The Impact Of Corticosteroids On Secondary Infection And Mortality In Critically Ill Covid-19 Patients

by

Andrea R. Levine

B.S., University of Maryland, 2007

M.D., University of Maryland, 2012

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This thesis was presented

by

Andrea R. Levine

It was defended on

July 27, 2021

and approved by

Thomas J. Songer, Assistant Professor, Department of Epidemiology, University of Pittsburgh Graduate School of Public Health

William G. Gain, Assistant Professor of Medicine, Division of Pulmonary, Allergy, and Critical Care Medicine, University of Pittsburgh School of Medicine

Thesis Advisor/Dissertation Director: Nancy W. Glynn, Associate Professor, Department of Epidemiology, University of Pittsburgh Graduate School of Public Health

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Andrea R. Levine, MS

University of Pittsburgh, 2021

ABSTRACT

Background: Corticosteroids are part of the treatment guidelines for COVID-19 and have been shown to improve mortality. However, the impact corticosteroids have on the development of secondary infection in COVID-19 is unknown. We sought to define the rate of secondary infection in critically ill patients with COVID-19 and to determine the effect of corticosteroid use on mortality in critically ill patients with COVID-19.

Study Design and Methods: One hundred and thirty-five critically ill patients with COVID-19 admitted to the Intensive Care Unit (ICU) at the University of Maryland Medical Center were included in this single-center retrospective analysis. Demographics, symptoms, culture data, use of COVID-19 directed therapies, and outcomes were abstracted from the medical record. The primary outcomes were secondary infection and mortality. Proportional hazards models were used to determine the time to secondary infection and the time to death.

Results: The proportion of patients with secondary infection was 63%. The likelihood of developing secondary infection was not significantly impacted by the administration of corticosteroids (HR 1.45, CI 0.75-2.82, p=0.28). This remained consistent in sub-analysis looking at bloodstream, respiratory, and urine infections. Secondary infection had no significant impact on the likelihood of 28-day mortality (HR 0.66, CI 0.33-1.35, p=0.256). Corticosteroid administration significantly reduced the likelihood of 28-day mortality (HR 0.27, CI 0.10-0.72, p=0.01).

Conclusion: Corticosteroids are an important and lifesaving pharmacotherapeutic option in critically ill patients with COVID-19 which have no impact on the likelihood of developing secondary infections. Confirming the safety of this relatively accessible pharmacotherapeutic option for critically ill patients with COVID-19 amongst a dearth of other effective pharmacotherapeutics of utmost public health significance.

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Preface

As of June 24, 2021, 3.89 million people have died from COVID-19. These were mothers and fathers, sisters, brothers, friends, and loved ones. These were pregnant women and young adults with promising futures. Patients died alone because we could not allow their family members to hold their hands as they took their final breath. The patients that I cared for during this pandemic have personally changed me as a pulmonary and critical care physician, and for that I am forever grateful. These patients made me work longer and harder and ask questions in an effort to provide them with better care. These patients simultaneously transformed me into a better doctor and a better scientist.

I would like to thank my committee members: Dr. Nancy Glynn, Dr. Thomas Songer, and Dr. William Bain, without whom I would not have had the strength or the stamina to complete this program. Their patience, guidance, and unrelenting belief in me has allowed me to complete my Masters in Epidemiology. To Dr. Glynn, specifically, her creativity, vision, and commitment to my training epitomizes a true mentor and educator and allowed me to complete this degree while simultaneously pursuing my clinical dreams. For that, I am forever grateful.

Lastly, to my wife, Dr. Noel Britton. She is my muse. She inspires me to work harder, push myself clinically, challenge myself as a physician and a scientist. She makes me a better human being. Chasing her has kept me motivated and moving, even in the darkest of days. She always reminds me that I am a doctor first but that research feeds my soul and my inquisitive mind. She has joined me on and supported me through every wild adventure and held my hand while I ran into the flames of the fire during the COVID-19 pandemic. “I carry your heart with me. I carry it in my heart. Whatever is done by me is your doing.”—E.E. Cummings.

1. INTRODUCTION

1.1 CORONAVIRUS PANDEMICS

Coronaviruses are often thought of as benign viruses which cause respiratory tract infections. Yet, three coronaviruses are known to cause severe and often fatal disease in humans. SARS-CoV first emerged in 2002 and was responsible for severe acute respiratory syndrome (SARS). The SARS-CoV pandemic impacted 33 countries, accounted for 8096 cases, and 774 deaths (case fatality rate of 9.5%). This pandemic was the result of a single spill over event which effectively was controlled by public health measures alone, in part because patients were critically ill during the period of time when they were more infectious. Thus, by 2004, the virus had disappeared[1]. MERS-CoV, first described in 2012, is responsible for the middle east respiratory syndrome (MERS). To date, there are 2566 cases of laboratory confirmed MERS-CoV-2 and 882 deaths (case fatality rate of 34.3%)[2]. This outbreak is ongoing because there remains continued spillover from camels causing ongoing primary infection in humans. In December of 2019, the first cases of the SARS-CoV-2 virus were reported in Wuhan, China. This was presumably due to a single spillover event which quickly spread throughout Asia. The first case was reported in the US on January 20, 2020 with the first US death on February 29, 2020. To date, there are 172 million laboratory confirmed cases of SARS-CoV-2 with 3.7 million deaths (case fatality rate of 2%).

1.2 SARS CoV-2

SARS-CoV-2 is an enveloped ß-coronavirus. The viral envelope is coated by a spike protein which binds to angiotensin-converting enzyme-2 (ACE-2) receptor of the target cell. The distribution of the ACE-2 receptor provides insight into the pathogenesis of the SARS-CoV-2 virus. ACE-2 receptors are found on the epithelium of the intestine, the kidneys, the blood vessels, and the lungs[3]. Critical illness from the SARS-CoV-2 virus is the result of an aberrant and deranged immune response.

1.3 COVID-19

COVID-19 is the disease caused by the SARS-CoV-2 virus. The virus is spread via respiratory droplets. Infection can be spread by pre-symptomatic, asymptomatic, and symptomatic carriers. 97.5% of infected patients have developed symptoms within 11.5 days of infection. Symptoms are variable and include fever, dry cough, shortness of breath, diarrhea, anosmia, dysgeusia, thromboembolic events, rashes, and fatigue. In severe cases, patients may go on to develop life threatening Acute Respiratory Distress Syndrome (ARDS) which is characterized by severe and refractory hypoxemia and pulmonary infiltrates. This is caused by capillary leak at the alveolar capillary interface, breakdown of the alveolar-capillary unit and a resultant flooding of the alveolar unit with a proteinaceous and inflammatory fluid. This summons an influx of neutrophils and macrophages into the alveolus which results in a profound and self-propagating inflammatory cascade.[4]

1.4 BURDEN OF DISEASE

Among all hospitalized patients with COVID-19, it is estimated that 33% will develop ARDS, 25% will require transfer to an intensive care unit (ICU), and 15% will require invasive mechanical ventilation. Of the patients who require care in an ICU, 60-80% require invasive mechanical ventilation and 75% meet the Berlin Criteria for ARDS. The ICU mortality rate for patients with COVID-19 is 40% and up to 60% in critically ill patients who require mechanical ventilation. Post-mortem histopathology confirms that up to 90% of non-survivors of COVID-19 died of ARDS.[5,6]

1.5 SECONDARY INFECTION IN CRITICALLY ILL PATIENTS

Secondary infection is defined as the occurrence of a second bacterial, viral, or fungal infection which develops during or after the initial infection. Secondary infection is common in the ICU. Approximately 13% of patients admitted to an ICU for sepsis, or life-threatening organ dysfunction secondary to an infection, will develop a secondary infection. This occurs, on average, within nine days of admission. Patients with sepsis who develop secondary infection are typically more severely ill on hospital admission. Furthermore, comorbid health conditions, respiratory insufficiency, the presence of a central venous catheter, the use of mechanical ventilation each independently increase the risk for ICU-acquired infection. Patients who develop a secondary infection have longer lengths of ICU stay (22 versus 5 days) and a worse 60-day mortality (44.2% versus 29.1%).[7]

Mechanistically, it is postulated that patients with sepsis who develop a secondary infection have a concurrent hyperinflammatory response and immune suppression.[8] Both pro- and anti-inflammatory responses occur early in sepsis and early death is often attributed to a profound and refractory hyperinflammatory state. Patients that survive this, however, may suffer from a delayed failure of the innate and adaptive immune system yielding profound immunosuppression. Spleen and lung derived immune cells harvested immediately after the death of patients with sepsis reveal a reduced production of pro- and anti-inflammatory cytokines and deranged and incompetent innate and adaptive immunity.[9]

1.6 SECONDARY INFECTION IN VIRAL PRIMARY INFECTION

Virus-mediated immunosuppression is widely described. This is an evolutionary strategy adopted by the virus to escape clearance by the host. The virus weakens the hosts innate immune response, making the host an optimal target for opportunistic pathogens.[10] This is perhaps best understood in the setting of the human immunodeficiency virus (HIV), ultimately causing robust immunosuppression traditionally manifested by host opportunistic infection. The viral-bacterial interaction is symbiotic, allowing the virus to survive while simultaneously increasing the pathogenicity of previously benign bacterial communities. The virus then utilizes bacterial components to invade target cells, and amidst an impaired immune response, the bacteria gain access to damaged and injured cells and tissue.[11,12]

History has been marked by numerous influenza pandemics which underscore the frequency and gravity of secondary infection in patient with a viral illness. In 1918, the Spanish flu infected nearly 50% of the world's population, leaving 40-50 million people dead. Pneumonia

due to bacterial secondary infection is thought to be the cause of death in 95% of these patients. This trend remained true in the 1957 Asian Influenza, 1968 Hong Kong Influenza, and 2009 Swine Influenza pandemics where bacterial secondary infection contributed significantly to the death toll.[12] Infection with SARS-CoV and MERS-CoV have also been complicated by bacterial secondary infection. Approximately 36% of patients with SARS and 56% of patients with MERS developed a secondary infection.[13,14]

