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Multimorbidity in primary care

Edited by
Sanghamitra Pati and Stefan Essig

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Multimorbidity in primary care

Topic editors
Sanghamitra Pati — Regional Medical Research Center (ICMR), India
Stefan Essig — University of Lucerne, Switzerland

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Editorial: Multimorbidity in primary care

Stefan Essig[1,2]* and Sanghamitra Pati[3]

[1]Center for Primary and Community Care, University of Lucerne, Lucerne, Switzerland, [2]Interface Policy Studies Research Consulting, Lucerne, Switzerland, [3]ICMR-Regional Medical Research Centre, Bhubaneswar, India

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Arch Mainous,
University of Florida, United States

*CORRESPONDENCE
Stefan Essig
✉ stefan.essig@unilu.ch

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Editorial on the Research Topic
Multimorbidity in primary care

Background

Multimorbidity, the coexistence of two or more chronic health conditions accompanied by reduced quality of life and increased healthcare utilization, and expenditure is a significant public health challenge. The prevalence of multimorbidity is on the rise, primarily due to an aging population, leading to diminished quality of life and life expectancy, along with an increased reliance on emergency or unplanned healthcare services. Managing multimorbidity requires continuous and coordinated care, thus posing substantial challenge for health systems and patients alike. The World Health Organization underscores the pivotal role of primary care in addressing multimorbidity (1). Primary care often being the first and frequent point of contact for patients with multimorbidity, has a critical role in providing quality of care for these individuals. In order to address the holistic needs of these population, primary care strengthening should be one of the key health system priorities. Toward this, understanding the role of primary care in effectively managing multimorbidity is essential for optimizing patient outcomes, enhancing healthcare delivery efficiency, and promoting patient-centered care.

Research

This editorial summarizes the contributing articles to the Research Topic "*Multimorbidity in primary care.*" We received a total of 38 manuscripts and were able to approve twelve of them for publication. Out of the twelve articles, eleven were original research and one was a perspective.

Overall, the studies collectively emphasize the intricate relationship between multimorbidity, healthcare delivery, patient experiences, and health outcomes in diverse populations and settings, underscoring the importance of understanding these dynamics to develop effective strategies for addressing the challenges posed by multimorbidity and enhancing patient care and outcomes.

Zhou et al. delved into the growing public health concern of hypertension in China, particularly examining self-care compliance, trust, and satisfaction among hypertensive patients. The study revealed a positive association between trust, satisfaction, and compliance, with insights that can guide interventions to enhance hypertension management. A similar study by Yun et al. examined the effects of regional healthcare disparities on complications in hypertensive patients in South Korea which highlighted the importance of identifying disparities to improve healthcare access and outcomes.

Su et al. addressed the public health issue of multimorbidity coexistence in older adults in China, examining its effects on all-cause mortality. The study, spanning a 10-year period, found that multimorbidity is associated with an increased risk of death in older individuals, with a more significant effect in those aged 80–94 years. Age heterogeneity is observed, emphasizing the need for tailored interventions to address multimorbidity in different demographic groups. Palo et al. assessed the prevalence and patterns of multimorbidity among chronic kidney disease patients in India, highlighting the need for regular screening and management of associated chronic conditions. Eyowas et al. found in Northwest Ethiopia that multimorbidity patients attending chronic outpatient care had higher rates of developing new conditions, hospitalization, and mortality; suggesting the need for future studies to understand the multimorbidity trajectories. Another study group in Ethiopia, Bambo et al., determined the prevalence and factors associated with postpartum anemia.

Craig et al. investigated the link between multimorbidity and health-related quality of life (HRQoL) in Jamaica. Using latent class analysis, the study identified four multimorbidity classes and assessed their impact on physical and mental dimensions of HRQoL, highlighting the differential effects of specific disease combinations and the mediating role of health service use. Furthermore, Lee et al. observed in Australia that functional limitation acts as a mediator between multimorbidity and HRQoL, underscoring the importance of improving functional status in patient care.

Onaisi et al. focused on statin prescription for cardiovascular primary prevention in primary care settings in the French region of Rhône-Alpes, examining the association between multimorbidity and appropriate statin prescription. The study found that multimorbidity alone does not determine appropriate statin prescription; rather, the presence of diabetes influenced prescription decisions, highlighting the importance of differentiating between diabetic and non-diabetic multimorbidity for improved prevention. Lüthi-Corridori et al. conducted a study to identify factors predicting length of hospital stay, mortality, and re-hospitalization within 6 months for patients admitted with pulmonary embolism in a Swiss hospital. They found that diabetes, among other factors, was associated with longer hospital stays. The study suggests that understanding these factors can aid clinicians.

van Pinxteren et al. explored the social dimensions of multimorbidity management among vulnerable populations in South Africa, indicating that the treatment burden and capacity for patients is a crucial step to redesign health systems. The perspective article of Sagan et al. shed light on the challenges faced by Central and Eastern European countries in catering to complex patients with chronic conditions and multimorbidity. Despite relatively younger populations, these countries experience high prevalence of chronic conditions, and the study identified key initiatives to improve care coordination, emphasizing the need for progress and learning from both successful and failed attempts.

Summary

To summarize, multimorbidity is a complex issue that affects patient-reported outcome measures, healthcare delivery, and patient experiences. Strengthening primary care would enable multimorbidity management through a holistic approach and may be the epicenter to provide continued and coordinated person-centered care. Primary healthcare providers often consider a holistic approach, taking into account individual diseases and their interactions, allowing for effective concurrent management of multiple morbidities, and resultant polypharmacy. Primary care being easily accessible provides a scope for better monitoring and prevention of chronic conditions and allows for timely interventions. Primary care providers prioritize patient involvement in decision-making, resulting in smooth transitions between specialties and settings. They also emphasize preventive care and health promotion, addressing modifiable risk factors, encouraging healthy behaviors, and providing routine screenings, all of which lead to better health outcomes and a higher quality of life for people with multimorbidity. We believe that these findings will assist researchers in better understanding multimorbidity in primary care.

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SE: Writing – original draft, Writing – review & editing. SP: Writing – original draft, Writing – review & editing.

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EDITED BY
Stefan Essig,
University of Lucerne, Switzerland

REVIEWED BY
Maddalena Illario,
University of Naples Federico II, Italy
Željko Reiner,
University Hospital Centre Zagreb,
Croatia

*CORRESPONDENCE
Racha Onaisi
✉ racha.onaisi@u-bordeaux.fr
Hubert Maisonneuve
✉ hubert.maisonneuve@unige.ch

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Multimorbidity and statin prescription for primary prevention of cardiovascular diseases: A cross-sectional study in general practice in France

Racha Onaisi[1]*, Roxane Dumont[2],
Jennifer Hasselgard-Rowe[3], David Safar[4], Dagmar M. Haller[5]
and Hubert Maisonneuve[5]*

[1]Department of General Practice, University of Bordeaux, Bordeaux, France, [2]Unit of Population Epidemiology, Division of Primary Care Medicine, Geneva University Hospitals, Geneva, Switzerland, [3]Faculty of Medicine, Institute of Global Health, University of Geneva, Geneva, Switzerland, [4]University College of General Medicine, University Claude Bernard Lyon 1, Lyon, France, [5]Faculty of Medicine, University Institute for Primary Care, University of Geneva, Geneva, Switzerland

Background: Statins are a first line, evidence-based yet underprescribed treatment for cardiovascular primary prevention. In primary care settings, multimorbidity is a complex situation which makes it difficult to apply prevention guidelines.

Aim: To assess the associations between multimorbidity and prescription of statins in accordance with the 2016 ESC recommendations ("appropriate prescription"), and to identify the factors and conditions associated with these prescriptions.

Design and setting: Cross-sectional prospective study in the French region of Rhône-Alpes among 40 general practitioners and their patients.

Methods: We examined the association between appropriate statin prescription and several patient characteristics, including multimorbidity, using multivariate logistic regression models.

Results: Between August 2017 and February 2019, 327 patients were included in the study. Seventy-four (22.6%) were on statin medication and 199 (60.9%) exhibited multimorbidity, defined as $\geq$2 diseases. Only 22.5% of eligible patients were prescribed statins for primary prevention. Diabetes was most strongly associated with appropriate statin prescription (aOR 8.10, CI 95: 3.81–17.80). Multimorbidity was not associated with appropriate statin prescription (aOR 1.31, CI 95: 0.54–3.26), except in the presence of diabetes which defined diabetic multimorbidity (aOR 10.46, CI 95: 4.87–23.35). Conversely, non-diabetic multimorbidity was associated with lower odds of being appropriately prescribed a statin (aOR 0.26, CI 95: 0.12–0.56).

Conclusion: Multimorbidity, in itself, does not seem to be a determinant factor for appropriate statin prescription. The latter appears to be determined by a patient's type of multimorbidity, especially the presence or not of diabetes. Differentiating between diabetic and non-diabetic multimorbidity may be a pragmatic way for GPs to improve primary prevention in a patient-centered and shared decision-making approach.

KEYWORDS

multimorbidity, cardiovascular diseases, primary prevention, statin, general practice

1. Introduction

Statin prescription is a cornerstone of primary cardiovascular prevention. In the primary care setting, multimorbidity is a complex situation which makes it difficult to apply prevention guidelines in daily practice (1–3). This study set out to understand the association between multimorbidity and the prescription of statins as primary prevention in primary care.

The World Health Organization defines multimorbidity as an association of two or more diseases that can impact a person's health status. Since many people consider this definition insufficient to summarize multimorbidity, numerous definitions can be found in the literature (4–6). Cardiovascular diseases and metabolic diseases, such as diabetes mellitus or obesity, are among the most represented health issues in patients with multimorbidity (7, 8). They are also the most common cause of death in Europe (9). Statin therapy for primary prevention in patients with high cardiovascular risk has been continuously recommended as a first line treatment (10, 11). Yet, despite evidence supporting use for primary prevention in high-risk patients, recent studies conducted in the United States and in Europe have found that statin therapy was prescribed in only 20–60% of eligible patients (12–14).

In primary care, a number of factors come into play when deciding whether or not to treat a multimorbid patient with statins: (i) the underuse of risk assessment scores (15), (ii) the poor applicability of single-diseased based guidelines (2), or (iii) the complex prioritization of health interventions (16–18).

To our knowledge, there is not much data about the associations between multimorbidity and statins under-prescription, and published data is sometimes contradictory (12, 19). For instance, in a recent study performed within the French-speaking population in Canada, multimorbidity was strongly associated with an increased likelihood of using statins for primary prevention (adjusted OR 3.76) (19). Yet, in that study, multimorbidity was assessed by using the number of chronic conditions declared by patients and was not further described. As far as cardiovascular prevention is concerned, the question remains: should asthma or osteoporosis influence statin prescription as much as diabetes and hypertension? We felt that these results needed to be explored further, so as to clarify the conditions that may constitute multimorbidity.

In this view, the aim of this study was therefore (i) to assess the associations between multimorbidity and the expected under-prescription of statins in accordance with guidelines for primary prevention, and (ii) to identify the factors and conditions associated with these prescriptions, in a primary care population.

To reach this aim we conducted a cross-sectional prospective study measuring the statin prescription rate in accordance with the 2016 European Society of Cardiology (ESC) guidelines on cardiovascular disease primary prevention (20), referred as "appropriate prescription" and the factors associated with the appropriateness of the prescription.

2. Materials and methods

2.1. Study population

We recruited general practitioners (GPs) in the French region of Rhône-Alpes using the snowball method, starting from a convenience sample of eight GPs affiliated within the primary care unit of Lyon University (France). We looked for maximum variation according to the following criteria: age, sex, duration of clinical practice, continuing medical education, type of practice (alone, group, pluri-professional structure), and participation in resident clerkships.

When a GP agreed to participate, a recruitment date was booked with a research assistant. On the day scheduled for the study, the research assistant was physically present in the GP practice. Patients were assessed for eligibility during their appointments with their GP, without modifying their scheduled consultations. Patients who agreed to participate were progressively included in the study until a maximum number of eight patients per GP was reached.

Patients were eligible if they had had their cholesterol levels measured during the preceding year, or had a statin prescription for primary prevention purposes, or presented at least one of the following cardiovascular risks: diabetes mellitus, family history of cardiovascular disease, active smoking, or high blood pressure.

Patients were excluded if they had a personal history of previous or current cardiovascular diseases (myocardial infarction, stroke, transient ischemic stroke, or peripheric arterial disease). They were also excluded if their cholesterol level had not been assessed in the previous 5 years.

2.2. Data collection

Data collection took place between August 2017 and February 2019. When eligible patients agreed to participate, a research assistant, or the GPs themselves, completed an anonymous questionnaire collecting sociodemographic data (age, sex, profession, and ethnicity), clinical data (weight, height, systolic blood pressure, cardiovascular risk factors, or diseases associated with cardiovascular risk), patients' self-perceived state of health, biological data (cholesterol levels, presence of microalbuminuria, and renal function), and current treatments (with a specific item focused on statin intake). The presence of multimorbidity was assessed using a list of 75 chronic conditions (21) which had been created to explore the prevalence of multimorbidity in a primary care population in the Swiss national study on multimorbidity and patterns of chronic conditions (22, 23). We considered multimorbidity to be present when the patients were suffering from two or more chronic conditions on the list.

To assess statin underprescription, we chose to calculate the rate of statins prescribed in accordance with the 2016 ESC guidelines on cardiovascular disease primary prevention, in our work referred to as "appropriate statin prescription." Appropriate statin prescription was calculated as the rate of patients prescribed statins among the total population of patients eligible for primary prevention with statin therapy. To ensure that the chosen guideline did not induce bias, we first compared the rates of statin therapy prescribed in accordance with ESC 2016 with the rates prescribed in accordance with other guidelines [French HAS 2017 (24), ESC 2019 (11), NICE (25), and AHA 2018/2019 (10)]. These guidelines all define at-risk patients, mainly relying on risk assessment scores, to determine which patients could benefit from statin therapy.

2.3. Sample size estimation

We calculated the sample size required for our study using the formula for proportions estimated with a given precision. Based on previous studies (12), we estimated that the maximum appropriate statin prescription rate was 62%. We wanted to be able to provide a 95% confidence interval width of 0.05 for the estimate. The minimum required sample was estimated at 377 patients. Statistical significance was set at a two-tailed p-value ≤ 0.05.

2.4. Statistical analysis

We compared sociodemographic and medical characteristics of participants with and without statin medication, using Fisher's exact test, Chi-squared and Student's T-test, as appropriate. Continuous quantitative variables were described by mean and standard deviation (SD) values. Discrete variables and categorical variables were described by frequency and proportion values.

To assess factors associated with appropriate statin prescription, we examined the associations between baseline clinical characteristics and compliance with the ESC 2016, using multivariate logistic regression models, and reported results as odds ratios (OR) and 95% confidence intervals (CI). Patients with statins prescribed according to the guidelines were compared to those not receiving any statin therapy. Several logistic regression models were tested, using two or more chronic conditions and three or more chronic conditions to define multimorbidity, including diabetes or not. Participants with missing data for at least one of the covariates were excluded from the models. All analyses were performed with R (version 4.0.3).

2.5. Ethical approval

This is not an interventional study. In line with the applicable French law at the time of the study design and data collection, ethical approval was not required.

3. Results

3.1. Characteristics of the study population

Five GPs declined participation (11%). The participating GPs invited a total of 330 patients to participate, three of them declined (0.9%) (**Figure 1**).

Among the 327 included patients who did not present any previous history of cardiovascular disease, 74 were on statin medication (22.6% of total study population). About half were more than 65 years old [$n = 99$ (30.4%) between 65 and 74 years old and $n = 67$ (20.6%) above 75], and 40.5% were male. More than half of the patients were considered multimorbid ($n = 199$, 60.9%). **Table 1** reports the characteristics of the total study population, stratified by statin use.

Patients on statin medication were more likely to be male (54.1 vs. 36.5%, $p = 0.01$), aged above 65 years old (67.5 vs. 46%,

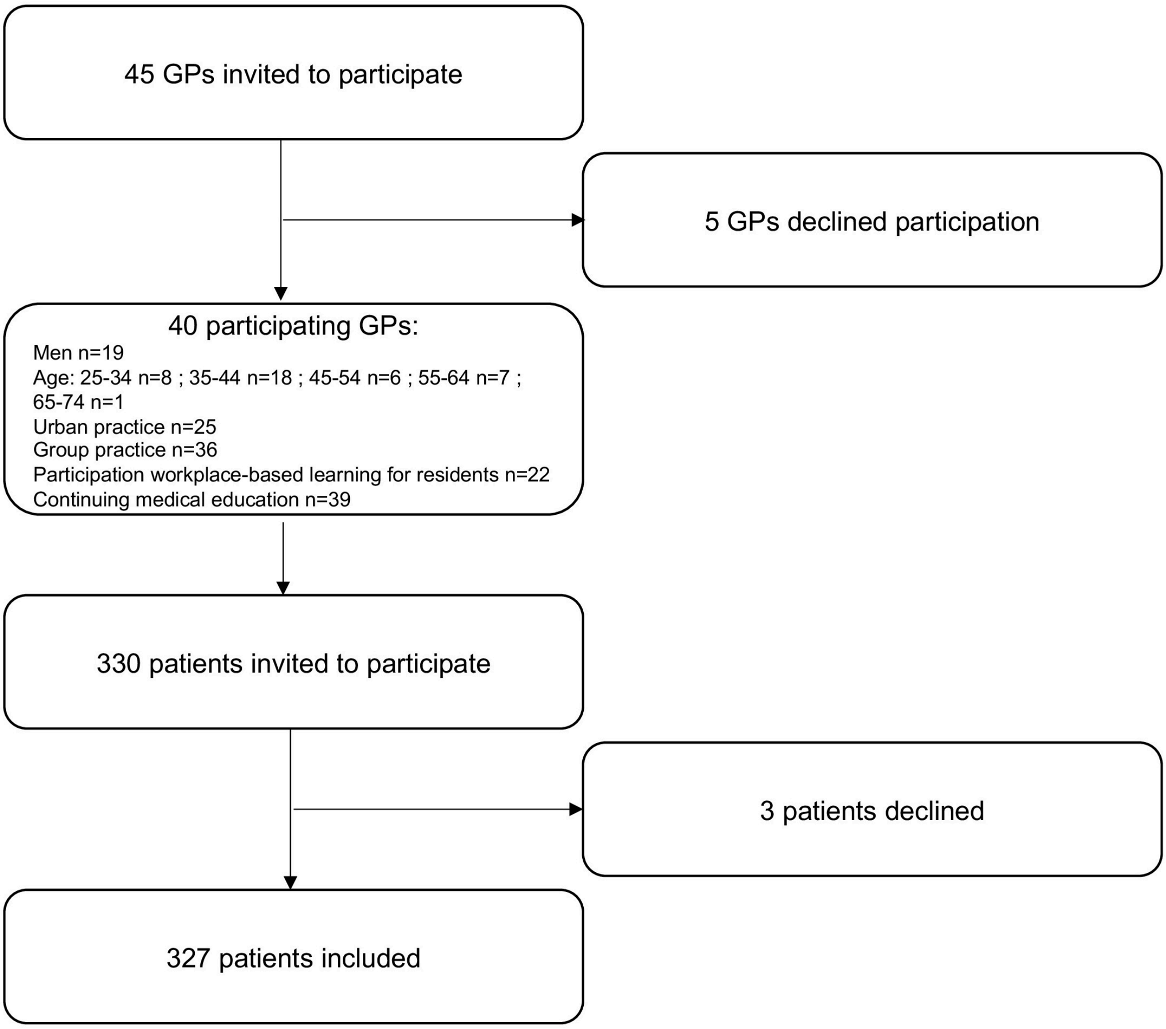

FIGURE 1
Flow-chart of general practitioners (GPs) and patients inclusions.

$p = 0.004$), and multimorbid (83.8 vs. 54.2%, $p < 0.001$). Among known cardiovascular risk factors, patients on statin medication were more likely to have diabetes mellitus (37.8 vs. 10.7%, $p < 0.001$) or treated hypertension (66.2 vs. 41.5%, $p < 0.001$). There were no significant differences between groups regarding family history of cardiovascular disease or active smoking.

3.2. Statins prescription in accordance with guidelines

The number of patients eligible for statin therapy varied between 157 and 281 depending on guidelines. Among the 262 patients for whom an indication for primary prevention statin therapy was found in accordance with the ESC 2016 recommendation, 59 were on medication, representing an estimated appropriate statin prescription rate of 22.5%.

No matter what guideline was taken into consideration, statin therapy for primary prevention was under-prescribed. The highest rate of appropriate statin prescription in our study population was estimated at 32.3% (AHA 2018/2019), with an even lower prescription rate estimated at 19.5% (HAS 2017) (**Table 2**).

3.3. Association between multimorbidity and appropriate statin prescription

In the univariate analysis, female patients were less likely to be treated in accordance with the guideline than male patients (OR = 0.54 [0.30–0.96]). Being between 65 and 74 years old (OR = 2.74 [1.43–5.34]), being treated for hypertension (OR = 2.93 [1.61–5.50]), exhibiting multimorbidity (OR = 3.19

TABLE 1 Characteristics of study population, stratified by statin use (*n* = 327).

	Without statin prescription *N* = 253	With statin prescription *N* = 74	Total *N* = 327	*p*-value[a]
	n (%)	*n* (%)	*n* (%)	
Sociodemographic characteristics				
Age				0.004
<65	136 (54.0)	24 (32.4)	160 (49.1)	
65–74	67 (26.6)	32 (43.2)	99 (30.4)	
≥ 75	49 (19.4)	18 (24.3)	67 (20.6)	
Sex				0.010
Male	93 (36.5)	40 (54.1)	133 (40.5)	
Female	160 (63.5)	34 (45.9)	194 (59.5)	
Ethnicity				0.861
White	231 (91.3)	66 (90.4)	297 (91.1)	
Black or African-American	17 (6.7)	6 (8.2)	23 (7.1)	
Other	5 (2.0)	1 (1.4)	6 (1.8)	
Health status				
Multimorbidity				
≥ 2 diseases	137 (54.2)	62 (83.8)	199 (60.9)	<0.001
≥ 3 diseases	78 (30.8)	42 (56.8)	120 (36.7)	<0.001
Self-perceived health status				0.054
Poor or mediocre	10 (4.3)	0 (0.0)	10 (3.2)	
Good	50 (21.3)	23 (31.5)	73 (23.7)	
Very good or excellent	175 (74.5)	50 (68.5)	225 (73.1)	
Risk factors for cardiovascular diseases				
Cholesterol levels				
Total [Mean (SD)]	217 (41)	186 (44)	210 (44)	<0.001
LDLc levels				<0.001
40–70 mg/dL	4 (1.6)	13 (17.6)		
70–99 mg/dL	29 (11.5)	26 (35.1)		
100–114 mg/dL	40 (15.8)	11 (14.9)		
>115 mg/dL	180 (71.1)	24 (32.4)		
HDLc [Mean (SD)]	0.60 (0.17)	0.53 (0.17)	0.58 (0.17)	0.006
≥ 40 mg/dL	227 (89.7)	57 (77)		0.008
Hypertension	*n* (%)	*n* (%)	*n* (%)	
Receiving a treatment for hypertension	105 (41.5)	49 (66.2)	154 (47.1)	<0.001
Systolic blood pressure level [Mean (SD)]	131.79 (13.77)	131.67 (12.61)	131.77 (13.49)	0.946
Diabetes	*n* (%)	*n* (%)	*n* (%)	
Type 2	27 (10.7)	28 (37.8)	55 (16.8)	<0.001
Type 1	5 (2.0)	6 (8.1)	11 (3.4)	0.027
Retinopathy	1 (0.4)	4 (5.4)	5 (1.5)	0.011
Neuropathy	33 (13.0)	8 (10.8)	41 (12.5)	0.756
Current smoker or former smoker for less than 3 years	51 (20.2)	14 (18.9)	65 (19.9)	0.945

(Continued)

TABLE 1 (Continued)

	Without statin prescription N = 253	With statin prescription N = 74	Total N = 327	p-value[a]
	n (%)	n (%)	n (%)	
Family history of cardiovascular disease	43 (17.0)	18 (24.3)	61 (18.7)	0.210
Renal function impairment with glomerual filtration rate (GFR) < 30 mL/mn	57 (23.0)	12 (16.2)	69 (21.4)	0.278
Body mass index (BMI)				0.086
<25	110 (45.1)	21 (31.8)	131 (42.3)	
25–29.9	81 (33.2)	31 (47.0)	112 (36.1)	
≥30	53 (21.7)	14 (21.2)	67 (21.6)	
Atrial fibrillation	11 (4.3)	6 (8.1)	17 (5.2)	0.325
HIV infection	6 (2.4)	1 (1.4)	7 (2.1)	0.939

[a] Fisher's exact test, Pearson's Chi-squared test or Student T, when appropriate.

TABLE 2 Rates of statin therapy prescribed in accordance with different guidelines.

	ESC 2016 (SCORE)	HAS 2017 (SCORE)	ESC 2019 (SCORE)	NICE(QRISK-2)		AHA 2018/2019(ASCVD)	
				QRISK > 5%	QRISK > 10%	ASCVD > 5%	ASCVD > 10%
Number of patients eligible for statin therapy (Ne)	262	185	281	264	202	190	127
Number of patients treated as recommended (Nt)	59	36	60	71	63	51	41
Appropriate statin prescription rate according to recommendation (Ne/Nt)	22.5%	19.5%	21.4%	26.9.0%	31.1%	26.8%	32.3%

[1.64–6.74]), were associated with an increased appropriate statin prescription.

Diabetes appeared to be the factor most strongly associated with appropriate statin prescription (OR = 8.00 [4.29–15.19]; *a*OR = 8.10 [3.81–17.80]), including in multimorbid patients. Indeed, in our multivariate models, diabetic multimorbidity was strongly associated with appropriate statin prescription (*a*OR = 10.46 [4.87–23.35]), while non-diabetic multimorbidity was associated with lower statin prescription for primary prevention, despite an indication for the treatment (*a*OR = 0.26 [0.12–0.56]) (**Table 3**).

Further analysis conducted in the multivariate models confirmed the major association between diabetes and appropriate statin prescription above multimorbidity status (**Supplementary material**).

Appropriate statin prescription was also more likely to be found in patients between 65 and 74 years old in multivariate models (*a*OR 2.45[1.09–5.64]), whereas being over 75 years old was not significantly associated with appropriate statin prescription.

4. Discussion

4.1. Key findings

As expected, statin therapy was under-prescribed among patients with an indication for primary prevention. There seems to be distinct categories of multimorbidity, as diabetic multimorbidity was strongly associated with appropriate statin prescription, while non-diabetic multimorbidity lowered the odds of being prescribed a statin for primary prevention in accordance with the guidelines.

4.2. Comparison with the existing literature

Our work raises questions about multimorbidity and how it might be dealt with by GPs in primary prevention contexts.

Among cardiovascular risk factors, diabetes appears to be the most significant factor taken into consideration. In the literature, a history of diabetes is found to be associated with

TABLE 3 Univariate and multivariate analysis of factors associated with appropriate statin prescription according to the 2016 European Society of Cardiology (ESC) guidelines.

	No statin therapy *N* = 261[†]	Appropriate statin therapy *N* = 57[‡]	Crude OR [95 CI]	Adjusted OR [95 CI]
	n (%)	*n* (%)		
Female	163 (62.5)	27 (47.4)	0.54 [0.30–0.96]*	0.58 [0.29–1.17][a]
Age				
<65	135 (52%)	19 (33.3)		
65–74	70 (27)	27 (47.4)	2.74 [1.43–5.34]*	2.45 [1.09–5.64]*[a]
≥75	55 (21)	11 (19.3)	1.42 [0.62–3.14]	1.23 [0.47–3.14][a]
Diabetes	36 (13.8)	32 (56.1)	8.00[4.29–15.19]**	8.10 [3.81–17.80]**[a]
BMI				
<25	110 (42.1)	17 (29.8)		
25–29.9	88 (33.7)	22 (38.6)	1.62 [0.81–3.27]	1.09 [0.48–2.46][a]
≥30	55 (21.1)	10 (17.5)	1.18 [0.49–2.70]	0.41 [0.14–1.08][a]
Treated hypertension	111 (42.5)	39 (68.4)	2.93 [1.61–5.50]**	1.75 [0.78–3.98][a]
Multimorbidity (≥2 diseases)	148 (56.7)	46 (80.7)	3.19 [1.64–6.74]**	1.31 [0.54–3.26][a]
Diabetic multimorbidity (diabetes + ≥1 additional disease)	29 (11.1)	31 (54.4)	9.54 [5.02–18.46]**	10.46 [4.87–23.35]**[b]
Non-diabetic multimorbidity (≥2 diseases)	119 (45.6)	15 (26.3)	0.43 [0.22–0.79]*	0.26 [0.12–0.56]**[b]
Non-diabetic multimorbidity (≥3 diseases)	64 (24.5)	8 (3.5)	0.50 [0.21–1.06]	0.31 [0.11–0.74]*[b]

[†] 1 missing data [‡] 2 missing data. **p*-value < 0.05 ***p*-value ≤ 0.001. [a] Adjusted on sex, age, BMI, treated hypertension, diabetes, and multimorbidity. [b] Adjusted on sex, age, BMI, treated hypertension.

higher odds of having a lipid screening, and with higher odds of appropriate statin prescription (14, 26), even though diabetic patients are also affected by statin under-prescription, both in our study and in two successive European surveys (27, 28). Our results stress that in comparison with other identified cardiovascular risk factors, diabetes seems to have a lot more weight in the prescription decision process. This might be explained by the fact that diabetic patients' cardiovascular risk may be considered moderate to high without using any assessment scores according to the European guideline (29). This in turn might make their eligibility for statin therapy in primary prevention more striking for practitioners, especially with regard to multimorbid patients.

Our findings in adjusted models underline the need to consider cardiovascular risk factors as confounding variables. Not only are they highly prevalent in multimorbid patients (7, 8), but when we calculated odds ratios adjusted for age, sex and the presence of treated hypertension, diabetes and body mass index (BMI), multimorbidity was no longer a determining factor for statin prescription for primary prevention purposes by itself. Unlike the diabetic patients, whether multimorbid or not, non-diabetic multimorbid patients are less likely to be prescribed an appropriate preventive statin therapy.

This underlines the fact that when it comes to primary prevention and cardiovascular diseases, considering multimorbidity as a homogeneous condition is overly simple and should be complemented by further detailed descriptive analyses. At a basic level, it would certainly be beneficial to differentiate between cardiovascular multimorbidity and non-cardiovascular multimorbidity as proposed by Déruaz-Luyet et al. (22). A recent Delphi-consensus study also proposed to use weighted measures of multimorbidity when focusing on risk adjustment (6).

There is only limited evidence of GPs clinical reasoning in situations of multimorbidity, particularly regarding the prioritization of health issues. Our findings question how risk assessment scores are used in daily practice and to what extent they influence prioritization in the context of multimorbidity. Liew et al. (15) found that GPs face difficulties in determining the practical implications of cardiovascular risk calculations, especially in patients already treated for risk factors, and this may be related to an "*understanding of the limited power of any risk score to make an individual prediction of risk highlighted in some guidelines.*" These difficulties could interfere with a common prioritization strategy, that consists in ranking health problems according to their impact on morbimortality (8).

We can hypothesize that it is not just cardio-vascular multimorbidity nor the global cardiovascular risk assessment, but rather the presence or absence of diabetes, that prevails in GPs decision-making about statin prescription for primary prevention (**Table 3** and **Supplementary material**). Differentiating between cardiovascular and non-cardiovascular multimorbidity could be a very pragmatic tool to guide the decision-making process in complex multimorbid situations. It could also constitute good-practice recommendations, with important clinical relevance (30), especially for non-diabetic multimorbid patients.

4.3. Strength and limitations

Despite a recruitment in only one region in France, several epidemiological data support the generalizability of our results. Indeed, the population structure in Rhône-Alpes is comparable to the nation-wide data in terms of sex-ratio (31) and age repartition (32). Though the standardized mortality rate above 65 years old is lower in Rhône-Alpes (37.5 vs. 38.4 ‰ for national data), main causes of death are comparable to national data, and cardiovascular diseases represent the second cause of death among people aged 65 and older (25% of deaths). Differences in standardized mortality rate could be explained by health disparities related to social determinants of health, as there is an important rate of intermediate occupations (33). Moreover, the rates of patients on statin medication and prevalence of multimorbidity at the time of inclusion are consistent with other epidemiological data in France and more generally in Europe (12, 23, 34). This suggests that our study population was comparable to other primary care populations across Europe. We are confident that our methodological choices in terms of GP sampling and prospective recruitment of participants strengthened the quality of the collected data. The higher appropriate statin prescription rates reported in American studies (14, 26) could be explained by the different risk assessment scores and guidelines applied there.

Our approach to multimorbidity is another strength of our study. (i) We used a robust tool to assess the presence of multimorbidity in primary care; (ii) our multivariate model included confounding variables as cardiovascular risk factors such as diabetes or treated hypertension; and (iii) we tested several categories of multimorbidity, which sharpened our analysis. Statin under-prescription in our sample is consistent with the existing literature (12).

We did not reach the target sample size. Recruitment and retention of physicians is an important issue for primary care research (35, 36). However, the assumption supporting the sample size estimation, based on a hospital sample, overestimated the rate of appropriate prescription. We found much lower appropriate statin prescription rate in our work (22.5 vs. 62%). This is not without consequences, as the closest to 50% the rate is, the larger the needed sample size is. Thus, we can assume that our final sample size might be sufficient and despite a smaller sample size than expected, our work provides insights into the associations between multimorbidity and appropriate statin prescription for primary prevention. As we found large, significant associations, particularly in relation to diabetes, we think our results remain valid. Yet, we may have missed smaller associations.

4.4. Implications for research and/or practice

Our work highlights the fact that in GPs' prescription habits for cardiovascular prevention in a context of multimorbidity, diabetes weighs more than multimorbidity (7, 37). Indeed, our findings reveal that within the term multimorbidity, the presence or absence of diabetes leads to opposite associations with our variable of interest. Our results underline the necessity to consider multimorbidity as a heterogeneous entity, especially when defining the outcomes of a study in the field of cardiovascular prevention.

Additional research exploring GPs' decision-making processes regarding the prescription of statin therapy for primary prevention purposes would help further understand and explain our findings, especially with regard to how they weigh different types of multimorbidity and cardiovascular risk levels. Our main outcome is based on appropriateness of statin prescription according to guidelines. However, as we underlined before, GPs are often confronted to a poor applicability of single-disease based guidelines in multimorbid patients (2), thus questioning the possible gap between guideline-recommended and clinically-relevant prescription. Defining diabetic multimorbidity as an entity, and differentiating between cardiovascular and non-cardiovascular multimorbidity situations may be a pragmatic way for GPs to improve primary prevention in a patient-centered and shared decision-making approach, for example through an integrated care model. Integrated care is particularly interesting in multimorbidity as it help avoid fragmentation of care, especially for patients with multimorbidity (38). First, differentiating between cardiovascular and non-cardiovascular multimorbid patients could help GPs and/or advanced nurse practitioners involved in multimorbid patients' care (39) to identify those most likely to need an extended cardiovascular risk assessment. An alert integrated in the medical record software could help increase practitioners' vigilance. Presence of diabetes in itself could also be a trigger, independently of associated chronic diseases as most diabetic patients have blood pressure issues or other risk factors, and are for the most part at high risk (27). Cardiovascular risk assessment guided by validated scores could be conducted by a medical assistant and registered in the shared medical electronic record. If high cardiovascular risk is confirmed, an automated alert could then warn the GP and/or the advanced practice nurse that a consultation should be organized and dedicated to discussing with the patient his cardiovascular risk level and the interventions that would be appropriate, in order to reach a shared understanding and agreement about the prescriptions that the GP could initiate. Not only advanced nurse practitioners could have the competencies to help better manage cardiovascular risk in multimorbid patients (39) but acceptability of coordinated care models between GPs and advance nurse practitioners seems high (40). Last, but not least, integrated care models also help improve both health outcomes–for example in patients with diabetes- and cost effectiveness of care (41, 42).

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. The patients/participants provided their written informed consent to participate in this study.

Author contributions

All authors listed have made a substantial, direct, and intellectual contribution to the work, and approved it for publication.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1089050/full#supplementary-material

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EDITED BY
Stefan Essig,
University of Lucerne, Switzerland

REVIEWED BY
Jernej Zavrsnik,
Community Health Center Dr. Adolf Drolc, Slovenia

*CORRESPONDENCE
Anna Sagan
✉ a.sagan@lse.ac.uk

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What is being done to respond to the rise of chronic diseases and multi-morbidity in Czechia, Hungary, Poland, and Slovakia?

Anna Sagan[1,2,3]*, Iwona Kowalska-Bobko[4], Lucie Bryndová[5], Martin Smatana[6], Ihor Chaklosh[4] and Pétér Gaál[7]

[1]European Observatory on Health Systems and Policies, London, United Kingdom, [2]London School of Economics and Political Science, London, United Kingdom, [3]London School of Hygiene and Tropical Medicine, London, United Kingdom, [4]Institute of Public Health, Jagiellonian University, Krakow, Poland, [5]Faculty of Social Sciences, Charles University, Prague, Czechia, [6]Faculty of Public Health, Slovak Medical University, Bratislava, Slovakia, [7]Health Services Management Training Centre, Semmelweis University, Budapest, Hungary

Although countries in central and eastern Europe (CEE) have relatively younger populations compared to the West, their populations are often affected by higher prevalence of chronic conditions and multi-morbidity and this burden will likely increase as their populations age. Relatively little is known about how these countries cater to the needs of complex patients. This Perspective piece identifies key initiatives to improve coordination of care in Czechia, Hungary, Poland, and Slovakia, including some pioneering and far-reaching approaches. Unfortunately, some of them have failed to be implemented, but a recent strategic commitment to care coordination in some of these countries and the dedication to rebuilding stronger health systems after the COVID-19 pandemic offer an opportunity to take stock of these past and ongoing experiences and push for more progress in this area.

KEYWORDS

chronic disease, multi-morbidity, care coordination, integrated care, Czechia, Hungary, Poland, Slovakia

Introduction

More than one out of three adults in the European Union (EU) report having a long-standing (chronic) illness or health problem, and an increasing proportion of the chronically ill people suffer from multi-morbidity, having two or more chronic conditions (1, 2). Multi-morbidity is most common among older people, with reported prevalence of up to 65% in people aged 65+ and up to 85% in people aged 85+ (2, 3). Increasing life expectancy means that the number of people afflicted with multiple health problems is likely to increase too.

Due to a variety of socio-economic, technological, demographic, and epidemiological factors, these problems have been more pronounced in Western Europe, leading to the emergence of various strategies and approaches to improve care for people with chronic conditions (2). So far these have been focused on specific diseases and medical specialties, including type 2 diabetes, asthma/chronic obstructive pulmonary disease

(COPD), cardiovascular diseases, cancer, and mental health problems, and hardly any have targeted multi-morbidity (2, 4). However, a variety of approaches has emerged to improve the organization and coordination of care for patients with complex chronic health needs, often involving primary care practices and focusing on multi-professional cooperation to better manage individual cases (2).

Countries in central and eastern Europe (CEE) have relatively younger populations compared to the West, but their populations often report higher prevalence rates of chronic conditions, such as diabetes, asthma, COPD, hypertension, and depressive disorders, and of multiple conditions (2), and population aging means this burden may further increase. Relatively little is known about how (and even if) these countries are responding to the changing disease patterns and the increasing burden of chronic diseases and multi-morbidity. In this context, this Perspective piece seeks to review the key efforts undertaken in Czechia, Hungary, Poland, and Slovakia in response to the rising prevalence of chronic conditions in their populations.

The hasty return to social health insurance after 1989

Health systems of Czechia, Hungary, Poland, and Slovakia followed similar historical trajectories. All four established Bismarckian-style social health insurance systems in the second half of the 19th century (5–8). After the Second World War, all four adopted the Soviet-style centralist system of state health care financed from general taxation, only to return to the Bismarckian model as quickly as possible after the fall of Communism. However, the 45 years spent under the Semashko system have left a legacy that is still visible to this day, including the relatively large numbers of hospital beds and the relative weakness of primary health care (PHC).

Under the Soviet model, health care was usually delivered by physicians with narrow specializations and provision was dominated by hospitals (9). Public polyclinics were the cornerstone of health care provision in the community, uniting primary and outpatient specialist services in one location and serving specified geographical (mostly urban) areas (10). The advantage of this set up was immediate access to specialists for the patients and opportunities for closer cooperation between primary and secondary care physicians. However, co-location of services was not accompanied by corresponding coordination mechanisms and this, together with the outdated facilities and equipment and low salaries, meant that care provided in polyclinics was of poor quality (10). Despite some initial health gains, mainly driven by the eradication of epidemic diseases thanks to the laboratory-based SANEPID (sanitary-epidemiological) service, the system proved unfit to cope with new challenges, including the rise of lifestyle-related non-communicable diseases (11).

The hasty return to social health insurance after 1989 was largely motivated by politics and ideology (9, 11, 12). It was accompanied by wide-ranging reform efforts, which included decentralization of health care administration, reducing the size of the hospital sector, expansion of private provision, especially in PHC, development of family medicine and general practice, changes in provider payment (with introduction of capitation payment in PHC and diagnosis-related groups (DRGs) in hospital care, counting among the key changes), strengthening of public health and improving quality of care (9). The speedy departure from the Soviet model meant that what came next was not always well thought through and some aspects of the old system, which perhaps could have been capitalized on and improved, were outright abandoned. For example, the dissolution of the centrally managed polyclinics resulted in many independent solo practices and ran counter to the trend to establish group practice and improve coordination between primary, specialist, long-term care and public health services that was emerging in much of western Europe (9). To this day, primary care remains relatively weak in many CEE countries, with narrow roles (e.g., limited use of minor surgery and diagnostics) and less prestige compared to specialist care, which, combined with limited gatekeeping, means that it is often bypassed in practice [see e.g., (5–8, 13)]. At the same time, the introduction of capitation fee as the main mode of payment for PHC has been blamed for under-provision of primary care services, and a rise in referrals to specialist care, while the introduction of DRGs in hospital care was criticized for obstructing coordination (9). At the start of 1990s, the health systems in CEE were largely based on an acute, episodic model of care concentrated in hospitals and were ill-equipped to deal with chronic diseases and multi-morbidity (9), and the reforms of the early the 1990s did little to rectify this situation. This does not mean, however, that the problem was not recognized, and all four countries have made attempts to optimize care pathways for patients with multiple chronic conditions.

A pioneering but failed care coordination initiative in Hungary

Hungary's Care Coordination System (CCS), introduced in 1998, was a truly pioneering initiative in the area of care coordination, not only in Hungary but also at the European level. The idea behind the CCS was to provide financial incentives to health care providers to coordinate their activities across levels of care for a population living in a geographically defined area (initially up to 200,000 people) (4, 14, 15). Hospitals, independent polyclinics, or groups of family doctors could become care coordinators and manage a virtual budget, based on weighted capitation, set by the National Health Insurance

Fund Administration (NHIFA). If, at the end of the year, the total cost of provided care was lower than this virtual budget, the coordinator would receive the difference and could use it for investments or other purposes (e.g., to increase salaries). To achieve maximum efficiency improvements and cost savings, all types of care coordinators had to collaborate with other health care providers in their region (social care providers were not part of the initiative but involving them was not prohibited either) to optimize patient pathways, for example by ensuring provision of appropriate outpatient care to reduce avoidable hospital admissions. Patients retained the right to choose providers outside of the CCS, but all payments made to these providers would be deducted from the virtual budgets. This limited incentives for the CCS to achieve savings by undertreating patients and meant that coordinators had financial responsibility for care received by all patients in their area, including care received outside of the CCS.

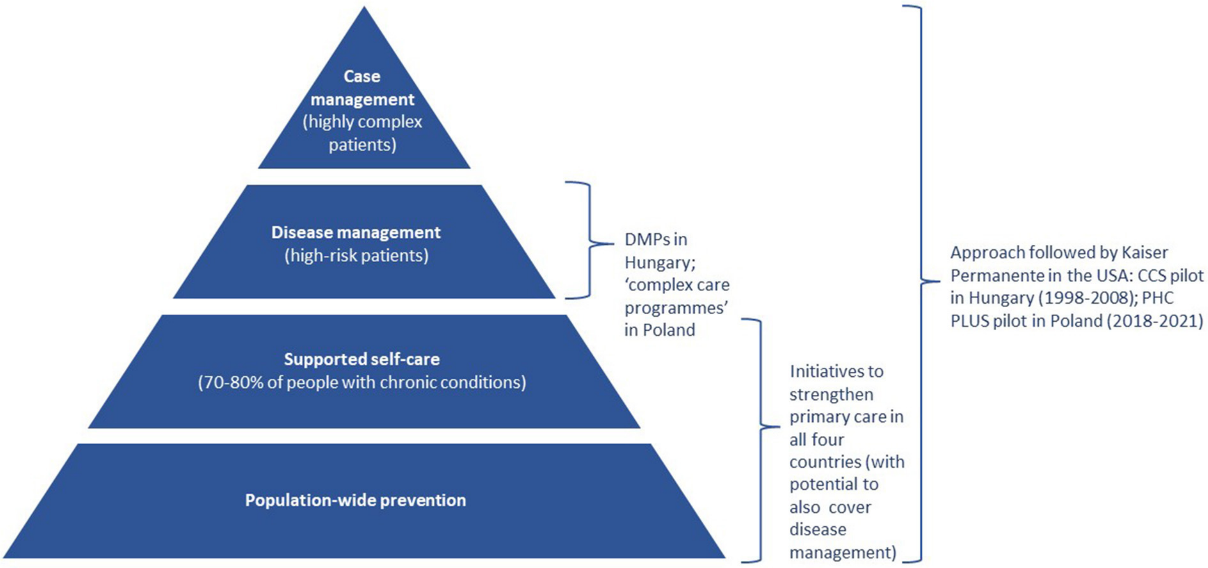
Various case management models were developed within the CCS to achieve savings. Both hospitals and independent polyclinics reported their activity data to the NHIFA for reimbursement purposes and care coordinators, using patients' social insurance identification numbers, could retrospectively reconstruct and optimize care pathways at the level of individual patients. At the same time, existing disease management programmes (DMPs) were also embedded into the CCS. These were originally developed with the support from the pharmaceutical or medical devices industries and were provided either within specialist outpatient units (e.g., diabetes care) or in dispensaries (e.g., in pulmonary dispensaries for asthma care). Coordinators would identify high risk individuals and include them in DMPs. Self-management was also encouraged within the CCS, with patient education and 24/7 consultation services provided by highly qualified nurses, including within the specific DMPs. As such, the CCS model was very comprehensive, catering to population groups of varying degrees of need, from supporting disease prevention in the general population to supporting individuals with highly complex needs, akin to the Kaiser Permanente approach in the USA and other population-based initiatives (16, 17) (Box 1).

The model was gradually rolled out to cover over 2.2 million inhabitants (over 20% of the population) by 2005. However, reform priorities soon changed and the new government (2006–2010) focused on introducing managed competition in the

BOX 1 Coordinated care initiatives in Czechia, Hungary, Poland, and Slovakia according to the risk profiles of the populations they serve.

Kaiser Permanente is a US non-profit health maintenance organization with a long track record in improving integration of health services (16). This is supported by tailoring provision to the needs and risk profiles of different groups of patients, as depicted in figure below (the so-called "Kaiser Triangle" or "Kaiser Pyramid"). There is thus a strong emphasis on disease prevention for the entire population (bottom layer of the triangle) and self-management (second layer); disease management and care pathways are available for patients with common conditions (third layer), and case management is offered to patients with the most complex needs (top layer).

Comparison of care coordination initiatives is not easy, including because similar programmes can use different nomenclatures in different countries. The Kaiser Triangle described above offers a simple framework for comparing these initiatives, by focusing on the different populations they serve that correspond to the different layers of the triangle. Some of the key care coordination initiatives pursued in Czechia, Hungary, Poland, and Slovakia, are shown in the figure below.



Key coordinated care initiatives in Czechia, Hungary, Poland, and Slovakia mapped onto the Kaiser Triangle. Source: Authors based on (17).

public health insurance system by replacing the NHIFA with multiple, partially private health insurers that were expected to compete for enrollees on the quality of services (6). This did not preclude the continuation of the CCS model, *per se*, but the government preferred to give the responsibility for care coordination to the private health insurance companies who could then implement coordination tools of their own choice. Political attention shifted to this new model, and despite the fact that the introduction of managed competition was turned down in a national referendum and eventually abandoned, the CCS was no longer pursued either and discontinued by 2008. Although the existing 16 CCS care coordinators (6 hospitals, 5 polyclinics, and 5 GP groups) supported the continuation of the model, both the government and the opposition were against the CCS which allowed care coordinators to retain achieved savings that were coming from an already tight health care budget.

Similar ideas were later pursued under the term "health coordination" (to make it distinct from the original "care coordination" and thus politically acceptable) within a European Union (EU) funded project implemented in 2014–2015. A conceptual framework for reintroducing care coordination was developed, complemented with health coordination guidelines and protocols. Health coordination offices were to be established at the level of micro regions, each covering approximately 50,000 inhabitants. These offices were meant to be initially separate, but the plan was to eventually locate them within health care providers (like in the CCS model) once the implementation of the model was approved. Unfortunately, another change in government meant that the proposals were again shelved. Some of these ideas were picked up in the primary care reform, which started in 2013 (see below), but these were much less far reaching compared to the "care coordination" and "health coordination" models described above.

Efforts to strengthen primary care

In all four countries, reforms aimed at strengthening PHC have been high on the policy agenda since the fall of Communism (9). Internationals agencies, such as the World Bank, the World Health Organization (WHO), and to a lesser extent the European Commission (EC) and bilateral donors, supported several initiatives designed to strengthen PHC in the region. Reforms of PHC continue, recently focusing more – at least in some countries – on shifting away from the solo practices and toward larger, multidisciplinary practices, which to some extent resembles the polyclinics model from the Soviet era (18).

