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Analysis of multimorbidity networks associated with different factors in Northeast China: a cross-sectional analysis

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ABSTRACT

Objectives This study aimed to identify and study the associations and co-occurrence of multimorbidity, and assessed the associations of diseases with sex, age and hospitalisation duration.

Design Cross-sectional.

Setting 15 general hospitals in Jilin Province, China.

Participants A total of 431 295 inpatients were enrolled through a cross-sectional study in Jilin Province, China.

Primary outcome measures The complex relationships of multimorbidity were presented as weighted networks.

Results The distributions of the numbers of diseases differed significantly by sex, age and hospitalisation duration ($p<0.001$). Cerebrovascular diseases (CD), hypertensive diseases (HyD), ischaemic heart diseases (IHD) and other forms of heart disease (OFHD) showed the highest weights in the multimorbidity networks. The connections between different sexes or hospitalisation duration and diseases were similar, while those between different age groups and diseases were different.

Conclusions CD, HyD, IHD and OFHD were the central points of disease clusters and directly or indirectly related to other diseases or factors. Thus, effective interventions for these diseases should be adopted. Furthermore, different intervention strategies should be developed according to multimorbidity patterns in different age groups.

Strengths and limitations of this study

- This study visually demonstrated the differences in multimorbidity according to sex, age group and hospitalisation duration.
- Adjusting the analysis of multimorbidity patterns to the individual level rather than disease level could identify and study the associations and co-occurrence of multimorbidity.
- The model can be applied to assess the patterns of multimorbidity associated with different factors, and provide meaningful information for clinicians.
- The results were based on a cross-sectional study in Jilin Province, China, which might limit the generalisability of the results.

INTRODUCTION

The term multimorbidity broadly refers to the presence of two or more health conditions (diseases) in a single individual.[1–4] With the continuing increase in life expectancy, multimorbidity has become a worldwide public health issue as it increases with age.[5] Additionally, multimorbidity is associated with increased adverse health outcomes such as poor quality of life, disability, hospitalisation, mortality and the concomitant use of healthcare resources and expenditure.[6–9] Furthermore, multimorbidity is also costly for both individuals and the healthcare system, with healthcare utilisation and costs increasing with each additional condition,[10–12] particularly in China, the world's most populous country.[13 14] Therefore, identifying the associations and co-occurrence of multimorbidity is an essential public health issue that requires urgent attention.

Most of the published literature on multimorbidity patterns focuses on disease level rather than individual level.[1 10 15] Adjusting the analysis of multimorbidity patterns to the individual level rather than disease level could identify and study the associations and co-occurrence of multimorbidity. Studying and treating diseases in isolation may not only lead to inefficiencies and duplication in the case of multimorbid patients but may also have serious implications if treatment for one disease contradicts that for another.[1] A multidimensional approach is required to understand the patterns of multimorbidity and recognise the associations between conditions within these patterns.

Furthermore, Aguado *et al*[16] pointed out that multimorbidity is a complex phenomenon that can be assessed using network analysis. Moreover, research on multiple disease networks has attracted increasing

attention in recent years. In their analysis of phenotyping networks, Hidalgo *et al*[17] reported that patients with highly connected diseases tended to die sooner. Glicksberg *et al*[18] observed race-specific disease networks based on a large-scale analysis of electronic medical records. In their multimorbidity network analyses, Kalgotra *et al* identified specific differences in disease diagnosis by sex and proposed questions for behavioural, clinical, biological and policy research; these researchers also identified specific differences in diagnoses among different population groups.[19 20]

However, these studies, while powerful and groundbreaking, did not adequately address the question of the associations of age, hospitalisation duration and diseases in their multimorbidity networks due to the limitations of their database. Thus, the present study aimed to identify and study the associations and co-occurrence of multimorbidity and provide meaningful information for clinicians. Another objective was to better understand the associations between common health conditions (diseases) to advance research into the mechanisms underpinning these common health conditions (diseases) associations. Finally, this study also assessed the associations of diseases with sex, age and hospitalisation duration.

