A Physician's Guide for Workers' Return to Work during COVID-19 Pandemic

Journal of Occupational and Environmental Medicine: Publish Ahead Print

DOI: 10.1097/JOM.0000000000002118

A Physician's Guide for Workers' Return to Work during COVID-19 Pandemic

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Running Title: Physician Guide to Return to Work during Pandemic

Sources of funding: None

Acknowledgments: The authors wish to acknowledge Alyssa B. Schultz, PhD for her editing of this manuscript.

Conflict of Interest: None

Statement of Clinical Significance

During COVID-19 pandemic, physicians are facing the challenges of deciding the risk of workers returning to the workplace. We developed guidelines for determining the risk of returning to work based on community risk , job risk and an individual worker's risk for the worker of developing significant COVID-19 disease.

ABSTRACT

Objective Higher risk for developing severe forms of COVID-19 has been associated with health risk factors and medical conditions which are common among workers globally. For at risk workers, return to work may pose unique risks which require protective policies and procedures.

Methods A review of the medical literature was conducted on health risk factors and medical conditions associated with increased COVID-19 morbidity and mortality.

Results The relative risk of acquiring and the severity of COVID-19 for workers is associated with three pillars: individual risk, workplace risk, and community risk. Matrices were developed to determine a worker's individual risk.

Conclusions A practical tool was developed for physicians managing COVID-19 relative risk in workers.

Keywords: Coronavirus Infections; Communicable Disease Control; Patient Isolation;

Pandemics; Chronic Disease, COVID-19

INTRODUCTION

Coronavirus disease (COVID-19) was declared as a pandemic by the World Health Organization (WHO) on March 11, 2020.[1] Common symptoms include fever, fatigue, cough, dyspnea, sore throat, headache, anosmia, hypogeusia or ageusia, asthenia, conjunctivitis and gastrointestinal issues (loss of appetite, diarrhea, nausea and vomiting). Although a significant number of patients are asymptomatic or have mild clinical symptoms at presentation, a small percentage of cases can progress to uncontrolled inflammatory response with acute respiratory distress syndrome or even multiple organ failure.[2-6] Some individuals are at high-risk for developing severe symptoms which are associated with significant morbidity and mortality, including the elderly, certain ethnicities (e.g. African Americans) and those affected by health risk factors and chronic diseases.[6-8] Specific organ damage has been described in COVID-19 patients, such as acute respiratory distress syndrome,[9] cardiovascular injuries (cardiac imbalance, coronary thrombosis, direct myocardial injury, arrhythmias and venous thromboembolism),[10-13] acute liver injury,[14,15] acute kidney injury and kidney replacement therapy,[16,17] and neurological complications (severe stroke, Guillain–Barre Syndrome, acute encephalitis, seizures and skeletal muscle injury)[18] that may represent a higher risk for those with pre-existing chronic health conditions.

In 2020, the global impact of COVID-19 posed unprecedented challenges to health agencies, governments, companies, healthcare systems, academia, and individuals. From the public health perspective, non-pharmaceutical interventions (NPIs) are an important strategy to mitigate the impact by slowing the epidemic spread, reducing peak healthcare demand, and protecting people at higher risk of acquiring the infection.[19] According to The Imperial College, physical distancing of people at high-risk groups is particularly effective at reducing severe outcomes. NPIs will need to be maintained until an effective COVID-19 vaccine becomes widely available.[19]

Based on clinical epidemiology studies, lists of health risk factors and medical conditions that predispose individuals to severe forms of COVID-19 have been developed and published by several health agencies such as WHO,[20] CDC,[21] NHS,[22] and others.

Examples of these risk factors include age, obesity, hypertension, and several health conditions such as diabetes - which are all prevalent among workers globally.[7] Using the 2017 Global Burden of Disease data, Clark et al.[7] estimated that 22% of the global population (1.7 billion people) have at least one underlying condition which increases the risk of severe COVID-19 and 4% of the global population (349 million people) are at greatly elevated risk for severe disease and necessitating hospitalization if they contract COVID-19.

For workers at increased risk who cannot work from home, return to work may expose them to COVID-19 going to and from work and at their workplaces. Strategies and guidelines are therefore needed to protect all workers, especially those at increased risk of COVID-19 complications. Governments around the world have generally not provided guidance on how to protect workers at increased risk nor assistance with decision-making about return to work for persons at heightened risk of complications and mortality from COVID-19.[23]

Occupational medicine specialists in a number of countries have developed medical guidelines to protect the health of workers until an effective preventive treatment or vaccine is available for COVID-19.[24-26] Nabeel and Fischman[27] proposed a four-step approach to guide return to work of individuals with high risk which includes: (1) assess the risk of exposure in the workplace which depends on the degree of interaction with people and the nature of job tasks; (2) identify the scope of individual risk and stratify the severity or the degree of control of the disease; (3) recommend protective measures in the workplace if work from home is not possible, and (4) advise workers on reduction strategies for modifiable risks (e.g. BMI, blood glucose, etc.). Coggon et al.[28] developed a risk model considering age, sex, ethnicity, smoking habits, and comorbidities to support decisions on occupational placement of workers in the UK during the pandemic. Larochelle[23] has proposed a framework for medical decisions about returning or continuing to work amidst the pandemic based on the risk of contracting SARS-CoV-2 at the workplace and the individual risk of complications and death if infected (both risks stratified as low, medium and high). The author suggested that patients with high risk in both domains should be counseled to stop working, those with high risk in one domain and medium risk in the other should mitigate exposure and consider

staying out of work, and all patients at work should be counseled to take precautions (use of mask, hand hygiene and PPE as recommended).

The purpose of this study is to develop a global framework to support physicians, companies, and governments on how to ensure the health and safety of workers at a higher risk of unfavorable outcomes of COVID-19 during the current pandemic, considering individual risk factors, workplace exposure risk, and the level of community transmission of SARS-Cov-2.

METHODS

A review of clinical and epidemiology COVID-19 studies was conducted. The literature search on July 15, 2020 utilized medical databases (PubMed and Scielo) with MESH terms including COVID-19: "covid19" OR "covid 19" OR "sarscov2" and MESH terms related to risk factors identified as associated with adverse COVID-19 outcomes: "smoking", "chronic disease", "diabetes", "pregnancy", "immunosuppression", "neurodegenerative diseases", "pulmonary disease, chronic obstructive", "asthma", "liver diseases", "obesity", "hypertension", "cancer", "heart disease", "COPD" and "asthma". In addition, a search with MESH terms including COVID-19 and "epidemiology" was conducted. We identified studies which described the prevalence and/or assessed the effects of sociodemographic factors, risk factors, and medical conditions associated with unfavorable COVID-19 related outcomes.

The criteria for high-risk individuals and their management from the US, Brazil and India were also reviewed, according to the dashboard provided by the Center for Systems Science and Engineering (CSSE) at Johns Hopkins University (JHU).[29] In addition, an internet search for the three most affected countries in Europe (UK, Spain and Italy) was conducted. The European continent became the epicenter for the pandemic following the first reported cases in China. Among the ten countries most affected by the COVID-19 pandemic, South Africa was the only country to our knowledge to release a specific recommendation for managing employees at increased risk for COVID-19.

Recommendations from Labor and Health & Safety government agencies regarding the risk of exposure to COVID-19 at workplaces were then reviewed. The risk that a worker may be exposed to in various work settings was quantified and stratified. The third step was to review indicators which quantified the level of transmission in the community and stratify the risk of exposure of the worker in a community. In conclusion, a framework was created which included three pillars of risk based on worker health factors, workplace risk, and community level risk.

RESULTS

The Individual Risk Pillar

The literature review is summarized in Tables 1 and 2. Seventy-three studies were reviewed, including sixty-six single country studies and seven reports with data from two or more countries. Almost half, thirty-six of the studies, were from China, followed by the US (21), Italy (10), Spain (6), France (4), UK and Mexico (3), South Korea (3) and Brazil and the Netherlands (2). The most common study methodology was cohort (33), followed by descriptive studies (22), meta-analysis and/or systematic review (14), case-control (3), and cross-sectional (1).

The descriptive studies examine associations between sociodemographic factors (age, male gender, non-white race/ethnicity), health risks (e.g., smoking, BMI) and chronic diseases (e.g., cardiovascular, hypertension, diabetes, chronic respiratory diseases, kidney diseases, cancer, immunosuppression and rheumatic diseases) and adverse COVID-19 outcomes. Despite raising concerns about reported risk factors, descriptive studies do not confirm a causal association of these factors with severe disease and death.[103] Cohort studies are more likely to prove etiology; in these studies, significant associations with adverse COVID-19 outcomes included older age (nineteen studies), male gender (seven studies), non-white race (two studies), cardiovascular diseases (eight studies), hypertension (ten studies), diabetes (seventeen studies), BMI greater than 30 kg/m^2 (three studies), cigarette smoking (one study), chronic respiratory diseases (eleven studies), chronic kidney diseases (six studies), cancer (nine studies), immunosuppression (three studies), liver diseases (three

studies), pregnancy (one study), organ transplantation (three studies), stroke and other neurologic (three studies), rheumatic diseases (one study), inflammatory bowel disease (one study), obstructive sleep apnea (one study) and association or combination of more than one disease and increasing risk (six studies). Three case-control studies were reviewed and reported associations of age (two studies), hypertension (one study), diabetes (one study), and obesity (one study) with COVID-19 complications. Among the ten meta-analyses reviewed, conclusions supported significant associations with complications for diabetes (five studies), cardiovascular diseases (three studies), chronic respiratory diseases (three studies), older age (three studies), male sex (two studies), smoking (two studies), hypertension (two studies), pregnancy, stroke and other neurologic conditions (both one study).

Table 3 presents a summary of guidelines for at-risk individuals published by several countries and legal guidelines and requirements for the management of at-risk workers. Governmental recommendations are generally in line with the published literature, based on age, health risk factors, and chronic medical conditions. However, there are several important differences. Some countries have been more specific and provided more detailed clinical criteria (UK[22,108] and South Africa[113]) while others provide only guidelines with few details (India,[107] Spain, [109] and Brazil[105]). Two countries created empirical risk categories: USA (increased risk and possibly at increased risk)[114] and UK (high risk or clinically extremely vulnerable and moderate risk or clinically vulnerable).[22] Legal requirements on management of high risk workers for employers differ by country, ranging from general protection measures, as Spain[110] and India[107] with no specific recommendations, to the US[104] with general recommendation that employers must consider, to the UK[108] and Brazil[106] with more specific obligations for employers to stringent requirements in South Africa,[113] which require employers to have policies and procedures to address the needs of vulnerable employees.

The Workplace Risk Pillar

The workplace in the era of the pandemic is being redesigned to reduce spread of the COVID-19 virus. A significant number of employees are working from home and are concerned about returning to work.[115,116] Baker et al.[117] estimated the number of workers in the US who are frequently exposed to infection and disease, and therefore COVID-19, in the

workplace more than once a month. Approximately 10% of US workers are exposed to disease or infection at least once per week, while 18.4% are exposed to disease or infection at least once per month. The majority of these workers are healthcare workers. Other occupations frequently exposed include police officers, correction officers, fire fighters, office and administrative support staff, educators, and community and social service workers. Mitigating the spread of COVID-19 through workplace policies and procedures is important in the overall strategy to limiting the spread of the pandemic. Understanding the estimated number of workers potentially exposed is useful in developing workplace specific strategies.[118]

The factors associated with the employee safely returning to the workplace in the context of COVID-19 have been categorized by Rafeemanesh et al.[118] as: (1) control measures including engineering controls, (2) administrative controls, and (3) personal protective equipment. Control measures include isolation of symptomatic individuals, proper ventilation, barriers between staff and clients/customers, using disposable tools and instruments, continuous cleaning, and disinfection. Administrative controls include preventing entry of sick workers, continuous training of staff on hygiene, reducing staff hours, and restricting staff gatherings. Personal protective equipment includes proper masks/respirators, eye protection, gloves, and special clothing.

