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Review Article

Sex and Gender Related Factors that Influence COVID-19 Disease in Terms of Predisposition, Acquisition, Morbidity and Mortality Rates

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Abstract

Undoubtedly, the pandemic of COVID-19 has changed most of our life aspects including social, health services, and economic aspects. There is culminating evidence supports the presence of sex and gender differences in acquisition of this infectious disease and its subsequent outcomes with males having the unfavorable rates and course. There is a paucity of data in terms of sex and gender incorporation by countries, researchers, and data providers. However, in this review, we highlighted the various factors standing behind the sex and gender differences and how could these factors influence the COVID-19 disease and its incidence rate and outcome in both sexes. We explore and discuss these factors in genetic, molecular, and clinical bases and, hence, these findings can be taken in consideration by researchers and decision makers. Nevertheless, more comprehensive analyses and studies are required to figure out this issue and of course this requires more attention in reporting disaggregated sex and gender data.

Keywords: *COVID-19; Cytokines; Gender; Sex; SARS-Cov-2*

Introduction

Since the start of COVID-19 pandemic with millions of peoples were affected all over the world, many studies, sources, and references have reported that males have more rates of infection with COVID-19 than females, however, this observation was thought be affected by other factors such as place, date, and study design [1-4]. Not only increased incidence and prevalence rates in males but also higher rates of morbidity, ICU admissions and mortality among males were observed (Table 1) [4-11]. Giving attention to the subject of sex and gender differences in predisposition to COVID-19 infection and its subsequent impact on disease course, outcome and treatment is an important issue. Sex and gender disaggregated data will help us to address numerous knowledge gaps, to improve our understanding of these sex related differences and their impact, to generate a perfect guidelines and policies, to improve the results of the ongoing experimental treatment studies, and finally to have a better and equitable response to this pandemic and future one. Unfortunately, most countries and data providers have not disaggregated data by sex and gender thus our understanding of this aspect is limited [7,12]. Notably, the exact mechanisms of these sex and gender differences are not completely understood and were influenced by multiple factors (Figure 1). In

this review, we discuss these factors and address their impact on COVD-19 disease in terms of disease predisposition, viral acquisition, and outcomes.

Genetic and molecular factors

One of the hypothesizes that strongly influences the sex-related disparities in COVID-19 outcomes is the sex-related difference in the genetic expressions regulating the immune response in which there is evidence demonstrating that a relevant number of genes involved in the positive regulation of innate and adaptive immune response are located on the X chromosome resulting in strong immune response, more protection, and less symptoms presentation [13]. In the opposite side, genetic variations among genes on the Y chromosome are suggested to negatively influence immune response, thus increasing susceptibility to infections in males compared to females [14]. Earlier studies have shown that SARS-CoV-2 utilizes angiotensin-converting enzyme-2 [ACE2] receptors at the surface of host cells as an entry point and this entry is enhanced by an enzyme named transmembrane serine protease-2 (TMPRSS2) [15-20]. Some reports showed that circulating levels of ACE2 are higher in healthy and comorbid men as compared to women [21]. The gene encoding ACE2 is located on the X chromosome, thus males are homozygous, and females are heterozygous [22,23]. This kind of gene expression put the females at a lower risk of infection and at the same time explains why females have lower incidence and burden of disease [16,24,25]. Interestingly, ACE2 has two biological forms, membrane-bound [more expressed in males, acts as viral receptor and worsens infection outcomes] and soluble-circulating form [more expressed in females, prevents viral attachment and mitigates infection outcomes] [26]. Females have higher levels of Angiotensin 1-7 (Ang1-7) which is considered to enable females to counteract inflammation induced by COVID-19, more effectively [27]. Moreover, there are some cell receptors that were recently described to interact with SARS-CoV-2 such as neuropilin-1 (NRP1) and cluster of differentiation 147 (CD147), however, genetic studies have demonstrated that these were not differentially expressed between males and females [28,29]. Various Signaling molecules were mentioned to interfere with the pathophysiology of SARS-CoV-2 infection, for example, the signal transducer and activator of transcription 1 (STAT1) is highly expressed in females with a protective effect and the extracellular signal-regulated kinase (ERK) is highly expressed in males with a negative effect, however, this needs more studies to confirm these results [30,31]. it is known that no difference between men and women has been found in the relative risk of thrombosis related to genetic risk factors and this is also applied when talking about COVID-19 infection and its thromboembolic effect [32].