1.7 SECONDARY INFECTION IS PREVALENT IN COVID-19

There is a strikingly high incidence of secondary infection that has been observed by our group as well as several others in patients with COVID-19. Ventilator associated pneumonias (VAPs), or pneumonia in patients who have been mechanically ventilated for more than 48 hours, have been reported in up to 50% of patients with COVID-19 who require mechanical ventilation. This is significantly higher than the typical 30% of patients who develop VAP with influenza.[15] Similarly, an unusually high incidence of blood stream infections has been reported in critically ill patients with COVID-19.[16] Patients who are critically ill from COVID-19 have prolonged ICU and hospital admissions, lengthy duration of mechanical ventilation, and a protracted need for central venous access, all of which far surpass the duration typically seen in non-COVID-19 ARDS and which are known risk factors for secondary hospital acquired infections.[6]

1.8 CORTICOSTEROIDS IN VIRAL PNEUMONIA

The use of corticosteroids in viral pneumonia has been widely debated. While corticosteroids suppress an often-deleterious inflammatory response, they also inhibit immune response and, thereby, slow pathogen clearance. The SARS-CoV virus and the MERS-CoV virus are known to trigger profound inflammatory states which induce ARDS. The inflammatory state persists long after viral clearance and is the etiology of multi-organ system failure. Thus, the use of an immunomodulator to protect a patient from the long-term and often devastating sequalae of the virus makes logical sense. However, corticosteroids are not without harm.

In a retrospective study of patients with MERS, patients who received corticosteroids were more likely to subsequently need mechanical ventilation, renal replacement therapy, and vasopressors. While this ultimately had no impact on 90-day mortality, patients who received corticosteroids did have impaired viral clearance.[17] Multiple corticosteroid studies were conducted in patients infected with the SARS-CoV virus, each indicating that corticosteroids caused harm.[18–21] Pulse dose methylprednisolone was associated with an increased 30-day mortality (adjusted OR 26.0 CI 4.4-154.8) as well as disseminated fungal infection and avascular necrosis. Patients who received corticosteroids had delayed viral clearance compared to patients who did not receive corticosteroids.[22–24]

The role of corticosteroids has been explored numerous times in patients with influenza. In ICU patients with H1N1, the use of corticosteroids increased the likelihood of developing a hospital acquired infection (OR 2.2, CI 1.1-4.5, $p<0.05$) and of ICU mortality (OR 3.8, CI 2.1-7.2, $p<0.01$).[25] Several subsequent studies confirmed the risk of using corticosteroids specifically in patients with ARDS secondary to influenza.[26–28] A systematic review and meta-analysis in influenza pooled 10 studies to include a total of 6548 patients. The risk ratio of mortality was 1.75

(CI 1.3-2.4, p=0.0002) in patents with influenza who received corticosteroids. Similarly, patients had longer lengths of ICU stay and were more likely to develop secondary bacterial or fungal infections compared to patients who did not receive corticosteroids. There was also prolonged viral shedding in patients with influenza who were treated with corticosteroids.[29]

In patients with ARDS, the most severe sequala of viral pneumonia, steroid therapy has been associated with higher mortality and a longer duration of mechanical ventilation. Patients with ARDS treated with steroids are more likely to develop bacterial pneumonia or invasive fungal infections.[26,27] Based on the increased likelihood for mortality, prolonged viral shedding, and increased risk of infection, the use of corticosteroids has, until recently, been discouraged in viral pneumonia.[30]

1.9 CORTICOSTEROIDS IN COVID-19 ARDS

Despite the initial warnings to avoid corticosteroids in patients with COVID-19, the United Kingdom based RECOVERY trial explored the role of dexamethasone as a therapeutic treatment option for this disease. Patients included in this trial were hospitalized with clinically suspected or laboratory confirmed COVID-19. Patients were randomized to receive either dexamethasone 6mg per day (N=2104) for 10 days or standard of care (N=4321). The mean age of the patients was 66.1 $\pm$ 15.7 years, 36% of the patients were female, 18% were Black, Asian, or from a minority ethnic group. The primary outcome was all-cause mortality at 28-days. Mortality was significantly reduced in patients who received dexamethasone (22.9% v. 25.7%, rate ratio 0.83, p<0.001). In a pre-specified sub-group analysis based on the degree of needed respiratory support, the mortality difference was the most significant in patients who required invasive mechanical ventilation

(N=1007) (29.3% vs. 41.4%, rate ratio 0.64, CI 0.51-0.81). Patients who were receiving dexamethasone also had a shorter duration of hospitalization and were more likely to be discharged alive at 28-days. The RECOVERY trial revolutionized the management of patients with COVID-19 ARDS and made the use of dexamethasone mainstay as part of the treatment protocol.[31] While practice changing, the RECOVERY trial failed to examine the impact that dexamethasone had on secondary infection in these patients and secondary infection ultimately impacted overall mortality.

A meta-analysis of seven randomized control trials which were terminated due to lack of equipoise after the publication of the RECOVERY trial further explored the role of corticosteroids in COVID-19 ARDS. Collectively, these studies assessed the role of various types of corticosteroids at different doses and durations on 28-day all-cause mortality in critically ill patients with COVID-19. The meta-analysis included 1703 patients from 12 countries. The average age and the proportion of female participants was included for each of the seven trials but the racial and ethnic composition of the patients was not included. The odds ratio for 28-day mortality was 0.66 [95% CI, 053-0.82, $p<0.001$] when comparing patients treated with corticosteroids to patients who did not receive corticosteroids. The mortality benefit was most robust and significant in patients who received dexamethasone (OR 0.64, CI 0.5-0.82). Similar to the RECOVERY trial, the mortality benefit was more significant in patients on invasive mechanical ventilation but not requiring support with vasoactive medications. There was no difference in mortality based on age or sex. Four of seven studies assessed for secondary infection[32]. However, the findings of the incidence of secondary infection or any relationship between secondary infection and outcomes were not published. This meta-analysis further

confirmed the mortality benefit of corticosteroids in COVID-19 ARDS but ignored the potential harm of secondary infection.

As a result of the findings of the RECOVERY trial, the CDC guidelines now strongly recommend the use of dexamethasone for patients with COVID-19, specifically those patients who are requiring mechanical ventilation. These recommendations are reiterated in the major society guidelines such as the Society of Critical Care Medicine (SCCM) European Respiratory Society (ERS)[33,34].

2.0 KNOWLEDGE GAPS

The incidence of secondary infection is striking in patients who are critically ill from COVID-19. This is likely due their prolonged hospital and ICU length of stay and the need for lengthy mechanical support and invasive lines and tubes. This may also be compounded by the known immunosuppressive nature of viral infection. Yet, the mainstay of therapy for patients with critical illness and ARDS secondary to COVID-19 is prolonged high dose immunosuppressive corticosteroid therapy. No studies have evaluated whether corticosteroid usage increases the risk of secondary infection in critically ill patients with COVID-19.

The costs and benefits of dexamethasone have also been studied primarily in a white patient population. The enrollment in the UK based RECOVERY trial closely mirrored the ethnic composition of the UK, more than 80% white. However, COVID-19 is known to disproportionally impact racial and ethnic minority groups. There is a higher rate of death from COVID-19 in the African American, Native American, and LatinX communities. In fact, more than 20% of cases in the US occur in the African American population and 33.8% in the LatinX population, although these groups account for only 13% and 18% of the US population, respectively[35]. African Americans have a two-fold higher rate of mortality from COVID-19. In the UK, 25% of patients requiring ICU support are Black or of other ethnic minority, despite the low proportion of these ethnicities in the UK population[36]. The unequal burden of disease in the minority populations is likely due to a combination of host and environmental factors[35]. Nevertheless, it is important to include the most at-risk population in clinical trials to determine whether the effects of pharmacotherapies are differentially beneficial in this patient population. While practice changing, the population of patients included in the RECOVERY trial did not accurately recapitulate the

population of patients most at risk of critical illness and mortality from COVID-19. The population of patients seen at the University of Maryland is primarily Black. Thus, exploring the role of corticosteroids specifically in the population of patients most susceptible to and at risk from mortality from COVID-19 is imperative and fills a large gap in our current knowledge about COVID-19 treatment.

3.0 PUBLIC HEALTH SIGNIFICANCE

As of June 24, 2021, there have been 179,702,827 known cases of COVID-19. Approximately 25-33% of patients will be admitted to the ICU for management of their COVID-19 illness[20,37]. Thus, worldwide, 59.9 million patients have required ICU admission for the treatment of COVID-19. Corticosteroids are considered the mainstem of treatment for patients who are critically ill with ARDS from COVID-19[31,33,34]. In a sub-group analysis, dexamethasone demonstrated a profound reduction in 28-day mortality, most apparent in mechanically ventilated patients. In contrast, there was a trend towards harm in using dexamethasone in patient who had no oxygen requirement[31]. Yet, steroids are being used ubiquitously all over the globe for COVID-19 absent any focus on the patient's severity of illness or potential adverse side effects of corticosteroids. Corticosteroids are readily available, highly affordable, and can be administered orally or intravenously which makes corticosteroids an ideal and enticing pharmacotherapeutic option for a global pandemic.

However, patients with COVID-19 have a marked incidence of secondary infection including bacterial and fungal bloodstream, respiratory, and urinary infections. Compared to a historical cohort of patients with ARDS secondary to influenza, the rate of VAP and bloodstream infection are significantly higher[15]. Corticosteroids are immunosuppressive and may place patients at a higher risk of secondary infections which is further compounded by the propensity for corticosteroids to yield hyperglycemia. The demographic composition of patients enrolled in the RECOVERY trial was disproportionately white with only a fraction of patients who were Black of LatinX. Yet these minority groups are unduly impacted by the COVID-19 pandemic[35]. These groups are concomitantly more effected by diabetes, with 12.5% of adult Hispanics in the US

having a diagnosis of diabetes, 11.7% of non-Hispanic Blacks, and 7.5% of non-Hispanic whites[38]. The mortality benefit presented in the RECOVERY trial may lack generalizability considering the trial omitted the members of the populations most at risk of getting and dying from COVID-19 and from suffering potential side effects from the proposed intervention.

