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Effect of ACE Inhibitors and ARBs in Severity of COVID-19 in Hypertensive Patients- A Retrospective Study.

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ABSTRACT

AIM: To study the disease severity of COVID-19 in hypertensive patients using ARBs and ACE inhibitors.

OBJECTIVES:

- To evaluate the correlation between the use of ARBs and ACEi and hypertensive COVID 19 patients.
- To assess the severity of disease in such patients

METHODS AND RESULTS: The data pertaining to NESCO jumbo covid facility, was retrospectively studied using electronic medical records available. Clinical outcomes were categorised using WHO classification of cases. The study includes 412 patients with hypertension of which 226 patients were on ACEi and ARBs. There was statistically no significant difference (p-0.749) in the severity of disease in patients using these drugs. Incidence of asymptomatic cases was higher in male patients.(p- 0.033)

CONCLUSION: There is no correlation between the use of ACEi and ARBs and clinical outcomes in COVID- 19 patients. Hence these drugs can be safely used in such patients.

KEY WORDS: COVID-19, ACEi (Angiotensin converting enzyme inhibitors), ARBs (angiotensin receptor blockers), RAAS (renin angiotensin aldosterone system), Hypertension.

I. INTRODUCTION:

In the late 2019, a novel corona virus, lead to the spread of a SARS Cov like infection in the city of Wuhan in China which was subsequently named by WHO as 2019-nCov causing COVID-19 (corona virus disease 2019) (1)(2). The high infectivity of the virus and the lack of vaccine lead to the rapid spread of virus resulting in the present situation of a global pandemic. As of November 2020, more than 63 million cases were recorded world wide.

SARS Cov2 shares structural similarity with SARS Cov and the binding affinity of SARS Cov2 with ACE 2 (angiotensin converting enzyme) receptor is similar to that of SARS Cov. Studies demonstrate that 83% of ACE 2 receptors are seen on the lung epithelium suggesting the respiratory distress caused by virus (3)(4).

Increased expression of ACE 2 receptors in various organs was found in connection with administration of ACE inhibitors and ARBs (angiotensin receptor blockers) in animal models (6). Urinary excretion of ACE 2 was seen in hypertensive patients treated with ARBs suggest that up regulation of receptors in human may occur (7). Although there is currently no evidence this could theoretically increase the viral load in COVID 19 and worsen the outcome (4)(5)(7). However, ACE2 acts as a gatekeeper for RAAS and helps in converting Angiotensin II to Angiotensin 1-7 hence diminishing its Angiotensin receptor 1 mediated deleterious effects(3-7). These conflicting views arise based on experimental studies and lack of clinical data on COVID-19.

Hypertension is one of the diseases which carry an increased risk for morbidity and mortality associated with COVID-19(8)(10). The Eighth Joint National Commission (JNC8) published evidence-based guidelines for the treatment of high blood pressure in adults, which recommended that ACE inhibitors are one of four drug classes recommended for initial therapy for adults with elevated blood pressure(9). This retrospective study was conducted to study the effect of ACE inhibitors and ARBs in COVID-19 severity in hypertensive patients.

II. METHODOLOGY:

Study design and participants:

The data pertaining to NESCO jumbo covid facility, Goregaon from June 2020 to September 2020 was retrospectively analysed to study the association between anti hypertensive drugs and COVID-19. A total of 412 patients were included in this study.

The criteria considered for inclusion of participants were: All COVID-19 patients with a history of hypertension and medication for the same who

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were tested positive using RT-PCR and rapid antigen tests; All the patients discharged from the facility. Patients with hypertension associated with other comorbidities; patients without a proper history of medication or discontinuation of medication during the stay at the facility were excluded from the study.

COVID-19 disease severity; Clinical management of COVID-19: interim guidance WHO

Mild	Symptomatic patients (Table 1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
Moderate disease	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air **Child** with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 (55). While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Severe disease	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air **Child** with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: • Central cyanosis or SpO2 < 90%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions (55,56). • Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40 (55). While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

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Hypertensives were categorised based on medical history available. Classification of severity of disease was done into asymptomatic, mild, moderate and severe based on "interim guidance for clinical management of COVID-19 given by world health organisation."

