Examination Of The Association Between C - Reactive Protein(crp) And Covid-19 Infection Severity And Length Of Hospitalization

Abdulahi Aremu Ayanwale
University of Texas at El Paso

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EXAMINATION OF THE ASSOCIATION BETWEEN C - REACTIVE PROTEIN (CRP) AND COVID-19 INFECTION SEVERITY AND LENGTH OF HOSPITALIZATION

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EXAMINATION OF THE ASSOCIATION BETWEEN C - REACTIVE PROTEIN (CRP) AND COVID-19 INFECTION SEVERITY AND LENGTH OF HOSPITALIZATION

by

ABDULAHI AYANWALE (MB:BS)

THESIS

Presented to the Faculty of the Graduate School of The University of Texas at El Paso in Partial Fulfillment of the Requirements for the Degree of

MASTER OF PUBLIC HEALTH

DEPARTMENT OF PUBLIC HEALTH SCIENCE
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Abstract

Introduction: Chronic stress can lead to many systemic complications and low-grade systemic inflammation including increased levels of inflammatory cytokines, such as C-reactive protein (CRP). CRP is a marker of systemic inflammation and is associated with depression and perceived stress. Elevations can result in ineffective immune responses, thereby increasing the risk of complications and mortality from infections. Recent evidence suggests that uncontrolled inflammatory responses associated with COVID 19 are a major determinant of disease severity. The COVID 19 is transmitted from one person to another through droplets from coughing, sneezing, talking, touching droplets on surfaces and contamination by hand-to-mouth routes. The mechanism by which the COVID 19 virus gain entrance into human system is through attaching to cells like the Angiotensin Converting Enzyme 2 (ACE2), cathepsin L, and Transmembrane serine protease isoform 2.

Purpose: The purpose of the study was to 1a) examine the relationship between CRP as proxy indicator of chronic stress, and Oxygen saturation to predict COVID 19 severity. 1b) and examine the relationship between CRP and the length of hospitalization to predict COVID 19 severity. 2) determine if gender moderates these relationships.

Methods: This retrospective study used medical records from patients admitted to the University Medical Center, El Paso, TX with COVID 19 (n=436 (272M/164F); age 57.3 ± 0.8 years; BMI 29.42 ± 0.3 Kg/m2). Chronic stress was measured by blood CRP level. Severity of COVID 19 infection was determined by the peripheral oxygen saturation (SpO₂) measured during the time of hospitalization. Length of hospitalization was determined by the number of days spent in the hospital. Patients were categorized into low CRP (< 3mg/L) vs. high CRP (≥3mg/L) groups and were compared using unpaired t-test and one-way ANOVA.
**Results:** Patients with low CRP level had greater COVID 19 severity, measured by SpO$_2$ (CRP<3; p-value = .019), and length of hospital stay was not statistically significant. The one-way ANOVA indicates that CRP was not statistically associated with length of hospitalization (p-value = .66).

**Conclusion:** lower levels of CRP are associated with worsened severity via SpO2 in COVID 19 patients. The practical implication is that CRP parameters should be considered in laboratory workup for COVID 19 patients, and treatment should focus on maximizing the healthcare resources during a pandemic. Healthcare resources are in high demand during the pandemic, and the resources can be judiciously maximized by classifying the patients based on the severity of COVID 19 symptoms.
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Chapter One

1.0 INTRODUCTION

1.1 Corona Virus Disease 2019 (COVID 19)

The etiology of the Coronavirus disease 2019 (COVID 19) is a ribonucleic acid (RNA) virus called severe acute respiratory syndrome coronavirus (SARS-CoV-2), which is a complex group of viruses. The outbreak of this common cold-like disease was first reported in Wuhan city, Hubei province in China in 2019 (Pascarella et al., 2020). The transmission of the COVID 19 virus occurs from one person to another through droplets from coughing, sneezing, talking, touching droplets on surfaces and contamination by hand-to-mouth routes (Ferretti et al., 2020). Symptoms of COVID 19 include cough, high temperature, loss of weight, headache, sore throat, and loss of smell. All ages are affected by the virus, but it is known to severely affect people with immunosuppression (Pascarella et al., 2020). The virus's incubation period ranges between about 2 to 12 days (Pascarella et al., 2020).

1.2 Mechanisms of COVID 19

The mechanism by which the COVID 19 virus gains entrance into human system is through attaching to cells via the Angiotensin Converting Enzyme 2 (ACE2), cathepsin L, and Transmembrane serine protease isoform 2 (Azevedo et al., 2020). However, ACE2 is the most common route of the entrance. The ACE2 is ubiquitous in most cells, and it serves as a receptor for the virus to gain entrance into the epithelial cells of the lung, heart, kidney tubules,
artery in smooth muscle cells, cells of the small intestine, and endothelial cells of blood vessels (Wang & Wang, 2021). The virus has a crown-like with Spike protein (S), Matrix protein (M) Nucleoprotein (N), and Envelope protein (E). The microscopic structure of the virus is shown in Figure 1. The virus makes use of the spike protein (S) by attaching to any cells carrying the ACE2 receptors to gain entrance into the human system (Wang & Wang, 2021).

1.3 COVID 19 Prevalence. In 2020, COVID 19 was classified as a worldwide pandemic. The confirmed cases, i.e., people who tested positive for the COVID 19, and the exposed cases are people in contact or within distance of the confirmed cases. The Johns Hopkins COVID 19 center showed 29845/100,000 confirmed cases, i.e., people who tested positive, of coronavirus globally. As of October 5th, 2021 there were reported 61.0/100,000 deaths. In October 5, 2021, the United States (U.S.) of America reached 13,173.0/100,000 confirmed cases with 211.4/100,000 deaths (COVID-19 United States Cases by County, 2020).

