ASSOCIATION OF IN-PATIENT OUTCOMES AND RENIN-ANGIOTENSIN-ALDOSTERONE SYSTEM INHIBITOR USE AMONG HOSPITALIZED HYPERTENSIVE PATIENTS WITH CORONAVIRUS DISEASE 2019 (COVID-19) IN A TERTIARY GOVERNMENT HOSPITAL

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ABSTRACT

Background and Objectives: RAAS inhibitors were speculated to increase expression of ACE2 receptors in the respiratory tract which was feared to lead to poorer outcomes among hypertensive patients infected with COVID-19. Current evidence has not confirmed Renin-Angiotensin-Aldosterone System inhibitors exposure as harmful in patients with COVID-19 infection. This study aims to determine the association between use of RAAS inhibitors and in-patient outcomes of adult hypertensive patients admitted for COVID-19.

Methodology: A cross-sectional analytical study using case records was done on adult hypertensive patients admitted for COVID19 starting from March 2020 to March 2021 in the Philippine General Hospital, a tertiary government hospital. The association of RAAS inhibitor use and in-patient outcomes was determined using Fisher's chi-square test.

Results: A total of 29.6% (n=671) patients admitted for COVID-19 were determined to be hypertensive. Majority of hypertensive COVID-19 patients were male (52%), elderly (58%) and with moderate disease severity (51%). The most common comorbidities were community acquired pneumonia (59%), type 2 diabetes mellitus (44%) and chronic kidney disease (22%). A total of 66% (n=442) of the hypertensive patients admitted for COVID were on RAAS inhibitors with Losartan (40%) as the most commonly used agent. RAAS inhibitor use was not found to be

associated with mortality (OR 0.74, 95% CI 0.57-1.10) and development of acute kidney injury (OR 1.12, 95% CI 1.12-1.69) among hypertensive COVID19 patients. However, RAAS inhibitor use was associated with decreased mortality among hypertensive patients classified with COVID-19 moderate disease (OR 0.42, 0.19-0.92, p-value 0.02).

Conclusion: RAAS inhibitor use was not associated with mortality and development of acute kidney disease.

Keywords: COVID-19, Hypertension, Renin-Angiotensin-Aldosterone System (RAAS) inhibitor

I. INTRODUCTION

Coronavirus Disease 2019 (COVID-19) continues to endanger global health resulting in almost five million deaths worldwide[1]. In the Philippines, the disease has infected almost three million people and caused over forty-three thousand deaths as of October 2021[2]. During the start of the pandemic, there was an emerging concern regarding the management of hypertension among patients infected by COVID-19[3]. Hypertension was identified as one of the most common comorbidities associated with higher risk of developing severe cases of COVID-19[4]. Renin-Angiotensin-Aldosterone System (RAAS) inhibiting agents, including Angiotensin Converting Enzyme Inhibitors (ACE-Is) and Angiotensin Receptor Blockers (ARBs), are one of the first line anti-hypertensive medications recommended for hypertension management[5]. However, the continued use of RAAS inhibitors was questioned in the setting of COVID-19. Similar to SARS, SARS-CoV-2 is believed to infect its host through specific binding to angiotensin-converting enzyme 2 (ACE2), expressed in the lung and other tissues[6]. Given this mechanism, speculation arose that use of RAAS inhibitors, particularly ACE inhibitors or angiotensin-receptor blockers, could lead to increased expression of ACE2 in the respiratory tract, leading to poorer outcomes. This was in contrast to a previous study using animal models, which showed that in acute lung injury, angiotensin II is upregulated by ACE and leads to severe lung failure through the angiotensin II type 1 receptor. Consequently, increased ACE2 expression by preexisting ARB treatment may be protective of SARS-CoV-2 infection[7]. Current evidence has not confirmed ACEI/ARB exposure as harmful in patients with COVID-19 infection[8-10], including the BRACE-CORONA trial which showed that continuing RAS-inhibitors in patients with severe COVID did not impact mortality[11].

Significance and Scope of the Study

Appropriate and individualized management for hypertension is essential for better outcomes. Establishing a relationship between use of RAAS inhibitors and adverse in-patient outcome among hypertensive patients hospitalized with COVID-19 would guide clinicians in providing optimal management. In this study, we determined the association between use of RAAS inhibitors and in-patient outcomes of adult hypertensive patients admitted for COVID-19 in a tertiary government hospital from March 2020 to March 2021.

