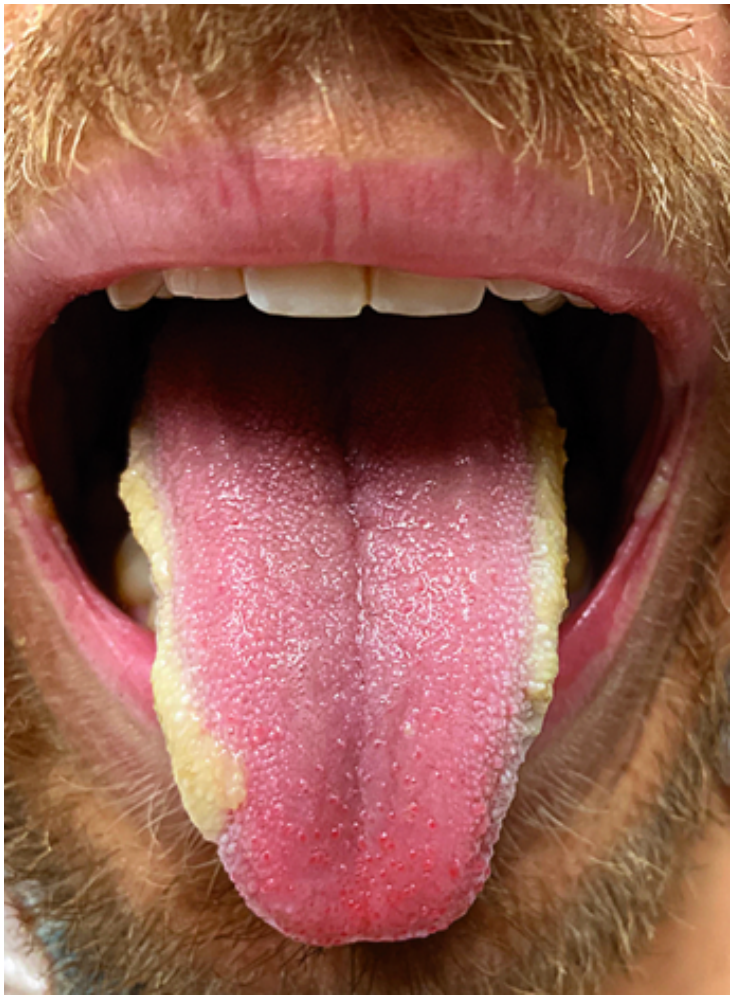
https://www.mdc-berlin.de/de/veroeffentlichungstypen/clinical-journal-club

Als gemeinsame Einrichtung von MDC und Charité fördert das Experimental and Clinical Research Center die Zusammenarbeit zwischen Grundlagenwissenschaftlern und klinischen Forschern. Hier werden neue Ansätze für Diagnose, Prävention und Therapie von Herz-Kreislauf- und Stoffwechselerkrankungen, Krebs sowie neurologischen Erkrankungen entwickelt und zeitnah am Patienten eingesetzt. Sie sind eingelanden, um uns beizutreten. Bewerben Sie sich!

A 26-year-old man presented to the emergency department with a 2-month history of an altered sense of taste associated with malaise, weight loss, and muscle cramps. Physical examination showed white, sharply demarcated, adherent plaques on the sides of the tongue. What is the diagnosis?



Oral hairy leukoplakia

Oral lichen planus

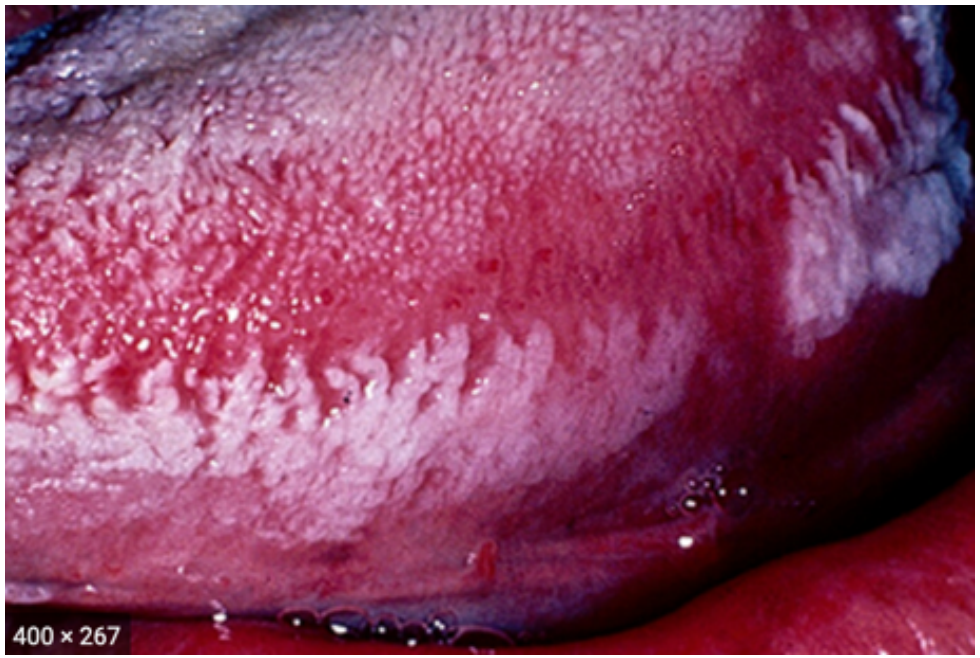
Human papillomavirus infection

Candidiasis

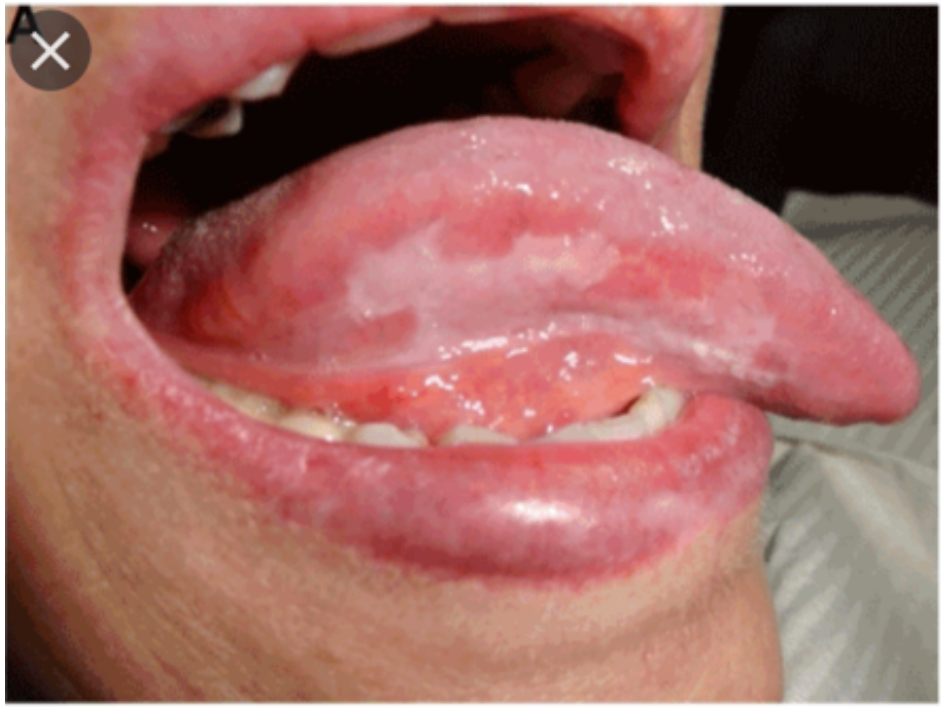
Uremic stomatitis

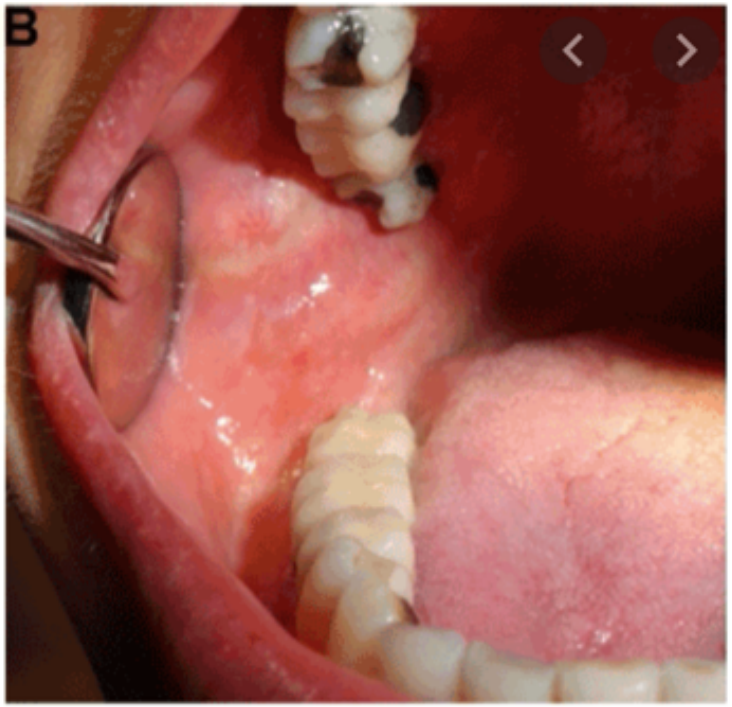
The correct answer is uremic stomatitis, a rare manifestation of long-standing uremia. This patient endorsed a history of chronic kidney disease secondary to vesicoureteral reflux. Laboratory tests showed a creatinine level of 22 mg per deciliter (reference range, 0.7 to 1.5) and a blood urea nitrogen level of more than 225 mg per deciliter (reference range, 9 to 20). The patient was initiated on hemodialysis with resolution of the lesions.

Die orale Haarleukoplakie, kurz OHL, ist eine weißliche Veränderung der Schleimhaut - meist am seitlichen Zungenrand - die durch eine Infektion mit dem Epstein-Barr-Virus ausgelöst wird. Sie tritt unter Immunsuppression, z.B. bei HIV-Infizierten oder Transplantatempfängern auf. Die orale Haarleukoplakie zeichnet sich durch mehrere Millimeter dicke, weiße, nicht abwischbare Beläge aus. Sie haben eine wellblechartige Oberfläche und sitzen am seitlichen Zungenrand und an der Zungenunterfläche. Die orale Haarleukoplakie ist meist asymptomatisch. Die Therapie erfolgt mit Virostatika wie Aciclovir, Foscarnet oder Valaciclovir. Zur dauerhaften Abheilung kommt es bei AIDS-Patienten jedoch erst unter einer hochaktiven antiretroviralen Therapie (HAART). Alternativ kann versucht werden, die Beläge abzubürsten. Supportiv können Vitamin-C-Lutschtabletten gegeben werden.



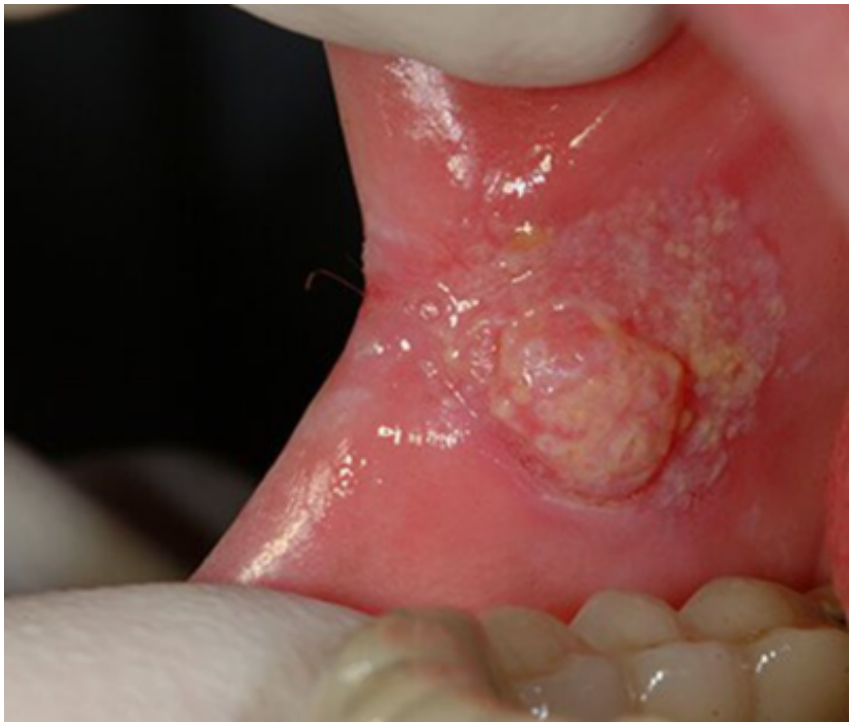
Der orale Lichen planus (OLP) ist mit einer Prävalenz von 0,1 - 4 Prozent eine der häufigsten Mundschleimhauterkrankungen innerhalb der adulten Bevölkerung (Siehe *). Die orale Erscheinungsform des Lichen planus (OLP) zeigt in einer Vielzahl der Fälle eine eindeutige klinische Morphologie sowie eine charakteristische Lokalisation. Der Lichen planus befällt ebenso die Genital- und die perianale Übergangsschleimhaut sowie den Pharynx. Selten wird die Konjunktiva oder der Oesophagus mit befallen. Jedoch führen untypische Manifestationen, abnorme Verteilungsmuster oder lichenoide Mundschleimhautveränderungen immer wieder zu Fehldiagnosen und klinischen Unsicherheiten. Die Entstehung des OLP als Resultat einer T-zellvermittelten lymphozytären Immunantwort auf veränderte Antigene innerhalb der Haut/Schleimhaut wird als möglicher Pathomechanismus diskutiert. Bis heute konnte diesbezüglich kein eindeutiger Auslöser für den OLP definiert werden, wobei genetische Prädispositionen in Betracht gezogen werden können.



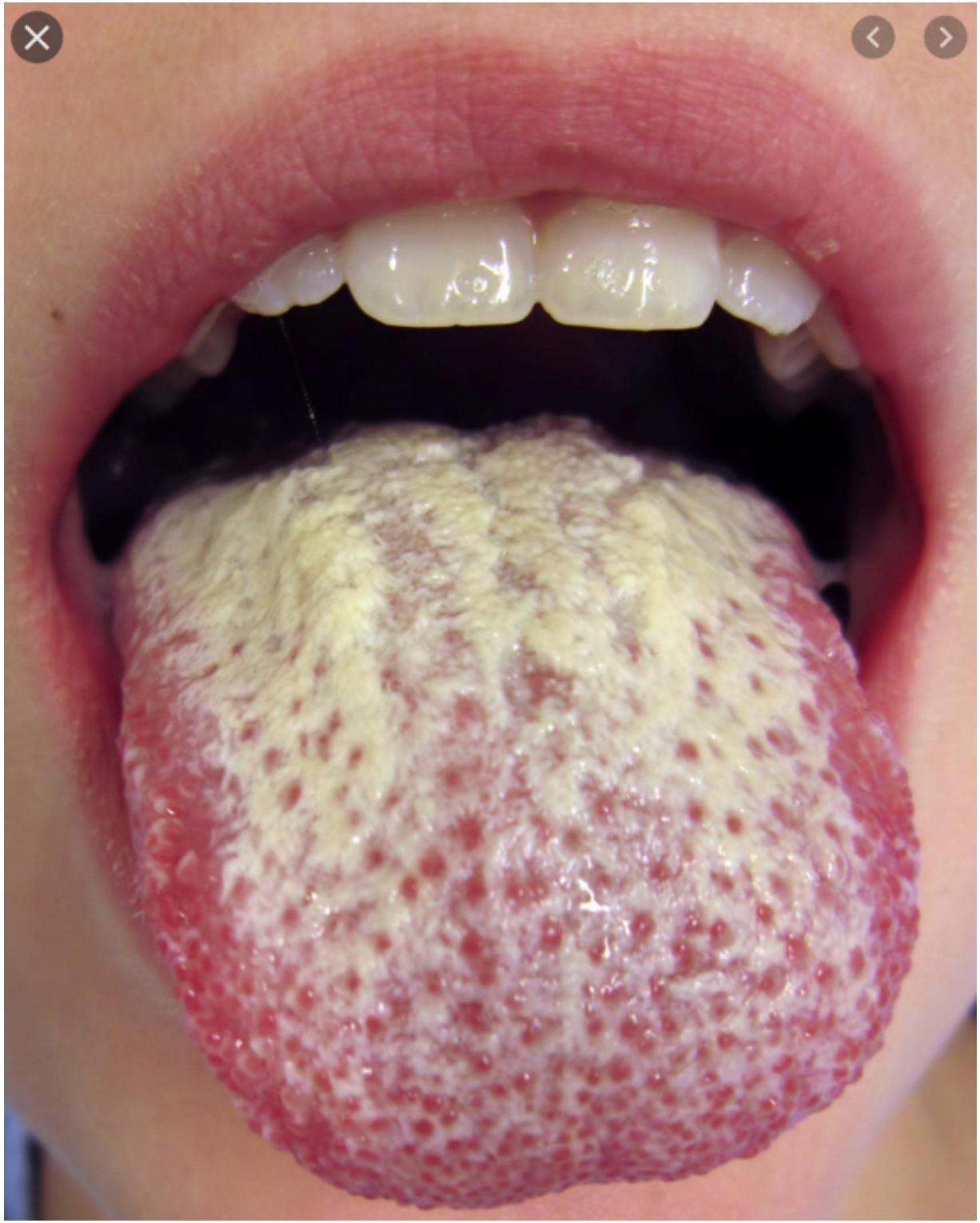


Oral HPV often has no symptoms. This means that people don't realize they're infected and are less likely to take the steps necessary to limit the spread of the disease. It's possible to develop warts in the mouth or throat in certain cases, but this is less common. This type of HPV can turn into oropharyngeal cancer, which is rare. If you have oropharyngeal cancer, cancer cells form in the middle of the throat, including the tongue, tonsils, and pharynx walls. These cells can develop from oral HPV. Early symptoms of oropharyngeal cancer include:

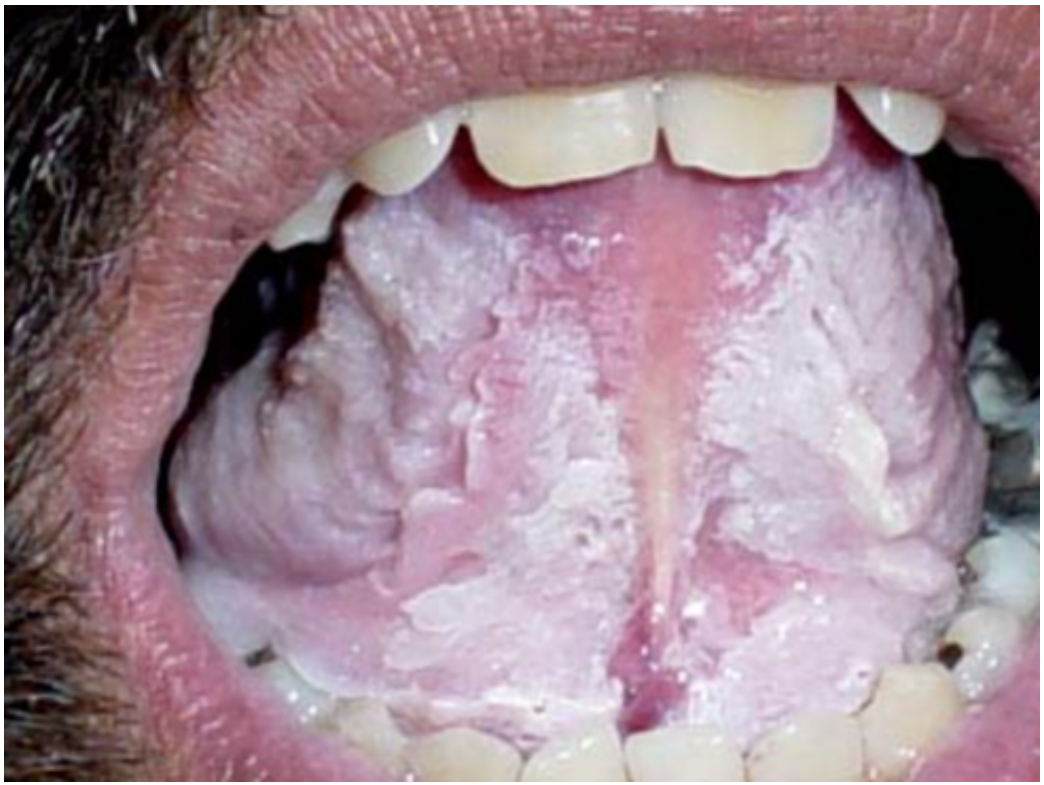
- trouble swallowing
- constant earaches
- coughing up blood
- unexplained weight loss
- enlarged lymph nodes
- constant sore throats
- lumps on the cheeks
- growths or lumps on the neck
- hoarseness



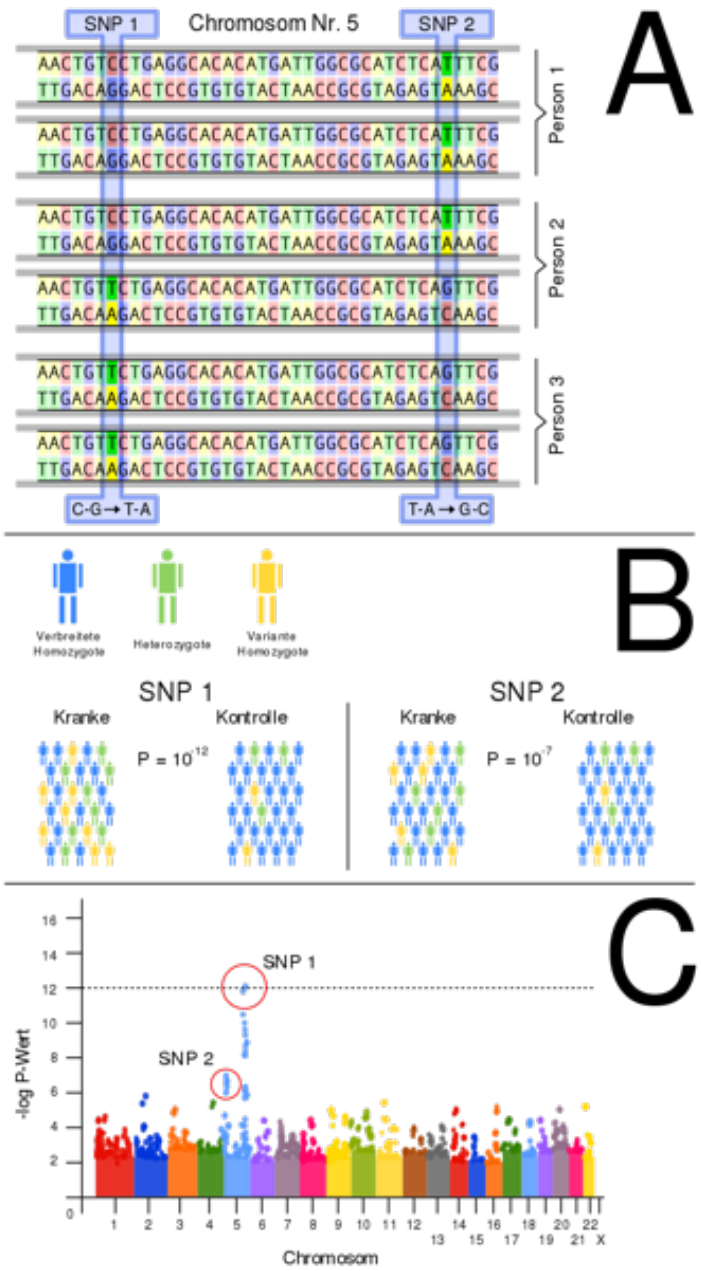
Eine Pilzinfektion der Mundhöhle ist eine Erkrankung, die man auf den ersten Blick nicht unbedingt erkennt. Sie ist meist harmlos, nicht immer schmerzhaft, kann aber sehr unangenehm sein und die Lebensqualität stark beeinträchtigen. Die Infektion wird durch Hefepilze – die sogenannten Candida-Hefen – hervorgerufen, die auf den Schleimhäuten der Mundhöhle siedeln. Daher stammen die Bezeichnungen orale Candidose (Kandidose) oder orale Candidiasis. Manchmal wird sie auch „Mundsoor“ genannt. Der häufigste Erreger ist Candida albicans. Viele Menschen haben Hefepilze in geringer Zahl auf den Schleimhäuten, ohne dass dies zu Problemen führt. Unter bestimmten Bedingungen können sich die Pilze allerdings stark vermehren. Die Pilzinfektion trifft häufig Menschen, die schwere Erkrankungen haben. Sie tritt aber auch als Nebenwirkung bestimmter Behandlungen auf.



Uremic stomatitis is a rarely reported oral mucosal disorder possibly associated with longstanding uremia in chronic renal failure patients. Since it was first mentioned by Lancereaux in 1887 and described by Barié in 1889,1 there have been only a small number of relevant reports in the literature. Four of 300 patients with uremia were observed to have probable uremic stomatitis in the 1930s, while in 1964 another 4 affected patients were reported from a group of 262 patients with renal disease. The clinical features of uremic stomatitis are poorly defined and are rarely detailed in relevant textbooks. The present report details the clinical and histopathological features of probable uremic stomatitis in a patient with longstanding chronic renal failure and reviews current knowledge of this unusual oral mucosal disorder.

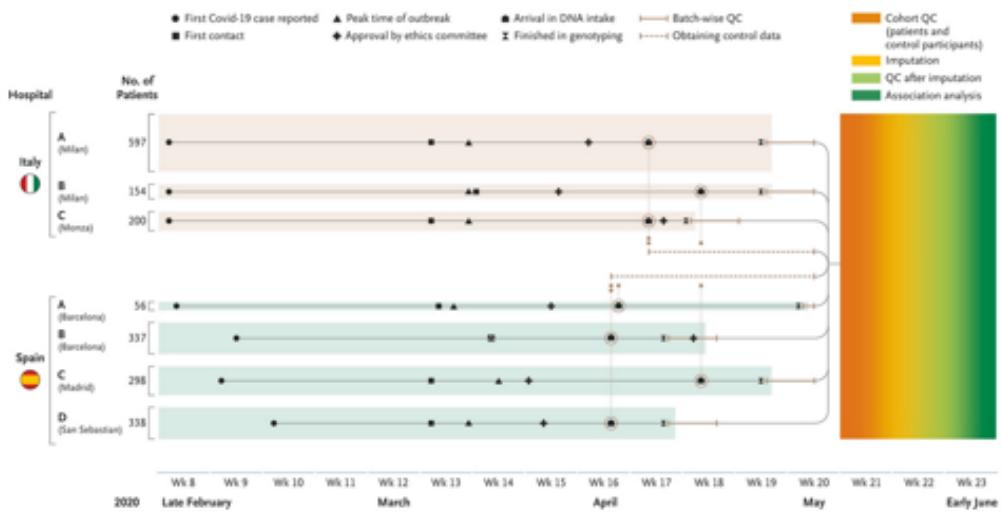


Eine genomweite Assoziationsstudie (GWAS, engl. Genome-wide association study) ist eine Untersuchung der genetischen Variation des Genoms eines Organismus – ausgelegt um einen bestimmten Phänotyp (zum Beispiel eine Krankheit) – mit bestimmten Haplotypen (bzw. Allelen) zu assoziieren. Das Ziel von GWAS ist es also letztlich die Allele (eine bestimmte Ausprägung eines Gens) zu identifizieren, welche gemeinsam mit einem Merkmal auftreten. Dabei werden nicht notwendigerweise die Gene direkt untersucht – v. a. aus ökonomischen Gründen nicht –, sondern wohldefinierte Marker (SNP, Single Nucleotide Polymorphism). Um diese zu detektieren wird vor allem auf Methoden wie Polymerase-Kettenreaktion und die isothermale DNA-Amplifikation mit allelspezifischen Oligonukleotiden gesetzt.
Das diploide menschliche Genom beispielsweise umfasst gut sechs Milliarden Basenpaare. Obwohl die Unterschiede zwischen zwei Menschen – im Vergleich zu anderen Species – extrem klein sind, wurden bisher mehr als 300 Millionen Polymorphismen gefunden (Datenbank Ensembl Variation 91). Die große Mehrheit dieser Polymorphismen liegen dabei als Einzelnukleotid-Polymorphismen (SNP) vor. Die größte Einschränkung der GWAS ist, dass nur Assoziationen von häufigen Haplotypen zu einem Phänotypen gefunden werden können – alle seltenen Varianten bleiben unentdeckt. Weiter ist zu betonen, dass GWAS nur korrelative Resultate liefern. Ein bestimmtes Allel eines Gens tritt gehäuft gemeinsam mit einem Phänotyp auf, was bedeutet, dass Gen und Merkmal 'irgendwie' in Verbindung miteinander stehen. Die Kausalität muss in weiteren Untersuchungen erst gezeigt oder gefunden werden. Auch werden heute nicht die Gene selber gefunden, sondern bloß Polymorphismen, die wiederum nur korrelativ mit den Genen zusammen auftreten.



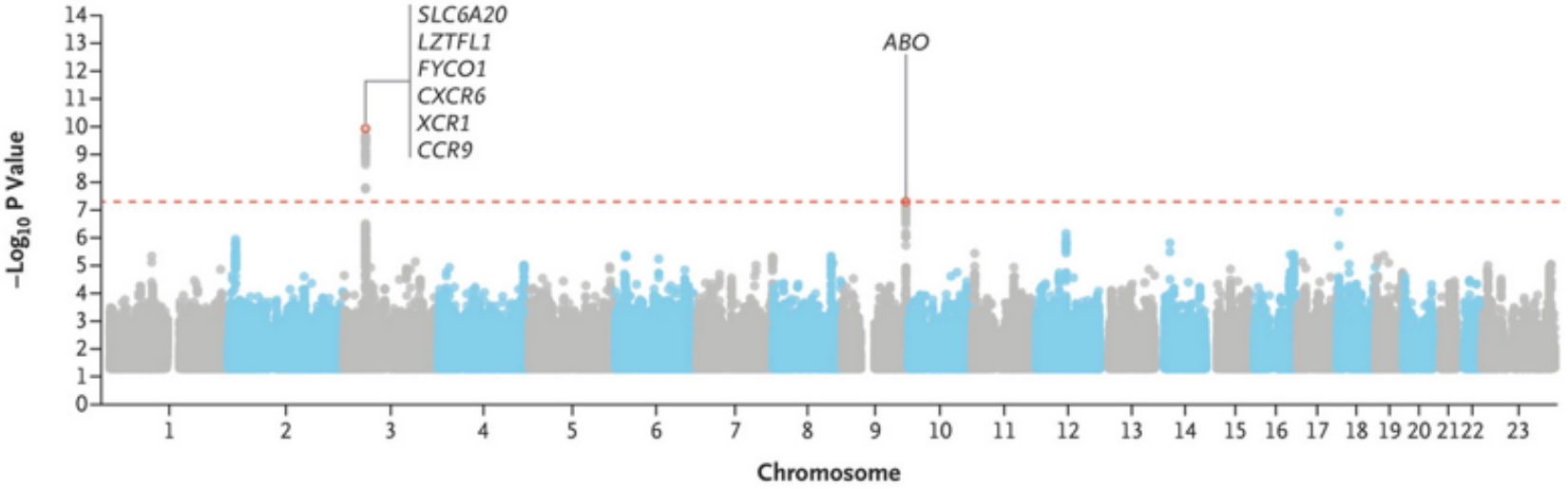
Genomewide Association Study of Severe Covid-19 with Respiratory Failure

There is considerable variation in disease behavior among patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19). Genomewide association analysis may allow for the identification of potential genetic factors involved in the development of Covid-19. We conducted a genomewide association study involving 1980 patients with Covid-19 and severe disease (defined as respiratory failure) at seven hospitals in the Italian and Spanish epicenters of the SARS-CoV-2 pandemic in Europe. After quality control and the exclusion of population outliers, 835 patients and 1255 control participants from Italy and 775 patients and 950 control participants from Spain were included in the final analysis. In total, we analyzed 8,582,968 single-nucleotide polymorphisms and conducted a meta-analysis of the two case–control panels.



The main events and milestones of the study are summarized in the plot. Samples from patients in three Italian hospitals (hospital A: Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan; hospital B: Humanitas Clinical and Research Center, IRCCS, Milan; and hospital C: UNIMIB School of Medicine, San Gerardo Hospital, Monza) and four Spanish hospitals (hospital A: Hospital Clínic and IDIBAPS, Barcelona; hospital B: Hospital Universitario Vall d'Hebron, Barcelona; hospital C: Hospital Universitario Ramón y Cajal, Madrid; and hospital D: Donostia University Hospital, San Sebastian) were obtained around the peak of the local epidemics, and ethics applications were quickly obtained by means of fast-track procedures (i.e., every local ethics review board supported studies of coronavirus disease 2019 [Covid-19] studies by providing rapid turn-around times, thus facilitating this fast de novo data generation). All the obtained blood samples were centrally isolated, genotyped, and analyzed within 8 weeks. Control data were obtained from control participants and from historical control data in Italy and Spain. The rapid workflow from patients to target identification shows the usefulness of GWAS, a standardized research tool that often relies on international and interdisciplinary cooperation. One center alone could not have completed this study, not to mention the increase in statistical power that was available because of the contribution of patients from multiple centers. The speed of data production depended heavily on laboratory automation, and the speed of analyses reflects existing analytic pipelines and the support of public so-called imputation servers (here, the Michigan imputation server of the G. Abecasis group). QC denotes quality control.

