COVID-19: MANAGEMENT IN ICU



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University Hospitals Leuven

COVID-19: MANAGEMENT IN ICU

Met alle Chinezen maar …

toch ook een beetje met den dezen!



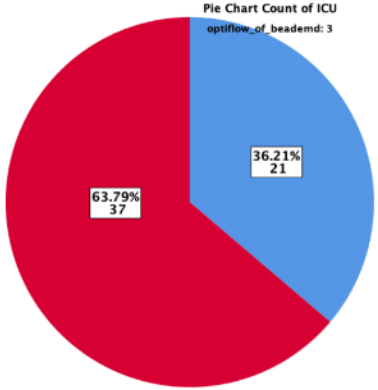
COVID-19: MANAGEMENT IN ICU

With all the “Chinesen” but ... also a little bit with “den dezen!”

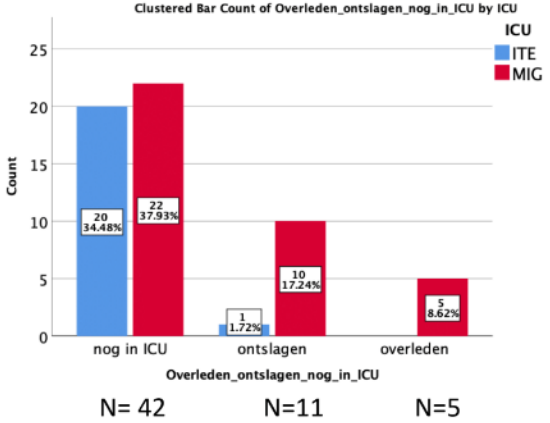


UZ Leuven data

Critically ill COVID patient with high oxygen need (HFNC/MV)



N=58
20% of all HOS

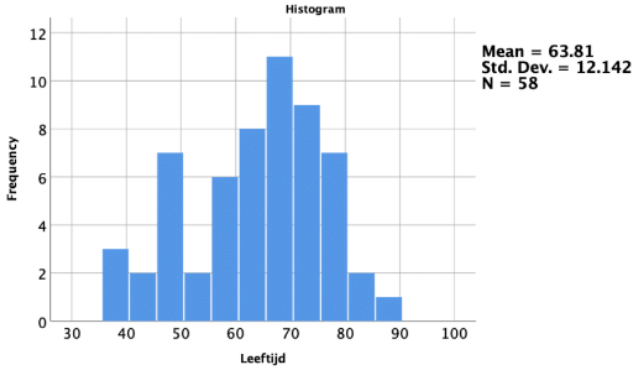


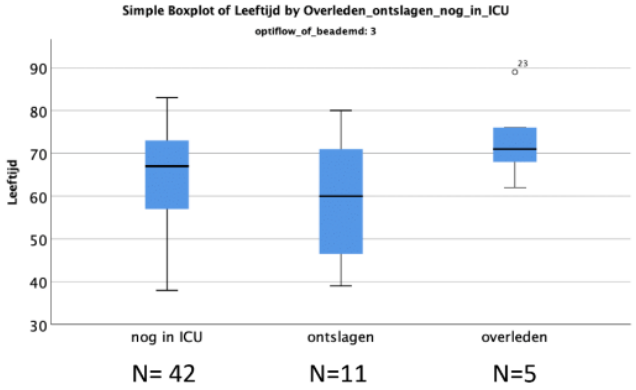
Most of them have one or more co-morbidities
Mortality in ICU: 25-62%

AML, Lymphoma, 2 ICH, MOF

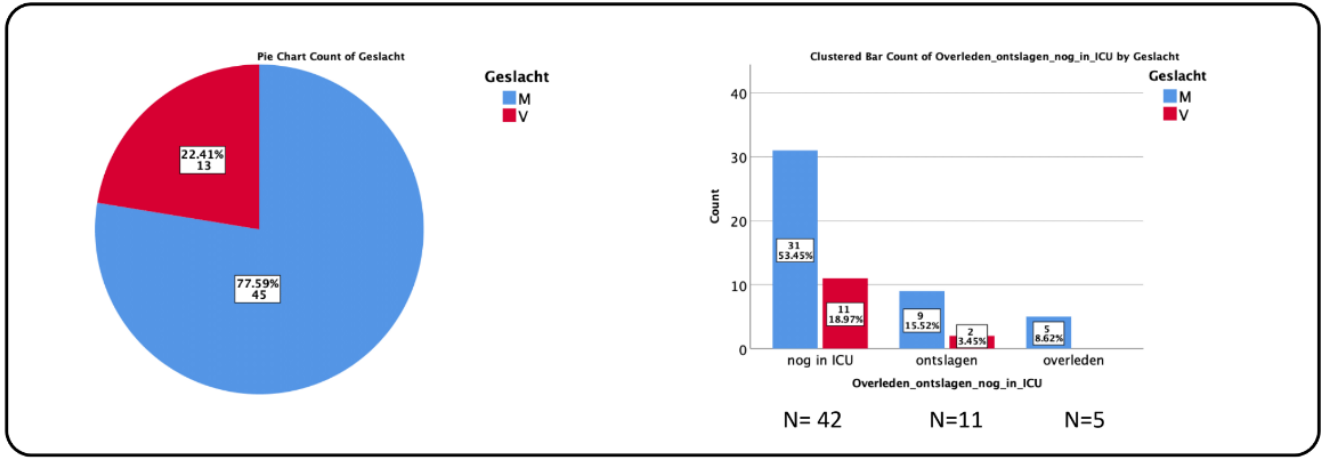
Reprinted with permission from my friendly colleague Prof Hermans

