

# **Field Epidemiology Training Program: Noncommunicable Disease COVID-19 Toolkit**

## **Literature Synthesis Report**

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# 1. Field Epidemiology Training Program: Noncommunicable Disease and COVID-19 Toolkit Overview

This resource is part of the Field Epidemiology Training Program (FETP): Noncommunicable Disease (NCD) and COVID-19 Toolkit. The Toolkit intends to build the capacity of Intermediate and Advanced FETP residents to incorporate NCDs within the context of their 2019 Novel Coronavirus Disease (COVID-19) pandemic response activities. The Toolkit includes a literature synthesis of key associations between COVID-19 illness (CLI) and NCD comorbidities, a list of field project topics and questions for investigation by intermediate and advanced level field epidemiologists and suggestions for types of data needed to conduct field projects, and two case study exercises, one for intermediate and one for advanced level field epidemiologists. For this Toolkit, the NCDs of primary interest are cardiovascular disease, diabetes, chronic obstructive pulmonary disease, cancers, and mental health. Please see the [U.S. Centers for Disease Control and Prevention \(CDC\) website](#) for a listing of medical conditions, including many NCDs and risk factors, that increase the risk of severe illness or mortality from CLI.<sup>1</sup>

## 2. Introduction

### 2.1 Background

NCDs are the leading causes of death and disability around the world.<sup>2</sup> In 2019, an estimated 42 million deaths (74.4% of global deaths) were attributable to noncommunicable diseases.<sup>3</sup> Seventeen million of these deaths are considered premature, occurring before the age of 70 years.<sup>3</sup> Over 85% of these premature deaths occur in low- and middle-income countries (LMICs).<sup>2</sup> NCDs are a category of generally chronic conditions that are associated with genetic, physiological, environmental, and behavioral risk factors.<sup>2</sup> The most common NCDs include cardiovascular disease, diabetes, cancers, and chronic respiratory disease.<sup>2</sup>

The COVID-19 pandemic has highlighted the underlying vulnerability that NCDs can create in affected populations.<sup>1</sup> The U.S. Centers for Disease Control and Prevention (CDC) have identified individuals with various NCDs as being at higher risk for more severe complications of COVID-19 disease compared to individuals without these conditions.<sup>1</sup> Residents participating in the FETPs are engaged in the COVID-19 response in countries around the world. An environmental scan conducted at the beginning of the development of the FETP: NCD COVID-19 Toolkit in October and November 2020 reviewed current FETP response activities and found that there were opportunities to further integrate consideration of NCDs as part of the COVID-19 response.

#### 2.1.1 Objective

This report seeks to summarize relevant evidence about NCD comorbidities and risk factors associated with CLI diagnosis, progression, and outcomes based on current literature at the time this review was conducted (up to October 2020). It is a rapid literature synthesis that draws from existing systematic reviews and meta-analyses across a range of relevant issues to identify findings of importance to FETP residents and their possible involvement in the COVID-19 response. This literature synthesis informed the development of the FETP: NCD COVID-19 Toolkit, which includes learning materials to equip FETP residents when responding to the COVID-19 pandemic. The information summarized in this review can enhance the knowledge of FETP program residents about NCDs, NCD intersections with CLI, and

opportunities to address these links. The rapid literature synthesis has a particular focus on NCDs and their risk factors with evidence of strong association with adverse CLI outcomes, specifically cardiovascular disease (including hypertension), diabetes, tobacco use, and obesity. This synthesis is intended to serve as a primer for a rapidly evolving body of literature, but not to be an exhaustive review of all published literature. Additionally, it is recommended that all readers consult more recently updated resources to identify any new developments. A few examples of such resources are the [CDC website on certain medical conditions that can increase risk for CLI severity and mortality](#), the [CDC website for healthcare providers on underlying medical conditions associated with high risk for severe CLI](#), and the [CDC website that summarizes the scientific evidence for conditions that increase risk of severe illness from CLI](#).<sup>1,4,5</sup>

### **2.1.2 Research Questions**

The following research questions were defined to guide the development of the scope and search strategy for this literature synthesis. They are:

1. How does the presence of NCDs (e.g., cardiovascular disease, chronic lung diseases, diabetes, chronic kidney disease, cancer) and their risk factors (e.g., obesity, smoking, alcohol, air pollution) affect COVID-19 progression and outcomes?
2. What are the impacts of CLI on NCDs?
3. What research methodologies and data sources have been used to examine the association between NCD and risk factor comorbidities with CLI?

## **3. Methodology**

This report synthesizes the results of systematic reviews and meta-analyses published between January 1 and October 15, 2020. Research Triangle Institute (RTI) International, a nonprofit research institute with expertise in health research and other technical services, conducted a systematic search of PubMed and the World Health Organization database of Global Literature on COVID-19. These databases do include articles that are published in pre-print databases, such as medRxiv. The search key terms included severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19, selected NCDs (cardiovascular disease, cerebrovascular disease, diabetes, chronic obstructive pulmonary disease, cancers, chronic kidney disease, obesity), and risk factors (smoking, air quality, alcohol, age, sex). RTI received the results of a systematic search conducted by Resolve to Save Lives (RTSL), which identified reviews, systematic reviews, and meta-analyses published between January 1 – August 28, 2020. RTI's subsequent searches included an update to RTSL's search for the period of August 29 – October 15, 2020, and a search to identify articles for additional NCDs and risk factors for the full time period (January 1 – October 15, 2020). The full search strategy is included in Appendix B.

