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Recommendations for the collection and analysis of data disaggregated by sex related to incidence, manifestations, response to therapies and outcomes in COVID-19 patients

ISS Working Group for Translational Research COVID-19

Version April 26, 2020

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Emerging data, either the infection rate as well as the lethality rate, highlight sex and gender differences in the context of the COVID-19 pandemic. The comprehension of the mechanisms underlying those differences will be important in designing gender-specific prevention and treatment strategies. Therefore, it is recommended to disaggregate by sex the collection and analysis of epidemiological and clinical data from COVID-19 patients, at national and international level.

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Introduction

Sex and gender (terms that refer respectively to the biological and socio-cultural characteristics of the individual) are important risk factors for both non-communicable and communicable diseases, such as infections. Women usually are more susceptible to viral infections than men, however disease outcome is worse in male than female individuals. The reasons behind this disparity may be linked to gender-related differences, i.e., the different social and behavioural habits that lead women to be more exposed to infectious diseases. In fact, it is well known that women are more involved in the informal care of sick family members and healthcare workers are mostly women.

However, the observed disparity in the severity of viral infections between male and female individuals is due to the sex-related differences, i.e., defined by biological factors. A crucial factor contributing to sex-related differences in viral infections is represented by the innate and adaptive immune response, stronger in women than in men. The main sex-specific determinants of immunity are:

i. Sex hormones, oestrogens and androgens, which play opposite effects, the first immunostimulants (and undergoing variations throughout life), the second immunosuppressive;

ii. genetic and epigenetic factors related to the enrichment on the X chromosome of gene expression regulators (e.g., microRNA) and gene encoding for proteins involved in the immune response to infections (e.g., Toll-like receptors, interleukins, chemokines).

Epidemiological data

Like other infectious diseases, a disparity between sexes has also been observed in COVID-19. In fact, epidemiological data available to date, highlight differences between men and women in SARS-CoV-2 clinical manifestations and disease outcome. In particular, data updated to February 24th2020, showed that in China men had a worse disease severity and a higher fatality rate (CFR) than women, that is 4,7% among men compared to 2,8% among women (1-3) (Figure 1).

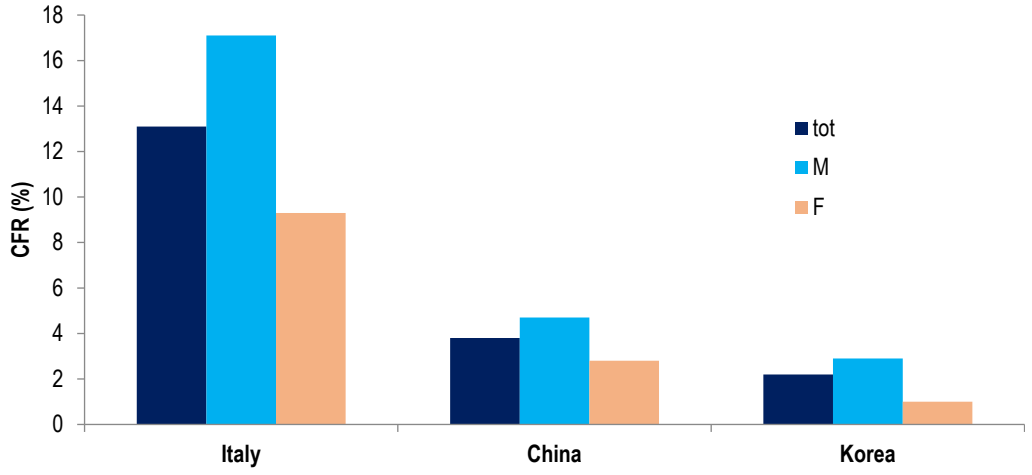

Figure 1. Total and sex-disaggregated COVID-19 case fatality rate (CFR) in Italy, China and Korea (Italian data are updated to April 23rd, Chinese ones to February 24th and Korean ones to April 18th, 2020)

Italian and Korean data confirm this trend with a higher fatality rate in men than women. Moreover, in both countries this trend remains constant in all age groups (4, 5) and sex disparity increases with age reaching the highest value among men over 70 years of age, except for over 89 years age group in which female population is numerically higher than male population (Figure 2).