The public health significance of this work extends far beyond US borders. It is also our responsibility, as a healthcare community and as stewards of public health, to identify drugs which are accessible and affordable to insured and uninsured patients within the US healthcare system and throughout the entire global community. Cases of COVID-19 are exponentially increasing in lower- and middle-income countries like India. In these countries, access to the vaccine has been scarce, living conditions may prohibit social distancing, and access to precious resources like oxygen and ICU beds are inadequate. Effective and affordable pharmacotherapies such as dexamethasone are vital to the survival of millions of people. However, we are seeing a rise in the cases of fungal infection in countries like India. The prevalence of mucor in India is 14 cases/100,000 people, nearly 70x the global prevalence. On May 29, 2021 there were more than 14,000 new cases of mucor[39]. A retrospective chart review study of 16 healthcare centers across India explored the relationship between COVID-19 and mucor. There was a 2.1-fold increase in the number of mucor cases in 2020 compared to the same time period the year prior. Risk factors for mucor included poorly controlled diabetes. The only unifying diagnosis in patients who had COVID-19 and developed mucor was COVID-19 and the majority of these patient (78.7%) received corticosteroids, often with excess doses or durations than recommended in the RECOVERY trial. The combination of a higher baseline prevalence of mucor, immunosuppression due to the SARS-CoV-2 virus, compounded by further immunosuppression by corticosteroids causing prolonged hyperglycemia may create the perfect milieu for mucor[40]. Thus, is it imperative

that we carefully administer glucocorticoids to the right patient population (critically ill and mechanically ventilated patients) when the benefit outweighs the risk. This calculation requires that we explore both the role that corticosteroids are playing in secondary infection and the access patients have to antibiotics and antifungals when performing these risk calculations.

4.0 OBJECTIVE

Exposure and outcome data was collected via a retrospective review of the Electronic Medical Record of critically ill patients with COVID-19 who were cared for at the University of Maryland Medical Center and R Adams Cowley Shock Trauma Center. We aimed to define the role that corticosteroids play in the incidence of secondary infection and the role that secondary infection plays in patient mortality in critically ill patients with COVID-19. We hypothesized that patients treated with corticosteroids will have a higher incidence of secondary infection and will be more likely to develop a secondary infection during the first 28 days of their hospitalization. We also hypothesized that patients who develop a secondary infection will have a higher mortality than patients who do not develop a secondary infection.

5.0 MATERIALS AND METHODS

5.1 STUDY DESIGN AND STUDY POPULATION

This was a retrospective cohort study of COVID-19 patients admitted to an Intensive Care Unit (ICU) at the University of Maryland Medical Center (UMMC) and R Adams Cowley Shock Trauma Center between March 14 and June 30 of 2020. The study was reviewed and approved by the University of Maryland, Baltimore, institutional review board (IRB). The requirement for written informed consent was waived by the IRB.

All patients included in this study have a confirmed diagnosis of SARS-CoV-2 by PCR testing. Patients were included in the study from the time that they arrived at their presenting hospital through death or hospital discharge. Patient demographics, laboratory, microbiology data, the use of COVID-19 directed therapies, and outcomes were abstracted by manual chart review from the medical record. Detailed study enrollment criteria are described in section 5.2 and in Figure 1.

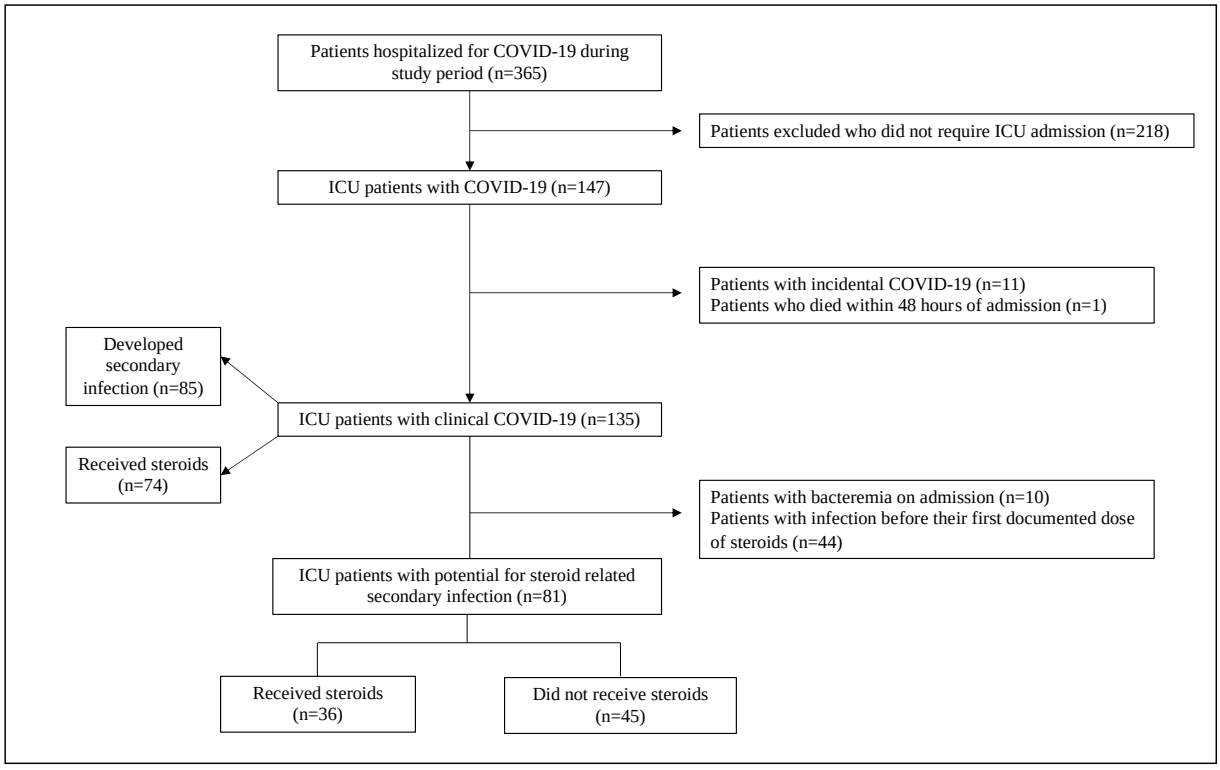

Figure 1: Study consort diagram.

5.2 EXCLUSION CRITERIA

5.2.1 Defining Exposure

Patients were defined as having been exposed to steroids if they received any steroid of any kind, dose, or duration during their hospitalization. Patients were excluded from this analysis if they had the outcome of interest prior to the exposure. In other words, patients who were co-infected on admission to the hospital or patients who developed a secondary infection in less than 48 hours after receiving corticosteroids were omitted from this analysis. The same exposure definition was used in the analysis of the effect of corticosteroids on mortality.

Secondary infection includes bloodstream, respiratory, or urinary infection. Bloodstream infection is be defined as positive blood culture without clear evidence of contamination. Respiratory infection is defined as a pathogen not considered to be a member of the normal respiratory flora isolated from the lower respiratory tract (sputum culture, tracheal aspirate, bronchoalveolar lavage). Urinary tract infection is defined as a pathogen obtained from the urine with greater than 100,000 colony forming units. Yeast in the sputum or urine was excluded. Cases of culture positivity were reviewed to confirm secondary clinical infection as determined by the expertise of the Infectious Disease consultant or Critical Care physician caring for the patient. Patients were determined to have secondary infection only when they had both culture positivity and sufficient clinical concern to warrant pharmacotherapeutic treatment. If individual patients developed multiple positive cultures during the hospital course, the first occurrence of a secondary infection was counted in the analysis.

5.2.2 Defining the Primary Outcome

There were two primary outcomes in this study: 1) secondary infection and, 2) mortality. The definition of secondary infection is outlined in section 5.2.1. Patients who were had a co-infection at the time of admission or within 48-hours of admission were excluded from the analysis of secondary infection. Furthermore, patients who had the outcome of secondary infection prior to or within 48-hours of receiving corticosteroids were also excluded from analysis of the impact of corticosteroids on secondary infection (Figure 1). Mortality was assessed using patient hospital records. Patients who died within 48-hours of admission were excluded from the time to event analysis as they were determined not to have had the opportunity to receive corticosteroids or develop a secondary infection.

5.2.3 Defining the Time at Risk

Data was extracted for each patient from the time of admission to the time of hospital discharge or death. Patients were considered at risk for secondary infection only if they did not have any evidence of infection, besides their COVID-19 illness, at hospital admission or within the first 48-hours of hospital admission (Figure 1). Evidence of infection is defined as positive culture data. Patients were considered to be at risk for secondary infection due to corticosteroids only if the infection developed >48 hours after the administration of steroids. Patients were considered at risk for mortality if they survived beyond the first 48-hours of their hospital admission.

5.3 STATISTICAL METHODS

We calculated descriptive statistics of demographic and clinical characteristics and performed comparisons between groups using the Chi-square test of independence for categorical variables and the Mann Whitney U test for discrete variables.[41,42] Time-to-event analyses were performed using univariate and multivariate proportional hazards models.

To assess the association between corticosteroid usage and secondary infection, we utilized Fine-Gray proportional hazards models (treating death as a competing risk).[43] We adjusted for potential clinical confounders that were biologically relevant (age). When assessing for the association between secondary infection and mortality and steroids and mortality, we used a Cox proportional hazard model adjusted for age as a biologically relevant potential clinical confounder.[44]

A post-hoc subgroup analysis was performed of the primary outcomes by two groups, as defined by characteristics at randomization: race and ethnicity. We used a Cox proportional hazard model adjusted for age as a biologically relevant potential confounder to assess the association between corticosteroid administration and secondary infection and corticosteroid administration and mortality.

