National COVID-19 Science Task Force (NCS-TF)
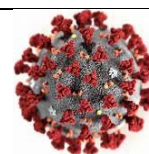
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Comment on updates: This is a short systematic review by the group, based on the work of N. Müller (USZ) and T. Fumeaux (SGI). The document was updated on 16.10.2020, based on new published evidence.	

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. The high number of infected patients around the world has led to the publication of a large amount of data. For each specific question, this policy brief includes the highest level and most updated available evidence, and highlight remaining uncertainties.

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, which is largest group in Switzerland. The hospitalization rate of SARS-CoV-2 infection is highly variable around the worldm depending on the structure of the population and the organization of the healthcare system. A modelling study from France suggests that around 3.6% of infected individuals are hospitalized (95% CrI: 2.1–5.6) (Salje). Since March 2020, 7.3 % of confirmed infections lead to an hospital admission in Switzerland (FOPH) :

15.10.2020, 8am	Total since the start of the epidemic
Laboratory-confirmed cases	71,317
Hospitalisations	5,208

Many risk factors associated with hospital admission have been described (Salje - Guan – Richardson – Zhou – Petrelli):

     - increasing age, with no specific limit (Salje – CDC – Lewnard - Petrelli)
     - male gender (RR 1.25, 95% CrI: 1.22–1.29) (Salje)

These data are concordant with the age and sex distribution of hospitalized patients in Switzerland (FOPH 15.10.2020) :


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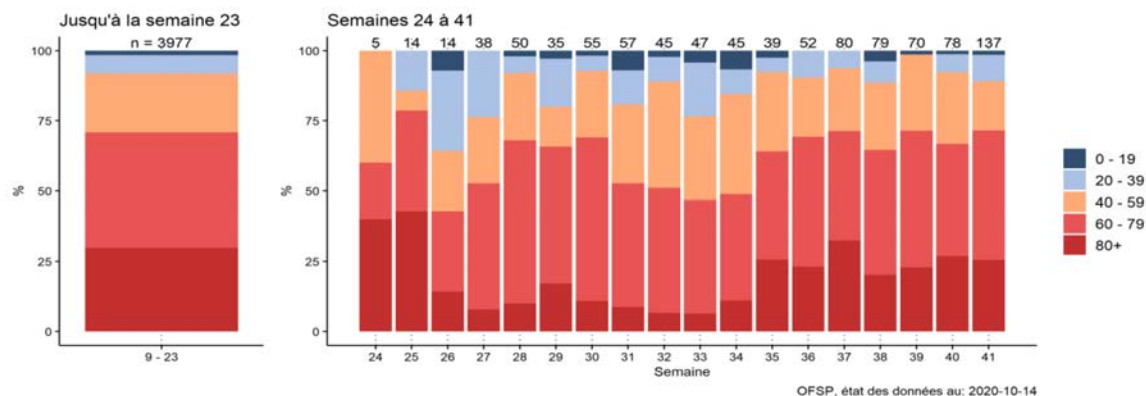
	Répartition des cas[1]
Semaines 9 à 23	
Femmes	40 %
Hommes	60 %
Total	100 %
Depuis la semaine 24	
Femmes	43 %
Hommes	57 %
Total	100 %

FOPH 15.10.2020

- Comorbidities :
     - hypertension and cardiovascular diseases (arrhythmia, heart failure, ischemic heart disease, chronic kidney disease) (Petrelli)
     - obesity is associated with a 2.13 increased risk (Popkin)
     - chronic respiratory disease, particularly COPD (RR 1.88, 95% CI, 1.4–2.4) (Alqahtani).
     - diabetes
     - smoking (RR 1.45, 95% CI: 1.03–2.04) (Alqahtani).

These risk factors are intertwined and sometimes merely associated with age. But, comorbidities are present in over 80 % of hospitalized patients in Switzerland, which is concordant with the published literature (Salive) :