The cornerstone of the primary care reform in Hungary, which was piloted between 2013–2017 with funding from the Swiss Contribution, was the horizontal integration of solo GP practices (usually composed of a doctor and a nurse) into group practices, comprising six or more single practices and with the additional involvement of other health professionals, such as dieticians, physiotherapists, public health experts and health mediators (19, 20). The integrated group practices retained their financial and organizational independence, but received extra funding to employ additional health professionals and provide more preventive services. The initiative was continued after the pilot ended in 2017, and in 2021 a national rollout started, also supported with additional funding. Pediatricians and dentists are now also allowed to join the group practices and higher funding is available for practices that opt for closer cooperation. The latter involves preparing a competency map and developing a plan for improving skills, equipment, and infrastructure in the practice, and providing additional surgery hours dedicated to prevention, and extra services, such as diagnostic tests, screening, and telemedicine. Case management and complex disease management programmes are not yet part of this initiative.

In Slovakia, a complex primary care reform plan was introduced in 2014 with the goal of overhauling the organization of primary care by 2030 (8). The plan was based on a proposal by the EC's Expert Panel that recommended to establish larger PHC teams or networks, resembling smaller polyclinics. These were referred to as Integrated Care Centers (ICCs) and were meant to integrate providers of outpatient care services by physically bringing them under one roof. This included PHC physicians, dentists, and gynecologists, at the minimum, and could also include other specialists and providers of social and public health services, depending on local needs. The Centers thus have the potential to become a one-stop shop for primary care services including basic diagnostic, preventive and social care services, providing continuous care for chronic patients and easing the burden on acute care hospitals (8). So far, progress has been slow, not least because practical implementation details have not been worked out. Eventually, in 2022, the Ministry of Heath developed a concept document for primary care, outlining the roles, processes (including coordination of tasks), competencies, and education of PHC doctors and nurses, financing and payment mechanisms, to provide the basis for strengthening of PHC in Slovakia. Once this document has been formally approved, implementation details will be progressively specified in dedicated guidelines.

An ambitious model of PHC reorganization was piloted in Poland between 2018 and 2021. The pilot, partly funded by the World Bank, sought to support development of multidisciplinary PHC teams, that besides a doctor and a nurse were to also include health educators, dieticians, and physiotherapists. While integration of solo GP practices into group practices (like in Hungary and Slovakia) was not explicitly encouraged, the pilot was more suited to larger practices, e.g., in terms of having established collaborations with specialist and in terms of ICT infrastructure, and few smaller practices, which dominate the Polish PHC landscape, met the formal requirements to join the pilot. The new model put much emphasis on health promotion and disease prevention, not only by including health educators and dieticians in PHC teams, but also by introducing periodic check-ups for qualifying registered patients (21). It also sought to increase the role of GPs in the management of chronic conditions by introducing DMPs for 11 most prevalent conditions in five areas (cardiology, diabetology, pulmonology, endocrinology, and rheumatology and neurology), including for diseases such as type 2 diabetes, chronic coronary heart disease, asthma, and COPD. It aimed to reduce referrals to specialists by allowing GPs to order extensive diagnostic and laboratory tests. If needed, GPs could consult with a range of cooperating specialists, while retaining the responsibility over the patient. Consenting patients would follow Individual Medical Care Plans that are tailored to their health condition(s) and are established jointly by the PHC team and the patient – the programme thus included elements of case management too (the top the Kaiser Pyramid; see Box 1). PHC teams were made responsible for coordinating patients' care pathways, including post-hospital treatment, with a new role of care coordinator introduced to that end. After the pilot was concluded, a national rollout was not pursued but the tested solutions are instead being implemented gradually and on a partly voluntary basis. Thus, in December 2021, all PHC practices were mandated to hire care coordinators, and in July 2022 the competencies of PHC doctors were extended to allow them to order a larger range of diagnostic tests. In October 2022, voluntary care coordination was introduced in four areas (as above but without rheumatology and neurology), with improved access to diagnostics and specialist consultations in these areas. This is in line with the World Bank's recommendations and is hoped to allow less-ready practices to learn from early implementers.

Poland also has various complex care programmes aimed at improving coordination of care for various diseases or groups of patients, which have been implemented over the past 15 years [see Table 1 in (22)]. However, some of these programmes are quite narrow, focusing mainly on diagnostics and specialist care, with only a few encompassing prevention and primary care services, or social care. The National Oncology Network, piloted since 2019, and the National Cardiology Network, piloted since 2021, have the ambition to offer a comprehensive range of services, from primary prevention to care for the most complex patients in their respective clinical areas, and to concentrate provision of highly specialist services in order to improve their quality. However, the role of PHC in the Oncology Network pilot has so far been minimal, even though many cancer patients in Poland are diagnosed too late to be successfully treated (23).

In the 2000's, an initiative that was similar to the Hungarian CCS model emerged in Czechia, but on a much lower scale than in Hungary, and showing more resemblance to UK's GP fundholding. Some regionally based health insurers gave their contracted GPs financial responsibility for selected, mainly outpatient health services consumed by their patients. The GPs were given virtual budgets to manage and could retain part of the savings if their average cost per patient was lower than the insurer's risk-adjusted average cost per member. These so-called "managed care projects" were administered by private parties contracted by the health insurers, and as part of the managed care support, GPs received regular feedback on their patients' care consumption and their own prescribing behavior, including how they compared to other GPs. The project had no central support and since it was not easy to achieve savings (the risk-adjustment formula on which the GP budgets were based was not well developed, and since there is not gatekeeping in the Czech system, patients could opt to see a specialist other than the one they were referred to by their GP) most participating health insurance funds have abandoned it by late 2000s. Nevertheless, some insurers still use benchmarking to compare their contracted GPs.

More recently, the Czech Ministry of Health has prioritized promoting primary care services by broadening the competencies of the GPs. Thus the remit of primary care has been progressively expanded, and since 2019 Czech GPs have been made responsible for patients with stabilized type 2 diabetes and patients who have recovered from cancer, and since 2020 for pre-diabetes care and early dementia detection. Provision of prevention, including vaccinations, and screening are also being incentivised with fee for service (FFS) payments, which now account for close to 40% of GPs' incomes (24), while the capitation rate has been progressively increased since the late 1990s.

Similarly to Poland, Czechia has also sought to concentrate provision of highly specialized care. Between 2008 and 2011, dedicated care networks for cancer, stroke, and cardiovascular disease patients were established, mainly covering specialist inpatient care (24, 25), and these have been further improved over the past decade. For example, Regional Oncology Groups were set up in 2017 to improve provision of cancer care, and the previously established Comprehensive Oncology Centers were charged with coordinating the full spectrum of cancer care within their regional group, including palliative care and home care services. Since 2019 the GPs have been included in these regional networks, after gaining responsibility for recovered cancer patients (see above) (24).

Care coordination as a strategic objective

Improving coordination of care is a relatively new objective in the strategic health system documents in the four countries. In Poland, it was only recognized as a strategic goal in 2021. The strategic framework document titled "Healthy Future. A Strategic Framework for the Development of the Health Care System for 2021–2027, with a perspective until 2030" (26) postulates establishing new models of coordinated care, including for older people and for people with mental health conditions, and structures, such as the National Oncology Network and the National Cardiology Network. Introduction of care coordinators within PHC, was also explicitly mentioned and it was already implemented at the end of 2021.

In Czechia, improved care coordination is one of the strategic goals of the Strategic Framework for the Health Care Development titled "Health 2030", which was first adopted by the Czech government in 2019 and later updated in 2020 in response to the COVID-19 pandemic (27). The Framework has seven priority areas, including continuation of the ongoing PHC reforms described above, implementation of coordinated care models, integration of health and social care, and development of community mental care.

In Slovakia and Hungary, care coordination was prioritized some years earlier – in 2013 in Slovakia and in 2011 in Hungary. Like now in Czechia, the main priority in Slovakia was to strengthen the role of PHC (28). The current government manifesto, approved in 2020, also supports improving coordination of care, including between health and social care sectors (29). In Hungary, the Semmelweis Plan from 2011 (30) was the first comprehensive strategic health policy document that addressed the question of the management of patient pathways across service providers. Interestingly, the earlier CCS reform has been a "stealth" reform, initiated by a wealthy businessman from a small town near Budapest, and later taken up by the Ministry of Health (31). However, with the exception of the PHC reform piloted in 2013–2017, which is currently being rolled out at the national scale, efforts to improve care coordination have been largely abandoned after 2014.

Discussion and conclusions

The concept of health systems resilience and how to improve it in practice have recently received increased attention both among health systems analysts and policy makers. This is mainly due to the occurrence of sudden and acute system shocks, such as the financial crisis and the COVID-19 pandemic, but more gradual strains and stresses, such as the rise of multiple chronic conditions, will also affect health systems resilience over time. Nevertheless, adapting to the changing disease patterns is by no means straightforward for several reasons. First, the fast pace of technological development demands increased specialization, while patients with multiple chronic conditions require integrated service provision across types and levels of care and sectors, such as health and social care. Second, care coordination is an elusive concept, with multiplicity of (often overlapping) terms, and its analysis is often overcomplicated with very broad frameworks, such as the one developed by the SELFIE (Sustainable integrated chronic care modeLs for multi-morbidity: delivery, FInancing and performancE) project (https://www.selfie2020.eu). Much simpler frameworks, such as the Kaiser Triangle used in this Perspective, can help map the various reforms by focusing on which population groups and health needs these initiatives attempt to cover. Third, long-term changes such as care coordination require long-term planning, and this is often obstructed by election cycles and politics. Fourth, fiscal decision makers often focus on achieving short-term cost savings; however, improving care coordination, while potentially decreasing costs by eliminating unnecessary services and reducing avoidable hospitalisations, can also increase health care costs by uncovering and addressing previously unmet needs. Focusing more on primary prevention, as the Kaiser model and some of the more comprehensive care coordination programmes do, can decrease the costs, albeit only in the (very) long term. Fifth, health care is a very complex and politically sensitive area from the perspective of high-level decision makers, and there seems to be a reluctance among the CEE politicians to experiment with new ideas, which have not been tried in other, more affluent countries in the West.

These are only some of the factors behind the mixed picture that we have found while analyzing coordinated care initiatives in Czechia, Hungary, Poland, and Slovakia. The former communist countries of Central and Eastern Europe are often considered to be lagging behind Western Europe in terms of health reforms, but the efforts we have identified here show that it is not the lack of innovative ideas that set health systems in the East and West apart, but rather the political and technical feasibility of the pursued policies. While Hungary and Poland have pursued more far-reaching coordinated care initiatives compared to Czechia and Slovakia, these efforts have so far failed. This was because of politics and changed priorities, or because the reform was too ambitious for the realities on the ground, such as the PHC PLUS reform in Poland, which was unsuited for small PHC practices that dominate in the country. Perhaps consulting with the Polish PHC doctors on the details of the reform would have helped achieve a more realistic pilot. In Czechia for example, the successful implementation of increased GP competencies has been ascribed to the efforts by the Ministry of Health to secure support from the professional association and medical societies affected by the reform.

Financial reasons have likely also played a role: health spending in all four countries is comparatively low among the EU countries (both in per capita terms and as %-age of GDP), and relatively little is spent on PHC, with the latter partly a reflection of the dominance of specialist care but also of the low numbers of PHC physicians. However, positive developments have been noted, both in terms of increasing the overall health spending and the remuneration and financial incentives for primary care doctors.

All four countries continue to pursue incremental reforms to strengthen PHC, and although these may be less far reaching, they nevertheless have potential to make a big difference to the lives of patients suffering from chronic diseases and prepare the ground for more ambitious reforms. Efforts to concentrate provision of specialist care in dedicated networks pursed in Czechia and Poland also have the potential to involve PHC providers and further bolster PHC in these countries. Strengthening care coordination has been recognized as a strategic priority in all four countries and the Recovery and Resilience Facility that was set up to aid EU Member States in the recovery from the COVID-19 pandemic, can now be used to support the realization of this goal. It is now a good time for Czechia, Hungary, Poland, and Slovakia to take stock of what has been tried so far, including revisiting the failed initiatives and reforms pursued in other countries, and use it as an opportunity to better prepare to meet the changing health needs of their populations. Paying more attention to the technical and political feasibility of innovative ideas could be the game changer for future health reforms.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

Conceptualization: AS. Resources and writing–original draft preparation: AS, IK-B, LB, MS, IC, and PG. Revisions: AS, LB, MS, and PG. Supervision: PG. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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EDITED BY
Stefan Essig,
University of Lucerne, Switzerland

REVIEWED BY
Hon Lon Tam,
The Chinese University of Hong Kong, China
Shiferaw Letta,
Haramaya University, Ethiopia

*CORRESPONDENCE
Chi Zhou
✉ zhouchi@hznu.edu.cn
Yin Dong
✉ 9597082@qq.com
Falin Zhao
✉ zhaofalin@hznu.edu.cn

†These authors have contributed equally to this work and share first authorship

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Relationship between self-care compliance, trust, and satisfaction among hypertensive patients in China

Chi Zhou[1]*†, Jingchun Chen[1]†, Fang Tan[2], Sihong Lai[1], Xu Li[1], Ke Pu[1], Jiahui Wu[1], Yin Dong[3]* and Falin Zhao[1]*

[1]Department of Health Management, School of Public Health, Hangzhou Normal University, Hangzhou, China, [2]School of Medicine and Health Management, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, China, [3]Department of Hospital Office, The People's Hospital of Yuhuan, Taizhou, China

Introduction: Hypertension is a growing public health concern worldwide. It is a leading risk factor for all-cause mortality and may lead to complications such as cardiovascular disease, stroke, and kidney failure. Poor compliance of hypertensive patients is one of the major barriers to controlling high blood pressure. Compliance is not ideal among Chinese patients, and increasing patient self-care compliance with hypertension is necessary.

Methods: This article analyzes the status of self-care compliance, trust, and satisfaction among Chinese hypertensive patients using cross-sectional data from Zhejiang Province. We use a multi-group structural equation model (MGSEM) to compare the interrelationships across genders.

Results: The study's findings show that the average trust, satisfaction, and compliance scores are 3.92 ± 0.55, 3.98 ± 0.61, and 3.33 ± 0.41, respectively. Female patients exhibit higher average total scores for trust and compliance than male patients. The SEM results indicate that trust has a direct positive association with compliance [$\beta = 0.242$, 95% CI: (0.068, 0.402)] and satisfaction [$\beta = 0.260$, 95% CI: (0.145, 0.367)], while their satisfaction is not directly associated with compliance. The results of MGSEM show that trust has an indirect effect on compliance in the male group through satisfaction [$\beta = 0.051$, $P < 0.05$, 95% CI: (0.012, 0.116)]. In the female group, trust has a direct effect on satisfaction [$\beta = 0.235$, $P < 0.05$, 95% CI: (0.041, 0.406)] and compliance [$\beta = 0.319$, $P < 0.01$, 95% CI: (0.086, 0.574)].

Discussion: This study reveals the mechanisms of self-care compliance, trust, and satisfaction among Chinese hypertensive patients. Its findings may serve as a reference for guiding primary healthcare providers to improve hypertension patients' compliance and implement gender-targeted health interventions.

KEYWORDS

self-care compliance, trust, satisfaction, hypertensive patients, China

1. Introduction

Hypertension is a crucial public health challenge worldwide (1). It is estimated that the number of people with high blood pressure will reach ∼2 billion by 2025 (2–4). Hypertension is the leading risk factor for all-cause mortality, and its complications include cardiovascular disease, stroke, and kidney failure, causing a heavy financial burden on families and society (5–10). In China, ∼250 million people suffer from hypertension and increased blood pressure, which may cause 24% of deaths and 14% of disability-adjusted life-years (11). Previous studies have shown that effective self-care management can significantly reduce blood pressure (10–12),

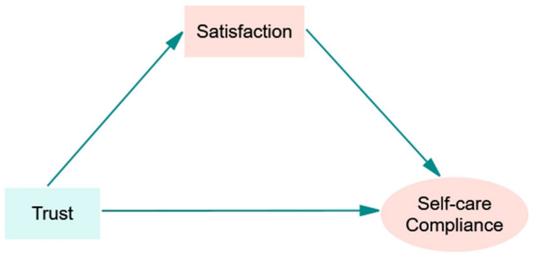

FIGURE 1
Structural framework of hypothesized relationships.

TABLE 1 Sample demographics ($N = 373$).

Variate	Frequency (N)	Composition ratio (%)
Age, mean ± SD	66.00 ± 10.41	
Gender, *N* (%)		
Male	205	55.0
Female	168	45.0
Education level, *N* (%)		
Primary school and below	229	61.4
High school	130	34.9
Junior college and above	14	3.8
Per capita monthly income, *N* (%)		
≤3,500 RMB	246	66.0
3,501–5,000 RMB	71	19.0
>5,000 RMB	56	15.0
Employment status, *N* (%)		
Unemployed	206	55.2
Employed	167	44.8
Insurance, *N* (%)		
Basic medical insurance for urban and rural residents	271	72.7
Other (business insurance, etc.,)	102	27.3
Duration of hypertension, *N* (%)		
<1 year	34	9.1
1–3 year	67	18.0
4–6 year	82	22.0
7–10 year	39	10.5
>10 year	151	40.5
Initial medical treatment, *N* (%)		
Community health services centers	263	70.5
Hospitals above the county level	64	17.2
Clinics or pharmacies	46	12.3
Have a family doctor, *N* (%)		
Yes	254	68.1
No	119	31.9

SD, standard deviation.

such as dietary salt reduction, physical activity, and potassium intake. However, the adoption of self-care behaviors and hypertension control rates are not ideal among Chinese patients (13–15).

As defined by Lahdenpera, self-care compliance means that patients collaborate proactively with healthcare personnel and change their lifestyle according to their recommendations (13, 14). High self-care compliance implies that patients are prone to adopt and maintain a healthy lifestyle to improve blood pressure control (15). In China, most patients with hypertension have low-to-medium levels of self-care compliance (16–19). For example, one study shows that 69.9% of Chinese hypertensive patients have a salt intake higher than 6 g/day, higher than that recommended by the World Health Organization (20). Most studies indicate that hypertension self-care compliance is associated with sociodemographic factors, such as gender, family income, and hypertension duration. However, the literature has devoted limited attention to other potentially influencing factors, such as patients' trust in physicians and patient satisfaction with healthcare services (13, 19).

Trust between doctors and patients are usually defined as the expectation that doctors provide high-quality healthcare services and prioritize patients' interests (21–23). A trusting doctor-patient relationship may increase the communication between patients and doctors, allowing patients to learn valuable medical information and knowledge related to disease management. Doctors may also enhance patients' confidence and vitality and lead them to actively participate in disease management, thus improving patient compliance (5, 24–26). Previous studies have reported that Chinese residents express moderate trust in primary care physicians (27, 28), and female patients are more likely to experience a high level of trust (29). Trust promotes patient satisfaction, and patients with sufficient trust in their physicians are more likely to feel satisfied with healthcare services (30, 31).

Patient satisfaction may be defined as consumption-related fulfillment due to healthcare service and may provide feedback on the technical level and service attitude of medical staff (32–34). Patient satisfaction is a crucial factor in the decision to treat and deliver healthcare services. It is associated with many outcome variables, such as advanced persistence and compliance, effectiveness and efficiency of self-care behavior, and improvement of prognosis (9, 35, 36). A study in China indicates that hypertensive patients have a medium satisfaction score; hence, efforts are needed to improve it (5).

Previous studies of trust, satisfaction, and compliance have focused on the relationship between any two of these factors. For example, a study targeting China has found a significant association between patient trust in their physicians and compliance with diet management and physical activity (2). Another study targeting Lebanon has reported that patients who feel more satisfied with healthcare services have higher hypertension compliance (6). However, quantitative studies that analyze the underlying mechanisms of these three factors among patients with a specific chronic disease are lacking. Exploring these mechanisms is crucial for improving chronic disease management.

To fill this research gap, the current study evaluates the status of patients' self-care compliance, trust, and satisfaction across genders and explores the relationships among patients' self-care compliance,

TABLE 2 The description of trust, satisfaction, and self-care compliance scores (mean ± SD).

Contents	Item	Average score of each item			*t*-value	*P*-value
		Total ($n = 373$)	Men ($n = 205$)	Women ($n = 168$)		
Trust	10	3.92 ± 0.55	3.86 ± 0.54	4.00 ± 0.56	−2.476	0.014
Competence	5	3.99 ± 0.57	3.92 ± 0.57	4.08 ± 0.56	−2.709	0.007
Benevolence	5	3.85 ± 0.64	3.80 ± 0.61	3.92 ± 0.67	−1.877	0.061
Satisfaction	5	3.98 ± 0.61	4.01 ± 0.61	3.95 ± 0.61	1.011	0.312
Self-care compliance	13	3.33 ± 0.41	3.29 ± 0.44	3.38 ± 0.36	−2.157	0.032
Intention	4	3.53 ± 0.53	3.50 ± 0.55	3.57 ± 0.51	−1.144	0.253
Lifestyle	3	2.76 ± 0.72	2.75 ± 0.73	2.77 ± 0.71	−0.227	0.821
Attitude	3	3.53 ± 0.52	3.49 ± 0.55	3.58 ± 0.48	−1.731	0.084
Responsibility	2	3.41 ± 0.72	3.48 ± 0.66	3.32 ± 0.76	2.155	0.032
Smoking	1	3.49 ± 1.04	3.07 ± 1.26	3.99 ± 0.08	−9.427	<0.001

TABLE 3 Correlation coefficients among study variables.

Variable	(1)	(2)	(3)
(1) Trust	1.000	-	-
(2) Satisfaction	0.249**	1.000	-
(3) Self-care compliance	0.120*	0.128**	1.000

Significant codes: $^{**}P < 0.01$; $^{*}P < 0.05$.

trust, and satisfaction using structural equation modeling (SEM), comparing gender differences.

We hypothesize that (1) trust and satisfaction directly predict self-care compliance, (2) trust directly predicts satisfaction, and (3) satisfaction mediates the role of trust and self-care compliance. Furthermore, due to differences in social and cultural roles, as well as the personality traits and knowledge of hypertension between men and women, we assume that differences may be observed between male and female patients in the above relationships.

2. Materials and methods

2.1. Participants and design

We conducted this cross-sectional study between June and August 2021. We collected the relevant data using self-administered questionnaires. We addressed two counties (Linping and Chunan) to represent both well- and less-developed GDP levels in Zhejiang Province. Each county featured two medical groups. We chose one hospital and 3–4 of its associated community health centers from each medical group. Thus, we selected four hospitals and 14 community health centers as investigation sites. We recruited residents waiting in the outpatient hall of each hospital/community health center. Participants met the following inclusion criteria: (1) aged 40 years or older, (2) diagnosed with hypertension and receiving antihypertensive therapy, (3) lived in the local area for more than 6 months, and (4) with no cognitive disability. We distributed a total of 450 questionnaires; 373 valid questionnaires were returned, with a response rate of 82.89%.

2.2. Measures

2.2.1. Trust

We constructed patient trust using the Wake Forest Physician Trust Scale (WFPTS) designed by Hall et al. (37) and the Chinese version by Dong et al. (28). This scale consists of 10 items and two domains: (1) competence (five items), referring to patients' judgment of physicians' professional knowledge and technical ability, and (2) benevolence (five items), indicating patients' perceived empathy from their physicians or emotional dependence on their physicians. Responses were rated on a five-point Likert scale, ranging from one ("strongly disagree") to five ("strongly agree"). In contrast, the negatively worded items (items two, three, and seven) were scored in reverse order ("1" = "strongly agree" and "5" = "strongly disagree"). The total score of the C-WFPTS ranges between 10 and 50, with a higher score indicating a higher level of trust in physicians. The reliability and validity of the C-WFPTS are adequate, with a Cronbach's alpha ranging between 0.728 and 0.789 (2, 38), and a Kaiser-Meyer-Olkin (KMO) value of 0.833 (5), suitable for evaluating the trust of Chinese patients in their physicians. The Cronbach's alpha of the scale is 0.827.

2.2.2. Satisfaction

We measured patient satisfaction using a self-developed questionnaire comprising five items: (1) "Are you satisfied with the time spent at treatment and the service process in this hospital?" (2) "Are you satisfied with the technical level and service attitude of medical staff in this hospital?" (3) "Are you satisfied with the burden of medical expenses in this hospital?" (4) "Are you satisfied with the primary health management services (e.g., health consultation, health education, and follow-up services)?" (5) "What about your overall satisfaction in this hospital?" Each question was rated on a five-point Likert scale ranging from one (strongly dissatisfied) to five (strongly satisfied), and the total score ranged from five to 25. Higher scores indicate higher patient satisfaction.

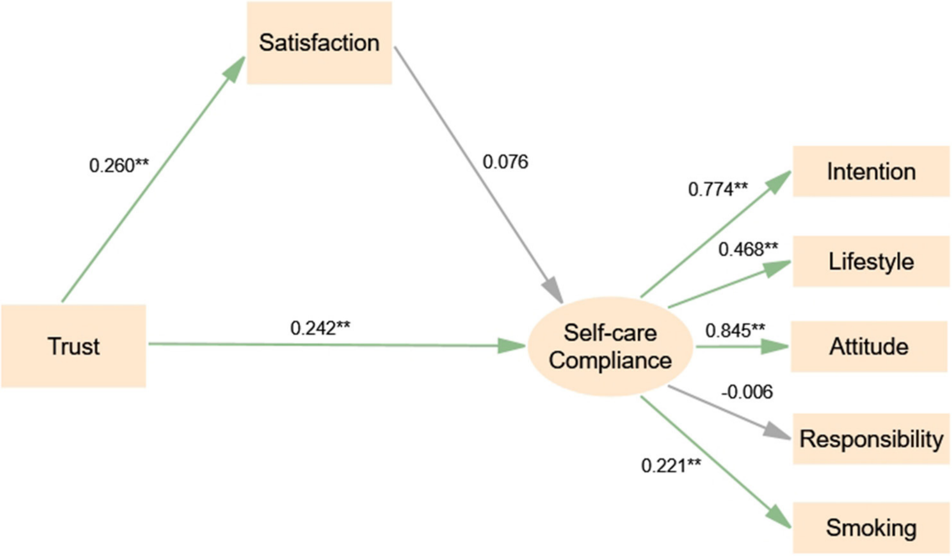

FIGURE 2
Structural equation model of trust, satisfaction and compliance (full sample). Significant codes: $^{**}P < 0.01$; $^{*}P < 0.05$.

2.2.3. Self-care compliance

We assessed patient self-care compliance using the Compliance of Hypertensive Patients Scale (CHPS) developed by Lahdenpera et al. (14). This scale consists of 13 items and five dimensions: intention (five items), lifestyle (three items), attitude (three items), responsibility (two items), and smoking (one item). Each item was rated on a four-point Likert scale ranging from one (poor compliance) to four (good compliance), and the total score ranged from 13 to 52. Higher scores indicate higher levels of self-care compliance. This scale has been verified as acceptable for measuring hypertension compliance in Chinese patients, with a Cronbach's alpha value of 0.859 (39). In this study, the Cronbach's α for this part is 0.765.

2.2.4. Covariates

Covariates in this study included the socio-demographic characteristics as follows: gender, age, education level (primary school and below, high school or junior college and above), employment status (unemployed or employed), type of medical insurance (medical insurance of urban and rural residents or others, e.g., business insurance), per capita monthly income (≤3,500, 3,501–5,000, or >5,000 RMB), duration of being diagnosed with hypertension (<1, 1–3, 4–6, 7–10, or >10 year), initial medical treatment (community health services centers, hospitals above the county level or clinics and pharmacies), and whether have a family doctor (yes or no).

2.3. Statistics analysis

We entered the data using Epidata 3.1 (the Epidata Association, Odense, Denmark) and analyzed them using IBM SPSS Statistics 26.0 (IBM Corporation, Armonk, NY, USA) and AMOS 24.0 (IBM, New York, NY, USA). First, we employed descriptive statistics to examine participant characteristics and the study's variables. We calculated the proportion and frequencies for categorical data (i.e., gender, district, and education level, among others), and we calculated means and standard deviations (SDs) for quantitative data (i.e., age, score of trust, satisfaction, and self-care compliance). Second, we used a *t*-test to verify the gender differences in trust, satisfaction, and self-care compliance. We employed Spearman's correlation to assess the correlations between the three variables of interest. Third, we used SEM to establish the measurement model outlined in Figure 1. We then used a multi-group structural equation model (MGSEM) to analyze the impact of the proposed variables across genders. We employed the Bootstrap maximum likelihood estimation method to compute the bias-corrected 95% confidence interval (95% CI). To evaluate the model fit, we applied the following criteria: a root mean squared error of approximation (RMSEA) of 0.08 or below, the goodness of fit index (GFI), comparative fit index (CFI), incremental fit index (IFI), and Tucker–Lewis's index (TLI) of 0.90 (40). We set the statistical significance at $P < 0.05$.

3. Results

3.1. Participants' sociodemographic characteristics

Table 1 reports the sociodemographic characteristics of the 373 participants. The average age of the participants is 66.00 ± 10.41 years old, 55.00% are male, 61.40% have primary school and below education level, and 66.00% have a monthly income of <3,500 RMB. In addition, 44.80% of participants are employed, 72.70% have basic medical insurance for urban and rural residents, 40.50% have suffered from hypertension for more than 10 years, 70.50% chose community health service centers as the initial medical treatment, and 68.1% have a family doctor.

TABLE 4 Direct, indirect, and total effects and bias-corrected 95% confidence intervals of the model.

	Total				Male				Female			
	b	SE	95% CI		b	SE	95% CI		b	SE	95% CI	
			Lower	Upper			Lower	Upper			Lower	Upper
Standardized direct effect												
Trust→ Satisfaction	0.260**	0.057	0.145	0.367	0.299**	0.075	0.146	0.435	0.235*	0.094	0.041	0.406
Trust→ Self-care compliance	0.242**	0.085	0.068	0.402	0.098	0.106	−0.096	0.313	0.319**	0.128	0.086	0.574
Satisfaction→ Self-care compliance	0.076	0.061	−0.042	0.199	0.171*	0.081	0.022	0.339	−0.023	0.083	−0.173	0.153
Standardized indirect effect												
Trust→ Satisfaction→ Self-care compliance	0.020	0.016	−0.042	0.056	0.051*	0.025	0.012	0.116	−0.005	0.022	−0.058	0.035
Standardized total effect												
Trust→ Self-care compliance	0.262**	0.083	0.096	0.420	0.149	0.106	−0.056	0.357	0.313**	0.129	0.083	0.571

Standardized estimating of 2,000 bootstrap sample.
SE, standard error; CI, confidence interval.
Significant codes: $^{**}P < 0.01$; $^{*}P < 0.05$.

3.2. Descriptive analysis of trust, satisfaction, and compliance scores

Table 2 presents the average scores for each variable. The total average score of the C-WFPTS is 3.92 ± 0.55. The average scores of the competence and benevolence domains are 3.99 ± 0.57 and 3.85 ± 0.64. The total average scores of satisfaction and CHPS are 3.98 ± 0.61 and 3.33 ± 0.41. For the domain scores of CHPS, intention (3.53 ± 0.53) and attitude (3.53 ± 0.52) have the highest average score, while lifestyle (2.76 ± 0.72) has the lowest average score. For the gender subgroup, female patients exhibit higher total average scores for C-WFPTS, and CHPS ($t = -2.476$, $P = 0.014$; $t = -2.157$, $P = 0.032$) than males.

3.3. Correlations between the study variables

Table 3 lists the correlation coefficients between the observed variables. Trust is positively correlated with satisfaction ($r = 0.249$, $P < 0.01$) and self-care compliance ($r = 0.120$, $P < 0.05$). Satisfaction is positively correlated with self-care compliance ($r = 0.128$, $P < 0.01$).

3.4. SEM results

The structural model has the following fit indices: chi-square = 2.727, df = 12, $p < 0.001$, CFI = 0.942, GFI = 0.975, IFI = 0.944, TLI = 0.899, and RMSEA = 0.068, indicating a good fit with the data, as shown in Figure 2. The results in Table 4 indicate that trust has a direct positive association with self-care compliance [$\beta = 0.242$, $P < 0.01$, 95% CI: (0.068, 0.402)], and trust is positively associated with satisfaction [$\beta = 0.260$, $P < 0.01$, 95% CI: (0.145, 0.367)].

We performed multi-group analyses using SEM by adding constraints ranging from equal structural weights across groups to equal structural weights, covariance, and residuals. The results of the three constraint models show that the chi-square value has no significant correlation with any of the model comparisons ($P = 0.299$, $P = 0.539$, $P = 0.668$), suggesting that the structural model is equivalent in the male and female group. As shown in Figures 3, 4 and Table 4, trust is a direct predictor of satisfaction both in male [$\beta = 0.299$, $P < 0.01$, 95% CI: (0.146, 0.435)] and female group [$\beta = 0.235$, $P < 0.05$, 95% CI: (0.041, 0.406)]. Satisfaction has a positive direct influence on self-care compliance in the male group [$\beta = 0.171$, $P < 0.05$, 95% CI: (0.022–0.339)], while we observe no significant difference in the female group. In addition, trust has an indirect effect on self-care compliance through satisfaction in the male group [$\beta = 0.051$, $P < 0.05$, 95% CI: (0.012–0.116)], while it is a direct predictor of self-care compliance in the female group [$\beta = 0.319$, $P < 0.01$, 95% CI: (0.086–0.574)].

4. Discussion

To the best of our knowledge, this is the first study to employ an SEM model to identify the relationship between trust, satisfaction, and self-care compliance among hypertensive patients, clarify the action mechanisms governing their relationships and compare the results across genders in China. The study's findings provide a reference for improving hypertension compliance.

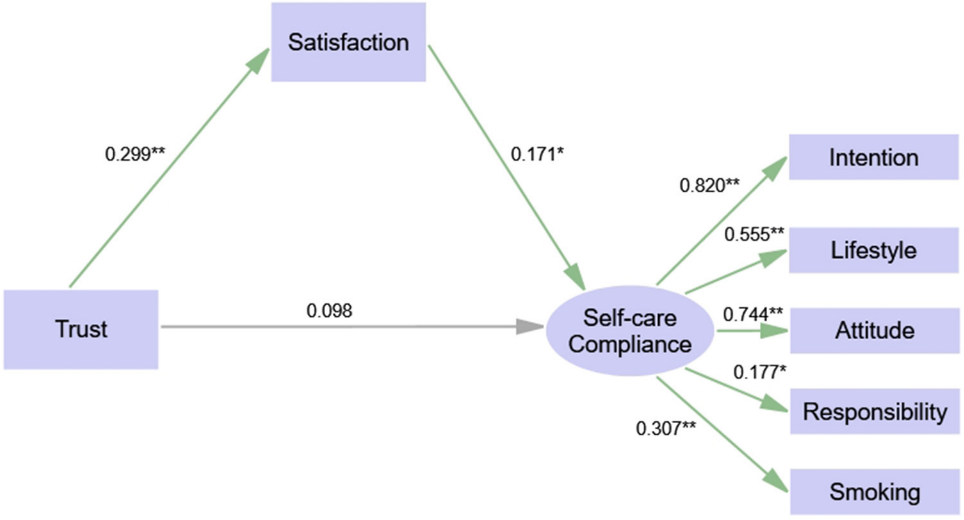

FIGURE 3
Structural equation model of trust, satisfaction and compliance (sub-sample: male). Significant codes: $^{**}P < 0.01$; $^{*}P < 0.05$.

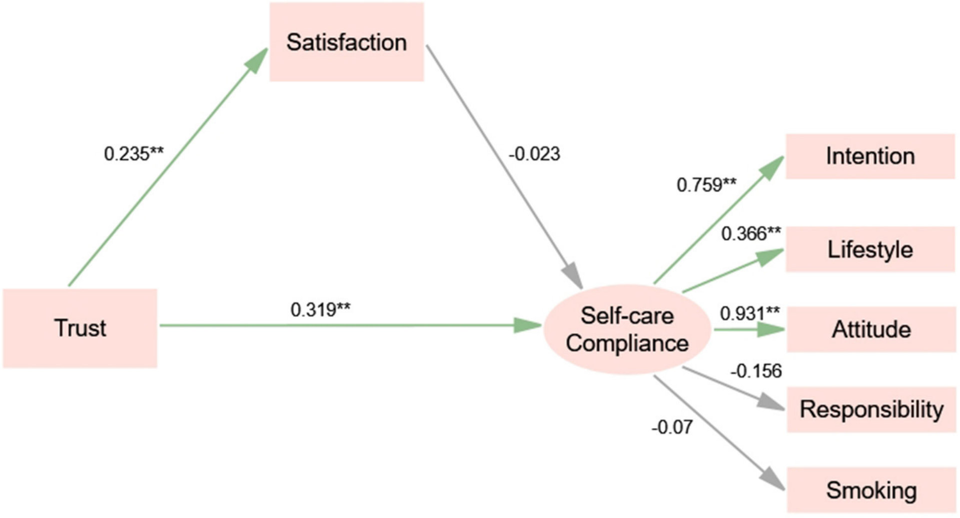

FIGURE 4
Structural equation model of trust, satisfaction and compliance (sub-sample: female). Significant codes: $^{**}P < 0.01$; $^{*}P < 0.05$.

The study's results indicate that the average CHPS is 3.33 points, in line with a study conducted in Hubei Province in China (39). The highest domain scores of CHPS are intention and attitude, and the lowest domain score is lifestyle. This finding aligns with previous studies (14, 41) and implies that participants may have a positive willingness and attitude to participate in hypertension health management but lack the motivation to take action. Female patients with hypertension have a higher total average CHPS score than male patients, in line with previous findings (41–43). This result may be because, compared with men, women undertake more housework and need to care for family members' health (44). Hence, they have more significant health responsibilities, are prone to higher compliance, and follow a healthier lifestyle (15, 43, 45). In addition, social and cultural factors discourage women from smoking and consuming alcohol in China, which may help maintain a healthy lifestyle (46).

This study finds a total average C-WFPTS score equal to 3.92. This result is slightly higher than the findings from China's western and central provinces (5, 29). One possibility is that the investigated hospital/community health centers in the eastern provinces exhibit higher levels of medical skills training and technology, and medical staff provides better treatment for chronic disease patients, gaining their trust (5, 16, 47). As noted by Chen et al., bridging the gap between the service capacity of primary care institutions and patients' demand for clinical and health services helps build a trustful partnership between doctors and patients (5). However, doctor-patient trust is lower in China than that observed in developed countries (48), especially the benevolence trust level (49, 50). One possible explanation is that the total number of Chinese healthcare professionals is insufficient, and they have a large medical service workload (38). As a result, they spend limited time communicating with patients to pursue service efficiency (2, 23), and patients are often unable to receive enough emotional support from their family doctors (24). Due to the impossibility to increase the number of healthcare professionals in a short time, it might be possible to improve the current situation of physician-patient trust by using text messaging and mobile app (51, 52), which provided a new way to bridge the relationship between physicians and patients. Additionally, this study also shows that female patients exhibit higher trust scores than male patients, in line with a previous study (53). This result may be because women are more sensitive to disease perception (42) and adopt more health-seeking behaviors (54, 55). Therefore, women have more opportunities to communicate with doctors and receive more medical information about their diseases, which helps build a trusted doctor-patient relationship (26, 56).

The SEM results show that trust positively influences self-care compliance among hypertensive patients for the whole sample, in line with existing studies (2, 6, 57). An adequate level of trust leads patients to share more information with doctors about their concerns. Hence, doctors can fully understand patients' attitudes and other potential barriers toward hypertension management and introduce measures for better self-care compliance (45, 58). Moreover, trust is a significant predictor of satisfaction. This result is consistent with the findings of Mahmoudian et al., who show that physicians' emotional and spiritual support, as well as mutual trust between doctors and patients, significantly impact patient satisfaction (24).

Different mechanisms affect the associations between trust, satisfaction, and self-care compliance across genders. The MGSEM results show that satisfaction only significantly affects self-care compliance in the male group. This finding may be due to male patients being more consumeristic in their interactions with the healthcare system and pursuing high-quality health services motivating them to follow up with physicians' instructions (59). In addition, our findings suggest that trust has an indirect positive influence on self-care compliance through satisfaction in the male group, while trust has a direct positive impact on self-care compliance in the female group. This finding confirms the results mentioned above, namely, a higher level of trust leads to better self-care compliance. In addition, compared with men, women are more likely to cognitively trust their doctors. This emotional trust leads them to cooperate with their physicians more actively and have higher compliance in their disease management (42, 60, 61). Men tend to think rationally, and their full trust in their doctors leads them to positively evaluate their treatment outcomes and enhance their motivation to follow doctors' medical advice (62).

Despite its contributions, this study has some limitations. First, the study is only conducted in rural areas in Zhejiang Province of China, which may limit the generalizability of its findings. Second, this cross-sectional study cannot reveal the causal relationship between the variables of interest. Third, we use self-assessed data to verify the research hypotheses. Finally, no objective indicators support the study's findings, which may be subject to answering or memory bias.

5. Conclusion

The total scores of patients' self-care compliance, trust, and satisfaction are close to those found by previous studies in China and may still be improved. Female patients have relatively higher self-care compliance and trust than males; hence, special attention should be devoted to male patients in health management. The progress of females' self-care compliance depends on doctor-patient trust, while males' depends on treatment outcome satisfaction through doctor-patient trust. The study's results indicate that gender differences must be considered when developing self-care compliance interventions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Hangzhou Normal University Ethics Board (No. 2019065). Written informed consent form was obtained from each participant prior to the enrolment. A copy of the signed consent form was given to each participant.

Author contributions

CZ and JC: visualization and writing—original draft. YD and FZ: visualization, writing—review and editing, and funding acquisition. FT, SL, XL, KP, and JW: data curation and formal analysis. All authors have read and agreed to the published version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.1085047/full#supplementary-material

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The impact of persistent precarity on patients' capacity to manage their treatment burden: A comparative qualitative study between urban and rural patients with multimorbidity in South Africa

Myrna van Pinxteren[1]*, Nonzuzo Mbokazi[1], Katherine Murphy[1], Frances S. Mair[2], Carl May[3,4] and Naomi Levitt[1]

[1]Chronic Disease Initiative for Africa, Department of Medicine, University of Cape Town, Cape Town, South Africa, [2]School of Health and Well-Being, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow, United Kingdom, [3]Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, London, United Kingdom, [4]NIHR North Thames Applied Research Collaboration, London, United Kingdom

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Dokuz Eylül University,
Türkiye

*CORRESPONDENCE
Myrna van Pinxteren
✉ Myrna.vanpinxteren@uct.ac.za

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Background: People living with multimorbidity in low-and middle-income countries (LMICs) experience a high workload trying to meet the demands of self-management. In an unequal society like South Africa, many people face continuous economic uncertainty, which can impact on their capacity to manage their illnesses and lead to poor health outcomes. Using precariousness – the real and perceived impact of uncertainty – as a lens, this paper aims to identify, characterise, and understand the workload and capacity associated with self-management amongst people with multimorbidity living in precarious circumstances in urban and rural South Africa.

Methods: We conducted qualitative semi-structured interviews with 30 patients with HIV and co-morbidities between February and April 2021. Patients were attending public clinics in Cape Town (Western Cape) and Bulungula (Eastern Cape). Interviews were transcribed and data analysed using qualitative framework analysis. Burden of Treatment Theory (BoTT) and the Cumulative Complexity Model (CuCoM) were used as theoretical lenses through which to conceptualise the data.

Results: People with multimorbidity in rural and urban South Africa experienced multi-faceted precariousness, including financial and housing insecurity, dangerous living circumstances and exposure to violence. Women felt unsafe in their communities and sometimes their homes, whilst men struggled with substance use and a lack of social support. Older patients relied on small income grants often shared with others, whilst younger patients struggled to find stable employment and combine self-management with family responsibilities. Precariousness impacted access to health services and information and peoples' ability to buy healthy foods and out-of-pocket medication, thus increasing their treatment burden and reducing their capacity.

Conclusion: This study highlights that precariousness reduces the capacity and increases treatment burden for patients with multimorbidity in low-income settings in South Africa. Precariousness is both accumulative and cyclic, as financial insecurity impacts every aspect of peoples' daily lives. Findings emphasise that current models examining treatment burden need to be adapted to accommodate patients' experiences in low-income settings and address cumulative precariousness. Understanding treatment burden and capacity for patients in LMICs is a crucial first step to redesign health systems which aim to improve self-management and offer comprehensive person-centred care.

KEYWORDS

multimorbidity (co-morbidity), treatment burden, qualitative research and analysis, low-income context, precarity

Background

Precariousness, the real and perceived impact of uncertainty, is a concept originally developed to determine the effects of economic insecurity and absence of state support on people's lives (1). It has since been extended to include the impact on people living under the threat of natural disasters and experiencing a lack of social and economic rights (1). Faced by continuous hardship, people who are "living on the edge" are more at risk of poverty, starvation, displacement, and exposure to violence without protection (2–4). Precariousness profoundly impacts people's health and well-being by reducing people's access to health care, health information and support networks (5–8). However, the impact of precariousness on patients with multimorbidity in low-middle countries (LMICs) is underexplored.

South Africa is a country with significant social and economic inequalities, scoring 63 on the Gini Coefficient index, amongst the highest in the world (9). These inequalities are caused by colonialization and the legacy of racial discrimination during apartheid, which deprived people of educational opportunities, jobs, adequate housing, and access to health care based on their racial classification (10–13). Almost 30 years post-apartheid, 34.5% of South Africans are unemployed, one in five South Africans rely on social welfare grants from the state (10, 14) and almost 20% of South African households have inadequate access to sufficient safe, and nutritious food (15). An estimated 25% of South Africans live in a township or slum setting and 14% of the population resides in informal dwellings, commonly called shacks (16). These social disparities, result in an increased burden of disease and poor health outcomes (10, 17).

With more than 8 million people receiving antiretroviral therapy (ART), South Africa has the highest number of people living with HIV (PLWH) in the world, whilst simultaneously experiencing a rising burden of non-communicable diseases (NCDs), most commonly diabetes, cardio-vascular diseases, hypertension and mental illness (18–21). These colliding epidemics are giving rise to patterns of multimorbidity, defined as two or more chronic conditions, disproportionately affecting socio-economically disadvantaged populations. The rising prevalence in multimorbidity has societal consequences, impacting the livelihood and futures of working populations and families (22). In the past 15 years, steep increases in NCDs have been reported in low-income groups, who also have the highest burden of HIV (23–25). Currently, of those seeking care in South Africa, the estimated prevalence of multimorbidity is between 22.6 and 48.4% (21, 26–28). More than 80% of South Africans use free public, state funded health services which are fragmented and not equipped to provide care for the long-term and complex treatment of multimorbidity patients (22, 29). Currently, no integrated care is offered for people living with HIV/NCD multimorbidity, and administration and consultation are taking place in separate clinics on separate days (30, 31). However, antiretroviral (ART) adherence clubs and differentiated HIV service delivery are offered free of charge to reduce waiting times and overcrowding in clinics (30, 32, 33). Availability of, access to and the quality of health services also differ between provinces and between urban and rural areas, underserving rural low-income households (34). Longstanding health system weaknesses have been exacerbated during the COVID-19 pandemic, as clinics are dealing with stock-outs of medication, interrupted services and staff shortages (35).

Responding to the rising burden of chronic communicable and NCDs in South Africa and increased prevalence of multimorbidity, the National Department of Health (NDoH) has developed initiatives to improve the integration of services at a primary care level, such as the Integrated Chronic Disease Management model (ICDM) (36). The ICDM model, informed by the WHO Innovative Care for Chronic Conditions Framework (ICCC), aims to streamline health care programmes on different levels: improve patients interactions on the micro-level, increase health organisation and community engagement on the meso-level, and restructure policies at the macro-level (37). It emphasises that optimal outcomes are achieved when there is both a partnership between patients, communities and health services and patients are empowered to take responsibility for their health. The ICDM model is currently being rolled out in 42 clinics in three of the nine South African provinces. Early evaluation studies have revealed a concern that patients with complex chronic conditions are expected to take on more responsibility for self-management, without receiving ongoing support delivered by health services (37, 38).

To further investigate the impact of multimorbidity in patients' lives, this paper explores the treatment burden experienced by people living with multimorbidity in South Africa, building on two theoretical models, the Burden of Treatment Theory (BoTT) and Cumulative Complexity Model (CuCoM) (39, 40). CuCoM explores the interaction between individual patients' workload and their capacity to manage this workload, whilst BoTT examines the role of the patient and their supporters in managing, caring, and supporting the work of being a patient and analyses how patient workload is distributed through and within social networks (39–41). These models have been developed and tested in high income countries and research on treatment burden in LMICs is scarce, but the few qualitative studies done in Sub-Saharan Africa report that patients with multimorbidity face several challenges when navigating their workload, due to inconsistent access to and poor quality of health care, insufficient health knowledge and stigma (30, 42, 43).

Applying both BoTT and CuCoM as a theoretical focus, this paper explores patients' agency to mobilise social and economic resources to effectively self-manage multimorbidity, in settings of precarity, and aims to understand if and how an absence of these resources can overwhelm patients and increase treatment burden, which in turn can lead to complications and ill-health (39, 44, 45).

Materials and methods

Study design

This paper is one of the outputs of a qualitative study "Exploring the treatment burden and capacity for self-care amongst people living with HIV/NCD multimorbidity in South Africa to inform the development of interventions to reduce workload and improve capacity" (EXTRA) (46). We used the method of in-depth, qualitative, individual interviews, which allowed an interpretivist narrative approach where participants were encouraged to share their life-stories and personal experiences of living with multimorbidity (47, 48). We used a semi-structured interview guide with open-ended questions adapted from the Burden of Treatment questionnaire (BTQ), BoTT and concepts from the CuCoM to explore individual patient and carer experiences (39, 40, 49). Questions were focused on the structural, spatial, and systemic factors that impact on patients' health care engagement and probed the role of social support networks in patients' self-management and how they coped with treatment burden (45, 50, 51). An extensive description of the methodological considerations is published elsewhere (46).

