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Factors associated with multimorbidity, polypharmacy, and medication regimen complexity among adults with hypertension at outpatient follow up departments of hospitals in south Gondar Zone, Ethiopia: An institution based multicentered cross-sectional study

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ABSTRACT

Objectives: Factors associated with multimorbidity, polypharmacy, and medication regimen complexity (MRCI) may vary from country to country. There are no such data in the present study settings. This study aimed to identify factors associated with multimorbidity, polypharmacy, and MRCI among hypertensive patients in public hospitals of South Gondar Zone.

Design: Multicentered cross sectional design

Setting: Public hospitals of Comprehensive specialized and primary hospitals, Ethiopia

Participants: Adult Hypertensive patients who had follow up and visited at outpatient clinics and selected by systematic random sampling from December 1, 2021, to February 30, 2022.

Data analysis: Data were collected through 65-items medication regimen complexity tool, interview, and checklist. Data were entered into SPSS version26, and analyzed using STATA 17. In adjusted analysis, statistical significance was set at $p<0.05$.

Results: We found participants from Nefas Mewucha hospital (AOR=0.3, 95% CI:0.15-0.59) and Mekane Eyesus hospital (AOR=0.17, 95% CI: 0.07-0.38), compared to Debre Tabor Comprehensive Specialized Hospital, polypharmacy (AOR=5.52, 95% CI: 1.49-20.39), medium (AOR=19.76, 95% CI: 5.86-66.56), and high MRCI (AOR=120.32, 95% CI: 33.12-437.07) were associated with multimorbidity. Multimorbidity (AOR=25.4, 95% CI: 7.48-86.23), controlled blood pressure (AOR=0.43, 95% CI: 0.19-0.92), and duration of hypertension therapy ≥5 years (AOR=2.12, 95% CI: 1.08-4.16) were predictor of polypharmacy. Whereas, controlled BP (AOR=0.48, 95% CI: 0.32-0.72), and multimorbidity (AOR=14.55, 95% CI: 9.00-23.52) were significantly associated with high MRCI.

Conclusion: A considerable hypertensive participants experienced multimorbidity, polypharmacy, and medication complexity. Polypharmacy, primary hospital setting, high MRCI were predictors of multimorbidity. On the other hand, multimorbidity, and controlled BP were predictor of polypharmacy and MRCI. Hypertensive patient care should consider multimorbidity, polypharmacy, and medication complexity.

Strength and limitation of the study

- It is the first in Ethiopia healthcare setting that identified factors associated with multimorbidity, polypharmacy, and MRCI among hypertensive patients.
- Multicentred design nature of the study is considered as an additional strength of the present study.
- However, this study has a limitation being cross sectional may not show true cause-effect relationship between outcome and predictors.
- Moreover, it did not consider inpatient settings, so the study is generalizable to hypertensive patients with chronic follow up at outpatient departments

INTRODUCTION

Multimorbidity is the co-occurrence of two and more chronic health conditions in an individual [1, 2]. It has become a major public health problem with prevalence ranges from 12.9% to 95.1% (3, 4). Multimorbidity has been linked with premature death, poor quality of life, healthcare utilization, age, body mass index, reduced kidney function, lower socioeconomic status, birth gender, suboptimal blood pressure control and polypharmacy [2, 3, 5-7].

The definition of polypharmacy has not been standardized, however, in literature, it has been commonly defined as the routine use of five or more concurrent medications. It comprises over the-counter, prescription, traditional, and complementary medicines [8]. Polypharmacy's prevalence has been increased worldwide, and associated with duration of treatment, comorbidity, chronic illness, and age [9, 10].

Medication regimen complexity includes dosage forms, dosing frequency, and additional instructions related to medications. It accounts for both prescription and over-the-counter medications to assess medication regimen complexity index [11]. This complexity is associated with clinical outcomes such as hospitalization, hospital readmission, medication adherence, blood pressure, age, and comorbidity [12-14].

There is limited data regarding factors associated with multimorbidity, polypharmacy, and medication regimen complexity among adults with hypertension in outpatient settings in Ethiopia. Therefore, the purposes of the present study were to identify factors associated with polypharmacy, medication regimen complexity and multimorbidity among adults with hypertension in the outpatient follow-up department in the South Gondar Zone.

METHODS

Study Area, Design, and Period

The study was conducted in one purposively, and three randomly chosen public hospitals in South Gondar Zone. According to 2007 census which was conducted by Central Statistical Agency (CSA), Ethiopia, this Zone has a total population of 2 051 738. Based on the 2011 CSA population projection, the South Gondar Zone has a total population of 2 239 077 (1 103 490 women and 1 135 587 men). An institution-based multicentered cross-sectional design was used, and data were collected from December 1, 2021, to February 30, 2022.

Study Participants

The source population embraced all adults with hypertension attending follow-up appointments at outpatient departments. The study population included those who received antihypertensive medications for at least 6 months and met the inclusion criteria. The study was conducted according to the guidelines for reporting observational studies, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [15].

Eligibility criteria

Inclusion criteria:

- Adults aged 18 years and above
- Receiving antihypertensive medications for at least six months
- Following up at outpatient departments of the study hospitals
- Willing to participate

Exclusion criteria:

- Cognitive impairment
- Hearing problems
- Admitted to inpatient wards

Sample Size Determination and Sampling Technique

There were no previous studies that we used to determine the sample size of the present study. Therefore, we used a single population proportion formula considering a 95% confidence interval, and a prevalence of 50% for outcomes. Then, we reached, a sample size of 384.

Accounting for a 10% non-response rate, the final sample size was 423. Debre Tabor Comprehensive Specialized Hospital, being the only specialized hospital in the zone, was selected purposively, while Addis Zemen Hospital, Nefas Mewucha Hospital, and Mekane Eyesus Hospital were chosen randomly. Proportional allocation and a systematic random sampling technique were applied, with a sampling interval of four; hence, every fourth participant was included until the desired sample size was achieved.

Study Variables

Dependent Variables: Multimorbidity, Medication regimen complexity index (MRCI), Polypharmacy

Independent Variables: Age, gender, residence, marital status, income, blood pressure status, educational status, number of medications, duration of treatment, health insurance, aerobic exercise

Operational definitions

Medication regimen complexity: comprised the dosage form, dosing interval, and additional instruction aspect to calculate the patient medication burden. It is quantified using 65 items Medication Regimen Complexity Index (MRCI): then, categorized into three levels: low (≤4), medium (5-8), and high (>8) MRCI scores [16].

Multimorbidity: Co-existence of two or more chronic conditions in an individual [1, 2].

Controlled blood pressure: Defined as BP <140/90 mmHg for individuals with hypertension without comorbidity, or BP <130/90 mmHg for those with diabetes mellitus, chronic kidney disease, or known cardiovascular diseases [17].

Regular aerobic exercise: Regular Aerobic Exercise: Participants engaged in activities like brisk walking, recreational swimming, cycling, and tennis for at least 150 minutes per week [18].

Polypharmacy: Routine use of five or more medications by a patient [8].

Data Collection Procedures

A questionnaire was developed and translated into Amharic, and back-translated into English for consistency. Interviews were conducted to gather socio-demographic and clinical characteristics not found in patient charts, such as monthly income, regular aerobic exercise, over-the-counter medications, marital status, educational level, and health insurance. A checklist was used to collect data on blood pressure level, dosage forms, dose frequency, number of medications, and additional administration instructions. The 65-item MRCI tool, including sections on dosage forms, dose frequency, and additional instructions with corresponding scores, was used to determine the MRCI [11].

The average of two BP readings taken two minutes apart during a visit was used to determine BP status [19].

Data Quality Control

To ensure data quality, we conducted a pretest, trained data collectors, and checked the filled questionnaires and checklists for completeness and correctness daily. The training covered the study objectives, methods, and ethical concerns.

Statistical Analysis

Data were entered and analyzed using Stata 17. We checked that no multicollinearity (variance inflation factor less than two). We checked the reliability of the 65 items MRCI tool for our study settings and found 0.7 value of Cronbach's alpha indicates the reliability of the tool. Categorical variables were described using frequencies, while means and standard deviation (SD) were used for continuous variables. After checking assumptions, ordinal for MRCI, and binary logistic regression for multimorbidity, and polypharmacy were employed to identify predictors associated with MRCI and multimorbidity, respectively. Variables with a p-value of less than 0.25 in univariate analysis were included in the multivariate analysis, and statistical significance was set at a p-value of <0.05.

Ethical consideration

The present study was approved from Institutional Research and Ethical Review Committee (IRERC), College of Health Sciences, Debre Tabor university (Ref: CHS/DTU1421//2021),

and conducted in accordance with the guidelines and standards of the declaration of Helsinki. IRERC gave us approval to receive verbal informed consent as the study does not have any known potential risk to participants. Therefore, Verbal consent was obtained from study participants after explaining the study's methods, and purpose. personal identifiers were anonymised to keep the participants' confidentiality.

Public and patient involvement

The general public and patients were not involved in the conceptualization, design, analysis, reporting, and dissemination of this study. Once their informed verbal consent was obtained, the adult hypertensive patients who were involved as study participants.

RESULTS

Socio-demographic and clinical characteristics of study participants

Four hundred twenty-three participants were included in the analysis of the study. The participants' age ranges from 23 to 90 years with mean ± standard error of 58.48±12.96 years, and majority of participants (59.8%) were female. The number of medications taken by each participant ranges from one to seven with mean ± SD of 2.65± 1.35.

Multimorbidity and polypharmacy were found in 46.3% and 12.06% of participants, respectively. Hypertension specific MRCI was low in 56.26%, medium in 40.43%, and high in 3.31% of participants. Concerning patient level MRCI, we found low in 20.80%, medium in 43.97%, and high in 35.22% (Table 1).

Table 1. Characteristics of study participants

Variable	Category of variable	Patient level Medication regimen complexity		
		Low	Medium	High
Sex	Female	55	114	84
	Male	33	72	65
Age in year	<65	65	109	96
	65+	23	77	53
Marital status	Single	4	15	8
	Married	60	123	10
	Divorced	7	19	6
	Widowed	17	29	31
Residence	Urban	55	114	98
	Rural	33	72	51
Income in Ethiopian birr	<6000	76	174	140
	6000+	12	12	9
Multimorbidity	Yes	4	69	123
	No	84	117	26
Religion	Christian	82	176	137
	Muslim	6	10	12
Education	Unable to read & write	56	105	87
	Can read &write	4	10	4
	Primary	9	38	26
	Secondary	5	15	12
	Higer education	14	18	20
Occupation	Farmer	16	30	24
	Merchant	11	37	29
	Daily labourer	1	2	0
	Retired	8	13	10
	Unemployed	38	89	69
	Employed	14	15	17
Multimorbidity	Yes	4	69	123
	No	84	117	26
Polypharmacy	Yes	0	0	51
	No	88	186	98
BP controlled	Yes	54	73	48
	No	34	113	101
Aerobic exercise	Yes	30	45	23
	No	58	141	126
Health insurance	Yes	58	132	115
	No	30	54	34
Study setting	Debre Tabor	22	71	57
	Nefas Mewucha	16	39	45
	Addis Zemen	34	35	31
	Estie	16	41	16
Therapy duration	<5 year	64	162	87
	5+ year	24	54	62

Patterns of multimorbidity

Type 2 diabetes mellitus was the most common comorbidity coexisting with hypertension, while the least encountered comorbidities included rheumatic fever, Parkinson's disease, fatty liver disease, and others. Others include: rheumatic fever, pulmonary tuberculosis, glaucoma, Parkinson's disease, fatty liver disease, degenerative aortic stenos, degenerative spondylosis, osteoarthritis, hypercalcemia, bilateral flank pain, schizophrenia, trigeminal neuralgia, and soft tissue injury (Table 2).

Table 2. Morbidities among hypertensive patients

Disorder	Frequency	Percent
Type 2 diabetes mellitus	52	21.40
Dyslipidemia	25	10.29
Dyspepsia	22	9.05
Hypertensive heart disease	21	8.64
Bronchial asthma	21	8.64
Rheumatoid arthritis	19	7.82
Peripheral neuropathy	19	7.82
Congestive heart failure	12	4.94
Ischemic stroke	10	4.12
Ischemic heart disease	7	2.88
Hyperthyroidism	6	2.47
Human immunodeficiency virus	5	2.06
Chronic kidney disease	3	1.23
Type 1 diabetes mellitus	3	1.23
Myalgia	3	1.23
Generalized tonic-clonic	3	1.23
Others (each 1[0.41%])	13	5.3

Others include: Rheumatic fever, Pulmonary tuberculosis, Glaucoma, Parkinson's disease, Faty liver disease, Degenerative aortic stenos, Degenerative spondylosis, Osteoarthritis, Hypercalcemia, Bilateral flank pain, Schizophrenia, Trigeminal neuralgia, and Soft tissue injury.

The most common body system morbidity encountered among the sampled study participants with hypertension was cardiovascular disorder, which accounted for 77 cases (31.69%). In contrast, the least common was special sense disorder, accounting for just 1 case (1%) (Fig. 1).

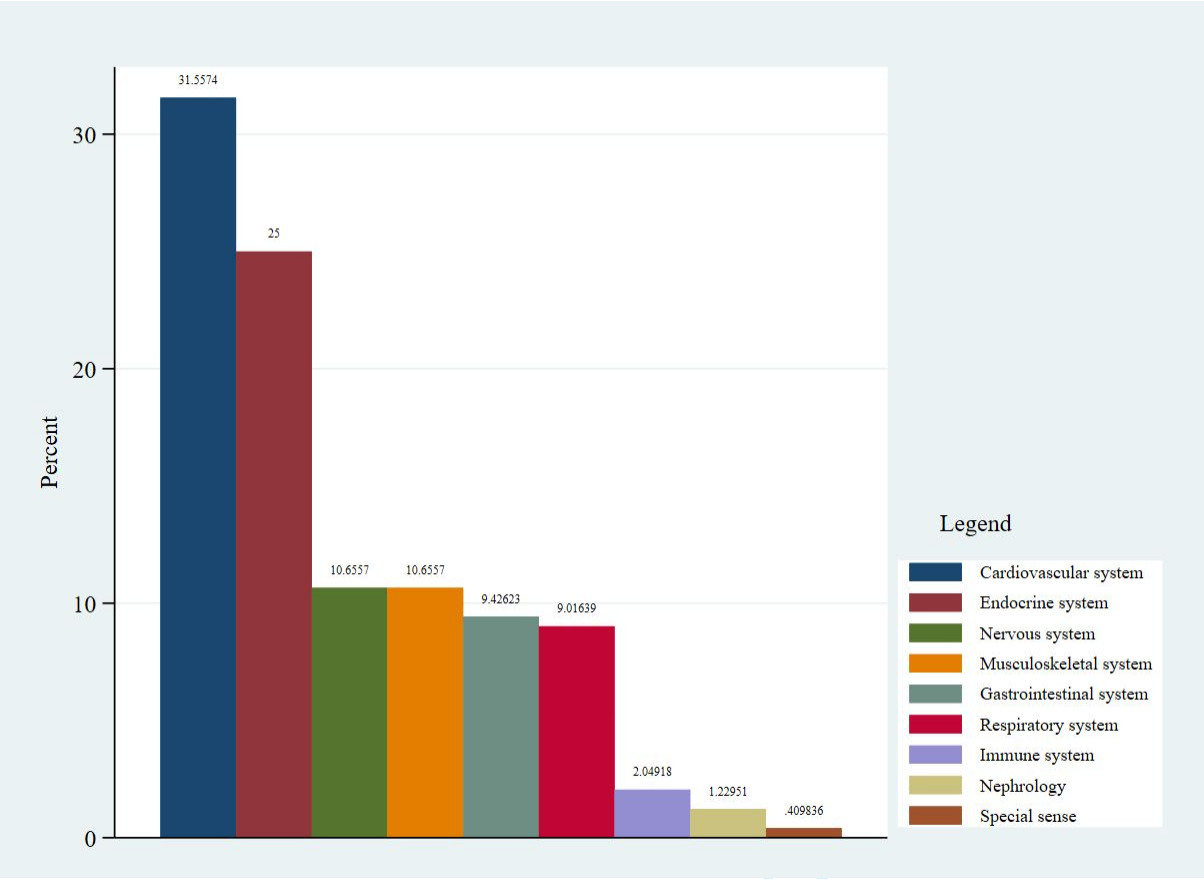

Fig. 1. Percent of body system disorders

Hypertension combined with type 2 diabetes mellitus was the most commonly observed multimorbidity, followed by hypertension combined with hypertensive heart disease. Conversely, hypertension combined with T2DM and HIV, hypertension combined with hypertensive heart disease and dyspepsia, and other combinations were the least frequently encountered multimorbidities among the study participants. Regarding the number of morbidities per participant, 53.9% had none, 35.22% had two, 10.4% had three, and 0.24% each had four and five morbidities. Others (each accounts 0.24%) include: hypertension +degenerative spondylosis, hypertension + type 2 diabetes mellitus + bilateral flank pain, hypertension + type 2 diabetes mellitus+ HIV, hypertension + hypertensive heart disease + dyspepsia, hypertension + type 2 diabetes mellitus + fatty liver disease, hypertension + type 2

diabetes mellitus + ischemic heart disease, hypertension + parkinson's disease + hypertensive heart disease, hypertension + glaucoma, hypertension + trigeminal neuralgia, hypertension + type 2 diabetes mellitus + chronic kidney disease, hypertension + rheumatoid arthritis + bronchial asthma, hypertension + schizophrenia, hypertension +hypocalcemia, hypertension+ type 2 diabetes mellitus +degenerative aortic stenosis, hypertension + peripheral neuropathy + HIV, hypertension +rheumatoid arthritis + hypertensive heart disease, hypertension + rheumatic fever, hypertension + soft tissue injury, hypertension + hypertensive heart disease + ischemic stroke +bronchial asthma + dyslipidemia, hypertension + osteoarthritis, hypertension + HIV + bronchial asthma, hypertension + hypertensive heart disease + pulmonary tuberculosis, and hypertension + dyslipidemia + congestive heart failure (Table 3).

Table 3. Pattern of multimorbidity among hypertensive patients

Multimorbidity		Frequency	Percent
Hypertension+T2 diabetes mellitus		30	7.09
Hypertension+Hypertensive heart disease		16	3.78
Hypertension+Dyspepsia		12	2.84
Hypertension+Rheumatoid arthritis		12	2.84
Hypertension+Dyslipidemia		11	2.60
Hypertension+Peripheral neuropathy		10	2.36
Hypertension+Bronchial asthma		10	2.36
Hypertension+Ischemic stroke		8	1.89
Hypertension+T2 diabetes mellitus+Dyslipidemia		7	1.65
Hypertension+Congestive heart failure		7	1.65
Hypertension+Hyperthyroidism		6	1.42
Hypertension+Peripheral neuropathy+Dyspepsia		3	.71
Hypertension+T2 diabetes mellitus+Peripheral neuropathy		3	.71
Hypertension+T2 diabetes mellitus+Bronchial asthma		3	.71
Hypertension+Generalized tonic-clonic epilepsy		3	.71
Hypertension+T1diabetes mellitus		3	.71
Hypertension+Myalgia		3	.71
Hypertension+Dyslipidemia+Rheumatoid arthritis		2	.47
Hypertension+Dyspepsia+Bronchial asthma		2	.47
Hypertension+Dyslipidemia+Bronchial asthma		2	.47
Hypertension+Rheumatoid arthritis+T2 diabetes mellitus		2	.47
Hypertension+Human immunodeficiency virus		2	.47
Hypertension+Chronic kidney disease		2	.47
Hypertension+Peripheral neuropathy+Rheumatoid arthritis		2	.47
Others		23	11.79
Number of multimorbidity	0	228	53.9
	2	149	35.22
	3	44	10.4
	4	1	.24
	5	1	.24

Factors associated with multimorbidity, Polypharmacy, and MRCI

In the final adjusted binary logistic regression, we found that polypharmacy, patient-level medication regimen complexity, and the study hospital were associated with the presence of multimorbidity.

