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Taking stock of the evidence:

COVID-19 and diabetes, hypertension, asthma, occupational lung diseases, coronary heart disease, heart failure and stroke

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SUMMARY

This evidence-based brief on COVID-19 and diabetes, hypertension, asthma, occupational lung diseases, coronary heart disease, heart failure and stroke was developed to inform the South African response, in the context of a country with multiple disease burdens, in particular, chronic infectious diseases and non-communicable diseases (NCDs) and an already overstretched health system.

A rapid review of international research, and experiences on risk, screening, management and support of people with these NCDs and COVID-19 was conducted. A comprehensive search strategy of multiple databases was used covering 1 October 2019 to 20 June 2020. We included 44 systematic reviews, 13 primary studies not included in the reviews and 26 ongoing studies. The systematic reviews and primary studies focused on risk of severe COVID-19, hospitalisation and death from COVID-19; impact of treatment and prognostic markers. None of the systematic reviews or primary studies assessed the risk of new COVID-19 cases and screening. None addressed occupational lung disease and few addressed asthma. A search was also done to identify relevant guidance documents.

Findings from systematic reviews and primary studies

- Hypertension, heart failure, diabetes, arrhythmia, and ischaemic heart disease were associated with the risk of hospitalisation.
- Hypertension was the most prevalent underlying disease in confirmed hospitalised COVID-19 cases.
- Pre-existing cardiovascular disease (CVD), hypertension, diabetes and cerebrovascular system diseases were associated with increased odds of severe COVID-19, ICU admission and death.
- Heart failure, arrhythmia and ischaemic heart disease were associated with risk of death.
- Asthma and other respiratory disease were associated with a higher risk of disease severity and death.
- Angiotensin-converting-enzyme inhibitors / Angiotensin receptor-blocking (ACEI/ARB) use was associated with lower mortality in patients with hypertension.
- Old age (≥ 60 years), males, CVD, hypertension, cerebrovascular disease and diabetes were independent prognostic factors for severe COVID-19 and death.
- Well-controlled diabetes in hospital was associated with lower risk of acute respiratory distress syndrome, acute heart injury, and acute kidney injury in patients with COVID-19.
- Uncontrolled diabetes was associated with higher mortality when corrected for age, sex, body mass index (BMI), smoking, index of multiple deprivation quintile, and comorbidities.
- Elevated cardiac troponin, C-reactive protein, Interleukin-6, D-dimer, Creatinine, Alanine transaminase, decreased lymphocyte count and reduced albumin were associated with increased mortality.
- None of the glucose lowering medications were associated with in-hospital death in multivariate analyses.

Limitations of systematic reviews and primary studies

- The studies included in the reviews were observational studies conducted in China with a few from Europe, Australia, Asia and USA, with probable overlap of participants across studies. The additional primary studies were largely from Europe and included large sample sizes but no primary studies were from Africa,
- The individual studies included in the reviews did not have unified approaches to data collection or outcome definitions for severity, and did not refer to prevalence of these NCDs in the population at large.
- About half of the included reviews and primary research studies had not been peer reviewed. They were pre-print.
- The overall ratings in the confidence of systematic review methods were generally low or critically low certainty using the AMSTAR 2 tool. Only a few reviews had a moderate certainty rating.
- For the primary observational studies, the inherent problem of confounding, selection and information biases, as well as random error due to small sample sizes, need to be taken into account when considering the findings.
- Ongoing studies cover a wider geographic area, include both clinical trials and systematic reviews on management strategies and will add to the evidence base.

Summary of guidance

- All included guidance documents were based on expert opinion or consensus. None were evidence-informed clinical practice guidelines.
- None of the guidance documents advocated screening or testing in people with these NCDs who do not have symptoms of COVID-19.
- The preventative measures to reduce risk for COVID-19 in people with these NCDs followed the guidance for the general population, but added specific elements such as working from home in certain groups, minimisation of face-to-face visits for routine care and the need for optimal NCD-related control.
- The provision of ongoing care highlighted the need to ensure patients with these NCDs have adequate supplies of medication, the use of virtual consultations and telemedicine to maintain contact, and awareness that they should contact the health services in the event of deterioration of their condition.
- Messages, in general, consisted of the need to live as healthily as possible, take medication as prescribed to ensure that the condition is well controlled, and to seek medical assistance if there was any deterioration in the condition, or if having symptoms that could indicate COVID-19.

Implications for policy and practice

SOUTH AFRICA
COVID-19 cases and co-morbidities

Sentinel hospital surveillance site data in all provinces (5 March – 21 June 2020) showed: 34% of hospitalised patients had one comorbid condition and 37% had two or more comorbid conditions. Hypertension and diabetes were the most common (in keeping with their prevalence in the country). Older age groups, male sex, admission in the public sector, comorbid hypertension, diabetes, chronic cardiac disease, chronic renal disease, malignancy, HIV and obesity were associated with in-hospital mortality in multivariate analysis. In addition, Western Cape Provincial routine public sector patient data on 3 456 253 adults with 12 522 confirmed COVID-19 cases and 435 COVID-19 deaths (1 March - 4 June 2020) confirmed that uncontrolled diabetes is associated with in hospital mortality.

Week 25 2020 COVID-19 sentinel hospital surveillance update
COVID-19 Special *Public Health Surveillance Bulletin, Vol 18, Suppl 2, 22 June*

The implications of the findings of this evidence brief need to be considered in the light of

- high rates of undiagnosed cases and poor levels of control for these NCDs, especially diabetes and hypertension in the country;
- the draft National NCD Strategic Plan for 2020-2025;
- the need for congruence with current guidelines for management of these NCDs, such as the Adult Primary Care Guideline (APC), APC-COVID and WHO guidance to deliver evidence based primary health care for people with NCDs; and
- the overarching National Department of Health plan to address the COVID-19 pandemic.

The implications and feasibility for implementation can be conceived of at the level of policy (meso), health system/practice (macro) and individual (micro) level.

PREVENTION

REDUCE THE RISK OF DEVELOPING COVID-19 Preventing COVID-19 infection is critical for people with NCDs and their families. Consideration could be given to risk stratification but should include all the usual preventative measures as well as maintaining a healthy lifestyle, limiting visits to health services and reducing the potential for exposure within health services.

SCREENING

SCREENING FOR COVID-19 IN PEOPLE WITH NCDs Testing/screening people with these NCDs for COVID-19 if asymptomatic is not indicated.

SCREENING FOR NCDs IN PEOPLE WITH CONFIRMED COVID-19 Screening hospitalised COVID-19 patients for diabetes and hypertension should be considered in order to improve their control with a view to reducing poor outcomes. How this screening should be undertaken needs operationalisation.

Consideration for screening non-hospitalised confirmed COVID-19 cases for diabetes and hypertension should be considered, as this has implications for their advice / support during self-isolation or need for observation and management.

TREATMENT

ONGOING CARE/HEALTH SYSTEMS Optimizing control of NCDs is key. Development of standard hospital NCD guidelines should be considered. The provision of health care requires reorganisation and includes the leveraging of ward based outreach teams where these exist, central dispensing units, team approach to improve delivery of person centred current guideline directed care and adherence to lifestyle related recommendations. For instance:

- informing patients of reason for limiting their access to routine care;
- providing adequate supplies of medication and other necessary equipment to reduce the frequency of clinic visits;
- providing guidance on when and how to access care for new or worsening symptoms or control;
- providing access to health promotion material, including adherence support;
- enabling virtual consultations, either by request from patient or vice versa; draw on the experiences of rural and remote health services;
- identifying those at heightened risk to give enhanced care to, e.g. to improve glycaemic control of people with poorly controlled diabetes or those self-isolating with an NCD and COVID-19;
- creating ways to monitor control that minimises risk for COVID-19;
- providing influenza and/or pneumococcal vaccinations if indicated;
- need for collection of data for tracking health care utilisation and quality improvement;
- continuing prescribed medication;
- continuing ACEI, which is not deleterious; and
- continuing steroids if needed for control of asthma.

MESSAGING

Patients need clear messaging to encourage healthy lifestyle even within the confines of home, adherence to COVID-19 prevention strategies, adherence to chronic medication as prescribed to ensure that the condition is well controlled, and self-care activities including monitoring and to seek medical assistance if there is any deterioration in the condition, or if having symptoms of COVID-19.

INTRODUCTION

The COVID-19 pandemic has had a massive impact globally. While it is a mild illness in the majority of people, countries and their health systems have struggled to respond to the challenges imposed by the pandemic. The intersection between non-communicable diseases (NCDs) and COVID-19 is one of the major global challenges. On the one hand, most health systems, including South Africa, have not responded fully to the needs of those living with or affected by NCDs, while on the other hand NCDs, in addition to age, have been identified as major risk factors for patients with poor outcomes when infected with COVID-19 (Kluge 2020, WHO 2020). The widespread introduction of measures to reduce the spread of COVID-19, such as social distancing, transport lockdowns, and closure of outpatient services, have resulted in disruption of routine NCD service delivery and maintenance of healthy lifestyle (Kluge 2020, WHO 2020, WHO NCDs 2020).

In South Africa the colliding epidemics of infectious diseases, such as HIV/AIDS and tuberculosis, and NCDs such as cardiovascular diseases (CVDs), diabetes, cancer, obesity, mental disorders and chronic respiratory conditions place an enormous burden on an already over stretched health system (Levitt 2011). This assessment of the evidence on COVID-19 and specific NCDs selected in collaboration with the National Department of Health (namely diabetes, hypertension, asthma, occupational lung diseases, coronary heart disease, heart failure and stroke) has been produced to inform the national response.

Key areas investigated by the brief

- Risk of COVID-19 in patients with these NCDs
- Increased risk of severe COVID-19, hospitalisation and death from COVID-19 in patients with these NCDs
- Screening for COVID-19 in patients with these NCDs
- Screening for NCDs in those diagnosed with COVID-19
- Management (including treatment) of COVID-19 in patients with these NCDs
- Prognostic markers in patients with these NCDs infected with COVID-19

METHODS

We conducted a rapid review of international research and experiences on COVID-19 and diabetes, hypertension, asthma, occupational lung diseases, coronary heart disease, heart failure and stroke. We also reviewed risk, screening, management and support of people with above mentioned NCDs and COVID-19. We included systematic reviews, primary studies and guidance documents (and expert opinions), written in English, on COVID-19 and the following pre-existing NCDs: diabetes, hypertension, asthma, occupational lung diseases, coronary heart disease, heart failure and stroke.

Using a comprehensive search strategy (see Appendix 1) combining terms for 'COVID-19' and 'diabetes or hypertension or asthma or occupational lung diseases or coronary heart disease or heart failure or stroke' we searched various databases from 1 October 2019 to 20 June 2020. Specifically, we searched the Cochrane COVID-19 Registry of Studies, Epistemonikos, Medline (PubMed) and Tripdatabase. We also checked evidence maps by EPPI Centre and Norwegian Institute for Public Health, as well as summaries of reviews published by Evidence Aid. The full search output was imported into Covidence software (Veritas Health Innovation 2020). Two researchers independently reviewed the search output and selected relevant studies for inclusion. Disagreements were resolved through discussion and reaching consensus. Researchers extracted data from included reviews and studies, assessed the quality of these, collated and organised the data according to the key areas listed above.

Results of the search

After the removal of 704 duplicates (i.e. records among the search output that appeared more than once), researchers independently screened 3 877 records and shortlisted 385 for full text eligibility assessment. Of these, we included 44 systematic reviews (Tables 1 to 3), 13 primary studies not included in the reviews (Table 4), guidance documents and 26 ongoing studies (Table 5).

FINDINGS FROM SYSTEMATIC REVIEWS AND PRIMARY RESEARCH STUDIES

The systematic reviews and primary research studies, not included in the reviews, focused on the following in patients with these NCDs: increased risk of severe COVID-19; hospitalisation and death from COVID-19; treatment impact and prognostic markers of good or poor outcome of COVID-19. None of the systematic reviews or primary studies assessed the risk of new COVID-19 cases or screening, and none addressed occupational lung disease. The studies included in the reviews were observational studies conducted in China (mainly) with a few studies from Europe, Asia, Australia and USA. None were conducted in Africa. Primary studies and ongoing studies covered a wider geographic area. Amongst the ongoing studies are both clinical trials and systematic reviews on management strategies.

The AMSTAR 2 (Shea et al 2017) overall ratings in the confidence of systematic review methods were generally at low or critically low certainty with only a few achieving a moderate certainty rating. Most reviews had one or more 'critical' weaknesses. For example, the protocols were not registered before starting the review, no list of excluding studies with reasons, risk of bias assessment of individual studies not done, not considering risk of bias when interpreting the results of the review, and not assessing for the presence and likely impact of publication bias. Where reviews covered similar topics, we focused on those with a higher AMSTAR 2 rating. For the primary observational studies, the inherent problem of confounding, selection and information biases, as well as random error due to small sample sizes, need to be taken into account when considering the findings.

In the section below, we integrate findings from the included reviews and primary studies. We report the relevant outcomes and 95% confidence intervals (CI). As systematic reviews provide the totality of the evidence we focus on reviews with better AMSTAR 2 certainty ratings first before primary studies not included in reviews. For meta-analysis, we report the number of studies which contributed and the I2 statistic, which describes the percentage variation across studies that is due to heterogeneity rather than chance.

Risk of hospitalisation in people with NCDs who have COVID-19

Only 2 primary studies conducted in Italy and the USA examined the risk of hospitalisation in people with NCDs who have COVID-19. In the cohort study (n=2 653) conducted by Rossi et al in Italy the risk of hospitalisation, after adjusting for age and sex, was higher in patients with heart failure (HR 1.6, 95% CI 1.2 to 2.1), arrhythmia (HR 1.5, 95% CI 1.2 to 1.9), ischemic heart disease (HR 1.3, 95% CI 1.0 to 1.7), diabetes (HR 1.5, 95% CI 1.3 to 1.9) and hypertension (HR 1.4, 95% CI 1.2 to 1.6). Age-specific risks of hospitalisation was higher in males than in females. The risk of hospitalisation was also increased in people with diabetes in a small retrospective study in the USA (n=49) (Shabto 2020).

