Journal of Cardiovascular Disease Research
ISSN: 0975-3583, 0976-2833 VOL15, ISSUE 09, 2024

ASSOCIATION OF HYPERTENSION AND ANTIHYPERTENSIVE TREATMENT WITH SHORT-TERM MORTALITY IN COVID-19 PATIENTS.

Akteruzzaman[1*], Wadud Chowdhury[2], Suman KS[3], Arnab KC[4], Anjuman Begum[5], Barua Sushanta[6].

1 Dr .Md. Akteruzzaman, MBBS, MD, Junior Consultant Cardiology, Sathkira Medical College Hospital, Sathkira, Bangladesh,mdakteruzzamansb27@gmail.com

2 Prof. Dr, Md. Wadud Chowdhury, MBBS, MD, Professor &Head of Cardiology, Dhaka , Medical College, Dhaka ,Bangladesh.drwadud@hotmail.com

3 Dr.Suman Kumar Saha, MBBS, MD, Assistant Professor of Cardiology, Dhaka Medical College, Dhaka ,Bangladesh.drsumankumarsaha74@gmail.com

4 Dr.Arnab Kumar Chowdhury, MBBS, MD, Medical officer Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh.
Arnabchowdhury2388@gmail.com

5 Dr.Anjuman Ara Begum, MBBS, MD, Junior Consultant, Mugda Medical College hospital, Dhaka, Bangladesh.jollysafed@gmail.com

6 Dr. Sushanta Barua, MBBS, MD, Assistant Registrar Department of Cardiology, National Institute of Cardiovascular Diseases, Dhaka, Bangladesh. sbarua330@gmail.com

Corresponding Address: Dr. Sushanta Barua,
MBBS , MD(Cardiology),Assistant Registrar,Department of Cardiology
National Institute of Cardiovascular Diseases,Sher-e-Bangla Nagar
Dhaka, Bangladesh
Sbarua330@gmail.com

Abstract:

Background: Hypertension is a prevalent comorbidity among hospitalized COVID-19 patients. The impact of hypertension and its management on COVID-19 outcomes remains controversial. This study aimed to evaluate the association between hypertension, antihypertensive treatment, and short-term mortality in COVID-19 patients.

Methods: A prospective cohort study was conducted among 260 adult COVID-19 patients admitted to the Department of Cardiology, Dhaka Medical College Hospital. Patient data, including demographic information, medical history, hypertension status, antihypertensive medication use, disease severity, and outcomes were collected. Short-term mortality was defined as in-hospital or 30-day mortality. Data were analyzed using SPSS 24.0.

Results: Hypertensive patients had significantly higher rates of ICU admission, longer hospital stays, and increased 30-day mortality compared to normotensive patients. Patients with hypertension who were not taking antihypertensive medication also exhibited worse outcomes. Conversely, those on RAAS inhibitors had lower ICU admission rates and shorter hospital stays. Multivariable analysis identified hypertension as an independent predictor of short-term mortality.

Conclusion: Hypertension is associated with increased morbidity and mortality in COVID-19 patients. Antihypertensive treatment, particularly with RAAS inhibitors, may mitigate some of these adverse effects. Further research is warranted to elucidate the complex relationship between hypertension, antihypertensive medications, and COVID-19 outcomes.

Keywords**:** ***Antihypertensive;COVID-19;Hypertension;RAAS.***

Introduction:

The emergence of COVID-19 in late 2019 has posed a significant global health challenge. With millions of cases and deaths reported worldwide, the virus has had a devastating impact [1].One critical area of concern lies in the interaction between COVID-19 and pre-existing medical conditions, particularly hypertension (high blood pressure). Hypertension is a widespread health concern, and its presence in COVID-19 patients appears to be associated with a greater risk of severe illness and mortality [2].However, the relationship between hypertension and COVID-19 outcomes is complex. Controversies surround the use of specific medications for hypertension management in these patients. ([3, 4]).This ongoing debate highlights the urgent need for further research to understand the impact of hypertension and antihypertensive drugs on COVID-19 outcomes. This study aims to address this gap in

knowledge specifically within the context of Bangladesh. By investigating the connection between hypertension, antihypertensive medication use, and short-term outcomes in hospitalized COVID-19 patients, this research will contribute valuable insights to guide patient care and improve clinical decision-making in our country.

