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The association between depression and anxiety with COVID-19 outcomes.

Erica Miller
University of Louisville

THE ASSOCIATION BETWEEN DEPRESSION AND ANXIETY WITH COVID-19 OUTCOMES

By:

Erica Miller

B.A., University of Louisville, 2019

A Thesis

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By the Following Thesis Committee:

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Dr. Kira C. Taylor, Ph.D., M.S.

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Dr. Kathy B. Baumgartner, M.A., M.S., Ph.D.

_____

Dr. Daniel R. DeMarco, Ph.D.

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ABSTRACT

THE ASSOCIATION BETWEEN DEPRESSION AND ANXIETY WITH COVID-19 OUTCOMES.

Erica Miller

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Previous studies have shown that mental disorders affect COVID-19 mortality. This study investigated the effect of depression and/or anxiety on COVID-19 outcomes. Depression/anxiety was defined by actively taking medication and/or diagnosis. The outcomes were ICU admission; ventilation; mortality; and time to mortality. Of 698 hospitalized patients, there were 204 (29%) defined to have either depression or anxiety. There were 109 deaths, and of those, 52 (48%) were diagnosed with depression/anxiety. Multivariable logistic regression and Cox proportional hazards models were used to examine associations. ICU admission and ventilation were not significantly associated with depression/anxiety. Depression/anxiety was associated with mortality (OR: 1.84, 95% CI: 1.15-2.93, p: 0.01) and time to mortality (HR: 1.60, 95% CI: 1.07-2.39, p: 0.02), adjusting for age, sex, and history of COPD. The association seemed driven by patients who were never admitted to the ICU. This study showed that depression/anxiety has a significant effect on COVID-19 mortality.

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I. INTRODUCTION

At the end of 2019, SARS-CoV-2 emerged in Wuhan, China causing coronavirus disease, COVID-19. Since its emergence, it has created a pandemic. Social distancing and isolation from others have been recommended practices to prevent and slow the spread of the virus. These practices may have helped reduce infections, but they may also have had a negative impact on mental health and resulted in increased depressive episodes among the affected populations. While there is evidence in the literature suggesting that COVID-19 is a risk factor for mental disorders, including depression, it is still not known whether depression prior to SARS-CoV-2 infection is a risk factor for adverse outcomes from COVID-19. In 2017, prior to the emergence of SARS-CoV-2, 7.9% of the adult population (18 years or older) were reported to have experienced at least one depressive episode [1]. As of October 20, 2021 there have been over 44,900,000 cases of COVID-19 diagnosed in the United States or around 13% of the total population [2]. These data demonstrate that both depression and COVID-19 are prevalent within the United States population, which creates an imminent public health concern.

Depression has been shown to be associated with increased levels of inflammatory markers including interleukin-6 and C-reactive protein, which may either increase or decrease the risk of COVID-19 adverse outcomes. Within Kentucky, during September 29th-October 11th, 2021, 30.9% of Kentucky residents who participated in the

Household Pulse Survey conducted by the National Center for Health Statistics reported symptoms of anxiety disorders and 28.6% reported symptoms of depressive disorder [3].

The objective of this study was to explore the potential association between depression and COVID-19 severity. Disease severity was measured through mortality, ventilation, and intensive care unit admission. This study is a retrospective cohort of individuals hospitalized with COVID-19 in nine different hospitals located in Louisville, KY. Mortality, ventilation, and intensive care unit (ICU) admission were each measured dichotomously and analyzed through logistic regression. Time to death was analyzed using Cox proportional hazards (PH) modeling. This study aimed to fill a gap in the literature investigating depression as a risk factor for COVID-19 outcomes.

II. OBJECTIVE, SPECIFIC AIMS, AND HYPOTHESES

The primary objective of the study was to assess the effect of depression and/or anxiety on COVID-19 severity outcomes and mortality. Effect modification and mediation by inflammatory markers Interleukin-6 (IL-6) and C-Reactive Protein (CRP) on depression and/or anxiety on COVID-19 mortality were also evaluated.

The specific aims of the study were:

Specific Aim 1: To evaluate the association between depression and/or anxiety with COVID-19 severity. For purposes of this study, any patient actively taking depression medication was defined as having depression. Similarly, in order to be defined as having anxiety, active anxiety medication use was required, however, unlike for depression, a diagnosis of anxiety was also required. COVID-19 severity was assessed through ventilation or ICU admission. *Hypothesis: There is a significant association between depression/anxiety and COVID-19 severity as measured by {1} ICU admission and {2} ventilation.*

Specific Aim 2: To evaluate the association between depression and COVID-19 mortality. Mortality was assessed through discharge status which was either alive or deceased. *Hypothesis: There is a significant association between depression and COVID-19 mortality.*

Specific Aim 3: To evaluate if inflammation, assessed through levels of the inflammatory markers IL-6 and CRP, acts as an effect modifier or mediator on the association between depression and/or anxiety and COVID-19 mortality. *Hypothesis: Inflammation will modify or mediate the association between depression and COVID-19 mortality.*

III. BACKGROUND AND LITERATURE REVIEW

Depression

Epidemiology and Burden of Depression

Depression is a serious mood disorder defined by experiencing persistent feelings of sadness and hopelessness and loss in interest in activities one once enjoyed. Other symptoms that are characteristic of depression include: a depressed mood most of the day; diminished interest or pleasure in all or almost all activities through the day; significant weight loss or decrease or increase in appetite; slowing down of thought and reduction of physical movement; fatigue or loss of energy; feeling worthless or excessive or inappropriate guilt; diminished ability to think or concentrate; and recurrent thoughts of death or suicidal thoughts or behavior [3]. Depression can be diagnosed after experiencing symptoms for at least two weeks. According to the Diagnostic and Statistical Manual of Mental Disorders, 5^{th} edition (DSM-5), an individual must experience five or more symptoms during the same two weeks and at least one of the symptoms should either be depressed mood or loss of interest or pleasure [3]. These symptoms must cause the individual clinically significant distress or impairment in social, occupational, or other important areas of functioning [3].

Depression can occur at any age. Diagnoses of depression in children are rare, but they increase in frequency through adolescence and young adulthood. Childhood

depression can present as prominent irritability rather than low mood. Many of the chronic mood and anxiety disorders in adults begin as high levels of anxiety in childhood [1]. For midlife or older adults, depression is often present as a comorbidity with diseases like diabetes, cancer, heart disease, and Parkinson's disease [1]. Such medical conditions can worsen the severity of depression. Clinically, the earlier the onset of the depressive episodes, the greater the risk of reoccurrence, chronicity, and impairment [4]. Between 50-80% of those who experience one significant episode will have recurrent episodes and intermittent subclinical symptoms while the risk of recurrence progressively increases with each episode [5, 6]. In 2019, among the adults aged 18 and older, females had a higher prevalence of a major depressive episode (9.6%) compared to males (6.0%) in the United States [7]. The highest prevalence of a major depressive episode was seen among adults who reported two ethnicities (13.7%) [7]. Among individuals who reportated a single ethnicity, it was highest among whites (8.5%) [7]. Adults aged 18-25 years old had the highest prevalence (15.2%) while adults aged 26-49 had a lower prevalence (8.9%) and adults aged 50 and over had the lowest prevalence (4.7%) [7].

Etiology of Depression

There are biological and social risk factors that are associated with depression. Genetics are a predecessor for biological risk factors for depression [8]. The differences between brain chemical compositions from neurotransmitters are a biological risk factor. Those who have a family history of depression, have a higher risk of a depression diagnosis. An individual with a twin diagnosed with depression has a 70% chance of developing depression [8]. A sleep disorder or serious illness like cancer, heart disease,

diabetes, cancer, stroke, or Alzheimer's disease are all considered biological risk factors as well [1].

