Landeskrankenhaus - Universitätsklinikum Graz

Stmk. Krankenanstaltenges.m.b.H. Medizinische Universität Graz

Medical University of Graz

Webinarreihe in Kooperation mit der ÖGP (10.05.2021)

Impfpräventable pulmonale Erkrankungen – Teil 1

Update COVID-19 und Influenza

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COVID-19 und Influenza (Same Same But Different?)

Merkmal	COVID-19 (SARS-CoV-2)	Influenza
Globale Verbreitung	Ja	
Pandemie-fähig	Ja	
Einfache Prävention möglich	Ja (Masken, Abstand, Hygiene)	
Symptomatik	Variable	
Fieber, Husten, MMA	Ja (aber nicht immer)	
Infektions-Promotor	Jüngere Menschen	
Risiko-Gruppen	Ältere, Polymorbide, Schwangere	
Diagnostik	PCR	
Nosokomiale Infektionen	Ja	
ICU-Letalität	27-40%	
Antivirale Therapie	Limitierte Wirksamkeit	
Impfungen	Verfügbar	
Booster-Impfungen nötig	Ja	

COVID-19 und Influenza (Same But Different Different)

Merkmal	COVID-19 (SARS-CoV-2)	Influenza
Erreger	Virus (Corona)	Virus (Orthomyxo)
Jährlich epidemisch	Nein	Ja
Hauptübertragungsweg	Aerosole > Tröpfchen	Tröpfchen > Aerosole
Basisreproduktionszahl R0	2-5	1-2
Inkubationszeit	5-6 Tage	1-2 Tage
Störung Geruch/Geschmack	Ja	Nein
Schwere CAP	Häufiger	Seltener als bei COVID
Therapie mit Immunsupp.	Ja	Nein
Therapie mit Antikoagulation	Ja	Nein
Sekundäre Infektionen	Seltener als bei Influenza	Häufiger
Postexpositionsprophylaxe	Nein	Ja
Hospital/ICU-Belastung	Ganzjährig	Saisonal (3 Monate)
Hospital-Letalität	17-22%	10-12%
Spätfolgen	Häufiger	Seltener als bei COVID
Tote pro Jahr in Österreich	Bis 9000	Bis 4500

Influenza Epidemiologie (Österreich Saison 2020/2021)

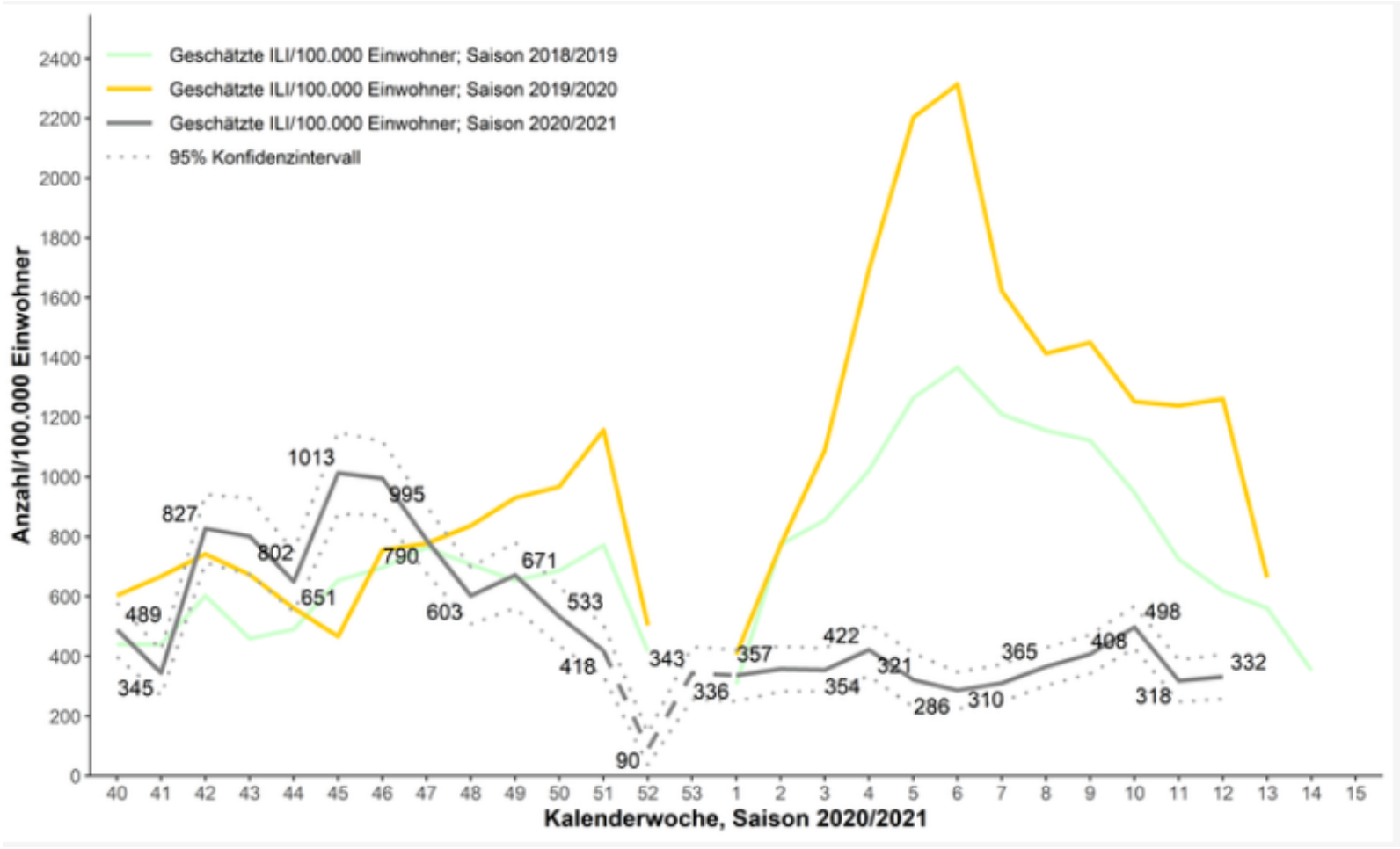
Tabelle 1: Geschätzte Anzahl der Todesfälle, assoziiert mit der saisonalen Influenza (IA) und mit Temperaturextremen (ET) inklusive 95 % Konfidenzintervall (KI) für die Saisonen 2015/2016-2019/2020 (jeweils KW 40-KW 20 des Folgejahres), Österreich.

Saison	Kalenderwoche	Anzahl geschätzte Todesfälle (95 % KI) assoziiert mit Influenza (IA)
2015/2016	40 - 20	259 (198; 326)
2016/2017	40 - 20	4.436 (4.242; 4.634)
2017/2018	40 - 20	2.851 (2.688; 3.016)
2018/2019	40 - 20	1.373 (1.246; 1.504)
2019/2020	40 - 20	834 (723; 950)

2020/2021 **vermutlich keine**

https://www.ages.at/themen/krankheitserreger/grippe/saison-202021/, abgerufen am 03.05.2021

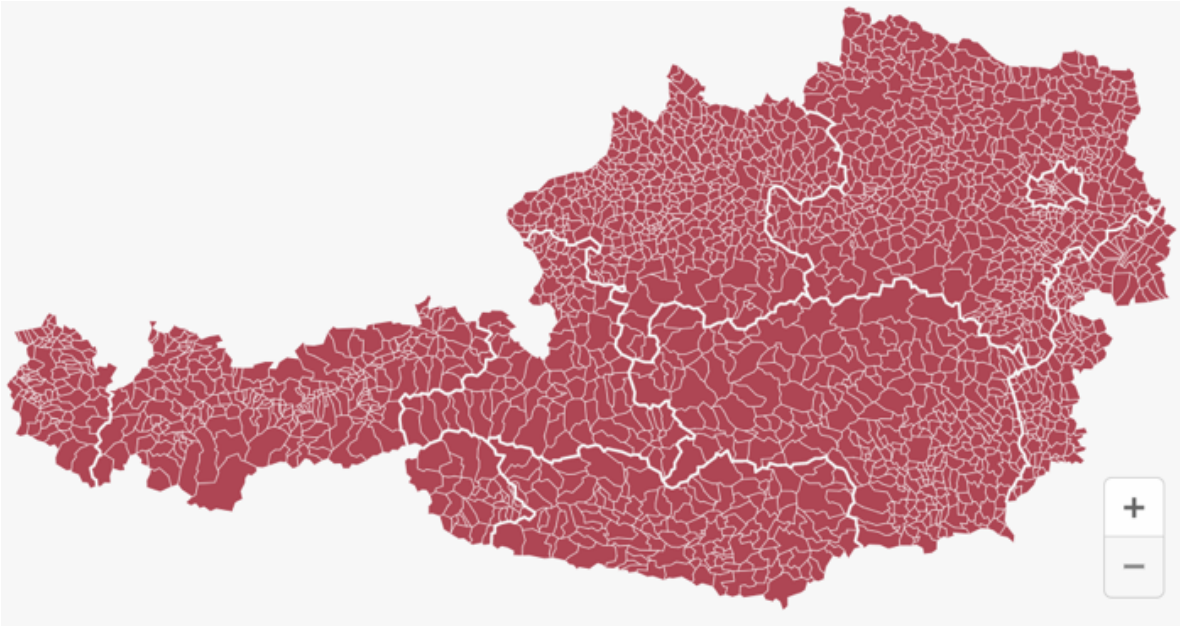
Influenza Epidemiologie (Österreich Saison 2020/2021)



https://www.ages.at/themen/krankheitserreger/grippe/saison-202021/, abgerufen am 03.05.2021

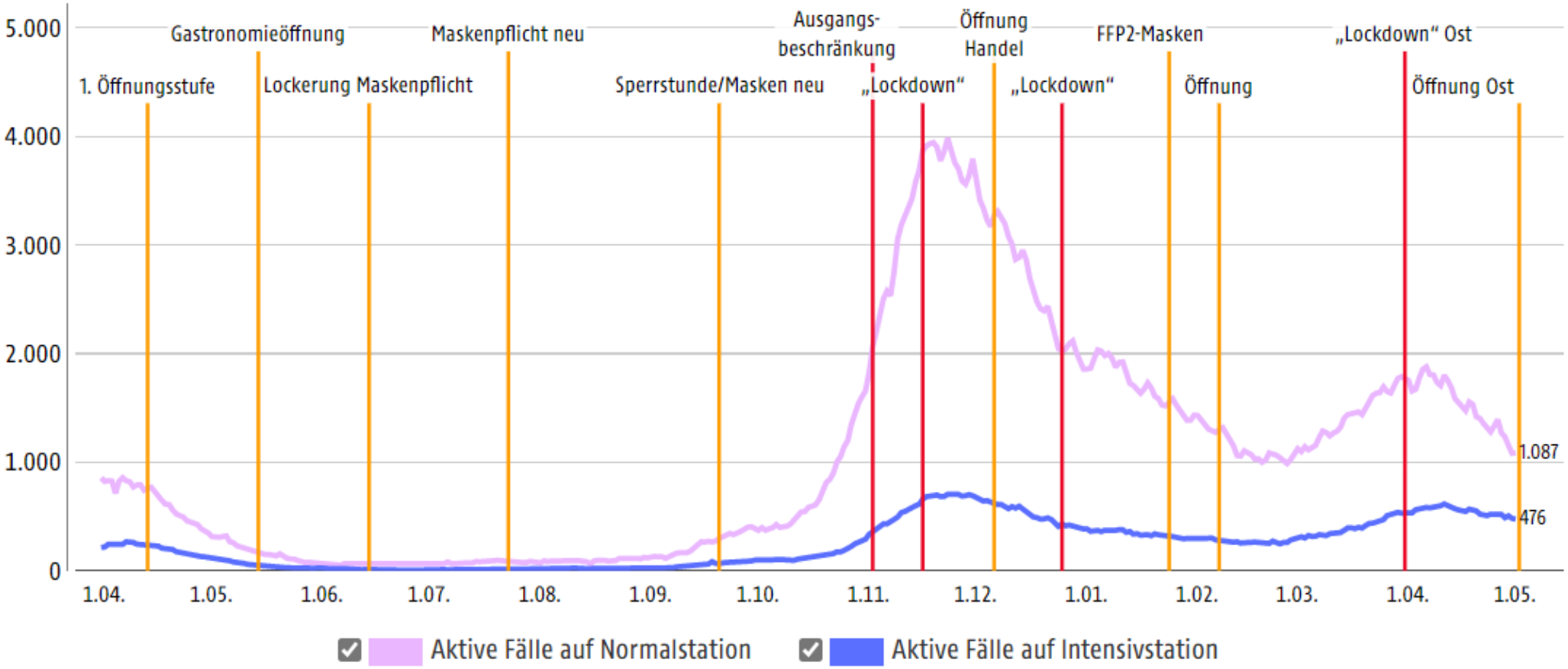
COVID-19 Epidemiologie (Österreich 27.02.2020 bis 03.05.2021)