Methodology of the Study

Study Design: A cohort study was conducted, following a group of patients with confirmed COVID-19 to assess health outcomes.

Study Setting: The study took place at the Department of Cardiology, Dhaka Medical College Hospital (DMCH), Dhaka, Bangladesh, over a 12-month period (May 2021 to April 2022).

Participants

Inclusion Criteria:

- Adults over 18 years old
- Confirmed COVID-19 infection via RT-PCR test
- Admitted to the study hospital
- With or without pre-existing hypertension

Exclusion Criteria:

- Neurological conditions (stroke, subarachnoid hemorrhage)
- Severe co-morbidities (liver/kidney disease, cancer, thyroid issues, etc.)
- Pregnancy
- Unwillingness to participate

Sample Selection

- **Sampling Method:** Purposive sampling was used, selecting participants who met the inclusion criteria.
- **Sample Size:** A total of 260 patients were enrolled in the study.

Data Collection

- **Ethical Approval:** The study received ethical approval from the relevant committee at Dhaka Medical College.
- **Data Collection Procedure:** All adult COVID-19 patients admitted to the cardiology department were screened for eligibility. Patients meeting the criteria were informed about the study and provided written consent. Demographic and health information (diabetes, dyslipidemia, heart disease, etc.) were collected. Clinical history, physical examination, and COVID-19 severity were assessed. Hypertension status and medication use were documented (previously diagnosed, medication details, etc.).Patients were categorized into groups based on hypertension and medication use. Short-term outcomes were monitored, including ICU admission, hospital stay duration and mortality (in-hospital or within 30 days).Data was collected via medical records, patient interviews and follow-up phone calls.

Data Collection Tools:

- A checklist for recording patient information
- A Bengali interview schedule with relevant questions
- A semi-structured questionnaire pre-tested on similar patients

Data Analysis: Data cleaning and verification were performed to ensure accuracy and completeness. Statistical analysis was conducted using SPSS version 24.Descriptive statistics summarized the patient population (frequencies for categorical variables, mean/median/standard deviation for continuous variables).Chi-square tests compared categorical variables between groups. Independent samples t-tests compared continuous variables between two groups. Univarate and multivariable logistic regression models were used to assess associations between factors and outcomes, adjusting for confounding variables. A significance level of $p < 0.05$ was considered statistically significant.

Results:

This study included 260 adult patients with RT-PCR-confirmed COVID-19, both with and without diagnosed hypertension, who were admitted to the Coronary Care Unit at the Department of Cardiology in DMCH. The majority of patients (35%) were aged 50-59 years, with a mean age of 55.68 ± 8.79 years. Hypertensive patients were significantly older than normotensive patients ($p < 0.05$).Male patients predominated, accounting for 150 (58%) of the participants, with a male-to-female ratio of 1.36:1. However, gender distribution did not differ significantly between hypertensive and normotensive patients ($p > 0.05$).

Most patients (70.8%) had moderate COVID-19 pneumonia, while 20% had severe and 9.2% had critical disease. Non-hypertensive patients were less likely to develop severe or critical COVID-19 ($p < 0.05$).

Both systolic and diastolic blood pressure were higher in the hypertension group ($p < 0.05$). However, heart rate and respiratory rate did not differ significantly between the two groups. Hypertensive patients had significantly higher Troponin-I and D-dimer levels compared to normotensive patients ($p < 0.05$).