Based on evaluation of workplace exposures, different occupations have been associated with a particular level of risk.[119] For example, by the nature of their work, healthcare workers are generally at the highest risk of COVID-19 infection whereas an outdoor agricultural worker is generally at low risk because they work independently and at a distance from co-workers (apart from risks associated with commuting and housing).[120] The U.S Occupational Health and Safety Administration has classified risk of occupational exposure from very high, high, medium, and lower risk.[104] Very high-risk occupations include healthcare workers performing aerosol-generating procedures and laboratory personnel and morgue workers performing autopsies. High occupational risk of exposure includes healthcare workers, medical transport workers, and mortuary workers who prepare bodies. Medium exposure risk jobs are those requiring contact within 6 feet/2-meters with

people who might be infected. Low risk jobs include those that do not require contact within 6 feet/2 meters of the public or co-workers (table 4).

The Community Risk Pillar

The third aspect that must be taken in consideration for managing the risk of workers is the level of community transmission of SARS-Cov-2, which reflects how prevalent the disease is in the community.[121,122] The risk of acquiring the disease is associated with the prevalence of disease where the individual lives and works.[123] To find out the level of community transmission, the physician must be aware of the available information and data which are provided by the World Health Organization, government health agencies around the world, research centers, and other sources. WHO has defined four transmission scenarios for COVID-19[124] and provides updated information for all countries as (1) no new cases, (2) sporadic cases, (3) clusters of cases, and (4) community transmission on its website.[125] Noticeably, current experience with COVID-19 indicates that in many regions with sporadic cases, aggressive testing strategies may reveal underlying community transmission.[126] CDC classifies levels of community transmission as (1) no to minimal community transmission, (2) minimal to moderate community transmission, when there is sustained transmission and potential risk for rapid increase in cases, (3) substantial, controlled transmission, when there is large scale but controlled community transmission, and (4) substantial, uncontrolled transmission, when there is large scale, uncontrolled community transmission, including communal settings.[127] EndCoronavirus is an international volunteer coalition with over 4,000 scientists, community organizers, citizens, and business owners operating since February 29, 2020. This organization offers guidelines and recommendations with the intent to help governments, communities, healthcare, institutions, families, and individuals to end the pandemic. The coalition´s website[128] includes data which classifies countries as "winning", "nearly there" and "need action". If available, more precise measures like number of daily cases per 100,000 (low<1, moderate 1-10, high 11-25, and critical >25) and percent of positive PCR tests (low <3%, moderate 3%-6%, high greater than 6%- 10%, and critical >10%) can be used by the physician to estimate the risk that a worker will be exposed at the community level.[129,130] The Johns Hopkins Coronavirus Resource Center (CRC)[131] provides

updated COVID-19 data and expert guidance by aggregating and analyzing data available from the US and other countries (cases, testing, contact tracing and vaccine efforts) to assist policymakers and healthcare professionals worldwide to respond to the pandemic. Their website includes the percentage of positive COVID-19 tests for most countries.

Table 5 summarizes data the physician should consider when defining the level of transmission in a community and determining the risk for a patient. The four levels of community spread listed in Table 5 are based on metrics published by WHO, CDC, Johns Hopkins University, and Harvard Global Health Institute. Other relevant indicators of community transmission such as R0 and herd immunity have not been considered in our model for stratifying the level of community transmission. At this time, there are no definitive reports on how to use such indicators to quantify risk. Additional research is needed to determine if such metrics should be included in worker risk models. Therefore, we recommend healthcare providers continue to focus primarily on metrics used to measure COVID-19 community transmission.

DISCUSSION

The Individual Risk Pillar

The literature review found a strong association with older age as an independent risk for severe forms and death of COVID-19. The risk for ICU admission and/or death increases exponentially with age which may be explained by immunosenescence,[132,133] 'inflammaging'[132,133] and reduced mucociliary clearance.[134] Male gender has also been reported in most studies as an independent risk factor for death and severe clinical forms of COVID-19, which may be related to a higher prevalence of chronic diseases, higher health risk behaviors, occupational exposure, and gender differences in the expression of angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) which have both been implicated on virus entry on target cells.[135,136] Race and ethnicity have been reported as independent risk factors in four studies (two cohorts and two descriptive) for higher mortality among non-white (Black, Hispanic and Asian). However, the reason for this

observation is not known at this time. Possible explanations include living conditions, health disparities, prevalence of comorbidities, and chronic stress.[137]

Obesity has been reported in several studies as an independent risk factor for COVID-19 morbidity and mortality. Notably, one study found a clear dose-response gradient between increasing BMI and a greater risk of virus complications,[50] which supports a cause and effect relationship. Another study found that obesity represented 49.5% of the total effect of diabetes on COVID-19 mortality.[34] Such findings may be related to effects on immunity, occurrence of comorbidities,[138] and effects on the respiratory system.[139] A consistent finding in our literature review was that smoking is associated with unfavorable COVID-19 outcomes, which can be related to several and probably interactive effects such as structural changes in the respiratory tract, impaired cell-mediated immunity in the alveolus, depletion of interleukin-1 and interleukin-6, reduced activity of natural killer (NK) cell in in peripheral blood, reduced level of circulating immunoglobulins, and depressed phagocyte activity.[140] However, immunologic abnormalities are reversible and expected to resolve within six weeks after stopping smoking[140] so all workers must be advised and supported to quit smoking during the COVID-19 pandemic.

Pre-existing cardiovascular disease (such as coronary artery disease, cardiomyopathy, valvular diseases and heart failure), have consistently been reported as a risk for poor COVID-19 outcomes. Of note, a study conducted in China found a very strong association (OR 21.4, $p<0.0001$)[101] between coronary heart disease and in-hospital death. Hypertension has been reported as an independent risk factor for unfavorable COVID-19 outcomes. It is not clear whether this increased risk is directly related to hypertension or to other associated comorbidities (cardiovascular disease, diabetes, obesity and others) or anti-hypertensive medication treatment.[141,142] Treatment resistant hypertension is associated with increased inflammatory biomarkers (interleukin-6, interleukin-1β, tumor necrosis factor-α and high-sensitivity C-reactive protein).[143] Hypertension might serve to enhance the systemic inflammatory response observed in patients with COVID-19. However, more research is needed to clarify the pathophysiological relation and associated risk, especially among patients with treatment resistant hypertension.[144] There has been initial concern about the

safety of angiotensin-converting-enzyme inhibitors (ACE inhibitors) and angiotensin II receptor blockers (ARBs), related to the intensification of ACE2 receptor expression, which could be associated with an increased risk of SARS-CoV-2 infection[145]. However, ACE2 receptors may protect against acute respiratory distress syndrome (ARDS) in COVID-19 patients[145] and more recent studies suggest that the use of renin-angiotensin-aldosterone system inhibitors is not associated with increased risk of severe forms of COVID-19.[146,147]

Diabetes is an independent predictor of COVID-19 severity and mortality, which may be due to the inhibition of neutrophil chemotaxis, altered cytokine production, phagocytic cell dysfunction, impaired T cell-mediated immune responses, and ineffective microbial clearance.[148] Hyperglycemia can also be a consequence of COVID-19 infection, caused by ACE2-dependent transient damage of pancreatic islets and exocrine tissue. Hyperglycemia and diabetes development during hospital admission have been reported.[149] Hyperglycemia at admission, without history of diabetes, was reported by Sardu et al.[83] as an independent risk factor for poorer outcomes. Current research highlights the importance of glycemic control during the COVID-19 pandemic and protective measures for workers with diabetes.

The respiratory diseases most studied have been COPD and asthma and one study also assessed interstitial lung diseases. COPD has consistently been identified in several studies as an independent risk factor for severe forms of COVID-19. While some studies found a significant association of asthma and poorer outcomes, others did not. Studies that reported a poorer outcome tended to combine asthma and COPD as one category (chronic respiratory diseases). Three studies which were limited to patients with asthma did not find an association with more severe COVID-19 lung involvement and poorer clinical outcomes. A large UK cohort study found a significant association of severe asthma and death of COVID-19.[91] Considering that COPD is associated with impaired local and systemic inflammatory response, reduced host immunity, microbiome imbalance, increased mucus production and structural lung damage as well as with increased risk of morbidity and mortality of respiratory infections,[150] COPD patients must be considered as high risk for complications from COVID-19. In the absence of additional research, moderate and severe asthma patients must also be considered at a higher risk.

Chronic kidney disease (CKD) has consistently been associated with severe forms of COVID-19 complications in several reports, including six cohort studies. In addition, CKD has an extensively documented association with cardiovascular disease (CVD), and CKD and CVD share common risk factors (diabetes mellitus, obesity, hypertension, smoking and dyslipidemia).[151] Our study suggests that patients who are undergoing treatment for some types of cancers (hematologic cancers and locally advanced and metastatic solid tumors) have more complications and higher death rates from COVID-19. However, this may not be the case for all types of cancer. Workers with cancer must be carefully evaluated to assess their risk level.

In this review, three cohort studies found a significant association of pre-existing chronic liver diseases with more severe COVID-19. Current research suggests that workers with chronic liver disease must be carefully evaluated to determine their risk level for COVID-19 complications and death. The few published studies of patients with rheumatic diseases, have indicated no elevated risk for COVID-19 complications. According to the American College of Rheumatology, there is currently no evidence that rheumatic diseases should be considered as a risk factor for unfavorable COVID-19 outcomes.[153] Immunosuppressive treatments must not be interrupted because exacerbation of rheumatic disease may lead to a systemic inflammatory state and organ specific manifestation of the underlying condition (especially kidney and lung) which may increase the risk of COVID complications.[153] There is currently insufficient evidence to draw definitive conclusions regarding the level of risk in patients with rheumatic diseases.

Active inflammatory bowel diseases and treatment for a disease flare are associated with COVID-19 complications and death. However, it is not clear if immunosuppressive therapy is also associated with morbidity and mortality. Available research suggests a possible association with concomitant corticosteroid therapy.[35] There are few published studies of organ transplantation recipients, but the current evidences suggests that organ transplant patients are at a significantly greater risk of complications and death and must be considered at very high risk for COVID-19 unfavorable outcomes.

We found no evidence that people living with HIV with good clinical and virologic control are at increased risk for severe forms of COVID-19. However, caution is warranted for HIV patients with high viral load, low CD4 cell count, severe disease, and those not using antiretroviral therapy[71] who may be at increased risk. Three cohort studies reported a significant association of pre-existing stroke and other neurologic diseases with morbidity and death from COVID-19. Current research strongly suggests that workers with stroke and other neurologic diseases must be considered at higher risk for complications of COVID-19. We found one study which suggested that sickle-cell disease (SCD) patients are at higher risk of COVID-19 complications.[76] More studies are necessary, but workers with SCD should be considered at high risk from COVID-19 because infection is the leading cause of morbidity and mortality among SCD patients.[154] One study reported a higher risk of hospital admission of patients with obstructive sleep apnea disorder,[40] but it is not clear if it is related to other comorbidities (obesity, cardiovascular diseases and diabetes).

Some studies reported similar risk among pregnant and non-pregnant patients and one cohort reported pregnancy among the risk factors associated with critical COVID-19 illness. Vertical transmission, and its long-term potential consequences cannot currently be excluded. At the present time, pregnancy, especially if associated comorbidities are present (obesity, hypertension, pre-eclampsia and diabetes), should be considered at higher risk until further studies are available.

