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Mechanism of sex related difference in COVID -19 lethality

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Abstract

Many countries have been affected with the resource of the international outbreak of COVID-19. Among Western countries, Italy has been mainly hit at the beginning of the pandemic, straight away after China. In Italy and elsewhere, female seem to be less affected than guys via skill of severe/fatal COVID-19 infection, regardless of their age. Although female and guys are affected in a distinctive way via the use of this infection, very few research consider extraordinary therapeutic strategies for the two sexes. Understanding the mechanisms underlying these versions might also moreover assist to come across high-quality and intercourse particular therapies. Here, we reflect on consideration on that different mechanisms are worried to explain this difference, in addition to the safety attributable to oestrogens. Several X-linked genes (such as ACE2) and Y-linked genes (SRY and SOX9) can also moreover provide an rationalization for intercourse differences. Cardiovascular comorbidities are amongst the main enhancers of virus lethality. In addition, the wide variety of sex-independent, non-genetic elements that can alternate susceptibility and mortality is enormous, and many special factors should be considered, which consists of gender and cultural habits in distinct countries.

Introduction

The outbreak of novel coronavirus disease 2019 (COVID-19) quickly turned into a pandemic, and Europe and U.S.A. have been particularly affected [Zhou et al. 2020b]. Sex differences are emerging in terms of case fatality (deaths/reported cases), and sex disaggregated data are now starting to be available for many countries. Looking at male/female ratio for death in confirmed cases it appears that the ratio is always above 1.1 in 34 out of the 35 countries that provide sex disaggregated data (only for Pakistan, the ratio is 0.9)[1]. Many European countries (Spain, Italy, England, Belgium, Greece, Denmark and The Netherlands) have a male/female ratio for death in confirmed cases equal or above 1.7, accessed on May 13th 2020)[2]. In particular, on May 11, 28.903 COVID-19 positive patients had died in Italy. Their mean age was 80 years. Deceased women were 10.934 (lethality 9.6%), whereas men were 17.018 (lethality 17.1%)[3]. For 951 Italian deaths, sex was not reported. The difference in lethality between sexes seems to suggest that women are less prone to develop severe complications that ultimately lead to death. The reasons for this sex-based tolerance are still unknown. Among Italian patients in the range 10-49 years, deceased women were about 84 over 32.345 (0.26% lethality), while in the range age of 50-90 years they were 7975/67.263 (11.9% lethality)[4]. Of note, men had a0.89% lethality (225 deaths over 25276 cases) in the range 10-49 years and 21.8% (15236/69844) in the range 50-90 years. Therefore, lethality seems to increase with age in both sexes, but it is 3.42 folds higher in young men than young women (10-49 years), and 1.84 folds in older men than in older women (50-90 years) accessed on May 13th 2020.

Although these are cumulative/raw data, they confirm that there is a reduced susceptibility of females to severe COVID-19 infection. Due to the differences between pre and post-menopausal phases [Horstman et al. 2012], it is reasonable to speculate that the potential role played by hormones may be present in protecting against severe outcome, but it is not the only factor. Therefore, we need to consider other possible reasons for this difference in sex-related lethality. First, is this difference confirmed also in populations from other countries? According to the latest publications, such differences in lethality between the 2 sexes have been shown elsewhere. For instance, in a number of different articles from China, similar data are reported [Chen et al. 2020a; Chen et al. 2020b; Guan et al. 2019; Huang et al. 2020; Wang et al. 2020; Zhou et al. 2020a][5]. In these studies, severe or deceased patients admitted to intensive care units (ICUs) were prevalently men, while women ranged between 30% [Huang et al. 2020] and 42.2% [Guan et al. 2019][6]. In the largest study available from China [Guan et al. 2019;], quite similar percentages to those reported for deceased women in Italy have been observed. Yet, in this latter study, the median age of patients was 47 years (IQR, 35-58)[7], and the distribution between sexes according to age was not reported. For the US, sex disaggregated data on case fatality are not available, but deaths were 57% for males and 43% for women[8].