Author, Reference	Country	No of patients	Results
Guan W J., *et al.* [3]	China	1590	Among confirmed cases of COVID-19, patients with any comorbidity yielded poorer clinical outcomes than those without.
Jin J., *et al.* [4]	China	43	Men with COVID-19 are more at risk for worse outcomes and death (death rate 60.5%-70.3%), independent of age.
Su W., *et al.* [5]	China	561	males are more likely than females to develop serious complications and progress to death.
Iaccarino G., *et al.* [6]	Italy	2378	Males required ICU admission due to COVID19 infection (74%), with a higher prevalence of comorbidities.
Palaiodimos L., *et al.* [8]	USA	200	Male sex, age, and BMI ≥ 35 kg/m^2 were significant predictors in the multivariate analysis for the outcome of intubation.
Grasselli G., *et al.* [9]	Italy	1591	The majority of ill patients were older men, mostly required mechanical ventilation and ICU mortality was 26%.
Asfahan S, *et al.* [11]	China	44,672	Age and co-morbidities correlated negatively with survival; male death rate was 63.8%
Takahashi T., *et al.* [15]	USA	98	Male patients had higher plasma levels of innate immune cytokines and was associated with worse outcomes
Qin L, *et al.* [60]	China	548	Males had higher mortality than females did (22.2% vs 10.4%), with hazard ratio of 1.923 (95% confidence interval, 1.181-3.130)
Vahidy F S., *et al.* [61]	USA	14,992	Males are more likely to have COVID-19, to have complications, to require ICU admission and mechanical ventilation, and had higher mortality than females, independent of age

Table 1: *Examples of studies with sex and gender related differences in outcomes available from literature.*

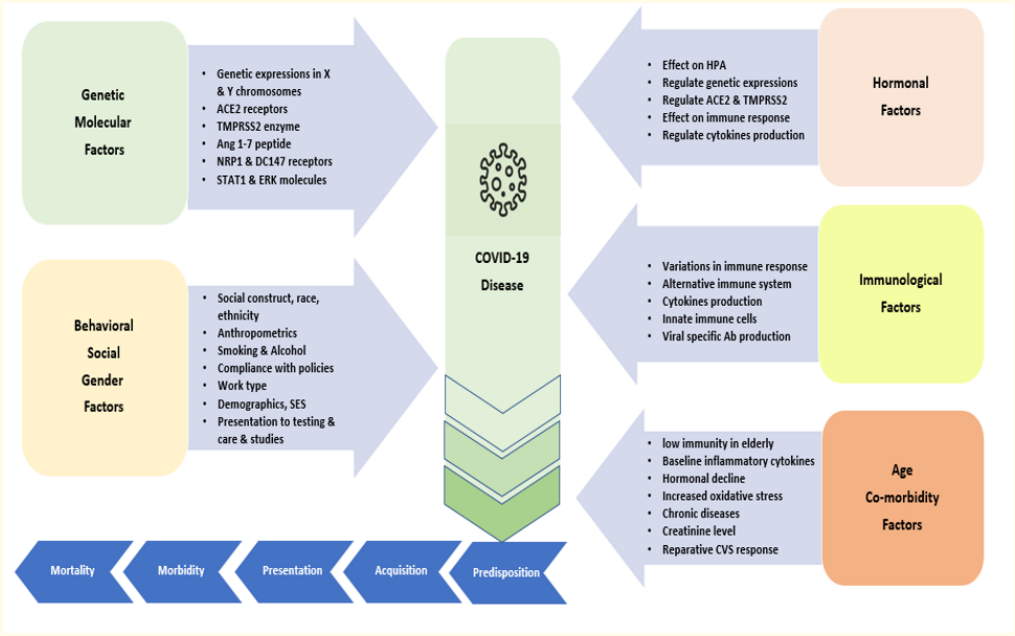


Figure 1: *Sex and gender related factors and their effect on COVID-19 disease course.*
Abbreviations: ACE2: Angiotensin-Converting Enzyme-2, TMPRSS2: Transmembrane Serine Protease-2, Ang1-7: Angiotensin 1-7, NRP1: Neuropilin-1, CD147: Cluster of Differentiation 147, STAT1: Signal Transducer and Activator of Transcription 1, ERK: Extracellular Signal-Regulated.

