The differential expression of the ACE2 receptor across ages and gender explains the differential lethality of SARS-Cov-2 and SARS and suggests possible therapy.

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Abstract

The fatality rate of SARS-Cov-2 escalates with age and is larger in men than women. I show that these variations are strongly correlated with the levels of the ACE2 protein in the lungs but surprisingly, despite ACE2 is the viral receptor, higher levels lead to lower fatality. This behaviour is consistent with a previous mathematical model that predicts that the speed of viral progression in the organism has a maximum and then declines with the receptor level. SARS-Cov-2 degrades ACE2 and thus worsens lung injury, causes vasoconstriction, thrombotic problems, and exacerbated inflammatory response. I developed a mathematical model based on the influence of ACE2 on viral propagation and on the negative effects of its degradation. The model fits SARS-CoV-2 fatality rate across age and gender with high accuracy ($r^2 \approx 0.9$). Rescaling the model parameters with the binding rates of the spike proteins of SARS-CoV and SARS-CoV-2 allows predicting the fatality rate of SARS-CoV across age and gender, in particular its higher severity for young patients, thus linking the molecular and epidemiological levels. These results support the suggestion that drugs that enhance the expression of ACE2, such as ACE inhibitors and angiotensin receptor blockers, constitute a promising therapy against the most adverse effects of CoViD-19. Furthermore, ACE2 is a candidate prognostic factor for detecting population that needs stronger protection.

The Covid-19 pandemics [1] is causing thousands of fatalities worldwide [2], creating a tremendous threat to global health. This disease presents a striking gradient of fatalities across age and a marked gender bias that determines much higher severity for males than for females. The first observation was generally attributed to the insurgence of comorbidities and the weakening of the immune system with age. The second observation was initially attributed to the fact that men tend to smoke more than women [3]. This gender difference is very marked in China where Covid-19 emerged but it is not so strong in other countries where it spread later, raising doubts on this explanation. Indeed many experts
wondered whether the gender difference should be attributed to some more fundamental biological difference yet to be discovered [4].

To make this issue more puzzling, the infection fatality rate (IFR) of the covid-19 disease was estimated to be around 1% [5,6]. This implies that, except in countries that applied extremely intensive tests, at least 80-90% of the infections have not been detected [6,7], presumably because the symptoms were mild enough to be confused with common cold. So, how does Covid-19 escalate from extremely weak symptoms in the youngest age cohorts, where the fatality rate almost vanishes and hospitalization is not needed, to 41% fatalities in male patients over 90 that had to be hospitalized, as reported in Italy [8]? And, more important, is it possible to treat the disease so that the severity of the most affected classes approaches that of the most protected ones?

Here I show that the variation of the case fatality rate (CFR), a commonly used proxy of the IFR, across age and gender is very strongly correlated with the level of the Angiotensin converting enzyme 2 (ACE2), the cellular receptor both of SARS and SARS-CoV-2 virus [1,11], in the lungs [12]. Although these data are obtained in rats, they are qualitatively similar to ACE2 mRNA expression in human tissues [13]. This correlation rationalizes the strong observed comorbidity between covid-19 and hypertension [3], since hypertension is negatively related with ACE2 levels, which favour vasodilation.

Surprisingly, the correlation between ACE2 and lethality is strongly negative: higher levels of the receptor decrease the lethality exponentially. The paradox is only apparent if we adopt a previously developed mathematical model of virus dynamics [14]. Stated in terms of receptor level, this model predicts that the speed of viral propagation is a non-monotonic function of the receptor that reaches a maximum and then decreases at high level. Here I extend this mathematical model for predicting the lethality of the SARS-CoV-2 infection based on the assumption that patients die if the virus degrades ACE2 in the lungs below a critical threshold before the immune system can control the infection.

ACE2 [15–17] is a key component of the Renin Angiotensin System (RAS) that regulates blood pressure and electrolyte homeostasis in blood [18] together with the homologous enzyme ACE, whose action it counteracts. While ACE cleaves angiotensin I (AngI) to produce angiotensin II (AngII), a peptide that binds to the AT1R receptor producing vasoconstriction and increasing blood pressure, ACE2 cleaves angiotensin II to angiotensin 1-7, a peptide with vasodilator effect, thereby reducing blood pressure. ACE2 protects the lungs from severe injury induced by acid aspiration or sepsis [19,20], and it counteracts the pro-inflammatory effect of AngII [26,27]. Upon viral entry the spike proteins of both SARS-CoV and SARS-CoV-2 cause the internalization and degradation of ACE2 that critically contributes to lung damage [20,21]. Decrease of ACE2 activity through SARS infection [22] or aging [23] exacerbate the severity of lung injuries and inflammatory lung diseases [21]. Dis-balance of ACE2 with respect to ACE, and the resulting high blood pressure are known to enhance the prothrombotic state [24,25] and the inflammatory state [26,27], producing symptoms frequently observed in severe SARS-CoV-2 patients.

The mathematical model that considers the influence of ACE2 on viral progression
and the negative effects of its degradation predicts the CFR of SARS-CoV-2 across six classes of age and gender in Italy, Spain and Germany, which span 3 orders of magnitude, with goodness-of-fit $r^2 \approx 0.90$. Importantly, the model fitted to SARS-CoV-2 and rescaled with the ratio between the binding rates of the spike proteins of SARS-CoV and SARS-CoV-2 allows predicting the SARS-CoV CFR with very good agreement. In particular, it predicts that SARS-CoV is relatively more severe for younger ages than SARS-CoV-2, as observed, suggesting that simple mathematical models can successfully bridge the molecular and the epidemiological level.

## Results

**Age- and gender-specific lethality is negatively correlated with ACE2 level**

Due to its relevance as the SARS receptor, the levels of the ACE2 protein in rat lungs were quantified by Xie et al. across three age classes of the two genders [12]. These authors found that the level of the ACE2 protein in the lungs strongly decays with age and it is generally larger for female than for male rats, with largest differences in the oldest cohort where the expression is almost double for female than for male rats.

Strikingly, the expression profile of ACE2 is very strongly anti-correlated with the lethality profile of SARS-CoV-2, as shown in Fig.1. This figure represents the level of the ACE2 protein in lung rats measured by Xie et al. (horizontal axis, data from Fig.2 of [12]) versus the case fatality ratio (CFR) of CoVid-19 registered in Italy [8], Spain [9] and Germany [10] in three uniform age classes (young, 0-29, middle-age 30-59 and old $> 60$; vertical axis) of the two genders. The data strongly support the exponential decrease of mortality with ACE2 concentration. The exponential fit is excellent, with $r^2 = 0.91$, 0.97 and 0.89, respectively, indicating that variations of ACE2 describe the largest part of the variation of the CFR.

As for other two-parameter fits tested in this work, the fitted exponent for Italy and Germany coincide within the error and the CFR differ only for a multiplicative factor, supporting the robustness of the data. Compared with these countries, data from Spain present higher mortality in the young ages. This can be attributed to the fact that the undetected cases are more frequent in classes where the disease is less severe but, puzzlingly, the estimated fraction of undetected cases is similar in Spain and Italy [6].