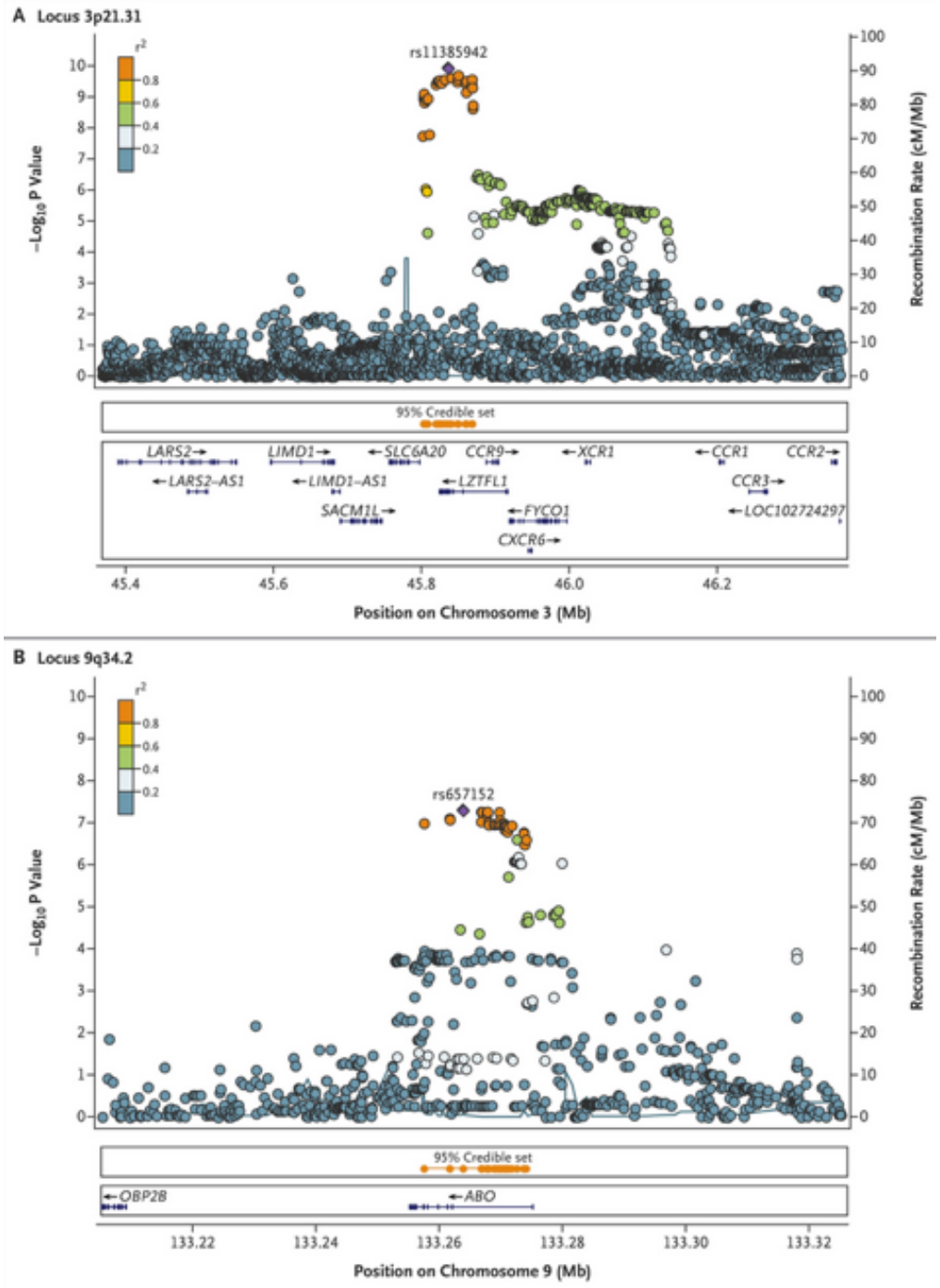
Characteristic	Italian Hospitals			Spanish Hospitals			
	A (N=503)	B (N=140)	C (N=192)	A (N=45)	B (N=228)	C (N=201)	D (N=301)
Median age (IQR) — yr	64 (54–76)	67 (57–75)	66 (56–74)	69 (59–75)	65 (56–72)	69 (60–79)	67 (57–75)
Female sex — no. (%)	159 (32)	39 (28)	51 (27)	13 (29)	78 (34)	50 (25)	124 (41)
Respiratory support — no. (%)							
Supplemental oxygen only	0	70 (50)	67 (35)	7 (16)	105 (46)	106 (53)	255 (85)
Noninvasive ventilation	399 (79)	25 (18)	89 (46)	6 (13)	7 (3)	16 (8)	0
Ventilator	104 (21)	45 (32)	33 (17)	31 (69)	116 (51)	77 (38)	46 (15)
ECMO	0	0	3 (2)	1 (2)	0	2 (1)	0
Hypertension — no./total no. (%)	166/503 (33)	71/140 (51)	109/192 (57)	26/45 (58)	113/228 (50)	112/199 (56)	114/301 (38)
Coronary artery disease — no./total no. (%)	21/503 (4)	25/140 (18)	25/192 (13)	4/45 (9)	14/228 (6)	35/199 (18)	15/301 (5)
Diabetes — no./total no. (%)	63/503 (13)	18/140 (13)	34/192 (18)	10/45 (22)	50/228 (22)	57/199 (29)	65/301 (22)



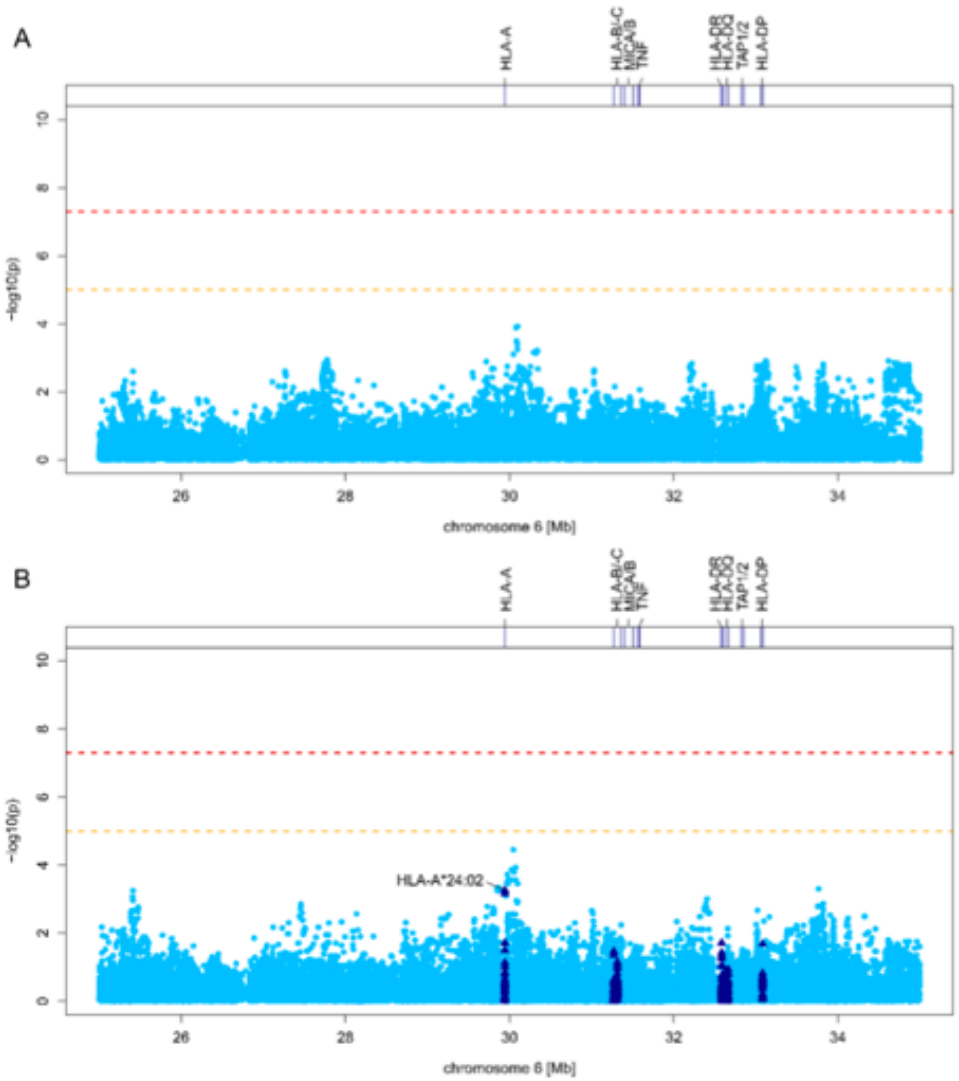
GWAS Summary (Manhattan) Plot of the Meta-analysis Association Statistics Highlighting Two Susceptibility Loci with Genomewide Significance for Severe Covid-19 with Respiratory Failure.

Chromosome and Analysis	Meta-analysis		Italian Panel				Spanish Panel			
	P Value	Odds Ratio (95% CI)	P Value	Odds Ratio (95% CI)	Allele Frequency		P Value	Odds Ratio (95% CI)	Allele Frequency	
					patient	control			patient	control
3p21.31†										
Main analysis	1.15×10^{-10}	1.77 (1.48–2.11)	1.98×10^{-7}	1.74 (1.27–2.38)	0.14	0.09	1.32×10^{-4}	1.85 (1.50–2.28)	0.09	0.05
Analysis corrected for age and sex	9.46×10^{-12}	2.11 (1.70–2.61)	7.02×10^{-8}	1.95 (1.53–2.48)	0.14	0.09	1.17×10^{-5}	2.79 (1.76–4.42)	0.09	0.05
9q34.2‡										
Main analysis	4.95×10^{-8}	1.32 (1.20–1.47)	2.90×10^{-6}	1.37 (1.20–1.57)	0.42	0.35	3.55×10^{-3}	1.26 (1.08–1.48)	0.42	0.35
Analysis corrected for age and sex	5.35×10^{-7}	1.39 (1.22–1.59)	5.31×10^{-5}	1.37 (1.17–1.60)	0.42	0.35	2.81×10^{-3}	1.45 (1.13–1.84)	0.42	0.35

On chromosome 3p21.31, the peak association signal covered a cluster of six genes (*SLC6A20*, *LZTFL1*, *CCR9*, *FYCO1*, *CXCR6*, and *XCR1*), several of which have functions that are potentially relevant to Covid-19. A causative gene cannot be reliably implicated by the present data. One candidate is *SLC6A20*, which encodes the sodium–imino acid (proline) transporter 1 (SIT1) and which functionally interacts with angiotensin-converting enzyme 2, the SARS-CoV-2 cell-surface receptor.
However, the locus also contains genes encoding chemokine receptors, including the CC motif chemokine receptor 9 (CCR9) and the C-X-C motif chemokine receptor 6 (CXCR6), the latter of which regulates the specific location of lung-resident memory CD8 T cells throughout the sustained immune response to airway pathogens, including influenza viruses. Flanking genes (e.g., *CCR1* and *CCR2*) also have relevant functions, and further studies will be needed to delineate the functional consequences of detected associations.



Bayesian fine-mapping analysis prioritized 22 and 38 variants for loci 3p21.31 (Panel A) and 9q34.2 (Panel B), respectively, with greater than 95% certainty. The linkage disequilibrium values were calculated on the basis of genotypes of the merged Italian and Spanish data sets derived from TOPMed (Trans-Omics for Precision Medicine) imputation. The positions in the genome assembly hg38 are plotted. The recombination rate is shown in centimorgans (cM) per million base pairs (Mb). The plot shows the names and locations of the genes; the transcribed strand is indicated with an arrow. Genes are represented with intronic and exonic regions. The purple diamond in each panel represents the variant most strongly associated with severe Covid-19 and respiratory failure.



Given its important role in several viral infections, we scrutinized the extended HLA region (chromosome 6, 25 through 34 Mb). There were no SNP association signals at the HLA complex that met even the significance threshold of suggestive association.

Dedicated analysis of the classical HLA loci showed no significant allele associations with either Covid-19 or disease severity (oxygen supplementation only or mechanical ventilation of any kind), and further analysis of heterozygote and divergent allele advantage or predicted number of HLA-bound SARS-CoV-2 peptides did not show significant associations with Covid-19 in this data set.

The pragmatic aspects leading to the feasibility of this massive undertaking in a very short period of time during the extreme clinical circumstances of the pandemic imposed limitations that will be important to explore in follow-up studies. For example, to enable the recruitment of study participants, a bare minimum of clinical metadata was requested. For this reason, extensive genotype–phenotype elaboration of current findings could not be conducted, and adjustments for all potential sources of bias (e.g., underlying cardiovascular and metabolic factors relevant to Covid-19) could not be performed. Furthermore, we have limited information about the SARS-CoV-2 infection status in the control participants; this concern is mitigated by the fact that the presence of susceptible persons in the control group would only bias the tests toward the null. In addition, few restrictions were imposed during inclusion, which led to genotyped samples having to be excluded owing to differing ethnic groups (population outliers). Further exploration of current findings, both as to their usefulness in clinical risk profiling of patients with Covid-19 and toward a mechanistic understanding of the underlying pathophysiology, is warranted.

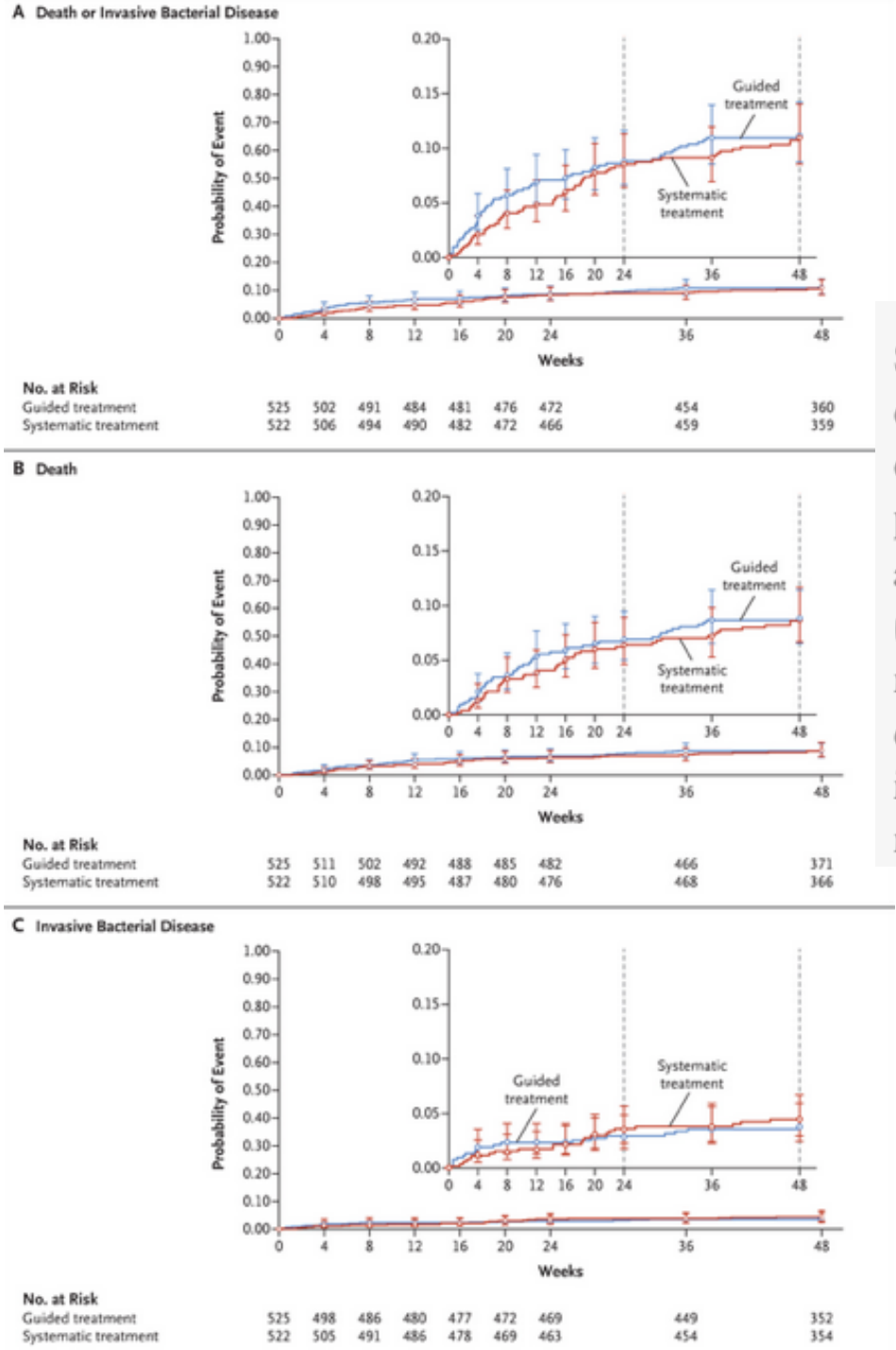
ABO (better off with O)

Systematic or Test-Guided Treatment for Tuberculosis in HIV-Infected Adults

In regions with high burdens of tuberculosis and human immunodeficiency virus (HIV), many HIV-infected adults begin antiretroviral therapy (ART) when they are already severely immunocompromised. Mortality after ART initiation is high in these patients, and tuberculosis and invasive bacterial diseases are common causes of death. We conducted a 48-week trial of empirical treatment for tuberculosis as compared with treatment guided by testing in HIV-infected adults who had not previously received ART and had CD4+ T-cell counts below 100 cells per cubic millimeter. Patients recruited in Ivory Coast, Uganda, Cambodia, and Vietnam were randomly assigned in a 1:1 ratio to undergo screening (Xpert MTB/RIF test, urinary lipoarabinomannan test, and chest radiography) to determine whether treatment for tuberculosis should be started or to receive systematic empirical treatment with rifampin, isoniazid, ethambutol, and pyrazinamide daily for 2 months, followed by rifampin and isoniazid daily for 4 months. The primary end point was a composite of death from any cause or invasive bacterial disease within 24 weeks (primary analysis) or within 48 weeks after randomization.

Characteristic	Treatment (N=525)	Treatment (N=522)
Baseline		
Female sex — no. (%)	221 (42.0)	215 (41.2)
Median age (IQR) — yr	35 (29–41)	35 (29–41)
Median body-mass index (IQR)†	19.6 (17.9–21.9)	19.7 (17.8–21.9)
Karnofsky performance-status score — no. (%)‡		
<80	27 (5.1)	27 (5.2)
≥80	497 (94.7)	494 (94.6)
Missing data	1 (0.2)	1 (0.2)
WHO clinical stage — no. (%)		
Stage 1	152 (29.0)	146 (28.0)
Stage 2	132 (25.1)	148 (28.4)
Stage >2	240 (45.7)	227 (43.5)
Missing data	1 (0.2)	1 (0.2)
Median CD4+ T-cell count (IQR) — cells/mm^3	28 (12–56)	32 (13–55)
CD4+ T-cell count — no. (%)		
≤50/mm^3	370 (70.5)	370 (70.9)
51–99/mm^3	155 (29.5)	152 (29.1)
Median plasma HIV-1 RNA level (IQR) — $\log_{10}$ copies/ml	5.5 (5.2–5.8)	5.4 (5.1–5.8)
Median hemoglobin level — g/dl	11.5 (9.9–13.4)	11.7 (9.9–13.2)
Positive plasma HBV surface antigen — no. (%)	47 (9.0)	48 (9.2)
Positive plasma HCV antibodies — no. (%)	36 (6.9)	35 (6.7)
Plasma ALT >2.5× ULN — no. (%)	49 (9.3)	36 (6.9)
Patients with tuberculosis symptoms according to WHO criteria — no. (%)§		
No symptoms	199 (37.9)	196 (37.5)
1 Symptom	155 (29.5)	150 (28.7)
2 Symptoms	90 (17.1)	103 (19.7)
3 Symptoms	62 (11.8)	58 (11.1)
4 Symptoms	18 (3.4)	15 (2.9)
Missing data	1 (0.2)	0
Follow-up		
Lost to follow-up — no. (%)	11 (2.1)	13 (2.5)
Follow-up time — person-yr	444	442
Initiated ART — no. (%)	523 (99.6)	510 (97.7)

Clinical End Points	Guided Treatment		Systematic Treatment		Adjusted Hazard Ratio (95% CI)†
	No. of First Events	Rate (95% CI)‡	No. of First Events	Rate (95% CI)‡	
Primary end point at 24 wk: composite of death from any cause or invasive bacterial disease	46	20.3 (14.5–26.2)	44	19.4 (13.7–25.1)	0.95 (0.63–1.44)§
Secondary end points at 24 wk¶					
Death from any cause	36	15.6 (10.5–20.8)	33	14.4 (9.5–19.3)	0.92 (0.57–1.47)
Invasive bacterial disease	15	6.7 (3.7–11.0)	18	8.0 (4.7–12.6)	1.19 (0.60–2.36)
Tuberculosis‖	93	47.2 (37.6–56.8)	15	6.7 (3.7–11.0)	0.15 (0.09–0.26)
IRIS	57	26.8 (19.8–33.7)	17	7.6 (4.4–12.1)	0.39 (0.22–0.69)
AIDS-defining events	62	29.3 (22.0–36.5)	46	21.3 (15.1–27.5)	0.73 (0.50–1.06)
Grade 3 or 4 adverse events**	125	65.5 (54.0–76.9)	166	94.3 (80.0–108.7)	1.39 (1.11–1.76)
Grade 3 or 4 drug-related adverse events**	37	16.9 (11.5–22.3)	89	44.7 (35.4–54.0)	2.57 (1.75–3.78)
Secondary end points at 48 wk¶					
Composite of death from any cause or invasive bacterial disease	58	13.3 (9.9–16.7)	56	12.8 (9.5–16.2)	0.97 (0.67–1.40)
Death from any cause	45	10.1 (7.4–13.5)	45	10.2 (7.4–13.6)	1.01 (0.67–1.52)
Invasive bacterial disease	19	4.4 (2.7–6.9)	22	5.1 (3.2–7.7)	1.15 (0.62–2.13)
Tuberculosis‖	99	26.2 (21.0–31.3)	18	4.2 (2.5–6.6)	0.17 (0.10–0.28)
IRIS	59	14.4 (10.7–18.1)	17	3.9 (2.3–6.3)	0.27 (0.16–0.47)
AIDS-defining events	72	17.7 (13.6–21.8)	52	12.6 (9.2–16.0)	0.71 (0.49–1.01)
Grade 3 or 4 adverse events**	143	39.8 (33.3–46.4)	179	54.7 (46.7–62.8)	1.32 (1.06–1.65)
Grade 3 or 4 drug-related adverse events**	39	9.3 (6.4–12.2)	94	24.9 (19.9–30.0)	2.59 (1.78–3.76)

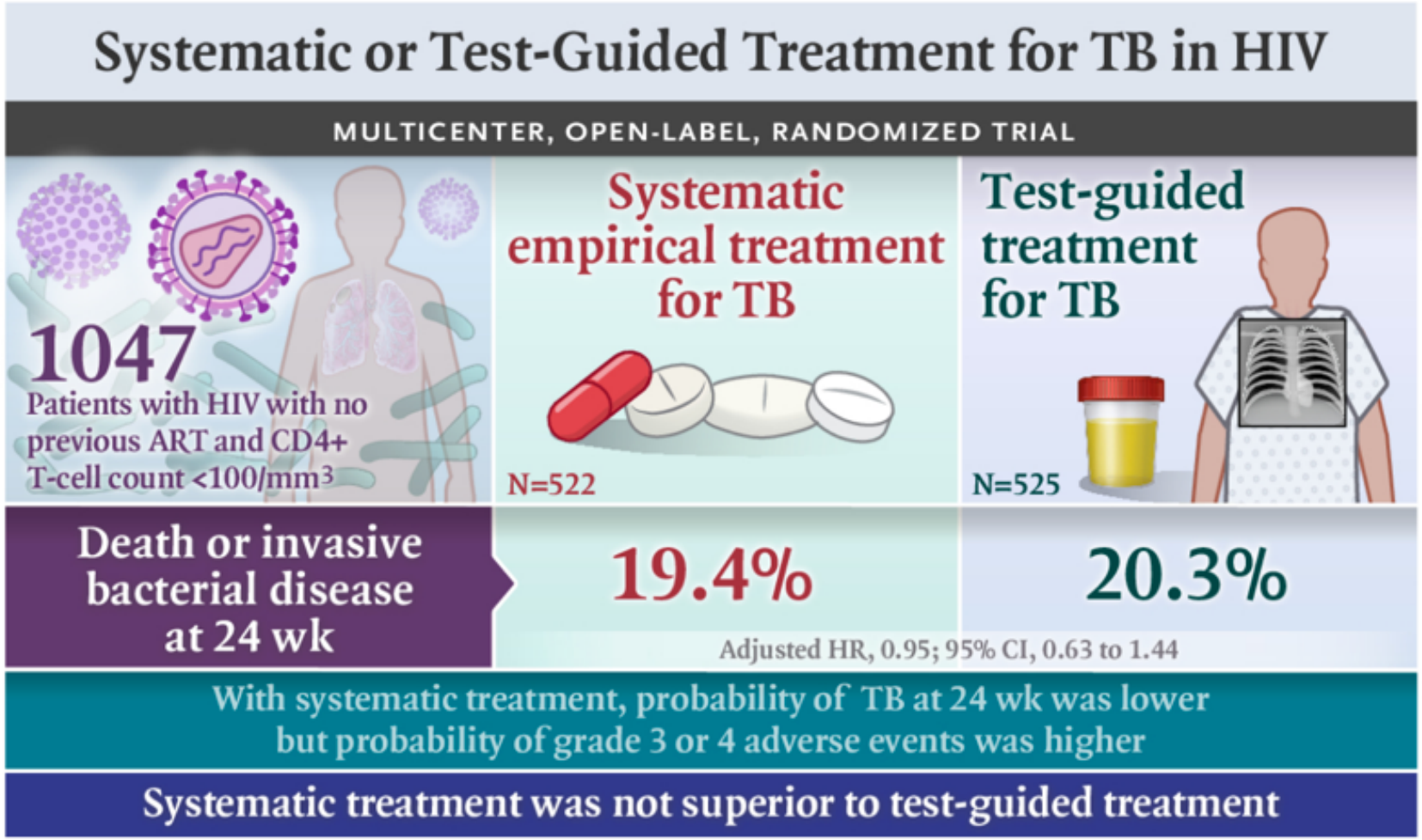


Shown are the Kaplan–Meier curves for the probability of the primary composite end point of death from any cause or invasive bacterial disease (Panel A) and the probability of the end-point components of death from any cause (Panel B) and invasive bacterial disease (defined as a bacteremia or clinical, biologic, or radiologic signs compatible with a bacterial infection of any solid organ or sterile space). In each panel, the inset shows the same data on an enlarged y axis. I bars represent 95% confidence intervals.

Serious Adverse Event	All Events (495 Events)*		Drug-Related Events (150 Events)†	
	Guided Treatment	Systematic Treatment	Guided Treatment	Systematic Treatment
	number of events			
Invasive bacterial infections	20	22	—	—
Isolated bacteremia	4	9	—	—
Bacterial pneumonia	8	4	—	—
Severe sepsis	2	4	—	—
Pyelonephritis	4	1	—	—
Necrotizing fasciitis	2	0	—	—
Bacterial enteritis	0	1	—	—
Salpingitis	0	1	—	—
Skin abscess	0	1	—	—
Appendicitis	0	1	—	—
Incident tuberculosis‡	50	17	—	—
Other AIDS-defining illnesses	31	39	—	—
Cryptococcosis	6	10	—	—
Nontuberculous mycobacteriosis	5	2	—	—
Pneumocystis pneumonia	5	6	—	—
Esophageal candidiasis	3	8	—	—
Cytomegalovirus retinitis	2	1	—	—
Isosporiasis	2	2	—	—
Cryptosporidiosis	1	3	—	—
Microsporidiosis	1	0	—	—
Progressive multifocal leukoencephalopathy	1	1	—	—
Kaposi's sarcoma	1	1	—	—
Solid tumors other than Kaposi's sarcoma	1	1	—	—
Wasting syndrome	3	4	—	—
Other grade 3 or 4 adverse events	119	197	45	105
Noninfectious transaminitis	26	43	17	39
Pruritus, rash, mucous ulcerations	8	35	8	34
Stevens–Johnson syndrome	2	3	2	3
Neutropenia	16	17	5	10
Anemia	7	14	1	4
Thrombopenia	0	3	0	1
Bicytopenia or pancytopenia	6	3	2	1
Neuropsychiatric disorders	5	6	4	3
Nonspecific acute fever	5	13	0	1
Nonspecific kidney failure	7	5	5	4
Vomiting	0	2	0	2
Hyperuricemia	0	1	0	1
Gynecomastia	1	2	1	2
Other	36	50	0	0
Total	220	275	45	105

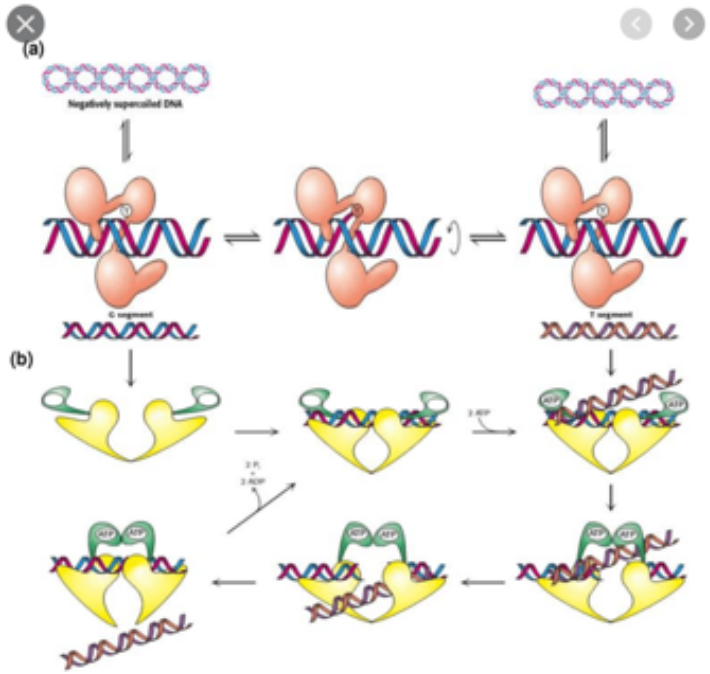
ADVERSE EVENTS

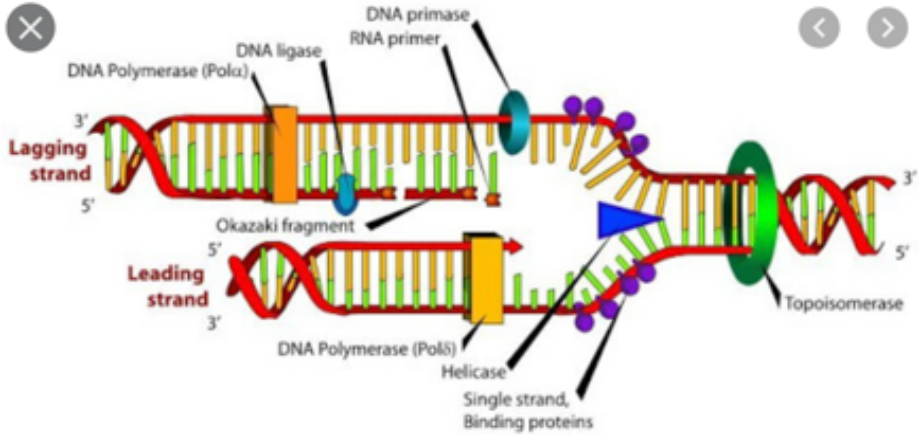
Overall, 495 serious adverse events (220 in the guided-treatment group and 275 in the systematic-treatment group) occurred in 322 patients (143 in the guided-treatment group and 179 in the systematic-treatment group), including 150 grade 3 or 4 drug-related adverse events (45 in the guided-treatment group and 105 in the systematic-treatment group) in 133 patients (39 in the guided-treatment group and 94 in the systematic-treatment group) (Table 3). The cumulative 24-week probability of grade 3 or 4 drug-related adverse events was 17.4% in the systematic-treatment group and 7.2% in the guided-treatment group (adjusted hazard ratio, 2.57; 95% CI, 1.75 to 3.78). Treatment for tuberculosis was stopped prematurely in 24 patients (4.6%) in the systematic-treatment group owing to adverse events. During follow-up, 79 cases of IRIS (59 in the guided-treatment group and 20 in the systematic-treatment group) occurred in 76 patients (59 in the guided-treatment group and 17 in the systematic-treatment group), including 60 cases of tuberculosis-associated IRIS (49 cases and 11 cases in the two groups, respectively).