Age distribution

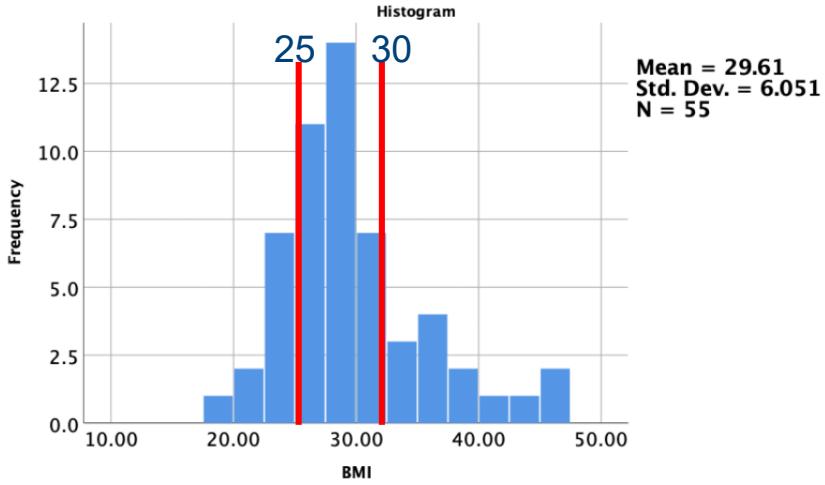


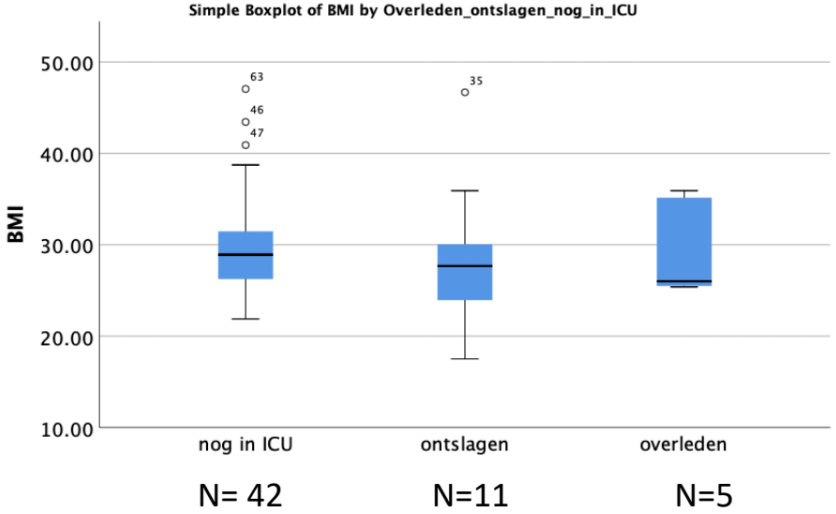


Sex

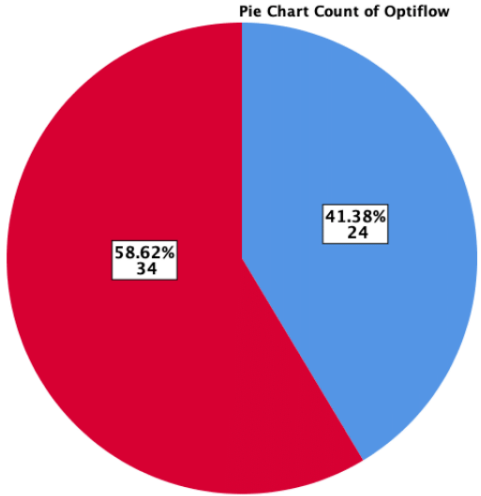

Pie Chart Count of Geslacht
Geslacht
M
V
22.41%
13
77.59%
45
Clustered Bar Count of Overleden_ontslagen_nog_in_ICU by Geslacht
Geslacht
M
V
Count
40
30
20
10
0
31
53.45%
11
18.97%
9
15.52%
2
3.45%
5
8.62%
nog in ICU
ontslagen
overleden
Overleden_ontslagen_nog_in_ICU
N= 42
N=11
N=5

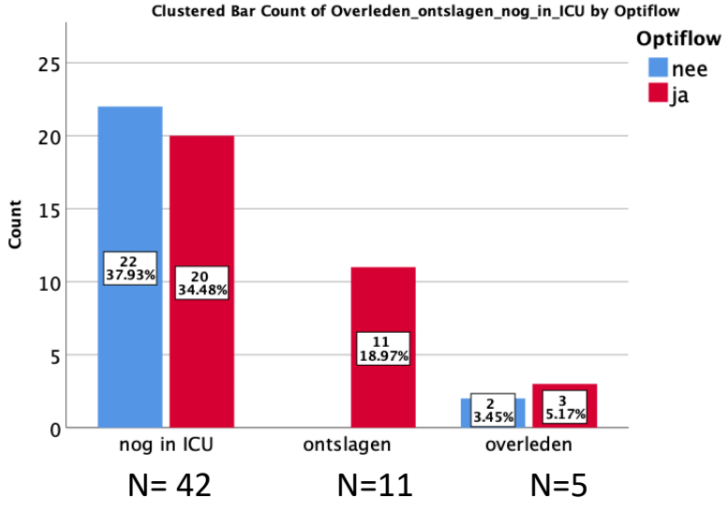
BMI


Histogram
25
30
Mean = 29.61
Std. Dev. = 6.051
N = 55
Frequency
12.5
10.0
7.5
5.0
2.5
0.0
10.00
20.00
30.00
40.00
50.00
BMI

