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The molecular basis of gender variations in mortality rates associated with the novel coronavirus (COVID-19) outbreak

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Abstract

Since the outbreak of the novel coronavirus disease (COVID-19) at the end of 2019, the clinical presentation of the disease showed a great heterogeneity with a diverse impact between different subpopulations. Emerging evidence from different parts of the world showed significantly poor outcome among males compared to female patients. A better understanding of the molecular mechanisms behind this difference might be a fundamental step for a more effective and targeted response to the outbreak. For that reason, here we try to investigate the molecular basis of the gender variations in mortality rates related to COVID-19 infection. To achieve this, we used our in-house pipeline to process publicly available lung transcriptomic data from 141 females compared to 286 males. After excluding Y specific genes, our results showed a shortlist of 73 genes that are differentially expressed between the two groups. Our results showed downregulation of a group of genes that are involved in the regulation of hydrolase activity including (AGTR1, CHM, DDX3X, FGFR3, SFRP2, and NLRP2), which is also believed to be essential for lung immune response and antimicrobial activity in the lung tissues in males compared to females. In contrast, our results showed an upregulation of angiotensin II receptor type 1 (AGTR1), a member of the renin-angiotensin system (RAS) that plays a role in angiotensin-converting enzyme 2 (ACE2) activity modulation. Interestingly, recent reports and experimental animal models highlight an important role of this receptor in SARS-Coronavirus lung damage as well as pulmonary edema, suggesting a possible role of its blockers like losartan and olmesartan as potential therapeutic options for COVID-19 infection. Finally, our results also showed a differential expression of different genes that are involved in the immune response including the NLRP2 and PTGDR2, further supporting the notion of the sex-based immunological differences.

Taken together, our results provide an initial evidence of the molecular mechanisms that might be involved in the differential outcomes observed between both genders during the COVID-19 outbreak. This might be essential for the discovery of new targets and more precise therapeutic options to treat COVID-19 patients from different clinical and epidemiological characteristics with the aim of improving their outcome.

Key words: COVID-19, gender, transcriptomics, RAS, hydrolase activity, sex-based immunological differences

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Introduction

Since the outbreak of the novel coronavirus disease (COVID-19) at the end of 2019, this disease has become a public health emergency with global impact that attract international interest [1].

Most of the COVID-19 patients were found to suffer from only mild to moderate symptoms reaching 81% of infected people and never need admission to hospital [2].

The other 19% of patients suffer from a more severe disease that on some occasion progress to critical condition. The fatality rate showed great variability between different populations, which was attributed to several factors including age as well as presence or absence of group of high prevalence co-morbidities including obesity, diabetes, cardiovascular diseases as well as chronic respiratory diseases [3]. Better understanding and early identification of risk factors that might predispose for a more aggressive clinical course might be essential for the adoption of more effective management strategies including early intensive care and adoption of more personalized therapeutic options.

Interestingly, and despite the fact that many reports from different parts of the world revealed an equal distribution of the cases between men and women, the mortality rate showed a significant difference between both genders with men forming around two-thirds of the deceased patients compared to only one third in women [4-6].

Indeed, the difference in the mortality rate can be attributed to some gender-related factors including hormonal variation, social and behavioural differences such as smoking and alcohol consumption habits, which might lead to increase the number of patients with comorbidities like cardiovascular and lung diseases [7].

Sex-based immunological differences were also suggested to play an important role in the variable mortality rate observed between both genders [8]. Interestingly, while the IgG antibody levels in both genders were found to be similar in the mild cases of COVID-19, female patients were found to have significantly higher levels of IgG antibodies in the more severe cases compared to the male patients [9].

Other mechanisms that were proposed to play a role in the higher vulnerability rate of males in COVID-19 pandemic is the gender-defined genetic polymorphisms and molecular variations [9]. In support to this notion, the angiotensin-converting enzyme 2 (ACE2), which was found to be essential for the COVID-19 virus to bind and enter to the host cells, including both the upper and lower respiratory tract [10], is located on the female sex chromosome [11]. Moreover, in vivo studies showed that ovariectomized females, in addition to males, are usually having higher levels of ACE2 activity compared to non-ovariectomized females. This might indicate a possible role of the sex hormones in regulating ACE2 activity [12].

