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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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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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 - Word counts: 2950
 - Keywords: Factor, multimorbidity, polypharmacy, medication complexity, Ethiopia

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

37 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.

41 Data analysis: Data were collected through 65-items medication regimen complexity tool,
42 interview, and checklist. Data were entered into SPSS version26, and analyzed using STATA
43 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.

60 • It is the first in Ethiopia healtheare setting that identified factors associated with multimorbidity, polypharmacy, and MRCI among hypertensive patients. 62 • Multicentred design nature of the study is considered as an additional strength of the present study. 64 • However, this study has a limitation being cross sectional may not show true cause-effect relationship between outcome and predictors. 66 • Moreover, it did not consider inpatient settings, so the study is generalizable to hypertensive patients with chronic follow up at outpatient departments 68 • 70 • 71 • 72 • 73 • 74 • 75 • 76 • 77 • 78 • 79 • 80 • 81 • 82 • 83 •	1 2 3 4	59	Strength and limitation of the study
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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.

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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].

31 32	127	Eligibility criteria
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34	128	Inclusion criteria:
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36	129	Adults aged 18 years and above
3/		
38	130	• Receiving antinypertensive medications for at least six months
39	131	• Following up at outpatient departments of the study hospitals
40 11	-	
41	132	Willing to participate
42 12		
45 11		
44 15	133	Exclusion criteria:
45		
40 17	134	Cognitive impairment
47		
49	135	Hearing problems
50	136	Admitted to inpatient wards
51	100	
52		
53	137	Sample Size Determination and Sampling Technique
54		
55	120	There were no previous studies that we used to determine the sample size of the present study
56	130	There were no previous studies that we used to determine the sample size of the present study.
57	139	Therefore, we used a single population proportion formula considering a 95% confidence
58		
59	140	interval, and a prevalence of 50% for outcomes. Then, we reached, a sample size of 384.
60		

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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].

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169 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].

178 The average of two BP readings taken two minutes apart during a visit was used to determine179 BP status [19].

180 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.

184 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.

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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, is ic Mk ing patient . (Table 1). 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).

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254 Table 1. Characteristics of study partie
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Variable	Category of variable	Patient level N complexity	ledication regi	men
		Low	Medium	High
Sex	Female	55	114	84
	Male	33	72	65
Age in year	<65	65	109	96
8	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	<6000	76	174	140
Ethiopian birr	6000+	12	12	9
Multimorbidity	Yes	4	69	123
v	No	84	117	26
Religion	Christian	82	176	137
- 8 -	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
1	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
v	No	84	117	26
Polypharmacv	Yes	0	0	51
VI V	No	88	186	98
BP controlled	Yes	54	73	48
	No	34	113	101
Aerobic	Yes	30	45	23
exercise	No	58	141	126
Health	Yes	58	132	115
insurance	No	30	54	34
Study setting	Debre Tabor	22	71	57
v O	Nefas Mewucha	16	39	45
	Addis Zemen	34	35	31
	Estie	16	41	16
Therapy	<5 year	64	162	87
duration	5+ vear	24	54	62

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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).

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	5	2.06
virus		
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

263 Table 2. Morbidities among hypertensive patients

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



275





Fig. 1. Percent of body system disorders

Hypertension combined with type 2 diabetes mellitus was the most commonly observed 277 multimorbidity, followed by hypertension combined with hypertensive heart disease. 278 Conversely, hypertension combined with T2DM and HIV, hypertension combined with 279 hypertensive heart disease and dyspepsia, and other combinations were the least frequently 280 encountered multimorbidities among the study participants. Regarding the number of 281 morbidities per participant, 53.9% had none, 35.22% had two, 10.4% had three, and 0.24% 282 each had four and five morbidities. Others (each accounts 0.24%) include: hypertension 283 +degenerative spondylosis, hypertension + type 2 diabetes mellitus + bilateral flank pain, 284 hypertension + type 2 diabetes mellitus+ HIV, hypertension + hypertensive heart disease + 285 59 dyspepsia, hypertension + type 2 diabetes mellitus + fatty liver disease, hypertension + type 2 286 60

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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).

	297	Table 3. Pa	attern of mu	ltimorbidity	among hyp	ertensive pa	atients
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Multimorbidity	Frequenc	Percen
	y	
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