Regarding the infection rate, no difference between men and women has been observed in China while in Korea women were more susceptible to SARS-CoV-2 infection (60% of confirmed cases are women according to data updated to 18 April) (5) (Figures 3 and 4). In Italy, a similar percentage of confirmed positive cases among the two sexes has been observed, in the 0-60 years age groups, while in the 60-80 years age groups infection cases predominate in men, with 32,235 confirmed cases in men vs. 20,988 in women (based on the data of the integrated surveillance of COVID-19 bulletin by ISS updated to April 23rd) (4). On the contrary, in over 90 years age groups, infection cases are higher in women than in men (9,429 women vs. 2,888 men). This gender disparity in COVID-19 cases distribution may be explained by the different demographic composition of various age groups and by the different levels of exposure to contagion related to occupations (for example, health workers among whom women predominate) or social habits (caregivers are mainly women).

No reliable data on gender differences in recovery rates are available so far, due to the lack of a clear definition of "recovered case", nor of the off-label effects of the therapies used, nor obviously, of the results of the on-going therapeutic protocols approved by the Italian Agency of Drug (*Agenzia Italiana del Farmaco*, AIFA) (about a dozen).

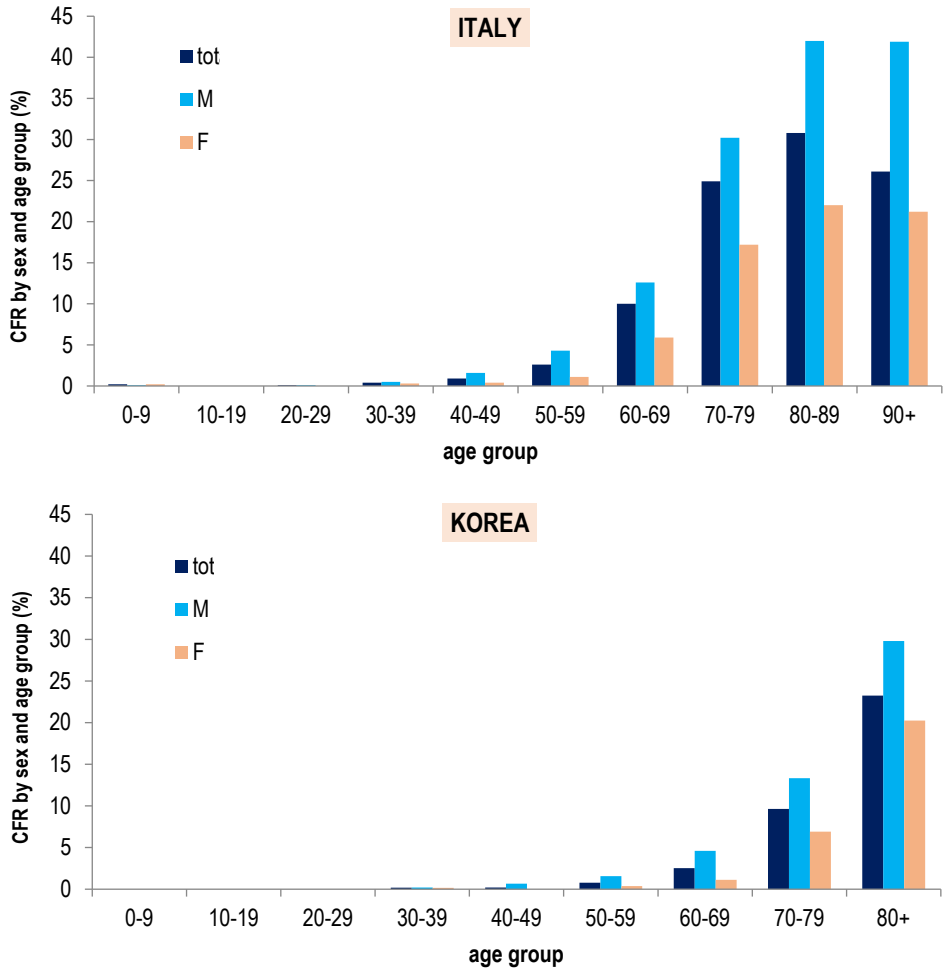

Figure 2. CFR by sex and age group in Italy and Korea

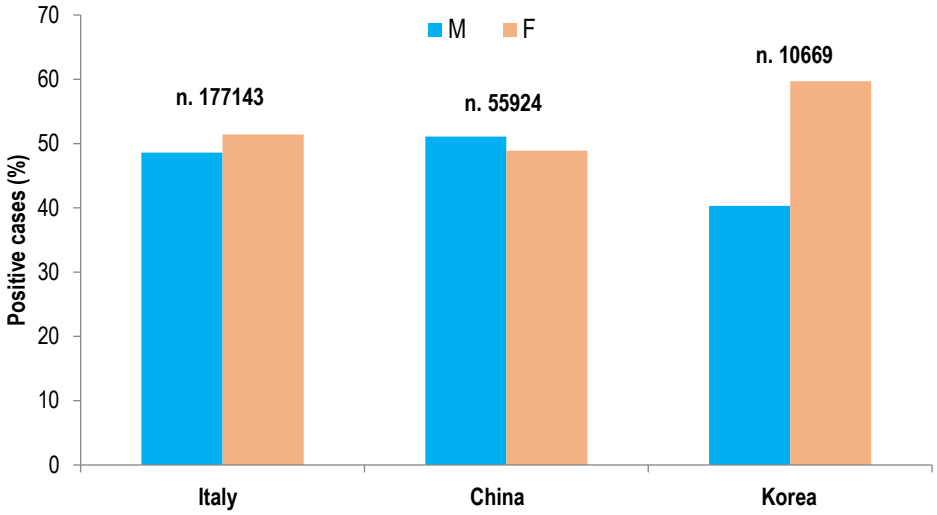

Figure 3. Sex-disaggregated confirmed positive cases in Italy, China and Korea
(Italian data are updated to April 23rd, Chinese ones to February 24th and Korean ones to April 18th, 2020)

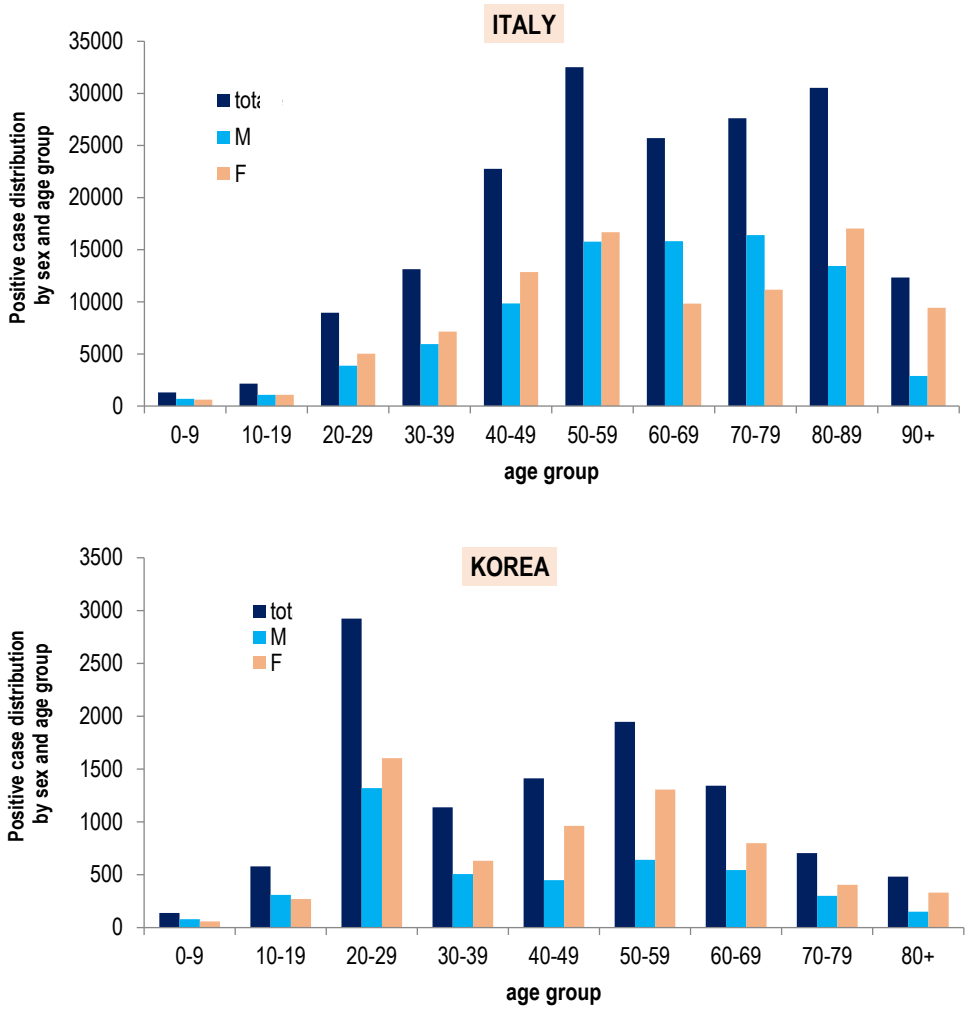

Figure 4. Figure 4. COVID-19 positive case distribution by sex and age group in Italy and Korea

From the above, it is clear that, from an epidemiological point of view, SARS-CoV-2 virus does not differ from other coronaviruses responsible for epidemics, such as SARS-CoV and MERS-CoV viruses. In fact, studies concerning the SARS and MERS epidemics, the first occurred in the years 2002-2003, the second in 2010, have reported a higher incidence, a worse disease severity and a higher fatality rate in men than in women, especially in the older age groups (6-8).