While those observations showed a possible role of gender-related genetic and molecular variations in determining the clinical behaviour including higher mortality rate in male

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patients compared to females, the full mechanisms underlying such differences still need to be more clarified.

Indeed, a better understanding of the molecular mechanisms that differentially affect males and females leading to variable infection vulnerability as well as mortality will be essential for the discovery of novel pathways and targets. This might help in the implementation of new therapeutic options aiding in a more effective, personalized and comprehensive approach to treat the COVID-19 outbreak.

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Methods

Differential expressed genes (DEGs) between males' and females' lung tissues

To have better understanding of the molecular basis of the variable gender-related response to COVID-19 infection and due to the fact that the lung tissue damage is an essential event in the disease pathogenesis, we investigated the differential expressed genes (DEGs) between lung tissues obtained from males and females using publicly available database (https://www.gtexportal.org/home/) BioJupies tool [13]. A schematic representation of the bioinformatics analysis is shown in figure (1).

Enriched Ontology Clustering of the identified DEGs

Enriched Ontology Clustering for the identified genes was performed to explore if the identified genes are sharing common pathways using the Metascape (a web-based tool used for comprehensive gene list annotation and analysis resource) [14], as shown in figure (1).

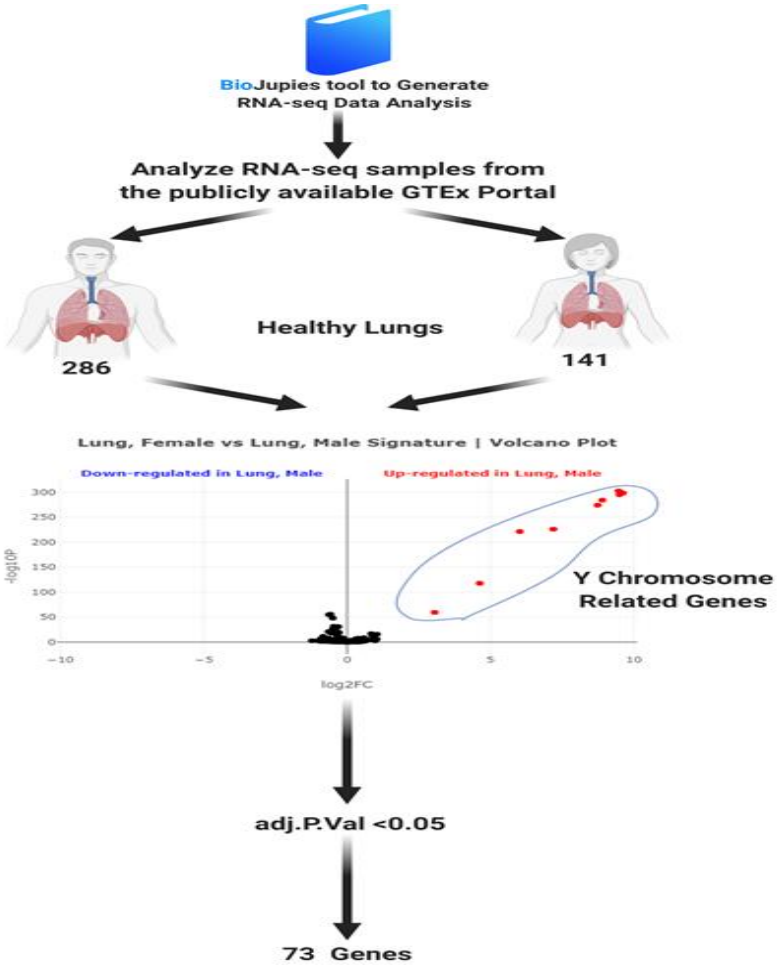

Figure 1: Schematic representation to bioinformatics analysis of differentially expressed genes in males compared to females' lung tissues using BioJupies tools [3]