Immunological factors

In general, it has been postulated that females appear to respond more vigorously to viral infections and produce more antibodies in response to infection and vaccination than males [33]. Infection with SARS-CoV-2 lead to host response that varies from a symptomatic or mild infection to a severe and lethal infection with cytokines storm initiating an inflammatory cascade that elaborate several cytokines, chemokines, and growth factors. One of the presumed reasons for this difference in host response is sex and gender factor. It has been found that males showed a significantly higher immune response, increased natural killer cells (NK cells) number, increased CD+8 cells number, and higher inflammatory cytokines production by macrophages, thereby, higher rates of morbidity and mortality [33,34]. This was explored in many studies that showed that males have significantly high inflammatory cytokines levels such asIL-6, IL-8, IL-18, and CCL-5 leading to increased disease severity [15,35]. Females have more activation of dendritic cells, increased CD+4 cells number, increased interferon (IFN) production, and activation of macrophages and neutrophils with consequent increase in phagocytotic activity [33]. The reason why females have less inflammatory response is unclear, but it has been assumed that females may have an alternative immune response such as virus-specific antibodies and innate immune cells that counteract theses harmful inflammatory cytokines [36].

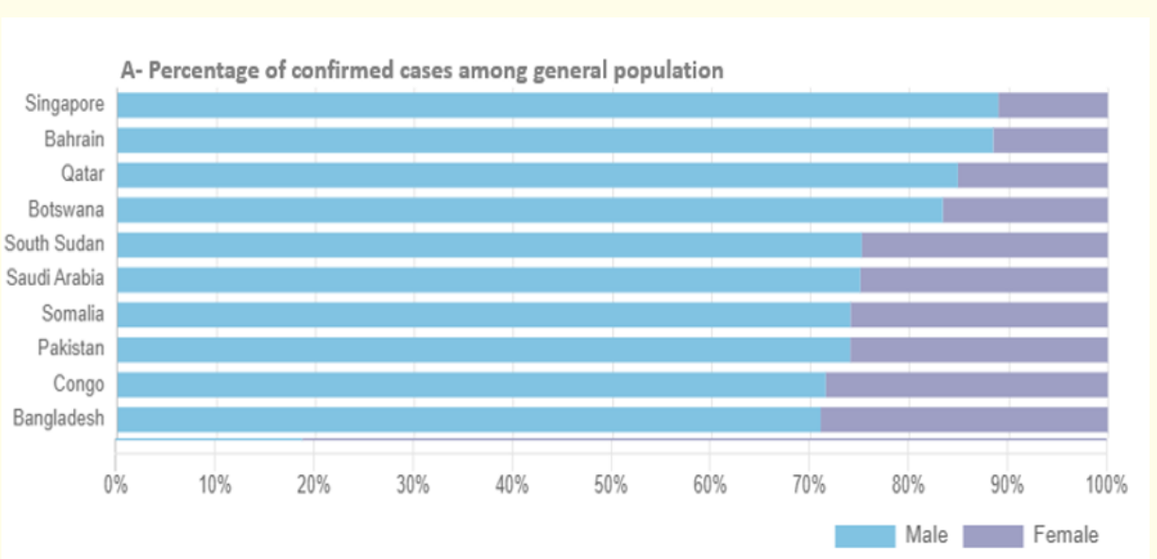
Hormonal factors

It has been found that testosterone hormone modulates the expression of gene encoding for transmembrane serine protease-2 (TMPRSS2), which enhances the entry of SARS-CoV-2 to host cell [16,37]. Also, testosterone has a suppressive effect on immune system and the hypothalamus-pituitary-adrenal (HPA) axis subsequently lead to higher rates of infection and disease progression in males [16,24,25,38].