Although the ACE2 protein levels were obtained in rats, a recent preprint that analysed the GTEx database found the same qualitative trends in human mRNA expression across several tissues: ACE2 expression tends to be higher in women than in men and tends to decrease with age [13]. Protein levels are more relevant for COVID-19 infection, but the trends are the same. Additional arguments that support the validity of rat data also for humans will be discussed later.

The GTEx database also shows that, despite lungs are the organ that is more severely
Figure 1: Expression of the ACE2 protein in lung rats (horizontal axis), normalized so that the highest expression is one, versus case fatality rate (vertical axis) of SARS-CoV-2 (Circles: Italy; triangles: Spain; diamonds: Germany) and SARS 2003 (open squares) in three age classes (young 0-29, middle-age 30-59 and old > 59) and two genders (male and female). The solid lines represent fits to the mathematical model (see text), the dashed lines represent predictions that rescale the models fitted to SARS-CoV-2 with the ratio between the binding rate constants of SARS and SARS-CoV-2 (see text).

damaged by COVID-19, they are not the tissue with the highest expression of ACE2 mRNA [30]. ACE2 expression is higher in tissues from reproductive organs, intestine, adipose tissue, kidney, hearth, thyroid, esophagus, breast, salivary glands and pancreas, among others. Some of these organs my be infected but they experience less damage, consistent with the negative correlation between ACE2 levels in lungs and lethality.

Mathematical model of covid-19 lethality

To rationalize the negative correlation between receptor expression and lethality I developed a mathematical model that assumes that Covid-19 deaths arise if the virus propagates through the upper respiratory tract (URT) reaching the lungs and it degrades the ACE2 receptor below a critical level before the immune system takes control.

The dynamics is crucial in this formulation. Since ACE2 is the viral receptor, we may expect that raising the ACE2 level enhance the rate at which SARS-CoV2 propagates in the organism and make the outcome of the infection worse. This reasoning lead to propose that drugs that stimulate the expression of ACE2, such as ACE inhibitors (ACE-
i) and angiotensin receptor blockers (ARB) that treat high blood pressure, may increase the risk of severe COVID-19 \[28,29\]. However, a mathematical model of viral progression shows that other outcomes are possible. Mathematical models of viral growth consider three processes: virus adsorption into susceptible cells, production of virus by infected cells after a delay time, and viral clearance by the immune system \[31\]. I shall translate here all the mathematical results in terms of receptor density, exploiting that the adsorption rate is proportional to the receptor level \( A \) expressed in susceptible cells times the association rate between the virus and the receptor, \( k_A \equiv kA \). In the simple mean-field version in which space is not considered, the model predicts that there is a minimal receptor density below which the virus does not grow and above that the initial growth rate of the virus is proportional to the adsorption rate \( kA \), implying that higher receptor levels accelerate the viral progression.

Nevertheless, virus propagate with finite velocity, and considering spatial diffusion modifies important predictions and parameters of the mathematical model. Luckily, the analytical solution of a mathematical model of viral infection in space is available \[32\]. This model was tested with experiments on the spread of bacteriophages in lysis plaques, but its mathematical formulation is conceptually equivalent to the above and can be directly applied to the present setting. As a function of the receptor level \( A \) (adsorption rate in the original paper), the authors describe two regimes: (1) when \( A \) is small the viral velocity \( v \) increases less than linearly with \( A \). (2) For intermediate \( kA \), large with respect to the delay time \( \tau \) but small with respect to the rate at which viral particles are produced, the viral velocity depends on the effective diffusion constant and it is almost independent of \( A \) \[32\], so that the viral progression is not enhanced by the expression of the receptor.

Importantly, the formulas presented in Ref. \[32\] are also valid in the third regime of very high receptor density, when \( kA \) is larger than the rate at which viral particles are produced, although this regime is not explicitly discussed. Counter-intuitively, in this regime the viral progression slows down with receptor density as \( v \propto 1/\sqrt{kA} \). This result is surprising: how can the virus progression be slowed down by increasing the receptor level? Since this is a mathematical model, the answer is readily found: in the model, viral particles are consumed when they enter a cell but the viral yield per infected cell does not increase when a cell is infected multiple times. Indeed, it was even proposed that multiple viral entries in the same cell interfere with viral replication. In fact, several viruses such as HIV \[33,34\], measles \[35\], influenza \[36\] and hepatitis B \[37\] downregulate their own receptor to prevent multiple viral entries. These observations support the idea that, after the infection is established, very fast adsorption is not advantageous for the virus, which also agrees with a recent study that demonstrated the protective effect of high adsorption rate through analytic computation, simulation and experiment \[38\]. All together, the mathematical model predicts the existence of a receptor level for which the viral progression is fastest.

Adopting these formulas it is possible to compute the time \( t_d \) after which the virus enters the lungs and degrades ACE2 below a critical level, causing the death of the patient,
as a function of the initial level of ACE2, $A$ (see Methods).

Next, I compute the lethality in each class as the probability that $t_d$ is smaller than the time $t_i$ needed by the immune system for neutralizing the virus. I model $t_i$ as a random variable, and consider two simple distributions: (1) The exponential distribution, which is the distribution with maximum entropy for given average value. (2) The Gaussian distribution, which is justified by the fact that the limit of the sum of independent random variables is a Gaussian variable and $t_i$ is the sum of intermediate steps in the maturation of the immune response. I neglect differences in immune system parameters from one age and gender class to the other in order to test if variations of the receptor level alone can explain the lethality data only through. This assumption is discussed later.

For the two tested distributions, it is easy to compute the lethality as a function of $A$ in the three possible dynamical regimes in which the viral velocity increases, is constant, and decreases with the receptor level $A$ (see Methods). In the increasing regime lethality is an increasing function of $A$. This behaviour contradicts the data and I shall not consider it further. If the velocity is constant the death probability is a decreasing function of $A$ because, at larger initial values, it takes more time to degrade the receptor below the critical level. I call this situation Model 1. If the velocity decreases the death probability is a decreasing function of $A$ even without considering this critical level (Model 2). Finally, Model 3 considers both the decrease of the velocity with $A$ and the effect of the critical level of ACE2. The three models, combined with the exponential and the Gaussian distribution, predict different functional forms of the CFR versus $A$ and they can be tested by fitting their predictions to the data (see Methods). Under both distributions, and for the CFR of all the tested countries, model 1 has the worst fit and model 3 the best. In particular, under the exponential distribution the relative quadratic error of the logarithm for models 1, 2 and 3 is 0.37, 0.19, 0.07, respectively, for Spain, 0.41, 0.30, 0.21 for Italy and 0.48, 0.23, 0.17 for Germany. Adopting the Gaussian distribution there is one additional parameter, with high risk of overfitting, but the ranking remains clear: 0.04, 0.01 and 0.01 for Spain, 0.10, 0.04 and 0.04 for Italy and 0.14, 0.06, 0.06 for Germany, so that model 1 performs the worst and it is not possible to discriminate models 2 and 3. See Methods and Supplementary Table 1 for further details. In all cases the fits are regularized through rescaled ridge regression [67] to reduce over-fitting. In summary, the hypothesis that the viral velocity decreases with the receptor density fits the data fairly well and it is preferable to the hypothesis of constant velocity, while present data do not allow assessing the effect of the critical level of ACE2.