COVID-19 Texas and El Paso. In October 2021, Texas had 14,018/100,000 confirmed cases, 226.2/100,000 deaths, and a positive test rate of 12.21% (COVID-19 United States Cases by County, 2020). El Paso’s County, in particular, was one of the top 50 counties with the most cases in the country, (i.e., 21,435.1/100,000 confirmed cases and 411.5/100,000 deaths) (COVID-19 United States Cases by County, 2020).

1.4 COVID 19 Hospitalization Rate. Between March, 2021 and October 2021 hospitalization rates were highest in El Paso County with 112 hospitalizations and 41 individuals in the
Intensive Care Unit (ICU). The individual most at risk for hospitalization were adults aged 50 to 80 years of age. Table 1 shows, particularly shows that individuals 60-69 years of age had the highest hospitalization rate at 21.56% (City of El Paso COVID-19 Cases | El Paso Strong).

Table 1. Hospital admission by age range of COVID-19 from March – October, 2021 (Source: City of El Paso COVID-19 Cases | El Paso Strong).

<table>
<thead>
<tr>
<th>AGE RANGE</th>
<th>Total</th>
<th>Number of Individuals Hospitalized by Gender</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Male</td>
</tr>
<tr>
<td>0-12</td>
<td>188</td>
<td>107</td>
</tr>
<tr>
<td>13-19</td>
<td>219</td>
<td>113</td>
</tr>
<tr>
<td>20-29</td>
<td>706</td>
<td>299</td>
</tr>
<tr>
<td>30-39</td>
<td>955</td>
<td>462</td>
</tr>
<tr>
<td>40-49</td>
<td>1378</td>
<td>799</td>
</tr>
<tr>
<td>50-59</td>
<td>2078</td>
<td>1189</td>
</tr>
<tr>
<td>60-69</td>
<td>2426</td>
<td>1328</td>
</tr>
<tr>
<td>70-79</td>
<td>1977</td>
<td>1106</td>
</tr>
<tr>
<td>80-89</td>
<td>1417</td>
<td>702</td>
</tr>
<tr>
<td>90+</td>
<td>445</td>
<td>208</td>
</tr>
<tr>
<td>TOTAL</td>
<td>11789</td>
<td>6313</td>
</tr>
</tbody>
</table>

1.5 Cost of COVID-19 on health care systems. The median days of hospitalization of an individual with pneumonia in addition to having COVID 19 is 22 days, which is reported to vary between 9 – 46 days. The cost of medical care due to COVID 19 has been estimated at an average of $3045 per person. The cost of hospitalization of confirmed case were further estimated to cost $14,366 per hospitalized patient. Thus, if 80% of the people in U.S. becomes infected it will cost an average of $254.4 billion (Bartsch et al., 2020).
Chapter Two

2.0 RECOMMENDED COVID 19 PREVENTION AND TREATMENTS

2.1 Prevention. The virus is a respiratory in nature and it can affect all organs of the body because it has a receptor called ACE that can gain entrance into all cells. The following are recommended means of prevention; stay at home/quarantine, stay away from asymptomatic people, stop nonessential trips, stay 6 feet or 2 meters when in a crowded place, change style of handshaking (e.g., use of fist bump vs. hand shake), frequently washing hands or using hand sanitizer after touching surfaces or nose or eye, use wipe to clean surfaces, and wearing masks (Lotfi et al., 2020).

Vaccines are also currently one of the most acceptable prevention measures for contracting COVID 19. Vaccines like Pfizer, Moderna, Johnson and Johnson and AstraZeneca are being used worldwide. The other therapeutic treatments are antimalaria (Hydroxychloroquine), Antibiotic (Azithromycin), Steroid (Prednisolone), Antiviral (Remdesivir, Lopinsvir) and Monoclonal Antibody (Tocilizumab) (Lotfi et al., 2020). In December 2020, the Pfizer vaccine was approved by the FDA for emergency use in the U.S. (Oliver, 2020). Two doses of the Pfizer vaccine are given intramuscularly 28 days apart for complete vaccination (Oliver, 2020). Each dose is 0.3ml in quantity. (Lotfi et al., 2020).

2.2 Treatments. Not all individuals who contract COVID-19 are hospitalized, therefore, treatments vary based on whether the individual is at home or in the hospital. The home treatment for mild symptoms of COVID-19 is self-quarantining for the duration of incubation of the virus and paracetamol for fever (McArthur et al., 2020). Individuals who are hospitalized undergo more intense treatments. Hospitalization typically assumes an individual is experiencing
severe symptoms of COVID-19. Treatments available in the hospital are Remdesivir, Oxygen, Plasma, and Monoclonal antibody. (Singhal, 2020). This treatment works by injection needles to administered the drugs and ventilating machine to administered oxygen and they must be carried out in the hospital by the health worker because of technically involved in the procedure. However, home care does not need technical know-how to administered the treatment.

2.3 Groups at most risk for COVID-19 infection.

2.3.1 Individuals with Comorbidities. Individual with comorbidities or underlining medical conditions are disproportionally affected by COVID 19. Individuals with comorbidities like diabetes, hypertension, chronic obstructive airway diseases, obesity, liver diseases, cardiovascular diseases, kidney diseases, cancer, and HIV have higher rates of COVID-19 and severity (Ejaz et al., 2020). Some people with comorbidities express high level of ACE2 receptor and the virus makes use of ACE 2 receptor to invade cells (Ejaz et al., 2020), thus, the virus recognizes their cells easily and they are at greater risk. Figure 2 illustrates the disparity of COVID-19 among individuals with comorbidities compared to those without.