Verstorbene Fälle (27.02.2020 bis 03.05.2021)	**ca. 10.000**
Aktuell im Krankenhaus (Normalstation)	**ca. 1.100**
Aktuell auf Intensivstationen	**ca. 500**



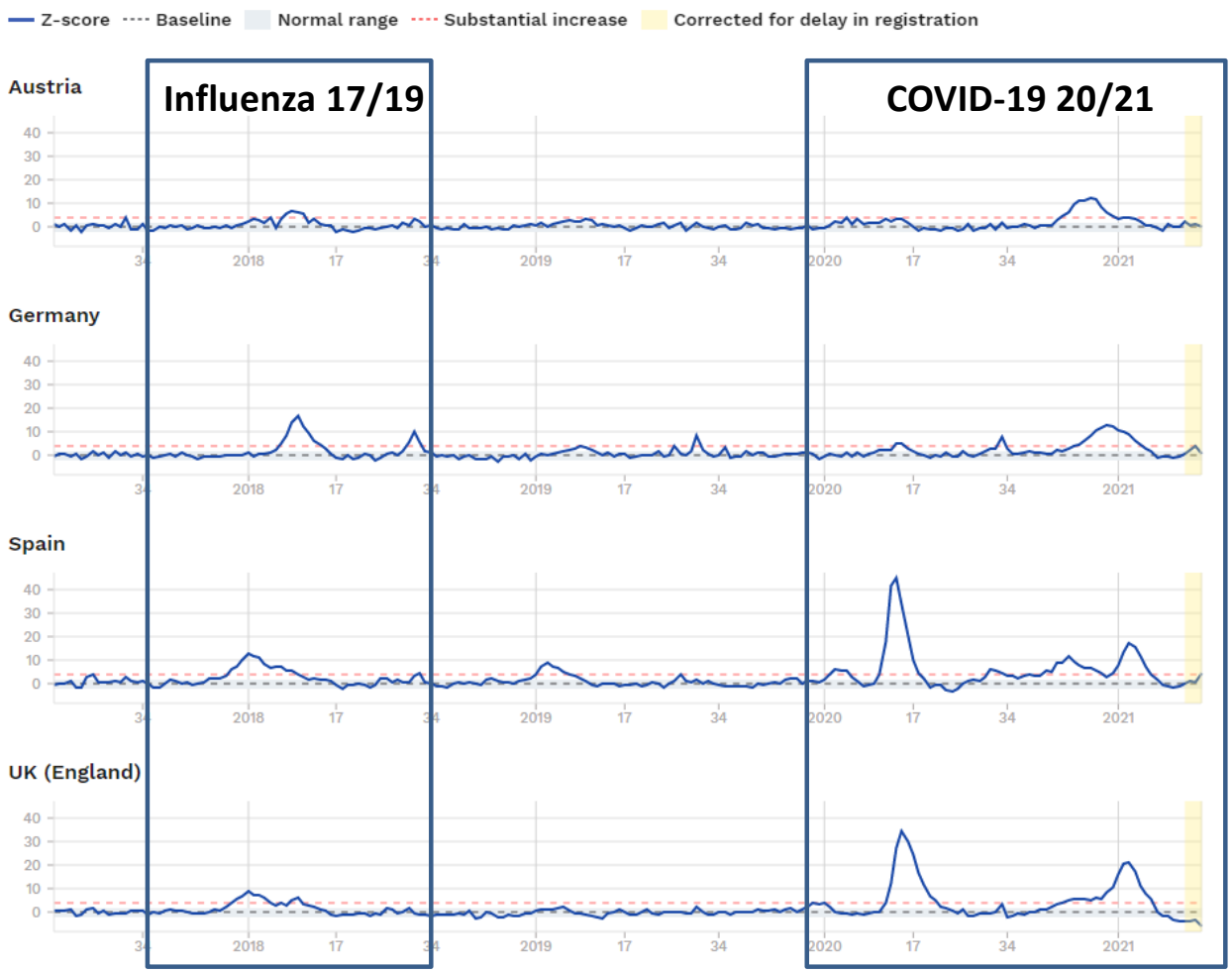
https://covid19-dashboard.ages.at, abgerufen am 03.05.2021

COVID-19 im Krankenhaus und auf ICU



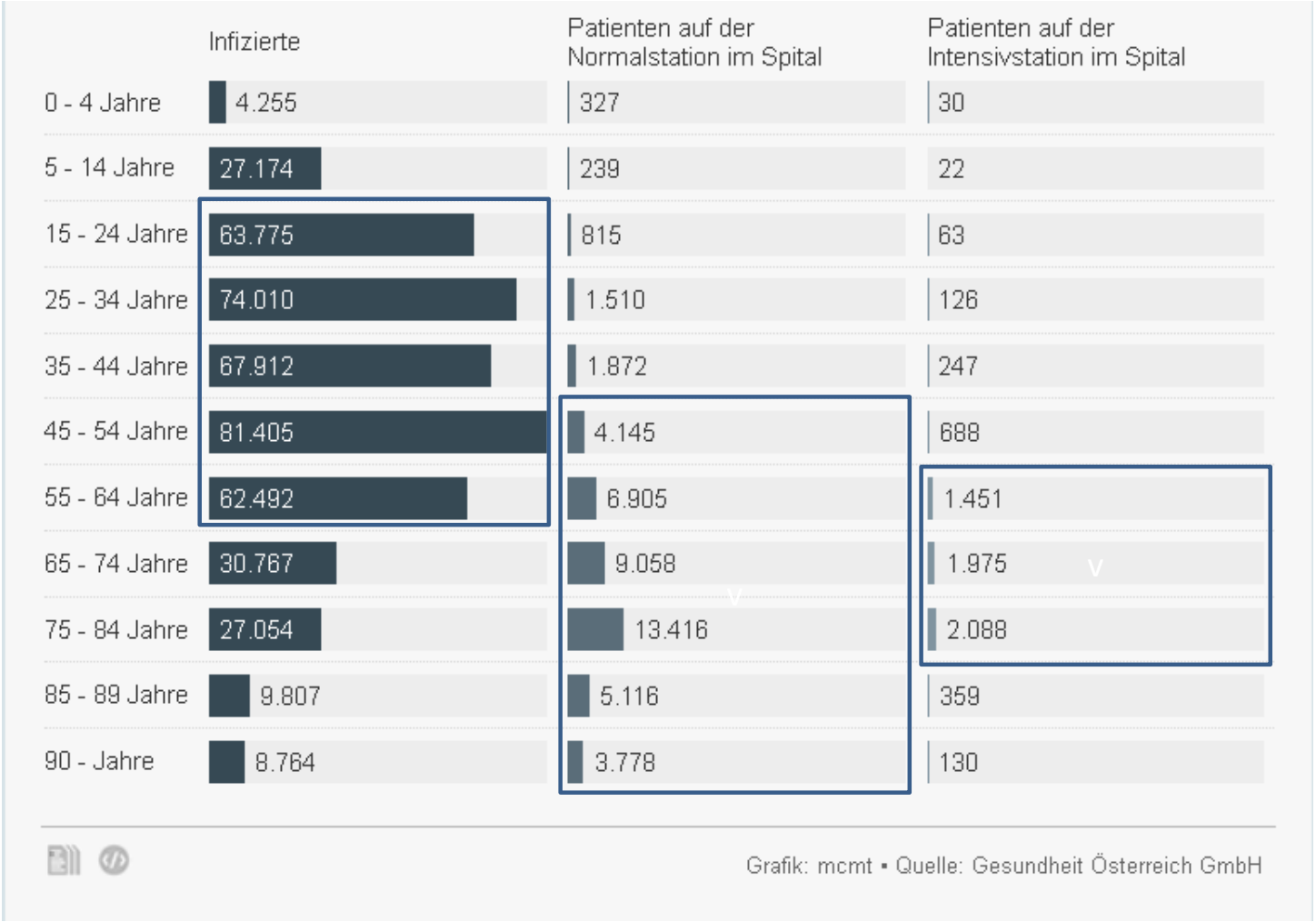
https://orf.at/corona/daten/oesterreich, Quelle AGES/EMS, abgerufen am 03.05.2021

Excess mortality Influenza 2017/2018 und COVID-19 2020/2021



https://www.euromomo.eu/graphs-and-maps#excess-mortality, abgerufen am 03.05.2021

