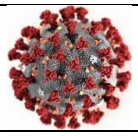
National COVID-19 Science Task Force (NCS-TF)	

Type of document: Review	
In response to request from: NCS-TF Advisory Board	**Date of request:** 19/04/2020
Expert groups involved: Clinical Group	**Date of response:** 01/05/2020
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Comment on planned updates: This is a short systematic review by the group, based on the work of N. Müller (USZ) and T. Fumeaux (SGI) and the Clinical Care Group. The literature search was updated on 01.05.2020. Data are regularly published, with a progressive increase in the methodological quality and better reproducibility, this document will therefore be updated after 4 weeks, and thereafter when necessary.	
Title: Risk factors for severe manifestations of SARS-CoV-2 infection	
Questions: Are there identified risk factors for a) hospitalization, b) ICU admission, and c) mortality in the context of COVID-19 and SARS-CoV-2 infection ?	

Summary: The evaluation of the risk of hospital and ICU admission, as well as the mortality associated with the COVID-19 is an important tool to plan the necessary resources to manage and care for patients, and to evaluate the consequences of the disease. Knowing associated risk factors will enable better care for patients, including advice regarding specific drugs either associated or as important not associated with an increased risk for mortality. Despite a high number of infected patients around the world, and many published data, the quality of these publications is generally low, with a risk of bias and confounding factors. Even though this should therefore be interpreted with great caution, and regularly evaluated, older age and cardiovascular and pulmonary comorbidities are associated with a higher risk of severe disease.

Main text:

Question 1. What are the identified risk factors for hospitalization in patients with SARS-CoV-2 infection?

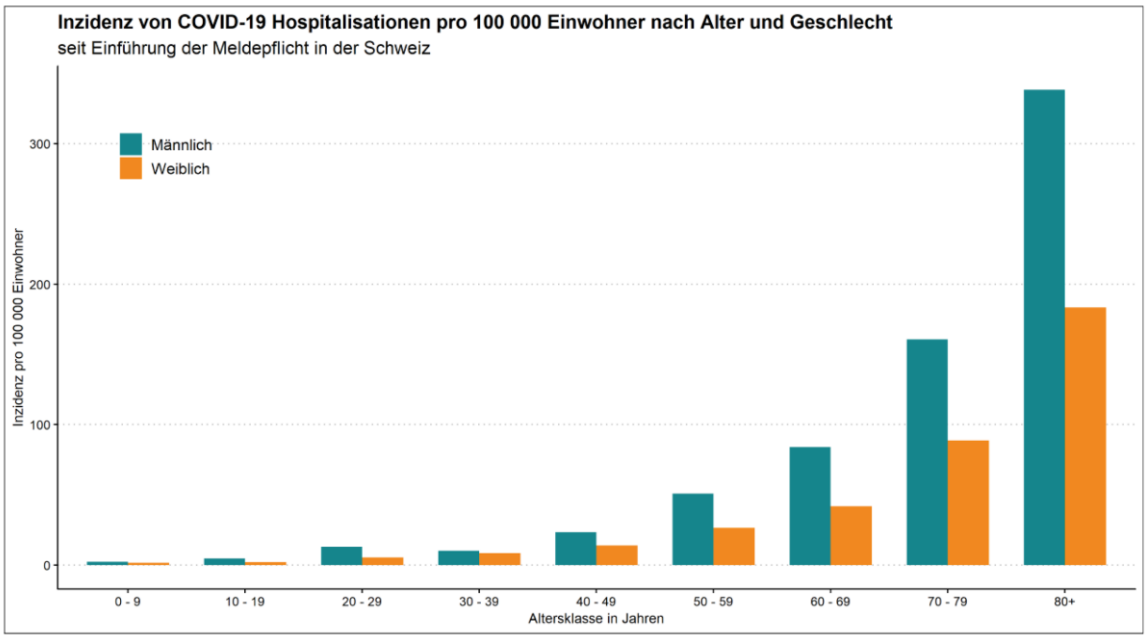
Introductory note: Hospitalizations for COVID-19 can be grouped into 4 categories: 1) medical reasons as direct consequence of SARS-CoV-2; 2) medical/social reasons, but not directly associated to SARS-CoV-2 , e.g. elderly patient not able to care for him/herself; 3) patients or physician-related causes: fear of the disease, or potential for adverse outcome, but no clinical necessity, and 4) for reasons of isolation or cohorting patients, without clinical necessity.