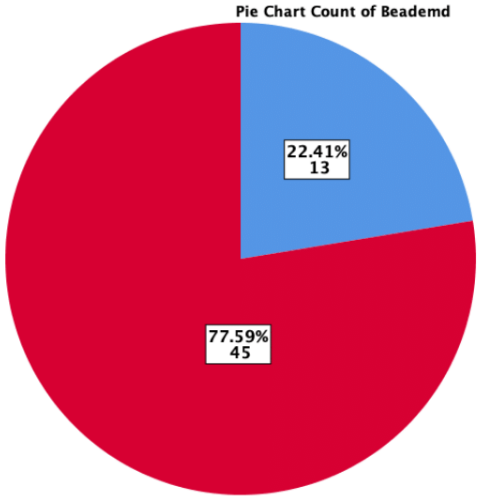

Simple Boxplot of BMI by Overleden_ontslagen_nog_in_ICU
BMI
50.00
40.00
30.00
20.00
10.00
63
46
47
35
nog in ICU
ontslagen
overleden
N= 42
N=11
N=5

Optiflow

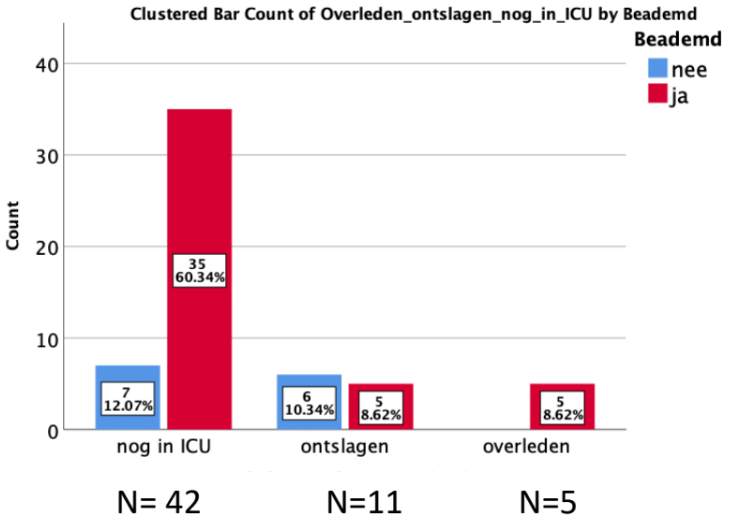

Pie Chart Count of Optiflow
Optiflow
nee
ja
41.38%
24
58.62%
34


Clustered Bar Count of Overleden_ontslagen_nog_in_ICU by Optiflow
Optiflow
nee
ja
Count
25
20
15
10
5
0
22
37.93%
20
34.48%
11
18.97%
2
3.45%
3
5.17%
nog in ICU
ontslagen
overleden
N= 42
N=11
N=5