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Deciphering Organ and Sex-Specific gene expression levels variation

The Genotype-Tissue Expression (GTEx) project (www.gtexportal.org) was used to evaluate the variation in the gene expression levels of the selected genes according to sex and organ including the lung and kidney [15]. Indeed, this platform includes the human transcriptomic data across different individuals and allow researchers to investigate the reference values of the gene expression levels for a range of normal primary tissues and organs. In addition, it allows the stratification of the gene expression levels with some clinical parameters including gender.

Deciphering Organ and Sex-Specific gene expression levels variation

The average expression of our candidate genes was evaluated across different cell population of human lung tissue using Lung Gene Expression Analysis Web Portal 'LungGENS', (https://research.cchmc.org/pbge/lunggens/) , which is a web-based tool used to investigate the expression levels of different genes in single-cell population.

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Results

Lung tissues showed a gender-related differential expression of genes

We compared the lung transcriptomic data of 141 females with 286 males. Our results showed 85 genes with significant variation in the expression levels between the two groups (Table 1). After excluding Y specific genes, 73 genes were selected.

Table 1: Top differential genes between males' and females' lung tissues

DDX43	KCNIP3	GEMIN8	SLC2A1	ITGAD	EFHC2	SYTL5
SFRP2	SLC4A3	CA5B	LANCL3	STS	KDM6A	
OOEP	AGTR1	RHOH	ZRSR2	RPS4X	PNPLA4	
GRM8	KRBOX1	NAP1L2	KDM5C	RNF183	ERCC6L	
NOX5	MRC2	PLIN4	FAM3B	UGT8	RIBC1	
SPESP1	MAN2C1	SMC1A	CEACAM6	SRRM4	LYPD6B	
AJAP1	CHM	EIF2S3	DDX3X	ARSD	AQP5	
FAM228A	TRAPPC2	SYAP1	GYG2	TNFRSF13B	NLRP2	
PTGDR2	UBA1	FGFR3	ADD2	CP	BEND2	
GPAT2	ZDHHC2	TXLNG	KEL	ZFX	MAP7D2	
MMEL1	EIF5	PRKX	EIF1AX	PCDHA1	SAA4	
PRPH2	OFD1	FBXL16	PLEKHG4B	HS6ST2	SAA2	

Significant pathways where the identified DEGs are differentially expressed between males' lung tissues compared to females'

Further analysis of the DEGs that differentiated between males' and females' lung tissues revealed an enrichment in pathways related to positive regulation of hydrolase activity (AGTR1, CHM, DDX3X, FGFR3, SFRP2, and NLRP2), which are important in lung physiology and inflammation. Pulmonary surfactant contains homeostatic and antimicrobial hydrolases which play a significant role in the terminal bronchioles and alveoli invading microbes control [16] (Figure 2).

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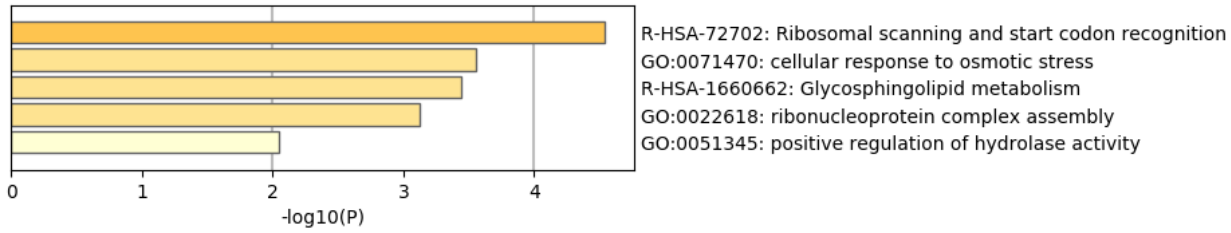