Setting

This study was conducted in two communities of low socio-economic status in South Africa, Gugulethu and Bulungula. The urban township of Gugulethu is located 15 km from Cape Town, in the Western Cape province. Gugulethu was established under the Group Area Act in 1953 as a segregated residential area for black Africans (52, 53). It is home for more than 100,000, mostly isiXhosa speaking residents who live in formal housing or shacks, as backyard dwellers. Compared to many other townships, Gugulethu is well-serviced, and schools, shops and clinics are easily accessible. Bulungula is a remote rural area in the coastal region in the Eastern Cape, previously part of a "homeland" designated for isiXhosa speaking black Africans under apartheid and ruled by proxy through traditional chiefs (54). It is one of the poorest and most underdeveloped areas in the country, with most people still living in traditional type housing with poor infrastructure, a shortage of basic amenities and few economic opportunities (55, 56). Health status in the Eastern Cape is poor: an estimated 20% of the population has HIV and hypertension prevalence rates are 49.8% (57). Women in the Eastern Cape also have the highest prevalence of diabetes in the country (18%) (57). In comparison, in the Western Cape, the estimated prevalence is 18% for HIV and 51.6% for hypertension (57). In addition, men in the Western Cape have the highest prevalence (13%) of diabetes in the country (57).

Data collection

Data was collected between February and April 2021. Participants were recruited from both and urban and rural South African township, allowing us to examine the differences in people's lived experiences and narratives (58). As experiences also might differ by age and sex, we included both females and males with various ages, socio-economic backgrounds, and education levels, using a purposive sampling method (59). The inclusion criteria were patients older than 18 years, with a confirmed diagnosis of HIV and at least one other chronic non communicable disease who use public health services In Gugulethu, participants were recruited from one community clinic (Gugulethu CHC). Potential participants were approached by a designated fieldworker who explained the study in everyday language and handed out an information sheet. If the person was interested, the fieldworker would collect phone numbers and set up an appointment for the interview (46). In Bulungula, participants and carers came from two villages supported by the Bulungula Incubator (BI), a local non-governmental organisation. Here, participants were approached by community health workers (CHWs) and when expressing interest, the interviews would be arranged. Semi-structured interviews were conducted by two researchers, Nonzuzo Mbokazi (NM) and Myrna van Pinxteren (MvP) in English or isiXhosa, two of the 11 official languages in South Africa. Each interview lasted between 30 and 90 min and was conducted in a COVID-19 compliant space in the clinic (Gugulethu) or in participants' homes (Bulungula) (60). All COVID-19 regulations were observed, including masking and social distancing (61). Questions focused on respondents' understanding of their conditions, experiences of the health services and relationships with their support networks. All interviews were audio-recorded and transcribed and translated by NM and MvP to form the data for analysis.

Data analysis

Informed by the BoTT and CuCoM, we undertook both inductive and deductive qualitative thematic analysis, guided by a framework approach (62–64). Data analysis was a constant interpretative process, consisting of the following steps: familiarisation, development of coding framework, charting, and further mapping and interpretation (65, 66). Included in the familiarisation phase was data management, assigning initial or open codes to each meaning unit in the transcripts to develop an understanding of what the participants are saying, and developing and refining a coding matrix or organisational schema, to then apply across the data set (46). To understand how, and to which extent concepts explored in BoTT and CuCoM were applicable to our context, we outlined the broad categories using the following constructs: (1) control conditions and enacting control, (2) structural factors, (3) patient capacity, (4) quality of life, and (5) impact of COVID-19. These categories derived from the open coding process and helped us organise, summarise, and condense the data. Table 1 outlines the different domains of treatment burden and elaborates on how these domains were experienced by our participants in urban and rural South Africa.

TABLE 1 Domains of treatment burden and the experiences of participants in Gugulethu and Bulungula.

Domains of treatment burden (BoTT and CuCoM)	Experiences of participants
Control conditions and enacting control: Including: sense-making (coherence), Practical help (skill-set workability), material and cognitive practices (interactional workability), enacting delegating work (collective action), monitoring (reflexive monitoring)	Learnings about conditions and treatments, how participants undertake self-care and what is required by participants to control conditions (including medication, clinic appointment and seeking health information)
Structural factors: Including: Exploitable resources (contextual integration), social capital (informational and material resources), opportunity (constraints agency), and control over services (structures agency)	Impact of socio-economic factors on the workload for participants, including the organisation of and access to healthcare facilities, relationships with HCPs, living conditions, geography, and culture
Patient capacity: Including: Building and retaining relational networks (extends agency), agency (general potential), social skill (securing co-operation) and structural resilience (potential to absorb adversity)	Explored participants' social networks, their individual capacity to cope with diagnoses and self-management, including individual agency, resilience, spiritual faith, and strategies to overcoming barriers
Quality of life: Including: expressing capacity, functional performance (potential to do the work)	Unpacked the impact of multiple chronic conditions on participants' physical, emotional, social, and financial wellbeing
Impact of COVID-19: Including: control over services, social capital (informational and material resources), mobilising capacity and opportunity (constraints agency)	Investigated the impact of COVID-19 lockdowns and regulations on participants' access to care and medication, social networks, and available economic resources

Using these broad categories, we then moved on to a deeper description, explanation and interpretation of the data and developed themes and sub-themes. To ensure rigour and trustworthiness of the study findings, we developed full transcripts that were checked by both MvP and NM for quality control. MvP and NM also developed fieldnotes and narrative memos comprised of summaries of data plus their own reflections and emerging interpretations, which were regularly discussed with all authors to further advance analysis (46). Further details on data analysis, reflexivity and positionality can be found in the qualitative methods paper (46).

Ethical aspects

This study strictly followed the guidelines from the Principles of Good Clinical Practice and the Declaration of Helsinki (67). Ethical approval for this study was obtained from the University of Cape Town (HREC 232/2020) and access to clinics was granted by the Western Cape Department of Health. In the Eastern Cape, we received approval from the (BI) to approach participants identified by community health workers (CHWs). Further detail of ethical considerations are published elsewhere (46).

Findings

We conducted a total of 30 semi-structured interviews with participants living with HIV and co-morbidities, 16 in Gugulethu, Western Cape and 14 in Bulungula, Eastern Cape (Tables 2, 3). We interviewed 9 men (2 in Bulungula, 7 in Gugulethu) and 21 women (9 in Gugulethu, 12 in Bulungula). All participants were South African citizens and spoke isiXhosa as their first language. The mean age was 56 years in Gugulethu and 50 years in Bulungula. Only one patient received private health care, 29 attended public health services. The most common co-morbidity was hypertension.

The multiple facets of treatment burden for people living with multimorbidity

Having two or more chronic conditions affected the everyday life of all participants, but the impact varied across field-sites, between illnesses and the severity of conditions. All respondents had to take antiretroviral therapy (ART) daily, preferably after taking food. Depending on the type of ART regimen, commonly reported side effects included stomach cramps, fatigue, and headaches. However, participants who had been on the same ART regimen for more than 5 years reported minimal side-effects. Aside from taking ART, participants also had to monitor and take medications for their other conditions, including pills for hypertension or insulin injections or metformin and some had to monitor their blood sugars to help manage their diabetes. Participants suffering from hypertension complained about fatigue, headaches, having low energy and feelings of anxiety, which impacted their functional performance. Respondents with diabetes felt the most burdened, as self-managing diabetes required dietary and lifestyle changes, including strictly monitoring their sugar intake and required taking food with medication. Respondents previously suffering from TB shared the challenges of taking multiple drug therapy, which had many side-effects.

Monthly clinic visits were scheduled for HIV consultations and blood tests were taken twice a year to monitor viral load. Policies recommend that blood pressure is measured during HIV check-ups, but a few participants commented that this is not always done. On the structure of services, participants commented that apart from hypertension check-ups, HIV care is still largely separated from NCD care and people living with diabetes, epilepsy and other heart conditions had to schedule multiple appointments a month to ensure all their different chronic conditions were being managed appropriately. One participant also attended a separate clinic for her depression check-ups. Respondents had to combine these visits with paid work, housework, farming, and childcare responsibilities. Although the burden for participants with three or more conditions was high, they tried their best to stay adherent, attend clinic appointments and stay positive about their treatment burden.

> "The best I can do is to adhere to the guidance from the nurses and not miss my clinic dates and take my medication duly. I have no stress about my conditions because I have accepted them." PU008 [M56]

TABLE 2 Participants characteristics Gugulethu, Cape Town.

Study ID	Sex	Age	Employment	Time HIV+	Co-morbidity	Carer present	Main type of support
PU001	Female	60	Unemployed	15 years	Diabetes/Asthma/Hypertension, Heart Condition	Yes	Cousin
PU002	Female	62	Unemployed	21 years	Diabetes/HIV	Yes	Son
PU003	Female	53	Retired	14 years	Stroke/Arthritis/ Asthma/ Depression/Hypertension	Yes	Daughter
PU004	Female	48	Unemployed	17 years	HIV/Hypertension/cellulitis	Yes	Friend
PU005	Female	63	Retired	25 years	HIV/Hypertension/TB in Hip	Yes	Partner
PU006	Female	61	Unemployed	18 years	HIV/Arthritis/Hypertension	Yes	Friend
PU007	Female	48	Unemployed	14 years	Hypertension	No	Husband
PU008	Male	56	Unemployed	19 years	Hypertension	Yes	Friend
PU009	Male	46	Employed	24 years	Diabetes/Hypertension/Depression	No	Wife
PU010	Male	57	Unemployed	19 years	Hypertension	Yes	Partner
PU011	Male	47	Self-employed	5 years	Hypertension	Yes	Partner
PU012	Female	57	Self-employed	18 years	Hypertension	No	None
PU013	Female	65	Retired	17 years	Hypertension/Diabetes/ liver failure	Yes	Partner
PU014	Male	72	Retired	7 years	Hypertension	No	None
PU015	Male	59	Unemployed	5 years	Hypertension/Diabetes	No	None
PU016	Male	46	Unemployed	26 years	Hypertension/Stroke	No	Brother and sister

TABLE 3 Participant characteristics Bulungula, Eastern Cape.

Study ID	Sex	Age	Employment	Time HIV+	Co-morbidity	Carer present	Main type of support
PR001	Female	61	Unemployed	9 years	Diabetes	Yes	Daughter
PR002	Female	59	Unemployed	18 years	Epilepsy	Yes	Daughter-in-law
PR003	Female	72	Retired	15 years	Hypertension	No	None
PR004	Female	60	EPWP	6 years	Heart condition	No	Daughter
PR005	Male	41	Farmer	8 years	Heart disease	No	Wife
PR006	Female	42	EPWP	6 years	Hypertension	Yes	Daughter
PR008	Female	40	Unemployed	9 years	Hypertension	No	Mother
PR009	Female	42	Unemployed	6 years	Hypertension	Yes	Sister-in-law
PR010	Female	63	Unemployed	15 years	Hypertension	No	None
PR011	Female	30	Unemployed	7 years	Hypertension	No	Mother
PR012	Female	48	Unemployed	7 years	Hypertension	No	Sister
PR013	Female	50	Unemployed	11 years	Hypertension	No	Sister
PR014	Male	34	Unemployed	6 years	Hypertension/ Stomach condition	Yes	Mother
PR015	Female	63	Unemployed	long time	Hypertension/Cancer	Yes	Daughter

Precariousness of income

A shortage of money, or losing income, influenced patient's capacity to self-manage their conditions. This lack of material resources limited their functional performance, but the extent of the impact varied between urban and rural areas, between younger and older patients and between men and women. Most patients over the age of 60 year relied on the income of an old-age grant, which is a maximum of R1890 per month (~92 GBP per month). Households would pool grant money and additional available income to buy groceries, out-of-pocket medication, pay for transport to the clinic or to cover costs for health emergencies.

> "The component of money is very difficult for me. We only have money at the end of the month [through a child support grant] for a short period of time. So, we take each day as it comes and try to not stress too much. Sometimes if I sell my mealies, I will have some bit of money, but it is not enough." PR05 [M40]

Between the urban and rural field-sites, there was a significant difference in expenditure for clinic visits and health emergencies. In Bulungula, participants mostly walked to the clinic and would spend R10 (0.50 GBP) to cross the river with the ferry. Although time-consuming due to the large distances, costs were manageable when budgeted for, but when a health emergency would arise, rural respondents would have to fork out a minimum of R500 (25 GBP) to hire a private vehicle to get to the hospital, almost one third of their monthly income. To make it through the rest of the month, they would borrow money from family or neighbours to increase their resources or rely on food donations for their daily meals. Being indebted to others weighed heavily on patients and they felt constantly guilty about incurring expenses for treatment and having to ask others for help.

> "I would walk to the road in extreme pain and get into the car which was R500. I do not even want to know the amount of debt my parents are in; I do not know how they will ever repay these debts they have incurred because of me and my illness." PR14 [M34]

Participants in Bulungula who did not receive a disability or old-age grant shared the family's child support grants for children or grandchildren (R460 per month, 23GBP) to cover household expenses. In this way, they were able to mobilise relational networks and increase their social capital. One advantage rural respondents had over urban participants was access to land for subsistence farming. This enabled them to grow their own crops and keep some livestock. However, as crops grow seasonally, participants complained about going hungry in August at the end of a long winter or when affected by drought. Although the land and produce were theirs, one participant shared that she struggled to produce her own crops, as she did not have the money to buy the seeds. Older participants complained that subsistence farming was strenuous on their ageing and ill bodies.

For participants in urban areas, grant support was also an important source of income, but some participants had formal employment or were self-employed. In general, urban areas in South Africa are better serviced and there are more job opportunities, but the demand on limited financial resources also differs, as there is rent to be paid and growing one own's food is more difficult. Several participants lost their income due to deteriorating health or were laid off during the COVID-19 pandemic, which impacted the availability of their economic resources. This was especially challenging for participants aged between 50 and 60 years, as they were too young to apply for an old-age grant and did not qualify for a disability grant, although they felt too old to start a new job. This left them in an extremely precarious position, especially when other family members were unemployed, or had passed away.

> "Since my husband passed away, there is no one who assists me. My youngest child is 20 and still at school. She needs help financially. So, I am alone, and I need financial help." PU012 [F57]

Economic insecurity and a shortage of exploitable resources required participants in both areas to plan their finances carefully and make difficult trade-offs when making spending decisions. The need for school clothes, shoes or unexpected costs for funerals would strain their already tight family budgets, forcing them to make compromises, including delaying care or walking to the clinic instead of taking public transport. Participants also reserved funds for out-of-pocket medication which were not dispensed by the public health services, including ointments for cellulitis or treatment for gout. Sometimes, pain tablets would not last the whole month and had to be substituted with aspirin or borrowed medication from others:

> "Right now, I am out of pills. I have asked my friend for pain pills. Mine ran out last week, I will only get more in April." PU002 [F62].

During the COVID-19 pandemic, urban patients also purchased immune boosters and vitamin C tablets to boost their immune systems, as recommended by government guidelines. These immune boosters were costly and not dispensed at government clinics.

> "I am paying for the boosters, vitamins, and stuff. To boost my body. At the pharmacy, they sell it for more than 30 rand, so I buy one at the time." PU007 [F48]

When experiencing income insecurity, every financial decision had to be carefully weighed, which meant that participants could not always prioritise their own health. Several patients admitted being hungry regularly, skipping meals or having to take ART on an empty stomach, which is not recommended. People with diabetes, who were urged to eat fresh, healthy, and non-fatty foods, struggled to adhere to the recommended diet, as fresh fruit and vegetables were unaffordable or would not be available all year around. A few patients took up extra work or rented out rooms to raise money to buy the recommended food.

> "I am getting an old age grant now. But I cannot say I am okay (financially), so I am selling sheep heads to add more, because I want to eat veggies like broccoli and spinach, the fresh foods." PU005 [F63]

Participants in Bulungula had little opportunity to make additional, cash income. They relied on occasional work through the Expanded Public Works Programme (EPWP) which is unskilled and low paid work, in addition to subsistence farming. This compelled them to ask family members or neighbours for food or money, reciprocating when they were able to. This was accepted as custom and understood as part of Ubuntu – an African centred form of social support which stresses the importance of being connected to one another through kinship and community (68). Respondents spoke of how after a long day travelling to and from the clinic, they could ask neighbours to share their evening meal, how harvested maize and other vegetables were shared amongst households and how members of the community often lent each other money for basic supplies. Some participants spoke about receiving remittances from family members who worked in the city. However, despite the goodwill of others, some families struggled to put food on the table, which impacted their health. One participant was annoyed by healthcare workers' apparent insensitivity to this situation:

> "I need more nutritious food, but we cannot always afford this kind of food. It is tough as I told you. So, the doctors think I am not committed to improving my health but what do I do if

> there is no money? In fact, this whole thing about eating healthy begins to irritate me because they act like they cannot see this rural area, there is nothing. This food they speak off, where are we supposed to get it?" PR014 [M34]

Through the social support structure of Ubuntu, rural participants were able to maintain relational networks, often through kinship ties, and get additional practical help, as they received money or food from neighbours.

In Gugulethu, participants who did not have relational networks to rely on, experienced extreme precariousness when losing employment but being ineligible for a grant. One male respondent, who lived alone struggled to put food on the table, which resulted in severe weight loss.

> "It is very hard, living without any work or a grant. I actually looked much better (before), this is not my face, this a face of hunger." PU015 [M59]

His lack of support structure resulted in a lack of exploitable resources, which impacted his social capital and capacity to self-manage his conditions.

Precarity of home and terrain

Living arrangements between urban and rural areas vary drastically. In rural Eastern Cape, traditional houses, or rondavels, are spread out over large areas of land. In urban Cape Town, people live in crowded settlements which are constantly expanding, due to ongoing urbanisation. Several urban participants lived in temporary, informal houses made of wood and corrugated iron, commonly known as shacks. These dwellings do not have sanitation or running water and people are compelled to share chemical toilets and communal taps with many others. This complicated their capacity to self-manage their conditions and compromised their overall health. Older and less mobile participants said they struggled to fetch water from outside taps or use outside toilets because of the uneven ground, the absence of pavements and poor lighting. One respondent, who had trouble walking due to complications of TB in her hip, commented:

> "I am staying in a hokkie (shack). I was using the wheelchair for some time, but that became too hard for me (moving about in the shack). If only I could get my own house. It is also not safe to stay here." PU005 [F63]

Other participants shared they were stressed as they did not have a permanent home and risked being evicted at any time by landlords from whom they rented temporary accommodation. For them, not having a permanent or formal address made it difficult to register for social services or receive deliveries, for example to get their medication delivered during lockdown. They were also located further from clinics, which increased their travelling times to the clinic, as well as the cost.

Rural participants did not experience such insecurity of tenure, as typically, the land they lived on had been settled by their families for several generations. However, many younger respondents were compelled to move to urban areas to seek education or jobs. One respondent spoke of how, when she was diagnosed with HIV and high blood pressure, she lost her job and had to move from the city to Bulungula to be closer to her family for support. She now lived in her sister's house, who worked in the city and assisted her and her daughter financially. Another participant shared that he was forced to relocate to Bulungula from urban Mthatha when he lost his job in 2015 after being shot. His loss of income meant that the whole family had to relocate to the village, where they did some farming and lived on the child support grant (CSG) from his sister.

> "We had an okay life, but all of that ended when I was shot. So, it has been hard having to adjust to a new way of life, I like my life here, my family is here but I wish we did not struggle. Everything here is very hard." PR14 [M34]

He described how his relocation had a severe impact on the workload involved in managing his HIV and hypertension. He had to walk very far to the nearest clinic, could not afford a varied diet and had to borrow money from neighbours to get transport to go to an urban clinic to get treatment for chronic stomach pains.

All participants in remote Bulungula experienced challenges due to the distance of clinics, lack of transport and unforgiving terrain, which constrained their agency and increased their treatment burden. All except two had to travel a full day to the clinic by foot, which required advance logistical and financial planning. They described how the journey to the clinic involved taking a ferry across the river mouth, walking through thick forest or along a beach and navigating steep hills on difficult paths. To make their appointments, they had to carry cash for the ferry, to buy food along the way or to find a place to spend the night half-way through their journey to make it more manageable.

> "I always try to ensure that I collect wood to sell so I can go to the clinic. Or if I cannot find anyone to sell to, I borrow money, even if I do not know how I am going to return it. I need R100 to go and come back, even if I do not eat, it's fine." PR06 [F46]

Participants in Bulungula also lacked basic amenities, such as running water within the home, and a lack of access to social services. Some patients had cell phones, but reception was limited and recharging difficult due to the lack of electricity. Data and airtime were also costly. Most rural respondents did not have access to mass media through TV or the internet. Consequently, respondents were relatively uninformed about their conditions and relied almost solely on the health information provided by clinic staff and community health workers (CHWs) from the Bulungula Incubator who visited patients at home.

> "The nurses tell us about what we should do and what we should not do, but we do not receive any papers with information to take home. Also, the Community Health Workers come and check on me and see how I am doing and share information with me." PR01[F61]

In addition, in rural areas low educational and literacy levels limited their ability to read pamphlets and posters at the clinics. This was very different in the urban areas, where participants had access to different media and had a higher level of literacy which enabled them to become more informed about their conditions.

Precarity and the threat of violence

A major concern, especially for female respondents, was their fear of being a victim of violence when travelling to the clinic, further impacting access to health services. Several female participants in Gugulethu said they feared being assaulted enroute to the clinic or being robbed of their medication when returning from the pharmacy at the clinic. To get ahead of the queue for the clinic, they had to travel very early in the morning but felt vulnerable when waiting outside the gates before the clinic opened, fearing being robbed by totsi's (thieves). During COVID-19, the situation worsened, as security officers at the clinic would only allow small groups of patients to enter the premises at a time, resulting in large crowds of patients gathering outside on the street with little security.

Participants from Bulungula complained that long distances and the limited available routes to the clinic posed risks for them and described how they tried to avoid travelling alone, as they were afraid of getting injured or assaulted when journeying across mountains or through forests. Sometimes, female respondents would wait for others to head out in the same direction, as they felt vulnerable walking on their own.

> "When you are ready to go home from the clinic, you need to look for someone who you can walk with. But if they take too long, you will just take the chance and go into the forest alone. That is a huge risk that all patients are faced with." PR012 [F48]

Not only did violence impact patients' access to health services, but gender-based violence (GBV) and substance abuse were mentioned in households in both settings. This wrecked participants' lives and fractured their relational networks. Tik (crystal methamphetamine) and alcohol addiction in families led to financial difficulties, intimate partner violence, mistrust, and stress. Some participants described how they felt unsafe living with abusive partners or family members, were afraid to leave their belongings when leaving the house and were not able to rely on their family members for help when experiencing a health emergency. One female was convinced that hearing that her son, only a teenager at the time, was on drugs, gave her a stroke.

> "It happened because my son, he was using drugs. I was so stressed. After that, I had a stroke." PU002 [F62]

Even though the patient recovered physically from the stroke, she still battled with anxiety and depression and was isolated from her social support system as she was afraid to leave the house, relying solely on care from her daughter. Similarly, when speaking about family relationships, another female respondent mentioned that her son, her main carer, overdosed and died at the age of 30. She mourned his death but was also relieved.

> "My son used to help me, but he was a drug user. Tik. It was terrible. When he was high, he would go crazy. He was being aggressive, hissing at you, biting you. He would steal my things, but then the next day he is helping me. But since he died, nobody is stealing my things now." PU005 [F63]

In the Eastern Cape, two female participants revealed that alcohol abuse by partners had negatively affected their marriages and financial circumstances. A large part of their income would be spent on beer and whiskey and when intoxicated, their partners would pick fights, physically and verbally abuse them, or leave the house for several days. One respondent cried when speaking about her marriage, as her husband fled home after stabbing his brother during a drunken brawl. She was mourning her brother-in-law's death, whilst trying to provide for her family on her own and keep her children in school. She was very distressed and worried about her future, but was grateful for the support of her sister-in-law, who made sure she kept adherent to her HIV and hypertension medication.

In Cape Town, three male respondents spoke about their own history with alcohol and drug use, which made them irresponsible and, in some cases, led to HIV infection. Two of them stopped drinking all together, as it interfered with their medication regimes and overall health. Beating their bad habits, these men now supported others to embrace a healthy lifestyle, increasing their capacity.

> "I had a neighbour; he was an alcoholic. He got this HIV while he was drunk. I changed that guy, he is right now. He quit alcohol, he is taking the ARVs now, so I made a difference in someone else's life." PU016[M46]

As recovered alcoholics, these participants gained a new sense of belonging through supporting others and in doing so, building new relational networks.

Precarity and insufficient health service support

Participants' capacity to manage the workload to live with HIV and other chronic conditions was affected by the type and level of support they received from their own relational networks and the structures provided by the state. Five urban participants complained that it was difficult to rely on the health services because of frequent stock outs of medication, which interrupted their self-management routines. The unavailability of monitoring tools was also reported, including blood pressure monitors and glucometers, and pillboxes to organise medication, which compromised their ability to control their conditions. Participants had to either buy their own supplies out of pocket or had to travel to the clinic to measure their blood pressure or glucose levels, which is time consuming and expensive. A patient with diabetes, who also had a partner with diabetes, said:

> "It would be very helpful to have a glucose meter at home, because we will be able to see, and read what our sugar levels are." PU013 [F65]

Information on their conditions was also not readily provided by the state health services. Participants felt that HIV information was more easily available, as they received counselling after their HIV diagnosis. However, health education and counselling after diagnosis of other chronic conditions, was scarce.

> "I receive a lot of pamphlets and information about HIV, but I do not have much about my other condition (mental health). I would like to know more about how to manage my other conditions." PU002 [F62]

Participants in rural Bulungula relied mostly on the health knowledge shared by the CHWs, who would inform them during home visits. The "nomakhayas" (CHWs in Isixhosa) visit patients at their homes to provide emotional support, share health information and remind them about their appointments. During the COVID-19 pandemic, they distributed masks and hand sanitizers and later coordinated the vaccination campaign. With health services far away and a lack of state support, the HCWs from the BI are a part of rural participants relational networks, as they assist with sense-making and self-monitoring their conditions. Participants greatly appreciated them:

> "I can talk to my nomakhaya. I tell her about the challenges I am facing, and she helps me make decisions and gives me advice. She also follows up to check I am not defaulting on treatment and keeping to all my clinic appointments." P06 [F42]

Compared to the continuous support offered by the CHWs in Bulungula, respondents in urban areas only occasionally spoke to a counsellor or social worker. Previously, HIV adherence clubs and peer-to-peer support groups, organised by local NGOs, were a part of urban participants' support networks, but these were discontinued during the COVID-19 pandemic. Few participants had personal relationships with health staff, partly due to short consultation times and high staff turnover. In contrast to the rural respondents, many of the urban patients expressed frustration with the staff at the clinic:

> "Every day they change things, they do not have the courtesy to tell you about what that change means, and when you ask – they shout at you sit here, go there and two hours passes, and you have not been helped and that is frustrating." PU014 [M72]

Although some participants expressed their discontent with staff attitudes, most frustration was caused by organisational mismanagement at the urban clinic, including a stock-out of medication, understaffing and high staff turnover, which made it difficult for patients to build relationships with health staff. Lost folders were another annoyance:

> "The clinic itself is fine, but the administration is horrible, they once lost my file for two months. I went without treatment for two months because they lost my folder." PU010 [M57]

For urban patients, the longstanding organisational issues in clinics were exacerbated during the COVID-19 pandemic, as clinics closed during the various lockdowns and patients did not always have access to their treatment, as medication was not delivered to everyone in need. This adversely affected patients' control over the health services and the capacity to adequately manage their multiple conditions, sometimes leading to serious health consequences and non-adherence to treatment.

Discussion

These findings illustrate the accumulative impact that precariousness has on the lives and treatment burden of people living with multimorbidity in urban and rural low-income settings in South Africa. Our analysis identified various dimensions of precariousness which negatively impacted on patients' capacity to self-manage multiple chronic conditions: these included economic insecurity, the threat of violence; difficult geographical terrain; insecure housing; and insufficient health service support.

Our findings echo results from other studies examining the impact of precariousness on patients in LMICs. These studies have similarly reported that limited financial resources, lack of insurance and financial instability are major barriers to self-management (69). Participants in other rural low-income settings have also reported experiencing a lack of health care providers and having to travel long distances to the clinic, commuting over rough terrain with poor road infrastructure whilst being at risk of violence (1, 69, 70).

This paper further illustrates that patient capacity to self-manage multimorbidity is complicated by the challenging biosocial complex in which people find themselves, as their health conditions have to be managed under conditions of health inequalities that are caused and sustained by a broad set of political, economic and social factors (28, 71). One patient summed this up by saying: "*the problem is not the treatment at the clinic, or staff, but the fact that the social conditions in the townships are bad. There is pollution, bad housing and hunger [PU009].*" Here, he highlights the structural inequalities experienced by South African patients, which even 25 years post-apartheid, are still prominent. Multiple chronic illnesses impacted every aspect of peoples' lives, as they constantly needed to consider the financial cost of care-seeking, the social cost of caring for family members and the emotional costs of negotiating with health providers and support networks (22, 72, 73).

Living in constant precariousness made it nearly impossible for patients to be structurally resilient – as the loss of a job, closure or relocation of the clinic, or death of a family member could push them "over the edge," as there is no financial buffer that can sustain them in times of need (74). Although most participants relied on state support through social grants, these barely covered basic food supplies, and often had to be shared within households. Especially in urban areas, this left participants between 50 and 60 years of age in extremely precarious positions, as they were considered "too healthy" to be on a disability grant and "too young" to qualify for an old-age grant. Disability grants are only paid to chronically ill patients who are unstable and sick; once they are on treatment and stable, they lose their grant, as they are considered "fit to work." Many participants considered this grant a "lifeline" and experienced stress and anxiety when it was withdrawn. Rural participants often relied on financial handouts from family, friends, and neighbours. This support was offered during health crises, but long-term, sustained financial help was rarely available, especially when participants were not able to reciprocate or pay back their debt.

Precariousness can be accumulative and cyclical in nature, as financial instability can lead to problems accessing health services, securing food and safe housing, and magnify tensions in relationships. This accumulation of precarity was amplified during the COVID-19 pandemic with its strictly imposed lockdowns when people experienced increased levels of economic uncertainty, disruption of health services; increased crime and intensified tension in relationships (75). Manderson and Warren (70) describe the cyclical nature of precariousness as "recursive cascades," encapsulating the impact that growing impoverishment has on increasing ill-health. Describing a three-tiered system, the recursive cascade explains how social and relational factors plus economic and practical resources worsen chronic conditions (70).

Whilst BoTT does include the need to mobilise material resources to navigate treatment burden (*exploitable resources*) and acknowledges how the lack of both informational and material resources (*social capital*) can put patients self-management and support structures under threat, findings in this paper describe that cyclical precariousness influences every aspect of patients' lives and ability to self-manage their health. Cyclical precariousness, in this LMIC context, is not just the inability to exploit opportunities to access health care resources but sums up the difficulties of managing long-term conditions when experiencing constant financial insecurities, which impact on patients' basic needs such as shelter, safety, food security and social support. Furthermore, the current BoTT does not sufficiently emphasise the impact that a lack of financial resources has on patients' ability to mobilise social support which in turn, diminishes social capital and self-management capacity. We would therefore suggest that the BoTT, which was developed in a high-income setting, needs to be adapted to include "cyclical precariousness" to make it a more applicable and useful theoretical model for use in LMIC contexts. Our findings suggest that cyclical precariousness negatively impacts patients' capacity to self-manage their conditions and in turn, increases their treatment burden, resulting in negative health outcomes (see Figure 1).

Although the precise terms are not used, the phenomena of cyclical precariousness and recursive cascades are also clearly reported in other treatment burden studies in LMICs, including amongst patients with chronic conditions in Ghana, Argentina and Malawi. These patients reported that due to financial constraints, patients struggled to cope with their treatment burden and keep up with the systems demands, due to a lack availability of health services (8, 42, 43). It is also important to recognise that chronic patients from vulnerable backgrounds are often compelled to prioritise their economic survival over controlling their health conditions (69). Underprivileged groups in HICs may similarly experience the impact of financial instability: For example, undocumented migrants in the US, who often rely solely on emergency care, are cut off from relational networks and have no access to government support (76, 77). After the financial crisis in 2008, many European countries cut welfare support, pushing vulnerable groups into precariousness, leading to homelessness, reliance on foodbanks and poorer health outcomes (1, 78, 79).

Cyclical precariousness also resulted in challenges for patients when navigating care in a siloed, disease focused, and overburdened health system, which perpetuates structural vulnerabilities, increases out-of-pocket costs and forces patients to be more reliant on their support networks (12, 80). As South Africa is attempting to move towards a patient-centred integrated care system, it is essential to consider the impact of precariousness on patients' capacity to self-manage chronic illnesses. As it stands, the ICDM model expects patients to take on more responsibility to self-manage their conditions, but does not consider the additional financial and social costs involved nor the increasing self-care demands of coping with multimorbidity compared to a single disease (36). In our study, it was clear that rural participants relied heavily on the support and guidance of HCWs. This increased their self-management capacity even when living in precarious conditions, as the CHWs informed them about their conditions, assisted with their treatment and offered emotional support. This suggests that CHWs could play an invaluable role in reengineering the primary healthcare system to improve chronic care

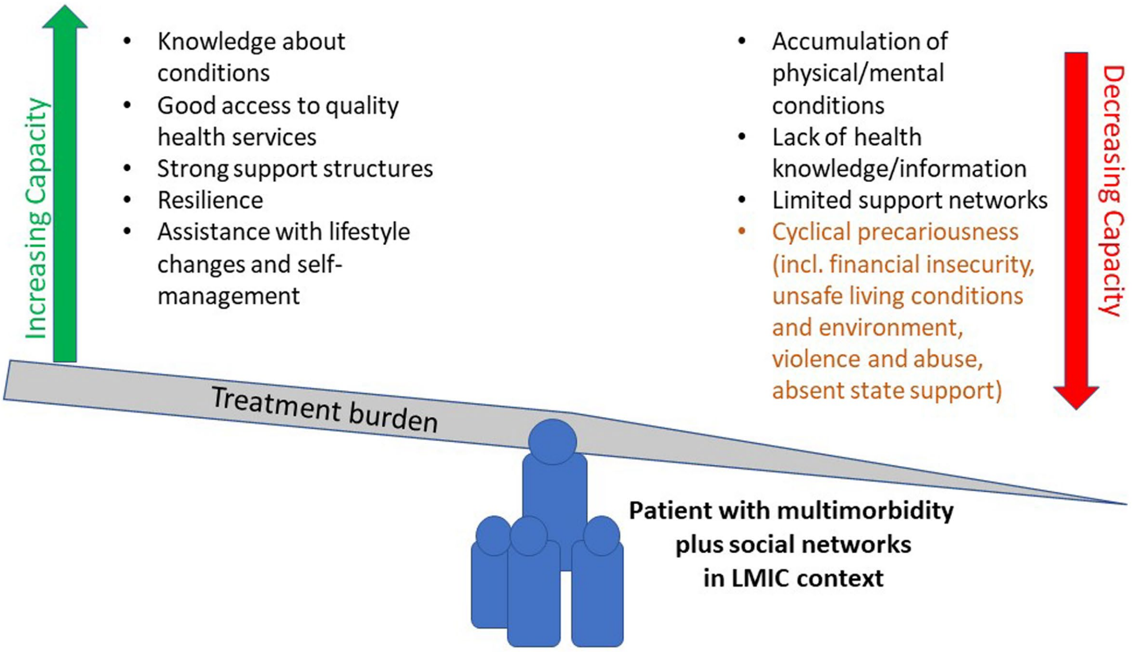

FIGURE 1
BoTT with the integration of cyclical precariousness.

particularly in the context of a growing population living with multimorbidity in these settings. Lastly, when informing patients about treatment for multimorbidity, communication channels and language should be carefully considered, as this study showed that literacy levels and access to media varied considerably between urban and rural participants.

Strengths and limitations

Our study has some limitations. Firstly, we intended to recruit an equal sample of men and women in the urban and rural areas, but only succeeded in including 2 men in the rural sample. This was due to the migration of men to urban areas for work, and their reduced engagement in HIV/NCD care compared to women (81, 82). Secondly, we only recruited two participants with self-reported depression, as mental illnesses are underreported in this context, and therefore our work cannot provide insights into additional issues experienced by people with mixed mental-and physical multimorbidity (83). Thirdly, all respondents lived with HIV/NCD multimorbidity, which means that we did not gain insights about the experience of patients with multimorbidity that did not include HIV as one of the combination of conditions, so additional work with patients with other patterns of multimorbidity would be worth exploring in future research. A key strength is the comparative nature of the study, as urban and rural interviews revealed a great variation within a common experience, which demonstrates its potential transferability or relevance to a wider or alternative setting. Participants accounts of living with multimorbidity differed, based on their culture, background, and social meanings. A further strength is the prolonged engagement within the study sites, as we regularly visited the clinic in Gugulethu and stayed in the local community of Bulungula for 2 weeks. Therefore, the data collected provided rich insights on peoples' treatment burden and we were able to reach data saturation in both settings as previously reported (46). The use of well-established theories of treatment burden to frame the research and analysis, enhances the potential for replication of this study in other settings (84).

Conclusion

Whilst we recognise that this is a small study and therefore findings cannot be generalised for the population, we believe that this study contributes meaningfully to the small body of literature that explores and advances our understanding of the personal, lived experiences of people with multimorbidity in low-income Sub-Saharan settings. Our work demonstrates that the CuCoM and the BoTT are viable theoretical underpinnings to investigate treatment burden in low-income settings. However, our findings also emphasise the impact of cyclical precariousness on patient workload and capacity, and we suggest that this aspect should be incorporated as an additional dimension to the BoTT. This could make the framework and future treatment burden measures more appropriate for use in South Africa. Our work also showed that support structures, especially in rural settings, positively impacted patients' self-management capacity, even when living in precariousness. To respond to the increased multimorbidity health needs in low-income settings in South Africa, the results point to the need to introduce a basic income grant that improves the standard of living, which can enhance self-management capacity and health outcomes. Actively including family and community support networks in self-management interventions can further increase capacity. To achieve person-centred care, support must be tailored to address the varying capacity of people to self-manage their multiple chronic illnesses.

Data availability statement

The data set used and analysed during this study is available from the corresponding author on reasonable request. Please contact Dr van Pinxteren, Myrna.vanpinxteren@uct.ac.za.

Ethics statement

The studies involving human participants were reviewed and approved by University of Cape Town Human Research Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

Author contributions

MP data collection and analysis, conceptualisation and write up of the paper. NM data collection and analysis, extensive intellectual input in the paper. KM conceptualisation of research project, extensive editing of the paper. FM conceptualisation of research project, extensive intellectual input, and editing. CM conceptualisation of research project, extensive intellectual input, and editing. NL conceptualisation of research project, extensive intellectual input, and editing. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Stefan Essig,
University of Lucerne, Switzerland

REVIEWED BY
Maddalena Illario,
University of Naples Federico II, Italy
Suman Kundu,
Vanderbilt University Medical Center,
United States
Zhongming Chen,
Weifang Medical University, China

*CORRESPONDENCE
Jinghui Zhu
✉ zhujh@wmu.edu.cn
Shichen Cui
✉ cuishichen@126.com

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Effects of multimorbidity coexistence on the risk of mortality in the older adult population in China

Zhili Su, Li Huang, Jinghui Zhu* and Shichen Cui*

School of Public Health and Management, Wenzhou Medical University, Wenzhou, China

Background: Multimorbidity coexistence is a serious public health issue affecting a significant number of older adults worldwide. However, associations between multimorbidity and mortality are rarely studied in China. We assessed the effects of multimorbidity coexistence on mortality among a nationwide sample of older adults from China.

Objective: We analyzed 10-year (2008–2018) longitudinal data of 12,337 individuals who took part in China, a nationwide survey of people aged 65 years and above. We used the Cox proportional hazard model to determine the effects of multimorbidity on the all-cause mortality risk. We also examined mortality risk between sex and age obtained through differential analysis.

Results: At baseline, 30.2, 29.9, and 39.9% of participants had 0, 1, and 2 or more diseases, respectively. The cumulative follow-up of this study was 27,428 person-years (median follow-up = 2.7 years; range, 0.01–11.3 years), with 8297 deaths. The HRs (95% CIs) for all-cause mortality in participants with 1, and 2 or more conditions compared with those with none were 1.04 (0.98, 1.10) and 1.12 (1.06, 1.18), respectively. The heterogeneity analysis indicated that, the mortality risk for 80–94 years and 95–104 years group with multimorbidity coexistence is 1.12 (1.05–1.21) and 1.11 (1.01–1.23), respectively, but the mortality risk for 65–79 years group with multimorbidity coexistence was not statistically significant. The heterogeneity analysis indicated that, the mortality risk for men and women in older adults with multimorbidity coexistence is 1.15 (1.06, 1.25) and 1.08 (1.01, 1.17), respectively.

Conclusion: Multimorbidity coexistence is associated with an increase in an increased risk of death in older individuals, with the effect being relatively significant in those aged 80–94 years.

KEYWORDS

elderly, multimorbidity coexistence, mortality, risk, cohort study

1. Introduction

According to the report in 2009, there were 113.09 million people aged 65 and above in China, accounting for 8.5% of the total population. By 2020, there will be 190.64 million people aged 65 and over in China, accounting for 13.5% of the total population (1). It means that the aging society is growing rapidly. The phenomenon of aging has led to a significant increase in chronic diseases, which in turn has led to an increase in the incidence of multimorbidity. Multimorbidity coexistence is the presence of two or more adverse health conditions or diseases occurring together in an individual (2–4). Multimorbidity is now a major public health problem worldwide, and its coexistence leads to high mortality rates, reduced physical functioning, disability, and poor quality of life, adding to the heavy burden on healthcare systems (5–9). A study found that 75% of individuals aged 65–74 years had multimorbidity, with the proportion increasing to 80% in those aged 75 years and older (10). Although multimorbidity coexistence has been recognized, it has still not been adequately studied. Most previous studies were cross-sectional and showed a correlation between multimorbidity and functional status; however, most studies had relatively small samples (11).

Therefore, this study systematically explores the impact of multimorbidity on mortality risk in older people through a prospective cohort study, filling a data gap in this area of multimorbidity and providing a scientific basis for developing prevention and control strategies for healthy aging management.

2. Data and methods

2.1. Data and sampling

This study used the dataset from the 2008–2018 Chinese Longitudinal Healthy Longevity Survey (CLHLS).

The CLHLS is a longitudinal survey of a nationally representative sample of Chinese people aged 65 and older with accurate quality (12).

The survey covered 23 provinces in China and collected extensive data on a large population of the oldest old individuals aged 80–112 and comparatively younger elderly individuals aged 65–79 to serve the needs of scientific research on the elderly people.

The 2008 survey was used as the baseline survey for this study, which included four periods of longitudinal data from 2008, 2011, 2014, and 2018. Exclusion criteria were as follows: first, 924 respondents who were younger than 65 and older than 104 years old at the baseline survey (2008) were excluded (13). Second, 2,554 respondents who were lost at the first follow-up and died before the 2008 survey time point were excluded. Finally, 1,139 respondents with missing data or outliers were excluded. The final sample of this study comprised 12,337 respondents with valid information. The flow chart is shown in Figure 1.

2.2. Multimorbidity assessment

In this study, elderly people with two or more diseases were classified as multimorbidity coexistence according to the method commonly used in previous studies (2–4). The diseases in this study are based on the CLHLS 2008 disease survey, in which respondents answered 19 chronic diseases collected from self-reported: hypertension, diabetes, heart disease, stroke and cerebrovascular, gastrointestinal ulcers, Parkinson's disease, bedsores, arthritis, dementia, epilepsy, cholecystitis, dyslipidemia, chronic nephritis, hepatitis, asthma, tuberculosis, glaucoma, cataracts, and cancer. We categorized study participants according to multimorbidity number at baseline as having either no disease group, single disease group, or multimorbidity (two or more diseases) group.

2.3. Outcome assessment

The main outcome of this study was all-cause mortality. Mortality risk was assessed using survival status and survival time calculated from months lived from the baseline (2008) to 2018. Survival is from the start of the survey in 2008 until their death or the time of the last follow-up visit. Lost visits were those in which the person or the elderly person's family could not be contacted or dropped out. The main outcome was all-cause mortality occurring during the follow-up survey in 2008–2018, with followed up every 3 years.

2.4. Covariates

Although the focus of this article was on the effects of multimorbidity coexistence on mortality, it was important to control for other factors so that the results would be reliable. Demographic, lifestyle, and physiological health characteristics were obtained, including age, sex, urban/rural residence, mode of residence, years of education, financial status, marital status, smoking, drinking, physical exercise, the ability to daily living (ADL), cognitive health, sleep status, and body mass index.

Age was divided into three groups: 65–79, 80–90, and 95–104 years. Mode of residence was dichotomized as living with family and others. Marital status is "married living with a spouse," while divorced, married not living with a spouse, widowed, and unmarried are classified as "other." The economic situation according to the question "your life is compared locally, belong to" was divided into "well-off," "average," and "poor." Current smoking, current alcohol drinking, and regular physical exercise were dichotomized as yes vs. no. Difficulty with ADLs is commonly used to gauge older people's daily performance in six basic activities: bathing, dressing, eating, using the toilet, free movement, and urine and defecation control. For ADL, a binary variable was constructed, with 1 representing having difficulty with any of the six ADLs and 0 representing having no difficulty with any of the six ADLs. Sleep duration was classified as <6 h, 6–10, and more than 10 h. BMI, defined as the weight (kg) in kilograms divided by the height (m) squared, were categorized as underweight (< 18.5), normal weight (18.5–23.9), and overweight or obese (≥ 24).

2.5. Statistical analysis

SPSS 27.0 software was used for data processing and statistical analysis in this study. Pearson's chi-square test was used for difference analysis between the groups. Kaplan–Meier survival curves demonstrate the risk of death for older people with different disease states, and log-rank tests are used to test for differences between groups. Cox proportional hazard regression was conducted longitudinally to investigate the relationship between multimorbidity and mortality risk. In addition, the relationship between multimorbidity and

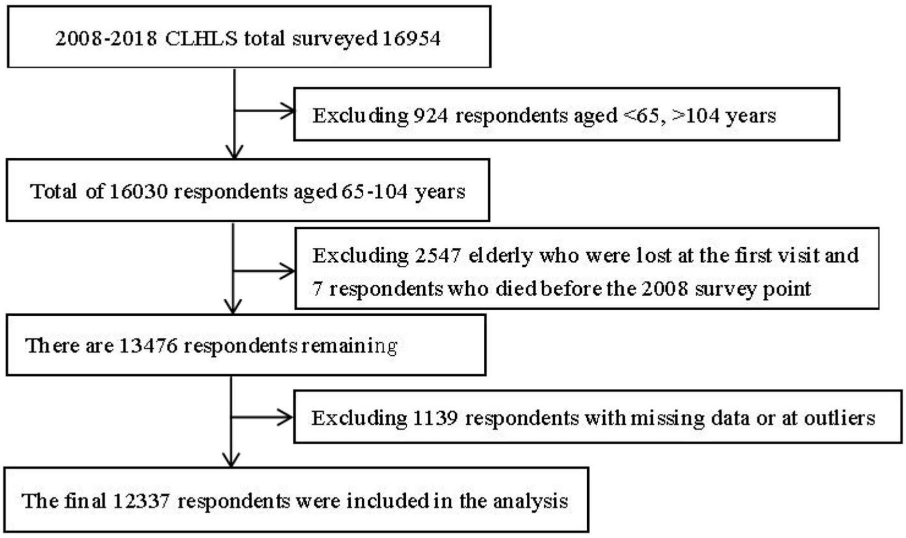

FIGURE 1
Flow chart for the inclusion of respondents.

mortality was explored based on stratifying age and sex. The hazard ratios (HRs) for all-cause mortality with 95% confidence intervals were expressed for the results. All statistical analyses were performed using a two-sided test with a test statistic of $a = 0.05$.

3. Results

3.1. Descriptive statistics

This study comprised a total of 12,337 participants at baseline. At the time of the survey, the M (P25, P75) was 87 (77, 94) years; 55.3% were female subjects, 61.7% were uneducated, and 63.3% lived in rural areas. Of these, 3,732 (30.2%), 3,686 (29.9%), and 4,919 (39.9%) were categorized as having no, single disease, and multimorbidity (two or more diseases), respectively. More than half of the participants with death were 80–94 years and female, rural, uneducated, ADL normal, and had multimorbidity (two or more diseases). The baseline characteristics of the survey respondents are shown in Table 1. There were statistical differences ($p < 0.05$) in age, residence, education, marital status, smoking, drinking, physical exercise, BMI, sleep duration, financial status, and ADL when comparing the deceased and surviving groups.

3.2. Mortality

During the 10-year follow-up, out of the 12,337 participants gathered at baseline, 8,297 (67.3%) were reported deceased. The study had a cumulative follow-up of 27,428 person-years (median follow-up of 2.7 years), a cumulative mortality rate of 67.3%, and a mortality density of 302.5 deaths per 1,000 person-years. As shown in Table 2.

3.3. Analysis of cox regression models of multimorbidity coexistence and mortality risk

Table 3 shows the HR of all-cause mortality according to multimorbidity. Regarding multimorbidity, those with no disease served as the reference group. Increased risk of mortality was significantly associated with multimorbidity. In Model 3, the HR was 1.04 (95% CI, 0.98–1.10) for one chronic disease and 1.12 (95% CI, 1.06–1.18) for multimorbidity.

The Kaplan–Meier survival curve (Figure 2) results showed that survival time M (P25, P75) was 2.7 (2.6, 2.7). Older people with multimorbidity had a higher mortality rate than those without disease, with a log-rank chi-square value of 69.4, $p < 0.001$, indicating a statistically significant difference.