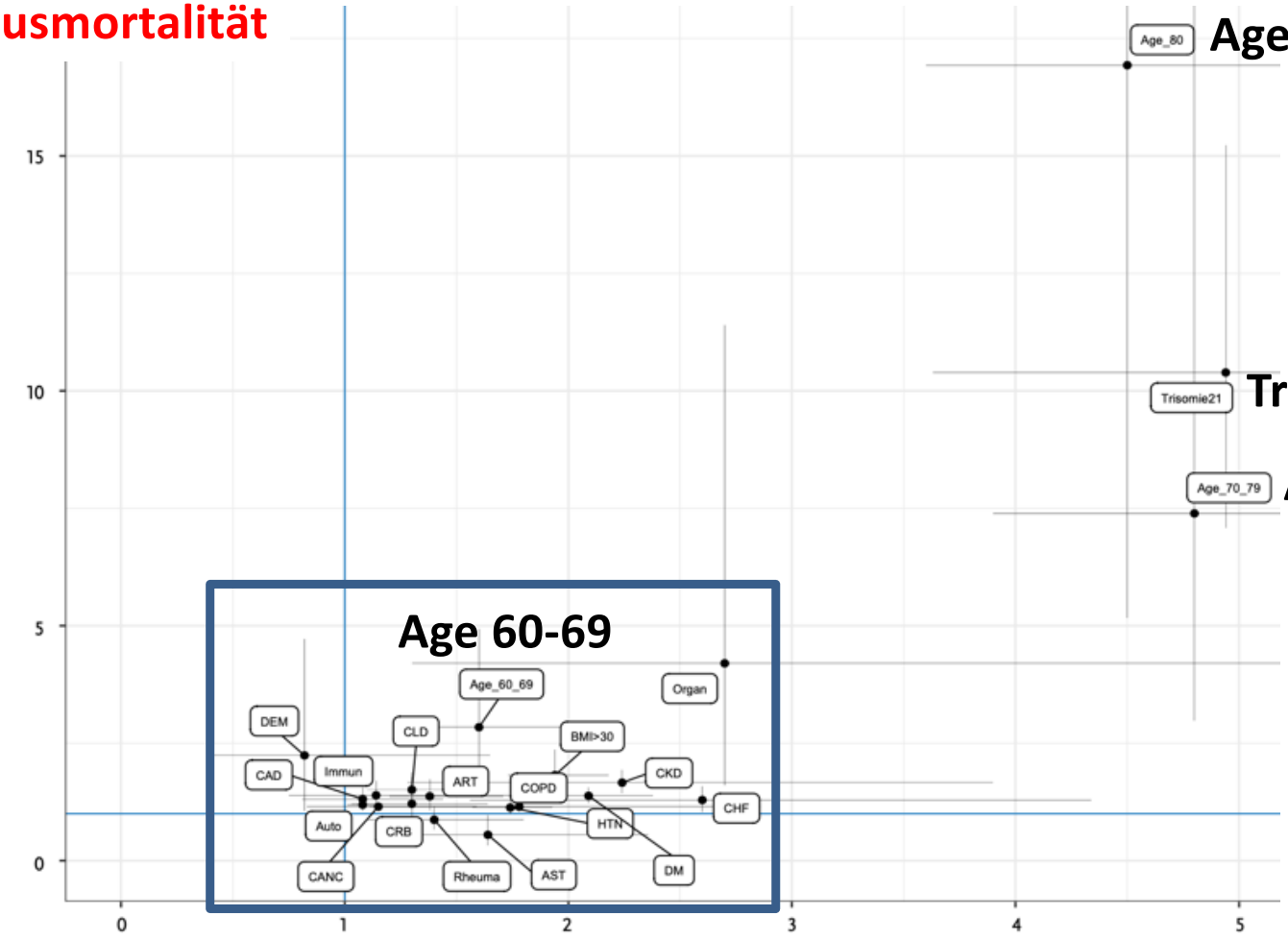
COVID-19 (Österreich März 2020 bis Februar 2021)



https://www.derstandard.at/story/2000126263769/wie-gross-das-risiko-ist-mit-covid-im-spital-zu; abgerufen am 03.05.2021

Risiken von Vorerkrankungen und Alter auf Hospitalisation und Mortalität von COVID-19

Krankenhausmortalität

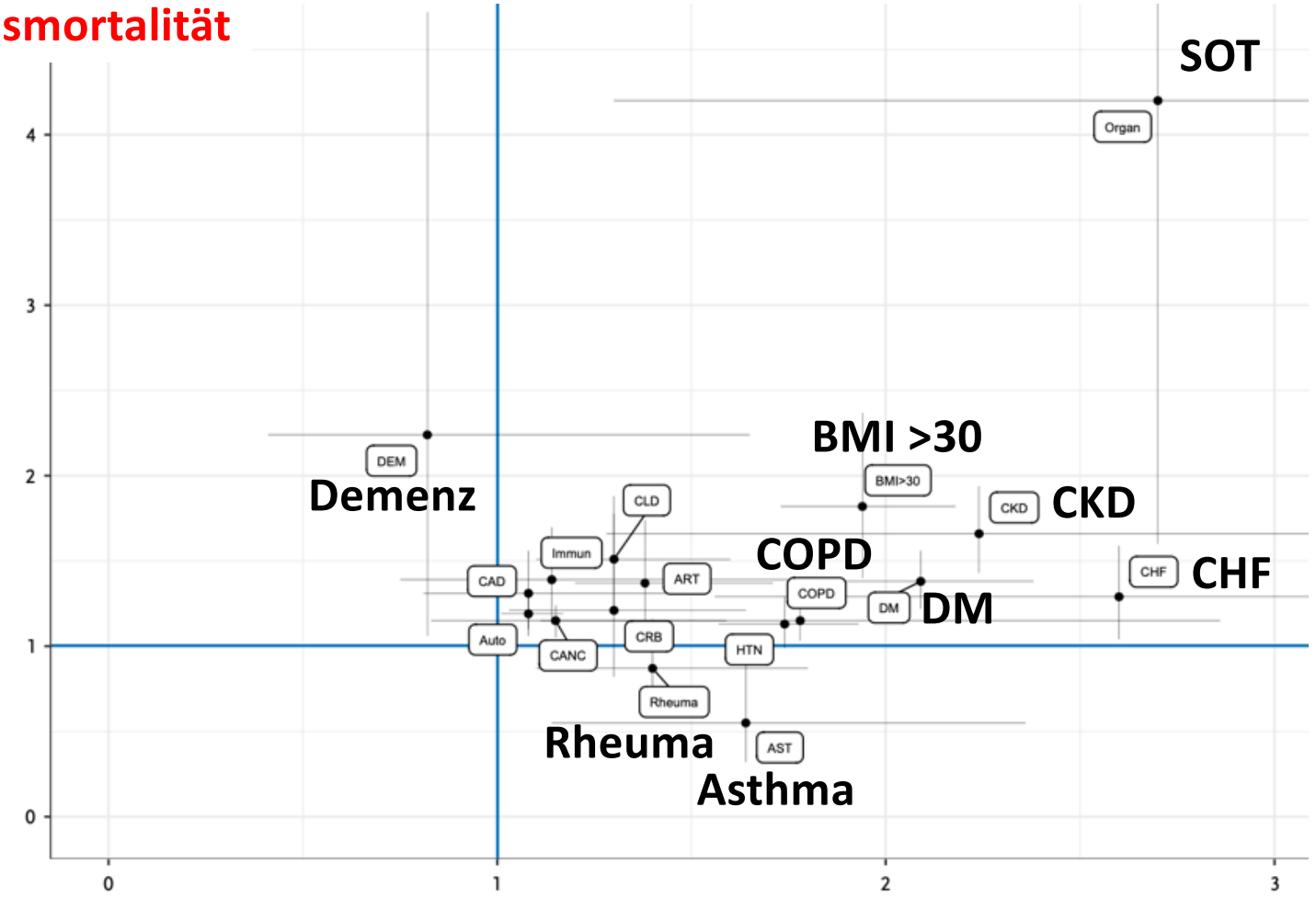


Hospitalisierung

Vygen-Bonnet S et al. Beschluss der STIKO zur 1. Aktualisierung der COVID-19-Impfempfehlung und die dazugehörige

Risiken von Vorerkrankungen und Alter auf Hospitalisation und Mortalität von COVID-19

Krankenhausmortalität



Hospitalisierung

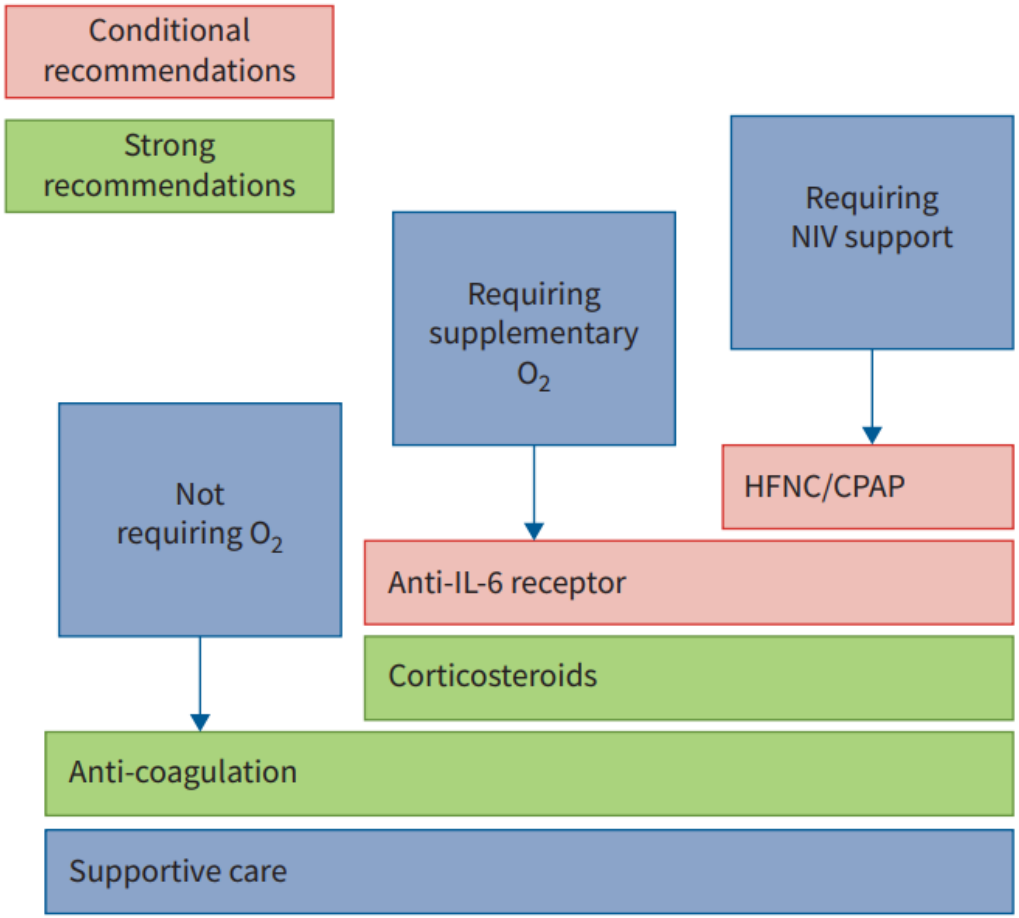
Vygen-Bonnet S et al. Beschluss der STIKO zur 1. Aktualisierung der COVID-19-Impfempfehlung und die dazugehörige

ERS COVID-19 Guideline 02/2021 (only positive recommendations)

Therapy (in hospital)	Recommendations	Strength of recommendation	Quality of Evidence
Corticosteroids (CC) Dexamethasone 6 mg/d for 10 d	**Offering CC pts. requiring O2 or ventilatory support**	**Strong**	Moderate
Anticoagulation (AC)	**Offering a form of AC to all pts.**	**Strong**	Very low
IL-6 receptor antagonist (aIL-6)	Offering aIL-6 pts. requiring O2 or ventilatory support	**Conditional**	Low
Noninvasive ventilatory support (HFNC or NIV)	HFNC or NIV for pts. with hypoxaemic respiratory failure without an immediate indication for invasive ventilation	**Conditional**	Very low
Remdesevir (RDV)	No recommendation is made regarding the use of RDV in pts. not requiring ventilatory support	None	Moderate

Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J 2021; 57: 2100048 [https://doi.org/10.1183/13993003.00048-2021].

ERS COVID-19 Guideline 02/2021 (only positive recommendations)



Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J 2021; 57: 2100048 [https://doi.org/10.1183/13993003.00048-2021].