Mechanical Ventilation

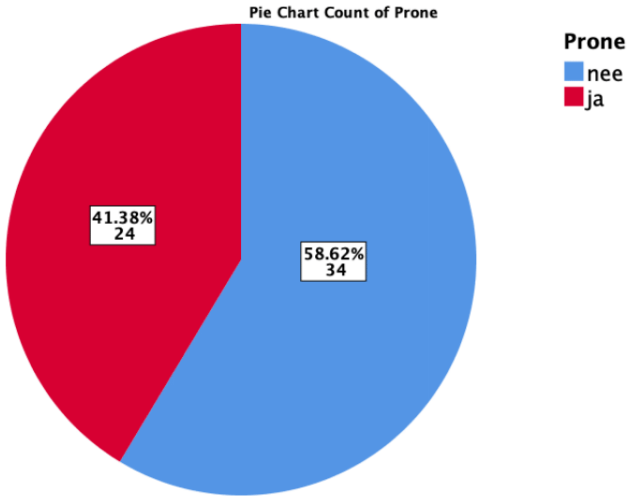


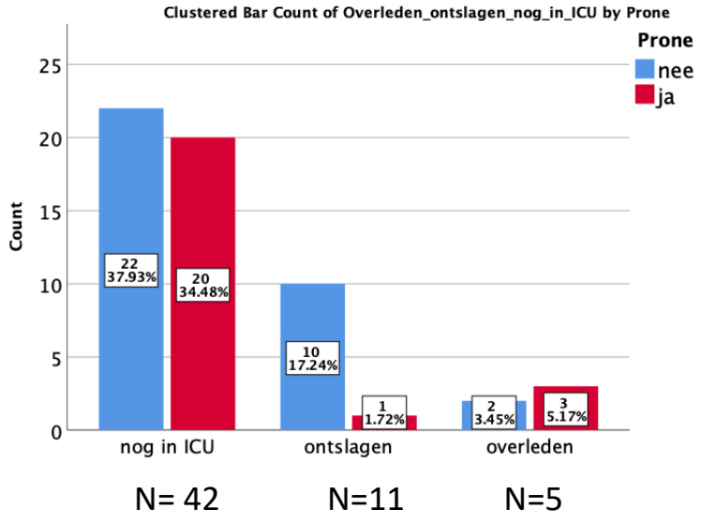
ECMO: 5



N= 42 N=11 N=5

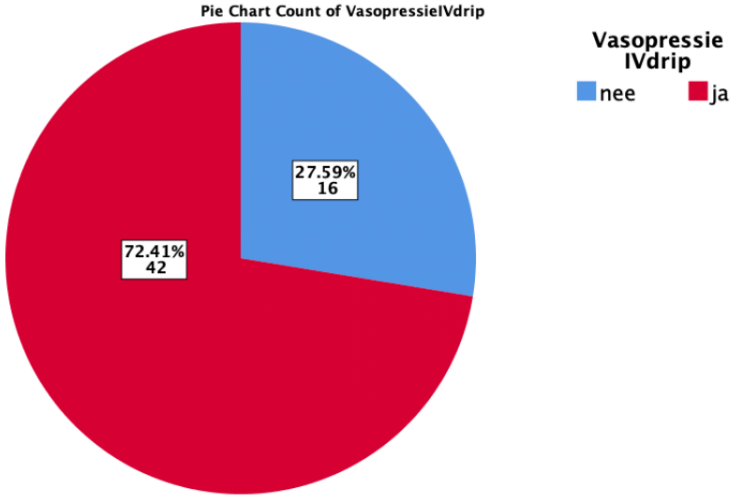
Prone

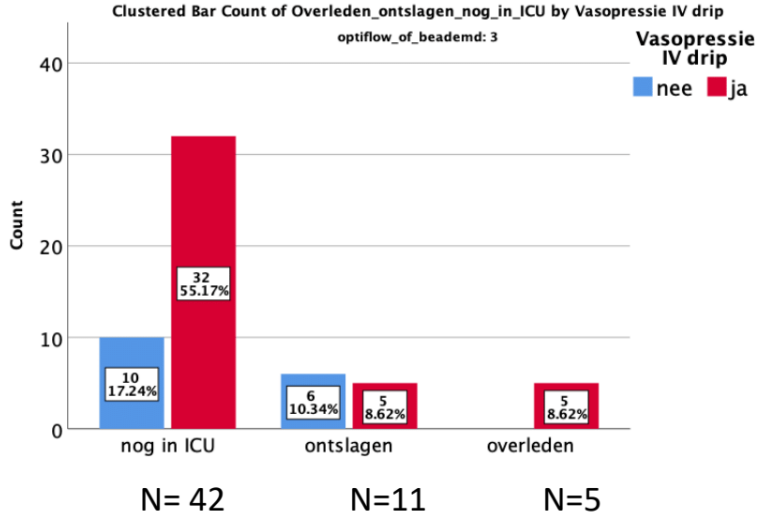




N= 42 N=11 N=5

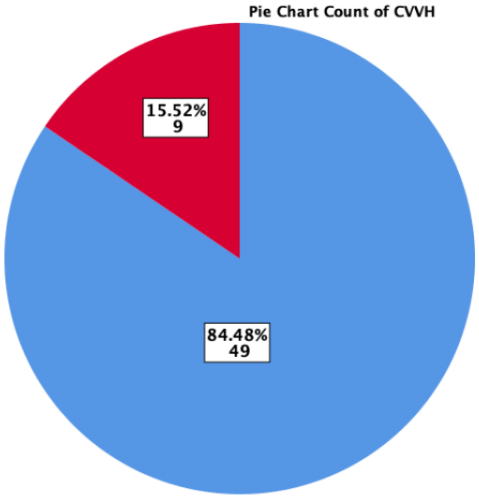
Vasopressie

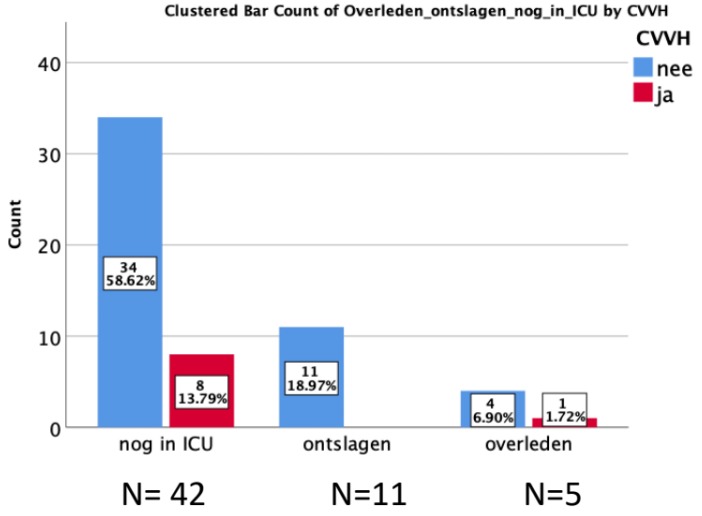




N= 42 N=11 N=5

CVVH





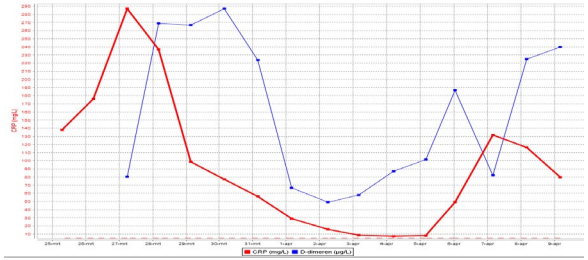
N= 42 N=11 N=5

Disease course





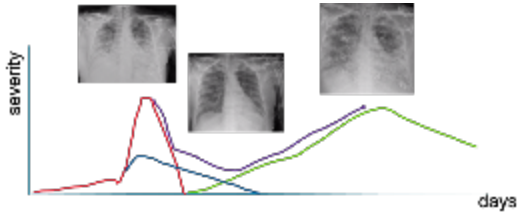




severity

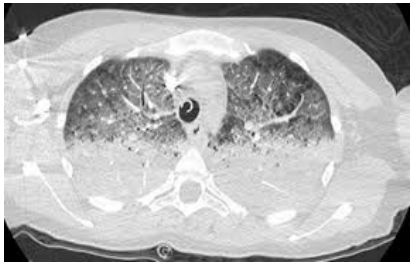
days

COVID-19 pneumonitis



Atypical ARDS → Pulmonary micro-thrombosis → “Typical” ARDS





Normal compliance
Dysregulation of perfusion
Low V/Q

Low compliance
Alveolar collapse
High right-left shunt

van de Veerdonk doi:10.20944/preprints202004.0023.v1

ICU management

GUIDELINES

Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19)