METHODS

Study population

This study analysed data obtained from the hospital information systems or electronic medical record systems of 15 general hospitals in Jilin Province, China. The research objects were inpatients between 1 January 2018 and 31 December 2018, and the final study comprised 516 399 inpatients. For each included inpatient, the extracted variables were sex, age, hospitalisation duration, disease names and International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) classifications. To ensure the effectiveness and representativeness of the constructed disease network, the original medical data set was preprocessed to eliminate invalid patient records, including the following: (1) inpatients with some conditions or diseases such as injury, poisoning, certain infectious or parasitic diseases and congenital malformations; and (2) diseases occurring in fewer than 1000 inpatients (as the disease network was constructed without considering rare diseases). Finally, this study included 72 diseases to explore multimorbidity in 431 295 inpatients.

Data collection

A multistage stratified random sampling method was used to obtain the sample data. First, through a comprehensive assessment of the geographical location, economic level and health service status of each city, Jilin, Changchun, Baicheng, Yanbian and Tonghua were finally included in the sample area, three general hospitals from each of these locations were then random selected. Finally, based on the administrative division, 15 general hospitals were selected as the monitoring institutions for this study. The inpatient data comprised continuous medical records, including indicators such as sex, age, hospitalisation duration, ICD-10 classification and disease name. To improve the data accuracy, we recruited and trained 20 people with proficiency in Excel software and medical backgrounds to form a professional team to check the accuracy of the basic information. Thirty general practitioners with more than 3 years of work experience confirmed that the names of the diseases matched the ICD-10 classifications.

Statistical analysis

The categorical variables in this study were expressed as counts and percentages. Rao-Scott-χ^2 tests were used to compare the distributions of the numbers of diseases and the complex relationships of multimorbidity were presented as weighted networks. The nodes represented diseases/factors, with the sizes of the nodes indicating their weight relative to all other diseases/factors. The edges represented the co-occurrence of a multimorbidity pair in the network, with the weight of the edge proportional to the prevalence of each pair. For inpatients with more than two diseases, the count of each multimorbidity pair would have an increment of 1 (eg, for an inpatient with ischaemic heart diseases (IHD), hypertensive disease (HyD) and cerebrovascular disease (CD), the multimorbidity pairs of IHD&HyD, IHD&CD and HyD&CD would increment by 1). The degree was defined as the number of nodes to which a focus node was connected, and was used to measure the node's participation in the network. The sparsity of the network was evaluated using the network density and average degree. The network density of an undirected graph with M edges and N nodes was defined as $2M/N(N-1)$, which described the proportion of potential connections $(N(N-1)/2)$ in a network with actual connections (M). The larger the network density (or average degree), the denser the network.[21–23] The networks were analysed using the R package *igraph*. All statistical analyses were performed using R V.3.6.1 (R Core Team (2014). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL http://www.R-project.org/). Statistical significance was set at $p<0.05$.

Patient and public involvement

Patients were not involved in the study based on anonymised data.

RESULTS

We analysed data from 431 295 inpatients in Jilin Province, China. As shown in table 1, the distributions of the numbers of diseases differed significantly by sex, age and hospitalisation duration ($p<0.001$). Additionally, the number of male inpatients was higher than that of female inpatients and the proportion of male inpatients with 2 or ≥3 diseases was higher than that of female inpatients. Further, the proportion of inpatients with one disease

Table 1 Descriptive characteristics of the inpatients according to the number of diseases

	n (%)	1	2	≥3	χ^2	P value
All inpatients	431 295 (100)	151 956 (35.23)	128 799 (29.86)	150 540 (34.9)		
Sex						
Male	216 248 (50.14)	71 712 (33.16)	67 498 (31.21)	77 038 (35.62)	856.93	<0.001
Female	215 047 (49.86)	80 244 (37.31)	61 301 (28.51)	73 502 (34.18)		
Age (years)						
0–	37 081 (8.60)	25 165 (67.86)	8745 (23.58)	3171 (8.55)	30 981.20	<0.001
18–	69 243 (16.05)	31 037 (44.82)	20 087 (29.01)	18 119 (26.17)		
45–	164 240 (38.08)	54 985 (33.48)	50 840 (30.95)	58 415 (35.57)		
65–	160 731 (37.27)	40 769 (25.36)	49 127 (30.56)	70 835 (44.07)		
Hospitalisation duration (days)						
0–	108 698 (25.20)	46 010 (42.33)	32 684 (30.07)	30 004 (27.60)	4809.34	<0.001
5–	108 680 (25.20)	40 716 (37.46)	31 081 (28.60)	36 883 (33.94)		
8–	101 756 (23.59)	30 118 (29.60)	31 934 (31.38)	39 704 (39.02)		
12–	112 161 (26.01)	35 112 (31.30)	33 100 (29.51)	43 949 (39.18)		

