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Spironolactone may provide protection from SARS-CoV-2: Targeting androgens, angiotensin converting enzyme 2 (ACE2), and renin-angiotensin-aldosterone system (RAAS)

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ABSTRACT

In coronavirus disease-19 (COVID-19), four major factors have been correlated with worse prognosis: aging, hypertension, obesity, and exposure to androgen hormones. Angiotensin-converting enzyme-2 (ACE2) receptor, regulation of the renin-angiotensin-aldosterone system (RAAS), and transmembrane serine protease 2 (TMPRSS2) action are critical for the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) cell entry and infectivity. ACE2 expression and RAAS are abnormal in hypertension and obesity, while TMPRSS2 is overexpressed when exposed to androgens, which may justify why these factors are overrepresented in COVID-19.

Among therapeutic targets for SARS-CoV-2, we hypothesized that spironolactone, a long used and safe mineralocorticoid and androgen receptors antagonist, with effective anti-hypertensive, cardioprotective, nephroprotective, and anti-androgenic properties may offer pleiotropic actions in different sites to protect from COVID-19. Current data shows that spironolactone may concurrently mitigate abnormal ACE2 expression, correct the balances membrane-attached and free circulating ACE2 and between angiotensin II and Angiotensin-(1-7) (Ang-(1-7)), suppress androgen-mediated TMPRSS2 activity, and inhibit obesity-related RAAS dysfunctions, with consequent decrease of viral priming. Hence, spironolactone may provide protection from SARS-CoV-2, and has sufficient plausibility to be clinically tested, particularly in the early stages of COVID-19.

Introduction

Specific characteristics of SARS-CoV-2 may explain the relative unsuccessfulness of the virus contention policies, including long virus shedding (20 days on average) [1] and period of incubation (up to 11 days) [2], the existence of multiple asymptomatic infections [1–3], and the prolonged surviving in surfaces and aerosol.

Although preliminary, consistent data elude to the fact that three major factors are atypically correlated with worse prognosis in SARS-CoV-2: hypertension, obesity, and androgen hormones.

Indeed, hypertension alone seems to be overrepresented in patients with acute respiratory distress syndrome (ARDS) due to Covid-19 (23.2%) when compared to type 2 diabetes *mellitus* (T2DM) (16.2%) and established coronary heart disease (5.8%), in addition to the approximate increase of 10% risk per year of age [4,5]. In China, where the prevalence of metabolic syndromes including obesity and T2DM are lower compared to Europe and USA, hypertension emerged as the strongest risk predictor for SARS-CoV-2 [6].

Obesity has been further identified as an important risk factor in SARS-CoV-2, which have been noticed after the pandemic spread to countries with higher prevalence of obesity. However, hypertension remained as an independent risk factor for respiratory severe manifestations in COVID-19 in obese patients, and was still prevailing in COVID-19 intensive care units (ICUs) in regions where obesity is highly prevalent.

Strong epidemiological data also supports the hypothesis that androgens are directly related to SARS-CoV-2 infectivity and pathogenesis. The larger incidence of severe COVID-19 in men compared to women is not fully justified by differences in the prevalence of metabolic disorders (obesity, T2DM, hypertension). Accordingly, pre-pubertal children show an imperative protection from SARS-CoV-2 infection, once this population is not exposed to androgens. Further, an indirect marker of dihydrotestosterone (DHT) activity and androgen receptor (AR) regulation and sensitivity, baldness has been clinically

