memo

COVID-19-EPIDEMIC :

COVID-19: The relationship between age, comorbidity and disease severity – a rapid review

Key messages

The findings in this memo are based on rapid searches in PubMed and Embase, as well as manual searches on websites of health authorities in selected countries. Two researchers shared tasks related to study selection and synthesis of results. In the current situation, there is an urgent need for identifying the most important evidence quickly. Hence, we opted for this rapid approach despite an inherent risk of overlooking key evidence or making misguided judgements.

Association between age and disease severity

Children are more mildly affected of COVID -19 than adults are. With increasing age, there seems to be an increasing proportion of COVID-19 patients who need hospitalization and who will need intensive care. Reports from many countries clearly show that the risk of dying from COVID-19 is higher among the elderly.

Association between comorbidity and disease severity

The incidence of many diseases appears higher among patients who die of COVID-19 than among those who survive. However, as chronic diseases are more common among older people, it is difficult to determine whether the increased risk among the elderly is due to comorbidity, age, or a combination of these factors.

Age and/or comorbidity?

We identified three studies analysing multiple risk factors using multivariate models, but the results do not provide clear answers as to whether age or comorbidity is the most important risk factor for serious illness. It seems reasonable to view age as an independent risk factor for death from COVID-19, but the results for other risk factors are more uncertain. It is difficult to draw firm conclusions about the relative importance of the various risk factors, as the available studies are small, with uncertain results. We expect that larger studies will soon be available, providing clearer answers about the relative importance of age and other risk factors for patients with COVID-19.

Contents

Problem statement

In connection with the ongoing COVID-19 outbreak, it is important to gather information about which patient groups are most at risk. The outbreak team at the Norwegian Institute of Public Health has asked us to prepare a quick survey and summary of the existing research on risk factors for developing serious illness. The main risk factors we focus on are age, comorbidity (such as cardiovascular disease, lung disease, diabetes and cancer), high blood pressure and obesity.

Method

We have undertaken a series of searches in PubMed and Embase for systematic reviews and other research articles. We also searched the websites of health authorities in selected countries.

Two researchers shared the task of reviewing search results, selecting, assessing and summarising the research results. The review was done individually and we only assessed the same studies if we believed it necessary.

Research librarian Elisabet Hafstad designed the literature searches.

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We have chosen this approach as it has been imperative to obtain the research results quickly, even though it is associated with a certain risk of overlooking important documentation and that we may make errors along the way.

This is the third rapid review which we have issued in response to the commission we received on 21 March 2020.

Results

The first part of the results chapter is a summary of 12 descriptive studies which report on the age distribution among patients who have died of COVID-19, the age distribution among patients who have required intensive care, the age distribution among patients who have been hospitalised and the corresponding rates of patients with various additional diseases (comorbidities).

In the second part of the results chapter, we summarize the findings from four studies that examined which risk factors are most important for predicting the severity of disease for patients with COVID-19.

Age distribution and prevalence of comorbidity among seriously ill patients

Age and lethality

Age distribution statistics among those who have lost their lives as a result of COVID-19 are available from several countries. A publication from the Chinese Centre for Disease Control reported 1,023 deaths and a clear correlation between age and lethality (case fatality rate – CFR) and between age and the actual number of deaths. Among COVID-19 cases the lethality (CFR) was 1.3% in the age group 50–59 years, increasing steadily with advancing age to be ten times as high (14.8%) among those over the age of 90 (1).

Reports from other countries, e.g. the United States, Italy, France and South Korea paint a similar picture, providing clear evidence that the risk of dying from COVID-19 is higher for the older population groups (2-6). Children seem to be far less severely affected (7).

Age and the need for intensive care

A report by the Centre for Disease Control in the US indicates the age distribution among COVID-19 patients who have been admitted to intensive care (2). Again, there is a clear gradient with an increasing rate of COVID-19 patients in need of intensive care with increasing age. A report from England, Wales and Northern Ireland concerning 196 patients with COVID-19 under intensive care shows an age distribution that is quite consistent with the figures from the US (8).

None of the 123 children mentioned in the U.S. report were admitted to intensive care (2). In a Chinese research paper reporting on 171 children with COVID-19, only three required intensive care. One of these children died. All three children that required intensive care had other underlying diseases (hydronephrosis, leukemia and intestinal invagination) (9).

Age and hospitalisation

The US report presents the age distribution among patients with COVID-19 who had been hospitalised, and the trend is the same as in intensive care: with increasing age, the proportion of COVID-19 cases requiring hospitalisation increases (2). Similar patterns have also been reported from Denmark (10).

Risk factors and comorbidity

The study by the Chinese Centre for Disease Control showed that comorbidity was far more common among those who died of COVID-19 than among those who survived the disease (1). Only 3% of the 44,672 patients with COVID-19 who were included in the study had elevated blood pressure, while 40% of those who died from COVID-19 had this condition. For cardiovascular disease, the corresponding rates were 4% and 32%, and for diabetes the rates were 5% and 20%.