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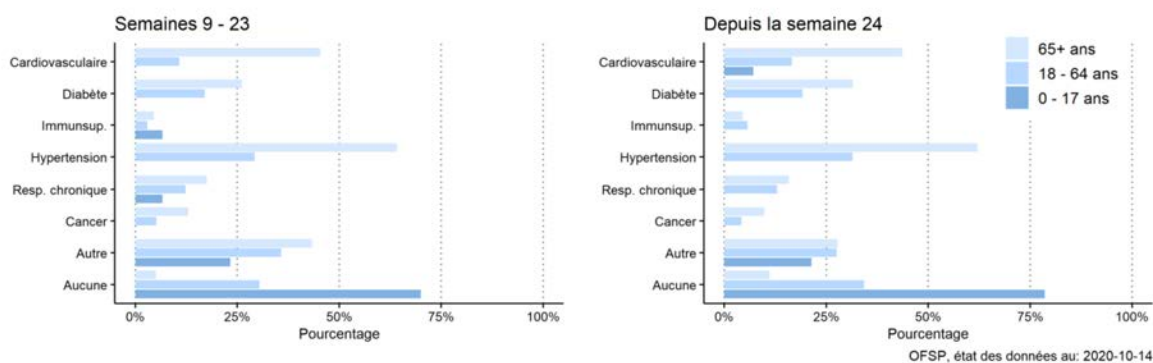
Some prognosis model have been published, but without external validation, limiting their use (Wynants).
An on-line calculator is available (https://riskcalc.org/COVID19Hospitalization/), but has not been validated for Swiss patients (Jehli)

Uncertainty: The risk of an adverse outcome and hospitalization increases with age, male sex, obesity, and with the number of cardiovascular and pulmonary co-morbidities. 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. No validated evaluation tool is available for the Swiss population to identify patients at high risk who may benefit from a preemptive of prophylactic therapy.

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

Introductory note: ICU admission is indicated for patients needing continuous monitoring or complex therapies, such as mechanical ventilation and other organ support, that are not available on regular wards. The proportion of patients who need to be admitted to the ICU has been reported to be between 5 to 25 % (Guan 2 – Grasselli - Salje). A recent meta-analysis reported a total of 17% of hospitalized patients requiring intensive care (33 studies, 7504 patients), 9% invasive ventilation (45 studies, 6933 patients) and 2% extra-corporeal membrane oxygenation (12 studies, 1,486 patients) (Grant).
Many factors **associated** with ICU admission are not risk factors but rather parameters determining the indication for ICU admission.

Epidemiologic factors associated with ICU admission:
- age is associated with the development of a severe disease needing ICU admission (MMWR – Grasselli – CDC - Lewnard), as an independent risk factor (OR, 1.03; 95% CI, 1.01-1.05) (Liang). A French modelling study confirmed this, but with a decrease of risk over 70 (Salje)
- male sex is associated with ICU admission risk (RR: 1.61, 95% CI: 1.56–1.67) (Salje), although not uniformly reported (Guan 2 – Grasselli – CDC)
- co-morbid conditions (chronic heart or lung disease, hypertension, diabetes) are present in 70-80 % patients (Grasselli - Jain). Globally, the number of comorbidities is an independent predictive factor for the development of severe disease (OR, 1.60; 95% CI, 1.27-2.00) (Liang)
- COPD seems to be associated with a significant risk (OR 17.8, 95 % Ci 6.56-48.2) (Jain)
- obesity is associated with a 1.74 higher risk of ICU admission (Popkin)
- cardiovascular disease and hypertension are associated with an increased risk of ICU admission of 4.4 and 3.7 times respectively (Jain).
- diabetes is associated with ICU admission and short term outcome (Roncon)
- cancer history is an independent predictor of the development of a severe infection (OR, 4.07; 95% CI, 1.23-13.43) (Liang)
- transplanted patients may have an increased risk, but this is not definitely proven
- Smoking is associated with more severe disease, and possibly with increased risk of ICU admission (Alqahtani)

Clinical presentation associated with ICU admission :
- acute hypoxemic respiratory failure (rarely with hypercapnia)
- dyspnea is an independent predictive factor for a severe disease, with an OR between 2 to 6 (Liang - Jain)
- hemoptysis is an independent predictive factor for a severe disease (OR, 4.53; 95% CI, 1.36-15.15) (Liang).