Social risk factors are as prevalent as biological risk factors. Individuals who were neglected or abused as children have a higher risk for major depression [5]. Women are more likely to develop major depression compared to men. Women are susceptible to depression during pregnancy, postnatal care, and menopause [1]. Lack of social support is another known social risk factor. Feeling excluded or alone can bring on an episode of depression to individuals who are susceptible to depression or mood disorders [4]. Major life events such as a new job, job loss, buying a house, divorce, moving, retiring, or losing a loved one can also trigger depressive episodes. Sadness is part of the grief cycle, but some people are more vulnerable to not moving out of this stage and this creates a depressive episode [1]. Abusing certain substances can increase the risk for depression. These substances include non-prescribed medications, alcohol, and illegal drugs. These can change the chemical composition of the brain and neurotransmitters linking social and biological risk factors [9]. Prescribed medications, including blood pressure medications, sleeping pills, steroids, and painkillers, have been linked to increased risk for depression like [9].

Pathophysiology of Depression

Human biological components have a distinct relation with depression. Genetic, neurological, hormonal, immunological, and neuroendocrinological mechanisms are some of the biological components that relate to depression [4]. Etiologic models that are based around the diathesis-stress models show which stressful situations trigger

depression in those who are predisposed based on biological and psychological characteristics [4]. Individuals with a first-degree relation to an individual with depression are 2.5 times more likely to develop major depression [10, 11]. Chronic stressors may prime the immune system, to make a heightened response to stress. It may also interfere with the capacity of the immune system to return to baseline after termination and show a dysregulation in the hypothalamus-pituitary-adrenal axis (HPA axis) [12]. A longitudinal birth cohort was followed in New Zealand exploring the effects of early childhood exposure on depression and inflammatory responses [13]. This cohort was followed into young adulthood and compared those without depression and without childhood maltreatment, those with depression and no maltreatment, those without depression and with maltreatment, and those with depression and with maltreatment [13]. Individuals who were depressed and maltreated were more likely to have higher levels of CRP compared amongst depressed individuals only [13].

The biological etiology relates to the pathophysiology. A meta-analysis was conducted to see the correlation between inflammation, the HP-axis, neurotrophic growth, and vitamin D. There were 230 controls and 2,333 participants from the Netherlands aged from 18-65 years old. Major depressive disorder (MDD) was grouped into 8 different categories, ranging from familial risk to chronic MDD. The study showed a linear increase of inflammatory markers (IL-6 and C-reactive protein), cortisol and a decrease of vitamin D across the whole sample population. Trends of dysregulation were found across stages for the at-risk individuals but not those who were in more progressive stages of MDD [14].

Anxiety

Overview of Anxiety

Anxiety has been defined as an individual fearing that he or she will act in a way that will be humiliating or embarrassing [4]. The National Comorbidity Study Replication (NCS-R) assessed data for anxiety disorders that included: panic disorder; generalized anxiety disorder; agoraphobia; specific phobia; social anxiety disorder; post-traumatic stress disorder; obsessive-compulsive disorder; and separation anxiety disorder [15]. Females had a higher prevalence (23.4%) than males (14.3%) [15]. Those who were aged 30-44 had the highest prevalence (22.7%), followed by those aged 18-29 (22.3%), then those 45-59 years old (20.6%), and finally those 60 or older (9.0%) [15]. A Dutch study investigated potential risk factors for adolescents. Sex, socioeconomic status, parental anxiety and depression, childhood adversity, temperament, body mass index, heart rate, blood pressure, and cortisol were the variables included [16]. They found that female sex, familial history, temperamental control, and low effortful control were significant predictors for anxiety in adolescents [16]. Blanco et al. conducted a study to examine whether the co-occurrence of anxiety disorders and MDD could be explained by an underlying latent factor and whether the risk factors exert their effect exclusively through this factor, directly on each other, or through a combination of effects at both levels [17]. It was concluded that low self-esteem, family history of depression, female sex, childhood sexual abuse, white race, years of education number of traumatic experiences, and disturbed family environment increased the risk of anxiety disorders and MDD through their effect on the latent factor [17].

Pathophysiology

Individuals with an anxiety disorder have a high comorbidity rate with other mood disorders including depression, and 90% of anxiety patients experience a form of depression in their lifetime [18]. The FDA has approved selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) for anxiety treatment [19]. These drug classes are the same as the ones used for depression medications. Anxiolytics like benzodiazepines can be used to minimize anxiety, but dependence can occur using this drug [20]. These could be less likely to be prescribed in comparison to SSRIs and SNRIs. Anxiety is one of the most common psychiatric disorders. Anxiety disorders occur more frequently in women with an approximate ratio of 2:1 [21]. Within the nervous system, there are specific mediators of anxiety which include: norepinephrine, serotonin, dopamine, and gamma-aminobutyric acid (GABA) [22]. The sympathetic nervous system mediates most of the symptoms [22].

The amygdala plays an important role in tempering fear and anxiety. Patients with anxiety disorders have been found to show a heightened amygdala response to anxiety cues like prefrontal cortex activation [22]. Common symptoms associated with anxiety are either cognitive, physiological, behavioral, or affective symptoms [22]. Tricyclic antidepressants, buspirone, and beta-blockers can also be treated to treat anxiety [22]. Persistent anxiety can also lead to cardiac events [22]. Since anxiety is fear-induced and a part of the sympathetic nervous system, there is cortisol released in response. With chronic cortisol release from anxiety, immunosuppression occurs [20].

COVID-19

COVID-19 Overview

SARS-CoV-2 is the causative agent of the coronavirus outbreak that occurred in late 2019 to early 2020. The disease as a result from SARS-CoV-2 infection is referred to as COVID-19 and is an upper respiratory syndrome with vast symptoms. It can take around 5 days to develop symptoms after exposure to the virus [23]. Common symptoms of COVID-19 are fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea [23]. The virus has the capability to infect anyone, but milder cases are generally seen in children and young adults. Those who are at higher risk of becoming a case are those who are pregnant, older, have underlying chronic medical conditions, have a substance abuse disorder, or are of Alaskan Non-Hispanic, American Indian Non-Hispanic, Black Non-Hispanic, or Hispanic ethnicity [24]. Underlying medical conditions that show a strong association include cancer [25], chronic kidney disease [26], chronic obstructive pulmonary disease [27], heart conditions [28], severe obesity with a BMI equal to or over 40 [29], pregnancy [30], sickle cell disease [31], smoking [32], solid organ transplant [33], and type 2 diabetes mellitus [34]. Within Kentucky, as of October 2021, the prevalence was approximately 16.5% [2].

Pathophysiology of COVID-19

The SARS-CoV-2 virus enters the cell by binding to the angiotensin-converting enzyme 2 (ACE-2) [35]. This virus uses its spike protein on the outside of the cell to recognize and bind to specific receptors on the host surface cell, resulting in virus entry to the cell [36]. SARS-CoV-2 forms a complex with ACE-2 which is ten times more

significantly associated together for binding affinity than SARS-CoV [37]. This is significantly greater than the threshold that is needed for the virus to cause disease [37]. There are studies that have shown that acute respiratory distress syndrome (ARDS) is the leading cause of mortality in coronavirus disease [38]. A cytokine storm is an essential mechanism of ARDS along with chronic unregulated systemic inflammatory stimulus, which is an outcome of the release of many of the pro-inflammatory markers like IL-6, tumor necrosis factor alpha, and interferon alpha [38]. Pathogen-associated molecular patterns (PAMPs) can be seen by pattern recognition receptors (PRRs). SARS-CoV-2 can stimulate a double-membrane vesicle synthesis, which possess no PRRs, and prevents the host cell from detecting RNA [39]. Using this mechanism, it continues replication and increases viral load and infection severity. In addition to being a respiratory disease, COVID-19 has neurological implications. Some of these implications include dizziness, headache, myalgias, hypogeusia, hyposmia, polyneuropathy, myositis, cerebrovascular diseases, encephalitis, and encephalopathy [40].

