Contemplating on the Etiology of COVID-19 Severity and Mortality Sex Differences

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Abstract
COVID-19 displays a sex-biased behavior with a higher rate of intensity and mortality in men. In that sense, COVID-19 deflects-off the typical trend of many viral infections which are characterized by a higher rate of intensity and prevalence in males, yet a higher female mortality rate. Severity and mortality rates of COVID-19 are associated with several underlying diseases, which exhibit significant self-sufficient male-biased dimorphism, thus are at times hypothesized to be the ones responsible to tilt mortality balance toward higher men death in COVID-19. Yet, similar comorbidities prevail in other viral infections, raising curiosity to what makes COVID-19 unique? The answer may lay in the involvement of renin-angiotensin system and ACE2 receptor in COVID-19 progression, 2 players which are significant contributors to the fatality of COVID-19. A structured difference is evident in the expression and function of RAS and ACE2 between the sexes, presumably tipping over mortality rate tendency toward male-risk factor.

Keywords
sex-biased, sexual dimorphism, COVID-19, SARS-Cov-2, ACE2, renin-angiotensin system (RAS), angiotensin-converting enzyme 2

COVID-19 displays sex-biased pattern with a higher rate of intensity and mortality in men. In that sense, COVID-19 deflects off the typical trend of many viral infections which are characterized by a higher rate of intensity and prevalence in males, yet a higher mortality rate in females.

Differences in pathology incident rate, disease progression, responsiveness to medical treatment and mortality rates are all part of what is well known in the medical jargon as sex-biased. Unequal female-to-male patient proportion is documented in the majority of life-threatening diseases or severe genetic disorders.¹² Viral infections similarly present sex differences, with a higher rate of intensity (viral burden, which often correlates with the severity of an active viral infection) and prevalence in males, presumably due to lower innate antiviral immune responses. A stronger immune system in females is often associated with a faster ease of viral burden and a higher antibodies production following vaccination. Yet, a vigorous immune response also accounts for a higher rate of autoimmune diseases, a more adverse reaction to vaccination and increased immune pathogenesis.³⁴ Adverse reaction in response to antiviral drugs is usually greater in females, being the outcome of differences in the pharmacokinetics and pharmacodynamics of antiviral drugs between the sexes. Primarily, due to a sex-related different function of the liver, kidney and fat metabolism, directly affect many parameters including drug absorption, distribution and metabolism.³⁵⁶ Furthermore, a higher female mortality rates and infection severity are reported. Higher female mortality rate is documented in many types of viral infections including Hantaviruses, Influenza A viruses (including children) and Measles.³⁷⁹

The Global Health 50/50 organization is collecting and constantly updating COVID-19 numbers of individuals infected and deceased, by country and by sex.¹⁰ Forty-one countries include sex information in their data, thus enabling sex-disaggregating. While the percentages of men and women infection and mortality slightly differ between the different countries, the tendency is unified. The rates of infected men and women are relatively similar with a slightly higher prevalence in women in the different countries, yet mortality rates...
deviate dramatically, ranging between ~1.5 to 2.5 times higher in men in comparison to women.\textsuperscript{10}

What do we know so far about COVID-19 mortality causes and how can we explain these sex differences?

COVID-19 severity and mortality rates are associated with age along with several underlying diseases including hypertension, cardiovascular diseases, obesity and diabetes.\textsuperscript{11-18} It is unclear whether these comorbidities are confounded by old age, or if indeed the physiological adverse side effects are a result of the underlying medical condition.\textsuperscript{12} Children seem to be less susceptible to COVID-19, they express less severe illness, death is extremely rare and they present almost 2 fold asymptomatic patients than adults.\textsuperscript{19-23} Potential explanations, yet to be further studied, focus on the still maturing immune system of children, which may respond differently to SARS-cov-2 infection; the differences in sex-hormones-mediated physiological processes, or on a deceptive asymptomatic infection display.\textsuperscript{19,24}