2 3 4 5	299	Factors associated with multimorbidity, Polypharmacy, and MRCI
6 7	300	In the final adjusted binary logistic regression, we found that polypharmacy, patient-level
8	301	medication regimen complexity, and the study hospital were associated with the presence of
9 10	302	multimorbidity.
11 12	303	Polypharmacy was significantly associated with a duration of hypertension treatment equal to
13 14	304	or greater than five years, multimorbidity, and controlled BP in the adjusted binary logistic
15 16	305	regression analysis.
17 18	306	We identified several factors associated with medication regimen complexity (MRCI) for
19 20	307	inclusion in a multivariate ordinal logistic regression analysis. These factors include the
21 22	308	presence of multimorbidity, controlled blood pressure (BP), duration of hypertension treatment
23	309	greater than five years, engaging in aerobic exercise, having health insurance, and an income
24 25 26	310	greater than 6000 Ethiopian Birr.
20 27 28	311	In the adjusted analysis, participants experiencing multimorbidity were fourteen times more
29	312	likely to have a complex medication regimen (AOR=14.55, 95% CI: 9.00-23.52, P<0.0001).
30 31	313	Furthermore, participants with controlled BP, based on WHO pharmacologic treatment of
32 33	314	hypertension guidelines (2021), were 52% less likely to have a complex medication regimen
34 35	315	(AOR=0.48, 95% CI: 0.32-0.72, P<0.0001) (Table 4).
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39	317	
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43 44 45	319	
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Variable	Variable	Outcome		COR (95% CI)	AOR (95% CI
	category	Patient M	IRCIa		
		≤4 5-8	3 >8		
Income	<6000 ETB	76 174	4 140	1	1
	≥6000 ETB	12 12	9	0.52(0.26-1.03)*	0.59(0.28-1.24)
Multimorbidity	No	85 1	17 26	1	1
	Yes	3 69	9 123	15.19(9.47-24.37)*	14.55(9.00-23.
Controlled BP	No	34 11	3 101	1	1
	Yes	54 73	48	0.46(0.32-0.67)+	0.48(0.32-0.72)
Aerobic exercise	No	58 14	41 126	1	1
	Yes	30 45	5 23	0.49(0.32-0.74)+	0.77(0.48-1.23)
Health insurance	No	30 5	4 34	1	1
	Yes	58 13	32 115	1.47(0.99-2.19)*	1.53(0.98-2.39)
Hypertension therapy	<5 years	64 13	32 87	1	1
	\geq 5 years	24 54	4 62	1.66(1.13-2.44)+	1.17(0.77-1.78)
		Polyphar	macy ^b		
		Absent	Present		
Study hospital	DCSH	126	24	1	1
Study noopitul	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.)
Hypertension therapy	<5 years	259	24	1	1
nypercension merupy	>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)
		Multimo	biditv ^b		
		Absent	Present		
1 99	<65 years	152	110	1	1
Age	<03 years	132	77	1 1 21(0 87 1 04)*	1 00(0 64 1 88)
Study hamital		50	01	1.31(0.07-1.94)	1.09(0.04-1.00
Study nospital	NMWH	59	91	1 0.51(0.30, 0.85) ⁺	
		56	44 1/	0.51(0.50-0.05) 0.53(0.32-0.88)+	0.50(0.15-0.59) 0.80(0.36-1.77)
	MFH	57	16	0.55(0.52-0.08) 0.18(0.09-0.35) ⁺	0.00(0.30-1.77) 0.16(0.07-0.38)
Aerobic exercise	No	165	160	1	1
		63	35	0.56(0.35-0.90)+	$\begin{bmatrix} 1 \\ 0.86(0.41 - 1.81) \end{bmatrix}$
Hypertension therapy	<5 years	169	11/	1	1
rippertension merapy	>5 years	59	<u>8</u> 1	$\frac{1}{2}$ 01(1 33-3 02)+	1 49(0 85-2 61)
Controlled BP	No	124	124	1	1
Controlled DI		104	124 71	$\begin{bmatrix} 1 \\ 0 & 69(0 & 47_1 & 03)^+ \end{bmatrix}$	1 12(0.64-1.05)
Polypharmacy	Absent	225	2	1	1.12(0.04-1.95
i orypnarmacy	Present	147	5 18	$24 49(7 49 80 08)^+$	552(1.40-20.2)
Patient MRCI		85	2	1	1
	$\left \frac{2}{5}\right ^{4}$	117	5 60	$12 38(1 35 25 26)^+$	10 76(5 87 66
	>8	$\frac{11}{26}$	172	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	120 22(22 12 4
	-0	20	123	77.34(33.43-293.07)	120.32(33.12-4

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

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 (\geq 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
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

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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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2 3 4	393	Author Contributions		
5 6 7	394	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.,		
7 8	395	F.N.D., G.T.A., T.A.M. and A.M.B. performed data entry, wrote, and edited the manuscript.		
9 10 11	396	All authors reviewed the manuscript and were responsible for all aspects of this work.		
12 13	397	Funding		
14 15 16	398	No specific fund for this study		
17 18 10	399	Disclosure		
20 21	400	Authors have declared that there is no conflict of interest		
22 23 24	401	Public and patient involvement		
25 26	402	The public and patients were not engaged in the design, conduct, reporting, and distribution of		
27 28	403	this research.		
29 30	404			
30 31 22	405	Patient consent for publication		
33 34	406	Not required.		
35 36 37	407	Ethical Approval		
38 39	408	Ethical approval for the present study was received from Institutional Research and Ethical		
40	409	Review Committee (IRERC), College of Health Sciences, Debre Tabor university, and		
41 42 43	410	conducted in accordance with the declaration of Helsinki.		
44 45 46	411	Data availability statement		
47 48	412	All necessary data are available within the manuscript and/or supporting materials		
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52 53	414	REFERENCES		
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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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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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 - Word counts: 3019
 - Keywords: Factor, multimorbidity, polypharmacy, medication complexity, Ethiopia