All records identified through these searches were uploaded to Rayyan, a software program used to facilitate and organize literature for systematic reviews by removing duplicates and screening by title and abstract.<sup>6</sup> Where there were gaps in the evidence identified through the systematic search, RTI conducted non-systematic searches to determine whether high-quality primary data were available that had not yet been included in a systematic review or meta-analysis. Based on these studies, RTI conducted a rapid analysis to synthesize key findings for each included NCD and risk factor. RTI reviewed the results of identified studies first to classify by the NCDs and/or risk factors that were included. RTI then noted the conclusions of

the article with regards to the associations between the NCDs and risk factors and COVID-19 severity and increased mortality.

For articles that included meta-analysis, RTI abstracted the estimated measure of association, either the odds ratio (OR) or relative risk (RR). When a single report was available for a measure of association, the estimate and associated confidence interval were presented. When the same measure of association (OR or RR) was reported for an outcome in multiple meta-analyses, RTI presented the range of estimates reported. This range is the highest and lowest estimates reported and does not reflect the results of any further meta-analysis.

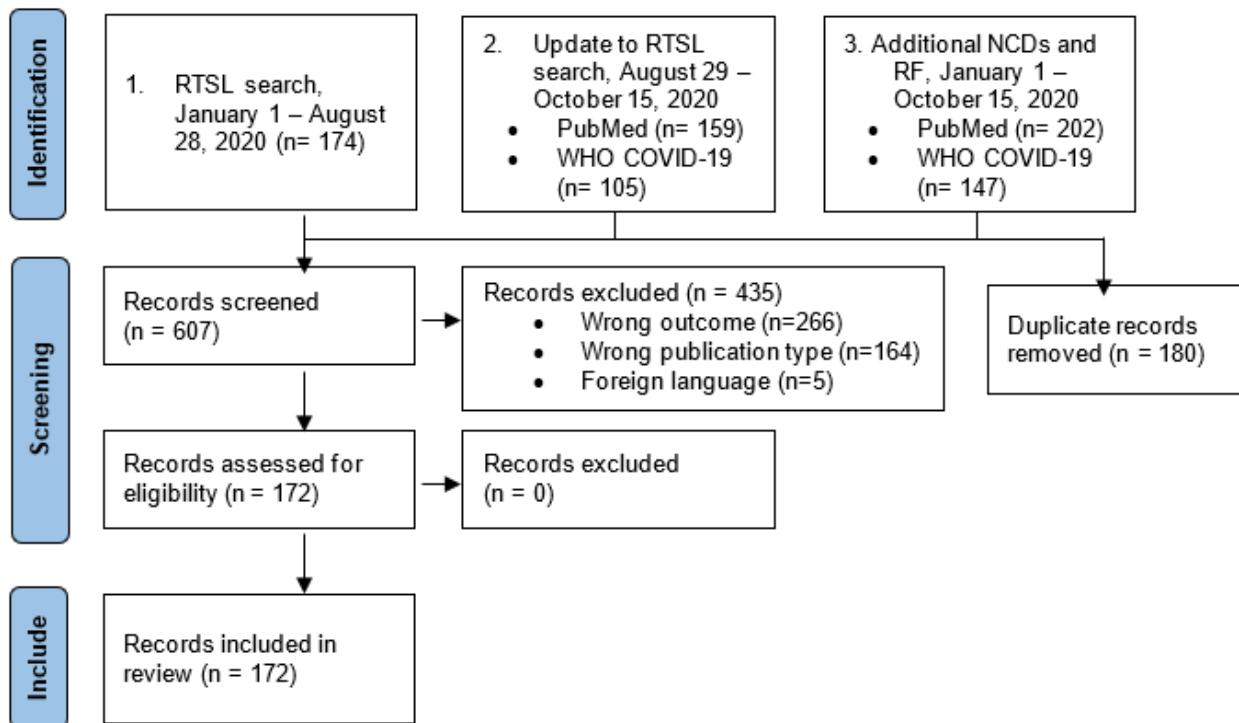
RTI also reviewed the discussion sections of these articles to capture information and identify additional references used about the hypothesized mechanisms for these associations. Lastly, RTI identified gaps in the literature that FETP residents may be well positioned to address. The aim of the synthesis was to summarize the current state of available knowledge relevant to FETP residents rather than to undertake a new meta-analysis to provide a definitive estimate of the strength of associations between NCD comorbidities and COVID-19 outcomes.

## 4. Results

### 4.1 Study Characteristics

The search identified 607 articles for title and abstract screening (Figure 1). Of these, 172 unique articles were identified as potentially relevant to the literature synthesis. A total of 135 of the 172 articles included meta-analysis of primary study results. Because this report is a rapid literature synthesis that is intended to serve as a primer for a rapidly evolving body of literature, comments on the results or underlying studies for all 172 articles were not included. The characteristics of a subset of articles are available in Appendix A. The citations for all 172 articles are included in Appendix C.

**Figure 1:** Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) flow chart of records reviewed on NCDs and COVID-19 Illness



The systematic reviews and meta-analyses reported the results of observational studies, with the most common methodologies being case series, prospective cohort studies, and case-control studies. These observational studies made comparisons of the prevalence of NCD comorbidities in populations with and without CLI and among patients with CLI who do and do not experience severe outcomes.