Several underlying conditions are suggested to interact with COVID-19 deterioration leading to ones’ death: lung injury leading to acute respiratory distress syndrome (ARDS); myocardial malfunction; and renin-angiotensin system (RAS) mediated kidney injury. Myocardial malfunction in COVID-19 patients may be the result of numerous causes: (i) hypoxia-induced lung injury which in turn may lead to oxidative stress and myocardial injury; (ii) CRS-mediated, (iii) and the binding of SARS-cov-2 spike (S) surface protein to Angiotensin-Converting Enzyme 2 (ACE2) receptor, abundant in myocardial cells, and a key regulator of renin-angiotensin system (RAS).\textsuperscript{13,25,26}

Both RAS and ACE2 undergo significant changes throughout aging and as part of the destructive changes accompanying COVID-19 comorbidity diseases.\textsuperscript{12,24} RAS is responsible for blood pressure regulation, systemic vascular resistance and electrolyte and fluid balance. As such it is highly significant in the various pathologies associated with COVID-19 risk.

In addition, cytokine release syndrome (CRS) is documented as an important cause of death in COVID-19 patients. Hyperinflammation and over-reaction of the immune system may lead to CRS response and consequently ARDS and death. Preliminary clinical trials explore the possibility to block cytokine storm deleterious effect by the blockage of IL-6 receptor, a key mediator of CRS\textsuperscript{13,27-30}

Indeed, the abovementioned underlying diseases all exhibit significant self-sufficient male-biased dimorphism, thus are hypothesized to be the ones responsible to tilt mortality balance toward higher men death in COVID-19.

Heart disease is well known for its higher occurrence rate in men. Cardiovascular disease (CVD) are substantially higher in men than women, yet it is the leading cause of death in women, worldwide. coronary heart disease (CHD) mortality is approximately 4 times higher in men than in premenopausal women, and is reduced to 2 fold in the aged population, ages 75-80 years. Finally, myocardial infarction (MI) in men is almost 3 times higher than in women at younger ages, but the incidence becomes more similar with increasing age.\textsuperscript{31-33} According to WHO report, hypertension prevalence is 25\% in men and 20\% in women, however this gap is gradually eliminated after menopause, up to the point that hypertension becomes more prevalent among the elderly women.\textsuperscript{34} Diabetes prevalence is on a rise, and the number of people diagnosed with diabetes was doubled between 1980 and 2017. Several studies have shown that diabetes is a stronger risk factor in women compared with men, both for CVD, MI and for CHD.\textsuperscript{35}

Yet, all this is equally true in the case of other viral infections such as Influenza A. Why do we not observe male-biased death in other viral infection? What makes COVID-19 unique? It seems the answer may lay in the involvement of RAS and ACE2 receptor in COVID-19 progression, 2 players which are significant contributors to the fatality of COVID-19 and presumably in a manner that is deadlier in men than in women.

Sex-bias is evident in the renin-angiotensin system (RAS) function and consequently in cardiovascular disease, hypertension, obesity, diabetes and diabetes-related renal pathologies. In these pathologies being a man is a risk factor in comparison to pre-menopausal women, yet after the onset of menopause, occurrence rate in women increases and becomes similar to that of men.\textsuperscript{36-39}

ACE2 belongs to the angiotensin-converting enzyme family. It secreted protein catalyzes the cleavage of angiotensin I into angiotensin 1-9, and angiotensin II into the vasodilator angiotensin 1-7. ACE2 protein was found in various human organs with a remarkable surface expression in lung alveolar epithelial cells and small intestine epithelia, as well as expression in vascular endothelium coronary and intrarenal vessels and in renal tubular epithelium.\textsuperscript{40,41} In contrast to ACE mRNA which is abundant in many human tissues, ACE2 mRNA shows tissue-specific expression profile in the testis, renal, the cardiovascular tissues, and the gastrointestinal system.\textsuperscript{31,42}