Etiology of COVID-19

SARS-CoV-2 shares 88% of its viral genome with two bat-derived coronaviruses but is more distant from SARS-CoV [41]. With the current data available, it appears that SARS-CoV-2 may initially have been hosted within bats that transferred to a pangolin or other wild animals sold at the Huanan market before spreading to humans [41]. Transmission from human-to-human contact is generally seen through breathing droplets from sneezing or coughing from infected individuals. The SARS-CoV strain from 2003 has been shown to remain infective on surfaces for up to four days while other

coronaviruses have been detected up until nine days on surfaces [42, 43]. Studies have shown that SARS-CoV2- can live on surfaces like stainless steel, plastic, glass, and cardboard for at least several hours [44-46]. Fomites and surfaces could be another route of transmission. The basic reproducibility, R_o, of this virus is between 2 and 3 consistently from data [47].

COVID-19 and Depression

With the emergence of COVID-19, social interactions have decreased, and many people no longer participate as often in common social activities. With limited interaction, depression and anxiety rates have increased. Etman et al. conducted a studying to estimate the prevalence of and risk factors associated with depression symptoms among US adults prior to and during the COVID-19 pandemic [48]. A nationally representative study was conducted and used 2 population-based surveys of US adults aged 18 and older. There were 1,441 participants that completed the COVID-19 and Life Stressors Impact on Mental Health and Well-being survey. This survey was conducted from March 21, 2020 to April 13, 2020. The prior prevalence for depression symptoms were derived from the National Health and Nutrition Examination Survey (NHANES) conducted from 2017 to 2018 [48]. The NHANES cohort had 5,065 participants. Depression symptom prevalence was 3-fold higher in all categories during the beginning COVID-19 pandemic compared to before the pandemic. Higher risk of depression symptoms during the COVID pandemic was associated with having a lower income (OR: 2.37, 95% CI: 1.26-4.43), having less than $5,000 in savings (OR: 1.52, 95% CI: 1.02-2.26), and exposure to more stressors (OR: 3.05, 95% CI 1.95-4.77).

A meta-analysis was conducted by Salari et al. looking at the prevalence of stress, anxiety, and depression in the general population during the COVID-19 pandemic. The systematic review and meta-analysis pulled articles from Science Direct, Embase, Scopus, PubMed, Web of Science, and Google Scholar [49]. The meta-analysis found that among 5 studies with a sample size of 9,074 that stress prevalence was 29.6% with 95% CI 24.3-35.4. The prevalence of anxiety among 17 studies with a sample size of 63,439 was 31.9% with 95% CI 27.5-36.7. The prevalence of depression among 14 studies with a sample size of 44,531 was 33.7% with 95% CI 27.5-40.6. This study shows that there is a high prevalence of depression during the COVID pandemic with is concordant with the work that Etman et al. performed.

Another study conducted by Mazza et al. examined the psychopathological impact that being infected with COVID-19 has on survivors. There were 402 adults within the cohort that were screened for psychiatric symptoms one-month after hospital treatment [50]. A clinical interview and self-report questionnaires were used to investigate post-traumatic stress disorder (PTSD), depression, anxiety, insomnia, and obsessive-compulsive (OC) symptomology. Baseline inflammatory markers were also collected. Overall, 56% scored in the pathological range for at least one clinical dimension, while 31% reported depression. Baseline inflammatory markers, screened through peripheral lymphocyte, neutrophil, and platelet counts, were positively associated with scores of depression and anxiety at follow-up showing that worsening inflammation with severity of depressive symptoms.

A study conducted by Wiemken et al. looked at depression as a risk factor for influenza severity for hospitalized adults. This study showed that non-elderly influenza patients with depression were found to have 3.8% decreased adjusted risk of major or severe loss of function compared to those without depression [51]. This was found to be statistically significant with 95% CI of 1.9%-5.7% and a P-value < 0.0001. Overall, the non-elderly patients with influenza infection, diagnosed with depression, had a decreased risk of more severe disease and lower odds of inpatient mortality. The proposed mechanism was that individuals who already have depression have increased pro-inflammatory cytokines. Death due to influenza is associated with increased inflammatory response to infection rather than overwhelming infection itself. Those with an increased inflammatory state may have negative regulatory networks which protect against excessive inflammation.

These studies suggest that with the emergence of the COVID-19 pandemic depressive symptoms have increased because of either the pandemic itself and isolation or through directly contracting COVID-19. Depression as a risk factor needed to be explored, which was the main objective of this study local to the Kentuckiana region.

Inflammation and Depression

The relationship between depression and inflammation is multifaceted. It has been suggested that patients with inflammatory disease are more likely to show higher rates of MDD, about one-third of people with MDD show elevated peripheral inflammatory markers, and patients treated with cytokines are at increased risk for developing

depression [52]. Inflammation is able to alter brain functioning and produces a pattern of symptoms known as sickness syndrome which mirrors depression [53].

Depression with Inflammatory Outcomes

A study conducted by Duivis et al in the Netherlands explored depressive symptoms and inflammatory markers through interleukin-6, C-reactive protein (CRP), and tumor necrosis factor [54]. There were 2,861 participants aged from 18-65 years old. There were 2,231 participants with current or past depression and/or anxiety diagnosis and 630 controls. The study was designed as a cohort with linear regression as the acting analysis accounting for age, sex, educational years, cardiovascular disease, diabetes, medication type, smoking status, alcohol intake, body mass index (BMI), and physical activity. When adjusting for demographics and health indicators, IL-6 and CRP were found to be statistically significant with a p-value <0.001 while the tumor necrosis factor was statistically significant with a p-value of 0.018 among those with a history of depression and/or anxiety compared to controls.

Another study conducted by Stewart et al. explored the effect on depressive symptoms and inflammatory outcomes. This study was a prospective cohort set in Pittsburgh with 263 participants aged 50-70 years old [55]. The covariates used in this study were age, sex, race, education level, smoking status, daily alcohol intake, BMI, high density lipoprotein cholesterol, triglycerides, fasting glucose, fasting insulin, diabetes, rheumatoid arthritis, and physical activity. Depressive symptoms were measured through the Beck Depression Inventory II questionnaire (BDI-II). Inflammation was assessed by measurement of IL-6 and CRP levels, at three different time points over

six years. One of the three data sets was not analyzed due to a clerical error. It was found that greater depressive symptom severity at baseline was associated with a larger 6-year increase in serum IL-6. In the studies' entirety, IL-6 and CRP were not associated with depressive symptoms measured by BDI-II .

Inflammation with Depression Outcomes

The other possibility is inflammation causing depression. Krogh et al. investigated the impact of exercise intervention on major depression in a cohort study with 169 participants [56]. Of these participants, 112 were diagnosed with MDD and 57 were health controls. At baseline, cytokines were measured as well as depression through the Hamilton depression rating scale. The participants with MDD were then randomized to either a 3-month exercise program or an attention control group performing low impact exercises. IL-6 and high-sensitivity CRP were the inflammatory makers measured. Age, sex, depression status, and education were the confounders assessed through the linear regression model. The results showed that overall, those with higher depressive symptoms had higher levels of high-sensitivity CRP and IL-6. Once controlling for lifestyle factors, the difference was no longer significant.

A study conducted by Lindqvist et al. explored oxidative stress and inflammation and their association with major depressive disorder. In this prospective cohort, there were 105 participants and tested to see response to antidepressants and inflammation markers among those unmedicated for major depression disorder and controls [57]. The inflammatory markers quantified in this study included IL-6, tumor necrosis factor, CRP, F2-isoprstanes, 8-OH 2-deoxyguanosine, glutathione peroxidase, glutathione, and

vitamin C. Controlled variables included sex, age, BMI, and smoking. Baseline blood samples were collected in addition to blood samples at 8 weeks after treatment and the participants were scored on the Hamilton Depression Rating Scale at both time points. Participants who were diagnosed with major depressive disorder showed higher levels of IL-6 ($p<0.001$), tumor necrosis factor ($p<0.001$), 8-OH 2-dexoyguanosine ($p=0.018$), and F2-isoprostanes ($p=0.012$). Those who were non-responders to the SSRI treatment had higher F2-isoprostanes at baseline ($p=0.006$) and after 8 weeks of treatment ($p=0.031$) compared to responders. Non-responders in the study showed an increase in 8-OH 2-deoxyguanosine ($p=0.021$ over the course of the study while responders showed a decrease in IL-6 levels ($p=0.019$).

