#### COVIP – a European multicenter study

# Outcomes and prognostic factors in coronavirus disease (COVID-19) in very old intensive care patients: COVIP

Both the preliminary reports of critically ill COVID-19 patients in Wuhan (China) and Italy reported a high risk of dying in patients with multimorbidity. Also, very old patients with SARS-CoV-2 infections suffered from high mortality rates (1). It is, however, unclear if age alone is an independent risk factor, or if co-morbid conditions and frailty trigger the adverse outcome.

In non-COVID-19 elderly patients admitted to the ICU, our European research group (2) found that the co-factors are more important than chronological age itself (3, 4). In patients with COVID-19, pretreatment with AT-2 blockers and ACE-inhibitors (5), but also nonsteroidal anti-inflammatory drugs such as ibuprofen (6) were suggested to be associated with adverse outcome. Furthermore, some groups reported a higher death rate in patients with concomitant cardiovascular disease (7) and diabetes (8).

This international multicenter study group, therefore, proposes to study the relationship between age, co-morbidities, pretreatment, frailty, and outcomes prospectively in a group of elderly patients receiving critical care for COVID-19. The results of this investigation will be essential to understand which factors can predict mortality in elderly COVID-19 patients to help to detect these patients early. Furthermore, the proposed study will also be a knowledge base necessary to guide triage decisions in the future. With this pandemic likely to continue for 18 months, it is paramount to identify independent risk factors early to facilitate both risk stratification and substantiate necessary triage decisions.

The pandemic begins in all European countries now, and decisive action of the research community is needed.

#### Aim

To describe important predictors for outcomes in a group of elderly patients admitted to the ICU with COVID-19.

#### Type of study:

This will be a purely prospective observational multinational study in Europe and Israel coordinated from Aarhus (Denmark), Bergen (Norway) and Duesseldorf (Germany)

#### Method:

All patients  $\geq$  70 years admitted to the ICU with proven COVID-19 will be included in the study. In addition to physiological data, we will also score for frailty (Clinical Frailty Scale) (6) and assess the Activities of Daily Life (Katz index, optional) (7). Also, we will record selected clinical and laboratory values, that have been measured routinely in the participating ICUs. There will be no extra blood sampling. These parameters will only be collected if they are available based on clinical measurements. Patients will be followed-up to hospital discharge. In addition, the time of survival and health-related quality of life (HRQOL, optional) will be documented at 3 months using telephone interviews and the form EQ-5D (8). Survivors and non-survivors will be studied w/r to factors important for survival.

In order to include most patients admitted, we will need to include a majority of patients without informed consent at admission since the majority will be in a state were acquiring informed consent will be impossible or inconvenient. Local regulations will apply if caregivers/family can give consent or we can use deferred consent in survivors. Caregiver consent must be allowed to give by telephone with signature by the treating physician because authorities may prohibit visiting patients. If consent is absolutely mandatory due to local law, informed consent will be taken. If the inclusion of a patient is impossible due to ward logistics or clinical priorities, the inclusion of a patient is also possible retrospectively.

All data will be completely anonymous after inclusion in the database (infrastructure established). Only the individual ICUs will have the list revealing patient ID. In order not to be able to identify patients in the database, only limited data will be registered, admission day is Day 1 and all times will relate to Day 1. No name of the ICU will be registered, just as a number, and the only country will be registered in the database. Later, each country will have access to its own data.

#### Statistical analysis

Descriptive statistics for the cohort (all) and subgroup (survivors/non-survivors) will be analyzed separately. In a regression analysis, factors important for short (hospital) and long-term (3 months) survival will be studied.

#### Variables to collect (see also Case Record Form):

- ICU number
- Consecutive number per ICU
- Country
- ICU admission date =1
- Date of consent
- Days in the hospital prior to ICU admission
- Days with symptom onset prior to hospital admission
- Age and gender
- Past medical history
  - Chronic heart failure yes/no with last ejection fraction
  - Diabetes yes/no
  - Ischemic heart disease yes/no
  - Renal insufficiency yes/no
  - Pulmonary comorbidity such as COPD yes/no
  - Arterial hypertension yes/no
    - Within ten days before admission: ACE Inhibitor use: yes/no
    - Within ten days before admission: Angiotensin receptor blocker use: yes/no
    - Pretreatment with NSAID within ten days before admission? yes/ no / unknown