Polypharmacy was significantly associated with a duration of hypertension treatment equal to or greater than five years, multimorbidity, and controlled BP in the adjusted binary logistic regression analysis.

We identified several factors associated with medication regimen complexity (MRCI) for inclusion in a multivariate ordinal logistic regression analysis. These factors include the presence of multimorbidity, controlled blood pressure (BP), duration of hypertension treatment greater than five years, engaging in aerobic exercise, having health insurance, and an income greater than 6000 Ethiopian Birr.

In the adjusted analysis, participants experiencing multimorbidity were fourteen times more likely to have a complex medication regimen (AOR=14.55, 95% CI: 9.00-23.52, P<0.0001). Furthermore, participants with controlled BP, based on WHO pharmacologic treatment of hypertension guidelines (2021), were 52% less likely to have a complex medication regimen (AOR=0.48, 95% CI: 0.32-0.72, P<0.0001) (Table 4).

Table 4. Univariate, and multivariate logistic analysis of predictors of MRCI, polypharmacy, and multimorbidity

Variable	Variable category	Outcome			COR (95% CI)	AOR (95% CI)
		Patient MRCI[a]				
		≤4	5-8	>8		
Income	<6000 ETB	76	174	140	1	1
	≥6000 ETB	12	12	9	0.52(0.26-1.03)*	0.59(0.28-1.24)
Multimorbidity	No	85	117	26	1	1
	Yes	3	69	123	15.19(9.47-24.37)*	14.55(9.00-23.52)+
Controlled BP	No	34	113	101	1	1
	Yes	54	73	48	0.46(0.32-0.67)+	0.48(0.32-0.72)+
Aerobic exercise	No	58	141	126	1	1
	Yes	30	45	23	0.49(0.32-0.74)+	0.77(0.48-1.23)
Health insurance	No	30	54	34	1	1
	Yes	58	132	115	1.47(0.99-2.19)*	1.53(0.98-2.39)
Hypertension therapy	<5 years	64	132	87	1	1
	≥5 years	24	54	62	1.66(1.13-2.44)+	1.17(0.77-1.78)
		Polypharmacy[b]				
		Absent		Present		
Study hospital	DCSH	126		24	1	1
	NMWH	87		13	0.78(0.38-1.62)*	1.06(0.47-2.38)
	ADZH	93		7	0.39(0.16-0.96)+	0.73(0.28-1.93)
	MEH	66		7	0.56(0.23-1.36)*	1.96(0.67-5.71)
Multimorbidity	No	225		3	1	1
	Yes	147		48	24.49(7.49-80.08)+	25.39(7.48-86.22)+
Hypertension therapy	<5 years	259		24	1	1
	≥5 years	113		27	2.58(1.43-4.66)+	2.12(1.08-4.16)+
Controlled BP	No	208		40	1	1
	Yes	164		11	0.42(0.19-0.92)+	0.42(0.19-0.92)+
		Multimorbidity[b]				
		Absent		Present		
Age	<65 years	152		118	1	1
	≥65 years	76		77	1.31(0.87-1.94)*	1.09(0.64-1.88)
Study hospital	DCSH	59		91	1	1
	NMWH	56		44	0.51(0.30-0.85)+	0.30(0.15-0.59)+
	ADZH	56		44	0.53(0.32-0.88)+	0.80(0.36-1.77)
	MEH	57		16	0.18(0.09-0.35)+	0.16(0.07-0.38)+
Aerobic exercise	No	165		160	1	1
	Yes	63		35	0.56(0.35-0.90)+	0.86(0.41-1.81)
Hypertension therapy	<5 years	169		114	1	1
	≥5 years	59		81	2.01(1.33-3.02)+	1.49(0.85-2.61)
Controlled BP	No	124		124	1	1
	Yes	104		71	0.69(0.47-1.03)+	1.12(0.64-1.95)
Polypharmacy	Absent	225		3	1	1
	Present	147		48	24.49(7.49-80.08)+	5.52(1.49-20.39)+
Patient MRCI	≤4	85		3	1	1
	5-8	117		69	12.38(4.35-35.26)+	19.76(5.87-66.56)+
	>8	26		123	99.34(33.45-295.07)+	120.32(33.12-437.07)+

Abbreviations: AOR, Adjusted odds ratio; COR, Crude odds ratio; ETB, Ethiopian birr; BP, Blood pressure; DCSH, Debre Tabor Comprehensive Specialized Hospital; NMWH, Nefas Mewucha Hospital, ADZH, Addis Zemen Hospital; MEH, Mekane Eyesus Hospital; MRCI, Medication regimen complexity index. Note: Superscript [a] indicates ordinal logistic regression was used while [b] shows binary logistic regression used, * indicates P<0.25 while + indicates P<0.05.

DISCUSSION

In the present study, we found that 46.3% of participants had multimorbidity, 12.06% experienced polypharmacy, and 35.22% had a high patient-level MRCI. Additionally, we identified associations between polypharmacy, patient-level MRCI, and the study hospital with multimorbidity. We also found that the duration of hypertension therapy, controlled blood pressure (BP), and multimorbidity were associated with polypharmacy, while controlled BP and multimorbidity were predictors of a high patient-level MRCI.

The magnitude of multimorbidity that we found is higher than the studies finding in Sweden (21.6%) [20], Japan (29.9%) [7], Hong Kong, China (40.4%) [6], but lower than the finding of studies in Bahir Dar, Ethiopia (54.8%) [21], Ghana (55%) [22], India (55%) [23], United Kingdom (73.9%) [5], and another study in China (56.7%) [24].

Concerning polypharmacy, our finding is lower than findings from Gondar, Ethiopia (46.6%) [25], Ghana (64.8%) [22], Somali Land (71%) [10], Saudi Arabia [(21%), (79%)] [9, 26], and Japan (22.3%) [7].

We found high patient level MRCI in 35.22% study participants, which is lower than the result of the study, Gondar, Ethiopia (57.2%) [25].

Participants with polypharmacy (≥5 medications) compared to having no polypharmacy were more likely to experience with multimorbidity in the present study. It is supported by study from Japan [7]. Moreover, participants exposed to medium, and high patient level MRCI compared to low patient level MRCI were more likely to experience multimorbidity. This finding is in line with the finding from Sweden [20]. Previous studies identified age, being male, and uncontrolled BP as predictor of multimorbidity [5, 6, 21], but those factors failed to associate with multimorbidity in our study.

We found that participants with hypertension treatment for five year and above were two times more likely to experience polypharmacy. This finding is supported by study from Saudi Arabia [9]. In addition, we found controlled BP, and presence of multimorbidity were predictor of polypharmacy, but we did not find similar studies to discuss the findings.

We found those participants who had controlled BP were 52% times less likely to have Medium and high patient level MRCI compared to those who had uncontrolled BP. This finding is similar with the finding of the study from Japan in which those participants who exposed to higher MRCI were more likely to have poor BP control [13]. We identified that participants

with multimorbidity were 14 times more likely to have medium, and high patient level MRCI. This result is in line with the study finding in Korea [27].

The observed difference between findings be attributed to difference in inclusion criteria, and distribution of sociodemographic characteristics of study participants. We determined multimorbidity, polypharmacy and MRCI specifically among hypertensive adults, but most of previous studies assessed multimorbidity [24], polypharmacy [10, 25, 26], and MRCI [25], among participants with any chronic conditions without considering the diagnosis of hypertension as a compulsory criterion for inclusion.

Strength and limitation of the study

The present study is the first in Ethiopia healthcare setting that identified factors associated with multimorbidity, polypharmacy, and MRCI among hypertensive patients. Multicentred design nature of the study is considered as an additional strength of the present study. However, this study has a limitation being cross sectional may not show true cause-effect relationship between outcome and predictors. Moreover, it did not consider inpatient settings, so the study is generalizable to hypertensive patients with chronic follow up at outpatient departments.

CONCLUSION

The present study showed a considerable number of hypertensive patients experienced multimorbidity, polypharmacy and patient level MRCI. We identified study setting being primary hospital, polypharmacy, and MRCI as predictors of multimorbidity. In addition, Multimorbidity, and controlled BP were predictors of polypharmacy, and MRCI in this study. Moreover, duration of hypertension treatment was significantly associated with polypharmacy. Therefore, hypertensive patients care should consider multimorbidity, polypharmacy, and MRCI to optimize their care.

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Author Contributions

T.S.Y., W.E.M., and A.M.B. designed the study and analyzed data. T.S.Y., Y.S.Y., S.B.D., F.N.D., G.T.A., T.A.M. and A.M.B. performed data entry, wrote, and edited the manuscript. All authors reviewed the manuscript and were responsible for all aspects of this work.

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Disclosure

Authors have declared that there is no conflict of interest

Public and patient involvement

The public and patients were not engaged in the design, conduct, reporting, and distribution of this research.

Patient consent for publication

Not required.

Ethical Approval

Ethical approval for the present study was received from Institutional Research and Ethical Review Committee (IRERC), College of Health Sciences, Debre Tabor university, and conducted in accordance with the declaration of Helsinki.

Data availability statement

All necessary data are available within the manuscript and/or supporting materials

REFERENCES

1. Mercer S FJ, Moffat K, Fischbacher-Smith D, Sanci L. Multimorbidity: technical series on safer primary care. World Health Organization.2016.
2. Skou ST MF, Fortin M, Guthrie B, Nunes BP, Miranda JJ, Boyd CM, Pati S, Mtenga S, Smith SM. Multimorbidity. Nature Reviews Disease Primers. 2022;8(1):48.

3. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PLoS One. 2014;9(7):e102149.
4. Chowdhury SR, Chandra Das D, Sunna TC, Beyene J, Hossain A. Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. EClinicalMedicine. 2023;57:101860.
5. Hirst JA, Ordonez Mena JM, O'Callaghan CA, Ogburn E, Taylor CJ, Yang Y, et al. Prevalence and factors associated with multimorbidity among primary care patients with decreased renal function. PLoS One. 2021;16(1):e0245131.
6. Wong MC, Wang HH, Cheung CS, Tong EL, Sek AC, Cheung NT, et al. Factors associated with multimorbidity and its link with poor blood pressure control among 223,286 hypertensive patients. Int J Cardiol. 2014;177(1):202-8.
7. Aoki T, Yamamoto Y, Ikenoue T, Onishi Y, Fukuhara S. Multimorbidity patterns in relation to polypharmacy and dosage frequency: a nationwide, cross-sectional study in a Japanese population. Sci Rep. 2018;8(1):3806.
8. WHO. World Health Organization. Medication safety in polypharmacy. Geneva.; 2019.
9. Alsanosi SM MA, Ahmadini HA, Qadhi RS, Ikram N, Felemban AH, Alqashqri HS, Hariri NH, Alhindi YZ, Ayoub N. Polypharmacy among patients with hypertension attending primary healthcare centres. Annals of Medicine and Surgery. 2023 Jun 1;85(6):. 2023;85(6):2545-9.
10. Sidamo T, Deboch A, Abdi M, Debebe F, Dayib K, Balcha Balla T. Assessment of polypharmacy, drug use patterns, and associated factors at the Edna Adan University Hospital, Hargeisa, Somaliland. Journal of tropical medicine. 2022;2022(1):2858987.
11. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. The Annals of pharmacotherapy. 2004;38(9):1369-76.
12. Alves-Conceicao V, Rocha KSS, Silva FVN, Silva ROS, Cerqueira-Santos S, Nunes MAP, et al. Are Clinical Outcomes Associated With Medication Regimen Complexity? A Systematic Review and Meta-analysis. The Annals of pharmacotherapy. 2020;54(4):301-13.
13. Wakai E IK, Kato C, Okuda M. Effect of number of medications and complexity of regimens on medication adherence and blood pressure management in hospitalized patients with hypertension. PLoS One. 2021;16(6):e0252944.
14. Wimmer BC, Johnell K, Fastbom J, Wiese MD, Bell JS. Factors associated with medication regimen complexity in older people: a cross-sectional population-based study. Eur J Clin Pharmacol. 2015;71(9):1099-108.
15. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The lancet. 2007 Oct 20;370(9596):1453-7.
16. Yeh A, Shah-Manek B, Lor KB. Medication Regimen Complexity and A1C Goal Attainment in Underserved Adults With Type 2 Diabetes. The Annals of pharmacotherapy. 2017;51(2):111-7.
17. Organization WH. Guideline for the pharmacological treatment of hypertension in adults. 2021.
18. Piercy KL, Troiano RP. Physical Activity Guidelines for Americans From the US Department of Health and Human Services. Circ Cardiovasc Qual Outcomes. 2018;11(11):e005263.
19. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.
20. Forslund T, Carlsson AC, Ljunggren G, Arnlov J, Wachtler C. Patterns of multimorbidity and pharmacotherapy: a total population cross-sectional study. Fam Pract. 2021;38(2):132-40.

21. Eyowas FA SM, Alemu S, Pati S, Getahun FA. Magnitude, pattern and correlates of multimorbidity among patients attending chronic outpatient medical care in Bahir Dar, northwest Ethiopia: the application of latent class analysis model. PLoS One. 2022;17(4):e0267208.
22. Kwakye AO KI, Oppong KG. Polypharmacy and its associated factors among patients with co-morbid hypertension and diabetes in a municipal hospital in Ghana. . Scientific African. 2024;23:e02028.
23. Pati S, Sinha R, Panda M, Puri P, Pati S. Profile of multimorbidity in outpatients attending public healthcare settings: A descriptive cross-sectional study from Odisha, India. J Family Med Prim Care. 2021;10(8):2900-14.
24. Zhong Y QG, Xi H, Cai D, Wang Y, Wang T, Gao Y. Prevalence, patterns of multimorbidity and associations with health care utilization among middle-aged and older people in China. . BMC public health.23(1):537.
25. Kassaw AT, Sendekie AK, Minyihun A, Gebresillassie BM. Medication regimen complexity and its impact on medication adherence in patients with multimorbidity at a comprehensive specialized hospital in Ethiopia. Frontiers in medicine. 2024;11:1369569.
26. Alwhaibi M, AlRuthia Y, Alhawassi TM, Almalag H, Alsalloum H, Balkhi B. Polypharmacy and comorbidities among ambulatory cancer patients: A cross-sectional retrospective study. Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners. 2020;26(5):1052-9.
27. Ji E, Ahn S, Choi J-Y, Kim C-H, Kim K-i. Effect of multimorbidity on hypertension management. Scientific Reports. 2023;13(1):18764.

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Factors associated with multimorbidity, polypharmacy, and medication regimen complexity among adults with hypertension at outpatient follow up departments of hospitals in south Gondar Zone, Ethiopia: An institution based multicentered cross-sectional study

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ABSTRACT

Objectives: Factors associated with multimorbidity, polypharmacy, and medication regimen complexity (MRCI) may vary across countries. Such data lack in the present study settings. This study aimed to identify factors associated with multimorbidity, polypharmacy, and MRCI among hypertensive patients in public hospitals of South Gondar Zone.

Design: Multicentered cross sectional design

Setting: Public hospitals of Comprehensive Specialized and primary hospitals, Ethiopia

Participants: Adult hypertensive patients who had follow up and visited at outpatient clinics and selected by systematic random sampling from December 1, 2021, to February 30, 2022.

Primary and secondary outcome measures: Medication regimen complexity was assessed using a 65-items medication regimen complexity tool. Sociodemographic data were collected through interview, while polypharmacy and clinical characteristics were documented using checklist. Data were entered into SPSS version26, and analyzed using STATA 17. Binary logistic regression model was used to determine AOR of factors associated with multimorbidity and polypharmacy. For factors influencing MRCI, an ordinal logistic regression used.

Results: We found participants from Nefas Mewucha hospital (AOR=0.3, 95% CI:0.15-0.59) and Mekane Eyesus hospital (AOR=0.17, 95% CI: 0.07-0.38), compared to Debre Tabor Comprehensive Specialized Hospital, polypharmacy (AOR=5.52, 95% CI: 1.49-20.39), medium (AOR=19.76, 95% CI: 5.86-66.56), and high MRCI (AOR=120.32, 95% CI: 33.12-437.07) were associated with multimorbidity. Multimorbidity (AOR=25.4, 95% CI: 7.48-86.23), controlled blood pressure (AOR=0.43, 95% CI: 0.19-0.92), and duration of hypertension therapy ≥5 years (AOR=2.12, 95% CI: 1.08-4.16) were predictor of polypharmacy. Whereas, controlled BP (AOR=0.48, 95% CI: 0.32-0.72), and multimorbidity (AOR=14.55, 95% CI: 9.00-23.52) were significantly associated with high MRCI. Concerning prevalence, multimorbidity, high MRCI, and polypharmacy was found in 46.1%, 35.22%, and 12.29% of participants, respectively.

Conclusion: A considerable hypertensive participants experienced multimorbidity (46.1%), polypharmacy (12.29%), and high medication complexity (35.22%). Polypharmacy, primary

hospital setting, high MRCI were predictors of multimorbidity. On the other hand, multimorbidity, and controlled BP were predictor of polypharmacy and MRCI. Hypertensive patient care should consider multimorbidity, polypharmacy, and medication complexity.

Strength and limitation of the study

- It is the first in Ethiopia healthcare setting that identified factors associated with multimorbidity, polypharmacy, and MRCI among hypertensive patients.
- Multicentred design nature of the study is considered as an additional strength of the present study.
- However, this study has a limitation being cross sectional that did not establish a true cause-effect relationship between outcome and independent factors.
- Moreover, exclusion of inpatient settings restricts the findings generalizability to adult hypertensive patients with chronic follow up at outpatient departments only
- Under representation of older adults and medication adherence were not adequately addressed, potentially affecting study results.

INTRODUCTION

Multimorbidity is defined as the co-occurrence of two or more chronic health conditions in an individual.[1, 2] It has become a major public health problem, with prevalence ranging from 12.9% to 95.1%.[3, 4] Multimorbidity has been linked with premature death, poor quality of life, increased healthcare utilization, advanced age, higher body mass index, reduced kidney function, lower socioeconomic status, birth gender, suboptimal blood pressure control and polypharmacy.[2, 3, 5-7]

The definition of polypharmacy has not been standardized; however, it is commonly defined in the literature as the routine use of five or more concurrent medications. This includes over-the-counter drugs, prescription medications, traditional remedies, and complementary medicines.[8] The prevalence of polypharmacy has been increased worldwide and is associated with factors such as duration of treatment, comorbidities, chronic illness, and advanced age.[9, 10]

Medication regimen complexity includes factors such as dosage forms, dosing frequency, and additional instructions related to medications. It accounts for both prescription and over-the-counter medications to calculate medication regimen complexity index.[11] This complexity is associated with clinical outcomes such as hospitalization, hospital readmission, medication adherence, blood pressure, age, and comorbidity. [12-14]

Literature has shown that the prevalence of multimorbidity varies across countries. Lifestyle and demographic factors contribute to the development of multimorbidity in diverse populations.[15] Unhealthy lifestyles[16] and lowerr socio-economic status[17, 18] have been associated with multimorbidity, which in turn contributes to polypharmacy. A study conducted in Saudi Arabia found that non-Saudi nationalities was associated with polypharmacy compared to Saudi nationals.[19] These suggest that factors associated with multimorbidity, polypharmacy and medication regimen complexity index may vary across countries.