Antidepressants and the Immune System

There has been a relationship established with depression and inflammation, but there are effects from antidepressants that play a role on the immune system as well. The interactions between the nervous system and immune systems are the main issue addressed by psychoneuroimmunology [58]. It has been suggested that antidepressants modulate immune response. One way they do this is by affecting the activation, proliferation, and survival of leukocytes [58]. The immunosuppressive effect of the HPA axis seems to be insufficient to reduce inflammation associated with depression, which can decrease the threshold of hypothalamic sensitivity to pro-inflammatory cytokines [59]. Antidepressant drugs are believed to have immunomodulatory properties as well as functioning as neurotransmitter transporters [58]. A study conducted by Dahl et al. measured blood cytokine levels before and after 12-week antidepressant therapy in 50

patients [60]. There was a significant reduction in the levels of cytokines, interleukin-6 and interferon gamma, from the baseline measure but did not significantly differ from the patients who were controls. Over the course of the study, 43 participants completed it and 30 were found to meet the recovered criteria. Those who met that criteria were the individuals who had statistically significantly reduced cytokines compared to their baseline measure. The 13 participants who did not meet the recovery criteria did not have statistically reduced cytokines compared to their baseline measure.

Other studies have shown contrary effects seen by Dahl et al. A study that treated in vitro of whole blood cultures with selective serotonin reuptake inhibitors (SSRIs) and mirtazapine, tetracyclic antidepressant, increased the production of cytokines [61]. Interleukin-1-beta, interleukin-6, and tumor necrosis factor alpha all showed increased inflammatory markers when measured while being treated with those drugs.

Chen et al. assessed the effect of antidepressants on plasma cytokines in 91 MDD patients compared to 90 healthy controls in a case-control study. Baseline plasma cytokines were measured in controls and patients, while patient's cytokines were also measured after completing the 8-week treatment of either venlafaxine or paroxetine [62]. After 8 weeks of treatment, the mean interferon gamma, tumor necrosis factor, IL-4, IL-5, and IL-8 were significantly lower in the venlafaxine group than the paroxetine ($p<0.001$). Paroxetine was found to increase the levels of IL-6 ($p=0.003$) the most in the non-remitter, those who were not in remission, group ($n=29$) than the remitter group ($n=21$).

Anxiolytics and the Immune System

Inflammation has been implicated in the pathogenesis of depression and anxiety. In a prospective cohort study with 42 participants conducted by Hou et al., the effects of SSRIs on peripheral cytokines in patients with first episode generalized anxiety disorder was investigated [63]. The patients were 18-60 years old, BMI between 18 and 30, 6 or more years of education, and a primary diagnosis of the first episode of general anxiety disorder. These patients did not have a history of taking either antidepressants or anxiolytics. Treatment lasted 12 weeks with either escitalopram (n=28) or sertraline (n=14). A sample of 10 mL of blood was taken before treatment at approximately the same time of day. The blood was analyzed for IL-1β, IL-6, IL-8, IL-12p70, and IFN-γ by an enzyme linked-immuno-absorbent assay. CRP was measured through immunological transmission turbidity. The same measure occurred 12 weeks after treatment. Anxiety was measured through the Generalized Anxiety Disorder Scale (GAD-7) and State Trait Anxiety Inventory.

For data analysis, treatment response was defined as a reduction in the GAD-7 score, differential between pre- and post-treatment, equal to or greater than 50%. No treatment response was defined as less than 50% reduction in the GAD-7 score. While controlling for BMI, smoking, and alcohol consumption, logistic regression on log-transformed CRP and IL-6 had a significant predict value for treatment response. While controlling for the same variables in either a Pearson or Spearman correlation model, it was demonstrated that there was a significant positive correlation between change in anxiety and change in peripheral inflammatory markers ($p < 0.05$). This finding

demonstrates patients with a greater reduction in anxiety also had a greater reduction in cytokine levels.

Costello et al. performed a systematic review and meta-analysis of the association between peripheral marks of inflammation and generalized anxiety disorder. The sources that were used were MEDLINE, EMBASE, PsycINFO, and Web of Science [64]. The eligibility criteria in this analysis were primary, quantitative research studies of people with a diagnosis of GAD assessed using a standardized clinical interview that measured peripheral inflammatory markers. Of the 1,718 studies identified, 14 of those met the criteria. The primary reason studies were rejected was due to the lack of diagnosis of GAD was recorded or inflammatory marker was measured. There were 1,118 patients with GAD with 10,623 controls. There were 16 cytokines evaluated. CRP (9/14), TNF- α (6/14), IL-6 (5/14), and IFN-γ (3/14) were the most common cytokines among this data set. The other cytokines were only analyzed in 2 or less studies. Significantly raised levels of CRP, IFN-γ, and TNF- α were reported in patients with GAD compared with controls in two or more studies. Ten further proinflammatory cytokines were reported to be significantly raised in GAD in at least one study. Five of the 14 different studies found no difference in the levels of at least one cytokine. CRP was the only cytokine with sufficient data for meta-analysis. It was found that CRP was significantly higher in people with GAD compared with controls.

Conclusion

These studies suggest that depression is associated with higher levels of inflammatory markers (IL-6 and CRP) and that inflammation can increase the risk of

depression. Cytokine storms have been showed to induce ARDS in patients with COVID-19. It has also been shown that antidepressants can either raise or lower cytokine levels. There are studies showing how COVID-19 induces depression, but there are no studies investigating depression as a risk factor of COVID-19 mortality or severity in the Kentuckiana region. Individuals with other inflammatory diseases like autoimmune diseases are at higher risk for more severe outcomes from COVID-19 disease; therefore, individuals with depression could be as well. This study will fill a gap in the literature by evaluating the association between depression and COVID-19 outcomes.

IV. METHODS

Study Design:

The data used in this study came from the Burden of COVID-19 study (Granting institution: University of Louisville; Principal Investigator: Dr. Julio Ramirez; IRB #20-0257). The purpose of the Burden of COVID-19 study was to assess the incidence, epidemiology, and clinical outcomes of patients in Kentuckiana diagnosed with COVID-19 [65]. The retrospective data was collected from Electronic Medical Records (EMR) from March-July 2020 within the hospital network in Kentuckiana [65].

Study Population:

The study population was located within the Kentuckiana region, focused on Louisville, KY and the surrounding areas. The Center for Excellence for Research in Infectious Diseases (CERID) at the University of Louisville maintains a retrospective cohort study of hospitalized patients infected with SARS-CoV-2 [66]. There were nine acute care hospitals located within Louisville, Kentucky [66] with 698 patients for the time period March 7th, 2020 to July 6th, 2020. Patients 18 years and older and who tested positive for SARS-CoV-2 by Polymerase Chain Reaction (PCR) test and admitted into the hospital were included.

Data Collection:

Reverse Transcriptase-Polymerase Chain Reaction testing was performed either by the University of Louisville Division of Infectious Diseases reference laboratory or at the associated lab of each hospital [66]. The CEIRD research team performed daily screenings of the hospital's EMR or from a daily report sent by the hospital to determine which patients had a confirmed or presumptive COVID-19 diagnosis. [66]. Information that was ascertained through either EMR or the daily report included COVID-19 test results; demographic and hospitalization data; past medical and social history; current medications; signs and symptoms; physical examination; laboratory, radiologic and microbiologic findings; management and therapies; in-hospital complications; and clinical outcomes [66].