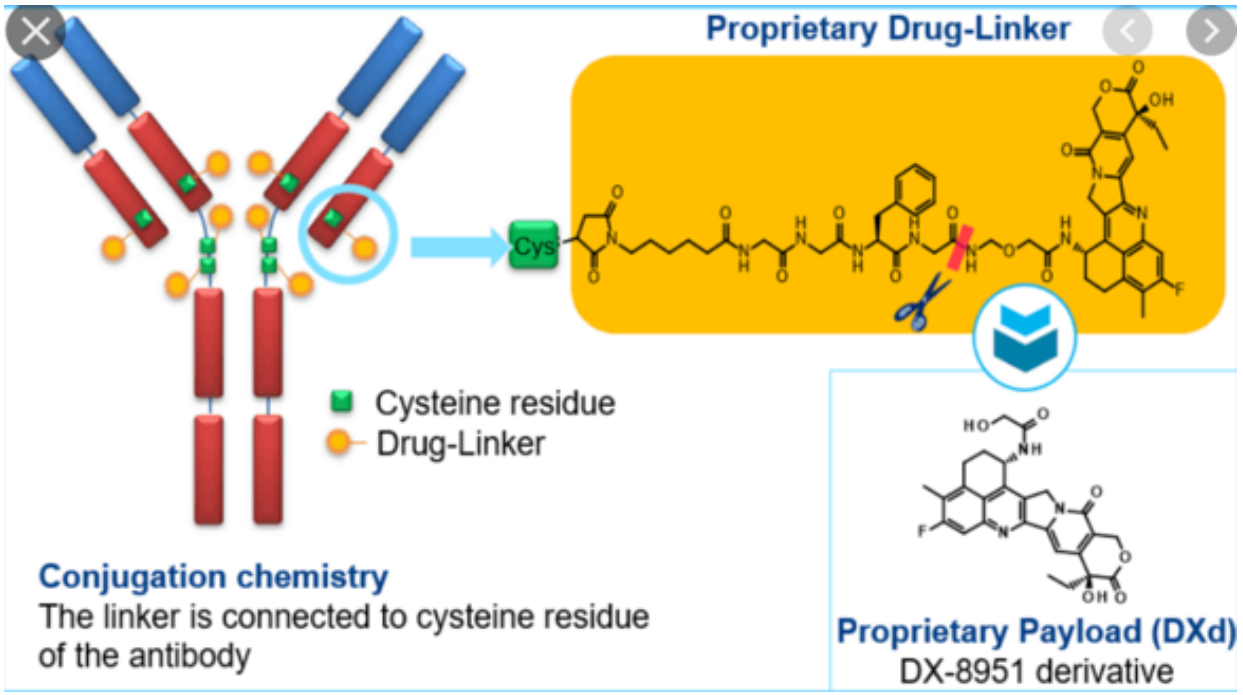
Handtuch schmeißen nicht besser als testen (aber auch nicht schlechter).

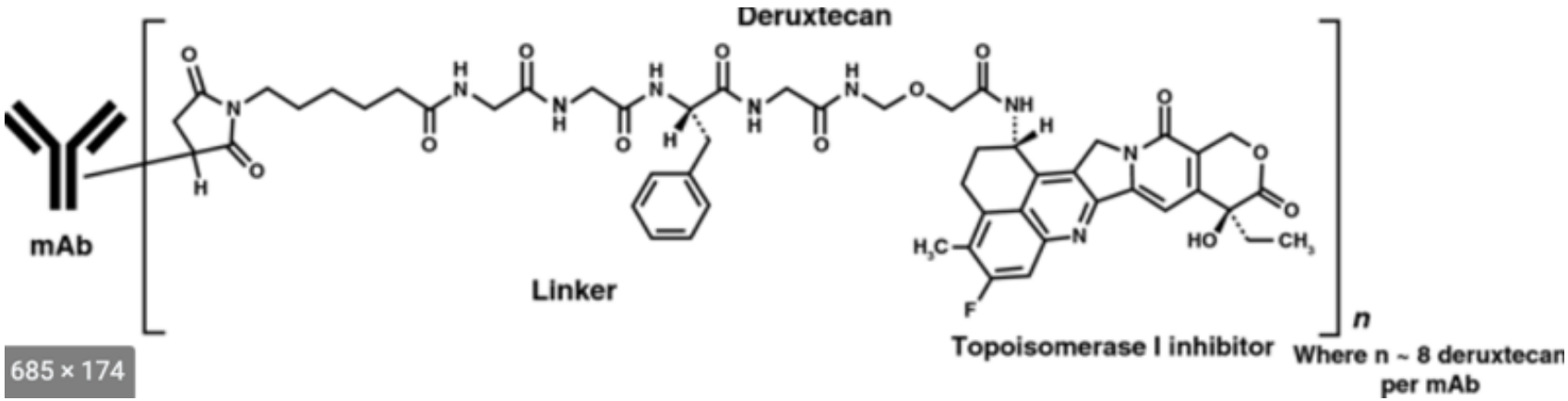
Topoisomerasen sind Enzyme, die für Änderungen der Topologie von DNA-Molekülen verantwortlich sind, welche bei einer Superspiralisierung notwendig sind. Man unterscheidet zwei übergeordnete Klassen:
Die bakterielle Topoisomerase I kann ausschließlich negative Superspiralisierung entspannen. Sie benötigt Magnesiumionen für ihre Aktivität. Prokaryotische Topoisomerasen I binden mittels einer Phosphotyrosinbindung kovalent an das 5'-Ende des Strangbruches. Dies konserviert die Energie der gespaltenen Bindung und ermöglicht es, die beiden Enden nach der Topoisomerisierung wieder zu verbinden. Für ihre Tätigkeit benötigt das Enzym keine Energie in Form von ATP.
Funktion der Topoisomerase II in Bakterien:
Die bakterielle Topoisomerase II bewirkt negative Superspiralisierung der DNA. Dadurch kann sie positiv superspiralisierte DNA entspannen und in relaxierte DNA negative Verdrillung einführen. Sie induziert dazu Doppelstrangbrüche; die negative Superspiralisierung geschieht unter ATP-Verbrauch. Antibiotika aus der Familie der Gyrasehemmer hemmen die Topoisomerase II und teilweise IV. Zytostatika wie Irinotecan zählen zu den Topoisomerasehemmern.





Trastuzumab deruxtecan is an antibody-drug conjugate that includes a human epidermal growth factor receptor 2 (HER2)-directed antibody trastuzumab and a topoisomerase I inhibitor conjugate deruxtecan (a derivative of exatecan).





Trastuzumab Deruxtecan in Previously Treated HER2-Positive Gastric Cancer

Trastuzumab deruxtecan (DS-8201) is an antibody-drug conjugate consisting of an anti-HER2 (human epidermal growth factor receptor 2) antibody, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor. The drug may have efficacy in patients with HER2-positive advanced gastric cancer. In an open-label, randomized, phase 2 trial, we evaluated trastuzumab deruxtecan as compared with chemotherapy in patients with HER2-positive advanced gastric cancer. Patients with centrally confirmed HER2-positive gastric or gastroesophageal junction adenocarcinoma that had progressed while they were receiving at least two previous therapies, including trastuzumab, were randomly assigned in a 2:1 ratio to receive trastuzumab deruxtecan (6.4 mg per kilogram of body weight every 3 weeks) or physician's choice of chemotherapy. The primary end point was the objective response, according to independent central review. Secondary end points included overall survival, response duration, progression-free survival, confirmed response (response persisting ≥4 weeks), and safety. An estimated 15 to 20% of advanced gastric and gastroesophageal junction cancers, which are especially prevalent in East Asia, have overexpression or amplification of human epidermal growth factor receptor 2 (HER2).

Characteristic	Trastuzumab Deruxtecan (N=125)	Physician's Choice of Chemotherapy (N=62)
Median age (range) — yr†	65 (34–82)	66 (28–82)
Female sex — no. (%)	30 (24)	15 (24)
Region — no. (%)		
Japan	99 (79)	50 (81)
South Korea	26 (21)	12 (19)
ECOG performance-status score — no. (%)‡		
0	62 (50)	30 (48)
1	63 (50)	32 (52)
Histologic subtype — no. (%)		
Intestinal	89 (71)	38 (61)
Diffuse	28 (22)	18 (29)
Other	8 (6)	6 (10)
HER2 expression — no. (%)§		
IHC 3+	96 (77)	47 (76)
IHC 2+ or ISH-positive	29 (23)	15 (24)
Primary site — no. (%)		
Stomach	108 (86)	55 (89)
Gastroesophageal junction	17 (14)	7 (11)
Sum of diameters of measurable tumors — no. (%)¶		
<5 cm	63 (50)	26 (42)
≥5 cm to <10 cm	34 (27)	22 (35)
≥10 cm	22 (18)	8 (13)
Missing data	6 (5)	6 (10)
No. of previous systemic therapies for advanced or metastatic disease — no. (%)‖		
2	66 (53)	38 (61)
3	34 (27)	18 (29)
≥4	25 (20)	6 (10)
Previous treatment — no. (%)		
Therapy containing trastuzumab	125 (100)	62 (100)
Therapy containing taxane	105 (84)	55 (89)
Therapy containing ramucirumab	94 (75)	41 (66)
Irinotecan or other topoisomerase I inhibitor	8 (6)	5 (8)
Immune checkpoint inhibitor	44 (35)	17 (27)

Figure S1. Study Design.

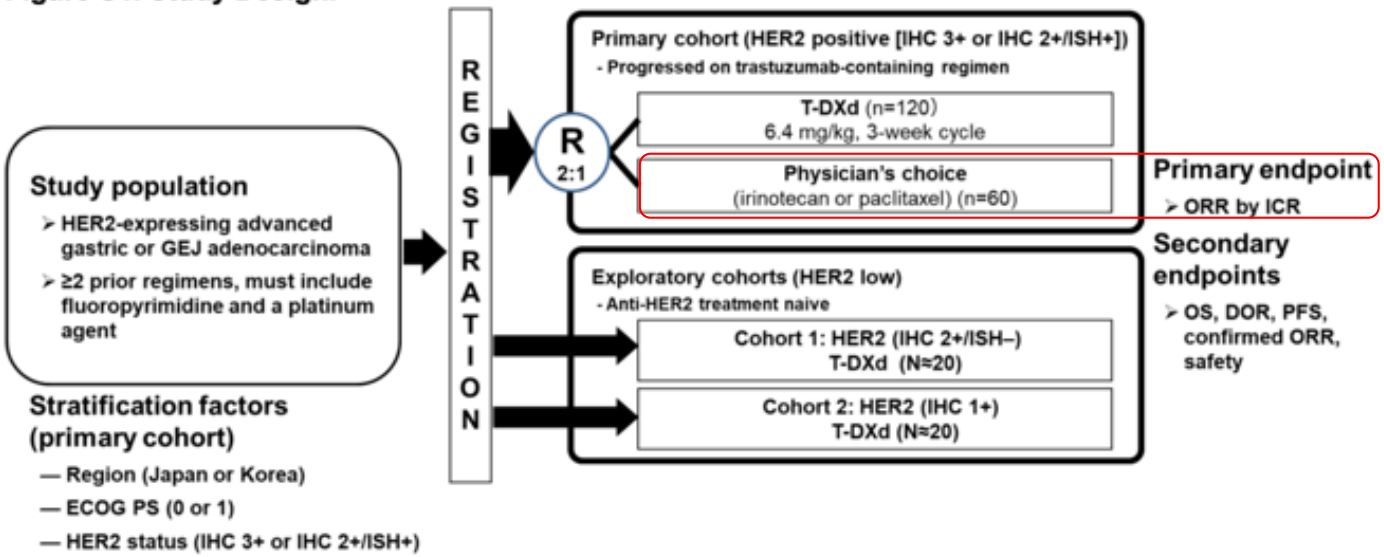
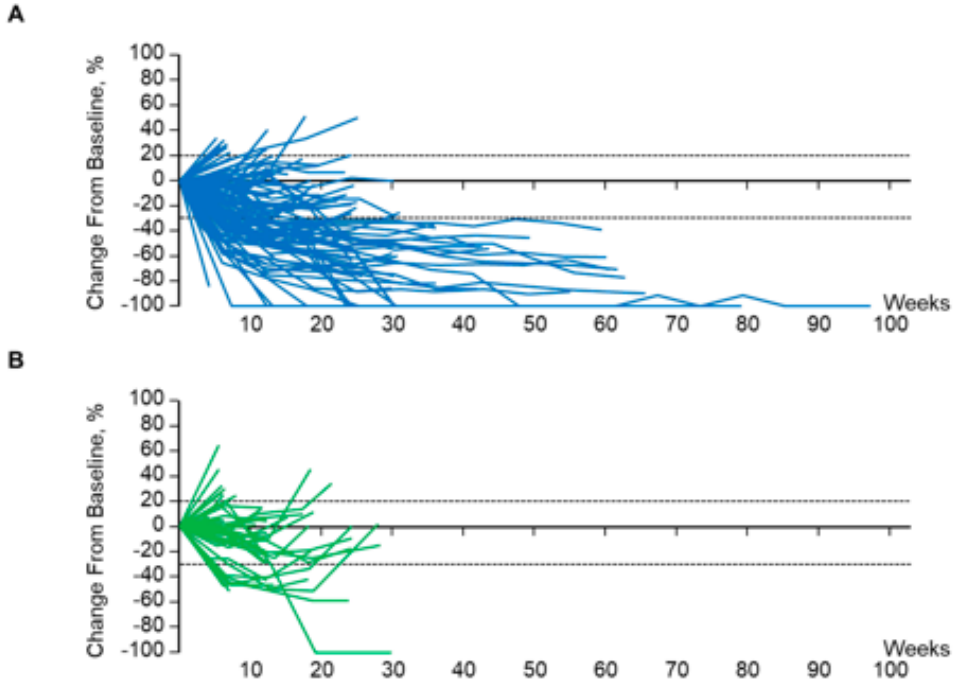


Figure S3. Spider Plot (changes from baseline in tumor burden, measured as the sum of tumor diameters) in (A) T-DXd Group and (B) Physician's Choice Group.



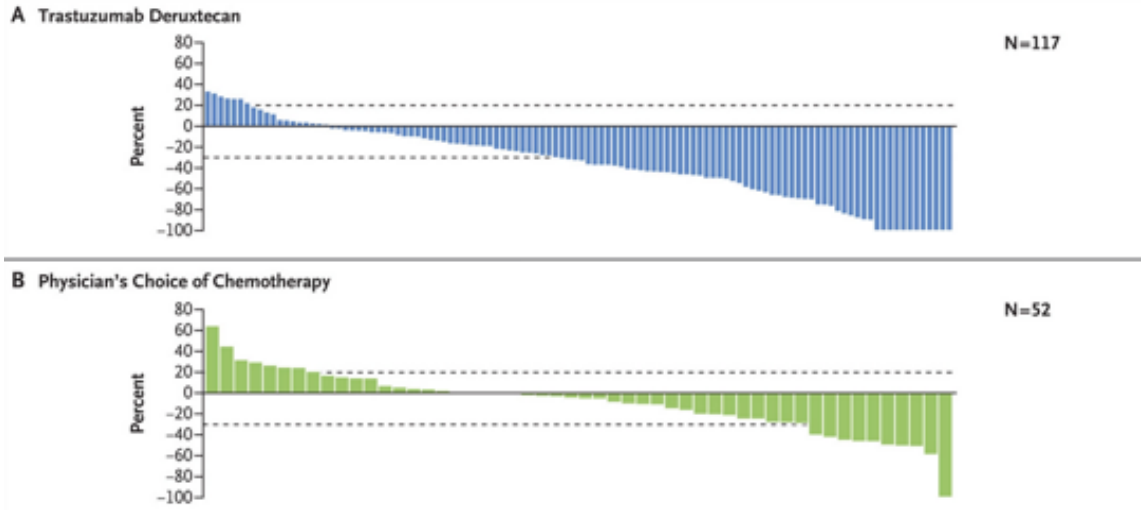
Taxane hemmen die Zellteilung und damit das Tumorwachstum, indem sie den Abbau des Spindelapparates hemmen und so diesen für seine essentielle Funktion in der Mitose unbrauchbar machen.
Die Mikrotubuli, welche den Spindelapparat ausbilden, sind essenziell für die Verteilung des verdoppelten Erbmaterials auf die beiden Tochterzellen im Verlauf der Zellteilung.

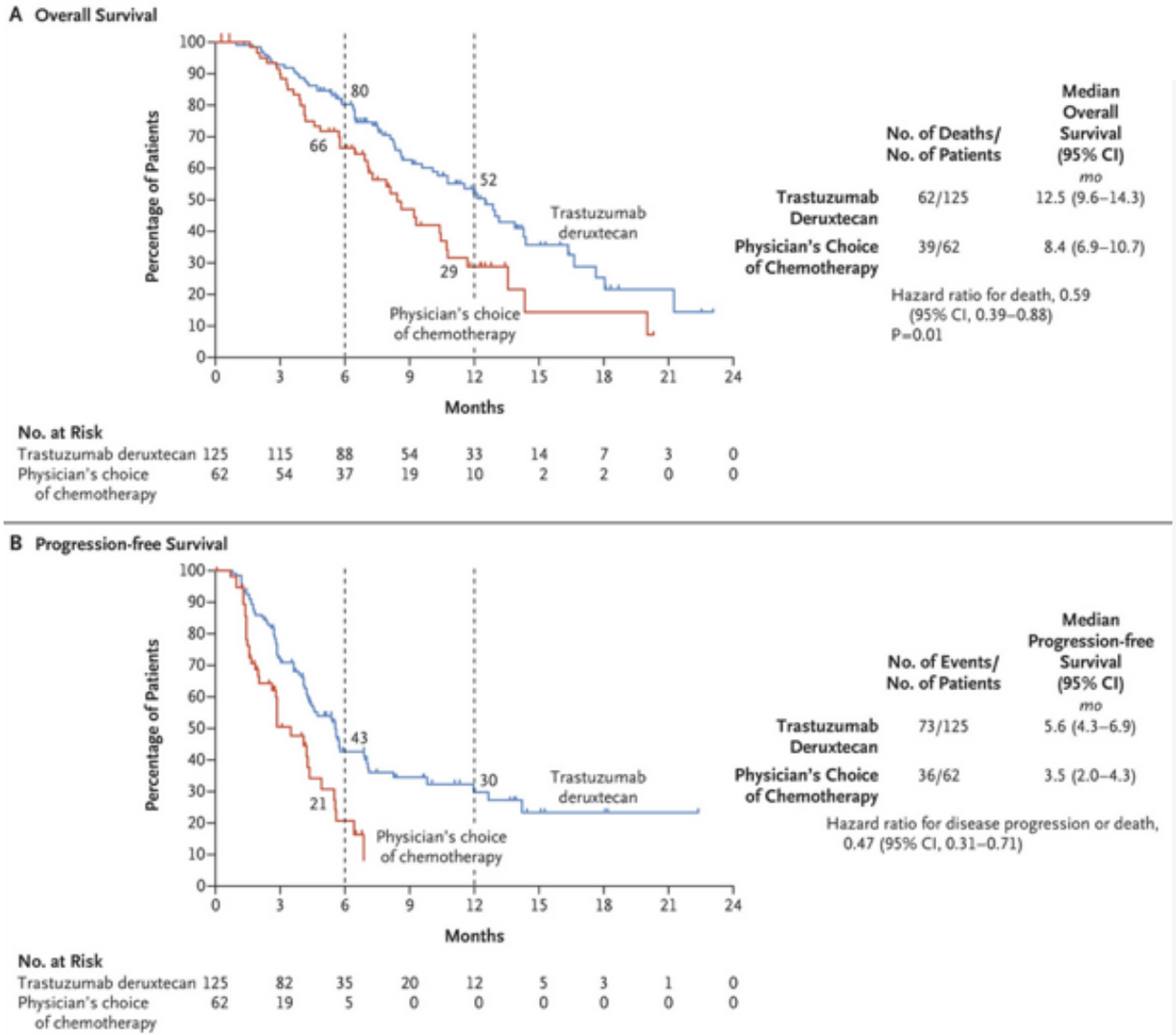
Irinotecan ist ein Arzneistoff, der zur Behandlung bestimmter Krebserkrankungen eingesetzt wird. Pharmakologisch ist Irinotecan ein Zytostatikum aus der Gruppe der Topoisomerase-Hemmer, chemisch stellt es ein halbsynthetisches Derivat des natürlich vorkommenden Pflanzeninhaltsstoffes Camptothecin dar.

Table 2. Summary of Efficacy.*

Variable	Trastuzumab Deruxtecan (N=119)	Physician's Choice of Chemotherapy (N=56)
Objective response†		
No. of patients	61	8
Percent of patients (95% CI)	51 (42–61)	14 (6–26)
Best response — no. (%)		
Complete response	11 (9)	0
Partial response	50 (42)	8 (14)
Stable disease	42 (35)	27 (48)
Progressive disease	14 (12)	17 (30)
Could not be evaluated	2 (2)	4 (7)
Confirmed objective response‡		
No. of patients	51	7
Percent of patients (95% CI)	43 (34–52)	12 (5–24)
Confirmed best response — no. (%)		
Complete response	10 (8)	0
Partial response	41 (34)	7 (12)
Stable disease	51 (43)	28 (50)
Progressive disease	14 (12)	17 (30)
Could not be evaluated	3 (3)	4 (7)
Confirmed disease control§		
No. of patients	102	35
Percent of patients (95% CI)	86 (78–91)	62 (49–75)

The line at 20% indicates progressive disease, and the line at −30% indicates a partial response. The analyses included patients who had both baseline and postbaseline target-lesion assessments according to independent central review. Six patients (two in the trastuzumab deruxtecan group and four in the physician's choice group) were excluded from this analysis because they did not undergo postbaseline tumor assessment.





In the analysis of overall survival (Panel A), 63 patients (50%) in the trastuzumab deruxtecan group and 23 (37%) in the physician's choice group had their data censored (tick marks). The two-sided Pvalue of 0.01 crossed the O'Brien–Fleming boundary of significance (0.0202 on the basis of the number of deaths). The percentages of patients who survived are shown at 6 months and 12 months. In the analysis of progression-free survival (Panel B), 62 patients (50%) in the trastuzumab deruxtecan group had progressive disease, as assessed on independent central review, and 11 (9%) had death as the first event; the corresponding values in the physician's choice group were 34 patients (55%) and 2 (3%). A total of 52 patients (42%) in the trastuzumab deruxtecan group and 26 (42%) in the physician's choice group had their data censored (tick marks). Data were censored for the following reasons: no baseline tumor assessment (for 1 patient in the trastuzumab deruxtecan group and for 2 in the physician's choice group), no postbaseline tumor assessment (for 1 and 3, respectively), receipt of new anticancer therapy (for 6 and 11), and missing of two consecutive tumor assessments (for 3 and 1); the remaining patients had data censored without an event. The percentages of patients who were free from disease progression or death are shown at 6 months and 12 months. Both analyses were stratified according to region.

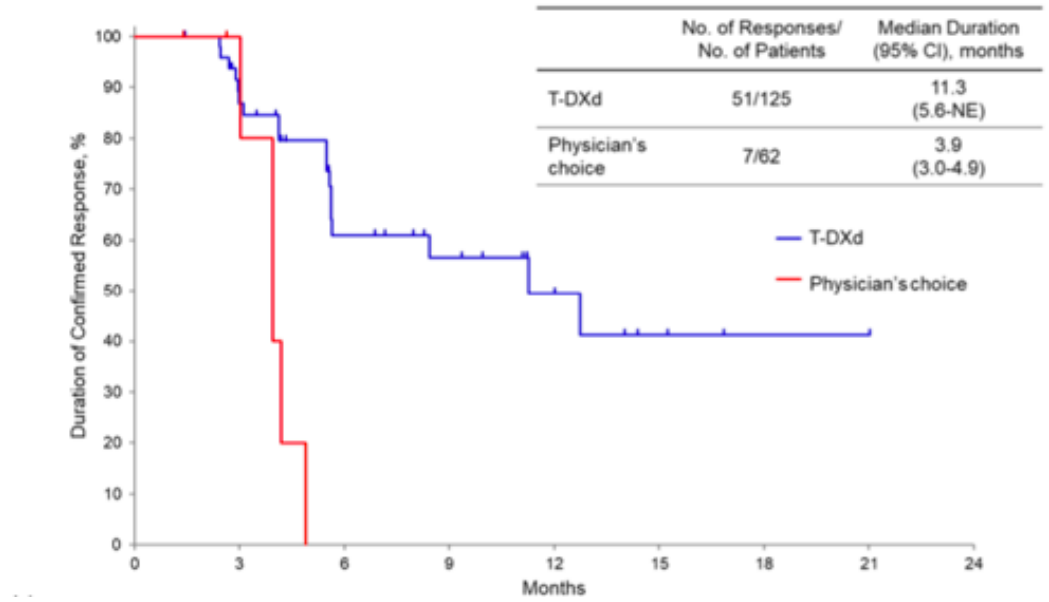
Adverse Events Occurring in at Least 20% of the Patients Treated with Trastuzumab Deruxtecan.

Preferred Term	Trastuzumab Deruxtecan (N=125)			Physician's Choice of Chemotherapy (N=62)		
	Any Grade	Grade 3	Grade 4	Any Grade	Grade 3	Grade 4
	number of patients (percent)					
Nausea	79 (63)	6 (5)	0	29 (47)	1 (2)	0
Neutrophil count decreased†	79 (63)	48 (38)	16 (13)	22 (35)	10 (16)	5 (8)
Decreased appetite	75 (60)	21 (17)	0	28 (45)	8 (13)	0
Anemia‡	72 (58)	47 (38)	0	19 (31)	13 (21)	1 (2)
Platelet count decreased§	49 (39)	12 (10)	2 (2)	4 (6)	1 (2)	1 (2)
White-cell count decreased¶	47 (38)	26 (21)	0	22 (35)	5 (8)	2 (3)
Malaise	43 (34)	1 (1)	0	10 (16)	0	0
Diarrhea	40 (32)	3 (2)	0	20 (32)	1 (2)	0
Vomiting	33 (26)	0	0	5 (8)	0	0
Constipation	30 (24)	0	0	14 (23)	0	0
Pyrexia	30 (24)	0	0	10 (16)	0	0
Alopecia	28 (22)	0	0	9 (15)	0	0
Fatigue	27 (22)	9 (7)	0	15 (24)	2 (3)	0
Lymphocyte count decreased‖	27 (22)	8 (6)	6 (5)	2 (3)	0	1 (2)

In this trial, the notable adverse events occurring with trastuzumab deruxtecan were myelosuppression and interstitial lung disease, which were managed by appropriate dose reduction or interruption. Although most gastrointestinal events were of low grade, hematologic events were more frequently of grade 3 or higher with trastuzumab deruxtecan than with chemotherapy. These toxic effects were often addressed with dose modification. Although HER2-targeted therapies, including trastuzumab, have been associated with cardiotoxic effects, this was not observed in our trial.

Discussion

This trial assessed the efficacy and safety of trastuzumab deruxtecan as compared with physician's choice of chemotherapy (irinotecan or paclitaxel) as third-line or later therapy in patients with HER2-positive gastric or gastroesophageal adenocarcinoma. The percentage of patients with an objective response was significantly higher in the trastuzumab deruxtecan group than in the physician's choice group (51% vs. 14%). A total of 10 patients in the trastuzumab deruxtecan group had a confirmed complete response, and overall survival was longer in the trastuzumab deruxtecan group than in the physician's choice group (median, 12.5 months vs. 8.4 months). The median duration of confirmed response was longer with trastuzumab deruxtecan than with physician's choice of chemotherapy (11.3 months vs. 3.9 months). The findings of this trial confirm those observed in a phase 1 trial of trastuzumab deruxtecan in patients with advanced HER2-positive gastric cancer (response according to investigator assessment, 43.2%; median progression-free survival, 5.6 months).



Renin–Angiotensin–Aldosterone System Blockers and the Risk of Covid-19

BACKGROUND

A potential association between the use of angiotensin-receptor blockers (ARBs) and angiotensin-converting–enzyme (ACE) inhibitors and the risk of coronavirus disease 2019 (Covid-19) has not been well studied.

METHODS

We carried out a population-based case–control study in the Lombardy region of Italy. A total of 6272 case patients in whom infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was confirmed between February 21 and March 11, 2020, were matched to 30,759 beneficiaries of the Regional Health Service (controls) according to sex, age, and municipality of residence. Information about the use of selected drugs and patients' clinical profiles was obtained from regional databases of health care use. Odds ratios and 95% confidence intervals for associations between drugs and infection, with adjustment for confounders, were estimated by means of logistic regression.

CONCLUSIONS

In this large, population-based study, the use of ACE inhibitors and ARBs was more frequent among patients with Covid-19 than among controls because of their higher prevalence of cardiovascular disease. However, there was no evidence that ACE inhibitors or ARBs affected the risk of COVID-19.

Renin–Angiotensin–Aldosterone System Inhibitors and Risk of Covid-19

BACKGROUND

There is concern about the potential of an increased risk related to medications that act on the renin–angiotensin–aldosterone system in patients exposed to coronavirus disease 2019 (Covid-19), because the viral receptor is angiotensin-converting enzyme 2 (ACE2).

METHODS

We assessed the relation between previous treatment with ACE inhibitors, angiotensin-receptor blockers, beta-blockers, calcium-channel blockers, or thiazide diuretics and the likelihood of a positive or negative result on Covid-19 testing as well as the likelihood of severe illness (defined as intensive care, mechanical ventilation, or death) among patients who tested positive. Using Bayesian methods, we compared outcomes in patients who had been treated with these medications and in untreated patients, overall and in those with hypertension, after propensity-score matching for receipt of each medication class. A difference of at least 10 percentage points was prespecified as a substantial difference.

CONCLUSIONS

We found no substantial increase in the likelihood of a positive test for Covid-19 or in the risk of severe Covid-19 among patients who tested positive in association with five common classes of antihypertensive medications.

Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19

BACKGROUND

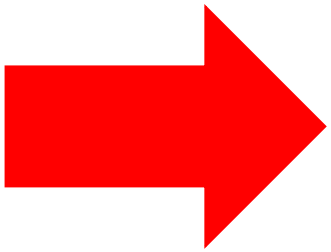
Coronavirus disease 2019 (Covid-19) may disproportionately affect people with cardiovascular disease. Concern has been aroused regarding a potential harmful effect of angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) in this clinical context.

METHODS

Using an observational database from 169 hospitals in Asia, Europe, and North America, we evaluated the relationship of cardiovascular disease and drug therapy with in-hospital death among hospitalized patients with Covid-19 who were admitted between December 20, 2019, and March 15, 2020, and were recorded in the Surgical Outcomes Collaborative registry as having either died in the hospital or survived to discharge as of March 28, 2020.

CONCLUSIONS

Our study confirmed previous observations suggesting that underlying cardiovascular disease is associated with an increased risk of in-hospital death among patients hospitalized with Covid-19. Our results did not confirm previous concerns regarding a potential harmful association of ACE inhibitors or ARBs with in-hospital death in this clinical context. (Funded by the William Harvey Distinguished Chair in Advanced Cardiovascular Medicine at Brigham and Women's Hospital.)



Expression of Concern: Mehra MR et al. Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2007621.

On May 1, 2020, we published "Cardiovascular Disease, Drug Therapy, and Mortality in Covid-19,"[1] a study of the effect of preexisting treatment with angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs) on Covid-19. This retrospective study used data drawn from an international database that included electronic health records from 169 hospitals on three continents. Recently, substantive concerns have been raised about the quality of the information in that database. We have asked the authors to provide evidence that the data are reliable. In the interim and for the benefit of our readers, we are publishing this Expression of Concern about the reliability of their conclusions.

Facit: Cardiovascular drugs do NOT appear to be an additive encumbrance in patients inflicted with Covid-19 disease

Covid-19 and Kidney Transplantation

At Montefiore Medical Center, we identified 36 consecutive adult kidney-transplant recipients who tested positive for Covid-19 between March 16 and April 1, 2020. A total of 26 recipients (72%) were male, and the median age was 60 years (range, 32 to 77). Fourteen recipients (39%) were black, and 15 recipients (42%) were Hispanic. Twenty-seven recipients (75%) had received a deceased-donor kidney; 34 recipients (94%) had hypertension, 25 (69%) had diabetes mellitus, 13 (36%) had a history of smoking tobacco or were current smokers, and 6 (17%) had heart disease. Thirty-five of the patients (97%) were receiving tacrolimus, 34 (94%) were receiving prednisone, and 31 (86%) were receiving mycophenolate mofetil or mycophenolic acid. Twenty-seven of the hospitalized patients (96%) had radiographic findings that were consistent with viral pneumonia, and 11 (39%) received mechanical ventilation. Six patients (21%) received renal replacement therapy. At a median follow-up of 21 days (range, 14 to 28), 10 of the 36 kidney-transplant recipients (28%) and 7 of the 11 patients who were intubated (64%) had died.