Figure 2. The frequency of comorbidity and its fatality in COVID 19 infection (Source; Ejaz et al., 2020)
Groups that face higher rates of comorbidities include many individuals of marginalized ethnic/racial groups. For example, Hispanics, African Americans, and Native American Indians are groups that have high rates of diabetes and obesity. These types of comorbidities may increase the risk of COVID-19 as these groups have been reported to disproportionately contract COVID-19. (Ejaz et al., 2020). These two factors make hospitalization and infections higher in them (CDC, 2020). According to the CDC, in 2021, Hispanics had the highest rates of COVID-19 cases, and second in death and hospitalization rates after American Indians populations (CDC, 2021). The hospitalization rate for American Indians, Hispanics, and African Americans was 3 times that compared to non-Hispanic (CDC, 2021).

2.3.2 Essential Workers. Another group of individuals that is most at risk for COVID-19 are people who work as essential workers but we do not have specific data on the group. Essential workers are individuals that must continue to work to serve the community regardless of quarantine guidelines. These employees are front line individuals that need to continue to work both for the community and to sustain family household incomes. The essential workers are in industries where they must be exposed to other individuals or in contact with high-risk surfaces (e.g., cleaning industries, food/grocery retail). Unfortunately, ethnic/racial minority groups make up a substantial number of essential workers (Martinez et al., 2021). In El Paso, there are high numbers of Hispanics employed as essential workers leading them to become at higher risk of COVID-19 infections compared to those that can work in quarantine mode. For instance, about 80% of agricultural and 40% of meatpacking workers are Hispanics (Martinez et al., 2021). These essential workers kept working during the peak of the pandemic and they are disproportionately affected (Martinez et al., 2021).
2.3.3 Biological sex (Men vs. Women). The COVID-19 deaths rate also

disproportionally affects men more than females generally. In a U.S. study conducted between

February and April 2020, a 60.6% mortality rate was recorded in men (Mukherjee & Pahan,

2021). Similar findings were indicated worldwide, with men having higher COVID-19 mortality

rates. Similar findings were reported in El Paso Texas. In El Paso, among adults 70 years of age,

males had 371 deaths compared to female with 210 deaths (See figure 3). While women have

marginally high cases compared to men in the U.S., men are reported to have higher rates of

severity, hospitalization, and mortality from COVID-19 than women. This disparity has been

explained as a result of higher expression of ACE2 in men than women. It is explained that

estrogen in women is a protective factor for the contraction of COVID-19. (Mukherjee & Pahan,

2021). Because ACE2 is inhibited by estrogen, the ACE2 receptor may be less available to

transmit the COVID-19 virus in women compared to men. (Mukherjee & Pahan, 2021).

Figure 3. COVID-19 related deaths by sex. (Image Source; City of El Paso COVID-19 Cases | El Paso Strong)
2.3.4 **Age in relation to risk for COVID-19 infection.** According to the CDC, adult 85 years or more and 18 – 64 years of age have a higher risk of contracting the virus compared to children ages 4 years and younger (CDC, 2020). Furthermore, people age 85 years and more are at the most significant risk of being hospitalized with COVID-19, while children less than 5 years old have the lowest of hospitalization. The mortality rates of COVID 19 in adults 85 years and more are also higher compared to children with COVID 19 (CDC, 2020).

2.4 **COVID 19 AND C-Reactive Protein (CRP)**

**CRP:** There is much interest in the association between CRP and COVID 19. Because the pathophysiological mechanism of the virus is through activation of the cytokine storm or excessive activation of the immune system, there is interest in the inflammatory response (Han et al., 2020). This inflammatory response of the virus leads to the release of markers like CRP, Interleukins (IL), Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), lymphocytes, etc. (Han et al., 2020), and the excess of these markers causes different symptoms and complications of COVID 19.

Studies have been conducted to examine the relationship between CRP and severe symptoms of COVID 19. Findings indicate that a high CRP level detected early in people infected with COVID 19 is an important indicator of COVID19 severity. Typically, Computerized Tomography (CT) is used to indicate severity but this research found better predictability of severity based on CRP levels (Tan et al., 2020). A meta-analysis study further found that a high CRP level, Lactate Dehydrogenases (LDH), and Lymphoma were also associated with the severe form of COVID 19 (Zhang et al., 2020).
In addition to the predictability of CRP in COVID 19 severity, there is interest in the stress physiological pathway. Stress stimulates different hormones and creates different pathways that are implicated in health outcomes. In addition to the inflammatory response, stress stimulates neuroendocrine hormones through the Hypothalamic-pituitary-axis (HPA) pathway to produces cortisol increasing central obesity, increases lipid level, and starts liver gluconeogenesis. These are often associated with the comorbid conditions mentioned earlier that put individuals at risk for COVID 19 (Hackett & Steptoe, 2017). Given that the populations identified as most at risk for COVID-19 are ethnic/racial minority groups, there may be rationale to examine CRP as a proxy to stress as these groups also are more likely to experience stressful livelihoods particularly during COVID-19. For example, the nature of ethnic/minority racial groups’ physically demanding jobs (i.e., working in factory, construction, grocery stores, truck drivers etc.) and underlying comorbidities may act as stressors that contribute to the CRP response (CDC, 2020). In a study by Ali, the value of CRP in hospitalized patient infected with COVID-19 was 41.8mg/L and no p-value was reported (Ali 2020).
The diagram below (Figure 4) illustrates the mechanism of stress. C-Reactive Protein (CRP) as an inflammatory marker implicated in stressful conditions, and this stressful condition can trigger the onset of conditions like diabetes or complicate existing diabetes. Substantial research has shown that individuals with significant inflammatory markers like CRP are at the risk of diabetes or new-onset diabetes and other medical complications (Malmo, 2016). Additionally, a meta-analysis study showed that a high CRP level in a patient with diabetes is significantly related to increased cardiovascular risk and all-cause mortality (Tian et al., 2019).