ERS COVID-19 Guideline 02/2021 – aIL-6 recommendation

Summary of evidence

- **8 randomised, controlled studies** comparing aIL-6 (a total of 3309 patients, more tocilizumab than sarilumab) vs. usual care (3038 patients)

- ERS meta-analysis identified **no significant effect of aIL-6 on mortality** (820/3309 (24.8%) with active treatment versus 893/3038 (29.4%) with usual care; OR 0.90, 95% CI 0.73–1.12

- However**: The two largest studies, RECOVERY and REMAP-CAP both demonstrated significant reductions in mortality**

- **Mechanical ventilation (MV) was reduced by 25% (OR 0.75, 95% CI 0.63–0.9, from 4 studies)**

- **Adverse events and serious adverse events were not increased.**

Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J 2021; 57: 2100048 [https://doi.org/10.1183/13993003.00048-2021].

ERS COVID-19 Guideline 02/2021 – aIL-6 recommendation

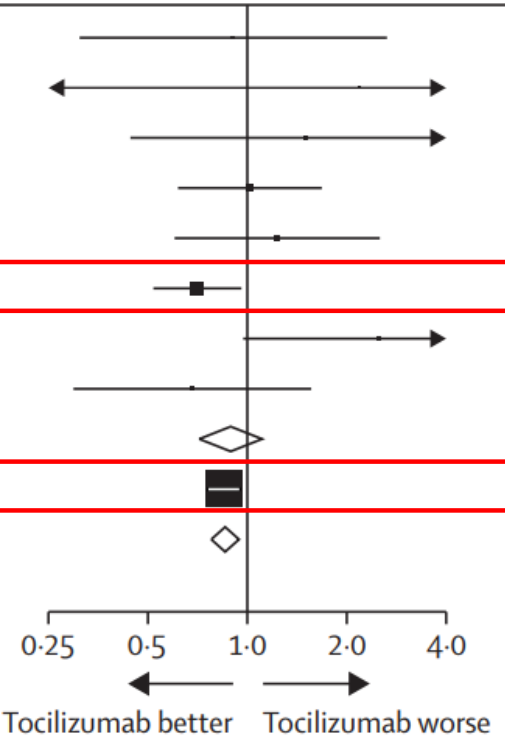
Die Studien:

1. Tocilizumab in Hospitalised Patients With COVID-19 Pneumonia. Rosas I, et al. medRxiv 2020.08.27.20183442; doi: https://doi.org/10.1101/2020.08.27.20183442 --> Inzwischen im NEJM 2021 Apr 22;384(16):1503-1516
2. Effect of Tocilizumab vs standard care on clinical worsening in patients hospitalised with COVID-19 Pneumonia A randomised controlled trial. Salvarani C, et al. JAMA Intern Med. Doi:10.1001/jamainternmed.2020.6615 Published online October 20, 2020.
3. Effect of Tocilizumab vs Usual Care in Adults Hospitalised With COVID-19 and Moderate or Severe Pneumonia A Randomised Clinical Trial. Hermine et al. JAMA Intern Med.
4. Efficacy of Tocilizumab in patients hospitalised with COVID-19. Stone et al. NEJM. 2020 Oct 21. Doi:10.1056/NEJMoa2028836
5. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. Gordon et al, https://www.medrxiv.org/content/10.1101/2021.01.07.21249390v1 --> Inzwischen N Engl J Med. 2021 Apr 22;384(16):1491-1502
6. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY) Preliminary results of a randomized controlled open-label platform trial. Horby et al https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1.full.pdf
7. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. Salama et al N Engl J Med. 2021 Jan 7;384(1):20-30
8. Effect of tocilizumab on clinical outcomes at 15 days in patients with severe or critical coronavirus disease 2019: randomised controlled trial. Veiga et al. BMJ 2021 Jan 20;372:n84. doi: 10.1136/bmj.n84.

Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J 2021; 57: 2100048 [https://doi.org/10.1183/13993003.00048-2021].

Meta–analysis of mortality in RECOVERY and other trials

	Deaths/patients randomly assigned (%)		Observed minus expected deaths*		Ratio of death rates, rate ratio (95% CI)
	Tocilizumab group	Usual care group	(O–E)	Var (O–E)	
CORIMUNO–TOCI[10]	7/64 (11%)	8/67 (12%)	–0·3	3·3	0·91 (0·31–2·65)
RCT–TCZ–COVID-19[11]	2/60 (3%)	1/66 (2%)	0·6	0·7	2·17 (0·22–21·3)
BACC Bay[12]	9/161 (6%)	(3/82) ×2† (4%)	1·0	2·6	1·51 (0·44–5·13)
COVACTA[9]	58/294 (20%)	(28/144) ×2† (19%)	0·3	15·3	1·02 (0·62–1·68)
EMPACTA[13]	26/249 (10%)	(11/128) ×2† (9%)	1·6	7·5	1·23 (0·60–2·52)
REMAP–CAP[15]	98/353 (28%)	142/402 (35%)	–14·2	40·8	0·71 (0·52–0·96)
TOCIBRAS[8]	14/65 (22%)	6/64 (9%)	3·9	4·3	2·51 (0·97–6·50)
COVINTOC[14]	11/91 (12%)	15/89 (17%)	–2·1	5·6	0·68 (0·30–1·56)
Subtotal: eight trials	**225/1337 (17%)**	**256/1396 (18%)**	**–9·3**	**80·1**	**0·89 (0·72–1·11)**
RECOVERY	621/2022 (31%)	729/2094 (35%)	–54·4	330·6	0·85 (0·76–0·94)
All trials	**846/3359 (25%)**	**985/3490 (28%)**	**–63·7**	**410·7**	**0·86 (0·78–0·94)**
					p=0·0017



Mortalität durch TCZ reduziert

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Horby et al. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0. PMID: 33933206; PMCID: PMC8084355.

ERS COVID-19 Guideline 02/2021 – aIL-6 recommendation

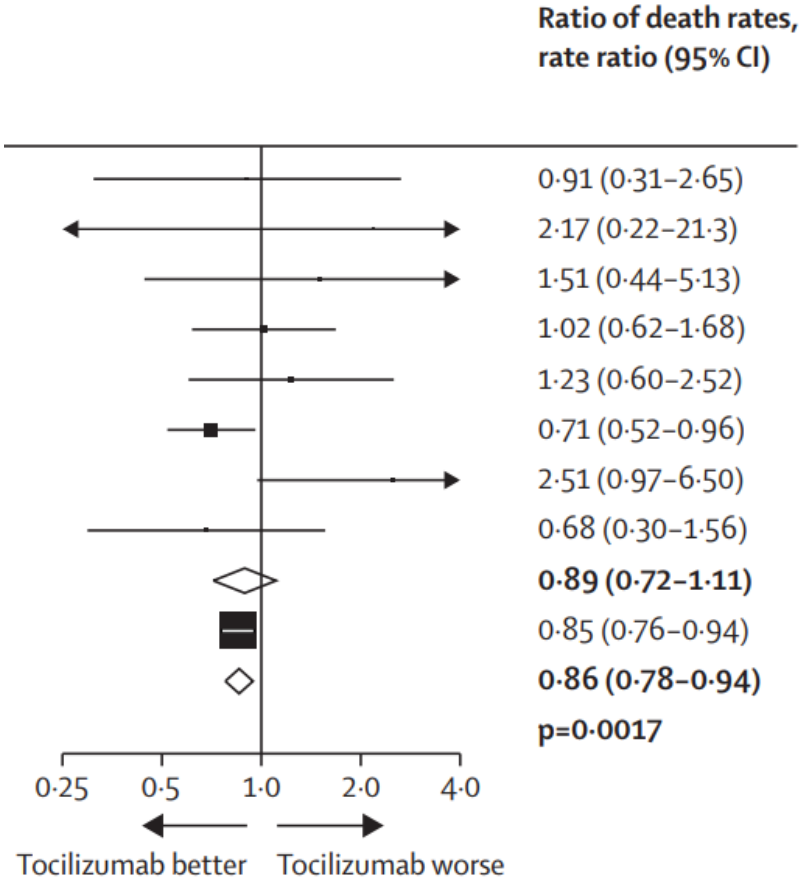
Die Studien:

Study/Autor/time	COVID19 CAP	Design	GC	TCZ	Control	primary outcome	Mortality	Clinical status	Male	Age, mean	MV	Benefits	Comment	Adverse events
1/Rosas COVACTA April - May 2020	SO2 ≤ 93% or OI ≤ 300 mmHg. Exclusion: TBC, bacterial, fungal, or viral infection other than SARS-CoV-2	RDBPCT (phase III)	19.4% (TCZ-group) vs. 28.5% (Placebo-group)	294	144 (placebo)	clinical status/score at day 28	After 28d no benefit	After 28d no benefit	70%	61	38% IMV	faster discharged or ready for dis- charge by day 28		No relevant difference
2/Salvarani RCT-TCZ-COVID-19 March - June 2020	OI 200-300 mmHg Exclusion: ICU admission, severe advanced age with multiple co- morbidities	ROLT	none	60	66 (standard of care)	Need invasive ventilation, death, clinical aggravation	After 14d no benefit	After 14d no benefit	61%	60	none	no	prematurely interrupted after an interim analysis for futility	No relevant difference
3/Hermine COR-IMUNO TOCI March - April 2020	≥ 3 L O2/min Exclusion: MV, ICU, bacterial infection, neutrophil <1.0 ×109/L, PLT < 50 G /L	BayROLT	33% (TCZ-group) vs. 61% (Control-group)	64	67 (usual care)	survival without need of HFO, MV at day 14	After 28d no benefit	After 4d no benefit	68%	64	none	Reduced the risk of MV or death by day 14 (HR 0.58 (90% CrI, 0.30 to 1.09))	TCZ reduced the risk of NIV, MV, or death by day 14. No difference on day 28 mortality.	No relevant difference
4/Stone BACC Bay	SO2 < 93% Exclusion: > 10 L O2/min, history of immunosuppressive Tx, diverticulitis	RDBPCT	11% (TCZ-group) vs. 6% (Control-group)	161	81 (placebo)	intubation or death	After 14d no benefit	After 14d no benefit	58%	60 (age > 65 34%)	none	no		No relevant difference
5/ Gordon REMAP-CAP March 9, 2020 (study start), April 19, 2020 (first TCZ), June, 2020 (first SAR) – Nov 19, 2020 GC were allowed from June 17, 2020,	Within 24h after starting organ support in ICU Exclusions: history of immunosuppressive Tx	BayROLT (Randoized, Embedded, Multifactorial Adaptive Platform Trial)	> 80% From the 158 pts. (13%) recruited before June 17, 41 were treated with 7-day hydrocortisone, 39 with shock-dependent hydrocortisone, and 78 without GC After June 17, 2020 93% had GC	353 (+48 SAR)	402 (usual care)	respiratory and cardiovascular organ support–free days, in-hospital death and days free of organ support to day 21	Improved 90-day survival in the pooled aIL6 group	more organ support–free days	73%	61	29% IMV, 42% NIV, 29% HFNO	Less time to ICU discharge hospital discharge	Median time to enrollment 1,2 d from hospital admission Median OI 117 GC dosage was not reported	No relevant difference
6/ Horby RECOVERY April 23, 2020 – January 24, 2021	SO2 < 92%, up to 21 days after prior randomization for other treatments with clinical evidence of progressive COVID-19. Exclusion: TBC, evidence for bacterial, fungal, or viral infection other than SARS-CoV-2	ROLPT	82% **Information on use of GC was collected from 18 June 2020 onwards** following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation prior to this date (and who were not allocated to dexamethasone) are assumed not to be receiving GC	2022	2094 (usual care)	28-day mortality reduced (RR 0.86; 95% CI 0.77-0.96; p=0.007); Data suggest that in pts. who are hypoxic Tx with a combination of a GC+TCZ would be expected to reduce mortality by about 33% for pts receiving simple O2 and nearly 50% for those receiving IMV; Based upon the ISARIC4C database, approximately 49% of hospitalised COVID-19 pts in the UK would meet our inclusion criteria and hence would benefit from tocilizumab.	28-day mortality reduced (RR 0.86; 95% CI 0.77-0.96; p=0.007); clear mortality benefit was seen in those receiving GC		66-69%	64	14% IMV, 41% non-invasive respiratory support (HFNO, CPAP, NIV)	More likely to be discharged from hospital alive within 28 days (RR 1,22; 95% CI 1,12-1.34; p<0·0001; less likely to get invasive ventilation or death (RR 0.85; 95% CI 0.78-0.93; p=0·0005).	no significant effect of TCZ on receipt of non-invasive respiratory support or IMV among those on no respiratory support at randomisation No significant effect on the rate of successful cessation of IMV among those on IMV at randomisation	No relevant difference
7/Salama EMPACTA	SO2 < 94% Exclusion: MV,	RDBPCT (phase III)	83-88%	249	128 (placebo)	Less mechanical ventilation or death by day 28 (HR, 0.55; 95% CI, 0.33 to 0.93)	After 28d no benefit		59%	56	none			No relevant difference
8/Veiga TOCIBRAS 8 May and 17 July 2020	SO2 < 93%, MV less than 24h	ROLT	69-73%	65	64		After 15d and 28d no benefit		68%	57	17% IMV			No relevant difference
9/Soin COVINTOC May 30, 2020, and Aug 31, 2020,	SO2 < 95% and respiratory rate >15/min	ROLT	91%	91	88		After 28d no benefit		85%	55	5% IMV, 23-31% NIV,			No relevant difference