General Objective

To determine the association between the use of RAAS inhibitor (ACEI, ARB) and in-patient outcomes of hospitalized hypertensive patients with COVID-19 in a tertiary government hospital.

Specific Objectives:

1. To describe the demographic profile of hypertensive inpatients with COVID-19
2. To identify the prevalence of RAAS inhibitor use among hospitalized hypertensive patients with COVID-19
3. To determine the association between the use of RAAS inhibitors and COVID-19 disease in-patient outcomes in terms of mortality and development of acute kidney injury

Operational Definition of Terms:

COVID-19 Patients

Patients diagnosed with the COVID-19 disease defined by having at least one positive result for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) by Reverse Transcription - Polymerase Chain Reaction (RT-PCR) assay from a nasopharyngeal/oropharyngeal swab or endotracheal aspirate specimen

Renin-Angiotensin-Aldosterone System (RAAS) Inhibitors

RAAS inhibitors are a group of drugs that act by inhibiting the renin-angiotensin-aldosterone system and include angiotensin-converting enzyme (ACE) inhibitors (i.e., Captopril, Enalapril), angiotensin-receptor blockers (ARBs) (i.e., Losartan, Telmisartan, Valsartan), and direct renin inhibitors.

Hypertension

A clinical diagnosis made after determination of an average of two or more seated blood pressure readings of systolic blood pressure ≥140mmHg and diastolic blood pressure ≥90mmHg during each of two or more outpatient visits[12]. In this study, this includes patients diagnosed with hypertension prior to infection with COVID-19 and were advised treatment with antihypertensive agents including, but not limited to, renin-angiotensin-aldosterone system inhibitors, beta blockers, calcium channel blockers and diuretics.

Acute Kidney Injury

Acute kidney injury diagnosis is determined by the clinician based on the following criteria: (1) Increase in serum creatinine by ≥0.3mg/dl within 48 hours; (2) Increase in

serum creatinine ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; (3) Urine volume <0.5 ml/kg/h for 6 hours[13].

Limitations of the Study

Outcomes after discharge and economic burden of hospitalization and overall management were not described. Changes in the definition/staging of COVID classification with the publishing of local COVID guidelines in July 2020 were not factored in during the analysis of the information.

II. METHODS

Study Design

This is a cross sectional analytical study that reviewed the case records of adult hypertensive patients admitted to the Philippine General Hospital for COVID-19 starting from March 2020 to March 2021.

Study Setting

The study was conducted in the Philippine General Hospital, a state-owned tertiary hospital located in Manila, Philippines, which was designated by the Department of Health as one of the COVID 19 referral centers. PGH has allotted wards and intensive care units for patients diagnosed with COVID-19. Patients admitted to these areas were received either from the hospital's emergency room or transferred from other institutions, quarantine centers or from home as organized by the Department of Health's One Hospital Transfer Command.

Population

A total of 2,264 charts were reviewed for all COVID 19 patients from March 2020 to March 2021 to include all hypertensive patients admitted for COVID-19 in PGH. Of those, 1593 charts were not included due to the following reasons: non-hypertensive, pregnant, pediatric or transferred to a quarantine facility.

Inclusion and Exclusion Criteria

Inclusion:

Records of adult patients (19 years old and above) with known hypertension admitted for or later known to have COVID-19 at the wards and intensive care units from March 2020 to March 2021 were reviewed. Patients who have used antihypertensives regularly prior to admission as determined by chart review or during hospital stay including those for whom medications were discontinued for whatever reason (i.e., shock or acute kidney injury) were included.

Exclusion:

Pregnant adult patients, patients with incomplete medical records and those transferred to a step-down quarantine facility were not included in the study.

Data Collection Process

Data collection was done through chart review of written and electronic medical records of all patients admitted at the COVID-19 wards/ICUs of PGH from March 2020 to March 2021. Patient charts were retrieved from the Medical Records Section and the computerized registry of admissions and discharges of PGH. The investigators reviewed each chart and included the charts of patients based on the aforementioned inclusion and

exclusion criteria (Figure 1). For patients included in the study, the following information were collected: age (years), sex, COVID-19 severity classification, baseline inflammatory markers (hsCRP, Ferritin, LDH, Interleukin-6), co-morbidities, anti-hypertensive medications used. The prevalence of RAAS inhibitor use among hospitalized hypertensive patients with COVID-19 patients was identified including the most commonly used agents. In-patient outcomes in terms of mortality and development of acute kidney injury were also gathered. Specific underlying causes of death were also documented whenever applicable. The COVID-19 severity classification indicated at the time in the chart by the physicians in charge was used as the basis for classifying patients in the study.