Given the importance of CRP in comorbid conditions that increase the risk of COVID 19, is it important to examine the association between CRP levels and COVID 19 severity. CRP is an inflammatory marker used to determine how to optimally manage and treat patients with COVID 19. In a retrospective cohort study, a high level of CRP, Interleukin-16 (IL-6), and procalcitonin (PCT) significantly showed that people infected with COVID 19 would have more severe symptoms rather than mild symptoms (Liu et al., 2020). The study also indicated that people with comorbidities like diabetes would have a high CRP level with severe symptoms of COVID 19 and some can also develop new onset diabetes and its complications (Liu et al., 2020). Triaging patients with
COVID 19 to receive optimal care and reduce severity is critical for recovery and streamlining health care for these patients. Thus, identifying factors that may be implicated in severity is important for the successful treatment of patients with COVID 19.


Chapter Three

3.1 BIOPSYCHOSOCIAL MODEL

The individuals with chronic health conditions are at higher risk of serious COVID 19 complications, hospitalizations, and mortality than individuals with no chronic disease conditions. Namely, individuals who are obese, diagnosed with diabetes, or other respiratory conditions experience serious and life-threatening effects/symptoms.

The CDC data confirmed that ethnic/racial groups are disproportionally affected with COVID 19 infections (CDC, 2020). In particular, there is a high rate of infections among Hispanics in the U.S. with diabetes and obesity comorbidities. Additionally, individuals with these comorbidities are shown to have severe COVID 19 and hospitalization rates.

In addition to comorbidities, factors like living in low socioeconomic status, lack of adequate access to health care/services (Martinez et al., 2021) and living in low resourced environments can be life stressors that can be an additional risk to one’s health (Martinez et al., 2021). Such life stressors do have an impact on the physiological response, including the CRP response. This is known as the biopsychosocial model. The biopsychosocial model suggests that physiology and social factors have an influence on individual biological system. Leger (2018) showed that physical stress and affective/emotional stress significantly have an immediate and long-term effect on physical health, that is, effects like chronic illness and later life functional limitation (Leger et al., 2018). Physiological dysregulation of hormones due to stress, have been implicated in physical health and persistent negative emotions/stress. The physiological dysregulation can lead to the over-stimulation of the heart and hypothalamic-pituitary-adrenal system (Leger et al., 2018).
Chronic stress, for example, can lead to many systemic complications and low-grade systemic inflammation, including increased levels of inflammatory cytokines, such as CRP (Liu et al., 2020). The CRP is also known as a marker of depression and perceived stress. Elevations can result in ineffective immune responses, thereby increasing the risk of complications and mortality from infections. Recent evidence suggests that uncontrolled inflammatory responses associated with COVID-19 are a major determinant of disease severity. See figure 4 above, on the influence of stress on human biopsychosocial system.
Chapter Four

4.1 GOALS AND OBJECTIVES

The current research between CRP and COVID-19 indicates a clear relationship (Liu et al., 2020). However, less is known about the relationship between CRP and COVID-19 among a predominately Hispanic population and more so between men and women. Thus, the objectives of this proposal are to:

1a) examine the relationship between CRP as an indicator of chronic stress, and Oxygen saturation to predict COVID-19 severity.
1b) and examine the relationship between CRP and the length of hospitalization to predict COVID-19 severity.
2) determine if gender moderates these relationships.

4.2 HYPOTHESIS

Hypothesis 1: High levels of CRP as a proxy indicator of stress is associated with COVID-19 severity, measured by oxygen saturation (i.e., SPO2).

Hypothesis 2: High levels of CRP is associated with longer hospitalization in people infected with COVID-19

Hypothesis 3: Gender moderates the association between CRP and severity and CRP and length of hospitalization from COVID-19 infection.
Chapter Five

5.0 METHODS

5.1 Study Sample

This is a retrospective cross-sectional study design and data from the University Medical Center (UMC), El Paso, Texas will be used to investigate the study objectives. Data were drawn from 858 patients admitted into the hospital in the year 2020. The sample size used for the study was 436 cases that include patient with CRP records. The eligibility criteria were adult males and females 18 years old or older, admitted to UMC and with a COVID-19 diagnosis. A total of 422 cases were excluded due to missing the CRP criteria.

5.2 Setting

The study was carried out in collaboration with The University of Texas at El Paso, UMC, and Texas Tech University in El Paso, Texas. All cases used in the analysis were diagnosed with COVID 19, and the data include clinical and laboratory records and patients’ demographics (e.g., age, sex, race/ethnicity, insurance) and health history. El Paso, Texas is located on the U.S./Mexico international border and is predominately Hispanic (82%). In 2021, the average yearly household income among low earner of family of four in El Paso was $48,700.00 (HUD, 2021). The use of this data has been approved by The University of Texas at El Paso Institutional Review Board.

5.3 Study Design. This is a retrospective cross sectional study design using patients admitted into the UMC El Paso, Texas for COVID-19 during 2020. The variables used for the
study include CRP as the exposure variable and severity of COVID 19 measured by Saturation of Peripheral Oxygen (SPO$_2$), and length of hospitalization stay (outcome variables).

5.3.1 Exposure Measures.

C-Reactive Protein (CRP). CRP as the exposure measure will be used as a proxy for determining patient’s stress level. The value of CRP less than 3mg/L is considered normal. The level of CRP was categorized into less 3mg/L and above or equal to 3mg/L. Less than 3mg/L was assigned low CRP level and above or equal to 3mg/L was assigned high CRP level. Anything above or equal to 3mg/L is indicative of high level of stress, and indirect assessment of psychological stress.

