Australian Government
National Health and Medical Research Council

NHMRC

National COVID-19 Health and Research Advisory Committee*

Date of report: 23 July 2020

Risk stratification of population groups in the context of COVID-19: hypertension and age evidence update

Focus

AHPPC asked NCHRAC to consider the available evidence on the risks of severe disease or death from COVID-19 that might clarify:

- if age alone is a risk factor, without underlying comorbidities, and
- whether hypertension is a risk factor, or whether it is only a risk factor if poorly managed.

This evidence brief is point in time and may need further review as more evidence is available, particularly on the association between comorbidities and the severity of COVID-19 disease and within the Australian context.

This evidence brief was developed by a working group of NCHRAC (see membership at **Attachment 1**).

Conclusions

NCHRAC conclusion 1: The available evidence shows that advancing age is a clear risk factor for severe disease or death from COVID-19, however, there is no clear age threshold at which a person becomes at risk of severe disease or death from COVID-19.

In drawing this conclusion, NCHRAC considered that as a person gets older, their risk of severe disease and death from COVID-19 increases with age. In a cohort study of primary care data (17 million patients) linked to COVID-19 notification data, risk of death from COVID-19 increased exponentially with age.[1] This aligned with results from a systematic review that found that every ten year increase in age increased the probability of severe disease by 6.6% (odds ratio (OR) 1.63, 95%CI 1.4–1.80) and death by 6.1% (OR 1.80, 95%CI 1.54–2.10).[2]

An example of the independent effect of age on increased risk of death from COVID-19 was demonstrated by Williamson *et al*[1]; data for age, including hazard ratios (HRs), are extracted and presented below.

---

* NHMRC is providing secretariat and project support for the Committee, which was established to provide advice to the Commonwealth Chief Medical Officer on Australia's health response to the COVID-19 pandemic. The Committee is not established under the NHMRC Act and does not advise the NHMRC CEO.

Extracted from Table 2: Hazard Ratios (HRs) and 95% confidence intervals (CI) for in-hospital COVID-19 death.[1]

	CPNS Death HR (95% CI)	
	Age-sex adj	**Fully adj**
Age		
18-<40	0.05 (0.04-0.08)	0.07 (0.05-0.10)
40-<50	0.27 (0.21-0.34)	0.31 (0.25-0.39)
50-<60	1.00 (ref)	1.00 (ref)
60-<70	2.61 (2.29-2.96)	2.09 (1.84-2.38)
70-<80	7.61 (6.78-8.54)	4.77 (4.23-5.38)
80+	26.27 (23.52-29.33)	12.64 (11.19-14.28)

Abbreviation: CPNS – COVID-19 inpatient hospital death notifications.

NCHRAC conclusion 2: According to the available evidence, it appears that hypertension is not a substantial risk factor for severe disease or death from COVID-19.

In drawing this conclusion, the working group noted that there is some variation in the published data on the association between hypertension and severe disease or death from COVID-19. At this point in time, there is no conclusive evidence that hypertension increases the risk of severe disease or death from COVID-19.

In reaching this conclusion, NCHRAC relied heavily on a population study of 17 million people registered with GP surgeries in England and included regardless of testing or COVID-19 status, which indicated measured high blood pressure or a history of diagnosed hypertension had little to no effect on disease severity, when adjusted for all other potential risk factors HR 0.95, 95%CI 0.89–1.01.[1] However, a population study of over 200,000 people from Korea who had made an insurance claim for COVID-19 testing, found that isolated hypertension (not defined) was associated with an increased risk of severe disease in a multivariate analysis (OR range 1.245–1.317).[3]

The working group acknowledges that hypertension is often associated with other risk factors that may increase the risk of severe COVID-19 disease but is unlikely to be an independent risk factor in its own right.

NCHRAC did not identify appropriate literature to determine whether untreated hypertension contributes to additional risk of severe disease or death from COVID-19. This conclusion should be reviewed periodically as new evidence becomes available.