- alterations in consciousness are associated with severe disease (OR, 4.71; 95% CI, 1.39-15.98) (Liang)

Laboratory findings associated with ICU admission :
- various laboratory parameters have been associated with ICU admission, mostly in observational series and univariate analysis, with high risk of bias.
- a large Chinese observational study identified several independent predictors (Liang) :
  - neutrophil-to-lymphocyte ratio (OR, 1.06; 95% CI, 1.02-1.10)
  - lactate dehydrogenase (OR,1.002; 95% CI, 1.001-1.004)
  - direct bilirubin (OR, 1.15; 95% CI, 1.06-1.24)
- a meta-analysis and meta-regression identified the following factors (Zhang JJY) :
  - raised leukocyte count (p<0.0001)
  - raised alanine aminotransferase (p=0.024) and aspartate transaminase (p=0.0040)
  - elevated lactate dehydrogenase (LDH) (p<0.0001)
  - increased procalcitonin (p<0.0001)

Chest imaging pattern associated with ICU admission :
- any chest radiographic abnormality is associated with the development of a severe disease (OR, 3.39; 95% CI, 2.14-5.38) (Liang)
- patients with an acute respiratory failure frequently have an ARDS pattern on CT-scan and lung ultrasound, but with no specific diagnostic or prognostic value

Predicting tools and nomograms :
- many tools were developed on small and selected populations (Gong – Liang), with poor overall quality and no prospective external validation, and therefore limited usefulness (Wynants)
- The PREDI-CO model has fair operative characteristics (sensitivity 80% (73%–85%), specificity 76% (70%–81%), positive predictive 69% (60%–74%) and negative predictive 85% (80%–89), even though it has not been validated for the Swiss population (Bartoletti).

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, and this may influence the ICU admission rate. Published data show that age, male sex, and comorbid conditions are significant risk factors, and acute respiratory failure at admission and/or ARDS pattern on chest imaging are associated with ICU admission. The use of predictive model is still not recommended for individual risk prediction for patients in Switzerland.

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

Introductory note: General mortality (case fatality) is estimated between 0.7 and 3.6 % (CEBM – Williamson – Verity), and the Infection Fatality Ratio (IFR) that was estimated around 0.65-0.70% (Salje - Verity) is probably lower, around 0.27 according to the WHO (Ioannidis). In Switzerland, the mortality of confirmed cases is 2.4 % at this stage. The mortality rate of hospitalized patients was initially estimated around 18.1% (95% CI: 17.8–18.4) (Salje), but is probably closer to 7%, according to a recent meta-analysis (Grant). ICU mortality varies very much and is reported to be 37 % in the US (Gupta) and 45 % in Lombardy (Grasselli 2), and around 24% in a recent registry including Swiss patients (Wendel-Garcia). The mortality in nursing home resident is probably around 35%.
Positive results of clinical trial could modify the therapy and influence the mortality rate and the associated risk.

Many factors associated with a higher mortality have been identified :

Factors associated with mortality in the general population (CDC 2020):
- Age is clearly associated with an increased risk the risk of dying (Knight - Lewnard – Petrelli - Williamson), from 0.001% under 20 to 10.1% over 80 (Salje).
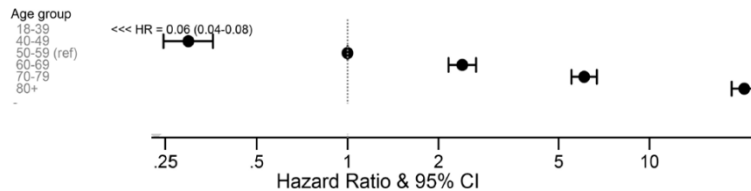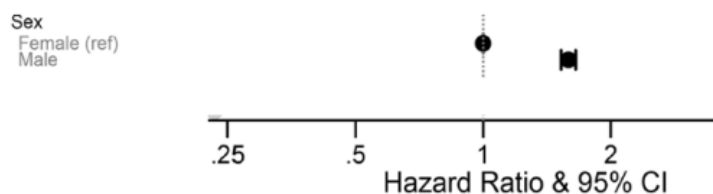

(Williamson)