30 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

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

37 Participants: Adult hypertensive patients who had follow up and visited at outpatient
38 clinics and selected by systematic random sampling from December 1, 2021, to February 30,
39 2022.

40 Primary and secondary outcome measures: Medication regimen complexity was 41 assessed using a 65-items medication regimen complexity tool. Sociodemographic data were 42 collected through interview, while polypharmacy and clinical characteristics were documented 43 using checklist. Data were entered into SPSS version26, and analyzed using STATA 17. Binary 44 logistic regression model was used to determine AOR of factors associated with multimorbidity 45 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.

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

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54 55	80
56 57 5°	81
58 59 60	82

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> 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.

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2 3 4	83	Strength and limitation of the study
5 6 7	84	• It is the first in Ethiopia healthcare setting that identified factors associated with
7 8	85	multimorbidity, polypharmacy, and MRCI among hypertensive patients.
9 10	86	• Multicentred design nature of the study is considered as an additional strength of the
11	87	present study.
12 13	88	• However, this study has a limitation being cross sectional that did not establish a true
14 15	89	cause-effect relationship between outcome and independent factors.
16 17	90	• Moreover, exclusion of inpatient settings restricts the findings generalizability to adult
17 18	91	hypertensive patients with chronic follow up at outpatient departments only
19 20	92	• Under representation of older adults and medication adherence were not adequately
21 22	93	addressed, potentially affecting study results.
23 24	94	
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109 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 overthe-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,

Medication regimen complexity includes factors such as dosage forms, dosing frequency, and additional instructions related to medications. It accounts for both prescription and over-thecounter 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 lifestyles¹⁶ 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.

2					
3 4	140	METHODS			
5 6 7	141	Study Area, Design, and Period			
8 9	142	The study was conducted in one purposively, and three randomly chosen public hospitals in			
10	143	South Gondar Zone. According to 2007 census which was conducted by Central Statistical			
11 12	144	Agency (CSA), Ethiopia, this Zone has a total population of 2 051 738. Based on the 2011 CSA			
13 14	145	population projection, the South Gondar Zone has a total population of 2 239 077 (1 103 490			
15	146	women and 1 135 587 men). An institution-based multicentered cross-sectional design was			
16 17 18	147	used, and data were collected from December 1, 2021, to February 30, 2022.			
19 20	148	Study Participants			
21 22	149	The source population embraced all adults with hypertension attending follow-up appointments			
$^{23}_{24}$ 150 at outpatient departments. The study findings were reported according to the gui					
 24 are empirical arpanetic arpanetic and analysis are experimentally are experiment					
					29 30
32 33	154	Inclusion criteria:			
34 35	155	Adults aged 18 years and above			
 Receiving antihypertensive medications for at least six months 					
37 38	157	• Following up at outpatient departments of the study hospitals			
39 40	158	Willing to participate			
41 42					
43	159	Exclusion criteria:			
44 45	160	Cognitive impairment			
46 47	161	Hearing problems			
48 49	162	Admitted to inpatient wards			
50 51 52	163	Sample Size Determination and Sampling Technique			
53 54	164	There were no previous studies that we used to determine the sample size of the present study.			
55	165	Therefore, we used a single population proportion formula considering a 95% confidence			
56 57	166	interval, and a prevalence of 50% for outcomes. Then, we reached, a sample size of 384.			
58 59 60	167	Accounting for a 10% non-response rate, the final sample size was 423. Debre Tabor			

168 Comprehensive Specialized Hospital, being the only specialized hospital in the zone, was 169 selected purposively, while Addis Zemen Hospital, Nefas Mewucha Hospital, and Mekane 170 Eyesus Hospital were chosen randomly. Proportional allocation and a systematic random 171 sampling technique were applied, with a sampling interval of four; hence, every fourth 172 participant was included until the desired sample size was achieved.

Study Variables

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

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

Operational definitions

181 Medication regimen complexity: comprised the dosage form, dosing interval, and additional 182 instruction aspect to calculate the patient medication burden. It is quantified using 65 items 183 Medication Regimen Complexity Index (MRCI): then, categorized into three levels: low (\leq 4), 184 medium (5-8), and high (>8) MRCI scores.²¹

Multimorbidity: Co-existence of two or more chronic conditions in an individual.^{1, 2}

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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.

