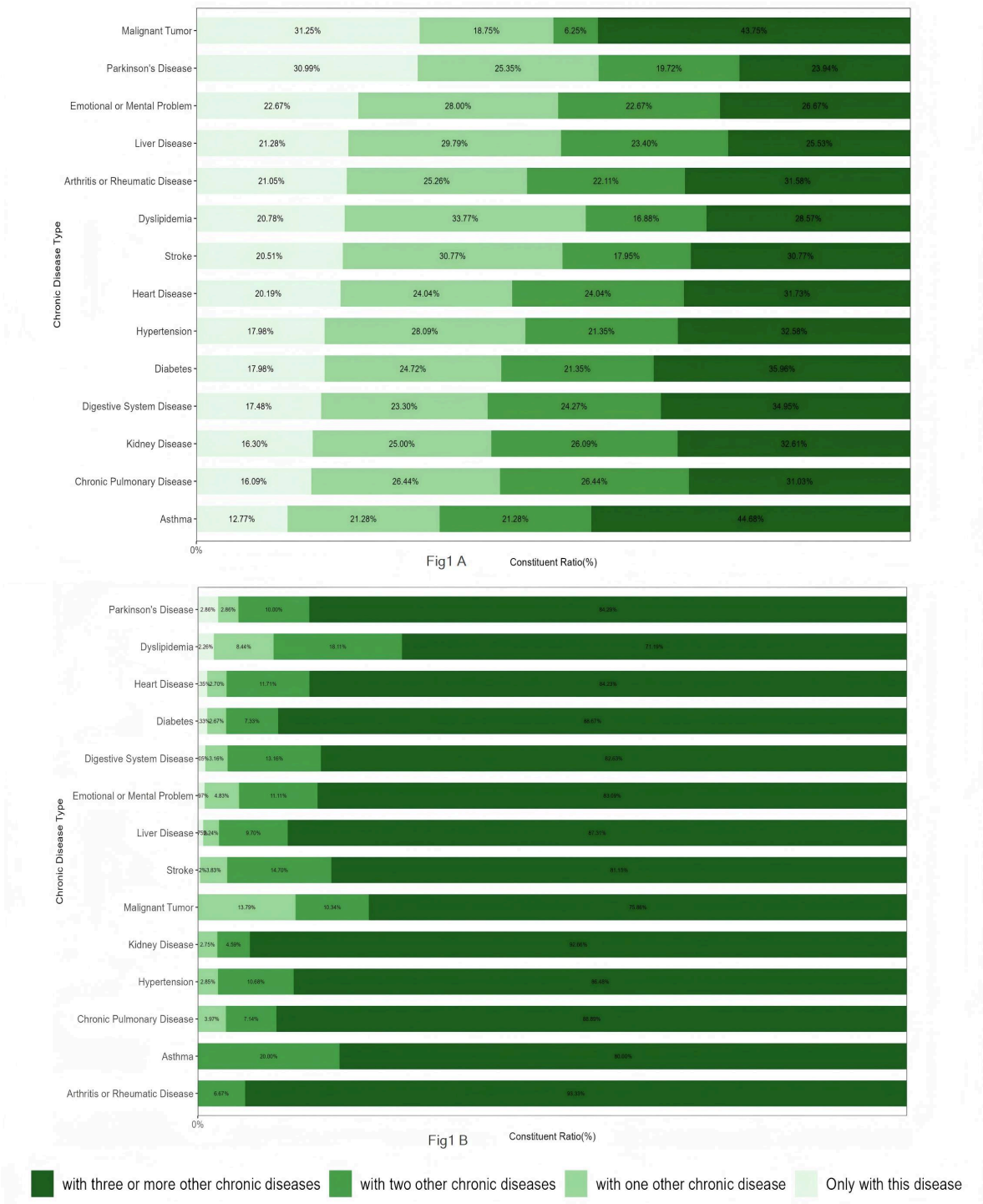


Figure 1

Stratified Distribution Characteristics of Single Disease Comorbidity for Somatic Chronic Conditions