Table I Sample Characteristics:

Age group (years)	**Hypertension**			
	Yes (n=112)%)	**No (n=148)(%)**	**Total (n=260)(%)**	**p-value**
Mean ±SD	56.46±9.43	53.87±8.89	55.68±8.79	**0.024 s ****
Gender				
Male	74(49%)	76(51%)	150(58%)	0.106 ns
Female	38(34%)	72(66%)	110(42%)	
Severity of COVID-19				

Moderate	44(24)	140(76)	184(70.8)	
Severe	48(92)	04(08)	52(20)	**p<0.001** [s]
Critical	20(83)	04(17)	24(9.2)	
Systolic BP (mmHg)	132.19±8.62	115.78±10.03		**<0.001** [s]
Diastolic BP	81.56±7.44	72.23±7.92		**<0.001** [s]
Heart rate (bpm)	76.59±6.52	76.51±6.40		0.92[ns]
Respiratory rate	25.21±5.44	24.88±5.16		0.612 [ns]
Biomarkers*				
WBC (x10^3/mm^3)	10.99±3.95	10.43±4.37		0.284 [ns]
Neutrophil (%)	68.61±12.41	64.29±13.90		0.01[s]
Lymphocyte (%)	22.42±10.92	22.42±10.92		0.097 [ns]
Troponin I (ng/mL)	0.04±0.03	0.02±0.01		**0.001** [s]
D-dimer(µg/mL)	2.59±2.28	1.63±1.48		**<0.001** [s]
LDH (IU/L)	397.71±187.68	397.78±210.77		0.998 [n]

Values are expressed as mean ±SD. p-value was determined by Independent sample t test.

p-value <0.05 was considered significant. ns = not significant (p>0.05), s= significant (p<0.05)

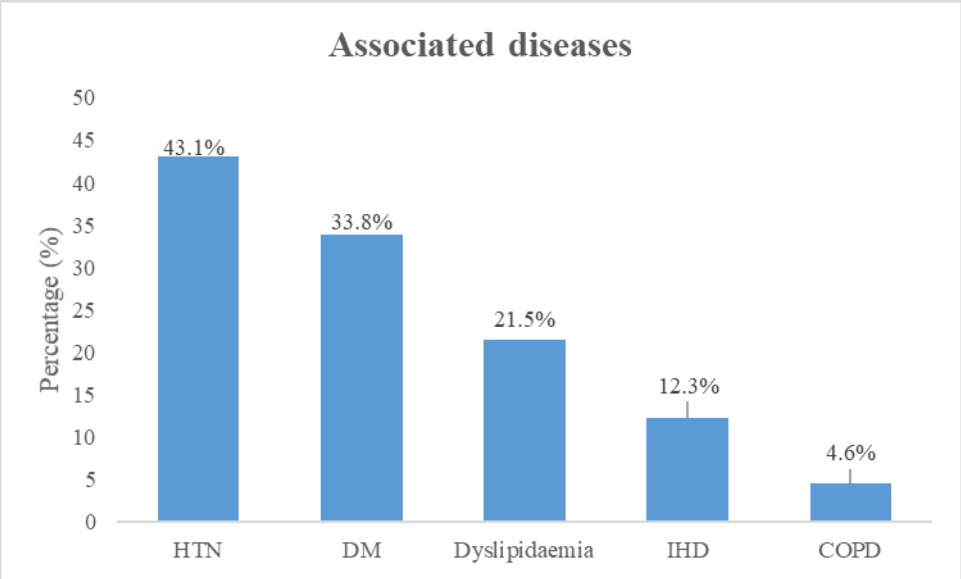

Figure 1: Associated diseases among study patients (n=260)

*Multiple response was considered

In this study, 112 patients (43.1%) had hypertension, followed in decreasing order diabetes mellitus (33.8%), dyslipidemia (21.5%), ischemic heart disease (12.3%) and COPD (4.6%), respectively.

Covid-19 patients with hypertension significantly needed more ICU support (44.64% vs 6.1%, p<0.001), longer hospital stay (16.97±2.43 vs 13.11±2.12 days, p<0.001) and higher 30-days mortality rate (25.9 vs 11.5%, p=0.003) compared to normotensive patients.