Biological sex. Biological sex (male vs. female) was included in the analysis to assess the role of gender on the relationship between CRP and severity of COVID-19. This information was gathered from the UMC medical record system. This study will see if there are any gender differences in the relationship between the exposure and outcome variables.

5.3.2 Outcome Measures

Severity – Saturation of Peripheral Oxygen (SPO$_2$). Severity was determined by oxygen saturation measurement (SPO$_2$). SPO$_2$ measures the level of oxygen circulation in the body system and measured using Pulse oximeter. The unit of measurement is a percentage (%). Level of SPO$_2$ between 95 – 100% is considered normal in the context of COVID-19 according to the CDC and level below 94% is considered abnormal (CDC, 2020). Individual with SPO$_2$ <94% is having difficulty with breathing and low SPO$_2$ is a measure of COVID-19 severity. For the purpose of analysis this was used as a continuous variable.
**Length of Hospital Stay.** Length of hospital stay was operationalized by number of days staying in the hospital for COVID-19 treatment. This was obtained through the data of hospital record. On average individuals with severe COVID-19 symptoms stay 15 or more days in the hospital. Therefore, longer hospitalization is measure of COVID-19 severity.

**Blood Pressure.** Blood pressure was classified into systolic and diastolic blood pressure as part of the vitals in admitted COVID-19 patients. This was obtained through the data of hospital record. Systolic blood pressure should not be more than 130mmHg and diastolic blood pressure should not be more than 90mmHg.

**Covariates.** Sociodemographic variables were used as covariates in the analysis. This includes, age, ethnicity will be adjusted in the analysis. Ethnicity was operationalized into three categories (Hispanic, Non-Hispanic and Unknown).

Table 2. Table of measures and their ranges.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measure</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposition variable</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td>&lt;3</td>
<td>≥3</td>
</tr>
<tr>
<td>Outcome variables</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPO2</td>
<td>&lt;.94</td>
<td>.95-1.0</td>
</tr>
<tr>
<td>Length of Hospitalization</td>
<td>5-10</td>
<td>≥11</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>≤130</td>
<td>&gt;130</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>≤90</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>
5.4 Database Management: The data for this project is under the supervision of the principal investigator (PI) Dr. Bajpeyi. Statistical data management will be overseen by the PI and his graduate student. Data quality checks and cleaning was conducted by Dr. Bajpeyi, his graduate student and the UMC research staff.

5.5 Statistical analysis. The analysis was carried out using GraphPad, descriptive statistical analysis will be conducted to determine comparisons between the sociodemographic variables and the exposure variable. To examine objective 1, a one-way ANOVA and unpaired t-test analysis will be conducted to determine the level of CRP (high vs low) against SPO2. The test is used to determine the level of significance between categorical and continuous variables. CRP is the categorical variable while SPO2 is the continuous variable. Additionally, a one-way ANOVA and unpaired t-test analysis will be conducted to determine the level of CRP against length of hospitalization, level of CRP against SPO2 and their interaction with biological sex. CRP as the categorical variable and length of hospitalization/SPO2 as the continuous variable, the test is to determine the level of significance of both variables as it relate to COVID-19 severity. Both analyses were conducted in the context of biological sex.

5.6 IRB Approval. The secondary data analysis will be submitted to The University of Texas at El Paso Institution Review Board (IRB) for Exemption consideration.
Chapter Six

6.0 RESULTS

6.1 Sample characteristics by CRP, SPO2, blood pressure and ethnicity

Table 3 shows the sociodemographic and clinical parameters of the patients. Four hundred and thirty-seven (N = 437) patients’ parameters were used for the analysis, of which sixty-two percent (n=272) were males, and thirty-eight were females (n=164). The median age for females was slightly higher (mean age = 58 ±16) than the males (mean age = 56.8 ±16.4) and was not statistically significantly different. The majority of cases included patients of Hispanic background (88.0%) and blood pressure was measured to aid in pointing out the severity of illness in the patients.

M = Mean, SE = Standard Error

<table>
<thead>
<tr>
<th>Table 3. Sociodemographic characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parameter</td>
</tr>
<tr>
<td>-----------------------------</td>
</tr>
<tr>
<td>Number(N) = 436</td>
</tr>
<tr>
<td>Age(years)</td>
</tr>
<tr>
<td>Ethnicity</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Non-Hispanic</td>
</tr>
<tr>
<td>Unknown</td>
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</tbody>
</table>
6.2 Clinical Parameters

In table 4 below using the one-way ANOVA, the one-way ANOVA was performed to determine the significance of the interaction of CRP with SpO₂ and days of hospitalization. The analysis revealed that there was a significant difference in SpO₂ between male and female (F = 3.33, p = .019). The analysis also revealed that there was a significant difference in diastolic blood pressure between male and female (F = 2.86, p = .037).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CRP &lt; 3 (n= 73)</th>
<th>CRP ≥3 (n= 364)</th>
<th>P-value(F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>Male (n=37)</td>
<td>Female (n=36)</td>
<td>Male (n=236)</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>36</td>
<td>236</td>
</tr>
<tr>
<td>SPO₂</td>
<td>93.03 ±0.72</td>
<td>95.36 ±0.32</td>
<td>91.82 ±0.49</td>
</tr>
<tr>
<td>Days of Hospitalization</td>
<td>6.16 ±0.94</td>
<td>6.75 ±2.37</td>
<td>9.08 ±0.56</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>127.9 ±4.71</td>
<td>128.9 ±5.02</td>
<td>133.0 ±1.48</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>79.43 ±2.87</td>
<td>73.67 ±2.24</td>
<td>76.50 ±0.84</td>
</tr>
</tbody>
</table>

Note: SpO₂ = a (Oxygen saturation), CRP = b (C-Reactive Protein).