There is limited data regarding factors associated with multimorbidity, polypharmacy, and medication regimen complexity among adults with hypertension in outpatient settings in Ethiopia. Therefore, the purpose of the present study was to identify factors associated with polypharmacy, medication regimen complexity and multimorbidity among adults with hypertension attending the outpatient follow-up department in the South Gondar Zone.

METHODS

Study Area, Design, and Period

The study was conducted in one purposively, and three randomly chosen public hospitals in South Gondar Zone. According to 2007 census which was conducted by Central Statistical Agency (CSA), Ethiopia, this Zone has a total population of 2 051 738. Based on the 2011 CSA population projection, the South Gondar Zone has a total population of 2 239 077 (1 103 490 women and 1 135 587 men). An institution-based multicentered cross-sectional design was used, and data were collected from December 1, 2021, to February 30, 2022.

Study Participants

The source population embraced all adults with hypertension attending follow-up appointments at outpatient departments. The study findings were reported according to the guidelines for reporting observational studies, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

Eligibility criteria

Inclusion criteria:

- Adults aged 18 years and above
- Receiving antihypertensive medications for at least six months
- Following up at outpatient departments of the study hospitals
- Willing to participate

Exclusion criteria:

- Cognitive impairment
- Hearing problems
- Admitted to inpatient wards

Sample Size Determination and Sampling Technique

There were no previous studies that we used to determine the sample size of the present study. Therefore, we used a single population proportion formula considering a 95% confidence interval, and a prevalence of 50% for outcomes. Then, we reached, a sample size of 384. Accounting for a 10% non-response rate, the final sample size was 423. Debre Tabor

Comprehensive Specialized Hospital, being the only specialized hospital in the zone, was selected purposively, while Addis Zemen Hospital, Nefas Mewucha Hospital, and Mekane Eyesus Hospital were chosen randomly. Proportional allocation and a systematic random sampling technique were applied, with a sampling interval of four; hence, every fourth participant was included until the desired sample size was achieved.

Study Variables

Dependent Variables: Multimorbidity, Medication regimen complexity index (MRCI), Polypharmacy

Independent Variables: Age, gender, residence, marital status, income, blood pressure status, educational status, number of medications, duration of treatment, health insurance, aerobic exercise

Operational definitions

Medication regimen complexity: comprised the dosage form, dosing interval, and additional instruction aspect to calculate the patient medication burden. It is quantified using 65 items Medication Regimen Complexity Index (MRCI): then, categorized into three levels: low (≤4), medium (5-8), and high (>8) MRCI scores.[21]

Multimorbidity: Co-existence of two or more chronic conditions in an individual.[1, 2]

Controlled blood pressure: Defined as BP <140/90 mmHg for individuals with hypertension without comorbidity, or BP <130/90 mmHg for those with diabetes mellitus, chronic kidney disease, or known cardiovascular diseases.[22]

Regular aerobic exercise: Regular Aerobic Exercise: Participants engaged in activities like brisk walking, recreational swimming, cycling, and tennis for at least 150 minutes per week.[23]

Polypharmacy: Routine use of five or more medications by a patient.[8] Fixed-dose combination (FDC) were accounted for in the methodology although no FDCs were identified in the medication regimens of participants. FDCs would have been counted as a single medication in the patient's regimen, regardless of the number of active ingredients, in cases where FDCs were present. This strategy helps to avoid overestimating the medication burden while considering the contribution of such combinations to the regimen complexity.

Chronic health condition: A chronic health condition is defined as a health problem that cannot be cured once acquired or one that persists for at least three months.[24]

Data Collection Procedures

A questionnaire was developed and translated into Amharic, and back-translated into English for consistency. Interviews were conducted to gather socio-demographic and clinical characteristics not found in patient charts, such as monthly income, regular aerobic exercise, over-the-counter medications, marital status, educational level, and health insurance. A checklist was used to collect data on blood pressure level, dosage forms, dose frequency, number of medications, and additional administration instructions. The 65-item MRCI tool, including sections on dosage forms, dose frequency, and additional instructions with corresponding scores, was used to determine the MRCI.[11]

The average of two BP readings taken two minutes apart during a visit was used to determine BP status.[25]

Data Quality Control

To ensure data quality, we conducted a pretest, trained data collectors, and checked the filled questionnaires and checklists for completeness and correctness daily. The training covered the study objectives, methods, and ethical concerns.

Statistical Analysis

Data were entered and analyzed using Stata 17. We checked that no multicollinearity (variance inflation factor less than two). We checked the reliability of the 65 items MRCI tool for our study settings and found 0.7 value of Cronbach's alpha indicates the reliability of the tool. Categorical variables were described using frequencies, while means and standard deviation (SD) were used for continuous variables. After checking assumptions, ordinal for MRCI, and binary logistic regression for multimorbidity, and polypharmacy were employed to identify predictors associated with MRCI and multimorbidity, respectively. Variables with a p-value of less than 0.25 in univariate analysis were included in the multivariate analysis, and statistical significance was set at a p-value of <0.05.

Ethical consideration

The present study was approved from Institutional Research and Ethical Review Committee (IRERC), College of Health Sciences, Debre Tabor university (Ref: CHS/DTU1421//2021), and conducted in accordance with the guidelines and standards of the declaration of Helsinki. IRERC gave us approval to receive verbal informed consent as the study does not have any known potential risk to participants. Therefore, Verbal consent was obtained from study participants after explaining the study's methods, and purpose. personal identifiers were anonymised to keep the participants' confidentiality.

Public and patient involvement

Patients and the public were not involved in the design of this study.

RESULTS

Socio-demographic and clinical characteristics of study participants

Four hundred twenty-three participants were included in the analysis of the study. The participants' age ranged from 23 to 90 years with mean ± standard error of 58.48±12.96 years, and majority of participants (59.81%) were female. The number of medications taken by each participant ranges from one to seven with mean ± SD of 2.65± 1.35.

Multimorbidity and polypharmacy were found in 46.10% and 12.29% of participants, respectively. Hypertension specific MRCI was low in 56.26%, medium in 40.43%, and high in 3.31% of participants. Concerning patient level MRCI, we found low in 20.80%, medium in 43.97%, and high in 35.22% (Table 1).

Table 1. Characteristics of study participants

Variable	Category of variable	Patient level Medication regimen complexity		
		Low	Medium	High
Sex	Female	55(13.00)	114(26.95)	84(19.86)
	Male	33(7.80)	72(17.02)	65(15.37)
Age in year	<65	65(15.37)	109(25.77)	96(22.70)
	65+	23(5.44)	77(18.20)	53(12.53)
Marital status	Single	4(0.95)	15(3.55)	8(1.89)
	Married	60(14.18)	123(29.08)	104(24.59)
	Divorced	7(1.65)	19(4.49)	6(1.42)
	Widowed	17(4.02)	29(6.86)	31(7.33)
Residence	Urban	55(13.00)	114(26.95)	98(23.17)
	Rural	33(7.80)	72(17.02)	51(12.06)
Income in Ethiopian birr	<6000	76(17.97)	174(41.13)	140(33.10)
	6000+	12(2.84)	12(2.84)	9(2.13)
Religion	Christian	82(19.39)	176(41.61)	137(32.39)
	Muslim	6(1.42)	10(2.36)	12(2.84)
Education	Unable to read & write	56(13.24)	105(24.82)	87(20.57)
	Can read &write	4(0.95)	10(2.36)	4(0.95)
	Primary	9(2.13)	38(8.98)	26(6.15)
	Secondary	5(1.18)	15(3.55)	12(2.84)
	Higer education	14(3.31)	18(4.26)	20(4.73)
Occupation	Farmer	16(3.78)	30(7.09)	24(5.67)
	Merchant	11(2.60)	37(8.75)	29(6.86)
	Daily labourer	1(0.24)	2(0.47)	0(0.00)
	Retired	8(1.89)	13(3.07)	10(2.36)
	Unemployed	38(8.89)	89(21.04)	69(16.31)
	Employed	14(3.31)	15(3.55)	17(4.02)
Multimorbidity	Yes	3(0.71)	69(16.31)	123(29.08)
	No	85(20.09)	117(27.66)	26(6.15)
Polypharmacy	Yes	0(0.00)	0(0.00)	52(12.29)
	No	88(20.80)	186(43.97)	97(22.93)
BP controlled	Yes	54(12.77)	73(17.26)	48(11.35)
	No	34(8.04)	113(26.71)	101(23.88)
Aerobic exercise	Yes	30(7.09)	45(10.64)	23(5.44)
	No	58(13.71)	141(33.33)	126(29.79)
Health insurance	Yes	58(13.71)	132(31.21)	115(27.19)
	No	30(7.09)	54(12.77)	34(8.04)
Study setting	Debre Tabor	22(5.20)	71(16.78)	57(13.48)
	Nefas Mewucha	16(3.78)	39(9.22)	45(10.64)
	Addis Zemen	34(8.04)	35(8.27)	31(7.33)
	Estie	16(3.78)	41(9.69)	16(3.78)
Therapy duration	<5 year	64(15.13)	132(31.21)	87(20.57)
	5+ year	24(5.67)	54(12.77)	62(14.66)

Patterns of multimorbidity

Type 2 diabetes mellitus was the most common comorbidity coexisting with hypertension, while the least encountered comorbidities included rheumatic fever, Parkinson's disease, fatty liver disease, and others. Others include: rheumatic fever, pulmonary tuberculosis, glaucoma, Parkinson's disease, fatty liver disease, degenerative aortic stenosis, degenerative spondylosis, osteoarthritis, hypercalcemia, bilateral flank pain, schizophrenia, trigeminal neuralgia, and soft tissue injury (Table 2).

Table 2. Morbidities among hypertensive patients

Disorder	Frequency	Percent
Type 2 diabetes mellitus	52	21.40
Dyslipidemia	25	10.29
Dyspepsia	22	9.05
Hypertensive heart disease	21	8.64
Bronchial asthma	21	8.64
Rheumatoid arthritis	19	7.82
Peripheral neuropathy	19	7.82
Congestive heart failure	12	4.94
Ischemic stroke	10	4.12
Ischemic heart disease	7	2.88
Hyperthyroidism	6	2.47
Human immunodeficiency virus	5	2.06
Chronic kidney disease	3	1.23
Type 1 diabetes mellitus	3	1.23
Myalgia	3	1.23
Generalized tonic-clonic	3	1.23
Others (each 1[0.41%])	13	5.3

Others include: Rheumatic fever, Pulmonary tuberculosis, Glaucoma, Parkinson's disease, Faty liver disease, Degenerative aortic stenos, Degenerative spondylosis, Osteoarthritis, Hypercalcemia, Bilateral flank pain, Schizophrenia, Trigeminal neuralgia, and Soft tissue injury.

The most common body system morbidity encountered among the sampled study participants with hypertension was cardiovascular disorder, which accounted for 77 cases (31.69%). In contrast, the least common was special sense disorder, accounting for just 1 case (0.41%) (Fig. 1).

Hypertension combined with type 2 diabetes mellitus was the most commonly observed multimorbidity, followed by hypertension combined with hypertensive heart disease. Conversely, hypertension combined with T2DM and HIV, hypertension combined with hypertensive heart disease and dyspepsia, and other combinations were the least frequently encountered multimorbidity among the study participants. Regarding the number of multimorbidity per participant, 53.9% had none, 35.22% had two, 10.4% had three, and 0.24% each had four and five morbidities. Others (each accounts 0.24%) include: hypertension +degenerative spondylosis, hypertension + type 2 diabetes mellitus + bilateral flank pain, hypertension + type 2 diabetes mellitus+ HIV, hypertension + hypertensive heart disease + dyspepsia, hypertension + type 2 diabetes mellitus + fatty liver disease, hypertension + type 2 diabetes mellitus + ischemic heart disease, hypertension + Parkinson's disease + hypertensive heart disease, hypertension + glaucoma, hypertension + trigeminal neuralgia, hypertension + type 2 diabetes mellitus + chronic kidney disease, hypertension + rheumatoid arthritis + bronchial asthma, hypertension + schizophrenia, hypertension +hypocalcemia, hypertension+ type 2 diabetes mellitus +degenerative aortic stenosis, hypertension + peripheral neuropathy + HIV, hypertension +rheumatoid arthritis + hypertensive heart disease, hypertension + rheumatic fever, hypertension + soft tissue injury, hypertension + hypertensive heart disease + ischemic stroke +bronchial asthma + dyslipidemia, hypertension + osteoarthritis, hypertension + HIV + bronchial asthma, hypertension + hypertensive heart disease + pulmonary tuberculosis, and hypertension + dyslipidemia + congestive heart failure (Table 3).

Table 3. Pattern of multimorbidity among hypertensive patients

Multimorbidity	Frequency	Percent
Hypertension+T2 diabetes mellitus	30	7.09
Hypertension+Hypertensive heart disease	16	3.78
Hypertension+Dyspepsia	12	2.84
Hypertension+Rheumatoid arthritis	12	2.84
Hypertension+Dyslipidemia	11	2.60
Hypertension+Peripheral neuropathy	10	2.36
Hypertension+Bronchial asthma	10	2.36

Hypertension+Ischemic stroke		8	1.89
Hypertension+T2 diabetes mellitus+Dyslipidemia		7	1.65
Hypertension+Congestive heart failure		7	1.65
Hypertension+Hyperthyroidism		6	1.42
Hypertension+Peripheral neuropathy+Dyspepsia		3	0.71
Hypertension+T2 diabetes mellitus+Peripheral neuropathy		3	0.71
Hypertension+T2 diabetes mellitus+Bronchial asthma		3	0.71
Hypertension+Generalized tonic-clonic epilepsy		3	0.71
Hypertension+T1diabetes mellitus		3	0.71
Hypertension+Myalgia		3	0.71
Hypertension+Dyslipidemia+Rheumatoid arthritis		2	0.47
Hypertension+Dyspepsia+Bronchial asthma		2	0.47
Hypertension+Dyslipidemia+Bronchial asthma		2	0.47
Hypertension+Rheumatoid arthritis+T2 diabetes mellitus		2	0.47
Hypertension+Human immunodeficiency virus		2	0.47
Hypertension+Chronic kidney disease		2	0.47
Hypertension+Peripheral neuropathy+Rheumatoid arthritis		2	0.47
Others		23	11.79
Number of multimorbidity	0 2 3 4 5	228 149 44 1 1	53.90 35.22 10.40 0.24 0.24

Factors associated with multimorbidity, Polypharmacy, and MRCI

In the final adjusted binary logistic regression, we found that polypharmacy, patient-level medication regimen complexity, and the study hospital were associated with the presence of multimorbidity.

Polypharmacy was significantly associated with a duration of hypertension treatment equal to or greater than five years, multimorbidity, and controlled BP in the adjusted binary logistic regression analysis.

We identified several factors associated with medication regimen complexity (MRCI) for inclusion in a multivariate ordinal logistic regression analysis. These factors include the presence of multimorbidity, controlled blood pressure (BP), duration of hypertension treatment greater than five years, engaging in aerobic exercise, having health insurance, and an income greater than 6000 Ethiopian Birr.

In the adjusted analysis, participants experiencing multimorbidity were fourteen times more likely to have a complex medication regimen (AOR=14.55, 95% CI: 9.00-23.52, P<0.0001). Furthermore, participants with controlled BP, based on WHO pharmacologic treatment of

hypertension guidelines (2021), were 52% less likely to have a complex medication regimen (AOR=0.48, 95% CI: 0.32-0.72, P<0.0001) (Table 4).

Table 4. Univariate, and multivariate logistic analysis of predictors of MRCI, polypharmacy, and multimorbidity

Variable	Variable category	Outcome			COR (95% CI)	AOR (95% CI)
		Patient MRCI[a]				
		≤4	5-8	>8		
Income	<6000 ETB	76	174	140	1	1
	≥6000 ETB	12	12	9	0.52(0.26-1.03)*	0.59(0.28-1.24)
Multimorbidity	No	85	117	26	1	1
	Yes	3	69	123	15.19(9.47-24.37)*	14.55(9.00-23.52)+
Controlled BP	No	34	113	101	1	1
	Yes	54	73	48	0.46(0.32-0.67)+	0.48(0.32-0.72)+
Aerobic exercise	No	58	141	126	1	1
	Yes	30	45	23	0.49(0.32-0.74)+	0.77(0.48-1.23)
Health insurance	No	30	54	34	1	1
	Yes	58	132	115	1.47(0.99-2.19)*	1.53(0.98-2.39)
Hypertension therapy	<5 years	64	132	87	1	1
	≥5 years	24	54	62	1.66(1.13-2.44)+	1.17(0.77-1.78)
		Polypharmacy[b]				
		Absent		Present		
Study hospital	DCSH	126		24	1	1
	NMWH	85		15	0.78(0.38-1.62)*	1.06(0.47-2.38)
	ADZH	94		6	0.39(0.16-0.96)+	0.73(0.28-1.93)
	MEH	66		7	0.56(0.23-1.36)*	1.96(0.67-5.71)
Multimorbidity	No	225		3	1	1
	Yes	146		49	24.49(7.49-80.08)+	25.39(7.48-86.22)+
Hypertension therapy	<5 years	258		25	1	1
	≥5 years	113		27	2.58(1.43-4.66)+	2.12(1.08-4.16)+
Controlled BP	No	206		42	1	1
	Yes	165		10	0.42(0.19-0.92)+	0.42(0.19-0.92)+
		Multimorbidity[b]				
		Absent		Present		
Age	<65 years	152		118	1	1
	≥65 years	76		77	1.31(0.87-1.94)*	1.09(0.64-1.88)
Study hospital	DCSH	59		91	1	1
	NMWH	56		44	0.51(0.30-0.85)+	0.30(0.15-0.59)+
	ADZH	56		44	0.53(0.32-0.88)+	0.80(0.36-1.77)
	MEH	57		16	0.18(0.09-0.35)+	0.16(0.07-0.38)+
Aerobic exercise	No	165		160	1	1
	Yes	63		35	0.56(0.35-0.90)+	0.86(0.41-1.81)
Hypertension therapy	<5 years	169		114	1	1
	≥5 years	59		81	2.01(1.33-3.02)+	1.49(0.85-2.61)
Controlled BP	No	124		124	1	1
	Yes	104		71	0.69(0.47-1.03)+	1.12(0.64-1.95)
Polypharmacy	Absent	225		146	1	1
	Present	3		49	24.49(7.49-80.08)+	5.52(1.49-20.39)+
Patient MRCI	≤4	85		3	1	1
	5-8	117		69	12.38(4.35-35.26)+	19.76(5.87-66.56)+
	>8	26		123	99.34(33.45-295.07)+	120.32(33.12-437.07)+

Abbreviations: AOR, Adjusted odds ratio; COR, Crude odds ratio; ETB, Ethiopian birr; BP, Blood pressure; DCSH, Debre Tabor Comprehensive Specialized Hospital; NMWH, Nefas Mewucha Hospital, ADZH, Addis Zemen Hospital; MEH, Mekane Eyesus Hospital; MRCI, Medication regimen complexity index. Note: Superscript [a] indicates ordinal logistic regression was used while [b] shows binary logistic regression used, * indicates P<0.25 while + indicates P<0.05.

DISCUSSION

In the present study, we found that 46.10% of participants had multimorbidity, 12.29% experienced polypharmacy, and 35.22% had a high patient-level MRCI. Additionally, we identified associations between polypharmacy, patient-level MRCI, and the study hospital with multimorbidity. We also found that the duration of hypertension therapy, controlled blood pressure (BP), and multimorbidity were associated with polypharmacy, while controlled BP and multimorbidity were associated with a high patient-level MRCI.