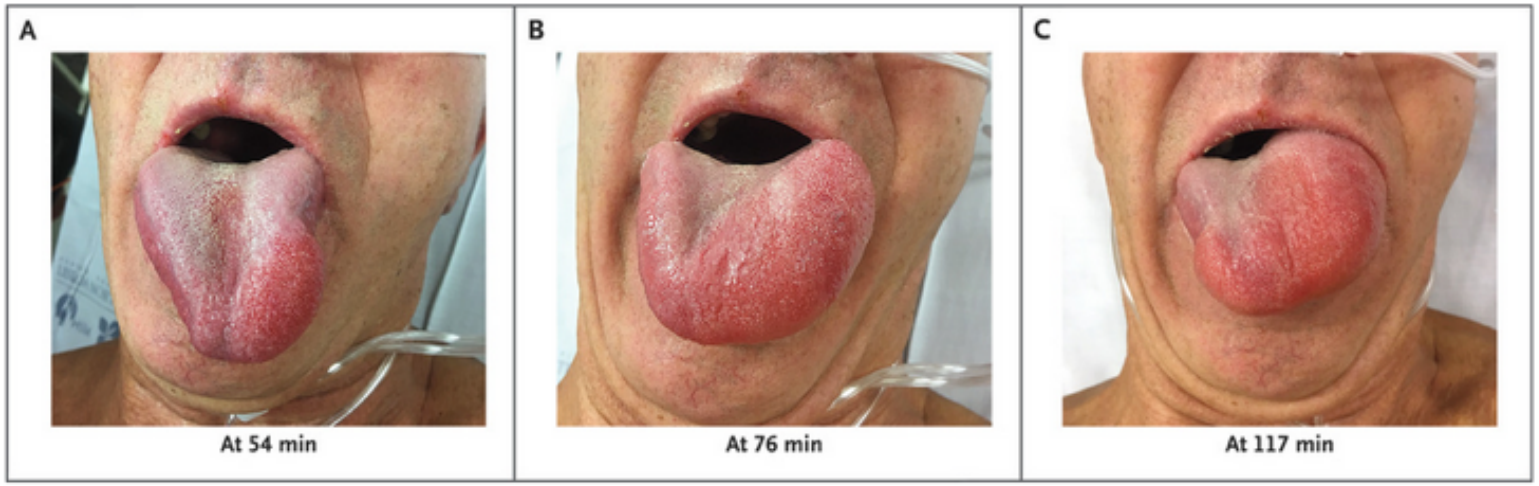
Variable	Value
Presenting symptom — no./total no. (%)	
Fever	21/36 (58)
Cough	19/36 (53)
Dyspnea	16/36 (44)
Myalgias	13/36 (36)
Diarrhea	8/36 (22)
Hospitalization — no./total no. (%)	28/36 (78)
Chest radiographic findings consistent with viral pneumonia — no./total no. (%)	27/28 (96)
Treatment — no./total no. (%)	
Withdrawal of antimetabolite	24/28 (86)
Withdrawal of tacrolimus	6/28 (21)
Hydroxychloroquine	24/28 (86)
Azithromycin	13/28 (46)
Leronlimab	6/28 (21)
Tocilizumab	2/28 (7)
High-dose glucocorticoids	2/28 (7)
Laboratory values	
White-cell count	
Median (range) — per mm^3	5300 (2100–14,700)
Patients with count <400 per mm^3 — no./total no. (%)	6/28 (21)
Lymphocyte count	
Median (range) — per mm^3	600 (100–1900)
Patients with count <1000 per mm^3 — no./total no. (%)	22/28 (79)
Platelet count	
Median (range) — per mm^3	146,000 (78,000–450,000)
Patients with count <150,000 per mm^3 — no./total no. (%)	12/28 (43)
CD3 cell count	
Median (range) — per mm^3	319 (34–1049)
Patients with count <706 per mm^3 — no./total no. (%)	19/28 (68)

Although effective treatment of Covid-19 is currently unknown, immunosuppressive management included withdrawal of an antimetabolite in 24 of 28 patients (86%). In addition, tacrolimus was withheld in 6 of the 28 severely ill patients (21%). Hydroxychloroquine was administered to 24 of these 28 patients (86%). Apixaban was administered to patients with d-dimer levels higher than 3.0 µg per milliliter. Six severely ill patients received the CCR5 inhibitor leronlimab (PRO 140, CytoDyn) on a compassionate-use basis, and 2 received the interleukin-6 receptor antagonist tocilizumab. Interleukin-6 levels were very elevated (range, 83 to 8175 pg per milliliter) when leronlimab was initiated (on day 0) in the 5 patients with elevated interleukin-6 levels; these levels decreased markedly 3 days later (range, 37 to 2022 pg per milliliter). However, only the 1 patient who had the lowest interleukin-6 level (at 83 pg per milliliter) remained in stable condition without intubation. Our results show a very high early mortality among kidney-transplant recipients with Covid-19 — 28% at 3 weeks as compared with the reported 1% to 5% mortality among patients with Covid-19 in the general population who have undergone testing in the United States and the reported 8 to 15% mortality among patients with Covid-19 who are older than 70 years of age.

CD4 cell count	
Median (range) — per mm^3	173 (6–507)
Patients with count <344 per mm^3 — no./total no. (%)	20/28 (71)
CD8 cell count	
Median (range) — per mm^3	132 (39–654)
Patients with count <104 per mm^3 — no./total no. (%)	8/28 (29)
Ferritin	
Median (range) — ng/ml	1230 (191–9259)
Patients with level >900 ng/ml — no./total no. (%)	10/28 (36)
D-dimer	
Median (range) — µg/ml	1.02 (0.32–5.19)
Patients with level >0.5 µg/ml — no./total no. (%)	16/28 (57)
Patients with level >3 µg/ml — no./total no. (%)	3/28 (11)
C-reactive protein	
Median (range) — mg/dl	7.9 (0.5–48.7)
Patients with level >5 mg/dl — no./total no. (%)	13/28 (46)
Procalcitonin	
Median (range) — ng/ml	0.2 (0.1–5.1)
Patients with level >0.2 ng/ml — no./total no. (%)	12/28 (43)
Lactate dehydrogenase	
Median (range) — U/liter	336 (158–309)
Patients with level >1.5 times upper limit of normal range — no./total no. (%)	10/28 (36)
Creatine kinase	
Median (range) — U/liter	145 (48–815)
Patients with level >200 U/liter — no./total no. (%)	9/28 (32)
Outcomes at a median of 21 days (range, 14–28) — no./total no. (%)	
Death	10/36 (28)
Intubation	11/28 (39)
Death after intubation	7/11 (64)
Renal replacement therapy	6/28 (21)
Remained hospitalized	12/28 (43)
Discharged from hospital	10/28 (36)

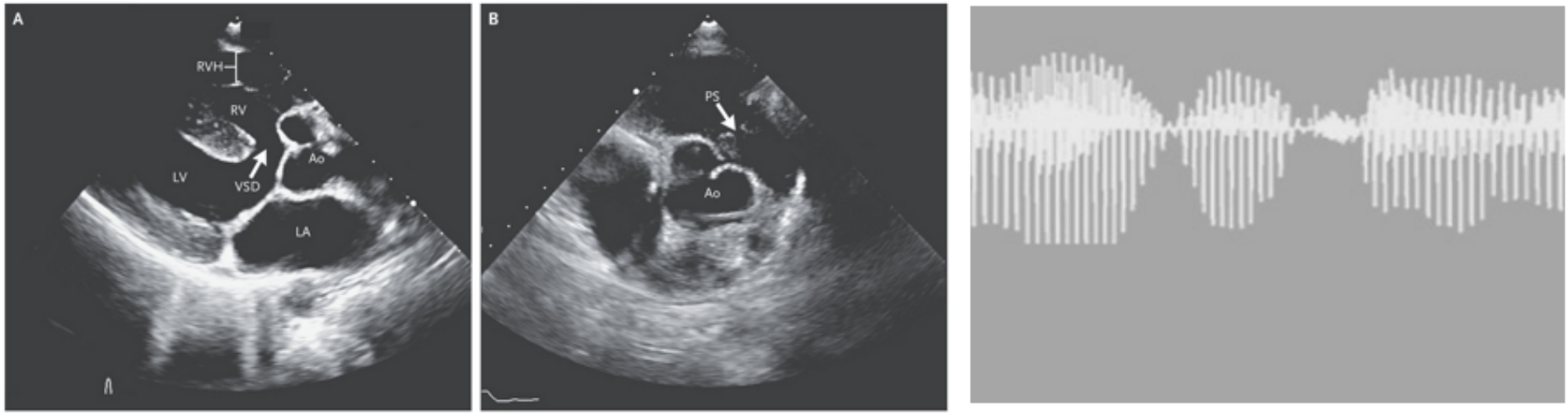
Mortality among kidney-transplant recipients with Covid-19 — 28% at 3 weeks as compared with the reported 1% to 5% mortality among patients with Covid-19 in the general population

Angioedema after t-PA Infusion



A 78-year-old man presented to the emergency department with weakness on the left side that had developed 90 minutes earlier. He had no history of use of angiotensin-converting–enzyme (ACE) inhibitors. An ischemic stroke in the territory of the right middle cerebral artery was diagnosed, and intravenous tissue plasminogen activator (t-PA) was initiated. Fifty-four minutes after the infusion was initiated, swelling of the left side of the tongue was noted (Panel A), and the t-PA was stopped. The swelling progressed (Panel B, 76 minutes after initiation of t-PA; Panel C, 117 minutes after initiation of t-PA). The patient had no shortness of breath or pain, and there was no evidence of airway compromise. Orolingual angioedema is a known potential adverse effect of t-PA. The swelling can be asymmetric at first and can develop in a location contralateral to the ischemic lesion. Orolingual angioedema may occur most often in patients who have had a stroke that involved the insula or in patients who have received treatment with an ACE inhibitor. The mechanism is incompletely understood. Treatment in this case included intravenous antihistamines and glucocorticoids, without advanced airway management. The tongue swelling resolved, but at a follow-up visit 3 months after presentation, some neurologic deficits resulting from the stroke remained.

Unrepaired Tetralogy of Fallot in Adulthood



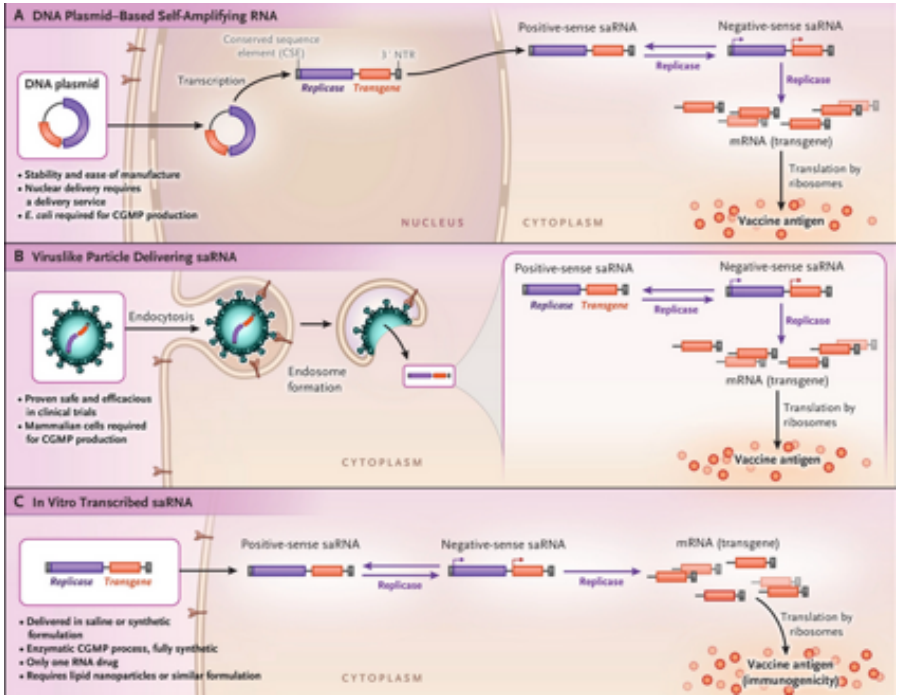
A 29-year-old man who had recently immigrated to the United States presented to the cardiology clinic with worsening exertional dyspnea, visual blurring, and headaches. These symptoms had been present since childhood, but he had not received regular medical care and the condition had not been diagnosed. The patient had found that his symptoms lessened when he squatted or after 30 minutes of rest. The oxygen saturation was 92% while the patient was breathing ambient air. The physical examination was notable for a harsh holosystolic murmur at the left sternal border with a sternal heave. There was no evidence of digital clubbing. Electrocardiography showed sinus rhythm with a right bundle-branch block. Laboratory studies showed a hemoglobin level of 20 g per deciliter (reference range, 13 to 17). Echocardiography (Panel A) showed the aorta (Ao) overriding a large ventricular septal defect (VSD) and right ventricular hypertrophy (RVH), along with subpulmonic stenosis (PS) (Panel B), all of which confirmed the diagnosis of tetralogy of Fallot. The characteristic murmur is due to right ventricular outflow obstruction. Squatting maneuvers increase systemic vascular resistance, resulting in reversal of shunting at the ventricular septal defect and therefore a reduction in symptoms. The patient underwent surgical repair including pulmonary valvotomy, closure of the septal defect, resection of muscle bundles in the right ventricular outflow tract, and patch augmentation of the infundibulum and main pulmonary artery. Two months later, he was recovering well without further episodes of dyspnea, visual disturbance, or headache.

Amplifying RNA Vaccine Development

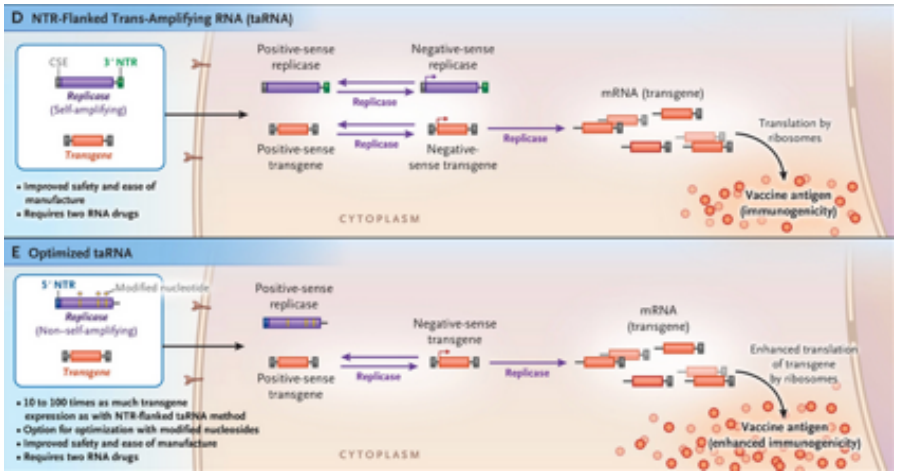
In the early 1990s, direct injection of nucleic acids (RNA or DNA) into the muscles of mice led to in vivo expression of proteins encoded by the injected nucleic acid. This finding, together with studies showing the elicitation of immune responses and protection against infection by means of the delivery of DNA that encodes pathogen proteins into the skin or muscle of mice, seeded the field of vaccinology such that only the coding sequence of a gene encoding a protein of a pathogen is necessary to create a vaccine. Early studies showed that both DNA and RNA vaccines induced immune responses. Delivery by plasmid (a small, circular extrachromosomal DNA molecule) initially emerged as the dominant strategy, and although the first clinical studies involving humans were mostly disappointing, advances in delivery and in the incorporation of immunostimulatory sequences (genetic adjuvants) have spurred new clinical trials and have informed strategies to develop vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (Covid-19).

Recent interest in messenger RNA (mRNA) vaccines has been fueled by methods that increase mRNA stability and protein production and improve delivery. These methods include the use of modified nucleosides as well as the development of nanoparticle-delivery technologies that stabilize mRNA, enhance cellular uptake, and improve the bioavailability of the mRNA once it is inside the cell. Avoidance of the risk of integration into the host genome is considered a comparative advantage of mRNA (with respect to DNA vaccines), although extensive studies have eased this concern about DNA vaccines. A clear advantage of mRNA vaccines is that, unlike DNA vaccines, they do not need to enter the nucleus to express the antigen. Instead, once inside the nucleus, a DNA vaccine will produce many copies of mRNA molecules, resulting in the production of more antigen per transfected cell. Of interest, then, are self-amplifying RNA vaccines, such as those involved in the strategy described by Beissert et al. to increase the yield of antigen expressed by mRNA vaccines.

Self-amplifying RNA vaccines are derived from the genome backbone of an alphavirus in which the genes encoding the viral RNA replication machinery are intact but those encoding viral structural proteins are replaced with a transgene encoding the vaccine antigen.



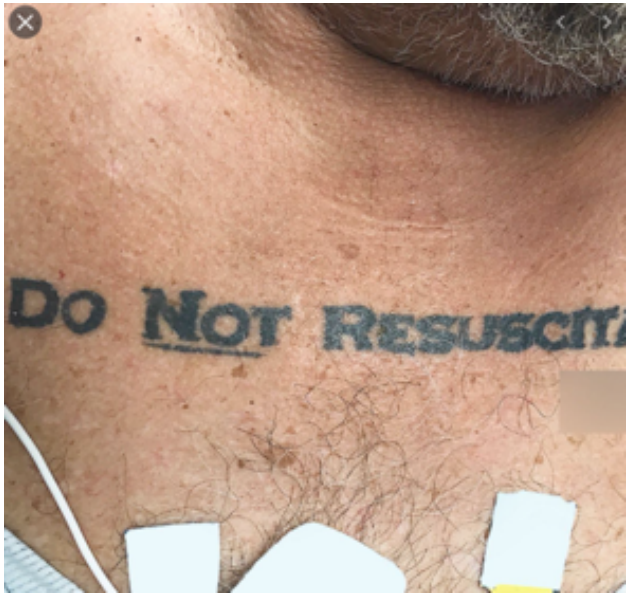
Obtaining Antigen Expression by Alphaviral Replicon RNA.
Plasmid DNA carries replicase genes (encoding proteins that replicate RNA) and the transgene (which encodes the vaccine antigen) into the nucleus, where it is transcribed, generating replicon RNA (the part that encodes replicase proteins). Replicon RNA is then transported to the cytoplasm, which is then followed by RNA self-replication (also called self-amplification), messenger RNA (mRNA) production, and translation of vaccine antigen (red) (Panel A). Viruslike RNA particles that are produced in a separate packaging step (not shown) deliver replicon RNA to the cytoplasm by means of receptor-mediated endocytosis (Panel B). In vitro transcribed replicon RNA is delivered to cells either in saline or in synthetic formulations (Panel C). Common to each approach, the replicase protein complex is translated from the upstream two thirds of the replicon RNA genome (purple). The replicase initiates RNA-dependent RNA polymerase–mediated transcription of a negative strand (−RNA) using the 3′ nontranslated (NTR) region (green) and, using the −RNA as a template, also transcribes a positive strand (+RNA) from the 5′ NTR region (green), as well as a subgenomic promoter (arrow) to initiate transcription into mRNA. Many antigen proteins (Ag) are translated directly from the mRNA by cytoplasmic ribosomes.



A dual strategy was described recently by Beissert and colleagues in which a replicon RNA encodes the replicase machinery “in trans” to the co-delivered antigen-encoding RNA (Panel D). The authors found immunogenicity when the replicase genes were flanked by NTR regions to facilitate intracellular replication (Panel E). They observed enhanced immunogenicity when the replicase genes were optimized for translational efficiency (and lacked flanking regions). CGMP denotes Current Good Manufacturing Processes, and *E. coli Escherichia coli*.

With the emergence of the Covid-19 pandemic, an mRNA vaccine was the first to enter clinical trials, with the first volunteers receiving the vaccine within 10 weeks after the genetic sequence of SARS-CoV-2 was released (www.modernatx.com/modernas-work-potential-vaccine-against-covid-19. opens in new tab). Nucleic acid vaccines are now a major hope for solving this pandemic crisis. This comes as no surprise. From their earliest conception, nucleic acid vaccines were recognized as a possible solution for a rapid pandemic response. The need for only the sequence of a pathogen in order to generate the vaccine and its simplicity in manufacture have long been recognized as superpowers in nucleic acid vaccines with regard to the delivery of a rapid response to an emerging epidemic. The ability of self-amplifying RNA vaccines, and now trans-amplifying RNA vaccines, to provide amplified and durable production of antigen in vivo, coupled with potent inherent innate immune-stimulating properties, adds to these powers and may provide the dose-sparing (i.e., getting the same immune responses with smaller doses of vaccine) that will probably be needed to meet global demands. We can only hope that their deployment will render the Covid-19 pandemic crisis into a more manageable challenge, saving lives and decreasing morbidity.

Eine Do-not-resuscitate-Anordnung, kurz DNR-Anordnung, ist eine mündlich oder schriftlich festgelegte Weisung an medizinisches Personal, dass eine Person grundsätzlich keine kardiopulmonale Reanimation (CPR) erhalten möchte.
Durch die zunehmenden Möglichkeiten der Lebensverlängerung wird die Frage nach dem Verzicht auf solche Maßnahmen relevant. Eine DNR-Anordnung soll in Notfallsituationen dazu dienen, den Patientenwillen umzusetzen. Aktuell (2019) gibt es keine allgemein bekannten Richt- oder Leitlinien zur DNR-Anordnung. Ob neben der CPR auch auf weitere Untersuchungen oder Behandlungen verzichtet werden soll, wird unterschiedlich bewertet. So wird mit einer DNR-Anordnung im weiteren Sinne oft auch die Einschränkung von Behandlungsumfang und -invasivität auf ein "sinnvolles" Maß gemeint.
Neben dem Patientenwunsch kann auch die medizinische Aussichtslosigkeit von Maßnahmen bzgl. des Erreichen eines therapeutischen Ziels eine Begründung für eine DNR-Anordnung sein.
Eine DNR-Anordnung darf nur durch einen erfahrenen Arzt erteilt werden, in der Klinik in der Regel durch einen Facharzt, im ambulanten Bereich vor allem durch den behandelnden Hausarzt. Neben dem Patienten sollten Familienmitglieder und Pflegepersonal in die Entscheidung einbezogen werden. In dem Gespräch werden Krankheitssituation, Prognose und Therapieziele besprochen und eine ärztliche Empfehlung abgegeben.
Die DNR-Anordnung muss so gestaltet sein, dass man auch unter Zeitdruck den Inhalt schnell und eindeutig erfassen kann.
Grundsätzlich sollten sie mit einer Gültigkeitsdauer versehen werden und in bestimmten zeitlichen Abständen reevaluiert werden. Eine DNR-Anordnung ist nicht gültig, wenn der Empfänger der Mitteilung relevante Zweifel bezüglich der Gültigkeit oder Authentizität hat. Bei jeder Änderung der prognostischen Situation bzw. Rahmenbedingungen ist eine Neubewertung notwendig.



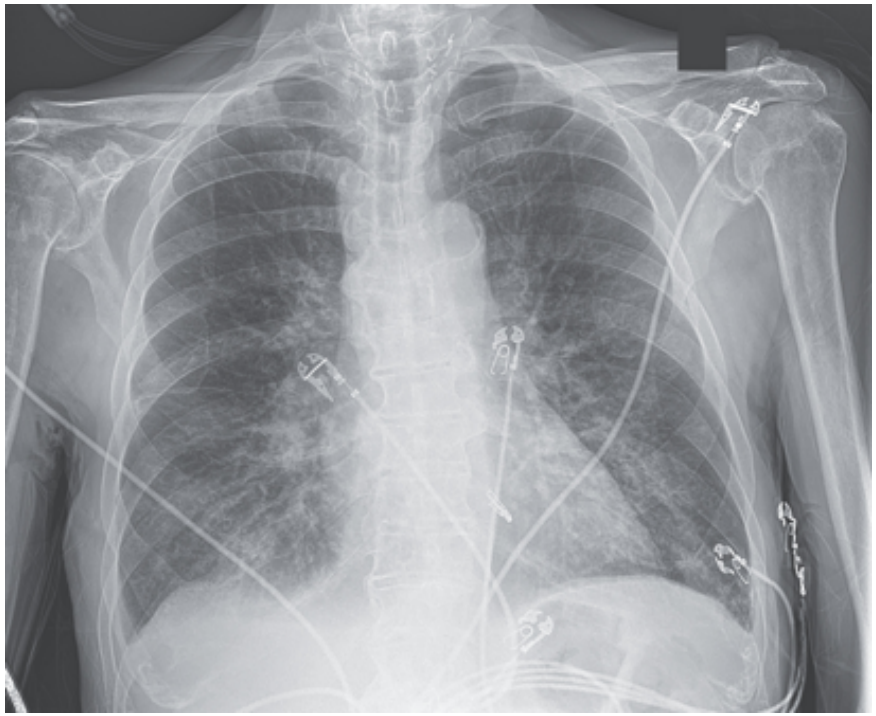
A 74-Year-Old Man with Acute Respiratory Failure and Unclear Goals of Care

A 74-year-old man with mantle-cell lymphoma was admitted to this hospital during the coronavirus disease 2019 (Covid-19) pandemic because of acute respiratory failure. One day before this admission, productive cough and dyspnea developed. The next day, when the patient was being evaluated at home by a visiting nurse, the oxygen saturation was 85% while he was breathing ambient air. Emergency medical services were called, and on their arrival, treatment with continuous positive airway pressure was initiated. The patient was transported by ambulance to this hospital. Four years before this admission, gastrointestinal bleeding had occurred because of a duodenal ulcer, resulting in hemorrhagic shock; 3 years before this admission, severe gastrointestinal bleeding had recurred because of an esophageal ulcer. At that time, an inpatient medical team had discussed goals of care with the patient, and a status of "do not resuscitate" (DNR) had been assigned. Three weeks before this admission, the patient had undergone transcatheter mitral valve repair for the treatment of mitral regurgitation. One week later, venetoclax therapy was initiated. Shortness of breath developed, and furosemide was administered. An inpatient medical team discussed goals of care with the patient, who explained that he had agreed to a DNR status several years earlier, when he had been "very sick and near death" and "in a different place"; a new status of "full code" was assigned.

Variable	Reference Range†	On Arrival, Emergency Department
Hematocrit (%)	41.0–53.0	28.5
Hemoglobin (g/dl)	13.5–17.5	8.8
White-cell count (per μl)	4500–11,000	9900
Differential count (per μl)		
Neutrophils	1800–7700	5020
Lymphocytes	1000–4800	3120
Monocytes	200–1200	1650
Eosinophils	0–900	10
Basophils	9–300	20
Platelet count (per μl)	130,000–400,000	176,000
Sodium (mmol/liter)	135–145	134
Potassium (mmol/liter)	3.4–5.0	5.0
Chloride (mmol/liter)	98–108	94
Carbon dioxide (mmol/liter)	23–32	27
Anion gap (mmol/liter)	3–17	13
Urea nitrogen (mg/dl)	8–25	40
Creatinine (mg/dl)	0.60–1.50	2.09
Glucose (mg/dl)	70–110	95
Alanine aminotransferase (U/liter)	10–55	17
Aspartate aminotransferase (U/liter)	10–40	31
Alkaline phosphatase (U/liter)	45–115	72
C-reactive protein (mg/liter)	<8.0	38.4
Lactic acid (mmol/liter)	0.5–2.0	1.9
Lactate dehydrogenase (U/liter)	110–210	262
D-dimer (ng/ml)	<500	1041

Venetoclax ist ein Arzneistoff für die Behandlung von Blutkrebs. Er ist der erste Vertreter der Wirkstoffklasse der Bcl-2-Hemmer und ist oral wirksam.

Furosemide, ceftriaxone, azithromycin, and oseltamivir were administered intravenously. Ninety minutes after the patient arrived in the emergency department, the oxygen saturation decreased to 74%, and the rate of supplemental oxygen was increased to 15 liters per minute. Preparations were made for intubation of the trachea and initiation of mechanical ventilation. The emergency department team was concerned about the likelihood of benefit of cardiopulmonary resuscitation (CPR) and intubation; an urgent palliative care consultation was requested.



Initial Chest Radiograph. A chest radiograph obtained on evaluation in the emergency department shows bibasilar patchy and interstitial opacities and small bilateral pleural effusions.

Prognosis and Goals of Care

I learned that this patient had some viable treatment options for his cancer but would probably die from the disease in less than a year. His oncologist thought that the respiratory failure was most likely due to congestive heart failure related to a poorly functioning mitral valve. Several weeks before this admission, the patient had been hospitalized with similar respiratory symptoms, which had improved with diuresis. The oncologist said that the patient had expressed a desire to try additional courses of cancer treatment and that intubation would be consistent with the patient's goal of getting back to baseline. However, we were concerned about the possibility that the patient had respiratory disease due to Covid-19, in which case he would probably not survive.

I put on personal protective equipment, called the patient's wife on my phone, and went into the room. The patient was breathing with the assistance of a nonrebreather face mask. He appeared frail and was having trouble talking. I briefly explained to him and his wife what he already knew — that he was having difficulty breathing and may soon need to be intubated. He replied to my medical summary with one-word answers, indicating that he wanted to "try" and that he was "positive." I said to him that I understood he wanted to receive medical care so that he could try to get better. He nodded in agreement.

During our conversation, the patient's wife confirmed my sense that the priority was to get through this episode of illness, and the patient again confirmed this goal with a nod. Therefore, I recommended the treatments that I thought would help him the most, including diuretic and antibiotic agents, as well as intubation if needed. I then discussed the treatments that I thought would be unlikely to help him. I explained that because of his overall health, if he became even sicker and began to die, he would be unlikely to survive CPR. I recommended to him that, under those circumstances, we focus on allowing a natural death to occur and that he have a DNR order in place. He agreed with this recommendation. I also explained what we knew about Covid-19 — that older adults with medical issues were unlikely to survive. Thirty minutes after this discussion, the patient was intubated in the emergency department and transferred to the intensive care unit (ICU).

Discussion of Management

Health care providers are frequently required to talk with very sick patients about CPR and intubation. These conversations are challenging. As clinicians, we deeply value patients' autonomy, and we want to do everything we can to help them get better. However, we do not want to cause harm with aggressive medical care that is highly unlikely to provide substantial benefit. As a result, we feel conflicted.

Adding to the complexity is the risk that patients will have certain misconceptions that lead them to choose unbeneficial treatments. On popular television medical dramas, the rate of survival immediately after CPR is 70%. Among those who survive, 72% are discharged from the hospital. Discussions about advance directives rarely occur. In real life, only 10% of patients who have out-of-hospital sudden cardiac arrest survive to hospital discharge, with many survivors having neurologic impairment. This rate is even lower among patients with serious coexisting conditions.

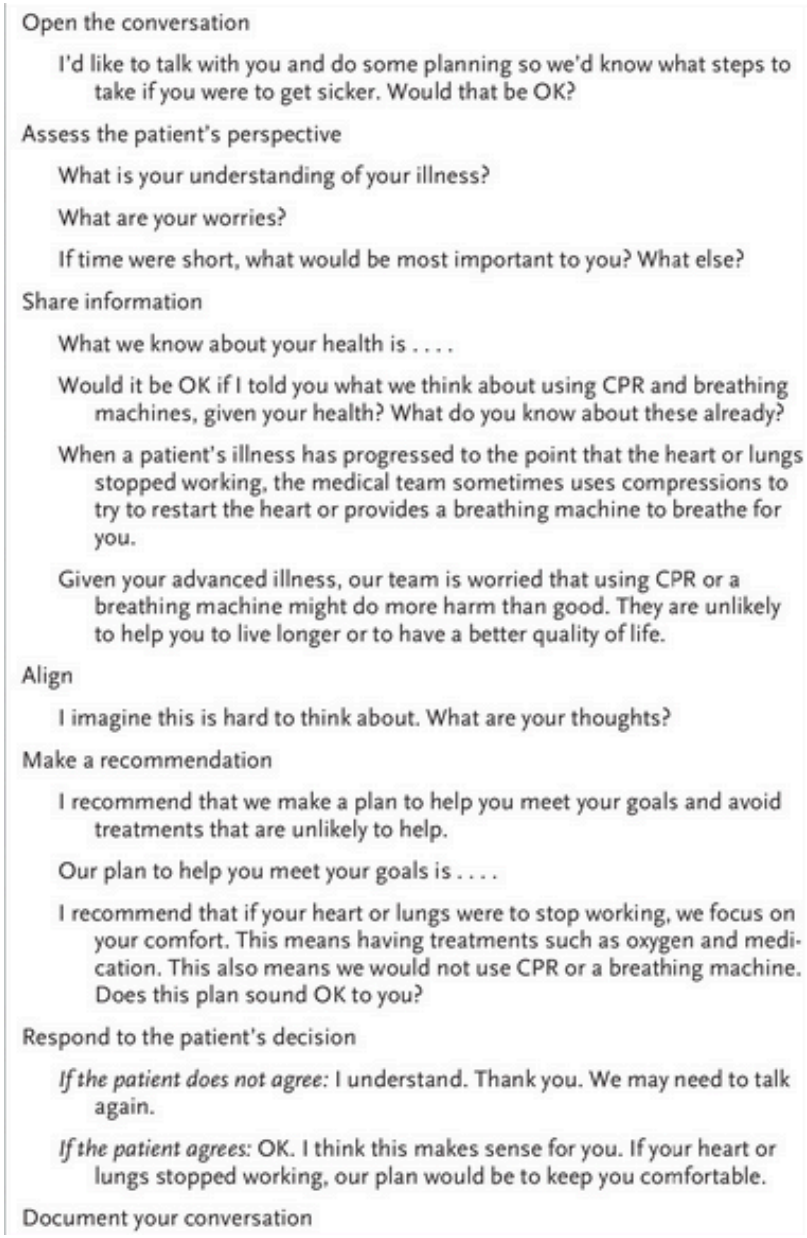
Goal for the Conversation	Indication
Information gathering	The patient has a stable condition and is likely to benefit from CPR and intubation, the patient has established a preference to limit CPR and intubation that needs to be confirmed, or it is the wrong time for a more in-depth conversation.
Shared decision making	The patient has an advancing illness, and it is unclear whether the benefits of CPR and intubation would outweigh the burdens because at this point the decision depends heavily on the patient's values and goals.
Informed consent	The patient is at risk for decompensation and death and is unlikely to benefit from CPR and intubation.