Term	Description	LogP	Log(q-value)	InTerm_InList	Symbols
R-HSA-72702	Ribosomal scanning and start codon recognition	-4.54091	-0.222	4/58	EIF1AX, EIF2S3, EIF5, RPS4X, DDX3X, GEMIN8
GO:0071470	cellular response to osmotic stress	-3.55394	0.000	3/42	AQP5, DDX3X, SLC2A1
R-HSA-1660662	Glycosphingolipid metabolism	-3.43638	0.000	3/46	STS, ARSD, UGT8
GO:0022618	ribonucleoprotein complex assembly	-3.12694	0.000	5/236	DDX3X, EIF2S3, EIF5, ZRSR2, GEMIN8
GO:0051345	positive regulation of hydrolase activity	-2.04604	0.000	7/777	AGTR1, CHM, DDX3X, EIF5, FGFR3, SFRP2, NLRP2

Figure 2: Top pathway enrichment for the differentially expressed genes between males' and females' lung tissues.

Genes related to the hydrolase activity are enriched in females' lung tissue compared to males'

Previous reports showed a possible role of several hydrolases in human lung tissues and alveolar lining fluid in modulating microorganism envelope suggesting their possible role in infection control [16]. For that reason, we further investigated the expression levels of genes involved in the lung hydrolase activity and were previously found to be differentially expressed using The Genotype-Tissue Expression (GTEx) project (www.gtexportal.org) portal. Interestingly, our results showed that CHM, DDX3X, FGFR3, and NLRP2 are more expressed in the lung tissues obtained from females compared to males. This might highlight a possible role of those genes in controlling the COVID-19 infection through the regulation of lung hydrolases (Figure 3).

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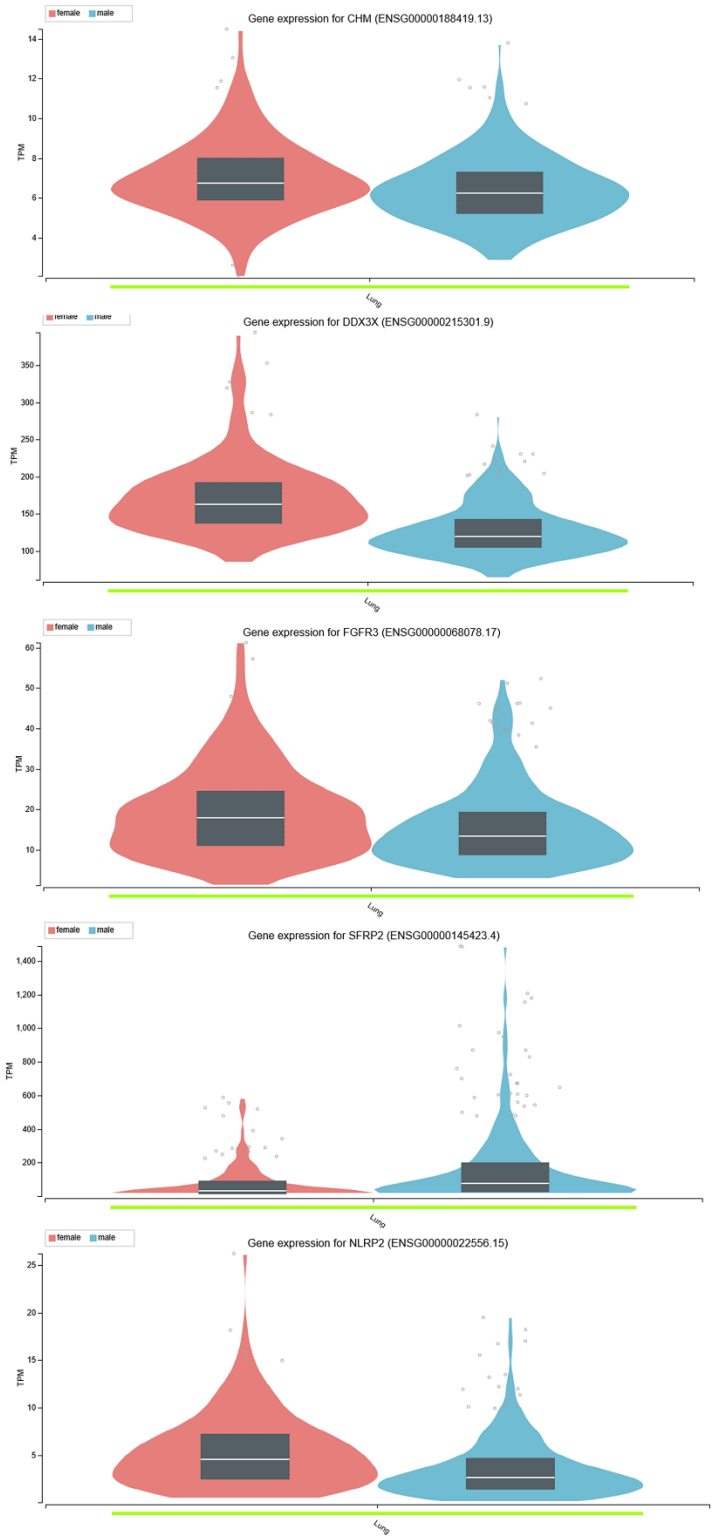