6.3 Relationship between CRP and SPO₂

Table 5. shows the results from the one-way ANOVA. A one-way ANOVA was performed to compare the effect CRP on SPO₂ and days of hospitalization. The one-way ANOVA revealed that...
there was statistically significant difference in SPO2 between CRP≥3 in male and female (F=3.33, p = .019). The table also shows that the days of hospitalization was not statistically significance using the same ANOVA tests.

Table 5. Relationship between CRP, SpO₂, days of hospitalization and blood pressure.

<table>
<thead>
<tr>
<th>Parameters</th>
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<th>CRP ≥3 (n= 364)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
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<td>Number</td>
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<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td></td>
<td>37</td>
<td>36</td>
<td>236</td>
</tr>
<tr>
<td>SPO2</td>
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<td>6.75 ±2.37</td>
<td>9.08 ±0.56</td>
</tr>
<tr>
<td>AGE (years)</td>
<td>51.08 ±2.6</td>
<td>57.78 ±2.61</td>
<td>57.57 ±1.07</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>127.9 ±4.71</td>
<td>128.9 ±5.02</td>
<td>133.0 ±1.48</td>
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<tr>
<td>Diastolic Blood Pressure</td>
<td>79.43 ±2.87</td>
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<td>76.50 ±0.84</td>
</tr>
</tbody>
</table>
Figure 5: relationship between CRP and SPO2 and interaction by biological sex.
6.4 Relationship between CRP and length of Hospitalization

Unpaired t-test (Table 6), The Mean value of SPO2 (M (M/F) = 93.03/95.36, SE(M/F) =±0.72/±0.32) was statistically significant different than the CRP <3 mean, t = (2.92), p = (.0047). In a surprising finding with the t-test, The Mean value of diastolic blood pressure (M(M/F) = 77.97/73.50, SE (M/F) =±1.86/ ±1.67) was statistically significant difference than both CRP mean, t = (2.24), p = (.02, .03). further t-test analysis shows no differences between men and women (CRP ≥ 3 p-value=.41) in relating to SpO₂ and days of hospitalization.

Table 6. Relationship between CRP, SPO₂, days of hospitalization and blood pressure.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CRP &lt; 3 (n=73)</th>
<th>CRP ≥3 (n=364)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Number</td>
<td>37</td>
<td>36</td>
</tr>
<tr>
<td>SPO₂</td>
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<td>95.36±0.32</td>
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<td>73.67±2.24</td>
</tr>
</tbody>
</table>
Figure 6: relationship between the level of CRP and length of Hospitalization moderated by gender.
In summary, Patients with low CRP level had greater COVID-19 severity, measured by SpO2 (CRP<3; p-value = .019), and length of hospital stay was not statistically significant. The one-way ANOVA indicates that CRP was not statistically associated with length of hospitalization (p-value = .66).
Chapter Seven

7.0 DISCUSSION

The summary from our findings showed that lower levels of CRP are associated with worsened symptoms of severity via SPO2 in the low range. These can be seen in the values/parameters in the result section that people that had a high level of CRP>3mg/L had no severe form of the disease and longer days of hospitalization.

In a study conducted in China, risk factors associated with severe symptoms of COVID-19 are Lymphopenia, CRP, hypertension, lactate dehydrogenase, elevated neutrophil, as well as symptoms such as difficulty in breathing, lethargy, and fatigue (Liu et al., 2020). The results from the study are in consistent with our finding on the inflammatory marker of CRP and the severity of symptoms. The people with low CRP levels had severe forms of COVID-19 infections.

The median days of hospitalization in an individual with pneumonia infected with COVID-19 is 22, which can vary between 9 - 46 days, while severe pneumonia is 25 days ranging between 14 - 44 days (Bartsch et al., 2020), and our study showed that the average days of hospitalization in patients with high and low CRP levels without pneumonia were 6-8 days averagely. Thus, our study has slight similarities to studies carried out in different parts of the world. Additionally, our findings showed that women above 60 years old are hospitalized more than younger women and this can be linked to the fact that older women have less female hormone (progesterone and estrogen) due to old age. Therefore, older women would not have the
protection from the virus just like men due to high affinity of the COVID-19 virus for the ACE2 cells.

Our study was carried out among the Hispanic-dominated community. It is expected to see the burden of the pandemic skewed in this direction; a large proportion of the Hispanic population was affected by the COVID-19 infection (CDC, 2021). In a study conducted in New York where the Hispanic population is not predominated, Hispanics have more hospitalization and death from the virus compared to white, and these can be attributed to the nature of their jobs, inadequate healthcare, pre-existing medical diseases, and immigration status (Macias Gill et al., 2020). In comparison with our findings, this study showed that a community dominated by a particular ethnicity does not indicate that the disease burden would be higher in such minority ethnic groups.

In our study, the male had a higher CRP level than the female, but abnormal SPO2 showed no appreciable contribution or difference between males and females. Men have more COVID-19 severity and hospitalization than women. Compared to the finding by Grasselli et al., among the critically ill patients in Italy, there was a decreased survival rate among older men with comorbidities requiring intubation (Grasselli et al., 2020). These findings showed that men are more impacted with COVID-19 than women.

The practical implication is that CRP parameters should be considered in laboratory workup for COVID-19 patients, and treatment should focus on maximizing the healthcare resources during a pandemic. Healthcare resources are in high demand during the pandemic because high volume of people is admitted due to COVID-19 infection, and we can judiciously
maximize the use of healthcare resources by classifying the patients based on the severity of symptoms from the virus infection.