The solid lines plotted in Fig.1 represent approximate fits of model 2 under the Gaussian distribution: $-\log(\text{CFR}) = aA - b\sqrt{A} + c$. They yield $r^2 > 0.92$ with only two free parameters, since the parameter $c$ was not fitted to reduce the error but it is necessary for obtaining the correct sign of the parameter $b$ (see Methods). The differences of parameters $a$ and $b$ between countries only slightly exceed the statistical errors. They may reflect the different incidence of undetected cases that affect different age classes differently (see Methods).

An important prediction of the model is that the fit parameters depend on the ad-
sorption constant per unit receptor, $k$, as $a \propto k$ and $b \propto \sqrt{k}$. Crucially, this prediction can be tested on the CFR of the 2003 SARS coronavirus [39], which also uses ACE2 as its cellular receptor. I hypothesize that the rate-limiting step in adsorption is the binding of the spike protein and the receptor, if their affinity is large enough to allow membrane fusion, a hypothesis supported by infection assays. Thus, I assume that $k$ is proportional to the binding rate constant between the spike and ACE2 that has been characterized with biochemical experiments. Equipped with these data, we rescale the fit parameters $a$ and $b$ obtained for SARS-CoV-2 to predict the corresponding parameters for SARS (see Methods) and multiply the predicted CFR times a global factor that accounts for the different fraction of undetected cases, which is the only free parameter. The prediction is very good, yielding relative quadratic error equal to 0.13, 0.08 and 0.010 using the fit parameters from Italy, Spain and Germany, respectively, see Fig.1, table 1 and Discussion.

It is natural to extend this analysis to the other coronavirus that uses ACE2 as receptor, NL63 [10], that causes common cold and is not generally associated with pneumonia. Its spike protein contains a very stable receptor binding domain of 120 residues (482-602) that was crystallized and showed high binding affinity for ACE2 [41]. However, the complete S1 domain of the spike (717 residues) is much less stable and its affinity for ACE2 is much smaller than for SARS-CoV [10, 42, 43]. Its affinity is so small that it was not possible to measure it with binding assays and it was conjectured that it is 10-100-fold smaller than that of SARS-CoV [42]. Since the CFR of SARS peaks for old females, whose normalized ACE2 is equal to 22% of the maximum value, and stays constant for old males with lower ACE2, the model predicts that this is the level at which SARS-CoV propagates fastest. If the binding affinity of the NL63 spike is at least ten times smaller, the ACE2 level at which NL63 propagates fastest is more than double the highest ACE2 level in the lungs, predicting that NL63 is in the regime in which ACE2 expression enhances its propagation. Consistently, NL63 infection is usually acquired during childhood [40], when the levels of ACE2 are higher. This analysis agrees with the apparently surprising data reported in Fig.3A of Ref. [40], which shows that ACE2 overexpression in 293T cells enhances NL63 infection three times more than SARS-CoV infection, indicating that higher receptor levels accelerate more the propagation of NL63 than that of SARS-CoV-2 despite the latter has higher binding affinity.

**Discussion**

This work suggests that variations of the level of the protein ACE2 in the lungs largely explain the variation of the lethality of the CoVid-19 disease across six age and gender classes whose CFR span 3 decades. ACE2 is used by the SARS-CoV-2 virus and the related SARS-Cov and NL63 virus as entry point in the cells, so that it has been proposed that its high concentration has an adverse effect and that drugs that stimulate ACE2 should be avoided in the context of the Covid-19 pandemics [28, 29]. Quite oppositely, we found that an increasing concentration of ACE2 decreases exponentially the lethality.
This result can be rationalized by a previous mathematical model that analytically predicts that the speed of viral progression in an infected organ reaches a maximum as a function of the receptor level and then decreases at higher values \[32\]. This happens because viral particles that enter cells that are already infected are consumed without increasing the viral yield. Furthermore, it has been proposed that multiple viral entries in the same cell hinder the maturation of viral particles. This effect is thought to underlay the evolution of mechanisms that limit the co-infection of the same cell by multiple viral particles by downregulating their own receptor after successful cell entry \[33–37\]. This tendency of some virus to downregulate their receptor was noted by Gurwitz for arguing against the idea that ACE2 expression favours SARS-CoV-2 infection \[44\].

Consistent with these results, the lungs are the organ where SARS-CoV-2 produces the largest damage but they rank only 19 among 54 human tissues for the expression level of ACE2, according to the GTEx database \[30\].

I developed a set of six mathematical models that predict the lethality of each age-gender class as a function of its ACE2 level in the lungs based on three elements. (1) The analytical prediction of how the receptor level influences viral propagation. (2) The hypothesis that the degradation of ACE2 is the main causative factor of the patients death, which occurs if the ACE2 level decays below a critical threshold before the immune system is able to control the infection. (3) The time necessary for the immune system to control the virus, which is modelled either as an exponential or as a Gaussian random variable. I neglected the dependence of these distributions on age and gender for two reasons. First, there are not reliable data on age- and gender-specific immune system parameters. Second and most important, I want to test the hypothesis that the levels of ACE2 alone are sufficient to determine the lethality profile without considering that the immune response weakens with age. This does not mean that the immune senescence is not important, but data can be explained even without considering it. The immune systems of male and female persons of middle age do not exhibit large differences, but their average ACE2 level and the SARS-CoV-2 lethality are different.

The resulting mathematical models provide excellent fits to the observed age and gender specific mortality rates, and the best model is the one that assumes that the propagation of the virus is slowed down by the receptor level, which fits data from the three countries with high accuracy \((r^2 > 0.92)\). Six data points is a small number, but the variation that they span is large and the agreement between data and model is very strong.

Strikingly, the fitted models also allow predicting the lethality profile across age and gender of the 2003 SARS-CoV outbreak from the measured ratio between the binding rate constants of the spike proteins of SARS and SARS-CoV-2, without free parameters except a global scale factor. The relative mean square error is 0.13, 0.08 and 0.010 using the fit parameters from Italy, Spain or Germany, respectively. Beside this surprising quantitative agreement, the most important aspect is the qualitative prediction that SARS has a higher relative incidence of mortality in young age with respect to old age compared with SARS-CoV-2 (the ratio is 22% compared with 1.3%). This is one of the most striking differences
between the two diseases, and we can qualitatively predict it from the fact that the SARS spike protein has smaller binding rate constant than SARS-CoV-2, bridging the molecular and the epidemiological level through a mathematical model of virus progression.

This prediction appears anti-intuitive: SARS is less efficient at binding its receptor, and nevertheless it is more lethal for younger ages. This comparison brings the worrying prediction that a mutation that decreases the binding affinity of the spike protein may generate a strain that is more lethal at younger ages.