Waleed Alhazzani[1,2], Morten Hylander Møller[3,4], Yaseen M. Arabi[5], Mark Loeb[1,2], Michelle Ng Gong[6], Eddy Fan[7], Simon Oczkowski[1,2], Mitchell M. Levy[8,9], Lennie Derde[10,11], Amy Dzierba[12], Bin Du[13], Michael Aboodi[6], Hannah Wunsch[14,15], Maurizio Cecconi[16,17], Younsuck Koh[18], Daniel S. Chertow[19], Kathryn Maitland[20], Fayez Alshamsi[21], Emilie Belley-Cote[1,22], Massimiliano Greco[16,17], Matthew Laundy[23], Jill S. Morgan[24], Jozef Kesecioglu[10], Allison McGeer[25], Leonard Mermel[8], Manoj J. Mammen[26], Paul E. Alexander[2,27], Amy Arrington[28], John E. Centofanti[29], Giuseppe Citerio[30,31], Bandar Baw[1,32], Ziad A. Memish[33], Naomi Hammond[34,35], Frederick G. Hayden[36], Laura Evans[37] and Andrew Rhodes[38*]

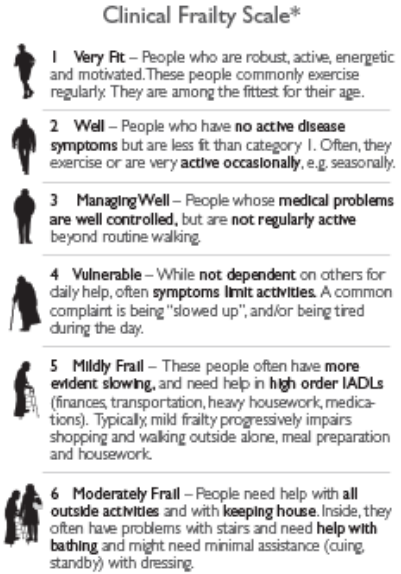
BUT: it is NOT influenza and it is NOT typical ARDS!

When to admit your patient to the ICU?

Should your patient be admitted to the ICU?

- comorbidities
- age?
- resources

Always consult ICU physician!



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.

3 **Managing Well** – People whose **medical problems are well controlled,** but are **not regularly active** beyond routine walking.

4 **Vulnerable** – 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.

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.



7 **Severely Frail** – **Completely dependent for personal care,** from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

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

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

Scoring frailty in people with dementia

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.

* 1. Canadian Study on Health & Aging, Revised 2008.
2.K. Rockwood et al. A global clinical measure of fitness and frailty in elderly people. CMAJ 2005;173:489-495.

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DALHOUSIE UNIVERSITY
Inspiring Minds

When to admit your patient to the ICU?

Fluctuations possible
Well-tolerated!
Clinical evaluation
Breathing pattern?

Early warning score for 2019-nCoV Infected Patients

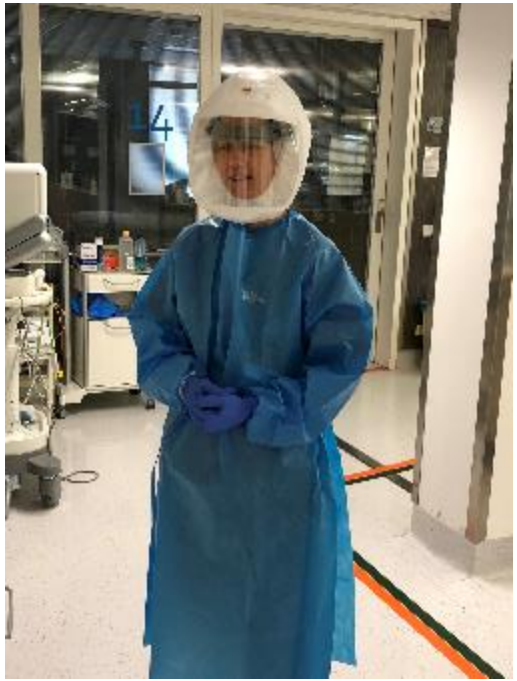
PARAMETERS	3	2	1	0	1	2	3
Age				<65			≥65
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Consciousness				Alert			Drowsiness Letargy Coma Confusion
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	

Early warning rules for 2019-nCoV Infected Patients

Score	Risk Grading	Warning Level	Monitoring Frequency	Clinical Response	Solution
0	/		Q12h	Routine Monitoring	/
1 - 4	Low	Yellow	Q6h	Bedside evaluation by nurse	Maintain existing monitoring/ Increase monitoring frequency/ Inform doctor
5 - 6 or 3 in one parameter	Medium	Orange	Q1-2h	Bedside nurse notifies doctor for evaluation	Maintain existing treatment/ Adjust treatment plan/ CCRRT* remote consultation
≥7	High	Red	Continuous	Bedside nurse notifies doctor for emergency bedside evaluation/ CCRRT remote consultation	CCRRT on-site consultation
≥7	High	Black	Continuous	✓ Patients are extremely severe with irreversible end-stage diseases facing death, such as serious irreversible brain injury, irreversible multiple organ failure, end-stage chronic liver or lung disease, metastatic tumors, etc. ✓ Should be discussed urgently by the expert group about the admission decision.	

Liao et al. Intensive Care Medicine 2020

Protect your people!





Oxygen therapy

- Target O2-saturation: 90-94%
- O2 delivery with flow as low as possible
- Oxygen need can fluctuate (eg fever, exercise,…)
- Initially clinically well-tolerated!
- If high flows are needed and no exclusion criteria for ICU admission, transfer if enough capacity

Oxygen therapy (in ICU)

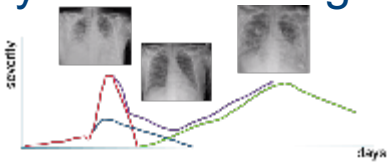
- **TRIAL** with:
  - High flow oxygen via nasal cannula (HFNC), start low (20l/min)
  - Non-invasive ventilation (CPAP, BiPAP)?
  - Don’t panic, but don’t delay intubation!
  - HFNC and auto-proning?