- If yes, pretreatment with
  - Ibuprofen
  - Diclofenac
  - ASS
  - Piroxicam
  - Naproxen
  - Indametacin
  - Coxib"
  - Metamizol
  - Paracetamol
- Ejection fraction [%] (last assessment)
- Pre-hospital condition (optional)
  - Living at (before hospital admission):
    - Own home (incl. with spouse)
    - Other home with family or caregiver
    - nursing home
    - hospital ward
    - other
    - unknown
  - Frailty as clinical frailty scale (CFS) (see attachment)
  - Not mandatory: Activity of daily life (ADL) (see attachment)

#### ICU Admission

- Bacterial co-infection confirmed yes/no
- First Blood gas analysis PaO2: \_\_ (under FiO2: \_\_ ) will create PaO2/FiO2 ratio
- SOFA with subsections as in VIP2
- Lowest thrombocyte count day 1
- Highest creatinine day 1
- Highest total bilirubin day 1
- Highest D-dimer day 1
- Inflammation (Not mandatory):
  - Highest Leucocyte count day 1
  - Lowest Lymphocyte count day 1
  - Highest Procalcitonin day 1
  - Highest CRP day 1
- Highest lactate day 1, highest lactate day 2

### During ICU stay

- Invasive ventilation Yes / no (if yes start on ICU day \_\_\_\_, duration \_\_\_\_days)
- Treatment with prone position: yes/no (if yes started at ICU day: \_\_)
- Tracheostomy yes/no (if yes ICU day \_\_\_\_)
- ECMO use
  - No / veno-venous / veno-arterial / unknown (if yes start on ICU day \_\_\_\_, duration \_\_\_days)

- Non-Invasive ventilation; (if yes start on ICU day \_\_\_\_, duration \_\_\_\_days)
- Vasoactive drugs (if yes start on ICU day \_\_\_\_, duration \_\_\_days)
- RRT (if yes start on ICU day \_\_\_\_, duration \_\_\_days)Cytokine filter system yes/no
- Use of:
  - Antibiotics yes/no
  - Corticosteroids yes/no
  - Antiviral drugs yes/no
  - Other experimental drugs yes/no
  - Other experimental trial (non-drug)
- Transfer for ECMO to another hospital
- EOL issues
  - Discussed yes/no/ no caregiver available
  - WH (day relative to ICU admission)
  - WD (as above)
- Outcome
  - ICU-outcome (dead/alive)
  - ICU length of stay (hours)
  - 30d Outcome (dead/alive)
  - 3 months follow up
  - Survival (dead/alive) if dead: Day in relation to ICU admission
  - If not dead day relative to ICU admission
  - Not mandatory: EQ 5D (see attachment)

## **References:**

- Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. February 2020. doi:10.1016/S2213-2600(20)30079-5.
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- Rockwood K, Stadnyk K, MacKnight C, McDowell I, Hébert R, Hogan DB. A brief clinical instrument to classify frailty in elderly people. *Lancet*. 1999;353(9148):205-206. doi:10.1016/S0140-6736(98)04402-X.
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- Måleinstrumentet EQ 5D https://www.fhi.no/kk/brukererfaringer/sporreskjemabanken/maleinstrumenteteq-5d/

#### **Clinical Frailty Scale**



**1 Very Fit** – People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

**2 Well** – People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g. seasonally.



**8 Very Severely Frail** – Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

7 Severely Frail - Completely dependent

(physical or cognitive). Even so, they seem

stable and not at high risk of dying (within

for personal care, from whatever cause



**9 Terminally III** – Approaching the end of life. This category applies to people with a life expectancy <6 months, who are not otherwise evidently frail.



**4 Vuinerable** – While not dependent on others for daily help, often symptoms limit activities. A common complaint is being "slowed up," and/or being tired during the day.

3 Managing Well – People whose medical problems are well controlled, but are not

regularly active beyond routine walking.



5 Mildly Frail – These people often have more evident slowing, and need help in high order IADLs (finances, transportation, heavy housework, medications). Typically, mild frailty progressively impairs shopping and walking outside alone, meal preparation and housework.



**6 Moderately Frail** – People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standby) with dressing.

#### Scoring frailty in people with dementia

~ 6 months).

The degree of frailty corresponds to the degree of dementia. Common **symptoms in mild dementia** include forgetting the details of a recent event, though still remembering the event itself, repeating the same question/story and social withdrawal.