Finally, the mathematical model predicts that the NL63 coronavirus, whose spike protein has much smaller binding affinity, is in a regime in which the receptor level enhances the viral progression. This is consistent with the fact that it is widespread among children that have the highest levels of the receptor, and with some apparently odd results reported in Ref. [40].

One limitation of the present work is that I used data of ACE2 protein expression obtained in rat lungs [12]. Nevertheless, a recent preprint that analysed the GTEx database [30] found the same qualitative trends of ACE2 mRNA expression in several human organs: ACE2 is more expressed in female than in male subjects, and its expression decays with age [13]. Furthermore, several arguments support the portability of expression data from rats to humans. First, there is an almost exact factor two between ACE2 expression in old female and male rats, as expected from the fact that the ACE2 gene is contained in the X chromosome both in rats and in humans, and females have two copies of it while males have only one. ACE2 is regulated by sex hormones [45], and the gender difference in level is very small for young rats, which suggests that young males compensate the disadvantage of having a single copy of the ACE2 gene overexpressing it. This may be a protective mechanism against cardio-vascular diseases (CVD), since some of the sex differences in CVD have been attributed to ACE2 [16]. Expression data show that this overexpression fades with age until the factor two gender-difference in ACE2 expression is reached at old age. These features (X chromosome location, compensatory overexpression in males that decays with age) are common between rats and humans. In contrast, a recent clinical study could not find significant differences in ACE2 expression between patients with acute respiratory distress syndrome (ARDS) of different age [47]. However, it is likely that the response to ARDS involves a complex dynamics of the RAS system to which ACE2 belongs. The clinical study measured the activity of RAS enzymes at only one time point for each patient, so that the dynamics may have obscured the individual differences.

Short after the discovery of ACE2, it was shown that this enzyme protects against lung damage in a mouse model of diffuse alveolar damage [19]. SARS and SARS-CoV-2 infections lead to degradation of ACE2, with detrimental effects on the lungs [20–22, 55]. Low levels of ACE2 increase the levels of AngII, which exacerbates the inflammatory response [26, 27], as it is observed in the most severe CoViD-19 cases, and they can also lead to the prothrombotic state that causes coagulation problems [24, 25], another frequent complication of CoViD-19 patients. Similar arguments were presented in two very recent papers that also propose that downregulation of ACE2 is the main responsible of the
complications arising in severe CoViD-19 cases [61,62].

Recent clinical studies in China and Italy support the beneficial role of ACE2 in protecting the lungs and mitigating the severity of COVID-19 [49, 50, 52, 54]. Already at the time of SARS, a retrospective meta-analysis found that the use of ACE-I provide a consistent reduction in risk of pneumonia compared with controls, in particular in patients with stroke and heart failure [56]. However, this protective role of ACE2 and of ACE-I and ARB that enhance its expression has been out-weighted by its role as entry point of SARS-Cov and SARS-Cov-2 in the cells, and it was speculated that ARB and ACE-I may favour the viral progression and should be avoided [28, 29]. Several medical societies expressed firm statements opposing this suggestion, arguing that it lacks sufficient evidence [58–60]. The current consensus is that data in humans are too limited to support either hypothesis that ACE-I and ARB may be detrimental or beneficial in COVID19 infections, but withdrawal of anti-hypertensive drugs in patients that need them may be harmful [53].

The strong negative correlation between ACE2 levels and lethality of SARS-Cov-2 found in this work, and the mathematical prediction that the receptor level does not enhance but it may even slow down the viral progression, support the clinical evidence that the effect of ACE2 on survival is positive and suggests two complementary protective roles of high ACE2 levels. On one hand, they are predicted to slow down the propagation of the virus, an effect conceptually similar to the one observed in recent experiments with soluble human ACE2 [57]. On the other hand, they alleviate the most severe complications of CoViD-19 and increase the time after which ACE2 is degraded below the critical level, giving more time to the immune system to fight against the virus. This work thus supports the idea that the drugs that upregulate ACE2 level, such as ACE inhibitors (ACE-I) and angiotensin receptor blockers (ARB) used to treat high blood pressure [15, 48], may reduce the lethality of old age classes towards the one of younger individuals and provide a promising treatment against the most adverse manifestations of CoViD-19. The same proposal has been recently advocated by Gurwitz and by Verdecchia et al. among others [44, 61], and critical trials sponsored by the University of Minnesota (NCT04312009, NCT04311177) started in April 2020. It would be desirable that other clinical trials join the effort to assess this rather promising treatment.

Finally, the results presented here suggest a prognostic role for the measurements of ACE2 levels, which may predict the severity of the disease already at an early stage and may allow detecting risk groups besides the elder. Indeed, hypertension is an important comorbidity of COVID-19 [3] that can be explained by the fact that both diseases are made more severe by lower levels of ACE2, supporting the hypothesis that individuals with low levels of ACE2 have to be protected more by the consequences of SARS-CoV-2 infection.
Materials and Methods

Case-fatality-rates and expression data

Case fatality rates (CFR) were taken from Ref. [8-10] for CoViD-19 in Italy, Spain and Germany, respectively, and from Ref. [39] for the 2003 SARS outbreak in Hong-Kong. At the beginning of an outbreak, CFR underestimate the true fatality rate because their calculation assumes that all people currently infected will recover, which unfortunately is not true. This effect may not be uniform across age-gender classes if patients of some classes tend to die more rapidly, as assumed by the model. However, at a late epidemic stage this effect is expected to be small. On the other hand, CFR overestimate the true fatality rate because of undetected cases that tend to lower the denominator. Since age-gender classes with higher lethality also tend to have more severe cases and less undetected cases, the overestimation is larger for classes with smaller lethality, with the consequence of reducing the differences among classes for larger fraction of undetected cases. The data currently available do not allow correcting for this bias, which may account for some of the differences in the fit parameters. The current data suggest that the fraction of undetected cases was roughly similar between Spain and Italy and it was much smaller for Germany [6].

Expression data presented in Ref. [12] were grouped in three age classes of 3 (young), 12 (middle) and 24 months (old). CFR were presented in bins of 10 years, and I grouped them in three equally spaced groups 0-29 (young), 30-59 (middle) and ≥ 60 years (old). Grouping the 20-29 years class with the middle age gave similar results with approximately exponential decrease of lethality with ACE2 expression.

For SARS CFR [39], ages were grouped differently: 0-44 (young), 45-74 (middle) and ≥ 75 (old). To compare these groups with those of SARS-CoV-2, I interpolated expression data of ACE2 $A$ for these groups as $A(0 - 44) = 0.667A(0 - 29) + 0.333A(30 - 59)$, $A(45 - 74) = 0.5A(30 - 59) + 0.5A(\geq 60)$ and $A(\geq 75) = 0.667A(\geq 60)$. Other schemes gave qualitatively similar results: The CFR decreases approximately exponentially with $A$ and the exponent is smaller than for SARS-CoV-2, which are the two important points made in the paper.

