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RESEARCH ARTICLE

Managing the dual burden: Pharmacoepidemiological insights into anti-diabetic and anti-hypertension medication use

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Abstract: The most prevalent non-communicable diseases that need long-term therapy include hypertension and diabetes mellitus. Mortality and morbidity rates increase when diabetes and hypertension are present together. These disorders must be taken into consideration in order to manage them successfully when they coexist. Both diabetes and hypertension are most likely to develop macrovascular and microvascular complications. Tight control of blood pressure is more helpful in diabetic-hypertensive patients than tight control of blood glucose levels. This study aims to learn about anti-diabetic and anti-hypertensive drug therapy, clinical outcomes, and how combination therapy affects the clinical outcome of diabetes with hypertension. It was a prospective single-centered observational study conducted among 300 Diabetic-Hypertensive patients. The mean age of the study was 58.8 years. According to this study, 56% were males and 44% were females. The commonly observed comorbidity conditions along with diabetes and hypertension were CKD (20.6%), UTI (15%), and Neuropathic diabetes (14%). The most affected occupations with diabetes and hypertension were Private Jobs (31%), Retired Employees (21%), and Homemakers (20%). The most prescribed drugs in diabetic-hypertensive patients were Metformin (7%), Metoprolol (11.7%), Metoprolol with Cilnidipine (5.6%), Metformin with Glimepiride (8.4%), Olmesartan with Amlodipine and Hydrochlorothiazide (8%), and Glimepiride with Metformin and Voglibose (6.3%). The conclusion of this study, males were more affected by diabetes and hypertension and mostly observed in the elderly. The anti-diabetic combination therapy and its clinical outcome are not associated with each other. The anti-hypertensive combination therapy and its clinical outcome are associated with each other.

Keywords: Diabetes mellitus; Hypertension; Monotherapy; Combination therapy; Anti-Hypertension drugs; Anti-Diabetic drugs

1. Introduction

Diabetes and hypertension are the most prevalent non-communicable diseases that are frequently seen together. When compared to normotensive and non-diabetic individuals, the co-existence of diabetes with hypertension is associated with a considerably higher risk (two-to-four-fold times) of cardiovascular disease, end-stage renal disease and mortality [1]. Diabetes mellitus is a carbohydrate metabolic disorder characterized by the body's reduced capacity to generate or respond to insulin and maintain normal blood sugar levels [2]. Systemic arterial hypertension (also known as hypertension) is characterized by persistently high blood pressure in the systemic arteries [3].

In India, an estimated 77 million individuals are diabetic and about 25 million are pre-diabetics (with a higher risk of getting diabetes) [4]. According to researchers, this number will rise to 134 million by 2045. Males get diabetes at a rate of 55.5% after age 20. Females account for 64.6% of the total [5]. India has one of the highest rates of hypertension prevalence, with about 30%of the Indian population suffering from hypertension [6]. It is estimated that one in every four people in India has hypertension [7]. But only approximately 12% of them have their blood pressure under control [8].

Diabetes is associated with both macrovascular (involving large vessels such as arteries and veins) and microvascular (involving small vessels, such as capillaries) complications. Hypertension is an important risk factor for diabetes-related vascular complications

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because hypertension is characterized by vascular dysfunction and injury [9]. Individuals with both diabetes and hypertension are more likely to develop macrovascular complications (coronary artery disease, myocardial infarction, stroke, congestive heart failure, peripheral vascular disease, and amputations) as well as microvascular complications (retinopathy, nephropathy, neuropathy) [10].

Tight blood glucose management only reduces the risk of microvascular complications, but tight blood pressure control reduces the risk of both micro and macrovascular complications. Strict blood pressure management is less expensive and easier for doctors and patients to implement than strict glucose control [11].

In diabetic hypertensive patients, the target blood pressure is 130/80mmHg. The dietary management was given alone, and then the pharmacological treatment was given if 130-139/80-89 mmHg or above. If the blood pressure is more than 140/90mmHg then both pharmacological treatment and dietary management should be given to the individual [11].