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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

235	Patients and the public were not involved in the design of this study.
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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, .c M. ng patiet. Table 1). 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).

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282 Table 1. Characteristics of study participants

Variable	Category of variable	Patient level Medication regimen		
		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	<6000	76(17.97)	174(41.13)	140(33.10)
Ethiopian birr	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		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)	9/(22.93)
BP controlled	Yes	54(12.77)	/3(1/.26)	48(11.35)
A	NO Var	34(8.04)	113(20.71)	101(23.88)
Aerobic	Yes	50(7.09)	45(10.64) 141(22.22)	23(5.44) 126(20.70)
exercise	NO Voz	58(13.71)	141(33.33) 122(21.21)	120(29.79) 115(27.10)
Health	Yes	38(13.71) 20(7.00)	132(31.21) 54(12.77)	113(27.19)
Study setting	Dobro Tobor	30(7.09)	$\frac{34(12.77)}{71(16.79)}$	57(12.49)
Study setting	Notes Mouraha	22(3.20) 16(3.79)	$\frac{11(10.78)}{20(0.22)}$	$3/(13.4\delta)$ 45(10.64)
	Addis Zomon	10(3.78) 37(8.04)	37(7.22) 35(8.27)	43(10.04) 31(7.22)
	Aduls Zeillell	34(0.04) 16(2.79)	33(0.27)	16(2.79)
Thorany	Lout <5 year	64(15, 12)	+1(7.07) 127(21.21)	10(3.76) 87(20.57)
duration	\sim ytal 5+ year	24(13.13)	54(12.77)	67(20.37)
	j J i year	24(3.07)	34(12.77)	102(14.00)

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285 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).

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

292 Table 2. Morbidities among hypertensive patients

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.

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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).

325 Table 3. Pattern of multimorbidity among hypertensive patients

Multimorbidity	Frequenc	Percent
	y	
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	11.7
Number of multimorbidity 0	228	53.9
2	149	35.2
3	44	10.4
4	1	0.24
5	1	0.24

327 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	Outco	ome	COR (95% CI)	AOR (95% CI)
	category	Patie	nt 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
<i>y</i>	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
Treatur Insurance	Ves	58	132 115	$1 1 47(0.99 2.19)^*$	1 53(0.98-2.39)
Humartancian tharany	105 (5 years	64	132 113	1.47(0.99-2.19)	1.55(0.98-2.59)
Hypertension therapy	<5 years	04	132 87 54 62	$\begin{bmatrix} 1 \\ 1 \\ ((1 \ 12 \ 2 \ 44))^{+} \end{bmatrix}$	
	≥5 years	24 D 1	<u> </u>	1.00(1.13-2.44)*	1.1/(0.//-1./8)
		Poly	bharmacy		
		Abse	nt 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	$2449(749-8008)^{+}$	25 39(7 48-86 22)+
Hypertension therapy	<5 years	258	25	1	1
ing percension energy	>5 years	113	27	$258(143-466)^+$	$212(1.08-4.16)^+$
Controlled BP	No	206	42	1	1
Controlled B1	Ves	165	10	$1 0 42(0 19 0 92)^+$	$1 0 42(0 19 0 92)^+$
	105	Multi	imorhidity	0.42(0.19-0.92)	0.42(0.19-0.92)
		Abse	nt Present		
Age	<65 years	152	118	1	1
	\geq 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
Trypertension therapy	>5 years	59	81	$201(133-302)^+$	1 49(0 85-2 61)
Controlled BP	No	124	124	1	1
Controlled B1	Ves	104	71	$0.69(0.47-1.03)^+$	1 12(0.64-1.95)
Polynharmaoy	Absent	225	116	1	1
i orypnarmacy	Dresent	3	140	$24 40(7 40 80 08)^+$	552(1 40 20 20)+
Detiont MDCI		05		24.47(7.47-00.00)	1
ratient WKCI	$\left \frac{\geq 4}{5}\right $	83	5		
	5-8		69	$12.38(4.35-35.26)^{+}$	19./b(3.8/-bb.5b) ⁺ 120.22(22.12.427.07) ⁺
	<i>></i> 8	26	123	99.34(33.45-295.07)*	$120.32(33.12-43/.07)^{+}$

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

361 Concerning polypharmacy, our finding is lower than those findings from studies conducted in
362 Gondar, Ethiopia (46.6%),³¹ Ghana (64.8%),²⁸ Somaliland (71%),¹⁰ Saudi Arabia [(21%),
363 (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 (\geq 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

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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 MRCI³¹ among participants with any chronic conditions, without requiring a hypertension diagnosis as a mandatory inclusion criterion.

390 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.