To sum up, currently available studies suggest that both young and older females are less susceptible to severe infection outcomes, regardless of their nationality. Both hospitalization in ICUs and death rates are different between sexes. Similar observations were already reported for other coronavirus epidemic .Despite this striking evidences for this infection, very few studies consider different therapeutic approaches for the two sexes. As no specific therapeutics are yet proposed to treat Covid-19 and control disease evolution, a better understanding of the pathogenic mechanisms in the two sexes induced by SARS-CoV-2 is mandatory to characterize new targets

Men are more prone to COVID-19 with higher mortalities

Both young and old women are dying less than matched age males. Beside hormone differences, which, however, do not appear to be the only factor, there are different potential mechanisms that may explain why women are less prone to severe COVID-19 infections.

The expression and activity of two factors may be considered, namely angiotensin-converting enzyme-2 (ACE2) and transmembrane protease, serine 2 (TMPRSS2) [Cheng et al. 2015; Kuba et al 2005][9]. While ACE2 is the receptor for the spike (S) protein of coronaviruses, TMPRSS2 splits the S-protein at sites S1/S2 and S2, favoring the attachment and fusion of the virus to cell membranes, respectively. ACE2 is largely expressed in organs mainly targeted and damaged by SARS-CoV-2 [Pagliaro and Penna 2005][10]. Both ACE2 and TMPRSS2 have been proposed as modulators of the different susceptibility to SARS-CoV in both sexes [Hoffmann et al. 2020]. Indeed, the expression of ACE2 seems reduced in post-menopausal women. However, in some studies, no differences were detected for ACE and ACE2 between the 2 sexes, while a lower ACE2 serum activity was observed in younger compared to older women [Fernández-Atucha et al. 2017][11]. ACE2 is located on the X chromosome, and is one of the genes escaping X inactivation [Tukiainen et al. 2017][12]. Therefore, it can be hypothesized that the second X chromosome could protect women from fatal polymorphisms that make the infection more aggressive in males, e.g. by favoring viral binding. Indeed, in a recent study, worse outcome in older COVID-19 patients has been attributed to the presence of lower ACE-2 levels and the subsequent upregulation of Angiotensin II (Ang II) proinflammatory pathways throughout the body, which could make patients more prone to systemic “deleterious” effects of Ang II [AlGhatrif et al. 2020][13]. ACE and ACE2 and their major products, Ang II and Ang-1-7, respectively, are linked in a sort of ying/yang process, when one decreases the other increases and viceversa [Pagliaro and Penna 2005; Koni and Miyamori 2007; Wakahara et al. 2016; Wang et al. 2015, 2016][14]. Whether ACE2 levels in the lung are related to the susceptibility and severity of COVID-19 infection is a matter of investigation [Gheblawi et al. 2020], and men may have higher expression of ACE2 in the lungs compared to women [Zhao et al. 2020][15], with potential important consequences on COVID-19 infections. Moreover, the different roles of membrane bound ACE2 and circulating ACE2 should be considered. Indeed, it has been proposed that soluble ACE2 could quench the coronavirus by limiting its attachment to cellular ACE2 [Monteil et al. 2020][16]. It is unknown whether circulating ACE2 levels in the two sexes are different. This would be an important piece of information as circulating ACE2 quenching the virus may limit the possibility for the virus to target other organs.