Most studies in these systematic reviews and meta-analyses were conducted in China and in high-income countries, such as the United States, and European countries, such as the United Kingdom, Italy, Spain, and Germany. Few studies were conducted in LMICs; however, of those included, the studies were conducted in Brazil, China, Mexico, and Thailand, which are classified as upper-middle income countries under the World Bank classification, and the Philippines, classified as a lower-middle income country.<sup>5</sup> Data for these studies were primarily collected from medical records in hospitals. A smaller number included studies that utilized data from infectious disease registries that covered populations outside of hospital settings.

The outcomes included in these studies were CLI severity and increased mortality. Disease severity was measured using a range of outcomes, including intensive care unit (ICU) admission and mechanical ventilation. Mortality was generally measured as in-hospital deaths while admitted for LI. Given the emerging nature of COVID-19 and that many studies were conducted using in-patient data, the outcomes included were all acute. Further investigation will be needed to assess chronic outcomes.

Review of the subset of studies included in Appendix A illustrates that the most common study designs were retrospective cohort, case series, prospective cohort, and cross-sectional. Consistent with these methodologies, the primary data source was medical and hospital records, rather than primary data collection from participants.

## **4.2 Pre-Existing NCD Comorbidities**

### **4.2.1 Chronic Kidney Disease**

A total of 13 articles examined chronic kidney disease (CKD) as a risk factor for CLI severity and increased mortality. CKD was associated with increased severity of CLI (OR 1.84-2.22<sup>7-10</sup>). Patients receiving dialysis or renal replacement therapy (RRT) were more likely to develop severe CLI (RR 26.02 [95% Confidence Interval (CI): 5.01-135.13]<sup>7</sup>) and to require intensive care (RR 14.22 [95% CI: 1.76-114.62]<sup>7</sup>) than patients not receiving RRT. Acute kidney injury was also associated with severe CLI (RR 8.12 [95% CI: 4.43-14.86]<sup>11</sup>) and ICU care (RR 5.90 [95% CI: 1.32-26.35]<sup>11</sup>) compared to patients without acute kidney injury. CKD was associated with increased mortality due to CLI (RR 3.25-7.10<sup>7,9,12</sup>) compared to patients without CKD. Patients receiving RRT were at increased risk of mortality (RR 12.95 [95% CI: 1.93-86.82]<sup>7</sup>) compared to those not receiving RRT. Acute kidney injury was associated with increased mortality (RR 13.38 [95% CI: 8.15-21.95]<sup>11</sup>) compared to those without acute kidney injury. The proposed mechanisms for these associations relate to the fact that CKD is associated with inflammation and impaired immune function.<sup>9,13</sup>

Additionally, angiotensin-converting enzyme 2 (ACE2), an enzyme attached to the membrane of cells located in several major organs, has been hypothesized as having a role in SARS-CoV-2 infection and disease severity, although further evidence is needed.<sup>14</sup> COVID-19 has been found to enter cells by binding to the ACE2 receptor, which can reduce ACE2 expression and lead to organ damage. The highest expression of ACE2 is in the kidneys.<sup>15</sup> After the SARS-CoV-2 virus enters the bloodstream, it may accumulate and bind in the kidneys that can result in organ damage.<sup>16</sup> However, results of a meta-analysis found no association between ACE2 use and higher mortality or worsening symptoms due to CLI.<sup>16</sup>

### **4.2.2 Cardiovascular Disease**

Cardiovascular disease (CVD), included in 45 articles, and hypertension, included in 49 articles, were associated with increased risk of CLI severity and mortality compared to patients without CVD or hypertension. Hypertension, an important risk factor for CVD, was associated with increased risk of developing severe CLI (RR 2.04 [95% CI: 1.69-2.47]<sup>17</sup>; OR 2.27-2.95<sup>18-22</sup>). Hypertension was also associated with increased risk of death (RR 2.21 [95% CI: 1.74-2.81]<sup>17</sup>; OR 2.42-3.67<sup>18,21-23</sup>).

CVD was associated with even greater risk of developing severe CLI (RR 5.05 [95% CI 4.36-5.85]<sup>19</sup>; OR 3.9-4.58<sup>20,21</sup>). CVD was associated with increased risk of death (RR 1.88 [95% CI: 1.41-2.51]<sup>24</sup>; OR 4.85-7.87<sup>21,23</sup>). Acute cardiac injury was associated with increased odds of severe COVID-19 (OR 6.28 [95% CI: 4.02-9.8]<sup>21</sup>) and death (OR 19.64-21.15<sup>21,23</sup>) compared to patients without acute cardiac injury.



A potential mechanism for this association is ACE2, which is the binding site for SARS-CoV-2 and how the virus enters cells. ACE2 protects against increases in blood pressure, so the introduction of SARS-CoV-2 could impede this function and result in cardiovascular complications.<sup>22</sup>

An additional hypothesis initially proposed was that common antihypertensive drugs (e.g., ACE inhibitors) can increase the expression of ACE2.<sup>17,18</sup> Increasing the expression of ACE2 might thereby provide more opportunities for SARS-CoV-2 to bind and spread. However, this mechanism was the subject of debate among experts<sup>25</sup> and results of a meta-analysis found no association between ACE inhibitor use and higher mortality or worsening symptoms due to CLI.<sup>26</sup> These results provide further evidence that it is safe to continue ACE inhibitors and/or angiotensin receptor blockers in patients who are taking these medications before hospitalization for CLI, and who do not have other indications to start or stop them.