The magnitude of multimorbidity observed in our study is higher than that reported in studies conducted in Sweden (21.6%),[26] Japan (29.9%),[7] and Hong Kong, China (40.4%),[6] but lower than findings from studies conducted in Bahir Dar, Ethiopia (54.8%),[27] Ghana (55%),[28] India (55%),[29] United Kingdom (73.9%),[5] and another study in China (56.7%).[30]

Concerning polypharmacy, our finding is lower than those findings from studies conducted in Gondar, Ethiopia (46.6%),[31] Ghana (64.8%),[28] Somaliland (71%),[10] Saudi Arabia [(21%), (79%)],[9, 32] and Japan (22.3%).[7]

We found high patient level MRCI in 35.22% of study participants, which is lower than the 57.2% reported in a study conducted in Gondar, Ethiopia. [31]

Participants with polypharmacy (≥5 medications) were more likely to experience multimorbidity compared to those without polypharmacy, a finding supported by a study from Japan.[7] Moreover, participants with medium or high patient level MRCI were more likely to experience multimorbidity compared to those with low patient level MRCI. This finding is in line with the finding from Sweden.[26] While previous studies have identified factors such as age, being male, and uncontrolled BP as predictor of multimorbidity,[5, 6, 27] these factors were not significantly associated with multimorbidity in our study.

We found that participants who had been undergoing hypertension treatment for five years or more were twice as likely to experience polypharmacy. This finding is supported by a study from Saudi Arabia.[9] In addition, we identified that controlled BP and presence of multimorbidity were associated with polypharmacy; however, we did not find comparable studies to further discuss these findings.

We found that those participants with controlled BP were 52% less likely to have Medium or high patient level MRCI compared to those with uncontrolled BP. This finding is similar with the finding of the study from Japan in which those participants with higher MRCI were more

likely to have poor BP control.[13] Additionally, we identified that participants with multimorbidity were 14 times more likely to have medium or high patient level MRCI, in line with a finding from a study in Korea.[33]

The observed differences between findings may be attributed to variations in inclusion criteria, and the sociodemographic distribution of study participants. In our study, we determined multimorbidity, polypharmacy and MRCI as well as associated factors specifically among hypertensive adults, whereas most of previous studies assessed multimorbidity,[30] polypharmacy,[10, 31, 32] and MRCI[31] among participants with any chronic conditions, without requiring a hypertension diagnosis as a mandatory inclusion criterion.

Strength and limitation of the study

The present study is the first in the Ethiopian healthcare setting that identified factors associated with multimorbidity, polypharmacy, and MRCI among adult hypertensive patients. The multicentred design enhances the generalizability of the findings to outpatient settings in diverse healthcare facilities. However, this study has a limitation being cross sectional which limits the ability to establish true cause-effect relationship between outcome and identified factors. Moreover, exclusion of inpatient settings restricts the generalizability of the findings to adult hypertensive patients receiving chronic care in outpatient departments only. Although we employed probability sampling techniques, higher proportion of population aged under 65 years included in the study may under represent factors associated with multimorbidity, polypharmacy and MRCI in older populations. Adherence to therapy was not assessed in our study, which might influence results of the study.

Clinical implication of the study findings

The high prevalence of multimorbidity (46.10%) in hypertensive patients highlights comprehensive care strategies. Healthcare providers should consider multiple chronic conditions when managing hypertension patients, as multimorbidity is often linked to more complex treatment regimens and adverse health outcomes. Adjusting treatment plans that address multimorbidity may improve patient outcomes and reduce complications. The observed high MRCI (35.22%) in our study indicates the need to simplify medication regimens without compromising treatment effectiveness whenever possible particularly in patients with multimorbidity. Healthcare providers should use strategy like combining medications with

fewer doses or using fixed dose combinations could help optimize treatment for patients with high MRCI.

Polypharmacy (12.29%) was strongly associated with multimorbidity, underscores the importance of regular medication reviews to minimize unnecessary polypharmacy, risk of drug interactions and side effects. Clinicians should monitor patients on multiple medications closely and regularly assess the appropriateness of each medication for patient's current health status.

The association of uncontrolled BP with both polypharmacy and high MRCI suggests that these patients may require more intensive treatment strategies including close monitoring of BP, medication adjustments and identifying the underlying cause. The association between longer duration of hypertension treatment (equal or greater than 5 years) and polypharmacy emphasizes the need for ongoing assessment of treatment effectiveness over time. Patients with long standing hypertension are more likely to develop additional comorbidities, so healthcare providers should ensure that the long-term hypertension management plan are regularly updated to reflect changes in patient's health and medication needs.

Based on our findings we recommend to strengthen integrated care model that involves physicians, pharmacists and nurses to address multimorbidity and optimize medication use. Emphasize should be given to patient centered care to simplify medication regimens and education on adherence and lifestyle modifications. Health systems should be strengthened to enhance the capacity of primary hospitals to manage hypertension and its comorbidities effectively. Further longitudinal research is needed to explore the long-term outcome of these findings. Health policy makers should address such challenges in designing guidelines for chronic disease management.

CONCLUSION

The present study showed a considerable number of hypertensive patients experienced multimorbidity, polypharmacy and patient level MRCI. We identified study setting being primary hospital, polypharmacy, and MRCI as predictors of multimorbidity. In addition, Multimorbidity, and controlled BP were predictors of polypharmacy, and MRCI in this study. Moreover, duration of hypertension treatment was significantly associated with polypharmacy. Therefore, hypertensive patients care should consider multimorbidity, polypharmacy, and MRCI to optimize their care.

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Author Contributions

T.S.Y., W.E.M., and A.M.B. designed the study and analyzed data. T.S.Y., Y.S.Y., S.B.D., F.N.D., G.T.A., T.A.M. and A.M.B. performed data entry, wrote, and edited the manuscript. T.S.Y. is the guarantor of this work. All authors reviewed the manuscript and were responsible for all aspects of this work.

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Authors have declared that there is no conflict of interest

Public and patient involvement

Patients and the public were not involved in the design of the study.

Patient consent for publication

Not required.

Ethical Approval

Ethical approval for the present study was received from Institutional Research and Ethical Review Committee (IRERC), College of Health Sciences, Debre Tabor university, and conducted in accordance with the declaration of Helsinki.

Data availability statement

All necessary data are available within the manuscript and/or supporting materials

REFERENCES

1. Mercer S FJ, Moffat K, Fischbacher-Smith D, Sanci L. Multimorbidity: technical series on safer primary care. World Health Organization.2016.
2. Skou ST MF, Fortin M, Guthrie B, Nunes BP, Miranda JJ, Boyd CM, Pati S, Mtenga S, Smith SM. Multimorbidity. Nature Reviews Disease Primers. 2022;8(1):48.
3. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PLoS One. 2014;9(7):e102149.
4. Chowdhury SR, Chandra Das D, Sunna TC, Beyene J, Hossain A. Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. EClinicalMedicine. 2023;57:101860.
5. Hirst JA, Ordonez Mena JM, O'Callaghan CA, Ogburn E, Taylor CJ, Yang Y, et al. Prevalence and factors associated with multimorbidity among primary care patients with decreased renal function. PLoS One. 2021;16(1):e0245131.
6. Wong MC, Wang HH, Cheung CS, Tong EL, Sek AC, Cheung NT, et al. Factors associated with multimorbidity and its link with poor blood pressure control among 223,286 hypertensive patients. Int J Cardiol. 2014;177(1):202-8.
7. Aoki T, Yamamoto Y, Ikenoue T, Onishi Y, Fukuhara S. Multimorbidity patterns in relation to polypharmacy and dosage frequency: a nationwide, cross-sectional study in a Japanese population. Sci Rep. 2018;8(1):3806.
8. WHO. World Health Organization. Medication safety in polypharmacy. Geneva.; 2019.
9. Alsanosi SM MA, Ahmadini HA, Qadhi RS, Ikram N, Felemban AH, Alqashqri HS, Hariri NH, Alhindi YZ, Ayoub N. Polypharmacy among patients with hypertension attending primary healthcare centres. Annals of Medicine and Surgery. 2023 Jun 1;85(6):. 2023;85(6):2545-9.
10. Sidamo T, Deboch A, Abdi M, Debebe F, Dayib K, Balcha Balla T. Assessment of polypharmacy, drug use patterns, and associated factors at the Edna Adan University Hospital, Hargeisa, Somaliland. Journal of tropical medicine. 2022;2022(1):2858987.
11. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. The Annals of pharmacotherapy. 2004;38(9):1369-76.

12. Alves-Conceicao V, Rocha KSS, Silva FVN, Silva ROS, Cerqueira-Santos S, Nunes MAP, et al. Are Clinical Outcomes Associated With Medication Regimen Complexity? A Systematic Review and Meta-analysis. The Annals of pharmacotherapy. 2020;54(4):301-13.

13. Wakai E IK, Kato C, Okuda M. Effect of number of medications and complexity of regimens on medication adherence and blood pressure management in hospitalized patients with hypertension. PLoS One. 2021;16(6):e0252944.

14. Wimmer BC, Johnell K, Fastbom J, Wiese MD, Bell JS. Factors associated with medication regimen complexity in older people: a cross-sectional population-based study. Eur J Clin Pharmacol. 2015;71(9):1099-108.

15. Nguyen H, Manolova G, Daskalopoulou C, Vitoratou S, Prince M, Prina AM. Prevalence of multimorbidity in community settings: A systematic review and meta-analysis of observational studies. Journal of comorbidity. 2019 Aug 20;9:2235042X19870934.

16. Fortin M, Haggerty J, Almirall J, Bouhali T, Sasseville M, Lemieux M. Lifestyle factors and multimorbidity: a cross-sectional study. BMC public health. 2014 Dec;14:1-8.

17. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, Glynn L, Muth C, Valderas JM. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PloS one. 2014 Jul 21;9(7):e102149.

18. Low LL, Kwan YH, Ko MS, Yeam CT, Lee VS, Tan WB, Thumboo J. Epidemiologic characteristics of multimorbidity and sociodemographic factors associated with multimorbidity in a rapidly aging Asian country. JAMA network open. 2019 Nov 1;2(11):e1915245-.

19. Balkhi B, AlQahtani N, Alwhaibi M, Alshammari TM, Alhawassi TM, Mahmoud MA, Almetwazi M, Ata S, Basyoni M, Aljadhey H. Prevalence and factors associated with polypharmacy use among adult patients in Saudi Arabia. Journal of Patient Safety. 2021 Dec 1;17(8):e1119-24.

20. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The lancet. 2007 Oct 20;370(9596):1453-7.

21. Yeh A, Shah-Manek B, Lor KB. Medication Regimen Complexity and A1C Goal Attainment in Underserved Adults With Type 2 Diabetes. The Annals of pharmacotherapy. 2017;51(2):111-7.

22. Organization WH. Guideline for the pharmacological treatment of hypertension in adults. 2021.

23. Piercy KL, Troiano RP. Physical Activity Guidelines for Americans From the US Department of Health and Human Services. Circ Cardiovasc Qual Outcomes. 2018;11(11):e005263.

24. US Department of Health and Human Services. Health, United States, 2010: with special feature on death and dying. Hyattsville (MD): Centers for Disease Control and Prevention, National Center for Health Statistics; 2011. Appendix, definition of "condition," p. 486–7. Available at: https://www.cdc.gov/nchs/data/hus/hus10.pdf. Accessed on: January 24, 2025.

25. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.

26. Forslund T, Carlsson AC, Ljunggren G, Arnlov J, Wachtler C. Patterns of multimorbidity and pharmacotherapy: a total population cross-sectional study. Fam Pract. 2021;38(2):132-40.

27. Eyowas FA SM, Alemu S, Pati S, Getahun FA. Magnitude, pattern and correlates of multimorbidity among patients attending chronic outpatient medical care in Bahir Dar, northwest Ethiopia: the application of latent class analysis model. PLoS One. 2022;17(4):e0267208.

28. Kwakye AO KI, Oppong KG. Polypharmacy and its associated factors among patients with co-morbid hypertension and diabetes in a municipal hospital in Ghana. . Scientific African. 2024;23:e02028.

29. Pati S, Sinha R, Panda M, Puri P, Pati S. Profile of multimorbidity in outpatients attending public healthcare settings: A descriptive cross-sectional study from Odisha, India. J Family Med Prim Care. 2021;10(8):2900-14.

30. Zhong Y QG, Xi H, Cai D, Wang Y, Wang T, Gao Y. Prevalence, patterns of multimorbidity and associations with health care utilization among middle-aged and older people in China. . BMC public health.23(1):537.

31. Kassaw AT, Sendekie AK, Minyihun A, Gebresillassie BM. Medication regimen complexity and its impact on medication adherence in patients with multimorbidity at a comprehensive specialized hospital in Ethiopia. Frontiers in medicine. 2024;11:1369569.

32. Alwhaibi M, AlRuthia Y, Alhawassi TM, Almalag H, Alsalloum H, Balkhi B. Polypharmacy and comorbidities among ambulatory cancer patients: A cross-sectional retrospective study. Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners. 2020;26(5):1052-9.

33. Ji E, Ahn S, Choi J-Y, Kim C-H, Kim K-i. Effect of multimorbidity on hypertension management. Scientific Reports. 2023;13(1):18764.

Figure legend

Fig 1. Percentage distribution of body system disorders

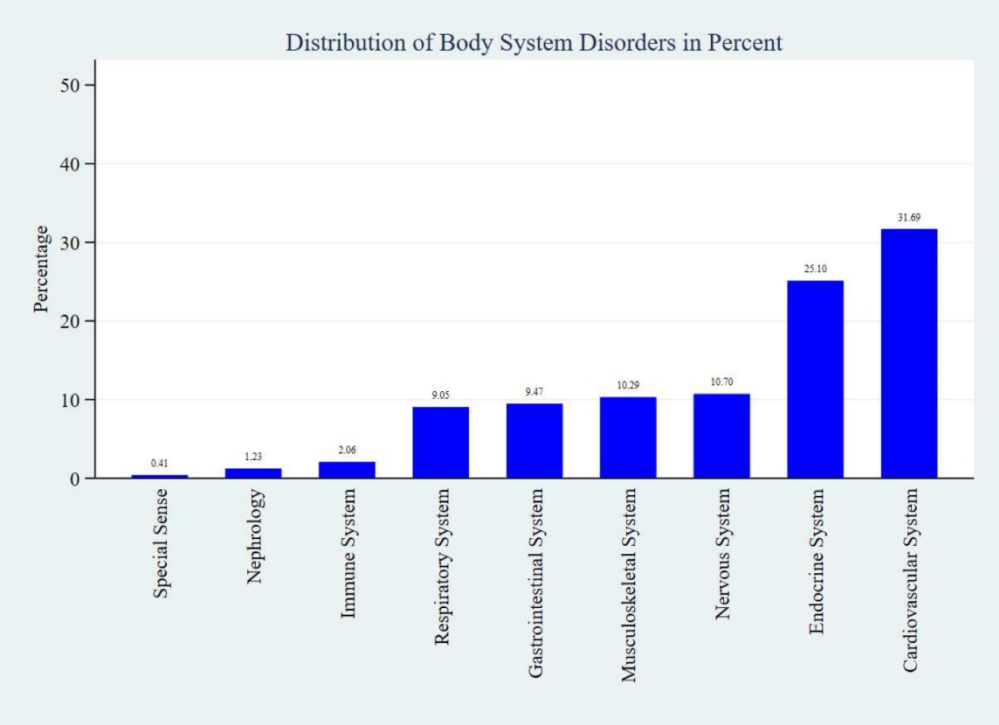

Fig 1. Percentage Distribution of Body System Disorders

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Clinical Factors Associated with Multimorbidity, Polypharmacy, and Medication Regimen Complexity among Adults with Hypertension: A Multicenter Cross-Sectional Study

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ABSTRACT

Objectives: Factors associated with multimorbidity, polypharmacy, and medication regimen complexity (MRCI) may vary across countries. However, such data are lacking in the present study setting. This study aimed to identify factors associated with multimorbidity, polypharmacy, and MRCI among adults living with hypertension in public hospitals of South Gondar Zone.

Design: Multicentered cross sectional design

Setting: Public hospitals of Comprehensive Specialized and primary hospitals, Ethiopia

Participants: Adults living with hypertension who had follow up visits at outpatient clinics and were selected by systematic random sampling from December 1, 2021, to February 30, 2022.

Primary and Secondary Outcome Measures: Medication regimen complexity was assessed using a 65-items medication regimen complexity tool. Sociodemographic data were collected through interview, while polypharmacy and clinical characteristics were documented using checklist. Data were entered into SPSS version26, and analyzed using STATA 17. Binary logistic regression model was used to determine AOR of factors associated with multimorbidity and polypharmacy. For factors influencing MRCI, an ordinal logistic regression used.

Results: We found participants from Nefas Mewucha hospital (AOR=0.3, 95% CI:0.15-0.59) and Mekane Eyesus hospital (AOR=0.17, 95% CI: 0.07-0.38), compared to Debre Tabor Comprehensive Specialized Hospital, polypharmacy (AOR=5.52, 95% CI: 1.49-20.39), medium (AOR=19.76, 95% CI: 5.86-66.56), and high MRCI (AOR=120.32, 95% CI: 33.12-437.07) were associated with multimorbidity. Multimorbidity (AOR=25.4, 95% CI: 7.48-86.23), controlled blood pressure (AOR=0.43, 95% CI: 0.19-0.92), and duration of hypertension therapy ≥5 years (AOR=2.12, 95% CI: 1.08-4.16) were associated with polypharmacy. Whereas, controlled BP (AOR=0.48, 95% CI: 0.32-0.72), and multimorbidity (AOR=14.55, 95% CI: 9.00-23.52) were significantly associated with high MRCI. The prevalence of multimorbidity, high MRCI, and polypharmacy was found in 46.1%, 35.22%, and 12.29% of participants, respectively.

Conclusion: A considerable proportion of participants with hypertension experienced multimorbidity, polypharmacy, and high medication complexity. Polypharmacy, primary hospital setting, and high MRCI were independent variables associated with multimorbidity. On the other hand, multimorbidity, and controlled BP were associated with polypharmacy and MRCI. Hypertension care should consider multimorbidity, polypharmacy, and medication complexity.

Strength and Limitation of the Study

- This study used objective measures to assess multimorbidity, polypharmacy and medication regimen complexity strengthens the methodological rigor.
- Multicentred design nature of the study is considered as an additional strength of the present study.
- However, this study has a limitation being cross sectional that did not establish a true cause-effect relationship between outcome and independent factors.
- Moreover, relatively small sample size and exclusion of inpatient settings restricts the findings generalizability to adult living with hypertension who have chronic follow up at outpatient departments only
- Under representation of older adults and medication adherence were not adequately addressed, potentially affecting study results.

INTRODUCTION

Multimorbidity is defined as the co-occurrence of two or more chronic health conditions in an individual.[1, 2] It has become a major public health problem, with prevalence ranging from 12.9% to 95.1%.[3, 4] Multimorbidity has been linked with premature death, poor quality of life, increased healthcare utilization, advanced age, higher body mass index, reduced kidney function, lower socioeconomic status, birth gender, suboptimal blood pressure control and polypharmacy.[2, 3, 5-7]

The definition of polypharmacy has not been standardized; however, it is commonly defined in the literature as the routine use of five or more concurrent medications. This includes over-the-counter drugs, prescription medications, traditional remedies, and complementary medicines.[8] The prevalence of polypharmacy has been increased worldwide and is associated with factors such as duration of treatment, comorbidities, chronic illness, and advanced age.[9, 10]

Medication regimen complexity includes factors such as dosage forms, dosing frequency, and additional instructions related to medications. It accounts for both prescription and over-the-counter medications to calculate medication regimen complexity index.[11] This complexity is associated with clinical outcomes such as hospitalization, hospital readmission, medication adherence, blood pressure, age, and comorbidity. [12-14]

Literature has shown that the prevalence of multimorbidity varies across countries. Lifestyle and demographic factors contribute to the development of multimorbidity in diverse populations.[15] Unhealthy lifestyles[16] and lowerr socio-economic status[17, 18] have been associated with multimorbidity, which in turn contributes to polypharmacy. A study conducted in Saudi Arabia found that non-Saudi nationalities was associated with polypharmacy compared to Saudi nationals.[19] These suggest that factors associated with multimorbidity, polypharmacy and medication regimen complexity index may vary across countries.