decreased with age, while the proportion of inpatients with ≥3 diseases increased. Moreover, the results of hospitalisation duration were similar to those for the age groups and the proportion of inpatients with ≥3 diseases increased with increasing hospitalisation duration.

Table 2 shows the abbreviations and proportions of the 72 diseases. Among the 72 diseases, the maximum and minimum percentages were 19.34 and 0.30, respectively. Additionally, IHD, HyD, CD, other forms of heart disease (OFHD) and malignant neoplasms (MNE) had frequencies exceeding 50 000.

Figure 1 shows a visual representation of the network according to sex, age and hospitalisation duration. Both sexes had notably more connections in the 45–64 years and 65– years age groups; however, female inpatients had more connections for the 18–44 years age group compared with that in male inpatients. Additionally, the 45–64 years and 65– years age groups had notably more connections with the hospitalisation duration, with the 65– years age group showing more connections to 12– days hospitalisation duration. Finally, the connections between different sexes and hospitalisation duration were similar.

Figure 2 shows the multimorbidity network for 72 diseases. CD, HyD, IHD and OFHD had notably high weights (illustrated by the sizes of the nodes). In addition, the 'IHD-OFHD-HyD' triangle and 'CD-HyD' exhibited notably high connections in the multimorbidity networks (illustrated by the thicknesses of the lines connected to these nodes). Although MNE had notably high weights, no high connections to other diseases were observed compared with those for other high-weight diseases.

As illustrated in figure 3, the 'IHD-OFHD-Male', 'IHD-OFHD-Female', 'CD-HyD-Male' and 'CD-HyD-Female' triangles showed notably high connections in the networks. Moreover, CD and diabetes mellitus (DME) had more notable connections with male inpatients compared with those in female inpatients.

Figure 4 shows the connections between different age groups and the 72 diseases. The older age group not only had more inpatients (illustrated by the sizes of the nodes) but also had more connections with other diseases (illustrated by the thicknesses of the lines connected to these nodes). Compared with other diseases, acute upper respiratory infections (AURI), influenza and pneumonia (IP) and OFHD had notably more connections with the <18 years age group. However, the 18–44 years age group had notably more connections to complications of labour and delivery (CLD), delivery (Del), maternal care related to the fetus and amniotic cavity and possible delivery problems (MCFAP), other maternal disorders predominantly related to pregnancy (OMDP) and metabolic disorders (MeD), and four of which were related to pregnancy and delivery. CD, HyD, IHD, OFHD and DME had notably more connections in the 45–64 years age group, and mainly cardiovascular and cerebrovascular diseases. In the 65– years age group, the 'CD-HyD-65–' and 'IHD-OFHD-65–' triangles showed the most network connections.

Figure 5 shows the networks for the different groups of hospitalisation duration and diseases. The weights were similar for the different groups of hospitalisation duration (illustrated by the node sizes). Moreover, CD, IHD, HyD, OFHD had more connections with the different groups of hospitalisation duration (illustrated by the thicknesses of the lines connected to these nodes).

DISCUSSION

A major strength of this study was that it used a large-scale, real-world clinical database of 431 295 inpatients in Jilin province, China. Additionally, the patterns of