The involvement of ACE2 gene in sexually biased pathologies was demonstrated in several experimental systems, for example, circulating ACE2 was significantly increased in diabetes female rats, while reduced ACE was detected within the kidney.\textsuperscript{43} Adipocyte ACE2 was concluded to protect female mice from obesity-hypertension, and to reduce the blood pressure response to systemic angiotensin II.\textsuperscript{44} These observations indicate that sex-related differences in the action of angiotensin II in hypertension and diabetes nephropathy, are attributed to similar sex-biased differences in RAS and specifically in the control of ACE2 and ACE balance.\textsuperscript{45}

Lately 3 manuscripts were published discussing COVID-19 sex differences in the context of ACE2 gene. Gagliardi et al, suggested a protective effect of estrogen presumably mediated via up-regulation of ACE2, in women infected with COVID-19, stressing my view of the importance of ACE2 AND RAS in COVID-19 sexually dimorphic behavior.\textsuperscript{46} Yet, while the role of estrogen and its protective effect is emphasized, one main issue is undiscussed—the age of the patients in question. As the vast majority of the sever and deceased women are at their postmenopausal phase, estrogen expression levels in them is expected to be similar to men’s level. Approximately 75\% of COVID-19 mortality rate occurs at the age of 65 years
old and above. The vast majority of COVID-19 sever cases and of COVID-19 deceased are 65 years old and older, and indeed 66% of the fatality rate differences between countries is explain by their age distribution.\textsuperscript{47} Thus, COVID-19 related differences between women and men, probably follows a far more complex mechanism than a straightforward estrogen-levels dependent.

Sharma et al and Scully et al, both addressing the role of ACE2 gene and ascribes a female protective role for this gene due to the fact that it is situated on X chromosome.\textsuperscript{48,49} X-chromosome located genes, obviously, not all express higher levels. The vast majority of those gene show a dosage compensation effect due to a random X inactivation of one of the female X chromosomes. ACE2, however belong to a relatively small group of X chromosome genes who are escapees, namely are expressed also from the inactive X chromosome. Yet, ACE2 is known to express an unusual heterogeneous sex-biased pattern with significant male-biased expression in several tissues.\textsuperscript{50} Thus, an a priori female-protective effect for ACE2 gene in COVID-19 cannot be concluded based solely on its chromosomal location without further experiments.

In conclusion, it is hypothesized that the larger portion of male death cases, up to 2.5 fold higher in some of the countries, is associated with a structured sex-related dimorphism expressed in the function of pathways and physiological micro-systems affected during SARS-cov-2 infection. In specific, attention is drawn to RAS and it associates - ACE2 tissue scattering, and CRS occurrence. While the topic of comorbidities and death occurrence in aged COVID-19 patients and those with underlying diseases is being constantly addressed, less is being said regarding the observed sexual dimorphism in COVID-19 death rate. Had underlying diseases were a main factor responsible for tipping over mortality rate tendency toward male-risk factor, we would have expected to see a similar pattern in other viral infections, especially in the case of Influenza A, which is characterized by higher rate of female mortality. As it is not the case, we ought to further study and search for those unique elements in COVID-19 pathologies which may account for the presented sex differences.

The characteristics of ACE2 and RAS as presenters of the differences between male and female in several systems is addressed. Thus, their role in the sex-biased pattern of COVID-19 is becoming convincing. Yet, the mechanism by which these differences are mediated, is clearly not a simple outcome of steroids’ induction or ACE2 gene X-chromosome location. Out of the many pathologies who express a wide array of differences between men and women (different types of cancer, asthma, autism, hypertension, cardiovascular diseases and many more others), the mechanism by which these biases are attained is still obscure.