This review will focus on group 1, by far the largest group in Switzerland, with very few patients, if at all, hospitalized for other reasons, as a way to avoid hospital overflow. In other countries, older patients at risk but without severe infection were often admitted. Therefore, in Switzerland, the possible bottleneck was never at the level of normal wards, but in the ICU.

Risk factors for hospitalizations/adverse outcome so far described are : Age, male gender, heart diseases (arrhythmia, heart failure, ischemic heart disease), hypertension, diabetes, chronic kidney disease, obesity, chronic respiratory disease and smoking, although the role of this last one has been questioned (Guan – Richardson – Zhou).

Many of these risk factors are intertwined and some were not uniformly recognized. Some of the factors may merely be associated with older age, such as comorbidities, the prevalence of which increases with age, from 50 % for persons under 65 to 82 % over 85 years (Salive). So far, careful multivariate analyses are missing, and prognosis models are still hampered by a relatively low number of patients, with a high risk of bias (Wynants). It is suggestive that any factor contributing to endothelial damage may be associated with an adverse outcome, a concept also partially supported by preliminary pathologic findings, although this has to be confirmed (Varga).

In Switzerland, of the total of 3705 hospitalized patients (FOPH daily brief 01.05.2020), 86% had at least one of the above described factors (hypertension, 52%, cardiovascular diseases 33% and diabetes 23%), only 14% having none. 61% were male. The age distribution of hospitalized patients shows that older age is associated with increased risk (FOPH daily brief 26.4.2020) :



Uncertainty: The risk of an adverse outcome and hospitalization increases with age and with the numbers of risk factors. However, it is not possible to identify a simple risk evaluation tool, as the risk increase is gradual and additional factors such as host response, inoculum, genetic factors, and others may play a role on the individual level. A validated risk evaluation tool would be of great value to select patients who would benefit the most from a new available therapy.

Question 2. What are the identified risk factors for ICU admission in patients with SARS-CoV-2 infection?

Introductory note: ICU admission is indicated for patients needing mechanical ventilation or other complex therapies or monitoring that are not possible on usual wards. It is generally reported that between 5 to 25 % of hospitalized COVID-19 patients are admitted to the ICU for a severe course, with a mean of 5-8 % (Guan 2 - Grasselli). Many of these factors are **associated** with ICU admission, not as risk factors, but rather as parameters that set the indication for ICU admission, for monitoring or therapy.

Epidemiologic factors associated with ICU admission:
- Male sex: not uniformly reported (Guan 2 – Grasselli – CDC)
- Age: mean age of 60 with variations, with 50 % > 65 in USA (MMWR – Grasselli)
- Co-morbidity present in 70-80 % patients (chronic heart or lung disease, hypertension, diabetes) (Grasselli)
- Diabetes is associated with ICU admission and short-term outcome (Roncon)
- Transplanted and oncologic patients may have an increased risk, but this is not definitely proven

Clinical presentation associated with ICU admission:
- Acute respiratory failure, mainly hypoxemic (rarely with hypercapnia)
- Septic shock, apparently less frequent than in other 'classical' Acute Respiratory Distress Syndrome, but to be confirmed

Laboratory value associated with ICU admission:
- Many descriptions of various parameters associated with ICU admission risk in observational series, in univariate analysis, but high risk of bias and few multivariate analysis
- Unclear association between laboratory value at admission and ICU admission risk

Chest imaging pattern associated with ICU admission:
- No clear risk identified, but patients with acute respiratory failure have an ARDS pattern on CT-scan and lung ultrasound, with no difference between moderate and severe ARDS