Prevalence of NCDs in hospitalised patients with COVID-19

Nine reviews of which four pre-print and five peer reviewed and published (Table 1), included observational studies conducted in China with a few in Europe, Asia and USA.

Hypertension was the most prevalent underlying disease in confirmed hospitalised COVID-19 cases (Emami et al). Six other reviews (Li et al, Nasiri et al, Tan et al, Wang B et al, Wang X et al and Yang et al) reported similar findings. The prevalence of asthma among patients diagnosed and hospitalised with COVID-19 was 3% (95%CI 0 to 14%) (Ghaythan et al.). None of the reviews reported on heart failure and stroke.

Amongst children under 18 years of age in the USA, Jose et al (pre-print review) reported that out of 345 children with COVID-19, 80 had at least one underlying condition. The most common underlying disease was “chronic lung diseases (including asthma)” in 40 children.

TABLE 1 *Prevalence of NCDs in confirmed hospitalised COVID-19 cases*

NCD	Occurrence (95%CI)	Number of studies	I^2	Review	AMSTAR 2 rating of review
Hypertension	16% (95%CI 10% to 24%)	7	84%	Emami et al	Moderate confidence
Cardiovascular disease	12% (95%CI 4% to 23%)	8	96%	Emami et al	Moderate confidence
Asthma	3% (95%CI 0 to 14%)	8	79%	Ghaythan et al.	Low confidence
Diabetes	8% (95%CI 7% to 9%)	6	0%	Emami et al	Moderate confidence
Respiratory system disease	1.5% (95%CI 1% to 2%)	6	0%	Yang et al	Low confidence

Increased risk of severe COVID-19 and death in patients with these NCDs

Thirty reviews of which 15 pre-print and 15 peer reviewed published (Table 2), included observational studies conducted in China with a few studies from Australia, Italy, France, Singapore, South Korea, Spain, UK and USA. In addition, 11 observational studies were included (Table 4): 3 retrospective cohorts (Chen 2020, Luo 2020, Zhu 2020) and a case series (Deng 2020) from China; 3 retrospective studies (Fadini 2020, Marfella 2020, Sardu 2020) and 1 prospective cohort (Rossi 2020) from Italy; 2 cohort studies from UK (Barron 2020; Williamson 2020) and 1 retrospective study from the USA (Shabto 2020).

Hypertension

Hypertension was associated with increased risk of severe COVID-19, ICU admission, poor outcome (including mortality, severe COVID-19, acute respiratory distress syndrome, need for ICU care and disease progression) and death in 17 systematic reviews (Chayakrit et al, Chen et al, Islam et al, Jain et al, Khan et al, Li et al, Lippi et al, Matsushita et al, Pranata et al, Parohan et al, Rahman et al, Shamshirian et al, Ssentongo et al, Wang et al, Xu et al, Zheng et al and Zuin et al).

The following table illustrates results of the most comprehensive meta-analysis, while considering AMSTAR 2 confidence ratings, for severe COVID-19, ICU admission, death and the composite poor outcome.

***TABLE 2** Hypertension and COVID-19 – disease severity and death*

Outcome	Measure of association (95%CI)	Number of studies	I^2	Review	AMSTAR 2 rating of review
Severe COVID-19	RR 2.04 95%CI 1.69 to 2.47	12	31%	Pranata et al	Moderate confidence
ICU admission	RR 2.11 95%CI 1.34 to 3.33	3	18%	Pranata et al	Moderate confidence
Death	OR 3.16 95% CI 2.51 to 3.97	19	44%	Islam et al	Moderate confidence
Composite poor outcome	RR 2.11 95%CI 1.85 to 2.40	30	44%	Pranata et al	Moderate confidence

Similarly, additional primary studies that focused on hypertension, reported that the risk of death increased in people with hypertension (Rossi 2020; Deng 2020).

Use of renin-angiotensin-aldosterone system (RAAS) inhibitors

Three reviews, one published (Guo et al, 9 studies) and two pre-print (Garg et al, 9 studies, and Ssentongo et al, 11 studies) assessed use of RAAS inhibitors. There was overlap in included observational studies (See Appendix 2). In all three reviews, based on results from observational studies, ACEI/ARB use was associated with lower mortality in patients with hypertension. Guo et al reported that ACEI/ARB treatment was not associated with disease severity (OR 0.71, 95 % CI 0.46–1.08, I^2 59%) compared to non-ACE/ARB treatment. Ssentongo et al reported that those with hypertension taking RAAS inhibitors were less likely to die from COVID-19 compared to those with hypertension not taking RAAS inhibitors (pooled relative risk (RR) = 0.65, 95% CI 0.45 to 0.94; 7 observational studies, I^2 80%).

Cardiovascular disease

Existing cardiovascular disease was associated with an increased risk of severe COVID-19, ICU admission and death in 11 systematic reviews (Aggarwal et al, Chayakrit et al., Islam et al, Jain et al, Khan et al, Li et al, Matsushita et al, Parohan et al, Ssentongo et al, Wang et al and Xu et al). Coronary heart disease (OR 4.19, 95%CI 1.27 to 13.80; 3 studies) (Shamshirian et al) was associated with ICU admission in COVID-19 patients. The odds of mortality was higher for COVID-19 patients with pre-existing heart failure (OR 3.98, 95% CI 2.96 to 5.35) (Khan et al).

Cardiovascular disease was also associated with increased poor composite outcome (mortality and severe COVID-19) (RR 2.23, 95% CI1.71 to 2.91, I2: 60%, 12 studies) (Pranata et al). Meta-regression, to examine the impact of moderator variables on study effect size, indicated that the association between CVD and the composite poor outcome was not influenced by gender (p=0.722), age (p=0.910), hypertension (p=0.218), cerebrovascular diseases (p=0.502), diabetes (p=0.062), and respiratory comorbidities (p=0.703).

The following table illustrates the findings of the most comprehensive meta-analysis, while considering AMSTAR 2 confidence ratings, for severe COVID-19, ICU admission and death.

***TABLE 3** Cardiovascular disease and COVID-19 – disease severity and death*

Outcome	Measure of association (95%CI)	Number of studies	I^2	Review	AMSTAR 2 rating of review
Severe COVID-19	OR 2.70 95% CI 1.52 to 4.80	3	Not reported	Jain et al	Low confidence
ICU admission	OR 4.44 95% CI 2.64 to 7.47	3	Not reported	Jain et al	Low confidence
Death	OR 3.32 95% CI 2.79 to 3.95	33	84%	Khan et al	Moderate confidence

In the primary studies, not included in the above-mentioned reviews, cardiovascular disease was also a risk factor for mortality (Deng, 2020; Williamson, 2020). Risk of death was also higher in patients with heart failure (HR 2.3, 95%CI 1.6 to 3.2), arrhythmia (HR 1.8, 95%CI 1.3 to 2.5) and ischemic heart disease (HR 1.7, 95%CI 1.2 to 2.5) (Rossi, 2020).

Diabetes

Diabetes was associated with severe COVID-19 and with increased mortality from COVID-19 in 11 reviews (Chayakrit et al, Huang et al, Islam et al, Kumar et al, Matsushita et al, Palaiodimos et al, Parohan et al, Rahman et al, Roncon et al, Xu et al and Zheng et al). Diabetes was also associated with composite poor outcome (comprised of mortality, severe COVID-19, acute respiratory distress syndrome (ARDS), need for ICU care and disease progression) (Huang et al). Meta-regression, to examine the impact of moderator variables on study effect size, showed that the association between diabetes and the composite poor outcome was affected by age and hypertension, but not gender, cardiovascular diseases and COPD.

The following table illustrates the most comprehensive meta-analysis, while considering AMSTAR 2 confidence ratings, for severe COVID-19, death and the composite poor outcome.

***TABLE 4** Diabetes and COVID-19 – disease severity and death*

Outcome	Measure of association (95%CI)	Number of studies	I^2	Review	AMSTAR 2 rating of review
Severe COVID-19	OR 3.02 95% CI 2.07 to 4.42	13	40%	Chayakrit et al	Low confidence
Death	OR 2.45 95% CI 1.82 to 3.30	21	49%	Islam et al	Moderate confidence
Composite poor outcome	RR 2.38 95%CI 1.88 to 3.03	30	62%	Huang et al	Critically low confidence

In line with findings from systematic reviews, primary studies also found that patients with diabetes had an increased risk of severe disease (Sardu 2020; Deng 2020) and mortality (Barron 2020; Zhu 2020, Chen 2020; Deng 2020; Williamson 2020) with the largest cohort study, from the UK, reporting that people with Type 1 and Type 2 diabetes had 3.50 (95%CI 3.15 to 3.89) and 2.03 (95%CI 1.97 to 2.09) times the odds respectively of dying in hospital with COVID-19 compared to those without diabetes adjusted for multiple factors (for age, sex, deprivation, ethnicity and geographical region), attenuated to 2·86 and 1·81 respectively when further adjusted for previous hospital admissions with coronary heart disease, cerebro-vascular disease or heart failure (Holman 2020).

A number of factors have been reported to be associated with mortality in people with diabetes and COVID-19; older age (adjusted odds ratio [aOR] 1.09 [95%CI 1.04 to 1.15] per year increase) and elevated C-reactive protein (aOR 1.12, 95%CI 1.00 to 1.24) (Chen 2020). In addition to age, Cariou et al (2020) found treated obstructive sleep apnoea (OR 2.80 [1.46, 5.38]), and microvascular (OR 2.14, 95% CI 1.16 to 3.94) and macrovascular complications (OR 2.54. 95% CI 1.44 to 4.50) were independently associated with the risk of death. Furthermore, Holman found the relationship between BMI and COVID-19 mortality was U-shaped: the HRs for BMI >40 kg/m^2 compared to 25-29.9 kg/m^2 were 2.15 (95% 1.37 to 3.36) and 1.46 (95% CI 1.50 to 1.79) for Type 1 and Type 2 diabetes respectively and for Type 1 diabetes and a BMI of 20 kg/m^2, compared to people with a BMI of 25 to 29·9 kg/m^2 the HR was 2.11 (95% CI 1.32 to 3.38) and for Type 2 diabetes the HR was 2.26 (95% CI 2.04 to 2.50).

A relationship between mortality and glycaemic control was found in three large cohort studies (Holman 2020, Williamson 2020, Zhu 2020). In the NHS-UK Open safety study, while controlled diabetes (HbA1c < 7.5% was associated with higher mortality HR 2.02 (1.89-2.16) when corrected for age and sex HR 1.50 (1.40-1.60) after adjustment for BMI, smoking, index of multiple deprivation quintile, and comorbidities, the HR was greater in uncontrolled diabetes (diabetes type unspecified) (HbA1c ≥ 7.5%) HR 3.61 (95%CI 3.34 to 3.90) and HR 2.36 (95%CI 2.18 to 2.56) after the same adjustments (Williamson 2020). Similarly, an increased risk for mortality with poor glycaemic control was found for both Type 1 and 2 diabetes in another UK cohort study (Holman 2020). Zhu et al (2020) found that well controlled diabetes (blood glucose from 3.9 to 10.0mmol/L) in hospital was associated with a lower mortality than poorly controlled DM (blood glucose> 10 mmol/l) (propensity score matching for other comorbidities that include hypertension, cardiovascular disease, cerebro-vascular disease and chronic kidney disease) adjusted HR 0.14 (95%CI 0.03 to 0.60). Smaller studies reported similar findings.

None of the glucose lowering medications (metformin, insulin, a-glycosidase, secretagogues, or dipeptidyl-peptidase-4 inhibitors (DPP-4i)) were associated with in-hospital death in multivariate analysis (Chen 2020, Fadini 2020), yet one small retrospective study in China (n=283) (Luo 2020) found that in-hospital mortality was lower in the metformin group (3/104 (2.9%) versus 22/179 (12.3%), P = 0.01). Marfella 2020 (n=78) found a negative association with hyperglycaemia and tocilizumab therapy in COVID-19 patients.

Cerebrovascular diseases

Khan et al found higher mortality among COVID-19 patients who had pre-existing cerebrovascular system diseases than their counterparts, and Pranata et al found that cerebrovascular disease, including stroke, was associated with increased poor composite outcome (mortality and severe COVID-19). The following table illustrates the most comprehensive meta-analysis, while considering AMSTAR 2 confidence ratings, for severe COVID-19 and death.

***TABLE 5** Cerebrovascular disease and COVID-19 – disease severity and death*

Outcome	Measure of association (95%CI)	Number of studies	I^2	Review	AMSTAR 2 rating of review
Severe COVID-19 and mortality	RR 2.04 95% CI 1.43 to 2.91	12	77%	Pranata et al	Moderate confidence
Death	OR 4.12 95% CI 3.04 to 5.58	15	26%	Khan et al	Moderate confidence

Similarly, an additional large cohort study from the UK by Williamson 2020 found that stroke/dementia was associated with higher risk of COVID-19 hospital death.

Respiratory disease

Respiratory disease was associated with severe COVID-19 and increased odds of death in three reviews (Islam et al, Khan et al, Zheng et al). Khan et al included chronic lung diseases, chronic obstructive pulmonary disease (COPD), ARDS, and tuberculosis as part of respiratory disease. Neither Islam et al nor Zheng et al specified the conditions that constituted respiratory disease. The following table illustrates the most comprehensive meta-analysis, while considering AMSTAR 2 confidence ratings, for severe COVID-19, ICU admission, death and the composite poor outcome.