Outcome Assessment:

Discharge status, either alive or dead, was extracted from the EMR and used to assess COVID-19 mortality. Time to death was evaluated by the date admitted into the hospital until date of death. COVID-19 severity was evaluated by ventilation and placement in the ICU. Both ventilation and ICU admission, were assessed as dichotomous variables, either receiving said treatment or not. Time on ventilation or time in ICU was not assessed.

Exposure Assessment:

The EMR listed the various depression medications, which included both brand name and generic drugs. These drugs were assessed separately based on active drug ingredient. The terms for SSRIs used to search the dataset were Celexa, citalopram,

Lexapro, escitalopram, fluoxetine, paroxetine, Zoloft, sertraline, vortioxetine, Viibryd, and vilazodone. For SNRIs the dataset search terms t were Cymbalta, duloxetine, desvenlafaxine, venlafaxine, and Savella. TCAs within the dataset were searched for using the terms amitriptyline and doxepin. Additional antidepressant medications not listed within those drug classes were searched for using the terms Wellbutrin, bupropion, Remeron, mirtazapine, and trazodone.

The medication class that was assessed for anxiety was benzodiazepines. The terms used to search within the dataset for benzodiazepines were alprazolam, clobazam, clonazepam, Diazepam, Ativan, lorazepam, and triazolam. The terms used to identify additional anxiolytics within the dataset were buspirone, Vistaril, hydroxyzine, prazosin, and pregabalin. An anxiety diagnosis was also determined by a recent diagnosis which was outlined by the CERID research team.

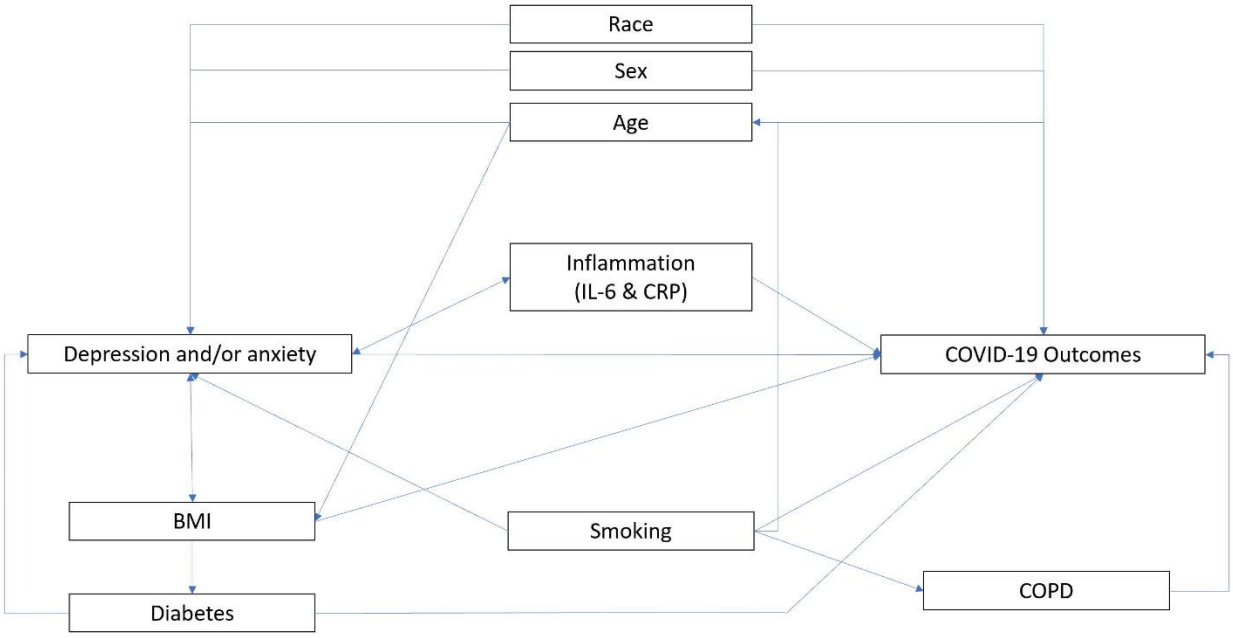
Some of the medications that were prescribed within this dataset for both anxiety and depression can be used for either diagnosis. Thus, it was not possible to accurately separate the diagnosis by the EMR, so a combined variable was created within this dataset for both depression and anxiety diagnosis. Exposure status was defined as having taken either medication or having either a depression/anxiety diagnosis. Duration of diagnosis of either depression or anxiety was not determined.

Confounding Assessment:

A confounding assessment was performed before interaction. Confounding was evaluated by removing a covariate from the full model and assessing whether there was a

10% difference in the reduced model's exposure odds ratio compared to the full model's exposure odds ratio. If there was a 10% difference, then the variable was considered a confounder. If the covariate was close to a 10% difference and the 95% confidence intervals were tighter than the full model's 95% confidence intervals, then the covariate was considered a confounder and kept within the model. Relevant covariates were chosen based on a directed acyclic graph (DAG) (Figure 1), which was guided by the literature review. The initial list of potential covariates included age, race, sex, BMI, smoking status, alcohol abuse, diabetes, asthma, and COPD.

Figure 1: Directed Acyclic Graph



Potential Mediation and Effect Modification:

Mediation and effect modification were assessed through inflammatory markers IL-6 and CRP levels between inflammation and depression and/or anxiety. Both inflammatory markers were analyzed through a sub-population as not every participant had data listed for these markers. Both markers had their concentration log-transformed to achieve a more normal distribution while running logistic regression for assessment. Mediation was assessed by comparing the difference between the inflammatory model to the odds ratio of a logistic regression model with the inflammatory marker to the odds ratio of a logistic model without the marker. Effect modification was assessed by adding an interaction term into the model. The interaction term consisted of the exposure multiplied by the inflammatory marker. If the p-value was less than 0.05 then it was concluded that there was interaction between the inflammatory marker and exposure on the outcome of interest.

Data Analysis:

Descriptive Statistics:

All of the analyses for this thesis were conducted in SAS 9.4. Descriptive statistics were calculated for the covariates to examine their distributions within this dataset. Univariate analyses were performed to examine the crude association between the covariates and the exposure. Student's T-test was used for normally, distributed continuous variables while the Chi-square test was used for categorical variables. The covariates that were included in the final multivariable models were chosen by data-based and theory-based methods. Covariates from the DAG that had an association with the

exposure with a p-value less than 0.1 were initially included in the multivariable model. Age and sex were included in the model regardless based on available literature.

Multivariable Models:

Logistic Regression:

The effect of depression, anxiety, or both was analyzed on mortality, ventilation, and ICU admission using separate multivariable logistic regression models. The models were evaluated for multicollinearity prior to confounding and interaction assessment. There were no issues with multicollinearity found in any of the models. To choose the remaining covariates, confounding was assessed prior to interaction because of the inability to explain biological pathways. Confounding was assessed by comparing the exposure's odds ratio of the full model to the exposure's odds ratio of a reduced model, which had one covariate removed. If there was more than a 10% change in the exposure's odds ratio or it was approaching a 10% difference and the 95%confidence intervals became narrower, then the variable was considered a confounder. Interaction was assessed by adding an interaction term to the final model used for analysis. The interaction term consisted of the exposure multiplied by the covariate of interest. If the p-value for the interaction term was less than 0.05, then it was concluded that there was interaction between the exposure and covariate on the outcome of interest. No statistically significant interactions were found between the covariates and the exposure. Covariates that were chosen for these different models, based on the criteria described above, were sex, age, and chronic obstructive pulmonary disease (COPD).

Mediation and effect modification were assessed using the different subsets based on available data for CRP and IL-6. Both inflammatory markers were log transformed to achieve a more normal distribution. The model that was used to assess mediation and effect modification was the final model for mortality. Mediation was assessed by adding the inflammatory marker to the model to examine the difference in the exposure's odds ratios of the regression models. The extent of mediation was evaluated by the percentage different between the exposure's odds ratio from the model including the inflammatory marker compared to the exposure's odds ratio from the model without the inflammatory marker. Effect modification was assessed by using an interaction term within the models. The interaction term used within the model was the exposure multiplied by either IL-6 or CRP. If there was a p value < 0.05 for the interaction term, then it was concluded to be an effect modifier.