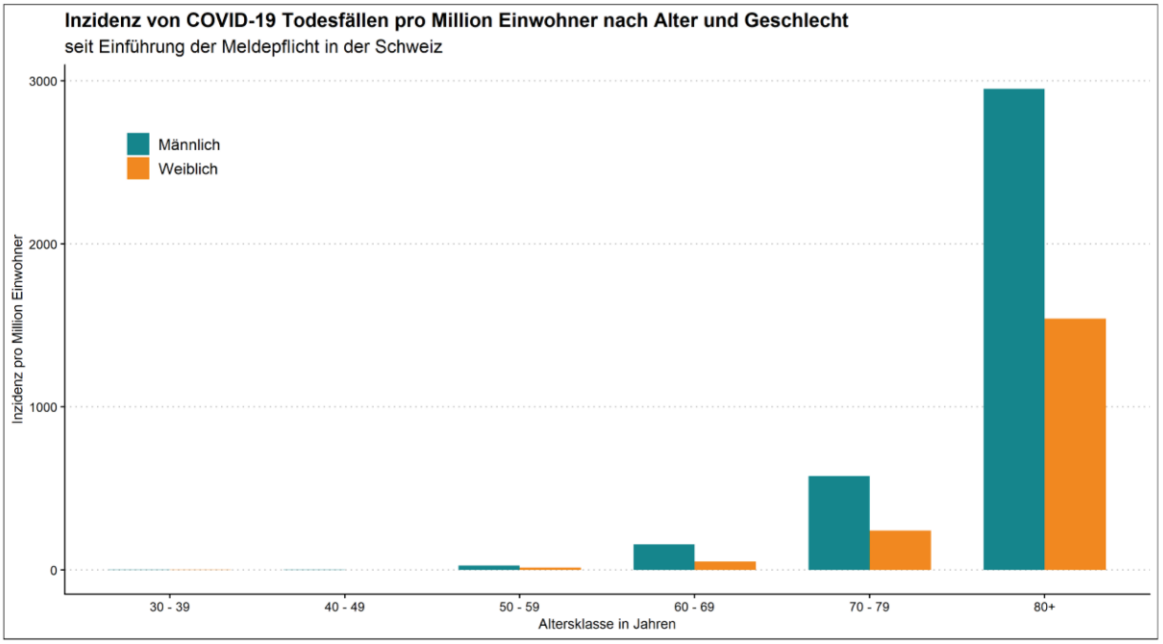
Predicting tools and nomograms:
- Many publications, mainly based on small and selected populations (Gong – Wynants)
- poor overall quality, no prospective external validations – limited usefulness (Wynants)

Uncertainty: ICU admission criteria may greatly vary between countries and institutions, depending on the number of available beds, the existence of intermediate care or step-down units, and the level of care. Moreover, the available data from observational studies are most of the time preliminary, mostly on small cohorts, with many missing data, and with a short follow-up. They are often not peer-reviewed yet. Eventually, multivariate analyses are rarely conducted to identify independent factors associated with ICU admission risk. Therefore, there is still uncertainty and firm conclusions are impossible regarding risk factors for ICU admission : nevertheless age, comorbid conditions, acute respiratory failure at admission, and an ARDS pattern on chest imaging are frequently present in ICU admitted patients. Ongoing clinical research will update this information, as series get larger and better methodology is applied.

Question 3. What are the identified risk factors for mortality in patients with SARS-CoV-2 infection?