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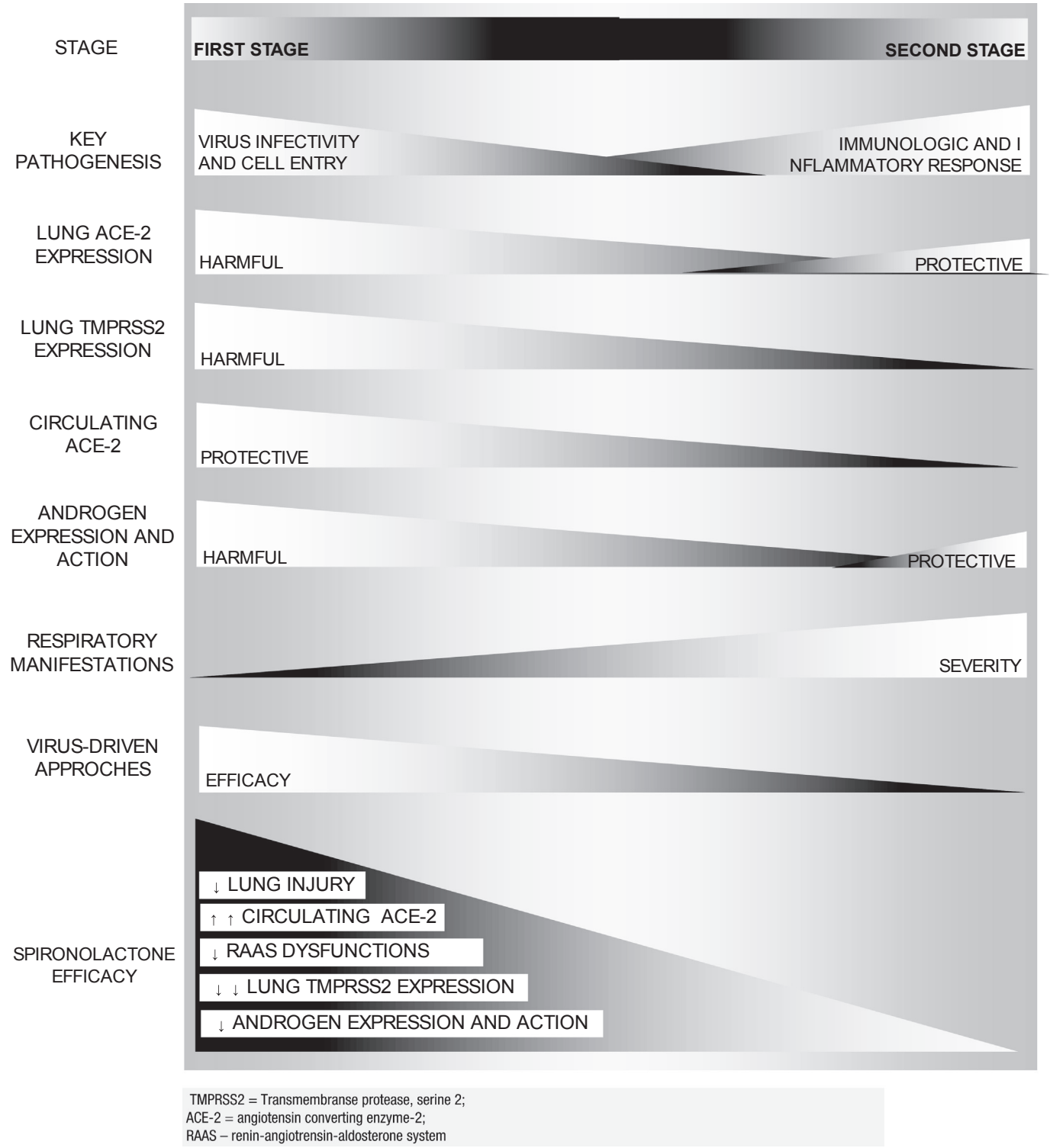

Fig. 1. COVID-19: Stages, key characteristics, ACE2 expression, and approaches.

observed to be particularly present in men that develop ARDS in COVID-19.

The presence of angiotensin-converting enzyme-2 (ACE2) receptor and transmembrane serine protease 2 (TMPRSS2) is mandatory for SARS-CoV-2 cell entry, while ACE2 and TMPRSS2 expression may modulate its infectivity. ACE2 and TMPRSS2 expressions abnormalities in hypertension and obesity, and exposure to androgens, respectively, may help justify why these are risk factors for COVID-19, as proposed by recent theories [7–10]. ACE2 and TMPRSS2 altered expressions can be concomitantly addressed by spironolactone and other mineralocorticoid antagonists, due to their actions in the renin-angiotensin-aldosterone system (RAAS) and as androgen antagonists, respectively, providing potential protection against SARS-CoV-2. Key characteristics of COVID-19 according to the timing of the infection is presented in Fig. 1.