Oxygen therapy (in ICU)



- Next step: **INTUBATION**
  - Perfect timing? Too early – too late
    - Rapid progression
    - Lack of improvement on high flow
    - Evolving hypercapnia
    - High work of breathing: excessive inspiratory effort or swings CVP (**Patient-Self inflicted lung injury**)
    - Hemodynamic instability
  - Strict procedures: intubation kits, RSI, experienced intubator, limit personnel,… .



Ventilation strategies

- Mostly **atypical** “ARDS” (but can evolve to “classical” type):
  - ***Lung protective strategies***: avoid ventilator induced lung injury!
    - TV 6 ml/kg IBW (4-8)
    - Pplat < 30 mmHg, driving pressure < 15 mmHg
    - (Very) high PEEP (cave: barotrauma, hypotension)
    - Recruitment maneuvers
  - High level of sedation and (intermittent) neuromuscular blocking agents frequently needed (shortage!). But as low as possible.
  - iNO?
  - ***Proning***!

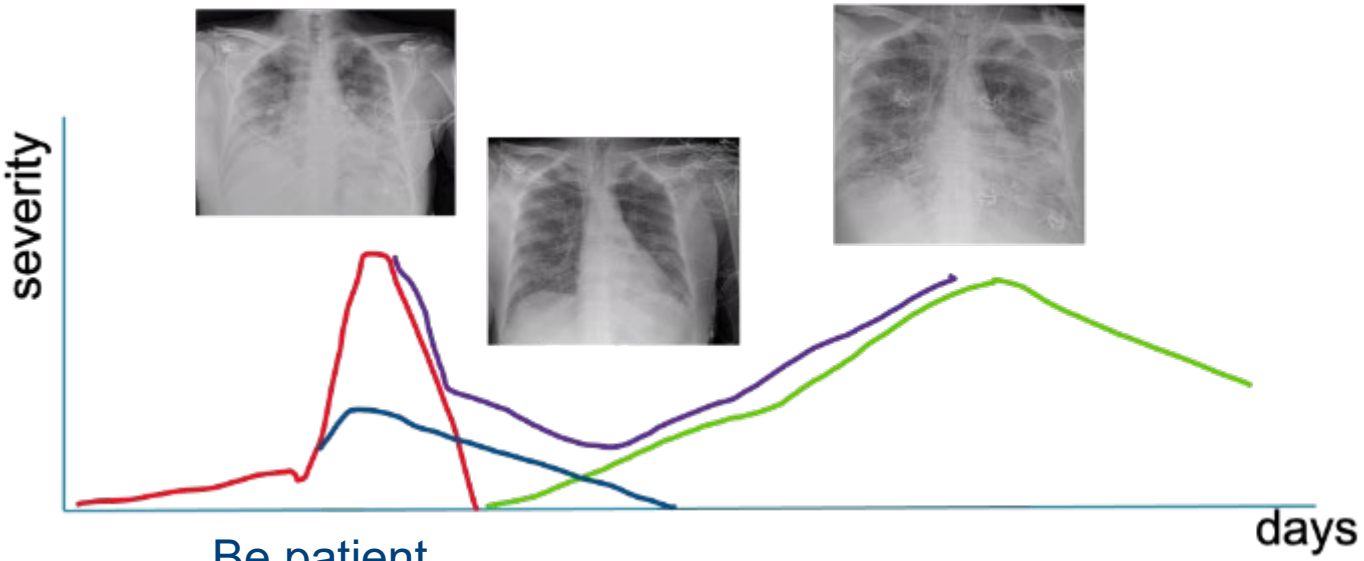
Prone ventilation

- Early, several days
- 12-16 hours
- Coordinate
- P/F <150, FiO2>60%, PEEP>5mmHg



ECMO as last resort

Weaning



Be patient
Avoid high tidal volume and high driving pressures
Wait until inflammation is better

Procoagulant effect of SARS-CoV-2

- D-dimer levels can be sky high and seem to correlate with the severity of disease (negative predictive marker)

Fibrinogeen	g/L	2.00 - 3.93	4.84	3.40		4.74	7.33				
D-dimeren	µg/L	≤ 500	> 128000	124556		111264	79262	24485	2426	1624	1502

Negative clinical evolution, followed by death

- Huge D-dimer levels seem to correlate with strong viral induced activation of the coagulation system
- Way of activation is unknown at the moment; no clear underlying DIC
- From our ICU experience: higher prevalence of acute VTE/PE, CVVH-filter clotting and ECMO-oxygenator clotting

Procoagulant effect of SARS-CoV-2

Anticoagulant Treatment is associated with decreased Mortality in Severe Coronavirus Disease 2019

Patients with coagulopathy – Tang et al., Journal of Thrombosis and Haemostasis, 2020

- 449 patients (China)
- Reduced mortality in profylactic heparin treated group with SOFA ≥ 6, D-dimers > 6 fold ULN; sepsis induced coagulopathy
- Mortality rises together with rising D-dimer levels
- LMWH-prophylaxis shows a better prognosis in severe SARS-CoV-19 disease

Occlusion and microthrombosis formation in small pulmonary vessels found in critically ill COVID-19 patients

Found on lung organ dissection – Luo et al., *Preprints* **2020**, 2020020407

Findings of acute pulmonary embolism in COVID-19 patients – Chen et al., Lancet Inf. Disease, 2020

- 25 patients (China): 10 out of them had acute PE
- Patients with COVID-19 pneumonia are indeed at high risk for acute pulmonary embolism
- The risk rises with the level of d-dimers; CT PA and or lower-limb ultrasonography should be performed
- No differences in PaO_2, $PaCO_2$ or SO_2 between PE positive and negative patients !

Effect of high PEEP and proning?