Introductory note: General mortality is estimated between 0.7 and 3 % (CEBM), with an ICU mortality reported to be 25-85 % and a nursing home resident death rate around 35 %. Factors associated with a higher mortality have been identified :

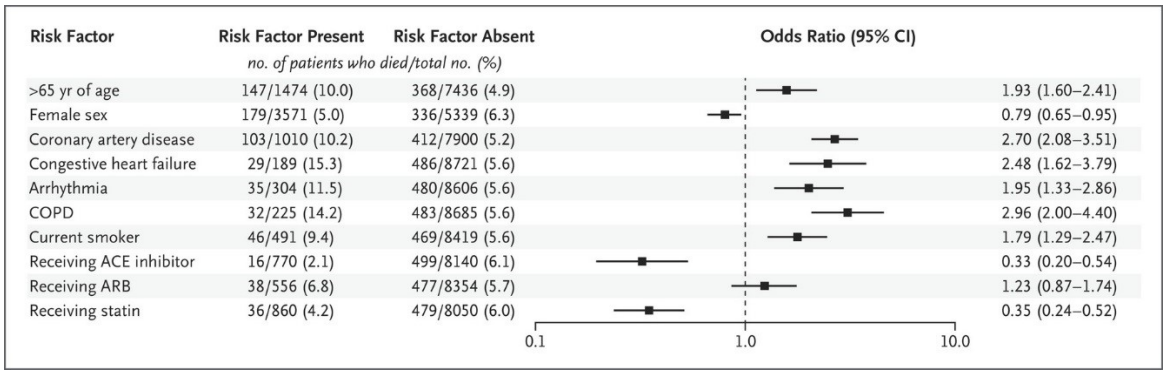
Factors associated with mortality in the population (CDC 2020):
- Age > 65: in Switzerland, age is clearly associated with an increased risk of death as shows in this graph:



Other associated factors (CDC) :
- Nursing home residency
- Comorbid condition
- Obesity (BMI > 40)
- Diabetes
- Chronic immunosuppression

Factors NOT associated with mortality in the population (Reynolds):
- Antihypertensive treatment, including ACE inhibitors and angiotensin-receptor blockers

Independent factors associated with mortality in hospitalized patients (Mehra – Liu - Ruan):
- Mehra identified age greater than 65 years (mortality of 10.0%, vs. 4.9% among those ≤65 years of age; odds ratio, 1.93; 95% confidence interval [CI], 1.60 to 2.41), coronary artery disease (10.2%, vs. 5.2% among those without disease; odds ratio, 2.70; 95% CI, 2.08 to 3.51), heart failure (15.3%, vs. 5.6% among those without heart failure; odds ratio, 2.48; 95% CI, 1.62 to 3.79), cardiac arrhythmia (11.5%, vs. 5.6% among those without arrhythmia; odds ratio, 1.95; 95% CI, 1.33 to 2.86), chronic obstructive pulmonary disease (14.2%, vs. 5.6% among those without disease; odds ratio, 2.96; 95% CI, 2.00 to 4.40), and current smoking (9.4%, vs. 5.6% among former smokers or nonsmokers; odds ratio, 1.79; 95% CI, 1.29 to 2.47) as independent predictors of mortality.