Estimated lethality (CFR) for patients with no other recorded disease was 0.9%, while the figure was significantly higher for patients with high blood pressure (6.0%), diabetes (7.3%), cardiovascular disease (10.5%), chronic lung disease (6.3%), and cancer (5.6%).

One challenge in the interpretation of these figures is that we cannot say whether the increased risk is linked to age or comorbidity, as the incidence of other disease also increases with age. It is also not clear from the studies whether patients receive treatment for their comorbidity and the extent to which the underlying disease is well regulated. The increased risk of becoming severely ill due to COVID-19 may either be due to increased age, comorbidity, inadequate treatment or a combination of these factors. To shed light on this, we also summarize results from studies that have tried to identify which risk factors best predict a more serious course of the disease (see the section *Age and comorbidity as predictors of disease severity* below).

Risk factors, comorbidity and the need for intensive care

We have only limited information on comorbidity among COVID-19 patients receiving intensive care. The only data we have found on this is from 196 intensive care patients in England, Wales and Northern Ireland (8). The data shows the following incidence of comorbidity: no patients with cardiovascular disease (0%), three with respiratory disease (1.6%), four with kidney disease (2.1%), none with liver disease

(0%), two with metastatic cancer (1.1%), two with haematological cancer (1.1%) and seven immunosuppressed patients (3.7%).

The report from England, Wales and Northern Ireland also provides data on the BMI distribution among intensive care patients: one patient (0.6%) <18.5, 49 patients (28%) between 18.5 and 25, 56 patients (32%) between 25 and 30, 58 patients (33%) with a BMI between 30 and 40, and 13 patients (7.3%) with a BMI above 40. For comparison, the average BMI in England is around 28 (11).

We also identified a review article which compiled data from four different studies (covering approximately 1,150 patients in total) to compare the prevalence of comorbidities among COVID-19 patients experiencing a severe or less severe course of the disease (12). The definition of severity varies slightly between the primary studies. The authors of the review article report that the prevalence of the following conditions was significantly higher among patients with severe illness than among patients with less serious illness: high blood pressure (OR 2.36; 95% CI: 1.46 to 3.83), diabetes (OR 2.07; 95% CI: 0.89 to 4.82), respiratory disease (OR 2.46; 95% CI: 1.76 to 3.44) and cardiovascular disease (OR 3.42; 95% CI: 1.88 to 6.22).

Age and comorbidity as predictors of disease severity

Earlier in the results chapter, we have shown that individual factors, such as age and underlying disease, can be linked to the risk of a severe course of disease. However, understanding how different risk factors affect one another can be challenging. The fact that advanced age is associated with higher severity of the disease may be due to several factors. On the one hand, advanced age can correlate with other risk factors, for example in that increased age mirrors increased frequency of comorbidity; but it is also possible that age is an independent risk factor.

To be able to say something about which risk factors best predict severity of the disease, we searched for studies in which the relationship between disease severity and risk factors was analysed using multivariate analyses, where one can control for age when investigating the effect of other explanation variables, and vice versa.

We found three studies that reported on results from multivariate analyses of age and other risk factors, such as predictors of disease severity.

Chen et al. studied 160 patients with COVID-19 (13). They compared background variables for 126 patients experiencing a mild course of the disease and 24 patients who became critically ill. The full-text version of the article is only available in Chinese, but from the English summary it is clear that known heart disease (OR 16.6; 95% CI 2.3 to 120.6) stood out as the main risk factor for critical illness in the multivariate analysis, while it seems that the impact of age was not as clear.

Dong et al. examined data from 135 patients (14). Here, too, the full-text version is only available in Chinese, so we have based our findings on the English summary. The 135 patients branched into two groups of either a severe or mild course of the disease, and here both advancing age (OR 1.04; 95% CI 1.01 to 1.07) and underlying chronic disease (OR 1.7; 95% CI 1.1 to 2.8) were identified as risk factors for severe disease in the multivariate analysis.

Zhou et al. included data from 191 patients hospitalised in Wuhan due to COVID-19 (15). Of the 191 patients, 137 were later discharged, while 54 patients died at the hospital. Multivariate comparisons of those who died and those who recovered showed that advancing age stood out clearly as an important independent factor (OR 1.10; 95% CI 1.03 to 1.17). They also found a correlation between heart disease and COVID-19 mortality, but the results were not as convincing (OR 2.14; 95% CI 0.26 to 17.79). Other risk factors we were interested in were not included in the multivariate analysis.

Seen together, the three studies do not provide a clear answer as to whether age or comorbidity is the main predictor of a serious course of the disease for COVID-19 patients. It appears that age is an independent risk factor for death due to COVID-19, and that the results are somewhat more uncertain for other risk factors, but this is difficult to determine given the lack of available data. One important reason why the results are uncertain is that relatively few patients are included in these studies, which makes it particularly difficult to distinguish a clear link between comorbidity and disease severity, as only some of the patients have underlying conditions – as opposed to age, which is a distinctive factor that can be determined for all of us.