Figure 3: The expression level of different genes related to the lung hydrolase activity between males' and females' lung tissues using The Genotype-Tissue Expression (GTEx) project (www.gtexportal.org) portal

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Angiotensin II type 1 receptor (AGTR1) is among the differential expressed genes between both genders and its expression is significantly higher in the lung tissue compared to kidney tissue.

Our short-listed genes also revealed the presence of AGTR1 among the gender-related differentially expressed genes. Interestingly, AGTR1 is one of the two G protein-coupled receptors essential for the physiological effects of angiotensin II (ANG II). Due to the fact that many reports highlight the role of human receptor ACE2, which also belongs to the renin-angiotensin system (RAS), in facilitating the binding of the SARS-CoV-2 to the host cells , we further analysed the mRNA expression levels of AGTR1 and AGTR2 in both kidney and lung tissues from normal individuals using The Genotype-Tissue Expression (GTEx) project (www.gtexportal.org) portal. Both receptors were shown to be upregulated in the lung tissue compared to the kidney tissue (Figure 4A, C). Next, we analysed their expression in the lung tissue stratified according to gender. Interestingly, our results revealed that while AGTR2 showed no significant difference in its expression between both genders, AGTR1 expression levels were higher in tissues obtained from male individuals compared to females (Figure 4B, D).