Mathematical model of viral propagation

The simplest mathematical model of viral propagation considers three populations: uninfected cells $U(t)$, free virus $V(t)$ that enter the cells with rate $k_A U(t)V(t)$ (adsorption) and are cleared with rate $c$, and infected cells $I(t)$ that produce new virus at rate $k_V Y I(t)$ ($Y$ stands for yield) after a delay $\tau$ called eclipse time, until they ultimately die [31]. Here I express the adsorption rate as a function of the receptor density $A$, $k_A = k_A$. The viral population cannot grow below the minimum receptor density given by $A^{\text{min}} = c/(kU_0Y)$ ($U_0$ is the initial concentration of susceptible cells). A spatially explicit version of this model in which virus diffuse through susceptible cells [14] was found amenable to ana-
lytical solution that explicitly gives the viral velocity \( v \) as a function of the model parameters \([32]\). Here I describe this solution in terms of the receptor density. The authors describe two regimes: (1) For small \( A \) \( (A < 1/(kU_0\tau Y)) \), \( A < 1/(kU_0k_V) \), the viral velocity increases with \( A \), but less then linearly, as \( v = 2\sqrt{D/kAU_0} \). (2) For intermediate receptor density \( 1/(kU_0\tau Y) < A < 1/(kU_0k_V) \) the viral velocity is given by \( v = \sqrt{2D/\tau} \), where \( D \) is the effective diffusion constant that depends on cell shape and density, and it is almost independent of \( A \) \([32]\) so that the viral progression is not enhanced by the expression of the receptor. (3) The formulas presented in the paper are also valid in the third regime of very high receptor density, when \( kA \) is larger than the rate at which viral particles are produced: \( A > 1/(kU_0\tau Y) \), \( A > 1/(kU_0k_V) \), although this regime was not explicitly discussed. Counter-intuitively, in this regime the viral progression slows down with receptor density as \( v = \sqrt{k_V/kAU_0} \).

The time that it takes for the virus to propagate through the upper respiratory tract (URT) can be estimated as \( t_U = l_U/v \). When the virus reaches the lungs, the number of infected cells grows with time as \( I(t) \propto (vt)^{d_F} \), where \( d_F \approx 2.35 \) is the fractal dimension of the lungs \([63]\), which are one of the classical examples of a fractal organ. As cells get infected, the receptor density in the lungs decreases as \( A(t) = A(0) \left(1 - I(t)/l_U^{d_F} \right) \) and it reaches the critical level \( A_c \) after the time \( t_L = (l_L/v)(1 - A_c/A_0)^{1/d_F} \approx l_L \left(1 - \frac{A_c}{A(0)} \right) \).

I used the approximation \( A_c \ll A(0) \), and \( A(0) \) is the receptor density at the beginning of the infection, which in the main text is simply denoted as \( A \). Summing these two times, I estimate the time at which death occurs as \( t_d \approx (1/v) \left[l_U + l_L \left(1 - \frac{A_c}{A(0)} \right) \right] \).

I consider three situations: (1) \( v \) is independent of \( A \); (2) \( v \) decreases as \( 1/\sqrt{kA} \) and almost all the cells in the lungs must be infected to produce the death, i.e. \( A_c = 0 \); (3) \( v \) decreases with \( A \) and \( A_c > 0 \). In each situation, the death time \( t_d \) depends on \( A \) as \( t_d \propto 1 - \frac{A_c}{d_F A} \) (Model 1), \( t_d \propto \sqrt{kA} \) (Model 2), \( t_d \propto \sqrt{k} \left(\sqrt{A} - \frac{A_c}{d_F A} \right) \) (Model 3).

In the model, death occurs if \( t_d \) is smaller than the time \( t_i \) needed by the immune system to control the virus, which is modelled either as an exponential (E) or a Gaussian (G) random variable. In the first case, the probability that \( t_i \) is larger than \( t_d \) can be computed as \( P_d = \exp(-t_d/T) \), where \( T \) is the average value of \( t_i \). In the Gaussian case, the probability is well approximated as \( P_d = C \exp \left(-(t_d - \mu)^2/(2\sigma^2) \right) \). Combining these expressions with the three models of \( t_d \) versus \( A \) and grouping together terms with the same power of \( A \), we obtain six mathematical models of the lethality \( P_d \) as a function of the initial level of ACE2 \( A \):

\[
-\ln(P_d) \approx \begin{cases} 
-\frac{a}{A} + b & \text{(1E)} \\
\frac{a}{A} - \frac{b}{A} + c & \text{(1G)} \\
\frac{a}{A} + b & \text{(2E)} \\
a\sqrt{A} + b & \text{(2G)} \\
\frac{a}{A} - \frac{b}{A} & \text{(3E)} \\
aA - b\sqrt{A} + c & \text{(3G)} 
\end{cases}
\]

\( a, b \) and \( c \) are positive fitting parameters. In Eq.(3G), there are five terms proportional to \( A, \sqrt{A}, 1/\sqrt{A}, 1/A \) and constant, corresponding to five fitting parameters. In order to
fit only three parameters, the same number as for the other Gaussian fits, I neglected the terms proportional to $1/A$ and constant, obtaining Eq. (3G), while neglecting the terms proportional to $1/A$ and $1/\sqrt{A}$ yields Eq. (2G).

**Fits of the model**

I determine the fitting parameters $a$, $b$, $c$ through regularized fits performed with rescaled ridge regression [67], which minimizes the quadratic error plus the term $\Lambda(a^2+b^2+c^2)$ that penalizes large values of the parameters. The regularization is necessary to avoid amplifying the noise due to covariant explanatory variables, as in the present case, and it allows more robust parameter estimation, often avoiding that they acquire unphysical values with incorrect sign, at the price of some bias. Rescaled ridge regression yields non vanishing parameters even in the limit of very large $\Lambda$, overcoming a drawback of other regularization schemes, and it fixes the parameter $\Lambda$ based on an analogy with statistical mechanics at the transition between the phase dominated by the noise and the one dominated by the bias. For ridge regression there is no analytic formula to determine the statistical error of the fitting parameters, therefore I applied a bootstrap approach, repeating the fit while eliminating each of the data points and computing the standard deviation of the fitting parameters numerically.

Despite these cautions, three-parameter fits of only six points are prone to overfitting, but when the Gaussian distribution was considered the two parameters fits yielded some parameters with incorrect sign. In these cases, I scanned different values of the constant $c$, I fitted $-\ln(P_d) - c = aA - b\sqrt{A}$ with only two free parameters and determined the parameter $c$ not by minimizing the error of the fit but by choosing a given value of the relative error on the parameters (50%).