Survival Analysis – Cox Proportional Hazards Regression Model:

A Cox proportional hazards model was used to conduct a survival analysis. The participants had a hospital admission date, hospital discharge date, discharge outcome, and death date recorded within their EMRs. The start time within this model was defined as the date of hospital admission and the stop time was either date of death or discharge status being alive. The proportional hazards assumption test was conducted to assess whether the PH assumption was met. If it was not met, Heaviside functions were used with an extended Cox model. Censorship was determined by survival while being discharged from the hospital and an event was death defined by the date of death. The

same covariates that were used within the logistic regression models were used within this model for consistency.

V. RESULTS

There were 922 participants enrolled from March 1st, 2020 to July 6th, 2020. Among those, 224 were excluded: 106 for being younger than 18, 114 for not being admitted to the hospital, and 4 for missing data on height, which was used for BMI calculation. There were 698 participants used for data analysis.

Descriptive Statistics

Among the 698 participants, 204 (29.2%) were diagnosed with either depression and/or anxiety. Table 1 shows the sample population stratified by depression or anxiety. Those who were diagnosed were more likely to be older (P= <0.0001), white (P= <0.0001), female (P = <0.0001), smokers (P = 0.0002), and have a higher BMI (P = 0.0265). Examining comorbidities, those with depression and/or anxiety were more likely to be diagnosed with diabetes (P = 0.0006); COPD (P = <0.0001); hypertension (P = <0.0001); hyperlipidemia (P = <0.0001); renal disease (P = 0.0035); and a prior cardiac event, which was defined as being diagnosed with either coronary artery disease, heart failure, atrial fibrillation, myocardial infarction, or deep vein thrombosis (P = <0.0001). Alcohol abuse (P = 0.67); asthma (P = 0.48); neoplastic disease (P = 0.16); and history of obstructive sleep apnea (P = 0.18) were not significantly associated with depression and/or anxiety.

Table 1. Patient Demographics and Medical History (n=698).

	Without either Depression or Anxiety	With either Depression or Anxiety	P-value[a]
N=698	494	204	
Demographic Characteristics			
Age, years (mean(SD))	55.3 (18.8)	69.2 (15.3)	<0.0001
18-44 (N, %)	159 (32.2)	13 (6.4)	
45-60 (N, %)	136 (27.5)	38 (18.6)	<0.0001
61-73 (N, %)	112 (22.7)	65 (31.9)	
74-102 (N, %)	87 (17.6)	88 (43.1)	
BMI, kg/m^2 (mean(SD))	31.5 (8.6)	30.1 (8.8)	0.0550
Healthy	111 (22.5)	67 (32.8)	
Overweight	132 (26.7)	45 (32.1)	0.0265
Obese	116 (23.5)	37 (18.1)	
Morbidly Obese	135 (27.3)	55 (27.0)	
Race (N, %)			
White	241 (48.8)	140 (68.6)	
Black	169 (34.2)	49 (24.0)	<0.0001
Other	84 (17.0)	15 (7.4)	
Sex (N, %)			
Female	245 (49.6)	137 (67.2)	<0.0001
Male	249 (50.4)	67 (32.8)	
History of Smoking (N, %)			
Never	344 (69.6)	110 (53.9)	
Current	48 (9.7)	23 (11.3)	0.0002
Former	102 (20.7)	71 (34.8)	
Alcohol Abuse (N, %)			
No Alcohol Abuse	458 (92.7)	191 (93.6)	0.67
History of Alcohol Abuse	36 (7.3)	13 (6.4)	
Comorbidities			
Diabetes (N,%)	142 (28.7)	86 (42.2)	0.0006
Asthma (N, %)	47 (9.5)	23 (11.3)	0.48
COPD (N, %)	47 (9.5)	54 (26.5)	<0.0001
Hypertension (N, %)	234 (47.4)	137 (67.2)	<0.0001
Hyperlipidemia (N, %)	139 (28.1)	98 (48.0)	<0.0001
Neoplastic Disease (N, %)	29 (5.9)	18 (8.8)	0.16
Renal Disease (N, %)	75 (15.2)	50 (24.5)	0.0035
History of Obstructive Sleep Apnea (N, %)	40 (8.1)	23 (11.3)	0.1828
Prior Cardiac Event (N, %)	124 (25.1)	84 (41.2)	<0.0001

[a] Categorical variables were assessed with the Chi-square test of independence. Continuous, normally distributed variables were assessed with Student's t-test.

Medication Frequency

There were 242 different instances where an antidepressant medication was reported, which includes the ones listed as miscellaneous. Citalopram/escitalopram (37) Sertraline (30), and Mirtazapine (32) were the most frequently used antidepressants among the patients (Table 2). There were 78 different instances were an anxiolytic medication as used, including the ones listed as miscellaneous. Lorazepam (16), Alprazolam (14), Hydroxyzine (13), and Clonazepam (11) were the most frequently used anxiolytics (Table 2). There were some name-brand and generic antidepressants and anxiolytics that were not taken but included within the medication list used by the Infectious Disease Department to search within the EMRs.

Table 2. Medication Frequency.

Medication	**Frequency**
Antidepressants	
SSRIs (Selective Serotonin Reuptake Inhibitor)	
Citalopram/Escitalopram	37
Sertraline	30
Fluoxetine	11
Lexapro	5
Paroxetine	4
Prozac	3
Celexa	2
Zoloft	2
Vortioxetine	1
Viibryd	1
Vilazodone	1

SNRIs (Serotonin-norepinephrine Reuptake Inhibitor)	
Venlafaxine/Desvenlafaxine	12
Duloxetine	12
Cymbalta	4
Savella	1
TCAs (Tricyclic Antidepressants)	
Amitriptyline	16
Doxepin	2
Miscellaneous	
Mirtazapine	32
Trazodone	21
Quetiapine	16
Bupropion	16
Wellbutrin	8
Seroquel	4
Remeron	1
Anxiolytics	
Benzodiazepines	
Lorazepam	16
Alprazolam	14
Clonazepam	11
Ativan	4
Diazepam	3
Clobazam	1
Triazolam	1
Miscellaneous	
Hydroxyzine	13
Buspirone	6
Pregabalin	5
Prazosin	3
Vistaril	1

The list of antidepressants or anxiolytics were also examined within this data set. For those taking either an antidepressant or anxiolytic, there were 122 patients taking one

medication; 56 were taking two medications; 17 were taking three medications; and 9 were taking four medications (Table 3).

Table 3. Number of Antidepressants or Anxiolytics per Patient.

Number of Medications	Frequency
1	122
2	56
3	17
4	9

Specific Aim 1: To evaluate the association between depression and COVID-19 severity.

The exposure of having a history of depression and/or anxiety was not significantly associated with ICU admission (OR: 1.01, 95% CI: 0.69-1.46) or with ventilation (OR: 1.19, 95% CI: 0.78-1.181) (Table 4). To further understand the clinical implications of the effect of depression/anxiety on mortality, the mortality model was stratified by ICU admission and interaction was assessed. Interaction between depression/anxiety and ICU admission did not yield a p-value <0.05 for statistical significance (p-value: 0.090). For those with depression/anxiety and did not enter the ICU, statistical significance was seen for association with mortality (OR: 5.18, 95% CI: 1.81-14.86) (Table 5). Once in the ICU, there was not a statistical significance between those with or without depression/anxiety (OR: 1.83, 95% CI: 0.98-3.40) (Table 5). This could be due to the fact that once one is admitted to the ICU, there is a higher mortality rate overall and comorbidities do not have much of an effect.

Specific Aim 2: To evaluate the association between depression and COVID-19 mortality and time to death.