Time to event analyses were depicted using Kaplan Meier curves. Two-sided p-values of less than 0.05 were considered to indicate statistical significance. All analyses were performed using the R programming environment (v.4.0.2).

6.0 RESULTS

6.1 CHARACTERISTICS OF THE STUDY POPULATION

From March through June 2020, 365 patients were hospitalized at UMMC for COVID-19, of which 147 were admitted to the ICU. Twelve patients were excluded from the analysis due to death within 48 hours (n=1) or incidental COVID-19 infection (n=11) (Figure 1). The mean age of the patients in the cohort was 52.3 years, 29.6% were female, 33.3% were Black or African American, 29.6% were White, 1.5% were Asian, 0.7% were Native Hawaiian or Other Pacific Islander, and 26% were designated as other. Fifty (37%) patients were Hispanic or Latino (Table 1).

Sixty-three percent of critically ill SARS-CoV-2 patients develop secondary infection. All patients included in this study required ICU level of care. As a whole, 83% of patients were mechanically ventilated, 7.4% required non-invasive positive pressure ventilation, 31.9% required high flow nasal cannula. Neuromuscular blockade was utilized in 43% of patients and 49.6% of patients were placed in the prone position. Twenty-four (17.8%) patients required extracorporeal membrane oxygenation (ECMO). Patients had prolonged ICU and hospital lengths of stay, averaging 22.4 and 26.8 days, respectively (Table 1).

Table 1: Patient Demographics

	All (N=135)
Age (years)	
Mean (SD)	52.3 (17.4)
Median [Q1, Q3]	52.0 [40.0, 64.0]
Female (%)	40 (29.6)
Race (%)	
Asian	2 (1.5)
Black of African American	45 (33.3)
Multiple Races	2 (1.5)
Native Hawaiian or Pacific Islander	1 (0.7)
Other	26 (19.3)
White	40 (29.6)
Hispanic (%)	50 (37)
COVID-19 Directed Therapies (%)	
Tocilizumab	24 (17.8)
Corticosteroids	74 (54.8)
Corticosteroids + Tocilizumab	19 (14.1)
Convalescent Plasma	23 (17)
Stem Cells	7 (5.2)
ARDS (%)	80 (59.3)
Required Mechanical Ventilation (%)	112 (83)
Non-Invasive Mechanical Ventilation (%)	10 (7.4)
High Flow Nasal Cannula (%)	43 (31.9)
Vasopressors (%)	84 (62.2)
Neuromuscular Blockade (%)	58 (43.0)
Prone Positioning (%)	67 (49.6)
ECMO (%)	24 (17.8)
ICU Length of Stay (days)	
Mean (SD)	22.4 (35.9)
Median [Q1, Q3]	17 [7.0, 28.3]
Hospital Length of Stay (days)	
Mean (SD)	26.8 (36.4)
Median [Q1, Q3]	20.5 [10.0, 31.0]
Mortality at 30-days from Admission (%)	25 (18.5)
Mortality at 60-days from Admission (%)	38 (28.1)

6.2 IMPACT OF STEROIDS ON SECONDARY INFECTION

The proportion of patients with secondary infection during their hospitalization was 63% (n=85). The average time from hospital admission, defined as admission to the initial presenting hospital, to positive culture data was 16.7 days, 11.2 days, and 20.8 days for blood, lower respiratory tract, and urine cultures, respectively. The primary steroid utilized was methylprednisolone (67%) dosed via the protocol described by Meduri (15, 16), followed by hydrocortisone (18.6%), dexamethasone (8.5%), betamethasone (5.7%), and prednisone (2.9%). Due to the timing of the data collection, no patients received dexamethasone dosing per the RECOVERY trial. Among all individuals who received corticosteroids, the average prednisone equivalent dose of steroids administered was 1360mg with a mean 12.9 days of >20mg prednisone equivalent doses.

In the subsequent time to secondary infection analysis, 54 of the 135 critically ill COVID-19 patients were excluded as they received corticosteroids within 48 hours of or after developing a secondary infection. The mean age of the patients included in the time to secondary infection analysis was 53.5 years, 35.8% were female, 2.5% Asian American, 37% African American, 37% White, 18.5% other, and 35.8% Hispanic or Latino (Table 2). Patients who received corticosteroids before developing infection received an average of 1210 mg of prednisone equivalent dose and received more than 20mg equivalents of prednisone for an average of 11.9 days. The odds that a patient with any positive culture data was exposed to steroids was 1.96 (CI 0.81-4.79, p=0.14). In the time to event analysis, there was no significant increase in the likelihood of secondary infection in patients who received corticosteroids (HR 1.45, CI 0.75-2.82, p=0.28) when adjusting for age (Figure 2). Similarly, there was no significant increase in the likelihood of bloodstream infection

(HR 2.54, CI 0.85-7.58, p=0.09), respiratory infection (HR 1.53, CI 0.65-0.72, p=0.27), or urinary infection (HR 1.06, CI 0.29-3.90, p=0.94).

Table 2: Demographics of Patients who Received Corticosteroids Prior to Secondary Infection

	All (N=81)	**Steroids (N=36)**	**No Steroids (N=45)**	***P*-value**
Age (years)				0.002
Mean (SD)	53.5 (18.4)	46.4 (15.8)	59.1 (18.5)	
Median [Q1, Q3]	53.0 [41.0, 61.0]	44.5 [35.8, 60.5]	61.0 [48.0, 73.0]	
Female sex, N (%)	29 (35.8)	10 (27.8)	19 (42.2)	0.27
Race, N (%)				0.08
Asian American	2 (2.5)	1 (2.8)	1 (2.2)	
Black or African American	30 (37.0)	10 (27.8)	20 (44.4)	
White	30 (37.0)	12 (33.3)	18 (40.0)	
Other	15 (18.5)	11 (30.6)	4 (8.9)	
Hispanic or Latino, N (%)	29 (35.8)	17 (47.2)	12 (26.7)	0.13

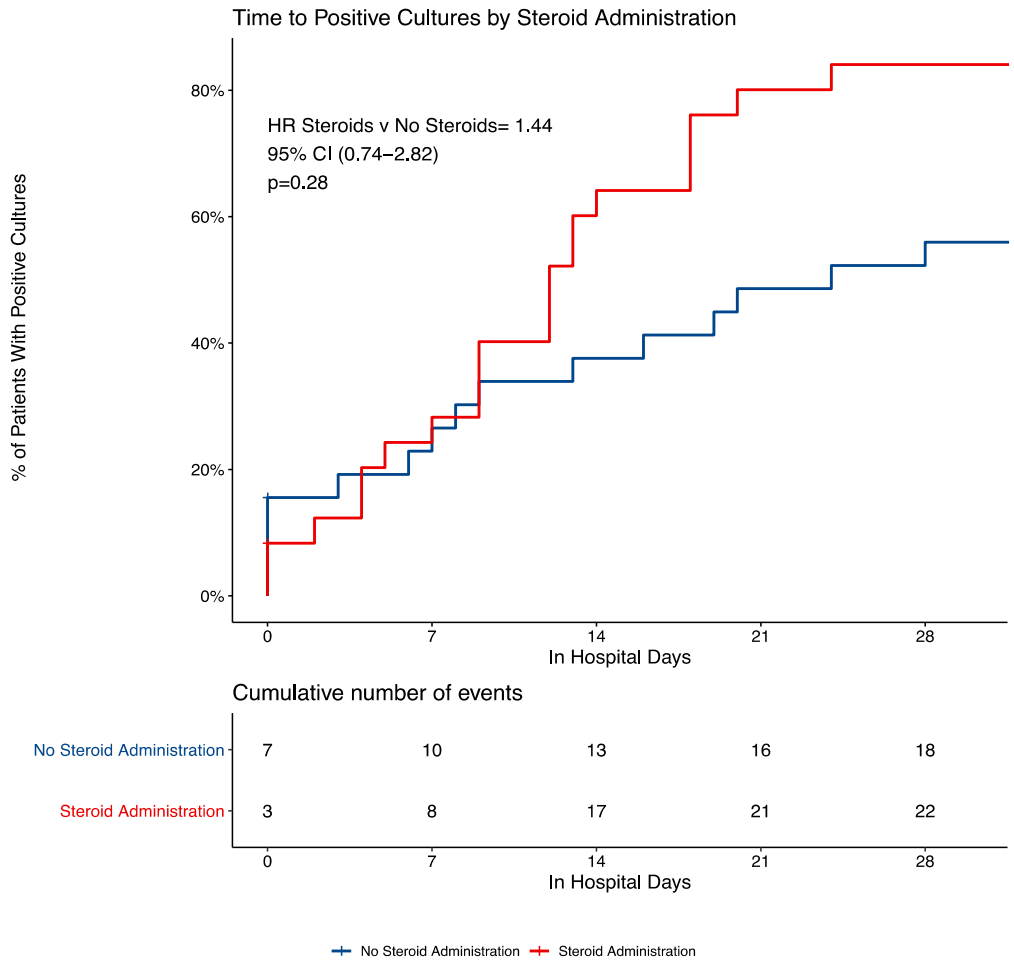

Figure 2: Kaplan-Meier curves examining time to positive culture by corticosteroid administration.Kaplan-Meier cuve is unadjusted. A Fine-Gray model was used to calculate the the adjusted HR which is adusted for age.

6.3 IMPACT OF SECONDARY INFECTION ON MORTALITY

The baseline demographics of all patients who developed a secondary infection are depicted in Table 3. The presence of secondary infection was not associated with the likelihood of 28-day mortality in an age-adjusted Cox proportional hazard estimate (HR 0.66, CI 0.33-1.35, p=0.26) (Figure 2). Similarly, the likelihood of mortality was not associated with the presence of bloodstream infection (HR 0.59, CI 0.31-1.13, p=0.11), respiratory infection (HR 0.59, CI 0.30-1.19, p=0.14), or urinary infection (HR 0.69, CI 0.30-1.58, p=0.38), when adjusting for age.