Four cohort studies reported that as the number of comorbidities increases, the risk of severe forms of COVID-19 complications also increases while two other cohort studies found that higher Charlson Comorbidity Index Scores were significantly associated with COVID-19 complications. These observations have important implications for physicians since multiple risk factors are frequently observed among workers.[155,156]

At this time, the knowledge about SARS-CoV-2 is incomplete and the literature in this area is rapidly evolving. However, based on our literature review, relevant risks that can be identified by healthcare providers to determine worker risk for COVID-19 morbidity and mortality include:

- Age over 60 years old; there is generally increasing risk with age;
- Male sex;
- Cardiovascular diseases, like CAD, CHF, cardiomyopathy and valvular diseases, especially if active and/or not well managed and compensated;
- Hypertension, especially if not responsive to treatment with three antihypertensive drug classes (usually a diuretic, a long-acting calcium channel blocker, and a blocker of the renin-angiotensin system) and/or with target organ damage;
- Diabetes types 1 and 2, with a greater risk if blood glucose is not within goal and/or with target organ damage;
- Obesity (BMI > 30 kg/ m^2), with greater risk with increasing BMI;
- Current smoking;
- Chronic respiratory diseases: COPD, interstitial lung diseases and moderate-to-severe asthma and cystic fibrosis;
- Significant chronic kidney disease;
- Cancer, especially in cases of hematologic cancers, locally advanced and metastatic solid tumors;
- Significant chronic liver disease;
- Pregnancy, especially those with associated comorbidities;
- Organ transplantation recipients;
- HIV patients with high viral load, low CD4 cell count, severe disease, and those not using antiretroviral therapy;
- Neurological diseases (e.g. stroke with significant functional limitation, etc.)
- Active inflammatory bowel diseases;
- Sickle-cell disease.

Table 6 illustrates the risk modeling we have developed to categorize workers according to individual

health risks.

Although there is an association with several health risks such as cigarette smoking and BMI and elevated risk for COVID-19 complications, there is no current evidence that mitigation of these risk factors results in lower risk of the severity of COVID-19. Nevertheless, it seems prudent to advise workers to modify such risk factors with the hope of attenuating their risk.

Our explanation for differences observed in higher risk worker definitions by official health agencies may be that it is difficult for any government to establish standards and guidance in an evolving science like the COVID-19 pandemic. The different recommendations and legal requirements to manage high-risk workers may reflect the differences in country culture, labor legislation, politics, and social security regulation. Healthcare workers in all countries must comply with local laws and regulations, however, physicians must keep in mind that COVID-19 research is constantly evolving and, similarly, medical decision making, and practice guidelines are also evolving.[122]

The Workplace Risk Pillar

Some evidence exists that a COVID-19 case may, in some settings, be work-related.[165] The risk of exposure to SARS-CoV-2 in the healthcare workplace is based on reported estimates of 150,000 healthcare professionals infected and at least 700 who have died in the US as of September 2020.[166] However, other factors must be considered. In addition, workers may contract the virus during travel to and from their jobs in crowded public or semiprivate transportation.[166] Protective measures adopted by the employer are effective to reduce viral dissemination in the workplace[167] and the absence of effective workplace controls has been associated with COVID-19 outbreaks in recently opened workplaces.[166] When managing a specific case of a high-risk worker, we recommend healthcare providers include an assessment of transportation used by the worker in addition to worksite control measures.

The Community Risk Pillar

Table 5 presents five definitions for the level of COVID-19 transmission in a particular country. These designations may be used by healthcare providers to determine

relative risk for managing high-risk workers. The WHO transmission status is available and periodically updated on the internet for almost all countries.[125] The CDC level of community transmission is not currently published and relies on a determination by the physician. Other metrics are available on endcoronavirus.org[128] and the Johns Hopkins[131] websites. It is not currently possible to estimate the future transmission of SARS-CoV-2. Several scenarios of peaks and valleys of COVID-19 incidence have been projected for the post-pandemic period until 2025.[168] Such projections depend in part on several factors such as intensity and timing of control measures, the degree of seasonal variation in transmission, the duration of immunity and the degree of cross-immunity between SARS-CoV-2 and other coronaviruses.[168] Precise measures of determining community activity, such as number of daily cases per 100,000 and percent of positive PCR testing should ideally be used by healthcare providers where available. We acknowledge that in several countries such data are not currently available.

Proposed framework

Table 7 summarizes four workplace options and guidelines for workers returning to work based on COVID-19 relative risk, considering individual, community, and workplace factors: (1) return to the workplace with standard recommendations, (2) return to the workplace with specific additional recommendations, (3) return to the workplace with specific work accommodation, and (4) currently stay out of the workplace. Figure 1 shows the proposed scheme, combining data on individual risk level and the OSHA classification of SARS-CoV-2 infection risk at work at the different levels of community transmission. Notably, community transmission level 3 and 4 have the same recommendations, because level 3 progresses to level 4 with more aggressive testing policies[126].

Larochelle proposed a matrix for determining the risk for workers of developing severe COVID-19 infection.[23] The matrix was a 3 x 3 matrix with 9 possible risk groups and interventions. One axis is the risk of contracting SARS-CoV-2 in the workplace rated as low, medium, and high. The other axis is the risk of death from COVID-19 as low, medium, and high. Each of the 9 boxes is assigned as A, B or C recommendation for how the healthcare

professional should advise a patient based on the 9-box risk. For example, a worker who is at high risk of contracting SARS-CoV-2 in the workplace and at high risk of death because of their health risk factors should be advised to consider stopping work if working remotely is not an option. We have expanded the Larochelle matrix[23] to include job risk ranked from 1 to 4 where 1 is low risk, for example workers who can work from home, to 4 for very high job risk for healthcare workers exposed to aerosol transmission from patients potentially infected with SARS-CoV-2. The individual employee risk of morbidity and mortality in the Larochelle model was expanded from 3 to 4 levels where 1 is relatively low risk and 4 is very high risk (see figure 1). The recommend four steps for using the proposed matrix in clinical practice is described in Figure 2 and summarized below:

- **Step 1:** Define community transmission level according to Table 5. If possible, physicians must consider data at the smallest geographic area available (e.g. city or state instead of country data). Precise measure of transmission such as percentage of positive tests and daily new cases per 100,000 people, if available, are preferred.
- **Step 2:** Define individual risk level. Using Table 3, classify each patient according to age and health risks. We suggest healthcare providers assign each worker a risk level and consider the highest level of relative risk for each worker. We acknowledge that comorbidity is common in workers who may have more than one medical conditions at level 2 and/or 3. In such situations, once research indicates that the relative risk increases as the number of comorbidities increase, the physician may assign the worker to level 4.
- **Step 3:** Define job risk level. Use Table 4 and investigate the patient information about job exposure. Beyond the definitions provided by OSHA, we recommend physicians investigate potential exposure on transportation and protective measures implemented by the employer. If the exposure at work is not at the higher levels, if exposure may occur at transportation and/or protective measures are not properly provided by the employer, the healthcare provider should assign the worker as exposed to a higher level. For high risk activities, if recommended PPE are not available, the physician should consider job exposure as very high.

- **Step 4:** Provide recommendations to the worker. Once all the three risk levels (individual, job, and community) are defined, using the proposed matrix (Figure 1), select the recommendation (A, B, C, or D) from the matrix box (Figure 1) and use the recommendations presented in Table 7 as a reference to define the medical management for each patient.

Limitations

We acknowledge several limitations of this literature review and proposed framework. We have stratified three different risk levels and there is a certain lack of precision for the definition of each level, that can be counterbalanced by the individual judgment of each physician. The medical literature on COVID-19 is rapidly evolving, so healthcare providers must keep current on research and practice guidelines with new information on risks for morbidity and mortality associated with health risks and chronic conditions. The reviewed studies used to stratify individual risk have been done with the general population and not limited to employed people. Therefore, the health risks for COVID-19 morbidity and mortality may not be applicable for a working population. The metrics to determine community and workplace risk may be incomplete and not applicable to all workers. Numerous medical conditions have not been studied which may contribute to the relative risk of morbidity and mortality from COVID-19. Workplace risk may, in some instances, be better characterized by the number of unusual lapses in protection rather than the usual practices associated with a particular industry. The matrices we developed for relative risk based on community, job and individual risk are empirical and will require prospective validation.

Conclusion

A practice tool for healthcare providers has been developed to determine a worker's relative risk of acquiring and the severity of COVID-19 based on individual risk, workplace risk, and community risk. Recommendations for managing workers based on these three risk pillars are illustrated in three matrices.

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Figure legend list

Figure 1 – Proposed worker guidelines based on community, job and individual risk for COVID-19 morbidity and mortality