Background

The conclusions represent the expert interpretation of relevant evidence as at 14 July 2020.

A summary of evidence considered is provided at **Attachment 2**.

Attachments

Attachment 1: Membership of the NCHRAC Risk Stratification of Population Groups in the context of COVID-19 Working Group

Attachment 2: Evidence summary

References

[1] The OpenSAFELY Collaborative, Williamson E, Walker AJ, Bhaskaran K, et al. OpenSAFELY: factors associated with COVID-19-related hospital death in the linked electronic health records of 17 million adult NHS patients. *MedRxiv* 2020 (posted 7 May 2020). DOI: https://doi.org/10.1101/2020.05.06.20092999 [Pre-print]

[2] Iscovich A, Ragusa M, Tortosa F, et al. Prognostic factors for severity and mortality in patients infected with COVID-19: A systematic review. *SSRN* 2020 (posted 24 Jun 2020). DOI: https://dx.doi.org/10.2139/ssrn.3627285 [Pre-print]

[3] Wonjun J, Huh K, Kang M, et al. Effect of Underlying Comorbidities on the Infection and Severity of COVID-19 in Korea: a Nationwide Case-Control Study. *J Korean Med Sci.* 2020 Jun 29; 25(25):e237. DOI: https://doi.org/10.3346/jkms.2020.35.e237 (published online 25 Jun 2020)

Australian Government
National Health and Medical Research Council

NHMRC

Attachment 1

NCHRAC Risk stratification of population groups in the context of COVID-19 Group

NCHRAC Members

Professor David Paterson – Chair

Professor Jonathan Carapetis AM

Professor Raina MacIntyre

Dr James Muecke AM

Invited Experts

Professor Josh Davis, President, Australasian Society for Infectious Diseases

Dr Jenny Firman, Deputy Chief Medical Officer, Department of Health

Dr Catherine Kelaher, Office of Health Protection, Department of Health

Professor Michael Reade AM, Professor of Military Medicine & Surgery, University of Queensland & Australian Defence Force Joint Health Command

Dr Katherine Woodthorpe AO, Chair – NHMRC Health Innovation Advisory Committee

Attachment 2

Systematic reviews of prognostic factors for COVID-19

1. Izcovich A, Ragusa M, et al. Prognostic Factors for Severity and Mortality in Patients Infected with COVID-19: A Systematic Review. The Lancet (pre-print). Posted 24th June 2020.
    a. Objective: to identify prognostic factors that may be used in decision-making related to the care of patients infected with COVID-19. Searched to 28th April 2020. Included 207 studies that assessed patients with confirmed or suspected SARS-CoV-2 infection and examined one or more prognostic factors for mortality or disease severity. Found with high or moderate certainty 49 variables that provide prognostic information. These have been grouped under demographic factors, patient history factors, physical examination factors and laboratory factors.
    b. Two reviewers assessed the risk of bias of individual included studies independently and in duplicate. Discrepancies were resolved by consensus. We used the Quality in Prognosis Studies (QUIPS) tool for prognostic factor studies.11 For "study confounding summary" and "statistical analysis and presentation domains", in order to assess adequacy of the multivariable models, we considered appropriate model adjustment as based on inclusion of age, one comorbidity (e.g. diabetes) and one parameter of disease severity (e.g. respiratory rate) at minimum. Risk of bias was high across most studies. 7 were judged as low risk of bias: Bai, Bi, Cummings, Docherty, Mehra and Rossi.
    c. For results see Table 1 in the complete manuscript. The following have been extracted from this table:

Table 1: Prognostic factors for mortality and/or severe COVID-19 disease extracted from Izcovich review