402 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

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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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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

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571 Figure legend

572 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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Secondary Subject Heading:	Cardiovascular medicine, Evidence based practice, Epidemiology
Keywords:	Hypertension < CARDIOLOGY, Drug Therapy, EPIDEMIOLOGIC STUDIES

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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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22 Word counts: 3019

Keywords: Factor, multimorbidity, polypharmacy, medication complexity, Ethiopia 23

29 ABSTRACT

30 Objectives: Factors associated with multimorbidity, polypharmacy, and medication regimen 31 complexity (MRCI) may vary across countries. However, such data are lacking in the present 32 study setting. This study aimed to identify factors associated with multimorbidity, 33 polypharmacy, and MRCI among adults living with hypertension in public hospitals of South 34 Gondar Zone.

Design: Multicentered cross sectional design

36 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.

40 Primary and Secondary Outcome Measures: Medication regimen complexity was 41 assessed using a 65-items medication regimen complexity tool. Sociodemographic data were 42 collected through interview, while polypharmacy and clinical characteristics were documented 43 using checklist. Data were entered into SPSS version26, and analyzed using STATA 17. Binary 44 logistic regression model was used to determine AOR of factors associated with multimorbidity 45 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.

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> **Conclusion:** A considerable proportion of participants with hypertension experienced 58 multimorbidity, polypharmacy, and high medication complexity. Polypharmacy, primary 59 hospital setting, and high MRCI were independent variables associated with multimorbidity. 60 On the other hand, multimorbidity, and controlled BP were associated with polypharmacy and 61 MRCI. Hypertension care should consider multimorbidity, polypharmacy, and medication 62 complexity.

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4	82	Strength and Limitation of the Study
5 6 7	83	• This study used objective measures to assess multimorbidity, polypharmacy and
7 8	84	medication regimen complexity strengthens the methodological rigor.
9 10	85	• Multicentred design nature of the study is considered as an additional strength of the
11	86	present study.
12 13	87	• However, this study has a limitation being cross sectional that did not establish a true
14	88	cause-effect relationship between outcome and independent factors.
16 17	89	• Moreover, relatively small sample size and exclusion of inpatient settings restricts the
18	90	findings generalizability to adult living with hypertension who have chronic follow up
19 20 21	91	at outpatient departments only
22	92	• Under representation of older adults and medication adherence were not adequately
23	93	addressed, potentially affecting study results.
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109 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 overthe-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,

Medication regimen complexity includes factors such as dosage forms, dosing frequency, and additional instructions related to medications. It accounts for both prescription and over-thecounter 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 lifestyles¹⁶ 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

141 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

153 Eligibility Criteria

154 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
- 9 162 Admitted to inpatient wards

163 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 **BMJ** Open

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.

s Study Variables

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

176 Independent Variables: Age, gender, residence, marital status, income, blood pressure status,
177 educational status, number of medications, duration of treatment, health insurance, aerobic
178 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 186 without comorbidity, or BP <130/90 mmHg for those with diabetes mellitus, chronic kidney 187 disease, or known cardiovascular diseases.²²

188 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.

198 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

207 The average of two BP readings taken two minutes apart during a visit was used to determine
208 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.

213 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.

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225 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.

233 Public and Patient Involvement

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21	234	Patients and the public were not involved in the design of this study.
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RESULTS

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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 \pm SD of 2.65 \pm 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 o (Table . , 43.97%, and high in 35.22% (Table 1).

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Variable	Category of variable	Patient level Medication regimen			
		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%	
8- ,	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	<6000	76(17.97%)	174(41.13%)	140(33.10	
Ethiopian birr	6000+	12(2.84%)	12(2.84%)	9(2.13%)	
Religion	Christian	82(19.39%)	176(41.61%)	137(32.3	
8	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(12.299	
vi v	No	88(20.80%)	186(43.97%)	97(22.939	
BP controlled	Yes	54(12.77%)	73(17.26%)	48(11.35°	
	No	34(8.04%)	113(26.71%)	101(23.88	
Aerobic	Yes	30(7.09%)	45(10.64%)	23(5.44%	
exercise	No	58(13.71%)	141(33.33%)	126(29.79	
Health	Yes	58(13.71%)	132(31.21%)	115(27.19	
insurance	No	30(7.09%)	54(12.77%)	34(8.04%	
Study setting	Debre Tabor	22(5.20%)	71(16.78%)	57(13.489	
	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	<5 year	64(15.13%)	132(31.21%)	87(20.579	
duration	5+ year	24(5.67%)	54(12 77%)	62(14 669	

 Type 1 diabetes mellitus

Generalized tonic-clonic

Others (each 1[0.41%])