Table II: Association of Hypertension with Short-term outcome between groups (n=260)

Short term outcome	Hypertension			
	Yes (n=112) N(%)	No (n=148) N(%)	Total (n=260) N(%)	p-value
ICU support				
Needed	50 (44.64)	9 (6.08)	59(22.69)	**<0.001[s] ***
Not needed	62 (55.36)	139 (93.92)	201(77.31)	
Hospital Stay (days)	16.97±2.43	13.11±12.12	15.04±2.46	**<0.001[s] ****
30-days mortality	29 (25.89)	17 (11.49)	46(17.69)	**0.003[s] ***

p-value was determined by *Chi square test and ** Independent sample t test. p-value <0.05 was considered significant. ns = not significant (p>0.05), s= significant (p<0.05)

COVID-19 patients with hypertension who were not taking any anti-hypertensive drugs also needed more ICU support (63.89% vs 35.53%, p=0.005), longer hospital stay (18.03±2.10 vs 16.47±2.42 days, p=0.001) and higher 30-days mortality rate (38.89 vs 19.74%, p=0.031) compared to those who were taking anti-hypertensive drugs.

Table III: Association of Anti-hypertensive treatment with Short-term out come between groups (n=112)

Short term outcome	Hypertensive patients getting Anti-hypertensive drugs			
	Yes (n=76) N(%)	No (n=36) N(%)	Total (n=112) N(%)	p-value
ICU support				
Needed	27 (35.53)	23 (63.89)	50 (44.64)	**0.005 s ***
Not needed	49 (64.47)	13 (36.11)	62 (55.36)	
Hospital Stay (days)	16.47±2.42	18.03±2.10	16.97±2.43	**0.001s ****
30-days mortality	15 (19.74)	14 (38.89)	29 (25.89)	**0.031s ***

p-value was determined by *Chi square test and ** Independent sample t test. p-value <0.05 was considered significant. ns = not significant (p>0.05), s= significant (p<0.05)

COVID-19 patients with hypertension who were taking RAAS inhibitor, needed lesser ICU support (22.22% vs 47.50%, p=0.022) and shorter hospital stay (15.78±1.64 vs 18,13±2.11 days, p<0.001

Table IV: Association of RAAS inhibitor with Short-term outcome between groups (n=76)

Short term outcome	Patients treated with RAAS inhibitor			
	Yes (n=36) N(%)	No (n=40) N(%)	Total (n=76) N(%)	p-value
ICU support				
Needed	8 (22.22)	19 (47.50)	27 (35.53)	**0.022^{s}** *
Not needed	28 (77.78)	21 (52.50)	49 (64.47)	
Hospital Stay (days)	15.78±1.64	18.13±2.11	16.47±2.42	**<0.001 ^{s}** **
30-days mortality	4 (11.11)	11 (27.50)	15 (19.74)	0.073^{ns} *

P-value was determined by *Chi square test and ** Independent sample t test. p-value <0.05 was considered significant. ns = not significant (p>0.05), s= significant (p<0.05).

Univariable logistic regression analysis showed that hypertension (OR=2.69, 95% CI= 1.393-5.20) and IHD (OR=2.89, 95% CI= 1.28-6.52) were the significant predictor for short-term mortality in COVID-19 patients.

Table V: Univariable logistic regression to detect odds ratio of variables for predicting short term mortality (n=260)

Predictor	OR	95% CI		p-value
		Lower	Upper	
DM	1.48	0.770	2.842	0.240 ns
HTN	**2.69**	**1.393**	**5.20**	**0.003 s**
Dyslipidemia	1.57	0.76	3.23	0.224 ns
IHD	**2.89**	**1.28**	**6.52**	**0.011 s**
COPD	2.45	0.706	8.52	0.158 ns
Neutrophil lymphocyte ratio	0.821	0.428	1.573	0.552 ns
CRP	0.703	0.186	2.66	0.603 ns
D-dimer	1.33	0.618	0.437	4.025 ns
Troponin-I	1.99	0.728	5.44	0.180 ns

p-value <0.05 was considered significant. ns = not significant (p>0.05), s= significant (p<0.05)

Multivariable logistic regression analysis showed that hypertension (OR=2.43, 95% CI= 1.18-5.04) was the independent predictor for short-term mortality in COVID-19 patients after adjusting DM, dyslipidemia, IHD, COPD, Troponin-I and D-dimer.