Prognostic factor	Mortality					Severe COVID-19 disease				
	Number of patients (studies)	Odds ratio (95%CI)	Risk without prognostic factor	Risk with prognostic factor	Certainty of the evidence	Number of patients (studies)	Odds ratio (95%CI)	Risk without prognostic factor	Risk with prognostic factor	Certainty of the evidence
Age Definition: 10 years increase	11962 (19)	1.80 (1.54-2.10)	9%	15.1% 6.1% increase in mortality. Between 4.2% more and 8.2% more	High	14456 (53)	1.63 (1.47-1.80)	13%	19.6% 6.6% increase in mortality. Between 5% more and 8.2% more	High
Sex Definition: male	31948 (58)	1.72 (1.5-1.98)	8%	13% 5% increase in mortality. Between 4% more and 8.2% more	Moderate	25032 (122)	1.53 (1.4-1.67)	10.8%	15.5% 4.7% increase in mortality. Between 3.7% more and 5.6% more	High
Arterial hypertension	31341 (52)	2.02 (1.71-2.38)	7%	13% 6% increase in mortality. Between 4.5% more and 7.3% more	High	20817 (94)	2.5 (2.21-2.92)	11.1%	23.3% 12.1% increase in mortality. Between 10.4% more and 14.4% more	Moderate
Low blood pressure Definition: SBP less than 90-100 mmHg	1269 (2)	6.7 (3.14-14.33)	9%	39.9% 30.9% increase in mortality. Between 14.7% more and 49.6% more	Moderate	480 (2)	1.29 (0.72-2.29)	NA	NA NA	NA

2. 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. JRAAS April-June 2020
    a. Objective: to investigate the association between hypertension and poor outcome in patients with COVID-19 pneumonia. Included 30 studies (6560 patients) of adult COVID-19 patients with information on hypertension and the composite poor outcome - mortality, severe COVID-10, ARDS, intensive care unit (ICU) care and disease progression.
    b. Risk of bias not assessed. Only 1 of the included studies was prospective
3. Wynants L et al. Prediction models for diagnosis and prognosis of covid-19: systematic review and critical appraisal
    a. Objective: to review and critically appraise published and preprint reports of prediction models for diagnosing covid-19 in patients with suspected infection, for prognosis of patients with covid-19, and for detecting risk of becoming infected with covid-19 or being admitted to hospital with the disease.
    b. Searched up to 7th April 2020. Study quality evaluated using Probast tool.
    c. Included 51 studies that developed or validated (66) multivariable covid-19 related prediction models.
    d. Evaluates models but does not report on results of the application of those models.
    e. Concludes that proposed models are “poorly reported, at high risk of bias, and their reported performance is probably optimistic”.

A number of systematic reviews were identified that are now out-of-date (searches conducted before May 2020) and were not considered further, including Zheng Z et al, Young BE et al, Martins-Filho PR et al and Yang J et al.

Studies of COVID-19 published after April 2020

Includes studies identified in a search of PubMed conducted on 10th July 2020 using the terms **((sars-cov-2) AND (hypertension)) AND (cohort study[MeSH Terms]).** The search resulted in 55 citations, and Table 2 below summarises those that met the following criteria:

- Have not yet been considered by the Izcovich and Ragusa review
- Conducted their search after April 2020
- Population included individuals diagnosed with COVID-19
- Reported outcome data for patients with/without hypertension
- >500 patients/participants
- Ideally conduct multivariate analysis
- Note: risk of bias for these studies has not been evaluated.

Table 2: Studies published since April 2020 reporting on COVID-19 and hypertension