A fourth study relevant to this issue was conducted by Wu et al. The authors examined 201 patients admitted to hospitals in Wuhan. Of the 201 patients, 84 developed acute respiratory distress syndrome, of which 44 subsequently died. Comparisons suggest that there was a stronger correlation between age and morbidity than between age and acute respiratory distress syndrome/ARDS, while there did not appear to be any such correlation linked to high blood pressure or diabetes (16). However, we cannot draw any definite conclusions about the weighting of the various risk factors as the available studies are small and the results carry great uncertainty.

Information about COVID-19 patients is being continuously collected. The Chinese have relatively detailed information about more than 70,000 patients in their central database (1), which would make it relatively easy to conduct multivariate analyses. We therefore assume that such analyses will soon be published based on data from a much larger number of patients than in the studies that we have discussed here. This would allow us to gain more solid knowledge about the relative importance of age and other risk factors for COVID-19 patients.

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Appendix

Search methods

PubMed – overviews of age groups/comorbidity:

(((((Coronavirus[mh] OR "Coronavirus Infections"[mh] OR "corona virus"[tw] OR coronavirus[tw] OR coronovirus[tw]) AND (novel[tw]OR 2019[tw] OR Wuhan[tw])) OR "COVID-19"[tw] OR COVID19[tw] OR CORVID-19[tw] OR CORVID19 OR nCoV[tw] OR "SARS-CoV-2"[tw] OR "SARS-CoV2"[tw] OR SARSCoV19[tw] OR HCoV-19[tw] OR WN-CoV[tw]) AND (Comorbidity[mh] OR comorbid*[tw] OR co-morbid*[tw] OR "Diabetes Mellitus"[mh] OR diabet*[tw] OR Hypertension[mh] OR hypertensi*[tw] OR "Heart Diseases"[mh] OR "heart disease"[tw] OR "heart diseases"[tw] OR "Cardiovascular Diseases"[mh] OR cardiovascular[tw] OR cardio-vascular[tw] OR Neoplasms[mh]OR cancer*[tw] OR immunosuppress*[tw] OR Aged[mh] OR "Middle Aged"[mh] OR "Young Adult"[mh] OR "age group"[tw] OR "age groups"[tw] OR elderly[tw] OR aged[tw] OR middleaged[tw] OR "old people"[tw])) AND systematic[sb]

4 hits

Main search, PubMed – age groups, without demarcation on publication type:

(((((Coronavirus[mh] OR "Coronavirus Infections"[mh] OR "corona virus"[tw] OR coronavirus[tw] OR coronovirus[tw]) AND (novel[tw]OR 2019[tw] OR Wuhan[tw])) OR "COVID-19"[tw] OR COVID19[tw] OR CORVID-19[tw] OR CORVID19 OR nCoV[tw] OR "SARS-CoV-2"[tw] OR "SARS-CoV2"[tw] OR SARSCoV19[tw] OR HCoV-19[tw] OR WN-CoV[tw]) AND (Aged[mh] OR "Middle Aged"[mh] OR "Young Adult"[mh] OR "age group"[tw] OR "age groups"[tw] OR elderly[tw] OR aged[tw] OR "old people"[tw] OR "young adult"[tw] OR "young adults"[tw] OR "young people"[tw]))

Limited to 2019-2020 (70 hits).

MEDLINE & Embase – regression analyses

Ovid MEDLINE (R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Daily and Versios®
1946 to March 20, 2020
Embase 1974 to 2020 March 20

1	(((corona virus OR coronavirus) ADJ3 (Wuhan OR 2019 OR novel)) OR "COVID-19" OR COVID19 OR CORVID-19 OR CORVID19 OR nCoV OR SARS-CoV-2 OR SARS-CoV2 OR SARSCoV19 OR HCoV-19 OR WN-CoV).mp	3453
2	(exp Regression Analysis/ OR Logistic Models/ OR Multivariate Analysis/ OR Risk Factors/ OR Protective Factors/) use ppezv OR (exp Regression Analysis/ OR exp Multivariate Analysis/ OR Risk Factor/ OR Protection/) use oemezd OR (regression* OR logistic OR multi-varia* OR multivaria* OR subgroup* OR ((risk OR protective) ADJ factor*) OR coefficient* OR (cox ADJ2 (analys* OR model*)) OR proportional hazard* OR least square*).mp	5823965
3	1 and 2	148
4	limit 3 to yr="2019 – Current" [MEDLINE: 51; Embase: 43]	94

Supplementary searches in PubMed

«Italy covid-19 age» (3 hits)
«covid-19 regression» (11 hits)

Completed 22−23 March 2020

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