Data collection:

Patients demographic characteristics and clinical data about the symptoms and severity of disease was collected from the electronic medical records available by a single investigator.

Statistical analysis :

Data obtained was compiled on a MS Office Excel Sheet (v 2019, Microsoft Redmond Campus, Redmond, Washington, United States).

Data was subjected to statistical analysis using Statistical package for social sciences (SPSS v 26.0, IBM).

Descriptive statistics like frequencies and percentage for categorical data, Mean & SD for numerical data has been depicted.

Comparison of frequencies of categories of variables with groups was done using chi square test.

For all the statistical tests, $p<0.05$ was considered to be statistically significant, keeping α error at 5% and β error at 20%, thus giving a power to the study as 80%.

III. RESULTS:

Participants:

In total 412 participants were considered for the study with a history of hypertension. The mean age was 57.9 years (SD -11.853) with minimum 31yrs and maximum 92 years(table:1) . Among these 412 participants 155(37.6%) were female and 257(62.4%) were male patients. 226 participants were on ACEi and ARBs, 186 participants were on other antihypertensives.

Table 1

	N	Minimum	Maximum	Mean	Std. Deviation
Age	412	31	92	57,99	11,853

Clinical outcomes based on use of use of ACEi and ARBs:

Among 412 participants 9%(37) were asymptomatic; 43.9%(181) cases were mild of which 84 participants were on ACEi and ARBs; 39.1%(161) cases were moderate of which 68 participants were on ACEi and ARBs ; 8%(33) were sere of which 17 participants were on ACEi and ARBs. There was a statistically non significant difference seen for the frequencies between the groups ($p>0.05$). Refer to table 2 and graph 1.

Clinical outcomes based on gender:

Of the 37 asymptomatic patients 9 were female and 28 were male; 81 were female and 100 were male among 181 mild cases, 56 were female and 105 were male of 161 moderate cases, 9 were female and 24 were male among the 33 severe cases. There was a statistically significant / highly significant difference seen for the frequencies between the groups ($p<0.01$, 0.05) with higher frequency for Asymptomatic in males. Refer to table 3 and graph.

Comparison of frequency of ACEI AND ARBs Y no * Severity based on WHO (table:2)

		Severity based on WHO				
		Asymptomatic	Mild	Moderate	Severe	Total
ACEI AND ARBs Y no	N	17	84	68	17	186
	Y	20	97	93	16	226
	Total	37	181	161	33	412

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Chi-Square	1,217	3	0,749

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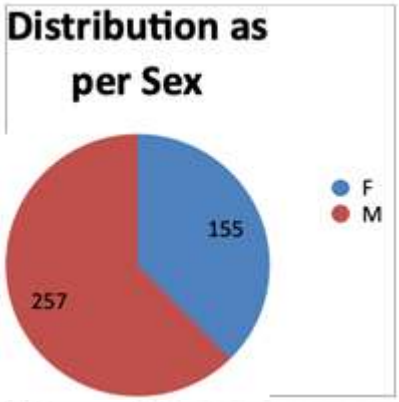