**Abbreviations**

Renin-angiotensin system (RAS); Angiotensin-Converting Enzyme 2 (ACE2); myocardial infarction (MI); coronary heart disease (CHD); Cardiovascular disease (CVD)

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**References**

1. Gloeckler Ries LA, Reichman ME, Lewis DR, Hankey BF, Edwards BK. Cancer survival and incidence from the surveillance, epidemiology, and end results (SEER) program. *Oncologist*. 2003;8(6):541-552.

2. Medicine UIo. Exploring the biological contributions to human health: does sex matter? *J Womens Health Gend Based Med*. 2001;10(5):433-439. doi:10.1089/152460901300233902

3. Klein SL. Sex differences in prophylaxis and therapeutic treatments for viral diseases. *Handb Exp Pharmacol*. 2012;(214):499-522. doi:10.1007/978-3-642-30726-3_22

4. Klein SL. Sex influences immune responses to viruses, and efficacy of prophylaxis and treatments for viral diseases. *Bioessays*. 2012;34(12):1050-1059. doi:10.1002/bies.201200099

5. Farkouh A, Riedl T, Gottardi R, Czaja M, Kautzky-Willer A. Sex-related differences in pharmacokinetics and pharmacodynamics of frequently prescribed drugs: a review of the literature. *Adv Ther*. 2020;37(2):644-655. doi:10.1007/s12225-019-01201-3

6. Ofotokun I, Chuck SK, Hitti JE. Antiretroviral pharmacokinetic profile: a review of sex differences. *Gend Med*. Jun 2007;4(2):106-119. doi:10.1016/s1550-8579(07)80025-8

7. Garene M. Sex differences in measles mortality: a world review. *Int J Epidemiol*. 1994;23(3):632-642. doi:10.1093/ije/23.3.632

8. Hardeil P, Kapetanstrataki M, Norman L, et al. Characteristics and mortality risk of children with life-threatening influenza infection admitted to paediatric intensive care in England 2003-2015. *Respir Med*. 2018;137:23-29. doi:10.1016/j.rmed.2018.02.012

9. Klein SL, Marks MA, Li W, et al. Sex differences in the incidence and case fatality rates from hemorrhagic fever with renal syndrome in China, 2004-2008. *Clin Infect Dis*. 2011;52(12):1414-1421. doi:10.1093/cid/cir232

10. TheGlobalHealth50/50organization. COVID-19 sex-disaggregated data tracker. http://globalhealth50.org/covid19

11. William D, Carlos SB. Obesity and its implications for COVID-19 mortality. *Obesity (Silver Spring)*. 2020;28(6):1005. doi:10.1002/oby.22818

12. Hanff TC, Harhay MO, Brown TS, Cohen JB, Mohareb AM. Is there an association between COVID-19 mortality and the renin-angiotensin system—a call for epidemiologic investigations. *Clin Infect Dis*. 2020;71(15):870-874. doi:10.1093/cid/ciaa329

13. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. The cytokine release syndrome (CRS) of severe COVID-19 and interleukin-6 receptor (IL-6 R) antagonist tocilizumab may be the key to reduce
the mortality. Int J Antimicrob Agents. 2020;46(1):111-116. doi:10.1016/j.ijantimicag.2020.105954

14. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-1062. doi:10.1016/S0140-6736(20)30566-3

15. Bonow RO, Fonarow GC, O’Gara PT, Yancy CW. Association of coronavirus disease 2019 (COVID-19) with myocardial injury and mortality. JAMA Cardiol. 2020;5(7):751-753. doi:10.1001/jamacardio.2020.1105

16. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality in hospitalized patients with COVID-19 in Wuhan, China. Intensive Care Med. 2020;46(5):846-848. doi:10.1007/s00134-020-05991-x

17. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;5(7):802-810. doi:10.1001/jamacardio.2020.0950

18. Deng Q, Hu B, Zhang Y, et al. Suspected myocardial injury in patients with COVID-19: evidence from front-line clinical observation in Wuhan, China. Int J Cardiol. 2020;311:116-121. doi:10.1016/j.ijcard.2020.03.087

