Letter to Editor

What is protecting females from COVID -19 related mortality - ᗇ

Pieter A. Doevendans[1,2,3]* and Yolande Appelman[4]

[1]UMCU Utrecht
[2]Central Military Hospital Utrecht
[3]Netherlands Heart Institute Utrecht
[4]Department of Cardiology, Amsterdam UMC, location VUMC University, Amsterdam The Netherland

*Address for Correspondence: Pieter A. Doevendans, Netherlands Heart Institute Utrecht, Netherlands, E-mail: P.Doevendans@umcutrecht.nl

Cite this article: Doevendans PA, Appelman Y. What is protecting females from COVID -19 related mortality. Int J Cardiovasc Dis Diagn. 2020;5(1): 001-002.

The world is in the grip of the COVID-19 pandemic and causes a high mortality and morbidity. Although it is early days to come to definite conclusions, we do see some interesting trends with respect to sex in relation to COVID mortality (very consistent) and morbidity (less consistent). In all age categories there is excess mortality in Males (M) compared to Females (F) except over the age of 90. It is obvious that age is the number 1 risk factor, but maybe sex is the second? This was demonstrated already in China in the first reports (F 2.8%; M 4.7%; fact 1.7), but we do see a comparable outcome in for instance the Netherlands (F 982 *vs* 1529 fact 1.6; https://www.rivm.nl/coronavirus-covid-19/actueel) Germany (F 592, M 1012 pts. fact 1.7; https://www.statista.com/statistics/1105512/coronavirus-covid-19-deaths-by-gender-germany/) and US (F 1991 *vs* M 2993 fact 1.5; https://www.cdc.gov/nchs/nvss/vsrr/COVID19/index.htm). The death toll is almost double in men, while also many females are developing complaints and reported sick. The most important data is retrievable on the internet but there is hardly any peer reviewed data or report out there. Here we used the data available on the internet on April 10th 2020.

The major limitation for an analysis could be that the statistics are incomplete, and more patients are dying at home. Incomplete data is highly likely as for instance in the Netherlands only people with proven COVID-19 are included in the statistics. Suspected cases are not included. In the Netherlands there is a marked difference by the official mortality numbers of proven cases (RIVM) versus a sharp increase in overall mortality reported through another Dutch agency, Central Bureau for Statistics (CBS). Part of the problem in the Netherlands is limited testing capacity, that is gradually picking up but must lead to major underreporting. Probably more countries have to deal with these issues. In addition, there could be a difference to access to our health facilities, where more males are being admitted, tested and treated. But if we assume that the lack of testing and access is comparable between males and females, women appear to have a much better chance to survive the disease compared to men.

It is interesting to consider the potential causes of this highly significant sex-based difference reported on various continents. Part of the explanation can be sought in looking at comorbidity. A very predominant co morbidity is Cardiovascular Disease (CVD), which is currently being used as a very wide definition. Of course, before we consider CVD an important risk factor, the data should be corrected for the expected prevalence in the elderly. If that correction is being made the dramatic effects of CVD for mortality will be limited. If we look at the distribution in the Netherlands, the table on COVID related mortality is more or less identical to the table on CV mortality; (https://www.hartstichting.nl/getmedia/41cf66bf-2107-44d6-b2c3-739fc465ec73/cijferboek.pdf) with a difference in absolute numbers. With respect to CVD corrected for age and sex the prevalence gives the impression that CVD indeed is an important discriminating factor, that accounts for a 50% difference in mortality. If we look at CVD in more detail, we are clearly in the dark as we lack the info at this moment to look at more specific diagnosis, like

whether hypertension, coronary artery disease, body mass index, ischemia or cardiac failure are the key issues. In the Netherlands the Dutch Cardiovascular Alliance embraced a national initiative from Prof F. Asselbergs to setup a more detailed registry to get specifically the additional information and correct diagnosis: Capacity (https://www. capacity-covid.eu). The remaining 50% in mortality gap, maybe related to differences in lifestyle and-or immune response. Several reports suggest there may be a relationship between Body Mass Index (BMI) and outcome. Yet it is difficult to get that info from the available reports on the internet. In a recent US obesity study, researchers looked at 3,615 patients admitted to their hospital from March 4th to April 4th 2020. The authors analyzed the BMI of the patients with confirmed COVID-19. A person with a BMI of 18 to 25 is considered normal weight, 25 to 30 is considered overweight, and over 30 is obese. The study showed that for patients aged < 60 years and a BMI from 30 to 34 were 2.0 times ($P < 0.0001$) and 1.8 times ($P = 0.006$) more likely to be admitted to acute and critical care, respectively, compared with individuals with a BMI under 30 https://www.cidrap.umn.edu/news-perspective/2020/04/new-york-obesity-appears-raise-covid-19-risk. For patients in the same age-group with a BMI over 35, the risk was 2.2 higher for acute and 3.6 times higher for critical care. In addition, a Chinese report published last month looked at 112 COVID-19 patients. Here, seventeen patients died of which fifteen (88%) were classed as being overweight or more. By comparison, only 18 of the 95 survivors (19%) were classed as overweight or above on the BMI scale. The effect of BMI and increased fat tissue could be related to the immune response and coagulation, potentially aggravating the individual response [1].

To continue on the immune system, there may be marked sex differences. Women, are better equipped with two X chromosomes and a more optimized immune system to coop with an infection, both at the level of the innate immune system and the delayed response [2-4]. It is not clear whether two X chromosomes or the absence of one Y chromosome is essential here.

In conclusion, it is crucial to protect the patient with CVD against COVID-19 infection, especially the elderly with attention for BMI. Yet more factors need to be considered to understand the difference in mortality between women and men.

REFERENCES

1. Peng YD, Meng K, Guan HQ, Leng L, Zhu RR, Wang BY, et al. Clinical characteristics and outcomes of 112 cardiovascular disease patients infected by 2019-nCoV. 2020; 48: E004. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/32120458

2. Trigunaite A, Dimo J, Jørgensen TN. Suppressive effects of androgens on the immune system. Cell Immunol. 2015; 294: 87-94. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/25708485

3. Agrawal M, Kern PA, Nikolajczyk BS. The Immune System in Obesity: Developing paradigms amidst inconvenient truths. Curr Diab Rep. 2017; 17: 87. **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/28812211

4. Appelman Y. The Y factor in the cardiac syndrome X. Netherlands Hear J. 2012; 20: 345-346 **PubMed:** https://www.ncbi.nlm.nih.gov/pubmed/22810625/