Although some animal and human studies suggest that TMPRSS2 is involved in determining severity of influenza [Cheng et al. 2015; Sakai et al. 2015][17], its role during coronavirus infections and in the modulation of COVID-19 severity is still unclear. Nevertheless, we must consider that TMPRSS2 is a testosterone regulated gene and may have a higher expression in men than in women [Tomlins et al. 2005][18].Moreover, several other X-linked genes (such as ILs, FOXP3XIST, TLR7) and Y-linked genes (SRY, SOX9) may explain sex differences [Ghosh and Klein 2017][19]. These and other immune regulatory genes encoded by the X and Y chromosomes may explain lower viral loads and reduced inflammation in women compared to men [Conti and Younes 2020][20]. In particular, the two X chromosomes seem to regulate the immune system even if one of them is inactive. The X chromosome regulates the immune system also acting on other proteins, including CD40L, CXCR3 and TLR8. These can be up-regulated in women and can determine the response to viral infections as well as to vaccinations. A Differentially Expressed Genes (DEGs) network was constructed to identify a specific gene signature characterizing SARS-CoV-2 infection [Fagone et al. 2020][21]. Intriguingly, ten DEGs were modulated by sexual hormones, as Androgen Receptor regulated 6 DEGs (while CCL20 and CXCL1 genes were up regulated; THBD, HEY2, BBOX1 and MYLK were down regulated genes); whereas Estrogen Receptor 1 regulates 4 DEGs (while C3 and EDN1 genes were up regulated; PDK4 and VTCN1 were down regulated DEGs)[22]. Also, CD4+ T cells number differs between sexes being higher in women with a better immune response [Conti and Younes 2020][23]. Finally, the number of sex-independent non-genetic factors that can change susceptibility and mortality is enormous, and many other factors are likely to be considered, including gender and cultural habits in different countries. For example, an Outbreak in the Republic of Korea determined a high incidence of case in women due to social and religious events occurring in those days. [Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020].

Immunological and inflammatory biomarkers

Morbidity and mortality associated with COVID-19 is mediated through severe viral stimulated irritation and developing tiers of inflammatory biomarkers and cytokines, frequently referred to as “cytokine storm.” Together with diminished lymphocyte counts, cytokine storm is consistently associated with large intense COVID-19 disease. Among these exhibiting an excessive inflammatory profile, older and male victims are overrepresented[24].

An early elevation in C-reactive protein (CRP) greater than 15mg/L Provides a marker of disorder severity and stages greater than 200 mg/L on admission are independently associated with 5 times the odds of death[25]. Males with severe COVID-19 reportedly have a greater CRP attention in contrast with females, independent of age andco-morbidities Of the numerous interleukins (IL)associated with COVID-19 severity, including IL-6, IL-2, IL-8, IL-10,45-47 and compared with females, younger and historic men with COVID-19 exhibit drastically higher IL-2 and tumor necrosis component alpha (TNFalpha), respectively, impartial of co-morbidities[26] [27] [28]. Moreover, data indicate that men with COVID-19 show larger regulation of pro-inflammatory cytokines, which include CCL14, CCL23,

IL-7, IL-16, and IL-18, the latter perhaps contributing to their greater susceptibility to developing cytokine storm and subsequent poorer COVID-19 outcomes[29 30]. Although IL-10, a cytokine with anti-inflammatory effects, has been proven to be greater amongst older males, a tremendous IL10 comments should be viewed an try to decrease excessive infection and consequent tissue damage. Further, greater IL-10 expression diminishes the exercise of antiviral T-cells. Whether biological sex differences regulate the associations among CRP and ILs and COVID-19 outcomes has but to be examined[31].

Adaptive immune response

Lymphocytes are amongst the first responders to viral agents, along with SARS-CoV-2, and are related with COVID-19 severity. Although average COVID-19 disease can be related with every prolonged or diminished lymphocyte counts, in excessive disease, lymphocytes are constantly decreased[32]. Although some COVID-19 research have endorsed that male intercourse is inversely associated with lymphocyte count, a meta-analysis of the advocate massive distinction in admission lymphocyte counts between victims with and barring immoderate COVID-19 penalties tested that lymphopenia and illness severity had been now no longer modified with the resource of way of the utilization of intercourse or co-morbidities[33]. A single-center Wuhan locate out about established that in ill patients, concentrations of SARS-CoV-2 immunoglobulin G have been notably larger in females compared with males, and remained so until four weeks from health facility admission[34]. Sex-specific adaptive immune response is generally well recognized, with female mounting higher antibody manufacturing and accelerated efficacious vaccine responses. Healthy females are acknowledged to have increased numbers of CD4þ T cells, giant CD4þ:CD8þ ratios, and increased numbers of activated T cells, cytotoxic T cells, and B cells compared with males, ensuing in a immediately response to the presence of infectious agents[35]. The function of intercourse steroids in the differential immune responses is supported through a locate out about indicating testosterone exerts an immunosuppressant effect, whereas estrogen would possibly moreover be every immune improving or immunosuppressive[36].