Table 2 Abbreviations and proportions of the 72 diseases

No	ICD-10 code range	Disease name	Abbreviation	Frequency	Percentage (%)
1	D60–D64	Aplastic and other anaemias	AOA	12 938	3.00
2	M00–M25	Arthropathies	Arth	8937	2.07
3	J00–J06	Acute upper respiratory infections	AURI	9014	2.09
4	D10–D36	Benign neoplasms	BNE	15 462	3.59
5	I60–I69	Cerebrovascular diseases	CD	68 144	15.80
6	D80–D89	Certain disorders involving the immune mechanism	CIM	1299	0.30
7	O60–O75	Complications of labour and delivery	CLD	6667	1.55
8	J40–J47	Chronic lower respiratory diseases	CLRD	15 772	3.66
9	D65–D69	Coagulation defects, purpura and other haemorrhagic conditions	CPH	2432	0.56
10	G80–G83	Cerebral palsy and other paralytic syndromes	CPPS	1819	0.42
11	I70–I79	Diseases of arteries, arterioles and capillaries	DAAC	8961	2.08
12	H30–H36	Disorders of choroid and retina	DCR	4609	1.07
13	L20–L30	Dermatitis and eczema	DE	1575	0.37
14	O80–O84	Delivery	Del	7782	1.80
15	K80–K87	Disorders of gallbladder, biliary tract and pancreas	DGBP	16 296	3.78
16	H25–H28	Disorders of lens	Dle	11 856	2.75
17	E10–E14	Diabetes mellitus	DME	46 510	10.78
18	N40–N51	Diseases of male genital organs	DMGO	6543	1.52
19	K35–K38	Diseases of appendix	DOA	4839	1.12
20	K70–K77	Diseases of liver	DOL	26 663	6.18
21	K65–K67	Diseases of peritoneum	DOP	2356	0.55
22	M40–M54	Dorsopathies	Dors	10 131	2.35
23	K20–K31	Diseases of oesophagus, stomach and duodenum	DOSD	21 127	4.90
24	K00–K14	Diseases of oral cavity, salivary glands and jaws	DOSJ	1803	0.42
25	E00–E07	Disorders of thyroid gland	DTG	7550	1.75
26	H43–H45	Disorders of vitreous body and globe	DVBG	1387	0.32
27	I80–I89	Diseases of veins, lymphatic vessels and lymph nodes, not elsewhere classified	DVLL	7191	1.67
28	G40–G47	Episodic and paroxysmal disorders	EPD	15 619	3.62
29	N00–N08	Glomerular diseases	GD	3234	0.75
30	H40–H42	Glaucoma	Gla	1962	0.45
31	K40–K46	Hernia	HI	3516	0.82
32	I10–I15	Hypertensive diseases	HyD	78 747	18.26
33	N70–N77	Inflammatory diseases of female pelvic organs	IDFP	3014	0.70
34	I20–I25	Ischaemic heart diseases	IHD	83 428	19.34
35	J09–J18	Influenza and pneumonia	IP	37 290	8.65
36	L00–L08	Infections of the skin and subcutaneous tissue	ISST	2403	0.56
37	J60–J70	Lung diseases due to external agents	LDEA	1328	0.31
38	O30–O48	Maternal care related to the fetus and amniotic cavity and possible delivery problems	MCFAP	8041	1.86
39	E70–E90	Metabolic disorders	MeD	43 477	10.08
40	C00–C97	Malignant neoplasms	MNE	56 980	13.21
41	D50–D53	Nutritional anaemias	NAN	1722	0.40
42	N80–N98	Non-inflammatory disorders of female genital tract	NDFG	10 227	2.37