Informed consent

If the patient is at risk for decompensation and death and our clinical judgment is that CPR or intubation is unlikely to be beneficial, then we shift to an informed-consent conversation in which we focus on our assessment of the low likelihood of benefit and the high risk.

In our willingness to make recommendations against medical interventions, we tend to treat decisions about CPR and intubation differently from decisions about other interventions. There are at least four reasons for this. First, because death might come sooner if the patient forgoes these interventions, we may think the decision is more value-laden than others. Second, because there is an anticipated delay between the discussion and the point at which the decision may become relevant, we may think the difficult recommendation is less urgent. Third, because we as the clinicians discussing the interventions are often unlikely to be the ones providing them, we may have a diminished a sense of the negative consequences of the interventions, which further reduces the urgency to recommend against them. Finally, we often worry that making recommendations against CPR and intubation will damage the relationship with the patient if the patient does not agree and will create an awkward or upsetting situation.

On the day after admission, testing of a nasopharyngeal specimen was negative for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2, the virus that causes Covid-19) but was positive for influenza A virus. Two days after presentation, after the family had conversations with the ICU team, the patient was extubated and died peacefully with full comfort measures.



Open the conversation

I'd like to talk with you and do some planning so we'd know what steps to take if you were to get sicker. Would that be OK?

Assess the patient's perspective

What is your understanding of your illness?

What are your worries?

If time were short, what would be most important to you? What else?

Share information

What we know about your health is . . . .

Would it be OK if I told you what we think about using CPR and breathing machines, given your health? What do you know about these already?

When a patient's illness has progressed to the point that the heart or lungs stopped working, the medical team sometimes uses compressions to try to restart the heart or provides a breathing machine to breathe for you.

Given your advanced illness, our team is worried that using CPR or a breathing machine might do more harm than good. They are unlikely to help you to live longer or to have a better quality of life.

Align

I imagine this is hard to think about. What are your thoughts?

Make a recommendation

I recommend that we make a plan to help you meet your goals and avoid treatments that are unlikely to help.

Our plan to help you meet your goals is . . . .

I recommend that if your heart or lungs were to stop working, we focus on your comfort. This means having treatments such as oxygen and medication. This also means we would not use CPR or a breathing machine. Does this plan sound OK to you?

Respond to the patient's decision

If the patient does not agree: I understand. Thank you. We may need to talk again.

If the patient agrees: OK. I think this makes sense for you. If your heart or lungs stopped working, our plan would be to keep you comfortable.

Document your conversation

nature medicine

LETTERS

https://doi.org/10.1038/s41591-020-0962-9

Check for updates

Age-dependent effects in the transmission and control of COVID-19 epidemics

The COVID-19 pandemic has shown a markedly low proportion of cases among children[1–4]. Age disparities in observed cases could be explained by children having lower susceptibility to infection, lower propensity to show clinical symptoms or both. We evaluate these possibilities by fitting an age-structured mathematical model to epidemic data from China, Italy, Japan, Singapore, Canada and South Korea. We estimate that susceptibility to infection in individuals under 20 years of age is approximately half that of adults aged over 20 years, and that clinical symptoms manifest in 21% (95% credible interval: 12–31%) of infections in 10- to 19-year-olds, rising to 69% (57–82%) of infections in people aged over 70 years. Accordingly, we find that interventions aimed at children might have a relatively small impact on reducing SARS-CoV-2 transmission, particularly if the transmissibility of subclinical infections is low. Our age-specific clinical fraction and susceptibility estimates have implications for the expected global burden of COVID-19, as a result of demographic differences across settings. In countries with younger population structures—such as many low-income countries—the expected per capita incidence of clinical cases would be lower than in countries with older population structures, although it is likely that comorbidities in low-income countries will also influence disease severity. Without effective control measures, regions with relatively older populations could see disproportionally more cases of COVID-19, particularly in the later stages of an unmitigated epidemic.

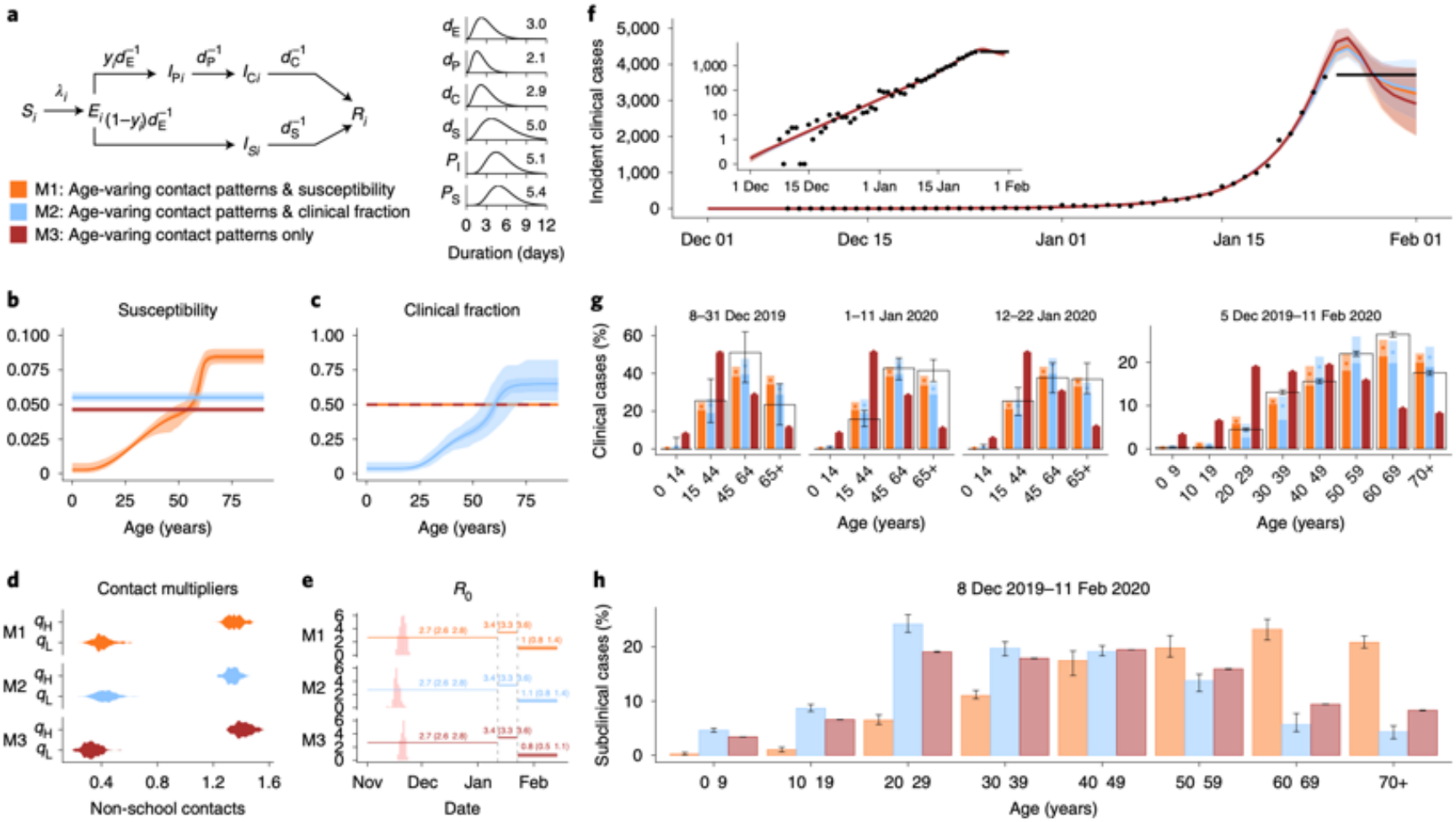


Fig. 1 | Fit of different model variants to data from Wuhan City, China. a, Model diagram and duration of disease states in days, where *d* parameters represent the duration of time in each disease state (see Methods), y_i is the fraction of infections that manifest as clinical cases in age group *i*, λ_i is the force of infection in age group *i*, P_I is the incubation period and P_S is the serial interval (see Methods). **b**, Susceptibility by age for the three models, with mean (lines), 50% (darker shading) and 95% (lighter shading) credible intervals shown. Age-specific values were estimated for model 1 (orange). Susceptibility is defined as the probability of infection on contact with an infectious person. **c**, Clinical fraction (y_i) by age for the three models. Age-specific values were estimated for model 2 (blue) and fixed at 0.5 for models 1 and 3. **d**, Fitted contact multipliers for holiday (q_H) and restricted periods (q_L) for each model showed an increase in non-school contacts beginning on 12 January (start of the Lunar New Year) and a decrease in contacts following restrictions on 23 January. **e**, Estimated R_0 values for each model. The red barplot shows the inferred window of spillover of infection. **f**, Incident reported cases (black) and modeled incidence of reported clinical cases for the three models fitted to cases reported by China Centers for Disease Control (CCDC)[1] with onset on or before 1 February 2020. Lines mark the mean and the shaded window is the 95% highest density interval (HDI). **g**, Age distribution of cases by onset date as fitted to the age distributions reported by Li et al.[27] (first three panels) and CCDC[1] (fourth panel). Data are shown in open bars and model predictions in filled bars, where the dot marks the mean posterior estimate. **h**, Implied distribution of subclinical cases by age for each model. Credible intervals on modeled values show the 95% HDIs; credible intervals on data for **g** and **h** show 95% HDIs for the proportion of cases in each age group.

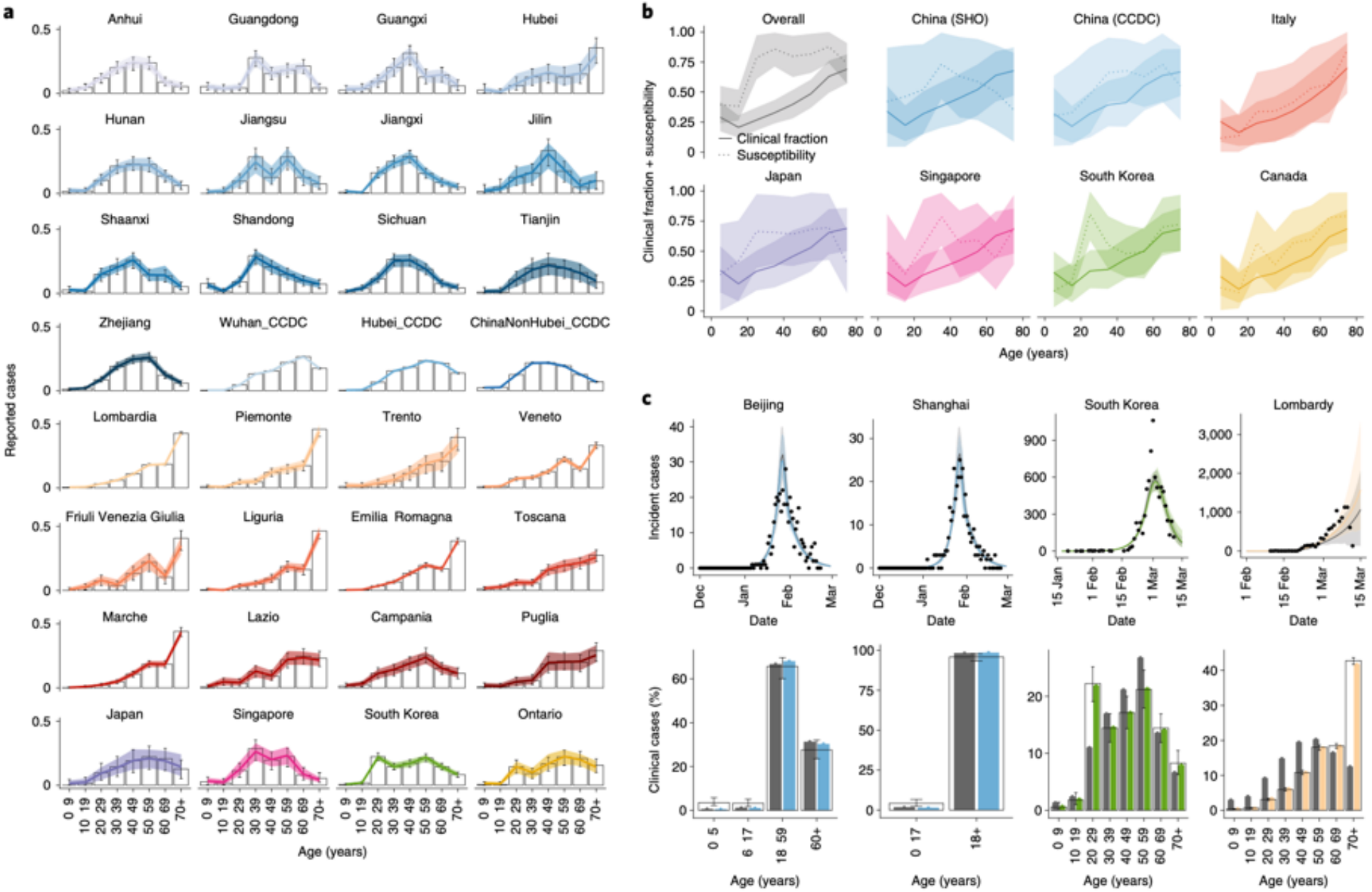


Fig. 2 | Estimating the age-specific symptomatic rate from age-specific case counts for six countries. a, Age-specific reported cases from 13 provinces of China, 12 regions of Italy, Japan, Singapore, South Korea and Ontario, Canada. Open bars are data and the colored lines are model fits with 95% HDI. **b**, Fitted mean (lines) and 95% HDI (shaded areas) for the age distribution in the clinical fraction (solid lines) and the age distribution of susceptibility (dashed lines) for all countries. The overall consensus fit is shown in gray. **c**, Fitted incidence of confirmed cases and resulting age distribution of cases using either the consensus (gray) or country-specific (color) age-specific clinical fraction from **b**.

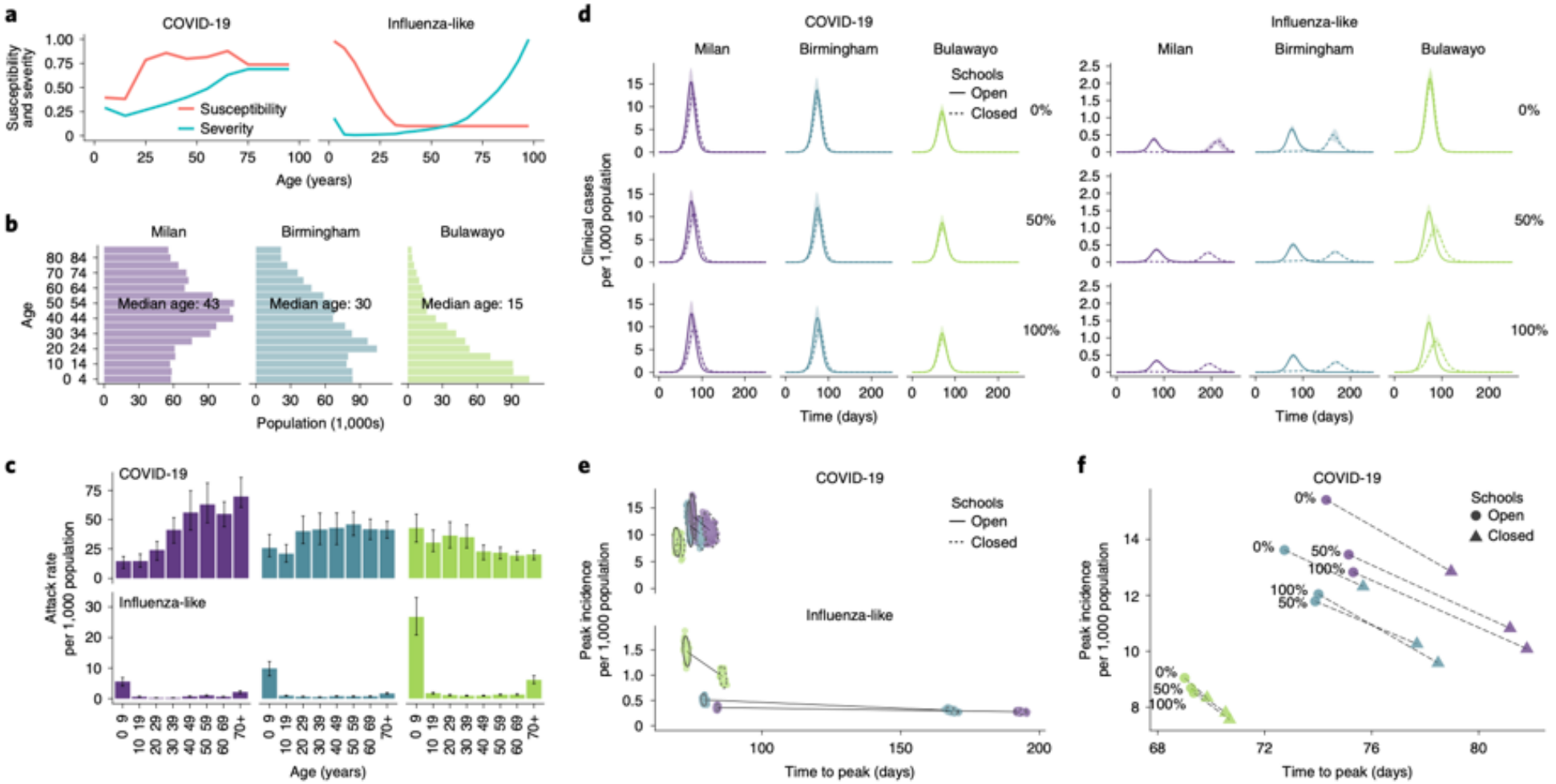


Fig. 3 | Effect of school closure under different demographics and subclinical infectiousness. a, Age dependence in clinical fraction (severity) and susceptibility to infection on contact for COVID-19 and for the influenza-like scenarios (simplified, based on ref. [44]) considered here. **b**, Age structure for the three exemplar cities. **c**, Age-specific clinical case rate for COVID-19 and influenza-like infections, assuming 50% infectiousness of subclinical infections. **d**, Daily incidence of clinical cases in exemplar cities for COVID-19 versus influenza-like infections. R_0 is fixed at 2.4. The rows show the effect of varying the infectiousness of subclinical infections to be 0%, 50% or 100% as infectious as clinical cases while keeping R_0 fixed. **e**, Change in peak timing and peak cases for the three cities, for either COVID-19 or influenza-like infections. **f**, Change in median COVID-19 peak timing and peak cases for the three cities, depending on the infectiousness of subclinical infections.

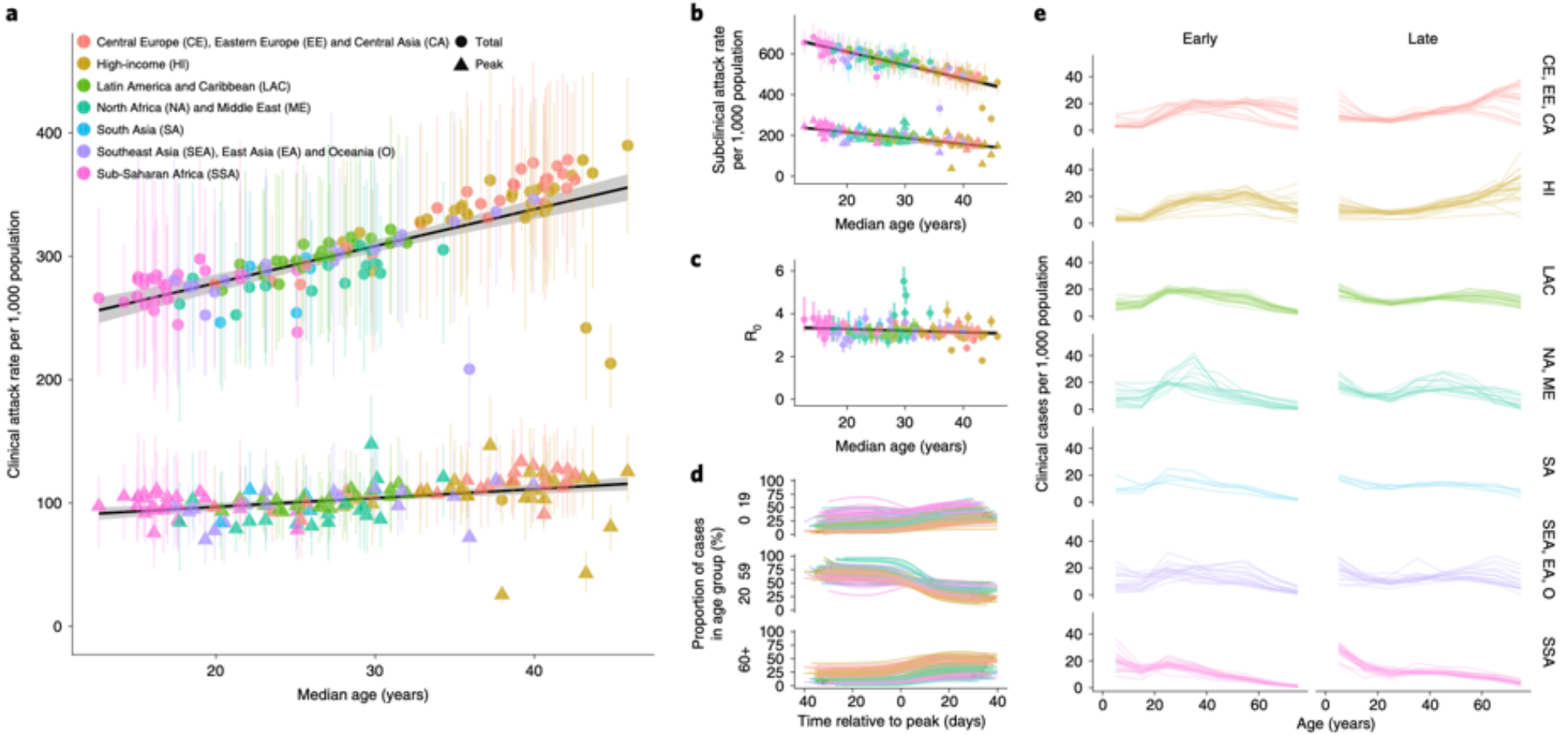


Fig. 4 | Implications for global preparedness. a, Expected clinical case attack rate (mean and 95% HDI) and peak in clinical case incidence for 146 countries in the Global Burden of Disease (GBD) country groupings[50] for an unmitigated epidemic. **b**, Expected subclinical case attack rate and peak in subclinical cases. **c**, Estimated basic reproduction number (R_0) in the capital city of each country assuming the age-specific clinical fraction shown in Fig. 2b and 50% infectiousness of subclinically infected people. **d**, Proportion of clinical cases in each age group at times relative to the peak of the epidemic. The 146 city epidemics were aligned at the peak, and colors mark the GBD groupings in **a**. **e**, Age distribution of the first and last thirds of clinical cases for 146 countries in GBD country groupings.

	Policy summary
Background	The distribution of confirmed COVID-19 cases has shown strong age dependence, with notably few cases in children. This could be because younger ages are less susceptible to infection and/or are less prone to showing clinical symptoms when infected. We used dynamic transmission models fitted to a range of available data on the age distribution of reported cases, and to studies that looked for infections among close contacts, to estimate the age-specific susceptibility to SARS-CoV-2 infection and the age-specific fraction of infections that develop full clinical symptoms of COVID-19.
Main findings and limitations	We find that those aged under 20 years are roughly half as susceptible to infection as those over 20 years of age, and that 79% of infections are asymptomatic or paucisymptomatic (that is, subclinical) in 10- to 19-year-olds, compared with 31% in those over 70 years of age. As with all modeling studies, further data generated during the epidemic could change our parameter estimates. Population mixing measured in contact surveys might not be representative of contact patterns made during the early phase of local epidemics. However, our estimates are consistent across countries and intervention contexts.
Policy implications	These results have implications for the likely effectiveness of school closures in mitigating SARS-CoV-2 transmission, in that these might be less effective than for other respiratory infections. There are also implications for the global expected burden of clinical cases; countries with a large number of children might need to account for decreased susceptibility and severity in burden projections.

Clinical impact of COVID-19 on patients with cancer (CCC19): a cohort study

Summary

Background Data on patients with COVID-19 who have cancer are lacking. Here we characterise the outcomes of a cohort of patients with cancer and COVID-19 and identify potential prognostic factors for mortality and severe illness.

Methods In this cohort study, we collected de-identified data on patients with active or previous malignancy, aged 18 years and older, with confirmed severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection from the USA, Canada, and Spain from the COVID-19 and Cancer Consortium (CCC19) database for whom baseline data were added between March 17 and April 16, 2020. We collected data on baseline clinical conditions, medications, cancer diagnosis and treatment, and COVID-19 disease course. The primary endpoint was all-cause mortality within 30 days of diagnosis of COVID-19. We assessed the association between the outcome and potential prognostic variables using logistic regression analyses, partially adjusted for age, sex, smoking status, and obesity. This study is registered with ClinicalTrials.gov, NCT04354701, and is ongoing.

Findings Of 1035 records entered into the CCC19 database during the study period, 928 patients met inclusion criteria for our analysis. Median age was 66 years (IQR 57–76), 279 (30%) were aged 75 years or older, and 468 (50%) patients were male. The most prevalent malignancies were breast (191 [21%]) and prostate (152 [16%]). 366 (39%) patients were on active anticancer treatment, and 396 (43%) had active (measurable) cancer. At analysis (May 7, 2020), 121 (13%) patients had died. In logistic regression analysis, independent factors associated with increased 30-day mortality, after partial adjustment, were: increased age (per 10 years; partially adjusted odds ratio 1·84, 95% CI 1·53–2·21), male sex (1·63, 1·07–2·48), smoking status (former smoker *vs* never smoked: 1·60, 1·03–2·47), number of comorbidities (two *vs* none: 4·50, 1·33–15·28), Eastern Cooperative Oncology Group performance status of 2 or higher (status of 2 *vs* 0 or 1: 3·89, 2·11–7·18), active cancer (progressing *vs* remission: 5·20, 2·77–9·77), and receipt of azithromycin plus hydroxychloroquine (*vs* treatment with neither: 2·93, 1·79–4·79; confounding by indication cannot be excluded). Compared with residence in the US-Northeast, residence in Canada (0·24, 0·07–0·84) or the US-Midwest (0·50, 0·28–0·90) were associated with decreased 30-day all-cause mortality. Race and ethnicity, obesity status, cancer type, type of anticancer therapy, and recent surgery were not associated with mortality.

Interpretation Among patients with cancer and COVID-19, 30-day all-cause mortality was high and associated with general risk factors and risk factors unique to patients with cancer. Longer follow-up is needed to better understand the effect of COVID-19 on outcomes in patients with cancer, including the ability to continue specific cancer treatments.

	Analysable population (n=928)
Age, years*	
Median	66 (57–76)
Range	18 to >90
<65	412 (44%)
65–74	237 (26%)
≥75	279 (30%)
Sex	
Female	459 (49%)
Male	468 (50%)
Not specified	1 (<1%)
Race and ethnicity†	
Non-Hispanic white	460 (50%)
Non-Hispanic black	148 (16%)
Hispanic	150 (16%)
Other or unknown	128 (14%)
Data missing	42 (5%)
Region of patient residence‡	
US-Northeast	375 (40%)
US-Midwest	203 (22%)
US-South	117 (13%)
US-West	116 (13%)
Canada	49 (5%)
Spain	68 (7%)
Smoking status†	
Never smoked	469 (51%)
Former smoker	326 (35%)
Current smoker	43 (5%)
Unknown	57 (6%)
Data missing	33 (4%)
Obesity status†	
Not specified	720 (78%)
Obese	172 (19%)
Data missing	36 (4%)
Number of comorbidities†	
0	132 (14%)
1	202 (22%)
2	231 (25%)
3	117 (13%)
≥4	192 (21%)
Unknown	23 (2%)
Data missing	31 (3%)
Type of malignancy§	
Solid tumours	758 (82%)
Breast	191 (21%)
Prostate	152 (16%)
Gastrointestinal	108 (12%)
Thoracic	91 (10%)
Gynaecological	49 (5%)
Renal cell carcinoma	45 (5%)
Endocrine	39 (4%)
Melanoma	38 (4%)

(Table 1 continues in next column)

	Analysable population (n=928)
(Continued from previous column)	
Head and neck	30 (3%)
Sarcoma	24 (3%)
Nervous system	12 (1%)
Solid tumour, not otherwise specified	43 (5%)
Haematological malignancies	204 (22%)
Lymphoid neoplasms	102 (11%)
Multiple myeloma	55 (6%)
Low-grade non-Hodgkin lymphoma	54 (6%)
Myeloid neoplasms	42 (5%)
High-grade non-Hodgkin lymphoma	27 (3%)
Acute myeloid leukaemia	13 (1%)
Acute lymphoblastic leukaemia	6 (1%)
Haematological malignancy, not otherwise specified	6 (1%)
Cancer status†	
Remission or no evidence of disease	422 (45%)
Present, stable, or responding to treatment	294 (32%)
Present, progressive disease	102 (11%)
Unknown	59 (6%)
Data missing	51 (5%)
ECOG performance status†	
0 or 1	614 (66%)
2	72 (8%)
3 or 4	46 (5%)
Unknown	167 (18%)
Data missing	29 (3%)
Type of anticancer therapy§	
None in the 4 weeks before COVID-19 diagnosis	553 (60%)
Non-cytotoxic therapy	206 (22%)
Targeted therapy	75 (8%)
Endocrine	85 (9%)
Immunotherapy¶	38 (4%)
Radiotherapy	12 (1%)
Surgery‖	2 (<1%)
Cytotoxic systemic therapy	160 (17%)
Unknown	9 (1%)
Recent surgery†	
None in the 4 weeks before COVID-19 diagnosis	811 (87%)
Yes‖	32 (3%)
Unknown	42 (5%)
Data missing	43 (5%)

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	Analysable population (n=928)
(Continued from previous page)	
Treatment of COVID-19†**	
Hydroxychloroquine alone	89 (10%)
Azithromycin alone	93 (10%)
Azithromycin plus hydroxychloroquine	181 (20%)
Neither	486 (52%)
Unknown	22 (2%)
Data missing	57 (6%)

Data are n (%), median (IQR), or range. Due to rounding, not all variables might add up to 100%. ECOG=Eastern Cooperative Oncology Group. *Age ≥90 years transformed into exact age of 90 years for reporting purposes. †These questions were optional in the survey, such that a proportion of results are missing. ‡US regions are census-tract defined. §Proportions might add up to more than 100% because some patients had more than one malignancy or received more than one treatment concurrently. ¶Includes checkpoint inhibitors, allogeneic haemopoietic stem-cell transplant, and adaptive cellular therapy. ‖Cancer surgeries are separated in the table for descriptive purposes but are combined with any recent surgery in the prognostic modelling. **Some patients were already taking these medications at the time of presentation: hydroxychloroquine (n=12 [1%]), azithromycin (n=26 [3%]), or both (n=23 [2%]).