In addition, low levels of testosterone in older males are associated with high cytokines levels such as CRP and various interleukins that contribute to worsening of the disease and fatality rates [15,24,25]. In the other hand, estrogen and progesterone hormones have an anti-inflammatory effect that oppose the production of several cytokines such as IL-6, IL-1β, and TNF-α [36,39,40]. Estrogen also promotes adaptive immune system and enhances the production of viral specific antibodies (IgGs) by B cells that lead to faster clearance of invading SARS-CoV-2 virus [15,24,25,41,42]. Downregulation of ACE2 receptor and TMPRSS2 expression and regulation of renin activity by estrogens were described in some reports [15,23]. Estradiol has a direct stimulatory effect on the hypothalamus-pituitary-adrenal [38]. In fact, ovariectomy increases the ACE2 expression in the females and estradiol replacement reduces the ACE2 expression [44]. These estrogenic effects explain the lower inflammatory responses and outcomes in females. Pregnant women tend to have less symptoms compared to nonpregnant women but higher rates of ICU admission and preterm birth [45]. It is suggested that there is a possible positive role of estrogens and a negative role of androgens on hemostasis and coagulation cascade consequently this suggests that in men the thrombotic risk is three folds higher compared to women due to these hormonal factors and this would exaggerate the preexisting thromboembolic tendency seen in COVID-19 infection in male patients [46].

Behavioral, social and gender factors

Social constructs such as gender, race, and ethnicity may influence an individual's lived experience and, therefore, exposure to and acquisition of SARS-CoV-2 [47]. Notably, the anatomical and physiological function of the respiratory system and the anthropometric measurements may differ between both sexes. Lung size is generally larger in men compared to women, hence, more battle ground area for SARS-Cov-2 to replicate and produce more effects [48]. Smaller body and face sizes in female limit perfect fitness of personal protective equipment [PPE] and N95 face masks, hence, more risk of exposure to infection [49]. Smoking was considered to be one of the contributing factors for increased severity of COVID-19 infection [50]. In addition, smoking was also considered to play a role in sex predisposition for COVID-19 infection. Worldwide, smoking rates are higher among males than females leading to parallel increase in incidence rates of COVID-19 infection in males [1,51]. Males showed less compliance with international precautions and public policies such as hygienic procedures and social distancing, thereby, more susceptible to get infection [1,50-53]. Males constitute the majority of hand power worldwide and the gathering in workplaces put them at a higher risk of exposure and infection with COVID-19 than females [1,5,15,50,52,54,55]. In the other hand, women constitute the majority in some jobs that might be closer to virus places such as healthcare workers (Figure 2) [56,57]. Other gender factors that should be taken in account when addressing sex and gender differences include rejection of social isolation and obligations, psychological stress, demographics, and poverty among COVID-19 patients [1,58-60]. In some parts of the world, males have probably easier access to health care and viral testing [61]. In addition, men also tend to present lately for testing and medical treatment thus increasing the rate of hospitalization among them. Based on the fact that females have less symptoms upon presentation, hence, less hospitalization rates, they are under-represented in research studies and thus the estimates to compare the efficacy of treatments might be inadequate [62,63]. One of the overlooked factors that affect the results of the reports that address the sex predisposition to COVID-19 infection is the ignorance of incorporating sex and gender data in the announced reports provided by some countries [7]. Nevertheless, based on the WHO and the Global Health 5050 Data Tracker reports from countries providing sex-disaggregated data, males have higher rate of morbidity and mortality (Figure 3) [12,64].