Zusammenstellung von H. Flick

Meta–analysis of mortality in RECOVERY and other trials

	Typ	CC	iMV	
CORIMUNO–TOCI[10]		**33-61%**	no	
RCT–TCZ–COVID-19[11]		no	no	
BACC Bay[12]	**RDBPC**	**6-11%**	no	
COVACTA[9]	**RDBPC**	**19-29%**	**38%**	
EMPACTA[13]	**RDBPC**	**83-88%**	no	
REMAP–CAP[15]		**>80%**	**29%**	**Mean Age 61**
TOCIBRAS[8]		**69-73%**	**17%**	
COVINTOC[14]		**91%**	**5%**	
Subtotal: eight trials				
RECOVERY		**82%**	**14%**	**Mean Age 64**
All trials				



RDBPC = randomized, double- blind, placebo-controlled
CC = corticorticoids
iMV = invasive mechanical ventilation

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Horby et al. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0. PMID: 33933206; PMCID: PMC8084355.

Mean Age of UK COVID-19 patients in hospital = 73 Jahre

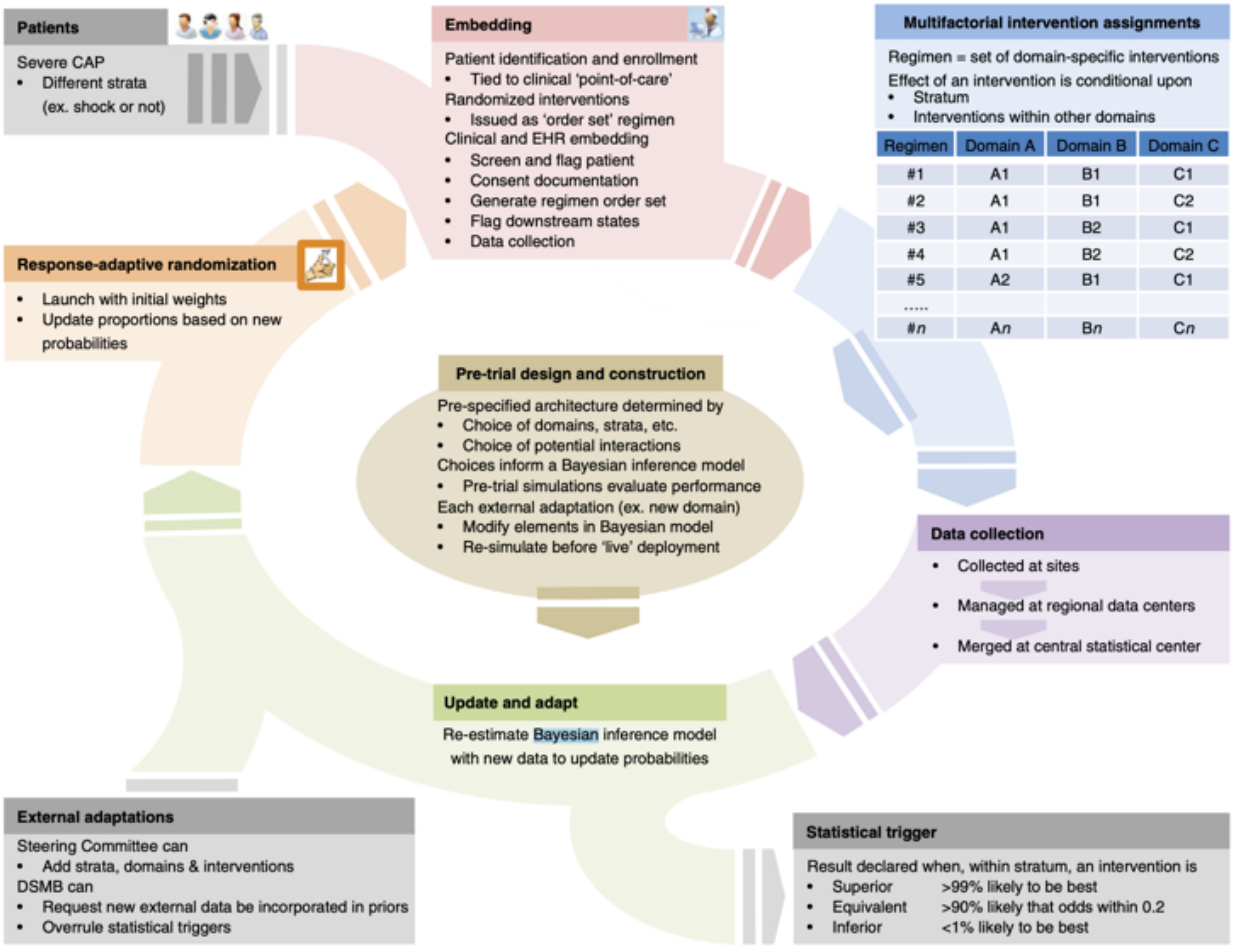
Baseline characteristics of 20 133 UK patients in hospital with COVID-19 between 6 February and 19 April 2020

Characteristics	Male	Female	All
Total No (%)	12 068 (59.9)	8065 (40.1)	20 133
Age at admission (n=20 133)			
Median (interquartile range)	72.0 (58.0-81.0)	74.0 (58.0-84.0)	72.9 (58.0-82.0)
Age (n=20 133)			
<18	180 (1.5)	130 (1.6)	310 (1.5)
18-39	534 (4.4)	533 (6.6)	1067 (5.3)
40-50	888 (7.4)	530 (6.6)	1418 (7.0)
50-59	1728 (14.3)	980 (12.2)	2708 (13.5)
60-69	2115 (17.5)	1181 (14.6)	3296 (16.4)
70-79	2972 (24.6)	1720 (21.3)	4692 (23.3)
≥80	3651 (30.3)	2991 (37.1)	6642 (33.0)

Docherty AB et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. BMJ. 2020 May 22;369:m1985. doi: 10.1136/bmj.m1985. PMID: 32444460; PMCID: PMC7243036

REMAP-CAP und RECOVERY

REMAP-CAP Randomized Embedded Multifactorial Adaptive Platform Trial



Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (Randomized Embed- ded Multifactorial Adaptive Platform for Community-acquired Pneumonia) study. Rationale and design. Ann Am Thorac Soc 2020;17:879-91

REMAP-CAP Randomized Embedded Multifactorial Adaptive Platform Trial

Pre-trial design and construction. The trial is designed by first specifying broad questions regarding the target population, potentially important subgroups, and the nature and type of interventions to be tested. Using an initial set of interventions, ordered within domains, and combined into regimens, an overarching Bayesian inference model is constructed, and Monte Carlo simulations of how the trial might unfold under alternative 'truths' regarding treatment effects, including heterogeneity of treatment effect across subgroups and treatment-by-treatment interactions.

R **Randomization.** Once the design is specified, sites are recruited and trained, appropriate oversight and approval is obtained, and all study execution procedures are deployed, the study launches. The trial begins by randomizing patients with fixed allocations to each treatment arm, proportional to the number of arms. Later, randomization weights are adjusted based on updated probabilities from the Bayesian inference model.

E **Embedding.** A key element of the design is tight integration with clinical operations, including using a clinical 'moment', or 'point-of-care' to flag and enroll patients and to deliver the treatment regimen as an 'order set'. Ideally, embedding will take advantage of electronic health record data, not only to help flag and enroll patients, but to deliver patient order sets and to facilitate on-going monitoring and data collection.

M **Multifactorial intervention assignments.**The treatment regimens themselves are assigned as a regimen, containing each randomized intervention within each domain. In settings with standard ICU order sets, the regimen would ideally be generated automatically, with inclusion of standard non-randomized ICU care elements as well as those randomized items that are part of REMAP-CAP.

A **Adaptation.**The heart of the trial is the monthly update of the Bayesian inference model. Each month, the SAC runs the Bayesian inferencemodel using the updated trial data to generate an updated posterior probability for all trial outcomes. If the model generates a probability that has crossed a predetermined threshold, it triggers a platform conclusion. Otherwise, the probabilities are used to update the randomizationweights.

P **Platform.** The entire trial is envisioned, like all adaptive platform trials, as a learning engine that can test multiple interventions both in parallel and sequentially. Thus, the focus is on the condition, CAP, itself, and not on any particular intervention. This approach allows a standard approach for enrollment and data collection to be built once and then run perpetually, providing numerous efficiencies.

Data collection. Data, ideally via the EHR, is uploaded to regional coordinating centers (RCCs), responsible for local data management and auditand feedback of sites. The RCCs forward data to the statistical analysis committee (SAC).