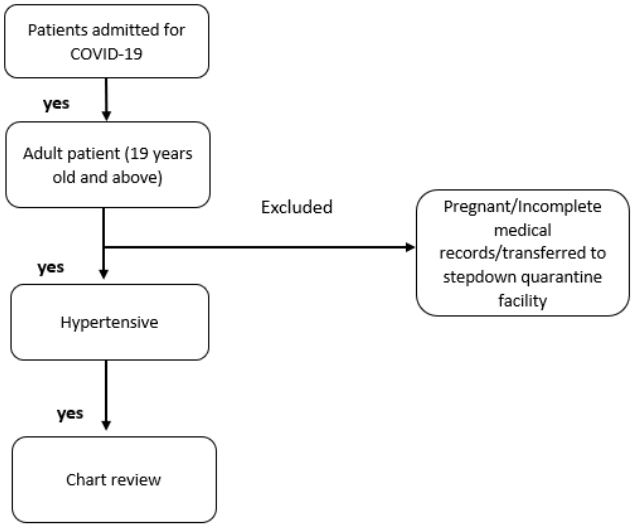

Figure 1. Chart review algorithm

Processing and Analysis

Data was encoded to an MS Excel file and imported to JASP 0.15 (Amsterdam, Netherlands) for analysis. Data was thoroughly checked for accuracy, completeness, and consistency by two independent investigators. A total of 671 charts were included after checking a total of 2,264 charts of admitted COVID19 patients from March 2020 to March

2021. All categorical variables were reported in terms of frequencies and percentages. Data with uneven distributions was reported in terms of median value. The association between RAAS inhibitor use based on COVID19 severity classification and in-hospital outcome in terms of development of AKI and mortality were determined using Fisher's exact test. A p-value of less than 0.05 was considered statistically significant for the tests. Mann-Whitney test was used to determine association of RAAS inhibitor use and COVID-19 severity for post-hoc analysis.

Ethical considerations

The study was submitted to and approved by the University of the Philippines Manila Research Ethics Board (UPM-REB).

III. RESULTS

A total of 29.6% (n=671) patients admitted for COVID-19 were determined to be hypertensive. Majority of hypertensive COVID 19 patients admitted were male (n=348, 52%), elderly (age > 60 years old) (n=377, 58%) and with moderate disease (n=345, 51%). The most common comorbidities identified amongst the study population included community acquired pneumonia (n=396, 59%), type 2 diabetes mellitus (n=295, 44%), chronic kidney disease (n=150, 22%), and heart failure (n=138, 21%). Baseline inflammatory markers for COVID 19 were not uniformly ordered for all patients, and results showed a wide range of values (Table 1).

TABLE 1.0 CHARACTERISTICS OF HYPERTENSIVE PATIENTS ADMITTED FOR COVID-19

Characteristics	Frequency (n = 671)
Age	
- <60	294 (42%)
- ≥60	377 (58%)
Sex	
- Male	348 (52%)
- Female	323 (48%)
COVID19 Classification	
- Mild	108 (16%)
- Moderate	345 (51%)
- Severe	164 (24%)
- Critical	54 (8%)
Comorbidities	
- Chronic Kidney Disease	150 (22%)
- Type 2 Diabetes Mellitus	295 (44%)
- Heart Failure	138 (21%)
- Stroke	92 (14%)
- Malignancy	41 (6%)
- Community Acquired Pneumonia	396 (59%)
- Chronic Obstructive Pulmonary Disease	19 (3%)
- Bronchial Asthma	54 (8%)
- Pulmonary Tuberculosis	90 (13%)
Inflammatory Markers	Median (Range)
- High Sensitivity C-Reactive Protein	57.97 mg/L (0 - 300)
- Ferritin	741 ng/mL (3.6 - 999)
- Lactate Dehydrogenase	340 U/L (124 - 13,310)
- Interleukin - 6	73 pg/ml (3 - 3149)

A total of 66% (n=442) of the hypertensive patients admitted for COVID were on RAAS inhibitors. Losartan (n=311, 70.3%) was the most commonly used RAAS inhibitor, followed by Telmisartan (n=56, 12.6%) and Enalapril (n=35, 7.9%). Among the non RAAS inhibitors, calcium channel blocker (n=450, 67%) was the most commonly used anti-hypertensive medication (Figure 2).