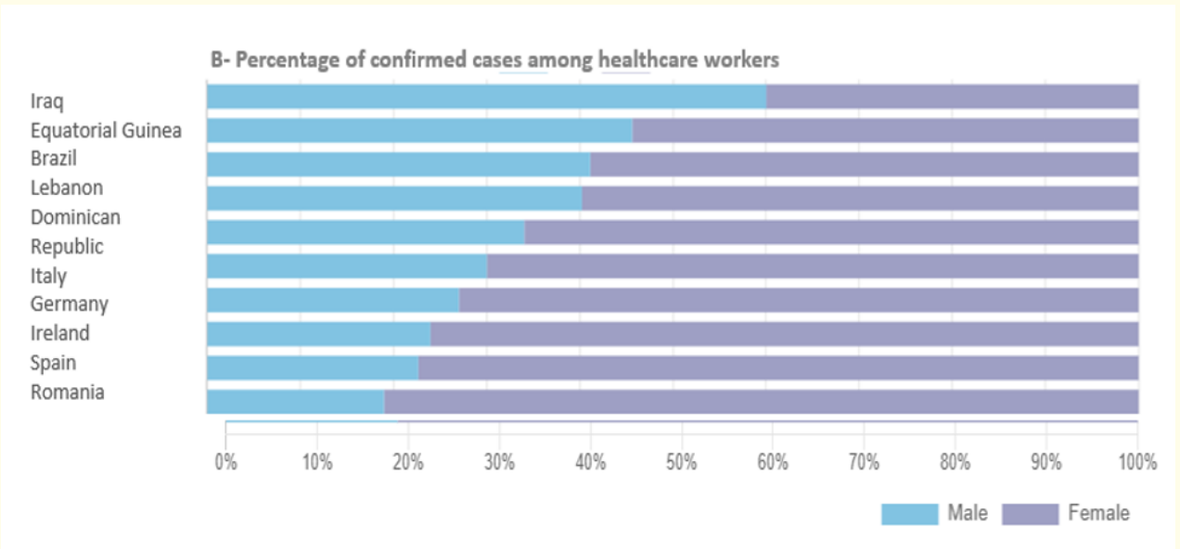
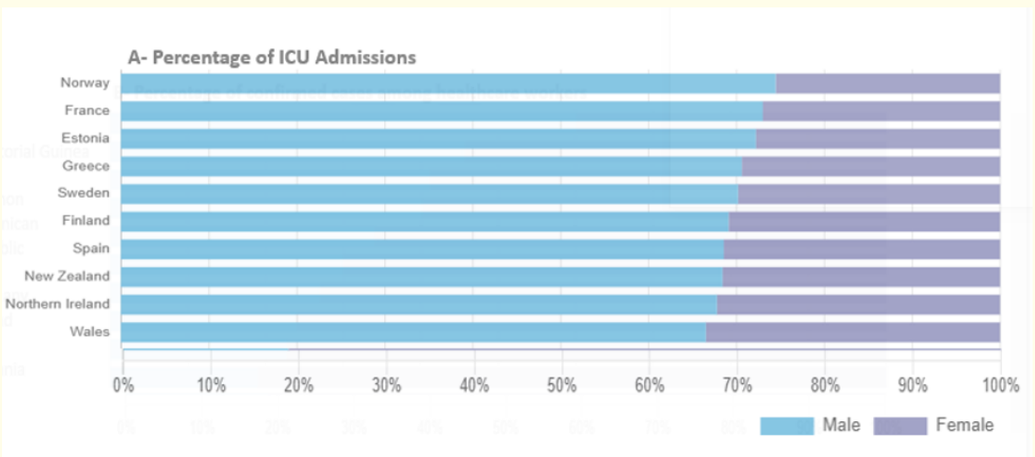


Figure 2: *Sex disaggregated data showing percentage of confirmed case of COVID-19 among general population and healthcare workers in several countries. Source: The COVID-19 Sex-Disaggregated Data Tracker- The sex, Gender and COVID-19 Project, GLOBAL HEALTH 5050; date accessed 18/09/2021.*



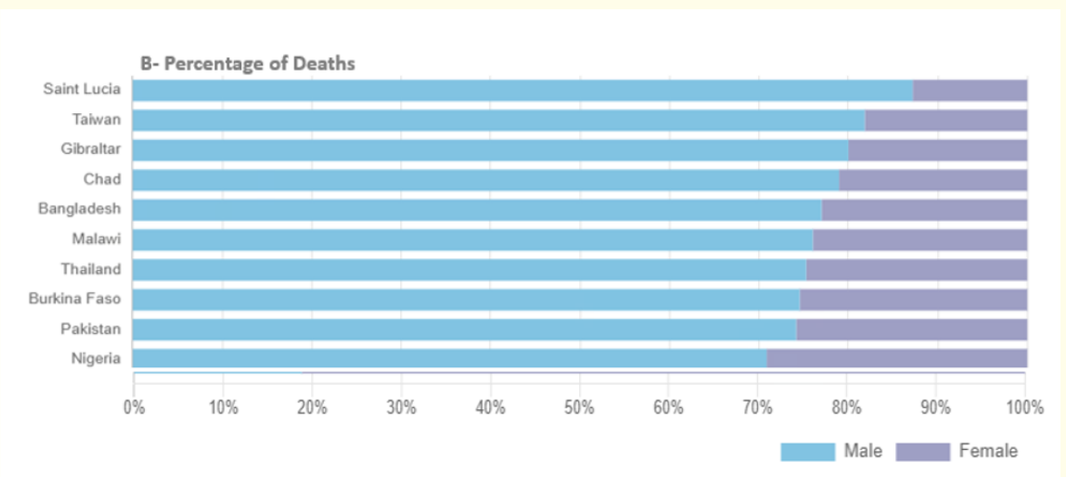


Figure 3: *Sex disaggregated data showing percentage of ICU admissions and deaths due to COVID-19 disease in several countries. Source: The COVID-19 Sex-Disaggregated Data Tracker- The sex, Gender and COVID-19 Project, GLOBAL HEALTH 5050; date accessed 18/09/2021.*