Table 1: **Patient demographic, clinical, and tumour characteristics**

	Died	Met composite endpoint	Admitted to an ICU	Required mechanical ventilation
Total (n=928)	121 (13%)	242 (26%)	132 (14%)	116 (12%)
Age, years				
<65 (n=412)	25 (6%)	68 (17%)	44 (11%)	38 (9%)
65–74 (n=237)	26 (11%)	60 (25%)	38 (16%)	34 (14%)
≥75 (n=279)	70 (25%)	114 (41%)	50 (18%)	44 (16%)
Sex*				
Female (n=459)	43 (9%)	101 (22%)	52 (11%)	45 (10%)
Male (n=468)	78 (17%)	141 (30%)	80 (17%)	71 (15%)
Race and ethnicity				
Non-Hispanic white (n=460)	71 (15%)	126 (27%)	60 (13%)	53 (12%)
Non-Hispanic black (n=148)	20 (14%)	42 (28%)	28 (19%)	25 (17%)
Hispanic (n=150)	16 (11%)	32 (21%)	18 (12%)	16 (11%)
Other or unknown (n=128)	12 (9%)	37 (29%)	24 (19%)	21 (16%)
Data missing (n=42)	2 (5%)	5 (12%)	2 (5%)	1 (2%)
Region of patient residence†				
US-Northeast (n=375)	55 (15%)	107 (29%)	56 (15%)	54 (14%)
US-Midwest (n=203)	19 (9%)	55 (27%)	38 (19%)	32 (16%)
US-South (n=117)	15 (13%)	30 (26%)	19 (16%)	17 (15%)
US-West (n=116)	19 (16%)	27 (23%)	14 (12%)	9 (8%)
Canada (n=49)	3 (6%)	11 (22%)	5 (10%)	4 (8%)
Spain (n=68)	10 (15%)	12 (18%)	0	0
Smoking status				
Never smoked (n=469)	44 (9%)	99 (21%)	54 (12%)	48 (10%)
Former smoker (n=326)	64 (20%)	116 (36%)	64 (20%)	55 (17%)
Current smoker (n=43)	5 (12%)	8 (19%)	4 (9%)	4 (9%)
Unknown (n=57)	6 (11%)	15 (26%)	9 (16%)	8 (14%)
Data missing (n=33)	2 (6%)	4 (12%)	1 (3%)	1 (3%)
Obesity status				
Not specified (n=720)	98 (14%)	190 (26%)	95 (13%)	83 (12%)
Obese (n=172)	20 (12%)	49 (28%)	36 (21%)	32 (19%)
Data missing (n=36)	3 (8%)	3 (8%)	1 (3%)	1 (3%)
Number of comorbidities				
0 (n=132)	3 (2%)	12 (9%)	6 (5%)	4 (3%)
1 (n=202)	13 (6%)	31 (15%)	18 (9%)	13 (6%)
2 (n=231)	41 (18%)	79 (34%)	42 (18%)	39 (17%)
3 (n=117)	24 (21%)	37 (32%)	20 (17%)	18 (15%)
≥4 (n=192)	31 (16%)	71 (37%)	41 (21%)	35 (18%)
Unknown (n=23)	5 (22%)	8 (35%)	4 (17%)	5 (22%)
Data missing (n=31)	4 (13%)	4 (13%)	1 (3%)	2 (6%)
Type of malignancy				
Solid tumour (n=654)	76 (12%)	151 (23%)	78 (12%)	70 (11%)
Haematological malignancy (n=167)	24 (14%)	58 (35%)	37 (22%)	28 (17%)
Multiple cancers‡ (n=107)	21 (20%)	33 (31%)	17 (16%)	18 (17%)

(Table 2 continues on next page)

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	Died	Met composite endpoint	Admitted to an ICU	Required mechanical ventilation
Cancer status				
Remission or no evidence of disease (n=422)	39 (9%)	95 (23%)	63 (15%)	55 (13%)
Present, stable, or responding to treatment (n=294)	41 (14%)	80 (27%)	40 (14%)	38 (13%)
Present, progressive disease (n=102)	25 (25%)	36 (35%)	12 (12%)	11 (11%)
Unknown (n=59)	11 (19%)	23 (39%)	14 (24%)	11 (19%)
Data missing (n=51)	5 (10%)	8 (16%)	3 (6%)	1 (2%)
ECOG performance status				
0 or 1 (n=614)	54 (9%)	135 (22%)	81 (13%)	81 (13%)
2 (n=72)	23 (32%)	31 (43%)	16 (22%)	8 (11%)
3 or 4 (n=46)	19 (41%)	22 (48%)	6 (13%)	5 (11%)
Unknown (n=167)	22 (13%)	51 (31%)	28 (17%)	21 (13%)
Data missing (n=29)	3 (10%)	3 (10%)	1 (3%)	1 (3%)
Type of anticancer therapy				
None in the 4 weeks before COVID-19 diagnosis (n=553)	75 (14%)	156 (28%)	91 (16%)	79 (14%)
Non-cytotoxic therapy (n=206)	23 (11%)	50 (24%)	24 (12%)	24 (12%)
Cytotoxic systemic therapy (n=160)	22 (14%)	35 (22%)	17 (11%)	12 (8%)
Unknown (n=9)	1 (11%)	1 (11%)	0	1 (11%)
Recent surgery				
None in the 4 weeks before COVID-19 diagnosis (n=811)	108 (13%)	212 (26%)	118 (15%)	104 (13%)
Yes (n=32)	6 (19%)	12 (38%)	6 (19%)	7 (22%)
Unknown (n=42)	4 (10%)	14 (33%)	6 (14%)	3 (7%)
Data missing (n=43)	3 (7%)	4 (9%)	2 (5%)	2 (5%)
Treatment of COVID-19				
Hydroxychloroquine alone (n=89)	11 (12%)	32 (36%)	18 (20%)	14 (16%)
Azithromycin alone (n=93)	12 (13%)	26 (28%)	15 (16%)	14 (15%)
Azithromycin plus hydroxychloroquine (n=181)	45 (25%)	86 (48%)	53 (29%)	51 (28%)
Neither (n=486)	41 (8%)	80 (16%)	39 (8%)	29 (6%)
Unknown (n=22)	7 (32%)	8 (36%)	2 (9%)	4 (18%)
Data missing (n=57)	5 (9%)	10 (18%)	5 (9%)	4 (7%)

Data are n (%). Due to rounding, not all variables might add up to 100%. The composite endpoint was a combination of death, severe illness requiring admission to hospital, admission to an ICU, or mechanical ventilation. ECOG=Eastern Cooperative Oncology Group. ICU=intensive care unit. *Data not shown for one patient, with sex not specified. †US regions are census-tract defined. ‡Any patient with two or more cancers reported, which could be solid, haematological, or both.

Table 2: **Primary and secondary outcomes by potential prognostic variables**

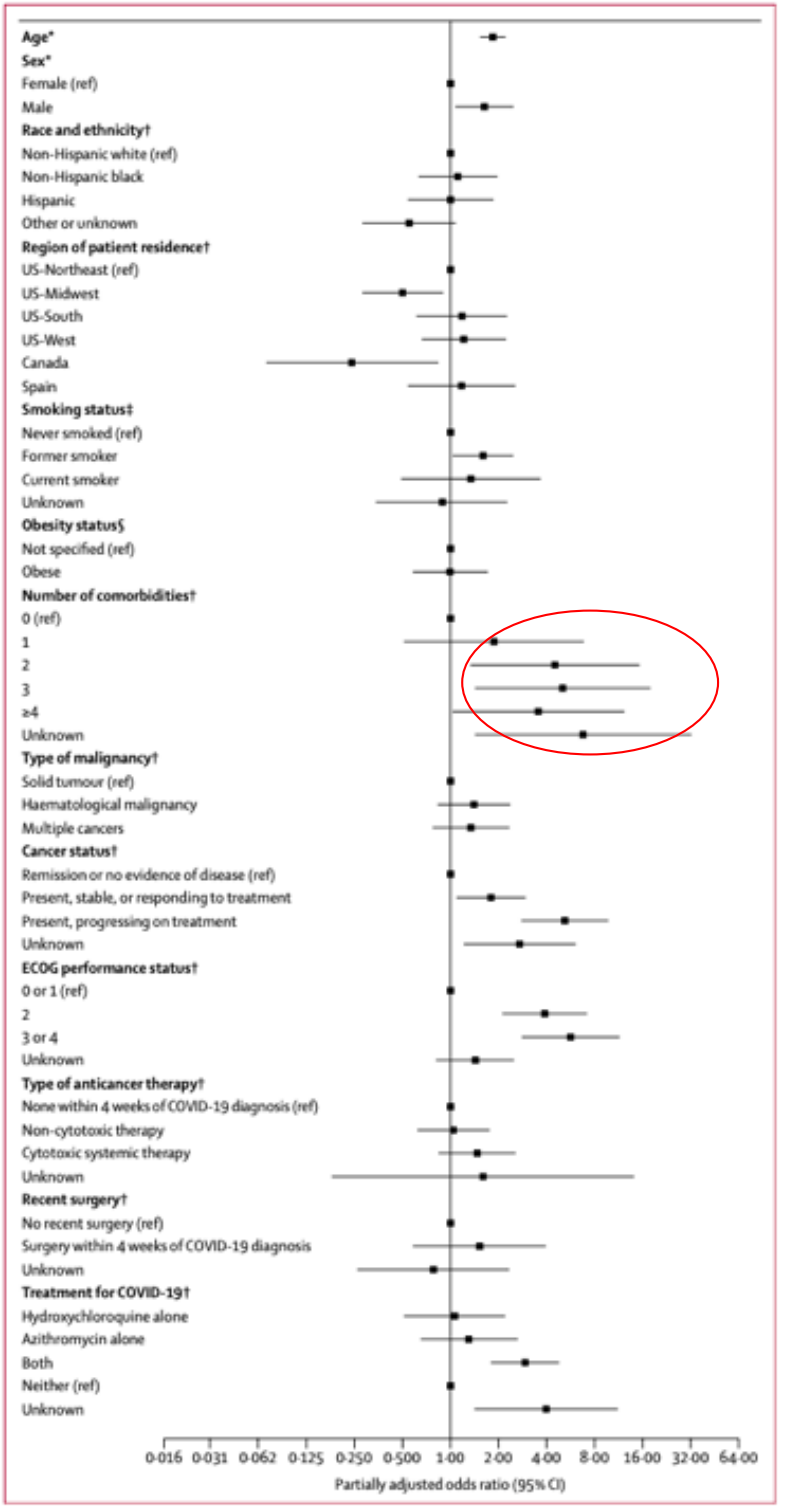
	Bivariable odds ratio	Multivariable partially adjusted odds ratio*
Age, per 10 years†	1·88 (1·58–2·24)	1·84 (1·53–2·21)
Sex		
Female	1 (ref)	1 (ref)
Male	1·94 (1·30–2·88)	1·63 (1·07–2·48)
Race and ethnicity		
Non-Hispanic white	1 (ref)	1 (ref)
Non-Hispanic black	0·85 (0·50–1·45)	1·11 (0·63–1·97)
Hispanic	0·65 (0·36–1·17)	1·00 (0·54–1·86)
Other or unknown	0·57 (0·30–1·09)	0·55 (0·28–1·08)
Region of patient residence‡		
US-Northeast	1 (ref)	1 (ref)
US-Midwest	0·60 (0·35–1·04)	0·50 (0·28–0·90)
US-South	0·86 (0·46–1·58)	1·18 (0·61–2·26)
US-West	1·14 (0·65–2·01)	1·21 (0·66–2·23)
Canada	0·38 (0·11–1·26)	0·24 (0·07–0·84)
Spain	1·00 (0·48–2·08)	1·17 (0·54–2·55)
Smoking status		
Never smoked	1 (ref)	1 (ref)
Former smoker	2·35 (1·55–3·55)	1·60 (1·03–2·47)
Current smoker	1·27 (0·47–3·39)	1·34 (0·49–3·67)
Unknown	1·14 (0·46–2·79)	0·89 (0·34–2·27)
Obesity status		
Not specified	1 (ref)	1 (ref)
Obese	0·84 (0·50–1·41)	0·99 (0·58–1·71)
Number of comorbidities		
0	1 (ref)§	1 (ref)§
1	3·12 (0·87–11·19)	1·87 (0·51–6·85)
2	9·52 (2·89–31·40)	4·50 (1·33–15·28)
3	11·54 (3·37–39·53)	5·04 (1·42–17·93)
≥4	8·77 (2·62–29·29)	3·55 (1·03–12·30)
Unknown	12·33 (2·71–56·01)	6·77 (1·42–32·33)
Type of malignancy		
Solid tumour	1 (ref)	1 (ref)
Haematological malignancy	1·28 (0·78–2·09)	1·40 (0·83–2·37)
Multiple cancers	1·86 (1·09–3·17)	1·34 (0·77–2·34)
Cancer status		
Remission or no evidence of disease	1 (ref)	1 (ref)
Present, stable, or responding to treatment	1·57 (0·98–2·49)	1·79 (1·09–2·95)
Present, progressive disease	3·07 (1·77–5·33)	5·20 (2·77–9·77)
Other or unknown	2·24 (1·06–4·71)	2·71 (1·21–6·09)

(Table 3 continues in next column)

	Bivariable odds ratio	Multivariable partially adjusted odds ratio*
(Continued from previous column)		
ECOG performance status		
0 or 1	1 (ref)	1 (ref)
2	4·84 (2·75–8·52)	3·89 (2·11–7·18)
3 or 4	7·33 (3·83–14·01)	5·66 (2·79–11·47)
Unknown	1·59 (0·93–2·73)	1·43 (0·81–2·50)
Type of anticancer therapy		
None in the 4 weeks before COVID-19 diagnosis	1 (ref)	1 (ref)
Non-cytotoxic therapy	0·80 (0·49–1·32)	1·04 (0·62–1·76)
Cytotoxic systemic therapy	1·02 (0·61–1·69)	1·47 (0·84–2·56)
Unknown	0·80 (0·10–6·46)	1·60 (0·18–14·14)
Recent surgery¶		
None in the 4 weeks before COVID-19 diagnosis	1 (ref)	1 (ref)
Yes	1·50 (0·60–3·74)	1·52 (0·58–3·96)
Unknown	0·66 (0·23–1·89)	0·78 (0·26–2·33)
Treatment of COVID-19		
Hydroxychloroquine alone	1·43 (0·71–2·90)	1·06 (0·51–2·20)
Azithromycin alone	1·56 (0·79–3·06)	1·30 (0·65–2·64)
Azithromycin plus hydroxychloroquine	3·42 (2·14–5·45)	2·93 (1·79–4·79)
Neither	1 (ref)	1 (ref)
Unknown	4·82 (1·84–12·60)	3·97 (1·41–11·19)

Data are odds ratio with 95% CI in parentheses. ECOG=Eastern Cooperative Oncology Group. *Age is adjusted for sex, smoking status, and obesity; sex is adjusted for age, smoking status, and obesity; smoking status is adjusted for age, sex, and obesity; obesity is adjusted for age, sex, and smoking status; and all other variables are adjusted for age, sex, smoking status, and obesity. †Age ≥90 years transformed into exact age of 90 years for modelling purposes; odds ratios are per 10-year age increment. ‡US regions are census-tract defined. §Precision of estimation for this category is poor due to small number of events in the reference group. ¶Includes any surgery, including cancer-specific surgeries, done within 4 weeks of COVID-19 diagnosis.

Table 3: **Bivariable and multivariable regression models of potential prognostic variables associated with 30-day all-cause mortality**



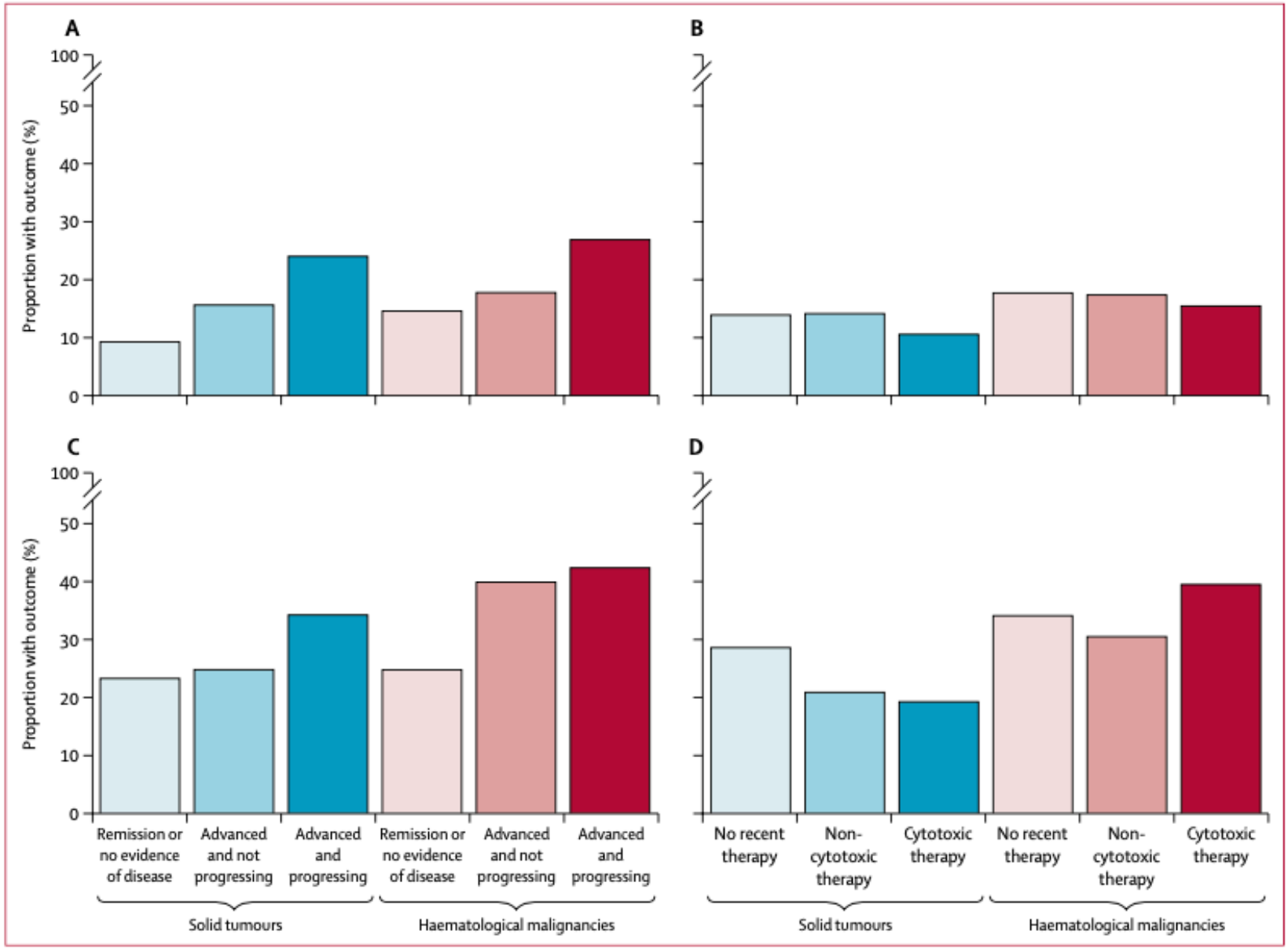


***Figure 2*: Primary and composite secondary outcome by cancer type, cancer status, and anticancer therapy**

Mortality as a function of cancer type and status (A) and cancer type and therapy type (B). Composite outcome as a function of cancer type and status (C) and cancer type and therapy type (D). Results are descriptive; no statistical analyses were applied.

Research in context

Evidence before this study

Very little evidence exists describing the natural history of patients with cancer who have COVID-19, the disease associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of May 7, 2020, the peer-reviewed literature was limited to small or single-institution case series; the largest series that we are aware of had 334 cases at a single institution. These case series are of insufficient size or breadth to draw statistical and generalisable conclusions about the factors that might be associated with better or worse outcomes for patients with cancer.

Added value of this study

To our knowledge, we report the largest series of patients with cancer and COVID-19 to date, including over 900 patients with a broad geographical distribution. The population is diverse in terms of age distribution, race and ethnicity, cancer status, and whether they are on active anticancer treatment. We found significant associations with increased 30-day all-cause mortality and the general factors of increasing age, male sex, former smoking, number of comorbidities, and receipt of azithromycin plus hydroxychloroquine; and the cancer-specific factors of moderate or poor Eastern Cooperative Oncology Group performance status and active (measurable) cancer. However, we cannot formally ascertain if the combination of hydroxychloroquine and azithromycin gives any clinical benefit or overall harm to patients, given the non-randomised nature of the study, and the possibility of other potential clinical imbalances.

Implications of all the available evidence

We identified several cancer-specific factors that are associated with increased 30-day all-cause mortality in patients with cancer and COVID-19, in addition to previously reported factors of age and sex in the general population. These findings have implications for patients and health-care providers who will be confronted with difficult decisions during the SARS-CoV-2 pandemic, such as whether to withhold or continue anticancer treatments, and whether to accelerate end-of-life planning under some circumstances.

COVID-19 mortality in patients with cancer on chemotherapy or other anticancer treatments: a prospective cohort study

Summary

Background Individuals with cancer, particularly those who are receiving systemic anticancer treatments, have been postulated to be at increased risk of mortality from COVID-19. This conjecture has considerable effect on the treatment of patients with cancer and data from large, multicentre studies to support this assumption are scarce because of the contingencies of the pandemic. We aimed to describe the clinical and demographic characteristics and COVID-19 outcomes in patients with cancer.

Methods In this prospective observational study, all patients with active cancer and presenting to our network of cancer centres were eligible for enrolment into the UK Coronavirus Cancer Monitoring Project (UKCCMP). The UKCCMP is the first COVID-19 clinical registry that enables near real-time reports to frontline doctors about the effects of COVID-19 on patients with cancer. Eligible patients tested positive for severe acute respiratory syndrome coronavirus 2 on RT-PCR assay from a nose or throat swab. We excluded patients with a radiological or clinical diagnosis of COVID-19, without a positive RT-PCR test. The primary endpoint was all-cause mortality, or discharge from hospital, as assessed by the reporting sites during the patient hospital admission.

Findings From March 18, to April 26, 2020, we analysed 800 patients with a diagnosis of cancer and symptomatic COVID-19. 412 (52%) patients had a mild COVID-19 disease course. 226 (28%) patients died and risk of death was significantly associated with advancing patient age (odds ratio 9·42 [95% CI 6·56–10·02]; p<0·0001), being male (1·67 [1·19–2·34]; p=0·003), and the presence of other comorbidities such as hypertension (1·95 [1·36–2·80]; p<0·001) and cardiovascular disease (2·32 [1·47–3·64]). 281 (35%) patients had received cytotoxic chemotherapy within 4 weeks before testing positive for COVID-19. After adjusting for age, gender, and comorbidities, chemotherapy in the past 4 weeks had no significant effect on mortality from COVID-19 disease, when compared with patients with cancer who had not received recent chemotherapy (1·18 [0·81–1·72]; p=0·380). We found no significant effect on mortality for patients with immunotherapy, hormonal therapy, targeted therapy, radiotherapy use within the past 4 weeks.

Interpretation Mortality from COVID-19 in cancer patients appears to be principally driven by age, gender, and comorbidities. We are not able to identify evidence that cancer patients on cytotoxic chemotherapy or other anticancer treatment are at an increased risk of mortality from COVID-19 disease compared with those not on active treatment.

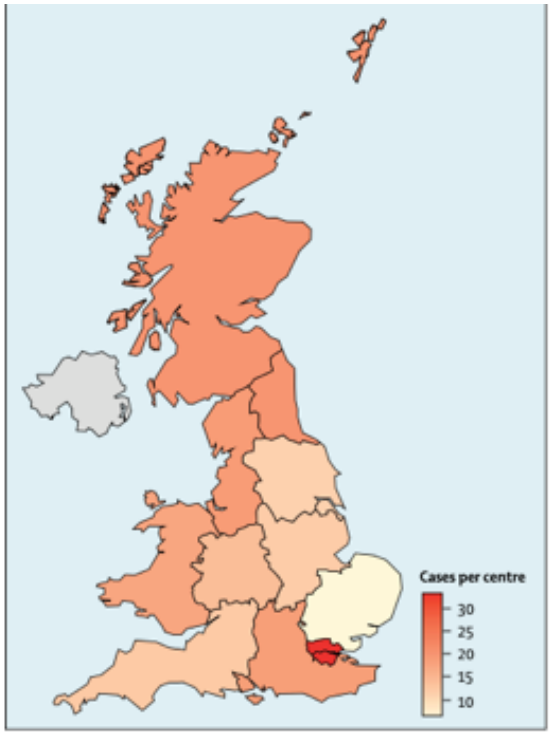


Figure 1: **Prevalence of COVID-19 in Scotland, Wales, and regions of England**
Data are the average numbers of cases from reports per cancer centre region, up to April 26, 2020. Grey indicates no data available.

	All patients (n=800)	Patients who died (n=226)	Patients who survived (n=574)
Sex			
Male	449 (56%)	146 (65%)	303 (53%)
Female	349 (44%)	80 (35%)	269 (47%)
Other*	2 (0%)	0 (0%)	2 (0%)
Age, years	69 (59–76)	73 (66–80)	66 (57–74)
Comorbidities			
Cardiovascular disease	109 (14%)	48 (21%)	61 (11%)
Chronic obstructive pulmonary disease	61 (8%)	24 (11%)	37 (6%)
Diabetes	131 (16%)	46 (20%)	85 (15%)
Hypertension	247 (31%)	92 (41%)	155 (27%)
None	169 (21%)	27 (12%)	142 (25%)
Other†	336 (42%)	108 (48%)	228 (40%)
No information	123 (15%)	28 (12%)	95 (17%)
Cancer type			
Lip, oral cavity, and pharynx	27 (3%)	4 (2%)	23 (4%)
Digestive organs	150 (19%)	42 (19%)	108 (19%)
Respiratory and intrathoracic organs	90 (11%)	32 (14%)	58 (10%)
Melanoma (skin)	27 (3%)	4 (2%)	23 (4%)
Breast	102 (13%)	18 (8%)	84 (15%)
Female genital organs	45 (6%)	5 (2%)	40 (7%)
Male genital organs	78 (10%)	30 (13%)	48 (8%)
Urinary tract	50 (6%)	16 (7%)	34 (6%)
Central nervous system	15 (2%)	3 (1%)	12 (2%)
Lymphoma	60 (8%)	20 (9%)	40 (7%)
Other haematological	109 (14%)	40 (18%)	69 (12%)
Other or unspecified‡	47 (6%)	12 (5%)	35 (6%)
Cancer stage			
Primary tumour localised	149 (19%)	40 (18%)	109 (19%)
Primary tumour locally advanced	78 (10%)	14 (6%)	64 (11%)
Metastatic	347 (43%)	103 (46%)	244 (43%)
Remission	21 (3%)	3 (1%)	18 (3%)
No information	205 (25%)	66 (29%)	139 (24%)

(Table 1 continues in next column)

	All patients (n=800)	Patients who died (n=226)	Patients who survived (n=574)
(Continued from previous column)			
Cancer treatment within 4 weeks of COVID-19 diagnosis			
Chemotherapy	281 (35%)	75 (33%)	206 (36%)
Hormone therapy	64 (8%)	21 (9%)	43 (7%)
Immunotherapy	44 (6%)	10 (4%)	34 (6%)
Radiotherapy	76 (10%)	18 (8%)	58 (10%)
Surgery	29 (4%)	7 (3%)	22 (4%)
Targeted treatment	72 (9%)	16 (7%)	56 (10%)
Other§	60 (8%)	13 (6%)	47 (8%)
None	272 (34%)	92 (41%)	180 (31%)
No information	10 (1%)	1 (0%)	9 (2%)
COVID-19 severity category			
Mild	412 (52%)	22 (10%)	390 (68%)
Severe	187 (23%)	59 (26%)	128 (22%)
Critical	173 (22%)	140 (62%)	33 (6%)
No information	28 (3%)	5 (2%)	23 (4%)
COVID-19 treatment			
Intensive therapy unit	53 (7%)	23 (10%)	30 (5%)

Data are n (%), or median (IQR). UKCCMP=UK Coronavirus Cancer Monitoring Project. ICD10=International Classification of Diseases. *Includes patients who do not identify as either male or female. †Includes comorbidities that were not listed in the table. ‡Includes ICD10 cancer types including malignant neoplasia of the bone and articular tissue, endocrine glands, mesothelioma and soft tissue, and any other tumour type that was not included in the table. §Includes cancer treatments that did not fall into the cancer treatment types defined in the table.

Table 1: **Clinical features of patients in the UKCCMP registry**

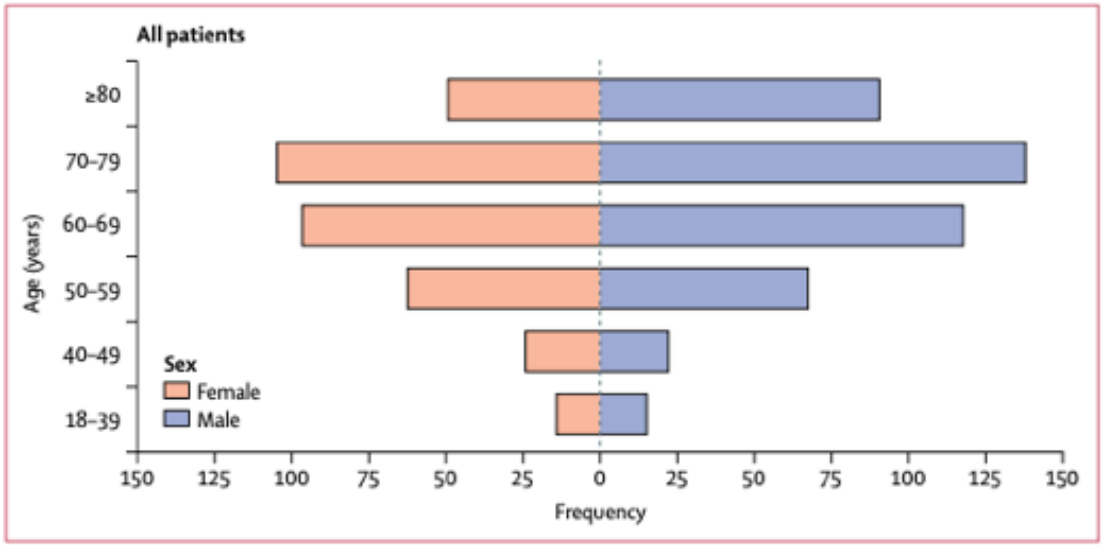


Figure 2: **Age distribution of patients with cancer in the cohort and relation to patient mortality**

	Odds ratio (95% CI)	p value
Anticancer treatment within 4 weeks of COVID-19 diagnosis		
Chemotherapy *vs* no chemotherapy	1·18 (0·81–1·72)	0·380
Hormone therapy *vs* no hormone therapy	0·90 (0·49–1·68)	0·744
Immunotherapy *vs* no immunotherapy	0·59 (0·27–1·27)	0·177
Radiotherapy *vs* no radiotherapy	0·65 (0·36–1·18)	0·159
Targeted treatment *vs* no targeted treatment	0·83 (0·45–1·54)	0·559
Cytotoxic chemotherapy		
Non-palliative chemo *vs* palliative chemo	0·40 (0·17–0·96)	0·040
Palliative first-line chemotherapy *vs* other line	0·84 (0·36–1·98)	0·690
Palliative chemotherapy *vs* no chemotherapy	1·48 (0·93–2·36)	0·102
Palliative chemotherapy *vs* no treatment	1·05 (0·63–1·76)	0·854

Multivariate analysis was done correcting for age, sex, and patient comorbidities.

Table 3: **Multivariate regression analysis and odds of death based recent anticancer treatment in patients in the UK Coronavirus Cancer Monitoring Project**

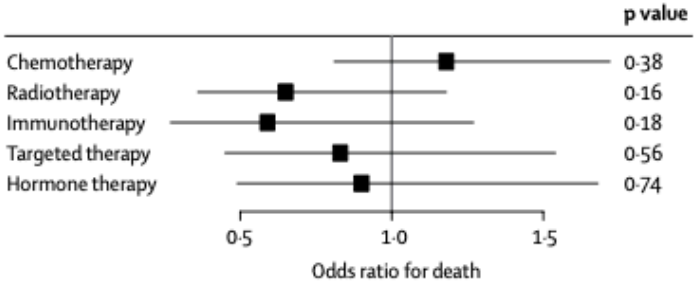


Figure 4: **Forest plots showing effect of anticancer treatments and mortality from COVID-19**

Odds ratios were adjusted for age, gender, and comorbidities. Whiskers indicated 95% CI.

	Odds ratio (95% CI)	p value	Adjusted p value
Sex	1·67 (1·19–2·34)	0·003	0·006
Age	9·42 (6·56–10·02)	<0·0001	<0·0001
Comorbidities			
Cardiovascular disease	2·32 (1·47–3·64)	0·0003	0·0019
Chronic obstructive pulmonary disease	1·80 (1·00–3·27)	0·063	0·375
Diabetes	1·61 (1·03–2·48)	0·032	0·190
Hypertension	1·95 (1·36–2·80)	0·0003	0·0015
Cancer type			
Lip, oral cavity, and pharynx	0·42 (0·13–1·21)	0·116	1·000
Digestive organs	0·91 (0·60–1·38)	0·680	1·000
Respiratory and intrathoracic organs	1·50 (0·91–2·45)	0·121	1·000
Melanoma (skin)	0·37 (0·12–1·14)	0·079	1·000
Breast	0·48 (0·28–0·84)	0·009	0·141
Female genital organs	0·31 (0·11–0·81)	0·010	0·148
Male genital organs	1·99 (1·14–3·48)	0·015	0·230
Urinary tract	1·10 (0·58–2·12)	0·745	1·000
Central nervous system	0·64 (0·15–2·32)	0·760	1·000
Lymphoma	1·30 (0·71–2·30)	0·373	1·000
Other haematological	1·57 (1·01–2·42)	0·040	1·000
Cancer stage			
Primary tumour localised	1·04 (0·67–1·64)	0·912	1·000
Primary tumour locally advanced	0·58 (0·29–1·09)	0·111	0·442
Metastatic	1·34 (0·90–2·01)	0·145	0·579
Remission	0·42 (0·10–1·43)	0·204	0·815
Cancer treatment within 4 weeks of COVID-19 diagnosis			
Chemotherapy	0·78 (0·55–1·11)	0·173	1·000
Hormone therapy	1·16 (0·64–2·06)	0·659	1·000
Immunotherapy	0·60 (0·27–1·24)	0·179	1·000
Radiotherapy	0·66 (0·37–1·17)	0·178	1·000
Surgery	0·83 (0·32–2·15)	0·825	1·000
Targeted treatment	0·56 (0·30–1·01)	0·058	0·525
COVID-19 severity score			
Mild	0·03 (0·02–0·05)	<0·0001	<0·0001
Severe	1·63 (1·10–2·40)	0·015	0·045
Critical	89·65 (41·64–209·83)	<0·0001	<0·0001
COVID-19 treatment			
Intensive therapy unit	1·95 (1·09–3·52)	0·027	0·027

Univariate analysis was done with presence compared with absence (reference) for each category except for sex and age. Male sex was compared with reference to female sex. A Bonferroni p value adjustment was done.