In diabetic-hypertensive individuals, thiazide-like diuretics are recommended for first-line treatment for treating hypertension [12] and angiotensin receptor blockers (ARB), calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACE inhibitors) have been long regarded as standard drugs in hypertension treatment. Beta-blockers are still used as adjuvant therapy in individuals who require multiple drug therapy and they are given to individuals such as tachycardia, heart failure, and ischemic heart disease [13]. Sodium-glucose cotransporter-2 inhibitors (SGLT-2 inhibitors) lower blood pressure by reducing kidney and heart damage. Glucagon-like peptide-1 receptor agonists (GLP1-RA) moderately lower blood pressure [14]. Dipeptide peptidase-4 inhibitors (DPP-4 inhibitors) also reduce blood pressure.

The study of the use of anti-diabetic drugs and antihypertensive drugs in hospitals confirms that rational treatment can improve clinical outcomes in the form of blood glucose levels and blood pressure levels, indicating that there is a significant relationship between the therapy given and clinical outcomes. We are interested in doing research on (i) how anti-hypertensive and anti-diabetic drugs are used in diabetic hypertensive outpatients. (ii) If there is any relationship between anti-diabetic or anti-hypertensive drugs and blood sugar levels or blood pressure levels in diabetic hypertensive outpatients.

2. Methodology

The study was a prospective single-centered observational study that was conducted in the Department of General Medicine at Trust Multispeciality Hospitals in Kakinada. The duration of the study was about 6 months from November 2022 to April 2023. This was a non-comparative observational study conducted on around 300 diabetic-hypertensive individuals. The sample data was collected according to the data collection form, as per the study criteria, the time taken to collect the data was about five and a half months, and the remaining time was allocated for the study Data's statistical analysis.

The study criteria include both males and females who have both diabetes and hypertension and all types of subjects who are currently receiving treatment at the hospital. The study criteria exclude those subjects who do not have either diabetes or hypertension, pregnant women, breastfeeding women, Pediatric patients, and subjects who are not receiving treatment in the same hospital. The data was collected from the subjects by taking their prescriptions, and by interviewing them after collecting their written informed consent forms. The data collection form consists of about patient's demographic details, co-morbid conditions, occupation, diagnosis, clinical outcome, and the anti-diabetic and anti-hypertensive drugs prescribed by the physician. The analysis of the study was done with respect to patient consent and other data collected from the public domain. Thus, the approval of the ethical committee was not required for further publication.

The data was collected from the subjects and arranged according to the study criteria and statistical analysis was conducted using Microsoft Excel. Simple statistics were used to analyze the study. The results of the study were expressed in percentages (%). To determine the relationship between anti-diabetic or anti-hypertensive drug therapy with blood glucose levels or blood pressure levels by using relative risk (measurement of risk). If the relative risk is more than 1 then positive outcome, relative risk is less than 1 then negative outcome.

3. Results and discussion

A 6-month single-centered, prospective observational study was conducted among 300 subjects who are diagnosed with both diabetes and hypertension in the department of general medicine at the Trust Multi-Speciality hospitals. Around 320 case sheets were collected, in some of them, the data was missing such as blood glucose levels and some of them are not willing to participate in the study. Thus, the total number of participants who are willing to participate in the study was 300. The descriptive statistics of the data are provided in Figure 1.