In Switzerland, age is clearly associated with an increased risk of death :
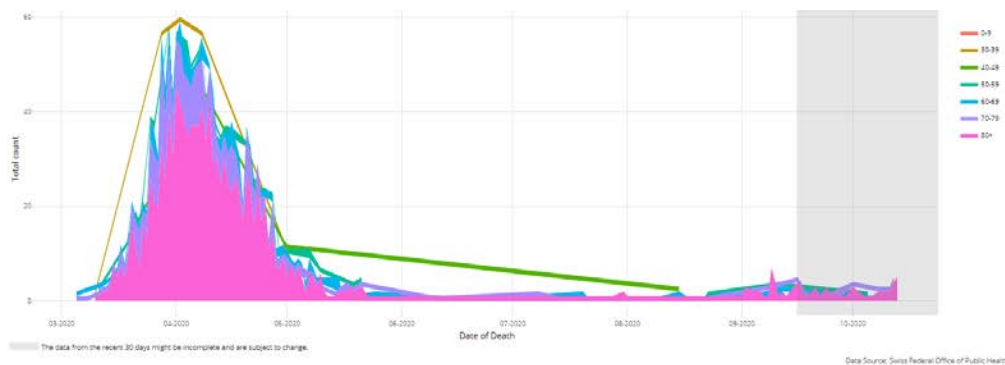
	Nombre de cas[1]	Âge médian	Fourchette
Semaines 9 à 23			
Femmes	43 %	86 ans	31-108 ans
Hommes	57 %	83 ans	0-102 ans
Total	100 %	84 ans	0-108 ans
Depuis la semaine 24			
Femmes	38 %	87 ans	56-101 ans
Hommes	63 %	82 ans	48-100 ans
Total	100 %	85 ans	48-101 ans

(FOPH Oct 15th 2020)

- male sex (Salje - Williamson) :

In Switzerland, a higher proportion of men is found among deceased people :

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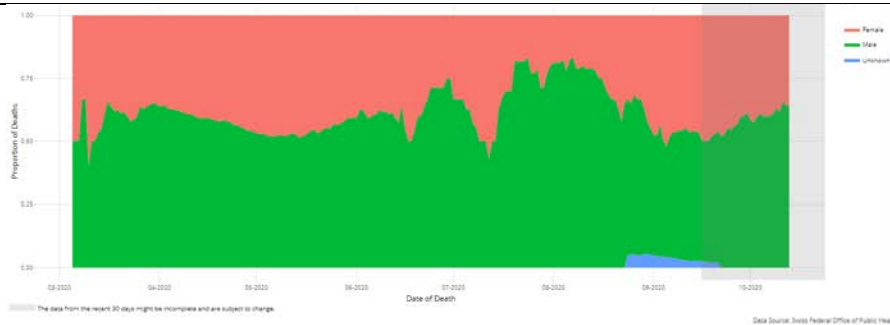
- Other factors associated with mortality :
  - obesity is associated with a 48 % increased risk of dying (Popkin -Williamson)

Williamson

  - comorbid conditions (CDC - Williamson), particularly :
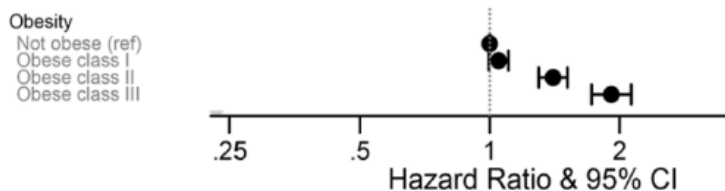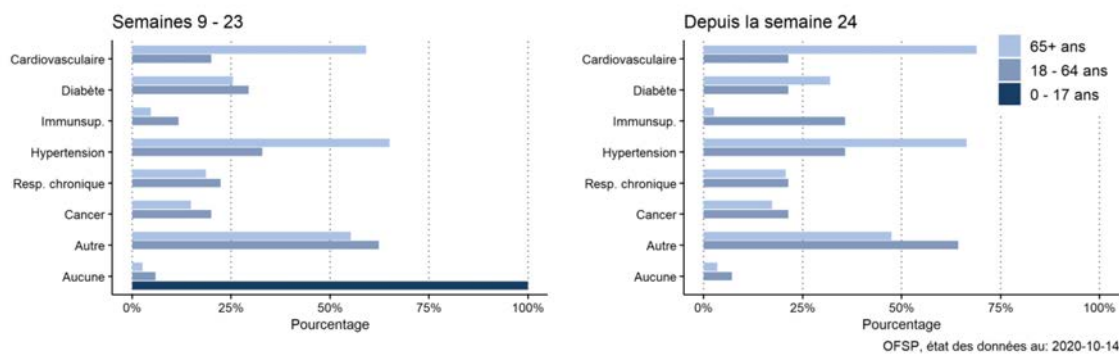   - heart failure (Petrelli)
    - dementia
    - chronic liver disease
    - diabetes (Petrelli – Williamson)
  - nursing home residency (CDC)
  - chronic immunosuppression (Williamson)
  - cancer (Petrelli - Williamson)

In Switzerland, the majority of deceased patient had at least one comorbitidy, in accordance with these data :