First author	Population	Country	Sample size	Hypertension Age Outcome/s	Abstract (or summary)	Citation and Link to article
Ji W	18 years or older, whose medical costs for COVID-19 testing were claimed until May 15, 2020 a nationwide retrospective case-control study Data extracted from insurance claims database of HIRA	South Korea	219,862 adults tested; 7341 positive, 954 severe	Hypertension: *isolated hypertension not defined but refers to ICD10* Age: not reported Outcome/s: a diagnosis of COVID-19; disease severity *defined as patients with a diagnosis confirmed by an RT-PCR test, who had claim data for oxygen therapy, mechanical ventilator, extracorporeal membrane*	**Objective:** to evaluate the underlying comorbidities associated with the diagnosis and severity of COVID-19. **Methods** COVID-19 diagnosis and infection severity were identified from reimbursement data using diagnosis codes and on the basis of respiratory support use, respectively. Odds ratios (ORs) were estimated using multiple logistic regression, after adjusting for age, sex, region, healthcare utilization, and insurance status. **Results** The COVID-19 group (7,341 of 219,961) was young and had a high proportion of female. Overall, 13.0% (954 of 7,341) of the cases were severe. The severe COVID-19 group had older patients and a proportion of male ratio than did the non-severe group. Diabetes (odds ratio range [ORR], 1.206–1.254), osteoporosis (ORR, 1.128–1.157), rheumatoid arthritis (ORR, 1.207–1.244), substance use (ORR, 1.321–1.381), and schizophrenia (ORR, 1.614–1.721) showed significant association with COVID-19. In terms of severity, diabetes (OR, 1.247; 95% confidential interval, 1.009–1.543), hypertension	J Korean Med Sci. 2020 Jun 29; 35(25): e237. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7324262/

				oxygenation, and cardiopulmonary resuscitation	(ORR, 1.245–1.317), chronic lower respiratory disease (ORR, 1.216–1.233), chronic renal failure, and end-stage renal disease (ORR, 2.052–2.178) were associated with severe COVID-19.	
Bravi F	All adults with SARS-CoV-2 infection in two Italian provinces were followed for a median of 24 days. Retrospective case control study	Italy	1603 (543 with hypertension)	Hypertension: not defined Explored based on treatment with ACE inhibitors or ARBs Age: yes Outcome/s: disease severity a. asymptomatic infection or mild disease, defined as fever or malaise plus at least one of the followings: sore throat, muscle pain, shortness of breath, dry cough, headache, conjunctivitis, and diarrhea, with no hospital admission; b. severe disease, requiring hospital admission, not in an intensive care unit; c. very severe or lethal disease, requiring admission in an intensive care unit and/or causing death.	**Objective:** to confirm the potential independent predictors of severe/lethal COVID-19, including treatment with ACE inhibitors and/or ARBs. **Methods and results** ARBs (Angiotensin II Receptor Blockers) and/or ACEi (Angiotensin-Converting Enzyme inhibitors) treatments, and hypertension, diabetes, cancer, COPD, renal and major cardiovascular diseases (CVD) were extracted from clinical charts and electronic health records, up to two years before infection. The sample consisted of 1603 subjects (mean age 58.0y; 47.3% males): 454 (28.3%) had severe symptoms, 192 (12.0%) very severe or lethal disease (154 deaths; mean age 79.3 years; 70.8% hypertensive, 42.2% with CVD). The youngest deceased person aged 44 years. Among hypertensive subjects (n = 543), the proportion of those treated with ARBs or ACEi were 88.4%, 78.7% and 80.6% among patients with mild, severe and very severe/lethal disease, respectively. At multivariate analysis, no association was observed between therapy and disease severity (Adjusted OR for very severe/lethal COVID-19: 0.87; 95% CI: 0.50–1.49). Significant predictors of severe disease were older age (with AORs largely increasing after 70 years of age), male gender (AOR: 1.76; 1.40–2.23), diabetes (AOR: 1.52; 1.05–2.18), CVD (AOR: 1.88; 1.32–2.70) and COPD (AOR: 1.88; 1.11–3.20). Only gender, age and diabetes also predicted very severe/lethal disease.	PLoS One. 2020 Jun 24;15(6):e0235248 http://dx.plos.org/10.1371/journal.pone.0235248 https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0235248
Gao C	All patients admitted with COVID-19 to Huo Shen Shan	China	2877 consecutive	Hypertension: diagnosis by the patient's physician	Objective: to test the hypothesis that treatment of hypertension, especially with RAAS inhibitors, might impact on the mortality of patients with COVID-19	Eur Heart J. 2020 Jun ;41(22):2058-2066. doi:

	Hospital. The hospital was dedicated solely to the treatment of COVID-19 in Wuhan, China Retrospective observational study		hospitalized patients	prior to the infection with SARS-CoV-2. These data were collected from patients' documented medical files. Age: yes Outcome/s: primary was all-cause mortality during hospitalization. Other included the time elapsed between onset of symptoms and discharge, the rates of use of invasive mechanical ventilation, and the severity of COVID-19 (mild, severe, or critical – all defined).	**Methods and results:** Hypertension and the treatments were stratified according to the medical history or medications administrated prior to the infection. Among 2877 hospitalized patients, 29.5% (850/2877) had a history of hypertension. After adjustment for confounders, patients with hypertension had a two-fold increase in the relative risk of mortality as compared with patients without hypertension [4.0% vs. 1.1%, adjusted hazard ratio (HR) 2.12, 95% confidence interval (CI) 1.17-3.82, P = 0.013]. Patients with a history of hypertension but without antihypertensive treatment (n = 140) were associated with a significantly higher risk of mortality compared with those with antihypertensive treatments (n = 730) (7.9% vs. 3.2%, adjusted HR 2.17, 95% CI 1.03-4.57, P = 0.041). The mortality rates were similar between the renin-angiotensin-aldosterone system (RAAS) inhibitor (4/183) and non-RAAS inhibitor (19/527) cohorts (2.2% vs. 3.6%, adjusted HR 0.85, 95% CI 0.28-2.58, P = 0.774).	10.1093/eurheartj/ehaa433. https://pubmed.ncbi.nlm.nih.gov/32498076/
Lee LYW	Patients with active cancer and symptomatic COVID-19 (surveillance registry) Prospective cohort	UK	800	Hypertension: ICD code Age: yes Outcome/s: all cause mortality, discharge from hospital	"risk of death was significantly associated with advancing patient age (odds ratio 9·42 [95% CI 6·56–10·02]; p<0·0001), being male (1·67 [1·19–2·34]; p=0·003), and the presence of other comorbidities such as hypertension (1·95 [1·36–2·80]; p<0·001) and cardiovascular disease (2·32 [1·47–3·64]).” Note above is the result of a univariate regression analysis.	Lancet. 2020 Jun 20;395(10241):1919-1926. doi: 10.1016/S0140-6736(20)31173-9. Epub 2020 May 28. https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/32473682/
Price-Haywood EG	Patients seen in integrated-delivery health system in Louisiana	USA	3626 (3481 with data on race); 1382 hospitalized	Hypertension: not defined Age: yes	Objective: to compare the clinical characteristics and hospital course of COVID-19 among black non-Hispanic and white non-Hispanic subpopulations in Louisiana. Clinical data extracted from electronic medical records system.	N Engl J Med. 2020 Jun 25; 382(26):2534-2543. doi: 10.1056/NEJMsa2011686. Epub 2020 May 27.

	March 1 - April 11, 2020 Retrospective, observational, cohort study seen at a single health facility			Outcome/s: length of hospital stay, death from any cause, survival to discharge	Unadjusted and multivariable models but hypertension not included in models. Reports blood pressure as a clinical characteristic.	https://www.nejm.org/doi/full/10.1056/NEJMsa2011686
Chen Y	retrospective study involving 904 patients with COVID-19 Aged 15-99 admitted to the Central Hospital of Wuhan who had reached an outcome	China	904	Hypertension: not defined "In the analysis of blood pressure–lowering medication, we included 71 patients with diabetes who also had COVID-19 and comorbid hypertension and who had available a history of blood pressure–lowering drug use." Age: yes Outcome/s: discharged from or died in hospital, poor prognosis (includes progression to severe or critical illness and in-hospital death)	Aim: evaluate the clinical characteristics of patients with COVID-19 with or without comorbid diabetes, and provide specific information about those cases regarding routine usage of glucose-lowering or blood pressure– lowering medicines, the medications most commonly used by patients with diabetes. See table 3 in manuscript for results of univariate and multivariate logistic regression. Hypertension appears to be significant in the univariate but did not remain significant in the multivariate analysis, for both all patients and the subset of diabetes patients, for the outcomes in-hospital death and poor prognosis.	Diabetes Care. 2020 Jul;43(7):1399-1407. doi: 10.2337/dc20-0660. Epub 2020 May 14. https://care.diabetesjournals.org/content/diacare/early/2020/05/13/dc20-0660.full.pdf
Nikpouraghdam M	Retrospective study of patients hospitalized with COVID-19	Iran (single centre)	2968	Hypertension Age Outcome/s	Aim: to characterize the epidemiological features of COVID-19 in Iran Reported frequency of comorbidities but no comparisons for the outcomes. Logistic regression for mortality conducted but unclear which variables were included.	J Clin Virol. 2020 Jun;127:104378. doi: 10.1016/j.jcv.2020.104378. Epub 2020 Apr 21.