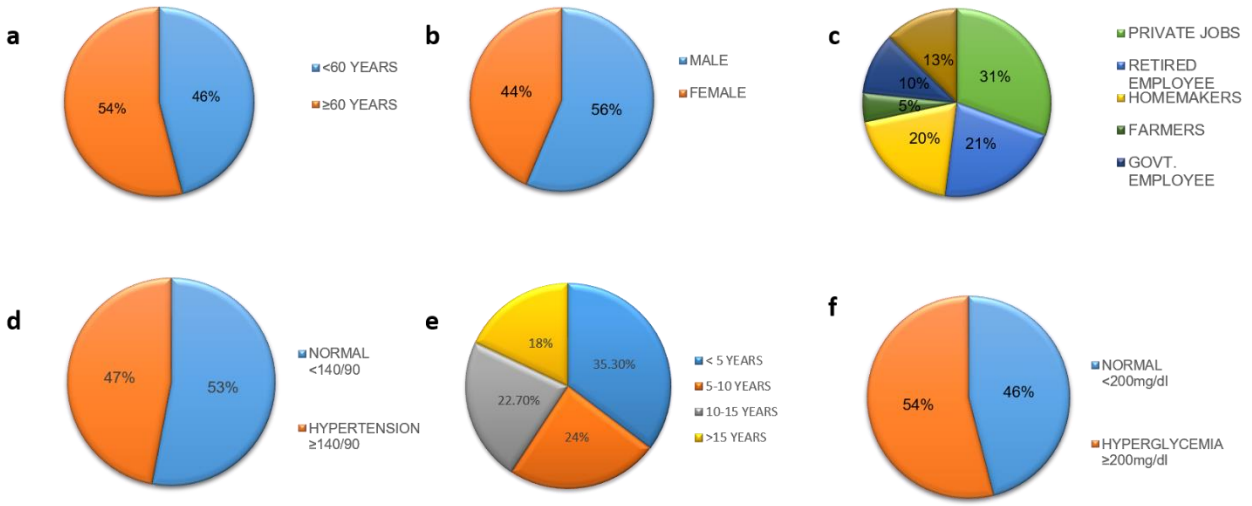

Figure 1. a. Age-wise distribution of Patients with Diabetes-Hypertension b. Gender-wise distribution of Patients with Diabetes-Hypertension c. Occupation-wise distribution of patients with Diabetes-Hypertension d. Blood pressure levels distribution among patients with Diabetes-Hypertension e. Duration of hypertension in patients with Diabetes-Hypertension f. Random blood sugar levels distribution among patients with Diabetes-Hypertension

3.1 Description of the data: A total of 300 participants data were grouped into <60 years and ≥60 years. In that, the observed data was found to be 138 (46%) patients were <60 years and 162 (54%) patients were ≥60 years were affected by both diabetes and hypertension, with an average age of 58.8 years. Thus, this study indicates that the age group above 60 has a higher chance of getting diabetes and hypertension. 168 (56%) patients were males and 132 (44%) patients were females. This indicates males were more prone to both diabetes and hypertension disorders when compared with females. 300 participants' data were grouped into categories based on their occupations. In that, the observed data was found to be 92 (30.6%) were private jobs, 64 (21.4%) were retired employees, 59 (19.6%) were homemakers, 38 (12.7%) were business, 32 (10.7%) were government employees, 15 (5%) were farmers. The uncontrolled blood pressure levels were observed among 159 (53%) patients and controlled blood pressure levels were observed among 141 (47%) patients. The uncontrolled blood sugar levels were observed in 138 (46%) patients and controlled random blood sugar levels were observed in 162 (54%) patients.

Table 1 shows the distribution of other comorbid conditions among 300 diabetes hypertensive patients. Diabetes hypertension with CAD 32 (11.4%), diabetes hypertension with CKD 62 (20.6%), diabetes hypertension with Dyslipidemia 32 (10.6%), diabetes hypertension with UTI 45 (15%), diabetes hypertension with neuropathic diabetes 42 (14%), diabetes hypertension with stroke 13 (4.4%), and only diabetes hypertension 72 (24%) were included in this study

Table 1. Duration of diabetes in patients with Diabetes-Hypertension

Duration of diabetes	No. of patients (n=300)
<5 years	122 (40.7%)
5-10 years	76 (25.3%)
10-15 years	45 (15%)
>15 years	57 (19%)

Table 2. Comorbidity-wise distribution among patients with Diabetes-Hypertension

Comorbidities	No.of patients (n=300)
HTN, DM	72 (24%)
HTN, DM, CAD	34 (11.4%)
HTN, DM, CKD	62 (20.6%)
HTN, DM, DYSLIPIDEMIA	32 (10.6%)
HTN, DM, UTI	45 (15%)
HTN, DM, Diabetic neuropathy	42 (14%)
HTN, DM, Stroke	13 (4.4%)

HTN: Hypertension DM: Diabetes mellitus CAD: Coronary artery disease

3.2 Frequency of antidiabetic drugs usage: Table 3, 4 and 5 shows, the classification of the anti-diabetic drugs prescribed for 300 diabetic-hypertension patients. In this study metformin 21 (7%) was the most prescribed monotherapy drug, followed by Glimepiride and Voglibose 11 (3.6%) and Linagliptin 3 (1%) was the least prescribed monotherapy drug. Metformin with Glimepiride 25 (8.3%), two anti-diabetic drugs in combination therapy were mostly prescribed, followed by Metformin with Sitagliptin 18 (6%), and Metformin with Acarbose 6 (2%) was the least prescribed two anti-diabetic drugs in combination therapy. Metformin with Glimepiride and Voglibose 19 (6.3%) is a three-diabetic drug combination that was mostly prescribed.