Age and comorbidity

It is well-known that older people have a more severe disease when infected with COVID-19 due to many factors such as low immunity, high baseline inflammatory cytokines (e.g. IL-6), low stress hormones and co-morbidities [65-67]. Surprisingly, high titers of neutralizing and antigen-binding antibodies have been found in elderly COVID-19 patients, it is still unknown whether such antibody response is protective, pathogenic, or just represent the expression of severe disease [67]. Noteworthy, because of the age-related hormonal decline and age-related increased oxidative stress, elderly men have higher COVID-19 induced endothelial injury and thromboembolism [68]. Furthermore, in many observational studies, it was noticed that males are more prone to have a severe disease than females, independently of age and comorbidities especially smoking-related comorbidities such as chronic lung diseases and ischemic heart diseases [4,10,11,50,61,69,70]. Older men with DM and kidney diseases have high levels of ACE2 thus are more susceptible to infection with COVID-19 virus [21]. It has been noticed that elevated levels of creatinine in blood samples of males compared to females were detected in patients with severe cases of COVID-19 which was positively correlated with increased mortality in male patients [4,71]. Some reports stated that female patients showed enhanced reparative response following cardiovascular injury induced by COVID-19 infection compared to male patients and this may explain the lower rate of deaths in females [72]. In fact, females tend to have more long-term disease manifestations, experience a higher rate of response to treatments and vaccination but a higher incidence of medication and vaccination side effects than males and the reason for that is not clear but might be attributed to biological differences, differences in therapeutic choices or differences in reporting [73-77].

Conclusion

This study highlighted the various interacting factors that influence the sex and gender disparities and predisposition for COVID-19 infection and how these factors affect the incidence rate, case fatality, and outcomes among both sexes. It showed that why males are infected more than females and why they have unfavorable COVID-19 outcomes. In the view of this study, we emphasize on the importance of incorporating the sex and gender data in all future national and international data, guidelines, recommendations, and clinical and therapeutic trials. Our experience from this pandemic mandate better understanding of all factors including sex and gender differences to make our interventions and decisions tailored with the impact of pandemic and its consequences in the future which will have a positive effect in all pandemic aspects including medical and economical aspects. We encourage all decision makers and researchers to include the disaggregated sex and gender data in all data sources and studies and to make it publicly available. Nevertheless, more comprehensive analyses and stronger studies are needed to address the sex and gender effects in COVID-19 disease and to investigate the possible role of sex-specific hormonal, immunological and genetic therapies in the treatment of COVID-19 disease or to combine it with the existing treatments.

Key Points

- Males have more rates of infection, morbidity and mortality with COVID-19 infection.
- Genes involved in the positive regulation of immune response are located on the X chromosome resulting in strong immune response while variations among genes on the Y chromosome are suggested to negatively influence immune response
- SARS-CoV-2 utilizes ACE2 receptors at surface of host cells as an entry point and this entry is enhanced by TMPRSS2 enzyme which have higher levels in males.
- Males showed exaggerated immune response with increased cytokines production, increased oxidative stress, and decreased reparative response following CVS injury which worsen the disease prognosis, while females have an alternative immune response such as virus-specific antibodies and innate immune cells that counteract harmful cytokines.
- Testosterone modulates the expression of TMPRSS2 genes, suppresses immune system and the HPA axis and increases cytokines production, hence, lead to higher rates of infection and disease progression in males, while estrogen downregulates the ACE2 and TMPRSS2 genes, stimulates adaptive immune response and HPA axis, and opposes harmful cytokines production leading to favorable prognosis in females.
- Gender and social construct factors that are prevalent in males and expected to increase the risk of infection include smoking, alcohol consumption, non-compliance with policies, anthropometrics, and more presentations to testing, care and studies.
- Co-morbidity and age-related factors such as low immunity, hormonal decline are more common in males and are positively correlated with increased mortality.

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Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Statement

The authors are accountable for all aspects of the work in ensuring that.

Conflicts of Interest

The authors have no conflicts of interest to declare.

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