**Prediction for SARS**

The models fitted to SARS-CoV-2 were rescaled in order to apply them to SARS-CoV, adopting the ratio between the binding rates of the spike proteins of both viruses to ACE2. The most precise measures available in the literature are $k_{\text{SARS-2}} = (2.3 \pm 1.4) \times 10^5 \text{nM}^{-1} \text{s}^{-1}$ and $k_{\text{SARS}} = (1.7 \pm 0.7) \times 10^5 \text{nM}^{-1} \text{s}^{-1}$ (table 1 in [66]). Although the error bars are huge, the greater rate constant of SARS-CoV-2 agrees with the more precisely determined binding affinity from the same table ($K_{\text{SARS-2}} = (1.2 \pm 0.1) \text{nM}$ and $K_{\text{SARS}} = (5.0 \pm 0.1) \text{nM}$), and from Ref. [65] that indicates that the spike protein of SARS-CoV-2 has greater affinity for ACE than the one of SARS-CoV. In that paper only one experiment was performed instead of five in Ref. [66] and the binding rate constant was greater for SARS-CoV, which is consistent with the large statistical errors measured in Ref. [66]. Thus, although the available data is quite noisy, the best available evidence suggests that the binding rate of SARS-CoV-2 spike protein is on the average faster than for SARS and the binding is more stable, which may also contribute to faster absorption giving the virus more time to perform membrane fusion.
For predicting the CFR of the 2003 SARS outbreak, I used the parameters of SARS-CoV-2 and rescaled them with the ratio between the kinetic binding constant $k^{cm}$ of the two spike proteins: $a_{SARS} = a_{SARS-2}/1.35$ and $b_{SARS} = b_{SARS-2}/\sqrt{1.35}$. I obtained the lethality profile as $\exp(-a_{SARS}A + b_{SARS}\sqrt{A})$, where $A$ is the ACE2 level of each gender and age class, and multiplied it times a constant factor that accounts for the different fraction of undetected cases, which was the only free parameter determined through a fit.

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References

[1] Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. (2020) A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 579 (7798): 270-273. doi:10.1038/s41586-020-2012-7

[2] https://github.com/CSSEGISandData/COVID-19/tree/master/csse_covid_19_data

[3] W. Guan et al. Clinical Characteristics of Coronavirus Disease 2019 in China. New Eng J Med 2020, DOI: 10.1056/NEJMoa200203

[4] https://www.the-scientist.com/news-opinion/why-some-covid-19-cases-are-worse-than-others-67160

[5] Verity, R. et al. Estimates of the severity of coronavirus disease 2019: a model-based analysis. The Lancet, published online (2020). https://doi.org/10.1016/S1473-3099(20)30257-7.

[6] Bastolla, U. How lethal is the novel coronavirus, and how many undetected cases are there? The importance of being tested. medRxiv 2020.03.27.20045062; doi: https://doi.org/10.1101/2020.03.27.20045062

[7] Seth Flaxman, Swapnil Mishra, Axel Gandey et al. Estimating the number of infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries. Imperial College London (2020), doi:https://doi.org/10.25561/77731
[8] Task force COVID-19 del Dipartimento Malattie Infettive e Servizio di Informatica, Istituto Superiore di Sanità. Epidemia COVID-19, Aggiornamento nazionale: 30 marzo 2020 (in Italian) https://www.epicentro.iss.it/coronavirus/bollettino/Bollettino-sorveglianza-integrata-COVID-19_2-aprile-2020.pdf

[9] Centro de Coordinacin de Alertas y Emergencias Sanitarias (Spain) Actualizacin n 76. Enfermedad por el coronavirus (COVID-19). 15.04.2020

[10] Coronavirus Disease 2019(COVID-19) Daily Situation Report of the Robert Koch Institute 28/04/2020 UPDATED STATUS FOR GERMANY.

[11] Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H (June 2004) Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. A first step in understanding SARS pathogenesis. The Journal of Pathology. 203 (2): 6317. doi:10.1002/path.1570

[12] Xie X, Chen J, Wang X, Zhang F, Liu Y (2006) Age- and gender-related difference of ACE2 expression in rat lung. Life Sci. 78:2166-71.

[13] Chen, J.; Jiang, Q.; Xia, X.; Liu, K.; Yu, Z.; Tao, W.; Gong, W.; Han, J.J. Individual Variation of the SARS-CoV2 Receptor ACE2 Gene Expression and Regulation. Preprints 2020, 2020030191 Chen, J.; Jiang, Q.; Xia, X.; Liu, K.; Yu, Z.; Tao, W.; Gong, W.; Han, J.J. Individual Variation of the SARS-CoV2 Receptor ACE2 Gene Expression and Regulation. Preprints 2020, 2020030191

[14] Fort J, Méndez V (2002) Time-delayed spread of viruses in growing plaques. Phys Rev Lett. 89:178101.

[15] https://en.wikipedia.org/wiki/Angiotensin-converting_enzyme_2

[16] Gene: ACE2, angiotensin I converting enzyme 2. National Center for Biotechnology Information (NCBI). U.S. National Library of Medicine. 2020-02-28

[17] Donoghue M, Hsieh F, Baronas E, Godbout K, Gosselin M, Stagliano N, Donovan M, Woolf B, Robison K, Jeyaseelan R, Breitbart RE, and Acton S. A Novel Angiotensin-Converting EnzymeRelated Carboxypeptidase (ACE2) Converts Angiotensin I to Angiotensin 1-9. Circulation Research. 87 (5): e1e9. doi:10.1161/01.RES.87.5.e

[18] Paz Ocaranza, M., Riquelme, J.A., Garca, L. et al. Counter-regulatory reninangiotensin system in cardiovascular disease. Nat Rev Cardiol 17, 116129 (2020). https://doi.org/10.1038/s41569-019-0244-8

[19] Imai Y, Kuba K, Rao S, Huan Y, Guo F, Guan B, Yang P, Sarao R, Wada T, Leong-Poi H, Crackower MA, Fukamizu A, Hui CC, Hein L, Uhlig S, Slutsky AS, Jiang C, Penninger JM (2005) Angiotensin-converting enzyme 2 protects from severe acute lung failure. Nature 436:112-6.
[20] Imai Y, Kuba K, Penninger JM (2008) The discovery of angiotensin-converting enzyme 2 and its role in acute lung injury in mice. Experimental Physiology. 93 (5): 5438. doi:10.1113/expphysiol.2007.040048.

[21] Jia H (2016) Pulmonary Angiotensin-Converting Enzyme 2 (ACE2) and Inflammatory Lung Disease. Shock. Augusta, Ga. 46 (3): 23948. doi:10.1097/SHK.0000000000000633.

[22] Kuba K, Imai Y, Rao S, Gao H, Guo F, Guan B, Huan Y, Yang P, Zhang Y, Deng W, Bao L, Zhang B, Liu G, Wang Z, Chappell M, Liu Y, Zheng D, Leibbrandt A, Wada T, Slutsky AS, Liu D, Qin C, Jiang C, Penninger JM (2005) A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 11:875-9.

[23] Schouten LRA, Helmerhorst HJF, Wagenaar GTM, Haltenhof T, Lutter R, Roelofs JJ, et al. Age-dependent changes in the pulmonary renin-angiotensin system are associated with severity of lung injury in a model of acute lung injury in rats. Crit Care Med. 2016;44:e122635.

[24] GY Lip (2000) Hypertension and the prothrombotic state. J Hum Hypertens. 14:687-90.

[25] Remkova A, Remko M (2010) The role of renin-angiotensin system in prothrombotic state in essential hypertension. Physiol Res. 59:13-23.