Table 3. Classification of anti-diabetic drugs prescribed in patients with Diabetes-Hypertension subjects receiving monotherapy

Class of drugs	Drug names	Prescribing frequency
Biguanides	Metformin	21 (7%)
SGLT-2 Inhibitor	Dapagliflozin	9 (3%)
DPP4 Inhibitor	Teneligliptin	4 (1.3%)
	Vildagliptin	5 (1.6%)
	Linagliptin	3 (1%)
α-glucosidase Inhibitor	Voglibose	11 (3.6%)
Meglitinide	Repaglinide	8 (2.6%)
Sulfonylureas	Gliclazide	10 (3.3%)
	Glimepiride	11 (3.6%)
	Total	82 (27.4%)

Table 4. Subjects receiving two anti-diabetic drugs in combination therapies

Class of drugs	Drug names	Prescribing frequency
Biguanide+DPP4 I	Metformin +Sitagliptin	18 (6%)
	Metformin + Teneligliptin	8 (2.7%)
	Metformin + Vildagliptin	17 (5.7%)
Biguanides+ Sulfonylureas	Metformin + Gliclazide	17 (5.7%)
	Metformin+ Glipizide	15 (5%)
	Metformin+ Glimepiride	25 (8.4%)
Biguanide+SGLT2 I	Metformin+ Dapagliflozin	11 (3.6%)
Biguanide+ α-glucosidase Inhibitors	Metformin + Acarbose	6 (2%)
SGLT2 I+ DPP4 I	Dapagliflozin + Sitagliptin	12 (4%)
Sulfonylureas+ α-glucosidase I	Gliclazide + Acarbose	15 (5%)
Biguanide+ Insulin	Metformin + Insulin	16 (5.3%)
SGLT2 I+ Insulin	Dapagliflozin + Insulin	17 (5.6%)
Sulfonylureas+ Insulin	Glimepiride+ Insulin	15 (5%)
	Total	192 (64%)

Table 5. Subjects receiving three anti-diabetic drugs in combination therapies

Class of drugs	Drug names	Prescribing frequency
Biguanide+ Sulfonylureas + α-glucosidase Inhibitors	Metformin+ Glimepiride+ Voglibose	19 (6.3%)
Biguanide+ Sulfonylurea+ Insulin	Metformin + Glimepiride+ Insulin	7 (2.3%)
	Total	26 (8.6%)

3.3 Antihypertensive drugs in usage: Table 6 shows the classification of the anti-hypertension drugs prescribed for 300 diabetic-hypertension patients. In this study, Metoprolol 35 (11.7%) was the most prescribed monotherapy drug, followed by Torsemide 24 (8%), and Ramipril and Metolazone 4 (1.3%) was the least prescribed monotherapy drug. Metoprolol with Cilnidipine 17 (5.6%) two anti-hypertension drugs in combination therapy was most prescribed, followed by Metoprolol with Olmesartan 14 (4.6%) and furosemide with spironolactone and Telmisartan with hydrochlorothiazide 3 (1%) was the least prescribed two anti-hypertensive drug in combination therapy. Olmesartan with hydrochlorothiazide and amlodipine 24 (8%) three anti-hypertensive drugs combination that were mostly prescribed.

Table 6. Classification of anti-hypertensive drugs prescribed in patients with Diabetes-Hypertension subjects receiving monotherapy

Class of drugs	Drug names	Prescribing frequency
Beta-blocker	Metoprolol	35 (11.7%)
	Carvedilol	22 (7.3%)
	Bisoprolol	5 (1.7%)
Diuretics	Torsemide	24 (8%)
	Eplerenone	8 (2.7%)
	Metolazone	4 (1.4%)
ARB	Telmisartan	18 (6%)
	Olmesartan	20 (20%)
	Losartan	6 (2%)
Alpha blocker	Prazosin	15 (5%)
Vasodilator	Clonidine	5 (1.7%)
ACE Inhibitor	Ramipril	4 (1.4%)
CCB	Cilnidipine	13 (4.4%)
	Total	179 (59.7%)

Table 7 and 8shows the relationship between monotherapy, dual therapy, and triple therapy of anti-hypertension drugs with clinical outcomes among 300 diabetic-hypertensive patients. 98 subjects with controlled blood pressure and 81 with uncontrolled blood pressure are receiving monotherapy. 48 subjects with controlled blood pressure and 33 subjects with uncontrolled blood pressure are receiving dual therapy. 22 subjects with controlled blood pressure and 18 subjects with uncontrolled blood pressure are receiving triple therapy (shown in Figure 2 and 3).