***TABLE 6** Respiratory disease and COVID-19 – disease severity and death*

Outcome	Measure of association (95%CI)	Number of studies	I^2	Review	AMSTAR 2 rating of review
Severe COVID-19	OR 5.15 95% CI 2.51 to 10.57	7	50%	Zheng et al	Critically low confidence
Death	OR 2.02 95% CI 1.80 to 2.26	28	71%	Khan et al	Moderate confidence

In the additional primary studies, asthma and other respiratory disease were associated with a higher risk for mortality in a large cohort study in the UK (Williamson 2020) with a HR 1.11 (95%CI 1.02 to 1.20) after all adjustments in those without recent oral steroid use and HR 1.25 (95%CI 1.08 to 1.44) in those with recent steroid use. Similarly, respiratory disease was also a risk factor for mortality in China (Deng 2020, large case series; not specifying the conditions constituting respiratory disease).

Prognostic markers in patients with these NCDs and COVID-19

Four reviews of which 3 pre-print and 1 peer reviewed published (Table 3), included observational studies conducted in China with a few studies from Australia, France, Hong Kong, Korea, Italy, Singapore and the USA. Beyond reviews we included, three observational studies, from France (Cariou 2020), Italy (Rossi 2020) and China (Chen 2020).

Kahathuduwa et al found that hypertension, fever and dyspnoea at presentation, and elevated C-reactive protein, predicted increased disease severity while increasing age and elevated lactate dehydrogenase predicted severity and case fatality. Bellou et al found that decreased lymphocyte count (OR 4.16, 95% CI 3.17 to 5.45) was associated with risk of severe COVID-19. Tian et al reported that those who died, compared to those who survived, differed on multiple biomarker levels on admission (see box).

Risk factors for poor prognosis (progression to severe or critical illness and in-hospital death) in patients with diabetes and COVID-19 were low albumin (aOR 0.91 [95% CI 0.83, 0.99]) and high C-reactive protein (aOR 1.16 [95% CI 1.01, 1.32]) (Chen 2020). Cariou 2020 (n=1 317) assessed a combined outcome of tracheal intubation for mechanical ventilation and/or death within 7 days of admission. In multivariable analyses with covariates prior to admission, BMI was associated with the combined outcome (OR 1.28 [1.10 to 1.47]). In multivariable analyses with covariates on admission, dyspnoea (OR 2.10 [1.31 to 3.35]), lymphocyte count (OR 0.67 [0.50 to 0.88]), C-reactive protein (OR 1.93 [1.43 to 2.59]) and AST (OR 2.23 [1.70 to 2.93]) levels were independent predictors of the same combined outcome. Age (OR 2.48 [1.74 to 3.53]), treated obstructive sleep apnoea (OR 2.80 [1.46 to 5.38]), and microvascular (OR 2.14 [1.16 to 3.94]) and macrovascular complications (OR 2.54 [1.44 to 4.50]) were independently associated with risk of death on day 7 (Cariou 2020).

Elevated levels of

- Cardiac troponin (+44.2 ng/L, 95% CI 19.0 to 69.4)
- C-reactive protein (+66.3 µg/mL, 95%CI 46.7 to 85.9)
- Interleukin-6 (+4.6 ng/mL, 95% CI 3.6 to 5.6)
- D-dimer (+4.6 µg/mL, 95% CI 2.8 to 6.4)
- Creatinine (+15.3 µmol/L, 95% CI 6.2 to 24.3)
- Alanine transaminase (+5.7 U/L, 95% CI 2.6 to 8.8)

Decreased levels of

- Albumin (-3.7 g/L, 95% CI -5.3 to -2.1)

GUIDANCE FOR SPECIFIC CONDITIONS

All included guidance documents were based on expert opinion or consensus. None were formal evidence-informed clinical practice guidelines.

None of the guidance documents advocated screening or testing in people with these NCDs without symptoms of COVID-19. The preventative measures to reduce risk for COVID-19 in these groups followed the guidance for the general population, but added specific elements such as working from home in certain groups, minimisation of visits for routine care, and the need for optimal NCD control. The provision of ongoing care highlighted the need to ensure patients have adequate supplies of medication, the use of virtual consultations and telemedicine to maintain contact, and awareness that they should contact the health services in the event of deterioration of their condition. Messages in general consisted of the need to live as healthily as possible, take medication as prescribed to ensure that the condition is well controlled, and to seek medical assistance if there was any deterioration in the condition, or if symptoms of COVID-19.

A summary of the guidance is provided below. Firstly, general guidance on risk reduction to reduce risk of becoming infected with COVID-19 followed by screening or testing for COVID-19 and general guidance for organisation of ongoing care. Secondly, we summarised disease specific guidance and general messages to the community for diabetes, asthma, CVD (including heart failure and hypertension). No specific guidance was found for people with known cerebrovascular disease.

Risk reduction

- Risk of infection increases with the presence of comorbidities and older age.
- Use of general preventative measures: social distancing, physical distancing, hand hygiene, respiratory etiquette, avoid touching of mouth, nose and eyes and use recommended face masks.
- Adapt health promotion activities (e.g. tobacco control and cessation, reduce harmful use of alcohol, physical activity, healthy diet and stress management).
- Vaccinations for influenza and/or pneumococcal if indicated.

Screening or testing for COVID-19

- From available information, individuals with hypertension, diabetes, CVD and asthma without symptoms suggestive of COVID-19 infection need not be tested.
- Screening is indicated where there are symptoms suggestive of COVID-19 infection, noting that the distinction between COVID-19 respiratory symptoms and an exacerbation of asthma from other causes can be challenging.

Organisation of ongoing care

- Ensure adequate medication supply: at least 2 or 3 months' medication based on stock availability.
- Rearrange routine visits.
- Use phone calls / WhatsApp as way for patients to keep in touch with their healthcare team.
- Continue self-monitoring at home, if possible.
- Minimise face-to-face contact by:
  - offering telephone, virtual consultations whenever possible;
  - contacting patients by text message or email;
  - encourage patients to avoid health facilities where possible –advise patient on symptoms requiring urgent care.
- If visiting the clinic, minimise time in the waiting area by:
  - cutting non-essential face-to-face appointments;
  - careful scheduling, texting patients when you are ready to see them;
  - outpatient waiting areas: physical distancing from other patients and from clinic administrative staff;
  - do routine bloods only if results are likely to change management; phone with results instead of arranging return visit.
- Ensure measures are in place for staff health and safety.

Specific guidance for people with asthma with COVID-19 infection

- Mild disease can be managed at home.
- Isolation for 14 days or until symptoms resolve (whichever one that is longer).
- For patients with asthma who may experience an acute exacerbation of their illness due to COVID-19, the use of metered dose inhalers, with or without a spacer, is preferred to the use of a nebuliser.
- Patients who do require a nebuliser should use it in a room that is isolated from other household members. Good ventilation for this area is recommended; this may be facilitated by opening the windows in the room.
- Patients requiring inhaled corticosteroids for the chronic management of asthma or COPD, or topical nasal corticosteroids for allergic rhinitis, should not discontinue these therapies due to COVID-19-related concerns.
- Similarly, patients who require a short course of oral corticosteroids for an asthma exacerbation should be given this therapy, notwithstanding concerns relating to corticosteroids and COVID-19.
- Patients should be advised when to seek medical attention- i.e. worsening of asthma or respiratory symptoms of COVID-19.

Specific guidance for people with diabetes and with COVID-19 infection

- Mild disease can be managed at home.
- Isolation for 14 days or until symptoms resolve (whichever one that is longer).
- Usual medication including medication for hypertension and lipid lowering should be continued.
- Usual self-care such as healthy eating, keeping as active as possible and checking for any acute diabetic foot problems.
- Regular glucose monitoring (if this is part of usual care programme) and keep a record for review with health care provider or be in touch with health provider to adjust treatment.
- If there are any symptoms and signs that are worsening, or blood sugar levels rising to stay above 10 mmol/l, person should seek medical attention.
- Contact the healthcare provider team by telephone or WhatsApp to avoid risk of deterioration of diabetes control.
- Sick day rules should be followed if fever or unwell.
- Ensure that family has glucagon injections and knows how to use it to manage severe hypoglycaemia in people with insulin treated diabetes.

Specific guidance for people with hypertension with COVID-19 infection

- Mild disease can be managed at home.
- Isolation for 14 days or until symptoms resolve (whichever one that is longer).
- Continue treatment with antihypertensive medication and maintain blood pressure according to the hypertension management guidelines.
- Ensuring sufficient medication on hand to treat high blood pressure and other health conditions.
- No need to adjust medication or stop ACE inhibitors or ARBs because of COVID-19 pandemic.
- Continue to monitor blood pressure at home if possible.
- No need for routine clinical review at a clinic during the COVID-19 pandemic.
- Use video or phone consultation if required.

Specific guidance for people with CVD and COVID-19 infection

- The risk of COVID-19 infection may be higher in chronic heart failure patients due to the advanced age and presence of several comorbidities.
- Patients with chronic coronary syndromes should continue to take aspirin for secondary prevention.
- Patients should be counseled to promptly report any new or concerning cardiac symptoms and not delay evaluation for severe symptoms.
- Guideline-directed medical therapy should be continued in chronic heart failure patients, irrespective of COVID-19.

Messages

General

- All general recommendation on infection prevention apply.
- It is best to stay at home as much as possible.
- If you do need to go outside for any of these reasons, you should still follow strict physical distancing measures and wear a cloth mask.
- Maintain a healthy lifestyle (e.g. eat healthy, quit smoking, restrict alcohol intake, get adequate sleep and keep physically active).
- Stay in touch with your family and friends but maintain social distancing.
- Keep hydrated. Many people, particularly older adults, do not consume adequate fluids.

Asthma

- During the pandemic, people with asthma should continue doing what they have been doing to keep asthma under control. They must inform their healthcare provider of any symptoms they may develop.
- Keep your asthma under control by following your asthma action plan.
- Ensure correct inhaler technique.
- Continue your current medications, including any inhalers with corticosteroids.
- Don't stop any medications or change your asthma treatment plan without talking to your healthcare provider.
- Discuss any concerns about your treatment with your healthcare provider.
- Ensure you have adequate supply of medication, at least a 30-day supply.
- Avoid your asthma triggers.
- Strong emotions can trigger an asthma attack. Take steps to help yourself cope with stress and anxiety.
- Contact your health care provider to ask about your symptoms.

Diabetes

- People with diabetes have a higher chance of being sicker and doing worse than most others if they are infected with COVID-19.
- Keep contact with people outside your household to a minimum. Only go out for: necessities like food, medicine, exercise and going to and from work, and only if you cannot work from home.
- It is important to take your diabetes medication regularly and monitor your blood sugars (if you have a glucose meter) to keep your blood sugars well controlled to reduce risk of infections and severity.
- Continue your other usual medication to ensure good control of cholesterol and blood pressure.
- If you have symptoms of COVID-19 or feel unwell such as vomiting or running a temperature or find that you are having symptoms of high or low blood sugars or problems with your diabetes contact your health provider.

Cardiovascular disease

- Take all your medicines as advised by your doctor or nurse.
- Do your best to follow all your medical advice on how to keep your condition well controlled.
- Seek medical help immediately if experiencing symptoms such as chest pain or new onset or worsening shortness of breath.
- If you have heart failure- continue to self-monitor your condition and record your weight first thing after you get out of bed in the morning.

Hypertension

- Continue taking your blood pressure medications as prescribed.
- If possible, measure your blood pressure at home.
- Do not change your treatment without first talking to your doctor or clinic.

If you have Hypertension and are over 60

- Be vigilant in observing our recommendations. Do not hesitate to get medical help if you develop symptoms.
- Take prescribed medications, follow all the recommendations already given and if necessary seek medical help.
- If you have hypertension, diabetes and high cholesterol (i.e. lipid disorders) (because people with hypertension quite often have diabetes and high cholesterol): keep taking all prescribed medications and follow all above general recommendations, including proper hydration and physical activity, to counteract the increased risk of COVID-19 infection and heart complications.
- If you have hypertension, asthma, and being a current or former smoker: be very sensitive to changes in how you feel, especially worsening of lung symptoms – shortness of breath/cough – and seek medical help rapidly.

LIMITATIONS

- The current novel coronavirus pandemic has led to a rapid increase in research to address the various questions related to the pandemic response. These include large numbers of systematic reviews and primary studies, often conducted in a hurry, and in the rush to provide answers, there has been a considerable duplication of research efforts.
- Despite conducting two searches for potential studies, further new studies may have become available since mid-June 2020.
- The systematic reviews predominantly included studies from China, with some studies from Asia, Europe and USA. No studies were from Africa.
- About half of the included reviews and primary research studies were pre-print (i.e. not peer reviewed).
- Only observational studies or reviews including observational studies were identified.
- Most studies were hospital-based.
- Few studies reported on asthma. The terms of reference for this project included asthma and occupational lung diseases but not chronic obstructive pulmonary disease or respiratory diseases in general, nonetheless we have reported on these when they were part of the reviews and primary studies included.
- Many of the primary studies are retrospective observational studies, included small numbers of patients with various lengths of follow-up, and did not have standardised methods for data collection and definition of variables (for example, the term 'severe outcome' differed by study). These primary studies form the basis of most of the systematic reviews, with meta-analyses limited by high heterogeneity with the source of this often not identified.
- One must take the inherent problem of confounding and selection and information biases in observational studies into account when considering the findings.
- The reviews do not consider the background prevalence of the various NCDs in the populations studied, nor for example with regards to diabetes or hypertension the level of control, medications used, complications of the condition prior to admission described, or whether the level of control in hospital (which can varies a lot from facility to facility) influenced outcomes.
- None of the included guidance documents were evidence-informed clinical practice guidelines.

IMPLICATIONS FOR POLICY AND PRACTICE

SOUTH AFRICA
COVID-19 cases and co-morbidities

Sentinel hospital surveillance site data in all provinces (5 March – 21 June 2020) showed: 34% of hospitalised patients had one comorbid condition and 37% had two or more comorbid conditions. Hypertension and diabetes were the most common (in keeping with their prevalence in the country). Older age groups, male sex, admission in the public sector, comorbid hypertension, diabetes, chronic cardiac disease, chronic renal disease, malignancy, HIV and obesity were associated with in-hospital mortality in multivariate analysis. In addition, Western Cape Provincial routine public sector patient data on 3 456 253 adults with 12 522 confirmed COVID-19 cases and 435 COVID-19 deaths (1 March - 4 June 2020) confirmed that uncontrolled diabetes is associated with in hospital mortality.