[26] Agarwal D, Dange RB, Raizada MK, Francis J. Angiotensin II causes imbalance between pro- and anti-inflammatory cytokines by modulating GSK-3β in neuronal culture. Br J Pharmacol. 2013 169:860-74. doi: 10.1111/bph.12177.

[27] Satou R, Penrose H2, Navar LG Inflammation as a Regulator of the Renin-Angiotensin System and Blood Pressure. Curr Hypertens Rep. 2018 20:100. doi: 10.1007/s11906-018-0900-0.

[28] Fang L, Karakiulakis G, Roth M (2020) Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med Available from: [http://dx.doi.org/10.1016/S2213-2600(20)30116-8](http://dx.doi.org/10.1016/S2213-2600(20)30116-8)

[29] Diaz JH (2020) Hypothesis: angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may increase the risk of severe COVID-19. Journal of Travel Medicine. doi:10.1093/jtm/taaa04

[30] https://gtexportal.org/home/gene/ACE2

[31] Smith, A.M.; Perelson, A.S. Influenza A virus infection kinetics: Quantitative data and models. Syst. Biol. Med. 2011, 3, 429445.
[32] V. Ortega-Cejas, J. Fort, V. Méndez and D. Campos (2004) Approximate solution to the speed of spreading viruses. Phys Rev E 69, 031909.

[33] Michel N1, Allespach I, Venzke S, Fackler OT, Keppler OT (2005) The Nef protein of human immunodeficiency virus establishes superinfection immunity by a dual strategy to downregulate cell-surface CCR5 and CD4. Curr Biol. 15:714-23.

[34] Bour S. Geleziunas R. Wainberg M.A. (1995) The human immunodeficiency virus type 1 (HIV-1) CD4 receptor and its central role in promotion of HIV-1 infection. Microbiol. Rev. 59: 63-93

[35] Schneider-Schaulies J. Schnorr J.J. Brinckmann U. Dunster L.M. Baczko K. Liebert U.G. Schneider-Schaulies S. ter Meulen V. (1995) Receptor usage and differential downregulation of CD46 by measles virus wild-type and vaccine strains. Proc. Natl. Acad. Sci. USA. 92: 3943-3947

[36] Marschall M, Meier-Ewert H, Herrler G, Zimmer G, Maassab HF (1997) The cell receptor level is reduced during persistent infection with influenza C virus. Arch Virol. 142:1155-64.

[37] Breiner K.M. Urban S. Glass B. Schaller H (2001) Envelope protein-mediated down-regulation of hepatitis B virus receptor in infected hepatocytes. J. Virol. 2001; 75: 143-150

[38] Eriksen RS, Svenningsen SL, Sneppen K and Mitarai N (2018) A growing micro-colony can survive and support persistent propagation of virulent phages. PNAS 115, 337-342.

[39] J. Karlberg, D. S. Y. Chong, and W. Y. Y. Lai (2004) Do Men Have a Higher Case Fatality Rate of Severe Acute Respiratory Syndrome than Women Do? Am J Epidemiol 159, 229-231 DOI: 10.1093/aje/kwh056

[40] Hofmann H, Pyrc K, van der Hoek L, Geier M, Berkhout B and Pöhlmann S (2005) Human coronavirus NL63 employs the severe acute respiratory syndrome coronavirus receptor for cellular entry. PNAS 102: 7988-7993. https://doi.org/10.1073/pnas.0409465102

[41] Kailang Wu, Weikai Li, Guiqing Peng, and Fang Li (2009) Crystal structure of NL63 respiratory coronavirus receptor-binding domain complexed with its human receptor PNAS 106 19970-19974; https://doi.org/10.1073/pnas.0908837106

[42] Mathewson, A. C., A. Bishop, Y. Yao, F. Kemp, J. Ren, H. Chen, X. Xu, B. Berkhout, L. van der Hoek, and I. M. Jones. 2008. Interaction of severe acute respiratory syndrome-coronavirus and NL63 coronavirus spike proteins with angiotensin converting enzyme-2. J. Gen. Virol. 89:2741-2745.
[43] Glowacka I, Bertram S, Herzog P, Pfefferle S, Steffen I, Muench MO, Simmons G, Hofmann H, Kuri T, Weber F, Eichler J, Drosten C, Pöhlmann S (2010) Differential downregulation of ACE2 by the spike proteins of severe acute respiratory syndrome coronavirus and human coronavirus NL63. J Virol. 2010 84:1198-205. doi: 10.1128/JVI.01248-09.

[44] Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics David Gurwitz. Drug development research 2020. https://doi.org/10.1002/ddr.21656

[45] Bukowska A, Spiller L, Wolke C, Lendeckel U, Weinert S, Hoffmann J, Bornfleth P, Kutschka I, Gardemann A, Isermann B, Goette A (2017) Protective regulation of the ACE2/ACE gene expression by estrogen in human atrial tissue from elderly men. Exp Biol Med 242:1412-1423. doi: 10.1177/1535370217718808.

[46] Gupte M, Thatcher SE, Boustany-Kari CM, Shoemaker R, Yiannikouris F, Zhang X, Karounos M, Cassis LA. Angiotensin converting enzyme 2 contributes to sex differences in the development of obesity hypertension in C57BL/6 mice. Arterioscler Thromb Vasc Biol 32: 13921399, 2012. doi:10.1161/ATVBAHA.112.248559.

[47] Schouten, L.R., van Kaam, A.H., Kohse, F. et al. Age-dependent differences in pulmonary host responses in ARDS: a prospective observational cohort study. Ann. Intensive Care 9, 55 (2019). https://doi.org/10.1186/s13613-019-0529-4

[48] C.M. Ferrario, J. Jessup, M.C. Chappell, D.B. Averill, K.B. Brosnihan, E.A. Tallant, D.I. Diz and P.E. Gallagher (2005) Effect of Angiotensin-Converting Enzyme Inhibition and Angiotensin II Receptor Blockers on Cardiac Angiotensin-Converting Enzyme 2. Circulation 111:26052610. https://doi.org/10.1161/CIRCULATIONAHA.104.510461

[49] Hao Cheng, Yan Wang, Gui-Qiang Wang (2020) Organ-protective effect of angiotensin-converting enzyme 2 and its effect on the prognosis of COVID-19. J Med Virol https://doi.org/10.1002/jmv.25785

[50] Anti-hypertensive Angiotensin II receptor blockers associated to mitigation of disease severity in elderly COVID-19 patients Yingxia Liu, Fengming Huang, Jun Xu, Penghui Yang, Yuhao Qin, Mengli Cao, Zhaoqin Wang, Xiaohe Li, Shaogeng Zhang, Lu Ye, Jingjun Lv, Jie Wei, Tuxiu Xie, Hong Gao, Kai-Feng Xu, Fusheng Wang, Lei Liu, Chengyu Jiang doi: https://doi.org/10.1101/2020.03.20.20039586

[51] Angiotensin II Receptor Blockers and Angiotensin-Converting Enzyme Inhibitors Usage is Associated with Improved Inflammatory Status and Clinical Outcomes in COVID-19 Patients With Hypertension. G Yang et al. MedRxiv preprint https://doi.org/10.1101/2020.03.31.20038935
[52] G.P. Rossi, V. Sanga, M. Barton (2020) Potential harmful effects of discontinuing ACE-inhibitors and ARBs in COVID-19 patients eLife, available online

[53] M. Vaduganathan, O. Vardeny, T. Michel, J.J.V. McMurray, M.A. Pfeffer and S.D. Solomon (2020) ReninAngiotensinAldosterone System Inhibitors in Patients with Covid-19. N Eng J Med, available online.