Based on anti – Factor Xa measurements in COVID-19 patients and available literature, UZ Leuven handles the following **profylactic anticoagulation** algorithm:

Profylactisch anticoagulatiebeleid bij gehospitaliseerde COVID-19 patiënten **UZ LEUVEN**		
Type COVID-patiënt	Anticoagulatiebeleid	Voorwaarden **dosis obv gewicht afronden naar boven**
ICU opname	Clexane **0,5 mg/kg, 2 keer per dag** Minstens 2 x 40 mg per dag (8 uur en 20 uur)	Bloedplaatjes > 50.000 Geen actieve bloeding
ICU CrCl < 30	Clexane **0,5 mg/kg, 1 keer per dag** Minstens Clexane 40 mg per dag	Bloedplaatjes > 50.000 Geen actieve bloeding
Non-ICU opname	Clexane **0,5 mg/kg, 1 keer der dag** Minstens Clexane 40 mg per dag	Bloedplaatjes > 50.000 Geen actieve bloeding
Non-ICU CrCl < 30	Clexane **0,5 mg/kg, 1 keer per dag** Minstens Clexane 40 mg per dag	Bloedplaatjes > 50.000 Geen actieve bloeding

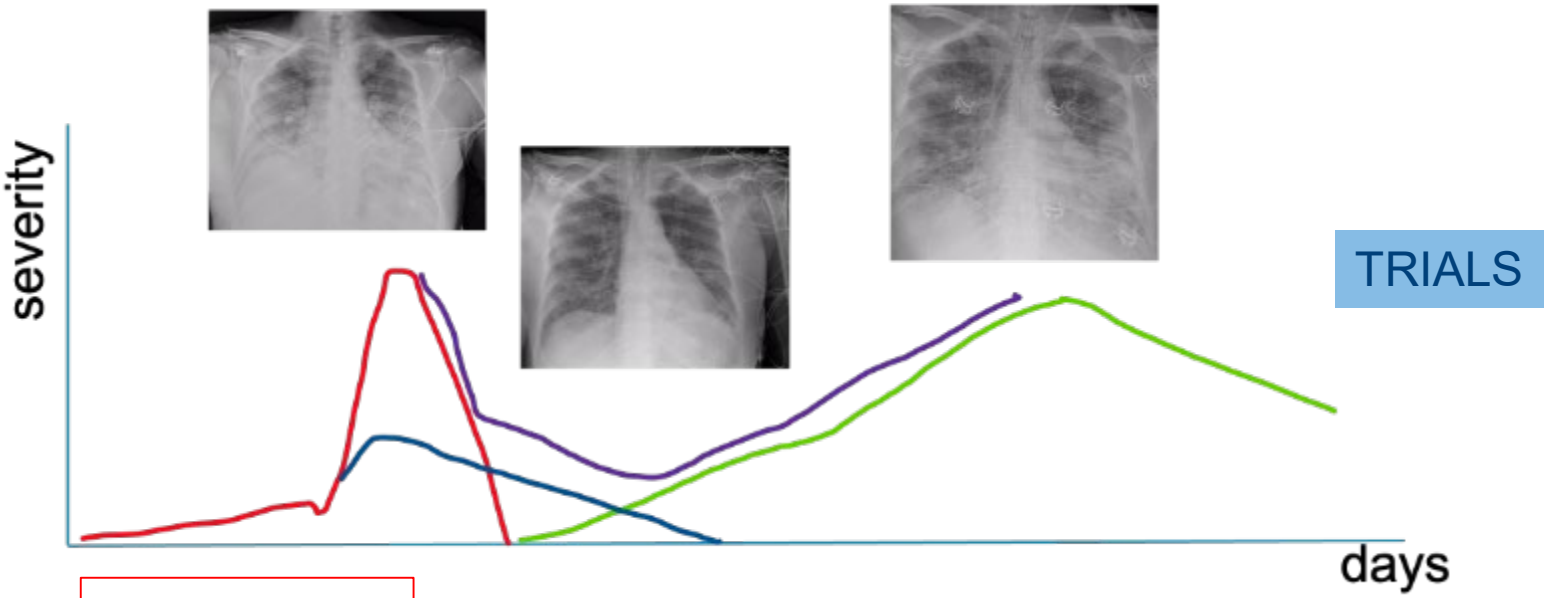
Continue profylaxis until recovery (even after discharge) in case of immobilisation, active cancer, history of VTE, …
We aim for higher anticoagulation levels for CVVH and VV-ECMO as compared to our normal ICU-standards: **aPTT levels around 60-70s, anti-Xa levels 0,3-0,5 IU/ml;** in case of therapeutic anticoagulation: **LMWH preferred**

Other supportive measures similar to ARDS

- ***Hemodynamic***: restrictive fluid administration and small doses norepinephrine, BUT:
  - Watch out for RV and impaired venous return (high PEEP)
  - Myocardial injury
  - Shock is rare
- ***Renal***: 15% AKI.
  - Thromboses CVVH
- ***Nutrition***: frequently high residual gastic volume
- ***Antibiotics***: start and stop early; culture if new inflammation (fungi?)
- ***Thrombosis***!



Other therapies



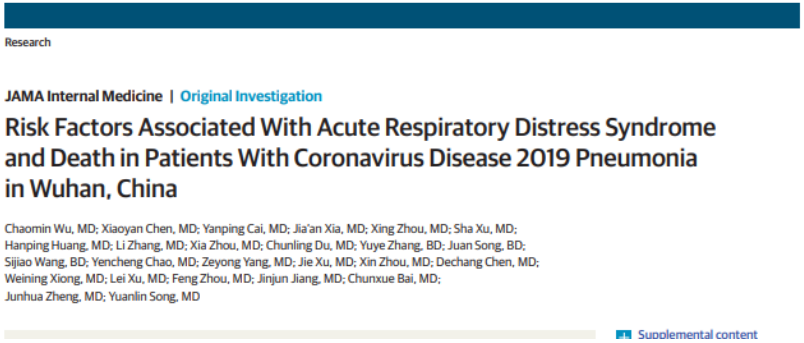
TRIALS

Anti-virals

Anti-inflammatory/coagulation

Steroids?