Table 2: **Univariate regression analysis and odds of death based on features of patients in the UK Coronavirus Cancer Monitoring Project**

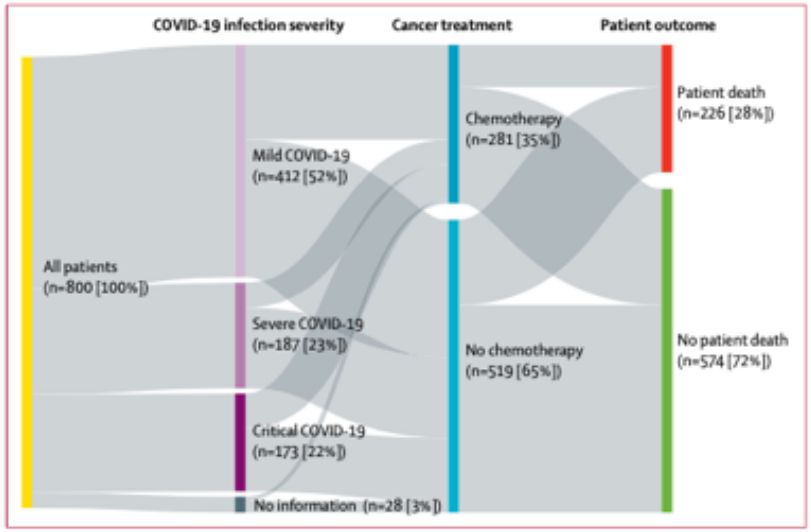


Figure 3: **Relationship of chemotherapy use within 4 weeks of confirmed COVID-19 and mortality and severity of disease course**

The vertical coloured bars denote the patient cohort, split into different groups. The grey horizontal bars denote associations between the different groups, with wider bars denoting more overlap.

Research in context

Evidence before this study

We searched PubMed for all studies related to the effect of severe acute respiratory syndrome coronavirus 2, the cause of COVID-19, on patients with cancer, using the search terms "COVID-19", "SARS-CoV-2", "cancer", "treatment", "chemotherapy", "immunotherapy", "radiotherapy", "targeted therapy", "outcomes," "death", "mortality", and "risk". We included publications in English only. To date, only two studies have described the effect of cancer treatments on COVID-19 outcomes. Both studies consist of small retrospective analyses from China in a few cancer centres. One study reported four patients who had chemotherapy or surgery in the past month, and identified that three had a clinically severe disease course. Another study described a cohort of 105 cancer patients with COVID-19, 17 of whom had received chemotherapy within the past 40 days and six had received immunotherapy. The authors reported that four of the six patients on immunotherapy had critical symptoms. No conclusions were drawn about chemotherapy and the authors stressed the importance of a further study with a large case population. In summary, to date, no high-quality evidence exists to identify risks from use of recent anticancer treatments during the COVID-19 pandemic.

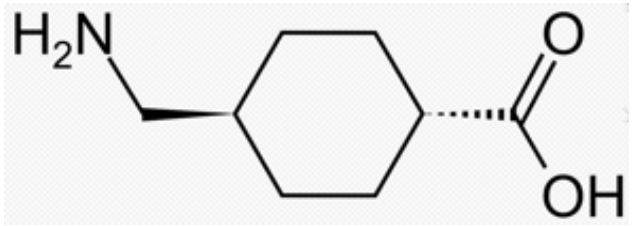
Added value of this study

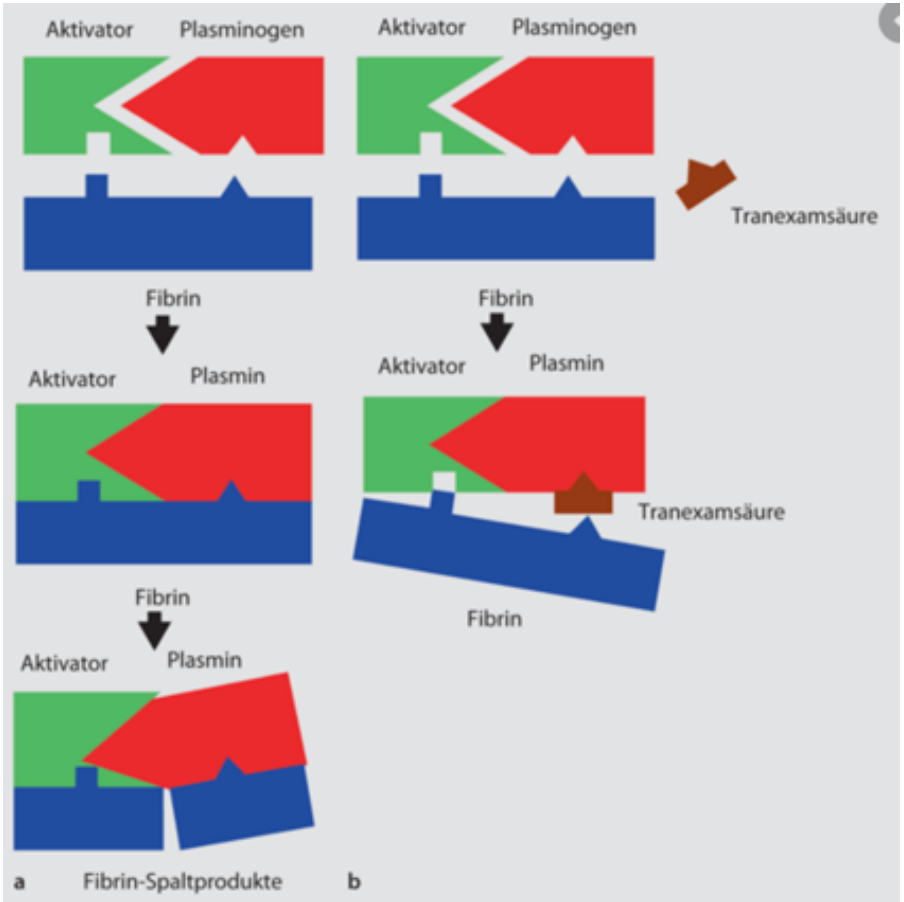
This UK Coronavirus Cancer Monitoring Project study is a national monitoring project. We have analysed the interaction between recent anticancer treatments and COVID-19 morbidity and mortality in the largest cohort of patients with cancer with COVID-19 presented to date, consisting of 800 patients. Recent chemotherapy use in patients with cancer before severe acute respiratory syndrome coronavirus 2 infection was not significantly associated with increased mortality. Although the numbers of patients are smaller, we did not observe any significant risk from recent use of immunotherapy, hormonal therapy, targeted therapy, or radiotherapy.

Implications of all the available evidence

Our data are strongly indicative that COVID-19 mortality in patients with cancer is principally driven by advancing age and the presence of other non-cancer comorbidities. At a population level, our data do not suggest that chemotherapy or anticancer treatments will necessarily increase the risk of mortality from COVID-19, and gives confidence to oncologists and other clinicians that delivery of effective anticancer regimens should continue during this difficult time.

Tranexamsäure (AMCHA oder TXA) ist eine Substanz, die in der Medizin zur Hemmung des Fibrinolysesystems verwendet wird. Der Wirkungsmechanismus beruht dabei auf einer Komplexbildung mit Plasminogen, wodurch dessen Bindung an die Fibrinoberfläche gehemmt wird. Damit resultiert letztlich eine Hemmung der Gerinnselauflösung (Fibrinolyse). Es wird daher als Antifibrinolytikum (Fibrinolysehemmer) bezeichnet. Tranexamsäure ist ein synthetischer Stoff, der der Aminosäure Lysin ähnelt. Er zählt wie ε-Aminocapronsäure und p-Aminomethylbenzoesäure zur Gruppe der sogenannten ε-Aminocarbonsäuren. Tranexamsäure blockiert die Bildung von Plasmin durch Hemmung der proteolytischen Aktivität der Plasminogenaktivatoren. Dadurch wird Plasmin in seiner Fähigkeit Fibrin zu lysieren behindert. Bei niedriger Dosis wirkt Tranexamsäure als kompetitiver Hemmer des Plasmins, bei hoher Dosierung als nicht-kompetitiver Hemmer. Alle ε-Aminocarbonsäuren wirken analog.





Effects of a high-dose 24-h infusion of tranexamic acid on death and thromboembolic events in patients with acute gastrointestinal bleeding (HALT-IT): an international randomised, double-blind, placebo-controlled trial

Summary

Background Tranexamic acid reduces surgical bleeding and reduces death due to bleeding in patients with trauma. Meta-analyses of small trials show that tranexamic acid might decrease deaths from gastrointestinal bleeding. We aimed to assess the effects of tranexamic acid in patients with gastrointestinal bleeding.

Methods We did an international, multicentre, randomised, placebo-controlled trial in 164 hospitals in 15 countries. Patients were enrolled if the responsible clinician was uncertain whether to use tranexamic acid, were aged above the minimum age considered an adult in their country (either aged 16 years and older or aged 18 years and older), and had significant (defined as at risk of bleeding to death) upper or lower gastrointestinal bleeding. Patients were randomly assigned by selection of a numbered treatment pack from a box containing eight packs that were identical apart from the pack number. Patients received either a loading dose of 1 g tranexamic acid, which was added to 100 mL infusion bag of 0·9% sodium chloride and infused by slow intravenous injection over 10 min, followed by a maintenance dose of 3 g tranexamic acid added to 1 L of any isotonic intravenous solution and infused at 125 mg/h for 24 h, or placebo (sodium chloride 0·9%). Patients, caregivers, and those assessing outcomes were masked to allocation. The primary outcome was death due to bleeding within 5 days of randomisation; analysis excluded patients who received neither dose of the allocated treatment and those for whom outcome data on death were unavailable. This trial was registered with Current Controlled Trials, ISRCTN11225767, and ClinicalTrials.gov, NCT01658124.

Findings Between July 4, 2013, and June 21, 2019, we randomly allocated 12 009 patients to receive tranexamic acid (5994, 49·9%) or matching placebo (6015, 50·1%), of whom 11 952 (99·5%) received the first dose of the allocated treatment. Death due to bleeding within 5 days of randomisation occurred in 222 (4%) of 5956 patients in the tranexamic acid group and in 226 (4%) of 5981 patients in the placebo group (risk ratio [RR] 0·99, 95% CI 0·82–1·18). Arterial thromboembolic events (myocardial infarction or stroke) were similar in the tranexamic acid group and placebo group (42 [0·7%] of 5952 *vs* 46 [0·8%] of 5977; 0·92; 0·60 to 1·39). Venous thromboembolic events (deep vein thrombosis or pulmonary embolism) were higher in tranexamic acid group than in the placebo group (48 [0·8%] of 5952 *vs* 26 [0·4%] of 5977; RR 1·85; 95% CI 1·15 to 2·98).

Interpretation We found that tranexamic acid did not reduce death from gastrointestinal bleeding. On the basis of our results, tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial.

	Tranexamic acid (n=5994)	Placebo (n=6015)
Age at randomisation, years		
Mean (SD)	58·1 (17·0)	58·1 (17·0)
<40	791 (13%)	779 (13%)
40–59	2356 (39%)	2333 (39%)
60–79	2078 (35%)	2130 (35%)
≥80	769 (13%)	773 (13%)
Sex		
Female	2142 (36%)	2124 (35%)
Male	3852 (64%)	3891 (65%)
Time from onset to randomisation, h		
Mean (SD)	21·4 (36·4)	22·5 (37·8)
≤3	960 (16%)	975 (16%)
>3–≤8	1607 (27%)	1551 (26%)
>8	3427 (57%)	3488 (58%)
Missing	0	1 (<1%)
Suspected location of bleeding		
Lower	674 (11%)	654 (11%)
Upper	5320 (89%)	5361 (89%)
Haematemesis		
Yes	4285 (72%)	4240 (71%)
No	1709 (29%)	1775 (30%)
Melaena or fresh blood per rectum		
Yes	4573 (76%)	4626 (77%)
No	1421 (24%)	1389 (23%)
Suspected variceal bleeding		
Yes	2694 (45%)	2739 (46%)
No	3300 (55%)	3276 (54%)
Suspected active bleeding		
Yes	5247 (88%)	5226 (87%)
No	747 (12%)	789 (13%)
Systolic blood pressure, mm Hg		
≥90	5222 (87%)	5216 (87%)
76–89	577 (10%)	577 (10%)
≤75	181 (3%)	201 (3%)
Missing	14 (<1%)	21 (<1%)

(Table 1 continues in next column)

(Continued from previous column)

	Tranexamic acid (n=5994)	Placebo (n=6015)
Heart rate, beats per min		
<77	812 (14%)	756 (13%)
77–91	1546 (26%)	1644 (27%)
92–107	1760 (29%)	1720 (29%)
>107	1864 (31%)	1885 (31%)
Missing	12 (<1%)	10 (<1%)
Signs of shock		
Yes	2574 (43%)	2648 (44%)
No	3420 (57%)	3367 (56%)
Rockall score		
1–2	1419 (24%)	1395 (23%)
3–4	2306 (38%)	2332 (39%)
5–7	2269 (38%)	2288 (38%)
Taking anticoagulants		
Yes	528 (9%)	500 (8%)
No	5422 (90%)	5466 (91%)
Unknown	44 (1%)	49 (1%)
Emergency admission		
Yes	5673 (95%)	5687 (94%)
No	321 (5%)	328 (6%)
Major comorbidities		
Cardiovascular	1108 (18%)	1132 (19%)
Respiratory	337 (6%)	324 (5%)
Liver	2432 (41%)	2532 (42%)
Renal	325 (5%)	310 (5%)
Malignancy	417 (7%)	382 (6%)
Other	999 (17%)	968 (16%)
Any comorbidity	4308 (72%)	4329 (72%)

Data are n (%) or mean (SD).

Table 1: **Baseline characteristics**

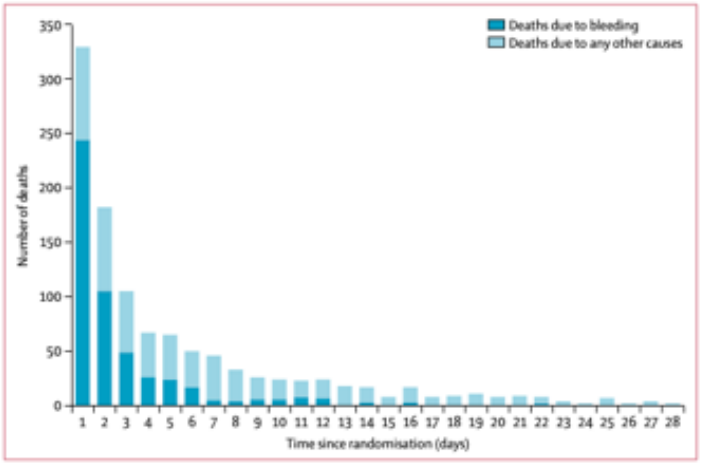


Figure 2: **Mortality by days from randomisation**

	Tranexamic acid (n=5956)	Placebo (n=5981)	Risk ratio (95% CI)
Death due to bleeding within 24 h	124 (2·1%)	120 (2·0%)	1·04 (0·81–1·33)
Death due to bleeding within 5 days	222 (3·7%)	226 (3·8%)	0·99 (0·82–1·18)
Death due to bleeding within 28 days	253 (4·2%)	262 (4·4%)	0·97 (0·82–1·15)
Rebleeding within 24 h*	41 (0·7%)	41 (0·7%)	1·00 (0·65–1·55)
Rebleeding within 5 days*	287 (4·8%)	315 (5·3%)	0·91 (0·78–1·07)
Rebleeding within 28 days*	410 (6·8%)	448 (7·5%)	0·92 (0·81–1·05)

Data are n (%) and risk ratio (95% CI). Death or rebleeding in hospital during follow-up. *Excludes 13 patients missing data on rebleed status or rebleed date.

***Table 2:* Effect of tranexamic acid on death due to bleeding and rebleeding**

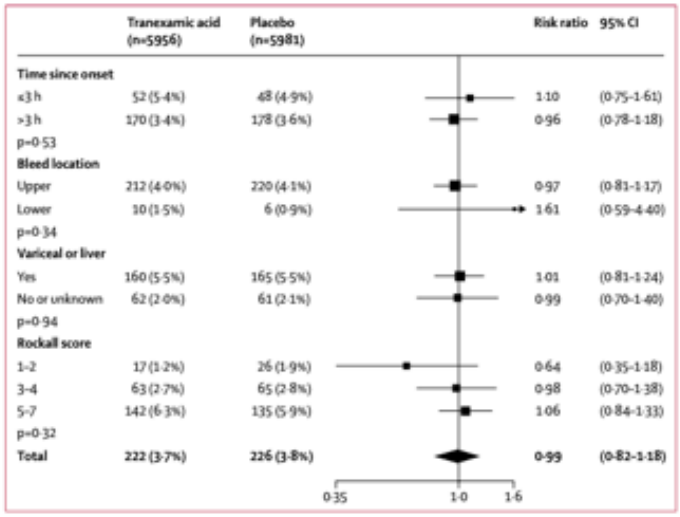


Figure 3: **Effect of tranexamic acid on death due to bleeding within 5 days**
Analysis stratified by time since bleeding onset, suspected bleed location, suspected variceal bleeding or comorbid liver disease, and Rockall score.

	Tranexamic acid (n=5956)	Placebo (n=5981)	Risk ratio (95% CI)
Bleeding	253 (4·2%)	262 (4·4%)	0·97 (0·82–1·15)
Thromboembolic event	26 (0·4%)	17 (0·3%)	1·54 (0·83–2·83)
Organ failure	109 (1·8%)	114 (1·9%)	0·96 (0·74–1·25)
Pneumonia	57 (1·0%)	42 (0·7%)	1·36 (0·92–2·03)
Sepsis	33 (0·6%)	49 (0·8%)	0·68 (0·44–1·05)
Malignancy	65 (1·1%)	40 (0·7%)	1·63 (1·10–2·42)
Other	21 (0·4%)	24 (0·4%)	0·88 (0·49–1·58)
All cause	564 (9·5%)	548 (9·2%)	1·03 (0·92–1·16)

Data are n (%) and risk ratio (95% CI). Death in hospital during follow-up.

***Table 3:* Effect of tranexamic acid on all-cause death**

	Tranexamic acid	Placebo	Outcomes
Interventions			
Diagnostic endoscopy	4781/5953 (80·3%)	4729/5978 (79·1%)	1·02 (1·00 to 1·03)
Therapeutic endoscopy	2542/5952 (42·7%)	2658/5978 (44·5%)	0·96 (0·92 to 1·00)
Diagnostic radiological procedure	1704/5953 (28·6%)	1744/5978 (29·2%)	0·98 (0·93 to 1·04)
Therapeutic radiological procedure	74/5953 (1·2%)	89/5978 (1·5%)	0·83 (0·61 to 1·13)
Surgical intervention	146/5953 (2·5%)	158/5978 (2·6%)	0·93 (0·74 to 1·16)
Any surgical, endoscopic, or radiological intervention	5216/5956 (87·6%)	5236/5981 (87·5%)	1·00 (0·99 to 1·01)
Any transfusion	4076/5951 (68·5%)	4129/5978 (69·1%)	0·99 (0·97 to 1·02)
Whole blood or red cells	3984/4076 (97·7%)	4018/4129 (97·3%)	1·00 (1·00 to 1·01)
Frozen plasma	930/4076 (22·3%)	993/4129 (24·0%)	0·93 (0·86 to 1·00)
Any platelets	219/4076 (5·4%)	255/4129 (6·2%)	0·87 (0·73 to 1·04)
Blood product transfusions			
Units of whole blood or red cells	2·8 (2·4)	2·9 (2·7)	−0·06 (0·05 to −0·18)
Units of frozen plasma	0·9 (2·4)	1·0 (2·6)	−0·05 (−0·01 to −0·23)
Units of any platelets	0·2 (0·9)	0·2 (1·0)	−0·02 (0·02 to −0·06)

Data for interventions are n/N (%) and risk ratio (95% CI); data for blood product transfusions are mean (SD) and difference in means (95% CI).

***Table 4:* Effect of tranexamic acid on the need for surgical, endoscopic, and radiological interventions or blood product transfusion**

	Tranexamic acid	Placebo	Outcomes
Complications			
Any thromboembolic event	86/5952 (1·4%)	72/5977 (1·2%)	1·20 (0·88 to 1·64)
Venous events (deep vein thrombosis, pulmonary embolism)	48/5952 (0·8%)	26/5977 (0·4%)	1·85 (1·15 to 2·98)
Deep vein thrombosis	23/5952 (0·4%)	12/5977 (0·2%)	1·92 (0·96 to 3·86)
Pulmonary embolism	28/5952 (0·5%)	16/5977 (0·3%)	1·76 (0·95 to 3·24)
Arterial events (myocardial infarction, stroke)	42/5952 (0·7%)	46/5977 (0·8%)	0·92 (0·60 to 1·39)
Myocardial infarction	24/5952 (0·4%)	28/5977 (0·5%)	0·86 (0·50 to 1·48)
Stroke	19/5952 (0·3%)	18/5977 (0·3%)	1·06 (0·56 to 2·02)
Renal failure	142/5951 (2·4%)	157/5978 (2·6%)	0·91 (0·73 to 1·14)
Liver failure	196/5952 (3·3%)	184/5977 (3·1%)	1·07 (0·88 to 1·30)
Respiratory failure	105/5952 (1·8%)	131/5978 (2·2%)	0·81 (0·62 to 1·04)
Cardiac event	100/5952 (1·7%)	89/5977 (1·5%)	1·13 (0·85 to 1·50)
Sepsis	210/5952 (3·5%)	216/5977 (3·6%)	0·98 (0·81 to 1·18)
Pneumonia	193/5952 (3·2%)	174/5978 (2·9%)	1·11 (0·91 to 1·36)
Seizure	38/5952 (0·6%)	22/5977 (0·4%)	1·73 (1·03 to 2·93)
Self-care capacity			
Days in ICU	0·4 (1·8)	0·4 (2·0)	−0·06 (0·01 to −0·13)
Katz score	5·5 (1·5)	5·5 (1·4)	−0·03 (0·02 to −0·09)

Data for complications are n/N (%) and risk ratio (95% CI); data for self-care capacity are mean (SD) and difference in means (95% CI). Thromboembolic events and complications are not mutually exclusive. ICU=intensive care unit.

***Table 5:* Complications and self-care capacity in study groups**

Research in context

Evidence before this study

Before this study a Cochrane systematic review and meta-analysis of randomised trials of tranexamic acid for upper gastrointestinal bleeding included seven trials with a total of 1654 patients. There was a large reduction in mortality with tranexamic acid (pooled risk ratio [RR] 0·61, 95% CI 0·42–0·89; p=0·01). However, given the small size of the included trials and the potential for selection and other biases, we considered this evidence to be hypothesis generating, requiring confirmation in larger trials. Furthermore, there was substantial uncertainty about the risk of thromboembolic events with tranexamic acid (pooled RR 1·86, 95% CI 0·66–5·24).

Added value of this study

The HALT-IT trial included 12 009 patients from 164 hospitals in 15 countries. Adult patients with significant upper or lower gastrointestinal bleeding were randomly assigned to receive tranexamic acid (1 g loading dose followed by 3 g maintenance dose over 24 h) or matching placebo. Tranexamic acid did not reduce death from gastrointestinal bleeding (RR 0·99, 95% CI 0·82–1·18) but was associated with an increased risk of venous thromboembolic events (1·85, 1·15–2·98) and seizures (1·73, 1·03–2·93).

Implications of all the available evidence

The most recent update of the Cochrane review included eight small randomised trials with 1701 participants and showed a reduction in mortality with tranexamic acid (RR 0·60, 95% CI 0·42–0·87). Although we cannot entirely rule out a modest increase or decrease in death due to bleeding with tranexamic acid, we can rule out the large mortality reduction suggested by the Cochrane review. Furthermore, tranexamic acid appears to increase the risk of venous thromboembolic events in patients with gastrointestinal bleeding. On the basis of our results, tranexamic acid should not be used for the treatment of gastrointestinal bleeding outside the context of a randomised trial. Our results highlight the unreliability of meta-analyses of small trials.

New directions in the treatment of opioid withdrawal

A Benjamin Srivastava, John J Mariani, Frances R Levin

The treatment of opioid withdrawal is an important area of clinical concern when treating patients with chronic, non-cancer pain, patients with active opioid use disorder, and patients receiving medication for opioid use disorder. Current standards of care for medically supervised withdrawal include treatment with μ-opioid receptor agonists, (eg, methadone), partial agonists (eg, buprenorphine), and α2-adrenergic receptor agonists (eg, clonidine and lofexidine). Newer agents likewise exploit these pharmacological mechanisms, including tramadol (μ-opioid receptor agonism) and tizanidine (α2 agonism). Areas for future research include managing withdrawal in the context of stabilising patients with opioid use disorder to extended-release naltrexone, transitioning patients with opioid use disorder from methadone to buprenorphine, and tapering opioids in patients with chronic, non-cancer pain.

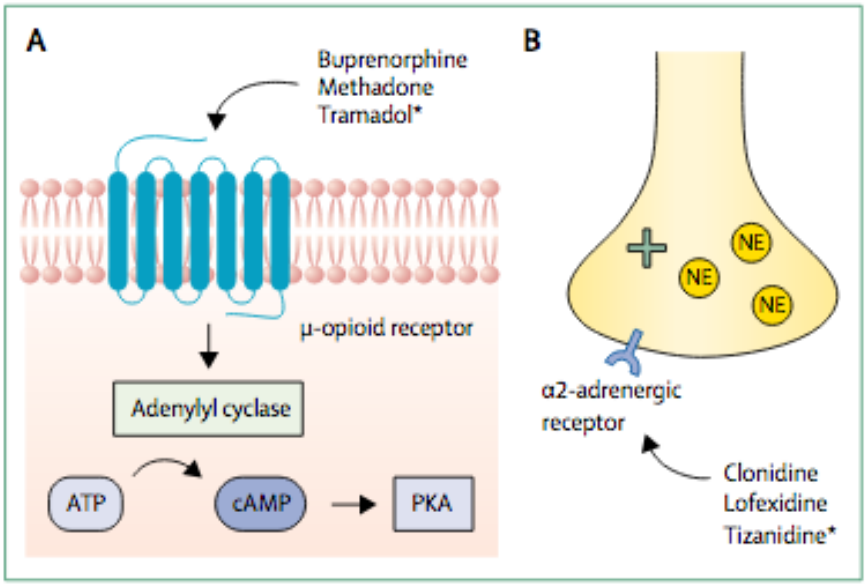


Figure 1: **Pharmacological mechanisms of agents used in the treatment of opioid withdrawal**

Acute opioid binding to the μ-opioid receptor inhibits the downstream cAMP (A), which recovers with chronic opioid use and further increases in withdrawal, leading to excess NE discharge from the noradrenergic neurons in the locus coeruleus (B). Therefore, treatment of withdrawal involves either attenuating the cAMP pathway through μ-opioid receptor agonism (A) or inhibiting excess NE discharge from locus coeruleus neurons through presynaptic α2-receptor agonism. ATP=adenosine triphosphate. cAMP=cyclic adenosine monophosphate. PKA=protein kinase A. NE=norepinephrine. *Not approved by the US Food and Drug Administration yet.

Panel 1: **Medically supervised withdrawal protocols for buprenorphine, clonidine, lofexidine, and methadone, along with recommendations for ancillary medications for symptoms**

Buprenorphine (begin when withdrawal symptoms emerge)[2,19,27]

- Day 1: 2–4 mg every hour for 4 h (total dose 8–12 mg)
- Day 2: 16 mg in divided doses (eg, 8 mg twice daily)
- Day 3–9: decrease by 2–4 mg per day as tolerated; add clonidine 0·1 mg every 4–6 h for breakthrough symptoms

Clonidine[2,19,27]

- Day 1: 0·1–0·2 mg every 4–6 h with a maximum dose of 1·2 mg
- Day 2 onward: taper by 0·1–0·2 mg per day

Lofexidine[32,33]

- Day 1: 0·54–0·72 mg every 6 h (total daily dose 2·16–2·88 mg)
- Day 2 onward: decrease each dose by 0·18 mg every 1–2 days

Methadone[2,19]

- Day 1: begin with 10 mg, increase by 10 mg every 6–8 h for maximum dose of 40 mg

Option 1:

- Days 2–4: decrease by 10 mg each day
- Days 5–8: decrease by 2 mg each day

Option 2:

- Days 2–8: decrease by 5 mg each day

Ancillary medications[27]

Anxiety

- Clonazepam 0·5–2·0 mg every 4–8 h (maximum 6 mg daily)

Muscle cramps

- Ibuprofen 400 mg every 4–6 h (maximum 2400 mg daily)

Nausea, vomiting, or diarrhoea

- Bismuth subsalicylate 2 tablets every hour (maximum 10 tablets daily)
- Ondansetron 8–16 mg every 8–12 h
- Prochlorperazine 5–10 mg every 3–4 h (maximum 40 mg daily)

Sleep

- Trazodone 50–150 mg at bedtime
- Zolpidem 10 mg at bedtime

Panel 2: Outstanding research questions and potential solutions in the treatment of opioid withdrawal

Managing withdrawal in patients with chronic, non-cancer pain (CNCP) undergoing opioid dose reduction or discontinuation[39-41]

- Lofexidine is being investigated as a treatment for withdrawal in patients with CNCP undergoing an opioid taper (NCT04070157)
- Trials investigating buprenorphine tapers for patients with CNCP who discontinue opioids are also underway (NCT02737826, NCT03156907)
- α2 agonists and ancillary medications might be most appropriate for patients with CNCP undergoing dose reduction (but not discontinuation)
- Buprenorphine might be most appropriate for patients with CNCP who discontinue opioids
- Tramadol might also be useful for the treatment of withdrawal during discontinuation but requires further study

Standardising the transition from methadone to buprenorphine[2,19,50]

- Buprenorphine microdosing has promise but requires evaluation in randomised controlled trials[51]

Improving induction rates onto extended-release naltrexone[8,9,56]

- Managing withdrawal symptoms with α2 agonists and other ancillary medications seems to be the most important factor, rather than reducing time to induction[56]
- Tizanidine with ancillary medications might hold promise[57]
- Lofexidine is being examined in outpatient transition to extended-release naltrexone (NCT04056182)
- Extended (21-day) buprenorphine taper followed by 2-day washout with ancillary medications and three oral naltrexone up-titrations before extended-release naltrexone administration is underway (NCT03711318)

Defining the optimal strategy to manage opioid withdrawal in patients who refuse medications for opioid use disorder or in situations in which medication is not available[10-13]

- Tramadol is an ideal medication given its low potency and relatively low abuse potential[38]

	Advantages	Disadvantages	Ideal situation for use
Buprenorphine	Better symptom control and treatment completion than α2 agonists; more accessible and safer than methadone	μ-opioid receptor agonist properties; potential for misuse; appears to not be helpful with extended-release naltrexone induction	Patients with OUD who will be stabilised on buprenorphine for OUD maintenance treatment; patients with OUD who will not be stabilised on MOUD (by choice or because of availability); patients with CNCP who undergo opioid discontinuation
Clonidine	Accessible, not scheduled; no substantial misuse potential	Substantial side-effect profile; hypotension and sedation; worse withdrawal symptom control compared with buprenorphine; only treats autonomic symptoms	Patients with OUD who will not be stabilised on MOUD (by choice or because of availability); transition to extended-release naltrexone (with substantial support and ancillary medications); patients with CNCP who undergo an opioid dose reduction
Lofexidine	Not scheduled; no substantial misuse potential; lower side-effect burden than clonidine	Side-effect burden still substantial; probably does not treat all withdrawal symptoms (just autonomic symptoms)	Patients with OUD who will not be stabilised on MOUD (by choice or because of availability); transition to extended-release naltrexone (with substantial support and ancillary medications); patients with CNCP who undergo an opioid dose reduction
Methadone	Better side-effect profile than clonidine	Needs to be dispensed at a licensed clinic; risk of misuse, diversion, and overdose; possibly requires a longer taper than with either α2 agonists or buprenorphine	Patients who will be stabilised on methadone for OUD maintenance treatment

CNCP=chronic, non-cancer pain. MOUD=medications for opioid use disorder. OUD=opioid use disorder.

Table: **Evaluation of withdrawal treatment by drug with indications for most appropriate use**

CNCP=chronic, non-cancer pain. MOUD=medications for opioid use disorder. OUD=opioid use disorder.