There is limited data regarding factors associated with multimorbidity, polypharmacy, and medication regimen complexity among adults with hypertension in outpatient settings in Ethiopia. Therefore, the purpose of the present study was to identify factors associated with polypharmacy, medication regimen complexity and multimorbidity among adults with hypertension attending the outpatient follow-up department in the South Gondar Zone.

METHODS

Study Area, Design, and Period

The study was conducted in one purposively, and three randomly chosen public hospitals in South Gondar Zone. According to 2007 census which was conducted by Central Statistical Agency (CSA), Ethiopia, this Zone has a total population of 2 051 738. Based on the 2011 CSA population projection, the South Gondar Zone has a total population of 2 239 077 (1 103 490 women and 1 135 587 men). An institution-based multicentered cross-sectional design was used, and data were collected from December 1, 2021, to February 30, 2022.

Study Participants

The source population embraced all adults with hypertension attending follow-up appointments at outpatient departments. The study findings were reported according to the guidelines for reporting observational studies, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

Eligibility Criteria

Inclusion criteria:

- Adults aged 18 years and above
- Receiving antihypertensive medications for at least six months
- Following up at outpatient departments of the study hospitals
- Willing to participate

Exclusion criteria:

- Cognitive impairment
- Hearing problems
- Admitted to inpatient wards

Sample Size Determination and Sampling Technique

There were no previous studies that we used to determine the sample size of the present study. Therefore, we used a single population proportion formula considering a 95% confidence interval, and a prevalence of 50% for outcomes. Then, we reached, a sample size of 384. Accounting for a 10% non-response rate, the final sample size was 423. Debre Tabor

Comprehensive Specialized Hospital, being the only specialized hospital in the zone, was selected purposively, while Addis Zemen Hospital, Nefas Mewucha Hospital, and Mekane Eyesus Hospital were chosen randomly. Proportional allocation and a systematic random sampling technique were applied, with a sampling interval of four; hence, every fourth participant was included until the desired sample size was achieved.

Study Variables

Dependent Variables: Multimorbidity, Medication regimen complexity index (MRCI), Polypharmacy

Independent Variables: Age, gender, residence, marital status, income, blood pressure status, educational status, number of medications, duration of treatment, health insurance, aerobic exercise

Operational Definitions

Medication regimen complexity: comprised the dosage form, dosing interval, and additional instruction aspect to calculate the patient medication burden. It is quantified using 65 items Medication Regimen Complexity Index (MRCI): then, categorized into three levels: low (≤4), medium (5-8), and high (>8) MRCI scores.[21]

Multimorbidity: Co-existence of two or more chronic conditions in an individual.[1, 2]

Controlled blood pressure: Defined as BP <140/90 mmHg for individuals with hypertension without comorbidity, or BP <130/90 mmHg for those with diabetes mellitus, chronic kidney disease, or known cardiovascular diseases.[22]

Regular aerobic exercise: Regular Aerobic Exercise: Participants engaged in activities like brisk walking, recreational swimming, cycling, and tennis for at least 150 minutes per week.[23]

Polypharmacy: Routine use of five or more medications by a patient.[8] Fixed-dose combination (FDC) were accounted for in the methodology although no FDCs were identified in the medication regimens of participants. FDCs would have been counted as a single medication in the patient's regimen, regardless of the number of active ingredients, in cases where FDCs were present. This strategy helps to avoid overestimating the medication burden while considering the contribution of such combinations to the regimen complexity.

Chronic health condition: A chronic health condition is defined as a health problem that cannot be cured once acquired or one that persists for at least three months.[24]

Data Collection Procedures

A questionnaire was developed and translated into Amharic, and back-translated into English for consistency. Interviews were conducted to gather socio-demographic and clinical characteristics not found in patient charts, such as monthly income, regular aerobic exercise, over-the-counter medications, marital status, educational level, and health insurance. A checklist was used to collect data on blood pressure level, dosage forms, dose frequency, number of medications, and additional administration instructions. The 65-item MRCI tool, including sections on dosage forms, dose frequency, and additional instructions with corresponding scores, was used to determine the MRCI.[11]

The average of two BP readings taken two minutes apart during a visit was used to determine BP status.[25]

Data Quality Control

To ensure data quality, we conducted a pretest, trained data collectors, and checked the filled questionnaires and checklists for completeness and correctness daily. The training covered the study objectives, methods, and ethical concerns.

Statistical Analysis

Data were entered and analyzed using Stata 17. We checked that no multicollinearity (variance inflation factor less than two). We checked the reliability of the 65 items MRCI tool for our study settings and found 0.7 value of Cronbach's alpha indicates the reliability of the tool. Categorical variables were described using frequencies, while means and standard deviation (SD) were used for continuous variables. After checking assumptions, ordinal for MRCI, and binary logistic regression for multimorbidity, and polypharmacy were employed to identify predictors associated with MRCI and multimorbidity, respectively. Variables with a p-value of less than 0.25 in univariate analysis were included in the multivariate analysis, and statistical significance was set at a p-value of <0.05.

Ethical Consideration

The present study was approved from Institutional Research and Ethical Review Committee (IRERC), College of Health Sciences, Debre Tabor university (Ref: CHS/DTU1421//2021), and conducted in accordance with the guidelines and standards of the declaration of Helsinki. IRERC gave us approval to receive verbal informed consent as the study does not have any known potential risk to participants. Therefore, Verbal consent was obtained from study participants after explaining the study's methods, and purpose. personal identifiers were anonymised to keep the participants' confidentiality.

Public and Patient Involvement

Patients and the public were not involved in the design of this study.

RESULTS

Socio-Demographic and Clinical Characteristics of Study Participants

Four hundred twenty-three participants were included in the analysis of the study. The participants' age ranged from 23 to 90 years with mean ± standard deviation (SD) of 58.48±12.96 years, and majority of participants (59.81%) were female. The number of medications taken by each participant ranges from one to seven with mean ± SD of 2.65± 1.35.

Multimorbidity and polypharmacy were found in 46.10% and 12.29% of participants, respectively. Hypertension specific MRCI was low in 56.26%, medium in 40.43%, and high in 3.31% of participants. Concerning patient level MRCI, we found low in 20.80%, medium in 43.97%, and high in 35.22% (Table 1).

Variable	Category of variable	Patient level Medication regimen complexity		
		Low	Medium	High
Sex	Female	55(13.00%)	114(26.95%)	84(19.86%)
	Male	33(7.80%)	72(17.02%)	65(15.37%)
Age in year	<65	65(15.37%)	109(25.77%)	96(22.70%)
	65+	23(5.44%)	77(18.20%)	53(12.53%)
Marital status	Single	4(0.95%)	15(3.55%)	8(1.89%)
	Married	60(14.18%)	123(29.08%)	104(24.59%)
	Divorced	7(1.65%)	19(4.49%)	6(1.42%)
	Widowed	17(4.02%)	29(6.86%)	31(7.33%)
Residence	Urban	55(13.00%)	114(26.95%)	98(23.17%)
	Rural	33(7.80%)	72(17.02%)	51(12.06%)
Income in Ethiopian birr	<6000	76(17.97%)	174(41.13%)	140(33.10%)
	6000+	12(2.84%)	12(2.84%)	9(2.13%)
Religion	Christian	82(19.39%)	176(41.61%)	137(32.39%)
	Muslim	6(1.42%)	10(2.36%)	12(2.84%)
Education	Unable to read & write	56(13.24%)	105(24.82%)	87(20.57%)
	Can read &write	4(0.95%)	10(2.36%)	4(0.95%)
	Primary	9(2.13%)	38(8.98%)	26(6.15%)
	Secondary	5(1.18%)	15(3.55%)	12(2.84%)
	Higer education	14(3.31%)	18(4.26%)	20(4.73%)
Occupation	Farmer	16(3.78%)	30(7.09%)	24(5.67%)
	Merchant	11(2.60%)	37(8.75%)	29(6.86%)
	Daily labourer	1(0.24%)	2(0.47%)	0(0.00%)
	Retired	8(1.89%)	13(3.07%)	10(2.36%)
	Unemployed	38(8.89%)	89(21.04%)	69(16.31%)
	Employed	14(3.31%)	15(3.55%)	17(4.02%)
Multimorbidity	Yes	3(0.71%)	69(16.31%)	123(29.08%)
	No	85(20.09%)	117(27.66%)	26(6.15%)
Polypharmacy	Yes	0(0.00%)	0(0.00%)	52(12.29%)
	No	88(20.80%)	186(43.97%)	97(22.93%)
BP controlled	Yes	54(12.77%)	73(17.26%)	48(11.35%)
	No	34(8.04%)	113(26.71%)	101(23.88%)
Aerobic exercise	Yes	30(7.09%)	45(10.64%)	23(5.44%)
	No	58(13.71%)	141(33.33%)	126(29.79%)
Health insurance	Yes	58(13.71%)	132(31.21%)	115(27.19%)
	No	30(7.09%)	54(12.77%)	34(8.04%)
Study setting	Debre Tabor	22(5.20%)	71(16.78%)	57(13.48%)
	Nefas Mewucha	16(3.78%)	39(9.22%)	45(10.64%)
	Addis Zemen	34(8.04%)	35(8.27%)	31(7.33%)
	Estie	16(3.78%)	41(9.69%)	16(3.78%)
Therapy duration	<5 year	64(15.13%)	132(31.21%)	87(20.57%)
	5+ year	24(5.67%)	54(12.77%)	62(14.66%)

Table 1. Characteristics of study participants

Patterns of Multimorbidity

Type 2 diabetes mellitus was the most common comorbidity coexisting with hypertension, while the least encountered comorbidities included rheumatic fever, Parkinson's disease, fatty liver disease, and others. Others include: rheumatic fever, pulmonary tuberculosis, glaucoma, Parkinson's disease, fatty liver disease, degenerative aortic stenosis, degenerative spondylosis, osteoarthritis, hypercalcemia, bilateral flank pain, schizophrenia, trigeminal neuralgia, and soft tissue injury (Table 2).

Table 2. Morbidities among hypertensive patients

Disorder	Frequency	Percent
Type 2 diabetes mellitus	52	21.40
Dyslipidemia	25	10.29
Dyspepsia	22	9.05
Hypertensive heart disease	21	8.64
Bronchial asthma	21	8.64
Rheumatoid arthritis	19	7.82
Peripheral neuropathy	19	7.82
Congestive heart failure	12	4.94
Ischemic stroke	10	4.12
Ischemic heart disease	7	2.88
Hyperthyroidism	6	2.47
Human immunodeficiency virus	5	2.06
Chronic kidney disease	3	1.23
Type 1 diabetes mellitus	3	1.23
Myalgia	3	1.23
Generalized tonic-clonic	3	1.23
Others (each 1[0.41%])	13	5.3

Others include: Rheumatic fever, Pulmonary tuberculosis, Glaucoma, Parkinson's disease, Faty liver disease, Degenerative aortic stenos, Degenerative spondylosis, Osteoarthritis, Hypercalcemia, Bilateral flank pain, Schizophrenia, Trigeminal neuralgia, and Soft tissue injury.

The most common body system morbidity encountered among the sampled study participants with hypertension was cardiovascular disorder, which accounted for 77 cases (31.69%). In contrast, the least common was special sense disorder, accounting for just 1 case (0.41%) (Fig. 1).

Hypertension combined with type 2 diabetes mellitus was the most commonly observed multimorbidity, followed by hypertension combined with hypertensive heart disease. Conversely, hypertension combined with T2DM and HIV, hypertension combined with hypertensive heart disease and dyspepsia, and other combinations were the least frequently encountered multimorbidity among the study participants. Regarding the number of multimorbidity per participant, 53.9% had none, 35.22% had two, 10.4% had three, and 0.24% each had four and five morbidities. Others (each accounts 0.24%) include: hypertension +degenerative spondylosis, hypertension + type 2 diabetes mellitus + bilateral flank pain, hypertension + type 2 diabetes mellitus+ HIV, hypertension + hypertensive heart disease + dyspepsia, hypertension + type 2 diabetes mellitus + fatty liver disease, hypertension + type 2 diabetes mellitus + ischemic heart disease, hypertension + Parkinson's disease + hypertensive heart disease, hypertension + glaucoma, hypertension + trigeminal neuralgia, hypertension + type 2 diabetes mellitus + chronic kidney disease, hypertension + rheumatoid arthritis + bronchial asthma, hypertension + schizophrenia, hypertension +hypocalcemia, hypertension+ type 2 diabetes mellitus +degenerative aortic stenosis, hypertension + peripheral neuropathy + HIV, hypertension +rheumatoid arthritis + hypertensive heart disease, hypertension + rheumatic fever, hypertension + soft tissue injury, hypertension + hypertensive heart disease + ischemic stroke +bronchial asthma + dyslipidemia, hypertension + osteoarthritis, hypertension + HIV + bronchial asthma, hypertension + hypertensive heart disease + pulmonary tuberculosis, and hypertension + dyslipidemia + congestive heart failure (Table 3).

Table 3. Pattern of multimorbidity among hypertensive patients

Multimorbidity		Frequency	Percent
Hypertension+T2 diabetes mellitus		30	7.09
Hypertension+Hypertensive heart disease		16	3.78
Hypertension+Dyspepsia		12	2.84
Hypertension+Rheumatoid arthritis		12	2.84
Hypertension+Dyslipidemia		11	2.60
Hypertension+Peripheral neuropathy		10	2.36
Hypertension+Bronchial asthma		10	2.36
Hypertension+Ischemic stroke		8	1.89
Hypertension+T2 diabetes mellitus+Dyslipidemia		7	1.65
Hypertension+Congestive heart failure		7	1.65
Hypertension+Hyperthyroidism		6	1.42
Hypertension+Peripheral neuropathy+Dyspepsia		3	0.71
Hypertension+T2 diabetes mellitus+Peripheral neuropathy		3	0.71
Hypertension+T2 diabetes mellitus+Bronchial asthma		3	0.71
Hypertension+Generalized tonic-clonic epilepsy		3	0.71
Hypertension+T1diabetes mellitus		3	0.71
Hypertension+Myalgia		3	0.71
Hypertension+Dyslipidemia+Rheumatoid arthritis		2	0.47
Hypertension+Dyspepsia+Bronchial asthma		2	0.47
Hypertension+Dyslipidemia+Bronchial asthma		2	0.47
Hypertension+Rheumatoid arthritis+T2 diabetes mellitus		2	0.47
Hypertension+Human immunodeficiency virus		2	0.47
Hypertension+Chronic kidney disease		2	0.47
Hypertension+Peripheral neuropathy+Rheumatoid arthritis		2	0.47
Others		23	11.79
Number of multimorbidity	0	228	53.90
	2	149	35.22
	3	44	10.40
	4	1	0.24
	5	1	0.24

Factors Associated with Multimorbidity, Polypharmacy, and MRCI

In the final adjusted binary logistic regression, we found that polypharmacy, patient-level medication regimen complexity, and the study hospital were associated with the presence of multimorbidity.

Polypharmacy was significantly associated with a duration of hypertension treatment five years or more, multimorbidity, and controlled BP in the adjusted binary logistic regression analysis.

We identified several factors associated with medication regimen complexity (MRCI) for inclusion in a multivariate ordinal logistic regression analysis. These factors include the presence of multimorbidity, controlled blood pressure (BP), duration of hypertension treatment five years or more, engaging in aerobic exercise, having health insurance, and an income greater than 6000 Ethiopian birr.

In the adjusted analysis, participants experiencing multimorbidity were fourteen times more likely to have a complex medication regimen (AOR=14.55, 95% CI: 9.00-23.52, P<0.0001). Furthermore, participants with controlled BP, as per the 2021 WHO pharmacologic treatment of hypertension guidelines were 52% less likely to have a complex medication regimen (AOR=0.48, 95% CI: 0.32-0.72, P<0.0001) (Table 4).

Table 4. Univariate, and multivariate logistic analysis of predictors of MRCI, polypharmacy, and multimorbidity

Variable	Variable category	Outcome			COR (95% CI)	AOR (95% CI)
		Patient MRCI[a]				
		≤4	5-8	>8		
Income	<6000 ETB	76	174	140	1	1
	≥6000 ETB	12	12	9	0.52(0.26-1.03)*	0.59(0.28-1.24)
Multimorbidity	No	85	117	26	1	1
	Yes	3	69	123	15.19(9.47-24.37)*	14.55(9.00-23.52)+
Controlled BP	No	34	113	101	1	1
	Yes	54	73	48	0.46(0.32-0.67)+	0.48(0.32-0.72)+
Aerobic exercise	No	58	141	126	1	1
	Yes	30	45	23	0.49(0.32-0.74)+	0.77(0.48-1.23)
Health insurance	No	30	54	34	1	1
	Yes	58	132	115	1.47(0.99-2.19)*	1.53(0.98-2.39)
Hypertension therapy	<5 years	64	132	87	1	1
	≥5 years	24	54	62	1.66(1.13-2.44)+	1.17(0.77-1.78)
		Polypharmacy[b]				
		Absent		Present		
Study hospital	DCSH	126		24	1	1
	NMWH	85		15	0.78(0.38-1.62)*	1.06(0.47-2.38)
	ADZH	94		6	0.39(0.16-0.96)+	0.73(0.28-1.93)
	MEH	66		7	0.56(0.23-1.36)*	1.96(0.67-5.71)
Multimorbidity	No	225		3	1	1
	Yes	146		49	24.49(7.49-80.08)+	25.39(7.48-86.22)+
Hypertension therapy	<5 years	258		25	1	1
	≥5 years	113		27	2.58(1.43-4.66)+	2.12(1.08-4.16)+
Controlled BP	No	206		42	1	1
	Yes	165		10	0.42(0.19-0.92)+	0.42(0.19-0.92)+
		Multimorbidity[b]				
		Absent		Present		
Age	<65 years	152		118	1	1
	≥65 years	76		77	1.31(0.87-1.94)*	1.09(0.64-1.88)
Study hospital	DCSH	59		91	1	1
	NMWH	56		44	0.51(0.30-0.85)+	0.30(0.15-0.59)+
	ADZH	56		44	0.53(0.32-0.88)+	0.80(0.36-1.77)
	MEH	57		16	0.18(0.09-0.35)+	0.16(0.07-0.38)+
Aerobic exercise	No	165		160	1	1
	Yes	63		35	0.56(0.35-0.90)+	0.86(0.41-1.81)
Hypertension therapy	<5 years	169		114	1	1
	≥5 years	59		81	2.01(1.33-3.02)+	1.49(0.85-2.61)
Controlled BP	No	124		124	1	1
	Yes	104		71	0.69(0.47-1.03)+	1.12(0.64-1.95)
Polypharmacy	Absent	225		146	1	1
	Present	3		49	24.49(7.49-80.08)+	5.52(1.49-20.39)+
Patient MRCI	≤4	85		3	1	1
	5-8	117		69	12.38(4.35-35.26)+	19.76(5.87-66.56)+
	>8	26		123	99.34(33.45-295.07)+	120.32(33.12-437.07)+

Abbreviations: AOR, Adjusted odds ratio; COR, Crude odds ratio; ETB, Ethiopian birr; BP, Blood pressure; DCSH, Debre Tabor Comprehensive Specialized Hospital; NMWH, Nefas Mewucha Hospital, ADZH, Addis Zemen Hospital; MEH, Mekane Eyesus Hospital; MRCI, Medication regimen complexity index. Note: Superscript [a] indicates ordinal logistic regression was used while [b] shows binary logistic regression used, * indicates P<0.25 while + indicates P<0.05.