Week 25 2020 COVID-19 sentinel hospital surveillance update
COVID-19 Special *Public Health Surveillance Bulletin, Vol 18, Suppl 2, 22 June*

The implications of the findings for policy and practice need to be considered in the light of

- high rates of undiagnosed cases and poor levels of control for these NCDs, especially diabetes and hypertension – in the country;
- the draft National NCD Strategic Plan for 2020-2025;
- the need for congruence with current guidelines for management of these NCDs such as the Adult Primary Care Guideline (APC) together with the recently developed APC-COVID and WHO guidance to deliver evidence based primary health care for people with NCDs; and
- the overarching National Department of Health plan to address the pandemic.

The implications are described for screening, reduction of risk for development of COVID-19 and poor outcome, provision for ongoing home-based care both for those infected with COVID-19 and those uninfected, and messaging at a community wide and individual level. The implications and feasibility for implementation can be conceived of at the level of policy (meso), health system/practice (macro) and individual (micro) level.

PREVENTION

REDUCE THE RISK OF DEVELOPING COVID-19 Preventing COVID-19 infection is critical for people with NCDs and their families. Consideration could be given to risk stratification but should include all the usual preventative measures as well as maintaining a healthy lifestyle, limiting visits to health services and reducing the potential for exposure within health services.

SCREENING

SCREENING FOR COVID-19 IN PEOPLE WITH NCDs Testing/screening people with these NCDs for COVID-19 if asymptomatic is not indicated.

SCREENING FOR NCDs IN PEOPLE WITH CONFIRMED COVID-19 Screening hospitalised COVID-19 patients for diabetes and hypertension should be considered in order to improve their control with a view to reducing poor outcomes. How this screening should be undertaken needs operationalisation.

Consideration for screening non-hospitalised confirmed COVID-19 cases for diabetes and hypertension should be considered, as this has implications for their advice / support during self-isolation or need for observation and management.

TREATMENT

ONGOING CARE/HEALTH SYSTEMS Optimizing control of NCDs is key. Development of standard hospital NCD guidelines should be considered. The provision of health care requires reorganisation and includes the leveraging of ward based outreach teams where these exist, central dispensing units, team approach to improve delivery of person centred current guideline directed care and adherence to lifestyle related recommendations. For instance:

- informing patients of reason for limiting their access to routine care;
- providing adequate supplies of medication and other necessary equipment to reduce the frequency of clinic visits;
- providing guidance on when and how to access care for new or worsening symptoms or control;
- providing access to health promotion material, including adherence support;
- enabling virtual consultations, either by request from patient or vice versa; draw on the experiences of rural and remote health services;
- identifying those at heightened risk to give enhanced care to, e.g. to improve glycaemic control of people with poorly controlled diabetes or those self-isolating with an NCD and COVID-19;
- creating ways to monitor control that minimises risk for COVID-19;
- providing influenza and/or pneumococcal vaccinations if indicated;
- need for collection of data for tracking health care utilisation and quality improvement;
- continuing prescribed medication;
- continuing ACEI, which is not deleterious; and
- continuing steroids if needed for control of asthma.

MESSAGING

Patients need clear messaging to encourage healthy lifestyle even within the confines of home, adherence to COVID-19 prevention strategies, adherence to chronic medication as prescribed to ensure that the condition is well controlled, and self-care activities including monitoring and to seek medical assistance if there is any deterioration in the condition, or if having symptoms of COVID-19.

KEY DEFINITIONS

AMSTAR 2	A widely accepted tool for critically appraising systematic reviews, with the purpose to judge the overall confidence in the results of the systematic review.
I2 statistic	Describes the % variation across studies that is due to heterogeneity rather than chance. Ranges from 0 to 100%, with the higher the I2 the greater the heterogeneity.
Meta-analysis	Statistical aggregation of several studies considered combinable.
Meta-regression	Used to examine the impact of moderator variables on study effect size.
Systematic review	Uses systematic, reproducible and transparent methods to identify, select and appraise the relevant studies, and analyse their findings. It can address different types of questions. Depending on the question, they may utilise different forms of evidence, including qualitative data and may evaluate simple and complex interventions.

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TABLES WITH DESCRIPTION OF INCLUDED RECORDS

Table 1 *Reviews on prevalence of NCDs in those hospitalised with COVID-19*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Clinical and epidemiological characteristics of Coronavirus Disease 2019 (COVID-19) patients	No	March 2020	Critically low	69	Not reported	China, Korea (5), USA (1), Germany, France, Australia, Italy, Singapore, Vietnam, Nepal, Hong Kong, and Taiwan. N=48,926	25.93% of the patients had comorbidities, among which hypertension was the most common (50.82%), followed by diabetes (20.89%), cardiovascular and cerebrovascular diseases (16.54%), respiratory system disease (9.70%) and malignancy (2.05%).	Shing Cheng Tan. Clinical and epidemiological characteristics of Coronavirus Disease 2019 2 (COVID-19) patients. medRxiv preprint https://doi.org/10.1101/2020.04.02.20050989
COVID-19 clinical characteristics, and sex-specific risk of mortality: Systematic Review and Meta-analysis	No	March 2020	Moderate	32	Case series Cross-sectional studies	China (31) Germany (1); N=4789	Most common comorbidities – pooled frequency: Hypertension (18.5 %, CI 12.7-24.4, 9 studies), cardiovascular diseases (14.9 %, CI 6.0-23.8, 12 studies), diabetes (10.8 %, CI 8.3-13.3, 11 studies).	Nasiri MJ et al. COVID-19 clinical characteristics, and sex-specific risk of mortality: Systematic Review and Meta-analysis. medRxiv. 2020 Jan 1.
Asthma and COVID-19 in Children - A Systematic Review and Call for Data	No	May 2020	Critically low	1	Morbidity Mortality Weekly Report	USA; n=2572	80 children had at least one underlying condition. The most common underlying disease was "chronic lung diseases (including asthma)" in 40 children, cardiovascular disease in 25 children, and immunosuppression in 10 children. Among the 295 cases for which data on both hospitalisation status and underlying medical conditions was available, 28/37 (77%) hospitalised patients had one or more underlying medical condition (including all six patients admitted to an ICU); compared to 30/258 (12%) patients who were not hospitalised.	Jose A. Castro-Rodriguez, Erick Forno. Asthma and COVID-19 in children – a systematic review and call for data. DOI: https://doi.org/10.1101/2020.05.04.20090845. URL: https://www.medrxiv.org/content/10.1101/2020.05.04.20090845v1
Prevalence and mortality of Lung Comorbidities Among Patients with COVID-19: A systematic review and meta-analysis	No	April 2020	Low	29	Observational retrospective	China (26) and USA (3) Total sample size=6261	Prevalence of asthma among patients diagnosed and hospitalised with COVID-19 3% (range 0-14%) (8 studies, I2 =79%, n=896). Prevalence of COPD among patients hospitalised with COVID-19 was estimated to be 2.2% (95% CI=0.02-0.03%) (22 studies, I2 =70%, n=6088). Prevalence lung cancer in patients among patients hospitalised with COVID-19 was 2.1% (95% CI=0.00-0.21%) (6 studies, I2 =93%, n=1724)	Ghaythan et al. Prevalence and mortality of Lung Comorbidities Among Patients with COVID-19: A systematic review and meta-analysis medRxiv 2020

Table 1 *Reviews on prevalence of NCDs in those hospitalised with COVID-19*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis	Yes	March 2020	Low	6	Retrospective studies	China; n=1558	Cardiovascular disease is a risk factor for patients with COVID-19 (OR:2.93, 95% CI: 1.73-4.96). COVID-19 patients with hypertension (OR: 2.29, 95% CI: 1.69-3.10) and diabetes (OR: 2.47, 95% CI: 1.67-3.66) had a higher risk of exacerbation.	Wang B et al. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. Aging (Albany NY). 2020a Apr 15;12(7):6049.
Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China	Yes	Feb 2020	Low	6	Observational studies	China; 1527 patients in total with sample sizes ranged from 11 to 1099	Most prevalent cardiovascular metabolic comorbidities were hypertension (17.1%, 95% CI 9.9–24.4%) and cardia-cerebrovascular disease (16.4%, 95% CI 6.6–26.1%), followed by diabetes (9.7%, 95% CI 6.9–12.5%). The results from the three included studies (with a total amount of 1278 patients) showed that hypertension accounted for 28.8% of ICU/ severe cases, but 14.1% of non-ICU/severe cases. The proportion hypertension and cardia-cerebrovascular disease were both higher in ICU/severe patients compared to the non-ICU/severe patients [hypertension: RR=2.03, 95% CI (1.54, 2.68), Z=5.04, P =0.09.	Li B et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. Clinical Research in Cardiology. 2020 Mar 11:1-8.
Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: A systematic review and meta-analysis	Yes	Feb 2020	Low	7	Not reported	China, n=1576	The most prevalent comorbidities were hypertension (21.1%, 95% CI: 13.0–27.2%) and diabetes (9.7%, 95% CI: 7.2–12.2%), followed by cardiovascular disease (8.4%, 95% CI: 3.8–13.8%) and respiratory system disease (1.5%, 95% CI: 0.9– 2.1%). Higher risk of hypertension (OR 2.36, 95% CI: 1.46–3.83), respiratory system disease (OR 2.46, 95% CI: 1.76– 3.44), and cardiovascular disease (OR 3.42, 95% CI: 1.88–6.22) were observed in the severe group. Diabetes (OR 2.07, 95% CI: 0.89-4.82).	Yang J et al. Prevalence of comorbidities and its effects in patients infected with SARS-CoV-2: a systematic review and meta-analysis. International Journal of Infectious Diseases. 2020 May 1;94:91-5.
Prevalence of diabetes mellitus in 2019 novel coronavirus: a Meta-analysis.	Yes	Feb 2020	Low	9	Retrospective studies	China, n=2007	Pooled prevalence of DM was 9% (95% CI 6%–12%) Prevalence of DM in moderate patients with 2019-nCoV was 7% (95% CI 4%–10%) Prevalence of DM in severe patients with 2019-nCoV was 17% (95% CI 13%–21%) The prevalence of DM in severe patients with 2019-nCoV was higher than that in moderate patients with 2019-nCoV (OR 2.49, 95% CI 1.70 to 3.64)	Wang X et al. Prevalence of diabetes mellitus in 2019 novel coronavirus: a Meta-analysis. Diabetes Research and Clinical Practice. 2020 May 11.

Table 1 *Reviews on prevalence of NCDs in those hospitalised with COVID-19*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Prevalence of Underlying Diseases in Hospitalised Patients with COVID-19: a Systematic Review and Meta-Analysis	Yes	Feb 2020	Moderate	10	Cross-sectional studies	China; n= 76993	Hypertension - most prevalent underlying disease in hospitalised COVID-19 cases. 16% (95%: CI: 10.15%-23.65%) of SARSCoV-2 infected cases were hypertensive. This information was reported in 7 studies; I2 84%. Cardiovascular disease - 8 studies, incidence was 12.11% (95%CI: 4.40% – 22.75%), I2=95.89%	Emami A et al. Prevalence of underlying diseases in hospitalised patients with COVID-19: a systematic review and meta-analysis. Archives of academic emergency medicine. 2020;8(1).

***AMSTAR overall rating of confidence in the results of the review**

High No or one non-critical weakness – the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest.

Moderate More than one non-critical weakness – the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review.

Low One critical flaw with or without non-critical weaknesses – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest.

Critically low More than one critical flaw with or without non-critical weaknesses – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

Table 2 *Reviews on increased risk of severe disease and death from COVID-19 in patients with NCDs*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression	Yes	April 2020	Critically low	30	Observational retrospective mainly, 1 prospective cohort	China n=6452	Mortality: DM was associated with mortality (RR 2.12 [1.44, 3.11], I2: 72%), 10 studies Severe disease: DM was associated with severe COVID-19 (RR 2.45 [1.79, 3.35], I2: 45%), 13 studies ARDS: DM was associated with ARDS (RR 4.64 [1.86, 11.58], I2: 9%) Disease progression: DM associated with disease progression (RR 3.31 [1.08, 10.14], I2: 0%), 2 studies ICU: DM was not associated with increased need for ICU care (RR 1.47 [0.38, 5.67], I2: 63%), 3 studies DM was associated with composite poor outcome (RR 2.38 [1.88, 3.03]; I2: 62%)	Huang I et al. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia - A systematic review, meta-analysis, and meta-regression [published online ahead of print, 2020 Apr 17]. Diabetes Metab Syndr. 2020;14(4):395-403. doi:10.1016/j.dsx.2020.04.018
Risk of ICU admission and morality risk in diabetic COVID-19 patients	Yes	March 2020	Critically low	8	Observational studies	China n=1853	Diabetic patients had an increased risk of ICU admission (OR: 2.79, 95 % CI 1.85–4.22, I2=46 %, 4 studies). Diabetic subjects were at higher mortality risk (OR 3.21, 95 % CI 1.82–5.64 , I2=16 %, 4 studies).	Roncon L et al. Diabetic patients with COVID-19 infection are at higher risk of ICU admission and poor short-term outcome. Journal of Clinical Virology. 2020 Apr 9:104354.