History of depression and/or anxiety was associated with mortality due to COVID-19 (OR: 1.84, 95% CI: 1.15-2.93) (Table 4). Among those who were not admitted into the ICU, 12.6% of the patients who were depressed died compared to the 1.6% who were not depressed (Table 5). Those who were admitted into the ICU, 46.8% of those who were depressed died compared to the 28.4% who were not depressed (Table 5). To determine the effect of history of depression and/or anxiety on time to death, a Cox proportional hazards model was used. The Kaplan-Meier curves were significantly different by the log-rank test (p=0.0022) (Figure 2). While examining the log-negative log survival curve to test the PH assumption, the graphs appeared mainly parallel and were concluded to meet the PH assumption (Figure 3). A Goodness of Fit statistical test was conducted, and the residuals were not correlated with time, also providing evidence that the PH assumption was met. Taking medications for depression and/or anxiety was associated with time to mortality, after adjusting for age, sex, and history of COPD (HR: 1.60, 95% CI:1.07-2.39) (Table 4).

Figure 2. Kaplan-Meier Curves

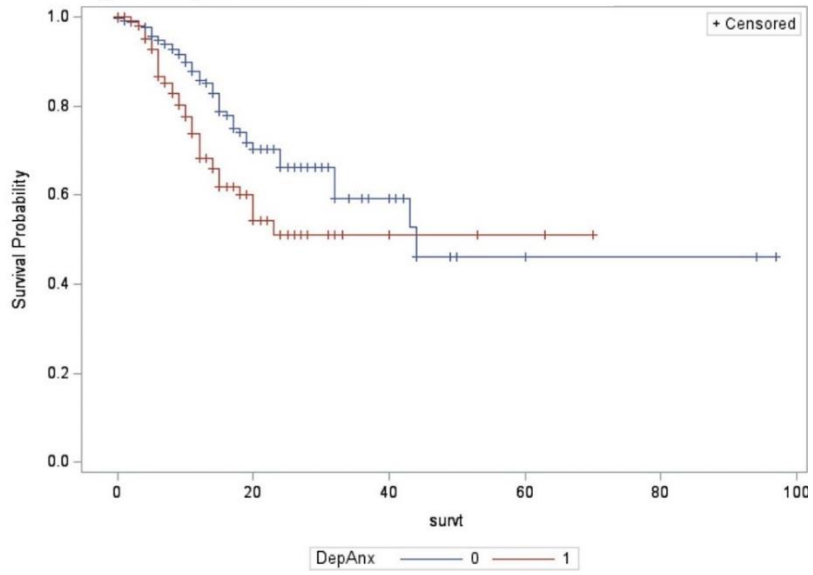


Figure 3. Log-Negative Log Survival Curves

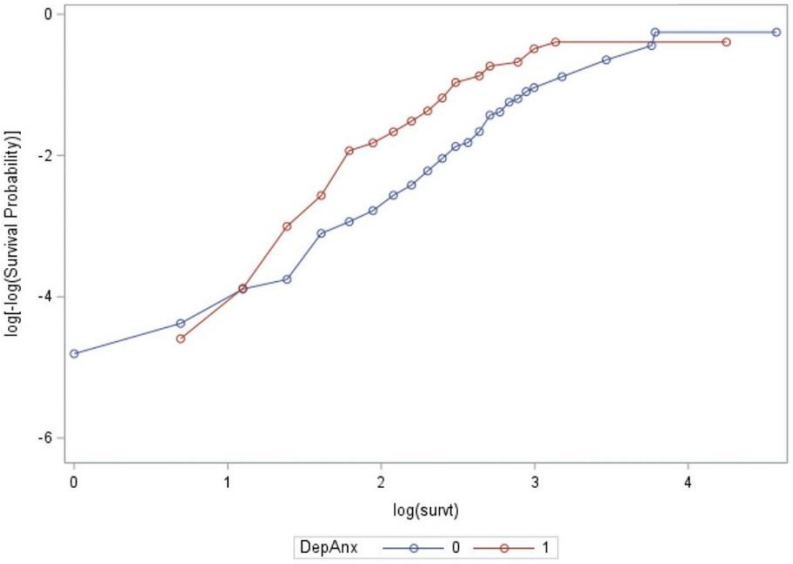


Table 4. Association Between Depression/Anxiety and COVID-19 Outcomes.

Outcome	OR[a,b]/HR[c]	95% Confidence Interval	P value
Mortality	1.84[b]	1.15-2.93	0.01
Ventilation	1.19[b]	0.78-1.81	0.42
ICU	0.95[b]	0.66-1.39	0.95
Time to Mortality	1.60[c]	1.07-2.39	0.02

[a]Adjusted for age, sex, and history of COPD.

[b]Odds Ratio
[c]Hazard Ratio

Table 5. Mortality Outcomes Stratified by ICU Admission

ICU Admission	Without Depression or Anxiety	With Depression or Anxiety	P value
Not admitted			
Alive (N,%)	306 (98.4)	111 (87.4)	<0.0001
Deceased (N,%)	5 (1.6)	16 (12.6)	
Admitted			
Alive (N,%)	131 (71.6)	41 (53.3)	0.0043
Deceased (N,%)	52 (28.4)	36 (46.8)	
Multivariable Model Stratified by ICU	**OR**	**95% CI**	**P value**
Not admitted	5.18	1.81-14.9	0.0022
Admitted	1.83	0.98-3.40	0.057

Specific Aim 3: To evaluate if inflammation, assessed through levels of the inflammatory markers IL-6 and CRP, acts as an effect modifier or mediator on the association between depression and COVID-19 mortality.

Different sub-populations were created and used for each inflammatory marker because the data for the inflammatory markers was not completed for all 698 participants. The same variables were retained as those for the logistic regression models. Only the mortality regression model was used to assess both sub-populations for both mediation and effect modification.

IL-6 mediation was evaluated by adding it to the model. There was about a 5% decrease in the odds ratio for the effect of depression and/or anxiety on mortality when IL-6 was added to the model. Effect modification was assessed by adding an interaction

variable between the exposure and IL-6. It was not found to be statistically significant, so no effect modification was determined (P = 0.16) (Table 6).

CRP mediation was evaluated by the same processes. There was about a 4% increase in the odds ratio for the effect of depression and/or anxiety on mortality when CRP was added to the model. Effect modification was assessed in the same fashion as stated above. It was not found to be statistically significant, so no effect modification was determined (P = 0.23) (Table 6).

Table 6. Effect of IL-6 and CRP Levels on the Association Between Depression and/or Anxiety and Mortality.

Inflammatory Marker	OR Inflammatory Marker Adjusted-No	95% CI	OR Inflammatory Marker Adjusted-Yes	95% CI	Effect Modification P-value
IL-6 (N=201)	1.98	0.86-4.51	1.88	0.77-4.45	0.16
CRP (N=457)	1.83	1.03-3.25	1.91	1.07-3.41	0.23

VI. DISCUSSION

This study's objective was to assess the effect of depression and/or anxiety on COVID-19 severity outcomes and mortality. Overall, depression and/or anxiety were not associated with ICU admission or ventilation. However, depression and/or anxiety were associated with mortality, with 84% higher odds of mortality, after adjusting for age, sex, and history of COPD (95% CI: 1.15-2.93). History of depression and/or anxiety were associated with time to mortality with 60% higher odds of mortality after adjusting for age, sex, and history of COPD (95% CI: 1.07-2.39). There was no meaningful mediation concluded or effect modification found for either IL-6 or CRP.

Depression and/or Anxiety and COVID-19 Outcomes

Although no significant associations were found between depression and/or anxiety and ICU admission or ventilation, there was a significant association with mortality and time to mortality due to COVID-19. Those who were diagnosed with depression may have been less likely to seek out treatment and to have experienced disease progression by the time treatment was sought. In this dataset of individuals hospitalized with COVID-19, approximately 29% were depressed overall; however, of those who died, about 48 % were depressed. Additionally, there seemed to be an inverse association with ICU admission; of those who died and were not admitted into the ICU, about 76% of those patients were depressed. For those who died and did not receive

ventilation, about 58% of those patients were depressed. These data suggest that depression and/or anxiety increases risk of mortality regardless of ICU admission or ventilation.