Continued

Table 2 Continued

No	ICD-10 code range	Disease name	Abbreviation	Frequency	Percentage (%)
43	K50–K52	Non-infective enteritis and colitis	NEC	13 421	3.11
44	G50–G59	Nerve, nerve root and plexus disorders	NPD	1964	0.46
45	F40–F48	Neurotic, stress-related and somatoform disorders	NSS	1532	0.36
46	D37–D48	Neoplasms of uncertain or unknown behaviour	NUB	3895	0.90
47	J20–J22	Other acute lower respiratory infections	OARI	7348	1.70
48	H49–H52	Disorders of ocular muscles, binocular movement, accommodation and refraction	OBAR	2967	0.69
49	D70–D77	Other diseases of blood and blood-forming organs	OBO	3116	0.72
50	M80–M94	Osteopathies and chondropathies	OC	5715	1.33
51	G30–G32	Other degenerative diseases of the nervous system	ODDNS	2133	0.49
52	K90–K93	Other diseases of the digestive system	ODDS	5737	1.33
53	K55–K63	Other diseases of intestines	ODI	17 525	4.06
54	N25–N29	Other disorders of kidney and ureter	ODKU	4442	1.03
55	G90–G99	Other disorders of the nervous system	ODNS	3302	0.77
56	J90–J94	Other diseases of pleura	ODP	5222	1.21
57	J95–J99	Other diseases of the respiratory system	ODRS	13 260	3.07
58	J30–J39	Other diseases of upper respiratory tract	ODRT	5612	1.30
59	N30–N39	Other diseases of urinary system	ODUS	9353	2.17
60	I30–I52	Other forms of heart disease	OFHD	67 632	15.68
61	O20–O29	Other maternal disorders predominantly related to pregnancy	OMDP	9398	2.18
62	O94–O99	Other obstetric conditions, not elsewhere classified	OOC	3138	0.73
63	O10–O16	Oedema, proteinuria and hypertensive disorders in pregnancy, childbirth and the puerperium	OPHD	1390	0.32
64	J80–J84	Other respiratory diseases principally affecting the interstitium	ORDI	1922	0.45
65	O00–O08	Pregnancy with abortive outcome	PAO	2809	0.65
66	I26–I28	Pulmonary heart disease and diseases of pulmonary circulation	PHPC	2135	0.50
67	N17–N19	Renal failure	RF	11 562	2.68
68	N10–N16	Renal tubulo-interstitial diseases	RTD	2710	0.63
69	H15–H22	Disorders of sclera, cornea, iris and ciliary body	SCIC	1412	0.33
70	M30–M36	Systemic connective tissue disorders	SCTD	2149	0.50
71	M60–M79	Soft tissue disorders	STD	2204	0.51
72	N20–N23	Urolithiasis	Uro	3961	0.92

ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th Revision.

multimorbidity were based on the entire eligible sample. Another strength was that individual level rather than disease level was considered as the unit of analysis.[15 24] This approach permits a more rational and realistic monitoring of participants than cohort studies to analyse multimorbidity patterns over time.[25] In the syndemics theory proposed by Singer,[26] the effects of the presence of multiple diseases on a patient's health differ from their individual independent efffects. In other words, the risk of multimorbidity is greater than the sum of single diseases. Furthermore, networks offer a more global picture because they include not only direct connections but also indirect associations, which provides more accurate information about multimorbidity. However, most current studies have compared different racial groups,[17 18] and few have evaluated the associations of disease patterns with sex, age and hospitalisation duration. The present study not only identified and studied the associations and co-occurrence of multimorbidity and provided meaningful information for clinicians but also

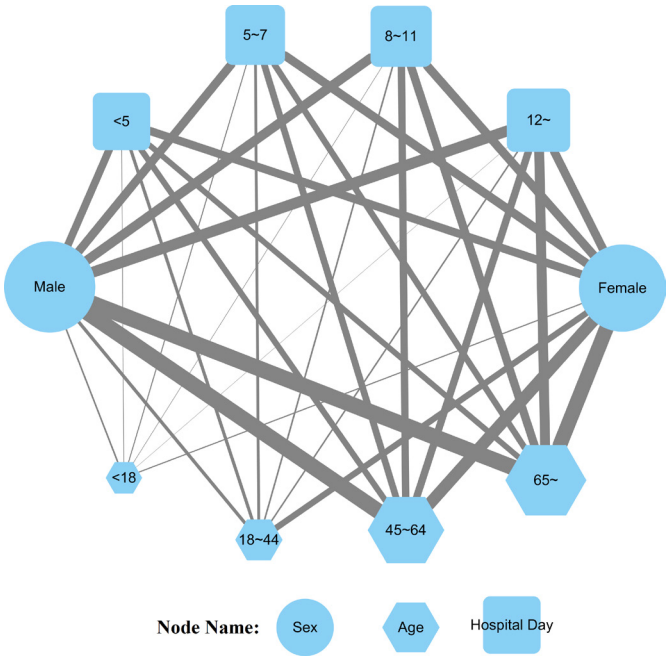

Figure 1 Network of sex, age and hospitalisation duration.

assessed the associations of diseases patterns with sex, age and hospitalisation duration.

Comparing the results of the present study to those by Hidalgo *et al*[17] on human phenotype using a dynamic network approach can be used to verify the reliability of the results of this study. Hidalgo *et al* found that many diseases were associated with HyD or IHD, consistent with the findings of the present study. Hidalgo *et al*[17] further demonstrated higher comorbidity for DME and HyD in black men compared with white men, and this study also confirmed more notable connections for DME in male inpatients compared with female inpatients.