19. Bialek S, Gierke R, Hughes M, McNamara LA, Pilishvili T, Skoff T. Coronavirus disease 2019 in children—United States, February 12–April 2, 2020. MMWR. 2020;69(14):422-426. US Department of Health and Human Services/Centers for Disease Control and Prevention. Accessed April 10, 2020. https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm

20. Dong Y, Mo X, Hu Y, et al. Epidemiology of COVID-19 among children in China. Pediatrics. 2020;145(6):e20200702. doi:10.1542/peds.2020-0702

21. Du RH, Liang LR, Yang CQ, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARS-CoV-2: a prospective cohort study. Eur Respir J. 2020;55(5):2000524. doi:10.1183/13993003.00524-2020

22. Ludvigsson JF. Systematic review of COVID-19 in children shows milder cases and a better prognosis than adults. Acta Paediatr. 2020;109(6):1088-1095. doi:10.1111/apa.15270

23. Qiu H, Wu J, Hong L, Luo Y, Song Q, Chen D. Clinical and epidemiological features of 36 children with coronavirus disease 2019 (COVID-19) in Zhejiang, China: an observational cohort study. Lancet Infect Dis. 2020;20(6):689-696. doi:10.1016/S1473-3099(20)30198-5

24. Lee PL, Hu YL, Chen PY, Huang YC, Hsueh PR. Are children less susceptible to COVID-19? J Microbiol Immunol Infect. 2020;53(3):371-372. doi:10.1016/j.jmii.2020.02.011

25. Ammirati E, Wang DW. SARS-CoV-2 inflames the heart. The importance of awareness of myocardial injury in COVID-19 patients. Int J Cardiol. 2020;303:64-65. doi:10.1016/j.ijcard.2020.03.086

26. Tan W, Aboulhosn J. The cardiovascular burden of coronavirus disease 2019 (COVID-19) with a focus on congenital heart disease. Int J Cardiol. 2020;309:70-77. doi:10.1016/j.ijcard.2020.03.063

27. Bizzarro M, Lagana AS, Aragona D, Unfer V. Inositol and pulmonary function. Could myo-inositol treatment downregulate inflammation and cytokine release syndrome in SARS-CoV-2? Eur Rev Med Pharmacol Sci. Mar 2020;24(6):3426-3432. doi:10.26355/eurrev_202003_20715

28. Henderson LA, Canna SW, Schulte GS, et al. On the alert for cytokine storm: immunopathology in COVID-19. Arthritis Rheumatol. 2020;72(7):1059-1063. doi:10.1002/art.41285

29. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J Autoimmun. 2020;111:102452. doi:10.1016/j.jaut.2020.102452

30. Mehta P, McAuley DF, Brown M, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-1034. doi:10.1016/S0140-6736(20)30628-0

31. Bhatnagar P, Wickramasinghe K, Williams J, Rayner M, Townsend N. The epidemiology of cardiovascular disease in the UK 2014. Heart. 2015;101(15):1182-1189. doi:10.1136/heartjnl-2015-307516

32. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. BMJ Glob Health. 2017;2(2):e000298. doi:10.1136/bmjgh-2017-000298

33. Millett ERC, Peters SAE, Woodward M. Sex differences in risk factors for myocardial infarction: cohort study of UK Biobank participants. BMJ. 2018;363:k4247. doi:10.1136/bmj.k4247

34. Di Giosia P, Giorgini P, Stamerra CA, Petrarca M, Ferri C, Sahbekkar A. Gender differences in epidemiology, pathophysiology, and treatment of hypertension. Curr Atheroscler Rep. 2018;20(3):13. doi:10.1007/s11883-018-0716-z

35. Glovac D, Fan W, Wong ND. Epidemiology of diabetes mellitus and cardiovascular disease. Curr Cardiovasc Rep. 2019;21(4):21. doi:10.1007/s11886-019-1107-y