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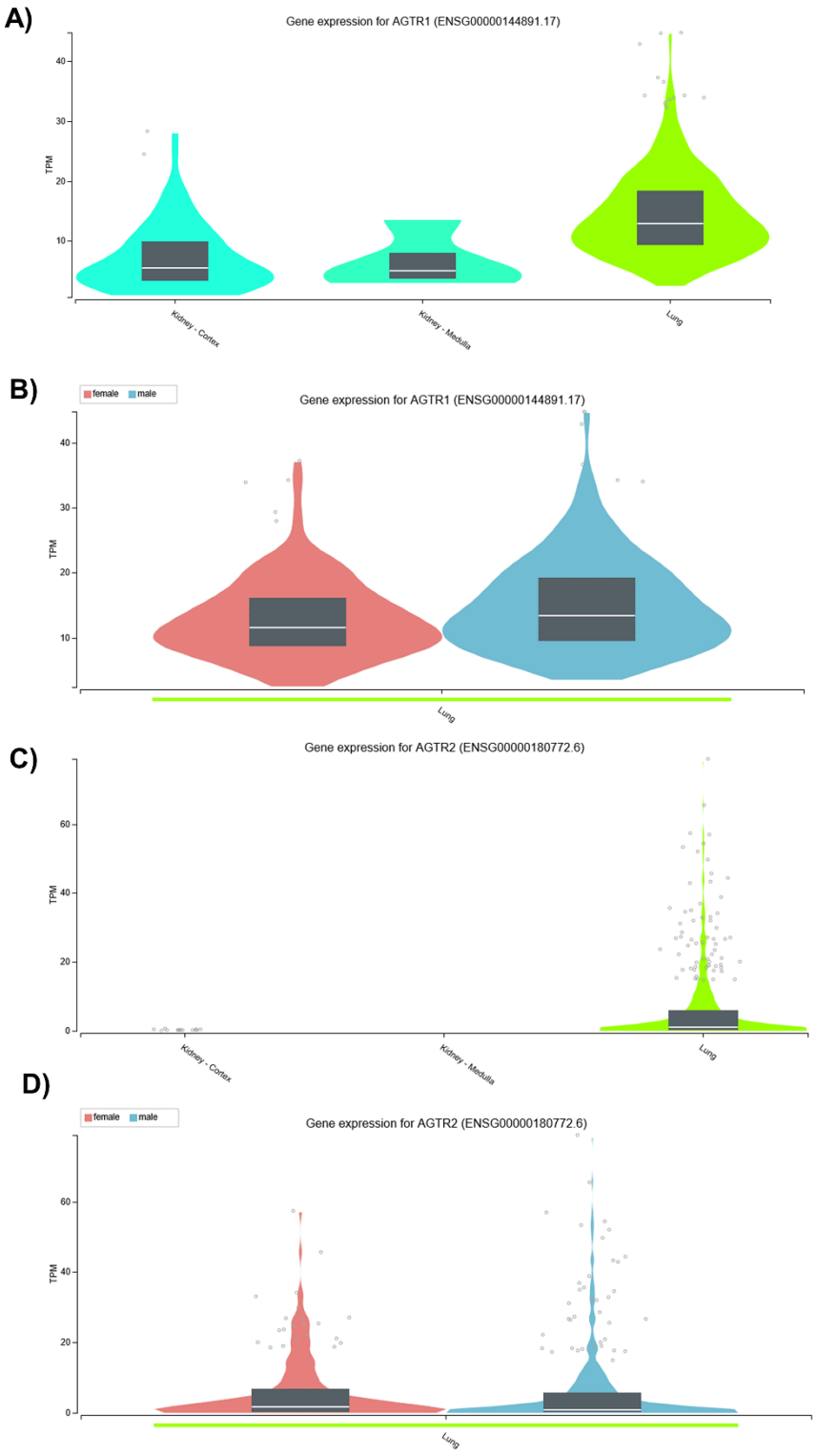

Figure 4: The mRNA expression levels of AGTR1 & AGTR2 in lung and kidney tissues using The Genotype-Tissue Expression (GTEx) project (www.gtexportal.org) portal

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The prostaglandin D2 receptor 2 (PTGDR2), involved in type 2 innate immune response and well known for its role in airway inflammation is another gender differential gene in the lung tissue

Another interesting gene that we also found in our short list is the prostaglandin D2 receptor 2 (PTGDR2). This gene is essential for cells involved in type 2 immune responses through its interaction with prostaglandin D2 (PGD2). Moreover, it is also known to play an essential role in the pathogenesis of asthma, through its role in induction of the pro-inflammatory cytokines and cationic proteases. Similar to AGTR1, PTGDR2 was also confirmed to be higher in the lung tissue compared to the kidney tissue (Figure 5A) and its expression to be upregulated in male individuals compared to females (Figure 5B).