Mehra et al. N Engl J Med, 2020

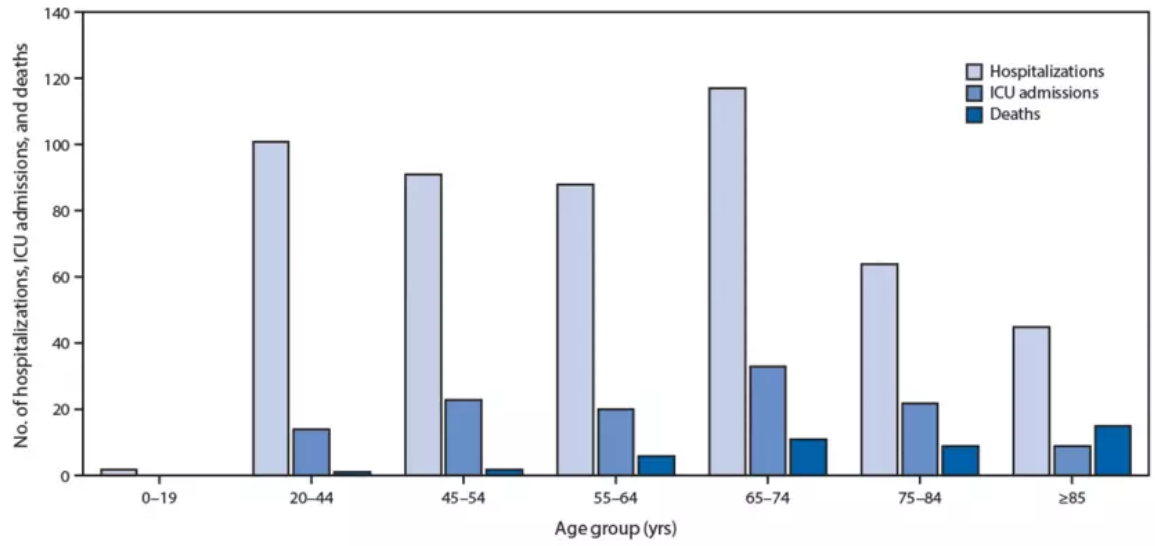
Factor NOT associated with mortality in hospitalized patients (Mancia – Mehra – Reynolds - Zhang):
- No increased risk of in-hospital death was found to be associated with the use of angiotensin-converting enzyme (ACE) inhibitors (2.1% vs. 6.1%; odds ratio, 0.33; 95% CI, 0.20 to 0.54) or the use of angiotensin receptor blockers (ARB) (6.8% vs. 5.7%; odds ratio, 1.23; 95% CI, 0.87 to 1.74) (Mehra).

Factors associated with mortality in the ICU:
- Age is reported to be associated with ICU mortality, with a clear increase in mortality by older age group (see graph below, CDC). Nevertheless, this association is seen only in univariate analysis, and confounding factors, such as comorbidities, probably explain most of this association.
- Acute respiratory distress syndrome and sepsis reported in 100% of patients with confirmed COVID-19 who died (Chen)
- Various prediction models or nomograms have been proposed, most of the time derived from small cohorts of selected patients, with a high risk of bias, no or poor external validation, limiting the value of these tools (Wynants)
- Data from patients admitted to the ICU in Switzerland (RISK-19- ICU registry, submitted data) suggest that very few factors are independently associated with the risk of dying.

Uncertainty: mortality data must be interpreted with caution, as the total incidence and prevalence of infected patients in the population is unknown, as death certificate do not always differentiate COVID-19 -related or non COVID-19 -related death, and as mortality data have often been published early on the course of the pandemic (Baud). The reported death rates are highly variable, depending on the country, the type of patients included (general population, nursing home residents, ICU patients), and the testing strategy (CEBM). Definite and reproducible data on mortality will probably be available in the aftermath of the pandemic

Recommendations from the Task Force:

Age and association with COVID-19 risk: Age is associated with an increased risk of hospitalization, ICU admission, although it cannot be determined if it is an independent risk factor:



source : CDC

Hospitalization Risk: Although age, male gender, comorbid state, chronic lung, heart or kidney disease, and diabetes have been associated with a higher risk of hospitalization, there are no validated prediction models that may help determine the proportion of patients needing an hospital admission, or helping identifying the individual at risk.

ICU Admission Risk: Risk factors for hospitalization are similarly associated with a high risk of ICU admission, with the addition of ARDS (clinical or radiological) presentation at admission, but there are no validated prediction rules that may help identify the patient at risk of ICU admission.

Mortality risk: A recent large study (Mehra) identified age and comorbidities as independent risk factors associated with mortality, however, there are at the present time no validated prediction rules for mortality risk evaluation, at the general population level, for hospitalized patients, and for ICU patients.

Open points for further discussion: With the evolution of the pandemic, and the results of larger registries, it is possible that prediction models could be validated in the near future, to help better stratify the risk in patients infected with SARS-CoV-2.
Also, the publication of results of ongoing clinical trials evaluating anti-viral and immunomodulation drugs may impact significantly the risk of hospitalization, ICU admission and death of COVID-19 patients.

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