7.1 Conclusion

CRP is associated with stress and continuous stress raises cortisol, which will now lead to the release of inflammatory markers like CRP. Racial/ethnic groups might experience a higher level of chronic stress in general due to the nature of their jobs. In addition, it may have gotten worse with changes that occurred by pandemics (e.g., socioeconomic challenges).

The idea of international cooperation against deadly and infectious diseases must be a priority for every country to prevent unnecessary morbidity, mortality, destruction of social life, unemployment, disruption of the educational system and destruction of the economy. Cooperation will allow the sharing of information between countries to prevent these losses. The world economy is in peril because countries failed to cooperate and follow the public health policy on the pandemic.

Countries worldwide need to invest in public health to help prepare the workforce needed to prevent the pandemic because pandemics will occur in the future. We must not be caught unaware of the next pandemic. Therefore, investment in public health schools and research in public health should be a priority by every country of the world.

CRP levels should be considered in blood test workup for COVID-19 patients, and treatment should direct at reducing inflammatory damage to lessen the severity of the virus.
7.2 Strength

Our study indicates that examining the CRP level of patients might help healthcare professionals identify patients who could suffer from severe COVID-19 and provide proper treatment promptly. The study was carried out in a Hispanic-dominated community. The study is a plus because most of the pandemic studies do not consider the group, the availability of 800 and above COVID-19 patients for the study in light of the pandemic. The CRP data in our study should be a crucial part of the COVID-19 pandemic from now on.

7.3 Limitations

Stress could not be assessed through psychological measures, and it is then used as a proxy measure called CRP as a physiological measure of stress. The study is a cross-sectional design, and this is a one-time study of the association between stress and CRP; stress is what the people had been undergoing for days, weeks, months and years. Then, a follow-up study would be an added advantage. We had limited covariates such as educational status, income level, jobs and health insurance in the study.

7.4 Future Directions

The future direction is to incorporate CRP inflammatory marker as triage in managing people infected with COVID-19 because this will help make use of hospital resources judiciously. In addition, triaging the patients infected with COVID-19 using CRP will enable health workers to determine the number of resources needed for anyone infected with the virus. We hope to carry out multiple linear regression analyses to investigate the effect of biological sex as a modifier between both CRP and length of hospitalization and CRP and SPO2. These will inform us how males or females modify the impact of the virus.
The study samples were predominately Hispanic along the border region, and we are planning to carry out such a study among Hispanic residing in the hinterland of the United States. This kind of future study can afford us to determine if the level of stress, CRP and COVID-19 vary across people.
Chapter Eight

8.0 STRATEGIC FRAMEWORK

8.1 Healthy Border 2020: The Healthy Border 2020 objectives aim to improve the U.S.-Mexico border health and quality of life in Texas, New Mexico, Arizona, and California from the U.S. From Mexico, Tamaulipas, Nuevo Leon, Coahuila, Chihuahua, Sonora, and Baja California.

- Infectious Disease: access to health; migration; poor hygiene, i.e., personal, housing; Poor diet and poor nutrition; environmental health, i.e., water, sewer; and access to information and education.

8.2 Healthy People 2020:

- In the years to come, the United States might encounter new and emerging problems in the field of infectious diseases and immunization. The public health infrastructure must be capable of responding to emerging threats. highly skilled professionals and state-of-the-art technology need to be in place to provide rapid response to the threat of epidemics.

- A coordinated strategy is necessary to understand, detect, control, and prevent infectious diseases. The new problems are:
  - New infectious diseases and agents will be detected, there should global collaboration due to migration, international travels, bioterrorism threats and movement of foods and agricultural products
  - Culturally competent public health preventive measures should be in place because of demographic diversity.
Chapter Nine

9.0 MPH Competencies

9.1 Evidence-based Approaches to Public Health:

- Apply epidemiological methods to the breadth of settings and situations in public health practice
- Select quantitative and qualitative data collection methods appropriate for a given public health context
- Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming, and software, as appropriate
- Interpret results of data analysis for public health research, policy or practice

9.2 Hispanic and border health concentration competencies:

- State the principles of prevention and control of disease and discuss how these can be modified to accommodate cultural values and practices in Hispanic and border communities.
- Differentiate quantitative health indicators in major communicable and non-communicable diseases in US/Mexico border vs non-border communities.
References


https://doi.org/10.1089/jwh.2020.8472


Oliver, S. E. (2020). The Advisory Committee on Immunization Practices’ Interim Recommendation for Use of Pfizer-BioNTech COVID-19 Vaccine — United States,

https://doi.org/10.15585/mmwr.mm6950e2


## APPENDIX

### TABLES

Table 1. Hospital admission by Age range of COVID-19

<table>
<thead>
<tr>
<th>AGE RANGE</th>
<th>Total</th>
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<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-12</td>
<td>188</td>
<td>107</td>
<td>81</td>
</tr>
<tr>
<td>13-19</td>
<td>219</td>
<td>113</td>
<td>106</td>
</tr>
<tr>
<td>20-29</td>
<td>706</td>
<td>299</td>
<td>407</td>
</tr>
<tr>
<td>30-39</td>
<td>955</td>
<td>462</td>
<td>493</td>
</tr>
<tr>
<td>40-49</td>
<td>1378</td>
<td>799</td>
<td>579</td>
</tr>
<tr>
<td>50-59</td>
<td>2078</td>
<td>1189</td>
<td>889</td>
</tr>
<tr>
<td>60-69</td>
<td>2426</td>
<td>1328</td>
<td>1098</td>
</tr>
<tr>
<td>70-79</td>
<td>1977</td>
<td>1106</td>
<td>871</td>
</tr>
<tr>
<td>80-89</td>
<td>1417</td>
<td>702</td>
<td>715</td>
</tr>
<tr>
<td>90+</td>
<td>445</td>
<td>208</td>
<td>237</td>
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<tr>
<td>TOTAL</td>
<td>11789</td>
<td>6313</td>
<td>4576</td>
</tr>
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</table>