DISCUSSION

In the present study, we found that 46.10% of participants had multimorbidity, 12.29% experienced polypharmacy, and 35.22% had a high patient-level MRCI. Additionally, we identified associations between polypharmacy, patient-level MRCI, and the study hospital with multimorbidity. We also found that the duration of hypertension therapy, controlled blood pressure (BP), and multimorbidity were associated with polypharmacy, while controlled BP and multimorbidity were associated with a high patient-level MRCI.

The magnitude of multimorbidity observed in our study is higher than that reported in studies conducted in Sweden (21.6%),[26] Japan (29.9%),[7] and Hong Kong, China (40.4%),[6] but lower than findings from studies conducted in Bahir Dar, Ethiopia (54.8%),[27] Ghana (55%),[28] India (55%),[29] United Kingdom (73.9%),[5] and another study in China (56.7%).[30]

Concerning polypharmacy, our finding is lower than those findings from studies conducted in Gondar, Ethiopia (46.6%),[31] Ghana (64.8%),[28] Somaliland (71%),[10] Saudi Arabia [(21%), (79%)],[9, 32] and Japan (22.3%).[7]

We found high patient level MRCI in 35.22% of study participants, which is lower than the 57.2% reported in a study conducted in Gondar, Ethiopia. [31]

Participants with polypharmacy (≥5 medications) were more likely to experience multimorbidity compared to those without polypharmacy, a finding supported by a study from Japan.[7] Moreover, participants with medium or high patient level MRCI were more likely to experience multimorbidity compared to those with low patient level MRCI. This finding is in line with the finding from Sweden.[26] While previous studies have identified factors such as age, being male, and uncontrolled BP as predictor of multimorbidity,[5, 6, 27] these factors were not significantly associated with multimorbidity in our study.

We found that participants who had been undergoing hypertension treatment for five years or more were twice as likely to experience polypharmacy. This finding is supported by a study from Saudi Arabia.[9] In addition, we identified that controlled BP and presence of multimorbidity were associated with polypharmacy; however, we did not find comparable studies to further discuss these findings.

We found that those participants with controlled BP were 52% less likely to have Medium or high patient level MRCI compared to those with uncontrolled BP. This finding is similar with the finding of the study from Japan in which those participants with higher MRCI were more

likely to have poor BP control.[13] Additionally, we identified that participants with multimorbidity were 14 times more likely to have medium or high patient level MRCI, in line with a finding from a study in Korea.[33]

The observed differences between findings may be attributed to variations in inclusion criteria, and the sociodemographic distribution of study participants. In our study, we determined multimorbidity, polypharmacy and MRCI as well as associated factors specifically among hypertensive adults, whereas most of previous studies assessed multimorbidity,[30] polypharmacy,[10, 31, 32] and MRCI[31] among participants with any chronic conditions, without requiring a hypertension diagnosis as a mandatory inclusion criterion.

Strength and Limitation of the Study

The present study is the first in the Ethiopian healthcare setting that identified factors associated with multimorbidity, polypharmacy, and MRCI among adult hypertensive patients. The multicentred design enhances the generalizability of the findings to outpatient settings in diverse healthcare facilities. However, this study has a limitation being cross sectional which limits the ability to establish true cause-effect relationship between outcome and identified factors. Moreover, exclusion of inpatient settings restricts the generalizability of the findings to adult hypertensive patients receiving chronic care in outpatient departments only. Although we employed probability sampling techniques, higher proportion of population aged under 65 years included in the study may under represent factors associated with multimorbidity, polypharmacy and MRCI in older populations. Adherence to therapy was not assessed in our study, which might influence results of the study. The relatively small sample size of this multicenter study may limit the generalizability of its findings to similar healthcare settings.

Clinical Implication of the Study Findings

The high prevalence of multimorbidity (46.10%) in adults living with hypertension highlights comprehensive care strategies. Healthcare providers should consider multiple chronic conditions when managing hypertension patients, as multimorbidity is often linked to more complex treatment regimens and adverse health outcomes. Adjusting treatment plans that address multimorbidity may improve patient outcomes and reduce complications. The observed high MRCI (35.22%) in our study indicates the need to simplify medication regimens without compromising treatment effectiveness whenever possible particularly in patients with multimorbidity. Healthcare providers should use strategy like combining medications with

fewer doses or using fixed dose combinations could help optimize treatment for patients with high MRCI.

Polypharmacy (12.29%) was strongly associated with multimorbidity, underscores the importance of regular medication reviews to minimize unnecessary polypharmacy, risk of drug interactions and side effects. Clinicians should monitor patients on multiple medications closely and regularly assess the appropriateness of each medication for patient's current health status.

The association of uncontrolled BP with both polypharmacy and high MRCI suggests that these patients may require more intensive treatment strategies including close monitoring of BP, medication adjustments and identifying the underlying cause. The association between longer duration of hypertension treatment (5 years or more) and polypharmacy emphasizes the need for ongoing assessment of treatment effectiveness over time. Patients with long standing hypertension are more likely to develop additional comorbidities, so healthcare providers should ensure that the long-term hypertension management plan are regularly updated to reflect changes in patient's health and medication needs.

Based on our findings we recommend to strengthen integrated care model that involves physicians, pharmacists and nurses to address multimorbidity and optimize medication use. Emphasize should be given to patient centered care to simplify medication regimens and education on adherence and lifestyle modifications. Health systems should be strengthened to enhance the capacity of primary hospitals to manage hypertension and its comorbidities effectively. Further longitudinal research with a large sample size is needed to explore the long-term outcomes of these findings. Health policy makers should address these challenges in designing guidelines for chronic disease management.

CONCLUSION

The present study showed that a considerable proportion of adults living with hypertension experienced multimorbidity, polypharmacy and patient level MRCI. We identified the primary hospital setting, polypharmacy, and MRCI as associated factors of multimorbidity. Additionally, multimorbidity, and controlled BP were associated with polypharmacy, and MRCI in this study. Furthermore, duration of hypertension treatment was significantly associated with polypharmacy. However, it is important to note that the relatively small sample size of the study may limit the generalizability of these findings. Therefore, hypertension care

should consider multimorbidity, polypharmacy, and MRCI to optimize their care, while recognizing that further research with a large sample size is needed to support these findings.

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Author Contributions

T.S.Y., W.E.M., and A.M.B. designed the study and analyzed data. T.S.Y., Y.S.Y., S.B.D., F.N.D., G.T.A., T.A.M. and A.M.B. performed data entry, wrote, and edited the manuscript. T.S.Y. is the guarantor of this work. All authors reviewed the manuscript and were responsible for all aspects of this work.

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Disclosure

Authors have declared that there is no conflict of interest

Public and Patient Involvement

Patients and the public were not involved in the design of the study.

Patient Consent for Publication

Not required.

Ethical Approval

Ethical approval for the present study was received from Institutional Research and Ethical Review Committee (IRERC), College of Health Sciences, Debre Tabor university, and conducted in accordance with the declaration of Helsinki.

Data Availability Statement

All necessary data are available within the manuscript and/or supporting materials

REFERENCES

1. Mercer S FJ, Moffat K, Fischbacher-Smith D, Sanci L. Multimorbidity: technical series on safer primary care. World Health Organization.2016.
2. Skou ST MF, Fortin M, Guthrie B, Nunes BP, Miranda JJ, Boyd CM, Pati S, Mtenga S, Smith SM. Multimorbidity. Nature Reviews Disease Primers. 2022;8(1):48.
3. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PLoS One. 2014;9(7):e102149.
4. Chowdhury SR, Chandra Das D, Sunna TC, Beyene J, Hossain A. Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. EClinicalMedicine. 2023;57:101860.
5. Hirst JA, Ordonez Mena JM, O'Callaghan CA, Ogburn E, Taylor CJ, Yang Y, et al. Prevalence and factors associated with multimorbidity among primary care patients with decreased renal function. PLoS One. 2021;16(1):e0245131.
6. Wong MC, Wang HH, Cheung CS, Tong EL, Sek AC, Cheung NT, et al. Factors associated with multimorbidity and its link with poor blood pressure control among 223,286 hypertensive patients. Int J Cardiol. 2014;177(1):202-8.
7. Aoki T, Yamamoto Y, Ikenoue T, Onishi Y, Fukuhara S. Multimorbidity patterns in relation to polypharmacy and dosage frequency: a nationwide, cross-sectional study in a Japanese population. Sci Rep. 2018;8(1):3806.
8. WHO. World Health Organization. Medication safety in polypharmacy. Geneva.; 2019.
9. Alsanosi SM MA, Ahmadini HA, Qadhi RS, Ikram N, Felemban AH, Alqashqri HS, Hariri NH, Alhindi YZ, Ayoub N. Polypharmacy among patients with hypertension attending primary healthcare centres. Annals of Medicine and Surgery. 2023 Jun 1;85(6):. 2023;85(6):2545-9.
10. Sidamo T, Deboch A, Abdi M, Debebe F, Dayib K, Balcha Balla T. Assessment of polypharmacy, drug use patterns, and associated factors at the Edna Adan University Hospital, Hargeisa, Somaliland. Journal of tropical medicine. 2022;2022(1):2858987.

11. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. The Annals of pharmacotherapy. 2004;38(9):1369-76.

12. Alves-Conceicao V, Rocha KSS, Silva FVN, Silva ROS, Cerqueira-Santos S, Nunes MAP, et al. Are Clinical Outcomes Associated With Medication Regimen Complexity? A Systematic Review and Meta-analysis. The Annals of pharmacotherapy. 2020;54(4):301-13.

13. Wakai E IK, Kato C, Okuda M. Effect of number of medications and complexity of regimens on medication adherence and blood pressure management in hospitalized patients with hypertension. PLoS One. 2021;16(6):e0252944.

14. Wimmer BC, Johnell K, Fastbom J, Wiese MD, Bell JS. Factors associated with medication regimen complexity in older people: a cross-sectional population-based study. Eur J Clin Pharmacol. 2015;71(9):1099-108.

15. Nguyen H, Manolova G, Daskalopoulou C, Vitoratou S, Prince M, Prina AM. Prevalence of multimorbidity in community settings: A systematic review and meta-analysis of observational studies. Journal of comorbidity. 2019 Aug 20;9:2235042X19870934.

16. Fortin M, Haggerty J, Almirall J, Bouhali T, Sasseville M, Lemieux M. Lifestyle factors and multimorbidity: a cross-sectional study. BMC public health. 2014 Dec;14:1-8.

17. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, Glynn L, Muth C, Valderas JM. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PloS one. 2014 Jul 21;9(7):e102149.

18. Low LL, Kwan YH, Ko MS, Yeam CT, Lee VS, Tan WB, Thumboo J. Epidemiologic characteristics of multimorbidity and sociodemographic factors associated with multimorbidity in a rapidly aging Asian country. JAMA network open. 2019 Nov 1;2(11):e1915245-.

19. Balkhi B, AlQahtani N, Alwhaibi M, Alshammari TM, Alhawassi TM, Mahmoud MA, Almetwazi M, Ata S, Basyoni M, Aljadhey H. Prevalence and factors associated with polypharmacy use among adult patients in Saudi Arabia. Journal of Patient Safety. 2021 Dec 1;17(8):e1119-24.

20. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The lancet. 2007 Oct 20;370(9596):1453-7.

21. Yeh A, Shah-Manek B, Lor KB. Medication Regimen Complexity and A1C Goal Attainment in Underserved Adults With Type 2 Diabetes. The Annals of pharmacotherapy. 2017;51(2):111-7.

22. Organization WH. Guideline for the pharmacological treatment of hypertension in adults. 2021.
23. Piercy KL, Troiano RP. Physical Activity Guidelines for Americans From the US Department of Health and Human Services. Circ Cardiovasc Qual Outcomes. 2018;11(11):e005263.
24. US Department of Health and Human Services. Health, United States, 2010: with special feature on death and dying. Hyattsville (MD): Centers for Disease Control and Prevention, National Center for Health Statistics; 2011. Appendix, definition of "condition," p. 486–7. Available at: https://www.cdc.gov/nchs/data/hus/hus10.pdf. Accessed on: January 24, 2025.
25. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.
26. Forslund T, Carlsson AC, Ljunggren G, Arnlov J, Wachtler C. Patterns of multimorbidity and pharmacotherapy: a total population cross-sectional study. Fam Pract. 2021;38(2):132-40.
27. Eyowas FA SM, Alemu S, Pati S, Getahun FA. Magnitude, pattern and correlates of multimorbidity among patients attending chronic outpatient medical care in Bahir Dar, northwest Ethiopia: the application of latent class analysis model. PLoS One. 2022;17(4):e0267208.
28. Kwakye AO KI, Oppong KG. Polypharmacy and its associated factors among patients with co-morbid hypertension and diabetes in a municipal hospital in Ghana. . Scientific African. 2024;23:e02028.
29. Pati S, Sinha R, Panda M, Puri P, Pati S. Profile of multimorbidity in outpatients attending public healthcare settings: A descriptive cross-sectional study from Odisha, India. J Family Med Prim Care. 2021;10(8):2900-14.
30. Zhong Y QG, Xi H, Cai D, Wang Y, Wang T, Gao Y. Prevalence, patterns of multimorbidity and associations with health care utilization among middle-aged and older people in China. . BMC public health.23(1):537.

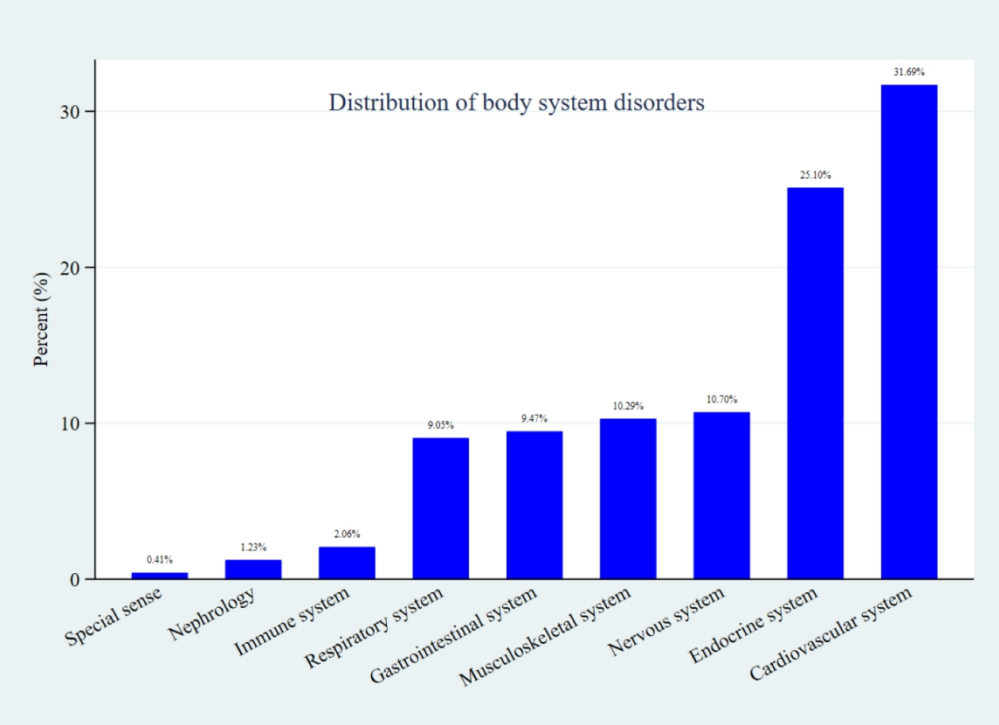
31. Kassaw AT, Sendekie AK, Minyihun A, Gebresillassie BM. Medication regimen complexity and its impact on medication adherence in patients with multimorbidity at a comprehensive specialized hospital in Ethiopia. Frontiers in medicine. 2024;11:1369569.

32. Alwhaibi M, AlRuthia Y, Alhawassi TM, Almalag H, Alsalloum H, Balkhi B. Polypharmacy and comorbidities among ambulatory cancer patients: A cross-sectional retrospective study. Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners. 2020;26(5):1052-9.

33. Ji E, Ahn S, Choi J-Y, Kim C-H, Kim K-i. Effect of multimorbidity on hypertension management. Scientific Reports. 2023;13(1):18764.

Figure legend

Fig 1. Percentage distribution of body system disorders



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Clinical Factors Associated with Multimorbidity, Polypharmacy, and Medication Regimen Complexity among Adults with Hypertension: A Multicenter Cross-Sectional Study

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ABSTRACT

Objectives: Factors associated with multimorbidity, polypharmacy, and medication regimen complexity (MRCI) may vary across countries. However, such data are lacking in the present study setting. This study aimed to identify factors associated with multimorbidity, polypharmacy, and MRCI among adults living with hypertension in public hospitals of South Gondar Zone.

Design: Multicentered cross sectional design

Setting: Public hospitals of Comprehensive Specialized and primary hospitals, Ethiopia

Participants: Adults living with hypertension who had follow up visits at outpatient clinics and were selected by systematic random sampling from December 1, 2021, to February 30, 2022.

Primary and Secondary Outcome Measures: Medication regimen complexity was assessed using a 65-items medication regimen complexity tool. Sociodemographic data were collected through interview, while polypharmacy and clinical characteristics were documented using checklist. Data were entered into SPSS version26, and analyzed using STATA 17. Binary logistic regression model was used to determine AOR of factors associated with multimorbidity and polypharmacy. For factors influencing MRCI, an ordinal logistic regression used.

Results: We found participants from Nefas Mewucha hospital (AOR=0.3, 95% CI:0.15-0.59) and Mekane Eyesus hospital (AOR=0.17, 95% CI: 0.07-0.38), compared to Debre Tabor Comprehensive Specialized Hospital, polypharmacy (AOR=5.52, 95% CI: 1.49-20.39), medium (AOR=19.76, 95% CI: 5.86-66.56), and high MRCI (AOR=120.32, 95% CI: 33.12-437.07) were associated with multimorbidity. Multimorbidity (AOR=25.4, 95% CI: 7.48-86.23), controlled blood pressure (AOR=0.43, 95% CI: 0.19-0.92), and duration of hypertension therapy ≥5 years (AOR=2.12, 95% CI: 1.08-4.16) were associated with polypharmacy. Whereas, controlled BP (AOR=0.48, 95% CI: 0.32-0.72), and multimorbidity (AOR=14.55, 95% CI: 9.00-23.52) were significantly associated with high MRCI. The prevalence of multimorbidity, high MRCI, and polypharmacy was found in 46.1%, 35.22%, and 12.29% of participants, respectively.

Conclusion: A considerable proportion of participants with hypertension experienced multimorbidity, polypharmacy, and high medication complexity. Polypharmacy, primary hospital setting, and high MRCI were independent variables associated with multimorbidity. On the other hand, multimorbidity, and controlled BP were associated with polypharmacy and MRCI. Hypertension care should consider multimorbidity, polypharmacy, and medication complexity.