In **moderate dementia**, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting.

In **severe dementia**, they cannot do personal care without help.

## Katz Index of Independence in Activities of Daily Living

ACTIVITIES	INDEPENDENCE:	DEPENDENCE:
POINTS (1 OR 0)	(1 POINT)	(0 POINTS)
	NO supervision, direction or personal	WITH supervision, direction, personal
	as <b>sista</b> nce	assistance or total care
BATHING	(1 POINT) Bathes self completely or needs	(0 POINTS) Needs help with bathing more
	help in bathing only a single part of the	than one part of the body, getting in or
	body such as the back, genital area or	out of the tub or shower. Requires total
POINTS:	disabled extremity.	bathing.
		-
DRESSING	(1 POINT) Gets clothes from closets and	(0 POINTS) Needs help with dressing self
	drawers and puts on clothes and outer	or needs to be completely dressed.
	garments complete with fasteners. May	
POINTS:	have help tying shoes.	
TOILETING	(1 POINT) Goes to toilet, gets on and	(0 POINTS) Needs help transferring to
	off, arranges clothes, cleans genital area	the toilet, cleaning self or uses bedpan or
	without help.	commode.
POINTS:		
TRANSFERRING	(1 POINT) Moves in and out of bed or chair	(0 POINTS) Needs help in moving from
	unassisted. Mechanical transferring aides	bed to chair or requires a complete
	are acceptable.	transfer.
POINTS:		
CONTINENCE	(1 POINT) Exercises complete self control	(0 POINTS) Is partially or totally
	over urination and defecation.	incontinent of bowel or bladder.
POINTS:		
FEEDING	(1 POINT) Gets food from plate into	(0 POINTS) Needs partial or total help
	mouth without help. Preparation of food	with feeding or requires parenteral feeding.
	may be done by another person.	
POINTS:		

**TOTAL POINTS** = \_\_\_\_\_ 6 = High (*patient independent*) 0 = Low (*patient very dependent*)

Slightly adapted from Katz, S., Down, T.D., Cash, H.R., & Grotz, R.C. (1970) Progress in the development of the index of ADL. *The Gerontologist*, 10(1), 20-30.

EQ-5D-51 by the caregiver			
Describing his/ber bealth today			
Please answer on behalf of the patient. Under each heading, mark ONE box that you think			
the patient would make to describe his/her own health TODAY if he/she were able to do.			
Mobility (walking about)			
He/she has no problems in walking about			
He/she has slight problems in walking about			
He/she has a moderate problems in walking about			
He/she has a severe problems in walking about			
He/she is unable to walk about			
Self-care			
He/she has no problems washing or dressing himself /herself			
He/she has slight problems washing or dressing himself /herself	•		
He/she has moderate problems washing or dressing himself /herself			
He/she has severe problems washing or dressing himself /herself			
He/she is unable to wash or dress himself /herself	•		
I rual activities (for example work, study, hourswork, family or leisure			
activities()			
He/she has no problems doing his/her usual activities			
He/she has slight problems doing his/her usual activities	-		
He/she has moderate problems doing his/her usual activities	-		
He/she has severe problems doing his/her usual activities	-		
He/she is unable to do his/her usual activities			
Pain / discomfort	1 		
He/she has no pain or discomfort	-		
He/she has slight nain or discomfort	-		
He/she has moderate pain or discomfort			
He/she has severe pain or discomfort	-		
He/she has extreme pain or discomfort	0		
····,-···	-		
Anxiety / Depression			
He/she is not anxious or depressed	•		
He/she is a slightly anxious or depressed	•		
He/she is moderately anxious or depressed			
He/she is a severely anxious or depressed			
He/she is extremely anxious or depressed			
We would like to know how good or bad his/her health is TODAY.			
<ul> <li>This scale is numbered from 0 to 100.</li> </ul>	The best health you can imagine 100		
<ul> <li>100 means the best health he/she can imagine.</li> </ul>	± 95		
<ul> <li>0 means the worst health he/she can imagine.</li> </ul>	so		
<ul> <li>Mark an X on the scale to indicate how his/her health is TODAY.</li> </ul>			
	- <u>+</u> ao		
	± 75		
	1 10		
	± 66		
	- <u>+</u> 50		
	± 45		
	1 35 1 1		
	20		
	± •		
	The warm health		
	you can inagine		
Now, please write the number you marked on the scale in the box below			