#### **4.2.3 Chronic Obstructive Pulmonary Disease**

A total of 15 articles included chronic obstructive pulmonary disorder (COPD). Having COPD was associated with increased risk of developing severe CLI (RR 1.88 [95% CI: 1.40–2.40]<sup>27</sup>; OR 3.70–6.42<sup>8,28–30</sup>) compared to not having COPD. Patients with COPD were also at increased risk of experiencing serious events, such as ICU admission, mechanical ventilation, and acute respiratory distress syndrome (ARDS) (OR 6.66–8.33<sup>20,30</sup>). COPD was associated with increased risk of death (RR 1.53 [95% CI: 1.03–2.28]<sup>24</sup>; OR 3.43–4.36<sup>30–32</sup>). The hypothesized mechanism for these adverse outcomes is that increased ACE2 expression among COPD patients may lead to increased susceptibility to COVID-19.<sup>30</sup> Additionally, COPD patients who have compromised lung function may be more vulnerable to respiratory infections.

#### **4.2.4 Cerebrovascular Disease**

Across the 25 articles that reported on cerebrovascular accident (CVA) defined as a history of “stroke,” CVA was associated with CLI severity and increased mortality compared to patients without such history. CVA history was associated with increased risk of severe CLI (OR 3.00 [95% CI: 2.10–4.30]<sup>33</sup>). Patients with a history of CVA were also at increased risk of myocardial injury when infected with SARS-CoV-2.<sup>33</sup> CVA was also associated with increased risk of mortality (RR 2.48 [95% CI: 2.14–2.86]<sup>24</sup>; OR 2.78–5.58<sup>24,33,34</sup>). The proposed mechanisms for this association include ACE2, which protects against increases in blood pressure. Patients with a history of stroke, including those who did and did not have hypertension prior to their stroke, are more vulnerable to future damage to blood vessels as a result of high blood pressure, which can lead to additional blood clots and strokes.<sup>35</sup> Additionally, damage to cardiomyocytes due to the SARS-CoV-2 virus could lead to a systemic inflammatory response.<sup>30</sup>

#### **4.2.5 Diabetes**

Type 2 diabetes was associated with increased risk of severe CLI outcomes, including death, compared to risk among individuals without type 2 diabetes. At the time that this review was conducted, none of the 60 identified studies assessed outcomes for patients with type 1 diabetes, gestational diabetes, or pre-diabetes. However, since this timeframe several studies have identified individuals with type 1 diabetes as being at high risk.<sup>36,37</sup>

Type 2 diabetes was associated with increased risk of severe CLI (RR 2.45–3.20; OR 2.52–2.78<sup>38,39</sup>). Patients with diabetes were at increased risk of severe events, such as ICU admission, mechanical ventilation, and ARDS (OR 3.07 [95% CI: 2.02–4.66]<sup>20</sup>). Type 2 diabetes was associated with increased risk of requiring intensive care (RR 1.88 [95% CI: 1.20–2.93]<sup>40</sup>). Patients with diabetes were also at increased risk of death (RR 1.61–2.12<sup>40,41</sup>;

OR 1.75–2.78<sup>20,31,38,42–44</sup>). A hypothesized mechanism for this risk is based upon the fact that hyperglycemia can cause diminished immune response and chronic inflammation.<sup>38,42,45</sup> People with diabetes may also have increased levels of ACE2, which increases opportunities for SARS-CoV-2 to bind and enter cells.<sup>45</sup>

#### **4.2.6 Cancer**

Cancer is associated with increased risk of CLI severity and death compared to patients who do not have cancer. The most frequently reported cancer among CLI patients was lung cancer (28% of cancer patients with CLI had lung cancer).<sup>44</sup> When considered as a disease category, cancers were associated with increased risk of severe CLI, defined based on clinical measures such as a respiratory rate below 30 breaths per minute or oxygen saturation below 93% (RR 1.76 [95% CI: 1.39–2.23]<sup>46</sup>; OR 2.17–3.91<sup>47–49</sup>), ICU admission (RR 1.56–2.88<sup>50,51</sup>; OR 3.10 [95% CI: 1.85–5.17]<sup>48</sup>), and mechanical ventilation (OR 4.86 [95% CI: 1.27–18.65]<sup>48</sup>). Cancers were also associated with increased risk of death (RR 1.66–2.31<sup>50,52</sup>; OR 2.25–2.97<sup>47,49,51,53</sup>). Patients with hematological malignancies had highest odds of death (OR 2.39 [95% CI: 1.17–4.87]<sup>53</sup>) followed by lung cancer patients (OR 1.83 [95% CI: 1.00–3.37]<sup>53</sup>) when compared to patients without cancer. Patients with hematological malignancies also had greater risk of death (hazard ratio (HR) 3.52 [95% CI: 2.41–5.14]<sup>53</sup>), when compared to patients with solid tumors (HR 1.56 [95% CI: 1.29–1.89]<sup>53</sup>).