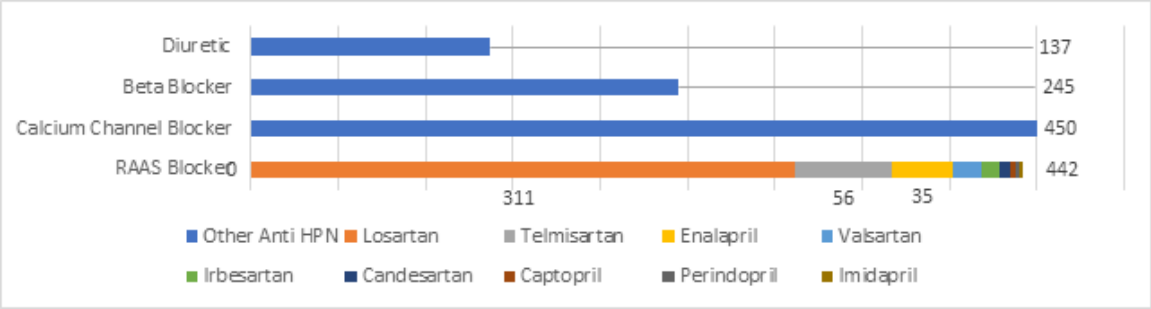

Figure 2. Anti-hypertensive Medication Use of Hypertensive Patients Admitted for COVID19

RAAS inhibitor use was not found to be associated with increased mortality and development of acute kidney injury among hypertensive COVID19 patients (Table 2-3). However, RAAS inhibitor use was associated with decreased mortality among hypertensive patients classified with COVID-19 moderate disease (OR 0.42, 0.19-0.92, *p* = 0.02) (Table 2). There was also no association found between RAAS inhibitor use and COVID-19 disease severity in post-hoc analysis *(p value = 0.48)*. The most common underlying cause of death among patients (n=156) was COVID19 infection (Table 4).

TABLE 2.0 ASSOCIATION OF RAAS INHIBITOR USE WITH IN-PATIENT MORTALITY AMONG COVID-19 PATIENTS

COVID Classification Severity	**Mortality**		
	OR	CI 95%	p-value
Mild	0.84	0.09-10.5	1.00
Moderate	0.42	0.19-0.92	0.02*
Severe	0.81	0.41-1.61	0.63
Critical	0.21	0.004-1.72	0.15
Total	0.74	0.51-1.10	0.12

TABLE 3.0 ASSOCIATION OF RAAS INHIBITOR USE WITH THE DEVELOPMENT OF ACUTE KIDNEY INJURY AMONG COVID-19 PATIENTS

COVID Classification Severity	Acute Kidney Injury		
	OR	CI 95%	p-value
Mild	0.87	0.23-3.65	1.00
Moderate	1.85	0.94-3.83	0.07
Severe	0.68	0.34-1.39	0.31
Critical	0.95	0.22-4.49	1.00
Total	1.12	0.75-1.69	0.63

TABLE 4.0 CAUSE OF DEATH

Underlying Cause of Death	Frequency (n = 156)
Acute Coronary Syndrome	17 (11%)
Acute Kidney Injury	1 (0.6%)
Aortic Dissection	1 (0.6%)
Community Acquired Pneumonia High Risk	10 (6%)
Chronic Kidney Disease	1 (0.6%)
Chronic Liver Disease	2 (1.3%)
COVID19	55 (35%)
Catheter Related Bloodstream Infection	1 (0.6%)
Cerebrovascular Disease	3 (1.9%)
Duodenal Ulcer	1 (0.6%)
Fatal Arrhythmia	1 (0.6%
Hospital Acquired Pneumonia	16 (10%)
Non-Hodgkin's Lymphoma	1 (0.6%)
Ruptured Aortic Aneurysm	1 (0.6%)
Unspecified	30 (19%)
TOTAL	141