36. Maric-Bilkan C, Manigrasso MB. Sex differences in hypertension: contribution of the renin-angiotensin system. Gend Med. 2012;9(4):287-291. doi:10.1016/j.gendmed.2012.06.005

37. Moritz KM, Cuffe JS, Wilson LB, et al. Review: sex specific programming: a critical role for the renal renin-angiotensin system. Placenta. 2010;31:S40-S46. doi:10.1016/j.placenta.2010.01.006

38. Sullivan JC. Sex and the renin-angiotensin system: inequality between the sexes in response to RAS stimulation and inhibition. Am J Physiol Regul Integr Physiol. 2008;294(4):R1220-R1226. doi:10.1152/ajpregu.00864.2007

39. White MC, Fleeman R, Arnold AC. Sex differences in the metabolic effects of the renin-angiotensin system. Biol Sex Differ. 2019;10(1):31. doi:10.1186/s13293-019-0247-5

40. Hamming I, Timens W, Bulthuis ML, Lely AT, Navis G, van Goor H. Tissue distribution of ACE2 protein, the functional receptor for SARS coronavirus. a first step in understanding SARS pathogenesis. J Pathol. 2004;203(2):631-637. doi:10.1002/path.1570

41. Donoghue M, Hsieh F, Baronas E, et al. A novel angiotensin-converting enzyme-related carboxypeptidase (ACE2) converts angiotensin I to angiotensin 1-9. Circ Res. 2000;87(5):E1-E9. doi:10.1161/01.res.87.5.e1
42. Harmer D, Gilbert M, Borman R, Clark KL. Quantitative mRNA expression profiling of ACE 2, a novel homologue of angiotensin converting enzyme. FEBS Lett. 2002;532(1-2):107-110. doi:10.1016/s0014-5793(02)03640-2

43. Yamaleyeva LM, Gilliam-Davis S, Almeida I, Brosnihan KB, Lindsey SH, Chappell MC. Differential regulation of circulating and renal ACE2 and ACE in hypertensive mRen2.Lewis rats with early-onset diabetes. Am J Physiol Renal Physiol. 2012;302(11):F1374-F1384. doi:10.1152/ajprenal.00656.2011

44. Shoemaker R, Tannock LR, Su W, et al. Adipocyte deficiency of ACE2 increases systolic blood pressures of obese female C57BL/6 mice. Biol Sex Differ. 2019;10(1):45. doi:10.1186/s13293-019-0260-8

45. Clotet-Freixas S, Soler MJ, Palau V, et al. Sex dimorphism in ANGII-mediated crosstalk between ACE2 and ACE in diabetic nephropathy. Lab Invest. 2018;98(9):1237-1249. doi:10.1038/s41374-018-0084-x

46. Gagliardi MC, Tieri P, Ortona E, Ruggieri A. ACE2 expression and sex disparity in COVID-19. Cell Death Discov. 2020;6:37. doi:10.1038/s41420-020-0276-1

47. Sudharsanan N, Didzun O, Bärnighausen T, Geldsetzer P. The contribution of the age distribution of cases to COVID-19 case fatality across countries: a 9-country demographic study. Ann Intern Med. 2020;M20-2973. doi:10.7326/m20-2973

48. Sharma G, Volgman AS, Michos ED. Sex differences in mortality from COVID-19 pandemic: are men vulnerable and women protected? JACC Case Rep. 2020;2(9):1407-1410. doi:10.1016/j.jaccas.2020.04.027

49. Scully EP, Haverfield J, Ursin RL, Tannenbaum C, Klein SL. Considering how biological sex impacts immune responses and COVID-19 outcomes. Nat Rev Immunol. 2020;20(7):442-447. doi:10.1038/s41577-020-0348-8

50. Tukiainen T, Villani AC, Yen A, et al. Landscape of X chromosome inactivation across human tissues. Nature. 2017;550(7675):244-248. doi:10.1038/nature24265