Table 2 *Reviews on increased risk of severe disease and death from COVID-19 in patients with NCDs*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis	Yes	Apr 2020	Critically low	33	Observational studies	30 China, 2 USA, 1 France. n=16,003 (8,849 (55%) Mainland China, 7,030 (44%) from USA, and 124 (1%) from France).	Covid-19 mortality - Diabetes associated with mortality of COVID-19 pooled odds ratio of 1.90 (95% CI: 1.37–2.64). Combined corrected pooled odds ratio of mortality or severity was 2.16 (95% CI: 1.74–2.68). Covid-19 severity - Diabetes was associated with severe COVID-19 with a pooled odds ratio of 2.75 (95% CI: 2.09–3.62) Prevalence of diabetes - The pooled prevalence of diabetes in patients with COVID-19 was 9.8% (95% CI: 8.7%–10.9%) (after adjusting for heterogeneity)	Kumar A et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews. 2020 May 6.
Hypertension in patients with coronavirus disease 2019 (COVID-19): a pooled analysis	Yes	March 2020	Critically low	13	Observational studies	China n=2893	Severe disease - Hypertension associated with an increased risk of severe COVID-19 (OR, 2.49; 95% CI, 1.98–3.12; I2 = 24%), 11 studies Meta-regression analysis, a correlation observed between an increase in mean age of patients with severe COVID-19 and an increased log OR of hypertension and COVID-19 severity (P = 0.03). Fatality - Hypertension was associated with higher mortality risk (OR, 2.42; 95% CI, 1.51–3.90; I2 = 0%).	Lippi G et al. Hypertension and its severity or mortality in Coronavirus Disease 2019 (COVID-19): a pooled analysis. Pol Arch Intern Med. 2020 Mar 31;10.
Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis	Yes	March 2020	Critically low	3	Observational studies	China, n=419	Prevalence of hypertension was 24.3% Risk of death: hypertensive patients with COVID-19 infections had a higher mortality risk compared with normotensive patients (OR 3.36, 95% CI 1.96- 5.74, I2 = 21%).	Zuin M et al. Arterial hypertension and risk of death in patients with COVID-19 infection: systematic review and meta-analysis. The Journal of Infection. 2020 Apr 11.
Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression	Yes	April 2020	Moderate	30	Observational retrospective	China n=6560	Meta-analysis showed that hypertension was associated with increased composite poor outcome (RR 2.11 (1.85, 2.40), p < 0.001; I 2 66%), severe COVID-19 (RR 2.04 (1.69, 2.47); I 2 31%), ARDS (RR 1.64 (1.11, 2.43), I 2 0%), ICU care (RR 2.11 (1.34, 3.33), I 2: 18%) and disease progression (RR 3.01 (1.51, 5.99), I 2 0%). Meta-regression analysis showed that association between hypertension and increased composite poor outcome was influenced by gender (p = 0.013), not by age (p = 0.233), CVD (p = 0.464), diabetes (p = 0.882) and COPD (p=0.094).	Pranata R et al. Hypertension is associated with increased mortality and severity of disease in COVID-19 pneumonia: A systematic review, meta-analysis and meta-regression. Journal of the Renin-Angiotensin-Aldosterone System. 2020 May; 21(2):1470320320926899.
Coronavirus disease 2019 (COVID-19) and cardiovascular risk: A meta-analysis.	Yes	April 2020	Low	13	Observational	China 49,076 confirmed COVID-19 cases (10,009 were severe cases and 7773 were non-severe cases)	The proportion of DM, HTN, CAD, HF and CVD events were higher in patients with severe COVID-19 disease compared to non-severe COVID-19 disease [DM: OR = 3.02, 95% CI (2.07–4.42), I 2 = 39.7%; HTN: OR = 4.56, 95% CI (1.96–10.59), I 2 = 91.7%; CAD: OR = 6.85, 95% CI (3.81–12.3), I 2 = 48.1%, HF: OR = 9.77, 95% CI (5.36–17.79), I 2 = 0%, CVD events: OR = 8.89, 95% CI (4.04–19.5), I 2 = 66.9%].	Krittanawong Chayakrit H, et al. Coronavirus disease 2019 (COVID-19) and cardiovascular risk: A meta-analysis. Progress in Cardiovascular Diseases 2020;In press: 2020

Table 2 *Reviews on increased risk of severe disease and death from COVID-19 in patients with NCDs*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis.	Yes	April 2020	Moderate	10	Case series (2), cohort studies (8)	China n=3118	Eight studies reported the relationship between underlying CVD and in-hospital mortality risk (2515 patients and 127 deaths) in unadjusted model. Overall, the summary estimate demonstrated that patients with CVD had an approximately fivefold higher risk of mortality compared with non-CVD patients (unadjusted OR 4.85, p p<0.001; 95%CI 3.06 to 7.70; I2=29.3%). Seven studies (2463 patients and 535 deaths) were included for the pre-existing hypertension and in-hospital mortality analysis with unadjusted ORs. The pooled unadjusted effect of hypertension on mortality risk was 3.67 (95% CI 2.31 to 5.83, I2=57.4%). For cardiac injury, all eight studies15 16 18–21 23 24 (1429 patients and 374 deaths) except one reported that acute cardiac injury was associated with a high mortality risk in unadjusted model. The pooled effect of these studies (unadjusted OR 21.15, 95%CI 10.19 to 43.94, I2=70.5%) showed that patients with elevated troponin levels had a higher mortality risk than those with normal troponin levels.	Li X et al. Impact of cardiovascular disease and cardiac injury on in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis. Heart. 2020 May 27.
The impact of 2019 novel coronavirus on heart injury: A systemic review and Meta-analysis	Yes	March 2020	Critically low	22	Retrospective observational data	China n= 4189	Infection severity: More severe COVID-19 infection is associated with higher mean troponin (SMD 0.53, 95% CI 0.30 to 0.75), with a similar trend for creatine kinase–MB, myoglobin, and NT-proBNP. Acute cardiac injury was more frequent in those with severe, compared to milder, disease (RR 5.99, 3.04 to 11.80). Meta regression suggested that cardiac injury biomarker differences of severity are related to history of hypertension (p = 0.030). Death: COVID19-related cardiac injury associated with higher mortality (summary RR 3.85, 2.13 to 6.96). hsTnI and NT-proBNP levels increased during the course of hospitalisation in non-survivors.	Li JW et al. The impact of 2019 novel coronavirus on heart injury: A Systematic review and Meta-analysis [published online ahead of print, 2020 Apr 16]. Prog Cardiovasc Dis. 2020;S0033-0620(20)30080-3. doi:10.1016/j.pcad.2020.04.008
Association of Cardiovascular Disease With Coronavirus Disease 2019 (COVID-19) Severity: A Meta-Analysis	Yes	Apr 2020	Critically low	18	Observational studies	China (16), USA (2) n = 4858 patients	COVID-19 severity: Pre-existing CVD was associated with increased risk of a severe form of COVID-19 (OR = 3.14; 95% CI 2.32-4.24; I2 = 0%) COVID-19 mortality: Pre-existing CVD was associated with overall risk of COVID-19 all-cause mortality (OR = 11.08; 95% CI: 2.59-47.32; I2 = 55%) Mortality in patients with severe COVID-19 disease – No association between previous history of CVD and mortality in severe COVID- 19 disease (OR = 1.72; 95% CI: 0.97-3.06, I2 = 0%)	Aggarwal G et al. Association of Cardiovascular Disease With Coronavirus Disease 2019 (COVID-19) Severity: A Meta-Analysis. Current Problems in Cardiology. 2020 Apr 28:100617.

Table 2 *Reviews on increased risk of severe disease and death from COVID-19 in patients with NCDs*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Comorbid Chronic Diseases and Acute Organ Injuries Are Strongly Correlated with Disease Severity and Mortality among COVID-19 Patients: A Systemic Review and Meta-Analysis	Yes	Apr 2020	Critically low	34	Observational	China n= 6,263 COVID-19 cases	Severe disease: Hypertension OR 2.92 (95% CI: 2.35, 3.64); CVD OR 3.84 (95% CI: 2.90, 5.07); Diabetes OR: 2.61; 95% CI: 2.05, 3.33)	Wang X et al. Comorbid Chronic Diseases and Acute Organ Injuries Are Strongly Correlated with Disease Severity and Mortality among COVID-19 Patients: A Systemic Review and Meta-Analysis. Research. 2020b Apr 19;2020:2402961.
Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis	Yes	March 2020	Critically low	13	Retrospective studies	China n=3027 patients with sample sizes ranged from 27 to 1099.	The proportion of diabetes, cardiovascular disease and respiratory disease was higher in critical/mortal group compared to the non-critical group [diabetes: OR = 3.68, 95% CI (2.68, 5.03); cardiovascular disease: OR = 5.19, 95% CI (3.25, 8.29); respiratory disease: OR = 5.15, 95% CI (2.51, 10.57)]. Hypertension in critical/mortal group [OR = 2.72, 95% CI (1.60, 4.64)].	Zheng Z et al. Risk factors of critical & mortal COVID-19 cases: A systematic literature review and meta-analysis. Journal of Infection. 2020 Apr 23.
Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis	Yes	March 2020	Critically low	21	Retrospective studies, national data	Singapore (1); China (20) Total of 47,344 patients (24,419 male and 22,925 females). The number of patients per study ranged from 12 to 44,672.	The prevalence of diabetes and hypertension comorbidities was 7.7 % (95CI 6.1–9.3 %, I2 64%) and 15.6 % (95CI 12.6–18.6 %, I2 80%), respectively. The incidence of cardiovascular disease 4.7 % (95CI 3.1–6.2 %, I2 77%). The percentage of severe cases in diabetes and hypertension cases was 44.5 % (95CI 27.0–61.9 %, I2 69%) and 41.7 % (95CI 26.4–56.9 %; I2 72%), respectively. The risks of severity and mortality rate ranged from 12.6 to 23.5 % and from 2.0 to 4.4 %, with pooled estimates at 18.0 and 3.2 %, respectively.	Yong Hu et al. Prevalence and severity of corona virus disease 2019 (COVID-19): A systematic review and meta-analysis. Journal of Clinical Virology 2020:127:104371. https://doi.org/10.1016/j.jcv.2020.104371.

Table 2 *Reviews on increased risk of severe disease and death from COVID-19 in patients with NCDs*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Impact of Cerebrovascular and Cardiovascular Diseases on Mortality and Severity of COVID-19–Systematic Review, Meta-analysis, and Meta-regression.	Yes	April 2020	Moderate	16	Retrospective observational mainly, one prospective cohort	China n=4448	Cerebrovascular disease was associated with increased poor composite outcome (RR 2.04 [1.43, 2.91], p<0.001; I2: 77%, p<0.001). Subgroup analysis revealed that cerebrovascular disease was associated with mortality (RR 2.38 [1.92, 2.96], p<0.001; I2: 0%, p=0.53). Cerebrovascular disease was borderline for severe COVID-19 (RR 1.88 [1.00, 3.51], p=0.05; I2: 87%, p<0.001). Cardiovascular disease was associated with increased poor composite outcome (RR 2.23 [1.71, 2.91], p p<0.001; I2: 60%, p=0.004) Subgroup analysis revealed that cardiovascular disease was associated with mortality (RR 2.25 [1.53, 3.29], p<0.001; I2: 33%, p=0.19) and severe COVID-19 (RR 2.25 [1.51, 3.36], p<0.001; I2: 76%, p=0.001). Meta-regression indicated that the association between cardiovascular disease and composite poor outcome was not influenced by gender (p=0.722), age (p=0.910), hypertension (p=0.218), cerebrovascular diseases (p=0.502), diabetes (p=0.062), and respiratory comorbidities (p=0.703).	Pranata R et al. Impact of Cerebrovascular and Cardiovascular Diseases on Mortality and Severity of COVID-19–Systematic Review, Meta-analysis, and Meta-regression. Journal of Stroke and Cerebrovascular Diseases. 2020 May 14:104949.
Risk factors for mortality of adult inpatients with Coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis of retrospective studies	Yes	March 2020	Low	6	Retrospective cohort design	China Sample size of studies varied from 172 to 20812 patients	Risk death: Older age (≥65 years) (combined effect size=2.39, 95% CIs=1.75-3.28, p<0.00, I2 =95.4%). Hypertension (combined effect size=3.29, 95% CIs=1.54-7.05, p=0.002, I2 =86.3%) Diabetes (combined effect size=3.11, 95% CIs=1.10-8.80, p=0.032, I2 =91.3%) COPD (combined effect size=7.69, 95% CIs=5.65-10.47, p<0.001, I2 =0.0%) CVDs (combined effect size=7.39, 95% CIs=2.88-18.96, p<0.001, I2=61.5%).	Parohan M et al. Risk factors for mortality in patients with Coronavirus disease 2019 (COVID-19) infection: a systematic review and meta-analysis of observational studies. The aging male : the official journal of the International Society for the Study of the Aging Male 2020;():1-9. 2020
Decreased Mortality of COVID-19 with Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients with Hypertension: A Meta-Analysis	Yes	May 2020	Critically low	9	Observational studies	China, n=3936	Disease severity of COVID-19: ACEI/ARB treatment was not associated with disease severity (OR 0.71, 95 % CI 0.46–1.08, I2 59% compared to non-ACE/ARB treatment Mortality of COVID-19: ACEI/ARB treatment was related to lower mortality of COVID-19 in patients with hypertension (OR 0.57, 95 % CI 0.38–0.84, I2 0)	Guo X et al. Decreased Mortality of COVID-19 with Renin-Angiotensin-Aldosterone System Inhibitors Therapy in Patients with Hypertension: A Meta-Analysis. Hypertension. 2020 May 27.