Cancer patients may be more vulnerable to CLI due to immunosuppression that results from common chemotherapy or radiation treatments.<sup>53–55</sup>

#### **4.2.7 Asthma**

The U.S. CDC has identified people with moderate to severe asthma as a group that may be particularly vulnerable to CLI.<sup>1</sup> However, data on the association between asthma and CLI are limited and inconsistent. While the CDC definition specifies that people moderate to severe asthma may be at risk, not all identified articles differentiated by severity of asthma. The search identified five articles that assessed asthma as a risk factor for CLI severity and increased mortality. Early studies conducted in China found that people with asthma were under-represented among CLI patients. Later studies from the United States and Europe have found people with asthma to be over-represented among CLI patients.<sup>56</sup> However, asthma was not associated with increased risk of hospitalization due to CLI after adjusting for age, sex, and other comorbidities (RR 0.96 [95% CI: 0.77–1.19]<sup>57</sup>). Across studies, asthma, defined as either all asthma or just moderate to severe asthma, was not significantly associated with increased risk of death compared to individuals without asthma after adjustment.<sup>12,29,57,58</sup> Initial concerns about the potential for inhaled corticosteroids and other asthma medications to increase risk of hospitalizations and other severe outcomes are not supported by data.<sup>57,58</sup> Although the mechanism is uncertain, it has been hypothesized that the inflammatory response that occurs for patients with asthma may be protective against CLI.<sup>56</sup>

#### **4.2.8 Obesity**

The search identified 23 articles that evaluated obesity as a risk factor for CLI severity and death. Obesity is defined as having a body mass index (BMI) greater than 30.0 kg/m<sup>2</sup>, and overweight as a BMI between 25.0 and 29.9 kg/m<sup>2</sup>.<sup>59</sup> Obesity was independently associated with increased risk of CLI severity and death compared to having a body mass index in the normal range. Individuals with obesity were more at risk of developing CLI than those who had healthy weight (OR 1.46 [95% CI: 1.30–1.65]<sup>60</sup>). Obesity and overweight (BMI ≥ 25.0) were associated with increased risk of severe CLI (RR 2.35 [95% CI: 1.43–3.86]<sup>61</sup>) and obesity was associated with increased risk of hospitalization (OR 2.13 [95% CI: 1.74–2.60]<sup>60</sup>),

and ICU admission (OR 1.74 [95% CI: 1.46–2.08]<sup>60</sup>). Compared to those with normal weight, individuals with obesity were at increased risk of ARDS compared to those with normal weight (obesity: OR 1.66 [95% CI: 1.21–2.28]<sup>62</sup>; severe obesity: OR: 1.78 [95% CI: 1.12–2.92]<sup>62</sup>). Obesity and overweight were associated with increased risk of death due to CLI (BMI  $\geq$  25.0: RR 3.52 [95% CI: 1.32–9.42]<sup>61</sup>; obesity: OR 1.48–1.55]<sup>60,63</sup>). While obesity is associated with several risk factors for severe CLI, including hypertension, CKD, and diabetes, it was an independent risk factor for these outcomes.<sup>60</sup> The hypothesized mechanism for this association is that obesity is associated with diminished immune function and inflammation.<sup>60</sup> Obesity is also associated with impaired immunological memory, which has implications for vaccine effectiveness.<sup>60</sup>

## **4.3 NCD Risk Factors**

### **4.3.1 Smoking**

The search identified 19 articles that examined smoking as a risk factor for CLI severity and increased mortality. Current cigarette smokers were at increased risk of severe CLI compared to non-smokers (RR 1.45 [95% CI: 1.03–2.04]<sup>27</sup>; OR 1.51–2.51<sup>28,30,39,64–67</sup>). Former cigarette smokers were also at increased risk of severe CLI compared to non-smokers (OR 2.17–3.46<sup>64,66</sup>), and smoking history was associated with increased risk of ICU admission ( $p=0.003$ <sup>67</sup>) compared to no smoking history. Any smoking history was also associated with COVID-19 death (RR 1.26 [95% CI: 1.20–1.32]<sup>68</sup>; OR 1.19 [95% CI: 1.05–1.34]<sup>69,70</sup>) in comparison to no smoking history.

Smoking is known to increase severity of respiratory infections and diminish immune function.<sup>68</sup> Additionally, smoking has been found to increase ACE2 expression.<sup>27,68</sup>

### **4.3.2 Air Quality**

No systematic reviews were identified that addressed the impact of air quality on CLI severity or increased mortality. Preliminary research indicated that the number of COVID-19 cases tends to be higher in areas with poor air quality compared to areas with better air quality.<sup>71</sup> Research conducted in England identified nitrogen oxide and ozone levels, which are markers of poor air quality associated with fossil fuels, to be associated with CLI death, even after adjusting for population density.<sup>72</sup> Evidence from prior outbreaks of other infections resulting in viral pneumonia suggest that air pollution can diminish the immune response.<sup>71</sup>

### **4.3.3 Alcohol**

No systematic reviews were identified that addressed the impact of alcohol consumption on CLI severity or death. Primary data on the association between alcohol use and CLI were not available. However, one study suggests that alcohol consumption can lower the body's immune response, and may increase vulnerability to CLI.<sup>73</sup>