3.4. Stratified analysis of the association between multimorbidity coexistence and mortality risk

Next, we examined the stratified analysis of age and gender on all-cause mortality. As shown in Table 4, concerning gender, we observed a positive association between gender and mortality in the fully adjusted model, with the HR for the risk of death from multimorbidity being 1.15 (95% CI, 1.06–1.25) for men and 1.08 (95% CI, 1.01–1.17) for women ($p < 0.05$) compared to the no disease group. For age, the HR for the risk of death due to multimorbidity was 1.12 (95% CI, 1.05–1.21) for 80–94 years old compared to the no disease group; the HR for the risk of death due to multimorbidity was 1.11 (95% CI, 1.01–1.23) for 95–104 years old ($p < 0.05$), but no differences in multimorbidity and mortality were observed by 65–79 years.

TABLE 1 Comparison of baseline characteristics of study participants by follow-up outcome, 2008–2018 (%).

Variables	Total (12,337)	Death (8297)	Survival (4040)	χ^2	*P*-value
Age (years)				3121.3	<0.001
65–79	3,632 (29.4%)	1,160 (14.0%)	2,472 (61.2%)		
80–94	5,765 (46.7%)	4,429 (53.4%)	1,336 (33.1%)		
95–104	2,940 (23.8%)	2,708 (32.6%)	2,32 (5.7%)		
Gender				3.06	0.08
Male	5,520 (44.7%)	3,667 (44.2%)	1,853 (45.9%)		
Female	6,817 (55.3%)	4,630 (55.8%)	2,187 (54.1%)		
Residence				56.5	<0.001
Urban	4,523 (36.7%)	2,853 (34.4%)	1,670 (41.3%)		
Rural	7,814 (63.3%)	5,444 (65.6%)	2,370 (58.7%)		
Living style				0.1	0.932
Living with family	10,182 (82.5%)	6,846 (82.5%)	3,336 (82.6%) 704		
Other	2,155 (17.5%)	1,451 (17.5%)	(17.4%)		
years of education				393.5	<0.001
≥1	4,728 (38.3%)	2,677 (32.3%)	2,051 (50.8%)		
0	7,609 (61.7%)	5,620 (67.7%)	1,989 (49.2%)		
Marital status				1130.7	<0.001
living with spouse	4,094 (33.2%)	1,928 (23.2%)	2,166 (52.9%)		
Other	8,243 (66.8%)	6,369 (76.8%)	1,874 (46.4%)		
Smoking				30.5	<0.001
No	1,0021 (81.2%)	6,852 (82.6%)	3,169 (78.4%)		
Yes	2,316 (18.8%)	1,445 (17.4%)	871 (21.6%)		
Drinking				19.8	<0.001
No	10,068 (81.6%)	6,861 (82.7%)	3,207 (79.4%)		
Yes	2,269 (18.4%)	1,436 (17.3%)	833 (20.6%)		
Exercise				277.6	<0.001
No	8,778 (71.2%)	6,297 (75.9%)	2,481 (61.4%)		
Yes	3,559 (28.8%)	2,000 (24.1%)	1,559 (38.6%)		
BMI (kg/m^2)				396.3	<0.001
18.5-23.9	6,354 (51.5%)	4,201 (50.6%)	2,153 (53.3%)		
< 18.5	3,984 (32.3%)	3,065 (36.9%)	919 (22.7%)		
≥24	1,999 (16.2%)	1,031 (12.4%)	968 (24.0%)		
Sleep status (hours)				211.3	<0.001
6-10	9,631 (78.1%)	6,273 (75.6%)	3,358 (83.1%)		
< 6	1,496 (12.1%)	985 (11.9%)	511 (12.6%)		
> 10	1,210 (9.8%)	1,039 (12.5%)	171 (4.2%)		
Economic status				22.1	<0.001
Wealthy	1,654 (13.4%)	1,072 (12.9%)	582 (14.4%)		
Average	8,455 (68.5%)	5,637 (67.9%)	2,818 (69.8%)		
Poor	2,228 (18.1%)	1,588 (19.1%)	640 (15.8%)		

(Continued)

TABLE 1 (Continued)

Variables	Total (12,337)	Death (8297)	Survival (4040)	χ^2	*P*-value
ADL				300.5	<0.001
Normal	9,067 (73.5%)	5,699 (68.7%)	3,368 (83.4%)		
Disorders	3,270 (26.5%)	2,598 (31.3%)	672 (16.6%)		
Morbidity				123.5	<0.001
No disease (0)	3,732 (30.2%)	2,283 (27.5%)	1,449 (35.9%)		
Single disease (1)	3,686 (29.9%)	2,451 (29.5%)	1,235 (30.6%)		
Multimorbidity (≥2)	4,919 (39.9%)	3,563 (42.9%)	1,356 (33.6%)		

TABLE 2 Deaths during the follow-up of survey respondents.

Grouping	Total number of people/occurrences	The cumulative follow-up person years	Cumulative mortality rate (%)	Death density/1000 person-years
Total	12,337/8297	2,7428	67.3	302.5
Gender				
Male	5,520/3667	12,531	66.4	292.6
Female	6,817/4,630	14,897	67.9	310.8
Age (years)				
65–79	3,632/1,160	5,478	31.9	211.8
80–94	5,765/4,429	15,579	76.8	284.3
95–104	2,940/2,708	6,371	92.1	425.1
Morbidity				
No disease	3,732/2,283	8,239	61.2	277.1
Single disease	3,686/2,451	8,356	66.5	293.3
Multimorbidity	4,919/3,563	1,0832	72.4	328.9

4. Discussion

This study showed the findings of the survival analyses examining the effect of multimorbidity coexistence on all-cause mortality among older people of the CLHLS cohort over a 10-year follow-up period. Multimorbidity is defined by the presence of two or more long-term conditions, which are those that cannot currently be cured but can be controlled through medications or other treatments. Multimorbidity increases with age, and the majority of people with multimorbidity are older people (14). Multimorbidity coexistence is a relatively common phenomenon for older people. In this study, a total of 19 chronic diseases were investigated in the elderly people over 65 years of age, and the prevalence of multimorbidity was found to be 39.9%, which is higher than the national prevalence of 28.06% and is based on five common chronic diseases (hypertension, diabetes, chronic obstructive pulmonary disease, asthma, and tumors) (15).

This study found that individuals with multimorbidity are at an increased risk of all-cause mortality compared with those with no disease and a single disease. Multimorbidity is an independent factor that increases the risk of death, and it can also be a strong predictor of mortality. These results were significant even after having controlled for demographic characteristics, lifestyle, and physiological health, a finding that is consistent with other studies (16–18). The mortality risk increased for two or more chronic diseases at 1.12 compared to the no chronic disease groups. Basu's study showed that the higher the number of chronic diseases, the higher the degree of disability (19). Other studies have also shown that multimorbidity coexistence will lead to increased dementia, and frailty in the elderly people, affecting the overall physical function and quality of life, even produce significant financial burden on healthcare systems (20–22).

In addition, this study further explored the relationship between multimorbidity and mortality risk in older people by gender and age group. The results showed that the risk of death from multimorbidity coexistence was high in both male and female older adults and that this risk of death was more pronounced in male older adults. The discrepancy can be attributed to the high burden of unhealthy lifestyle factors in male subjects compared with female subjects, like most male subjects who smoke and drink alcohol, which in turn leads to a higher risk of death (23). This is consistent with the results of the analysis of chronic diseases based on Chinese death surveillance data from 2004 to 2018; the results show that at present and

TABLE 3 Cox proportional risk regression model for factors influencing death in older people.

Morbidity	Model 1		Model 2		Model 3	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
No disease	1.00		1.00		1.00	
Single disease	1.07 (1.01–1.13)	0.02	1.03 (0.98–1.10)	0.21	1.04 (0.98–1.10)	0.19
Multimorbidity	1.19 (1.13–1.26)	<0.001	1.10 (1.05–1.17)	<0.001	1.12 (1.06–1.18)	<0.001

HR, hazard ratio; 95% CI, 95% confidence interval. Model 1: corrected for sex, age, place of residence, and mode of residence; Model 2: further adjusted for education, marriage, smoking, alcohol consumption, exercise, economics, and ADL; Model 3: further adjusted for sleep, and BMI.

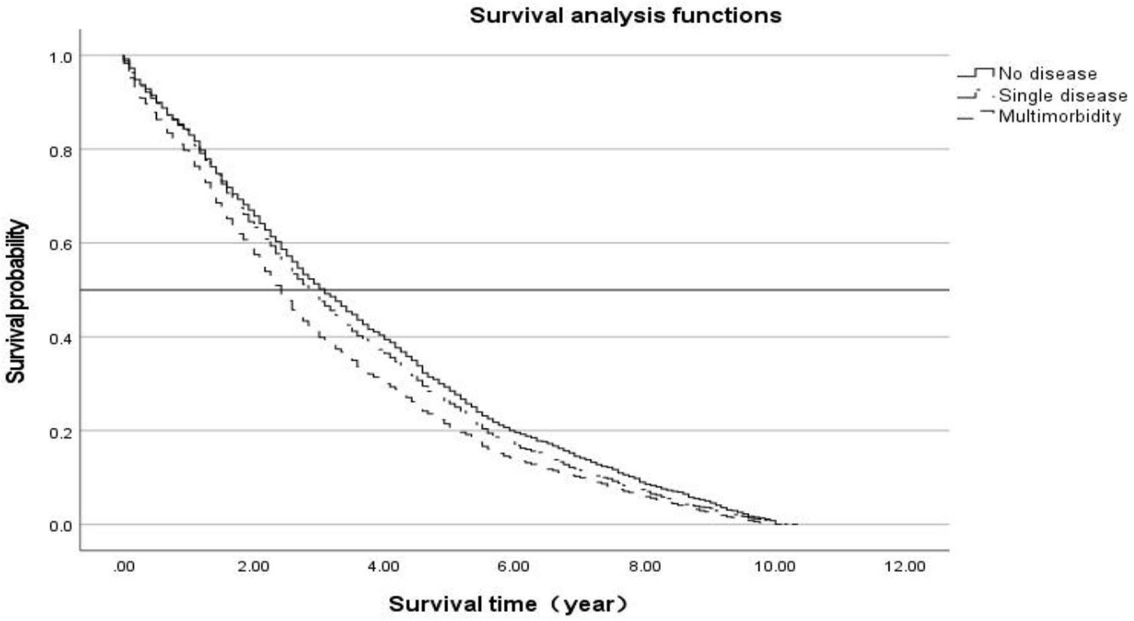

FIGURE 2
Kaplan–Meier survival curve.

in future, the male age-standardized mortality rate is higher than that in female subjects (24). The age analysis found no differences in multimorbidity and mortality observed by 65–79 years old, compared to the no disease or single disease. The risk of death due to multimorbidity for 80–94 years old and 95–104 years old is statistically significant, with a significant risk of death among 80–94 years old compared to 95–104 years old. Similar to previous studies (25, 26), these findings showed that multimorbidity was more likely to occur among those of older age than those of younger age. This may be because the elderly people are gradually aging with the increase of age, with reduced immunity, and degenerative changes were observed in each system organ, resulting in the increased risk of suffering from multiple chronic diseases.

In summary, the accelerated effect of multimorbidity on elderly people's health, and the gender and age difference of the effect should cause great attention to all sectors of society. In the context of disease transition and aging society, multimorbidity coexistence has become a key factor hindering the improvement of the health level of elderly people in China, Older people "live long," but it is necessary to make them "live well." Currently, there is no effective treatment for multimorbidity and still needs frequent general practice consultations, complex and structured care, as well as coordination between health and social sectors (27). From the National Institute for Health and Care Excellence (NICE) record an approach to care that takes account of multimorbidity, involving a personalized assessment and the development of an individualized management plan (28). This study aimed to improve quality of life by reducing treatment burden, adverse events, and unplanned or uncoordinated care. Focusing on the quality of life and symptoms of patients with multimorbidity became the main target.

This study analyzed the effects of multimorbidity coexistence on the all-cause mortality risk. In addition, the relationship between multimorbidity and mortality was explored based on stratifying age and gender. Relevant conclusions can provide some reference for paying clinical attention to key risk groups and providing intervention measures in future. However, there are some shortcomings in this study. First, the study examines the number of diseases rather than the pattern of diseases, which needs to be supplemented by further research. Second, the data limitations of this study do not allow for a detailed

TABLE 4 Stratified analysis of multimorbidity coexistence and mortality risk in older people.

Variables	HR	95% CI	*P*-value
Gender			
Male			
No disease	1.00		
Single disease	1.041	0.96–1.13	0.338
Multimorbidity	1.153	1.06–1.25	<0.001
Female			
No disease	1.00		
Single disease	1.028	0.95–1.11	0.504
Multimorbidity	1.084	1.01–1.17	<0.032
Age (years)			
65–79			
No disease	1.00		
Single disease	1.115	0.96–1.29	0.14
Multimorbidity	1.083	0.94–1.25	0.28
80–94			
No disease	1.00		
Single disease	1.029	0.95∼1.11	0.458
Multimorbidity	1.124	1.05∼1.21	0.002
95–104			
No disease	1.00		
Single disease	1.021	0.92–1.14	0.71
Multimorbidity	1.108	1.01–1.23	<0.045

Adjusted to Model 3.

examination of individual disease subsections. Finally, the data used for multimorbidity were self-reported by patients, which may underestimate the chronic disease status of the study population.

5. Conclusion

This study analyzed the effect of multimorbidity on all-cause mortality using data from a 10-year cohort of the CLHLS. This study showed that individuals with multimorbidity are at an increased risk of all-cause mortality compared with those diseases alone, especially in 80–94 years and male elderly adults. Therefore, patients with multimorbidity must be provided with integrated assessment and treatment.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found at: Chinese Longitudinal Healthy Longevity Survey (CLHLS).

Ethics statement

The studies involving human participants were reviewed and approved by the Biomedical Ethics Committee, Peking University (IRB00001052-13074). The patients/participants provided their written informed consent to participate in this study.

Author contributions

ZS and LH designed the research and directed its implication. ZS prepared, analyzed the data, and drafted the manuscript. JZ and SC revised the manuscript together. All authors have read and approved the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Sanghamitra Pati,
Regional Medical Research Center (ICMR),
India

REVIEWED BY
Tanuwong Viarasilpa,
Mahidol University,
Thailand
Iva Pruner,
University of Belgrade,
Serbia

*CORRESPONDENCE
Giorgia Lüthi-Corridori
✉ giorgia.luethi-corridori@ksbl.ch

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Risk factors for hospital outcomes in pulmonary embolism: A retrospective cohort study

Giorgia Lüthi-Corridori[1,2]*, Stéphanie Giezendanner[1,2,3], Cedrine Kueng[1,2], Maria Boesing[1,2], Anne B. Leuppi-Taegtmeyer[1,2,4], Munachimso Kizito Mbata[1], Philipp Schuetz[2,5] and Joerg D. Leuppi[1,2]

[1]Cantonal Hospital Baselland, University Center of Internal Medicine, Liestal, Switzerland, [2]Faculty of Medicine, University of Basel, Basel, Switzerland, [3]Centre for Primary Health Care, University of Basel, Basel, Switzerland, [4]Department of Patient Safety, Medical Directorate, University Hospital Basel, Basel, Switzerland, [5]Cantonal Hospital Aarau, University Department of Medicine, Aarau, Switzerland

Background: Pulmonary embolism (PE) is not only a life-threatening disease but also a public health issue with significant economic burden. The aim of the study was to identify factors—including the role of primary care—that predict length of hospital stay (LOHS), mortality and re-hospitalization within 6months of patients admitted for PE.

Method: A retrospective cohort study was conducted with patients presenting to a Swiss public hospital with PE diagnosed at the hospital between November 2018 and October 2020. Multivariable logistic and zero-truncated negative binomial regression analyses were performed to assess risk factors for mortality, re-hospitalization and LOHS. Primary care variables encompassed whether patients were sent by their general practitioner (GP) to the emergency department and whether a GP follow-up assessment after discharge was recommended. Further analyzed variables were pulmonary embolism severity index (PESI) score, laboratory values, comorbidities, and medical history.

Results: A total of 248 patients were analyzed (median 73 years and 51.6% females). On average patients were hospitalized for 5 days (IQR 3–8). Altogether, 5.6% of these patients died in hospital, and 1.6% died within 30 days (all-cause mortality), 21.8% were re-hospitalized within 6 months. In addition to high PESI scores, we detected that, patients with an elevated serum troponin, as well as with diabetes had a significantly longer hospital stay. Significant risk factors for mortality were elevated NT-proBNP and PESI scores. Further, high PESI score and LOHS were associated with re-hospitalization within 6months. PE patients who were sent to the emergency department by their GPs did not show improved outcomes. Follow-up with GPs did not have a significant effect on re-hospitalization.

Conclusion: Defining the factors that are associated with LOHS in patients with PE has clinical implications and may help clinicians to allocate adequate resources in the management of these patients. Serum troponin and diabetes in addition to PESI score might be of prognostic use for LOHS. In this single-center cohort study, PESI score was not only a valid predictive tool for mortality but also for long-term outcomes such as re-hospitalization within 6 months.

KEYWORDS

LOHS, pulmonary embolism, risk factors, length of hospital stay, multi morbidity, rehospitalization, in hospital death

1. Introduction

Pulmonary embolism (PE) is a serious, potentially life-threatening health condition that represents the third major cause of cardiovascular death behind myocardial infarction and cerebrovascular accidents (1, 2). PE can be considered a central public health issue since it is associated with a substantial economic burden (3–6).

The exact incidence rate for PE is not available but estimates range from 39 to 115 per 100,000 population. Additionally, as the incidence of PE rises with age, PE rates can be expected to continue increasing even further due to the rapidly ageing population in high-income countries, and therefore to significantly impact morbidity, mortality, and healthcare costs (6, 7). Most nations have an urgent dilemma in the realm of public health: how to address the difficulties brought on by the rise in the number of PE patients while utilizing the available medical resources to better fulfill their medical demand without impacting on cost and overtreatments.

Over the past decades, the incidence rate of PE has increased in Europe, whereas the mortality rate and the length of hospital stay (LOHS) have slightly decreased, due to advances in treatments and diagnostics (8–12). In a retrospective, Italian cohort study of 328 patients with PE, despite a trend in reduction in LOHS, the mean and median have not significantly decreased, due to a very small percentage (3%) of patients who received an ultra-early discharge and a large percentage of patients who were discharged within 6 days (31.5%) (13). LOHS is considered a crucial characteristic for health reports when it comes to the management and evaluation of inpatients and is a significant signal for the assessment of hospitals' service quality (14). Several factors can influence LOHS in patients with PE such as sociodemographic, health-related characteristics and hospital care-related features (15–17). Due to the wide variability of influencing factors, there is no uniform approach to predict the length of stay for PE.

The primary aim of the study was to identify which factors may affect the length of stay of patients admitted for PE. The identification of patient characteristics influencing LOHS may allow decision-makers to plan hospital management accordingly.

Particularly we retrospectively explored if the primary outcome length of hospital stay for PE was influenced by commonly available sociodemographic and health-related variables measurable at entry time.

Although a reduced length of stay decreases hospital costs, it might negatively affect the quality of care. For this reason, as secondary outcomes, we analyzed factors associated with all-cause mortality (in hospital or 30 days mortality) and rehospitalization within 6 months.

2. Materials and methods

2.1. Design and setting

Our study was conducted in the cantonal hospital of Baselland (KSBL), a district general hospital covering a stable population of 280,000 in Northwest Switzerland. We undertook a retrospective cohort study with 378 consecutive patients hospitalized at the KSBL at the medical or surgical ward and who received the diagnosis of pulmonary embolism (according to the primary International Classification of Disease codes) during their hospital stay between November 2018 and October 2020. We were able to access the electronic case notes of 378 patients to retrieve presenting symptoms and clinical signs that have been associated with PE. Further, sociodemographics, vital signs, comorbidities and discharge variables (mortality and re-hospitalization) were assessed.

2.2. Inclusion and exclusion criteria

Data of these patients were individually reviewed. Patients were included in the study if a new PE was the main reason for their hospitalization and their diagnosis was confirmed by computer tomographic pulmonary angiogram (CTPA), scintigraphy or duplex ultra-sound by a specialist (deep vein thrombosis (DVT) combined with PE specific symptoms) within 12 h after presentation. Alternatively, they were also included if confirmatory, diagnostic imaging was performed later, but anticoagulant treatment was started within 12 h after presentation to the hospital due to high clinical suspicion of PE.

The following patients were excluded:

- Denied research consent.
- PE only as a suspected diagnosis and never confirmed with any imaging method.
- Primarily hospitalized for another reason, and PE was diagnosed after >12 h.
- Transferred from/to another hospital and therefore no complete case documentation.

After the application of the eligibility criteria, 248 patients were included in the analysis.

2.3. Statistical analyses

The outcome variables comprised LOHS (primary outcome), all-cause mortality in hospital and 30 days, and re-hospitalization within 6 months (secondary outcomes).

To minimize the risk of bias, optimism, and overfitting, no data-driven selection of variables was done. We selected potential predictors based on the literature and on clinical knowledge. Two researchers conducted a literature review and consulted clinical experts in the field. All variables are included in Table 1. Predictors included the PESI score based on age at entry, sex, history of cancer, history of chronic lung disease, history of heart failure, respiratory rate, hypothermia (below 36 degrees Celsius), systolic blood pressure (BP) <100 mmHg, heart rate (HR) ≥110 bpm, O_2 saturation (SpO_2) below 90%, altered mental status, and respiratory rate ≥ 30/min (18).

Abbreviations: BMI, Body mass index; BP, Blood pressure; BPM, Beats per minute; CI, Confidence interval; CTPA, Computed tomography pulmonary angiogram; DVT, Deep vein thrombosis; GP, General practitioner; HR, Heart rate; ICD, International Classification of Diseases; IQR, Interquartile range; IRR, Incident risk ratio; KSBL, (Kantonsspital Baselland) cantonal hospital of Baselland; LOHS, Length of hospital stay; NT-proBNP, N-terminal pro b-type natriuretic peptide; OR, Odds ratio; PE, Pulmonary embolism; PESI, Pulmonary embolism severity index; ROC, Receiver operating characteristic; SD, Standard deviation; VTE, Venous thromboembolism.

TABLE 1 Patient characteristics.

Demographic	All (*n*=248)	Missing *n* (%)
Age at diagnosis, median (IQR) in years	73 (62–81.5)	--
Gender (female)	128 (51.6%)	--
Insurance type		
General	199 (80.2%)	--
Half-private	30 (12.1%)	--
Private	19 (7.7%)	--
Vital signs		
Heart rate (bpm), mean (SD)	92.1 (19.7)	--
Tachycardia (>100 bpm)	76 (30.6%)	--
Blood pressure systolic (mmHg), mean (SD)	140.7 (24.9)	--
Blood pressure diastolic (mmHg), mean (SD)	83.1 (14.1)	--
Hypotension (<100/60 mmHg), *n* (%)	11 (4.4%)	--
Hypertension (>140/90 mmHg), *n* (%)	124 (50%)	--
Respiratory rate (/min) mean (SD)	20.4 (5.7)	35 (14.1%)
Hypothermia (<36°C), *n* (%)	9 (3.6%)	--
Oxygen saturation, mean (SD)	93.8 (4.8)	--
Oxygen requirement	36 (14.5%)	--
Comorbidities	229 (92.3%)	--
Dyslipidemia, *n* (%)	44 (17.7%)	--
Diabetes, *n* (%)	37 (14.9%)	--
Cardiovascular disease, *n* (%)	86 (34.7%)	--
Heart failure, *n* (%)	5 (2%)	--
Chronic lung disease, *n* (%)	44 (17.7%)	--
Rheumatic disease, *n* (%)	30 (12.1%)	--
Mental disease, *n* (%)	55 (22.2%)	--
Altered mental status, *n* (%)	5 (2.2%)	--
Active cancer, *n* (%)	30 (12.1%)	--
Medical history		
Previous VTE, *n* (%)	58 (23.4%)	--
Previous PE, *n* (%)	26 (10.5%)	--
Previous DVT, *n* (%)	44 (17.7%)	--
History of cancer, *n* (%)	50 (20.2%)	--
History of hypertension, *n* (%)	126 (50.8%)	--
PESI		
PESI score, mean (SD)	96.8 (31.4)	--
PESI retrospectively calculated, *n* (%)	200 (81%)	
Laboratory values		
NT-proBNP, (ng/L) median (IQR)*	499 (125–2,479)	70 (28.2%)
Troponin-T hs (ng/L), median (IQR)**	16.95 (7.22–44.38)	94 (37.9%)
Entry and discharge circumstances		
Housing situation before admission		
Private home, *n* (%)	211 (85.1%)	--
Care facility, *n* (%)	37 (14.9%)	--
Sent by GP, *n* (%)	122 (49.2%)	--
Follow-up with GP, *n* (%)	72 (29%)	Data of 14 patients missing (died)
Discharge destination		Data of 14 patients missing (died)
Private home, *n* (%)	200 (80.6%)	
Care facility, *n* (%)	34 (13.7%)	
Rehabilitation unit, *n* (%)	21 (8.5%)	Data of 14 patients missing (died)
Outcomes		
Length of stay, in nights, median (IQR)	5 (3–8) Median 5 (3–8)	--
Rehospitalization at KSBL within 6 months after discharge, *n* (%)	51 (21.8%)	Data of 14 patients missing (died)
Death	18 (7.3%)	--
Death (in hospital death)	14 (5.6%)	--
Death (30 days mortality)	4 (1.6%)	--

*NT-proBNP normal range < 125 ng/L.
**Troponin-T hs < 14 ng/L.

Other variables of interest were body mass index (BMI), a medical history of dyslipidemia, diabetes, or previous PE. Laboratory values of interest were serum N-terminal pro B-Type natriuretic peptide (NT-proBNP) and Troponin-T high-sensitive (hs). The analysis of LOHS was primarily on patients that were discharged alive, a sensitivity analysis was performed on the full data set.

Further, the housing situation before admission and admission *via* another doctor (usually the GP) were entered into the models. For re-hospitalization outcome, we further entered the variable if GP follow-up was suggested and the LOHS.

For descriptive statistics as measures of central tendency, we displayed mean and standard deviation (SD) in case of normal distribution and median with interquartile range in case of skewed distribution, which was assessed through histograms assessment. For categorical variables we reported absolute and relative frequencies.

Variables with missing values were imputed using the k-Nearest Neighbor algorithm [function knn.impute from the R package "bnstruct" (19)]. A zero-truncated negative binomial regression was conducted to estimate the LOHS and its association with potential risk factors using the R package "VGAM." As a sensitivity analysis, all regression models were additionally performed on the original, non-imputed data set.

Logistic regression models were created to estimate the risk of death and rehospitalization, and its association with potential risk factors.

All statistical analyses were performed using R, version 4.0.3 statistical software (R Foundation for Statistical Computing). All *p*-values reported were 2-sided; statistical significance was defined as $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 378 patients were identified who received the diagnosis of pulmonary embolism during their hospital stay. After the exclusion of 24 patients who declined research consent, 15 patients in which the diagnosis was not confirmed with imaging methods, 67 patients who were diagnosed more than 12 h after admission, and a further 24 who had incomplete diagnostic documentation, 248 cases were analyzed. The patient characteristics are shown in Table 1.

The median age at admission was 73 years (range 19–96) and 51.6% were female. The majority of the patients had general insurance (80%). Vital signs measured at admission revealed that the mean HR was 92.1 but one third of the patients presented to the hospital with tachycardia (30.6%). The average blood pressure was 141/83 mmHg, while half of the patients had hypertension while only a minority of the patients had hypotension, (4.4%). Body temperature was usually in the normal range and oxygen saturation was on average 93.7%, but some of the patients needed oxygen supply at entry (14.5%).

The majority of the patients had comorbidities (92.3%), the three most frequent disease types were: cardiovascular (34.7%), mental (22.2%) and chronic lung diseases (17.7%). Patients' history revealed that previous VTE occurred in 23.4%, the most frequent one was DVT, followed by PE whereas 12 patients had both (4.8%).

Pulmonary embolism severity index (PESI) score was calculated at admission in 19% of the cases, in the remaining 81% of the cases the PESI score was calculated retrospectively. The mean of the PESI score was 96.8 (SD = 31.4). Regarding the laboratory values, NT-proBNP was measured in 71.8% of the patients and the values had a median of 499 ng/l (IQR 125–2,479), whereas troponin-T hs was measured in 62% of the patients with a median of 16.9 ng/l (6.84–46.2).

Before admission most of the patients lived independently, but 14.9% were admitted from a care facility. Almost half of the patients were sent to the hospital by a GP (49.2%). After the discharge, a follow-up with a GP was organized in 29% of all cases. The majority of the patients returned to their private homes (80.6%) while 13.7% were transferred to a care facility or a rehabilitation center (8.5%).

Out of 248 hospitalized patients with pulmonary embolism, 14 patients died during the hospital stay and were excluded from regression analyses with outcome LOHS and re-hospitalization. Patients with PE who did not die within the hospital stayed for a median of 5 days (IQR 3–8). Additionally, four patients died within 30 days (1.6% of the total patients) and rehospitalization at KSBL within 6 months after discharge occurred in 21.8% of the cases.

3.2. Prediction of LOHS

Our primary aim was to identify factors that predict LOHS. Table 2 provides coefficient estimates for predictors of LOHS in patients who did not die. Regression coefficients are shown as incident risk ratio (IRR). Patients with higher PESI scores (IRR = 1.068, 95%CI [1.034–1.104], value of $p < 0.001$), higher troponin values [IRR = 1.433, 95%CI (1.189–1.727), value of $p < 0.001$], and with diabetes [IRR = 1.293, 95%CI (1.007–1.66), value of p 0.044] had significantly longer LOHS.

TABLE 2 Results of multivariable zero-truncated negative binomial regression model for length of hospital stay (LOHS) estimation in pulmonary embolism survivors (n=234).

	LOHS prediction	IRR (95%CI)	Pr(>|z|)
(Intercept):1	5.899	2.422 (1.742–5.722)	0.004
PESI score (per 10 points)	**6.273**	**1.068 (1.034–1.104)**	**<0.001**
NT-proBNP (per 1,000 units)	6.012	1.021 (0.997–1.045)	0.089
Troponin-T hs (per 100 units)	**8.297**	**1.433 (1.189–1.727)**	**<0.001**
Pervious PE	6.485	1.107 (0.829–1.478)	0.492
Previous DVT	5.482	0.924 (0.724–1.178)	0.522
Diabetes	**7.517**	**1.293 (1.007–1.66)**	**0.044**
Cardiovascular diseases	6.904	1.183 (0.969–1.443)	0.098
Dyslipidemia	5.041	0.842 (0.66–1.075)	0.168
BMI	6.039	1.026 (0.87–1.209)	0.763
Housing situation before admission	5.104	0.854 (0.656–1.112)	0.241
Sent by doctor	5.98	1.015 (0.846–1.217)	0.873

Statistically significant variables $p < 0.05$.

The LOHS prediction at the intercept (5.899 days) is the LOHS when all covariates are at 0 (for categorical covariates) or at their mean (for continuous covariates). The predicted LOHS of the model for each variable is presented for one unit increase. If the PESI score increases by one unit (on the original scale per 10 points), the predicted LOHS increases from 5.89 to 6.27 days. A higher increase occurs when the Troponin increases by one unit (on the original scale per 100 n/L) the predicted LOHS rise to 8.3 days. People with diabetes compared to those without tend to stay two nights longer, assuming all other variables are held constant.

Our secondary aims included the analyses of factors associated with mortality and rehospitalization rates. The results of the univariate logistic regression models for mortality, adjusted for PESI score, are displayed in Table 3. Higher PESI scores and NT-proBNP values were significantly associated with mortality in patients with pulmonary embolism [OR 1.617, 95%CI (1.359–1.981), value of $p < 0.001$ and OR 1.091, 95%CI (1.012–1.171) value of p 0.013, respectively]. No other variable was found to be statistically significant in the association with the mortality rate.

The results of our secondary multivariable analysis concerning rehospitalization rate are reported in Table 4. The odds for rehospitalization within 6 months in KSBL were also significantly higher for patients with a higher PESI score and for patients with a higher LOHS [OR 1.183, 95%CI (1.041–1.353) value of p 0.012 and OR 1.099, 95%CI (1.031–1.183) value of p 0.007, respectively]. No other variable was found to be statistically significant in the association with rehospitalization.

4. Discussion

This retrospective observational cohort study of patients with PE showed that LOHS is influenced by PESI score, serum troponin values

TABLE 3 Results of univariate logistic regression model for mortality (in-hospital or within 30days) in pulmonary embolism (*n*=18).

	OR (95%CI)	Pr(>|z|)
PESI score	**1.617 (1.359–1.981)**	**<0.001**
NT-proBNP	**1.091 (1.012–1.171)**	**0.013**
Troponin-T hs	0.139 (0.003–1.949)	0.249
Previous DVT	0.41(0.022–2.322)	0.408
Diabetes	0.782 (0.152–2.979)	0.74
Cardiovascular diseases	1.628 (0.537–5.073)	0.388
Dyslipidemia	0.341 (0.043–1.611)	0.229
BMI	0.443 (0.117–1.399)	0.199
Housing situation before admission (care facility)	1.443 (0.367–4.715)	0.575
Sent by doctor	1.423 (0.454–4.715)	0.548
LOHS	1.056 (0.967–1.137)	0.172

All variables were adjusted for pulmonary embolism severity index (PESI) score. Statistically significant variables $p < 0.05$.

TABLE 4 Multivariable logistic regression model for rehospitalization in pulmonary embolism (*n*=51).

	OR (95%CI)	Pr(>|z|)
PESI score	**1.183 (1.041–1.353)**	**0.012**
NT-proBNP	0.934 (0.831–1.03)	0.546
Troponin-T hs	0.853 (0.265–1.926)	0.957
Previous PE	0.522 (0.116–1.772)	0.339
Previous DVT	1.346 (0.495–3.456)	0.545
Diabetes	1.917 (0.733–4.893)	0.175
Cardiovascular diseases	1.871 (0.873–4.013)	0.106
Dyslipidemia	0.525 (0.181–1.372)	0.208
BMI	0.747 (0.36–1.437)	0.404
Housing situation before admission (care facility)	0.815 (0.279–2.139)	0.69
Sent by doctor	1.019 (0.501–2.076)	0.959
Follow up with GP	1.352 (0.626–2.869)	0.435
LOHS	**1.099 (1.031–1.183)**	**0.007**

Statistically significant variables $p < 0.05$.

and diabetes. Other factors such as medical history, other types of comorbidities and whether the patients were sent to the hospital by a GP were not associated with longer LOHS.

Pulmonary embolism severity index score is a validated prognostic model for PE devised by Aujesky and colleagues (20). Originally it was developed to predict 30-day mortality using 11 clinical criteria [age at entry, sex, history of cancer, history of chronic lung disease, history of heart failure, respiratory rate, hypothermia (below 36 degrees Celsius), systolic blood Pressure <100 mmHg, heart rate ≥110 bpm, oxygen saturation below 90%, altered mental status, and respiratory rate ≥ 30 breaths per minute (20)]. The PESI score was also implemented to identify low-risk patients who might be treated outside the hospital and consequently be eligible for early discharge (18). In line with other studies, our results also confirm the prognostic validity of the PESI score in predicting the length of hospital stay (21, 22). The role of PESI in LOHS was confirmed by Rodriguez et al. (23), however the impact of the single items composing the score was unclear. For this reason, in our study, we have also analyzed the items of the PESI score separately and we found that age, sex heart rate over 110 bpm, oxygen saturation <90% and heart failure were significantly predictive for LOHS (for more details see Table A1 in the appendix).

A strong finding of our research is that serum troponin was statistically significant in association with LOHS, despite the model being controlled for cardiovascular disease. This trend was noted by Muktar et al. in 2018 where patients who had long LOHS had higher values of cardiac biomarkers compared to those with short LOHS, but no statistically significant difference was found in their study, possibly due to the small sample size (22). Elevated cardiac troponins are known to indicate subendothelial ischemia in the right ventricle (24) and to be associated with right ventricular dysfunction and pulmonary hypertension in acute PE (25, 26). These complications may explain the found association with extended LOHS.

Another point worth discussing is the fact that diabetes was the only health condition associated with longer LOHS. Previous studies have investigated the relationship between diabetes and PE incidence (27) or demonstrated that patients with diabetes have worse outcomes compared to patients without diabetes, especially in terms of mortality (28) or hospitalization rate (29). A recent study by Schmitt et al. found that PE patients with diabetes had prolonged LOHS (30), which is confirmed by our results. So, despite advances in treatments, diabetes is still associated with a higher risk of adverse outcomes and healthcare providers should take this finding into account. Although PE patients who also suffer from diabetes are at elevated risk for adverse events and a complicated clinical course (30, 31), further studies are required in order to clarify the underlying mechanisms and impact of disturbed glucose metabolism on the generation and clinical outcome of PE in light of LOHS.

The study followed up patients until late 2020 (the first year of the COVID-19 pandemic), however only one case out of 248 in our sample was tested positive for the SARS-CoV-2 virus. The reason why the proportion of patients with a positive test is low relies on our inclusion criteria, since we selected patients who were hospitalized with pulmonary embolism as their main diagnosis (reason for hospitalization). The majority of patients hospitalized with COVID-19 received a different ICD code as their main diagnosis and are not captured in our cohort.

Our secondary aim was to assess which factors were associated with morality rate. The overall in-hospital (5.6%) and the 30-days mortality rate (5.6 and 1.6%) observed in this study, were relatively low compared to that reported in recent studies by Matskiv et al. and by Jiménez et al. (32) (11.9 and 5.4%, respectively). Our results showed that mortality was associated with elevated values of NT-proBNP in addition to the PESI score. As previously stated, the PESI score is the most validated prognostic model for PE in predicting mortality and our study confirms this association and is in line with previous publications (17, 18, 20, 21, 33, 34).

The role of biomarkers in all-cause mortality of patients with pulmonary embolism has been debated. A meta-analysis by Lega et al. (35) showed that higher level of NT-proBNP was associated with higher risk of adverse outcomes, all-cause mortality among them. Interestingly in our research, we detected a difference between the role of NT-proBNP and troponin values. As previously discussed, our study revealed that higher serum troponin was significantly associated with LOHS whereas NT-proBNP was associated with mortality. The meta-analysis of Klok et al. (36) found that high concentrations of BNP in PE patients were associated with complicated in-hospital course and death, while LOHS was analyzed in particular. Another meta-analysis by Beccatini et al. (37) showed that elevated values of troponin were indicator of high risk for short-term death in patients with acute PE, but the study limited his research to troponin values only and did not include NT-proBNP values. In a recent Swiss study by Benmachiche et al. (38) results revealed that patients with high levels of NT-proBNP were at higher risk of in-hospital mortality and longer LOHS, regardless of their clinical characteristics. Although in other conditions like acute coronary syndrome, the level of NT-proBNP provided better predictive power than troponin (39), this difference in PE patients has still to be established. Ultimately, the precise role of biomarkers in early risk stratification is fundamental since PE may present with a wide spectrum of symptoms but in some cases with no evident symptoms. Biomarkers might be fundamental in order to detect a serious condition and allow consequently treatment adjustment with more aggressive therapy.

Our secondary outcomes included rehospitalization rates. We detected that in our study population rehospitalization within 6 months was significantly influenced by PESI score and in addition by LOHS but not by other factors. PESI score has been validated in studies with a relatively short-term follow-up (30 and 90 days mortality), (17, 33, 40) one study showed its accuracy in predicting long-term prognosis (6 month and 1 year mortality) (33) but its accuracy in predicting long term outcome in terms of rehospitalization in 6 months has not been established. The role of LOHS and its association with the risk of rehospitalization has been debated in research (41–44). Literature suggests that both short length of stay and long length of stay can be associated with rehospitalization rates. On one hand, a shortening of the length of stay could point to the so colloquially called “bloody” discharges, where the patient is not yet in a sufficient state of health or still has open problems (45, 46). On the other hand, a longer length of stay could be associated with rehospitalizations because it could occur especially in critically ill people and multimorbid elderly patients, who are subsequently exposed to a higher risk of readmission (41, 43). In order to test the association of LOHS with rehospitalization we visualized the frequency of rehospitalization versus LOHS and detected rather a linear tendency, as the LOHS increased so did the percentage of rehospitalization rates (Figure 1). For the above-mentioned reasons, we included LOHS in our model as a continuous variable and did not dichotomize it in short versus long length of hospital stay. The explanation for such tendency is that patients with pulmonary embolism hospitalized in KSBL are on average old and multimorbid patients. The positive aspect of these results is that patients were usually not discharged too early and a short length of stay did not result in a higher risk of rehospitalization.

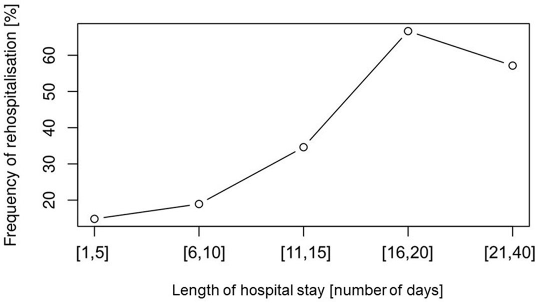

FIGURE 1
Frequency of rehospitalization versus length of hospital stay (LOHS). Rehospitalization rates increases with longer length of hospital stay in approximately lineal relationship.

In all our analyses the PESI score had significant influence on LOHS, mortality and rehospitalization. PESI score is an essential parameter for determining how to proceed with the patient (e.g., outpatient treatment, surveillance) (47). Therefore, whenever it is not calculated, the patient is at risk of being under- or overtreated. By definition, the PESI score is used to predict 30 day mortality and is a widely validated model that uses clinical parameters to stratify patients into five risk levels (20).Unfortunately, in our study PESI score was only calculated at the time of admission in 19% of the cases, in the remaining 81% of the cases the PESI score was calculated retrospectively.

Published audits on the management of PE patients only cover very particular aspects of the process, for instance, the use of clinical decision rules (48) or treatment strategies (49) or only look at single subsegmental PE (50) and do not focus on the frequency of the PESI score calculation. Therefore, do not know if the proportion is representative of usual practice. In our opinion, the fact that the PESI score is poorly reported can be due to two factors: either other indicators are given priority in the emergency department, or the PESI was actually calculated but not entered into the patients’ records.

The criteria that make up the score refer to easily accessible information and vital signs that can be measured by a GP. Moreover, the score is of high importance in predicting not only severity and mortality but also LOHS and the likelihood of re-hospitalization. Therefore, we believe that it may be appropriate for GPs who suspect pulmonary embolism to already calculate the PESI when sending a patient to the hospital.

4.1. Comparison between multivariable models and sensitivity analysis

In our study we assessed the association between PESI score in addition to other risk factors and we also assessed the parameters composing the PESI score alone. As displayed in the Appendix Figure A1 LOHS prediction the receiver operating characteristic (ROC) curve shows a higher accuracy for the model with other parameters in addition to PESI score compared to the model with PESI score alone and this is valid both for 5 days prediction (median LOHS) and for 8 days prediction (the upper IQR).

The sensitivity analysis on the full data for the prediction of LOHS did not give any other predictor except for NT-proBNP which was predictive for in-hospital death. The sensitivity analysis on the full data for the prediction of the PESI items only on LOHS shows the same results as the analysis performed on the patients that were discharged alive.

4.2. Strengths, limitations, and further research

Despite the availability of a large amount of data regarding the prognosis of PE patients, only a few studies have investigated possible predictors of LOHS in these patients (15, 21, 51). The novelty of our study is that the analysis did not limit its focus just to the PESI score. Our analysis looked at a broader range of variables (demographic, health-related risk factors and the role of primary care) as well as the PESI score and determined their associations with outcomes of interest. The data collection involving manual extraction of information was conducted by a doctor alone but subsequently, the parameters forming the PESI score were reviewed independently by two researchers. The characteristics of the sample of this study are comparable with other cohorts with a bigger sample size, for example in our study the median age was 73 years 52% were female and 50% had hypertension as a comorbidity. In a German study from 2018 with almost 1 million PE patients, the median age was 72, 54% were female and 43% had hypertension (8).

All statistical analyses that were primarily performed on imputed data have also been applied to the non-imputed dataset, the statistical significance of the variables with missing data did not differ in the two models. The sensitivity analysis demonstrated that the internal validity of our research was not impacted by missing data.

There are some limitations to this study. As a retrospective study design, the data quality depends on precise documentation in the patient files. Particularly we assumed that if the PESI score was not reported, the clinician did not calculate it, so we could have underestimated the percentage of patients with a PESI calculation at entry to hospital. Additionally, information about rehospitalization within 6 months was only possible within KSBL: due to privacy policy, it was not possible to access information about rehospitalizations in other hospitals. However, in Switzerland readmissions usually occur within the same hospital; a Swiss study has shown that only 17% of unplanned readmissions occurred at a different hospital (41). Our results concerning mortality and rehospitalization rates must be interpreted carefully since their occurrence was relatively low (18 and 51 patients, respectively).

Further research to prospectively validate the statistical model's accuracy in predicting LOHS—ideally in multicenter studies with a larger sample size—is needed.

5. Conclusion

Understanding the factors that are associated with LOHS in patients with PE has clinical implications and may help healthcare providers to deliver efficient care and to allocate adequate resources in the management of these patients. In summary, the results of this study showed that the PESI score is a major predictor of LOHS, mortality and rehospitalization in PE patients. Diabetes is an additional risk factor that healthcare providers should be aware of. Even though cardiac biomarkers and comorbidities are predictors of LOHS, their role in defining mortality and rehospitalization is yet to be established. Moreover, our study confirmed the essential role of PESI score calculation in the management of PE patients, clinicians and GPs should be aware of and perform the calculation as soon as PE is diagnosed.

Data availability statement

The dataset presented in this article is not readily available because it contains sensitive human personal data. All data generated were analyzed during this study and the results included in this article. Further inquiries can be directed to the corresponding author. Requests to access the datasets should be directed to JL, joerg.leuppi@ksbl.ch.

Ethics statement

The studies involving human participants were reviewed and approved by Nordwest- and Zentralschweiz ethic commission (Project-ID 2021–00964). The ethics committee waived the requirement of written informed consent for participation.

Author contributions

GL-C and CK were responsible of data collection. GL-C, SG, and MB were responsible for data analysis. GL-C, SG, and JL were responsible for designing the study. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Appendix

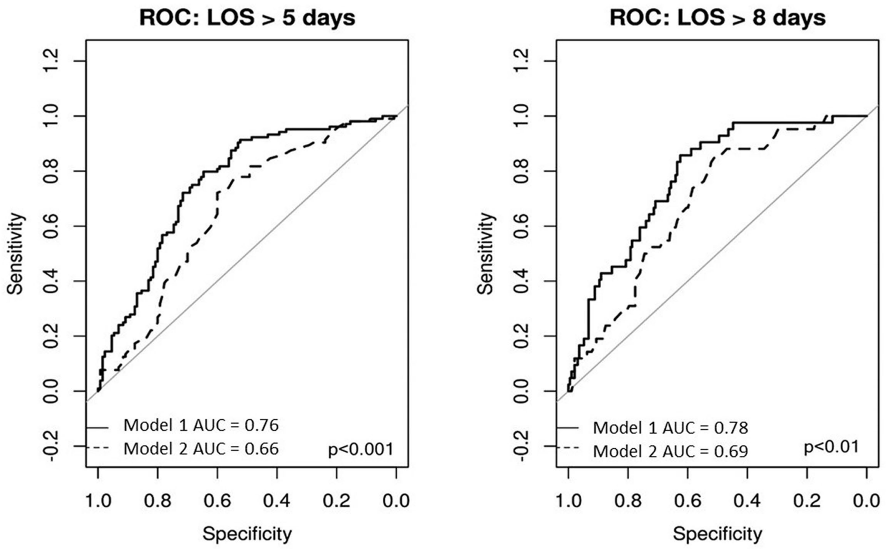

FIGURE A1
Receiver operating characteristic (ROC) curve accuracy of the models to predict 5days and 8days length of hospital stay. For both 5days and 8days prediction, model 1 showed higher accuracy than model 2. Model 1 includes the following variables: pulmonary embolism severity index (PESI) score, body mass index (BMI), a medical history of dyslipidemia, diabetes or previous PE, NT-proBNP and troponin-T hs, housing situation before admission and admission *via* GP. Model 2 only includes the PESI score. Pulmonary embolism severity index score is based age at entry, sex, history of cancer, history of chronic lung disease, history of heart failure, respiratory rate, hypothermia [below 36°C], systolic blood pressure (BP) <100mmHg, heart rate (HR) ≥110bpm, oxygen saturation below 90%, altered mental status, and respiratory rate≥30 breaths per minute (18).

TABLE A1 Multivariable zero-truncated negative binomial regression model for length of hospital stay (LOHS) estimation in pulmonary embolism survivors with pulmonary embolism severity index (PESI) items separately assessed (*n*=234).

	LOHS prediction	IRR (95%CI)	Pr(>|*z*|)
Intercept	4.638	1.774(1.148–2.742)	0.01
Age	**5.207**	**1.138 (1.071–1.21)**	**<0.001**
Sex	**5.864**	**1.296 (1.083–1.55)**	**0.005**
History or active cancer	4.72	1.02 (0.829–1.255)	0.851
BP systolic < 100 mmHg	5.452	1.197 (0.761–1.883)	0.436
Heart rate ≥ 110 bpm	**6.139**	**1.361 (1.075–1.724)**	**0.01**
Respiratory rate ≥ 30 breaths/min	4.876	1.058 (0.707–1.583)	0.783
Oxygen < 90%	**6.188**	**1.373 (1.109–1.699)**	**0.004**
Chronic lung disease	5.107	1.114 (0.878–1.414)	0.375
Altered mental status	5.003	1.089 (0.51–2.324)	0.826
Hypothermia < 36°C	4.821	1.045 (0.612–1.782)	0.872
Heart failure	**9.345**	**2.113 (1.165–3.832)**	**0.014**

The analysis of the items composing the PESI score showed that age, sex, heart rate over 110 bpm, oxygen saturation <9% and heart failure were significantly associated with LOHS. Statistically significant variables $p < 0.05$.