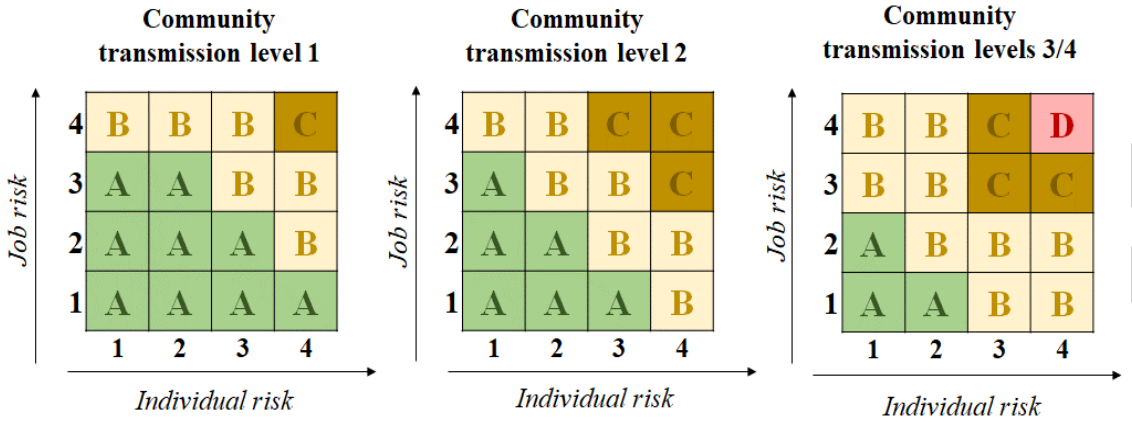

Figure 2 – Steps in the use of the proposed risk matrix

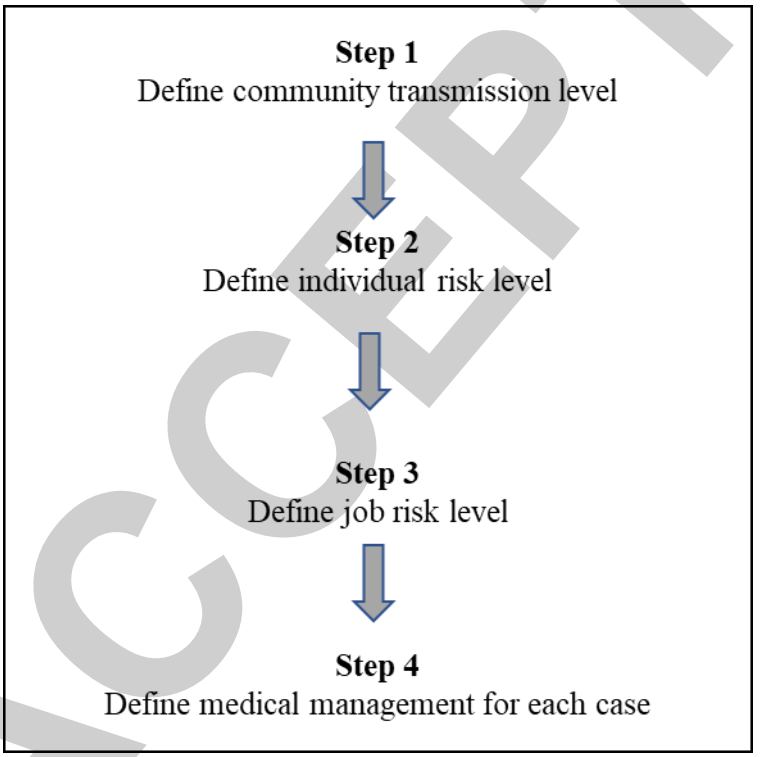

Table 1 – Summary, characteristics and key findings of 73 studies reviewed

Author	Sample	Methodology	Country	Findings
Aggarwal et al.[30]	4,858	Meta-analysis of studies about association of CVD with severe diseases and increased mortality in COVID-19 patients	China and USA	Previous cardiovascular disease was significantly associated with a higher risk of a severe disease (OR = 3.14; 95% CI 2.32-4.24) and death outcome (OR = 11.08; 95% CI: 2.59-47.32), but not significantly associated with mortality in severe form of COVID-19 (OR = 1.72; 95% CI: 0.97-3.06)
Akalin et al.[31]	36	Cohort of adult kidney-transplant recipients with COVID-19 (median follow-up of 21 days)	USA	96% of patients had radiographic findings suggestive of viral pneumonia. During follow up, 39% needed intubation and mechanical ventilation, 21% needed renal replacement therapy and 28% died
Alberici et al.[32]	20	Cohort of long-term kidney transplant patients with COVID-19 (median follow-up of 7 days)	Italy	At baseline all cases had fever, 1 had dyspnea; 50% of all cases had bilateral infiltrates Chest X-ray, 35% had unilateral infiltrates and 15% had no infiltrates. During follow up, 87% had radiological worsening and among those 73% needed oxygen therapy. Six patients had acute kidney injury and one needed hemodialysis. Five patients died after a median period of 15 days
Assaad et al.[33]	302	Retrospective cohort study of cancer patients with suspected COVID-19 (median follow-up time of 25 days)	France	18.2% of patients tested positive for SARS-COV-2. 9.9% of patients died during the observation period among all patients, 21% died in the PCR positive group and 10% in the negative group. Detection of SARS-COV-2 on RT-PCR was not associated with an increased death rate. 80% of cancer patients who died had metastatic disease (in both groups). Receiving any cancer treatment on the last 30 days was not associated to increased risk of death.
Bello-Chavolla et al.[34]	51,633	Retrospective cohort of COVID-19 cases	Mexico	Age ≥65 years (HR 2.02, p<0.001), diabetes (HR 1.34, p<0.001), early-onset diabetes (<40 years) (HR 2.86, p<0.001), obesity (HR 1.25, p<0.001), chronic kidney disease (HR 1.99, p<0.001), COPD (HR 1.40, p<0.001), immunosuppression (HR 1.27, p=0.007) were significantly associated to increased lethality in COVID-19 cases. In patients with diabetes mellitus, mortality was higher in those with concomitant comorbidities (immunosuppression, COPD, CKD, hypertension) and those aged over 65 years. Diabetes mortality was partially mediated by obesity, the effect of obesity represented 49.5% of the total effect of diabetes.
Bezzio et al.[35]	79	Prospective observational cohort study with adults with	Italy	55% had COVID-19 pneumonia, 36% were hospitalized, 13% needed mechanical ventilation and 11% died. Active IBD was associated with severe COVID-19

		Inflammatory bowel disease and COVID-19		outcomes and all patients were under treatment for a disease flare. Ulcerative Colitis was significantly associated with COVID-19 pneumonia, but not with death. 38% had at least one comorbidity: hypertension (11%), coronary heart disease (6%), COPD (6%), ankylosing spondylitis (3%), rheumatoid arthritis (1%), multiple sclerosis (1%), undifferentiated connective tissue disease (1%), Hypothyroidism 1 (1%). Charlson Comorbidity Index distribution: 0 (54%), 1 (18%), 2 (15%), 3 (8%), 4 (4%), 5 (1%). Risk of COVID-19 pneumonia was significantly associated with age over 65 years (OR 5.87, p=0.03), Ulcerative Colitis (OR 2.91, p=0.03), IBD disease activity (OR 10.25, p=0.003) and Charlson Comorbidity Index score >1 (OR 2.91, p=0.04). COVID-19-related death was significantly associated with age over 65 years (OR 19.6, p=0.002), IBD disease activity (OR 8.45, p=0.02) and Charlson Comorbidity Index score >1 (OR 16.66, p=0.01).
Cai et al.[36]	383	Case series of adults with COVID-19 admitted to a hospital	China	Overweight (OR 1.84, p=.05) and obesity (OR 3.40, p=0.007) were significantly associated to severe forms of COVID-19. Comparing obese and normal weight man, the obese were at increased odds of developing severe forms (OR 5.66, p=0.003).
China CDC[37]	44,672	Descriptive and exploratory analysis of cases in China until 2/11/2020.	China	Overall case-fatality rate (CFR) was 2.3% but higher for those with underlying medical conditions: cardiovascular diseases (10.5%), diabetes (7.3%), chronic respiratory disease (6.3%), hypertension (6.0%) and cancer (5.6%). CFR was also higher for older age groups (0.2% 0-40 years, 0.4% 40-19 years, 1.3% 50-59 years, 3.6% 60-69 years. 8% 70-80 years and 14.8% > 80 years).
Chen et al.[38]	274	Retrospective case series of patients with COVID-19 (113 who died and 161 who recovered)	China	Male sex was more frequent among deceased patients (73% vs 55%). Deceased patients were significantly older than recovered (media age 68 vs 51) years. Among deceased cases: hypertension (48% vs 24%), diabetes (21% vs 14%), cardiovascular disease (14% vs 4%), chronic lung diseases (10% vs 4%), cancer (4% vs 1%), cerebrovascular disease (4% vs 0%) and chronic kidney disease (4% vs 1%)
Chen et al.[39]	9	Case series (retrospective review of medical records)	China	All 9 pregnant women in the third trimester underwent caesarean section. The clinical characteristics of COVID-19 infection during pregnancy were similar to those reported for non-pregnant adults. None of the nine patients developed severe pneumonia or died.
Chhiba et al.[40]	1,526	Retrospective	USA	14.4% of cases has asthma. Asthma was not

		cohort of COVID-19 cases		significantly associated to a higher risk of hospitalization (RR 0.96, p=0.71). Diabetes (RR 1.16; 95% CI: 1.00-1.36), and obstructive sleep apnea (RR 1.23; 95% CI: 1.01-1.49) were significantly associated to a higher risk hospital admission regardless of asthma status.
Choi et al.[41]	293	Cohort study with COVID-19	South Korea	Among all cases, reported comorbidities were: hypertension (9.9%), diabetes mellitus (7.2%), allergic disease (13.0%), chronic lung disease (5.8%), peripheral vascular disease (4.4%), cancer (2.4%), liver disease (1.7%), congestive heart failure (2.0%), cerebrovascular disease (1.7%), rheumatic disease 2 (0.7%), acute myocardial infarction (0.3%), kidney disease (0,3%). 12.3% cases were classified as the progression group and 87.7% as the improvement/stabilization group. Risk factors significantly associated to poorer outcomes were older age (49.5 vs. 27.0 years old, p < 0.001), hypertension (HR 3.56, p<0.001) and diabetes mellitus (HR 6.59, p<0.001)
Christensen et al.[42]	4,48	Retrospective cohort	Denmark	Comorbidities 10 years before COVID-19 data were used to calculate the Charlson Comorbidity Index Score (CCIS), which categorizes comorbidities and calculates a single comorbidity score for a patient (diagnosis considered are: myocardial infarction, heart failure, cerebrovascular disease, peripheral vascular disease, diabetes, dementia, hemi- or paraplegia, rheumatic disease, peptic ulcer, COPD, chronic renal disease, liver disease, cancer, metastatic cancer, HIV/AIDS). The distribution of cases by CCIS was 0: 65.0%, 1-2: 24.8%, 3-4: 6.4% and >4: 3.8%. On the entire sample, 17.8% had severe outcome and 9.3% died. The risk of severe forms significantly increased with CCIS>0: CCIS 1–2: OR 1.76 (95% CI 1.43-2.16), CCIS 3-4: OR 2.36 (95% CI 1.74-3.18) and CCIS > 4: OR, 2.67 (95% CI 1.87-3.81). The risk of death also significantly increased with CCIS>0: CCIS 1–2: OR (95% CI 1.57-2.9), CCIS 3-4: OR 3.00 (95% CI 2.06-4.38) and CCIS > 4: OR 3.85 (95% CI 2.51-5.90]
Cummings et al.[43]	257	Prospective observational cohort of critically ill patients.	USA	67% were men and 82% had at least one chronic illness: hypertension (63%), diabetes (36%) and obesity (46%). Older age (HR 1·31, CI 95%1·09–1·57), hypertension chronic (HR 1·58 CI 95% 0·89–2·81), cardiac disease (HR 1·76 CI 95% 1·08–2·86) and chronic pulmonary disease (COPD or interstitial lung disease) (HR 2·94 CI 95% 1·48–5·84) were significantly associated with in-hospital mortality.
Della Gatta et	51	Systematic	China	No cases in the first trimester, 2 in the

al.[44]		review of pregnant with COVID-19 reported cases		second trimester, 49 in the third trimester. One 30-year-old patient with no comorbidities and diagnosis of at 34 weeks develop server form of COVID-19 and intrauterine fetal demise has occurred. 48 neonates (1 set of twins) were in good condition at birth. One neonate was delivered by cesarean 34 weeks of gestational age and died 9 days after delivery and perinatal infection could not be excluded.
Docherty et al.[45]	20,133	Prospective cohort with minimal follow-up time of two weeks.	UK	77% had comorbidities: chronic cardiac disease (31%), uncomplicated diabetes (21%), non-asthmatic chronic pulmonary disease (18%) and chronic kidney disease (16%). Increasing age [50-59 years (HR 2.63, p<0.001); 60-69 years (HR 4.99, p<0.001); 70-79 years (HR 8.51, p<0.001); ≥80 years (HR 11.09, p<0.001)], male sex (female sex was significantly associated with lower mortality – HR 0.81, p<0.001), chronic cardiac disease (HR 1.16, p<0.001), chronic non-asthmatic pulmonary disease (HR 1.17, p<0.001), chronic kidney disease (HR 1.28, p<0.001), obesity (HR 1.33, p<0.001), stroke (HR 1.17, p=0.001), dementia (HR 1.40, p<0.001), cancer (HR 1.13, p=0.017), and liver disease (HR 1.51, p<0.001) were associated with higher mortality.
Du et al.[46]	179	Prospective cohort of patients with COVID-19 pneumonia.	China	Age > 65 years (OR 3,765), cardiovascular and cerebrovascular diseases (OR 2,464) were associated with higher mortality.
Ebekozien et al.[47]	64	Preliminary report of observational study among patients with type 1 diabetes and COVID-19 and COVID-19–like symptoms (with test pending or unavailable)	USA	The most common outcome for both groups was diabetic ketoacidosis (45.5% in the confirmed COVID-19 group and 13.3% the suspected or test pending group). Median HbA1c in the COVID-19–like group was 8.0% and in the in the COVID-19–positive was 8.5%. Over 50% of all cases had hyperglycemia, and nearly one-third of patients experienced DKA. Comorbidities among all cases were: obesity (39.4%), hypertension or cardiovascular disease (12.1%), asthma (7.9%), Hashimoto thyroiditis (4.8%) and hyperlipidemia (4.8%)
Fadini et al.[48]	Not available	Meta-analysis of studies reporting the prevalence of diabetes among people infected with the SARS-CoV-2 and its impact on disease severity or progression	Italy and China	A relatively lower prevalence of diabetes among COVID-19 cases has been observed in Italy and China, compared to general population. Pooled rate ratio of diabetes among patients with severe COVID-19 compared to those with the better outcome was 2.26 (95% CI 1.47–3.49) among six studies in China. Among 355 with who died of COVID-19 in Italy, the prevalence of diabetes was 35.5% and the rate ratio among patients who died of SARS-CoV-2 infection compared to the general