### **4.3.4 Age**

Increasing age was positively associated with increased risk of severe CLI, ICU admission, developing ARDS, and mechanical ventilation.<sup>39,74</sup> A total of 52 articles identified in the review assessed older age as a risk factor for CLI death. Older age was also associated with increasing risk for death due to CLI.<sup>74,75</sup> People over 65 years of age had significantly greater risk of death due to CLI than those younger than 65 (OR 4.59 [95% CI: 2.61–8.04]<sup>31</sup>). These associations are consistent with outcomes of past coronavirus outbreaks, including SARS and MERS.<sup>74</sup> Older age is associated with a decline in immune response to viral infection and a longer proinflammatory response.<sup>31</sup> Older age may also be associated with an increased risk of other comorbidities that can result in negative outcomes, such as ARDS.<sup>31</sup>

### **4.3.5 Sex**

The search identified ten articles that examined sex as a risk factor for CLI severity and increased mortality. Men were at greater risk of severe outcomes of CLI than women. Male sex was associated with increased risk of severe CLI than female sex (RR 1.20 [95% CI: 1.13–1.27]<sup>74</sup>; OR 1.22 [95% CI: 1.01–1.49]<sup>39</sup>). Male sex was associated with increased risk of ICU admission (RR 1.29 [95% CI: 1.13–1.47]<sup>74</sup>), developing ARDS (RR 1.15 [95% CI: 1.01–1.30]<sup>74</sup>), and requiring mechanical ventilation compared to female sex (RR 1.35 [95% CI: 1.11–1.64]<sup>74</sup>). Male sex was also associated with increased risk of mortality (RR 1.23 [95% CI: 1.14–1.33]<sup>74</sup>; OR 1.50 [95% CI: 1.06–2.12]<sup>31</sup>). Potential mechanisms for this association include hormonal differences by sex, X-chromosome linked genes such as ACE2, and Y-chromosome linked genes that are associated with the immune response.<sup>39,76</sup> Sex differences may also occur in the social and cultural behaviors that influence exposure to SARS-CoV-2, such as participation in religious gatherings, which if crowded could increase risk of exposure.<sup>76</sup>

## **4.4 NCD Complications of COVID-19**

Pre-existing NCDs can increase risk for severe outcomes of CLI; likewise, CLI can result in serious complications of the NCD conditions. Although it is still too early to fully understand the long-term outcomes of the COVID-19 pandemic, preliminary studies have documented serious acute outcomes that may result in chronic health complications.<sup>77,78</sup> These lasting effects are referred to as “long COVID.”<sup>79</sup> Additional long-term complications of CLI may include neurological or psychiatric effects, but these were not within the scope of this review’s search strategy and did not appear in any articles identified by the search. The evidence regarding the long-term complications of CLI is continuously evolving and readers are encouraged to refer to the latest evidence for any updates and new developments.

### **4.4.1 Lung Complications**

Acute lung injury is among the most common complications of CLI and was discussed in three articles identified by the search. An estimated 30% of CLI patients in the ICU developed severe lung complications, such as lung edema and ARDS.<sup>80</sup> An estimated 5% of total people infected with CLI developed ARDS.<sup>81</sup> SARS-CoV-2 binds the ACE2 receptors in the lungs, which may be the mechanism for complications such as lung edema, acute lung injury, and ARDS.<sup>82,83</sup>

### **4.4.2 Acute Kidney Injury**

Many patients who have severe CLI develop kidney damage such as acute kidney injury (AKI).<sup>16</sup> A total of seven articles identified included AKI. AKI is more common among patients with severe CLI than with mild CLI.<sup>8</sup> The estimated incidence of AKI among COVID-19 patients was 8.4%–9.4%.<sup>10,13</sup> The odds of death among CLI patients with AKI were estimated to be 13.33 higher than the odds among patients without AKI (95% CI 4.05–43.91).<sup>13</sup>

### **4.4.3 Acute Cardiac Injury**

Cardiac complications of CLI include acute cardiac injury and heart failure. Cardiac complications, such as acute cardiac injury, were discussed in nine identified articles. In a systematic review of cardiovascular complications among patients with severe CLI, the estimated frequency of acute cardiac injury and heart failure was 25.3% and 23.7%, respectively.<sup>21</sup>

#### **4.4.4 Acute Ischemic Stroke**

While a history of cerebrovascular disease is a risk factor for CLI severity and increased mortality, acute ischemic stroke is also a potential complication of CLI and was included in nine of the identified articles. The estimated incidence of acute ischemic stroke among CLI patients was 1.1%–1.2%.<sup>84</sup> The mortality rate for patients who have an acute ischemic stroke was estimated to be high (38.0%–44.2%).<sup>84,85</sup> Acute stroke risk was higher for patients with severe CLI than mild CLI (RR 4.18 [95% CI: 1.70–10.25]<sup>86</sup>).

## 5. Conclusions

This synthesis of systematic reviews and meta-analyses published between January 1 and October 15, 2020, identified evidence indicating that pre-existing NCD comorbidities and NCD risk factors are associated with increased risk for severe CLI and death. In addition to these NCD comorbidities and risk factors, individual characteristics, such as older age and male sex, were significant risk factors for severe CLI and death. Available evidence within the period of review did not suggest that asthma increases risk of severe CLI or death, although data were limited and inconsistent. Alcohol intake as a risk factor had not been well studied within the period of review. Initial studies from the COVID-19 pandemic suggest SARS-CoV-2 infection can result in acute injury of the lungs, kidney, and heart, and in acute ischemic stroke. The impact of these comorbidities and risk factors, and the high and rising burden of NCDs around the world, underscore the importance of integrating attention to NCDs in the COVID-19 pandemic response through surveillance and analytic activities.