Vitamin D

Apart from its position in calcium homeostasis via improving calcium reabsorption from the gut, nutrition D modulates inflammatory pathways associated with viral infections. Meta-analyses point out that vitamin D deficiency increases the threat of acute viral respiratory infection and community acquired pneumonia, and that supplementation can also forestall higher respiratory tract infections.90 Vitamin D was once observed to minimize with age, and the strongest protecting impact of supplementation used to be found in those with the lowest 25-hydroxyvitamin D [25(OH) D] levels at baseline[37]. Whether sex modified the effect of supplementation on top respiratory tract infection threat was once now not examined[38].American men are uncommonly evaluated for this deficiency and often do no longer receive sufficient supplementation, especially those who are older or overweight Ecological studies advise a nice correlation between nations with low suggest concentrations of 25(OH) D and higher COVID-19 infection and mortality rates. A Swiss cohort learn about of 109 patients stated that 25(OH)D degrees were drastically decrease in patients with SARS-CoV-2 in contrast with those who had been uninfected, even though the association did no longer substantially range when stratified with the aid of sex and age older than 70 years[39]. A large analysis of 348,598 UK Biobank members established that no matter a univariate affiliation between 25(OH) D tiers and the odds of COVID-19, following multivariable adjustment, the association used to be no longer significant. Modification by means of age or intercourse used to be no longer investigated. It is conceivable that decrease nutrition D stages might also contribute to worse disease located in older guys compared with younger or woman individuals, however there is inadequate epidemiologic proof in help of this thesis. Given the pretty minimal dangers of vitamin D supplementation, some experts have encouraged vitamin D supplementation as a COVID-19 preventive strategy, particularly in at hazard elderly populations Ecological studies advise a nice correlation between nations with low suggest concentrations of 25(OH)D and higher COVID-19 infection and mortality rates. A Swiss cohort learn about of 109 patients stated that 25(OH)D degrees were drastically decrease in patients with SARS-CoV-2 in contrast with those who had been uninfected, even though the association did no longer substantially range when stratified with the aid of sex and age older than 70 years. A large analysis of 348,598 UK Biobank members established that no matter a univariate affiliation between 25(OH)D tiers and the odds of COVID-19, following multivariable adjustment, the association used to be no longer significant. Modification by means of age or intercourse used to be no longer investigated. It is conceivable that decrease nutrition D stages might also contribute to worse disease located in older guys compared with younger or woman individuals, however there is inadequate epidemiologic proof in help of this thesis. Given the pretty minimal dangers of vitamin D supplementation, some experts have encouraged vitamin D supplementation as a COVID-19 preventive strategy, particularly in at hazard elderly populations[40].

Sex Hormones, Menopause, and Hormone Replacement Therapy

Sex variations that are constant at some point of the life cycle are likely chromosomal/genetic in origin, whereas those that show up with puberty and then fade with getting older are suggestive of hormonal effects. Sex steroids, along with testosterone, estrogen, and progesterone are strong regulators of immune and inflammatory responses due to the presence of sex hormone responsive sequences in the respective genes. Estrogen at some stage in pre menopause has anti-inflammatory effects, attended by means of decrease tiers of IL-6, IL-8, and TNF-alpha. Conversely, the physiologic decline of estrogen degrees at some stage in herbal menopause outcomes in extended levels of IL6, IL-8, and TNF-alpha. Estrogen depletion or oophorectomy in mice infected with SARS-CoV led to a worse prognosis in contrast with regular estrogen producing mice. Clinical research show that infection resolves greater rapidly in female as in contrast with men, and these differences are thought to be due to hormonal results on neutrophil apoptosis and bone marrow production.Taken together, accessible research provide robust proof that estrogen exerts substantial anti-inflammatory responses, therefore suggesting a viable therapeutic function of hormone alternative therapy in older women. Similarly, low tiers of testosterone in aged guys have been associated with up regulation of inflammatory markers and feasible accelerated chance of lung damage, as nicely as respiratory muscle catabolism and improved want for assisted ventilation. As superior age stays one of the most important risks for bad COVID-19 outcomes, future lookup tackle the function of hormone alternative therapy in elderly girls and guys who are diagnosed with COVID-19.