Possible mechanisms of gender differences

Among the mechanisms concurring to determining the gender disparity in SARS-CoV-2 fatality, differences in lifestyle, such as smoking addiction, more frequent in men, should be considered. In addition, pre-existing comorbidities, such as hypertension, cardiovascular disease and chronic lung diseases (COPD) that were commonly found among severe and lethal COVID-19 cases, are often more frequent and more severe in men.

However, the observed sex-disparity is mainly due to biological factors. As mentioned above, women generally mount prompter and more intense innate and adaptive immune responses, and this could play an important role in COVID-19 progression, which is diverging in the two sexes.

Female and male sex hormones, especially oestrogens and androgens, have not only an immunomodulatory effect, but in the SARS-CoV-2 case, they could be involved in the infection mechanism itself. In fact, the virus enters target cells of the respiratory system by directly binding to ACE2 (Angiotensin Converting Enzyme 2) receptor, an enzyme that regulates vasoconstriction and is expressed by several tissues, such as the pulmonary epithelium, where it plays a protective role against damage caused by infection, inflammation and stress. SARS-CoV-2, by binding to ACE2, decreases the level of this receptor, rendering it unavailable for the lung protective role.

To note, oestrogens upregulate ACE2 receptor expression, suggesting that this enzyme can play its protective role, especially in the lungs, even in infected individuals, at least in women of childbearing age. On the other hand, androgens seem to have a pathogenic role by modulating the expression of cellular enzymes, such as the serine protease TMPSSR2, involved in the phase of infection, subsequent to receptor binding, i.e. viral entry, promoting infection spread in the lungs.

Genetic milieu also plays a crucial role in sex- related differences in many diseases. It is known that female mammalian cells carry two X chromosomes while male ones carry one X chromosome and one Y chromosome. To prevent redundant expression of X-linked double-copy genes, a random inactivation of one of the two X chromosomes occurs in female cells. Since this mechanism is imperfect some chromosomal regions escape inactivation and, consequently, genes encoded in these regions are over-expressed in female sex. ACE2 is encoded on the X chromosome in those regions usually escaping inactivation, thus suggesting its overexpression in women which may thus be protected from the severe outcome and death associated to COVID19.

Conclusions

Consequent to the certainties and hypotheses on COVID-19, the importance of carrying out further specific studies, also retrospective, is evident, in order to: i) evaluate the role of innate and adaptive immune responses and sex hormones in determining gender-related differences in this pandemic –such as the role of using hormone replacement therapy (HRT) in women affected by COVID-19 – and ii) understand the role of X-chromosome inactivation (XCI) escaping genes and of their regulators , such as microRNAs. The aim is not only to identify sex-specific pathogenetic determinants of COVID-19 susceptibility and disease progression but also to provide tools of knowledge for the development of personalized therapy.

Understanding sex/gender-related mechanisms correlated to pandemic should not be considered an additional option to research but a fundamental issue to ensure impartial and effective global health interventions for each individual. With a view to global health, all countries should urgently align and face this fact to conduct health interventions for COVID-19 (9).

In order to understand gender differences and find more appropriate solutions to reduce the impact of COVID-19 on women and men, we propose, at international, national and regional level, to:

- systematically collect and report gender and age- disaggregated data on COVID-19;
- take into account gender perspectives in research design to allow an evaluation of the safety and efficacy of diagnostic tools, candidate or already used drugs and vaccines;
- report all the data on COVID-19 related research, disaggregated by sex in peer-reviewed publications
- obtain guarantees for the application of a gender sensitive approach by research funding agencies and ethics committees;
- perform a comparative analysis of gender-disaggregated data, for example on lethality, obtained by our and other countries.

For the latter point, we aim to collect international data, also through the collaboration with the International Gender Medicine Society (IGM), in order to get a complete picture of gender differences in all countries, to understand whether and how climatic and environmental differences, habits and lifestyles, different health systems, therapies and patient care can influence disease susceptibility and outcome.

In the long-term, once we have emerged from the emergency, understanding the mechanisms underlying gender and sex differences will allow us to understand why some people are more at risk than others, to identify predictive markers of disease severity and to find the best personalized therapy, according to gender.

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