Angus DC, Berry S, Lewis RJ, et al. The REMAP-CAP (Randomized Embed- ded Multifactorial Adaptive Platform for Community-acquired Pneumonia) study. Rationale and design. Ann Am Thorac Soc 2020;17:879-91

REMAP-CAP

3301 assessed

895 **(27%)** randomized

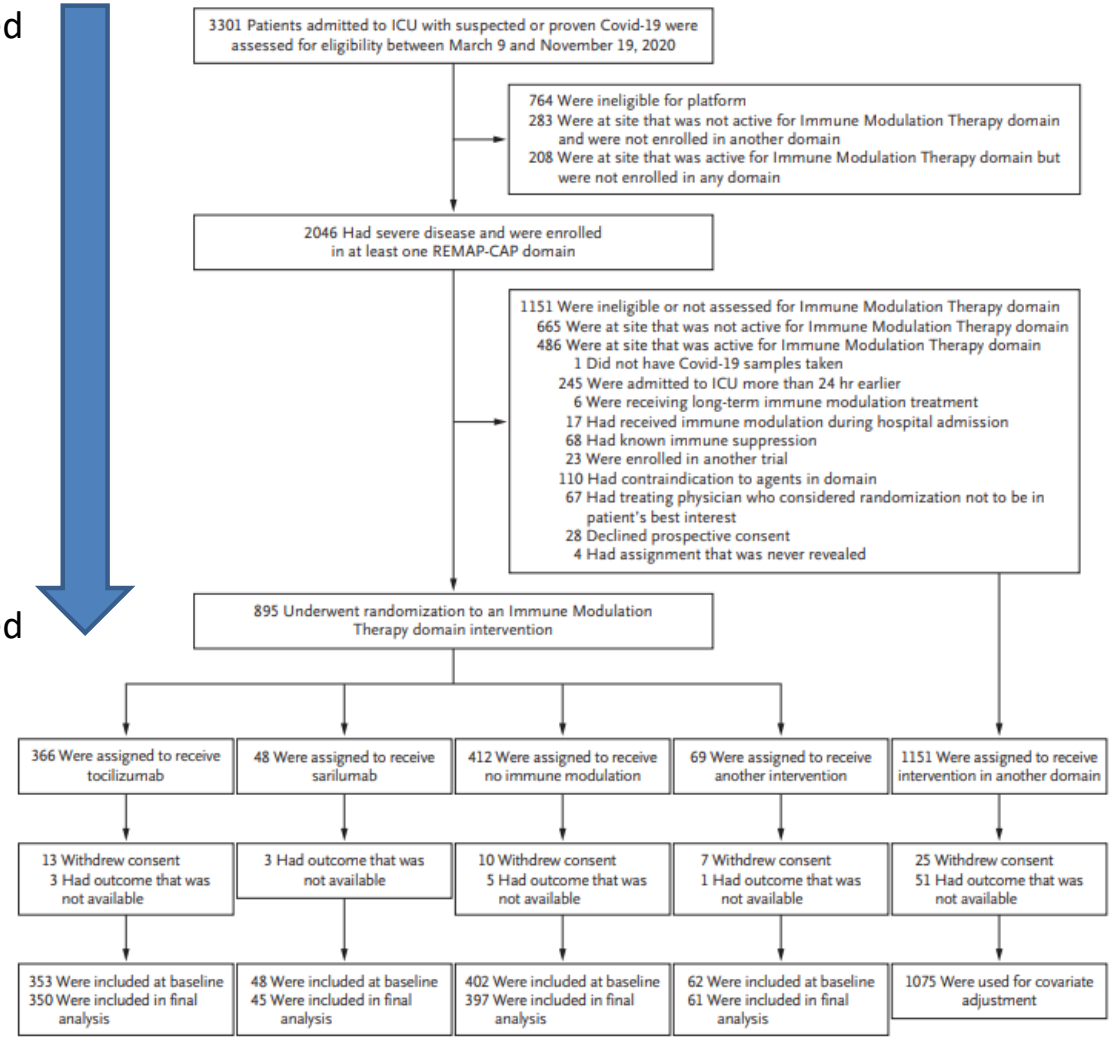


Table 1. Baseline Characteristics of the Patients in the Immune Modulation Therapy Domain.*

Characteristic	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)†	All Patients (N=865)‡
Age — yr	61.5±12.5	63.4±13.4	61.1±12.8	61.4±12.7
Male sex — no. (%)	261 (74)	39 (81)	283 (70)	629 (73)
Race or ethnic group — no./total no. (%)§				
White	160/228 (70)	29/39 (74)	206/279 (74)	420/580 (72)
Asian	41/228 (18)	8/39 (21)	47/279 (17)	99/580 (17)
Black	12/228 (5)	1/39 (3)	9/279 (3)	23/580 (4)
Mixed	2/228 (1)	0/39	5/279 (2)	7/580 (1)
Other	13/228 (6)	1/39 (3)	12/279 (4)	31/580 (5)
Body-mass index¶				
Patients evaluated	342	39	377	815
Median (IQR)	30.5 (26.9–34.9)	29.2 (26.0–33.8)	30.9 (27.1–34.9)	30.5 (26.8–34.9)
APACHE II score‖				
Patients evaluated	337	42	381	820
Median (IQR)	13 (8–19)	10 (7–16)	12 (8–18)	12 (8–19)
Confirmed SARS-CoV-2 infection — no./total no. (%)**	284/345 (82)	44/47 (94)	334/394 (85)	715/847 (84)
Median time to enrollment (IQR)				
From hospital admission — days	1.2 (0.8–2.8)	1.4 (0.9–2.8)	1.2 (0.8–2.8)	1.2 (0.8–2.8)
From ICU admission — hr	13.1 (6.6–19.0)	16.0 (11.4–20.8)	14.0 (6.8–19.5)	13.6 (6.6–19.4)
Acute respiratory support — no./total no. (%)				
None or supplemental oxygen only	1/353 (<1)	0/48	2/402 (<1)	3/865 (<1)
High-flow nasal cannulae	101/353 (29)	17/48 (35)	110/402 (27)	249/865 (29)
Noninvasive ventilation only	147/353 (42)	23/48 (48)	169/402 (42)	359/865 (42)
Invasive mechanical ventilation	104/353 (29)	8/48 (17)	121/402 (30)	254/865 (29)
Vasopressor support — no./total no. (%)	63/353 (18)	4/48 (8)	79/402 (20)	163/865 (19)
Pa_{O_2}/Fi_{O_2}				
Patients evaluated	335	35	354	780
Median (IQR)	115 (89–162)	126 (99–157)	118 (89–169)	116.5 (89–165)
Laboratory values††				
C-reactive protein				
Patients evaluated	207	37	244	533
Median (IQR) — μg/ml	150 (85–221)	136 (105–204)	130 (71–208)	136 (79–208)
D-dimer				
Patients evaluated	159	20	172	385
Median (IQR) — ng/ml	832 (461–1763)	828 (355–1435)	1010 (500–2115)	910 (480–1916)

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. **Gordon** AC et al. N Engl J Med. 2021 Apr 22;384(16):1491-1502. doi: 10.1056/NEJMoa2100433. Epub 2021 Feb 25. PMID: 33631065; PMCID: PMC7953461

REMAP-CAP

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Patients evaluated	335	35	354	780
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REMAP-CAP

Table 4.1: Summary of the number of sites and patients randomized within each country

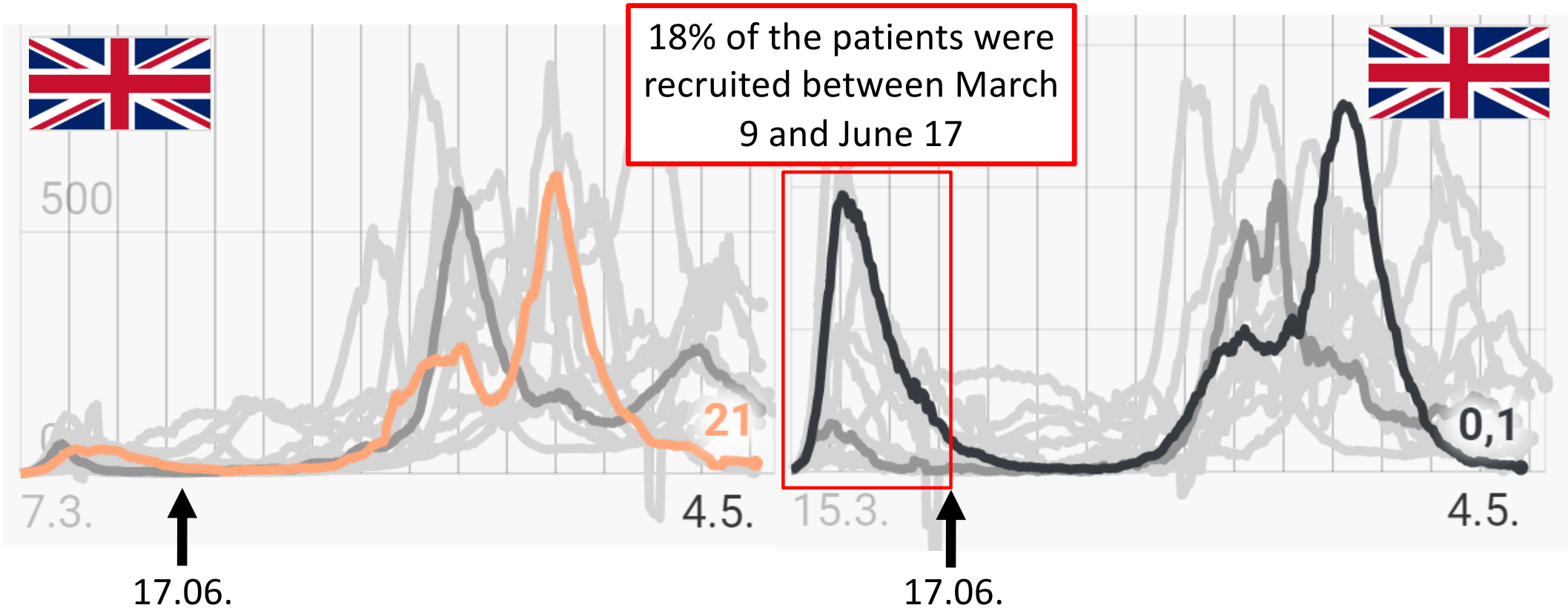
Region	Country	All Domains			Immune Modulation Domain		
		Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes	Number of Sites	Number of Patients Randomized	Number of Patients w/ Outcomes
Americas	Canada	21	148	119	1	4	4
	United States of America	2	94	94			
Europe	France	3	11	11			
	Germany	2	4	4			
	Ireland	2	34	34	2	9	9
	Netherlands	7	96	94	7	68	66
	Portugal	1	3	3			
	United Kingdom	121	1405	1378	88	698	688
Middle East	Saudi Arabia	1	114	114	1	83	83
Oceana	Australia	22	73	68	1	1	1
	New Zealand	5	9	9	2	2	2

Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19 – Preliminary report. **Gordon** AC et al. N Engl J Med. 2021 Apr 22;384(16):1491-1502. doi: 10.1056/NEJMoa2100433. Epub 2021 Feb 25. PMID: 33631065; PMCID: PMC7953461