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Postpartum anemia and its determinant factors among postnatal women in two selected health institutes in Gondar, Northwest Ethiopia: A facility-based, cross-sectional study

Getachew Mesfin Bambo[1,2]*, Samuel Sahile Kebede[1,2], Chomaw Sitotaw[3], Elias Shiferaw[1] and Mulugeta Melku[1,4]

[1]Department of Hematology and Immunohematology, School of Biomedical and Laboratory Sciences, University of Gondar, Gondar, Ethiopia, [2]Department of Medical Laboratory Science, College of Health Sciences, Mizan-Tepi University, Mizan, Ethiopia, [3]University of Gondar Comprehensive Specialized Hospital Laboratory, Gondar, Ethiopia, [4]College of Medicine and Public Health, Flinders University, Adelaide, SA, Australia

Background: Anemia is highly prevalent globally and disproportionately affects postnatal women. It is a significant cause of maternal mortality and morbidity globally.

Objective: The main aim of this study was to determine the extent of postpartum anemia and associated factors among postnatal women in two selected health facilities in Gondar, Northwest Ethiopia.

Methods: A facility-based, cross-sectional study was conducted among 282 postnatal women from March to May 2021. A systematic sampling technique was used to recruit study participants from each institute. Sociodemographic, obstetric, and clinical data were collected through a semi-structured questionnaire. A venous blood sample was collected to determine the red blood cell parameters. A thin blood smear preparation was performed to examine blood morphology. In addition, direct wet mount and formalin-ether sedimentation techniques were used for stool examination to identify intestinal parasites. Data were entered into EpiData and exported to Stata 14 for statistical analysis. Descriptive statistics were presented in text, tables, and figures. A binary logistic regression model was used to identify factors associated with postpartum anemia. A p-value <0.05 was considered statistically significant.

Results: The proportion of postpartum anemia was 47.16%; 95% CI; 41.30–53.03 with moderate, mild, and severe anemia accounting for 45.11, 42.86, and 12.03%, respectively. The majority of the anemia (94%) was of the normocytic normochromic type. It was associated with postpartum hemorrhage (AOR=2.23; 95% CI: 1.24–4.01), cesarean section (AOR=4.10; 95% CI: 2.11–7.78), lack of iron and folate supplementation during pregnancy (AOR=2.12; 95% CI: 1.17–4.02), and low diet diversity level (AOR=1.83; 95% CI: 1.05–3.18).

Conclusion: The prevalence of anemia was found to be a major public health concern. Iron and folate supplementation during pregnancy, improved management of PPH, an effective cesarean section with post-operative care,

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EDITED BY
Sanghamitra Pati,
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REVIEWED BY
Nihar Ranjan Mishra,
All India Institute of Medical Sciences,
Kalyani (AIIMS Kalyani), India
Afra Alkan,
Ankara Yıldırım Beyazıt University, Türkiye

*CORRESPONDENCE
Getachew Mesfin Bambo
✉ gmesfin007@gmail.com;
✉ getachewmesfin@mtu.edu.et

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and taking a diversified diet will reduce the burden. Therefore, identified factors should be considered to prevent and control postpartum anemia.

KEYWORDS

determinant factors, postpartum anemia, postnatal women, Ethiopia, postpartum hemarrhage

Introduction

Anemia is defined as a decrease in the mass of red blood cells (RBCs) or a low level of hemoglobin (Hb) relative to the normal reference range. The World Health Organization (WHO) defines it as Hb < 12.0 gm/dl in adult, non-pregnant women. However, there is no well-defined agreement for postpartum anemia (PPA), nonetheless, which is still defined as Hb < 12 gm/dl (1, 2). The postpartum period is defined as the first 6 weeks following childbirth (3).

Anemia is also defined as tissue hypoxia due to inadequate oxygen delivery in the tissue. The pathophysiology of anemia is multi-factorial and complex, which might be associated with a predisposition in genes for Hb, enzymatic deficiencies, chronic and acute blood loss, nutrient deficiencies, infection, hemorrhage, chronic disease, bone marrow disorders, and other factors. This may be due to inadequate or defective erythropoiesis from food shortages, bone marrow infiltration, inflammation, or hereditary Hb disorders and severe erythrocyte loss related to hemolysis and acute blood bleeding (4, 5).

Indeed, iron deficiency is the most common micronutrient deficiency and the most common cause of anemia in the world. About half (50%) of the cases of anemia are attributed to iron deficiency. Iron deficiency anemia (IDA) is more prevalent in low-income countries (6). Anemia is a serious problem and challenge in the world that can affect about one-third of people around the world (women, young children, and individuals with long-term diseases) in both developed and developing countries (7, 8). It is a fact that anemia is more prevalent among children and women of reproductive age, including postnatal women, and can cause morbidity and mortality in women in addition to fetal consequences (9).

Anemia is a significant cause of maternal mortality and morbidity on a global scale. It affects 38% of pregnant women and 29% of non-pregnant women, with the highest proportion in central and west Africa (56%) (10). Around 500 million women of reproductive age are affected by anemia, which is a major public health challenge for low- and middle-income countries (11). One of the developing countries, Ethiopia, had the highest rates of maternal deaths in 2016, with 412 women dying for every 10,000 live births (12). This mortality is mainly associated with prolonged iron loss due to postpartum hemorrhage (PPH), which is a leading predictor of cardiac arrhythmias (13, 14). It is also associated with lower global household income, cognitive and psychological impairment, poor quality of life, emotional instability, and postpartum depression (1, 15).

In addition, PPA has the highest risk of endometritis and thrombotic complications secondary to iron deficiency and local ischemia (16, 17). Furthermore, the prevalence of anemia among lactating women has increased from 23.03 to 28.3% in Ethiopia over the past two and a half decades (2011–2016) (18). PPA is primarily linked to poor economic development, obstetric problems, and low nutritional status. Evidence suggests that obstetric factors are a significant source of PPA, leading to morbidity and mortality in women of reproductive age (19). During delivery, women experienced traumatic processes, leading to PPH. Different studies investigated the risk factors for PPA, including PPH, maternal residence, blood loss, and maternal level of education. This could be attributed to active bleeding during delivery, which causes a drop in Hb levels both before and after delivery (20).

It is also characterized by their socioeconomic context. Higher prevalence rates (57.2%) of anemia among rural women aged 20 years and older were observed in India (21). PPA is also a common problem in countries with stronger economies (22). Low maternal education levels, poor socioeconomic status, and living in rural areas all play a significant role in the development of anemia in women (23). Women with low dietary diversity had a higher risk of anemia (24). During pregnancy, improved and increased adherence to iron and folic acid was found to reduce the possible risk of anemia in postnatal women. Vitamin and mineral deficiencies may worsen during pregnancy due to increased energy and nutrient demands, causing adverse outcomes for both mother and child (25).

In addition to this, anemia in women of reproductive age is a significant issue, and the WHO has set a global goal of attaining a 50% reduction in anemia in women of reproductive age by 2025 (26). To achieve the WHO target, addressing anemia in postnatal women is of great importance. However, there are only a few rigorous studies conducted on PPA in Africa, particularly in Ethiopia. Although blood morphology is helpful in the diagnosis and categorization of the pathophysiology of anemia (27). In addition, parasitic infection is an independent predictor of anemia. However, the available studies did not reveal this. As a result, this study highlighted important findings that can help improve the maternal healthcare system.

Abbreviations: ANC, Antenatal Care; AOR, Adjusted Odds Ratio; BMI, Body Mass Index; CI, Confidence Interval; COR, Crude Odds Ratio; CS, Cesarean Section; DDS, Dietary Diversity Score; FAO, Food and Agricultural Organization; G/dl, gram per deciliter; Hb, hemoglobin; HCT, hematocrit; HIV, human immunodeficiency virus; IDA, iron deficiency anemia; IP, intestinal parasite; IQR, interquartile range; K3-EDTA, tri-potassium ethylene diamine tetra-acetic acid; KM, kilometer; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; Ml, milliliter; PNC, postnatal care; PPA, postpartum anemia; PPH, postpartum hemorrhage; QC, quality control; RBC, red blood cell; RDW, red cell distribution width; RPM, revolutions` per minute; UGCSH, University of Gondar Comprehensive Specialized Hospital; WHO, World Health Organization.

Methods

Study area, design, and period

A facility-based cross-sectional study was conducted in the town of Gondar, in the Amhara regional state, from March to May 2021. Gondar has one hospital and eight public health centers. The estimated population projection for Gondar was 362,000 in 2020 (28). Gondar is situated about 727 kilometers (km) northwest of Addis Ababa and 185 km from the city of Bahir Dar. It is located at an altitude of 2,133 meters above sea level at 12° 36′ north and 37° 28′ east, latitude and longitude, respectively (29).

Population

Source and study population: All postnatal women in Gondar were considered as the source population. All postnatal women who gave birth and attended the postnatal care (PNC) clinic at the Gondar Health Center and the University of Gondar Comprehensive Specialized Hospital (UGCSH) and were available during the data collection period were considered as the study population.

Sample size determination

The sample size was determined by a single population proportion formula, considering a 5% margin of error at 95% CI, and by taking the 24.3% prevalence reported in the previous study (30):

$$N = (Z\alpha / 2)^2 \left(\frac{\mathrm{p}(1-\mathrm{p})}{\mathrm{d}^2} \right)$$

where N = the desired sample size, z = 1.96, standard normal distribution value at 95% CI corresponding to a significant level of alpha, and d = acceptable margin of error.

$$N = (1.96)^2 \left(\frac{0.243(0.76)}{(0.05)^2} \right) = 282$$

The total sample size calculated for this study was 282 postnatal women.

Sampling technique

Of the nine public health facilities, two of them, the Gondar Health Center and the UGCSH, were selected using a simple random sampling technique. Using the monthly postnatal women numbers from both facilities (450 from UGCSH and 180 from the Gondar Health Center), the interval value was calculated by dividing the estimated total number of women within the calculated sample size (1890/282 = 6.7) by the proportionate population size in each health facility. For instance, the estimated total number of women in UGCSH during the study period (900) was divided by the interval (4.46) to yield a proportionate sample, which was approximately 201, and the same method was used for the Gondar Health Center, where 81 postnatal women were recruited. Then, a systematic sampling technique was employed, using an interval of four based on the corresponding sample size from each health facility. The lottery method was applied to select the first four participants, and every four women were interviewed until the allocated sample size was achieved (Figure 1).

Inclusion criteria and exclusion criteria: All postnatal women who delivered in the selected health institutions and volunteered to participate were included in the study. Women with a medical history of hypertension, kidney disease, human immunodeficiency virus (HIV), or hepatitis B, too ill to give informed consent, receiving any form of hematinic, or those who had been recently transfused were excluded from the study.

Variables

Dependent variables: Anemia was a dependent variable. Before determining whether a woman was anemic or not, altitude was considered. The adjustment for altitude was made to account for the decrease in blood oxygen saturation. The Hb level was adjusted using the following formula: (adjustment = −0.032 (altitude * 0.0032808) + 0.022 (altitude * 0.0032808)^2 and adjHb = Hb − adjustment (when adjustment >0)) (31).

Independent variables: Socio-demographic variables (maternal age, educational level, residence, marital status, religion, family size, occupation), obstetric variables (parity, frequency of antenatal care (ANC) visits, history of abortion and malaria infection, place and mode of delivery, iron and folate supplementation during pregnancy, PPH, intestinal parasites (IP), family planning, birth within 5 years), and nutritional variables such as dietary diversity, weekly meat consumption, daily fruit and vegetable consumption, coffee and tea drinking habits were considered as independent variables.

Operational definitions

High dietary diversity: Consumption of at least 7 foods from 10 food groups (32, 33).

Low dietary diversity: Consumption of four or fewer foods from 10 food groups (32, 33).

Minimal dietary diversity: Consumption of at least five foods from 10 food groups (33, 34).

Postpartum anemia: Adjusted Hb levels of postnatal women below 11 gm/dl within 24 h and 12gm/dl up to 6 weeks after the birth period result in postpartum anemia, which is further classified as mild (adjHb = 11–11.9 gm/dl), moderate (adjHb = 8–10.9gm/dl) and severe (adjHb <8 gm/dl) (1, 2).

Postpartum hemorrhage: Bleeding during delivery is classified as mild (500-1,000 ml), moderate (1000–2000 ml), and heavy (>2000 ml) postpartum hemorrhage.

Data collection techniques

After obtaining written informed consent, socio-demographic variables such as age, educational attainment, marital status,

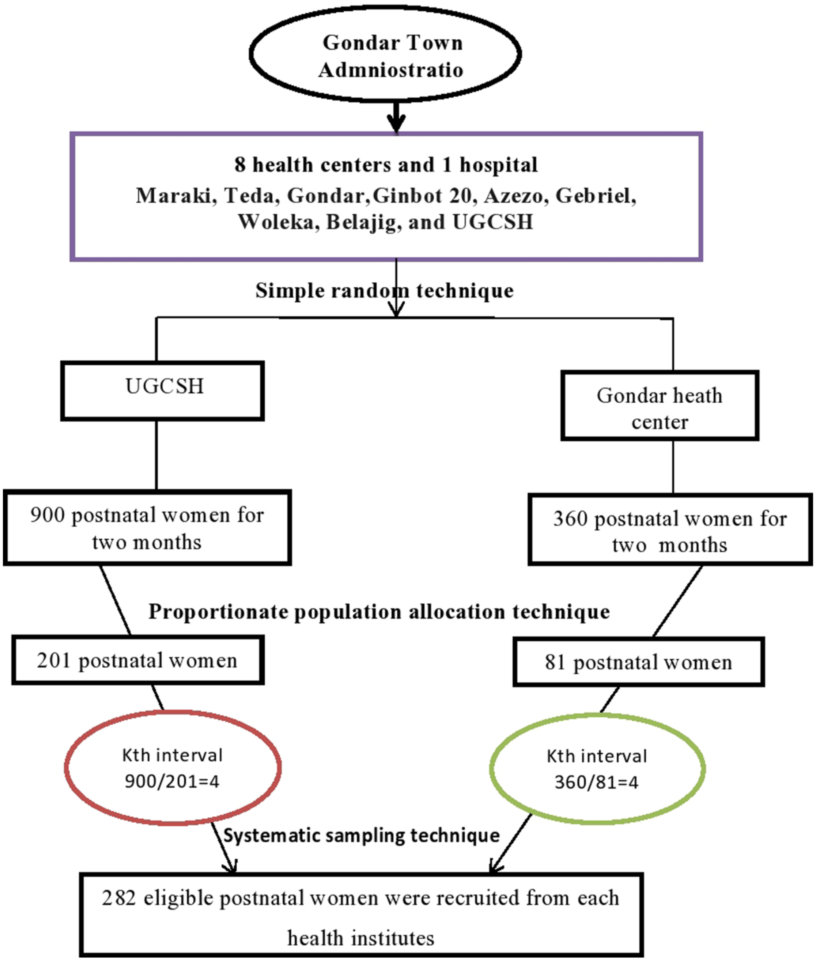

FIGURE 1
Schematic presentation of sampling technique.

occupation, and related characteristics of postnatal women were collected through face-to-face interviews using a pre-tested, semi-structured questionnaire at the obstetric and gynecological wards and PNC units of UGCSH and the Gondar Health Center. Obstetric and clinical data were collected using physical examinations, chart reviews, and laboratory tests. Detailed information on the history of abortion and malaria infection, and iron and folic acid supplements during pregnancy, were collected from the charts. According to the guidelines of the Food and Agriculture Organization (FAO), a Dietary Diversity Score (DDS) was assessed.

Blood sample collection and analysis: A 5 ml venous blood sample was collected by well-trained laboratory personnel using standard aseptic procedures and sent to the hematology laboratory. The blood sample was placed in a labeled tri-potassium ethylenediaminetetraacetic acid (K3-EDTA) tube. An automated, compact 5-part differential hematology analyzer (Beckman Coulter UniCel DxH 800) was used to determine hematological parameters. A drop of blood from a confirmed anemic woman was put on a microscopic slide, and a thin smear was prepared. The smear was stained with undiluted Wright's staining solution based on standard operating procedures. It was then air-dried, labeled with an identification number, and examined under a microscope with a 100X oil immersion objective by well-trained hematologists. RBC shape, size, color, and cellular inclusions were carefully evaluated for morphologic examination.

Stool sample collection and examination: Pea-sized stool samples were collected from each study participant using a clean, wide-mouth, leak-proof stool cup. Wet mount preparation and the formol-water concentration technique were used to detect IP. Fresh stool samples were mounted on a microscope slide with a wooden applicator stick and emulsified with a drop of physiological saline (0.85% w/v NaCl). The concentration technique was used on the remaining samples for the concentration of IP.

The fecal sample was emulsified in 10 ml of formol-water (10% v/v) in a screw-cap bottle. The suspension was strained into a conical tube by using gauze to extract large fecal particles and centrifuged at 1500 rpm for 3 min. Then, it was re-suspended by using 4–3 ml of formol water and 3–4 ml of ether or ethyl acetate and centrifuged at 3,000 rpm for 1 min. Finally, the supernatant was removed, and the sediment was examined under the microscope. A stool examination was performed according to standard operating procedures. Any helminth eggs, larvae, or cyst stages were detected. All samples were collected through laboratory tests using the participants' laboratory information checklist.

Data quality management: The questionnaire was prepared in English, translated into the local language (Amharic), and then translated back into English for consistency. Prior to data collection, the data collection tool was pretested on 14 volunteer postnatal women at UGSCH. There were inaccuracies in the measurement of body mass index (BMI), which was therefore omitted. Prior to data collection, orientation was provided to data collectors. During the data collection process, there was close monitoring to ensure data accuracy and consistency. Following blood collection, to avoid hemolysis, the blood was applied to the wall of the test tube. Data were collected by well-trained health professionals (five midwives and three laboratory staff).

Prior to running the participants' sample, the accuracy of the hematology analyzer was checked with high-, normal-, and low-quality control (QC) materials. All reagents were checked for expiration dates and prepared according to the manufacturer's instructions. A morphological examination was carried out on the known mean corpuscular volume (MCV) and mean corpuscular Hb concentration (MCHC) of healthy individuals to ensure the quality of the staining reagent. The stool wet mount and suspension were made within the appropriate concentration of sample and reagents. Fresh stool samples were observed within 30 min of collection. Finally, all results were documented and registered with the correct value and units.

Data processing, analysis, and interpretation

The data were checked for completeness and consistency. Then, they were coded and double-entered into EpiData, version 4.6.0.0, before being imported into Stata, version 14.0, for analysis. The data was cleaned, and preliminary analyses were carried out. Descriptive statistics were summarized using frequency, percentage, median, mean, interquartile range (IQR), and standard deviation for presentation in text, tables, and figures. A binary logistic regression model was used to assess factors associated with the outcome variable. Variables with a *p*-value of ≤ 0.25 were adjusted for multivariable analysis. In the model, a backward variable selection was used. The *Hosmer* and *Lemeshow* post-estimation statistical test was performed to check the goodness of fit. A *p*-value ″ 0.05 was considered statistically significant.

Results

Socio-demographic characteristics

A total of 282 postpartum women were included in this study. The median age of the participants was 28 years, with an IQR of 24–30. Approximately 62.8% of the participants were between the ages of 25 and 34. Three-fourths (75.9%) of the respondents were from urban areas. One-third (29.4%) of respondents were illiterate. Of the total participants, 242 (85.8%) were married (Table 1).

Obstetric and clinically related characteristics

Of the total study population, 162 (57.5%) women were multiparous. A total of 159 (56.4%) of the participants had experienced PPH. The majority of women, 256 (90.8%) individuals, had at least one ANC visit during pregnancy, with 62.9% of them having at least 4. Most (98.2%) of the women had delivered at a health facility. A total of 209 (74.1%) had a vaginal delivery (Table 2).

Dietary characteristics

More than half of the women (150, or 53.2%) had low dietary diversity. A total of 114 (40.4%) women ate meat at least once per week. More than half of the women (158, or 56%) consumed fruit and vegetables at least once a day. A total of 229 women (81.2%) had the habit of drinking coffee; 183 of them (79.9%) preferred to do so 30 min after food consumption (Table 3).

Laboratory findings

The median adjusted Hb value of the women was 12.1 gm/dl (IQR: 10.8–13.1 gm/dl). A total of 126 (69.5%) women had an RBC count $\geq 4.0 \times 10^9$/l with a mean value of $4.21 \pm 0.78 \times 10^9$/l. The median HCT value was 38.3% (IQR = 34.8–41.5%) with 68.4% ≥ 36%. The result of the stool examination showed that 84 (29.8%) of them were positive for at least one IP. A. *lumbercoid* was the predominant one, with a proportion of 46.4% (Table 4 and Figure 2).

TABLE 1 Socio-demographic characteristics of post-natal women in Gondar town, Northwest Ethiopia, 2021 (*n*=282).

Variables	Categories	*n*	%
Age	15–24	81	28.72
	25–34	177	62.77
	35–49	24	8.51
Maternal educational status	Unable to read and write	83	29.43
	Primary school	70	24.82
	Secondary school	55	19.50
	College and above	74	26.24
Maternal residence	Urban	214	75.89
	Rural	68	24.11
Maternal occupation	Farmer	48	17.02
	Private	72	25.54
	Governmental employee	47	16.67
	Others	115	40.78
Maternal family size	≤4	183	64.89
	5–8	99	35.11
Maternal marriage status	Single	18	6.38
	Married	242	85.82
	Divorced	13	4.61
	Widowed	9	3.20
Maternal religion	Orthodox	244	86.52
	Protestant	11	3.90
	Muslim	27	9.57

Others for maternal occupation represent students, unemployed, merchants, housewives, daily laborers and non-governmental organization workers *n*: represents for frequency and % indicates percentage.

TABLE 2 Obstetric and clinical characteristics of postnatal women in Gondar town, Northwest Ethiopia, 2021 (*n*=282).

Variables	Categories	*n*	%
Parity	Primipara	120	42.55
	Para 2–4	147	52.13
	Grand multiparous	15	5.32
PPH	Yes	159	56.38
	No	123	43.62
Severity of PPH	Mild	70	24.82
	Moderate	62	21.99
	Severe	27	9.57
Place of delivery	At home	5	1.77
	Health institution	277	98.23
Mode of delivery	Vaginal	209	74.11
	CS	73	25.89
ANC follow up	Yes	256	90.78
	No	26	9.22
Frequency of ANC visit	<4 times	95	37.21
	≥4 times	161	62.89
Family planning	Yes	234	82.98
	No	48	17.02
Birth within 5 years	Yes	110	39.01
	No	172	60.99
History of recent abortion	Yes	39	13.83
	No	243	86.17
History of recent malarial infection	Yes	52	18.44
	No	230	81.56
Iron and folate supplementation	Yes	208	73.76
	No	74	26.24

ANC, Antenatal care; CS, cesarean section. *n* represents for frequency and % indicates percentage.

TABLE 3 Nutritional characteristics of postnatal women in Gondar town, Northwest Ethiopia, 2021 (*n*=282).

Variables	Categories	*n*	%
Diet diversity level	Low	150	53.19
	Medium	118	41.84
	High	14	4.96
Weakly meat	At least once	114	40.43
consumption	Less than once	168	59.57
Daily fruit and vegetable consumption	At least once	158	56.03
	Less than once	124	43.97
Tea drinking	Yes	191	67.73
	No	91	32.27
Tea taking habit	After 30 min of food	160	83.77
	Immediately after food	31	16.23
Coffee drinking	Yes	229	81.21
	No	53	18.79
Coffee taking habit	After 30 min of food	183	79.91
	Immediately after food	46	20.09

n: represents for frequency and % indicates percentage.

TABLE 4 Laboratory findings of postnatal women in Gondar town, Northwest Ethiopia, 2021 (n=282).

Laboratory tests	Categories	*n*	%
RBC count	$\geq$4.0 × 10^9/L	196	69.50
	<4.0 × 10^9/L	86	30.50
HCT value	≥36%	193	68.44
	24–35.9%	77	27.30
	<24%	12	4.23
MCV	80–100 fl	259	91.84
	<80 fl	14	4.96
	>100 fl	9	3.20
MCH	<27 pg	24	8.51
	≥27 pg	258	91.49
MCHC	≥32 gm/dl	274	97.16
	<32 gm/dl	8	2.84
RDW	11–15%	207	73.40
	>15%	75	26.60
RBC morphology	Normocytic normochromic	125	94.00
	Microcytic hypochromic	5	3.75
	Macrocytic normochromic	3	2.25
Stool examination	Positive for intestinal parasite (IP)	84	29.79
	Negative for IP	198	70.21

NB; RBC, red blood cell; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; IP, intestinal parasite; L, liter; Pg, picogram; Fl, femtolitre; Gm/dl, gram per deciliter; RDW, red blood cell distribution width.

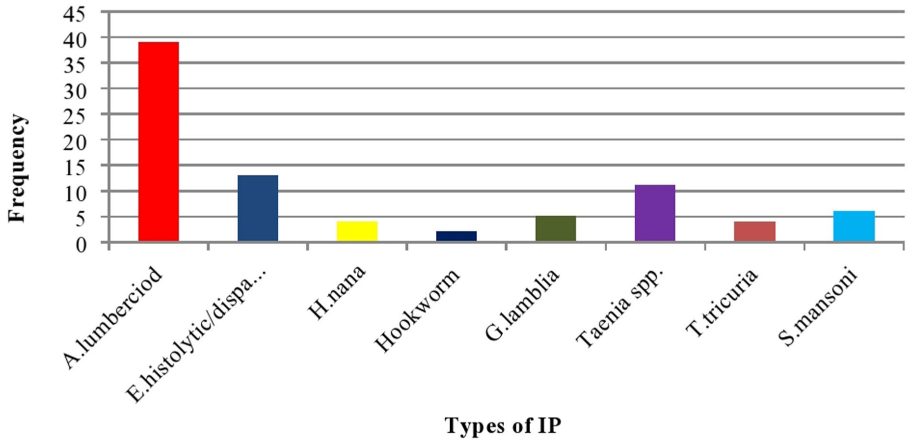

FIGURE 2
Bar graph showing the type of identified IP among postnatal women in Gondar town, Northwest Ethiopia, 2021 (n=282).

Prevalence, severity, and morphologic characteristics of PPA

Prevalence and severity: The overall prevalence of PPA anemia was 133 (47.16%; 95% CI: 41.30–53.03). Individuals with anemia were further classified into three categories: mild anemia (57, or 42.86%), moderate anemia (60 or 45.11%), and severe anemia (16, or 12.03%) (Figure 3).

Morphological characteristics of PPA

Based on the blood film reports, out of the total of 133 anemic women, the majority (125, or 94%) had a normocytic, normochromic blood picture. A total of 5 (3.76%) had a microcytic hypochromic blood picture, while 3 (2.24%) had a macrocytic blood picture (Table 4).

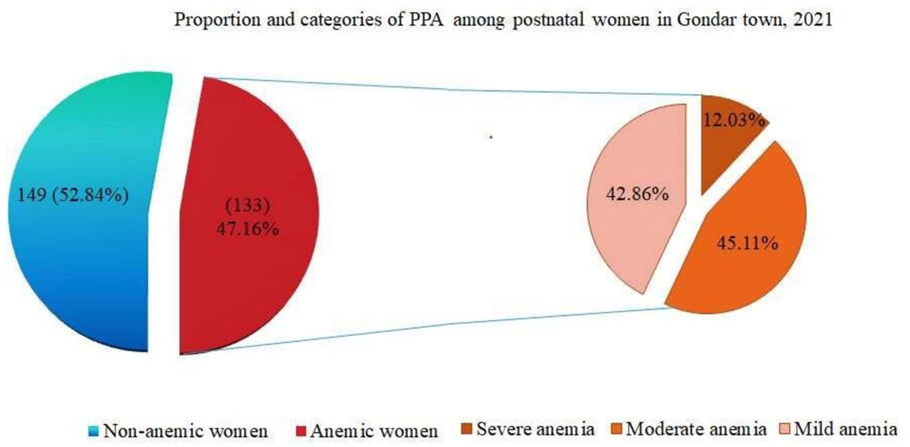

FIGURE 3
Pie of pie chart showing proportion and severity of PPA among postnatal women in Gondar town, 2021 (*n*=282).

Determinants of PPA in postpartum women

In univariate analysis, all variables were insignificant except PPH, mode of delivery, iron and folate supplementation during pregnancy, and level of dietary diversity. Women who experienced PPH (AOR = 2.23; 95% CI: 1.24–4.01), delivered *via* CS (AOR = 4.10; 95% CI: 2.11–7.78), did not take iron and folate supplementation during pregnancy (AOR = 2.12; 95% CI: 1.17–4.02) and had a low dietary diversity level (AOR = 1.83; 95% CI: 1.05–3.18) were at higher risk of PPA (Table 5).

Discussion

A number of factors have been associated with PPA. The change in Hb during the postpartum period would play an important role in providing baseline information. Thus, the current study aimed to assess the magnitude and factors associated with PPA among postnatal women in two selected health facilities in Gondar.

In this study, the prevalence of anemia among postnatal women was 47.16% (95% CI: 41.30–53.03). The finding was consistent with the results of studies conducted in southern India (47.3%) (35) and southeastern Kokang, Myanmar (56.3%) (36). In terms of severity, moderate anemia (45.11%) was common in this study. This finding was in line with a similar study conducted in India, which found 49.8% of moderate anemia types and 26% of mild anemia types (37).

On the other hand, the prevalence was lower than in studies conducted in Asia [eastern rural Myanmar (60.3%) (38) and India (76.2%; 95% CI; 70.4–81.4%) (38)]. This difference may be due to teff injera, a staple food consumed by most Ethiopian mothers (39), which contains more iron. In addition, it could be the coexistence of numerous contributing factors in rural Myanmar women like low family income, lack of primary education, hunger, drinking spring or river water, or drinking unboiled water, which could lead to anemia (38). It could be due to the fact that women in rural areas have poor socioeconomic status and, therefore, do not have access to iron-rich foods (40). Instead, given that the postpartum period is characterized by accelerated erythropoiesis and RBC mass expansion, it is possible that the hemodilution effect subsides and Hb levels return to normal in the participants in this study (35). Another reason for the discrepancy could be the difference in sample sizes, which were 227 and 733 in the India and Myanmar studies, respectively (38, 41).

The prevalence reported from the current study was higher than studies conducted in Japan (10.5%) (42), Spain, Mancha-Centro Hospital (16.4%) (22), northern Kenya (25%) (43), Ghana (16%) (44), Bhaktar, Nepal (20%) (45), Ethiopia – in Tigray (16.5%) (46), Sidama (19%) (47), Addis Ababa – at the Tikur Anbessa Specialized and Gandhi Memorial Hospitals (30%) (48), and in Debre Markos (24.3%) (30). The disparity may be due to differences in the geographical, cultural, clinical, and nutritional factors of women. In addition, different cutoff points were used to define PPA. Since there is no universally accepted definition of PPA, different researchers use different cutoff points, such as Hgb < 11 mg/dl at 24 h in Spain [Mancha-Centro Hospital (22) and in Debre Markos (30)]. In Madrid, Hgb < 10 mg/dl is used to indicate PPA for up to 6 weeks (49). In addition, there may be a difference in postpartum screening time. If the postpartum period is extended, mothers will have more time to recover from anemia or have their Hb levels increase (30). Iron is expected to improve in lactating women due to decreased iron requirements and reduced blood loss associated with amenorrhea (50).

According to RBC morphological findings, the majority of anemic women had a normocytic normochromic blood picture (94%), followed by a microcytic hypochromic (3.24%) and a macrocytic blood picture (2.24%). Possible causes include acute bleeding, or early iron deficiency (51).

Postpartum hemorrhage, iron and folate supplementation during pregnancy, CS, and low dietary diversity were found to be significantly associated with PPA. In this study, the prevalence of anemia was found to increase in women who experienced PPH. The odds of PPA were 2.2 times higher among women who had experienced PPH (AOR = 2.23; 95% CI: 1.24–4.01) than their counterparts. Probably, uterine atony, uterine inversion, coagulopathy, vaginal tears, uterine laceration, and retained tissue or placenta may expose women to cycles of bleeding, which can lead to Hb declines. The majority of studies showed Hb and HCT declines in the context of overt PPH. Excessive blood loss during and after delivery, in addition to

TABLE 5 Logistic regression showing factors associated with PPA in Gondar town, Northwest Ethiopia, 2021 (*n*=282).

Independent variables	Categories	PPA		COR [95% Conf. Interval]	AOR [95%Conf. Interval]
		Yes	No		
Maternal age	15–24	36	45	1.00	1.00
	25–29	56	59	1.18 (0.60–1.95)	1.42 (0.74–2.72)
	30–49	41	45	1.14 (0.63–2.10)	1.30 (0.62–2.74)
Residence	Urban	96	118	1.00	1.00
	Rural	37	31	1.47 (0.85–2.54)	0.97 (0.48–1.95)
Educational status	Unable to read and write	37	46	0.99 (0.53–1.88)	0.96 (0.46–2.04)
	Primary	38	32	1.48 (0.77–2.8)	1.02 (0.49–2.12)
	Secondary	25	30	1.04 (0.51–2.08)	1.16 (0.53–2.52)
	College and above	33	41	1.00	1.00
Marital status	Single	19	21	1. 02 (0.52–1.99)	1.05 (0.49–2.22)
	Married	114	128	1.00	1.00
Parity	Primipara	63	57	1.00	1.00
	Multiparous	70	92	0.69 (0.43–1.12)	0.48 (0.23–1.01)
PPH	Yes	95	64	3.32 (2.02–5.45)***	2.23 (1.24–4.01)**
	No	38	85	1.00	1.00
Mode of delivery	Vaginal	78	131	1.00	1.00
	CS	55	18	5.13 (2.37–9.36)***	4.10 (2.11–7.78)***
Iron and folate supplementation	Yes	89	119	1.00	1.00
	No	44	30	1.96 (1.14–3.36)**	2.12 (1.17–4.02)**
Births in 5 years	Yes	44	66	0.63 (0.39–1.01)	0.66 (0.34–1.29)
	No	89	83	1.00	1.00
ANC follow up	Yes	116	140	1.00	
	No	17	9	2.28 (0.98–5.30)	2.01 (0.69–6.24)
Tea drinking	Yes	97	94	1.60 (0.94–2.62)	1.05 (0.57–1.94)
	No	36	55	1.00	1.00
Diet diversity level	Low	83	67	2.03 (1.26–3.27)***	1.83 (1.05–3.18)*
	Minimal diet	50	82	1.00	1.00

PPA, postpartum anemia; PPH, postpartum hemorrhage; AOR, adjusted odds ratio; COR, crude odds ratio; CS, cesarean section; Conf. Interval, confidence interval.
*, **, *** = p-values < 0.05, <0.01.

insufficient erythropoiesis, may also cause a drop in Hb throughout the postpartum period (35).

Compared to mothers who gave birth *via* the vaginal route, mothers who gave birth *via* CS had four times higher odds of anemia (AOR = 4.10; 95% CI: 2.11–7.78). The findings were in agreement with a similar study conducted in Tigray, which discovered that vaginal birth was associated with a lower risk of anemia (AOR = 0.13; 95% CI: 0.038–0.454) (52). This potentially traumatic surgical procedure could cause women to suffer a major hemorrhage, leading to PPH. Surgery is a key determinant of blood loss. Postoperative anemia, defined as a blood loss of more than 500 ml, is a common complication that affects 80–90% of people who have had major surgery (53).

The results of this study also suggested that women who were not supplemented with iron and folate during their pregnancy had twice as many chances of developing PPA as those who were (AOR = 2.12; 95% CI: 1.17–4.02). This conclusion was supported by studies from India (AOR = 3.53; 95% CI: 1.18–11.37) and Ethiopia (35, 54). The possible explanation would be that iron is the most important nutrient for hematopoiesis and that, when taken throughout pregnancy, it has the capacity to reduce anemia, even during delivery. The depletion of stored iron during pregnancy may also be a factor because of the high demand for iron during childbirth (30).

Women with a low level of dietary diversity were 83% more likely to suffer from anemia than those with a minimum level of dietary diversity (AOR = 1.83; 95% CI: 1.05–3.18). This finding was consistent with a study conducted among lactating women in Jimma District (AOR = 2.32; 95% CI: 1.65–5.72) (24). This could be due to inadequate dietary intake, leading to an iron, vitamin B12, folate, and vitamin A deficiency. Another reason could be a lack of protein and iron-containing foods such as eggs and meat, which could lead to an iron deficiency (36).

Many studies from Ethiopia and abroad discovered that inadequate and missed ANC follow-ups, multiparity, and low education levels were independent predictors of PPA (24, 54–58). However, these factors were not associated with PPA in this study.

Strengths and limitations

The women's hemoglobin concentration was adjusted for altitude. To make the sampling more representative, the probability sampling technique was used. Furthermore, the study estimates were done with the appropriate statistical analysis. As a result, we are confident that this study provides more precise and generalizable results that policymakers and program managers may use to develop action strategies for this issue.

Furthermore, anemia has been associated with antepartum hemorrhage (30), but this association has not been investigated. Due to budgetary constraints, we were unable to measure anemia indicators for further categorization. As a result, we were unable to identify the type of anemia.

Conclusion and recommendations

The prevalence of PPA in this study was a major public health concern. One in two postnatal women was found to be anemic with an adjusted Hb concentration below 12 g/dl. Iron and folate supplementation and the administration of uterotonics such as oxytocin during the third stage of labor will prevent PPH and PPA. To reduce the burden of anemia among postnatal women, health education and promotion of iron and folate supplements during pregnancy, in addition to dietary diversity practices, need to be combined with women's long-term income-generating activities. Anemia in women who have had cesarean deliveries may also be avoided by efficient CS delivery, a positive long-term health outlook following CS, and postoperative monitoring. Thus, due attention must be given to reduce the magnitude of PPA through effective antepartum, intrapartum, and postpartum maternal care. In addition, further research is required to address the limitations of this study.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by Ethical approval and consent to participate. The research was conducted after ethical clearance was secured with reference number of SBMLS/2747 from Ethical Review Committee of School of Biomedical and Laboratory Sciences, College of Medicine and Health Sciences, University of Gondar. In addition, permission was obtained from each selected health institution. Moreover, informed consent was secured from each study participants and the obtained data were strictly confidential. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

Author contributions

GB conceived the idea, wrote the proposal, performed the data analysis and interpretation, wrote the initial draft, and revised subsequent drafts. MM and ES provided advice on study design, data analysis, and interpretation, and reviewed and commented on subsequent drafts. SK and CS participated in data collection and laboratory processing, and assisted in drafting the manuscript. MM and ES revised and edited the manuscript. All authors approved the submitted version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Frank A. Orlando,
University of Florida, United States

REVIEWED BY
Rohan Mehta,
University of Florida, United States
Nivedita Kamath,
St. John's Medical College Hospital, India

*CORRESPONDENCE
Subrata Kumar Palo
✉ drpalsubrat@gmail.com

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Prevalence and pattern of multimorbidity among chronic kidney disease patients: a community study in chronic kidney disease hotspot area of Eastern India

Subrata Kumar Palo[1]*, Soumya Ranjan Nayak[1], Debadutta Sahoo[1], Swetalina Nayak[1], Ashis Kumar Mohapatra[1], Aviram Sahoo[1], Pujarini Dash[1] and Sanghamitra Pati[2]

[1]Model Rural Health Research Unit, ICMR-RMRCBB, Cuttack, India, [2]ICMR-Regional Medical Research Centre, Bhubaneswar, India

Introduction: Chronic kidney disease (CKD) is mostly asymptomatic until reaching an advanced stage. Although conditions such as hypertension and diabetes can cause it, CKD can itself lead to secondary hypertension and cardiovascular disease (CVD). Understanding the types and prevalence of associated chronic conditions among CKD patient could help improve screening for early detection and case management.

Methods: A cross sectional study of 252 CKD patients in Cuttack, Odisha (from the last 4years CKD data base) was telephonically carried out using a validated Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC) tool with the help of an android Open Data Kit (ODK). Univariate descriptive analysis was done to determine the socio-demographic distribution of CKD patients. A Cramer's heat map was generated for showing Cramer's coefficient value of association of each diseases.

Results: The mean age of participants was 54.11 (±11.5) years and 83.7% were male. Among the participants, 92.9% had chronic conditions (24.2% with one, 26.2% with two and 42.5% with three or more chronic conditions). Most prevalent chronic conditions were hypertension (48.4%), peptic ulcer disease (29.4%), osteoarthritis (27.8%) and diabetes (13.1%). Hypertension and osteoarthritis were found to be most commonly associated (Cramer's V coefficient=0.3).

Conclusion: Increased vulnerability to chronic conditions among CKD patients make them at higher risk for mortality and compromised quality of life. Regular screening of CKD patient for other chronic conditions (hypertension, diabetes, peptic ulcer disease, osteoarthritis and heart diseases) would help in detecting them early and undertake prompt management. The existing national program could be leveraged to achieve this.

KEYWORDS

CKD, multimorbidity, GFR, chronic conditions, Cramer's coefficient

Introduction

Chronic kidney disease (CKD) is defined as a decrease in Glomerular Filtration Rate (GFR) to less than 60 mL/min/1.73m^2 for at least 3 months, irrespective of cause (1, 2). It was estimated, around 13% of the world's population has CKD. Additionally, prevalence estimates imply the problem is 15% greater in low- and middle-income nations compared to high-income ones (3). CKD is mostly asymptomatic until its stage is advanced (4) and so, the documented cases presenting to hospitals represent the tip of the iceberg. As the disease stage progresses, it leads to many complications that include CVD (myocardial infarction, ischemic stroke, peripheral vascular disease, valvular disease and arrhythmias), anemia, bone mineral disease, volume overload and electrolyte imbalances (5). On the other hand, diseases such as hypertension and diabetes mellitus are known risk factors for CKD (6, 7). Hence, CKD is often linked to multimorbidity (3). Multimorbidity is defined as presence of two or more chronic conditions in the same individual at a point in time (8). Research study among older age group (>60 years) has shown multimorbidity to be prevalent in 73.9% of general participants and 86% among participants having CKD (any stage) (9). The presence of multimorbidity especially among CKD patients increases the risk of complications and influences the prognosis greatly leading to longer hospital stays, greater health-care expenses, mortality, polypharmacy and low quality of life (4, 10). Early detection of associated morbidities through detailed evaluation in the community and their prompt management will undoubtedly aid in preventing the potential consequences (10). As in other lower middle income countries (LMICs), multimorbidity has become the norm among Indian adults. Data on the prevalence and pattern of multimorbidity among CKD patients in India, particularly in a rural setting, are nonetheless lacking. Decision-making about the degree of multimorbidity in CKD patients in India is therefore hindered by contradicting clinical guidelines, particularly in a rural setting (11, 12). Because of this, contemporary health care programs urgently need guidance concerning the pattern and prevalence of multimorbidity.

In India, many states have hotspot regions for CKD including Odisha, an Eastern state (13). Badamba and Narasinghpur blocks of Cuttack district, Odisha, are in the limelight for CKD burden for last more than a decade and have brought the attention of researchers, program implementers and policy makers to prevent and control it (14). With this backdrop, a research study was carried out to determine prevalence of multimorbidity among CKD patients and explore the pattern of chronic conditions among CKD population of the said areas. This will primarily aid policy makers in identifying which other disease areas' recommendations should be taken into account when incorporating renal disease recommendations. This study was done through Model Rural Health Research Unit (MRHRU) established in the catchment area of this CKD hotspot.

Materials and methods

A cross-sectional study was conducted among the diagnosed CKD patient in the catchment area of MRHRU at Tigiria, a block of Cuttack district, Odisha. Under the study, a total of 674 CKD patients diagnosed between (January 2017–January 2021) were line listed after collecting data from the healthcare management information system (HMIS) database of community health centers of both the study blocks. Among all the patients, 97 were deceased, 99 were bed ridden and 221 could not be contacted (incorrect phone number). Finally, among the 257 CKD patients contacted for the study, 5 declined to participate, and a total of 252 interested participants who verbally consented for the study were enrolled, with a non-response rate of 1.95%.

Data collection tool

A standardized structured schedule 'Multimorbidity Assessment Questionnaire for Primary Care (MAQ-PC)' was used for data collection. This is a validated tool for community based assessment of multimorbidity (15). Additionally, socio-demographic information was collected using a standardized tool. Considering the COVID-19 pandemic related restrictions during the study period, data were collected telephonically by the trained field investigators using an android based Open Data Kit (ODK) platform.

Statistical analysis

Univariate descriptive analysis was done to determine the socio-demographic distribution of CKD patients tabulated by *n* (%) and confidence interval. To assess the distribution of associated disease with number of chronic conditions, a bivariate descriptive table was presented with *n* (%). A Cramer's heat map was generated by estimating Cramer's V coefficient value by using R studio 2021.09.1 to assess the association between diseases among participants having two or more chronic conditions other than CKD.

Results

The mean age of the study participants was 54.11 (±11.57) years, ranging from20 to 86 years. While 52.4% were in the (40–59) age group, 37.7% were 60 or above and 9.9% were in the 20-39 age group. The majority (83.7%) were male, 97.6% of participants were Hindus and 91.5% were married. While most of the participants (88.2%) were from rural villages, 84.9% of participants were literate,69.1% of participants belonged to below poverty line (BPL) and 44.1% had monthly family income less than 6,000 Indian rupees. The detailed socio-demographic distribution of study participants is presented in Table 1.

Among 252 study participants, 234 (92.9%) had other chronic conditions apart from CKD (multimorbidity). Upon analyzing for the number of chronic conditions associated at the individual level, 18 (7.1%) had no other chronic condition, 61 (24.2%) had one additional chronic condition, 66 (26.2%) had two additional chronic conditions and 107 (42.5%) had three or more additional chronic conditions among CKD patients. The distribution of number of associated chronic conditions is presented in Figure 1.

Among the participants with multimorbidity, the major associated disease conditions included hypertension (48.41%), peptic ulcer

TABLE 1 Distribution of participants according to socio-demographic characteristics.

Socio-demographic characteristics	Participant (*N*=252) *n* (%)	95% Confidence interval
Age group		
20–39	25 (9.92%)	(6.52–14.29%)
40–59	132 (52.38%)	(46.01–58.68%)
60 above	95 (37.70%)	(31.69–43.99%)
Gender		
Male	211 (83.73%)	(23.25–78.58%)
Female	40 (15.94%)	(11.58–20.98%)
Religion		
Hindu	245 (97.61%)	(94.36–98.87%)
Islam	6 (2.39%)	(0.87–5.11%)
Marital status		
Currently married	226 (91.50%)	(87.29–94.66%)
Never married	11 (4.45%)	(2.24–7.82%)
Widow/Widower	10 (4.05%)	(1.95–7.31%)
Ethnicity		
General	76 (30.77%)	(25.07–36.93%)
OBC	111 (44.94%)	(38.62–51.37%)
Other	60 (24.29%)	(19.07–30.13%)
Residence		
Urban	29 (11.84%)	(8.07–16.55%)
Rural	216 (88.16%)	(83.44–91.92%)
Education		
Illiterate	36 (15.13%)	(10.82–20.32%)
Literate	202 (84.87%)	(79.67–89.17%)
House type		
Kutcha	58 (24.37%)	(19.05–30.33%)
Pucca	94 (39.50%)	(33.24–46.01%)
Semi pucca	86 (36.13%)	(30.02–42.59%)
Monthly family income		
Below 6,000	101 (44.10%)	(37.56–50.79%)
Above 6,000	128 (55.90%)	(49.20–62.43%)
Poverty status		
Above poverty line (APL)	73 (30.93%)	(25.09–37.25%)
Below poverty line (BPL)	163 (69.07%)	(62.74–74.90%)

disease (29.4%), osteoarthritis (27.8%) and diabetes mellitus (13.1%). The prevalence of different chronic conditions among CKD patients is depicted in Figure 2.

Upon further analysis of the associated morbidities according to number of chronic conditions among the participants with multimorbidity, a total of 346 co-morbid conditions were identified. Out of those, 15 (4.3%) were among participants having one additional chronic condition, 68 (19.6%) were among participants having two additional chronic conditions and 263 (76%) were among participants having three or more additional chronic conditions.

Among participants having one associated chronic condition, hypertension and peptic ulcer disease were the major associated conditions. Among participants with two associated morbidities, hypertension, osteoarthritis and peptic ulcer disease were the major conditions. Among participants with three or more additional comorbidities, hypertension, peptic ulcer disease, osteoarthritis and diabetes mellitus were the major associated conditions. The detailed distribution of chronic conditions is presented in Table 2.

We further analyzed the co-occurrence of different diseases among the study participants having two and more additional chronic conditions. To find out this association between diseases, the eight most prevalent chronic conditions were considered to run a Cramer heat map (refer to Figure 2; Table 2). Cramer's V coefficient lies between 0 and 1, where 0 indicates no association between diseases and 1 indicates a perfect strong association between the diseases. The highest crammer's V coefficient value (0.3) was between hypertension and osteoarthritis. Crammer's V coefficient value of 0.2 was observed between diabetes mellitus and peptic ulcer disease, chronic backache and osteoarthritis, osteoarthritis and peptic ulcer disease, and diabetes mellitus and dementia. Among other diseases, the Crammer's V coefficient value was either 0.1 or 0. The association between morbidities is depicted in Figure 3 below.

Discussion

With improved life expectancy, aging people are also at increased risk for chronic illnesses such as hypertension, diabetes mellitus, cancer, chronic kidney disease and mental health problems (16). In addition to aging, unhealthy lifestyles and unplanned exposure to urban environments attribute to the occurrence of non-communicable diseases (17). Due to limited research studies on multimorbidity among CKD patients, the present study has explored the prevalence of other chronic conditions among CKD patients in the hotspot area of Odisha, Eastern India. Additionally, we assessed the pattern of other chronic conditions among CKD patients.