To note, we are learning more about COVID-19 and CLI every day. This synthesis drew upon research included in systematic reviews and meta-analysis published up to October 15, 2020 and there may be subsequent new findings in relation to CLI and NCD comorbidities and risk factors as the science evolves. It is recommended that researchers should review the latest research while in the development phase of their projects to ensure that new findings are considered. An example of such a resource is the [U.S. Centers for Disease Control and Prevention \(CDC\) website](#), which provides a listing of medical conditions, including many NCDs and risk factors, that increase the risk of severe illness or death from CLI.<sup>1</sup>

### 5.1 Gaps that FETP Residents May Address

There are several gaps in knowledge around CLI and NCD comorbidities that FETP residents may fill within their response activities and program requirements. Residents across all three levels participate in surveillance activities, ranging from collecting surveillance data at the frontline level to conducting surveillance system evaluations at the advanced level.<sup>87-89</sup> As part of these evaluations, residents may be able to recommend integration of NCD comorbidity data collection as an opportunity to strengthen the health information system. FETP residents have helped to develop systems and processes for case investigation and contact tracing, including associated data collection forms, and may thereby be well positioned to integrate NCDs into these investigation and response activities. Such investigations may help understand associations between NCD comorbidities and risk factors at the population level and allow local health authorities to recommend policies and programs to strengthen the local COVID-19 response. Looking forward, these activities also have potential to strengthen the healthcare response to the rising burden of NCDs over time.

At the time of the review, most studies reviewed were undertaken in high-income countries in North America and Europe and in China with few studies in LMICs. The studies conducted in China primarily analyzed medical records from patients in urban hospitals and did not cover rural settings that might more closely reflect the situation of other LMIC populations. There is an opportunity for FETP residents to contribute to generating data and findings in LMICs relating to NCD comorbidities and CLI. The studies included in this systematic reviews and meta-analyses were largely case series and retrospective cohort studies of patients receiving care in hospitals. As a result, the follow up periods for these studies were short in duration (most less than 1 month) and patients with more severe cases of CLI were predominant in the study samples. Additional studies related to the medium and longer-term outcomes for patients with mild to moderate CLI are needed. As part of their planned epidemiological studies, intermediate and advanced FETP residents may have an opportunity to collect and analyze data to help fill these gaps and generate important evidence relating to their context.

As the prevalence of COVID-19 increases, analytical studies with larger study populations may be feasible. These larger studies will allow for more precise estimates of the impact of NCD comorbidities and risk factors. The rise in prevalence of COVID-19 in many countries and establishment of more centralized registries for COVID-19 cases may allow advanced residents to conduct aggregate analyses of CLI outcomes for different NCD comorbidities and risk factors. This shift from case-based analyses to larger data sets may allow these residents to help improve the knowledge base for their country and the various populations within.

Finally, few of the included studies of NCD comorbidities and risk factors accounted for potential confounding by age and sex, multi-morbidity (patients that have several concurrent NCDs, like diabetes and hypertension), or by multiple risk factors (e.g., obesity and NCDs, smoking and lung cancer). Residents may contribute to addressing this knowledge gap in two key ways: first, by increasing the available data on NCDs and potential confounding risk factors as a result of their surveillance and outbreak investigation activities; and second, by conducting data analyses that explore and account for these potentially confounding factors.

## **5.2 Recommendations for FETP**

- FETP curriculum could include content instruction on NCDs as risk factors for severe CLI outcomes and for potential long-term complications of SARS-CoV-2 infection.
- Training could prepare residents to establish or improve surveillance systems, both in healthcare facilities (e.g., patient disease registries) and at the community level to include NCD comorbidities and risk factors.
- For FETP advanced residents, instruction on investigation of NCD comorbidities could include strategies for detecting and addressing confounding variables in analyses, along with content on what the confounding factors are likely to be.
- FETP residents can expand the research literature by collecting data on SARS-CoV-2 infections, CLI outcomes, and comorbidities in LMICs and disseminating their findings.
- Mentorship support is needed to guide residents to address potential challenges with data availability and analysis and interpretation of confounding factors.

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## Appendix A: Characteristics of Selected Articles (published between January 1 – October 15, 2020)

First Author	Title	Countries	Data Sources	Study Designs
Fang <sup>74</sup>	Epidemiological, comorbidity factors with severity and prognosis of COVID-19: a systematic review and meta-analysis	China, Japan, Singapore	Hospital records	-
Jain <sup>90</sup>	Predictive symptoms and comorbidities for severe COVID-19 and intensive care unit admission: a systematic review and meta-analysis	China	Hospital records	Retrospective cohort,
Lippi <sup>18</sup>	Hypertension in patients with coronavirus disease 2019 (COVID-19): a pooled analysis	China	Hospital records	Not specified
Mantovani <sup>45</sup>	Diabetes as a risk factor for greater COVID-19 severity and in-hospital death: A meta-analysis of observational studies	China, United States, Israel, France, Italy, Norway, Thailand, Australia, Korea, United Kingdom	Hospital records	Cross-sectional, cohort, case-control
Momtazmanesh <sup>21</sup>	Cardiovascular disease in COVID-19: a systematic review and meta-analysis of 10,898 patients and proposal of a triage risk stratification tool	-	-	Case series, retrospective cohort, prospective cohort, population-based surveillance