REMAP-CAP

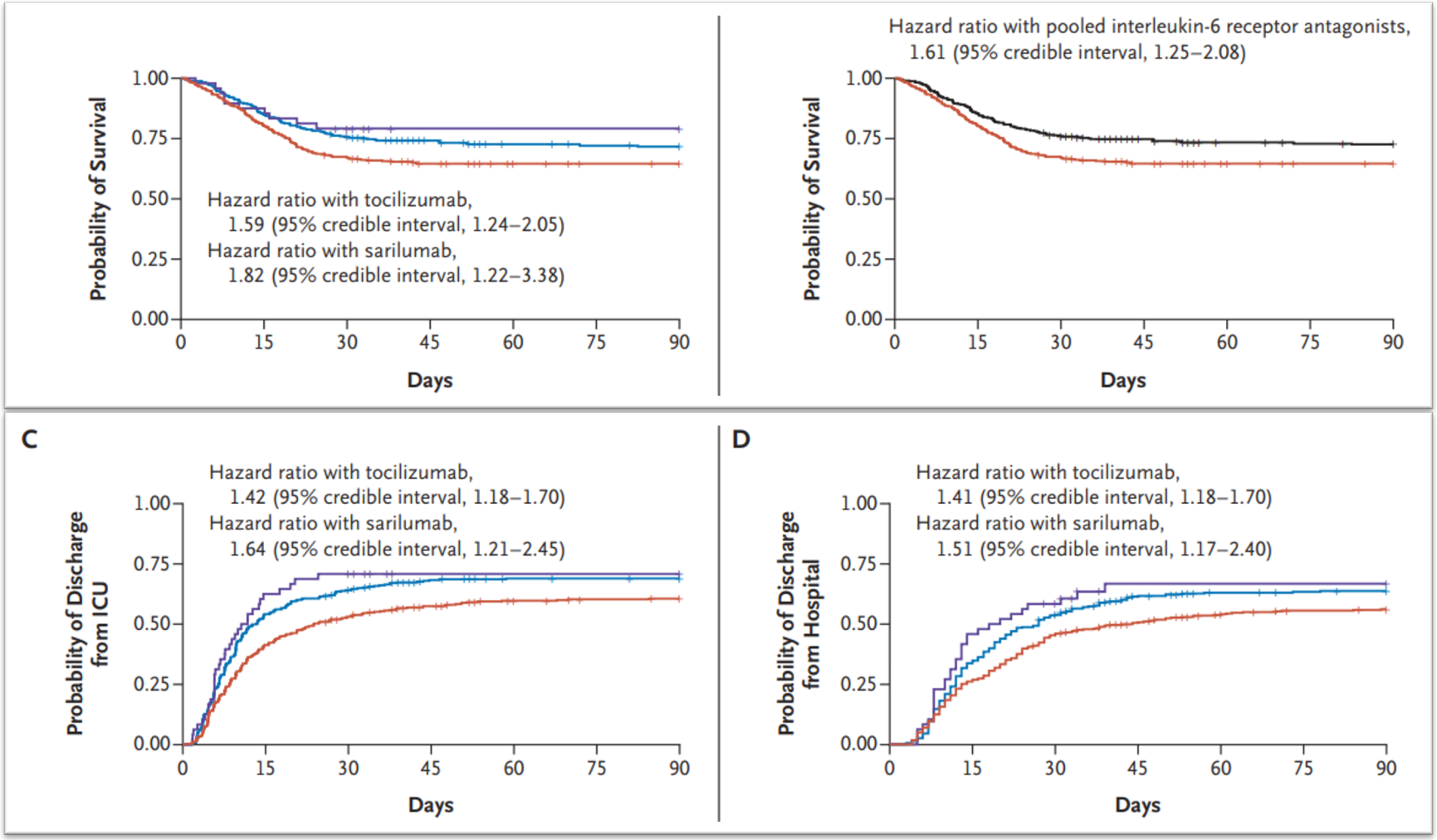
Bestätigte **Fälle** pro 100.000 in 7 Tagen in UK

COVID-19 Tote pro 100.000 in 7 Tagen in UK



https://www.derstandard.at/story/2000124389425/aktuelle-zahlen-coronavirus-oesterreich-weltweit, abgerufen am 05.05.2021

REMAP-CAP



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RECOVERY

RECOVERY
Randomised Evaluation of COVID-19 Therapy

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This national clinical trial aims to identify treatments that may be beneficial for people hospitalised with suspected or confirmed COVID-19

GLOBAL CUMULATIVE TOTALS

39749 Participants

181 Active sites

Peter Horby, Professor of Emerging Infectious Diseases and Global Health

A range of potential treatments have been suggested for COVID-19 but nobody knows if any of them will turn out to be more effective in helping people recover than the usual standard of hospital care which all patients will receive. The RECOVERY Trial is currently testing some of these suggested treatments:

- Regeneron's antibody cocktail (a combination of monoclonal antibodies directed against coronavirus)
- Baricitinib (an immunomodulatory drug used in rheumatoid arthritis)
- Dimethyl fumarate (an immunomodulatory drug used in psoriasis and multiple sclerosis).

Data from the trial are regularly reviewed so that any effective treatment can be identified quickly and made available to all patients. Please see our news page for results that RECOVERY has already found. The RECOVERY Trial team will constantly review information on new drugs and include promising ones in the trial.

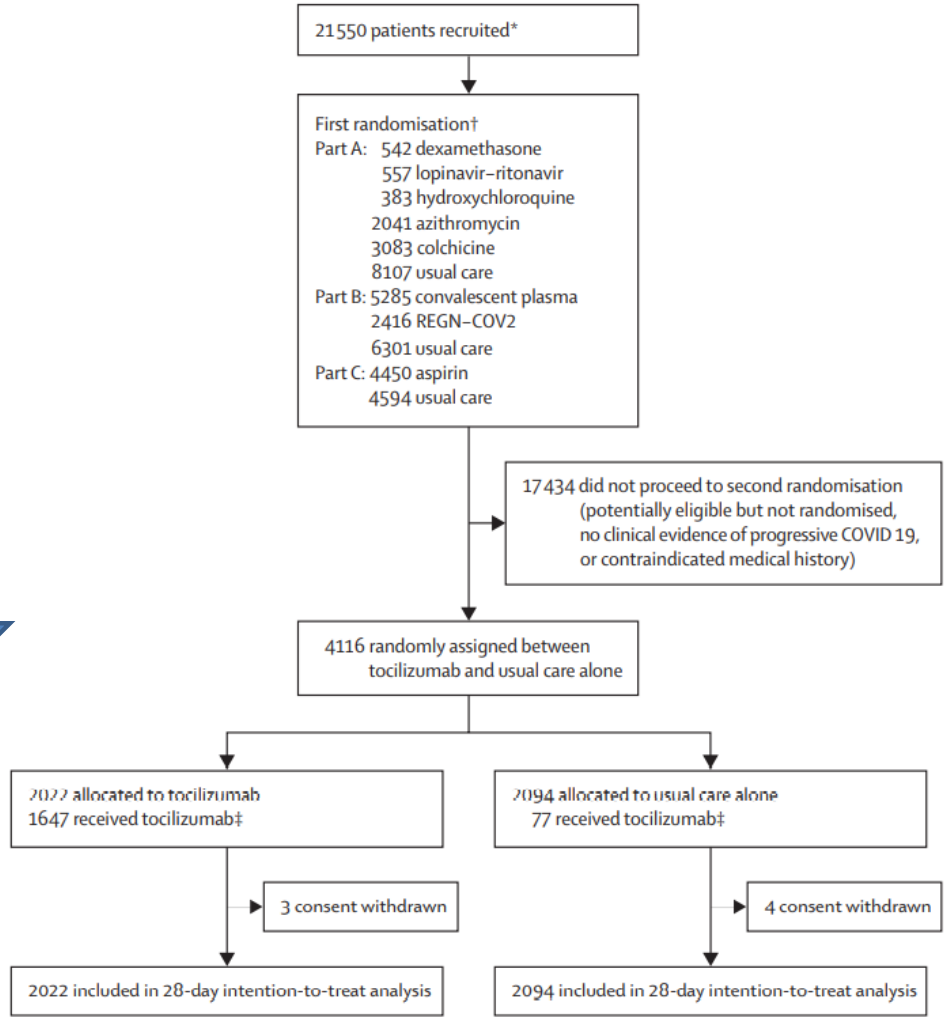
https://www.recoverytrial.net

RECOVERY

21550 recruited

4116 **(19%)** randomized

Flow of participants through the RECOVERY trial



Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Horby et al. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0.

RECOVERY

	Tocilizumab (n=2022)	Usual care (n=2094)
Part A allocation		
Usual care	839 (41%)	869 (41%)
Lopinavir/ritonavir	51 (3%)	64 (3%)
Dexamethasone	49 (2%)	45 (2%)
Hydroxychloroquine	37 (2%)	38 (2%)
Azithromycin	197 (10%)	177 (8%)
Use of systemic corticosteroids^		
Yes	1664 (82%)	1721 (82%)
No	357 (18%)	367 (18%)
Unknown	1 (<1%)	6 (<1%)

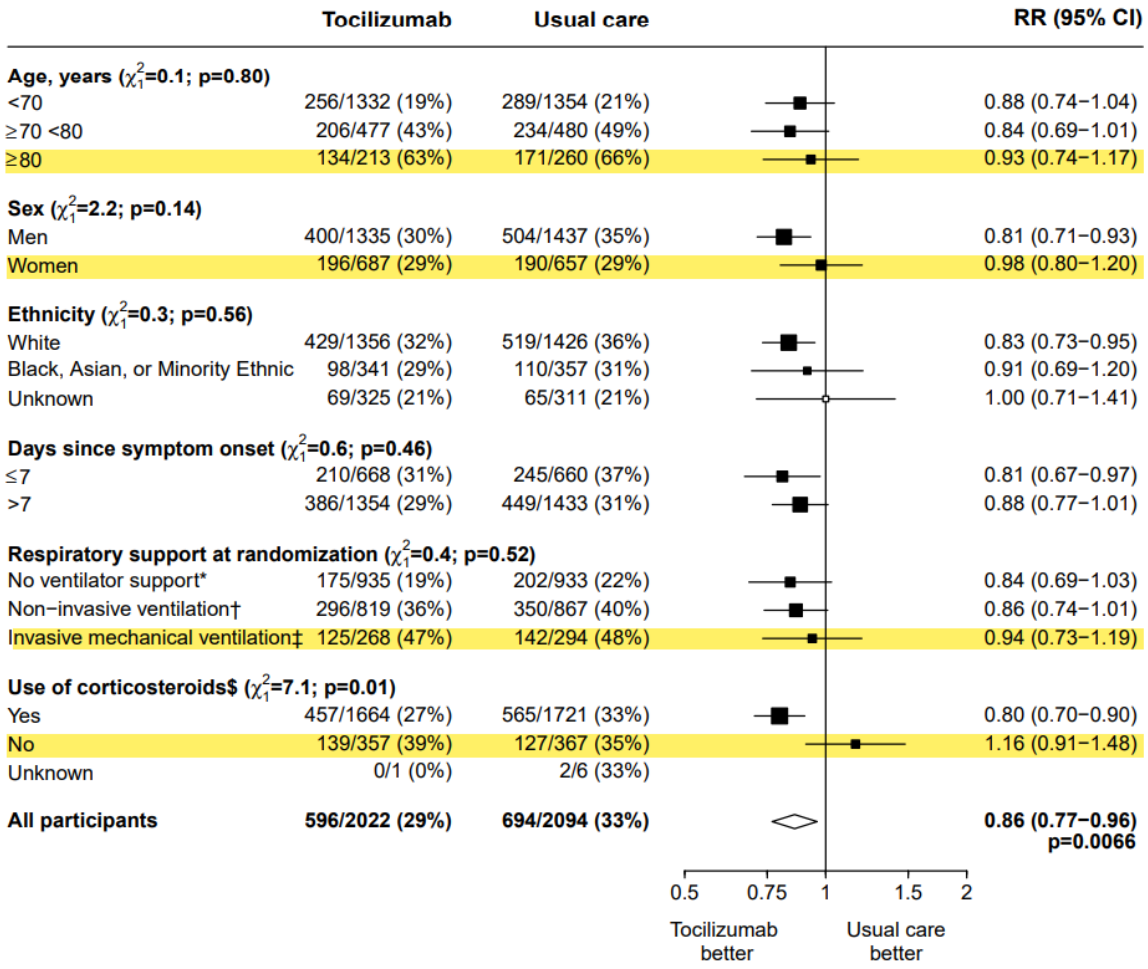
Data are mean (SD), n(%), or median (IQR). Information on sex, ethnicity, and SARS-CoV-2 test result were recorded on the main randomisation form when patients first entered the study. All other information was recorded on the second randomisation form (when patients were randomly assigned to tocilizumab vs. usual care alone). * includes 3 pregnant women. † Includes 9 patients not receiving any oxygen and 1859 patients receiving low-flow oxygen. ‡ includes patients receiving high-flow nasal oxygen, continuous positive airway pressure, or other non-invasive ventilation). § Includes patients receiving invasive mechanical ventilation or extra-corporeal membranous oxygenation. ¶ Defined as requiring ongoing specialist care. || Defined as estimated glomerular filtration rate <30 mL/min/1.73m² $ 2631 and 1615 participants were randomised into parts B and C of the first randomisation respectively. ^Information on use of corticosteroids was collected from 18 June 2020 onwards following announcement of the results of the dexamethasone comparison from the RECOVERY trial. Participants undergoing first randomisation prior to this date (and who were not allocated to dexamethasone) are assumed not to be receiving systemic corticosteroids.