CKD patients have a high prevalence of multimorbidity because CKD is a systemic disorder. In our study, we found that the majority of participants had two or more other chronic conditions in addition to CKD. This finding is supported by a study conducted in the UK with 1741 participants, which revealed that the majority of participants had two or more chronic conditions in addition to CKD (18). Our study also showed that about one-fifth of the participants had one or more other chronic conditions in addition to CKD, which is supported by a study among primary care patients that found 26 and 29% of all participants had one and two other chronic conditions, respectively, in addition to CKD (18). As the kidneys are responsible for filtering waste products, electrolyte balance, and important endocrine system functions, progression of CKD can cause toxin accumulation, electrolyte imbalances, and certain endocrine dysfunctions. As a result, CKD progression can cause disruptions to numerous metabolic pathways. While the sodium dysregulation, increased sympathetic nervous system, and

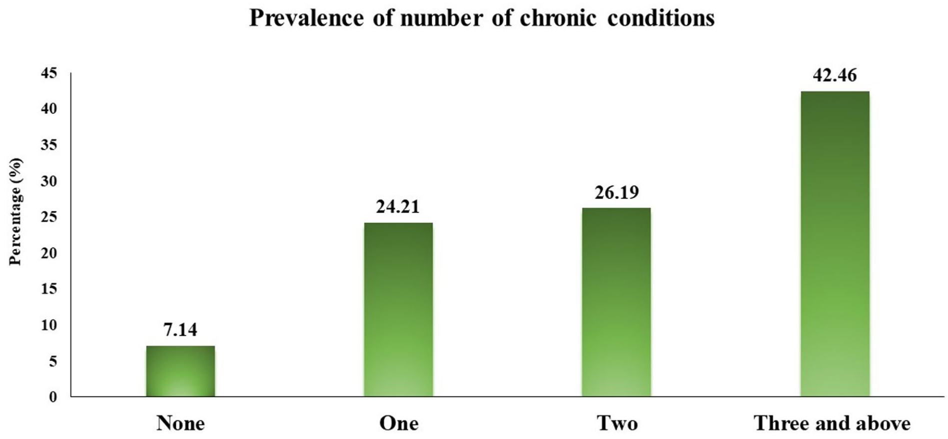

FIGURE 1
Distribution of number of other chronic conditions among participants.

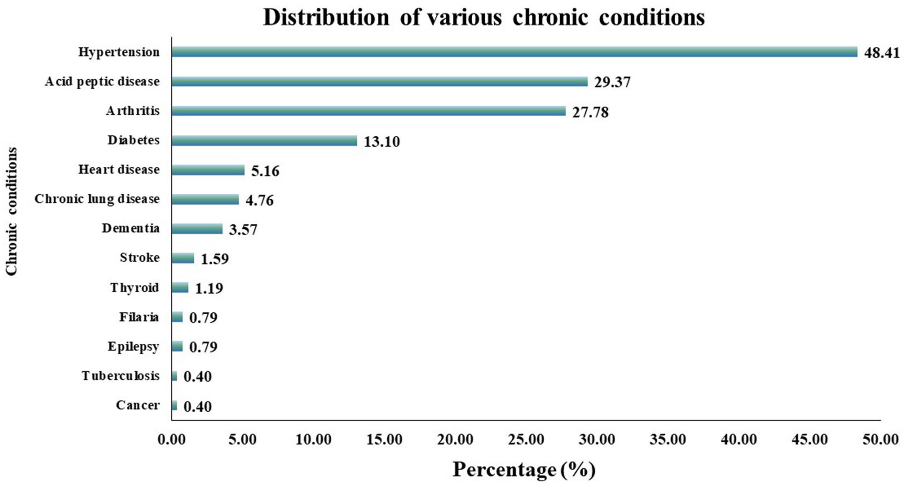

FIGURE 2
Prevalence of various chronic conditions among CKD participants with Multimorbidity.

alterations in the renin-angiotensin aldosterone system caused by CKD have primarily been associated with hypertension (19), these pathologic conditions could lead to the occurrence of other chronic diseases.

The presence of additional chronic conditions leads to an increased risk of mortality and a poor quality of life (18). The most prevalent associated disease conditions that we found were hypertension followed by peptic ulcer disease, osteoarthritis and diabetes mellitus. This finding was also reflected by a community based study from North Kerala which found the chronic conditions among CKD patient include hypertension (61.4%), diabetes (47.3%), cardiovascular disease (30.6%), chronic obstructive pulmonary disease (10%), malignancies (2.6%), and retinopathy (28%) (20). Both Studies found that hypertension is the most common co-morbid condition, and this correlates with the pathophysiology of CKD-associated hypertension where renin-angiotensin-aldosterone system (RAAS) over expression accompanied by eGFR reduction results in sodium and water retention (19).

Whereas CKD is an attributing factor for many other non-communicable diseases such as cardiovascular diseases, hypertension, anemia, bone mineral, volume overload and electrolyte imbalances (5), diseases such as hypertension and diabetes mellitus are risk factors for CKD (8). In addition, studies have shown that consumption of NSAIDs is another important CKD risk factor (21). Patients suffering from osteoarthritis often take pain medicines such as non-steroidal anti-inflammatory drugs (NSAIDs). Also, these drugs cause peptic ulcer diseases (22, 23). In this context, we also observed a higher association between hypertension and osteoarthritis, diabetes and peptic ulcer disease, and osteoarthritis and peptic ulcer disease. This clearly indicates that CKD patients are more vulnerable for having multimorbidity because of the risk factors involved, nature and complications of the disease, and the medications prescribed and consumed.

TABLE 2 Distributions of number of associated disease conditions according to presence of number of chronic conditions.

Chronic conditions	None or One comorbidity	Two comorbidities	Three and above comorbidities
Hypertension	7 (46.7%)	28 (41.2%)	87 (33.1%)
Acid peptic	4 (26.7%)	11 (16.2%)	59 (22.4%)
Osteoarthritis	1 (6.7%)	21 (30.9%)	48 (18.2%)
Diabetes mellitus	2 (13.3%)	3 (4.4%)	28 (10.6%)
Heart disease	1 (6.7%)	1 (1.5%)	11 (4.2%)
Chronic lung disease	0	2 (2.9%)	10 (3.8%)
Dementia	0	0	9 (3.4%)
Stroke	0	0	4 (1.5%)
Thyroid	0	0	3 (1.1%)
Filaria	0	0	2 (0.8%)
Epilepsy	0	0	2 (0.8%)
Tuberculosis	0	1 (1.5%)	0
Cancer	0	1 (1.5%)	0
Total	15 (4.3%)	68 (19.7%)	263 (76%)

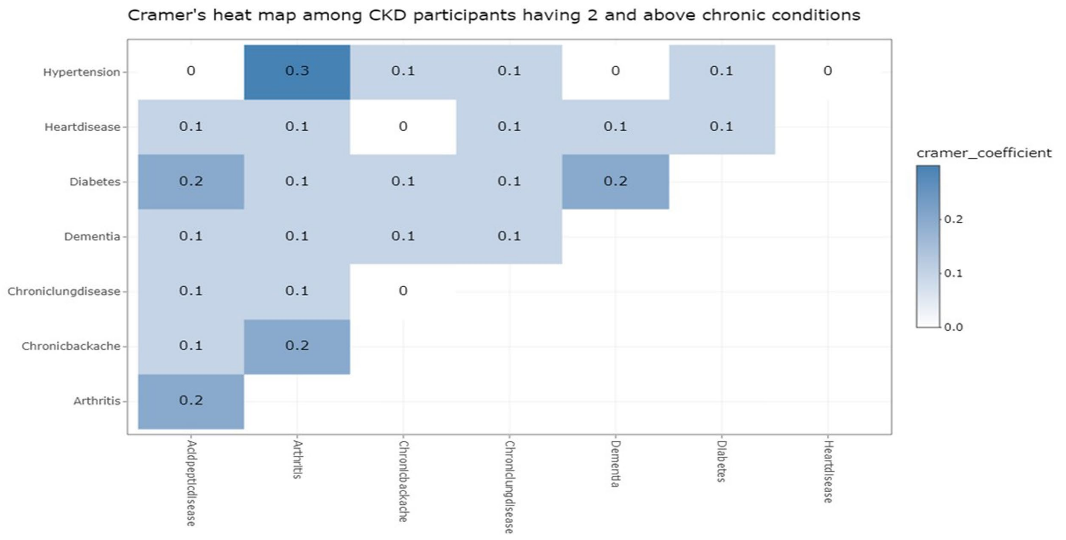

FIGURE 3
Crammer's heat map showing the association between chronic conditions.

Conclusion

In view of increased vulnerability for different chronic conditions among CKD patients leading to their higher risk of mortality and morbidity, it is critically important to regularly screen the CKD patient for hypertension, diabetes, peptic ulcer disease, osteoarthritis and heart diseases especially in CKD hotspot areas. Early detection of these chronic conditions and their prompt management could help in improving their quality of life and mortality. The current national program for prevention and control of cancer, diabetes mellitus, CVD and stroke (NPCDCS) through established health and wellness centers could be leveraged for this purpose.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by ICMR-Regional Medical Research Centre, Institutional Human Ethics Committee. Written informed consent to participate in this study was provided by the participants'.

Author contributions

SKP, SP, DS, SN, and SRN: conceptualization, design of the study, acquisition, and writing original draft. SRN, DS, SN, AM, and AS: data collection, data curation, statistical analysis, and writing original draft. SKP, DS, PD, and SP: intellectual content, study supervision, critical review, and draft editing. SKP, SRN, DS, SN, AM, AS, PD, and SP: integrity of any part of the work are appropriately investigated and resolved. All authors approved the final draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Sanghamitra Pati,
Regional Medical Research Center (ICMR),
India

REVIEWED BY
Kerryn Butler-Henderson,
RMIT University, Australia
Fiona Boland,
Royal College of Surgeons in Ireland, Ireland

*CORRESPONDENCE
Fantu Abebe Eyowas
✉ fantuabebe@gmail.com

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Multimorbidity and adverse longitudinal outcomes among patients attending chronic outpatient medical care in Bahir Dar, Northwest Ethiopia

Fantu Abebe Eyowas[1]*, Marguerite Schneider[2], Shitaye Alemu[3] and Fentie Ambaw Getahun[1]

[1]School of Public Health, College of Medicine and Health Sciences, Bahir Dar University, Bahir Dar, Ethiopia, [2]Alan J. Flisher Centre for Public Mental Health, Department of Psychiatry and Mental Health, University of Cape Town, Cape Town, South Africa, [3]School of Medicine, College of Medicine and Health Sciences, University of Gondar, Gondar, Ethiopia

Background: Multimorbidity is becoming more prevalent in low-and middle-income countries (LMICs). However, the evidence base on the burden and its longitudinal outcomes are limited. This study aimed to determine the longitudinal outcomes of patients with multimorbidity among a sample of individuals attending chronic outpatient non communicable diseases (NCDs) care in Bahir Dar, northwest Ethiopia.

Methods: A facility-based longitudinal study was conducted among 1,123 participants aged 40+ attending care for single NCD (n=491) or multimorbidity (n=633). Data were collected both at baseline and after 1year through standardized interviews and record reviews. Data were analyzed using Stata V.16. Descriptive statistics and longitudinal panel data analyzes were run to describe independent variables and identify factors predicting outcomes. Statistical significance was considered at p-value <0.05.

Results: The magnitude of multimorbidity has increased from 54.8% at baseline to 56.8% at 1year. Four percent (n=44) of patients were diagnosed with one or more NCDs and those having multimorbidity at baseline were more likely than those without multimorbidity to develop new NCDs. In addition, 106 (9.4%) and 22 (2%) individuals, respectively were hospitalized and died during the follow up period. In this study, about one-third of the participants had higher quality of life (QoL), and those having higher high activation status were more likely to be in the higher versus the combined moderate and lower QoL [AOR1=2.35, 95%CI: (1.93, 2.87)] and in the combined higher and moderate versus lower level of QoL [AOR2=1.53, 95%CI: (1.25, 1.88)].

Conclusion: Developing new NCDs is a frequent occurrence and the prevalence of multimorbidity is high. Living with multimorbidity was associated with poor progress, hospitalization and mortality. Patients having a higher activation level were more likely than those with low activation to have better QoL. If health systems are to meet the needs of the people with chronic conditions and multimorbidity, it is essential to understand diseases trajectories and of impact of multimorbidity on QoL, and determinants and individual capacities, and to increase their activation levels for better health improve outcomes through education and activation.

KEYWORDS

multimorbidity, quality of life, panel data, ordinal regression, Ethiopia

Background

Multimorbidity is usually defined as the occurrence of two or more coexisting chronic conditions in an individual (1).

Multimorbidity is a growing global challenge with substantial impacts on individuals, health systems and the society (1). Recent reviews reported a pooled prevalence of 42.4% in high-income countries (HICs) (2), 43% in Latin America and Caribbean (3) and 36.4% in low-and middle-income countries (LMICs) (4). The magnitude of chronic multimorbidity in a recent facility based study in northwest Ethiopia was 54.8% (5).

Although mechanisms underlying the development of multimorbidity are complex, the increasing burden of multimorbidity is due to population aging and changes in lifestyle risk factors, notably physical inactivity and obesity (6). Studies in HICs have also shown that multimorbidity is socially patterned, where it mainly affects and occurred much earlier in populations with socio-economic deprivation in HICs (7, 8) and in the wealthiest quintile group in LMICs (9). The rising incidences of multimorbidity in LMICs is further influenced by the presence of adverse environmental and early life stressors linked to poverty, limited social infrastructure and poorer coping mechanisms, which ultimately lead to occurrences of chronic diseases and multimorbidity at earlier ages (1).

Non communicable diseases (NCDs) multimorbidity is associated with many adverse consequences, including death at younger age (10–12), impairments of physical and social functioning (13, 14), poor quality of life (15–17), high cost of care (18) and higher rates of adverse effects of treatment and complex interventions (19).

The management of multimorbidity is much more complicated and demanding for the health system, patients and their family (20). Although people with multiple chronic conditions require an ongoing and integrated care over a period of years or decades, they often receive a care that is fragmented and ineffective (21–24).

Despite the challenges of generating a universal management algorithm for every possible combination of chronic conditions, most models have common features (25). The overarching care principles involve integration and coordination of care, patient-centered interventions and optimization of medication therapy (25–30). Some of the models that were reported to be effective in improving outcomes of patients with multimorbidity in HICs include the patient centered medical homes (PCMH) (31), the Salford Integrated Care Program (SICP) (32), the whole system intervention (CARE Plus) (33) and patient activation (PA) (34, 35).

People who have the highest patient activation (PA) levels, including knowledge, confidence and skills to manage their own health tend to have better health outcomes than those who have a more passive approach (36, 37). Patient activation has been used to tailor self-management support interventions to improve behavioral and health-related outcomes for patients with multiple chronic conditions (38). Evidence shows higher levels of patient activation are associated with better self-management, better health outcomes, and lower healthcare costs (34). Conversely, lower patient activation scores are associated with lower QoL (38, 39). However, the authors did not find evidence on the implementation of these or other effective models of managing multimorbidity in the LMICs context. The challenges of managing multimorbidity might even be higher in LMICs where health systems are overwhelmed by high burden of communicable diseases (such as HIV, TB and Malaria) and maternal, neonatal and nutritional health problems (40). On the other hand, health systems in LIMCs are largely configured with conventional one-size fits all chronic disease care (26), which often is inadequate to meet the needs of patients with chronic multimorbidity (41). Directly applying intervention models from HICs to LMICs is not feasible as primary care is organized in different ways across countries and even within different regions of a given country (42).

In the face of struggling to fight against communicable and non-communicable diseases, and maternal childhood health problems, the emergence of multimorbidity in Ethiopia poses a serious burden to the health system. Health services in Ethiopia are largely organized around single conditions and hospital doctors who specialize in one condition or area of the body often manage patients with one condition in mind, although many people, especially as they get older, will end up with more than one diagnosed condition.

Therefore, patients with multimorbidity remain inadequately managed and suffer adverse consequences, including poor quality of life, impaired functioning, hospitalization and mortality.

Despite the huge challenge multimorbidity brings to the health system in Ethiopia, substantial evidence gaps remain on the burden of multimorbidity, and its impacts on longitudinal patient outcomes. The need for understanding the trajectories and impacts of multimorbidity in the LMICs context has been emphasized (43, 44).

Objective

This study aimed to determine the longitudinal outcomes of patients with multimorbidity using HRQoL as the main outcome and associated factors among a sample of individuals attending chronic outpatient NCDs care in Bahir Dar, northwest Ethiopia.

Methods and materials

This is a multi-center facility based longitudinal study conducted both in public and private health facilities in Bahir Dar City, Ethiopia. This study is part of an ongoing research and detail of the methods applied in this study has been published elsewhere (45).

Study setting and population

This study was conducted in five hospitals (three public and two private) and three private specialty clinics in Bahir Dar city. These facilities provide the bulk (~80%) of chronic NCDs care for the people living in the city and surrounding areas. Although chronic NCDs care and management is presumed to be provided in a relatively uniform fashion using the national NCDs treatment guideline (46), the nature of patients vising these facilities may vary and there remains a substantial difference in the quality and affordability of NCDs care between public and private health facilities in the country.

Sample size

Sample size for the baseline study

The input values α (type I error = 0.05), power ($1-\beta = 90$), confidence level (95%) and the estimated non-response and attrition during follow-up (20%) were used to estimate the sample size required for measuring the variables. Compared to other methods, the sample size yielded by the general linear multivariate model with Gaussian errors (GLIMMPSE) sample size and power calculator formula (32–34) was chosen for its adequacy to answer all the quantitative study objectives. Based on the given assumptions and the approach we used, the calculated sample size required was calculated as 600. As the nature of participants is likely to be different by the type of facility (public or private) where they receive care, we employed stratification to ensure fair representation in the sample for important sub-groups analysis. Hence, a design effect of 2 was considered to avoid the possible loss of sample power during stratification. Adding 20% to the possible loss to follow-up (considering the longitudinal study) and nonresponse, the sample size needed was calculated to be 1,440.

Sample size for the end line study

All of the patients that were enrolled for the baseline study ($n = 1{,}432$, 99.4%) were approached for the end line study. However, we obtained data only from 79% ($n = 1{,}123$) of the participants studied at baseline. The person-time data was 2,556 as calculated through Stata to assume a longitudinal panel data.

Sampling procedure

A two-stage stratified random sampling method was employed for recruiting facilities and participants. The sample size from each facility was determined based on the notion of probability proportional to size (PPS) using the pool of chronic NCD patients (≥ 40 yrs) registered for follow-up over the year preceding our assessment (January–December 2020) in each participating facility.

Only facilities who were providing chronic NCDs care by general practitioners or specialist physicians for at least a duration of 1 year prior to the data collection were considered. Older adults (40 years or more) diagnosed with at least one NCD and were on chronic diseases follow up care for at least 6 months prior to the study period were recruited for the study. Pregnant women and individuals who were too ill to be interviewed and admitted patients were excluded.

Participants enrolled for the baseline study (from March 15 to April 30, 2021) were invited 1 year later for the follow up study from March 15 to April 30, 2022. Contact information (mobile numbers and medical registration numbers) of patients involved in the baseline study were documented to contact them for the follow-up study. Printed copies of contact addresses of patients were given to the data collectors to sort out appointment dates of patients and to also remind patients to come for the study. All the participants agreed for the baseline study were informed about our plan to contact them 1 year from the baseline assessment. We used Kobo toolbox software to accurately match the end line data (period 2) with the baseline data (period 1) (47).

Data on QoL, patient activation (PA) score and multimorbidity were collected at two points on the same individual. However, some key outcome data such as mortality, hospitalization and perceived progress over time were collected only at the end of the follow up period.

Definition and measurement of the primary outcome variable (HRQoL)

HRQoL (stated as QoL in this study) is defined as individuals' perception of their position in life in the context of physical, psychological and social functioning and well-being (48). QoL at two points (baseline and end line) was measured using the interviewer-administered short form (SF-12 V2) assessment tool (49, 50).

The SF-12 tool is extensively validated and widely used generic tool for measuring QoL in multimorbidity across different contexts, including Sub-Saharan Africa (51–53). The tool was translated and pilot tested according to the study protocol we published (45). The tool measures eight health aspects, namely physical functioning (PF), role limitations due to physical health problems (RP), bodily pain (BP), general health perceptions (GH), vitality (VT), social functioning (SF), role limitations due to emotional problems (RE), and mental health (psychological distress and psychological well-being) (MH). Two summary measures are derived from the SF-12: physical health (Physical Component Summary-PCS) and mental health (Mental Component Summary-MCS). However, owing to the possibility of correlation (lack of uni-dimensionality) between the PCS and MCS scores, some studies criticized the use of these scoring algorithms and recommended raw sum scores instead (54, 55). The use of a single raw sum score enables a consistent assessment of the impact of multimorbidity and how this varies across a given population (56). Thus, we applied this approach for analyzing the QoL data.

First, we reverse coded the scores for items 1, 9 and 10 and computed the raw total. The overall scores were scaled from 0 to 100, with 0 representing worst health (57). Although popularly used in previous studies, the notion of fitting linear regression models to summarize categorical data such as the QoL data has been questioned (55, 58). The linear regression models may potentially lose important variability in the data particularly when the QoL data is collected by Liker-type scales such as the SF-12 tool (59, 60). Recent advances in the field recommend the interpretation of QoL rather as a categorical (group continuous) variable than as a metric variable (58). Studies suggest that ordinal regression models (OLR) are superior to other method for analyzing ordinal data, including health-related QoL data (58, 61). Hence, we ranked the scaled QoL scores into three ordered and non-overlapping categories as per the recommendation (60) as poor QoL (a scaled value <75), moderate QoL (scaled value from 75 to 89.9) and high QoL (scaled value from 90 to 100) and fitted into the longitudinal OLR and proportional odds (PPO) models.

Measurement of independent variables

Sociodemographic characteristics

Except for age, the data on gender, education, residence and occupation were taken from the baseline records. In addition, outcomes were compared based on the baseline QoL, gender and method of data collection.

Non communicable diseases and NCDs multimorbidity

As explained in the study protocol (5), multimorbidity was operationalized as the co-occurrence of two or more of the chronic NCDs. List of NCDs considered in this study were determined based on our review study (62) and includes hypertension, diabetes, heart diseases (heart failure, angina and heart attack), stroke, bronchial asthma, chronic obstructive pulmonary diseases (COPD), depression and cancer.

Information on these chronic conditions was assessed through a question about ever being diagnosed with the disease by a health professional. The specific question was "have you ever been told by a health professional/doctor that you have (disease name)?" responses were either yes (scored as "1") or no (score as "0"). Participants were also prompted to report up to three additional chronic conditions they are living with if any. To improve the quality of data obtained from interviews (63, 64), we reviewed medical records of all the study participants. At the time of the follow-up data collection, participants were asked if they are diagnosed with new (additional) NCD/s (since the baseline) and patient charts were reviewed to corroborate the information obtained from interviews if patients reported to have any. In addition to the interview and review of medical records, we used a locally validated patient health questionnaire (PHQ-9) (65) to assess mental health status. Possible PHQ-9 scores range from 0 to 27 and patients scoring 10 or more were classified as having depression (66).

In addition, data on factors potentially related to developing new NCD and multimorbidity, including age, gender and activation level were explored.

Patient activation score

Patient activation (PA) refers to the motivation, knowledge, skills and confidence that equip adults to be actively engaged in their health and healthcare (67). PA score was measured using validated tools (67, 68). The tool contains 13 statements answered on a 4-point Likert-type scale about managing one's health and summed to a 100-point scale, with higher scores reflecting higher levels of activation (69). The score was classified into four stages, the lowest category being poor activation ($\leq 47.0 =$ stage 1, 47.1–55.1 = stage 2, 55.2–67.0 = stage 3 and $\geq 67.1 =$ stage 4). We omitted the 'not applicable' option as it was not chosen by any of the participants at baseline.

Those who fall into Level 1 are defined as passive recipients of care who do not understand that they can play an active role in their own healthcare. Level 2 includes patients who lack the basic knowledge and confidence to effectively self-manage (for example they may not understand the treatment options available to them or what their medications do). Level 3 includes those who have a basic knowledge about their health but they lack the confidence and skills to engage in positive self-management behaviors. Level 4 is for patients who have the knowledge and confidence to self-manage but who may need support during times of personal stress or health crisis (70). The PA level has been found to be a valid and reliable measure in people with long-term conditions, including in patients with multimorbidity in different contexts (71).

Measurement of other outcome variables

Hospitalization

Participants were asked if they were hospitalized (at least once) due to the chronic condition/s they are living with. Responses were recorded as yes if they were hospitalized and no if not. The factors associated with hospitalization, including the type and number of NCDs were also studied. We used binary logistic regression models adjusting for age and gender to check if NCDs and multimorbidity are associated with hospitalization.

Perceived progress

We asked participants to rate their progress since the baseline status. They indicated their progress (symptom burden) over time using a rating scale (poor or deteriorating progress, fair progress and very good or excellent progress) as proposed (72).

Mortality

We reviewed medical records and contacted patient family members (using the telephone number we recorded at baseline) to collect the mortality data.

Data collection tools and procedures

The tools we used to collect the baseline data were utilized to gather the follow-up data. The tools were piloted tested and standardized according to the study protocol (45). For the sake of a more efficient and accurate data collection, aggregation and statistical analysis, the follow-up data were also collected by the Kobo Toolbox software (47). Patients were interviewed and assessed following their regular consultation appointment. Physicians and nurses working in the chronic care unit were involved to facilitate the data collection process. However, data were primarily collected by graduate nurse professionals.

After obtaining consent from the participants, information on self-reported newly diagnosed medical condition/s, activation status, QoL and depression level was collected by interviewer administered questionnaires. Finally, we reviewed medical records of participants who have had a new diagnosis and those of patients reported to have died during the follow up period.

Data were collected by face-to-face interviews ($n = 913$, 81.2%) and telephone interviews ($n = 211$, 18.8%). The t-test shows no statistically significant differences in the mean age between the two method of data collection employed (p-value = 0.497).

Data quality assurance

Data were collected from multiple sources using pilot tested and standardized instruments. Eight of the 10 data collectors that were recruited for the baseline study and two newly recruited data collectors were oriented together and employed to collect the end line data. The data collection process was monitored by trained supervisors and the principal investigator. We used Kobo toolbox software to collect real time data and monitor the validity of the information uploaded to the server daily (47).

Data analysis

The data from the Kobo toolbox server were downloaded into an excel spreadsheet and migrated to SPSS V. 21 for cleaning before being exported to Stata V. 17 for analysis. The end line data were linked to the baseline data to form the panel data.

The authors did not do imputations to account for the missing data due to the addition of a 20% sample for the possible loss during follow up and non-response and because of the probability that the missing were at random.

We ran descriptive statistics to characterize distributions of the study participants, patient reported outcomes and associated factors. All descriptive analyzes were weighted to account for the stratified sampling. In our analysis, age and social support scores were treated as continuous variables.

Sensitivity analysis was conducted using chi squared test to check whether the data collected by face-to-face interview (81.2%) and telephone interview (18.8%) have statistical difference. No difference was observed between the two based on multimorbidity status ($\chi^2 = 7.2$, $p = 0.065$) and QoL ($\chi^2 = 2.29$, $p = 0.130$) measured at baseline.

Descriptive statistics were also used to characterize and compare the distributions of PA levels and QoL levels between the baseline and end line period. For the sake of clarity, we have also computed the means and SDs of both these response variables. We checked multicollinearity of independent variables while fitting multivariable models (VIF = 1.02).

Most QoL data are measured by Likert-type scales, and the scores were treated as if they are continuous (equal distance between levels) and normally distributed (61). However, evidence shows that such data possess skewed distributions and it is unknown whether the distances between two successive or alternative levels (categories) are equal (73). Hence, analyzing ordinal data as if they are metric (continuous) can systematically lead to biased effect-size estimates, inflated errors rates and inaccurate parameter estimates (55, 74). In addition, collapsing the categories to suit for binary regression is inappropriate for ordered outcomes such as the QoL (59, 60). Hence, more sensitive and comprehensive models are required. Evidence suggests that the ordinal regression models are superior to the methods commonly used to analyze data of an ordered nature (75, 76). The ordinal models provide better theoretical interpretation and numerical inference than the metric (linear) models for ordered outcomes (77, 78). Based on this, QoL was treated as an ordered outcomes and categorized as low, moderate and high, and coded as 0, 1 and 2, respectively, as described above. However, as our data did not satisfy the parallel lines regression assumptions, we fitted the partial proportional odds model. The model treats the data in two categories (as Panel 1 vs. 2 and 3 or panel 1 and 2 vs. 3).

Our data were measured at two points in time. Considering the correlation between outcomes measure at different times, we fitted an ordered logistic panel data analysis model. Panel data analysis is useful to control unobserved characteristics that do not change over time (time invariance variables) (79).

The data measured at two periods were reshaped from wide to long format. Then, the authors set Stata to handle the longitudinal panel data by using the *xtset* command (*xtset* facility type year). We had 2,246 person time data for this analysis.

Facility type was the panel variable and year (2021 to 2022) the time variable. We obtained the following output, signifying the data were strongly balanced (all individuals have data at two times).

```
xtset facility type year
       panel variable: participant ID (strongly balanced)
              time variable: year, 2021 to 2022
                     delta: 1 unit
```

To explore the relationship between predictor and outcome variables, we fitted both fixed and random effect models.

The model we fitted is described below.

$Y_{it} = \alpha + \beta_k X_{kit} + uit + \varepsilon it$ *where*

i = individual and t = time (from March 2021–March 2022)

α is the intercept

Y_{it} is the dependent variable (either QoL)

X_{kit} represents the k^{th} independent and control variable

B_k is the coefficient for respective independent and control variables

uit is the impact of the i^{th} individual (not a measured variable)

εit is the error

As we recruited a random sample of study participants, we performed both fixed effect and random effect regressions, then we compared them using the Hasuman test. The null hypothesis states that the error terms are not correlated. That means a significant test (p-value <0.05) in the Hausman test implies that the error terms are not correlated. Hence, the fixed effect model is preferred. If the test result is not significant, however, the random effect model is plausible (79). The Hausman test in our model indicates that the null hypothesis be rejected (p-value = 0.110). Hence, the random effect model is appropriate. We have further checked whether the random effect model is preferred to the simple OLS by running the Breusch-Pagan Lagrange Multiplier (LM) test. The null hypothesis is that variation across entities is zero (no panel effect). The LM test in our analysis showed a significant (p-value = 0.001) implying the random effect model is appropriate (80).

We used logistic regression analysis adjusting for age and sex to identify factors associated with development of new NCDs, multimorbidity and adverse outcomes such as hospitalization, poor progression and mortality.

Results

Characteristics of the study participants

Of the 1,432 participants who were enrolled in the baseline study, 1,123 (78.5%) patients agreed to participate for the follow up study. They ranged in age from 41 to 93 years (mean 57.1 ± 11.8 years, median 55 years), with a slightly higher percentage of women (50.9%) versus men (49.1%; Table 1). The primary reason for non-response were absenteeism on the date of follow-up and difficulty in tracing them *via* telephone calls (n = 19.06%), death of the participant (n = 22, 1.54%) and refusal (n = 9, 0.98%). There was no statistically significant difference between the attendees and the lost to follow up groups with regard to age (p-value = 0.504), gender (p-value = 0.400), multimorbidity status (p-value = 0.097) and the mean baseline QoL scores (p-value = 1.000).

Newly diagnosed NCDs and the change in the patterns of multimorbidity

During the follow up period, 44 (3.9%) patients reported to have one or more newly diagnosed NCDs, with, a higher proportion (n = 34, 72.3%) of them having multimorbidity at baseline. There was a statistically significant difference in the probability of developing new NCDs between having multimorbidity and single morbidity at baseline (p-value = 0.003). In addition, there was a 2% increase in the magnitude of multimorbidity during the follow up period. In other words, the magnitude of multimorbidity has increased from 54.8% at baseline to 56.8% as measured at the follow

TABLE 1 Socio-demographic characteristics of study participants attending chronic outpatient NCDs care in Bahir Dar, Ethiopia.

Variables	Frequency	Percentage
Age in years		
≤44	190	16.9
45–54	310	27.6
55–64	314	28.0
65+	309	27.5
Sex		
Male	552	49.1
Female	572	50.9
Residence		
Urban (Bahir Dar)	651	58.0
Other towns	287	25.5
Rural	185	16.5
Religion		
Orthodox Christian	1,033	91.9
Muslim	85	7.6
Others	6	0.5
Marital status		
Currently married	844	75.1
Single*	280	24.9
Education no		
Formal education	594	52.8
Primary	121	10.8
Secondary	145	12.9
College level and above	264	23.5
Occupation		
Housewife	267	23.8
Employed	223	19.8
Farmer	153	13.6
Trader	263	23.4
Retired	110	9.8
Unemployed	108	9.6
Wealth index (SES)		
Low	403	35.9
Middle	337	29.9
High	384	34.2
QoL		
Poor	426	37.9
Moderate	320	28.5
High	378	33.6

*Never married, divorced, widowed and separated.

up period. It was also observed that about 17% of those having multimorbidity had three or more NCDs, a 2 % increase from the baseline status (15.2%).

Hypertension (19.6%), heat failure (19.6%) and chronic kidney diseases (15.2%) were the most frequently newly diagnosed NCDs during the follow up (Figure 1).

Factors associated with occurrence of newly diagnosed NCDs

Having multimorbidity and being in the overweight or obese BMI category at baseline were the factors predicting development of new NCDs. However, only the presence of multimorbidity at baseline remained a statistically significant factor in the adjusted model. The odds of having a new NCD diagnosis was 2.5 times higher among patients that had multimorbidity at baseline compared to those who had single morbidity. However, participants' age and sex were not associated with development of new NCDs during the one-year follow up (Table 2).

Perceived Progress

The majority ($n = 659$, 58.6%) of the participants reported that they had a good progress compared to their status at baseline. While about one third ($n = 374$, 33.3%) reported to have a fair progress and 91 patients (8.1%) had poor and deteriorating progresses.

Hospitalization

Nearly 10% of the patients were admitted during the follow-up because of one or more of the NCDs they were living with. Presence of three or more chronic NCDs (AOR: 3.64, 95%CI = 2.15, 6.17) compared with having single NCD, and those who reported to have a deteriorating progress (AOR: 12.42, 95%CI = 6.97, 22.14) or fair progress (AOR: 2.82, 95%CI = 1.72, 4.60) since the baseline were more likely than their counterparts to have hospital admission (Table 3).

Mortality

Of the total number of patients whose status was known ($n = 1{,}160$, 82%), 22 (2%) patients were reported to have died during the course of the one-year follow up.

Patient activation status

The PA scores were summed and scaled into a 100-point scale to compute the mean PA value. The mean score was 76.0 ± 23.2. According to the standard classification (81), the majority (45.8%) were classified under the highest activation category (score ≥ 67.1), followed by those in level two 26.1% (score 47.1–55.1), 18.4% in level one (score < 47.0) and 9.7% in level three (score 55.2–67.0; Table 4). For the sake of simplifying the interpretation of its effect on QoL on the ordered logistic regression (proportional odds) model, we classified the PA score into two groups: high (≥55.2) and low (≤55.1). In this sense, the proportion of participants in the high and low category was 55.5 and 44.5%, respectively. We observed that activation level

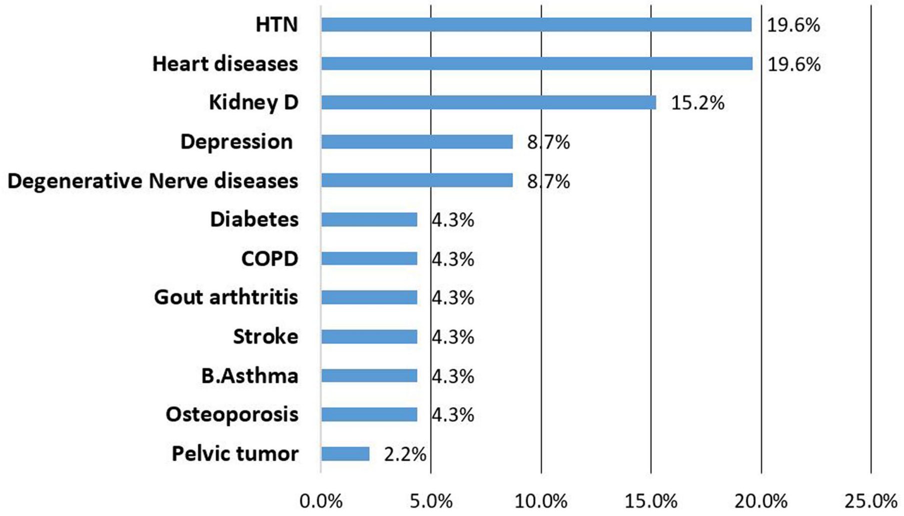

FIGURE 1
List of newly identified NCDs among patients attending NCDs care follow up, Bahir Dar Ethiopia.

TABLE 2 Factors Associated with development of new NCDs among patients attending outpatient NCD care follow up, Bahir Dar Ethiopia.

Variables	New NCDs		*p*-value	Crude odds ratio (95%CI)	*p*-value	Adjusted odds ratio (95%CI)
	Yes (%)	No (%)				
Age in years			0.881	0.99 (0.97, 1.02)	-	
Sex						
Male	27 (4.9)	524 (95.1)	Base		-	
Female	17 (3)	554 (97)	0.102	0.59 (0.32, 1.11)	0.188	0.64 (0.33, 1.24)
BMI (baseline)						
Underweight	1 (0.3)	149 (99.7)	0.132	0.21 (0.03, 1.59)	0.129	0.21 (0.03, 1.60)
Normal weight	18 (3.1)	566 (96.9)	Base		-	
Overweight or obese	25 (6.6)	353 (93.4)	0.011	2.22 (1.19, 4.14)	0.153	1.61 (0.84, 3.08)
Multimorbidity at baseline						
Yes	34 (5.4)	599 (94.6)	0.004	2.81 (1.34, 5.73)	0.017*	2.52(1.18, 5.38)
No	10 (2)	481 (98)	Base		-	

*Statistically significant at *p*-value < 0.05 in the adjusted model.

fluctuated over time. Based on the Pearson correlation test, the correlation between the baseline and end line PA score was 0.065, implying no strong correlation between the two measurements.

Quality of life

The majority (37.9%) of participants had a lower QoL and there was a modest increase from the baseline level (33.5%). In this study, about one-third (33.6) of the patients had better QoL and 28.5% of them had moderate QoL.

Factors associated with QoL

We assessed the effect of key independent variables through fitting an ordered longitudinal panel data analysis model. As indicated in the method section above the random effect model is appropriate for the data at hand and the output of the model is shown below (Table 4).

Compared to males, females had lower odds of being in the higher level of QoL versus the combined lower and moderate QoL and in the combined higher and moderate levels of QoL versus the lower level of QoL, given the other variables are held constant in the model [AOR1 = AOR2: 0.99, (95%CI: 0.82, 1.22)]. Similarly, a person living with multimorbidity had a lower odds of being in the higher level of QoL versus the combined lower and moderate QoL and in the combined higher and moderate levels of QoL versus the lower level of QoL, given the other variables are held constant in the model [AOR1 = AOR2: 0.89, (95%CI: 0.73, 1.09)]. However, none of these association are statistically significant. Further, age has no statistically significant association with QoL in our analysis.

On the other hand, PA score has shown a statistically significant association with QoL in both panels. For individuals having a higher levels of PA score, the odd of being in the higher category of QoL

TABLE 3 Factors associated with hospitalization among patients on chronic NCDS care follow up, Bahir Dar Ethiopia.

Variables	Hospitalization		*p*-value	COR (95%)	*p*-value	AOR (95%)
	Yes	No				
Age			0.941	1.00 (0.98. 1.02)		
Morbidity						
Single NCD	33	452	Base			
2 NCDs	33	415	0.738	1.09 (0.66, 1.79)	0.811	1.06 (0.63, 1.79)
3 or more NCDs	40	151	<0.001	3.63 (2.21, 5.96)	<0.001**	3.64 (2.15, 6.17)
Perceived progress						
Poor/deteriorating	33	58	<0.001	12.36 (7.01, 21,78)	<0.001**	12.42 (6.97, 22.14)
Fair progress	44	330	<0.001	2.89 (1.78,4.72)	<0.001**	2.82 (1.72, 4.61)
Good progress	29	630	Base			
Baseline PAM level						
Level 1	16	147	0.358	1.32 (0.73, 2.41)		
Level 2	15	120	0.350	0.75 (0.40, 1.34)		
Level 3	10	95	0.796	0.89 (0.38, 2.98)		
Level 4	65	654	Base			

**Statistically significant at *p*-value < 0.001 in the adjusted model.

TABLE 4 Factors associated with QoL in longitudinal panel ordered logistic regression model.

Independent variables	QoL (Panels)			
	Panel one (1 Vs. 2 and 3)		Panel two (1 and 2 *Vs* 3)	
	Coefficients	AOR 1 (95%CI)	AOR2(95%CI)	*p*-value
Sex [Female vs. male (Ref)]	Constant (OR1 = OR2)	0.99 (0.82, 1.22)	0.99 (0.82, 1.22)	0.897
Age in years	Constant (OR1 = OR2)	1.00 (0.99, 1.01)	1.00 (0.99, 1.01)	0.949
Multimorbidity [yes vs.no (Ref)]	Constant (OR1 = OR2)	0.89 (0.73, 1.09)	0.89 (0.73, 1.09)	0.266
PAM [high vs. low (Ref)]	Coefficients not constant (OR1 ≠ OR2)	2.35 (1.93, 2.87)	1.53 (1.25, 1.88)	<0.001**

**Statistically significant at *p*-value < 0.05 in both panels using the random effect model.

versus the combined moderate and lower QoL was 2.4 times higher [AOR1: 2.35, (95%CI: 1.93, 2.87)]. Likewise, the odds of being in the combined higher and moderate QoL versus lower QoL was 1.5 times higher for individuals having a higher level of PA score [AOR2: 1.53, (95%CI: 1.25, 1.88)] (Table 4).

Discussion

This study broadly assessed the progress and outcomes of patients attending chronic outpatient NCD care in Bahir Dar, Ethiopia.

It was found that multimorbidity is common and those having multimorbidity at baseline were more likely than individuals with single morbidity to develop new NCDs over the course of the 12 month follow up period. This may be explained by the possibility that individuals living with multimorbidity already have enough of the risk factors to developing more NCDs (44), or because of the probability that they would find it difficult to make lifestyle modifications while burdened with existing multiple conditions, or may be due to complications arising from poor management of the underlying NCDs. Other studies have also reported a higher rate of cumulative incidence of NCDs among multimorbid individuals than their counterparts in LMICs (82, 83). The findings with regard to the challenges and burdens that patients with multimorbidity face are consistent with previous studies in LMICs (1, 82).

The magnitude of multimorbidity increased from 54.8% at baseline to 56.8% by the end of the one-year follow up. A 2 % increase in the burden of multimorbidity implies that the course of developing multimorbidity is rapid and that if not properly managed, individuals with single morbidity will eventually develop multimorbidity. While living with single NCDs is challenging by itself, the addition of one or more chronic NCDs during the course of treatment may complicate patient management and result in poor clinical outcomes, including disability, poor quality of life and mortality (84). Studies have shown that timely screening and prevention of risk factors and person-centered management of index conditions help to prevent or delay occurrences of comorbidity and multimorbidity (1, 83). Although not shown in our study, previous evidence has shown that individuals with high activation level are less likely than their counterparts to develop additional morbidities during the course of their treatment (34, 69).

Monitoring the clinical progress of individuals attending chronic care is instrumental to prevent adverse outcomes and modify interventions to improve management and outcomes (82). The authors observed that the majority had higher levels of perceived progress of their conditions from the baseline status. A significant proportion (8.1%) of the participants had poor or deteriorating progress. Unless immediate action is taken, those in the latter category will suffer poor outcomes. Perhaps, those who reported to have a fair progress may progress to a deteriorating status if not managed properly. Evidence shows that carefully implemented preventive and management strategies help avoid adverse progresses and development of secondary or tertiary conditions (83, 85).

In this study, the authors found that nearly 10% of participants were hospitalized at least once during the one-year follow up due the chronic condition/s they were living with. Consistent with previous literature (86, 87), individual having multimorbidity at baseline, including those with three or more chronic conditions were more likely than individuals with single morbidity to experience hospitalization during the course of their follow up care. In agreement with previous studies (88), a dose–response relationship between the number of chronic diseases and hospitalization was also observed in this study. Other researchers argue that most multimorbidity related hospitalizations are avoidable, and their occurrence warrants a lack of care coordination and the lack of care quality, possibly because of fragmentation when addressing the problems in individuals living with multiple conditions (86).

During the one-year follow up, 22 (~2%) patients were reported to have died. Although it was difficult to ascertain the cause death of these individuals, a higher proportion (64%) of them had multimorbidity at baseline and participants' death was not attributable to their age. Longitudinal studies consistently reported an increasing odd of mortality among individuals with multimorbidity compared to those without multimorbidity (82, 89). Higher mortality risk in those with multimorbidity indicates the need for tailored, person-centered integrated care interventions and better access to holistic healthcare for improving the wellbeing and survival of these group (90). However, in contrast to previous studies (91), neither the number of chronic conditions nor specific disease combinations are associated with mortality in our study. This might be related to the relatively short period of follow up and small sample of the deceased individuals in our analysis.

A sufficient degree of activation is required for patients with multiple chronic diseases for adequate self-management practices (92). A higher level of PA, that allows patients to take on the role of managing their own health and healthcare (70),is associated with better outcomes such as improved QoL, compliance to medication regiments, proper self-management and reduced chance of unplanned hospitalization and mortality (69, 93). In this study, it was found that the majority (55%) had higher level of PA. However, given the high and growing burden of multimorbidity, there seem a missed opportunities to enhance activation among patients attending chronic follow up care. This may result in a more rapid progression to development of more NCDs and associated complications (93).

As observed in our study, activation level may fluctuate over time and can be affected by disease progression, background of patents and quality of healthcare (94). Hence, it is important to understand individual circumstances and changes in the progression of their condition and support activation levels and behaviors sufficient to maintain their wellbeing and improve outcomes as suggested by previous literature (38).

Health related QoL is one of the outcomes that could be predicted by individuals' activation status (95). In this study, it was found that a higher proportion (38%) of the participants had poor QoL with 33.6% reporting good QoL. Although it is not possible to determine causation, higher levels of PA predicted higher levels of QoL in our study. This finding is consistent with previous studies (37). This association illuminates a possible entry point for developing strategies to increase patient activation levels, thereby increasing QoL and improving health outcomes (95). Moreover, Racheli Magnezi et al. (95) found that patient activation intervention was particularly effective for those with PA scores at Levels 1 and 2 (i.e., the less activated patients) and any changes in PA levels were directly associated with changes in health status, with improvement in patient activation leading to better health outcomes. Activation of patients with chronic conditions can routinely be monitored and enhanced through providing instructions and specific caretaking tasks, building their confidence and encouraging patients to take additional actions, until they are finally able to manage their own conditions (81, 95).

However, unlike their effect on the QoL at baseline, age and multimorbidity did not show a statistically significant association with QoL in the longitudinal study. This variation may be partly explained by the difference in the way the survey data were handled (i.e., we used longitudinal panel data for this study and cross-sectional data at baseline) to analyze the impact of these factors on QoL at the end line. The slight changes in the levels of QoL from the baseline might have contributed to the loss of significance of these variables. Further research is need to corroborate or refute this observation.

Implication of research, policy and practice

The main goal of health care for the people living with chronic conditions and multimorbidity is to support them achieve a better QoL, improved wellbeing and survival (28, 96). However, a significant number of patients attending chronic care in the study area experienced a range of adverse outcomes, including development of new NCDs and multimorbidity, poor disease progression, poor QoL, hospitalization and mortality. This implies living with chronic NCDs and associated multimorbidity has profound impacts on individuals, and that the health system does not seem to be well prepared to adequately respond to individual patient needs. The provision of patient-centered care in which all healthcare providers work together with patients to ensure coordination, consistency and continuity of care over time is essential (97). This will in turn improve the wellbeing and survival of the people with multimorbidity in the study area.

Given the positive association between PA level and QoL, it is desirable to determine and devise strategies to increase activation status. The notion of patient activation is relatively new in the study context and there is a need to experiment its effects in improving outcomes of patients in the chronic care landscape and beyond.

Strength and limitations of the study

Our study has the advantage of involving a broad group of health facilities and patients receiving chronic NCDs care. Guided by a published study protocol, this longitudinal study provided strong insight on the course and patterns of disease progression, the impact of multimorbidity on important patient outcomes such as hospitalization and mortality, and the level and predictors of QoL using robust methodologies. Our ability to determine activation levels of patients would encourage service providers to measure and intervene with mechanisms to increase PA. However, the findings of this facility-based study may not exactly represent the underlying epidemiology of multimorbidity and its impact in the general population. In addition, although the sensitivity analysis does not show variations, the data collected from a portion of patients by telephone interview might not be an exact replica of the data obtained from face-to-face interviews. However, adequacy of the sample size and parsimony of the methods we employed would make our study robust.

Conclusion and recommendations

The likelihood of developing new NCDs and multimorbidity is high. Multimorbidity is not only high in the study area, but also it associated with worst patient outcomes, including hospitalization and mortality, compared to those with single NCDs. This study revealed that the highest proportion of individuals with multimorbidity had poor QoL. On the other hand, patients having a higher level of PA level were more likely to have better levels of QoL. If health systems in LMICs are to meet the needs of the people with chronic conditions and multimorbidity, it is essential to understand the long- term, life course determinants of different multimorbidity trajectories, and to help improve individual capacity and activation levels. Replicating the evidence on the effect of patient activation on QoL and determining outcomes and predictors of people living with chronic NCDs and multimorbidity longitudinally is recommended. It is also imperative to replicate the methods that were employed to measure and analyze QoL data in this study in order to facilitate comparison and further development of the approaches.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by College of medicine and health sciences, Bahir Dar University internal review board. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements. All study subjects provided verbal consent to participate in this study.