Strength and Limitation of the Study

- This study used objective measures to assess multimorbidity, polypharmacy and medication regimen complexity strengthens the methodological rigor.
- Multicentred design nature of the study is considered as an additional strength of the present study.
- However, this study has a limitation being cross sectional that did not establish a true cause-effect relationship between outcome and independent factors.
- Moreover, relatively small sample size and exclusion of inpatient settings restricts the findings generalizability to adult living with hypertension who have chronic follow up at outpatient departments only
- Under representation of older adults and medication adherence were not adequately addressed, potentially affecting study results.

INTRODUCTION

Multimorbidity is defined as the co-occurrence of two or more chronic health conditions in an individual.[1, 2] It has become a major public health problem, with prevalence ranging from 12.9% to 95.1%.[3, 4] Multimorbidity has been linked with premature death, poor quality of life, increased healthcare utilization, advanced age, higher body mass index, reduced kidney function, lower socioeconomic status, birth gender, suboptimal blood pressure control and polypharmacy.[2, 3, 5-7]

The definition of polypharmacy has not been standardized; however, it is commonly defined in the literature as the routine use of five or more concurrent medications. This includes over-the-counter drugs, prescription medications, traditional remedies, and complementary medicines.[8] The prevalence of polypharmacy has been increased worldwide and is associated with factors such as duration of treatment, comorbidities, chronic illness, and advanced age.[9, 10]

Medication regimen complexity includes factors such as dosage forms, dosing frequency, and additional instructions related to medications. It accounts for both prescription and over-the-counter medications to calculate medication regimen complexity index.[11] This complexity is associated with clinical outcomes such as hospitalization, hospital readmission, medication adherence, blood pressure, age, and comorbidity. [12-14]

Literature has shown that the prevalence of multimorbidity varies across countries. Lifestyle and demographic factors contribute to the development of multimorbidity in diverse populations.[15] Unhealthy lifestyles[16] and lowerr socio-economic status[17, 18] have been associated with multimorbidity, which in turn contributes to polypharmacy. A study conducted in Saudi Arabia found that non-Saudi nationalities was associated with polypharmacy compared to Saudi nationals.[19] These suggest that factors associated with multimorbidity, polypharmacy and medication regimen complexity index may vary across countries.

There is limited data regarding factors associated with multimorbidity, polypharmacy, and medication regimen complexity among adults with hypertension in outpatient settings in Ethiopia. Therefore, the purpose of the present study was to identify factors associated with polypharmacy, medication regimen complexity and multimorbidity among adults with hypertension attending the outpatient follow-up department in the South Gondar Zone.

METHODS

Study Area, Design, and Period

The study was conducted in one purposively, and three randomly chosen public hospitals in South Gondar Zone. According to 2007 census which was conducted by Central Statistical Agency (CSA), Ethiopia, this Zone has a total population of 2 051 738. Based on the 2011 CSA population projection, the South Gondar Zone has a total population of 2 239 077 (1 103 490 women and 1 135 587 men). An institution-based multicentered cross-sectional design was used, and data were collected from December 1, 2021, to February 30, 2022.

Study Participants

The source population embraced all adults with hypertension attending follow-up appointments at outpatient departments. The study findings were reported according to the guidelines for reporting observational studies, Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[20]

Eligibility Criteria

Inclusion criteria:

- Adults aged 18 years and above
- Receiving antihypertensive medications for at least six months
- Following up at outpatient departments of the study hospitals
- Willing to participate

Exclusion criteria:

- Cognitive impairment
- Hearing problems
- Admitted to inpatient wards

Sample Size Determination and Sampling Technique

There were no previous studies that we used to determine the sample size of the present study. Therefore, we used a single population proportion formula considering a 95% confidence interval, and a prevalence of 50% for outcomes. Then, we reached, a sample size of 384. Accounting for a 10% non-response rate, the final sample size was 423. Debre Tabor

Comprehensive Specialized Hospital, being the only specialized hospital in the zone, was selected purposively, while Addis Zemen Hospital, Nefas Mewucha Hospital, and Mekane Eyesus Hospital were chosen randomly. Proportional allocation and a systematic random sampling technique were applied, with a sampling interval of four; hence, every fourth participant was included until the desired sample size was achieved.

Study Variables

Dependent Variables: Multimorbidity, Medication regimen complexity index (MRCI), Polypharmacy

Independent Variables: Age, gender, residence, marital status, income, blood pressure status, educational status, number of medications, duration of treatment, health insurance, aerobic exercise

Operational Definitions

Medication regimen complexity: comprised the dosage form, dosing interval, and additional instruction aspect to calculate the patient medication burden. It is quantified using 65 items Medication Regimen Complexity Index (MRCI): then, categorized into three levels: low (≤4), medium (5-8), and high (>8) MRCI scores.[21]

Multimorbidity: Co-existence of two or more chronic conditions in an individual.[1, 2]

Controlled blood pressure: Defined as BP <140/90 mmHg for individuals with hypertension without comorbidity, or BP <130/90 mmHg for those with diabetes mellitus, chronic kidney disease, or known cardiovascular diseases.[22]

Regular aerobic exercise: Regular Aerobic Exercise: Participants engaged in activities like brisk walking, recreational swimming, cycling, and tennis for at least 150 minutes per week.[23]

Polypharmacy: Routine use of five or more medications by a patient.[8] Fixed-dose combination (FDC) were accounted for in the methodology although no FDCs were identified in the medication regimens of participants. FDCs would have been counted as a single medication in the patient's regimen, regardless of the number of active ingredients, in cases where FDCs were present. This strategy helps to avoid overestimating the medication burden while considering the contribution of such combinations to the regimen complexity.

Chronic health condition: A chronic health condition is defined as a health problem that cannot be cured once acquired or one that persists for at least three months.[24]

Data Collection Procedures

A questionnaire was developed and translated into Amharic, and back-translated into English for consistency. Interviews were conducted to gather socio-demographic and clinical characteristics not found in patient charts, such as monthly income, regular aerobic exercise, over-the-counter medications, marital status, educational level, and health insurance. A checklist was used to collect data on blood pressure level, dosage forms, dose frequency, number of medications, and additional administration instructions. The 65-item MRCI tool, including sections on dosage forms, dose frequency, and additional instructions with corresponding scores, was used to determine the MRCI.[11]

The average of two BP readings taken two minutes apart during a visit was used to determine BP status.[25]

Data Quality Control

To ensure data quality, we conducted a pretest, trained data collectors, and checked the filled questionnaires and checklists for completeness and correctness daily. The training covered the study objectives, methods, and ethical concerns.

Statistical Analysis

Data were entered and analyzed using Stata 17. We checked that no multicollinearity (variance inflation factor less than two). We checked the reliability of the 65 items MRCI tool for our study settings and found 0.7 value of Cronbach's alpha indicates the reliability of the tool. Categorical variables were described using frequencies, while means and standard deviation (SD) were used for continuous variables. After checking assumptions, ordinal for MRCI, and binary logistic regression for multimorbidity, and polypharmacy were employed to identify predictors associated with MRCI and multimorbidity, respectively. Variables with a p-value of less than 0.25 in univariate analysis were included in the multivariate analysis, and statistical significance was set at a p-value of <0.05.

Ethical Consideration

The present study was approved from Institutional Research and Ethical Review Committee (IRERC), College of Health Sciences, Debre Tabor university (Ref: CHS/DTU1421//2021), and conducted in accordance with the guidelines and standards of the declaration of Helsinki. IRERC gave us approval to receive verbal informed consent as the study does not have any known potential risk to participants. Therefore, Verbal consent was obtained from study participants after explaining the study's methods, and purpose. personal identifiers were anonymised to keep the participants' confidentiality.

Public and Patient Involvement

Patients and the public were not involved in the design of this study.

RESULTS

Socio-Demographic and Clinical Characteristics of Study Participants

Four hundred twenty-three participants were included in the analysis of the study. The participants' age ranged from 23 to 90 years with mean ± standard deviation (SD) of 58.48±12.96 years, and majority of participants (59.81%) were female. The number of medications taken by each participant ranges from one to seven with mean ± SD of 2.65± 1.35.

Multimorbidity and polypharmacy were found in 46.10% and 12.29% of participants, respectively. Hypertension specific MRCI was low in 56.26%, medium in 40.43%, and high in 3.31% of participants. Concerning patient level MRCI, we found low in 20.80%, medium in 43.97%, and high in 35.22% (Table 1).

Variable	Category of variable	Patient level Medication regimen complexity		
		Low	Medium	High
Sex	Female	55(13.00%)	114(26.95%)	84(19.86%)
	Male	33(7.80%)	72(17.02%)	65(15.37%)
Age in year	<65	65(15.37%)	109(25.77%)	96(22.70%)
	65+	23(5.44%)	77(18.20%)	53(12.53%)
Marital status	Single	4(0.95%)	15(3.55%)	8(1.89%)
	Married	60(14.18%)	123(29.08%)	104(24.59%)
	Divorced	7(1.65%)	19(4.49%)	6(1.42%)
	Widowed	17(4.02%)	29(6.86%)	31(7.33%)
Residence	Urban	55(13.00%)	114(26.95%)	98(23.17%)
	Rural	33(7.80%)	72(17.02%)	51(12.06%)
Income in Ethiopian birr	<6000	76(17.97%)	174(41.13%)	140(33.10%)
	6000+	12(2.84%)	12(2.84%)	9(2.13%)
Religion	Christian	82(19.39%)	176(41.61%)	137(32.39%)
	Muslim	6(1.42%)	10(2.36%)	12(2.84%)
Education	Unable to read & write	56(13.24%)	105(24.82%)	87(20.57%)
	Can read &write	4(0.95%)	10(2.36%)	4(0.95%)
	Primary	9(2.13%)	38(8.98%)	26(6.15%)
	Secondary	5(1.18%)	15(3.55%)	12(2.84%)
	Higer education	14(3.31%)	18(4.26%)	20(4.73%)
Occupation	Farmer	16(3.78%)	30(7.09%)	24(5.67%)
	Merchant	11(2.60%)	37(8.75%)	29(6.86%)
	Daily labourer	1(0.24%)	2(0.47%)	0(0.00%)
	Retired	8(1.89%)	13(3.07%)	10(2.36%)
	Unemployed	38(8.89%)	89(21.04%)	69(16.31%)
	Employed	14(3.31%)	15(3.55%)	17(4.02%)
Multimorbidity	Yes	3(0.71%)	69(16.31%)	123(29.08%)
	No	85(20.09%)	117(27.66%)	26(6.15%)
Polypharmacy	Yes	0(0.00%)	0(0.00%)	52(12.29%)
	No	88(20.80%)	186(43.97%)	97(22.93%)
BP controlled	Yes	54(12.77%)	73(17.26%)	48(11.35%)
	No	34(8.04%)	113(26.71%)	101(23.88%)
Aerobic exercise	Yes	30(7.09%)	45(10.64%)	23(5.44%)
	No	58(13.71%)	141(33.33%)	126(29.79%)
Health insurance	Yes	58(13.71%)	132(31.21%)	115(27.19%)
	No	30(7.09%)	54(12.77%)	34(8.04%)
Study setting	Debre Tabor	22(5.20%)	71(16.78%)	57(13.48%)
	Nefas Mewucha	16(3.78%)	39(9.22%)	45(10.64%)
	Addis Zemen	34(8.04%)	35(8.27%)	31(7.33%)
	Estie	16(3.78%)	41(9.69%)	16(3.78%)
Therapy duration	<5 year	64(15.13%)	132(31.21%)	87(20.57%)
	5+ year	24(5.67%)	54(12.77%)	62(14.66%)

Table 1. Characteristics of study participants

Patterns of Multimorbidity

Type 2 diabetes mellitus was the most common comorbidity coexisting with hypertension, while the least encountered comorbidities included rheumatic fever, Parkinson's disease, fatty liver disease, and others. Others include: rheumatic fever, pulmonary tuberculosis, glaucoma, Parkinson's disease, fatty liver disease, degenerative aortic stenosis, degenerative spondylosis, osteoarthritis, hypercalcemia, bilateral flank pain, schizophrenia, trigeminal neuralgia, and soft tissue injury (Table 2).

Table 2. Morbidities among hypertensive patients

Disorder	Frequency	Percent
Type 2 diabetes mellitus	52	21.40
Dyslipidemia	25	10.29
Dyspepsia	22	9.05
Hypertensive heart disease	21	8.64
Bronchial asthma	21	8.64
Rheumatoid arthritis	19	7.82
Peripheral neuropathy	19	7.82
Congestive heart failure	12	4.94
Ischemic stroke	10	4.12
Ischemic heart disease	7	2.88
Hyperthyroidism	6	2.47
Human immunodeficiency virus	5	2.06
Chronic kidney disease	3	1.23
Type 1 diabetes mellitus	3	1.23
Myalgia	3	1.23
Generalized tonic-clonic	3	1.23
Others (each 1[0.41%])	13	5.3

Others include: Rheumatic fever, Pulmonary tuberculosis, Glaucoma, Parkinson's disease, Faty liver disease, Degenerative aortic stenos, Degenerative spondylosis, Osteoarthritis, Hypercalcemia, Bilateral flank pain, Schizophrenia, Trigeminal neuralgia, and Soft tissue injury.

The most common body system morbidity encountered among the sampled study participants with hypertension was cardiovascular disorder, which accounted for 77 cases (31.69%). In contrast, the least common was special sense disorder, accounting for just 1 case (0.41%) (Fig. 1).

Hypertension combined with type 2 diabetes mellitus was the most commonly observed multimorbidity, followed by hypertension combined with hypertensive heart disease. Conversely, hypertension combined with T2DM and HIV, hypertension combined with hypertensive heart disease and dyspepsia, and other combinations were the least frequently encountered multimorbidity among the study participants. Regarding the number of multimorbidity per participant, 53.9% had none, 35.22% had two, 10.4% had three, and 0.24% each had four and five morbidities. Others (each accounts 0.24%) include: hypertension +degenerative spondylosis, hypertension + type 2 diabetes mellitus + bilateral flank pain, hypertension + type 2 diabetes mellitus+ HIV, hypertension + hypertensive heart disease + dyspepsia, hypertension + type 2 diabetes mellitus + fatty liver disease, hypertension + type 2 diabetes mellitus + ischemic heart disease, hypertension + Parkinson's disease + hypertensive heart disease, hypertension + glaucoma, hypertension + trigeminal neuralgia, hypertension + type 2 diabetes mellitus + chronic kidney disease, hypertension + rheumatoid arthritis + bronchial asthma, hypertension + schizophrenia, hypertension +hypocalcemia, hypertension+ type 2 diabetes mellitus +degenerative aortic stenosis, hypertension + peripheral neuropathy + HIV, hypertension +rheumatoid arthritis + hypertensive heart disease, hypertension + rheumatic fever, hypertension + soft tissue injury, hypertension + hypertensive heart disease + ischemic stroke +bronchial asthma + dyslipidemia, hypertension + osteoarthritis, hypertension + HIV + bronchial asthma, hypertension + hypertensive heart disease + pulmonary tuberculosis, and hypertension + dyslipidemia + congestive heart failure (Table 3).

Table 3. Pattern of multimorbidity among hypertensive patients

Multimorbidity		Frequency	Percent
Hypertension+T2 diabetes mellitus		30	7.09
Hypertension+Hypertensive heart disease		16	3.78
Hypertension+Dyspepsia		12	2.84
Hypertension+Rheumatoid arthritis		12	2.84
Hypertension+Dyslipidemia		11	2.60
Hypertension+Peripheral neuropathy		10	2.36
Hypertension+Bronchial asthma		10	2.36
Hypertension+Ischemic stroke		8	1.89
Hypertension+T2 diabetes mellitus+Dyslipidemia		7	1.65
Hypertension+Congestive heart failure		7	1.65
Hypertension+Hyperthyroidism		6	1.42
Hypertension+Peripheral neuropathy+Dyspepsia		3	0.71
Hypertension+T2 diabetes mellitus+Peripheral neuropathy		3	0.71
Hypertension+T2 diabetes mellitus+Bronchial asthma		3	0.71
Hypertension+Generalized tonic-clonic epilepsy		3	0.71
Hypertension+T1diabetes mellitus		3	0.71
Hypertension+Myalgia		3	0.71
Hypertension+Dyslipidemia+Rheumatoid arthritis		2	0.47
Hypertension+Dyspepsia+Bronchial asthma		2	0.47
Hypertension+Dyslipidemia+Bronchial asthma		2	0.47
Hypertension+Rheumatoid arthritis+T2 diabetes mellitus		2	0.47
Hypertension+Human immunodeficiency virus		2	0.47
Hypertension+Chronic kidney disease		2	0.47
Hypertension+Peripheral neuropathy+Rheumatoid arthritis		2	0.47
Others		23	11.79
Number of multimorbidity	0	228	53.90
	2	149	35.22
	3	44	10.40
	4	1	0.24
	5	1	0.24

Factors Associated with Multimorbidity, Polypharmacy, and MRCI

In the final adjusted binary logistic regression, we found that polypharmacy, patient-level medication regimen complexity, and the study hospital were associated with the presence of multimorbidity.

Polypharmacy was significantly associated with a duration of hypertension treatment five years or more, multimorbidity, and controlled BP in the adjusted binary logistic regression analysis.

We identified several factors associated with medication regimen complexity (MRCI) for inclusion in a multivariate ordinal logistic regression analysis. These factors include the presence of multimorbidity, controlled blood pressure (BP), duration of hypertension treatment five years or more, engaging in aerobic exercise, having health insurance, and an income greater than 6000 Ethiopian birr.

In the adjusted analysis, participants experiencing multimorbidity were fourteen times more likely to have a complex medication regimen (AOR=14.55, 95% CI: 9.00-23.52, P<0.0001). Furthermore, participants with controlled BP, as per the 2021 WHO pharmacologic treatment of hypertension guidelines were 52% less likely to have a complex medication regimen (AOR=0.48, 95% CI: 0.32-0.72, P<0.0001) (Table 4).