Myalgia

2 3	282						
4 5 6 7	283	Patterns of Multimorbidity					
8 9	284	Type 2 diabetes mellitus was the most common comorbidity coexisting with hypertensity					
10 11	285	while the least encountered comorb	pidities included rheumatic	fever, Parkinson's disease, fatty			
12	286	liver disease, and others. Others in	clude: rheumatic fever, pul	monary tuberculosis, glaucoma,			
13 14	287	Parkinson's disease, fatty liver dise	ase, degenerative aortic ste	nosis, degenerative spondylosis,			
15 16	288	osteoarthritis, hypercalcemia, bilate	eral flank pain, schizophren	ia, trigeminal neuralgia, and soft			
17	289	tissue injury (Table 2).					
18 19 20	290	Table 2. Morbidities among hype	ertensive patients				
21		Disorder	Frequency	Percent			
22		Type 2 diabetes mellitus	52	21.40			
24 25		Dyslipidemia	25	10.29			
26 27		Dyspepsia	22	9.05			
28		Hypertensive heart disease	21	8.64			
29 30		Bronchial asthma	21	8.64			
31 32		Rheumatoid arthritis	19	7.82			
33		Peripheral neuropathy	19	7.82			
34 35		Congestive heart failure	12	4.94			
36 37		Ischemic stroke	10	4.12			
38		Ischemic heart disease	7	2.88			
39 40		Hyperthyroidism	6	2.47			
41 42		Human immunodeficiency virus	5	2.06			
42		Chronic kidney disease	3	1.23			

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.

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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).

	Multimorbidity	Frequenc	Percent
		y	
	Hypertension+T2 diabetes mellitus	30	7.09
	Hypertension+Hypertensive heart disease	16	3 78
	Hypertension+Dyspersia	12	2.84
	Hypertension+Bheumatoid arthritis	12	2.01
	Hypertension+Dyslinidemia	11	2.01
	Hypertension+Dyshiputenna Hypertension+Derinheral nauronathy	10	2.00
	Hypertension+Pronchial asthma	10	2.30
	Hypertension+Isohomia strako	Q	1.80
	Hypertension+T2 diabates mollitus+Dyslinidamia	7	1.65
	Hypertension + Congestive beaut feilure	7	1.05
	Hypertension+Congestive heart failure	1	1.03
	Hypertension+Hypertnyrolaism	6	1.42
	Hypertension+Peripheral neuropatny+Dyspepsia	3	0.71
	Hypertension+12 diabetes mellitus+Peripheral neuropathy	3	0./1
	Hypertension+12 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
		149	35.22
	3	44	10.40
	4	1	0.24
	5	1	0.24
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# 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).</li>
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).</li>

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

Variable	Variable	Outcome Patient MRCI ^a		COR (95% CI)	AOR (95% CI)
	category				
		≤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	$147(099-219)^*$	1 53(0 98-2 39)
Hypertension therapy	<5 years	64 132	87	1	1
riypertension therapy	>5 years	24 $54$	62	$1 66(1 13-2 44)^+$	1 17(0.77-1.78)
		Polynharm	acv ^b	1.00(1.1 <i>3⁻2</i> . <b>T</b> )	1.1/(0.//-1./0)
			10 y		
~		Absent Pr	esent		
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
	$\geq$ 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)+
		Multimorbi	dity ^b		
		Absent Pr	esent		
Δσε	<65 years	152	118	1	1
nge	>65 years	76	77	$1 31(0 87 1 94)^*$	1 09(0.64-1.88)
Study hospital		50	01	1.51(0.87-1.94)	1
Study hospital	NMWH	56	11	$0.51(0.30, 0.85)^+$	$\begin{bmatrix} 1 \\ 0.20(0.15, 0.50)^{+} \end{bmatrix}$
		56	44	0.51(0.30-0.85)	0.30(0.15-0.57)
		50	44 16	0.35(0.32-0.88) 0.18(0.00.0.25) ⁺	0.80(0.30-1.77) 0.16(0.07.0.29) ⁺
A analia amanaiga		165	10	0.18(0.09-0.33)	0.10(0.07-0.38)
Aerodic exercise		105	25	$\begin{bmatrix} 1 \\ 0.56(0.25, 0.00) + \end{bmatrix}$	$\begin{bmatrix} 1 \\ 0.96(0.41, 1.91) \end{bmatrix}$
II.montongion 4	105	160	<u> </u>	1	1
rrypertension therapy	> years	109	114 01	$\begin{bmatrix} 1 \\ 2 & 01(1 & 22 & 2 & 02) \pm \end{bmatrix}$	$\begin{bmatrix} 1 \\ 1 & 40(0.95, 2.61) \end{bmatrix}$
	≥5 years	39	81	2.01(1.55-5.02)	1.49(0.85-2.61)
Controlled BP	INO Var	124	124		
D 1 1	Yes	104	/1	0.69(0.47-1.03)*	1.12(0.64-1.95)
Polypharmacy	Absent	225	146		
	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	$9934(3345-29507)^+$	$12032(3312-43707)^+$

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.</li>

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#### **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

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We found high patient level MRCI in 35.22% of study participants, which is lower than the
 384 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

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400 likely to have poor BP control.¹³ Additionally, we identified that participants with
401 multimorbidity were 14 times more likely to have medium or high patient level MRCI, in line
402 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 MRCI³¹ among participants with any chronic conditions, without requiring a hypertension diagnosis as a mandatory inclusion criterion.