Stokes (CDC)	COVID-19 cases reported to CDC	USA	1,320,488	Hypertension: not reported Age: yes Outcome/s: hospitalization, ICU admission and death		https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html
Williamson (OpenSAFELY)	Cohort of all adults currently registered with GP surgeries with at least 1 year of prior follow up.	England	17,425,445 adults	Hypertension: raised blood pressure defined as either a prior coded diagnosis of hypertension or the most recent recording indicating systolic BP >= 140 mmHg or diastolic BP >= 90 mmHg. Age: yes Outcome/s: primary outcome is death in hospital among people with confirmed COVID-19	Covariates included: - health conditions in UK guidance, immunodeficiency, and emerging risk factors (including raised blood pressure) - age, sex, BMI, smoking status - other comorbidities including raised blood pressure or a diagnosis of hypertension Results: see Table 2 and Figure 3 There was no association between hypertension and in-hospital death (HR 0.95, 0.89-1.01). There was a clear trend by age.	Preprint https://www.medrxiv.org/content/10.1101/2020.05.06.20092999v1
Petrilli CM et al	Prospective cohort	USA (New York City)	5279	Hypertension: Age: yes Outcome/s: a) admission to hospital, b) critical illness (composite of care in ICU, use of mechanical ventilation, discharge	Objective: to describe outcomes of people admitted to hospital with COVID-19 disease, and the clinical and laboratory characteristics associated with severity of illness. Predictors: patient characteristics, medical history, vital signs and laboratory results. In multivariable analysis the factors most strongly associated with hospital admission were age, heart failure, male sex, chronic kidney disease and increase in BMI. Also significant was hypertension.	https://www.bmj.com/content/369/bmj.m1966

				to hospice, of death) , c) discharge to hospice care or death.	Of those admitted to hospital, factors most associated with critical illness were age, BMI and male sex. Diabetes was also significant. Hypertension was not significant. (Table 3) In a competing risk model for mortality hypertension was not significant.	
Kim et al	Cohort of hospitalised adults identified through COVID-NET (CDC's Coronavirus Disease 2019- Associated Hospitalization Surveillance Network)	USA	2491 (discharged or died in hospital) 1428/2488 with hypertension	Hypertension: not defined. Age: yes Outcome/s: ICU admission and in-hospital mortality	Objective: to describe risk factors for severe outcomes among adults hospitalised with COVID-19 Factors independently associated with ICU admission included age, male sex, obesity, diabetes and immunosuppression; and for mortality included age, diabetes, CLD, CVD, neurologic disorders, renal disease and immunosuppression. See Table 3. Hypertension was not a significant risk factor in the model. Note: most patients in the available data set have not reached an outcome	Preprint (CDC COVID-NET) Interim Analysis of Risk Factors for Severe Outcomes among a Cohort of Hospitalized Adults Identified through the U.S. Coronavirus Disease 2019 (COVID-19)-Associated Hospitalization Surveillance Network (COVID-NET) https://www.medrxiv.org/content/10.1101/2020.05.18.20103390v1