Author contributions

FE, FG, MS, and SA conceived and designed this study. FE, FG, and MS participated in the data analysis and interpretation of the findings. FE drafted the manuscript. FG and MS contributed in revising the manuscript. MS undertook an English language check as she is a native English speaker. All authors critically reviewed and approved the final manuscript for submission.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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EDITED BY
Redhwan Ahmed Al-Naggar,
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REVIEWED BY
Nicholas Schiltz,
Case Western Reserve University, United States
Svetlana Puzhko,
Bielefeld University, Germany

*CORRESPONDENCE
Tiara Marthias
✉ tiara.marthias@unimelb.edu.au

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Functional limitation as a mediator of the relationship between multimorbidity on health-related quality of life in Australia: evidence from a national panel mediation analysis

John Tayu Lee[1,2,3], Marie Ishida[4], Tilahun Haregu[4], Sanghamitra Pati[5], Yang Zhao[4,6], Raffaele Palladino[1,7,8], Kanya Anindya[9], Rifat Atun[2,10], Brian Oldenburg[11,12] and Tiara Marthias[5,13]*

[1]Department of Primary Care and Public Health, Imperial College London, London, United Kingdom, [2]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, MA, United States, [3]College of Health and Medicine, Australian National University, Canberra, ACT, Australia, [4]Nossal Institute for Global Health, Melbourne School of Population and Global Health, The University of Melbourne, Parkville, VIC, Australia, [5]ICMR Regional Medical Research Centre, Bhubaneswar, Odisha, India, [6]The George Institute for Global Health China, Beijing, China, [7]Department of Public Health, University "Federico II" of Naples, Naples, Italy, [8]Interdepartmental Center for Research in Healthcare Management and Innovation in Healthcare (CIRMIS), University "Federico II" of Naples, Naples, Italy, [9]School of Public Health and Community Medicine, Institution of Medicine, Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden, [10]Countway Library, Harvard Medical School, Boston, MA, United States, [11]Implementation Science Lab, Baker Heart and Diabetes Institute, Melbourne, VIC, Australia, [12]School of Psychology and Public Health, La Trobe University, Melbourne, VIC, Australia, [13]Department of Health Policy and Management, Faculty of Medicine, Public Health and Nursing, Gadjah Mada University, Yogyakarta, Indonesia

Objective: The inverse relationships between chronic disease multimorbidity and health-related quality of life (HRQoL) have been well-documented in the literature. However, the mechanism underlying this relationship remains largely unknown. This is the first study to look into the potential role of functional limitation as a mediator in the relationship between multimorbidity and HRQoL.

Methods: This study utilized three recent waves of nationally representative longitudinal Household, Income, and Labor Dynamics in Australia (HILDA) surveys from 2009 to 2017 (n = 6,814). A panel mediation analysis was performed to assess the role of functional limitation as a mediator in the relationship between multimorbidity and HRQoL. The natural direct effect (NDE), indirect effect (NIE), marginal total effect (MTE), and percentage mediated were used to calculate the levels of the mediation effect.

Results: This study found that functional limitation is a significant mediator in the relationship between multimorbidity and HRQoL. In the logistic regression analysis, the negative impact of multimorbidity on HRQoL was reduced after functional limitation was included in the regression model. In the panel mediation analysis, our results suggested that functional limitation mediated ~27.2% ($p < 0.05$) of the link between multimorbidity and the composite SF-36 score for HRQoL. Functional limitation also mediated the relationship between the number of chronic conditions and HRQoL for each of the eight SF-36 dimensions, with a proportion mediated ranging from 18.4 to 28.8% ($p < 0.05$).

Conclusion: Functional status has a significant impact on HRQoL in multimorbid patients. Treatment should concentrate on interventions that improve patients' functioning and mitigate the negative effects of multimorbidity.

KEYWORDS

chronic disease, multimorbidity, mediation, functional limitation, comorbidity

Introduction

Australians are living longer lives than ever before, but many are dealing with multiple chronic diseases, resulting in a low health-related quality of life (1–3). With an aging population and increased risk factor exposure, the prevalence of multimorbidity, defined as the coexistence of two or more long-term conditions, is expected to rise further in Australia (4–7). Recent national studies in Australia found that the prevalence of non-communicable diseases (NCDs) was $\sim$ 25% for those aged 50–54, and this percentage increased to 50% for those aged 70 and above, based on only 12 self-reported NCDs (8, 9). It is also worth noting that multimorbidity is highly socioeconomically patterned in Australia, as it is in many other high-income countries, with lower socioeconomic groups or aboriginal groups having a higher prevalence of multimorbidity (10). Multimorbidity imposes heavy costs on the patients, their families, the healthcare system, and society as a whole (11–14).

Health-related quality of life (HRQoL) is an important health outcome metric that assesses an individual's subjective physical and mental health. HRQoL, according to the WHO definition, is frequently multifaceted, encompassing both physical and mental health, and represents individuals' wellbeing in the context of their culture and values (15, 16). HRQoL is frequently assessed in clinical settings and health surveys to track patient wellbeing and progress toward national health goals (17–20). Poor HRQoL is associated with increased healthcare utilization, suboptimal treatment outcomes, and an increased risk of death (19, 21, 22).

Several studies, including high-level systematic reviews, have suggested that multimorbidity reduces HRQoL (23–25). A number of long-term health conditions were found to have a negative impact on HRQoL after controlling for confounding variables (23, 25). Numerous studies have discovered a link between functional limitation and poor HRQoL, with the risk of poor HRQoL increasing as functional limitation increases (26–28). However, it is unclear how much adjusting for functional limitation modifies or reduces the relationship between multimorbidity and HRQoL. Multimorbidity appears to be independently associated with poor HRQoL in the majority of studies reported to date, even after adjusting for functional limitation, though the magnitude of the association appears to be less significant when functional limitation is included in the models (23, 24, 28, 29). Similarly, multimorbidity does not fully explain the link between functional limitation and poor HRQoL.

Until now, the complex relationship between multimorbidity, functional function, and HRQoL has received insufficient attention. A mediation analysis is a statistical model that looks at the relationships between two variables and how much they are mediated by a third variable (e.g., the mediator). In the current epidemiological and public health literature, this methodology is widely used to assess the mechanism by which disease affects health outcomes. To address this important evidence gap in the literature, this is the first longitudinal study to investigate the role of functional limitation in the influence of multimorbidity on HRQoL using three waves of nationally representative data in Australia. This study looks specifically at the role of functional limitation as a mediator in the relationship between multimorbidity and HRQoL in a population-based sample of Australian adults.

Methods

Sample and data

This study utilized three waves of longitudinal data from Waves 9 (2009), 13 (2013), and 17 (2017) of the Household, Income, and Labor Dynamics in Australia (HILDA) survey. The HILDA survey is a nationally representative, household-based panel study that collects information on the health, wellbeing, socioeconomics, and labor market dynamics of Australian residents over the course of their lives. Commenced in 2001, data were collected annually through interviews with individuals aged 15 years and above from the selected households. Wave 1 (2001) data were collected from 13,969 individuals, and a sample top-up of 4,009 individuals was added in wave 11 (2011). A detailed description of the survey objectives and methods is provided elsewhere (30). In this study, respondents who participated in all three waves (Waves 9, 13, and 17) are included in the sample and dropped those with any missing data on covariates, leaving 6,814 respondents.

HRQoL (outcome variable)

HILDA survey contains 36-item short questionnaires deriving from SF-36 Health Survey, which is a widely used instrument for assessing HRQoL. SF-36 includes eight dimensions of scale scores ranging from 0 to 100 (a higher score indicates better health) that measure physical and mental health: physical functioning (PF), role physical (RF), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). The overall health status of the individual was based on the overall SF-6D score, which is derived from the SF-36. Finally, these scores were converted to binary variables with a threshold of 25th percentile as 1 indicating poor health and 0 indicating better health.

TABLE 1 Sample characteristics from wave 17 (year 2017).

		Number of individual respondents (%)
Total		6,814 (100)
Gender	Male	3,168 (46.5)
	Female	3,646 (53.5)
Age group	15–29	786 (11.5)
	30–49	2,337 (34.3)
	50–59	1,442 (21.2)
	60+	2,249 (33.0)
Marital status	Married/defacto	4,901 (71.9)
	Not married	1,913 (28.1)
Indigenous status	Non-Indigenous	6,708 (98.4)
	Indigenous	106 (1.6)
State	New South Wales	1,912 (28.1)
	Victoria	1,679 (24.6)
	Queensland	1,524 (22.4)
	South Australia	600 (8.8)
	Western Australia	672 (9.9)
	Tasmania	214 (3.1)
	Northern Territory	56 (0.8)
	Australian Capital Territory	157 (2.3)
Locality	Urban	5,831 (85.6)
	Rural	983 (14.4)
SEIFA	Highest	1,535 (22.5)
	Second highest	1,464 (21.5)
	Middle	1,352 (19.8)
	Second lowest	1,321 (19.4)
	Lowest	1,147 (16.8)
Number of chronic diseases	None	3,760 (55.2)
	1	1,747 (25.6)
	2	814 (12.0)
	3+	493 (7.2)
Functional limitation	No	5,405 (79.3)
	Yes	1,409 (20.7)

Multimorbidity (exposure variable)

The physical conditions included in HILDA were as follows: arthritis/osteoporosis, asthma, cancer, chronic bronchitis/emphysema, type 1 diabetes, type 2 diabetes, heart disease, high blood pressure/hypertension, and any other serious circulatory condition, depression/anxiety, and "other mental illnesses." Respondents who answered affirmatively to the question "Have you been told by a doctor or nurse that you have any of these conditions?" were defined as reporting a health condition. We counted the number of self-reported health conditions to quantify the number of physical conditions (0, 1, 2, 3, 4, etc).

Functional limitation (mediator)

The HILDA survey questionnaire inquired about respondents' functional limitations. Respondents were classified as having functional limitations if they answered yes to the following question: "Do you have any long-term condition, impairment or disability that restricts you in your everyday activities, and has lasted or is likely to last, for 6 months or more?."

Covariates

The covariates of this study are as follows: sex (men and women), age group (18–29, 30–39, and 40–49), marital status (married/cohabitating and single/separated/divorced/widowed), geographical region of Australia by state (New South Wales, Victoria, Queensland, Western Australia, South Australia, Tasmania, Northern Territory, and Australian Capital Territory), and locality (urban and rural). Socioeconomic status was obtained using the quintile of Socio-Economic Indexes for Areas (SEIFA) relative to socioeconomic advantage/disadvantage (SEIFA = 1: lowest SES group; SEIFA = 5: highest SES group).

Statistical analysis

We adopted a panel mediation study design to explore the role of functional limitations (2013) on the relationships between multimorbidity and HRQoL using three waves of panel datasets. We performed the analysis following the steps suggested by Baron and Kenny, which consists of a series of panel data regression analyses (31). We examined the relationship between multimorbidity and HRQoL measures; the association between functional limitation and multimorbidity; and the association between HRQoL and multimorbidity and functional limitation. Based on the results, we identified the set of associations that meet the mediation criteria: (1) The multimorbidity is significantly associated with the functional limitation; (2) multimorbidity is significantly associated with HRQoL; (3) functional limitation is significantly associated with the HRQoL; and (4) the association between the multimorbidity and HRQoL is attenuated when the mediator is included in the model. To confirm the mediation effect, separate mediation models using the Stata paramed program (32) were adopted for each selected HRQoL measure, including each dimension of SF-36. The paramed command performs causal mediation analysis using parametric regression models and is based on a counterfactual approach. We further reported the estimated natural direct effect (DE), natural indirect effect (IE), and marginal total effect (TE) on the odds ratio scale. Percent mediation was estimated as the ratio of natural logarithms of

TABLE 2 Sample characteristics against outcome variables from wave 17.

		Mean number of NCDs	Prevalence of Disability (%)	Prevalence of Low HRQoL (%)
Total		0.74	20.70	24.76
Gender	Male	0.72	21.60	22.35
	Female	0.77	19.90	26.84
Age group	15–29	0.16	8.14	19.85
	30–49	0.31	11.71	20.78
	50–59	0.70	17.82	23.93
	60+	1.44	36.15	31.13
Marital status	Married/defacto	0.71	19.10	21.06
	Not married	0.85	24.80	34.20
Indigenous status	Non-Indigenous	0.75	20.62	24.54
	Indigenous	0.73	24.53	38.68
State	New South Wales	0.78	21.53	23.93
	Victoria	0.69	17.69	25.13
	Queensland	0.75	21.11	25.18
	South Australia	0.87	23.96	26.79
	Western Australia	0.74	21.84	23.48
	Tasmania	0.87	26.17	30.84
	Northern territory	0.38	14.29	10.71
	Australian capital territory	0.55	14.65	21.02
Locality	Urban	0.74	20.10	25.11
	Rural	0.78	24.00	22.66
SEIFA	Highest	0.56	14.14	18.24
	Second highest	0.65	17.35	19.81
	Middle	0.74	20.71	25.00
	Second lowest	0.84	21.65	28.77
	Lowest	1.03	32.43	34.87

the difference between TE and DE divided by TE. Furthermore, we examined the mediation effect of functional limitation across different dimensions of HRQoL outcomes by performing the same analysis on each HRQoL component. All estimates from mediation analysis were bootstrapped with 500 replications to obtain bias-corrected 95%CI.

All statistical analyses were performed using Stata 15 Corp. The panel data mediation analysis was conducted using the Stata paramed program, and a significance was set at 0.05. All statistical models were adjusted for the covariates mentioned above.

Results

Table 1 presents the sample characteristics of this study. Of 6,814 participants, 53.5% were women, 71.9 were married/*de facto*, and 85.6% were residing in urban areas. In total, 55.2% reported not having any NCD, while 7.2% reported having three or more NCDs and 20.7% of the sample reported disability.

The participant's characteristics against key indicators are presented in Table 2. The mean number of NCDs was 0.74 for the overall sample. The number of NCDs and the prevalence of functional limitation were higher among the older age group and those with lower socioeconomic status. Finally, the proportion of low HRQoL showed a similar trend with functional limitation. The prevalence of low HRQoL was 24.8% among the overall sample. It was higher among people from the lower socioeconomic area (34.9%). However, women showed a higher prevalence of low HRQoL (26.8%), while men showed a higher prevalence of disability (21.6%).

Table 3 shows the descriptive statistics of the HRQoL outcomes (overall HRQoL as well as the eight individual dimensions). The table also showed the univariate relationship among the number of NCDs, functional limitation, and HRQoL outcomes. The analysis found that having a higher number of NCDs was linked to poorer HRQoL outcomes, as demonstrated by the lower scores on the SF-6D (OR = 1.74, $p < 0.05$) and physical functioning (OR = 2.11, $p < 0.05$) scales. Additionally, the second equation revealed a

TABLE 3 Mediation analysis using the method by Baron and Kenny.

	Equation 1		Equation 2		Equation 3 (include both number of NCDs and functional limitation in the regression model)			
	Number of NCDs		Number of NCDs		Number of NCDs		Functional limitation	
	OR	*p*-value	OR	*p*-value	OR	*p*-value	OR	*p*-value
Overall poor HRQoL	1.74	<0.001			1.52	<0.001	3.70	<0.001
By component of HRQoL								
Physical functioning	2.11	<0.001			1.84	<0.001	4.51	<0.001
Role physical	1.74	<0.001			1.51	<0.001	3.85	<0.001
Bodily pain	1.74	<0.001			1.52	<0.001	3.93	<0.001
General health	2.08	<0.001			1.86	<0.001	3.36	<0.001
Vitality	1.64	<0.001			1.47	<0.001	2.75	<0.001
Social function	1.69	<0.001			1.48	<0.001	3.29	<0.001
Role emotion	1.53	<0.001			1.38	<0.001	2.41	<0.001
Mental health	1.45	<0.001			1.32	<0.001	2.25	<0.001
Functional limitation			1.94	<0.001				

TABLE 4 Results from panel mediation analysis.

	Direct effect		Indirect effect		Total effect		% mediated by disability
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	
Overall HRQoL	1.52 (1.42, 1.65)	<0.01	1.17 (1.14, 1.21)	<0.01	1.78 (1.65, 1.92)	<0.01	27.4
By components of HRQoL							
Physical functioning	1.84 (1.71, 2.00)	<0.01	1.21 (1.17, 1.25)	<0.01	2.22 (2.03, 2.41)	<0.01	23.5
Role physical	1.51 (1.40, 1.63)	<0.01	1.18 (1.15, 1.22)	<0.01	1.78 (1.65, 1.93)	<0.01	28.5
Bodily pain	1.52 (1.41, 1.62)	<0.01	1.18 (1.15, 1.22)	<0.01	1.80 (1.67, 1.94)	<0.01	28.8
General health	1.86 (1.72, 2.01)	<0.01	1.15 (1.13, 1.19)	<0.01	2.14 (1.97, 2.33)	<0.01	18.4
Vitality	1.47 (1.36, 1.58)	<0.01	1.12 (1.10, 1.15)	<0.01	1.65 (1.53, 1.78)	<0.01	23.1
Social function	1.48 (1.37, 1.60)	<0.01	1.15 (1.12, 1.19)	<0.01	1.71 (1.59, 1.84)	<0.01	26.9
Role emotion	1.38 (1.29, 1.49)	<0.01	1.10 (1.08, 1.13)	<0.01	1.52 (1.42, 1.64)	<0.01	23.1
Mental health	1.32 (1.24, 1.43)	<0.01	1.09 (1.07, 1.12)	<0.01	1.44 (1.35, 1.55)	<0.01	23.9

significant correlation between the number of NCDs and functional limitation (OR: 1.94, $p < 0.05$). The third equation, which included both HRQoL measures and functional limitation in the model, revealed that the number of NCDs and functional limitation were both significantly associated with poor HRQoL outcomes. It is important to note that when functional limitation is included in the model, the magnitude of the effect between multimorbidity and HRQoL decreases in all measures, indicating that the impact of the number of NCDs on HRQoL outcomes was partially mediated by functional limitation.

Overall SF-6D score

Table 4 and Figure 1 show DE, IE, and TE of functional limitation on the overall SF-6D score and each dimension of SF-36. The number of NCDs was associated with lower overall HRQoL scores (OR^{TE}:1.78, 95%CI: 1.65–1.92), with 27.2% mediated by functional limitation. The decomposition of total effects indicated statistically significant NDE (OR^{DE}: 1.52, 95%CI: 1.42–1.65) and IE (OR^{IE}: 1.17, 95%CI: 1.14–1.21).

Each HRQoL dimensions

We also investigated the role of functional limitation in each dimension of the SF-36 separately. The most significant result was observed for physical functioning (OR^{TE}: 2.22, 95%CI: 2.03–2.41) and general health (OR^{TE}: 2.14, 95%CI: 1.97, 2.33), the associations of which were 23.9 and 18.4%, respectively, mediated by functional limitation. Functional limitation showed the largest

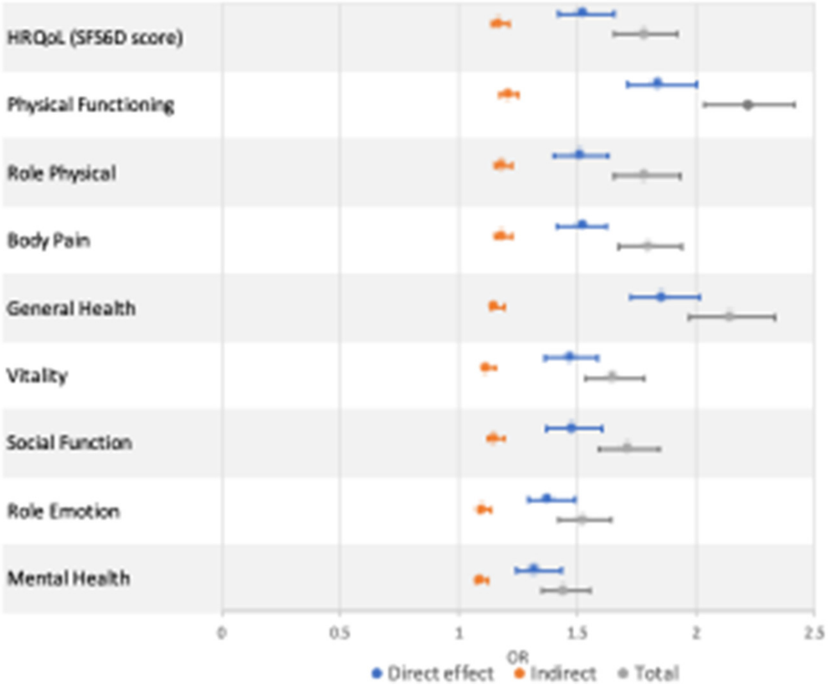

FIGURE 1
Direct, indirect, and total effect of multimorbidity on HRQoL.

mediation effect of the association between the number of NCDs and role physical (28.7%). Consistent results were found in other SF-36 domains (body pain: 28.2%, vitality: 22.6%, social function: 26.1%, role emotion: 22.8%, mental health: 23.6%).

Discussion

Principal findings and interpretation

This is the first study that uses a panel data study design to investigate the role of functional limitation as a mediator in the relationship between multimorbidity and health-related quality of life in Australia. We found clear evidence that functional limitation acts as a partial mediator on the relationships between multimorbidity and the overall HRQoL score as well as each SF-6D dimension, with the percentage of mediation ranging from 18 to 28%.

The possible explanation is that disabled older adults or those with greater functional limitations have a negative impact on their self-care ability, physiological activities, and social interaction, all of which have a negative impact on their physical and mental health, reducing HRQoL. Multimorbidity, functional limitation, and disability all have a negative impact on HRQoL outcomes (26, 28, 33, 34). Although it is widely assumed that multimorbidity is associated with poorer HRQoL, the mechanisms through which multimorbidity negatively affects HRQoL through functional limitation or disability have not been thoroughly investigated. Our findings show that functional limitation plays a role in mediating the relationship between multimorbidity and HRQoL.

Clinical implications

Multimorbidity has been found to have a negative impact on the health-related quality of life of patients, partly due to its association with functional decline. Therefore, managing functional limitations effectively could help maintain the HRQoL of patients with multimorbidity. This implies a need for a more comprehensive approach to managing both conditions and recognizing their equal importance, which could ultimately improve the overall wellbeing of patients. In clinical practice, a thorough assessment of the various types of functional limitations in patients with multimorbidity could help guide appropriate preventive and supportive care, not only to maintain HRQoL but also to prevent further decline in function dependence.

Limitations

This study has several limitations, including the use of self-reported measures which may be subject to recall and social desirability bias. Although a well-validated questionnaire was used to measure HRQoL, subjective measures may not fully capture the objective reality of patients' health status. Additionally, the study is not causal and only identified associations between variables. Although panel data was used, unobserved confounding variables cannot be completely ruled out. Notably, important clinical factors such as disease severity and duration of the illness were not included in the study, which could have affected the relationship between multimorbidity and HRQoL.

Furthermore, the mechanisms underlying the relationship between multimorbidity and HRQoL are complex and may involve multiple mediators. While the current study focused on function limitation as a mediator, other mediators such as psychological distress or social isolation may also play vital roles. Further research utilizing more comprehensive measures and sophisticated statistical techniques, such as structural equation modeling, may offer more insights into the mechanisms underlying the relationship between multimorbidity and HRQoL.

Conclusion

This study contributes to the existing literature to understand the mediating effect of functional limitation and disability on the relationships between multimorbidity and HRQoL. Our study highlights the importance of improving patients' functional ability and preventing disability for patients with multimorbidity to improve their HRQoL. Therefore, healthcare that improves the management of patients with multimorbidity should include interventions that aim to encourage patients to participate in physical activity and increase social participation. Given the important mediating role, our study highlights that functional limitation or disability might be considered an intermediate outcome for evaluating interventions aimed at managing multimorbidity.

Data availability statement

The study utilized HILDA survey in Australia, which can be apply for access to the dataset through the following link: https://melbourneinstitute.unimelb.edu.au/hilda.

Author contributions

The aim of the research was developed by JL and MI. The methodology development and analysis were conducted by JL, MI, and TH. JL and MI drafted the manuscript draft. SP, YZ, RP, KA, RA, and BO contributed to all sections. All authors reviewed, edited, and commented on multiple versions of the manuscript. All authors contributed to the article and approved the submitted version.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Appendix

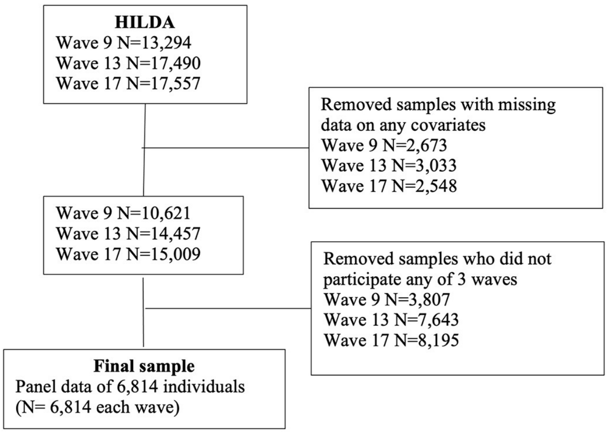

FIGURE A1
Sample flowchart.

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EDITED BY
Sanghamitra Pati,
Regional Medical Research Center (ICMR),
India

REVIEWED BY
Tanveer Rehman,
Regional Medical Research Center (ICMR),
India
Yu Xiao,
Chengdu No. 4 People's Hospital, China

*CORRESPONDENCE
Sung-In Jang
✉ JANGSI@yuhs.ac

[†]These authors have contributed equally to this work and share first authorship

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Effect of regional medical disparities on complications in patients with hypertension: Cox's proportional hazard models

Choa Yun[1†], Minah Park[2,3†], Jae Hong Joo[4], Soo Hyun Kang[5], Sung Hoon Jeong[6], Chung-Mo Nam[7], Eun-Cheol Park[2,7] and Sung-In Jang[2,7*]

[1]Department of Biostatistics and Computing, College of Medicine, Yonsei University, Seoul, Republic of Korea, [2]Institute of Health Services Research, Yonsei University, Seoul, Republic of Korea, [3]Department of Preventive Medicine, Eulji University School of Medicine, Daejeon, Republic of Korea, [4]Department of Health Informatics and Biostatistics, Yonsei University Graduate School of Public Health, Seoul, Republic of Korea, [5]Department of Preventive Medicine, Gachon University College of Medicine, Incheon, Republic of Korea, [6]Department of Rehabilitation Medicine, Seoul National University Hospital, Seoul, Republic of Korea, [7]Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Republic of Korea

Objective: Complications associated with hypertension can be alleviated by providing necessary medical services. However, there may be disparities in their provision depending on regional differences. Thus, this study aimed to examine the effects of regional healthcare disparities on complications in patients with hypertension in South Korea.

Methods: Data from the National Health Insurance Service National Sample Cohort (2004–2019) were analyzed. The position value for the relative composite index was used to identify medically vulnerable regions. The diagnosis of hypertension within the region was also considered. The risk of complications associated with hypertension included cardiovascular, cerebrovascular, and kidney diseases. Cox proportional hazards models were used for statistical analysis.

Results: A total of 246,490 patients were included in this study. Patients who lived in medically vulnerable regions and were diagnosed outside their residential area had a higher risk of complications than those living in non-vulnerable regions and were diagnosed outside the residential area (hazard ratio: 1.156, 95% confidence interval: 1.119–1.195).

Conclusion: Patients living in medically vulnerable regions who were diagnosed outside their residential areas were more likely to have hypertension complications regardless of the type of complication. Necessary policies should be implemented to reduce regional healthcare disparities.

KEYWORDS

hypertension, adverse effect, healthcare disparity, complications, Cox proportional hazards models

1. Introduction

The prevalence of hypertension is high worldwide. If not treated properly, hypertension can lead to complications, including cardiovascular disease (1), cerebrovascular disease, and kidney disease (2). However, if well managed, disabilities and premature death can be prevented (3). In 2010, the worldwide prevalence of hypertension was estimated to be 1.39 billion persons, representing 31% of all adults (4). Since South Korea is becoming the fastest-aging country worldwide3, there is a greater likelihood of an increase in the prevalence of hypertension. According to the Korea Hypertension Fact Sheet 2021, among the adult population (aged ≥20 years), it was estimated that 28% have hypertension. Compared with that in 2002, the number of people diagnosed with hypertension increased from 3.0 million to 10.1 million in 2019 (5).

Despite the seriousness of hypertension, it can be treated with proper and effective management (6). Especially among patients with chronic diseases, continuity of care is known to result in better patient satisfaction and outcomes (7). However, managing chronic diseases becomes much more difficult for people residing in rural areas (8) because the population composition, socioeconomic conditions, and distribution of medical facilities are different and the use of medical care varies (9). As of 2022, Seoul, the capital of South Korea, had 4.8 doctors per 1,000 inhabitants, and except for metropolitan cities (Busan, Daegu), all the other areas had an average of less than 3.2 doctors per 1,000 inhabitants (10). In addition, in a study on amenable deaths for specific districts conducted in 2018, the death rate in Seochogu (a district in Seoul) was 25.8 per 100,000 people, whereas the death rate in Hapcheon-gun (a county in Gyeongsangnam-do) was 112.2 per 100,000 people, a 4.3 fold difference (11).

Considering that hypertension requires ongoing treatment, a process of identifying medical gaps by region is necessary to avoid potential complications. Various approaches have been taken to assess the healthcare gap according to the region. For example, a study of all-cause mortality among patients with hypertension was conducted based on the years of life lost according to region (11). Another study assessed disparities according to socioeconomic status (12). However, the results of these studies were reported by region without considering other factors; therefore, there is a need to assess the overall effect of healthcare factors on complications of hypertension.

Therefore, our study aimed to estimate the effect of regional healthcare disparities using the position value for relative composite (PARC) index on complications and morbidity events among patients with hypertension in the Korean population using data from the Korean Health Insurance Service.

2. Materials and methods

2.1. Data and study population

The data used in this study were obtained from the National Health Insurance Service National Sample Cohort (NHIS-NSC) (13) from 2002 to 2019. However, to prevent the effects of other comorbid conditions, the period 2002–2003 was designated as a washout period. In addition, to identify patients with newly diagnosed hypertension, those who were diagnosed with hypertension in 2002–2003 and those diagnosed with hypertension complications in 2002–2003 were excluded. Finally, the data from 2004 to 2019 were used. After these exclusions, the total study population included 246,490 individuals.

2.2. Ethical consideration

This study was reviewed and approved by the International Review Board of Yonsei University's Health System (number: Y-2020-0031) and adheres to the tenets of the Declaration of Helsinki. The NHIS-NSC data do not contain any identifying information; hence, additional approval for written informed consent was not required.

2.3. Variables

The variables of interest in this study were medically vulnerable regions and diagnosis of hypertension within these regions. The medically vulnerable regions were identified using PARC indicators. These indicators have enabled the identification of healthcare levels by region in Korea (14). Details regarding analytical methods are provided in past literature (15–20).

PARC is an objective indicator that can identify relative locations compared with other regions using the positioning method. The PARC value ranges from −1 to 1. If the value is 1, it indicates superior healthcare levels in the region; 0 indicates average healthcare levels; and −1 indicates worst healthcare levels when compared with the mean value of the entire region. In other words, the closer the value is to-1, the lower the level of healthcare in the region than the average level of healthcare in the entire region, while the closer the value is to 1, the higher the average healthcare level of the entire region. In this study, when the PARC value was less than −0.33, it was classified as a medically vulnerable region (14).

The primary dependent variable in this study was hypertension complications among hypertension patients (International Classification of Diseases 10th revision codes: I10, I11, I12, I13, and I15). The complications included cardiovascular disease (ICD-10: I20, I21, I46, I48, and I50), cerebrovascular disease (ICD-10: I60, I61, I62, I63, and G45), and chronic kidney disease (ICD-10: N18.5).

The other covariates included sex (male/female), age (under 10, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, and over 70 years), type of insurance coverage (NHI/medical aid), income (low/middle/high), Charlson's comorbidity index (CCI) (0, 1, 2+), and types of healthcare facility (tertiary hospital/primary care hospital).

2.4. Statistical analysis

Continuous variables are reported as means and standard deviations and were compared using Student's t-test or analysis of variance for multiple groups, as appropriate. Categorical variables are reported as counts and percentages and were compared using the χ^2 test. The primary analysis tested whether a statistical interaction was present between the residential region and diagnosis area regarding the event of the complication survival, which was defined as the time from diagnosis of essential hypertension to the time complications occurred. Cox proportional hazards models were fitted to our results, and adjusted estimations were reported. In the presence of an interaction effect (residential region× diagnosis area), statistical significance was considered at $p < 0.05$. After considering the level of each interaction term as one group and dividing it into four groups—vulnerable and outside region, vulnerable and inside region, non-vulnerable and outside region, and non-vulnerable and inside region—univariate and multivariate Cox proportional hazards model analyses were performed. Additionally, Cox proportional hazards models for subgroups were used to calculate the hazard ratio (HR) for complication events, including cardiovascular, kidney, and cerebrovascular diseases, with adjustments for potential confounders. All statistical analyses were performed using SAS version 7.1 Enterprise (SAS Institute, Cary, NC), and all p-values were two-sided with a significance level of 0.05.

3. Results

The study cohort comprised 246,490 participants (Table 1). Table 1 shows the descriptive statistics of baseline characteristics by group. Patients who lived in vulnerable regions and were diagnosed outside the regions comprised 4.47% (11,007) of the participants, and those from non-vulnerable regions who were diagnosed inside the region comprised 49.05% (120,893).

We fitted multivariate Cox proportional hazards models to examine the presence of an interaction effect. In this model, the interaction term between the residential region (vulnerable vs. non-vulnerable) and the diagnosis area (outside vs. inside) was significant in the adjusted models (p for interaction = 0.005) (Supplementary Table S1). Since the interaction term was significant, we compared HRs for our outcome in the four groups defined in the methods using univariate and multivariate Cox proportional hazards models. Table 2 shows that the vulnerable and outside region group had the highest rate of complications, and there was a significant association between patients who were included in this group and the risk of complications when compared with that in the reference group (unadjusted HR for complications, 1.465; 95% CI, 1.418–1.513; $p < 0.0001$ and adjusted HR for complications, 1.156; 95% CI, 1.119–1.195; $p < 0.0001$).

TABLE 1 Baseline characteristics by group (residential region×diagnosis area).

	Group				*p*-value
	Vulnerable and outside region (*n* =11,007, 4.47%)	Vulnerable and inside region (*n* =19,760, 8.02%)	Non-vulnerable and outside region (*n* =94,830, 38.47%)	Non-vulnerable and inside region (*n* =120,893, 49.05%)	
	n (%)	*n* (%)	*n* (%)	*n* (%)	
Sex					<0.0001
Male	5,512 (4.38)	8,721 (6.94)	52,253 (41.56)	59,232 (47.11)	
Female	5,495 (4.55)	11,039 (9.14)	42,577 (35.25)	61,661 (51.00)	
Income					
Low	1,895 (4.73)	3,324 (8.29)	14,613 (36.45)	20,261 (50.54)	<0.0001
Middle	4,854 (4.56)	9,170 (8.61)	39,654 (37.22)	52,857 (49.61)	
High	4,258 (4.26)	7,266 (7.28)	40,563 (40.62)	47,775 (47.84)	
Coverage type					<0.0001
NHI, employed/self-employed	4,779 (3.91)	7,919 (6.48)	50,383 (41.21)	59,171 (48.40)	
Medical aid	6,228 (5.01)	11,841 (9.53)	44,447 (35.78)	61,722 (49.68)	
Age (years)					<0.0001
Under 10	166 (25.78)	353 (12.30)	1,002 (34.90)	1,350 (47.02)	
10–19	83 (6.65)	52 (4.16)	527 (42.19)	587 (47.00)	
20–29	262 (5.36)	118 (2.41)	2,648 (54.18)	1859 (38.04)	
30–39	630 (3.51)	618 (3.44)	8,812 (49.12)	7,880 (43.92)	
40–49	1709 (3.30)	2,622 (5.06)	21,166 (40.83)	26,342 (50.82)	
50–59	2,674 (3.86)	4,631 (6.69)	20,833 (35.00)	29,701 (49.90)	
60–69	2,962 (4.98)	6,024 (10.12)	20,833 (35.00)	29,701 (49.90)	
Over 70	2,521 (6.47)	5,342 (13.72)	13,172 (33.83)	17,902 (45.98)	
Charlson comorbidity index					<0.0001
0	4,371 (4.50)	6,981 (7.19)	40,444 (41.67)	45,270 (46.64)	
1	3,312 (1.34)	6,283 (8.29)	28,501 (37.60)	37,709 (49.74)	
Over 2	3,324 (4.52)	6,496 (8.82)	25,885 (35.16)	37,914 (51.50)	
Healthcare facility					<0.0001
Tertiary Hospital	4,953 (7.56)	2,751 (4.20)	35,293 (53.89)	22,499 (34.35)	
Primary Care Hospital	6,054 (3.34)	17,009 (9.40)	59,537 (32.89)	98,394 (54.36)	

TABLE 2 Cox proportional hazard regression models of time to complication event.

	Univariate		Multivariate	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Group				
Vulnerable and Outside region	1.465 (1.418, 1.513)	<0.0001	1.156 (1.119, 1.195)	<0.0001
Vulnerable and Inside region	1.146 (1.116, 1.177)	<0.0001	1.045 (1.017, 1.073)	0.0015
Non-vulnerable and Outside region	1.149 (1.131, 1.167)	<0.0001	1.042 (1.025, 1.059)	<0.0001
Non-vulnerable and Inside region	Ref		Ref	
Sex				
Male	1.3001 (0.986, 1.015)	0.9184	1.158 (1.139, 1.177)	<0.0001
Female	Ref		Ref	
Income				
Low	0.981 (0.960, 1.003)	0.0876	1.036 (1.013, 1.059)	0.0017
Middle	0.936 (0.922, 0.951)	<0.0001	1.021 (1.005, 1.037)	0.0113
High	Ref		Ref	
Coverage type				
NHI, employed/ self-employed	0.847 (0.834, 0.859)	<0.0001	0.954 (0.937, 0.970)	<0.0001
Medical aid	Ref		Ref	
Age (years)				
Under 10	1.310 (1.234, 1.390)	<0.0001	1.435 (1.352, 1.523)	0.0001
10–19	0.094 (0.072, 1.121)	<0.0001	0.092 (0.071, 0.119)	<0.0001
20–29	0.186 (0.170, 0.204)	<0.0001	0.183 (0.166, 0.200)	<0.0001
30–39	0.297 (0.285, 0.309)	<0.0001	0.302 (0.290, 0.315)	<0.0001
40–49	0.403 (0.394, 0.413)	<0.0001	0.413 (0.402, 0.423)	<0.0001
50–59	0.535 (0.524, 0.547)	<0.0001	0.535 (0.524, 0.547)	<0.0001
60–69	0.722 (0.707, 0.737)	<0.0001	0.714 (0.700, 0.729)	<0.0001
Over 70	Ref		Ref	
Charlson comorbidity index				
0	0.623 (0.612, 0.635)	<0.0001	0.667 (0.655, 0.679)	<0.0001
1	0.806 (0.792, 0.820)	<0.0001	0.824 (0.810, 0.838)	<0.0001
Over 2	Ref		Ref	
Healthcare facility				
Tertiary Hospital	1.646 (1.621, 1.671)	<0.0001	1.707 (1.680, 1.734)	<0.0001
Primary Care Hospital	Ref		Ref	

The results of the χ^2 test indicated that each complication rate was significantly different among the four groups ($p < 0.0001$) (Table 3). In addition, on examining the subgroups, it was observed that patients diagnosed outside their residential area and those living in medically vulnerable areas had the highest rate of all complications (cardiovascular disease: 2640 [24.0%]; kidney disease: 262 [2.4%]; cerebrovascular disease: 1928 [17.5%]).

Table 4 shows the overall HR (95% CI) and *p*-value of the fitted multivariate Cox proportional hazards models with adjustments for potential confounders for the subgroup analysis. For cardiovascular and cerebrovascular diseases, the vulnerable and outside region group had the highest rate of complications when compared with the reference group (adjusted HR for cardiovascular disease, 1.167; 95% CI, 1.120–1.215; $p < 0.0001$ and adjusted HR for cerebrovascular disease, 1.162; 95% CI, 1.108–1.219; $p < 0.0001$). However, the non-vulnerable and outside region group had the highest rate of complications when compared with the reference group for kidney disease (adjusted HR, 1.124; 95% CI, 1.106–1.196; $p < 0.0002$). The HR for cardiovascular and kidney diseases was higher in the group with the first diagnosis outside the residential area, regardless of whether they were medically vulnerable. In contrast, the HR for cerebrovascular diseases was higher in the medically vulnerable group than in the diagnosis group.

4. Discussion

In this study, we examined the effects of regional medical disparities on complications in patients with hypertension. Our results

TABLE 3 General characteristics of study subjects for hypertension complications.

	Hypertension complications											
	Complications		*p*-value	Cardiovascular disease		*p*-value	Kidney disease		*p*-value	Cerebrovascular disease		*p*-value
	Yes	No		Yes	No		Yes	No		Yes	No	
	n (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
Group			<0.0001			<0.0001			<0.0001			<0.0001
Vulnerable and Outside region	4,100 (37.3)	6,907 (62.8)		2,640 (24.0)	8,367 (76.0)		262 (2.4)	10,745 (97.6)		1928 (17.5)	9,079 (82.5)	
Vulnerable and Inside region	6,341 (32.1)	13,419 (67.9)		3,791 (19.2)	15,969 (80.8)		326 (1.7)	19,434 (98.3)		3,330 (16.9)	16,430 (83.1)	
Non-vulnerable and Outside region	28,353 (29.9)	66,477 (70.1)		18,768 (19.8)	76,062 (80.2)		2,123 (2.2)	92,707 (97.8)		12,114 (12.8)	82,716 (87.2)	
Non-vulnerable and Inside region	33,846 (28.0)	87,047 (72.0)		21,533 (17.8)	99,360 (82.2)		2,184 (1.8)	118,709 (98.2)		15,520 (12.8)	105,373 (87.2)	
Sex			<0.0001			<0.0001						<0.0001
Male	35,033 (27.9)	90,685 (72.1)		22,562 (18.0)	103,156 (82.0)		2,957 (2.4)	122,761 (97.6)		15,064 (12.0)	110,654 (88.0)	
Female	37,607 (31.1)	83,165 (68.9)		24,170 (20.0)	96,602 (80.0)		1938 (1.6)	118,834 (98.4)		17,828 (14.8)	102,944 (85.2)	
Income			<0.0001			<0.0001			0.2322			<0.0001
Low	11,316 (28.2)	28,777 (71.8)		7,140 (17.8)	32,953 (82.2)		757 (1.9)	39,336 (98.1)		5,204 (13.0)	34,889 (87.0)	
Middle	30,428 (28.6)	76,107 (71.4)		19,257 (18.1)	87,278 (81.9)		2,112 (2.0)	104,423 (98.0)		13,981 (13.1)	92,554 (86.9)	
High	30,896 (30.9)	68,966 (69.1)		20,335 (20.4)	79,527 (79.6)		2026 (2.0)	97,836 (98.0)		13,707 (13.7)	86,155 (86.3)	
Coverage type			<0.0001			<0.0001			0.0356			<0.0001
NHI, employed/ self-employed	31,940 (26.1)	90,312 (73.9)		20,970 (17.2)	101,282 (82.9)		2,355 (1.9)	119,897 (98.1)		13,429 (11.0)	108,823 (89.0)	
Medical aid	40,700 (32.8)	83,538 (67.2)		25,762 (20.7)	984,765 (79.3)		2,540 (2.0)	121,698 (98.0)		19,463 (15.7)	104,775 (84.3)	
Age (years)			<0.0001			<0.0001			<0.0001			<0.0001
Under 10	1,159 (40.4)	1712 (59.6)		707 (24.6)	2,164 (75.4)		36 (1.3)	2,835 (98.7)		613 (21.4)	2,258 (78.6)	
10–19	58 (4.64)	1,191 (95.4)		45 (3.6)	1,204 (96.4)		7 (0.6)	1,242 (99.4)		7 (0.6)	1,242 (99.4)	
20–29	464 (9.49)	4,423 (90.5)		322 (6.6)	4,565 (93.4)		94 (1.9)	4,793 (98.1)		75 (1.5)	4,812 (98.5)	
30–39	2,724 (15.18)	15,216 (84.8)		1859 (10.4)	16,081 (89.6)		325 (1.8)	17,615 (98.2)		773 (95.7)	17,167 (4.3)	
40–49	10,815 (20.86)	41,024 (79.1)		7,245 (14.0)	44,594 (86.0)		762 (1.5)	51,077 (98.5)		4,066 (92.2)	47,773 (7.8)	
50–59	18,910 (27.31)	50,337 (72.7)		12,510 (18.1)	56,737 (81.9)		1,148 (1.7)	68,099 (98.3)		8,025 (88.4)	61,222 (11.6)	
60–69	22,621 (38.0)	36,899 (62.0)		14,452 (24.3)	45,086 (75.7)		1,592 (2.7)	57,928 (97.3)		10,995 (81.5)	48,525 (18.5)	
Over 70	15,889 (40.8)	23,048 (59.2)		3,592 (24.6)	29,345 (75.4)		931 (2.4)	38,006 (97.6)		8,338 (78.6)	30,599 (21.4)	

(Continued)

TABLE 3 (Continued)

	Hypertension complications											
	Complications			Cardiovascular disease			Kidney disease			Cerebrovascular disease		
	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value	Yes	No	*p*-value
	n (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
Charlson comorbidity index			<0.0001			<0.0001			<0.0001			<0.0001
0	17,424 (18.0)	79,642 (82.0)		10,626 (11.0)	86,440 (89.0)		1,129 (1.2)	95,937 (98.8)		7,405 (7.6)	89,661 (92.4)	
1	22,262 (29.4)	53,543 (70.6)		14,128 (18.6)	61,677 (81.4)		1,486 (2.0)	74,319 (98.0)		9,838 (13.0)	65,967 (87.0)	
Over 2	32,954 (44.8)	40,665 (55.2)		21,978 (29.9)	51,641 (70.2)		2,280 (3.1)	71,339 (96.9)		15,649 (21.3)	57,970 (78.7)	
Healthcare facility			<0.0001			<0.0001			<0.0001			<0.0001
Tertiary Hospital	25,980 (39.7)	39,516 (60.3)		17,411 (26.6)	48,085 (73.4)		1979 (3.0)	63,517 (97.0)		11,107 (17.0)	54,389 (83.0)	
Primary Care Hospital	46,660 (25.8)	134,334 (74.2)		29,321 (16.2)	151,673 (83.8)		2,916 (1.6)	178,078 (98.4)		21,785 (12.0)	159,209 (88.0)	

showed that patients living in medically vulnerable regions and those diagnosed outside their residential areas were more likely to have hypertension complications. In particular, for each individual complication, the results also showed that patients living in medically vulnerable regions and those diagnosed outside their residential areas were more likely to have a higher HR.

The results of this study are similar to those of studies conducted in other countries. For example, in China, which has a similar prevalence of hypertension to South Korea, treatment and control are worse in rural areas (21). In Romania, prevalence of hypertension is higher and general control of hypertension is lower in rural areas than in urban areas (22). In the United States, the prevalence of hypertension and current medication use is higher in rural areas due to lack of healthcare workers and a higher prevalence of obesity, lack of physical activity, and smoking (23).

The reason for the higher risk of hypertension complications may be disparities in access to care. With regard to hypertension management, counseling and education by health clinics and doctors are known to affect the recognition and treatment rate of hypertension (24). However, those in rural areas have limited access to healthcare personnel (25) and this problem is also present in Korea. While the number of doctors per 100 beds in metropolitan cities was 14.17 and the number of nurses was 60.95, in rural areas, the number of doctors was 6.36 and the number of nurses was 26.67 (26), which indicated a large gap in the access to healthcare personnel. In the case of departments, except for orthopedics, those in rural areas have limited access to other departments (27).

According to the subgroup analysis, patients living in medically vulnerable regions who were diagnosed outside their residential areas were more likely to have a higher risk of hypertension complications from cardiovascular, kidney, and cerebrovascular diseases. Although patient differences in characteristics, the overall prevalence could be attributed to medical access issues. Rural areas are known to have transportation issues and limited access to care, resulting in a higher likelihood of fewer hospital visits and under-diagnoses (28). As cardiovascular and cerebrovascular diseases are time-sensitive diseases with a "golden time" for the use of appropriate treatment (29, 30) implementation of timely and appropriate medical resources in both internal and external medical institutions is important (29). However, as patients in vulnerable regions and those who have been diagnosed outside their region have a significant shortage of these resources, there is a higher probability that they are more affected than other groups.

In the case of kidney disease, managing and controlling blood pressure is the best prevention method (31); therefore, accessibility and performance of primary care services are important (32). However, in South Korea, there is a preference for hospitals over clinics (33); thus, there has been a constant decrease in the number of clinics in rural areas over the past years (34). These factors may have had a greater effect on people diagnosed outside their region. This may indicate that a person's most frequently used healthcare facility is outside their region, making accessibility much more difficult.

This study has some limitations. First, due to the use of medical claims data, factors such as obesity, physical activity, and smoking rate could not be considered. However, in South Korea, there are relatively small differences in the smoking rate (35), obesity (36) and amount of

TABLE 4 Cox proportional hazard regression models of time to complication event for specific hypertension complications.