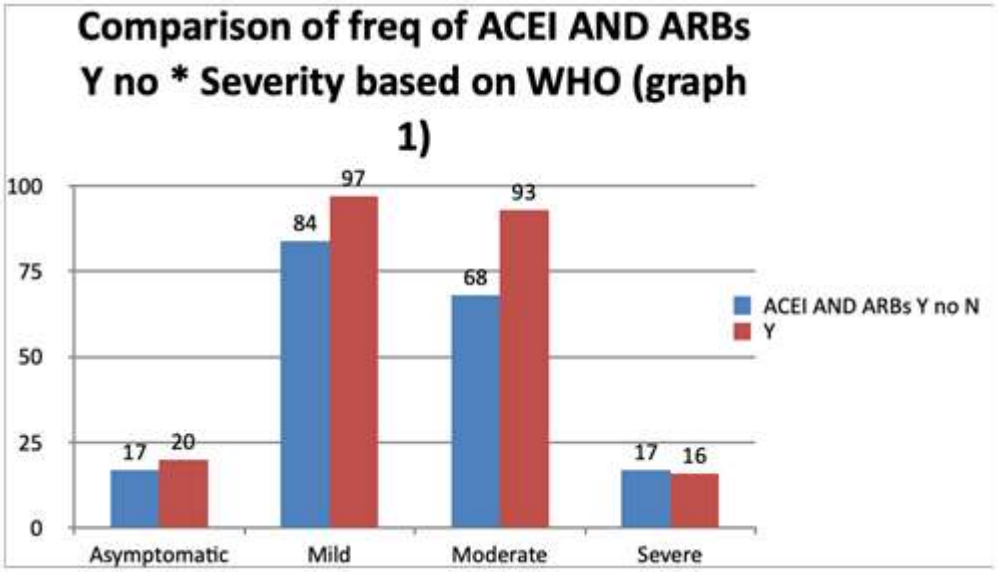

Comparison of frequency of Sex * Severity based on WHO (table 3)

		Severity based on WHO				
		Asymptomatic	Mild	Moderate	Severe	Total
Sex	F	9	81	56	9	155
	M	28	100	105	24	257
	Total	37	181	161	33	412

Chi-Square Tests			
	Value	df	Asymp. Sig. (2-sided)
Chi-Square	8,767	3	.033*

IV. DISCUSSION:

The use of ACEI/ARBs has been a controversial issue during the ongoing COVID-19 pandemic. This is due to the fact that cellular entry point for SARS Cov 2 being ACE 2 receptor and the possibility of up regulation of these receptors due to continual use of these drugs. Conversely, there is a down regulation of ACE 2 receptors by

SARS Cov 2 so the use of these drugs help in increasing the ACE 2 receptors preventing lung injury (4-7). In the present retrospective study, we found no association between the use of ACEI/ARBs and severe clinical outcomes in COVID-19. This is in contrast with the study conducted by Liabeuf et al.,(11). They found out that the use of renin angiotensin system Inhibitors was associated with 1.73 times increased risk in outcomes of COVID-19.

Choi KH et al., (12) conducted a similar study and found that there was a lower risk of severe clinical outcomes with use of ACEI/ARBs compared to other anti hypertensive drugs (aOR-0.43). Feng Z et al.,(13) conducted a multi centric study in south china and obtained similar results to study conducted by Choi KH et al., that hypertensives without ACEI/ARBs is an independent risk factor for developing severe pneumonia (aOR- 2.07). Dalan R et al., (14) studied the association of pharmacotherapy in diabetes and hypertension as risk factors for severity in COVID-19. They concluded that the use of ACEI was associated with decreased admission of patients into ICU. Similarly Zhang P et al.,(15) found a decreased in-hospital mortality in patients using ACEI/ARBs.

Felice et al., (16) conducted a study to evaluate the association of use of ACEI/ARBs and clinical deterioration in COVID 19 in an Italian cohort of 133 hypertensives. They found that chronic use of these drugs is not associated with increased severity of the disease which is similar to results in present study. Similar to the present study, Son M et al.,(17) found out that there is no association between use of RAAS inhibitors in severity and risk for COVID-19; Shah et al., (18) found that baseline use of ACEI/ARBs is not associated with severity of disease in African-American population.

Hasan et al.,(19) conducted a systematic review and meta- analysis on Mortality and Disease Severity Among COVID- 19 Patients Receiving Renin- Angiotensin System Inhibitors, they concluded that there is no increased risk associated with use of these drugs.

Soleimani A et al (20) studied effects of angiotensin receptor blockers (ARBs) on in-hospital outcomes of patients with hypertension and confirmed or clinically suspected COVID-19. They found no sex disparity in outcomes of patients; few studies found a poorer outcomes in male patients (21) this is in contrast to present study which shows there is an increased of asymptomatic cases in male population. These differences could be due to differences in selection of sample or type of study conducted.

V. LIMITATIONS:

The present study is a retrospective study and does not involve any follow up of the cases. A randomised controlled trial could be conducted to draw further conclusions and avoid all the possible confounding factors.

VI. CONCLUSION:

Among the hypertensive patients in COVID-19 the use of ACEI/ARBs is not associated with increased risk of severe clinical outcomes of the disease. This study demonstrates that as there is no possible association RAAS inhibitors should not be discontinued in hypertensive patients with COVID-19.

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