Table 3: Demographics of Patients who Developed Secondary Infection.

	All (N=135)	**Co-Infection (N=85)**	**No Co-Infection (N=50)**	***P*-value**
Age (years)				0.53
Mean (SD)	52.3 (17.4)	51.9 (14.3)	53.3 (22.4)	
Median [Q1, Q3]	52.0 [40.0, 60.0]	51.0 [41.0, 62.0]	57.0 [35.0, 72.0]	
Female sex, N (%)	40 (29.6)	23 (27.1)	17 (34.0)	0.22
Race, N (%)				0.44
Asian American	2 (1.5)	1 (1.2)	1 (2.0)	
Black or African American	45 (33.3)	26 (30.6)	19 (38.0)	
White	40 (29.6)	26 (30.6)	14 (28.0)	
Native Hawaiian/Pacific Islander	1 (0.7)	1 (1.2)	0 (0)	
Other	26 (19.3)	21 (24.7)	5 (10.0)	
Multiple Races	2 (1.5)	1 (1.2)	1 (2.0)	
Hispanic or Latino, N (%)	50 (37.0)	38 (44.7)	12 (24.0)	0.14

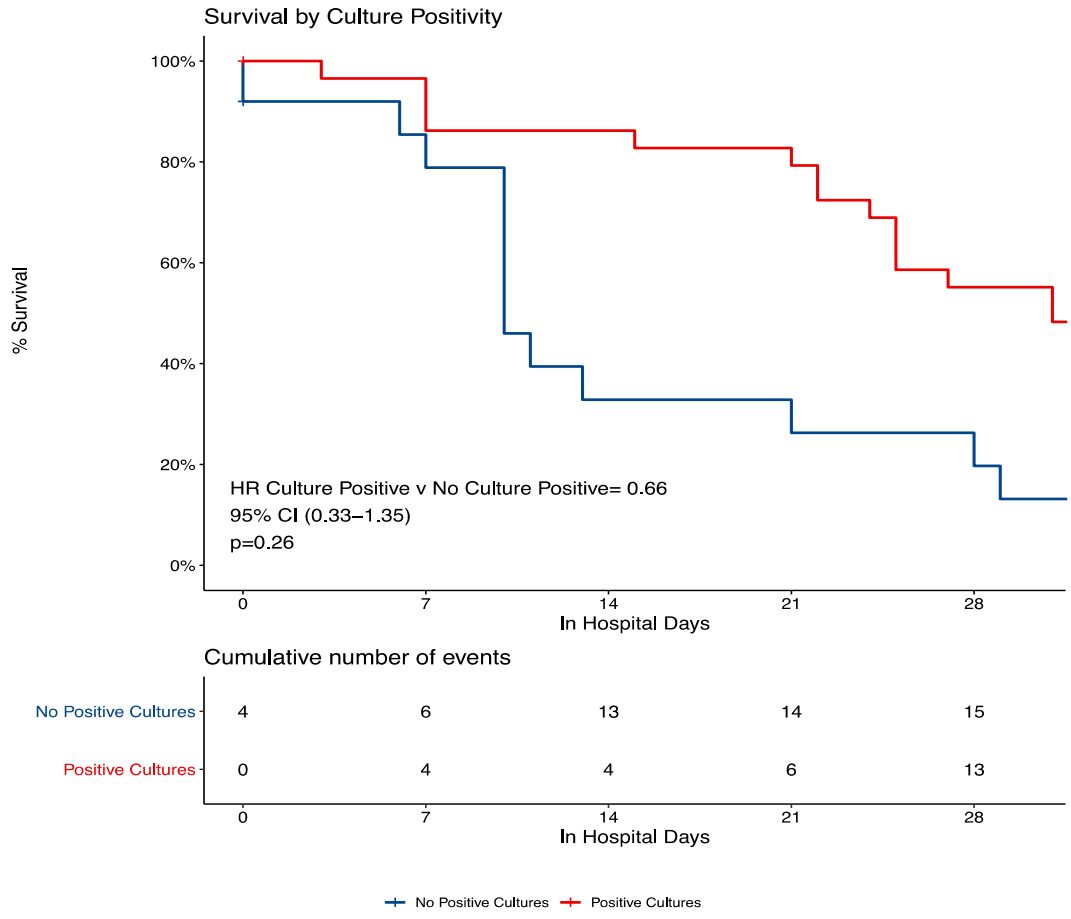

Figure 3: Kaplan-Meier curves examining time to mortality by the presence of secondary infection. The Kaplan-Meier curve is unadjusted and the hazard ratio is adjusted for age.

6.4 IMPACT OF CORTICOSTEROIDS ON MORTALITY

Seventy-four patients (55%) received corticosteroids during their hospitalization (Table 4). Thirty-three percent of these patients were Black. Thirty-seven percent were Hispanic. The demographic composition of this group more closely reflects the ethnic and minority makeup of patients globally effected by COVID-19. An unadjusted Cox proportional hazard estimate of 28-day mortality indicates that there is a 68% reduction in the likelihood of mortality during the 28-day period in patients treated with corticosteroids (HR 0.32, 0.17-0.58 p<0.001) (Figure 3). This finding remains significant in an age-adjusted Cox proportional hazard estimate (HR 0.27, CI 0.10-0.72, p=0.01).

Table 4: Demographics of All Patients who Received Corticosteroids

	All (N=135)	**Steroids (N=74)**	**No Steroids (N=61)**	***P*-value**
Age (years)				0.01
Mean (SD)	52.3 (17.4)	49.2 (14.7)	54.2 (20.9)	
Median [Q1, Q3]	52.0 [40.0, 60.0]	48.5 [39.3, 60.0]	59.0 [35.0, 72.0]	
Female sex, N (%)	40 (29.6)	16 (21.6)	24 (39.3)	0.01
Race, N (%)				0.12
Asian American	2 (1.5)	1 (1.4)	1 (1.6)	
Black or African American	45 (33.3)	21 (28.4)	24 (39.3)	
White	40 (29.6)	22 (29.7)	18 (29.5)	
Native Hawaiian/Pacific Islander	1 (0.7)	1 (1.4)	0 (0)	
Other	26 (19.3)	21 (28.4)	5 (8.2)	
Multiple Races	2 (1.5)	1 (1.4)	1 (1.6)	
Hispanic or Latino, N (%)	50 (37.0)	36 (48.6)	14 (23.0)	0.05

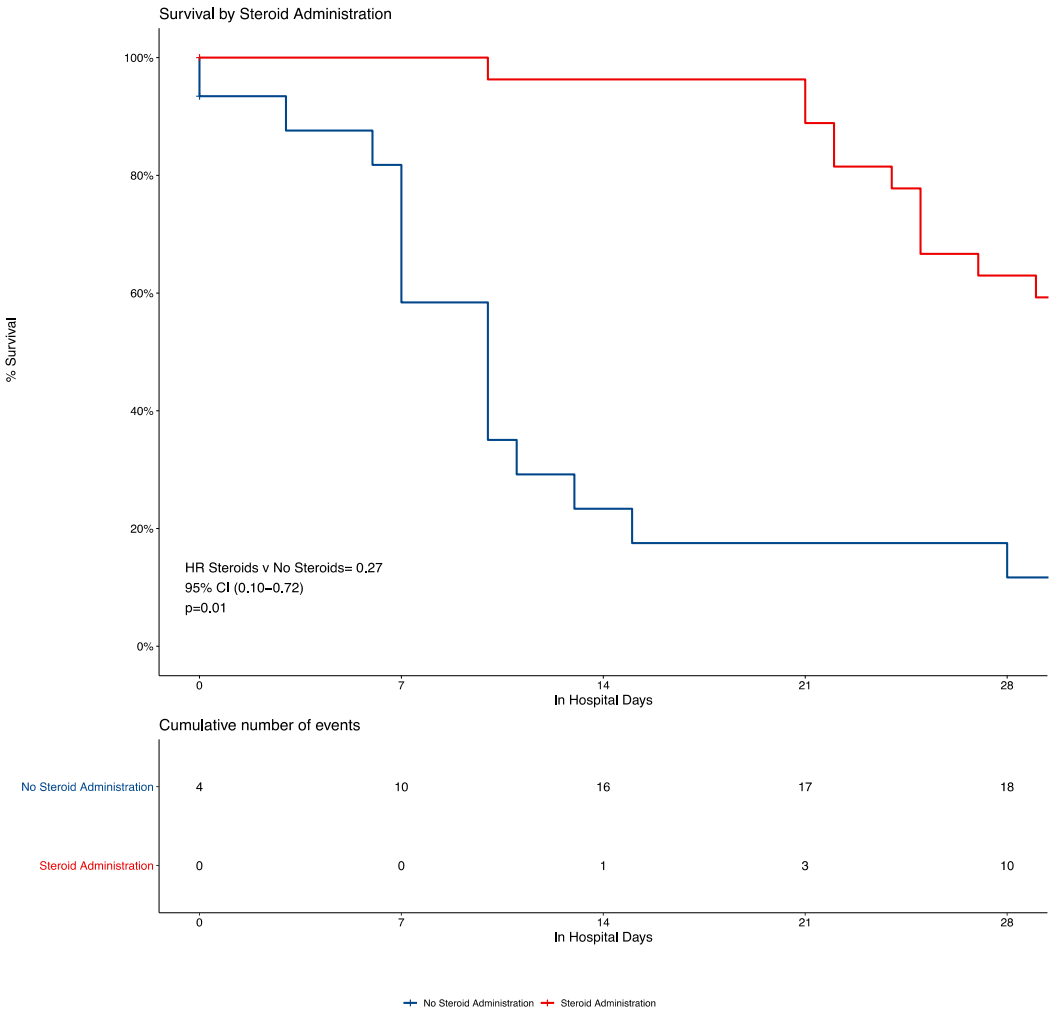

Figure 4: Kaplan-Meier curve examining time to mortality by corticosteroid administration. The Kaplan-Meier curve is unadusted. A Cox proportional Hazard Model was used to calculate the adjusted HR which is adjusted for age.