Table 2. Showing the Variable measure

<table>
<thead>
<tr>
<th>Variable</th>
<th>Measure</th>
<th>Unit</th>
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</thead>
<tbody>
<tr>
<td>CRP</td>
<td>&lt;3</td>
<td>≥3</td>
</tr>
<tr>
<td>SPO2</td>
<td>&lt;.94</td>
<td>.95-1.</td>
</tr>
<tr>
<td>Length of Hospitalization</td>
<td>5-11</td>
<td>&gt;11</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>≤130</td>
<td>&gt;130</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>≤90</td>
<td>&gt;90</td>
</tr>
</tbody>
</table>
Table 3. Sociodemographic characteristics.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Male</th>
<th>Female</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number(N) = 436</td>
<td>272</td>
<td>164</td>
<td></td>
</tr>
<tr>
<td>Age(years)</td>
<td>56.8 ±16.4</td>
<td>58 ±16</td>
<td>0.45</td>
</tr>
<tr>
<td>Ethnicity</td>
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</tr>
<tr>
<td>Hispanic</td>
<td>244</td>
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<tr>
<td>Non-Hispanic</td>
<td>21</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>2</td>
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</tbody>
</table>

Table 4. Clinical Parameters.

Table 4. Clinical Parameters; blood pressure, SPO2\textsuperscript{a}, hospitalization and CRP\textsuperscript{b} values by gender (N=436).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CRP &lt; 3 (n= 73)</th>
<th></th>
<th>CRP &gt;3 (n= 364)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male (n=37)</td>
<td>Female (n=36)</td>
<td>Male (n=236)</td>
<td>Female (n=128)</td>
</tr>
<tr>
<td>Number</td>
<td>37</td>
<td>36</td>
<td>236</td>
<td>128</td>
</tr>
<tr>
<td>SPO2</td>
<td>93.03 ±0.72</td>
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</tr>
<tr>
<td>Days of Hospitalization</td>
<td>6.16 ±0.94</td>
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<td>8.26 ±0.89</td>
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<tr>
<td>Systolic Blood Pressure</td>
<td>127.9 ±4.71</td>
<td>128.9 ±5.02</td>
<td>133.0 ±1.48</td>
<td>130.0 ±1.90</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>79.43 ±2.87</td>
<td>73.67 ±2.24</td>
<td>76.50 ±0.84</td>
<td>73.34 ±1.13</td>
</tr>
</tbody>
</table>
Note: SPO2 = a (Oxygen saturation), CRP = b (C-Reactive Protein).

Table 5. Relationship between CRP, SPO2, days of hospitalization and blood pressure.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>CRP &lt; 3 (n=73)</th>
<th>CRP &gt;3 (n= 364)</th>
<th>ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>37</td>
<td>36</td>
<td>236</td>
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<table>
<thead>
<tr>
<th>Parameters</th>
<th>CRP &lt; 3 (n=73)</th>
<th>CRP &gt;3 (n=364)</th>
<th>t-test</th>
</tr>
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<tbody>
<tr>
<td>Number</td>
<td>37</td>
<td>36</td>
<td>236</td>
</tr>
<tr>
<td>SPO2</td>
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<td>Days of Hospitalization</td>
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<td>0.07</td>
</tr>
<tr>
<td>Systolic Blood Pressure</td>
<td>127.9 ±4.71</td>
<td>128.9 ±5.02</td>
<td>0.88</td>
</tr>
<tr>
<td>Diastolic Blood Pressure</td>
<td>79.43 ±2.87</td>
<td>73.67 ±2.24</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Table 6. Relationship between CRP and Length of Hospitalization
FIGURES

*Figure 1.* The microscopic structure of the COVID 19 virus *(Source: Udugam et al., 2020)*

*Figure 2.* The frequency of comorbidity and its fatality in COVID 19 infection *(Source: Ejaz et al., 2020)*
Figure 3. COVID-19 related deaths by sex. (Image Source: City of El Paso COVID-19 Cases | El Paso Strong)

Figure 4. The mechanism of stress (Image Source: Hackett & Steptoe, 2017)
Figure 5: relationship between CRP and SPO2 and interaction by biological sex
Figure 6: relationship between the level of CRP and length of Hospitalization moderated by gender.
Vita

Abdulahi Ayanwale

I obtained Master of Public Health (MPH) at the University of Texas at El Paso, United States of America with distinction. December, 2021. Thesis title: “examination of the association between c-reactive protein (CRP) and COVID 19 infection severity and length of hospitalization”. I graduated with Bachelor of Medicine, Bachelor of Surgery (June, 2015) from the University of Lagos, Nigeria. Thesis title: “Lifestyle factors that affect Pregnant women during antenatal clinic visit in Gbagada, General Hospital, Lagos”.

I worked as Graduate Teaching Assistant, Department of Public Health, University of Texas at El Paso, September 2019 – December 2021. Responsibilities include: assisting professors with preparation and grading undergraduate courses. Practicum under the mentorship of Dr. Martinez, School of Nursing, University of Texas at El Paso, June – August, 2021. Responsibilities include: Preparation of manuscript for publication, IRB download and documentation, Infographic design. Graduate Research Assistant to Professor Sobin, Department of Public Health, university of Texas at El Paso, March – June, 2020. Responsibilities include: measured suspected locations with lead contaminants.

I was awarded; Sandy Tayler Endowed Fellowship, University of Texas at El Paso, July 2021 and Endowment Scholarship, University of Lagos, September 2009.

I am a medical doctor and belonged to the Medical and Dental Council of Nigeria (MDCN), married to a lovely pharmacist with a son.