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

Independent factors associated with mortality in hospitalized patients (Liu – Ruan - Docherty) :
- increasing age, starting from 50 year old
- sex: female sex is associated with decrease mortality : HR 0.81 (CI 0.75 to 0.86) (Docherty - Knight)
- coronary artery disease : OR 2.70 (95% CI 2.08 - 3.51)
- heart failure : OR 2.48 (95% CI 1.62 - 3.79)
- cardiac arrhythmia : OR 1.95 (95% CI 1.33 - 2.86)

- COPD : OR 2.96 (95% CI 2.00 - 4.40)
- current smoking : OR 1.79 (95% CI 1.29 to 2.47)
- smoking and COPD have also been associated with increased mortality in a meta-analysis (Alqahtani)
- obesity (Docherty)

		Hazard ratio (95% CI)	Hazard ratio (95% CI)	P value
Age on admission (years)	<50			
	50-59		2.63 (2.06 to 3.35)	<0.001
	60-69		4.99 (3.99 to 6.25)	<0.001
	70-79		8.51 (6.85 to 10.57)	<0.001
	≥80		11.09 (8.93 to 13.77)	<0.001
Sex at birth	Female		0.81 (0.75 to 0.86)	<0.001
Chronic cardiac disease	Yes		1.16 (1.08 to 1.24)	<0.001
Chronic pulmonary disease	Yes		1.17 (1.09 to 1.27)	<0.001
Chronic kidney disease	Yes		1.28 (1.18 to 1.39)	<0.001
Diabetes	Yes		1.06 (0.99 to 1.14)	0.087
Obesity	Yes		1.33 (1.19 to 1.49)	<0.001
Chronic neurological disorder	Yes		1.17 (1.06 to 1.29)	0.001
Dementia	Yes		1.40 (1.28 to 1.52)	<0.001
Malignancy	Yes		1.13 (1.02 to 1.24)	0.017
Moderate/severe liver disease	Yes		1.51 (1.21 to 1.88)	<0.001

Docherty

Factor NOT associated with mortality in hospitalized patients (Mancia – Reynolds – Zhang P) :
- antihypertensive treatment, including ACE inhibitors and angiotensin-receptor blockers

The 4C Mortality Score proposed by the WHO, based on the ISARIC cohort, is a risk stratification model for the prediction of death in hospitalized patients (Knight). It categorises patients in low, intermediate, high, or very high risk of death, based on easy-to-obtain parameters, but it has not been validated for Swiss patients :

Variable	4C Mo
Age (years)	
<50	—
50-59	+2
60-69	+4
70-79	+6
≥80	+7
Sex at birth	
Female	—
Male	+1
No of comorbidities*	
0	—
1	+1
≥2	+2
Respiratory rate (breaths/min)	
<20	—
20-29	+1
≥30	+2
Peripheral oxygen saturation on room air (%)	
≥92	—
<92	+2
Glasgow coma scale score	
15	—
<15	+2
Urea (mmol/L)	
≤7	—
7-14	+1
>14	+3
C reactive protein (mg/dL)	
<50	—
50-99	+1
≥100	+2

*Comorbidities were defined by using Charlson comorbidity index, with the addition of clinician defined obesity.   (Knight)
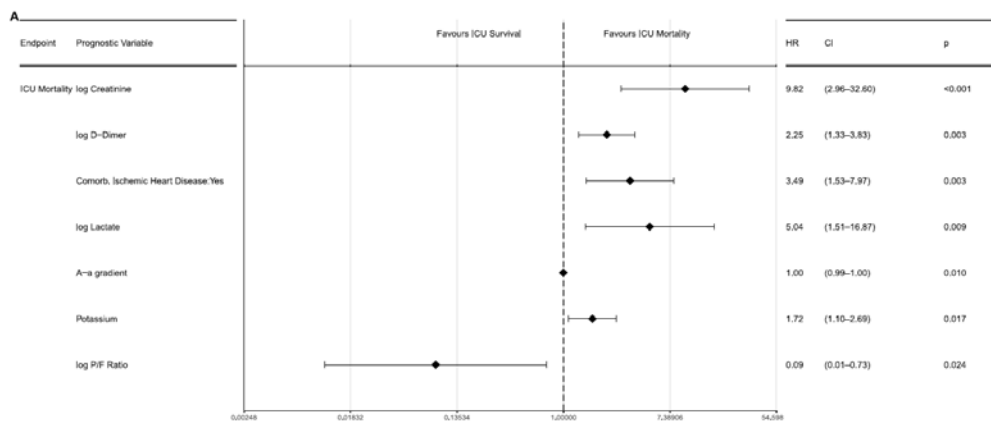
Factors associated with mortality in the ICU :
- age is associated with ICU mortality (CDC – Qian – Grasselli 2 - Gupta), as an independent factor, with an hazard ratio of 1.75 (95% CI, 1.60-1.92) (Grasselli 2), and an OR of 11.15 (95%CI, 6.19-20.06) for over 80 years vs less than 40 (Gupta).