Hypothesis

Spironolactone: May the multi-purpose drug provide protection from SARS-CoV-2?

Spironolactone, a safe anti-hypertensive and anti-androgenic drug used since 1959 that acts as potassium-sparing diuretic drug by antagonizing mineralocorticoid receptors (MRs), tend to disclose favorable patterns of the RAAS and ACE2 expression, reduces TMPRSS2 activity due to its antiandrogenic activity, and may prevent acute lung injuries due to its pleiotropic effects. We hypothesize that spironolactone my offer protection for some of the populations at highest risk for severe COVID-19, including obesity, bald males (that present enhanced TMPRSS2 expression), and hypertension.

Evaluation of the hypothesis

ACE2 expression in COVID-19: why hypertension and obesity are risk factors?

Whether the atypical increased risk related to hypertension in COVID-19 is derived from hypertension *per se*, due to secondary lung alterations resulted from the effects of increased blood pressure on tissues, or if the unexpected risk related to hypertension is actually secondary to the effects of chronic exposure to speicific classes of antihypertensives, is uncertain.

The large percentage of patients with hypertension undertaking angiotensin-converting enzyme inhibitors (ACEi's) or angiotensin receptor blockers (ARBs) [11–13] has been hypothesized to be the main underlying mechanism that could justify the peculiar severity of COVID-19 in hypertension, due to their inherent actions in the RAAS, that could indirectly increase the availability of surface-attached ACE-2 in the lung endothelium, potentially leading to enhanced coupling of SARS-CoV2 to ACE-2 and its consequent cell entry in the early stage of COVID-19. However, despite the initial reports that have correlated ACEi and ARB with increased risk of severe manifestations in COVID-19, further findings including systematic reviews and meta-analyses failed to demonstrate these correlations [14–16].

While ARB and ACEi disclosed inconsistent findings on COVID-19 related outcomes, the fact that hypertension, regardless of its control, has been shown to be an important and independent risk factor for COVID-19 severity, remains to be explained. Unlike diabetes, which the level of control based on the HbA1c predicts COVID-19 outcomes, hypertension did not show the same sort of correlation, and this should be considered for further analyses [5].

Among the multiple mechanisms proposed to justify the severity of COVID-19 related to obesity, the disruption of the RAAS system, ACE2 expression and activity, and the balance between the hypertensive and pro-inflammatory angiotensin II and angiotensin receptor-1 (AT1) axis, and the anti-inflammatory Angiotensin-[1-7] and its Mas receptor, a G-coupled receptor, may explain the particular increased SARS-CoV-2 infectivity in this population.

Hypertension and obesity are two major representatives of the key importance of the dysfunctions-related RAAS abnormalities for the development of the SARS-CoV-2 infectiveness.

In regards with ACE2 expression, membrane-attached ACE2 should be differentiated from freely circulating ACE2 due to their likely distinct roles in RAAS and COVID-19. While membrane ACE2 is expressed broadly [17–20], particularly in the lungs, kidney, heart, testicles, and gut, circulating ACE2 levels are low and its functional role in the lungs seems not to be clinically relevant, when under physiological conditions [21]. Despite the discussion on the clinical relevance under physiological conditions, the fact that epithelial type II cells of the lungs represent up to 80% of the total ACE2 expression in the body [22] is of clinical importance in pathologies that require the participation of ACE2 to occur. Indeed, absence of ACE2 expression led to full resistance to SARS-CoV infection [23,24]. Particularly, the receptor binding domain (RBD) of the SARS-CoV2 has a stronger interaction with angiotensin converting enzyme 2 (ACE2), compared to other virus infections from the same family [25–29], and any increase of ACE2 expression may potentially amplify the virus capacity to entry the cells.