Table 4. Univariate, and multivariate logistic analysis of predictors of MRCI, polypharmacy, and multimorbidity

Variable	Variable category	Outcome			COR (95% CI)	AOR (95% CI)
		Patient MRCI[a]				
		≤4	5-8	>8		
Income	<6000 ETB	76	174	140	1	1
	≥6000 ETB	12	12	9	0.52(0.26-1.03)*	0.59(0.28-1.24)
Multimorbidity	No	85	117	26	1	1
	Yes	3	69	123	15.19(9.47-24.37)*	14.55(9.00-23.52)+
Controlled BP	No	34	113	101	1	1
	Yes	54	73	48	0.46(0.32-0.67)+	0.48(0.32-0.72)+
Aerobic exercise	No	58	141	126	1	1
	Yes	30	45	23	0.49(0.32-0.74)+	0.77(0.48-1.23)
Health insurance	No	30	54	34	1	1
	Yes	58	132	115	1.47(0.99-2.19)*	1.53(0.98-2.39)
Hypertension therapy	<5 years	64	132	87	1	1
	≥5 years	24	54	62	1.66(1.13-2.44)+	1.17(0.77-1.78)
		Polypharmacy[b]				
		Absent		Present		
Study hospital	DCSH	126		24	1	1
	NMWH	85		15	0.78(0.38-1.62)*	1.06(0.47-2.38)
	ADZH	94		6	0.39(0.16-0.96)+	0.73(0.28-1.93)
	MEH	66		7	0.56(0.23-1.36)*	1.96(0.67-5.71)
Multimorbidity	No	225		3	1	1
	Yes	146		49	24.49(7.49-80.08)+	25.39(7.48-86.22)+
Hypertension therapy	<5 years	258		25	1	1
	≥5 years	113		27	2.58(1.43-4.66)+	2.12(1.08-4.16)+
Controlled BP	No	206		42	1	1
	Yes	165		10	0.42(0.19-0.92)+	0.42(0.19-0.92)+
		Multimorbidity[b]				
		Absent		Present		
Age	<65 years	152		118	1	1
	≥65 years	76		77	1.31(0.87-1.94)*	1.09(0.64-1.88)
Study hospital	DCSH	59		91	1	1
	NMWH	56		44	0.51(0.30-0.85)+	0.30(0.15-0.59)+
	ADZH	56		44	0.53(0.32-0.88)+	0.80(0.36-1.77)
	MEH	57		16	0.18(0.09-0.35)+	0.16(0.07-0.38)+
Aerobic exercise	No	165		160	1	1
	Yes	63		35	0.56(0.35-0.90)+	0.86(0.41-1.81)
Hypertension therapy	<5 years	169		114	1	1
	≥5 years	59		81	2.01(1.33-3.02)+	1.49(0.85-2.61)
Controlled BP	No	124		124	1	1
	Yes	104		71	0.69(0.47-1.03)+	1.12(0.64-1.95)
Polypharmacy	Absent	225		146	1	1
	Present	3		49	24.49(7.49-80.08)+	5.52(1.49-20.39)+
Patient MRCI	≤4	85		3	1	1
	5-8	117		69	12.38(4.35-35.26)+	19.76(5.87-66.56)+
	>8	26		123	99.34(33.45-295.07)+	120.32(33.12-437.07)+

Abbreviations: AOR, Adjusted odds ratio; COR, Crude odds ratio; ETB, Ethiopian birr; BP, Blood pressure; DCSH, Debre Tabor Comprehensive Specialized Hospital; NMWH, Nefas Mewucha Hospital, ADZH, Addis Zemen Hospital; MEH, Mekane Eyesus Hospital; MRCI, Medication regimen complexity index. Note: Superscript [a] indicates ordinal logistic regression was used while [b] shows binary logistic regression used, * indicates P<0.25 while + indicates P<0.05.

DISCUSSION

In the present study, we found that 46.10% of participants had multimorbidity, 12.29% experienced polypharmacy, and 35.22% had a high patient-level MRCI. Additionally, we identified associations between polypharmacy, patient-level MRCI, and the study hospital with multimorbidity. We also found that the duration of hypertension therapy, controlled blood pressure (BP), and multimorbidity were associated with polypharmacy, while controlled BP and multimorbidity were associated with a high patient-level MRCI.

The magnitude of multimorbidity observed in our study is higher than that reported in studies conducted in Sweden (21.6%),[26] Japan (29.9%),[7] and Hong Kong, China (40.4%),[6] but lower than findings from studies conducted in Bahir Dar, Ethiopia (54.8%),[27] Ghana (55%),[28] India (55%),[29] United Kingdom (73.9%),[5] and another study in China (56.7%).[30]

Concerning polypharmacy, our finding is lower than those findings from studies conducted in Gondar, Ethiopia (46.6%),[31] Ghana (64.8%),[28] Somaliland (71%),[10] Saudi Arabia [(21%), (79%)],[9, 32] and Japan (22.3%).[7]

We found high patient level MRCI in 35.22% of study participants, which is lower than the 57.2% reported in a study conducted in Gondar, Ethiopia. [31]

Participants with polypharmacy (≥5 medications) were more likely to experience multimorbidity compared to those without polypharmacy, a finding supported by a study from Japan.[7] Moreover, participants with medium or high patient level MRCI were more likely to experience multimorbidity compared to those with low patient level MRCI. This finding is in line with the finding from Sweden.[26] Study participants who had follow up visits at primary care hospitals were less likely to experience multimorbidity compared to those who had follow up visits at comprehensive specialized Hospital. This finding is supported by a study conducted in India, which reported that multimorbidity varied between different healthcare settings, such as public versus private care setting.[33] Additionally, a study conducted in Sri Lank found that higher multimorbidity in tertiary care than in primary setting although the difference was not statistically significant.[34] While previous studies have identified factors such as age, being male, and uncontrolled BP that associated with multimorbidity,[5, 6, 27] these factors were not significantly associated with multimorbidity in our study.

We found that participants who had been undergoing hypertension treatment for five years or more were twice as likely to experience polypharmacy. This finding is supported by a study

from Saudi Arabia.[9] In addition, we identified that controlled BP and presence of multimorbidity were associated with polypharmacy; however, we did not find comparable studies to further discuss these findings.

We found that those participants with controlled BP were 52% less likely to have Medium or high patient level MRCI compared to those with uncontrolled BP. This finding is similar with the finding of the study from Japan in which those participants with higher MRCI were more likely to have poor BP control.[13] Additionally, we identified that participants with multimorbidity were 14 times more likely to have medium or high patient level MRCI, in line with a finding from a study in Korea.[35]

The observed differences between findings may be attributed to variations in inclusion criteria, and the sociodemographic distribution of study participants. In our study, we determined multimorbidity, polypharmacy and MRCI as well as associated factors specifically among hypertensive adults, whereas most of previous studies assessed multimorbidity,[30] polypharmacy,[10, 31, 32] and MRCI[31] among participants with any chronic conditions, without requiring a hypertension diagnosis as a mandatory inclusion criterion.

Strength and Limitation of the Study

The present study is the first in the Ethiopian healthcare setting that identified factors associated with multimorbidity, polypharmacy, and MRCI among adult hypertensive patients. The multicentred design enhances the generalizability of the findings to outpatient settings in diverse healthcare facilities. However, this study has a limitation being cross sectional which limits the ability to establish true cause-effect relationship between outcome and identified factors. Moreover, exclusion of inpatient settings restricts the generalizability of the findings to adult hypertensive patients receiving chronic care in outpatient departments only. Although we employed probability sampling techniques, higher proportion of population aged under 65 years included in the study may under represent factors associated with multimorbidity, polypharmacy and MRCI in older populations. Adherence to therapy was not assessed in our study, which might influence results of the study. The relatively small sample size of this multicenter study may limit the generalizability of its findings to similar healthcare settings.

Clinical Implication of the Study Findings

The high prevalence of multimorbidity (46.10%) in adults living with hypertension highlights comprehensive care strategies. Healthcare providers should consider multiple chronic

conditions when managing hypertension patients, as multimorbidity is often linked to more complex treatment regimens and adverse health outcomes. Adjusting treatment plans that address multimorbidity may improve patient outcomes and reduce complications. The observed high MRCI (35.22%) in our study indicates the need to simplify medication regimens without compromising treatment effectiveness whenever possible particularly in patients with multimorbidity. Healthcare providers should use strategy like combining medications with fewer doses or using fixed dose combinations could help optimize treatment for patients with high MRCI.

Polypharmacy (12.29%) was strongly associated with multimorbidity, underscores the importance of regular medication reviews to minimize unnecessary polypharmacy, risk of drug interactions and side effects. Clinicians should monitor patients on multiple medications closely and regularly assess the appropriateness of each medication for patient's current health status.

The association of uncontrolled BP with both polypharmacy and high MRCI suggests that these patients may require more intensive treatment strategies including close monitoring of BP, medication adjustments and identifying the underlying cause. The association between longer duration of hypertension treatment (5 years or more) and polypharmacy emphasizes the need for ongoing assessment of treatment effectiveness over time. Patients with long standing hypertension are more likely to develop additional comorbidities, so healthcare providers should ensure that the long-term hypertension management plan are regularly updated to reflect changes in patient's health and medication needs.

Based on our findings we recommend to strengthen integrated care model that involves physicians, pharmacists and nurses to address multimorbidity and optimize medication use. Emphasize should be given to patient centered care to simplify medication regimens and education on adherence and lifestyle modifications. Health systems should be strengthened to enhance the capacity of primary hospitals to manage hypertension and its comorbidities effectively. Further longitudinal research with a large sample size is needed to explore the long-term outcomes of these findings. Health policy makers should address these challenges in designing guidelines for chronic disease management.

CONCLUSION

The present study showed that a considerable proportion of adults living with hypertension experienced multimorbidity, polypharmacy and patient level MRCI. We identified the primary hospital setting, polypharmacy, and MRCI as associated factors of multimorbidity. Additionally, multimorbidity, and controlled BP were associated with polypharmacy, and MRCI in this study. Furthermore, duration of hypertension treatment was significantly associated with polypharmacy. However, it is important to note that the relatively small sample size of the study may limit the generalizability of these findings. Therefore, hypertension care should consider multimorbidity, polypharmacy, and MRCI to optimize their care, while recognizing that further research with a large sample size is needed to support these findings.

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Author Contributions

T.S.Y., W.E.M., and A.M.B. designed the study and analyzed data. T.S.Y., Y.S.Y., S.B.D., F.N.D., G.T.A., T.A.M. and A.M.B. performed data entry, wrote, and edited the manuscript. T.S.Y. is the guarantor of this work. All authors reviewed the manuscript and were responsible for all aspects of this work.

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Disclosure

Authors have declared that there is no conflict of interest

Public and Patient Involvement

Patients and the public were not involved in the design of the study.

Patient Consent for Publication

Not required.

Ethical Approval

Ethical approval for the present study was received from Institutional Research and Ethical Review Committee (IRERC), College of Health Sciences, Debre Tabor university, and conducted in accordance with the declaration of Helsinki.

Data Availability Statement

All necessary data are available within the manuscript and/or supporting materials

REFERENCES

1. Mercer S FJ, Moffat K, Fischbacher-Smith D, Sanci L. Multimorbidity: technical series on safer primary care. World Health Organization.2016.
2. Skou ST MF, Fortin M, Guthrie B, Nunes BP, Miranda JJ, Boyd CM, Pati S, Mtenga S, Smith SM. Multimorbidity. Nature Reviews Disease Primers. 2022;8(1):48.
3. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, et al. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PLoS One. 2014;9(7):e102149.
4. Chowdhury SR, Chandra Das D, Sunna TC, Beyene J, Hossain A. Global and regional prevalence of multimorbidity in the adult population in community settings: a systematic review and meta-analysis. EClinicalMedicine. 2023;57:101860.
5. Hirst JA, Ordonez Mena JM, O'Callaghan CA, Ogburn E, Taylor CJ, Yang Y, et al. Prevalence and factors associated with multimorbidity among primary care patients with decreased renal function. PLoS One. 2021;16(1):e0245131.
6. Wong MC, Wang HH, Cheung CS, Tong EL, Sek AC, Cheung NT, et al. Factors associated with multimorbidity and its link with poor blood pressure control among 223,286 hypertensive patients. Int J Cardiol. 2014;177(1):202-8.
7. Aoki T, Yamamoto Y, Ikenoue T, Onishi Y, Fukuhara S. Multimorbidity patterns in relation to polypharmacy and dosage frequency: a nationwide, cross-sectional study in a Japanese population. Sci Rep. 2018;8(1):3806.
8. WHO. World Health Organization. Medication safety in polypharmacy. Geneva.; 2019.

9. Alsanosi SM MA, Ahmadini HA, Qadhi RS, Ikram N, Felemban AH, Alqashqri HS, Hariri NH, Alhindi YZ, Ayoub N. Polypharmacy among patients with hypertension attending primary healthcare centres. Annals of Medicine and Surgery. 2023 Jun 1;85(6):. 2023;85(6):2545-9.

10. Sidamo T, Deboch A, Abdi M, Debebe F, Dayib K, Balcha Balla T. Assessment of polypharmacy, drug use patterns, and associated factors at the Edna Adan University Hospital, Hargeisa, Somaliland. Journal of tropical medicine. 2022;2022(1):2858987.

11. George J, Phun YT, Bailey MJ, Kong DC, Stewart K. Development and validation of the medication regimen complexity index. The Annals of pharmacotherapy. 2004;38(9):1369-76.

12. Alves-Conceicao V, Rocha KSS, Silva FVN, Silva ROS, Cerqueira-Santos S, Nunes MAP, et al. Are Clinical Outcomes Associated With Medication Regimen Complexity? A Systematic Review and Meta-analysis. The Annals of pharmacotherapy. 2020;54(4):301-13.

13. Wakai E IK, Kato C, Okuda M. Effect of number of medications and complexity of regimens on medication adherence and blood pressure management in hospitalized patients with hypertension. PLoS One. 2021;16(6):e0252944.

14. Wimmer BC, Johnell K, Fastbom J, Wiese MD, Bell JS. Factors associated with medication regimen complexity in older people: a cross-sectional population-based study. Eur J Clin Pharmacol. 2015;71(9):1099-108.

15. Nguyen H, Manolova G, Daskalopoulou C, Vitoratou S, Prince M, Prina AM. Prevalence of multimorbidity in community settings: A systematic review and meta-analysis of observational studies. Journal of comorbidity. 2019 Aug 20;9:2235042X19870934.

16. Fortin M, Haggerty J, Almirall J, Bouhali T, Sasseville M, Lemieux M. Lifestyle factors and multimorbidity: a cross-sectional study. BMC public health. 2014 Dec;14:1-8.

17. Violan C, Foguet-Boreu Q, Flores-Mateo G, Salisbury C, Blom J, Freitag M, Glynn L, Muth C, Valderas JM. Prevalence, determinants and patterns of multimorbidity in primary care: a systematic review of observational studies. PloS one. 2014 Jul 21;9(7):e102149.

18. Low LL, Kwan YH, Ko MS, Yeam CT, Lee VS, Tan WB, Thumboo J. Epidemiologic characteristics of multimorbidity and sociodemographic factors associated with multimorbidity in a rapidly aging Asian country. JAMA network open. 2019 Nov 1;2(11):e1915245-.

19. Balkhi B, AlQahtani N, Alwhaibi M, Alshammari TM, Alhawassi TM, Mahmoud MA, Almetwazi M, Ata S, Basyoni M, Aljadhey H. Prevalence and factors associated with polypharmacy use among adult patients in Saudi Arabia. Journal of Patient Safety. 2021 Dec 1;17(8):e1119-24.

20. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. The lancet. 2007 Oct 20;370(9596):1453-7.

21. Yeh A, Shah-Manek B, Lor KB. Medication Regimen Complexity and A1C Goal Attainment in Underserved Adults With Type 2 Diabetes. The Annals of pharmacotherapy. 2017;51(2):111-7.

22. Organization WH. Guideline for the pharmacological treatment of hypertension in adults. 2021.

23. Piercy KL, Troiano RP. Physical Activity Guidelines for Americans From the US Department of Health and Human Services. Circ Cardiovasc Qual Outcomes. 2018;11(11):e005263.

24. US Department of Health and Human Services. Health, United States, 2010: with special feature on death and dying. Hyattsville (MD): Centers for Disease Control and Prevention, National Center for Health Statistics; 2011. Appendix, definition of "condition," p. 486–7. Available at: https://www.cdc.gov/nchs/data/hus/hus10.pdf. Accessed on: January 24, 2025.

25. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71(6):1269-324.

26. Forslund T, Carlsson AC, Ljunggren G, Arnlov J, Wachtler C. Patterns of multimorbidity and pharmacotherapy: a total population cross-sectional study. Fam Pract. 2021;38(2):132-40.

27. Eyowas FA SM, Alemu S, Pati S, Getahun FA. Magnitude, pattern and correlates of multimorbidity among patients attending chronic outpatient medical care in Bahir Dar, northwest Ethiopia: the application of latent class analysis model. PLoS One. 2022;17(4):e0267208.

28. Kwakye AO KI, Oppong KG. Polypharmacy and its associated factors among patients with co-morbid hypertension and diabetes in a municipal hospital in Ghana. . Scientific African. 2024;23:e02028.

29. Pati S, Sinha R, Panda M, Puri P, Pati S. Profile of multimorbidity in outpatients attending public healthcare settings: A descriptive cross-sectional study from Odisha, India. J Family Med Prim Care. 2021;10(8):2900-14.

30. Zhong Y QG, Xi H, Cai D, Wang Y, Wang T, Gao Y. Prevalence, patterns of multimorbidity and associations with health care utilization among middle-aged and older people in China. . BMC public health.23(1):537.

31. Kassaw AT, Sendekie AK, Minyihun A, Gebresillassie BM. Medication regimen complexity and its impact on medication adherence in patients with multimorbidity at a comprehensive specialized hospital in Ethiopia. Frontiers in medicine. 2024;11:1369569.

32. Alwhaibi M, AlRuthia Y, Alhawassi TM, Almalag H, Alsalloum H, Balkhi B. Polypharmacy and comorbidities among ambulatory cancer patients: A cross-sectional retrospective study. Journal of oncology pharmacy practice : official publication of the International Society of Oncology Pharmacy Practitioners. 2020;26(5):1052-9.

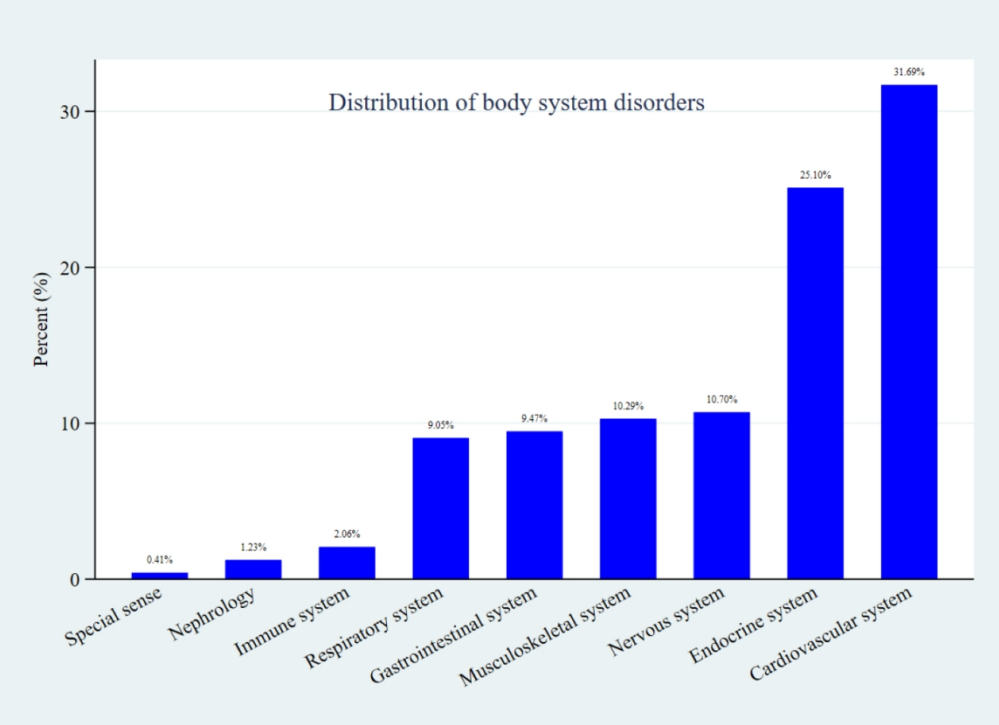
33. Pati S, Swain S, Knottnerus JA, Metsemakers JF, van Den Akker M. Magnitude and determinants of multimorbidity and health care utilization among patients attending public versus private primary care: a cross-sectional study from Odisha, India. International journal for equity in health. 2020; 19:1-2.

34. Alwis I, Rajapaksha B, Jayasanka C, Dharmaratne SD. Morbidity profile and pharmaceutical management of adult outpatients between primary and tertiary care levels in Sri Lanka: a dual-centre, comparative study. BMC Primary Care. 2024;25(1):200.

35. Ji E, Ahn S, Choi J-Y, Kim C-H, Kim K-i. Effect of multimorbidity on hypertension management. Scientific Reports. 2023;13(1):18764.

Figure legend

Fig 1. Percentage distribution of body system disorders



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