Table 7. Subjects receiving two anti-HTN drugs in combination therapies

Class of drugs	Drug names	Prescribing frequency
CCB+ β-blocker	Cilnidipine+ Metoprolol	17 (5.6%)
	Amlodipine + Metoprolol	12 (4%)
ARB+ β-blocker	Olmesartan +Metoprolol	14 (4.6%)
	Telmisartan+ Metoprolol	10 (3.4%)
ARB+ CCB	Telmisartan+ Cilnidipine	8 (2.6%)
	Olmesartan + amlodipine	6 (2%)
β-blocker + ACEI	Metoprolol+ Ramipril	4 (1.4%)
ARB+ Diuretic	Telmisartan+ Hydrochlorothiazide	3 (1%)
	Losartan+ Hydrochlorothiazide	4 (1.4%)
Two diuretics	Furosemide+ Spironolactone	3 (1%)
	Total	81 (27%)

Table 8. Subjects receiving three anti-HTN drugs in combination therapies

Class of drugs	Drug names	Prescribing frequency
ARB+ Diuretics+ CCB	Olmesartan+ Hydrochlorothiazide+ Amlodipine	24 (8%)
	Telmisartan+ Hydrochlorothiazide+ Amlodipine	16 (5.3%)
	Total	40 (13.3%)