While expression and availability of attached ACE2 is directly correlated with Covid-19 severity during the first stage of viral replication, the free circulating form of ACE2 may couple to SARS-CoV2 and hamper its entry in the pulmonary endothelium. It has been hypothesized that recombinant human soluble ACE2 could play a protective role against the development of severe manifestations, ARDS, and death in Covid-19, which has been clinically demonstrated by the beneficial effects of recombinant ACE2 in the prevention of coronaviruses-induced lung injury [30–34], despite its unaffordability for regular medical use. Under physiological conditions, circulating plasma ACE2 may not be present in levels sufficient to protect membrane-attached ACE2 from coupling to SARS-COV2 [30]. However, under particular conditions including soluble ACE2 and drugs that increase its levels in the plasma, its protective actions may become relevant. Hence, a speculative ratio between attached ACE2 availability and expression, and freely circulating ACE2 could predict the lung pathogenicity of Covid-19, although methods to assess this ratio have not been developed and validated to date. Hence, as mentioned, the differences between plasma and membrane ACE2 should not be ignored.

Together with the aberrancies in ACE2 expression, another hypothesis has postulated that an unbalance between angiotensin II and angiotensin 1–7 levels and effects would also be responsible for the severity of clinical manifestations [35–37].

Due to the high level of uncertainty regarding the expression and activity of ACE2 in different organs during COVID-19, hypotheses regarding the correlations between ACE2 and COVID-19 severity should be generated from epidemiological data, which is consistent with the overrepresentation of obesity and hypertension. Fig. 2 depicts a hypothetical model of the first stage of (SARS-CoV-2 infectivity and replication) under different *scenarios* of physiological, untreated hypertension, use of different drug classes, and hyperandrogenism.

Androgen-driven theory to explain overrepresentation of males in severe COVID-19

Despite the lack of clinical data of the androgen effects on SARS-CoV-2, its strong mechanistic plausibility and corresponding epidemiological data provide theoretical basis for an androgen mediated SARS-CoV-2 infectiveness [8].

The androgen-regulated transmembrane protease serine 2 (TMPRSS2) is the important enzyme that cleaves the spike protein of the virus and the ACE2 receptor for viral cell entry [8]. Male mice are known to be extremely more vulnerable to SARS-CoV infection [38].

Recent American data showed a drastic difference of over 6 times more male fatalities in a very productive age range (40–49 years) and approximately two times more male admissions from 30 to 49 years [39].

SARS-CoV-2 entry into type II pneumocytes in the lung is driven by androgens [8–10]. This theory explains the findings that females and pre-puberty subjects are relatively protected from COVID-19 ARDS. Interestingly, infants under one year old may have increased risk of COVID-19 complications, which is in accordance with the occurrence of the mini-puberty *i.e.*, a transient expression of androgens at this age. In their report, the authors provide a detailed hypothesis of the molecular mechanisms of COVID-19 disease mediated by androgens. Among the drugs mentioned as potential candidates to test, spironolactone, a steroidal androgen receptor competitive blocker, was singled out as a possible safe and potentially effective alternative. Fig. 2 shows a hypothetical scenario of the first stage of COVID-19 in hyperandrogenic states.