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Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Renin-angiotensin-aldosterone system inhibitors and mortality in patients with hypertension hospitalised for COVID-19: a systematic review and meta-analysis	No	May 2020	Critically low	11	Cohort, case control, case series	China, Italy, USA, France, 61,268 patients	Taking RAAS inhibitors –death pooled RR= 0.65, 95% CI 0.45 to 0.94; 7 observational studies, I2 80%.	Ssentongo A et al. Renin-angiotensin-aldosterone system inhibitors and mortality in patients with hypertension hospitalised for COVID-19: a systematic review and meta-analysis. medRxiv. 2020 Jan 1.
Association of Renin Angiotensin System Blockers with Outcomes in Patients with Covid-19: A Systematic Review and Meta-analysis.	No	May 2020	Critically low	15	Observational studies	China- 9, USA- 2, Italy- 2, Spain- 1, multinational- 1, 23,822 COVID-19 positive patients [n = 6,650 on ACEI/ ARB, n = 17,172 not on ACEI/ ARB] were included	In-hospital mortality- ACEI/ARB use was associated with lower mortality [0.64 (0.45-0.89)] in patients with hypertension. Severe/critical illness odds of severe/critical illness [0.76(0.52-1.12); p=0.16] compared with non-ACEI/ARB users in patients with hypertension	Garg A et al. Association of Renin Angiotensin System Blockers with Outcomes in Patients with Covid-19: A Systematic Review and Meta-analysis. medRxiv. 2020:2020.05.23.20111401.
Cardiovascular Diseases and COVID-19 Mortality and Intensive Care Unit Admission: A Systematic Review and Meta-analysis	No	March 2020	Critically low	16	Four studies were case-control and four and eight of them were cross-sectional and cohort studies	Not reported, n=3473	Mortality: Hypertension (OR: 1.92, 95% CI 1.92-2.74) (7 studies), Heart Failure (OR: 11.73, 95% CI 5.17-26.60) (3 studies), Other cardiovascular disease (OR: 1.95, 95% CI 1.17-3.24) (4 studies) Overall CVDs (OR: 3.37, 95% CI 2.06-5.52) (8 studies) ICU admission: Coronary heart disease (OR: 4.19, 95%CI 1.27-13.80) (3 studies, I2 69%), Cardiovascular disease (OR: 4.17, 95%CI 2.52-6.88) (6 studies), Hypertension (OR: 2.69, 95%CI 1.55-4.67) (9 studies, I2 69%)	Shamshirian A et al. Cardiovascular Diseases and COVID-19 Mortality and Intensive Care Unit Admission: A Systematic Review and Meta-analysis. medRxiv. 2020 Jan 1.
COVID-19: The relationship between age, comorbidity, and disease severity – a rapid review	No	Not reported	Critically low	12	Descriptive studies	China, England, Wales, Northern Ireland	One study showed that comorbidity was far more common among those who died of COVID-19 than among those who survived the disease. Comorbidity as a risk factor of disease severity: known heart disease (OR 16.6; 95% CI 2.3 to 120.6, 1 study, n=160) advancing age (OR 1.04; 95% CI 1.01 to 1.07) underlying chronic disease (OR 1.7; 95% CI 1.1 to 2.8, 1 study, n=135) Heart disease and COVID-19 mortality - OR 2.14; 95% CI 0.26 to 17.79	Brurberg K et al. COVID-19: The relationship between age, comorbidity and disease severity – a rapid review. Oslo: Norwegian Institute of Public Health, 2020.

Table 2 *Reviews on increased risk of severe disease and death from COVID-19 in patients with NCDs*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Systematic review and meta-analysis of predictive symptoms and comorbidities for severe COVID-19 infection	No	March 2020	Low	7	Retrospective cohort studies	China Sample size ranged from 40 to 1099	Severe disease: pORs of COPD (6.42, 95% CI 2.44- 16.9) CVD (2.70, 95% CI 1.52 – 4.80) Hypertension (1.97, 95% CI 1.40 – 2.77). ICU admission: pORs of COPD 17.8 (95% CI 6.56 – 48.2) CVD 4.44 (95% CI 2.64 – 7.47) Hypertension 3.65 (95% CI 2.22 – 5.99)	Jain V et al. Systematic review and meta-analysis of predictive symptoms and comorbidities for severe COVID-19 infection. medRxiv. 2020 Jan 1.
The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis	No	April 2020	Critically low	25	Observational studies	China Most studies with sample size <300	Factors associated with severe COVID-19 were male sex (10 studies; pooled RR=1.73, [95%CI 1.50-2.01]), hypertension (8 studies; 2.87 [2.09-3.93]), diabetes (9 studies; 3.20 [2.26-4.53]), and CVD (10 studies; 4.97 [3.76-6.58]).	Matsushita K et al. The relationship of COVID-19 severity with cardiovascular disease and its traditional risk factors: A systematic review and meta-analysis. medRxiv. 2020 Jan 1.
Age-adjusted associations between comorbidity and outcomes of COVID-19: a review of the evidence	No	Not reported	Critically low	7	Mostly cohort designs	China; Sample sizes ranged from 171 to 1,590	In one study, after adjusting for age and smoking status, patients with hypertension at admission were 58% more likely to reach the composite endpoint (ICU admission, invasive ventilation, or death) than those without hypertension (HR 1.58, 95% CI: 1.07-2.32). Another study found that the presence of hypertension at hospital admission was associated with 2.71 times the odds of severe disease (ICU admission), in a retrospective cohort of 487 patients, after adjusting for age, sex, and time from symptom onset to admission. In studies examining diabetes mellitus as a comorbidity, the authors did not distinguish between Type 1 and Type 2 diabetes. One study found that hospitalised COVID-19 patients with diabetes had a 59% increased risk of the composite endpoint (ICU admission, invasive ventilation, or death) (HR 1.59, 95% CI: 1.03-2.45), after adjusting for age and smoking status. Another study found that those with diabetes were more likely to die in hospital, and point estimates were not materially different when adjusted for additional comorbidities as well as age (HR=2.84 cf. 2.80).	Mason KE et al. Age-adjusted associations between comorbidity and outcomes of COVID-19: a review of the evidence. medRxiv. 2020 Jan 1.
Risk factors for severe corona virus disease 2019 (COVID-19) patients: a systematic review and meta analysis	No	March 2020	Critically low	20	Observational studies	China; sample size ranged from 21 to 1099	Severe COVID-19: Diabetes – OR = 3.04 [2.01, 4.60] Hypertension – OR = 2.31 [1.68, 3.18] Coronary heart disease – OR = 2.76 [1.39, 5.45] Chronic obstructive pulmonary disease – OR = 3.56 [1.33, 9.54].	Xu L et al. Risk factors for severe corona virus disease 2019 (COVID-19) patients: a systematic review and meta-analysis. medRxiv. 2020 Jan 1.

Table 2 *Reviews on increased risk of severe disease and death from COVID-19 in patients with NCDs*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Effects of pre-existing morbidities on occurrence of death among COVID-19 disease patients: A systematic review and meta-analysis	No	May 2020	Moderate	36	Majority were retrospective (26), seven prospective studies	China (35), Australia (1) Sample size ranged from 7 to 8910, total size = 36 398	Prevalence of pre-existing morbidity among COVID-19 patients: Approximately 36.5% of the total COVID-19 patients reported that they had hypertension, 22.0% had diabetes, 11.9% had cardiovascular disease, 4.1% had chronic lung disease, 2.3% had COPD, 11.0 % had hyperlipidemia, and 3.0% had chronic kidney disease. Effects of pre-existing morbidity on deaths in COVID-19 patients: Cardiovascular system disease (OR: 3.32, 95% CI: 2.79-3.95; I2 = 83.8%, 33 studies), Immune and metabolic disorders (OR: 2.39, 95% CI: 2.00-2.85; I2 = 64.5%, 31 studies), Respiratory system disease (OR: 2.02, 95% CI: 1.80-2.26; I2 = 71.2%, 28 studies), Cancers (OR: 2.22, 95% CI: 1.63-3.03, I2 = 67.7%, 20 studies), Cerebrovascular system diseases (OR: 4.12, 95% CI: 3.04-5.58, 15 studies)	Khan et al. Effects of underlying morbidities on the occurrence of deaths in COVID19 patients: A systematic review and meta-analysis
Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis	No	March 2020	Critically low	9	Observational studies	China	COVID-19 severity Hypertension OR=2.3, 95% CI (1.76, 3.00) I2=50%, n=1936 Diabetes OR 2.67 [1.91, 3.74] I2=42%, n=1936 Coronary heart disease 2.85 [1.68, 4.84], I2 =0%, n=1720	Chen Y et al. Effects of hypertension, diabetes and coronary heart disease on COVID-19 diseases severity: a systematic review and meta-analysis. medRxiv. 2020 Jan 1.
Clinical and historical features associated with severe COVID-19 infection: a systematic review	No	April 2020	Low	63	Observational cohort studies	China (57), USA (2), 1 each Italy, France, South Korea, and Singapore; 17648 patients with sample sizes from 12 to 4103 patients, with a mean of 280.	Hypertension - state that 22 of the 33 papers reported an association between hypertension and disease severity. No other data Diabetes - state that 13 of the 32 papers reported an association between diabetes and disease severity. No other data Cardiovascular disease - state that 16 of the 25 papers reported an association between CVD and disease severity. No other data Stroke – state that 5 of the 12 papers reported an association between stroke and disease severity. No other data	Pigoga JL et al. Clinical and historical features associated with severe COVID-19 infection: a systematic review. medRxiv. 2020 Jan 1.
The association of cardiovascular disease and other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis	No	May 2020	Critically low	19	Cohort and case control	China (17), Italy (1), 1 multi country Sample size ranged from 28 to national data of 44 672	Coronary heart disease, hypertension, congestive heart failure, and cancer increased the risk of mortality from COVID-19. The risk of mortality: Coronary heart disease (RR= 2.40, 95%CI=1.71-3.37, n=5) Hypertension (RR=1.89, 95%CI= 1.58-2.27, n=9). Cancer (RR=1.93 95%CI 1.15-3.24, n=4) Congestive heart failure (RR=2.66, 95%CI 1.58-4.48, n=3)	Ssentongo P et al. The association of cardiovascular disease and other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. medRxiv. 2020 Jan 1.

Table 2 *Reviews on increased risk of severe disease and death from COVID-19 in patients with NCDs*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Diabetes is associated with increased risk for in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis comprising 18,506 patients	No	May 2020	Critically low	14	Observational studies (twelve retrospective and two prospective)	5 Asia, 5 USA, 4 in Europe 18,506 patients: 3,713 diabetics and 14,793 non-diabetics.	Patients with diabetes were associated with a higher risk of death compared to patients without diabetes (OR: 1.65; 95% CI: 1.35–1.96; I2 77.4%).	Palaiodimos L et al. Diabetes is associated with increased risk for in-hospital mortality in patients with COVID-19: a systematic review and meta-analysis comprising 18,506 patients. medRxiv. 2020 Jan 1.
Risk Factors of the Severity of COVID-19: A Meta-Analysis	No	April 2020	Critically low	10	Retrospective observational studies	China Sample size ranged from 34 to 1099	Diabetes - 10 studies (n=2240) - COVID severity - RR =1.57; 95% CI 1.25 to 1.98. Heterogeneity I2=54% Hypertension - 9 studies (n=2220) - COVID severity - RR=1.79; 95% CI 1.57 to 2.04 Heterogeneity, I2=0%	Rahman A, Sathi NJ. Risk Factors of the Severity of COVID-19: a Meta-Analysis. medRxiv. 2020 Jan 1.
Association of age, sex, comorbidities, and clinical symptoms with the severity and mortality of COVID-19 cases: a meta-analysis with 85 studies and 67299 cases	No	May 2020	Moderate	85	Observational retrospective mainly	China (69), USA (8), Italy (6), South Korea (1), Iran (1) N= 67299	Patients having at least one comorbidity had 3.46-times risk of death than survived patients (OR = 3.46, 95% CI =2.56-4.67). A total of 31% death was found due to hypertension in comparison to the survival (6.77%) with hypertension, and the chance of death was found 3.16-times higher in comparison to survival patients with hypertension (OR = 3.16, 95% CI = 2.51-3.97). The proportion of death in cerebrovascular disease and cardiovascular disease was also higher than the survival rate with these diseases (12.92% vs. 14.78% death, OR = 5.84, 95% CI = 3.63-9.39), OR = 4.67, 95% CI = 3.22-6.77, respectively). Covid-19 patients with diabetes and respiratory disease had 2.45 and 2.68, times more risk of death, respectively, compared to survival with these diseases.	Islam MS et al. Association of age, sex, comorbidities, and clinical symptoms with the severity and mortality of COVID-19 cases: a meta-analysis with 85 studies and 67299 cases. medRxiv. 2020 Jan 1.

Table 3 Reviews on prognostic markers in patients with these NCDs when they have COVID-19

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Predictors of mortality in hospitalised COVID-19 patients: A systematic review and meta-analysis	Yes	Apr 2020	Critically low	14	Retrospective studies	China 13 (n=2025), USA 1 (n=2634 combining data from 12 hospitals).	Presence of comorbidities hypertension (OR 2.5; 95% CI 2.1-3.1), coronary heart disease (OR 3.8; 95% CI 2.1-6.9) and diabetes (OR 2.0; 95% CI 1.7-2.3) associated with higher risk of death amongst COVID-19 patients. Those who died, compared to those who survived, differed on multiple biomarker levels on admission - elevated levels of cardiac troponin (+44.2 ng/L, 95% CI 19.0-69.4; P=0.0006); C-reactive protein (+66.3 µg/mL, 95% CI 46.7-85.9; P<0.00001); interleukin-6 (+4.6 ng/mL, 95% CI 3.6-5.6; P<0.00001); D-dimer (+4.6 µg/mL, 95% CI 2.8-6.4; P<0.00001); creatinine (+15.3 µmol/L, 95% CI 6.2-24.3; P=0.001) and alanine transaminase (+5.7 U/L, 95% CI 2.6-8.8; P=0.0003); & decreased levels of albumin (-3.7 g/L, 95% CI -5.3 to -2.1; P<0.00001)	Tian W et al. Predictors of mortality in hospitalised COVID-19 patients: A systematic review and meta-analysis. Journal of Medical Virology. 2020 May 22.
Case fatality rate in COVID-19: a systematic review and meta-analysis	No	March 2020	Critically low	29	Observational studies	China (28) Singapore (1) 2,090 patients	Prevalence of combined severe or critical illness in COVID-19 Patients with existing Type 2 Diabetes Mellitus: coefficient 3.6, standard error (SE) 2.2, 95% CI -0.6 to 7.9, Z 1.7, P value 0.093, I2 93% Patients with existing hypertension: coefficient 8.4, standard error (SE) 2.5, 95% CI 3.6 to 13.2, Z 3.4, P value <0.001, I2 89% Patients with existing cardiac disease: coefficient 4.8, standard error (SE) 2.6, 95% CI -0.4 to 10.0, Z 1.8, P value 0.07, I2 92% Prevalence of critical illness in COVID-19 Patients with existing Type 2 Diabetes Mellitus: coefficient 0.6, standard error (SE) 2.2, 95% CI -3.8 to 4.9, Z 0.3, P value 0.794, I2 90% Patients with existing hypertension: coefficient 8.4, standard error (SE) 2.5, 95% CI 3.5 to 13.3, Z 3.3, P value <0.001, I2 75% Patients with existing cardiac disease: coefficient 6.7, standard error (SE) 3.0, 95% CI 0.9 to 12.6, Z 2.3, P value 0.023, I2 86% Case-fatality rate in COVID-19 Patients with existing Type 2 Diabetes Mellitus: coefficient -4.2, standard error (SE) 4.8, 95% CI -13.5 to 5.3, Z -0.9, P value 0.4, I2 85% Patients with existing hypertension: coefficient 6.1, standard error (SE) 3.1, 95% CI -0.002 to 12.1, Z 2.0, P value 0.05, I2 63% Patients with existing cardiac disease: coefficient 6.3, standard error (SE) 5.6, 95% CI -4.7 to 17.3, Z 1.2, P value 0.264, I2 87%	Chanaka Kahathuduwa et al. Case fatality rate in COVID-19: a systematic review and meta-analysis. DOI: 10.1101/2020.04.01.20050476.