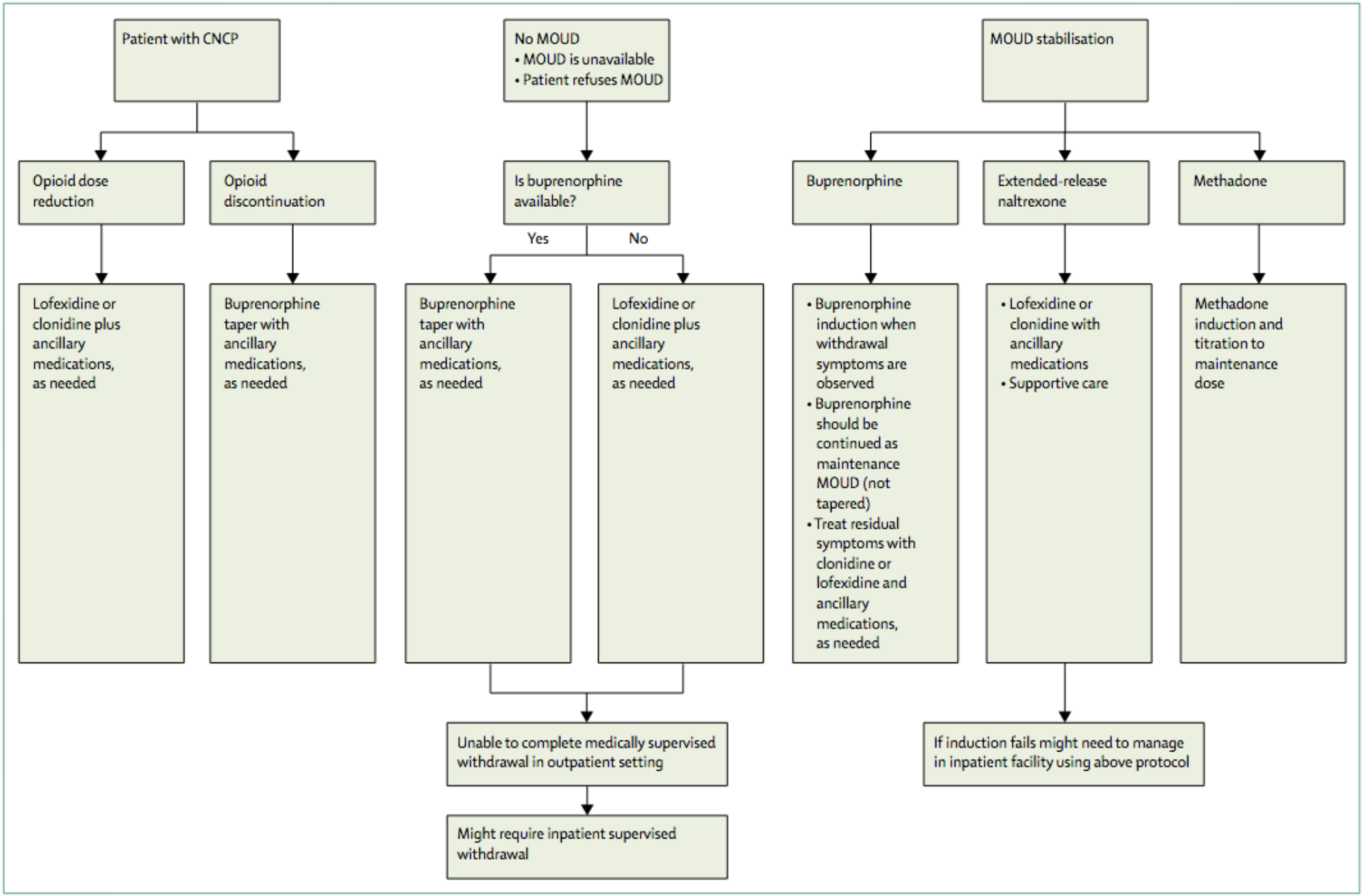


Figure 2: **Algorithm for the treatment of medically supervised opioid withdrawal**

CNCP=chronic, non-cancer pain. MOUD=medications for opioid use disorder.

Panel 3: Approaches that do not show promise or for which evidence is minimal

μ-opioid receptor antagonist treatment[8,61]

When a μ-opioid receptor antagonist (ie, naloxone or naltrexone) is administered before the onset of opioid withdrawal, although initially the severity of withdrawal is increased, the duration is shortened by several days. In a 2017 Cochrane review, Gowing and colleagues reviewed nine studies (five outpatient, four inpatient) comparing α2-adrenergic agonist (clonidine or lofexidine) therapy combined with a μ-opioid receptor antagonist (naloxone or naltrexone) for opioid withdrawal. Peak withdrawal severity appeared to be greater in the combination groups taking a μ-opioid receptor antagonist and an α2 agonist but average withdrawal severity was generally lower in these groups than in the groups taking only α2 agonists. Differences in treatment retention were inconsistent, although delirium was reported in two studies after the first dose of naltrexone. Ultimately, the authors concluded that although μ-opioid receptor antagonist treatment protocols are feasible, whether they reduce withdrawal duration, improve treatment retention, or lead to greater success of oral naltrexone stabilisation, when compared with α2-adrenergic agonist protocols, is unclear. Further, a higher degree of care might be required due to the initial, precipitated withdrawal symptoms, which can include severe nausea, vomiting, and diarrhoea.

Calcium channel blockers: gabapentin and pregabalin[62–68]

Gabapentin is a γ-aminobutyric-acid (GABA) analogue that acts pharmacologically as an n-type calcium channel blocker. Early evidence showed that adjunctive gabapentin was associated with reductions in post-surgical morphine, and data from clinical trials showed that gabapentin could reduce withdrawal symptoms and, when compared with placebo, was associated with reductions in opioid use. A more recent study compared gabapentin (1600 mg daily) with pregabalin (450 mg daily), another GABA analogue and voltage-gated calcium channel blocker, and placebo as adjunctive treatment to a buprenorphine taper over 4 weeks in 50 patients with opioid use disorder undergoing medically supervised withdrawal in an outpatient setting. Neither gabapentin nor pregabalin was superior to placebo for withdrawal symptom severity (as measured by Short Opiate Withdrawal Scale scores).

Ibogaine[69–74]

Ibogaine is a psychedelic alkaloid with a varied pharmacological profile, including serotonin reuptake inhibition and weak activity at the μ-opioid, κ-opioid, and N-methyl-D-aspartate receptors. The literature suggests that the primary reason for which ibogaine is used is for treatment of withdrawal, although the mechanism of action in treating opioid withdrawal remains unclear, as ibogaine does not have typical μ-opioid receptor agonist effects (and does not have downstream effects consistent with μ-opioid receptor agonism), nor does it have affinity for α-adrenergic receptors. Given that ibogaine is illegal in the USA and many other countries, it has not been studied in high-quality, randomised clinical trials; thus current evidence is restricted to open-label and retrospective studies. In one retrospective chart review of patients undergoing medically supervised withdrawal with ibogaine in an inpatient setting and two prospective open-label studies, withdrawal symptoms decreased substantially. Alhough adverse effects were not reported in the prospective studies, clinically significant cardiovascular and neuropsychiatric side-effects of ibogaine are well documented and would probably caution against its implementation.

Kratom[75–80]

Kratom (*Mitragyna speciosa*) is a plant indigenous to southeast Asia that contains several indole alkaloids, principally mitragynine and 7-hydroxymitragynine, with variable pharmacological properties including agonism at the μ-opioid, δ-opioid, and κ-opioid receptors. Kratom is currently regulated in the USA as a dietary supplement and is banned in the UK. Emerging evidence indicates that kratom, like other opioids, can lead to tolerance and withdrawal on cessation and is subject to misuse; kratom withdrawal has been managed successfully with clonidine and buprenorphine, and kratom overdose has been successfully reversed with naloxone. Recently, in the USA, it has been used in non-medical settings for reducing, or abstaining from, heroin use, managing chronic pain, and managing opioid withdrawal. However, it has not been evaluated for safety and efficacy in randomised controlled trials and is not available as a pharmaceutical grade product.

Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe respiratory complications of COVID-19

In March 2020, the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial was established as a randomised clinical trial to test a range of potential treatments for COVID-19, including low-dose dexamethasone (a steroid treatment). Over 11,500 patients have been enrolled from over 175 NHS hospitals in the UK.

On 8 June, recruitment to the dexamethasone arm was halted since, in the view of the trial Steering Committee, sufficient patients had been enrolled to establish whether or not the drug had a meaningful benefit.

A total of 2104 patients were randomised to receive dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days and were compared with 4321 patients randomised to usual care alone. Among the patients who received usual care alone, 28-day mortality was highest in those who required ventilation (41%), intermediate in those patients who required oxygen only (25%), and lowest among those who did not require any respiratory intervention (13%).

Dexamethasone reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75; p=0.14).

Based on these results, 1 death would be prevented by treatment of around 8 ventilated patients or around 25 patients requiring oxygen alone.

Given the public health importance of these results, we are now working to publish the full details as soon as possible.

Peter Horby, Professor of Emerging Infectious Diseases in the Nuffield Department of Medicine, University of Oxford, and one of the Chief Investigators for the trial, said: 'Dexamethasone is the first drug to be shown to improve survival in COVID-19. This is an extremely welcome result. The survival benefit is clear and large in those patients who are sick enough to require oxygen treatment, so dexamethasone should now become standard of care in these patients. Dexamethasone is inexpensive, on the shelf, and can be used immediately to save lives worldwide.'

Martin Landray, Professor of Medicine and Epidemiology at the Nuffield Department of Population Health, University of Oxford, one of the Chief Investigators, said: 'Since the appearance of COVID-19 six months ago, the search has been on for treatments that can improve survival, particularly in the sickest patients. These preliminary results from the RECOVERY trial are very clear – dexamethasone reduces the risk of death among patients with severe respiratory complications. COVID-19 is a global disease – it is fantastic that the first treatment demonstrated to reduce mortality is one that is instantly available and affordable worldwide.'

For interview requests, please contact: Genevieve Juillet, Media Relations Manager (Research and Innovation), University of Oxford, gen.juillet@admin.ox.ac.uk.

Dexamethason (9-Fluor-16α-methylprednisolon) ist ein künstliches Glucocorticoid, das entzündungshemmend u nd dämpfend auf das Immunsystem wirkt. Es gehört zu den langwirkenden Glukokortikoiden, wirkt rund 25-mal stärker als die körpereigenen Produkte[

Cell

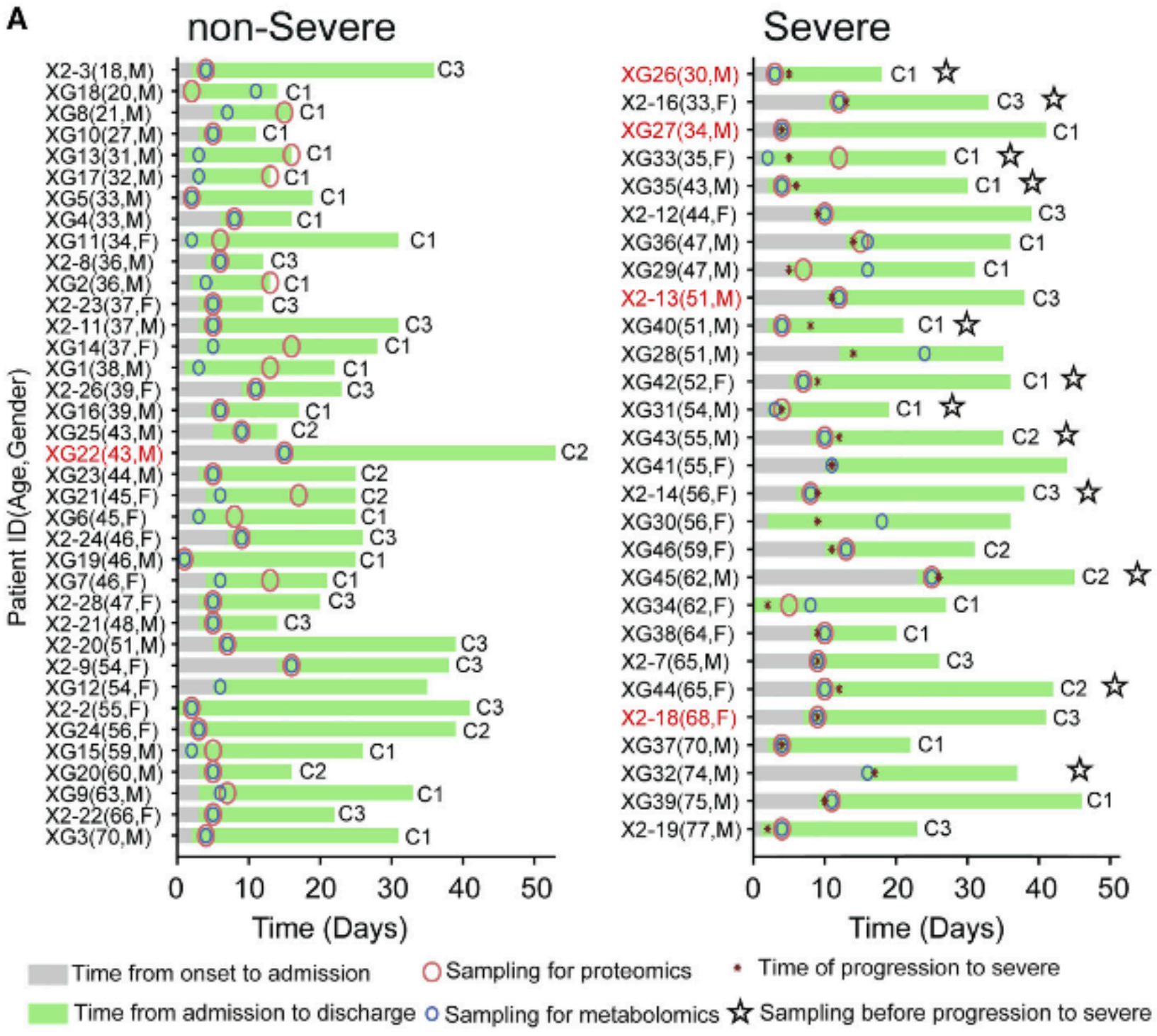
CellPress

Article

Proteomic and Metabolomic Characterization of COVID-19 Patient Sera

SUMMARY

Early detection and effective treatment of severe COVID-19 patients remain major challenges. Here, we performed proteomic and metabolomic profiling of sera from 46 COVID-19 and 53 control individuals. We then trained a machine learning model using proteomic and metabolomic measurements from a training cohort of 18 non-severe and 13 severe patients. The model was validated using 10 independent patients, 7 of which were correctly classified. Targeted proteomics and metabolomics assays were employed to further validate this molecular classifier in a second test cohort of 19 COVID-19 patients, leading to 16 correct assignments. We identified molecular changes in the sera of COVID-19 patients compared to other groups implicating dysregulation of macrophage, platelet degranulation, complement system pathways, and massive metabolic suppression. This study revealed characteristic protein and metabolite changes in the sera of severe COVID-19 patients, which might be used in selection of potential blood biomarkers for severity evaluation.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non-Severe
Severe
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XG18(20,M) C1
XG8(21,M) C1
XG10(27,M) C1
XG13(31,M) C1
XG17(32,M) C1
XG5(33,M) C1
XG4(33,M) C1
XG11(34,F) C1
X2-8(36,M) C3
XG2(36,M) C1
X2-23(37,F) C3
X2-11(37,M) C3
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XG1(38,M) C1
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0 10 20 30 40 50
Time (Days)
0 10 20 30 40 50
Time (Days)
Time from onset to admission
Time from admission to discharge
Sampling for proteomics
Sampling for metabolomics
Time of progression to severe
Sampling before progression to severe

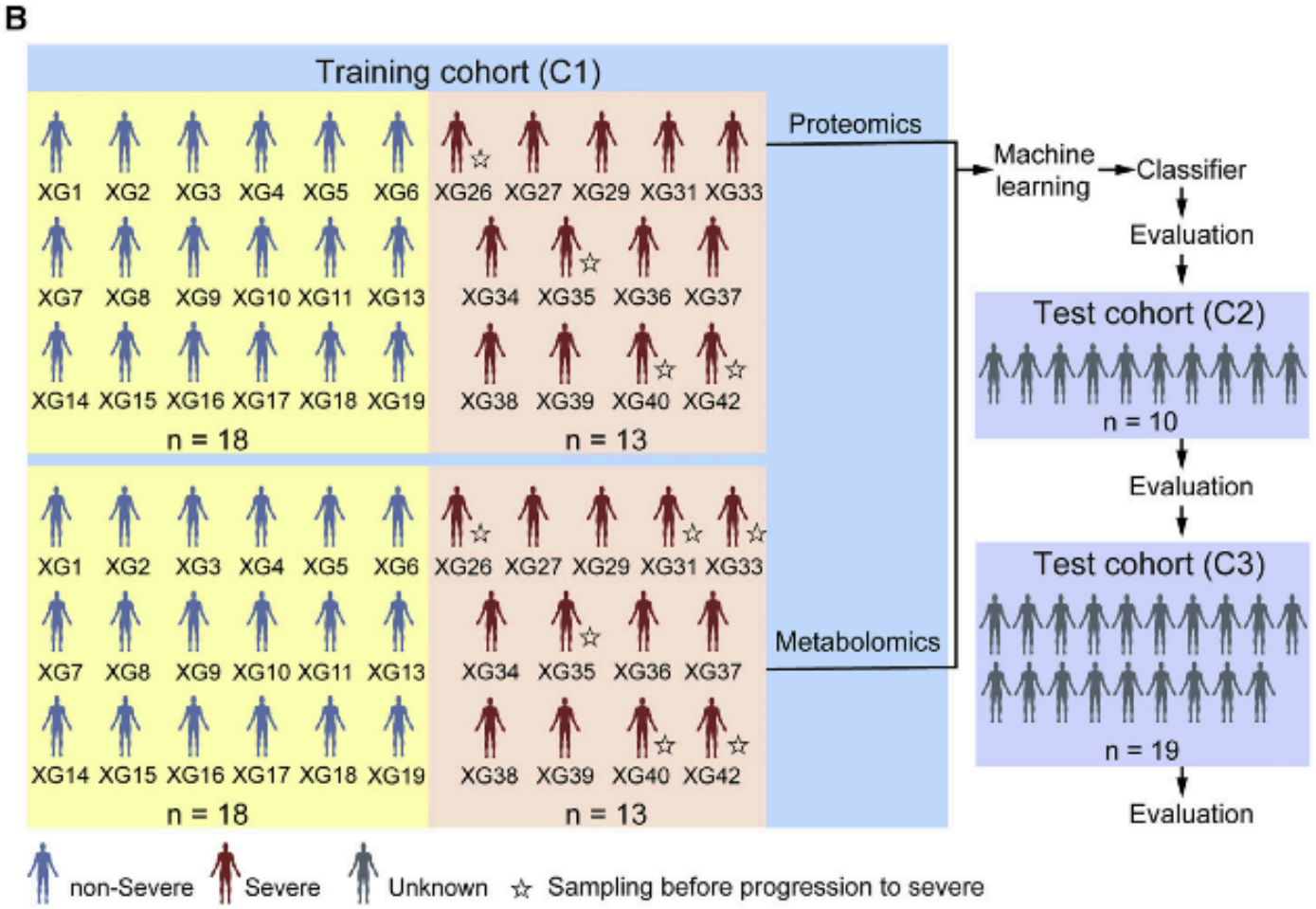


Figure 1. Summary of COVID-19 Patients and Machine Learning Design

(A) Summary of COVID-19 patients, including non-severe (n = 37) and severe (n = 28) patients with more details in Table S1. Patients labeled in red (y axis) indicate chronic infection of hepatitis B virus.

(B) Study design for machine-learning-based classifier development for severe COVID-19 patients. We first procured samples in a training cohort (C1) for proteomic and metabolomic analysis. The classifier was then validated in an independent test cohort (C2), followed by a second test cohort (C3).

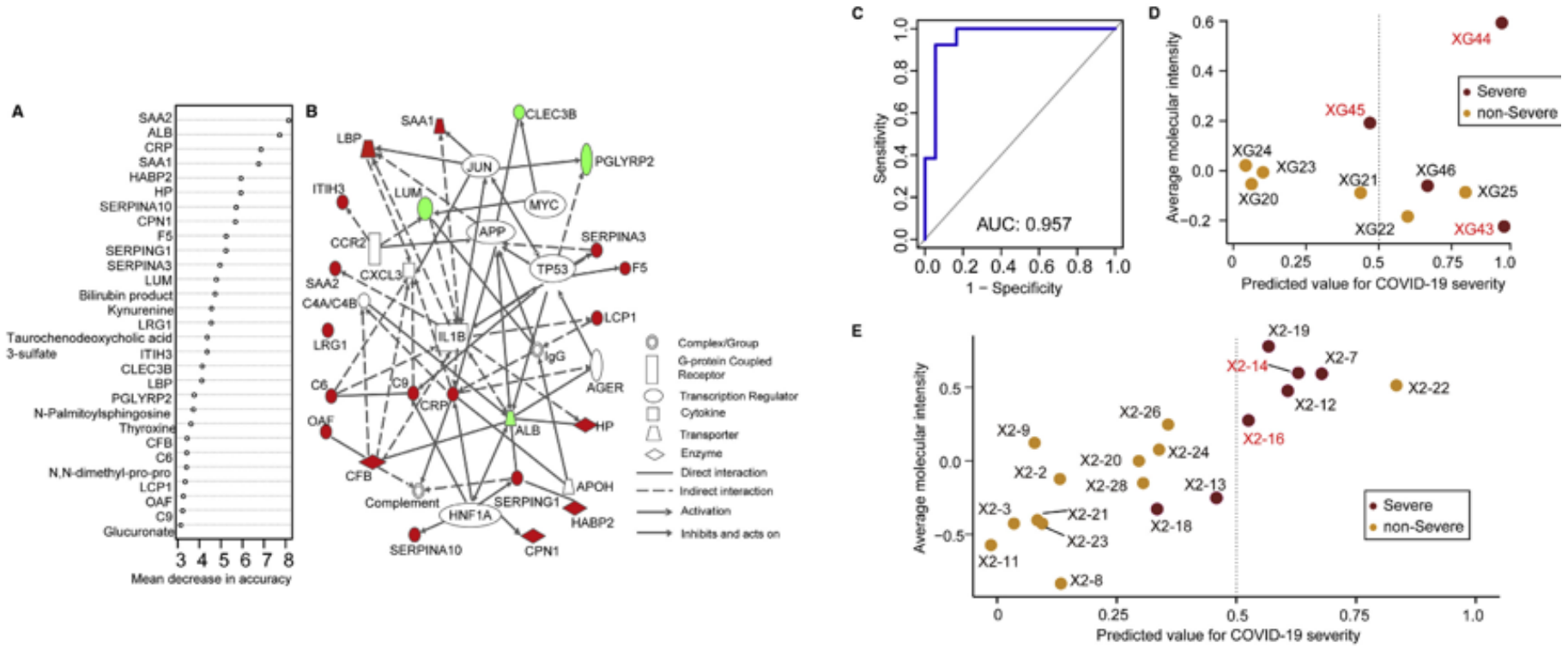


Figure 2. Separation of Severe and Non-severe COVID-19 Patients by Machine Learning of Proteomic and Metabolomic Features

(A) Top 22 proteins and 7 metabolites prioritized by random forest analysis ranked by the mean decrease in accuracy.

(B) Network of prioritized proteins appeared in the classifier. Red and green nodes indicate upregulated and downregulated molecules, respectively. White nodes represent molecules not detected in our dataset.

(C) Receiver operating characteristic (ROC) of the random forest model in the training cohort (C1).

(D) Performance of the model in the test cohort (C2) of 10 COVID-19 patients.

(E) Performance of the model in the test cohort (C3) containing 19 COVID-19 patients. Patients labeled in red received serum test before they were diagnosed as severe.

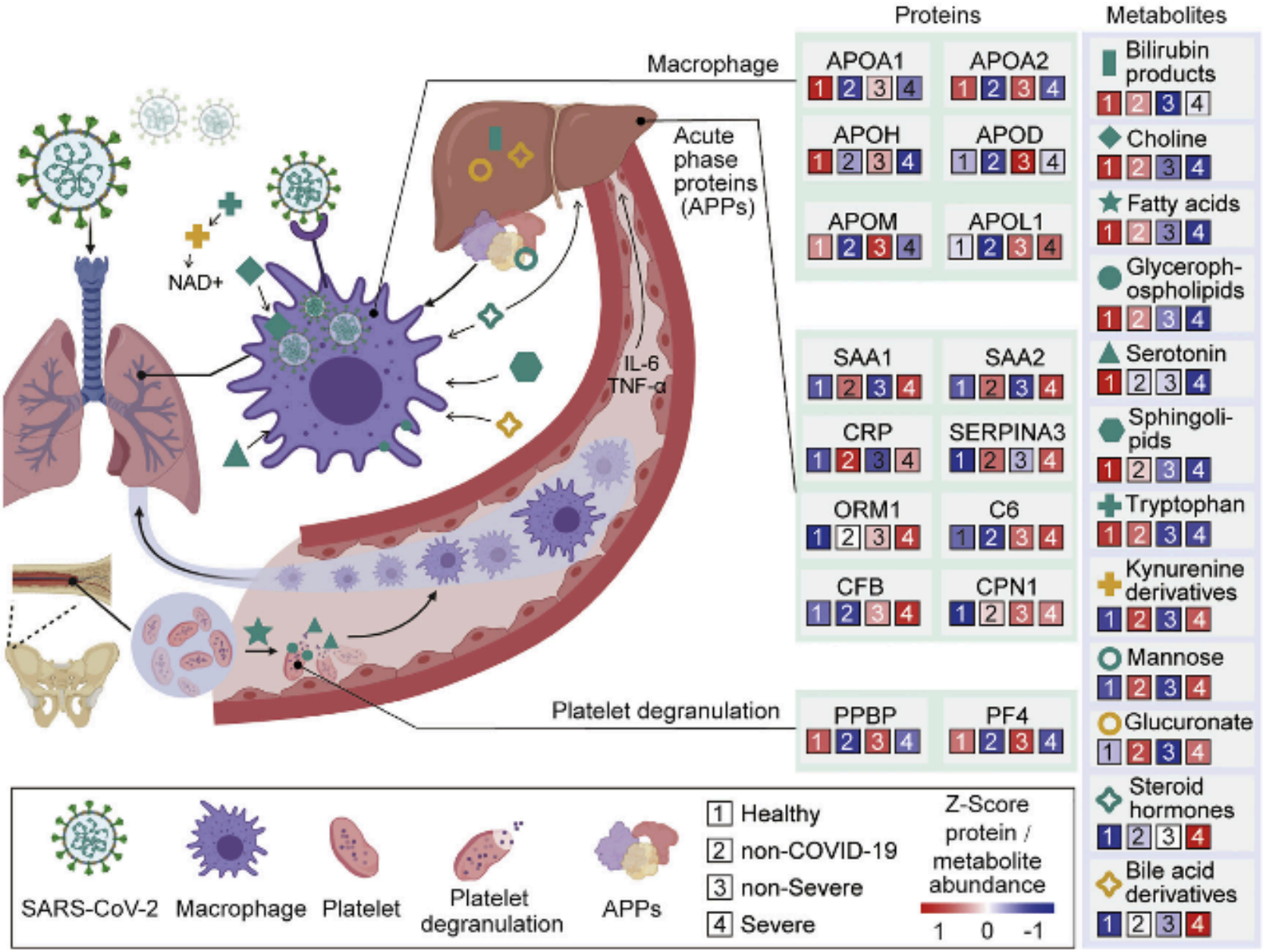
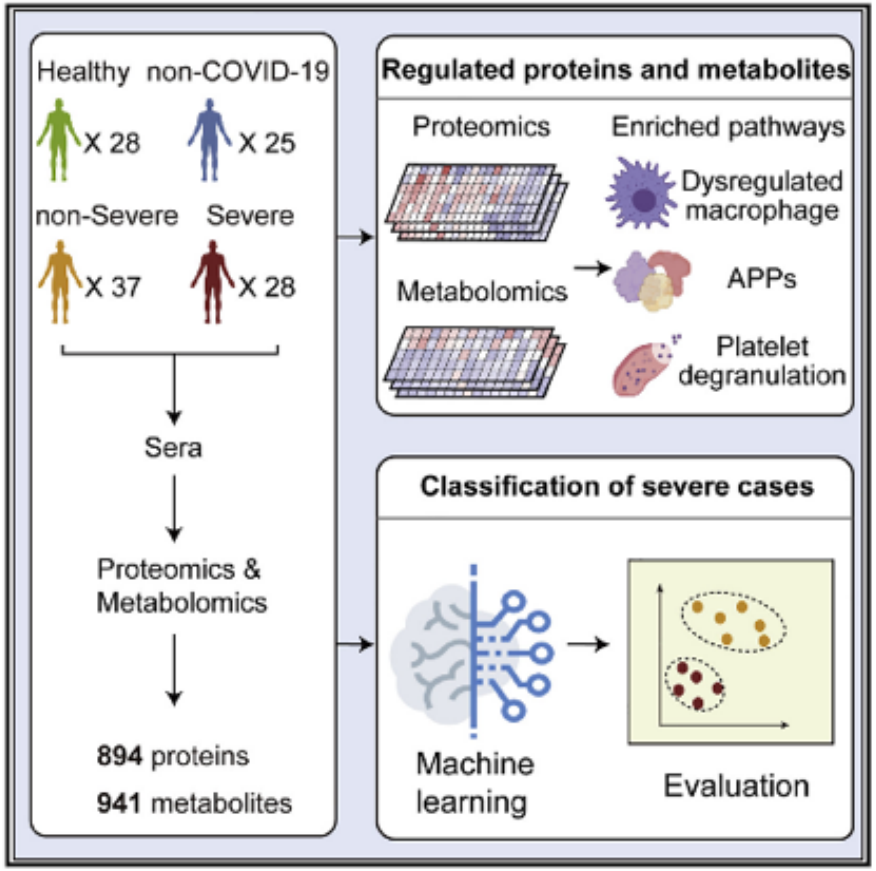


Figure 5. Key Proteins and Metabolites Characterized in Severe COVID-19 Patients in a Working Model

SARS-CoV-2 may target alveolar macrophages via ACE2 receptor, leading to an increase of secretion of cytokines including IL-6 and TNF-α, which subsequently induce the elevation of various APPs such as SAP, CRP, SAA1, SAA2, and C6, which are significantly upregulated in the severe group. Proteins involved in macrophage, lipid metabolism, and platelet degranulation were indicated with their corresponding expression levels in four patient groups.

Graphical Abstract



Highlights

- 93 proteins show differential expression in severe COVID-19 patient sera
- 204 metabolites in COVID-19 patient sera correlate with disease severity
- A model composed of 29 serum factors shows patient stratification potential
- Pathway analysis highlights metabolic and immune dysregulation in COVID-19 patients

In Brief

Proteomic and metabolomic analysis of COVID-19 sera identifies differentially expressed factors that correlate with disease severity and highlights dysregulation of multiple immune and metabolic components in clinically severe patients.

An unusual cause of breast hypertrophy: pseudoangiomatous stromal hyperplasia secondary to contraceptive implant

Sara Allen, Chandler S Cortina

A 24-year-old woman attended our clinic reporting pain, soreness, swelling, and masses in both her breasts. She said that the problems had developed over the previous 3 months. She noted that while both breasts were enlarged, her right breast had doubled in size.

She was not taking any medication, but she did have an etonogestrel—a progestagen only—contraceptive implant put in 6 months earlier. Around the time the implant was put in, she also had a lump in her right breast; a biopsy found it to be benign proliferative breast tissue. She had no significant medical or social history and there was no history of breast or ovarian cancer in her family.

On examination, we found the patient's breasts were asymmetrical; both were erythematous, tender, and had focal, palpable, mobile masses (figure). The skin of both breasts had a peau d'orange pattern. We found no axillary or supraclavicular lymphadenopathy. At this initial assessment, we were concerned for possible inflammatory breast cancer; a diagnostic mammogram and an ultrasound (figure) showed large bilateral masses. Given the skin findings, the rapid growth, and the large, irregular, and heterogeneous nature of the masses, our radiologist assigned a Breast Imaging-Reporting and Data System category of 5—indicating that we considered the lesion highly suspicious of malignancy.

Histopathological examination of samples taken from both breasts, using core-needle biopsies, showed prominent pseudoangiomatous stromal hyperplasia (PASH) and mammary hamartomas.

We then removed the implant, and 1 week later, the patient reported significant reduction in breast size, pain, pressure, and erythema. We advised her against future use of exogenous hormonal therapies with the aim of reducing the likelihood of recurrence. She is planning to have both masses excised and oncoplastic reconstructive surgery carried out.

PASH masses can resemble breast cancer both on examination and at imaging, and tissue sampling is imperative for diagnosis. PASH is a hormone-sensitive process and rapid progression can occur with sudden hormonal changes, which given the timeline we believe was the case with our patient—the contraceptive implant being the source of the excess hormone. PASH should be considered as an important differential diagnosis of breast hypertrophy in a premenopausal patient, particularly in the context of changes to the hormonal milieu.

The risk of developing breast cancer is not increased with PASH, and so follow-up using standard mammographic screening is recommended (video).

Contributors

We both provided care and diagnosed the patient. We both contributed equally to writing the Clinical Picture and taking the photographs. Written consent for publication was obtained from the patient.

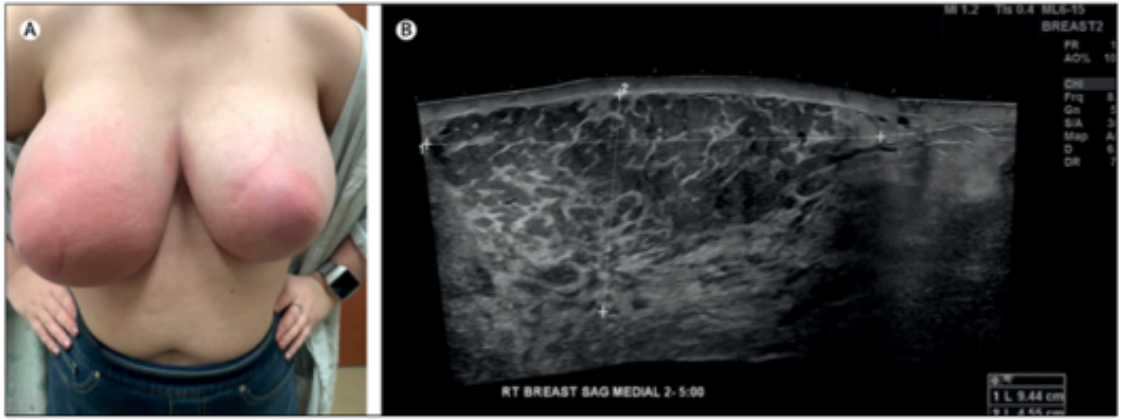


Figure: **Pseudoangiomatous stromal hyperplasia secondary to contraceptive implant**

Asymmetrical, erythematous, tender, and enlarged breasts (A). An ultrasound shows a heterogeneous mass with skin thickening—measuring 9·44 cm × 4·55 cm—in the right breast (B).