				population was 1.75
Fredi et al.[49]	143	Single-center observational study of patients with rheumatic diseases and confirmed or possible COVID-19 and case control study	Italy	72% of patients with confirmed COVID-19 developed pneumonia and were hospitalized. 10% of patients with confirmed or suspected COVID-19 (ten in those with confirmed COVID-19 and two in those with suspected COVID-19). Deceased patients with confirmed COVID-19 were older than survivors (median age 78.8 years vs 65.5, p=0·0002). No differences were found in sex, comorbidities, or therapies between the survivors and non-survivors. In the case control study no significant differences were found in duration of hospital stay, comorbidities prevalence and death rates.
Gao et al. [50]	150	Case control study (75 obese and 75 non-obese COVID-19 patients)	China	Obese cases had lower lymphocyte counts and higher levels of plasma C-reactive protein (early indicators of severe COVID-19), longer hospital stay (median 23 vs 18, p= 0.037) and greater proportion of severe clinical presentation (33.3% vs 14.7%, p=0.007). Obesity was significantly associated with a higher risk of severe COVID-19 (adjusted OR 3.00, 95% CI 1.22-7.38). There was a clear dose-response relationship between increasing values of BMI and percentage of cases with severe COVID-19: each 1-unit increase in BMI was also associated with a 12% increase in the risk of having severe forms of COVID-19.
García-Pachón et al.[51]	168	Descriptive study of adults with COVID-19 admitted to a hospital	Spain	Prevalence of asthma among COVID-19 cases: 2.4%, COPD prevalence: 7.1%. The prevalence of asthma and COPD was similar to the expected for general population in the country.
Grandbastien et al.[52]	106	Monocentric, retrospective, cohort study of cases admitted to one hospital	France	Among 106 patients with COVID-19, 23 had asthma. Asthma was not significantly associated to more involvement of lung parenchyma on CT scan (OR 0.90, p=0.786), to a higher risk of being admitted to an ICU (OR 1.065; p=0.92) and higher risk of exacerbation before and during hospital admission (generalized linear mixed-effect model, p=0,09)
Grasselli et al.[53]	1,591	Retrospective observational study of 1591 consecutive patients admitted to ICU.	Italy	82% (95% CI 79.98%-83.82%) were male, median age was 63 years, 86% of patients ha8d at least one comorbidity: 49% hypertension, 21% cardiovascular disease (cardiomyopathy and heart failure), 18% hypercholesterolemia, 17% diabetes type, 2, 8% cancer (active neoplasia and neoplasia in remission), 4% COPD, 3% chronic kidney disease, 3% chronic liver disease and 20% others (anemia, asthma, inflammatory bowel disease, epilepsy, chronic respiratory insufficiency, endocrine disorders, connective tissue diseases, neurologic disorders, chronic pancreatitis,

				immunocompromise and organ transplant).
Grasselli et al.[54]	3,988	Retrospective cohort of COVID-19 patients admitted to a hospital	Italy	Hospital mortality rate were 12/1000 patients-days and ICU mortality rate was 27/1000. Median age was 63 years old and 79.9% of patients were male. 60.5% at least one comorbidity: hypertension (42.1%), hypercholesterolemia (16.5%) heart disease (16.2%), type 2 diabetes (12.9%), cancer (8.3%), COPD (2.3%), chronic kidney disease (2.2%), liver disease and (2.2%). Older age (HR 1.75; 95%CI 1.60-1.92), male sex (HR 1.57; 95%CI 1.31-1.88), COPD (HR 1.68; 95%CI 1.28-2.19), hypercholesterolemia (HR 1.25; 95%CI 1.02-1.52) and type 2 diabetes (HR 1.18; 95%CI, 1.01-1.39) were independent factors significantly associated to higher mortality rates.
Guan et al.[55]	1,099	Descriptive and exploratory study of cases	China	Mean age was 48.9 years, 57.3% patients were male, 23.7% had at least one coexisting disorder, the most common were hypertension (15%), diabetes (7.4%), coronary heart disease (2.5%), hepatitis B infection (2.1%), cerebrovascular disease (1.4%), COPD (1.1%), cancer (0.9%), chronic renal disease (0.7%) and immunodeficiency (0.1%).
Guan et al.[56]	1,590	Retrospective case study	China	25.1% reported at least one comorbidity. Reported comorbidities were hypertension (16.9%), other cardiovascular diseases (3.7%), cerebrovascular diseases (1.9%), diabetes (8.2%), HBV infection (1.8%), COPD (1.5%), chronic kidney diseases (1.3%), cancer (1.1%) and immunodeficiency (0.2%). No patient reported asthma. At least one comorbidity was more frequent in severe cases than in non-severe cases (32.8% versus 10.3%). Severe clinical presentation was observed in 19.3% of patients with comorbidities vs 4.5% of those without. Among patients with at least one comorbidity the hazard ratio of severe forms was 1.79 (95% CI 1.16–2.77) and 2.59 (95% CI 1.61–4.17) among those with two or more comorbidities. The HR of each comorbidity was: COPD: 2.681 (95% CI 1.424–5.058), diabetes 1.586 (95% CI 1.028–2.449), hypertension 1.575 (95% CI 1.069–2.322), cancer 3.501 (95% CI 1.604–7.643).
Gupta et al.[57]	2,215	Multicenter cohort study of COVID-19 patients admitted to ICUs at 65 hospitals	USA	35.4% of patients died. Older age (80 vs <40 years OR 11.15, 95%CI, 6.19-20.06), male sex (OR 1.50, 95%CI 1.19-1.90), obesity (40 vs <25 OR 1.51, 95%CI 1.01-2.25), coronary artery disease (OR 1.47, 95%CI 1.07-2.02), cancer (OR 2.15, 95%CI 1.35-3.43), liver disease (OR 2.61, 95%CI 1.30–5.25) and CKD (OR 2.43, 95%CI 1.46–4.05) were significantly associated to a higher risk of death.

Haroun-Díaz et al.[58]	80	Case description (assessment of COVID-19 effects on severe asthma patients)	Spain	COVID-19 was confirmed on 3 patients (3.75%). None of the 3 cases developed ARDS and did not require ICU admission or oxygen therapy
Hoek et al.[59]	23	Descriptive study of COVID-19 cases in solid organ transplantation recipients	Netherlands	23 SOT recipients: 15 kidney, 4 heart, 3 lung, 1 kidney-after-heart and 1 liver. All patients had a baseline immunosuppressive treatment. 83% of patients were hospitalized, 2 among 23 were admitted to an ICU and 5 patients died of COVID-19. Mortality was higher among patients with higher Clinical Frailty Scale (CFS) scores (5.8 vs 1.92 for survivors).
Huang et al.[60]	6,452	Systematic review, meta-analysis, and meta-regression of diabetes and COVID-19 cases	China	Meta-analysis showed that diabetes was significantly associated with worst outcomes (RR 2.38 p<0.001), mortality (RR 2.12, p<0.001), severe disease (RR 2.45, p<0.001), ARDS (RR 4.64, p=0.001) and disease progression (RR 3.31, p=0.04). Meta-regression showed that association between diabetes and worst outcome was affected by age (p=0.003) and hypertension (p<0.001).
Ioannidis et al.[61]	226,017	Cross-sectional survey of countries with 800 or more deaths of COVID-19 as of April 24, 2020	13 USA states and 14 countries	Individuals <40 accounted for <1.3% of all COVID-19 deaths in European countries and Canada and 0.4–2.3% in the US states. However, in Mexico and India were a much larger proportion. Patients <65 accounted for 4.5–11.2% of COVID-19 deaths in Canada and European countries, 8.3–22.7% in US States, and were most deaths in India and Mexico. Individuals 80 years or older accounted for the majority of deaths in Europe (except Ireland) and Canada, in the US there was variability across states (39–63%). In Mexico, they accounted for 8.3% of deaths (no data on India). Patients <65 had 30- to 100-fold lower risk of COVID-19 death than those 65 or older in 11 European countries and Canada, 16- to 52-fold lower risk in US locations, and less than 10-fold in India and Mexico.
Kammar-García et al.[62]	13,842	Retrospective cohort	Mexico	38.8% of cases were hospitalized, among those admitted to a hospital 55.5% were admitted to an ICU and 11.4% were intubated. 45.3% had at least one comorbidity, 26% had 1 comorbidity, 12.9% had 2 comorbidities and 6.4% had 3 or more comorbidities. 95.6% of patients without comorbidities survived while 88.5% of those with 1 comorbidity, 81.8% of those with 2 comorbidities and 73.7% of those with 3 or more comorbidities survived. Survival was significantly decreased as the number of comorbidities increased (log-rank Mantel-Cox, p<00001). Survival analysis showed that comorbidity determines survival regardless of age. The risk of hospital admission (OR 3.1, 95% CI

				2.7-3.7), pneumonia (OR 3.02, 95% CI 2.6-3.5), ICU admission (OR 2, 95% CI 1.5-2.7) and death (HR 3.5, 95% CI 2.9-4.2) was significantly increased in cases with three or more comorbidities than in patients with 1, 2 or no comorbidities.
Kasraeian et al.[63]	87	Systematic review and meta-analysis of cases with COVID-19 pneumonia and pregnancy	China	78% of the pregnant women showed mild or moderate COVID-19. Clinical presentation of COVID-19 pneumonia was similar to the observed among other adult populations. 92% underwent cesarean section. No pregnancy loss was observed. No evidence of vertical transmission was found.
Khalil et al.[64]	2,567	Systematic review and meta-analysis of clinical features and pregnancy outcomes of COVID-19 in pregnancy	USA, China, Spain, Italy, France, Brazil and Netherlands	73.9% were in the third trimester. 21.8% had preterm birth (before 37 weeks), most of them indicated by a doctor (18.4%). ICU admission was necessary in 7.0% and intubation in 3.4%. Maternal mortality was low (0.9%). At least one comorbidity was reported in 32.5%: obesity 38.2%, smoker 3.3%, asthma 8.8%, hypertension 4.2%, cardiac disease 3.2%. Admission to ICU was significantly associated to comorbidities (beta=0.007, p<0.05), maternal age >35 (beta=0.007, p<0.01). Positive RT-PCR in neonates' nasal swab was observed in 1.4%.
Killerby et al.[65]	531	Retrospective study 220 hospitalized and 311 outpatient adults with COVID-19	USA	Age over 65 years (OR 3.4, 95% CI 1.6–7.4), black race (OR 3.2, 95% CI 1.8–5.8), diabetes mellitus (OR 3.1, 95% CI 1.7–5.9), male sex (OR 2.4, 95% CI 1.4–4.1), smoking (OR 2.3, 95% CI 1.2–4.5) and obesity (OR 1.9, 95% CI 1.1–3.3) were significantly associated with hospitalization.
Kumar et al.[66]	16,033	Meta-analysis with studies from three countries	China, USA, France	Calculated pooled prevalence of diabetes: 11.2% (95% CI: 9.5%e13.0%). Calculated pooled odds ratio of association of diabetes mellitus with severe forms was 2.16 (1.74-2.68; p < 0.01). Calculated pooled odds ratio of association of diabetes mellitus with death was 1.90 (1.37-2.64; p<0.01).
Lee et al.[67]	800	Prospective cohort study of patients with active cancer and symptomatic COVID-19	UK	28% patients died, with death principally attributable to COVID-19 in 93% of patients. The risk of death was significantly associated with older age (median 73 years vs 66 years; p<0.001) and with higher comorbidities including cardiovascular disease (21% vs 11%, p<0.001) and hypertension (41% vs 27%; p<0.001). Chemotherapy, immunotherapy, hormonal therapy, radiotherapy and targeted therapies were associated to a higher risk of death.
Li et al.[68]	548	Cohort study of severe cases.	China	Fatality rates estimated to be 1.1% in nonsevere cases and 32.5% in severe cases. Age over 65 years old (OR 2.2, 95% CI 1.5-3.5) and hypertension (OR 2.0, 95% CI 1.3-3.2) were significantly associated with severe clinical presentation and age 65