6.5 RE-EVALUATION OF THE FINDINGS IN RACIAL AND ETHNIC MINORITY POPULATIONS

6.5.1 Race, Corticosteroids, and Secondary Infection

We explored the role of race on the relationship between corticosteroid administration and secondary infection. In a Cox proportional hazard model, there was no significant effect of corticosteroids on secondary infection, adjusting for race (HR 1.71, CI 0.89-3.29, p=0.11). Similarly, corticosteroids had no significant impact on the outcome of secondary infection when adjusting for both race and age (HR 1.58, CI 0.75-3.34, p=0.225). In a sub-analysis of Black patients only (n=30), corticosteroids had no impact on the development of secondary infection (HR 2.31, CI 0.70-7.54, p=0.17).

6.5.2 Ethnicity, Corticosteroids, and Secondary Infection

When the effect of corticosteroid administration on secondary infection was adjusted for ethnicity and for both ethnicity and age, there was no significant effect of corticosteroids on the likelihood of developing secondary infection (HR 1.47, CI 0.77-2.82, p=0.25 and HR 1.38, CI 0.68-2.80, p=0.37). In the subgroup analysis of Hispanic patients only, corticosteroids did not impact the likelihood of developing secondary infection, when adjusting for age (HR 0.90, CI 0.31-2.62, p=0.85).

6.5.3 Race, Corticosteroids, and Mortality

We explored the impact of race on the relationship between corticosteroids and mortality. In a subgroup analysis of Black patients (n=45), a Cox proportional hazards model adjusting for age demonstrated a 73% reduction in the likelihood of 28-day mortality with the administration of corticosteroids (HR 0.27, CI 0.07-0.96, p=0.02) (Figure 5). This finding was significant in a second subgroup analysis of all non-white patients (n=76) (HR 0.22, CI 0.077-0.67, p=0.006), when adjusting for age (Figure 6).

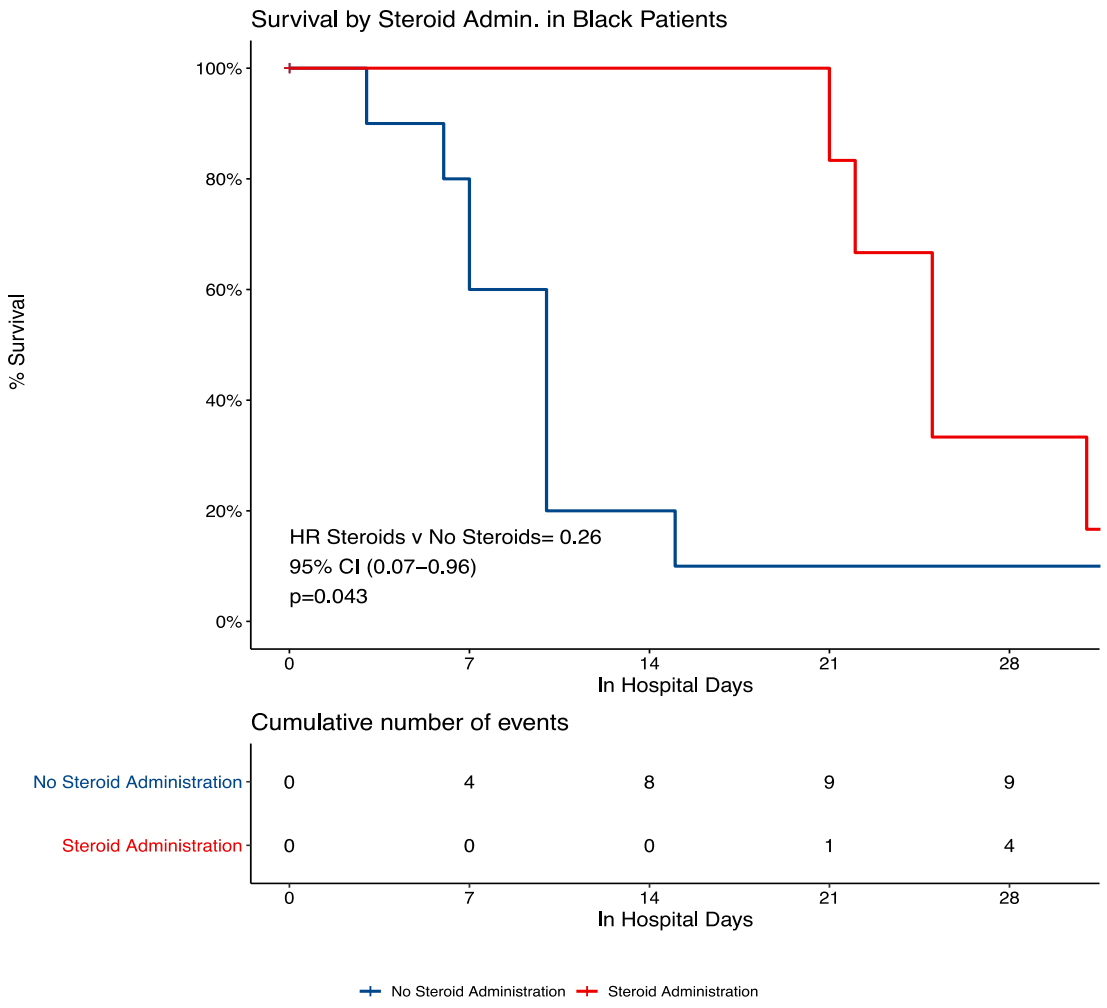

Figure 5: Kaplan-Meier curve examining time to mortality by corticosteroid administration in a subgroup of Black patients. The Kaplan-Meier curve is unadjusted. A Cox proportional hazard model was used to calculate the adjusted HR which is adjusted for age.

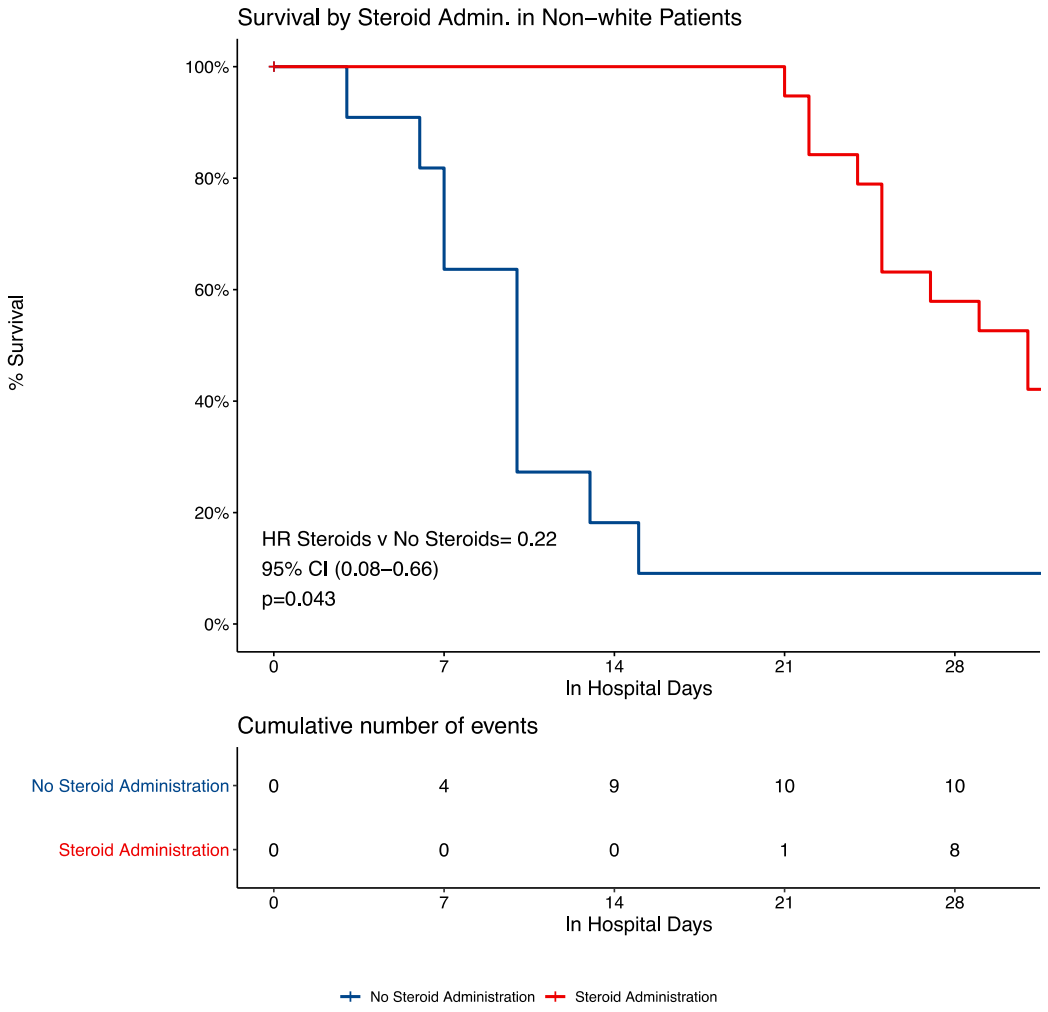

Figure 6: Kaplan-Meier curve examining time to mortality by corticosteroid administration in a subgroup of non-white patients. The Kaplan-Meier curve is unadjusted. A Cox proportional hazard model was used to calculate the adjusted HR which is adjusted for age.