### 409 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. 

44 422 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 

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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, whilerecognizing that further research with a large sample size is needed to support these findings.

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data collectors for providing internet for literature access and ethical approval, allowing data
collection, and participating in data collection in this study.

### 468 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.

### 473 Funding

474 No specific fund for this study

#### **Disclosure**

476 Authors have declared that there is no conflict of interest

### **Public and Patient Involvement**

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

### **Patient Consent for Publication**

481 Not required.

### 482 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.

### 486 Data Availability Statement

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

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# **BMJ Open**

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

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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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22 Word counts: 3019

Keywords: Factor, multimorbidity, polypharmacy, medication complexity, Ethiopia 23

## 29 ABSTRACT

30 Objectives: Factors associated with multimorbidity, polypharmacy, and medication regimen 31 complexity (MRCI) may vary across countries. However, such data are lacking in the present 32 study setting. This study aimed to identify factors associated with multimorbidity, 33 polypharmacy, and MRCI among adults living with hypertension in public hospitals of South 34 Gondar Zone.

**Design:** Multicentered cross sectional design

36 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.

40 Primary and Secondary Outcome Measures: Medication regimen complexity was 41 assessed using a 65-items medication regimen complexity tool. Sociodemographic data were 42 collected through interview, while polypharmacy and clinical characteristics were documented 43 using checklist. Data were entered into SPSS version26, and analyzed using STATA 17. Binary 44 logistic regression model was used to determine AOR of factors associated with multimorbidity 45 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. 

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> **Conclusion:** A considerable proportion of participants with hypertension experienced 58 multimorbidity, polypharmacy, and high medication complexity. Polypharmacy, primary 59 hospital setting, and high MRCI were independent variables associated with multimorbidity. 60 On the other hand, multimorbidity, and controlled BP were associated with polypharmacy and 61 MRCI. Hypertension care should consider multimorbidity, polypharmacy, and medication 62 complexity.

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4	82	Strength and Limitation of the Study
5 6 7	83	• This study used objective measures to assess multimorbidity, polypharmacy and
7 8	84	medication regimen complexity strengthens the methodological rigor.
9 10	85	• Multicentred design nature of the study is considered as an additional strength of the
11	86	present study.
12 13	87	• However, this study has a limitation being cross sectional that did not establish a true
14	88	cause-effect relationship between outcome and independent factors.
16 17	89	• Moreover, relatively small sample size and exclusion of inpatient settings restricts the
18	90	findings generalizability to adult living with hypertension who have chronic follow up
19 20 21	91	at outpatient departments only
22	92	• Under representation of older adults and medication adherence were not adequately
23	93	addressed, potentially affecting study results.
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## 109 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 overthe-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, 

Medication regimen complexity includes factors such as dosage forms, dosing frequency, and additional instructions related to medications. It accounts for both prescription and over-thecounter 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 lifestyles¹⁶ 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**

## 141 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

153 Eligibility Criteria

154 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
- 9 162 Admitted to inpatient wards

## 163 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.

s Study Variables

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

176 Independent Variables: Age, gender, residence, marital status, income, blood pressure status,
177 educational status, number of medications, duration of treatment, health insurance, aerobic
178 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 186 without comorbidity, or BP <130/90 mmHg for those with diabetes mellitus, chronic kidney 187 disease, or known cardiovascular diseases.²²

188 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.

## **198 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 

207 The average of two BP readings taken two minutes apart during a visit was used to determine
208 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.

## 213 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.

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## 225 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.

## 233 Public and Patient Involvement

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21	234	Patients and the public were not involved in the design of this study.
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### RESULTS

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## 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  $\pm$  SD of 2.65 $\pm$  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 o (Table . , 43.97%, and high in 35.22% (Table 1). 

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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 vear	<65	65(15.37%)	109(25.77%)	96(22.70%
8- /	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	<6000	76(17.97%)	174(41.13%)	140(33.10
Ethiopian birr	6000+	12(2.84%)	12(2.84%)	9(2.13%)
Religion	Christian	82(19.39%)	176(41.61%)	137(32.39
8	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(12.299
	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	Yes	30(7.09%)	45(10.64%)	23(5.44%
exercise	No	58(13.71%)	141(33.33%)	126(29.79
Health	Yes	58(13.71%)	132(31.21%)	115(27.19
insurance	No	30(7.09%)	54(12.77%)	34(8.04%
Study setting	Debre Tabor	22(5.20%)	71(16.78%)	57(13.489
. 0	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	<5 year	64(15.13%)	132(31.21%)	87(20.57
1 4	5	24(5 (70/)	54(12 770/)	62(11 66)