				years (HR 1.7, 95% CI 1.1-2.7) or more and hyperglycemia (HR 1.8, 95% CI 1.1-2.8) were associated to death in severe cases.
Liang et al.[69]	710	Retrospective cohort study throughout the country.	China	Age (OR 1.03, 95% CI 1.01-1.05), number of comorbidities (chronic obstructive pulmonary disease, diabetes, hypertension, coronary artery disease, cerebrovascular disease, hepatitis B, cancer, chronic renal disease, immunodeficiency disease, and pregnancy - OR 1.6 95% CI, 1.27-2.00) and cancer history (OR 4.07, 95% CI 1.23-13.43) were significant predictors of critical illness.
Liang et al.[70]	18	Prospective cohort of COVID-19 cases	China	1% of COVID-19 cases a had a medical history of cancer. 25% of cancer patients had done surgery or chemotherapy on the last month and 75% were cancer recovered in medical follow up. Patients with cancer had a more severe baseline CT findings, deteriorated significantly faster than those without cancer (median time to severe events 13 days vs 43 days, p<0.0001) and significantly higher risk or severe outcomes (39% vs 8%, p=0.0003). Lung cancer patients did not have a higher risk of severe events compared with patients with other cancers.
Mirzaei et al.[71]	252	Systematic review of COVID-19 and HIV co-infection	China, Italy, Spain, Turkey, Uganda, USA	80.9% were male, mean age was 52.7 years and 98% were on antiretroviral therapy. Reported co-morbidities: hypertension (39.3%), obesity or hyperlipidemia (19.3%), chronic obstructive pulmonary disease (18.0%), and diabetes (17.2%). 66.5% presented mild to moderate symptoms. Despite death among COVID19-HIV co-infected patients was high (14.3%) data suggest that mortality risk factors are related to older age and other comorbidities and not due to HIV.
Nie et al.[72]	671	Descriptive study	China	22.4% of cases had comorbidities: 10.4% had cardiovascular diseases (of whom 85.7% had hypertension), 1.8% had diabetes, 2.5% had respiratory diseases. Cardiovascular diseases (including hypertension), diabetes and respiratory diseases were not significantly associated to with higher COVID-19 severity. Older age was significantly associated to with higher COVID-19 severity (OR 1.026, p=0.003). 2 of 3 pregnant patients had severe disease.
Ortiz-Brizuela et al.[73]	309	Prospective cohort study with 140 inpatients and 169 outpatients	Mexico	Compared to outpatients, inpatients were older and had more diabetes (22.9% vs. 5.3%, p<0.001) and hypertension (32.1% vs. 9.5%, p<0.001). Admission to ICU was significantly associated with diabetes (41.4% vs. 18%, p=0.016)
Pachiega et al.[74]	276,703	Observational study	Brazil	83% of deaths cases were over 60 years old and 58.6% were male. Estimated prevalence of comorbidities in deaths was 83% (95% CI: 79 – 87). Comorbidities

				observed: chronic heart diseases (35%), diabetes (28.7%), asthma/COPD (8.2%), kidney diseases (5.9%), stroke (5.3%), hypertension (5.1%), obesity (4.4%) immunosuppressive diseases (3.8%), cancer (0.6%)
Palmieri et al.[75]	3,032	Descriptive study patients who died of COVID-19	Italy	368 death cases were < 65 years old and 2,644 were > 65 years old. 4.1% of cases had no comorbidities, 15% had 1, 21.4% had 2 and 59.6% had 3 or more. Reported prevalence of comorbidities: ischemic heart disease (28.2%), atrial fibrillation (22.5%), heart failure (16.2%), hypertension (68.3%), type 2 diabetes (30.1%), dementia (15.8%), COPD (16.4%), cancer (15.8%), chronic liver disease (4.0%), chronic renal failure (20.4%), dialysis (1.8%), HIV (0.2%), autoimmune diseases (3.8%), obesity (11%). Patients over 65 years had more comorbidities than those <65 years (3.3 ± 1.9 vs. 2.5 ± 1.8, p<0.001). 10.9% patients <65 years had no comorbidities compared to 3.2% patients ≥65 years.
Panepinto et al.[76]	178	Case series describing patients with sickle cell disease and COVID-19	USA	Median age of cases was 26 years old. 6% were asymptomatic, 54% had mild disease, 18% had moderate disease, 17% had severe disease and 5% had critical disease. 69% were hospitalized, 11% were admitted to an ICU and 7% died.
Patanavanich et al.[77]	11,590	Meta-analysis	China, Korea and USA	Smoking was significantly associated with an increased with COVID-19 progression (OR 1.91, p=0.001). Limitations in various articles suggest that the risk of smoking may be even higher.
Pereira et al.[78]	90	Retrospective study with solid organ transplantation patients and COVID-19	USA	76% of patients were hospitalized. 19% patients did not need oxygen therapy, 29% required nasal cannula, 12% non-rebreather mask, high flow nasal cannula or BIPAP and 35% were intubated and needed mechanical ventilation. 18% of all patients died.
Petrilli et al.[79]	5,279	Prospective cohort study	USA	51.9% cases were admitted to hospital. 62.9% of entire sample reported at least one chronic condition. Observed comorbidities: hypertension (42.7%), diabetes (22.6%), asthma/COPD (14.9%), chronic kidney disease (12.3%), cancer (7.6%), coronary artery disease (13.3%), heart failure (7%), hyperlipidemia (32.5%) and obesity (BMI 30-39: 29.4% and BMI>40: 5.9%). Risk factors significantly associated with hospital admission were: age > 75 (OR 37.9, p<0.001), age 65-74 (OR 8.7, p<0.001), heart failure (OR 4.4, p<0.001), male sex (OR 2.8, p<0.001), chronic kidney disease (OR 2.6, p<0.001), obesity (BMI 30-39 OR 1.8, p<0.001; BMI>40 OR 2.4, p<0.001), hypertension (OR 1.8, p<0.001) and diabetes (OR 2.2, p<0.001). Risk factors significantly associated with critical

				illness were: age (65-74 OR 1.7, p=0.004; >75 OR 2.3, p<0.001), male sex (OR 1.5, p<0.001), heart failure (OR 1.9, p<0.001), BMI over 40 (OR 1.5, P=0.03) and diabetes (OR 1.2, p=0.03)
Richardson et al.[80]	5,700	Descriptive analysis of cases admitted to hospitals in NY.	USA	Comorbidities were observed in 88% of hospitalized patients and the most common were hypertension, obesity and diabetes.
Rivera-Izquierdo et al.[81]	238	Retrospective case series of patients hospitalized for COVID-19	Spain	25.6% of patients died. No patients under 50 years old died. The risk factors significantly associated with a greater hazard of death were age (3% increase per 1-year increase in age) and diabetes mellitus (HR 2.42, 95%CI 1.43–4.09).
Robilotti et al.[82]	423	Cohort study of cancer patients with COVID-19	USA	40% of cases were admitted to hospital, 20% had severe respiratory illness and 9% needed mechanical ventilation. Case fatality was 12% on the entire sample, 24% for those admitted to a hospital and 35% for those admitted to an ICU. Age > 65 (OR 1.82, p=0.004), smoking (current/former) (OR 1.60 p=0.022), race non-white (OR 1.62, p=0.029), hematologic cancer (OR 2.49, p=0.003), cardiac disorder (OR 1.86, p=0.015), chronic kidney disease (OR 1.84, p=0.003), chronic lymphopenia or corticosteroids (OR 1.85, p=0.030), ICI (immune checkpoint inhibitors) therapy (OR 2.84, p=0.013) were associated to a higher risk of hospitalization and severe respiratory illness. Age > 65 (OR 1.67, p=0.024), smoking (current/former) (OR 1.78 p=0.007), cardiac disorder (OR 2.02, p=0.002), chronic kidney disease (OR 1.68, p=0.02) and ICI therapy (OR 2.38 p=0.005). Receiving chemotherapy on the last month, major surgery and metastatic cancer were not significantly associated to a higher risk of severe forms of COVID-19. Seven pediatric patients had mild presentation and no complication was observed.
Sardu et al.[83]	59	Cohort of COVID-19 pneumonia patients with normal glycemia a and hyperglycemia at baseline	Italy	D-dimer levels were significantly higher in patients with hyperglycemia than in those with normal glycemia (p<0.001). COVID-19 patients with diabetes and patients with hyperglycemia had a higher risk of severe form of disease than patients without diabetes and normoglycemia. Few patients with hyperglycemia with or without previous DM were free from severe disease compared with patients with normoglycemia without previous diabetes (p<0.02).
Shi et al.[84]	306	Case-control study 153 patients with COVID-19 patients and	China	Patients with diabetes had a higher prevalence of hypertension (56.9% vs 28.8%), cardiovascular disease (20.9% vs 11.1%), and cerebrovascular disease (7.8% vs 1.3%), all P< 0.05. Diabetes patients

		diabetes matched with 153 sex and age-matched COVID-19 controls admitted at two tertiary hospitals		were more likely to be admitted to ICU (17.6% vs 7.8%, p<0.05) and to have ARDS (24.8% vs 11.1%), acute cardiac injury (30.7% vs 17.0%), secondary infections (24.2% vs 11.1%), shock (20.9% vs. 10.5%), and acute kidney injury (12.4% vs 3.3%), all p<0.05. For all cases, hypertension, cardiovascular disease and chronic pulmonary disease were independently associated with in-hospital death. Diabetes (HR 1.58, 95% CI 0.84–2.99). After adjustment diabetes was not statistically significantly associated with in-hospital death. Among patients with diabetes, age over 70 years (HR 2.39, 95% CI 1.03–5.56) and hypertension (HR 3.10, 95% CI 1.14–8.44) were associated with in-hospital death.
Stokes et al.[85]	1,320,488	Descriptive (case surveillance)	USA	14% were hospitalized, 2% were admitted to an ICU and 5% died. Comorbidities reported: cardiovascular disease (32%), diabetes (30%) and chronic lung disease (18%), renal disease (7.6), immunocompromised (5.3%), neurologic/neurodevelopmental disability (4.8%). 45% of patients reporting at least one health condition were hospitalized vs 7.6% among those who did not report underlying conditions. 19.5% of cases with comorbidities died vs 1.6% of those without comorbidities.
Suleyman et al.[86]	463	Case series (retrospective review) of patients from a healthcare System	USA	94% patients had at least 1 comorbidity: 63.7% hypertension, 39.3% chronic kidney disease and 38.4% diabetes. Male sex (OR 2.0, p=0.001), severe obesity (OR, 2.0, p=0.02) and chronic kidney disease (OR, 2.0, p=0.006) were significantly associated with ICU admission and age >60 years (OR 3.5, p<0.001), severe obesity (OR 3.2, p<0.001), CKD (OR 2.4, p<0.001), and cancer (OR 2.5, p=0.01) were independently associated with the need for mechanical ventilation.
Sun et al.[87]	244	Retrospective case-control study among patients over 60 years old	China	58.5% in the discharged group and 32.2% in the deceased group were female. Comorbidities prevalence: 21% had diabetes and 14.4% had coronary heart disease. Older age (OR 1.122, p=0.037 was significantly associated with increased risk for death.
Vila-Córcoles et al.[88]	1,547	Population-based retrospective cohort with adults over 50 years-old	Spain	Among 349 positive cases, the most common reported comorbidities were: hypertension (58,7%), hypercholesterolemia (35%), heart disease (33%), diabetes (26,9%) and obesity (26,1%). A higher incidence of COVID-19 was observed among patients with neurologic disease, atrial fibrillation, chronic renal disease, heart disease, chronic respiratory disease, diabetes and cancer. An