6.5.4 Ethnicity, Corticosteroids, and Mortality

We explored the role of ethnicity on the relationship between corticosteroids and mortality using a subgroup of Hispanic patients (n=50). In this subgroup, corticosteroids have no significant

impact on the likelihood of 28-day mortality in an unadjusted model or in a model adjusted for age (HR 0.39, CI 0.032-4.67, p=0.46).

6.6 THE ROLE OF PROVIDER VARIABILITY ON OUTCOMES

Each critically ill COVID-19 patients may have been cared for by a multitude of critical care physicians and infectious disease doctors. This introduced the possibility of bias and inconsistencies based on routine practice variation. At the University of Maryland, however, two distinct intensive care units housed critically ill patients with COVID-19, the Medical Intensive Care Unit (MICU) and the Biocontainment Unit (BCU). A highly consistent group of critical care and infectious disease providers practice within these two distinct units and there is no overlap in providers who practice both in the BCU and in the MICU. The practice patterns, including who to treat with corticosteroids and when, who to treat with antibiotics and when, are fairly homogenous with each of the two units even across providers. As such, we could distill practice variation into the difference between the BCU and the MICU, rather than exploring the practice variation between individual providers. Corticosteroid use and secondary infection, based on the unit in which the patient was cared for, is represented in Table 5, 6 and 7, respectively. We performed a Cox proportional hazards model adjusting for the unit where the patient was cared for. Corticosteroid use had no impact on the likelihood of developing secondary infection, when adjusting for the intensive care unit where the patient was cared for (HR 1.49, CI 0.80-2.79, p=0.21). Furthermore, there was no significant effect of corticosteroids on secondary infection when adjusting for both intensive care unit and age (HR 1.46, CI 0.74-2.91, p=0.28).

Table 5: Total number of patients administered corticosteroid in each ICU.

N=128	**MICU (N=52)**	**BCU (N=76)**
Corticosteroid Administration n (%)	25 (48)	49 (64)

Table 6: Corticosteroid administration by ICU of patients who had the potential to develop secondary infection after corticosteroid administration.

N=81	**MICU (N=36)**	**BCU (N=45)**
Corticosteroid Administration n (%)	13 (36)	23 (51)

Table 7: Number of patients with secondary infection in each of ICU of the population of patients with potential corticosteroid-related secondary infection.

N=81	**MICU (N=36)**	**BCU (N=45)**
Secondary Infection n (%)	13 (36)	29 (64)

We further assessed the role that practice variation may have played on the relationship between corticosteroid exposure and 28-day mortality. The number of deaths in each unit are depicted in Table 8. When adjusting for BCU or MICU status, there remains a 68% reduction in the likelihood of 28-day mortality in patients who receive corticosteroids (HR 0.32, CI 0.17-0.63, p=0.001). These findings are preserved when adjusting for both age and intensive care unit (HR 0.28, CI 0.11-0.72, p=0.009).

Table 8: Mortaity in each ICU.

N=128	**MICU (N=52)**	**BCU (N=76)**
Mortality n (%)	16 (31)	27 (35)

7.0 DISCUSSION

This study shows that critically ill SARS-CoV-2 patients have a high proportion of secondary infection (63%). Previous studies have estimated that the proportion of secondary infection varies from 5% to 40%, with critically ill patients falling towards the higher end of that range.[45–56] We hypothesize that the increased proportion of secondary infection in our population is related to the higher level of critical illness. The vast majority of the patients in the study required mechanical ventilation and those who did not required non-invasive mechanical ventilation or high flow nasal cannula. This study population, thus, reflects an exceedingly high acuity population. Our work demonstrates that the use of corticosteroids does not impact the likelihood of developing secondary infection. Furthermore, secondary infection does not impact the patient's likelihood of mortality. This work also re-demonstrates that corticosteroids dramatically reduced 28-day mortality. The mortality benefit of corticosteroids remains true despite provider practice variation and in a subgroup of Black and non-white patients.

Secondary infection research is subject to an important epidemiological principle known as competing risks. This concept is imperative in COVID-19 where the rate of mortality is high (>35% in ICU patients in our study) and frequently occurred relatively early in the disease process, with over 30% of deaths occurring in the first two weeks of the hospitalization. Without accounting for competing risks, the previously published studies assessing risk of secondary infection are likely inaccurate.[57] Our work utilized the Fine-Grey competing risk model to account for this epidemiological principle and, thus, allowed for more accurate exploration of the relationship between corticosteroids and secondary infection and provided an improved estimate of time to secondary infection.

Prior to COVID-19, the safety and effectiveness of corticosteroids for ARDS were debated.[58–63] The RECOVERY trial, while practice changing in terms of bringing corticosteroids use to the forefront of COVID-19 therapeutics, did not report the incidence of secondary infections.[31] Our work specifically evaluates whether corticosteroid use is associated with the rate of secondary infection in critically ill COVID-19 patients and found no increase in the likelihood of bloodstream, respiratory tract, or urinary infections in patients treated with corticosteroids. Our findings parallel two recently published randomized clinical trials which administered corticosteroids in COVID-19 and explored secondary infection as a secondary outcome.[47,48] While these trials were terminated early due to the publication of the RECOVERY trial, they found no increase in secondary infection in patients treated with corticosteroids.[47,48] Furthermore, despite the high proportion of secondary infection in our study cohort, secondary infection was not significantly associated with the rate of 28-day mortality. These results provide reassurance to clinicians apprehensive of the infection risk of corticosteroid use in COVID-19.

Our data echoes the findings of the recently published RECOVERY trial and reinforces not just the safety but the efficacy of corticosteroids in the most critically ill patients hospitalized with COVID-19. The RECOVERY trial reported that mechanically ventilated patients with COVID-19 are 46% less likely to die if treated with dexamethasone, when adjusting for age.[31] In a Cox proportional model adjusted for age, we demonstrate a 73% reduction in 28-day case-fatality rate with steroid administration among our cohort. When additionally controlling for mechanical ventilation, our effect remains highly significant, demonstrating a 74% reduction in case fatality. Patients included in this analysis primarily received methylprednisolone followed by hydrocortisone, suggesting this mortality benefit may be a class effect rather than the effect of a particular corticosteroid. The survival benefit of corticosteroids on 28-day case-fatality in the most

critically ill patients, amid the absence of evidence to suggest that corticosteroids are associated with secondary infection or that secondary infection worsens patient survival, tips the scales heavily in favor of the use of corticosteroids for the critically ill patient with COVID-19.

This research contributes to a previously identified gap in the knowledge regarding the risk and benefit of corticosteroids in racial and ethnic monitories such as Black and Hispanic patients. Our patient population was significantly more diverse than the primarily white RECOVERY trial population and includes the patients most likely to have diabetes and, thus, be at risk from hyperglycemia and the population most severely impacted by the COVID-19 pandemic. Despite the more diverse population, use of corticosteroids was not associated with secondary infection. Furthermore, we demonstrated the mortality benefit of corticosteroids in a population of patients that appropriately included the highest risk patient population. These findings confirm the need for much larger trials which enroll a diverse population of patients.

Our work was able to further support corticosteroids as a therapeutic option for COVID-19 but was unable to elucidate the exact etiology of the high proportion of secondary infections in critically ill patients with COVID-19. It is uncertain what role the SARS-CoV-2 virus itself has played immunologically in the propensity for secondary infections in COVID-19. The rate of secondary infection as well as the dramatic and reproducible mortality benefit of corticosteroids in COVID-19 points to a distinct phenotype of ARDS which benefits from the use of anti-inflammatory therapy[31,32,64]. Besides immunological properties of the virus itself, COVID-19 related logistics are likely contributory to the high proportion of secondary infection. Patients are often cared for in negative pressure units rather than negative pressure rooms and based on available resources, multiple ICU patients may be cohorted in a single room. This has the potential to propagate infection transmitted by providers and equipment between patients. There are no clear

guidelines on how to maintain traditional contact precautions in a negative pressure unit while donned in full personal protective equipment. The exceedingly high proportion of secondary infection, therefore, may be related to a yet unidentified property of the SARS CoV-2 virus compounded by evolving infection prevention strategies.

The generalizability of this study is limited in that it is a single-center retrospective cohort study conducted in an urban hospital in the United States. Corticosteroid administration strategies and infection rates are subject to institution-specific practices. For example, the UMMC was forced to cohort patients at the height of the COVID-19 pandemic in negative pressure units. The role that this played in the rate of secondary infection is not yet defined. Regarding the analysis of the association between corticosteroids with the outcomes of secondary infection and mortality, no patients enrolled in the study died within the first 48 hours of inclusion and all patients with the outcome of secondary infection received corticosteroids at least 48 hours prior to their first positive culture. Thus, each patient had ample opportunity to receive corticosteroids. In fact, approximately 30% of patients enrolled received corticosteroids within the first 24 hours of presentation to the hospital (Figure 7). This significantly diminishes concern for immortal time bias in our analysis.

The results of this study are strengthened by the high level of acuity of the population, the relatively large number of patients included in the analysis, the diverse patient demographics, as well as the rigorous definition of secondary infection. Furthermore, the statistical analysis appropriately accounted for competing risks, resulting in a more accurate estimation of the time to secondary infection. Our findings contribute to the growing body of research exploring corticosteroid treatment in COVID-19.