 Type 1 diabetes mellitus

**Generalized tonic-clonic** 

Others (each 1[0.41%])

Myalgia

2 3	282							
4 5 6 7	283	Patterns of Multimorbidity						
8 9	284	Type 2 diabetes mellitus was the	most common comorbidity	y coexisting with hypertension,				
10 11	285	while the least encountered comorb	pidities included rheumatic	fever, Parkinson's disease, fatty				
12	286	liver disease, and others. Others in	clude: rheumatic fever, pul	monary tuberculosis, glaucoma,				
13 14	287	Parkinson's disease, fatty liver dise	ase, degenerative aortic ste	nosis, degenerative spondylosis,				
15 16	288	osteoarthritis, hypercalcemia, bilateral flank pain, schizophrenia, trigeminal neuralgia, and soft						
17	289	tissue injury (Table 2).						
18 19 20	290	<ul> <li>Table 2. Morbidities among hypertensive natients</li> </ul>						
21		Disorder	Frequency	Percent				
22		Type 2 diabetes mellitus	52	21.40				
24 25		Dyslipidemia	25	10.29				
26 27		Dyspepsia	22	9.05				
28		Hypertensive heart disease	21	8.64				
29 30		Bronchial asthma	21	8.64				
31 32		Rheumatoid arthritis	19	7.82				
33		Peripheral neuropathy	19	7.82				
34 35Congestive heart failure12				4.94				
36 37		Ischemic stroke	10	4.12				
38		Ischemic heart disease	7	2.88				
39 40		Hyperthyroidism	6	2.47				
41 42		Human immunodeficiency virus	5	2.06				
42		Chronic kidney disease	3	1.23				

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.

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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). 

 

	Multimorbidity	Frequenc	Percent
		y	
	Hypertension+T2 diabetes mellitus	30	7.09
	Hypertension+Hypertensive heart disease	16	3 78
	Hypertension+Dyspersia	12	2.84
	Hypertension+Bheumatoid arthritis	12	2.01
	Hypertension+Dyslinidemia	11	2.01
	Hypertension+Dyshiputenna Hypertension+Derinheral nauronathy	10	2.00
	Hypertension+Pronchial asthma	10	2.30
	Hypertension+Isohomia strako	Q	1.80
	Hypertension+T2 diabates mollitus+Dyslinidamia	0	1.65
	Hypertension + Congestive beaut feilure	7	1.05
	Hypertension+Congestive heart failure	1	1.03
	Hypertension+Hypertnyrolaism	6	1.42
	Hypertension+Peripheral neuropatny+Dyspepsia	3	0.71
	Hypertension+12 diabetes mellitus+Peripheral neuropathy	3	0.71
	Hypertension+12 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
		149	35.22
	3	44	10.40
	4	1	0.24
	5	1	0.24
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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	Outcome		COR (95% CI)	AOR (95% CI)
	category	Patient MR	CIa		
		≤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
Tieutin insurance	Ves	58 132	115	$1 47(0 99-2 19)^*$	1 53(0 98-2 39)
Hypertension therapy	<5 years	64 132	87	1	1
Typertension merapy	<5 years	24 132	62	$1 \\ 1 \\ 6 \\ 6 \\ (1 \\ 1 \\ 2 \\ 4 \\ 4)^+$	1 1 17(0 77 1 78)
	<u>></u> 5 years	24 34	02 b	1.00(1.15-2.44)	1.1/(0.77-1.78)
		Forypharm	acy~		
		Absent Pr	resent		
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
2	Yes	146	49	24.49(7.49-80.08)+	25.39(7.48-86.22)+
Hypertension therapy	<5 years	258	25	1	1
51 15	>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	$0.42(0.19-0.92)^+$	$0.42(0.19-0.92)^+$
		Multimorb	idityb		
		Absent Pr	esent		
•			110	1	1
Age	<65 years	152	118		
	≥ 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
	Yes	63	35	$0.56(0.35-0.90)^+$	0.86(0.41-1.81)
Hypertension therapy	<5 years	169	114	1	1
	\geq 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
J P J	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)+	$120 32(33 12437 07)^+$
11 · · · · · · · · · · · · · · · · · ·	11	1 11	143	(J).JT(JJ.TJ-293.07)	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.

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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

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We found high patient level MRCI in 35.22% of study participants, which is lower than the
 384 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

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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 MRCI³¹ among participants with any chronic conditions, without requiring a hypertension diagnosis as a mandatory inclusion criterion.

5 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.

428 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

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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.

460 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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474 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
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- 482 Authors have declared that there is no conflict of interest
- **Public and Patient Involvement**
- 484 Patients and the public were not involved in the design of the study.

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- 486 Patient Consent for Publication
 - 487 Not required.

488 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.

492 Data Availability Statement

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

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45	606	Figure legend
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