Innate Immune System

Total white cell count number was once less consistently extended amongst COVID-19 sufferers who required intensive care unit admission or died in contrast with sufferers who did not. These studies did not look at the impact of intercourse on this relationship, a question that deserves attention as there are sex-specific differences in blood leukocyte composition within the conventional population. In the latter population, adult males have higher baseline numbers of total leukocytes, monocytes, neutrophils, eosinophils, and basophils in contrast with females. The total leukocyte and neutrophil counts amplify regularly till the age of fifty five years in males. Women have a bimodal distribution in total leukocyte counts, with the lowest counts occurring round menopause.These recognized intercourse differences, collectively with the presence of underlying co-morbidities and concurrent infections, possibly make contributions to the inconsistent findings regarding white blood cell counts suggested in contemporary COVID-19 studies. The neutrophil to lymphocyte ratio (NLR) is a generic marker of infection and appears to mirror the severity of COVID-19, specially among sufferers older than 50 years of age. A single-center retrospective analysis observed t hat more males had an NLR above 11.75, which was once associated with a lower survival rate .The NLR famous distinct sexual dimorphism in the popular population. Females 50 age years or youthful have a higher NLR compared with men of the identical age and intercourse and age on the prognostic compared with older females. The NLR is higher for men than girls older than the age of 50 years. The effects of cost of NLR require in addition investigation. Sex variations may additionally have important implications in the efficacy of therapeutics that goal unique viral signaling pathways. Notably, toll-like receptors (TLRs), which up regulate type 1 interferon (IFN), an important shielding mechanism against viral infections, can also be up to 10-fold greater in females in contrast with males.

Conclusion

The greater COVID-19 case fatality rate and expanded severity of sickness in men in distinction with ladies is in all likelihood due to a mixture of behavioral/lifestyle hazard factors, prevalence of co-morbidities, aging, and underlying organic intercourse differences. Several comorbidities, which disproportionally showcase up in men, in all opportunity make contributions to worse COVID-19 outcomes, and troubles have been expressed whether or no longer ACE inhibitors or angiotensin receptor blockers may additionally also in addition exert terrible penalties in COVID-19. Experimental and epidemiologic proof is conflicting as to whether or not or no longer the use of ACE inhibitors and angiotensin receptor blockers up regulate ACE2 expression and influences susceptibility to contamination and/or disorder severity. Randomized scientific trials in enchancment can also in addition inform suggestions about the use of such treatment in COVID-19 victims and whether or not or now not or no longer this will vary with the beneficial resource of sex. Based on the on hand literature, we conclude that biological sex differences can also affect the pathogenic mechanisms of COVID-19, the hazard for infection, and the severity of the disease, its outcomes, and its biomarkers. Indeed, experimental and epidemiologic evidence suggests that most of the biomarkers that have been tested in the context of the danger of contamination and the severity of COVID-19 range via intercourse at baseline within wholesome populations. However, the role of biological intercourse and risk for contamination and ailment severity is complex and accessible statistics are now not uniformly consistent. A extremely good instance is that of the immune response: though females usually have an overall better immune response, males are more in all likelihood to improve the cytokine storm related with negative COVID-19 outcomes. Further investigation into immunomodulation by intercourse hormones, age, and X linked gene expression may additionally help explain the worse survival of men, and may also become aware of sex-specific threat factors for SARS-CoV-2 infection and the course, outcomes, and prognosis for COVID-19.

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