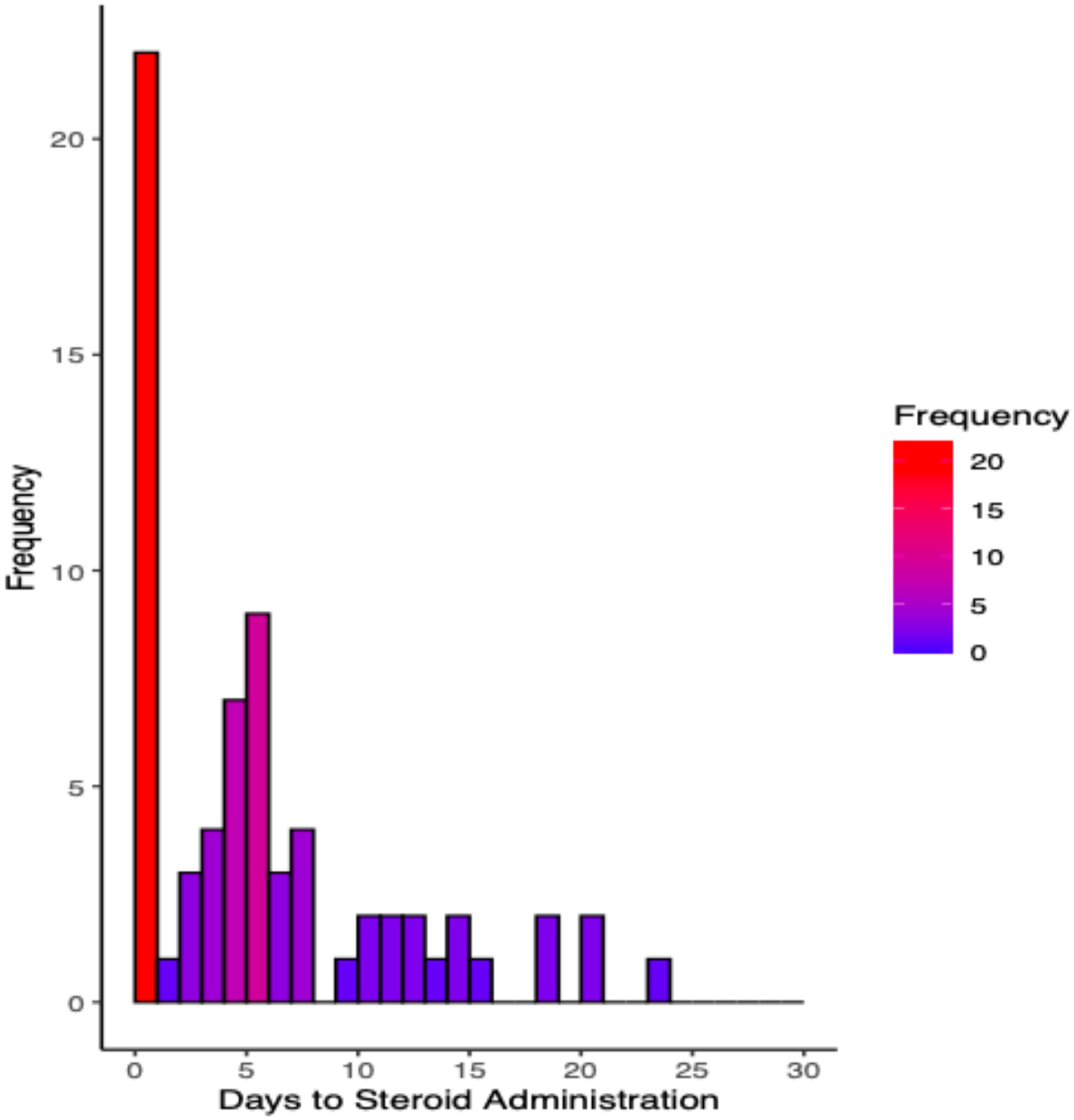

Figure 7: Histogram of time from hospital admission to corticosteroid administration.

7.1 CORTICOSTEROIDS COMBINED WITH OTHER COVID-19 THERAPIES

Further studies should focus on longer term outcomes of both morbidity and mortality in critically ill patients receiving corticosteroids, whether the addition of COVID-19 directed therapies (i.e., tocilizumab) contribute to secondary infection, and the risk of corticosteroid use in regions where fungal infection may be more prevalent. Tocilizumab, for example, an anti-IL-6 receptor monoclonal antibody now has an Emergency Use Authorization (EAU) for the treatment of COVID-19. Tocilizumab induces further immunosuppression, specifically through the IL-6 pathway. Reassurance, therefore, that corticosteroids are not predisposing patients to secondary infection is critical before adding a second immunosuppressive agent in critically ill patients. This work, conducted as a retrospective chart review, was unable to account for the use of other COVID-19 directed therapies in the evaluation of secondary infection or mortality as data on the timing of other COVID-19 directed therapies was not collected. This made it impossible to determine the temporal relationship between each exposure (COVID directed therapies, corticoid steroid administration) and the study's outcomes of interest (co-infection, mortality).

7.2 COMPARING METHYLPREDNISOLONE TO DEXAMETHASONE

Recent studies have compared the mortality benefit of methylprednisolone to dexamethasone in patients with COVID-19. Methylprednisolone achieves higher lung tissue concentration than dexamethasone[65]. Yet, dexamethasone is routinely used for COVID-19 ARDS based on the findings of the RECOVERY trial and the prior work by Villar non-COVID-19 ARDS[31,58]. However, due to the timing of our data collection, our patients primarily received

methylprednisolone and we observed a more robust mortality benefit than was seen with dexamethasone in the RECOVERY trial[31]. A recent observational study comparing the mortality benefit of methylprednisolone to that of dexamethasone in mechanically ventilated patients revealed a more significant reduction in mortality with the use of methylprednisolone compared to dexamethasone, 31% v. 54% (RR 0.48, 95% CI 0.24-0.95, p=0.04)[66]. A small prospective randomized control trial further explored the benefit of methylprednisolone compared to dexamethasone. Patients were randomized in a 1:1 ratio to receive either dexamethasone 6mg/day for 10 days or methylprednisolone for 10 days. A total of 86 patients were enrolled, 44 to the methylprednisolone group and 42 to the dexamethasone group. There were no significant differences between the two groups at randomization. There was an improvement in the 9-point ordinal score in the group treated with methylprednisolone compared to the group treated with dexamethasone at five and 10 days. In terms of 28-day mortality, 15 patients died in the dexamethasone group (37.5%) compared to eight patients in the methylprednisolone group (18.6%). Patients who received methylprednisolone had a significant reduction in length of hospital stay (7.43 v. 10.52, p=0.002) and the need for mechanical ventilatory support (18.2 v. 38.1, p=0.040) when compared to patients who received dexamethasone[67]. Combined with our findings, this points to a need for a randomized controlled trial comparing methylprednisolone to dexamethasone in patients with COVID-19 ARDS.

7.3 MINORITY GROUPS AND COVID-19

More than 80% of the patients enrolled in the RECOVERY trial were white. Racial and ethnic minorities were primarily excluded from this trial based on the population demographics of

the United Kingdom. Thus, it remained unclear whether the mortality benefit seen with dexamethasone would translate to these vulnerable patient populations which are most heavily impacted by COVID-19. Our study population was 70% racial minority, including 30% Black. Our results from a subgroup analysis of Black patients revealed a significant mortality benefit to receiving corticosteroids. In fact, when you compare the effect of corticosteroids on the subgroup of Black patients to the primarily white mechanically ventilated patients in the RECOVERY trial, the likelihood of mortality is reduced by 73% in the subgroup of Black compared to a 46% reduction in a mostly white population. This finding was even more robust amongst the larger subgroup of non-white patients (78% v. 46% reduction in likelihood of mortality). This mortality benefit occurs without any increased likelihood of secondary infection in patients treated with corticosteroids. Our study population also included 37% Hispanic patients. This population represents an additional under-represented minority in the RECOVERY trial. In this subgroup analysis, there was no significant impact on the likelihood of mortality with the administration of corticosteroids. This alludes to a still unidentified genetic, socioeconomic, or environmental difference in the response to corticosteroids between ethnic groups and also may reflect our relatively small sample size of only 50 Hispanic people in the subgroup.

The analysis of the effect of corticosteroids on secondary infection and mortality in minority racial groups is semi re-assuring, albeit grossly underpowered due to the small sample sizes. In Black patients, specifically, there is a significant and robust effects of corticosteroids reducing the likelihood of mortality. Black patients have been disproportionally impacted by the COVID-19 pandemic. Prior work in asthma, a disease whose mainstay of treatment is corticosteroids, has uncovered racial/ethnic-specific differences in terms of corticosteroid responsiveness with Black patients having less of a response to the same dose of corticosteroids[68].

It is imperative that patients from all ethnic and racial backgrounds be represented in clinical trials to avoid any generalization of drug effects amongst populations with unquantifiable variability in genetic and environmental factors. While this work suggests that the mortality benefit to Black and non-white patients is at least as robust as the effect seen in white patients, larger randomized clinical trials must be conducted which proportionally include the patient populations most impacted by a particular disease state and to further determine if Hispanic and other ethnic minority patients benefit from corticosteroids for COVID-19.

7.4 PRACTICE VARIATION

While we were unable to account for the individual practice variation between providers, we were able to account for practice variation between intensive care units. Generally, providers within a single intensive care unit tend to have similar practice patterns and their clinical service time is typically isolated to a single intensive care unit. Similarly, consultants are often housed within a single intensive care unit. This is especially true at the University of Maryland where there is little cross-pollination between the MICU and the BCU. Therefore, we could use these intensive care units as surrogates for practice patterns. Our analysis suggests that there is no difference in the relationship between corticosteroid administration and the development of secondary infection when controlling for the particular ICU for which the patient received their care, and ipso facto, for the variations in practice in those units. This would suggest that corticosteroids, independent of practice patterns, do not contribute to secondary infection and yield a significant mortality benefit and makes our findings more generalizable to providers and intensive care units outside of the University of Maryland.

8.0 CONCLUSION

The development of secondary infections is a commonly feared corticosteroid-related complication. The results of this study should conciliate those fears. Furthermore, the presence of a secondary infection does not increase the COVID-19 case fatality. The use of corticosteroids, a lifesaving therapy for many critically ill patients with COVID-19, should be accompanied by heightened awareness but not trepidation regarding the risk of secondary infection. This is of utmost public health significance during a global pandemic when the pharmacotherapeutic options are limited and the morbidity and mortality of the virus are so high.

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