Of great interest regarding the pre-clinical data regarding how

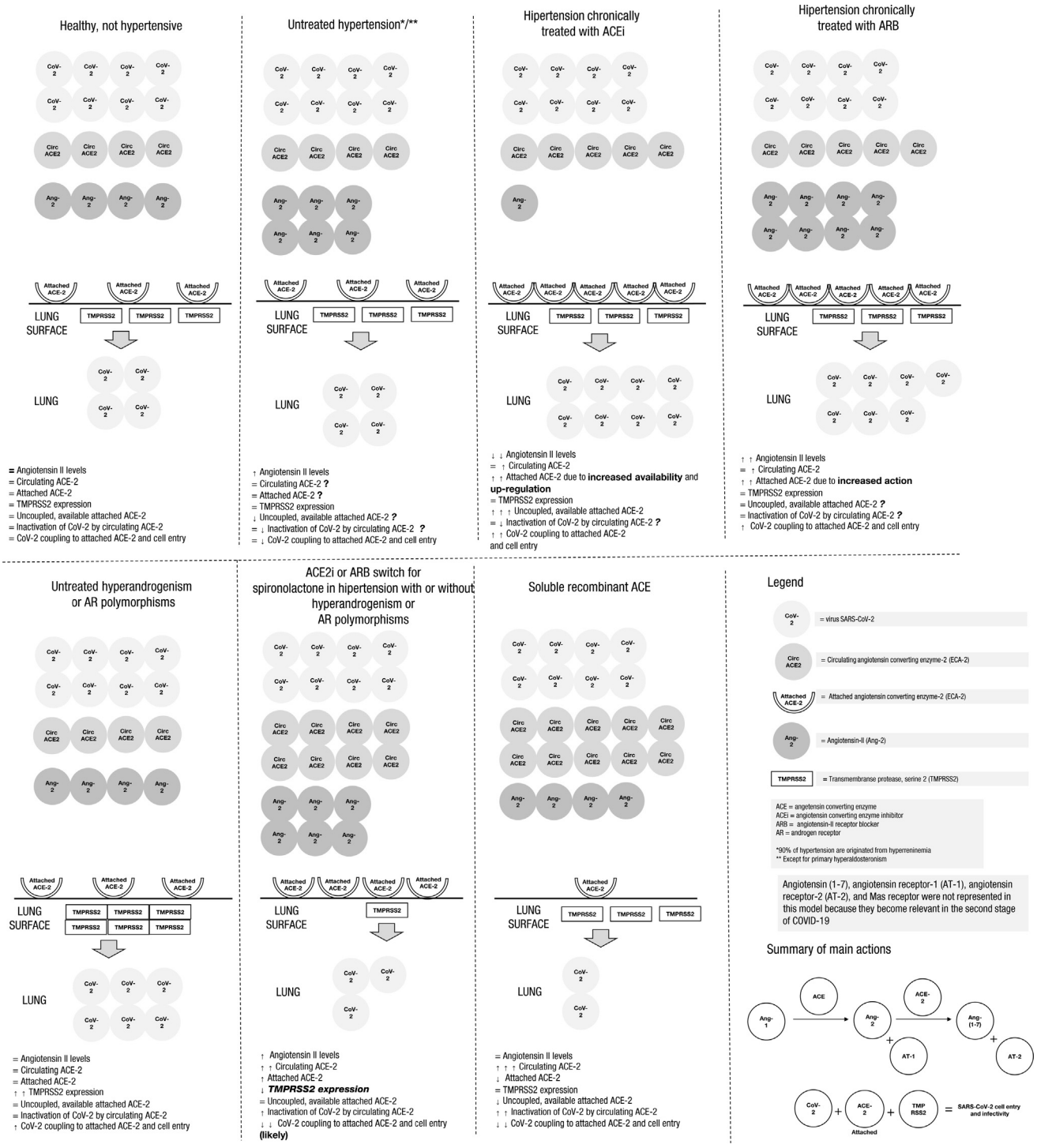

Fig. 2. Simplified hypothetical model of the proposed *scenarios* in the first stage of COVID-19, during SARS-CoV-2 cell infection and replication period.

androgen blockade impacts survival, the non-steroidal androgen receptor blocker flutamide was the only drug to date that demonstrated in experimental model male mice survival from lethal dose of SARS-CoV [40]. Other drugs, such as remdesivir, failed to demonstrate male mice survival and based their conclusions on female mice analysis [41].

Consequences of the hypothesis and discussion

Spironolactone: a multi-purpose drug that may provide protection from SARS-CoV-2

Spironolactone is currently the main representative of the potassium-sparing diuretic class of drugs, may be as effective as ACEi and ARB to maintain normal blood pressure [42,43], addresses heart function, and provides cardio- and renoprotection [44–49]. Unlike ACEi and ARB, that specifically increase lung membrane-attached ACE2 expression, spironolactone tend to disclose favorable patterns of ACE2

expression, including a more extensive increase of circulating ACE2 when compared to membrane-attached ACE2, enhancing its potential protective role in SARS-CoV-2, once plasma ACE2 may couple to SARS-CoV-2 and avoid its entry in the cells [50–55], and may downregulate the androgen-mediated TMPRSS2 due to its antiandrogenic activity [56–58], without the adverse events of male sexual castration. In addition, spironolactone has been demonstrated to mitigate the detrimental effects of obesity on the RAAS [58–65], including hyperactivation of the RAAS due to increased angiotensinogen production by adipose tissue and imbalance towards angiotensin-2-AT-1 axis, possibly reducing obesity-related COVID-19 complications, and has direct specific anti-inflammatory effects in the lungs, possibly reducing acute lung injuries [66–73].