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY) Preliminary results of a randomized controlled open-label platform trial. Horby et al. https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1.full.pdf

RECOVERY

Effect of allocation to tocilizumab on 28–day mortality by baseline characteristics

- Kein Effekt bei > 80 J.
- **Kein Effekt bei Frauen???**
- Kein Effekt bei iMV
- Kein Effekt ohne GC???



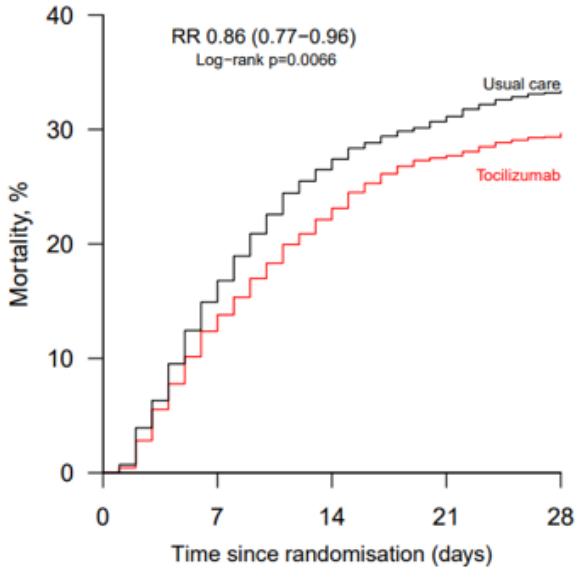
	Tocilizumab	Usual care	RR (95% CI)
Age, years (χ^2_1=0.1; p=0.80)			
<70	256/1332 (19%)	289/1354 (21%)	0.88 (0.74–1.04)
≥70 <80	206/477 (43%)	234/480 (49%)	0.84 (0.69–1.01)
≥80	134/213 (63%)	171/260 (66%)	0.93 (0.74–1.17)
Sex (χ^2_1=2.2; p=0.14)			
Men	400/1335 (30%)	504/1437 (35%)	0.81 (0.71–0.93)
Women	196/687 (29%)	190/657 (29%)	0.98 (0.80–1.20)
Ethnicity (χ^2_1=0.3; p=0.56)			
White	429/1356 (32%)	519/1426 (36%)	0.83 (0.73–0.95)
Black, Asian, or Minority Ethnic	98/341 (29%)	110/357 (31%)	0.91 (0.69–1.20)
Unknown	69/325 (21%)	65/311 (21%)	1.00 (0.71–1.41)
Days since symptom onset (χ^2_1=0.6; p=0.46)			
≤7	210/668 (31%)	245/660 (37%)	0.81 (0.67–0.97)
>7	386/1354 (29%)	449/1433 (31%)	0.88 (0.77–1.01)
Respiratory support at randomization (χ^2_1=0.4; p=0.52)			
No ventilator support*	175/935 (19%)	202/933 (22%)	0.84 (0.69–1.03)
Non–invasive ventilation†	296/819 (36%)	350/867 (40%)	0.86 (0.74–1.01)
Invasive mechanical ventilation‡	125/268 (47%)	142/294 (48%)	0.94 (0.73–1.19)
Use of corticosteroids$ (χ^2_1=7.1; p=0.01)			
Yes	457/1664 (27%)	565/1721 (33%)	0.80 (0.70–0.90)
No	139/357 (39%)	127/367 (35%)	1.16 (0.91–1.48)
Unknown	0/1 (0%)	2/6 (33%)	
All participants	**596/2022 (29%)**	**694/2094 (33%)**	**0.86 (0.77–0.96) p=0.0066**

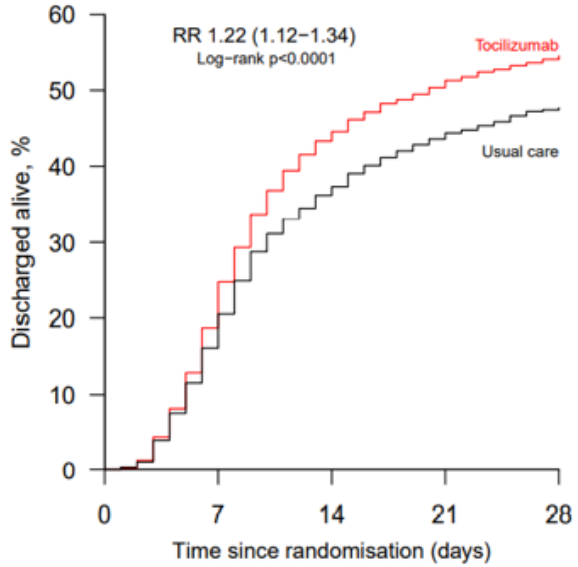
Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY) Preliminary results of a randomized controlled open-label platform trial. Horby et al. https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1.full.pdf

RECOVERY

Table 2: Effect of allocation to tocilizumab on main study outcomes

	Treatment allocation			
	Tocilizumab (n=2022)	Usual care (n=2094)	RR (95% CI)	p value
Primary outcome				
Total: 28-day mortality	596 (29%)	694 (33%)	0.86 (0.77-0.96)	0.0066
Secondary outcomes				
Median time to being discharged alive, days	20	>28		
Discharged alive from hospital within 28 days	1093 (54%)	990 (47%)	1.22 (1.12-1.34)	<0.0001
Receipt of invasive mechanical ventilation or death*	571/1754 (33%)	687/1800 (38%)	0.85 (0.78-0.93)	0.0005
Invasive mechanical ventilation	215/1754 (12%)	273/1800 (15%)	0.81 (0.68-0.95)	0.01
Death	471/1754 (27%)	552/1800 (31%)	0.88 (0.79-0.97)	0.01





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The data suggest that in patients with hypoxia and significant inflammation, treatment with **corticosteroid plus tocilizumab reduces mortality by about 33% for patients requiring simple oxygen and nearly 50% for those requiring invasive mechanical ventilation**.

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Zurück zur ERS

ERS COVID-19 Guideline 02/2021 – aIL-6 recommendation

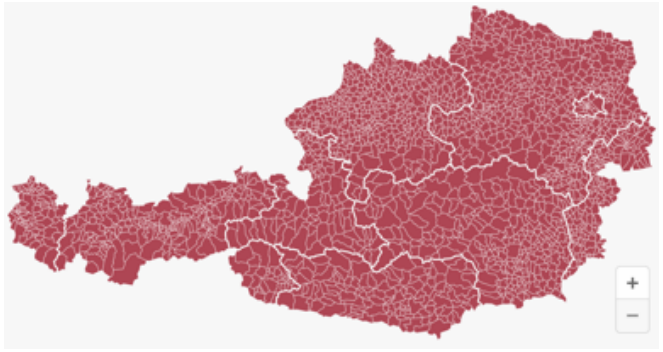
- Anti-IL-6 reduces the risk of mechanical ventilation or death in hospitalised patients.
- No major safety concerns.
- As corticosteroids (CC) are also recommended for pts. requiring O2 and ventilatory support, would be expected to be given to pts. also receiving CC **in nearly all cases**.
- aIL-6 is relatively expensive, but it is expected the benefits will outweigh the costs.

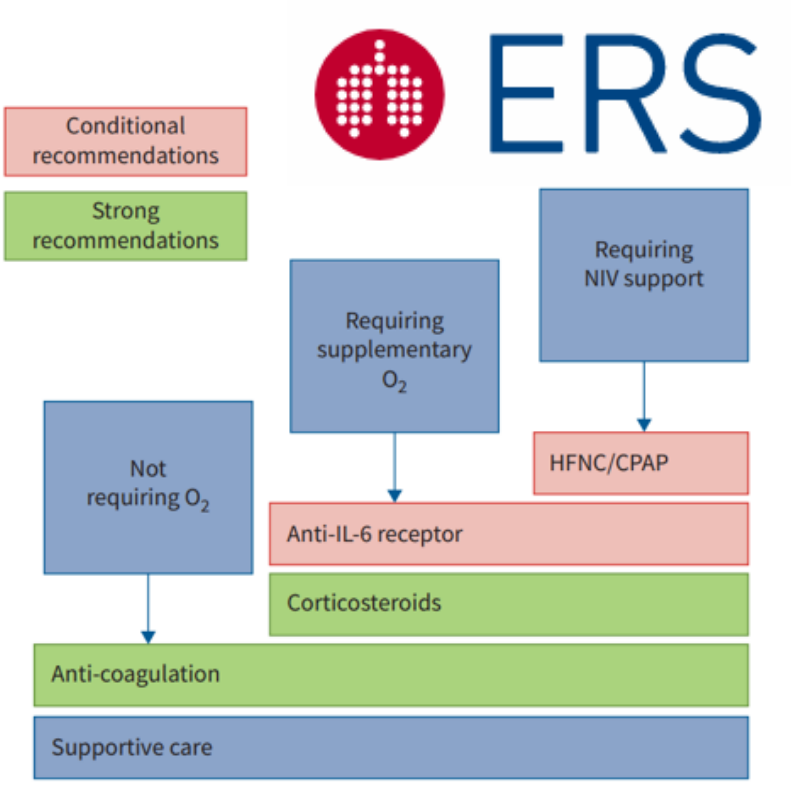
- **The panel considers that currently it is hard to identify the optimal patient population to benefit from this treatment:**

  Patient populations most likely to benefit (see inclusion criteria REMAP-CAP)
  - those receiving O2 and who are progressing despite CC Tx;
  - those in the first 24 h after receiving ventilatory support;
  - those are considered at high risk of future requirement for ventilatory support.

Chalmers JD, Crichton ML, Goeminne PC, et al. Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J 2021; 57: 2100048 [https://doi.org/10.1183/13993003.00048-2021].

Update COVID-19 und Influenza - Zusammenfassung





REMAP-CAP

RECOVERY
Randomised Evaluation of COVID-19 Therapy

Landeskrankenhaus - Universitätsklinikum Graz

Stmk. Krankenanstaltenges.m.b.H. Medizinische Universität Graz

Medical University of Graz

Vielen Dank für die Aufmerksamkeit

Fragen?

Holger Flick
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holger.flick@medunigraz.at