[54] T.C. Hanff, M.O. Harhay, T.S. Brown, J.B. Cohen, A.M. Mohareb (2020) Is There an Association Between COVID-19 Mortality and the Renin-Angiotensin System—a Call for Epidemiologic Investigations. Clin Infect Dis 2020 Mar 26 (available online)

[55] Nicholls J, Peiris M (2005) Good ACE, bad ACE do battle in lung injury, SARS. Nature Med. 11: 8212. doi:10.1038/nm0805-821.

[56] Caldeira D, Alarcao J, Vaz-Carneiro A, Costa J (2012). Risk of pneumonia associated with use of angiotensin converting enzyme inhibitors and angiotensin receptor blockers: systematic review and meta-analysis. BMJ. 345: e4260. doi:10.1136/bmj.e4260.

[57] V. Monteil et al. (2020) Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. Cell, available online

[58] Position Statement of the ESC Council on Hypertension on ACE-Inhibitors and Angiotensin Receptor Blockers. European Society of Cardiology (ESC). 13 March 2020. Lay summary Medscape.

[59] EMA advises continued use of medicines for hypertension, heart or kidney disease during COVID-19 pandemic. European Medicines Agency (EMA). 27 March 2020. Lay summary Medscape.

[60] HFSA/ACC/AHA Statement Addresses Concerns Re: Using RAAS Antagonists in COVID-19. American College of Cardiology (ACC). 27 March 2020. Lay summary Medscape.

[61] Verdecchia P, Cavallini C, Spanevello A and Angeli F (2020) The pivotal link between ACE2 deficiency and SARS-CoV-2 infection. Eur J Intern Med. 2020 Apr 20 doi: 10.1016/j.ejim.2020.04.037

[62] Ciaglia E, Vecchione C, Puca AA (2020) COVID-19 Infection and Circulating ACE2 Levels: Protective Role in Women and Children. Frontiers in Pediatrics 8:206 https://www.frontiersin.org/article/10.3389/fped.2020.00206

[63] E.R. Weibel (1991) Fractal geometry: A design principle for living organisms, Am J Physiol 261 L361L369.
[64] R. Yan, Y. Zhang, Y. Li, L. Xia, Y. Guo, Q. Zhou (2020) Structural basis for 
the recognition of the SARS-CoV-2 by full-length human ACE2. Science (2020) 
eabb2762 DOI: 10.1126/science.abb2762

[65] D. Wrapp, N. Wang, K.S. Corbett, J.A. Goldsmith, C-L. Hsieh, O. Abiona, B.S. 
Graham, J.S. McLellan (2020) Cryo-EM structure of the 2019-nCoV spike in the 
prefusion conformation. Science 367, 1260-1263. DOI: 10.1126/science.abb2507

[66] Walls AC1, Park YJ1, Tortorici MA2, Wall A3, McGuire AT4, Veesler D (2020) 
Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell. 
pii: S0092-8674(20)30262-2. doi: 10.1016/j.cell.2020.02.058

Andersen, K.G., Rambaut, A., Lipkin, W.I. et al. The proximal origin of SARS-
CoV-2. Nat Med (2020). https://doi.org/10.1038/s41591-020-0820-9

[67] Bastolla U, Dehouck Y. (2019) Can conformational changes of proteins be repre-
sented in torsion angle space? A study with rescaled ridge regression. J Chem Inf 
Model 59:4929-4941. doi:10.1021/acs.jcim.9b00627
| Fit | $v(A)$ | $A_{cr}$ | $P(t_i)$ | $-\ln(P_d)$ | Error | $a^c$ | $b^c$ | $c^c$ | Data |
|-----|--------|----------|---------|------------|------|------|------|------|------|
| exp |        |          |         |            |      |      |      |      |      |
| 1E  | Const  | $> 0$    | E       | $-\frac{a}{A} + b$ | 0.37 | 5.2  | 1.1  | 1.0  | ES   |
| 2E  | Decr   | $> 0$    | E       | $-\frac{a}{A} + b$ | 0.19 | 5.7  | 0.1  | 0.3  | ES   |
| 3E  | Decr   | 0        | E       | $a\sqrt{A} + b$    | 0.07 | 6.8  | 0.6  | 0.3  | ES   |
| 1G  | Const  | $> 0$    | G       | $\frac{a}{A^2} - \frac{b}{A} + c$ | 0.04 | 0.2  | 2.5  | 0.5  | ES   |
| 2G  | Decr   | 0        | G       | $aA - b\sqrt{A} + c$ | 0.01 | 6.1  | 0.7  | 0.4  | ES   |
| 3G  | Decr   | $> 0$    | G       | $aA - b\sqrt{A} + \frac{c^2}{\sqrt{A}}$ | 0.01 | 7.0  | 0.7  | 0.1  | ES   |
| 2G2 | Decr   | 0        | G       | $aA - b\sqrt{A} + c$ | 0.01 | 6.9  | 1.1  | 0.5  | ES   |
| 2G1 | Decr   | 0        | G       | $aA - b\sqrt{A} + c$ | 0.08 | 5.09 | 0.97 | 0.01 | SA   |

Table 1: **Fit results.** (a) Type of fit. (b) Dependence of viral velocity on receptor level $A$. I test only the constant and decreasing regime because the increasing regime contradicts the data. (c) Critical level of ACE2 below which the patient dies. If $A_{crit} = 0$ death happens later and the CFR depends less on the initial level of ACE2. (d) Distribution of the response time of the immune system, either exponential (E) or Gaussian (G). (e) Functional form of the logarithm of the death probability (estimated as CFR) versus the initial receptor level $A$ computed with the mathematical model under hypothesis b, c and d. (f) Relative mean square error $1 - r^2$ of the fit regularized with re-scaled ridge regression (i.e. the error is not the minimal possible), imposing that all fit parameters are positive. (g-i) Fit parameters and statistical error computed with bootstrapping. (j) Fitted CFR data. ES=Spain, IT=Italy, DE=Germany, SA=SARS 2003 Hong Kong. In fit 2G2 only the parameters $a$ and $b$ are fitted while $c$ is set to get a given value of the relative error of the parameters. In fit 2G1, for the 2003 SARS, only the multiplicative parameter $c$ is fitted while $a$ and $b$ are predicted based on the corresponding parameters of Spain, Italy and Germany and the ratio between the kinetic rate constant of the spike proteins of SARS-Cov and SARS-Cov-2. Note that two-parameter fits from Italy and Germany coincide within the error except for a multiplicative factor (additive in the logarithm) despite the fraction of undetected cases of the two countries are very different.