Table 3 *Reviews on prognostic markers in patients with these NCDs when they have COVID-19*

Review title	Peer-reviewed publication Yes / No	Date search	Methodological quality (AMSTAR 2 tool)*	Number included studies	Types of studies	Where studies conducted, number participants	Findings	Citation
Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis	No	Feb 2020	Critically low	30	Retrospective, observational studies (19 single-center and 11 multi-center studies)	China 27, 3 United States, Australia and Korea 53 000 patients	The predictor for disease severity included old age (≥ 50 yrs, odds ratio [OR] = 2.61; 95% CI, 2.29-2.98), male (OR =1.348, 95% CI, 1.195-1.521), smoking (OR =1.734, 95% CI, 1.146-2.626) and any comorbidity (OR = 2.635, 95% CI, 2.098-3.309), especially chronic kidney disease (CKD, OR = 6.017; 95% CI, 2.192-16.514), chronic obstructive pulmonary disease (COPD, OR = 5.323; 95% CI, 2.613-10.847) and cerebrovascular disease (OR = 3.219; 95% CI, 1.486-6.972). Old age (≥ 60 yrs, RR = 9.45; 95% CI, 8.09-11.04), followed by cardiovascular disease (RR = 6.75; 95% CI, 5.40-8.43) hypertension (RR = 4.48; 95% CI, 3.69-5.45) and diabetes (RR = 4.43; 95% CI, 3.49-5.61) were found to be independent prognostic factors for the COVID-19 related death.	Xianxian Zhao et al. Incidence, clinical characteristics and prognostic factor of patients with COVID-19: a systematic review and meta-analysis. DOI: https://doi.org/10.1101/2020.03.17.20037572.
Risk factors for adverse clinical outcomes in patients with COVID-19: A systematic review and meta-analysis	No	April 2020	Critically low	88	Hospital-based observational studies	6 of the 88 conducted outside China (France, Hong Kong, Italy, Singapore, USA)	Severity and progression of disease, admission to ICU, need for mechanical ventilation: Elevated C-reactive protein (OR, 6.46; 95% CI, 4.85 – 8.60), decreased lymphocyte count (OR, 4.16; 95% CI, 3.17 – 5.45), cerebrovascular disease (OR, 2.84; 95% CI, 1.55 – 5.20), chronic obstructive pulmonary disease (OR, 4.44; 95% CI, 2.46 – 8.02), diabetes mellitus (OR, 2.04; 95% CI, 1.54 – 2.70), hemoptysis (OR, 7.03; 95% CI, 4.57 – 10.81), and male sex (OR, 1.51; 95% CI, 1.30 – 1.75) were associated with risk of severe COVID-19. Presence of chronic comorbid disorders also increased the risk of severe COVID-19, ICU admission	Bellou V et al. Risk factors for adverse clinical outcomes in patients with COVID-19: A systematic review and meta-analysis. medRxiv. 2020 Jan 1.

Table 4 *Primary studies not included in the reviews*

Research question / objective	Peer reviewed publication	Type of study	Sample size	NCD	Where study conducted	Risk of bias	Findings	Citation
Increased risk of severe COVID-19, hospitalisation and death from COVID-19 in patients with these NCDs								
Type 1 and 2 diabetes and associations with in-hospital death with COVID-19	No	Cohort study	61,414,470	Diabetes	England, UK	Low risk bias	23,804 COVID-19 related deaths occurred - one third in people with diabetes: 7,466 (31·4%) Type 2 and 365 (1·5%) Type 1. Crude mortality rates per 100,000 persons over the 72 days for the overall population and Type 1 and Type 2 diabetes were 38·8 (38·3-39·3), 138·3 (124·5-153·3), and 260·6 (254·7-266·6) respectively Adjusted for age, sex, deprivation, ethnicity and geographical region, people with Type 1 and Type 2 diabetes had 3·50 (3·15-3·89) and 2·03 (1·97-2·09) times the odds respectively of dying in hospital with COVID-19 compared to those without diabetes	Barron E et al. Type 1 and Type 2 diabetes and COVID-19 related mortality in England: a whole population study.
Association between plasma glucose levels and clinic outcomes in COVID-19 patients with type 2 diabetes	Yes	Multi-centered, retrospective cohort study	7,337	Diabetes	China	Retrospective No pre-hospital data	In-hospital death rate was significantly higher in patients with pre-existing type 2 diabetes (T2D) relative to the non-diabetic individuals (7.8% versus 2.7%, p < 0.001) Crude HR 28-day all-cause mortality in the diabetic group versus non-diabetic individuals was 2.90 (95% CI, 2.21–3.81; p < 0.001) Well-controlled BG (glycaemic variability within 3.9 to 10.0mmol/L) was associated with lower mortality compared to individuals with poorly controlled BG (upper limit of glycaemic variability exceeding 10.0 mmol/L) (adjusted HR, 0.14) during hospitalisation. T2D required more medical interventions Oxygen inhalation (76.9% versus 61.2%), non-invasive ventilation (10.2% versus 3.9%), and invasive ventilation (3.6% versus 0.7%) were also applied significantly more frequently to the individuals with T2D compared to the patients without T2D	Zhu L et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell metabolism. 2020 May 1.

Table 4 *Primary studies not included in the reviews*

Research question / objective	Peer reviewed publication	Type of study	Sample size	NCD	Where study conducted	Risk of bias	Findings	Citation
Age- and sex-specific prevalence of SARS-CoV-2 disease (COVID-19) and its prognostic factors.	No	Prospective cohort study	2653	Diabetes/ heart failure/ hypertension/ IHD	Italy	Based only on routinely collected data for hospitalisations to define comorbidity; have no information on treatments administered in hospital or prescribed at home	Age-specific risks of hospitalisation was higher in males than in females by a factor of 2 or more Hospitalisation rate was 40.5%, Case fatality rate was 8.5%. Immigration status (as represented by place of birth) was found to be associated with hospitalisation, with patients born abroad having a 40% higher risk Risk of hospitalisation was higher in patients with heart failure (HR 1.6, 95% CI 1.2 to 2.1), arrhythmia (HR 1.5, 95% CI 1.2 to 1.9), dementia (HR 1.2, 95% CI 0.9 to 1.8), ischemic heart disease (HR 1.3, 95% CI 1.0 to 1.7), diabetes (HR 1.5, 95% CI 1.3 to 1.9), hypertension (HR 1.4, 95% CI 1.2 to 1.6), and COPD (HR 1.9, 95% CI 1.4 to 2.5) AT-1 inhibitors and ACE inhibitors, exposure to these drugs appeared to be associated with a modest increase in hospitalisation but not death Risk of death higher in patients with heart failure (HR 2.3, 95% CI 1.6 to 3.2), arrhythmia (HR 1.8, 95% CI 1.3 to 2.5), dementia (HR 1.8, 95% CI 1.1 to 2.8), ischemic heart disease (HR 1.7, 95% CI 1.2 to 2.5), diabetes (HR 1.6, 95% CI 1.1 to 2.2), and Hypertension (HR 1.6, 95% CI 1.2 to 2.1) Age-specific risks of death was higher in males than in females by a factor of 2 or more	Giorgi Rossi P et al. Characteristics and outcomes of a cohort of SARS-CoV-2 patients in the province of Reggio Emilia. Italy. medRxiv. 2020;2020(13.20063545).
Effects of optimal glycaemic control in patients with hyperglycaemia affected by Covid-19	Yes	Retrospective study	59	Diabetes	Italy	Small sample size	Patients with hyperglycaemia and patients with diabetes had a higher risk of severe disease than those without diabetes and with normoglycemia. Patients with hyperglycaemia treated with insulin infusion had a lower risk of severe disease than patients without insulin infusion Patients with hyperglycaemia treated without insulin infusion had increased mortality than those treated with insulin infusion	Sardu C et al, Outcomes in Patients With Hyperglycemia Affected by Covid-19: Can We Do More on Glycemic Control? Diabetes Care. 2020 May 19.

Table 4 *Primary studies not included in the reviews*

Research question / objective	Peer reviewed publication	Type of study	Sample size	NCD	Where study conducted	Risk of bias	Findings	Citation
Characteristics and outcomes of patients with diabetes and covid-19 in association with glucose-lowering medication	Yes	Retrospective cohort study	904	Diabetes	China	Limitations in classifying trueSARS-CoV-2-negativecases	Risk factors for higher mortality of patients with diabetes and COVID-19 were older age (adjusted odds ratio [aOR] 1.09 [95% CI 1.04, 1.15]) and elevated C-reactive protein (aOR 1.12 [95% CI 1.00, 1.24]). Elevated glucose was associated with higher mortality in all patients (aOR 1.08 [95% CI 1.01, 1.16]; P50.033) and in patients without diabetes (aOR 1.19 [95% CI 1.01, 1.41]; P 5 0.040), however, it was not associated with in-hospital death or poor prognosis in patients with diabetes and COVID-19 Increasing odds of in-hospital death in all patients with COVID-19 associated with diabetes (OR 2.51 [95% CI 1.53, 4.13]) Risk factors for poor prognosis in patients with diabetes and COVID-19 were low albumin (aOR 0.91 [95% CI 0.83, 0.99]; P50.030) and high CRP (aOR 1.16 [95% CI 1.01, 1.32]; P 5 0.033) Insulin usage (aOR 3.58 [95% CI 1.37, 9.35]; P 5 0.009) was associated with poor prognosis Insulin and no-insulin groups showed no significant difference in the percentages of those with severe and critical illness on admission (16.90% [12 patients] in the insulin group vs. 10.20% [5 patients] in the no-insulin group; P 5 0.426). Multivariable regression analyses - none of the glucose lowering medications (metformin, insulin, a-glycosidase, secretagogues, or DPP-4 inhibitors) were associated with in hospital death	Chen Y et al. Clinical characteristics and outcomes of patients with diabetes and COVID-19 in association with glucose-lowering medication. Diabetes Care. 2020 May 13.
To explore the clinical risk factors associated with death.	Yes	Case series	44,672	Cardiovascular disease, hypertension, diabetes, respiratory disease, and cancers	China	No comparison group	Cardiovascular disease (RR = 6.75, 95%CI = 5.40–8.43, p < 0.001), hypertension (HR = 4.48, 95%CI = 3.69–5.45, p < 0.001), diabetes (RR = 4.43, 95%CI = 3.49–5.61, p < 0.001), respiratory disease (RR = 3.43, 95%CI = 2.42–4.87, p < 0.001), and cancers (RR = 2.926, 95%CI = 1.34–6.41, p = 0.006) were the risk factors for fatality of patients with COVID-19.	Deng G et al. Clinical determinants for fatality of 44,672 patients with COVID-19. Critical Care. 2020 Dec;24(1):1-3.
To determine factors associated with risk of death from COVID-19	No	Cohort study	17,425,445	Diabetes, asthma, heart disease, respiratory disease, Hypertension,	England	Covers 40% of the population, but may not yet be fully representative	Most comorbidities were associated with higher risk of COVID-19 hospital death, including diabetes (2.36 (2.18-2.56)) (with a greater HR for those with recent HbA1c >= 58 mmol/mol), asthma (1.25 (1.08-1.44)) (with a greater HR for those with recent use of an oral corticosteroid), respiratory disease (1.78 (1.67-1.90)), and chronic heart disease (1.27 (1.20-1.35)). There was no association between hypertension (defined as a recorded diagnosis, or high blood pressure at the last measurement) and outcome (HR 0.95, 0.89-1.01). However, in sensitivity analyses, diagnosed hypertension was associated with slightly increased risk (HR 1.07, 1.00-1.15) while high blood pressure (≥140/90 mmHg) at the most recent measurement was associated with lower risk (HR 0.61, 0.56-0.67).	Williamson E et al. Open SAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. medRxiv. 2020 Jan 1.