				increased risk of acquiring COVID-19 was significantly associated with heart disease (HR: 1,47, p=0,045) and chronic respiratory disease (HR: 1,75, p=0,05)
Wang et al.[89]	138	Case series of COVID-19 pneumonia cases	China	46.4% patients had one or more chronic diseases: hypertension (31.2%), diabetes (10.1%), cardiovascular disease (14.5%), cancer (7.2%), cerebrovascular disease (5.1%), COPD (2.9%), chronic kidney disease (5.5%), chronic liver disease (2.9%), HIV infection (1.4%). Patients admitted to ICU care were significantly older (median age 66 vs 51; p<0.001) and had more underlying diseases: hypertension, diabetes, cardiovascular disease and cerebrovascular disease.
Wang et al.[90]	1,558	Meta-analysis	China	COVID-19 patients with hypertension (OR 2.29, p<0.001), diabetes (OR 2.47, p<0.001) or COPD (OR 5.97, p<0.001) had a higher risk of exacerbation. Cardiovascular disease (OR 2.93, p<0.001) and cerebrovascular disease e (OR 3.89, p=0.002) were significantly associated with severe COVID-19. Liver disease, cancer and kidney disease were not significantly associated with severe COVID-19.
Williamson et al.[91]	5,683	Cohort study from 2/1 to 4/25/2020 encompassing general population and deaths cases of COVID-19	UK	Death from COVID-19 was significantly associated with older age [60-70 (HR 2.09 95% CI 1.84-2.38), 70-80 (HR 4.77 95% CI 4.23-5.38), >80 (HR 12.64 95% CI 11.19-14.28)], male sex (HR 1.99, 95%CI 1.88-2.10), uncontrolled diabetes (HR 2.36, 5% CI 2.18-2.56), severe asthma (HR 1.25, CI 1.08-1.44), obesity [class I (HR 1.27 95% CI 1.18-1.36), class II (HR 1.56 95% CI 1.41-1.73), class III (HR 2.27 95% CI 1.99-2.58), liver disease (HR 1.61 95% CI 1.33-1.95), stroke/dementia (HR 1.79 95% CI 1.67-1.93), other neurological (HR 2.46 95% CI 2.19-2.76), kidney disease (HR 1.72 95% CI 1.62-1.83), organ transplant (HR 4.27 95% CI 3.20-5.70), spleen diseases (HR 1.41 95% CI 0.93-2.12), Rheumatoid/Lupus/ Psoriasis (HR 1.23 95% CI 1.12-1.35), other immunosuppressive condition (HR 1.69 95% CI 1.21-2.34). Ethnicity had a significant effect on the risk of death of COVID-19 for black people (HR 1.71, 95% CI 1.44-2.02) and Asian people (HR 1.62, 95% CI 1.43-1.82)
Wu et al.[92]	201	Retrospective cohort from 12/25/2019 to 1/26/2020	China	41.8% developed ARDS and of those, 52.4% died. Comorbidities prevalence: hypertension (19.4%), diabetes 22 (10.9%), cardiovascular disease 8 (4.0%), liver disease 7 (3.5%), nervous system disease 7 (3.5%), chronic lung disease 5 (2.5%), chronic kidney disease 2 (1.0%) and cancer (0.5%). Age ≥65 years significantly associated with higher risks of developing

				ARDS (HR 3.26, 95% CI 2.08-5.11) and death (HR 6.17, 95% CI, 3.26-11.67). Compared with patients with and without ARDS, ARDS cases had a higher proportion of hypertension (13.7%, p=0.02) and diabetes (13.9%, p=0.002).
Wu et al.[93]	926	Meta-analysis of diabetes and COVID-19 cases	China	A strong association between diabetes and mortality of COVID-19 patients was found: OR 1.75 (95% CI 1.31–2.36, p=0.0002).
Xu et al.[94]	703	Retrospective observational study of patients admitted to tertiary hospitals in China between 01/10/2020 and 3/13/2020.	China	Death and other adverse outcomes groups were older, more males and had more comorbidities, especially with > 2 comorbidities (cardiovascular disease, diabetes, hypertension, COPD, chronic liver disease, chronic kidney disease and malignancy).
Yamada et al.[95]	210	Retrospective cohort of patients with chronic kidney disease and COVID-19	USA	CKD patients had a higher risk of severe disease (RR 2.51, p<0.001) and death (RR 2.05, p<0.001) without adjusting age groups. A significant increased risk of mortality was found in CKD patients when stratifying by age groups among age from 60 to 79 (RR 1.80, 95% CI 1.15–2.83), but not in patients age 80 or older (RR 1.15 95% CI 0.71–1.86). Significant higher risk of death was found when CKD was associated to other comorbidities: atrial fibrillation (OR 2.13, 95% CI 1.03–4.43), heart failure (OR 2.09, 95% CI 1.16–3.77) and ischemic heart disease (OR 2.87, 95% CI 1.04–3.36)
Yang et al.[96]	710	Single-centered, retrospective, observational study, of adult patients with COVID-19 admitted to ICU	China	Compared with survivors, non-survivors were older (64.6 vs 51.9) and were more likely to have chronic medical illnesses (53% vs 20%. Comorbidities and risk factors among survivors and non-survivors were chronic cardiac disease (10%), chronic pulmonary disease (8%), cerebrovascular disease (13.5%), diabetes (17%), cancer (4%), dementia (2%), malnutrition (2%) and smoking (4%).
Zaigham & Andersson[97]	108	Systematic review all case reports and series of COVID-19 and pregnancy	China, Sweden, USA, Korea & Honduras	3 ICU admissions were reported but no maternal deaths. 1 neonatal death and one intrauterine death were also reported. Most mothers were discharged with no major complications, severe maternal morbidity and perinatal deaths were reported. Vertical transmission of the COVID-19 could not be ruled out
Zhang et al.[98]	869	Retrospective cohort, single-center study of COVID-19 cases	China	616 (70.9%) were discharged and 95 patients (10.9%) were transferred to due to worsening disease. Comorbidities reported: hypertension (10.5%), diabetes (2.4%) and COPD/asthma (1.6%). Cases with comorbidities had a significantly higher risk of condition worsening (HR, 2.733, p=0.001)
Zhao et al.[99]	2,002	Meta-analysis	China	Pooled OR of COPD for the development of severe COVID-19 was 4.38 (95% CI

				2.34-8.20). Pooled OR of COPD for death of COVID-19 was 1.93 (95% CI 59-7.43). OR of current smoking the development of severe COVID-19 was 1.98 (95% CI: 1.29-3.05).
Zheng et al.[100]	3,027	Meta-analysis	China	Male sex (OR 1.76, p<0.00001), age 65 or older (OR 6.06, p<0.00001) and smoking (OR 2.51, p=0.0006) were significantly associated with disease progression. Diabetes (OR 3.68, p<0.00001), hypertension (OR = 2.72, p=0.0002), cardiovascular disease (OR 5.19, p<0.00001), respiratory disease (OR 5.15, p<0.00001) were significantly associated with critical/mortal disease.
Zhou et al.[101]	171	Retrospective, multicenter cohort study of adult inpatients (from 12/29/2019 to 1/31/2020	China	48% patients had comorbidity: hypertension (30%), diabetes (19%) and coronary heart disease (8%). Older age (OR 1.14), coronary heart disease (OR 21.4, p<0·0001), hypertension (OR 3.05, p=0.0010), diabetes (OR 2.85, p=0·0062) were significantly associated with in-hospital death.
Zhu et al.[102]	7,337	28 days retrospective cohort of inpatient cases focusing on the association between plasma glucose levels and outcomes in COVID-19 patients with T2D	China	Prevalence of T2D was similar to the country prevalence. T2D was significantly correlated with ARDS. The in-hospital death rate was significantly higher in patients with T2D relative to the non-diabetic individuals (HR 1.70, p< 0.001). Compared to the poor controlled group, the well-controlled group had less frequent occurrences of ARDS, acute heart injury, acute kidney injury, septic shock and DIC. Death rate was significantly lower in the well-controlled group.

Table 2 – Overview of risk factors and conditions studied in the 73 articles reviewed

Author	Type of Study	Age	Sex	Race	CVD	HBP	DM	Obesity	Smoking	CRD	CKD	Cancer	HIV	Liver disease	Pregnancy	Organ Transplantation	neurologic Rheumatic disease	IBD	SCD	OSA	Association / Score
Aggarwal et al.[30]	Meta-analysis				X																
Akalin et al.[31]	Cohort															X					
Alberici et al.[32]	Cohort															X					
Assaad et al.[33]	Cohort											X									
Bello-Chavolla et al.[34]	Cohort	X	X				X	X		X	X										X
Bezzio et al.[35]	Cohort	X																X			X
Cai et al.[36]	Descriptive							X													
China CDC[37]	Descriptive	X			X		X			X											
Chen et al.[38]	Descriptive	X	X		X	X	X			X	X	X					X				
Chen et al.[39]	Descriptive														X						
Chhiba et al.[40]	Cohort						X			X										X	
Choi et al.[41]	Cohort	X				X	X														
Christensen et al.[42]	Cohort												X								X
Cummings et al.[43]	Cohort	X			X	X				X											
Della Gatta et al.[44]	Systematic review														X						
Docherty et al.[45]	Cohort	X			X			X		X	X	X		X			X				
Du et al.[46]	Cohort	X			X												X				
Ebekozien et al.[47]	Descriptive						X														
Fadini et al.[48]	Meta-analysis							X													
Fredi et al.[49]	Descriptive	X															X				
Gao et al. [50]	Case-control							X													
García-Pachón et al.[51]	Descriptive									X											
Grandbastien et al.[52]	Cohort									X											

Grasselli et al.[53]	Descriptive	X	X		X	X	X		X	X	X	X		X		X		X			
Grasselli et al.[54]	Cohort	X	X				X			X											
Guan et al.[55]	Descriptive	X	X		X	X	X			X	X	X									
Guan et al.[56]	Cohort					X	X			X		X									X
Gupta et al.[57]	Cohort	X	X		X			X			X	X		X							
Haroun-Díaz et al.[58]	Descriptive									X											
Hoek et al.[59]	Descriptive															X					
Huang et al.[60]	Meta-analysis	X				X	X														
Ioannidis et al.[61]	Cross-sectional	X																			
Kammar-García et al.[62]	Cohort																				X
Kasraeian et al.[63]	Meta-analysis														X						
Khalil et al.[64]	Systematic review														X						
Killerby et al.[65]	Cohort	X	X	X			X		X												
Kumar et al.[66]	Meta-analysis						X														
Lee et al.[67]	Cohort											X									
Li et al.[68]	Cohort	X				X	X														
Liang et al.[69]	Cohort	X			X	X	X			X		X			X						X
Liang et al.[70]	Cohort											X									
Mirzaei et al.[71]	Systematic review												X								
Nie et al.[72]	Descriptive	X																			
Ortiz-Brizuela et al.[73]	Cohort	X				X	X														
Pachiega et al.[74]	Descriptive	X	X		X	X	X	X		X	X	X					X				
Palmieri et al.[75]	Descriptive	X			X	X	X	X		X	X	X	X	X				X			
Panepinto et al.[76]	Descriptive																		X		
Patanavanich et al.[77]	Meta-analysis								X												
Pereira et al.[78]	Descriptive															X					
Petrilli et al.[79]	Cohort	X	X		X	X	X	X			X										

Richardson et al.[80]	Descriptive	X	X	X	X	X	X	X		X	X	X		X							
Rivera-Izquierdo et al.[81]	Cohort	X					X														
Robilotti et al.[82]	Cohort											X									
Sardu et al.[83]	Cohort						X														
Shi et al.[84]	Case-control	X				X	X														
Stokes et al.[85]	Descriptive	X	X	X	X		X			X	X						X				
Suleyman et al.[86]	Descriptive																				
Sun et al.[87]	Case-control	X																			
Vila-Córcoles et al.[88]	Cohort	X			X					X											
Wang et al.[89]	Descriptive	X											X								
Wang et al.[90]	Meta-analysis	X	X		X	X	X			X							X				
Williamson et al.[91]	Cohort	X	X	X			X	X		X	X	X		X		X	X	X			
Wu et al.[92]	Cohort	X				X	X														
Wu et al.[93]	Meta-analysis						X														
Xu et al.[94]	Descriptive	X	X		X	X	X			X	X	X		X							X
Yamada et al.[95]	Cohort										X										
Yang et al.[96]	Descriptive	X			X		X		X	X		X					X				
Zaigham & Andersson[97]	Systematic review														X						
Zhang et al.[98]	Cohort	X	X			X	X			X											
Zhao et al.[99]	Meta-analysis									X											
Zheng et al.[100]	Meta-analysis	X	X		X		X		X	X											
Zhou et al.[101]	Cohort	X			X	X	X														
Zhu et al.[102]	Cohort						X														

Table 3 – Summary of criteria and management guidelines for at risk workers published by country health authorities