No routine steroids, except for other indications
Data from other viral pneumonia (influenza, MERS, SARS)
Hyperglycemia, opportunistic infections, longer viral shedding



Research

JAMA Internal Medicine | Original Investigation

Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China

Chaomin Wu, MD; Xiaoyan Chen, MD; Yanping Cai, MD; Jia'an Xia, MD; Xing Zhou, MD; Sha Xu, MD; Hanping Huang, MD; Li Zhang, MD; Xia Zhou, MD; Chunling Du, MD; Yuye Zhang, BD; Juan Song, BD; Sijiao Wang, BD; Yencheng Chao, MD; Zeyong Yang, MD; Jie Xu, MD; Xin Zhou, MD; Dechang Chen, MD; Weining Xiong, MD; Lei Xu, MD; Feng Zhou, MD; Jinjun Jiang, MD; Chunxue Bai, MD; Junhua Zheng, MD; Yuanlin Song, MD

Supplemental content

Retrospective cohort
N=201

Mortality steroids vs no steroids: 23/50 (46%) vs 21/34 (61,8%)

Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial

*Jesús Villar, Carlos Ferrando, Domingo Martínez, Alfonso Ambrós, Tomás Muñoz, Juan A Soler, Gerardo Aguilar, Francisco Alba, Elena González-Higueras, Luís A Conesa, Carmen Martín-Rodríguez, Francisco J Díaz-Domínguez, Pablo Serna-Grande, Rosana Rivas, José Ferreres, Javier Belda, Lucía Capilla, Alec Tallet, José M Añón, Rosa L Fernández, Jesús M González-Martín for the dexamethasone in ARDS network**

Summary

Background There is no proven specific pharmacological treatment for patients with the acute respiratory distress syndrome (ARDS). The efficacy of corticosteroids in ARDS remains controversial. We aimed to assess the effects of dexamethasone in ARDS, which might change pulmonary and systemic inflammation and result in a decrease in duration of mechanical ventilation and mortality.

Methods We did a multicentre, randomised controlled trial in a network of 17 intensive care units (ICUs) in teaching hospitals across Spain in patients with established moderate-to-severe ARDS (defined by a ratio of partial pressure of arterial oxygen to the fraction of inspired oxygen of 200 mm Hg or less assessed with a positive end-expiratory pressure of 10 cm H_2O or more and FiO_2 of 0·5 or more at 24 h after ARDS onset). Patients with brain death, terminal-stage disease, or receiving corticosteroids or immunosuppressive drugs were excluded. Eligible patients were randomly assigned based on balanced treatment assignments with a computerised randomisation allocation sequence using blocks of 10 opaque, sealed envelopes to receive immediate treatment with dexamethasone or continued routine intensive care (control group). Patients in the dexamethasone group received an intravenous dose of 20 mg once daily from day 1 to day 5, which was reduced to 10 mg once daily from day 6 to day 10 [illegible] groups were ventilated with lung-protective mechanical ventilation. Allocation concealment was [illegible] sites during the trial. Primary outcome was the number of ventilator-free days at 28 days, defined [illegible] days alive and free from mechanical ventilation from day of randomisation to day 28. Secondary [illegible] cause mortality 60 days after randomisation. All analyses were done according to the intention-to-tre study is registered with ClinicalTrials.gov, NCT01731795.

Findings Between March 28, 2013, and Dec 31, 2018, we enrolled 277 patients and randomly assigned 139 patients to the dexamethasone group and 138 to the control group. The trial was stopped by the data safety monitoring board due to low enrolment rate after enrolling more than 88% (277/314) of the planned sample size. The mean number of ventilator-free days was higher in the dexamethasone group than in the control group (between-group difference 4·8 days [95% CI 2·57 to 7·03]; p<0·0001). At 60 days, 29 (21%) patients in the dexamethasone group and 50 (36%) patients in the control group had died (between-group difference –15·3% [–25·9 to –4·9]; p=0·0047). The proportion of adverse events did not differ significantly between the dexamethasone group and control group. The most common adverse events were hyperglycaemia in the ICU (105 [76%] patients in the dexamethasone group *vs* 97 [70%] patients in the control group), new infections in the ICU (eg, pneumonia or sepsis; 33 [24%] *vs* 35 [25%]), and barotrauma (14 [10%] *vs* 10 [7%]).

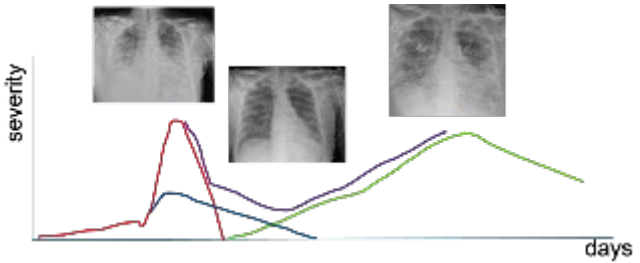
Interpretation Early administration of dexamethasone could reduce duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS.

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Steroids?

Consider:

- Low dose (0,5-1 mg methylprednisolone/kg/dag for 5-7 days)
- At day 5-10?
- “new inflammation” with high CRP, ferritine,… (Hemofagocytic lymphohistiocytosis?)
- Clinical worsening
- After exclusion of new infection (VAP, Fungi,…)



Challenges

- Lack of capacity (bed, ventilators, staff, nurses)
- Lack of medication (sedatives, muscle relaxantia, antibiotics,…)
- Lack of PPE
- Lack of patience (not patients!)

Life after ICU??

Thanks to everyone and take care!