These findings are in keeping with a 2020 U.K cohort study, which reported that a pre-pandemic depression diagnosis was significantly associated with mortality (aOR: 2.67, 95% CI: 2.03-3.54) [67]. Another 2020 study based on electronic record data reported a higher death rate (8.5%) for COVID-19 patients with a recent diagnosis of a mental disorder compared with COVID-19 patients with no evidence of a mental disorder (4.7%), and more so when compared with patients with no COVID-19 infection and no mental disorder diagnosis (1.4%) [68]. A meta-analysis of studies examining pre-existing mental disorders found that mood disorders were significantly associated with mortality among those with a SARS-CoV-2 infection (OR: 1.99, 95% CI: 1.46-2.71), but antidepressant use was only significant in models with no adjustment for potential confounders [69]. Anxiety disorders were not associated with an increased risk of mortality (OR: 1.07, 95% CI: 0.73-1.56), but anxiolytic use was (aOR: 1.47, 95% CI: 1.15-1.88) [69]. No increased risk of ICU admission was found in this meta-analysis for those with a mental disorder (aOR: 1.33, 95% CI: 0.87-2.04) [69]. The meta-analysis also concluded that those with severe mental disorders had higher COVID-19 mortality estimates (aOR: 1.55 95% CI:1.30-1.85) compared to patients with other mental disorders (aOR: 1.09, 95% CI: 0.92-1.29) [69]. Overall, this evidence suggests that the effect of depression and/or anxiety on COVID-19 mortality may be increased for those actively taking medication or with a severe mental illness diagnosis.

Depression and/or Anxiety and Inflammatory Markers

There was no significant effect modification found by either inflammatory marker on the effect of depression and/or anxiety with COVID-19 mortality. Some mediation was seen from both markers. Including IL-6 in the multivariable model decreased the effect of depression and/or anxiety on mortality, while including CRP increased the effect of depression and/or anxiety on mortality. The mediation seen by IL-6 is not what has been seen in some previous studies [54, 55, 70], but the mediation by CRP does relate to previous studies [54, 55, 70]. Other studies have shown that antidepressants decrease cytokine activity like IL-6 [60, 62]. By decreasing cytokine activity through antidepressant medication, this could reduce the potential for a cytokine storm, which would lead to ARDS and death [36] therefore, potentially explaining the reduced effect on the association of depression and/or anxiety on mortality. Both inflammatory markers were significantly associated with COVID-19.

Strengths and Limitations

This study has multiple strengths. First, this is one of the few studies to explore the effect that depression and/or anxiety has on COVID-19 outcomes in the Kentuckiana region. This is also the first study to assess mediation and effect modification by IL-6 and CRP. This study will add to the developing literature and lead to discussions about the biological pathways that could lead to such associations.

Another strength was the use of PCR to identify those with a SARS-CoV-2 infection. Using this tool, it reduced misclassification on those admitted into the hospital

with a COVID-19 diagnosis. One final strength of this study is the region. Kentucky is a good place for this study having a vaccination rate of 51.7% and within the 10-14.9% 7-day positivity rate for COVID-19 compared to the United states average of 6.18% [71]. A recent study reported depression within Kentucky at 28.6% while the United States prevalence was 7.8% [3, 8]. This study assists doctors within the region to understand the possible consequences of depression and anxiety which may lead to adjusting the treatment of those who are hospitalized with COVID-19. Treatment could be altered by screening for depression/anxiety and observing severity symptoms to treat those symptoms sooner.

There are limitations in this study that should be noted. Mental health diagnoses were classified based on only medication use as reported in the EMR, which may have resulted in misclassification. Cases of depression or anxiety as well as prescribed medication may have been missed. For example, some patients within this study could be misclassified by not having depression or anxiety but could have the diagnosis while not actively taking medicine. Other participants may have been actively taking the medication, but it was not listed within the EMR. The medication list may not have been extensive enough to include all possible medications.

The population was restricted to those who were hospitalized, affecting external validity because we were not able to examine the effect of depression and/or anxiety on the risk of COVID-19 infection. Differential misclassification could occur with mortality by misclassifying the cause of death. A third limitation is that literature was emerging while this study was progressing, and residual confounding may be present given the

limited number of studies with sufficient duration to assess the influence of a large number of covariates.

Future Research

Since the emergence of SARS-CoV-2 and the beginning of this study, different screening tools have been developed and implemented. Testing sites are more widely available and accessible for more screening opportunities. With these screening opportunities, both symptomatic and asymptomatic patients could be recruited for a prospective cohort study. Once enrolled based on a positive SARS-CoV-2 PCR result, questionnaires regarding symptoms and mental health status could be administered. This would expand the sampling population to outside of just those hospitalized, and address classification of individuals based on mental health status. Further research is also needed to understand the biological pathway to explain the association between depression and/or anxiety and mortality. This would allow for research opportunities to examine the effect of depression on less severe COVID-19 outcomes such as being symptomatic versus asymptomatic and risk of hospitalization.

Conclusion

COVID-19 remains a significant public health concern as recent and on-going studies provide evidence of an association between depression/anxiety and COVID-19 outcomes. This literature is still developing as COVID-19 long-term effects and mechanisms are being discovered.

From this study, it was concluded that there was an association between depression and/or anxiety with mortality and time to mortality from COVID-19 diagnosis. There was no association concluded with depression and/or anxiety with ICU admission or ventilation. There was no meaningful mediation found from either IL-6 or CRP on the effect of depression and/or anxiety and mortality. There was no effect modification by inflammatory markers on depression and/or anxiety. These results will add to the evolving literature on the association of mental disorders and COVID-19 outcomes and can be built upon for future research with different methods and developing technologies.

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CURRICULUM VITA

Erica R Miller
12705 Charles Farm Circle, Apt 201, Louisville, KY 40299 | C: (502) 377-6747 | ermill06@louisville.edu

Academic History:

Master of Science: Specialization in Epidemiology **December 2021**
University of Louisville – Louisville, KY. United States
3.7 GPA

Bachelor of Arts: Major: Biology. Minor: Psychology
University of Louisville - Louisville, KY, United States **May 2019**
3.2 GPA
Worked in the Remold lab in the Shumaker Research Building.
Multiple classes focusing in microbiology, virology, and biology.

High School Degree:
Butler Traditional High School – Louisville, KY
4.0 GPA
Member of NHS, GSP Scholar.

Experience:

Eurofins Microbiology

04/2018 to Current

Associate Research Scientist & Analytical Services Manager – Louisville, KY

- Aseptic techniques applied through all parts of sampling handling from preparation to cultural confirmation.
- Project manager for a LEAN transformation.
- Sterile media preparation.
- PCR experience.
- Microbial cultural confirmation.
- Various research projects with the site Microbiologist.
- Research presentations at accredited conferences.
- Assists with methodology improvements.

Skills*:*

- Computer proficiency
- Microsoft Offic

- File record/maintenance
- Proficient in math
- PCR experience
- Quality system maintenance

Publications

- "Keeping the Environment Safe: RT-PCR Detection of Synthetic SARs-CoV-2 on Stainless Steel Over Time". Erica R Miller, Alex Angel, Cynthia Forseman Ph.D., Brian Beck, Daniel R. DeMarco Ph.D. *AOAC*.October 2020.
- "Detection if Inoculated SARS-CoV-2 Virus Analogue from the Surfaces of Raw and Heat-Processed Meat Products." Erica Miller, Daniel DeMarco, Alex Angel, Cynthia Forsman, J. David Legan, Megan Brown, and Richard Higby. *IAFP*. 2021.
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