Country	Agencies	Criteria	Management recommendation
USA	CDC[21] OSHA[104]	• Age >60 years old • Underlying medical conditions at an increased risk: ✓Cancer ✓Chronic kidney disease ✓COPD ✓Immunocompromised state from solid organ transplant ✓Obesity ✓Serious heart conditions (CHF, CAD and cardiomyopathies) ✓Sickle cell disease ✓Type 2 diabetes mellitus • Underlying medical conditions possibly at an increased risk ✓Asthma (moderate-to-severe) ✓Cerebrovascular disease (affects blood vessels and blood supply to the brain) ✓Cystic fibrosis ✓Hypertension or high blood pressure ✓Immunocompromised state (weakened immune system) from blood or bone marrow transplant, immune deficiencies, HIV, use of corticosteroids, or use of other immune weakening medicines ✓Neurologic conditions, such as dementia ✓Liver disease ✓Pregnancy ✓Pulmonary fibrosis (having damaged or scarred lung tissues) ✓Smoking ✓Thalassemia (a type of blood disorder) ✓Type 1 diabetes mellitus	• Employers should develop plans that consider and address the level(s) of risk associated with different worksites • General protective measures must be implemented (social distancing, use of masks and hand/respiratory hygiene)
Brazil	Ministry of Health[105] Secretary of Labor[106]	• Age > 60 years old • Severe or decompensated heart diseases (heart failures, CAD, arrhythmias and hypertension • Severe or decompensated lung diseases (COPD, asthma, oxygen-dependent) • Immunocompromised state • Advanced kidney disease (stages 3, 4 or 5) • Diabetes (according to physician opinion) • High-risk pregnancy	• High-risk workers must work from home if possible or measures to reduce exposure must be implemented • A list of high-risk employees must be available if requested by labor inspection • General protective measures must be implemented (social distancing, use of masks and hand/respiratory hygiene)
India	Ministry of Health and Family Welfare[107]	• Age > 60 years old • Diabetes • Hypertension • Cardiac disease • Chronic lung disease • Cerebrovascular disease • Chronic kidney disease • Immunosuppression • Cancer	• High-risk workers must adopt general protective measures (social distancing, use of masks and hand/respiratory hygiene) at workplaces
UK	National Health System[22] Health and Safety Executive[108]	• High risk (clinically extremely vulnerable) ✓Organ transplant ✓Chemotherapy or antibody treatment for cancer, including immunotherapy ✓Intense course of radiotherapy (radical radiotherapy) for lung cancer ✓Targeted cancer treatments that can affect the immune system (such as protein kinase inhibitors or PARP inhibitors) ✓Blood cancer (leukemia, lymphoma or myeloma) ✓Bone marrow or stem cell transplant in the past 6 months or taking immunosuppressant medicine ✓Severe lung condition (cystic fibrosis, severe asthma or severe COPD) ✓Severe combined immunodeficiency (SCID) or sickle cell disease ✓High doses of steroids or immunosuppressant medicine ✓Serious heart condition and are pregnant • Moderate risk (clinically vulnerable) ✓Age 70 or older ✓Not severe lung disease (asthma, COPD, emphysema or bronchitis)	• Clinically extremely vulnerable workers must not return to work before specific dates. • After specific dates, employees can return to work if workplace is COVID-secure. If possible, they should work from home.

		✓Heart disease (such as heart failure) ✓Diabetes ✓Chronic kidney disease ✓Liver disease (such as hepatitis) ✓Neurologic diseases (Parkinson's disease, motor neuron disease, multiple sclerosis or cerebral palsy) ✓Use of medicine that can affect the immune system (such as low doses of steroids) ✓Severe obesity (BMI 40 or above) ✓Pregnancy	
Spain	Ministry of Health[109] Ministry of Labor[110]	• Risk factors for COVID-19 complications ✓Older age ✓Heart diseases and hypertension ✓Diabetes ✓COPD ✓Cancer ✓Immunosuppression ✓Pregnancy ✓Obesity ✓Smoking ✓Other chronic diseases	• General protective measures must be implemented ET AL. workplaces (communication, social distancing, use of masks and hand/respiratory hygiene)
Italy	Ministry of Health[111] Ministry of Labor and Social Policies[112]	• Risk factors for death of COVID-19 ✓Older age ✓Hypertensive heart disease ✓Diabetes ✓Coronary heart diseases ✓Cancer ✓Organ transplant recipients	• High-risk worker, if certified by local health authority may take medical leave during COVID-19 pandemic according to country legislation
South Africa	National Department of Health[113]	• Risk factors for serious complications and severe illness from COVID-19 ✓60 years and older ✓One or more of the underlying commonly encountered chronic medical conditions (of any age) particularly if not well controlled: ▪ Chronic lung disease: moderate to severe asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, idiopathic pulmonary fibrosis, active TB and post-tuberculous lung disease (PTLD) ▪ Diabetes (poorly controlled) or with late complications ▪ Moderate/severe hypertension (poorly controlled) or with target organ damage ▪ Serious heart conditions: heart failure, coronary artery disease, cardiomyopathies, pulmonary hypertension; congenital heart disease ▪ Chronic kidney disease being treated with dialysis ▪ Chronic liver disease including cirrhosis ▪ Severe obesity (BMI of 40 or higher) ▪ Immunocompromised as a result of cancer treatment, bone marrow or organ transplantation, immune deficiencies, poorly controlled HIV or AIDS, prolonged use of corticosteroids and other immune weakening medications ▪ >28 weeks pregnant (and especially with any comorbidity)	• Employers should have a policy and procedures to address the needs of vulnerable employees. • These measures need to consider the work environment and activities and include: • Ensuring that potential exposure to the SARS-CoV-2 virus is eliminated or minimized • If potential exposure cannot be eliminated the employer should explore other ways of temporary workplace accommodation that prevent the risk of infection. • If the accommodation is not possible, consider work from home. • If the above steps are not possible, adopt leave procedures according to country legislation.

Table 4 – Occupational risk stratification.[104]

Risk level	OSHA designation	Description	Examples
4	Very high	Jobs with high risk of exposure to confirmed or suspected sources of Sars-Cov-2 during medical, laboratory or postmortem procedures	. Healthcare personnel carrying out procedures such as intubation, bronchoscopy, dental procedures and invasive sample collection on suspected or confirmed COVID-19 patients . Healthcare personnel collecting or handling specimens from confirmed or suspected COVID-19 patients . Morgue workers performing autopsies on the bodies of people with confirmed or suspected COVID-19
3	High	Jobs with high risk of exposure to known or suspected sources of COVID-19	. Healthcare staff (e.g., physicians, nurses, physiotherapists, nutritionists and others who must enter patients' rooms) providing care to confirmed or suspected COVID-19 patients (except when performing aerosol-generating procedures) . Medical transportation workers moving confirmed or suspected COVID-19 patients in enclosed vehicles. . Mortuary workers involved in preparing bodies of deceased people who are known to have suspected of confirmed COVID-19 at the time of their death.
2	Medium	Jobs with contact within 6 feet with people who may be infected with SARS-CoV-2, but who are not confirmed or suspected COVID-19 patients (general public)	. School workers, high-volume retail workers and other high-population-density work environments
1	Lower risk (caution)	Jobs that do not require contact with confirmed or suspected COVID-19 patients nor contact within 6 feet of general public	. All occupations with minimal contact with the public and other coworkers

Table 5 – Levels of community transmission

	1	2	3	4
WHO transmission status	No new cases	Sporadic cases	Clusters of cases	Community transmission
Level of Community Transmission (CDC)	No to minimal community transmission	Minimal to moderate community transmission	Substantial, controlled transmission	Substantial, uncontrolled transmission
Country status at endcoronavirus.org	Winning	Nearly there	Nearly there	Need action
Country or state % of positive tests at coronavirus.jhu.edu/testing	≤ 3%	3% - 6%	6% - 10%	> 10%
Daily new cases per 100,000 people (if available)	< 1	1<10	10 - 25	>25

Table 6 – Individual health risk matrix

Risk factors	**Severity levels (clinical criteria)**			
	1	**2**	**3**	**4**
Age	< 60	≥ 60 & < 65	≥ 65 & <70	≥ 70
Sex	Female	Male	No current evidence	No current evidence
Smoking	Non-smoker	No current evidence	Current smoker	Current smoker
Diabetes	No diabetes	Well managed with diet and oral hypoglycemics without target organ damage	Well managed with diet and insulin without target organ damage	Poorly managed (with hyperglycemia) and/or with target organ damage
BMI	BMI < 30	BMI ≥ 30 and < 35	BMI ≥ 35 & ≤ 39.9	BMI ≥ 40 or BMI > 35 & ≤ 39.9 with metabolic syndrome
Hypertension	Normal blood pressure, no treatment	Hypertension diagnosis, well controlled	Hypertension diagnosis, poorly controlled	Resistant hypertension not responsive to treatment with three antihypertensive drug classes and/or with target organ damage
COPD	No disease	Stage 1[157]	Stage 2[157]	Stages 3 and 4[157]
Asthma	No history or past asthma with no symptoms	Mild asthma[158,159]	Moderate asthma[158,159]	Severe asthma[158,159]
Other respiratory diseases	No disease	No current evidence	Interstitial lung disease with only mild to moderate physiological Impairment[160]	Severe interstitial lung disease[160] or cystic fibrosis
Cardiomyopathy/ Valvular heart disease	No disease or only predisposing etiologic factor	Mild condition without evidence of hemodynamic repercussion	Moderate condition without evidence of hemodynamic repercussion	Moderate condition with evidence of hemodynamic repercussion or Use of blood thinners or severe condition
Congestive Heart Failure	No disease	Classes I and II and well controlled[161]	Classes III and well controlled[161]	Class IV or classes II and III poorly controlled[161]
Coronary Artery Disease	No disease	Coronary event > 60 days without resulting limitation of	Coronary event > 60 days with slight limitation of physical activity well controlled with	Recent (<60 days) and/or with marked limitation or inability to carry on any physical

		physical activity[162]	treatment[162]	activity[162]
Renal disease	No disease	Stages 1[163]	Stages 2 or 3[163]	Stages 4 or 5; and/or dialysis[163]
Cancer	No disease	No current evidence	No current evidence	Hematologic cancers, locally advanced and metastatic solid tumors
Liver diseases	No disease	Mild condition	Moderate condition without evidence of liver failure	Severe conditions and/or liver failure (hepatic encephalopathy)
Pregnancy	Non-pregnant	Pregnant < 28 weeks	Pregnant >= 28 weeks or 30 days after delivery with no comorbidities	Pregnant ≥ 28 weeks or 30 days after delivery with comorbidities
Organ transplantation	No transplant	No transplant	No transplant	Organ transplantation recipients
HIV	No disease	HIV with normal CD4 cell count and using antiretroviral therapy	HIV with low CD4 cell count, severe disease and those not using antiretroviral therapy	HIV with low CD4 cell count, severe disease and those not using antiretroviral therapy
Neurological diseases (stroke and others)	No disease	Mild condition	Moderate condition	Severe condition
Inflammatory Bowel Disease	No disease	Clinical remission (asymptomatic)	Mild or moderate disease with few symptoms[164]	Severe disease[164]
Sickle-cell disease	No current evidence	No current evidence	No current evidence	Homozygous sickle cell disease

Table 7 – Workplace guidelines for workers

A **In the workplace with standard** **recommendations**	• Frequent hand hygiene (water & soap, alcohol gel available) • Use of cloth (fabric) masks • Respiratory hygiene • Cough and sneeze etiquette • Physical distancing (6 feet/ 3 meters at work, cafeteria, etc.)
B **In the workplace with specific** **recommendations**	• Standard recommendations plus: ✓ Surgical masks and face shield at work ✓ Clean and disinfect frequently touched surfaces ✓ Individual transportation ✓ Encourage optimal management of health condition(s) ✓ Follow-up with Occupational Health service (if available) ✓ Determine if vaccinations are up to date (e.g. influenza, pneumonia) ✓ Special precautions in case of contact with suspected or confirmed cases
C **In the workplace with work** **accommodation**	• Work from home or • Other work accommodation (such as work at specific location, go to the workplace a few days in the week, isolating the worker in a safer environment to perform work such as plexiglass or enclosure or other accommodations arranged in consultation with an occupational expert)
D **Out of workplace**	• Work from home or • Sick leave (disability benefit according to local regulation) or • Other leave