Previous studies have shown that sex significantly affects multimorbidity.[19 27 28] In the present study, the proportion of multimorbidity was much higher in male inpatients than in female inpatients, a finding consistent with those of other studies.[29–31] Further, the disease associations in networks of both sexes revealed different disease associations according to sex. In the present study, 'CD-HyD' and 'IHD-OFHD' showed more connections

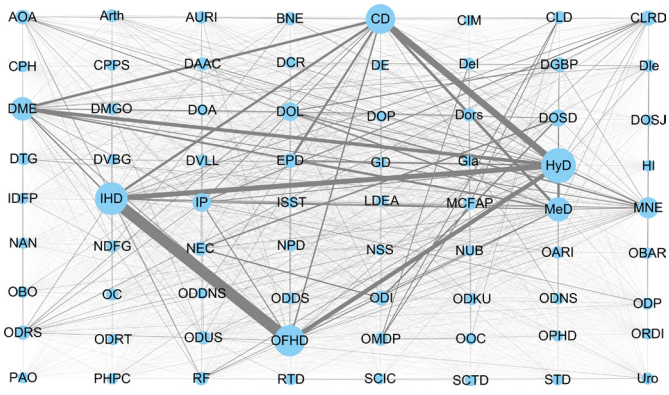

Figure 2 Multimorbidity networks for 72 diseases.

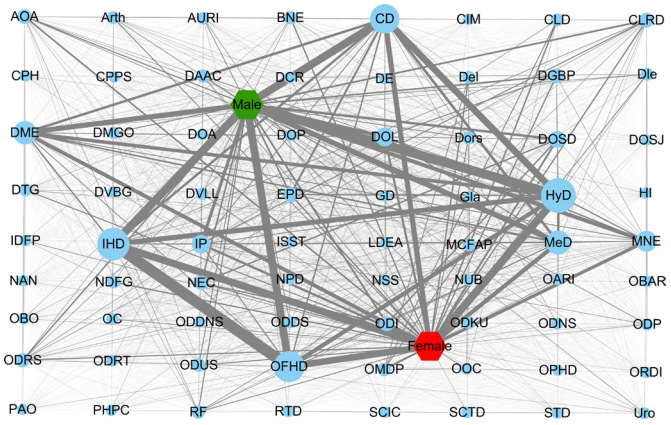

Figure 3 Multimorbidity networks with sex for 72 diseases.

with male inpatients and female inpatients, respectively. The connection between CD and HyD in both sexes has been well documented in the literature.[32] Additionally, CD and HyD share common risk factors such as obesity,[33 34] smoking and drinking.[35] Furthermore, CD and DME showed more connections with male inpatients than female inpatients, also consistent with the findings of other studies.[17 36 37]

Multimorbidity is often attributed to the ageing process, with a prevalence of approximately 62% in individuals aged 65–74 years and 81.5% in those older than 85 years of age.[38] A previous study showed an increasing tendency in the prevalence of multimorbidity in older adults.[39 40] The present study observed similar results, with more patients in the 65–74 years age group (table 1 and illustrated by the sizes of the nodes in figure 4). This may be due to higher body immunity and function in younger people compared with those in older people, thus, the proportion of diseases was lowest in the 0–17 years age group.

Furthermore, the main diseases differed across age groups; for instance, AURI and IP showed more connections in the <18 years age group. Other studies also found similar results.[41–43] Thus, more attention should be paid to respiratory system diseases in patients <18 years. Furthermore, CLD, Del, MCFAP, OMDP and MeD showed notably more connections in the 18–44 years age group.