Table-VI: Multivariable logistic regression for short term mortality with confounding factors (n=260)

Predictor	OR	95% CI		p-value
		Lower	Upper	
DM	1.159	.558	2.410	0.692 ns
HTN	**2.433**	**1.175**	**5.040**	**0.017 s**
Dyslipidemia	1.813	.827	3.976	0.137 ns
IHD	2.841	0.967	6.955	0.052 ns
COPD	3.925	.933	14.911	0.055 ns
D-dimer	1.061	.314	3.583	0.924 ns
Troponin-I	1.061	.343	3.278	0.918 ns

p-value <0.05 was considered significant. ns = not significant (p>0.05), s= significant (p<0.05)

Discussion

This study investigated the association between hypertension and its treatment with short-term mortality in COVID-19 patients. Our findings support previous research, suggesting that:

Hypertension is a risk factor: COVID-19 patients with hypertension experienced worse outcomes, including increased need for intensive care, longer hospital stays and higher mortality rates compared to those with normal blood pressure. This aligns with prior studies demonstrating a link between hypertension and negative COVID-19 outcomes [1-5].

Comorbidities and age play a role: Underlying conditions like diabetes and dyslipidemia were prevalent in our hypertensive group, potentially contributing to poorer outcomes. Additionally, hypertensive patients tended to be older, another established risk factor for severe COVID-19

[6]. Hypertensive patients had significantly higher Troponin-I and D-dimer compared to normotensive patients ($p < 0.05$).Previous studies also found that in-hospital mortality of COVID-19 patients were closely linked to elevated serum troponin-I [7,8,9]and D-dimer[10,11,12,13,14]. In the current study, hypertensive patients who were not taking any anti-hypertensive agents had also needed more ICU support (63.89% vs 35.53%, $p=0.005$), longer hospital stay duration (18.03±2.10 vs 16.47±2.42 days, $p=0.001$) and higher 30-days mortality rate (38.89 vs 19.74%, $p=0.031$) compared to those who were taking anti-hypertensive agents. Similarly, Gao et al. also found that individuals who received antihypertensive medications prior to admission had a reduced death rate than those who did not (Gao et al. 2020). Hence, despite the limited clinical evidence suggesting that antihypertensive medications can affect COVID-19 prognosis, this study recommends that it is better to continue standard antihypertensive medications in accordance with the European Society of Cardiology (ESC) Council [15]. In the present study, patients who were taking RAAS inhibitor, needed lesser ICU support (22.22% vs 47.50%, $p=0.022$) and shorter hospital stay (13.11±2.12 vs 16.86±2.53 days, $p<0.001$).

Uncontrolled hypertension worsens prognosis: Hypertensive patients not taking medications had significantly worse outcomes compared to those on medication. This finding suggests the importance of managing hypertension for optimal COVID-19 prognosis, as observed by Gao et al. [2].

RAAS inhibitors and mortality: There was no significant difference in mortality between patients taking RAAS inhibitors and those on other antihypertensive. While some studies suggest a potential benefit of RAAS inhibitors [8-10], the evidence is inconclusive, and our results align with Gao et al. who found no significant difference in mortality based on RAAS inhibitor use [2].Furthermore, Ferrario [16] hypothesized that the use of antihypertensive drugs- ACEIs and ARBs may enhance ACE2 expression, making patients more vulnerable to viral host cell entry and proliferation. However, changes in serum or pulmonary ACE2 levels in response to ACEIs or ARBs, have shown conflicting and limited evidence from laboratory or clinical investigations (Vaduganathan et al. 2020).

Limitations:

This study is observational, and causal relationships cannot be definitively established. More research is needed to explore the mechanisms behind the observed associations.

Conclusion:

Hypertension is a significant risk factor for severe COVID-19 outcomes. Our findings highlight the importance of managing hypertension and continuing antihypertensive medications during the pandemic. While the role of RAAS inhibitors remains unclear, current evidence suggests no reason to discontinue their use. Further research is warranted to elucidate the specific effects of different antihypertensive medications on COVID-19 prognosis.

Acknowledgment:

Acknowledge to study participant

Conflict of interest: none

REFERENCES

1.Lu, H., Stratton, C.W. & Tang, Y.W., 2020. Outbreak of pneumonia of unknown etiology in Wuhan, China: The mystery and the miracle. Journal of Medical Virology, 92(4), 401–402.