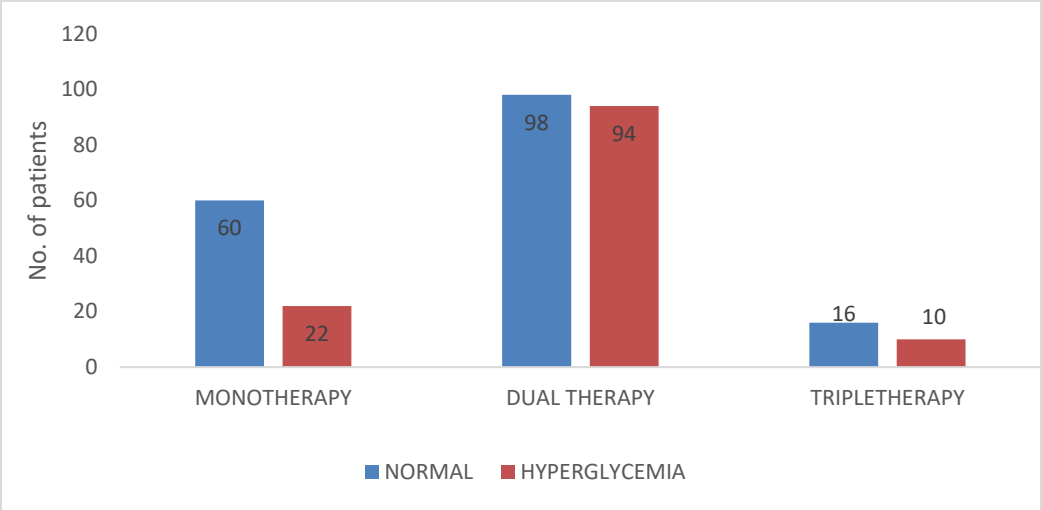

Figure 2. Relationship to anti-diabetic therapy with blood glucose levels

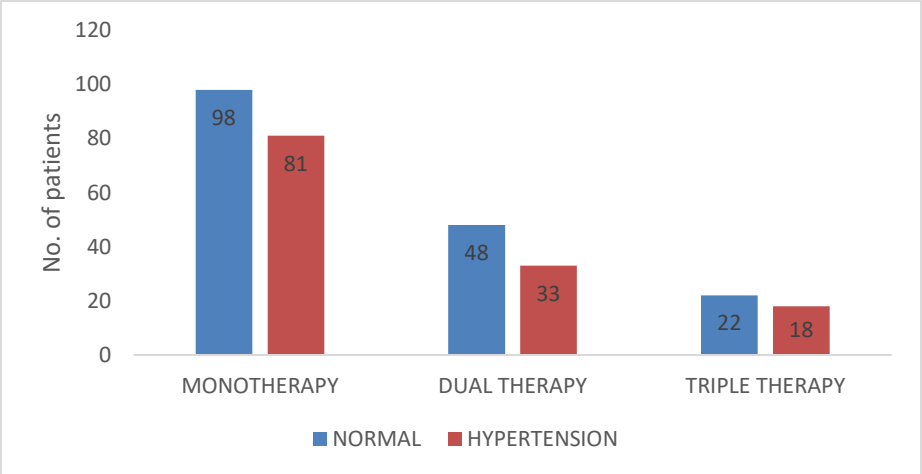

Figure 3. Relationship to anti-hypertension therapy with blood pressure levels

3.4 Antidiabetic drug usage: Table 9 shows, the relationship between monotherapy, dual therapy, and triple therapy of anti-diabetic drugs with clinical outcomes among 300 diabetic-hypertensive patients. 56 subjects with controlled blood sugar and 26 subjects with Hyperglycemia are receiving monotherapy. 98 subjects with controlled blood sugar and 94 subjects with Hyperglycemia receive dual therapy.16 subjects with controlled blood sugar and 10 with Hyperglycemia are receiving triple therapy.

3.5 Relative risk: Table 9 shows the relative risk of monotherapy and combination therapy of anti-diabetic drug therapy with random blood sugar levels in diabetic-hypertensive patients is 0.765. If the relative risk was less than 1, then there is no association between the therapy and the outcome.

Table 9. Relative risk of monotherapy and combination therapy of anti-diabetic drug therapy with blood glucose levels in diabetic-hypertension patients

Type of therapy	Subjects with normal blood glucose levels	Subjects with hyperglycemia	Total (n=300)	Relative risk
Anti-DM Combination therapies	156 (71.55%)	62 (28.44%)	218	0.977
Anti-DM Monotherapy	60 (73.17%)	22 (26.82%)	82	

Table 10 shows, the relative risk of monotherapy and combination therapy of anti-hypertension drug therapy with blood pressure levels 300 in diabetic-hypertensive patients is 1.056. The relative risk was greater than 1, then there is an association between the therapy and the outcome.

Table 10 Relative risk of monotherapy and combination therapy of anti-hypertensive drug therapy with blood pressure levels in diabetic-hypertensive patients

Type of therapy	Subjects with normal blood pressure levels	Subjects with hypertension	Total (n=300)	Relative risk
Anti-HTN Combination therapies	70 (57.85%)	51 (42.14%)	121	1.056
Anti-HTN Monotherapy	98 (54.74%)	81 (45.25%)	179	

4. Conclusion

The two most prevalent non-communicable diseases in the general population were diabetes and hypertension. Metformin (7%), Metoprolol (11.7%), Metoprolol with Cilnidipine (5.6%), Metformin with Glimepiride (8.4%), Olmesartan with Amlodipine and Hydrochlorothiazide (8%) and Glimepiride with Metformin and Voglibose (6.3%) were the medicines that were most frequently prescribed to diabetics with hypertension. Although there was no correlation between the anti-diabetic drug therapy and its clinical outcome, there was a correlation between the anti-hypertensive drug therapy and its clinical outcome.

Compliance with ethical standards

Acknowledgements

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Conflict of interest statement

The authors declare there isn't any conflict of Interest..

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Author's short biography

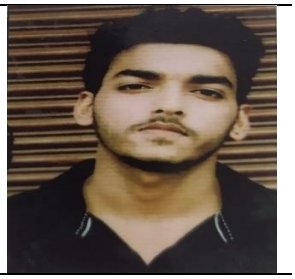
Laxmi Renuka Chikkala -As an intern in Trust Multi-speciality hospital, during this research, I collected specific data of only diabetic- hypertensive patients that falls under our aim of research from both inpatients and outpatients case files.

Priyanka Kandregula

Prepared the introduction part and explained the disease condition and their comorbidity. Drafted the methodology and helped the group with the analysis of collected data to interpret the results.

Naruttam Debnath

Worked on the methodology:-Analysed all the data collected and prepared a graphical presentation with tables with different values that we got, indicating different conditions of the patients classifying them in different groups ,for a better understanding of the case using the statistical tools.



Bipin Sah

Studied all the data collected with the reference of the graphical values and tables and came to the conclusion and made up the results of this research.