	Cardiovascular disease		Kidney disease		Cerebrovascular disease	
	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Group						
Vulnerable and Outside region	1.167 (1.120, 1.215)	<0.0001	1.081 (0.949, 1.231)	0.2413	1.162 (1.108, 1.219)	<0.0001
Vulnerable and Inside region	0.992 (0.958, 1.027)	0.6575	0.876 (0.780, 0.985)	0.0268	1.148 (1.105, 1.192)	<0.0001
Non-vulnerable and Outside region	1.080 (1.058, 1.102)	<0.0001	1.124 (1.056, 1.196)	0.0002	0.984 (0.960, 1.009)	0.2088
Non-vulnerable and Inside region	Ref		Ref		Ref	
Sex						
Male	1.061 (1.040, 1.083)	<0.0001	1.864 (1.749, 1.987)	<0.0001	1.065 (1.039, 1.090)	<0.0001
Female	Ref		Ref		Ref	
Income						
Low	0.931 (0.906, 0.957)	<0.0001	1.110 (1.020, 1.208)	0.0160	1.044 (1.010, 1.079)	0.0102
Middle	0.942 (0.923, 0.961)	<0.0001	1.071 (1.007, 1.139)	0.0288	1.062 (1.037, 1.087)	<0.0001
High	Ref		Ref		Ref	
Coverage type						
NHI, employed/self-employed	0.987 (0.966, 1.008)	0.2360	0.886 (0.830, 0.946)	0.0003	0.904 (0.882, 0.928)	<0.0001
Medical aid	Ref		Ref		Ref	
Age (years)						
Under 10	1.248 (1.156, 1.348)	<0.0001	0.781 (0.559, 1.089)	0.1454	1.202 (1.107, 1.305)	<0.0001
10–19	0.150 (0.112, 0.201)	<0.0001	0.196 (0.093, 0.413)	<0.0001	0.027 (0.013, 0.057)	<0.0001
20–29	0.263 (0.235, 0.294)	<0.0001	0.654 (0.527, 0.811)	0.0001	0.072 (0.057, 0.091)	<0.0001
30–39	0.398 (0.378, 0.419)	<0.0001	0.624 (0.548, 0.712)	<0.0001	0.196 (0.182, 0.211)	
40–49	0.521 (0.505, 0.538)	<0.0001	0.509 (0.461, 0.563)	<0.0001	0.344 (0.331, 0.358)	<0.0001
50–59	0.667 (0.649, 0.686)	<0.0001	0.562 (0.514, 0.614)	<0.0001	0.494 (0.479, 0.510)	<0.0001
60–69	0.866 (0.844, 0.889)	<0.0001	0.859 (0.791, 0.932)	0.0003	0.750 (0.729, 0.772)	<0.0001
Over 70	Ref		Ref		Ref	
Charlson comorbidity index						
0	0.492 (0.481, 0.504)	<0.0001	0.603 (0.561, 0.649)	<0.0001	0.519 (0.505, 0.534)	<0.0001
1	0.710 (0.695, 0.725)	<0.0001	0.799 (0.748, 0.853)	<0.0001	0.710 (0.692, 0.728)	<0.0001
Over 2	Ref		Ref		Ref	
Healthcare facility						
Tertiary Hospital	1.838 (1.802, 1.874)	<0.0001	1.755 (1.653, 1.864)	<0.0001	1.552 (1.515, 1.590)	<0.0001
Primary Care Hospital	Ref		Ref		Ref	

physical activity (37) between rural and urban areas; hence, it is unlikely that there is confounding by these factors. Nevertheless, these factors should be considered in future studies. Second, factors such as history of hypertension prescription and continuity of care could not be considered in this study. Future studies should consider these factors.

However, our study has some major strengths. To the best of our knowledge, this was the first study to investigate regional medical disparities in complication morbidity events in patients with hypertension using the PARC index. In addition, since all Korean citizens are required to enroll in the National Health Insurance Service, the NHIS datasets provide nationally representative data.

Our findings suggest that patients who live in medically vulnerable regions and are diagnosed outside their residential area are more likely to have a complication of hypertension, including cardiovascular and cerebrovascular disease. Therefore, necessary policies should be implemented to reduce regional healthcare disparities.

Data availability statement

The datasets GENERATED/ANALYZED for this study can be found in the NHIS REPOSITORY https://nhiss.nhis.or.kr/bd/ab/bdaba000eng.do;jsessionid=65hUSEvUQ4RZuiKJOf9ggWNyYYMW wCUCBKUkhbpCMifjCNazbC9wHff1VfMi61cp.primrose22_servlet_engine10.

Ethics statement

The studies involving human participants were reviewed and approved by International Review Board of Yonsei University's Health System. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Author contributions

CY and MP contributed to conception and design of the study. CY performed the statistical analysis. MP wrote the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2023.1138017/full#supplementary-material

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Multimorbidity patterns and health-related quality of life in Jamaican adults: a cross sectional study exploring potential pathways

Leslie S. Craig[1], Colette A. Cunningham-Myrie[2], Katherine P. Theall[3], Jeanette Gustat[4], Julie H. Hernandez[5] and David R. Hotchkiss[5]*

[1]Department of Medicine, School of Medicine, Tulane University, New Orleans, LA, United States, [2]Department of Community Health and Psychiatry, University of the West Indies, Mona, Jamaica, [3]Department of Social, Behavioral, and Population Sciences, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, United States, [4]Department of Epidemiology, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, United States, [5]Department of International Health and Sustainable Development, School of Public Health and Tropical Medicine, Tulane University, New Orleans, LA, United States

Introduction: Multimorbidity and health-related quality of life (HRQoL) are intimately linked. Multiple chronic conditions may adversely affect physical and mental functioning, while poorer HRQoL may contribute to the worsening course of diseases. Understanding mechanisms through which specific combinations of diseases affect HRQoL outcomes can facilitate identification of factors which are amenable to intervention. Jamaica, a middle-income country with high multimorbidity prevalence, has a health service delivery system dominated by public sector provision via a broad healthcare network. This study aims to examine whether multimorbidity classes differentially impact physical and mental dimensions of HRQoL in Jamaicans and quantify indirect effects on the multimorbidity–HRQoL relationship that are mediated by health system factors pertaining to financial healthcare access and service use.

Materials and methods: Latent class analysis (LCA) was used to estimate associations between multimorbidity classes and HRQoL outcomes, using latest available data from the nationally representative Jamaica Health and Lifestyle Survey 2007/2008 (N=2,551). Multimorbidity measurement was based on self-reported presence/absence of 11 non-communicable diseases (NCDs). HRQoL was measured using the 12-item short-form (SF-12) Health Survey. Mediation analyses guided by the counterfactual approach explored indirect effects of insurance coverage and service use on the multimorbidity–HRQoL relationship.

Results: LCA revealed four profiles, including a *Relatively Healthy* class (52.7%) characterized by little to no morbidity and three multimorbidity classes characterized by specific patterns of NCDs and labelled *Metabolic* (30.9%), *Vascular-Inflammatory* (12.2%), and *Respiratory* (4.2%). Compared to the *Relatively Healthy* class, *Vascular-Inflammatory* class membership was associated with lower physical functioning (β=−5.5; p<0.001); membership in *Vascular-Inflammatory* (β=−1.7; p<0.05), and *Respiratory* (β=−2.5; p<0.05) classes was associated with lower mental functioning. Significant mediated effects of health service use, on mental functioning, were observed for *Vascular-Inflammatory* (p<0.05) and *Respiratory* (p<0.05) classes.

EDITED BY
Stefan Essig,
University of Lucerne, Switzerland

REVIEWED BY
Giuseppe Lassandro,
University of Bari Aldo Moro, Italy
Rowena Katherine Merritt,
University of Kent, United Kingdom
Fantu Abebe,
Bahir Dar University, Ethiopia
Matteo Scopetti,
Sapienza University of Rome, Italy

*CORRESPONDENCE
David R. Hotchkiss
✉ hotchkis@tulane.edu

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Conclusion: Specific combinations of diseases differentially impacted HRQoL outcomes in Jamaicans, demonstrating the clinical and epidemiological value of multimorbidity classes for this population, and providing insights that may also be relevant to other settings. To better tailor interventions to support multimorbidity management, additional research is needed to elaborate personal experiences with healthcare and examine how health system factors reinforce or mitigate positive health-seeking behaviours, including timely use of services.

KEYWORDS

non-communicable diseases (NCD), multimorbidity (MM), health-related quality of life, Jamaica, latent class analysis (LCA)

Introduction

Health-related quality of life (HRQoL), a subjective, multidimensional construct encompassing functioning and well-being in physical, emotional, and social domains (1–3), has been further described by Mayo as a "measure of the value assigned to duration of life as modified by impairments, functional states, perceptions and opportunities, as influenced by disease, injury, treatment and policy" (3, 4). Given chronicity of non-communicable diseases (NCDs), coupled with the potential for poorer physical and mental functioning to erode individual self-management capacity, intensify care demands, and contribute to a worsening of the course of diseases, HRQoL outcomes have important implications for the management of prevalent multimorbidity (i.e., the co-occurrence of two or more NCDs) and prevention of additional conditions (1, 5, 6).

Systematic reviews have consistently documented a strong, inverse relationship between the number of medical conditions and physical HRQoL domains (1, 7). Associations between multimorbidity and mental HRQoL domains are more varied, however, with some studies reporting no statistically significant relationship while others have indicated significant declines in patients with 3 or more concurrent diagnoses (1, 7). Yet, while the body of literature on multimorbidity and HRQoL is growing, commonly cited limitations of available evidence include the frequent exclusion of psychiatric diagnoses from multimorbidity measurement, paucity of data from low- and middle-income country (LMIC) settings, and the reliance on simple counts of diseases (1, 7). Further, despite the existing consensus on the association of prevalent multimorbidity with poorer physical HRQoL domains, there is less agreement regarding the mechanistic pathways underlying poor HRQoL outcomes and the factors that may be amenable to intervention (8).

Aspects of the health system, including instruments that support financial access to care (e.g., insurance coverage) and "hassles" associated with health system interaction (e.g., seeking information, scheduling visits, interacting with health care providers) (8, 9), have been suggested as factors that may present opportunities for intervention along the multimorbidity–HRQoL pathway. Researchers have posited that specific combinations of diseases may have differential effects on patient's experiences with accessing, using, and enacting, care with potential to differentially affect outcomes (5, 8). A systematic review of qualitative data exploring patient's subjective experiences of multimorbidity identified financial burdens and frequent healthcare use among the most pressing components of individual experiences in managing the burden and treatment of multimorbidity (9). Specifically, individuals reported that financial pressures were exacerbated by need for private insurance, as this typically shaped user charges and the amount to be reimbursed, while frequent service use negatively impacted the subjective experience of multimorbidity, by serving as a reminder of all health problems currently faced (9).

Improved understanding of the mechanisms through which health system factors, pertaining to financial access and service use, influence quality of life outcomes, can better guide the allocation of resources and organization of care, with important implications for multimorbidity prevention and control. This research used data from the Jamaica Health and Lifestyle Survey 2007/2008 (JHLS-II) to examine the contribution of health system factors to the multimorbidity–HRQoL relationship in Jamaica, a middle-income country in the Caribbean region with a high prevalence of multimorbidity that is disproportionately borne by women (10). Indeed, nationally representative, comprehensive lifestyle surveys such as JHLS-I (2000/2001) and the JHLS-II have been conducted, over the past few years, to better quantify the burden of NCDs and inform targeted action, including the 2012–2017 NCD strategic plan (11). At the time of manuscript preparation, JHLS-III 2016/2017 were not available and the JHLS-II remained the latest available nationally representative dataset for in-depth investigation.

Health service delivery in Jamaica is facilitated through a broad network of primary, secondary, and tertiary care facilities and involves a mix of public and private sectors, with the former being the main provider of public health and hospital services while the latter dominates ambulatory service and pharmaceutical supply provision (10, 12). Recognizing that medication costs account for a substantial portion of out-of-pocket spending, the Government of Jamaica introduced two government programs, funded by government taxes, to enhance financial access to drugs: the Jamaica Drug for the Elderly Programme (JADEP) and the National Health Fund (NHF) (12). JADEP provided subsidies for specific drugs covering select chronic illnesses, for all Jamaican residents over the age of 60, while the NHF provided subsidies to its beneficiaries for the treatment of selected NCDS, without age restrictions (13). Private health insurance schemes are also available and voluntary, with the majority being employer-provided or employer-funded with co-payment by employees.

As illustrated in the conceptual framework below (Figure 1), multimorbidity class membership was hypothesized to affect HRQoL (assessed via the SF-12 Health Survey instrument, using summary

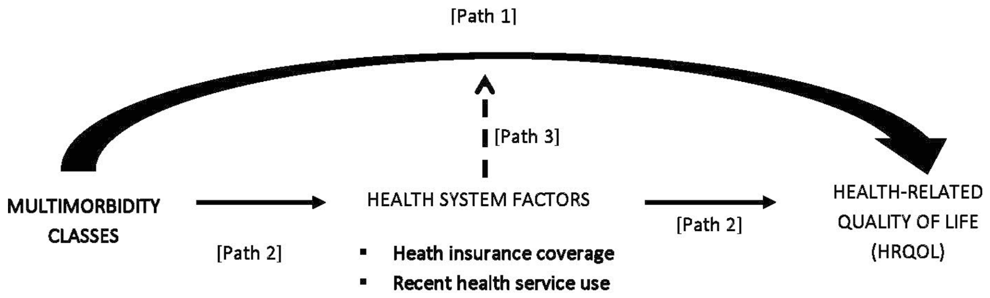

FIGURE 1
Conceptual framework to guide data analysis (1) Path 1 tests the direct association of multimorbidity class membership on health-related quality of life (HRQoL), (2) Path 2 tests the indirect association of health system factors reflecting financial access to care (i.e., insurance coverage) and health service utilization (i.e., recent health service use) on HRQoL, and (3) Path 3 tests the moderation effect of health system factors on the multimorbidity–HRQoL relationship.

measures of physical functioning and mental functioning) in the Jamaican population both directly and indirectly, through three main pathways. First, given evidence of a significant inverse relationship between the number of chronic conditions and physical HRQoL domains (1, 7), we hypothesized that multimorbidity classes reflecting a higher number of conditions would be associated with lower physical and mental health functioning (Path 1). Second, given independent effects of the health system reflecting financial access to care (i.e., insurance coverage) and health service utilization (i.e., recent health service use), we hypothesized that by minimizing financial stress and enabling better health-seeking behaviour, insurance coverage would mediate (i.e., lessen) the impact of multimorbidity on physical and mental dimensions of HRQoL (Path 2) while, due to challenges navigating the health system, recent service use would mediate (i.e., intensify) the multimorbidity–HRQoL relationship via a negative effect on mental health functioning (Path 2). Finally, we hypothesized that interactions between multimorbidity and health system factors would moderate the multimorbidity–HRQoL relationship, either by mitigating (in the case of insurance coverage) or reinforcing (in the case of health service use) its effects on health outcomes (Path 3).

Materials and methods

Data

Secondary analysis of JHLS-II data was performed. Study design, recruitment, sampling, and data collection procedures for the JHLS-II have been previously described (13). Briefly, 2,848 individuals, 15–74 years old of age, were recruited between November 2007 and March 2008 to participate in this nationally representative, interviewer-administered, cross-sectional survey (13, 14). Participant recruitment was guided by a multi-stage cluster sampling design and based on random selection of clusters (enumeration districts) proportional to the size of the population within all parishes in Jamaica (13). Trained interviewers used structured questionnaires and standardized protocols to collect demographic, medical history, and health behaviour data, and obtain physical (i.e., height, body weight, hip circumference, and waist circumference), and biological (i.e., blood pressure, blood glucose, and total cholesterol) measurements (13, 14).

Measures

In this study, four categories of variables were operationalized:

(1) **Exposure**: multimorbidity class membership,
(2) **Outcomes**: HRQoL, relating to physical and mental domains,
(3) **Mediators of the multimorbidity–HRQoL relationship**: health system factors reflecting financial access to care and health care utilization, and
(4) **Covariates**: covariates included socio-demographic characteristics, economic circumstances, and health behaviours with well-documented associations with quality-of-life outcomes.

Multimorbidity class membership

Binary indicators reflecting the presence/absence of 11 NCDs were used to categorize the population into latent class (i.e., multimorbidity) segments, based on the relative probabilities that individuals within the class have a particular NCD. These indicators of multimorbidity class membership have been previously described (15, 16). In brief, only those NCDs with the greatest burden in this population, defined as a prevalence of 1% or higher in each sex, were included as indicators: hypertension, obesity, hypercholesterolemia, diabetes, asthma, arthritis, cardiovascular disease, mental health disorders, chronic obstructive pulmonary disease (COPD), stroke, and glaucoma. Self-reported diagnosis of bronchitis/pneumonia served as a proxy for COPD and, in keeping with guidance on multimorbidity measurement (17), cardiovascular (i.e., heart disease, myocardial infarction, and circulation problems) and mental health (i.e., depression, anxiety, psychosis, and other mental health problems) conditions were grouped together to reflect cardiovascular diseases and mental health disorders, respectively.

Health-related quality of life (HRQoL)

HRQoL was measured using the SF-12 Health Survey instrument, a 12-item short-form that captures eight dimensions of health (i.e., Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health) and can be used to generate two summary subscale scores reflecting physical and mental HRQoL functioning: the Physical Component

Summary (PCS-12) and Mental Component Summary (MCS-12) scores (18). The SF-12 captures eight dimensions of health, with the PCS-12 generally measuring Physical Functioning, Role Limitations due to Physical Health Problems, Bodily Pain, and General Health domains, while the MCS-12 predominantly reflects Vitality (i.e., energy/fatigue), Social Functioning, Role Limitations due to Emotional Problems, and Mental Health (i.e., psychological distress and psychological well-being) (19). Summary HRQoL measures of physical and mental health remain a valuable approach to the measurement of health and functional status, and recommendations urge use of traditional SF-12 scoring and procedures for their derivations (20). In accordance with these recommendations (19), PCS-12 and MCS-12 subscale scores were weighted, aggregated and standardized, to achieve a mean score of 50 and standard deviation (SD) of 10, and allow for meaningful comparison with each other (19). PCS-12 and MCS-12 scores were set to missing if an individual was missing data on any one of the SF-12 items, and mean substitution for missing values used. Higher scores were indicative of better HRQoL (2).

Health system factors

Individual-level health system factors included indicators of health insurance coverage and health service use. For health insurance coverage, binary indicators of public coverage (based on enrolment in either the NHF or JADEP) and private insurance coverage reflected better financial access to needed medications and health services, respectively. Based on data availability, a binary indicator of recent health service use was created using a proxy measure based on reports of the last blood pressure measurement being taken in the 6 month period prior to the survey.

Covariates

Socio-demographic, economic, and behavioural factors noted to impact quality of life outcomes were defined (1). Self-reported socio-demographic characteristics included age in years (treated as continuous), sex (male/female), full-time employment (yes/no), and having attained at least secondary level education or higher (yes/no). For economic circumstances, principal component analysis (PCA) was used to generate quintiles ranging from poorest to wealthiest, based on (yes/no) responses to questions on ownership of household assets (i.e., gas/electric stove, refrigerator or freezer, microwave oven, telephone, radio, television set, cable, satellite dish, bicycle, motorbike, car, computer, washing machine, sewing machine, fan, air conditioner, compact disk (CD) player, stereo equipment, record player, and video cassette recorder), and living conditions (i.e., number of members per sleeping room). This wealth index was then dichotomized to reflect discrete high vs. low groups, specifying those in the top 60% versus the bottom 40% (21). Health behaviours reflected past or current tobacco use (yes/no), current alcohol drinkers (yes/no) and low physical activity levels (yes/no). Physical activity levels were defined using metabolic equivalent (MET) levels based on walking, moderate-intensity activity, and vigorous-intensity activity scores from the International Physical Activity Questionnaire (IPAQ)-Short Form (22). Based on established cut-offs, categories reflecting high (i.e., ≥7 or more days of any combination of walking, moderate-or vigorous-intensity activities accumulating at least 3,000 MET-minutes/week), moderate (i.e., ≥5 days of any combination of walking, moderate-or vigorous-intensity activities achieving a minimum of at least 600 MET-minutes/week) or low (i.e., no activity or some activity reported but not enough to meet moderate or high levels) levels of activity were derived (22), and the former two categories collapsed to create the binary, low physical activity levels indicator.

Ethics approval and consent to participate

The JHLS-II survey and study protocol were approved by the Ministry of Health, Jamaica and the University of the West Indies/University Hospital of the West Indies Ethics Research Committee (ECP 169, 14/15). Written informed consent was obtained from all adult study participants and, for participants under 18 years of age, written consent was received from a parent and/or legal guardian. All study procedures were performed in accordance with institutional guidelines and confidentiality of all participants and national data were protected within legal limits.

Statistical approach

Descriptive statistics were examined using proportions for categorial variables and means with 95% confidence intervals (CIs) for continuous variables. Base sampling weights, calculated as the product of the inverse of the probability of selecting a household and the inverse of the probability of selecting a primary sampling unit, were applied to account for sampling design and non-response. Further, post-stratification weights, calculated as the number of persons in the Jamaican population between the ages of 15–74 years, represented by each individual in the sample within 5 year age-sex categories, were used. In keeping with recommendations (23), regressions were unweighted. All analyses were performed using Stata v.15 software (StataCorp, College Station, TX).

Latent class analysis (LCA)

Multimorbidity classes were identified using LCA, a reductionist strategy that uses a person-centred approach to identify segments of the population with diverging disease profiles (24). First, a series of models, with a progressively increasing number of latent classes, were fit to the data. Baseline model selection was driven by comparison of model fit statistics (i.e., likelihood-ratio G^2 statistic and parametric bootstrap likelihood ratio test) and information criteria (i.e., Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), adjusted BIC) in addition to visual inspection of probability plots to evaluate the meaningfulness and distinctiveness of resultant latent class solutions (25). A description of the methodology used to determine baseline model selection can be found in Craig et al. 2020 (15).

Next, a Bayes' theorem-based approach was used to estimate the effect of multimorbidity class membership on physical and mental HRQoL domains. This involved fitting the latent class model with the outcome included as a covariate, and then using Bayes' theorem to reverse the direction of the effect and empirically derive the class-specific distribution of mean PCS-12 and MCS-12 scores, via kernel density estimation (26). Pairwise tests and corresponding *values of p*, with statistical significance set at $p < 0.05$, were used to compare each multimorbidity pattern with the reference class and test the null hypothesis that scores were equal. All statistical analyses were carried out via Stata v.15 software, using the LCA Stata Plugin (27) and the LCA_Distal_BCH Stata function (28) as needed.

Multivariable regression analysis

Following LCA, individuals were assigned to their best fit class based on their maximum posterior probability. Multivariable regression methods were then used to further examine the multimorbidity–HRQoL relationship, separately for physical and mental domains, while controlling for important confounders known to affect quality of life outcomes (7).

Mediation analyses

To investigate the role of health system factors on HRQoL outcomes, the counterfactual approach to mediation analysis, developed by Valeri and VanderWeele (29), was used. This approach allows the total effect of multimorbidity on HRQoL to be decomposed into direct and indirect effects, using models with interactions (e.g., between multimorbidity classes and health system factors) and non-linearities (e.g., binary mediators such as insurance coverage and recent health service use) (29). Analyses were performed in Stata using the *paramed* program, which is based on the mediation macro developed by Valeri and VanderWeele (29). Multimorbidity classes were recoded as separate binary indicators (i.e., *Metabolic*, *Vascular-Inflammatory*, and *Respiratory*) to accommodate programming requirements for operationalization of the exposure variable. To satisfy identifiability assumptions regarding no confounding (29), key socio-demographic, economic, and health behaviour covariates were included in the regression. Potential interactions between multimorbidity classes and health system factors were tested for their effects on HRQoL and included where significant. Natural direct and indirect effects were estimated by fitting a linear regression model for the continuous outcome and a logistic regression model for the binary mediator, respectively (29). From these combined models, estimates for the natural direct effects, natural indirect effects, and total effects (i.e., the sum of the natural direct and indirect effects) were determined, along with bias-corrected bootstrap confidence intervals (via bootstrap procedures with 1,000 replications) (29). The proportion of the multimorbidity–HRQoL relationship mediated through health system factors was calculated as the ratio of the natural indirect effect to the total effect.

Results

Sample characteristics

Multimorbidity latent classes

Only participants with complete information on the presence or absence of the 11 NCD multimorbidity indicators were included in the analytic sample. There were no statistically significant differences between those with complete ($n = 2{,}551$) and those with missing data ($n = 311$) with respect to age, sex, or region of residence. Fit statistics, information criteria, entropy scores and model interpretability together suggested that the four-class solution was the optimum baseline model. Briefly, the G^2 statistic, Akaike Information Criteria (AIC) and the adjusted Bayesian Information Criteria (BIC) reached their lowest in the four-class model. The four-class solution's entropy score also indicated precision in class prediction and, upon examination, allowed for meaningful interpretation of resultant latent classes. Latent class prevalences and item-response probabilities (i.e., the estimated probability of reporting a particular NCD, given membership in a particular latent class) for the four-class model have been fully described in an earlier publication (15) and are illustrated in Table 1. In summary, the final classes were labelled: *Relatively Healthy* (52.7%) – characterized by individuals with very low probability of any of the 11 NCDs; *Metabolic* (30.9%) – characterized by individuals with a high probability of hypertension and obesity, and somewhat moderate probability of hypercholesterolemia; *Vascular-Inflammatory* (12.2%) – characterized by individuals with the highest probability of hypertension, obesity, hypercholesteremia and diabetes, in addition to a high probability of arthritis and cardiovascular disease; and *Respiratory* (4.2%) – characterized by individuals with the highest probability of asthma and COPD.

Health system factors

A significantly larger proportion of the sample had private health insurance compared to public coverage through subsidies (18.8% vs. 10.1%; $p = 0.008$) (Figure 2). Specifically, 13.7% of the study population had enrolled in the NHF while only 4.2% had enrolled in JADEP; among those over 60 years, 27.0% were enrolled in JADEP. Compared to their *Relatively Healthy* counterparts (18.8%), the *Metabolic* class was less likely ($p = 0.034$) and the *Vascular-Inflammatory* class more likely ($p = 0.003$) to own private insurance. All multimorbidity classes were significantly more likely than their *Relatively Healthy* counterparts ($p \leq 0.001$) to have public insurance coverage (i.e., be enrolled in either of the government subsidized programs). Similarly, all multimorbidity classes were significantly more likely than their *Relatively Healthy* counterparts to have had a recent health service visit ($p < 0.001$).

Distribution of mean HRQoL subscale scores

Mean PCS-12 and MCS-12 scores for the survey population were 51.3 (SD = 8.5) and 49.5 (SD = 9.0), respectively. Table 2 presents mean PCS-12 and mean MCS-12 scores, given latent class membership. Individuals in the *Metabolic* and *Vascular-Inflammatory* classes scored 2.7 ($p < 0.001$) and 13.4 ($p < 0.001$) points lower on the PCS-12 subscale, respectively, than their *Relatively Healthy* counterparts. There were no statistically significant differences in mental health functioning scores according to latent class membership.

Multivariate regression analyses

Following assignment of individuals to their best fit class based on their maximum posterior probability, regression estimates indicated that, compared to those in the *Relatively Healthy* class, membership in the *Vascular-Inflammatory* class ($\beta = -5.5$; $p < 0.001$) was associated with significantly lower PCS-12 scores (Table 3). For MCS-12, individuals in the both *Vascular-Inflammatory* class ($\beta = -1.7$; $p < 0.05$) and *Respiratory* class ($\beta = -2.5$; $p < 0.05$) had significantly lower mental functioning scores than their *Relatively Healthy* counterparts.

Results of the multivariate model further indicated that higher educational attainment ($\beta = 1.4$; $p < 0.001$) and full-time employment ($\beta = 1.5$; $p < 0.001$) were associated with higher PCS-12 scores, while low levels of physical activity ($\beta = -0.9$; $p < 0.01$) were associated with lower PCS-12 scores. Being in the top 60% wealth quintile ($\beta = 1.2$;

TABLE 1 Four-latent-class model of multimorbidity.

	Latent class			
	1	2	3	4
	Relatively healthy	Metabolic	Vascular inflammatory	Respiratory
Latent class prevalences	0.53	0.31	0.12	0.04
Item-response probabilities	**Probability of a Yes response**			
Hypertension	0.05	**0.58**	**0.80**	0.14
Obesity	0.20	**0.39**	**0.56**	**0.53**
Hypercholesterolemia	0.05	0.23	**0.36**	0.20
Diabetes mellitus	0.00	0.17	**0.36**	0.08
Asthma	0.07	0.02	0.06	**0.45**
Arthritis	0.03	0.04	**0.43**	0.05
Cardiovascular disease	0.02	0.00	**0.41**	0.10
Mental health disorders	0.02	0.01	0.07	0.12
COPD	0.02	0.00	0.05	**0.41**
Stroke	0.00	0.01	0.10	0.00
Glaucoma	0.00	0.02	0.07	0.00
Mean number of NCDs reported (95% CI)	0.40 (0.36, 0.45)	1.60 (1.53, 1.67)	3.40 (3.23, 3.56)	2.86 (2.72, 3.00)

*Item-response probabilities ≥ 0.35 in boldface to facilitate interpretation.

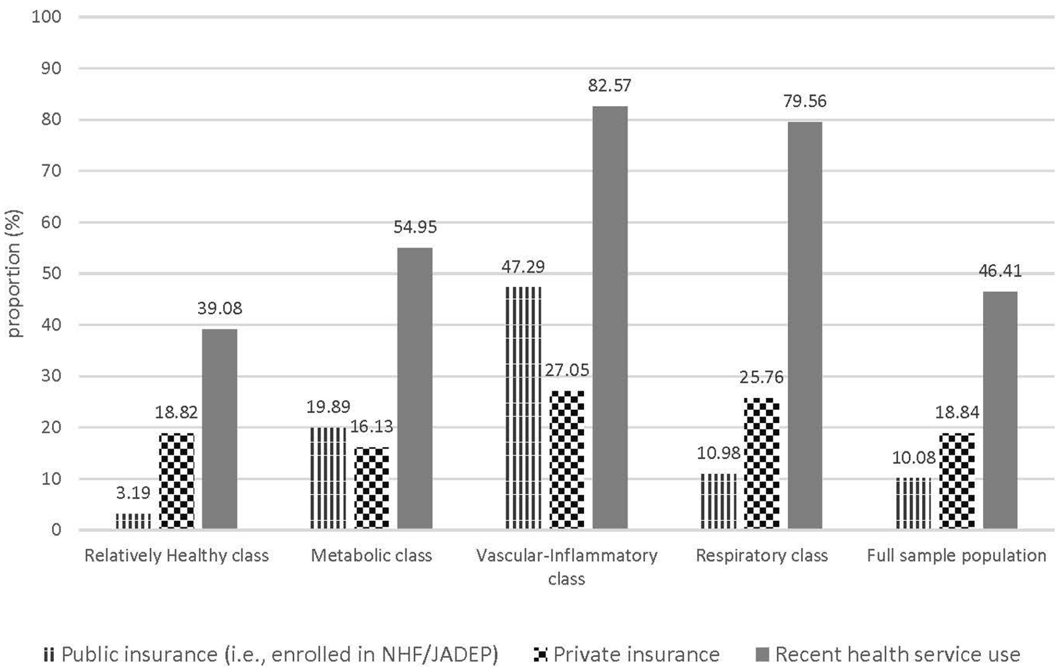

FIGURE 2
Health Insurance coverage and recent health service encounters, according to class membership.

$p < 0.001$) was associated with higher MCS-12 scores. Conversely, being female ($\beta = -2.6$; $p < 0.001$) and self-reporting past or current use of tobacco ($\beta = -1.9$; $p < 0.001$) were associated with lower MCS-12 scores. Advancing age was associated with lower PCS-12 scores ($\beta = -0.1$; $p < 0.001$), but higher MCS-12 scores ($\beta = 0.1$; $p < 0.001$). Public insurance coverage through subsidies was associated with lower PCS-12 scores ($\beta = -2.7$; $p < 0.001$) while private insurance coverage was associated with higher MCS-12 scores ($\beta = 1.1$; $p < 0.05$). Recent health service use was associated with lower scores on the MCS-12 subscale ($\beta = -1.0$; $p < 0.01$).

TABLE 2 Mean HRQoL subscale scores, according to latent class.

Latent class	Physical component summary (PCS-12) score			Mental component summary (MCS-12) score		
	Mean score	95% CI	value of *p*	Mean score	95% CI	value of *p*
Relatively healthy	53.85	(53.37, 54.33)	[ref]	49.56	(48.94, 50.19)	[ref]
Metabolic	51.13	(50.13, 52.12)	<0.001	50.49	(49.50, 51.48)	0.179
Vascular-inflammatory	40.48	(38.64, 42.32)	<0.001	48.56	(47.07, 50.05)	0.211
Respiratory	52.56	(49.46, 55.65)	0.435	45.62	(41.49, 49.75)	0.074

p-values based on Wald chi-squared tests.

TABLE 3 Multivariate regression analysis of effect of multimorbidity class membership on HRQoL outcomes.

	Physical component summary (PCS-12) score (*N*=2,499)	Mental component summary (MCS-12) score (*N*=2,499)
	β (95% CI)	β (95% CI)
Multimorbidity class		
Relatively healthy	[ref]	[ref]
Metabolic	−0.13 (−0.89, 0.62)	−0.27 (−1.16, 0.63)
Vascular-inflammatory	−5.48*** (−6.66, −4.29)	−1.69* (−3.09, −0.28)
Respiratory	−0.35 (−2.41, 1.70)	−2.53* (−4.97, −0.09)
Age, years	−0.11*** (−0.14, −0.09)	0.06*** (0.03, 0.09)
Female sex	−0.26 (−0.99, 0.48)	−2.60*** (−3.47, −1.73)
Secondary level or higher	1.39*** (0.64, 2.15)	−0.67 (−1.57, 0.23)
Employed full-time	1.46*** (0.84, 2.07)	0.21 (−0.53, 0.94)
Top 60% wealth quintile	0.51 (−0.13, 1.16)	1.42*** (0.66, 2.19)
Currently use alcohol	0.66* (0.00, 1.32)	−0.76 (−1.55, 0.02)
Past or present smoker	−0.39 (−1.10, 0.33)	−1.88*** (−2.73, −1.03)
Low levels of physical activity	−0.93** (−1.53, −0.32)	−0.55 (−1.27, 0.17)
Private insurance coverage	−0.18 (−1.00, 0.65)	1.11* (0.14, 2.09)
Public insurance coverage	−2.69*** (−3.66, −1.73)	0.17 (−0.97, 1.31)
Recent health service use	−0.53 (−1.18, 0.11)	−1.03** (−1.80, −0.27)

CI, confidence interval. Estimates based on non-missing data (<1% missing across all variables). $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.

Mediation analyses

Results of the mediation analyses for PCS-12 and MCS-12 scores are presented in Tables 4, 5, respectively. As noted above, significant total effects were observed between the *Vascular-Inflammatory* class and PCS-12 scores, while lower MCS-12 scores were significantly associated with membership in both the *Vascular-Inflammatory* and *Respiratory* classes (Table 3).

For physical functioning, there was some mediation by public insurance coverage (Table 4), with 4.8% of the total effect of the *Vascular-Inflammatory* class on PCS-12 scores mediated by enrolment in government subsidized programs ($\beta_{\text{total}} = -5.7$, $p < 0.001$; $\beta_{\text{indirect}} = -0.3$, $p < 0.01$). There were no statistically significant indirect effects mediated by recent service use or private insurance coverage.

With regard to mental health outcomes, the total effects of the *Vascular-Inflammatory* class and the *Respiratory* class on MCS-12 scores both appeared to be mediated by recent health service use (Table 5). The proportions mediated through recent service use were 13.3 and 10.0%, for the association between MCS-12 scores and membership in the *Vascular-Inflammatory* class ($\beta_{\text{total}} = -1.7$, $p < 0.05$; $\beta_{\text{indirect}} = -0.2$; $p < 0.05$) and the *Respiratory* class ($\beta_{\text{total}} = -2.5$, $p < 0.05$; $\beta_{\text{indirect}} = -0.3$; $p < 0.05$), respectively. There were no statistically significant indirect effects on MCS-12 scores by insurance coverage for either the *Vascular-Inflammatory* or *Respiratory* classes.

Discussion

This study used LCA to explore the distribution of HRQoL outcomes conditional on multimorbidity class membership and explore the role of health system factors in mediating this relationship. Findings indicate that beyond the accumulation of an increasing *number* of conditions, risk of adverse HRQoL outcomes is further modified by the *types* of disease combinations. Specifically, the study illustrated that specific disease profiles are differentially associated with poorer physical functioning, with the *Metabolic* class and the *Vascular-Inflammatory* class scoring 2.7 ($p < 0.001$) and 13.4 ($p < 0.001$) points lower, respectively, than their counterparts in the *Relatively*

TABLE 4 Mediation analysis: effects of multimorbidity on the PCS-12 subscale scores.

	Natural direct effect	Natural indirect effect	Marginal total effect
	β (95% CI[†])	β (95% CI[†])	β (95% CI[†])
Vascular-inflammatory class			
Mediator: recent service use[a,¥]	−5.38*** (−6.80, −3.98)	−0.17 (−0.26, 0.02)	−5.49*** (−6.93, −4.15)
Mediator: private insurance[b]	−5.66*** (−7.17, −4.24)	0.16 (−0.05, 0.57)	−5.50*** (−6.93, −4.08)
Mediator: public insurance[c,¥]	−5.38*** (−6.73, −3.86)	−0.27** (−0.53, −0.14)	−5.66*** (−7.03, −4.17)

PCS-12, physical component summary score. [†]Bias-corrected confidence interval. [¥]The exposure–mediator interaction was not significant at the $p < 0.05$ level and not included in the model.

[a]Adjusted for age, sex, education, employment, wealth, current alcohol use, past or present smoking status, physical activity level, public insurance coverage, and private insurance coverage.

[b]Adjusted for age, sex, education, employment, wealth, current alcohol use, past or present smoking status, physical activity level, public insurance coverage, and recent service use.

[c]Adjusted for age, sex, education, employment, wealth, current alcohol use, past or present smoking status, physical activity level, private insurance coverage, and recent service use.

TABLE 5 Mediation analysis: effects of multimorbidity on the MCS-12 subscale scores.

	Natural direct effect	Natural indirect effect	Marginal total effect
	β (95% CI[†])	β (95% CI[†])	β (95% CI[†])
Vascular-Inflammatory class			
Mediator: recent service use[a,¥]	−1.44* (−2.85, −0.11)	−0.22* (−0.42, −0.08)	−1.66* (−3.01, −0.37)
Mediator: private insurance[b,¥]	−1.44* (−3.00, −0.19)	0.09 (0.02, 0.25)	−1.35* (−2.90, −0.09)
Mediator: public insurance[c,¥]	−1.44* (−2.82, −0.11)	0.01 (−0.10, 0.15)	−1.42* (−2.75, −0.13)
Respiratory class			
Mediator: recent service use[a,¥]	−2.24 (−5.48, 0.55)	−0.25* (−5.39, −0.06)	−2.49* (−5.57, 0.33)
Mediator: private insurance[b,¥]	−2.24 (−5.44, 0.51)	−0.02 (−0.12, 0.06)	−2.25 (−5.48, 0.43)
Mediator: public insurance[c]	−2.10 (−6.24, 1.48)	−0.38 (−2.65, 1.45)	−2.48 (−5.52, 0.63)

MCS-12, mental component summary score. [†]Bias-corrected confidence interval. [¥]Exposure–mediator interactions were not significant at the $p < 0.05$ level and not included in the models.

[a]Adjusted for age, sex, education, employment, wealth, current alcohol use, past or present smoking status, physical activity level, public insurance coverage, and private insurance coverage.

[b]Adjusted for age, sex, education, employment, wealth, current alcohol use, past or present smoking status, physical activity level, public insurance coverage, and recent service use.

[c]Adjusted for age, sex, education, employment, wealth, current alcohol use, past or present smoking status, physical activity level, private insurance coverage, and recent service use.

Healthy class. After controlling for important confounders, results continued to implicate multimorbidity patterns as important determinants of physical functioning and well-being, with membership in the *Vascular-Inflammatory* class associated with lower PCS-12 scores, compared to membership in the *Relatively Healthy* class. For mental health functioning, results of the multivariate regression analyses indicated that multimorbidity patterns were also important determinants of psychological well-being, with significant inverse relationships observed between MCS-12 scores and membership in both the *Vascular-Inflammatory* and *Respiratory* classes. Given that the mean number of NCDs reported among members of the *Vascular-Inflammatory* and *Respiratory* classes was 3.40 and 2.86, respectively, this finding is further in keeping with evidence of poorer functioning, along mental HRQoL domains, following 3 or more concurrent diagnoses (1). Findings also indicated low levels of private and public insurance coverage and alluded to relatively high health system interactions (i.e., high proportions of respondents with a recent health care visit), particularly among those with varying patterns of multimorbidity.

Findings from this study indicate that membership in the *Vascular-Inflammatory* class (characterized by very high probability of hypertension, obesity, hypercholesteremia, and diabetes, in addition to an increased likelihood of self-reported arthritis and cardiovascular disease) is associated with particularly increased vulnerability to poor quality of life outcomes, across both physical and mental domains. A Canadian study among 238 primary care patients (18 years or older) explored differential impacts of varying combinations of conditions, grouped by anatomical domain, with HRQoL outcomes and similarly concluded that vascular, upper gastro-intestinal and musculoskeletal systems have strong negative effects on physical dimensions of HRQoL (30). Given that the PCS-12 subscale is heavily weighted towards HRQoL aspects reflecting physical functioning, general health and pain, these findings suggest that interventions targeting physical therapy and pain management may promote better disease control and quality of life outcomes for members of the *Vascular-Inflammatory* class. Importantly, researchers have noted that living with a chronic disease does not preclude mental well-being attainment and urge identification of individual strengths, assets and motivations to inform resource-centered interventions (31). Accordingly, given that the MCS-12 subscale is heavily weighted towards HRQoL aspects reflecting energy, social engagement, and emotional well-being, more investigation is needed to understand how *Vascular-Inflammatory* and *Respiratory* patterns differentially affect energy levels, social functioning, and mental well-being, in order to support more holistic care interventions that promote better psychosocial adaption and resilience. A systematic review of 10 randomized controlled trials of interventions to improve outcomes for patients with multimorbidity, indicated that strategies targeting quality of life outcomes and functional difficulties were most promising, with evidence of a statistically significant reduction in mortality 2 years post-intervention

(32). Given that individuals in the *Vascular-Inflammatory* class appear to be at greatest risk for both poor physical and mental health functioning, further investigation into the role of health system factors in reinforcing or mitigating poor outcomes is also warranted.

In considering entry points for interventions to support improved multimorbidity management via better physical functioning and emotional wellbeing, results of mediation analyses highlight possible pathways. There was a significant mediated effect through recent health service use, on the relationship between multimorbidity and mental health functioning, for individuals in both the *Vascular-Inflammatory* and *Respiratory* classes. This finding corroborated the hypothesis that prior health care use would mediate the multimorbidity–HRQoL association negatively, reflecting personal frustrations, and health system hassles that have been reported in the international literature (9) among primary care patients with prevalent multimorbidity. A small, yet statistically significant mediated effect through public insurance coverage was also observed, indicating that enrolment in either the NHF or JADEP was associated with lower physical functioning. This finding may reflect a limitation of cross-sectional analyses which challenge temporal ordering of exposure and outcome, as it is not clear why access to medications would be associated with lower physical functioning. One possible explanation lies in the nature of these government subsidized programs, where the JADEP caters to populations over the age of 60 years (where physical limitations are more common) while the NHF is a needs-based program with enrolment conditional on the confirmed diagnosis of disease. It is thus likely that persons seek the benefits of these programs after their illnesses have reached a more advanced stage where physical limitations become apparent and pharmaceutical intervention is more urgent. Findings may also reflect sub-optimal utilization of the NHF or JADEP programs, as study data suggest relatively low enrolment, hinting at minimal uptake of benefits provided by these government schemes. Regardless, this finding underscores the need for timely access to services and medications to better support the management of multiple co-existing morbidities and prevent the accumulation of new ones.

Researchers have suggested that multiple chronic conditions may act additively or synergistically to adversely affect health outcomes (1, 30, 33). Data from middle-income countries indicate that multimorbidity (based on disease counts) is positively associated with higher levels of healthcare utilisation (34) but inversely associated with quality-of-life outcomes (35). Further, chronicity of NCDs and the dynamic nature of health and well-being predispose multimorbid individuals to negative feedback cycles, where poorer quality of life outcomes reduce capacity to manage multiple conditions and facilitate the accumulation of new ones (5). Comprehensive care frameworks acknowledge HRQoL as a critical patient-related outcome, with implications for reducing the burden of prevalent conditions and promoting treatment compliance (36). Minimizing risk of adverse health outcomes in this vulnerable sub-group of persons with multimorbidity requires a deeper look into health-seeking behaviours, coping strategies and the role of enabling factors (e.g., insurance) in alleviating concerns regarding access to and use of care. While national efforts to reduce access barriers (i.e., following establishment of the NHF and JADEP programs) were implemented in 2008, when the Government of Jamaica abolished user fees in public facilities, the ensuing increased demand has challenged service quality, with reports of long wait times, insufficient supplies and inadequate human resources, prompting private care-seeking among Jamaicans of all income groups, including the poorest quintiles (12). In the absence of systematic research on the role of health system factors on multimorbidity management and HRQoL outcomes, anecdotal reports suggest that public health clinics in Jamaica are typically overburdened with serving large numbers of the population, such that clients experience difficulty scheduling appointments outside of a usual 3–6 month window in addition to challenges concerning inconsistent drug availability and limited surgical intervention within the public domain. Future qualitative work would allow for better elaboration of the personal experiences of Jamaicans with prevalent multimorbidity, as well as challenges and concerns regarding financial access to services and medication.

Strengths and limitations

There are several strengths and limitations of this study. At the time of writing, these data represented the latest available population-level collection, since results of the JHLS-III were not yet available, and the technical report not finalized. Given that NCDs continue to dominate the health and economic burden for Jamaica (37), and the wider Caribbean region (38, 39), findings from this study remain relevant by providing insights for public health planning, policy, and clinical intervention. The cross-sectional study design challenges the temporal ordering assumptions needed for mediation analysis, which require that the exposure (i.e., multimorbidity) preceded the mediator (i.e., health system factors) which, in turn, preceded the outcome (i.e., scores on the HRQoL subscales). The Bayes' theorem-based approach is recommended as a robust technique for modelling the effect of latent classes on a distal outcome (26), and use of this approach to examine the distribution of mean PCS-12 and MCS-12 scores, conditional on class membership, is a strength of this study. Yet, this model does not allow for statistical control of potential confounders or formal tests of mediation. Further, while the maximum probability assignment method has been widely used throughout the literature to estimate the associations between latent class membership and distal outcomes and has been noted to produce less biased estimates compared to other classify-analyze approaches, this method fails to account for uncertainty in class membership (26). Simulation studies indicate that maximum probability assignment approaches often attenuate effects of the exposure on the outcome (26), suggesting that the impact of multimorbidity patterns on HRQoL outcomes may be even greater than estimated here. These limitations must be borne in mind in interpretation of the results.

Limitations in the definition and measurement of indicators must also be considered. Ideally, health service use would have been operationalized using a measure reflecting the number of visits made within a specified period, to better capture frequency of use and the increased service utilization that has come to be associated with multimorbidity. The recent health care service use indicator used in this study was a convenience measure (based on a blood pressure measurement by a health professional in the past 6 months), with selection determined by JHLS-II questionnaire availability. Limitations of this binary indicator are acknowledged, including failure to capture the type of health care service used (e.g., primary, secondary, and tertiary), the purpose of the visit (i.e., routine vs. emergency consultation) or the number of health visits made within a given time period. In addition, few indicators were dichotomized based on arbitrary cut-points (e.g., top 60% vs. bottom 40% wealth quintile). Further, despite inclusion of several covariates deemed relevant, residual confounding due to omission of potentially important social (e.g., social support), disease-related (e.g., severity of diseases, number of medications being used), and health system (e.g., quality of care, hospitalization) factors, beyond those included in the study, may have occurred. Studies note that important factors impacting the multimorbidity–HRQoL relationship may include the presence of coexisting acute conditions, time since diagnosis of chronic diseases, and the prognosis of health conditions (1). These variables were not available in the dataset and not accounting for them could have potentially biased the effect estimates observed here.

Conclusion

This study identified differential effects of specific combinations of diseases on HRQoL outcomes, demonstrating the clinical utility and epidemiological value of latent classes (i.e., multimorbidity patterns) in estimating risk of poor mental and physical functioning, and highlighting health system factors that represent opportunities for intervention. In order to better tailor interventions to support management of multiple conditions, additional research is needed to further elaborate personal experiences with healthcare and examine how health system factors reinforce and/or mitigate positive health-seeking behaviours, including timely use of health services.

Data availability statement

The data analyzed in this study is subject to the following licenses/restrictions: the datasets used and/or analysed during the current study are not publicly available as the authors are still using the data for other analyses. However, data will be made available from the corresponding author upon reasonable request. Requests to access these datasets should be directed to DH, hotchkis@tulane.edu.

Ethics statement

The studies involving human participants were reviewed and approved by the Ministry of Health, Jamaica and the University of the West Indies/University Hospital of the West Indies Ethics Research Committee (ECP 169, 14/15). Written informed consent to participate in the study was obtained from all adult study participants and, for participants under 18 years of age, was provided by the participants' parent and/or legal guardian.

Author contributions

LC conceptualized the paper, developed the analytic strategy, and analysed the data and interpreted the findings. CC-M, KT, JG, JH, and DH critically revised the paper for important contextual background and intellectual content. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

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Glossary

AIC	Akaike Information Criteria
BIC	Bayesian Information Criteria
CD	Compact disk
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
HRQoL	Health-related quality of life
IPAQ	International Physical Activity Questionnaire
JADEP	Jamaica Drug for the Elderly Programme
JHLS-II	Jamaica Health and Lifestyle Survey 2007/2008
LCA	Latent class analysis
MCS-12	Mental Component Summary
MET	Metabolic equivalent
NCD	Non-communicable disease
NHF	National Health Fund
OR	Odds ratio
PCA	Principal components analysis
PCS-12	Physical Component Summary

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