2. Gao, C., Cai, Y., Zhang, K., et al. (2020). Association of hypertension and antihypertensive treatment with COVID-19 mortality: a retrospective observational study. European Heart Journal, 41(22), 2058–2066.

3.Semenzato, L., Botton, J., Drouin, J., Baricault, B., Vabre, C., Cuenot, F., et al., 2021. Antihypertensive Drugs and COVID-19 Risk: A Cohort Study of 2 Million Hypertensive Patients. Hypertension, 77(1), 833–842.

4. Chouchana, L., Beeker, N., Garcelon, N., Rance, B., Paris, N., Salamanca, E., et al., 2021. Association of Antihypertensive Agents with the Risk of In-Hospital Death in Patients with Covid-19. Cardiovascular Drugs and Therapy, 1(1), 1–6.

5.Abayomi, A., Osibogun, A., Kanma-okafor, O., Idris, J., Bowale, A., Wright, O., et al., 2021.

Morbidity and mortality outcomes of COVID-19 patients with and without hypertension in Lagos , Nigeria : a retrospective cohort study. 6(1),1-18.

6. Fang, X., Li, S., Yu, H., Wang, P., Zhang, Y., Chen, Z., et al., 2020. Epidemiological, comorbidity factors with severity and prognosis. Aging, 12(13), 12493–12503.

7.Lombardi, C.M., Carubelli, V., Iorio, A., Inciardi, R.M., Bellasi, A., Canale, C., et al., 2020. Association of Troponin Levels with Mortality in Italian Patients Hospitalized with Coronavirus Disease 2019: Results of a Multicenter Study. JAMA Cardiology, 5(11), 1274–1280.

8.Salvatici, M., Barbieri, B., Cioffi, S.M.G., Morenghi, E., Leone, F.P., Maura, F., et al., 2020. Association between cardiac troponin I and mortality in patients with COVID-19. Biomarkers, 25(8), 634–640.

9.Wibowo, A., Pranata, R., Akbar, M.R., Purnomowati, A. & Martha, J.W., 2021. Prognostic performance of troponin in COVID-19: A diagnostic meta-analysis and meta-regression. International Journal of Infectious Diseases, 105, 312–318.

10.Chen, H., Guo, J., Wang, C., Luo, F., Yu, X., Zhang, W., et al., 2020. Clinical characteristics and intrauterine vertical transmission potential of COVID-19 infection in nine pregnant women: a retrospective review of medical records. The Lancet, 395(10226), 809–815.

11.Guan, W.-J., Liang, W.-H., Zhao, Y., Liang, H.-R., Chen, Z.-S., Li, Y.-M., et al., 2020. Comorbidity and its impact on 1590 patients with COVID-19 in China: a nationwide analysis. The European respiratory journal, 55(5),1-2.

12.Tang, N., Li, D., Wang, X. & Sun, Z., 2020. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. Journal of Thrombosis and Haemostasis, 18(4), 844–847.

13.Vidali, S., Morosetti, D., Cossu, E., Luisi, M.L.E., Pancani, S., Semeraro, V., et al., 2020. D-dimer as an indicator of prognosis in SARS-CoV-2 infection: a systematic review. ERJ Open Research, 6(2), 00260–02020.

14.Wang, D., Hu, B., Hu, C., Zhu, F., Liu, X., Zhang, J., et al., 2020. Clinical Characteristics of

138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - Journal of the American Medical Association, 323(11), 1061–1069.

15. de Simone, G. (2020). Position statement of the ESC council on hypertension on ACE-inhibitors and angiotensin receptor blockers. European Society of Cardiology.

16.Ferrario, C.M., Jessup, J., Chappell, M.C., Averill, D.B., Brosnihan, K.B., Tallant, E.A., et al., 2005. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. Circulation, 111(20), 2605–2610.

17.Vaduganathan, M., Vardeny, O., Michel, T., McMurray, J.J. V, Pfeffer, M.A. & Solomon, S.D., 2020. Renin-Angiotensin-Aldosterone System Inhibitors in Patients with Covid-19. The New England journal of medicine, 382(17), 1653–1659.