Age-specific outcomes over time

(Quian)
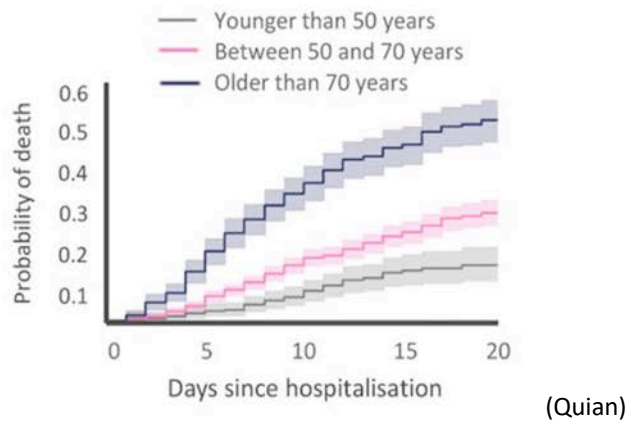
- acute respiratory distress syndrome (ARDS) and sepsis reported in 100 % of dying ICU COVID-19 patients (Chen)
- male sex (HR1.57; 95%CI, 1.31-1.88), high oxygen (HR, 1.14; 95%CI, 1.10-1.19) and PEEP (HR, 1.04; 95%CI, 1.01-1.06) need, low PaO2:FiO2 ratio (HR, 0.80; 95%CI, 0.74-0.87) on ICU admission are independently associated with ICU mortality (Grasselli 2 - Gupta)
- history of chronic obstructive pulmonary disease (HR, 1.68; 95%CI, 1.28-2.19), hypercholesterolemia (HR, 1.25; 95%CI, 1.02-1.52), and type 2 diabetes (HR, 1.18; 95%CI, 1.01-1.39), higher body mass index (>40 vs <25: OR, 1.51; 95%CI, 1.01-2.25), and active cancer (OR, 2.15; 95%CI, 1.35-3.43) are also independently associated with higher mortality (Grasselli 2 - Gupta)
- no validated prediction models has been validated, as they were derived from small cohorts of selected patients, with a high risk of bias, no or poor external validation (Wynants)
- data from patients admitted to the ICU in Switzerland (Wendel-Garcia) show that very few factors are independently associated with the risk of dying :

Endpoint	Prognostic Variable	Favours ICU Survival	Favours ICU Mortality	HR	CI	p
ICU Mortality	log Creatinine			9.82	(2.96–32.60)	<0.001
	log D–Dimer			2.25	(1.33–3.83)	0.003
	Comorb. Ischemic Heart Disease:Yes			3.49	(1.53–7.97)	0.003
	log Lactate			5.04	(1.51–16.87)	0.009
	A–a gradient			1.00	(0.99–1.00)	0.010
	Potassium			1.72	(1.10–2.69)	0.017
	log P/F Ratio			0.09	(0.01–0.73)	0.024

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

clearly associated with an increased risk of dying. As already mentioned, therapies with proven efficacy could modify the mortality and associated risks

Recommendations from the Task Force

There is a clear and probably independent association of age, male sex, and obesity for hospitalization, ICU admission, and mortality

Hospitalization Risk: Although age, male gender, obesity, 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 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 dyspnea and ARDS (clinical or radiological) presentation at admission. However, published prediction models have not been validated in the Swiss population, so that they should be used very cautiously to identify the patient at risk for ICU admission.

Mortality risk: Age, male sex, obesity and chronic cardiovascular and lung disease, and ARDS presentation, have been associated with an unfavorable outcome. The 4C score is a simple prediction tool proposed by the WHO, but that has not been specifically validated in the Swiss population.

Open points for further discussion: Anti-viral and/or immunomodulating drugs use (mainly dexamethasone and remdesivir) may impact significantly the risk of ICU admission and death of COVID-19 patients in the months to come, but the amplitude of change is difficult to evaluate at this point.

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