Table 4 *Primary studies not included in the reviews*

Research question / objective	Peer reviewed publication	Type of study	Sample size	NCD	Where study conducted	Risk of bias	Findings	Citation
Outcomes of COVID-19 positive patients with diabetes managed as outpatients	Yes	Retrospective study	49	Diabetes	USA	Small sample size; selection bias	Rate of hospitalisation for patients with diabetes in ECVOMC was double the rate of hospitalisation for all ECVOMC patients	Shabto JM et al. Characteristics and Outcomes of COVID-19 Positive Patients with Diabetes Managed as Outpatients. Diabetes Research and Clinical Practice. 2020 May 22:108229.
Whether DPP-4 inhibitors might be protective against COVID-19 among people with type 2 diabetes	No	Retrospective study	403	Diabetes	Italy	Concern re representativeness of sample; ascertainment bias	Type 2 diabetes patients with COVID-19 who were on DPP-4i had a similar disease outcome as those who were not. Proportion of DPP-4i users among patients with COVID-19 pneumonia was 11.3% (95% C.I. 5.8-20.7) and 10.3% (95% C.I. 7.5-13.9) among diabetic patients hospitalised for pneumonia of other aetiology (OR 1.11. p=0.967).	Fadini GP et al. Exposure to DPP-4 inhibitors and COVID-19 among people with type 2 diabetes. A case–control study. Diabetes, Obesity and Metabolism. 2020 May 28.
Association between Metformin Treatment with Decreased Mortality in COVID-19 Patients with diabetes	Yes	Retrospective study	283	Diabetes	China	Small sample size; retrospective	In-hospital mortality was lower in the metformin group (3/104 (2.9%) versus 22/179 (12.3%), P = 0.01) Fasting blood glucose level of the metformin group was higher than that of the no-metformin group at admission and was under effective control in both groups after admission	Luo P et al Metformin Treatment Was Associated with Decreased Mortality in COVID-19 Patients with Diabetes in a Retrospective Analysis. The American Journal of Tropical Medicine and Hygiene. 2020 May 21:tpmd200375.
The effects of TCZ on outcomes in hyperglycaemic Covid-19 patients with moderate-to-severe respiratory illness.	No	Retrospective study	78	Diabetes	Italy	Retrospective; small sample size	At admission, higher IL-6 levels were found in hyperglycaemic patients that persisted even after TCZ administration. Also, in the risk-adjusted Cox regression analysis, TCZ in hyperglycaemic patients failed to attenuate the risk of severe outcomes as it did in normoglycaemic patients (P < 0.009). Moreover, Kaplan–Meier analysis showed that hyperglycaemic patients without a diabetes diagnosis had an increased risk of severe disease compared with both normoglycaemic and hyperglycaemic patients with a previous diabetes diagnosis. Moreover, there was evidence that optimal Covid-19 infection management with TCZ is not achieved during hyperglycaemia in both diabetic and non-diabetic patients.	Marfella R et al. Negative impact of hyperglycaemia on tocilizumab therapy in Covid-19 patients. Diabetes & Metabolism. 2020 May 21.

Table 4 *Primary studies not included in the reviews*

Research question / objective	Peer reviewed publication	Type of study	Sample size	NCD	Where study conducted	Risk of bias	Findings	Citation
Type 1 and Type 2 diabetes and COVID-19 related mortality in England: a cohort study in people with diabetes	No	Cohort	265,090 people with Type 1 and 2,889,210 people with Type 2	Diabetes	UK	lack of accurate population level data on tests for COVID-19	The degree of hyperglycaemia was strongly associated with risk of death related to COVID-19 after adjusting for other risk factors. In this population of people with diabetes, there was a U- shaped relationship with body mass index. Impaired renal function was associated with an increased risk of COVID-19 related death.	Holman N, et al. Type 1 and Type 2 diabetes and COVID-19 related mortality in England: a cohort study in people with diabetes.
Prognostic markers of good or poor outcome in patients with these NCDs when they have COVID-19								
The precise diabetes-related phenotype associated with covid-19 severity in people with diabetes	No	Prospective observational study	1317	Diabetes	France	Low and highly unlikely for selection, information and confounding bias.	Characteristics prior to admission associated with combined tracheal intubation for mechanical ventilation and/or death within 7 days of admission: sex, BMI and previous treatment with RAAS blockers In multivariable analyses with covariates prior to admission, only BMI remained positively associated with the combined tracheal intubation for mechanical ventilation and/or death within 7 days of admission (OR 1.28 [1.10, 1.47]). On admission, dyspnoea (OR 2.10 [1.31, 3.35]), lymphocyte count (OR 0.67 [0.50, 0.88]), C-reactive protein (OR 1.93 [1.43, 2.59]) and AST (OR 2.23 [1.70, 2.93]) levels were independent predictors of the combined tracheal intubation for mechanical ventilation and/or death within 7 days of admission Age (OR 2.48 [1.74, 3.53]), treated obstructive sleep apnoea (OR 2.80 [1.46, 5.38]), and microvascular (OR 2.14 [1.16, 3.94]) and macrovascular complications (OR 2.54 [1.44, 4.50]) were independently associated with risk of death on day 7.	Cariou B et al. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia. 2020 May 29:1.

***Table 5** Ongoing studies*

Country	Type of study	NCD	Research question / objective / aim / purpose	Add ongoing study URL
Increased risk of hospitalisation and death from COVID-19 in patients with NCDs - 5				
France	Cohort	HPT	To assess the risk of moderate to serious COVID-19 infections in patients using synthetic anti-malarial drugs (AMD) or anti-hypertensive drugs (Angiotensin receptor-blocking/Angiotensin-converting-enzyme inhibitors). To examine the risk of moderate to serious COVID-19 infections according of age, sex, co-morbidities, level of exposure of AMD, geographical locations and underlying comorbidities.	https://clinicaltrials.gov/ct2/show/NCT04356417
Switzerland	Cohort	CVD, diabetes, hypertension, dyslipidaemia	To characterise the clinical course of adult inpatients with COVID-19 and concomitant cardiovascular affection in a worldwide, multi-centre PCHF registry	https://clinicaltrials.gov/ct2/show/NCT04390555
Sweden	Case control	Diabetes, hypertension	Risk Factors of Critical Care Admission and Intensive Care Mortality	https://clinicaltrials.gov/ct2/show/NCT04390074
-	Systematic review	HPT	The association of comorbid hypertension with poorer progression in patients with COVID-19	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020179861
-	Systematic review	Diabetes	COVID-19 susceptibility and sequelae in diabetes and obesity: a systematic review and meta-analysis	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020180730
Management of COVID-19 in patients with these NCDs - 11				
Italy	Clinical trial	Presence of one or more comorbidities	The objectives of this study are: to demonstrate the superiority of COVID-19 convalescent plasma (CCP) plus standard therapy (ST) over ST alone, to prevent progression of pneumonia in COVID-19 patients aged ≥65 with chronic comorbidities	https://www.clinicaltrials.gov/ct2/show/NCT04374526
Ireland	Clinical trial	Hypertension	To randomise patients with primary (essential) hypertension who are already taking ACEi/ARB to either switch to an alternative BP medication or continue with the ACEi/ARB that they have already been prescribed.	https://www.clinicaltrials.gov/ct2/show/NCT04330300
USA	Clinical trial	Diabetes mellitus / blood glucose measurement >126 mg/dl AND EITHER history of hypertension and/or ischemic heart disease and/or heart failure	To determine the effects of standard of care treatment vs. standard of care plus AT-001 on cardiac structure and function and in-hospital survival in patients hospitalised for management of COVID-19 infection.	https://clinicaltrials.gov/ct2/show/NCT04365699
Italy	Clinical trial	Diabetes	The Effect of Sitagliptin Treatment in COVID-19 Positive Diabetic Patients	https://www.clinicaltrials.gov/ct2/show/NCT04365517
USA	Clinical trial	Diabetes	Effects of Dipeptidyl Peptidase 4 (DPP4) Inhibition on COVID-19 Patients With Type 2 Diabetes	https://www.clinicaltrials.gov/ct2/show/NCT04341935
Israel	Clinical trial	Diabetes	Efficacy and Safety of Dipeptidyl Peptidase-4 Inhibitors in Diabetic Patients With Established COVID-19	https://clinicaltrials.gov/ct2/show/NCT04371978
France	Case control	Hypertension	To analyze the associations between COVID-19 and hypertension, and treatments with angiotensin converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARBs)	https://clinicaltrials.gov/ct2/show/NCT04374695
Italy	Case control	Diabetes	Sitagliptin Treatment in Diabetic COVID-19 Positive Patients	https://www.clinicaltrials.gov/ct2/show/NCT04382794

Table 5 Ongoing studies

Country	Type of study	NCD	Research question / objective / aim / purpose	Add ongoing study URL
-	Systematic review	Diabetes	Is chloroquine plus azithromycin strategy safe and effective for the treatment of novel coronavirus (COVID-19) pneumonia in diabetic patients?	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020179573
-	Systematic review	Hypertension	Can hypertension patients with COVID-19 continue to use angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs)? Does taking these two drugs increase the chance of infection with COVID-19 in hypertensive patients?	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=177067
-	Systematic review	Acute stroke	Is Traditional Chinese Medicine safe and effective for COVID-19 patients with ischemic stroke?	https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=179679
Prognostic markers of good or poor outcome in patients with these NCDs when they have COVID-19 - 10				
Switzerland	Cohort	CVD	The primary aim of this study is to gather observational data, starting from February 1st 2020 until the end of the pandemic, to compare clinical outcomes COVID+ hospitalised patients at HUG or in a care center in Geneva with pre-existing or newly onset CVD, to COVID+ hospitalised patients at HUG or in a care center in Geneva without pre-existing CVD	https://clinicaltrials.gov/ct2/show/NCT04384029
China	Case control	Hypertension	The impact of hypertension and hypertension treatment on the severity and prognosis of patients with covid-19.	https://clinicaltrials.gov/ct2/show/NCT04318301
China	Case control	Diabetes	A Single-centre Retrospective Study to Find Prediction Factors Related to Mortality of COVID-19 Patients by Univariate and Multivariate Analysis	https://clinicaltrials.gov/ct2/show/NCT04365634
Italy	Case control	At least one of Hypertension, Obesity &/or diabetes, CVD, COPD	The primary end-point of is to assess the recovery rate in patients with diagnosis of Covid-19 pneumonia. Among the other secondary end-points, we intend to find the predictors of the time to clinical improvement or hospital discharge in patients affected by Covid-19 pneumonia.	https://clinicaltrials.gov/ct2/show/NCT04324684
USA	Case control	CVD	A retrospective, observational, case-control study looking for cardiovascular manifestations of COVID-19, including laboratory evidence of myocardial injury, electrocardiographic changes, arrhythmias and echocardiographic abnormalities. Include the role of pre-existing CVD comorbidities in clinical course of COVID-19.	https://clinicaltrials.gov/ct2/show/NCT04335630
China	Case series	Diabetes	Application of flash glucose monitoring to evaluate the effect of hyperglycaemia and glycaemic variability on prognosis in patients with novel coronavirus pneumonia (COVID-19)	https://apps.who.int/trialsearch/Trial2.aspx?TrialID=ChiCTR2000030436
-	Systematic review	Diabetes	The association of comorbid diabetes mellitus with poorer progression in patients with COVID-19 remain controversial.	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=178048
-	Systematic review	Diabetes	What are the genetic polymorphisms that are associated with the worst outcome of COVID-19 in patients with diabetes mellitus?	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181311
-	Systematic review	Diabetes	How do maternal, perinatal, and post-perinatal outcomes from Covid-19 in women with diabetes and gestational diabetes compare to normoglycaemic pregnancies?	https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020180186
-	Systematic review	Hypertension	Is hypertension an independent prognostic factor for poor outcomes in COVID-19 patients?	https://www.crd.york.ac.uk/PROSPERO/display_record.php?RecordID=180040

APPENDICES

Appendix 1 Search strategy

Medline (PubMed) – https://www.ncbi.nlm.nih.gov/pubmed/

#1 SARS-Cov2

#2 (COVID19 OR COVID-19 OR "COVID 19")

#3 "COVID-19" [Supplementary Concept]

#4 #1 OR #2 OR #3

#5 (diabetes or hypertension or asthma or occupational lung diseases or coronary heart disease or heart failure or stroke)

#6 "Diabetes Mellitus"[Mesh]

#7 "Hypertension"[Mesh]

#8 "Asthma"[Mesh]

#9 "Lung Diseases"[Mesh]

#10 "Coronary Disease"[Mesh]

#11 "Heart Failure"[Mesh]

#12 "Stroke"[Mesh]

#13 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12)

#14 #5 OR #13

#15 #4 AND #14 Filters: Publication date from 2019/10/01 to 2020/05/31; Humans

Cochrane COVID-19 Study Register – https://covid-19.cochrane.org/

diabetes OR hypertension OR asthma OR "occupational lung diseases" OR "coronary heart disease" OR "heart failure" OR stroke AND 1 Oct '19 – 31 May '20

Epistemonikos – https://www.epistemonikos.org/

(advanced_title_en:((SARS-Cov2 OR COVID19 OR "COVID 19" OR COVID-19)) OR advanced_abstract_en:((SARS-Cov2 OR COVID19 OR "COVID 19" OR COVID-19))) AND (advanced_title_en:((diabetes OR hypertension OR asthma OR "occupational lung diseases" OR "coronary heart disease" OR "heart failure" OR stroke)) OR advanced_abstract_en:((diabetes OR hypertension OR asthma OR "occupational lung diseases" OR "coronary heart disease" OR "heart failure" OR stroke))) [Filters: protocol=no, min_year=2019, max_year=2020]

Trip Database – https://www.tripdatabase.com/

(SARS-CoV2 OR COVID19 OR "COVID 19" OR COVID-19) AND (diabetes or hypertension or asthma or "occupational lung diseases" or "coronary heart disease" or "heart failure" or stroke)

Appendix 2 Mapping studies included in reviews on the use of renin-angiotensin-aldosterone system (RAAS) inhibitors

Studies included in reviews	Reviews		
	Garg	Ssentongo	Guo
Bean D		x	
Conversano A	x		
De Abajo	x		
Feng Y	x		x
Guo T	x	x	
Huang Z		x	x
Ip A		x	
Li J	x	x	x
Li X	x		
Mancia G	x	x	
Mehra MR	x	x	
Mehta N	x	x	
Meng J	x	x	x
Peng Y	x		x
Reynolds HR	x		x
Richardson S		x	
Wang Y, Lu	x		
Yang G	x	x	x
Zhang L, Sun		x	
Zhang P	x	x	x
Zheng Z		x	