IV. DISCUSSION

The controversy regarding the use of RAAS inhibitors in the setting of COVID-19 stems from the pathophysiologic mechanism of COVID-19 disease. SARS-CoV2, the causative agent of COVID-19, enters the human host through the use of a functional receptor - angiotensin converting enzyme 2 (ACE 2) receptor, found most commonly in the airways [14-15]. While the use of RAAS blockers such as ACEIs and ARBs, and their effect on the natural history of COVID 19 remains to be fully elucidated, it has been noted in earlier experimental models, that RAAS blocker use upregulates ACE2 receptors, posing a higher risk of contracting COVID-19 and leading to poorer outcomes[6]. However, recent experimental studies involving both animal and human tissues found that ACE2 receptor activity in the potential key target site (i.e., respiratory tract) for SARS-CoV-2 infection was not significantly modified by RAAS blockers[16-17]. Recent studies also suggest that RAAS inhibitor use likely poses no greater risk of contracting COVID-19 than individuals not on these medications[17]. The heterogeneity of data and lack of long-term evaluation of these experimental studies have led to further investigation at various centers managing patients admitted for COVID. In our local setting, RAAS inhibitor use was not associated with COVID-19 severity and mortality. Our data is consistent with the findings found in several observational studies, systematic reviews and meta-analyses wherein RAAS inhibitor use did not increase the risk and severity of COVID-19 infections nor did it lead to poorer outcomes [8, 18-25]. This finding is also supported by the BRACE-CORONA trial wherein preliminary reports showed that there is no evidence that RAAS inhibitor use during COVID-19 infection affects disease outcome [26].

In our study, RAAS inhibitor use among patients with moderate disease severity was associated with decreased mortality (OR = 0.42, 95% CI 0.19 - 0.92). This was

consistent with the findings of lower risk of mortality found in observational studies and meta-analyses [27-29.] Potential protective mechanism of RAAS inhibitor use was hypothesized to be from its inhibition of Ang II generation and AT1R function, and the enhanced activity of both Ang II/AT1R and AEC2/Ang 1–7/MasR axis with the endpoint production of Ang 1-7. The increased ACE2 expression seen in RAAS inhibitor use also promotes the production of Ang 1-7. Previous experimental studies have supported that Ang 1–7 protects against lung injury. RAAS inhibitors may contribute to the attenuation of lung injury or inflammation via the induction of Ang 1–7 in COVID-19 patients. This finding still needs further investigation in randomized controlled trials to clear up whether RAAS inhibitor use is protective or harmful [30].

We also found out that there is no association between RAAS inhibitor use and development of acute kidney injury among hypertensive patients admitted for COVID-19. The same finding was seen in a multi-center cohort study which found RAAS inhibitor use prior to hospitalization was not associated with AKI [31]. This is in contrast to the latest published data wherein exposure to RAAS inhibitors is associated with higher risk of COVID-19 related acute kidney injury. Though the use of RAAS inhibitors is renoprotective in the long-term, it can adversely affect renal function in the acute setting of physiological stress, such as in the setting of COVID-19 infection, via its effect on periglomerular hemodynamics, systemic blood pressure and natriuresis [32].

Several studies and guidelines promote the use of ACEI and ARBs for hypertensive patients with or without related comorbidities such as heart failure, chronic coronary disease or chronic kidney disease. The use of ACEI or ARB can be as high as up to 33% among urban dwellers in the Philippines as of 2013 data[33]. Hypertension itself has been identified as being one of the most frequent comorbidities associated with

COVID-19 Infection with increased prevalence of up to three or four-fold for those requiring intensive care, advanced airway and even with poor outcome[34]. Some researchers suggest shifting to other antihypertensives without ACE2 expression increasing activity such as calcium channel blockers[35]. While other groups note the tradeoff of switching to non-ACEI and ARB antihypertensives may be related with loss of protective mechanisms and perhaps increase in cardiovascular mortality in COVID-19 patients. Multiple specialty societies however, such as the European Society of Cardiology, European Society of Hypertension, Heart Failure Society of America and American College of Cardiology and American Heart Association have recommended continuing the use of these drugs for patients diagnosed with COVID-19[36]. The findings of lack of association between RAAS inhibitor use and in-patient mortality and development of acute kidney injury supports the said recommendations.

V. CONCLUSION

RAAS inhibitor use is not associated with increased mortality and development of acute kidney injury. Moreover, RAAS inhibitor use may be associated with decreased mortality among hypertensive patients with moderate COVID-19 disease severity. We recommend further studies with a larger population to test these findings.

VI. ACKNOWLEDGMENT

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