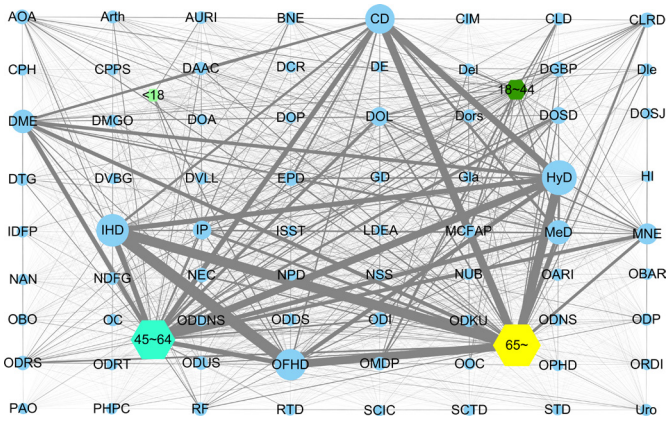

Figure 4 Multimorbidity networks with age for 72 diseases.

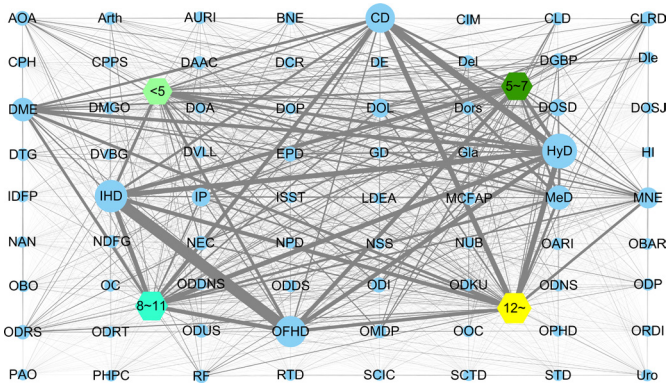

Figure 5 Multimorbidity networks with hospitalisation duration for 72 diseases.

This finding is likely related to the age at which women have children; and other studies have shown that women often develop metabolic disorders during pregnancy.[44] Thus, more attention should be given to female health. Moreover, the health challenges faced by the 45–64 years age group are more complex than those faced by other age groups because body immunity and function decline with age. Additionally, the population in this age group is under substantial mental stress, leading to feelings of exhaustion and illness. Therefore, multimorbidity studies individuals aged 45–64 years cannot be overlooked, particularly those on CD, HyD, IHD, OFHD and DME. Although this age group had a denser multimorbidity network, the 'CD-HyD-65–' and 'IHD-OFHD-65–' triangles showed more connections than those of other combinations. These findings suggest that different intervention strategies should be developed according to multimorbidity patterns in different age groups.

Finally, the results of this study showed that the stronger the disease connection to other diseases, the stronger the connection to the longer duration of hospitalisation. For example, HyD showed more marked connections with other diseases and a stronger connection with the group of patients with longer hospitalisation duration. Other studies have reported similar results. Specogna *et al*[45] observed that patients with spontaneous intracerebral haemorrhage arriving at the hospital with HyD were 31% more likely to stay in the hospital beyond 1 week per visit compared with non-hypertensive patients.

This study had some limitations. First, the study participants were inpatients in Jilin Province, which could not represent the patterns of multimorbidity in other places. Second, this study investigated only sex, age and hospitalisation duration; however, other factors not considered in this study might have impacted multimorbidity. Finally, diseases occurring in fewer than 1000 inpatients were excluded, which might have caused bias.

CONCLUSION

The results of this study visually demonstrated the differences in multimorbidity according to sex, age group and hospitalisation duration. Adjusting the analysis of multimorbidity patterns to the individual level revealed that IHD, HyD, CD and OFHD were the central points of disease clusters and were directly or indirectly related to other diseases and factors. Thus, accurate identification and effective intervention for these diseases should be adopted in the healthcare system. Furthermore, the government and relevant departments should develop different intervention strategies according to multimorbidity patterns in different age groups. Finally, the multimorbidity patterns were more consistent with clinical practice, allowing the effective management of patients with multimorbidity.

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Contributors JY and XY had the original idea for the study and carried out the design. JY and XY provided valuable insight regarding the methodological approach and organization of the manuscript. JY, YL and ZZ carried out the statistical analysis and reviewed the consistency of data included in the paper. JY and YL drafted the manuscript. JY, HJ, PC and YQ revised the manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the ethics committee of the School of Public Health, Jilin University (Reference Number: 2018-07-06).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. These data were from a survey conducted by the School of Public Health, Jilin University in Jilin Province in 2018. Because of relevant regulations, the data cannot be shared.

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