<b>First Author</b>	<b>Title</b>	<b>Countries</b>	<b>Data Sources</b>	<b>Study Designs</b>
Parohan <sup>31</sup>	Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies	China, Italy, Iran	-	Prospective cohort, retrospective cohort
Popkin <sup>60</sup>	Individuals with obesity and COVID-19: A global perspective on the epidemiology and biological relationships	Bangladesh, Kuwait, Mexico, USA, Brazil, Spain, China, France, UK, Finland, Italy, Brazil, Israel, Thailand, Switzerland, Denmark, Romania	Medical records	Cross-sectional, cohort, case-control
Pranata <sup>17</sup>	Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis, and meta-regression	-	-	Retrospective cohort, prospective cohort
Reddy <sup>68</sup>	The effect of smoking on COVID-19 severity: A systematic review and meta-analysis	United States, China, UK, Italy	Hospital records	Cohort, case series,
Tan <sup>84</sup>	COVID-19 and ischemic stroke: a systematic review and meta-summary of the literature	United States, Italy, France, United Kingdom, Spain, Turkey, China, Philippines	Medical records	Case series, retrospective cohort
Varikasuvu <sup>38</sup>	Diabetes and COVID-19: A pooled analysis related to disease severity and mortality	China, Italy, France, United States,	Medical records	Retrospective cohort, prospective cohort, case series



<b>First Author</b>	<b>Title</b>	<b>Countries</b>	<b>Data Sources</b>	<b>Study Designs</b>
Venkatesulu <sup>53</sup>	A systematic review and meta-analysis of cancer patients affected by a novel coronavirus	China, United States, UK, Italy, Spain, France	Medical records, primary data collection	Retrospective, clinical trials
Yamakawa <sup>85</sup>	Clinical Characteristics of Stroke with COVID-19: A Systematic Review and Meta-Analysis	China, Italy, United States, Spain, Netherlands, France	Hospital records	Retrospective cohort, case series
Yu <sup>33</sup>	Cardio-Cerebrovascular Disease is Associated with Severity and Mortality of COVID-19: A Systematic Review and Meta-Analysis	United States, Spain, Oman, China, Italy, Brazil, Iran, Greece	Medical records	Retrospective cohort, prospective cohort
Zaki <sup>44</sup>	Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: A systematic review	China, Mexico, United States	Medical records	Cross-sectional, cohort
Zhang <sup>22</sup>	Association of hypertension with the severity and fatality of SARS-CoV-2 infection: A meta-analysis	China	-	Retrospective cohort

- Indicates characteristics not reported in manuscript or supplemental materials

## Appendix B: Search Strategy

Search	Databases	Dates	Search Terms
1. RTSL search	PubMed	January 1– August 28, 2020	(COVID-19 OR SARS-COV-2 OR Coronavirus) AND (hypertension OR "high blood pressure" OR cardiovascular OR myocarditis OR troponin OR coronary heart disease OR chronic kidney disease OR smoking OR tobacco OR "chronic obstructive pulmonary disease" OR "COPD" OR "air pollution")
2. Update to RTSL search	PubMed, WHO Global Literature on COVID-19	August 29– October 15, 2020	("systematic review" OR "meta-analysis" OR "meta-analysis") AND ("COVID-19" OR COVID OR coronavirus OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2") AND (Diabetes OR diabetic OR "cardiovascular disease" OR hypertension OR "high blood pressure" OR "raised blood pressure" OR "heart disease" OR stroke OR "chronic kidney disease" OR "heart failure" OR "coronary artery disease" OR cardiomyopathy OR "respiratory disease" OR "chronic lung disease" OR "COPD" OR "chronic obstructive pulmonary disease" OR cancer) OR (Obesity OR overweight OR obese OR smoking OR tobacco OR alcohol OR "air pollution" OR "air quality" OR "unhealthy diet" OR "sedentary behavior" OR "physical inactivity" OR "physical activity")
3. Search for additional NCDs and risk factors	PubMed, WHO Global Literature on COVID-19	January 1– October 15, 2020	("systematic review" OR "meta-analysis" OR "meta-analysis") AND ("COVID-19" OR COVID OR coronavirus OR "SARS-CoV-2" OR "severe acute respiratory syndrome coronavirus 2") AND (Diabetes OR diabetic OR cancer OR alcohol OR air pollution OR air quality OR "unhealthy diet" OR "sedentary behavior" OR "physical inactivity" OR "physical activity")

## Appendix C: Identified Articles

- Abbasi, J. (2020). "Large Meta-analysis Digs Into Obesity's COVID-19 Risks." Jama.
- Abdi, A., et al. (2020). "Diabetes and COVID-19: A systematic review on the current evidences." Diabetes Res Clin Pract **166**: 108347.
- Afshar, Z. M., et al. (2020). "Fatality rate of COVID-19 in patients with malignancies: a systematic review and meta-analysis." J Infect **81**(2): e114-e116.
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