Notably, since spironolactone mostly targets the virus entry in the cells, which is the hallmark of the first phase of Covid-19, spironolactone should be preferably administrated in the earlier stages of the infection, prior to the complications of respiratory manifestations, when SARS-CoV-2 activity becomes secondary and the exacerbated inflammatory response is the responsible for the Covid-19 induced ARDS.

Discussion

The current COVID-19 pandemic urges for rapid responses to change its course and mortality rate. The learnings of the mechanisms of SARS-CoV-2 cell entry and infectivity, which meet corresponding epidemiological data and identification of risk factors, allowed more precise predictions regarding efficacy of drugs proposed to protect from COVID-19.

Among current options, researchers should preferably focus on existing drugs that have been long used, i.e., to repurpose old drugs for COVID-19, due to five major reasons that are inherent to these molecules: 1. The short- and long-term safety profile of these drugs are known, whereas can only be obtained after longer studies with new molecules; 2. Risks are known, which allow directed monitoring and allows, in opposition to newly released drugs, for which multi-organ and multi-risk monitorization is recommended due to the little known effects, particularly because very few have been tested in large populations; 3. Contraindications are known, avoiding the use on those that may present harms, in contrast to the lack of awareness of the contraindications of new drugs, among which several contraindications can only be detected in large-scale studies; 4. Clinicians are familiarized with the clinical management of old drugs, including posology, monitoring for risks, contraindications, and potential complications, which is desirable since the number of infected subjects does not allow COVID-19 to be managed within specialized centers; on the contrary, general practitioners, family medicine physicians, and all medical doctors should be skilled to manage these patients, which is unfeasible in case novel molecules unfamiliar to medical community is largely used; 5. The cost of new, patented drugs is unaffordable by public health systems, and unlikely has favorable cost-effectiveness, since the level of evidence of benefits is too weak compared to costs due to the insufficient time of studies to provide supporting data for their use massively.

The above-mentioned advantages of old drugs are imperative for the massive clinical use of these drugs against COVID-19. In this regard, oppositely to other alternatives, that may cause undesired harms that led to questionings regarding their use, spironolactone offers solid safety, extensive effectiveness, and has strong plausibility that meets according *in vitro*, *in vivo*, and clinical evidence that spironolactone provides active protection for those organs centrally affected in COVID-19: lungs, heart, and kidneys.

In addition, as demonstrated in the present article, unlike the majority of the current proposed drugs, that only offer potential protection in the first stage of COVID-19, during SARS-CoV-2 viral replication and spread, spironolactone has demonstrated actions that may provide protection during all three stages of COVID-19, since it may reduce SARS-CoV-2 infectivity, inhibit cytokine and inflammatory storm as an overresponse to the virus, and alleviate lung, heart, and kidney injuries, for the first, second, and third stages of COVID-19, respectively.

To us, there is sufficient data to support the employment of spironolactone for large-scale studies, and an empirical alternative for compassionate use due to the lack of relevant risks [74,75].

Perspectives and conclusion

Abnormal ACE2 expression, angiotensin II and angiotensin 1–7 imbalance, and androgen activity seem to be key regulators of SARS-CoV-2 infectivity, in accordance with epidemiological observations. Since spironolactone exhibits concurrent actions in the modulation of ACE2 expression that would direct- and indirectly avoid SARS-CoV-2 cell entry, in the increase of angiotensin 1–7 levels, that can attenuate the harms of the overexpression of angiotensin II-AT-1 axis, and as an anti-androgenic agent, that would decrease viral priming through TMPRSS2 activity, spironolactone seems to be an ideal candidate drug for the prophylactic and early treatment of SARS-CoV-2.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability statement and data deposition

There is no additional data associated with the present manuscript.

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