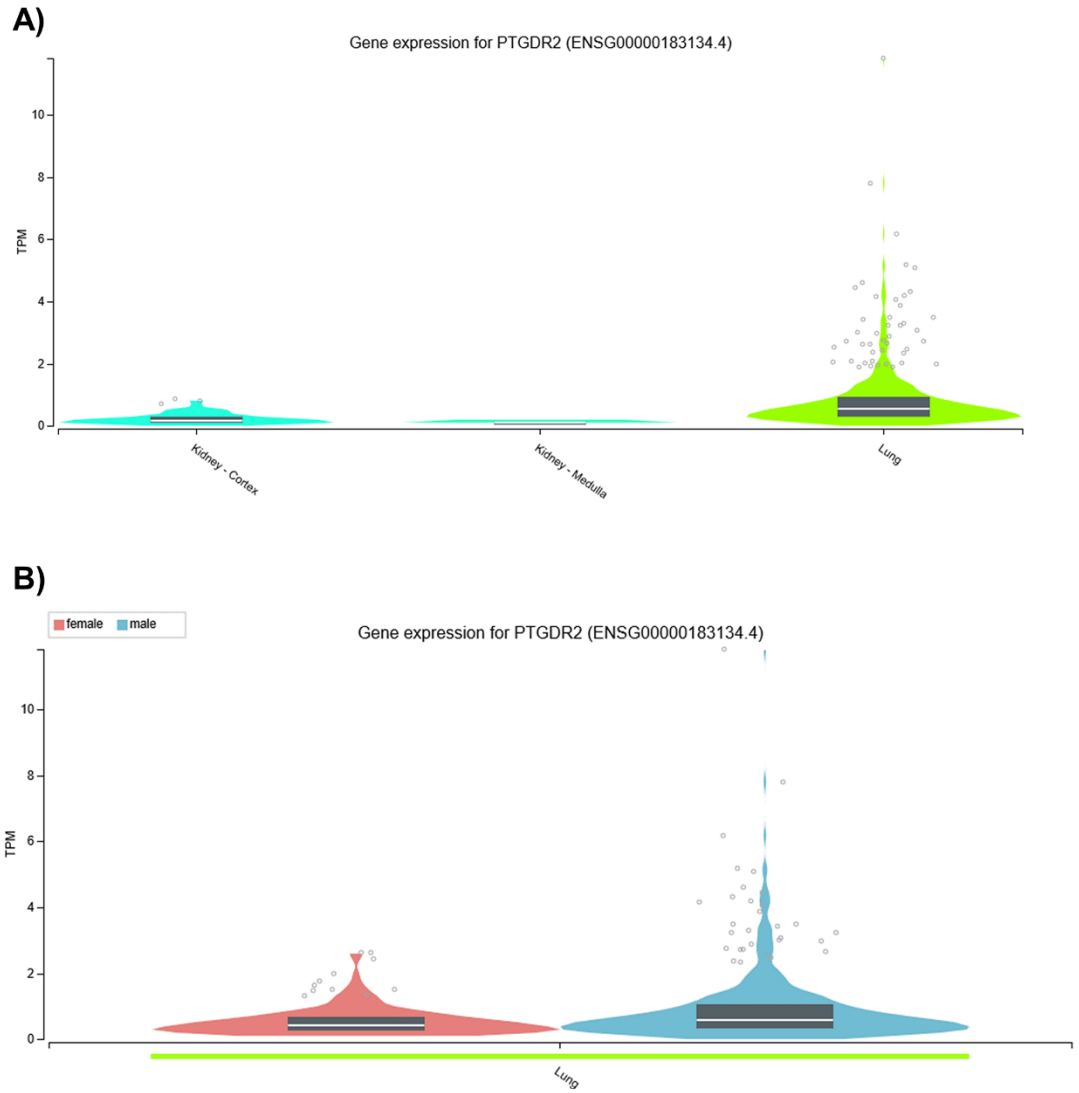

Figure 5: The mRNA expression levels of PTGDR2 in lung and kidney tissues using The Genotype-Tissue Expression (GTEx) project (www.gtexportal.org) portal

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Cellular localization of the different identified gene candidate

Next, and to have better idea about the cellular localization of the different gene candidate in the lung tissue , we investigate the gene expression levels of those genes using single-cell profiling of human lung tissues (the LGEA portal: https://research.cchmc.org/pbge/lunggens/mainportal.html). Our results showed a variable expression of the candidate genes in different cell populations. Interestingly, all genes were expressed in the alveolar type I (AT1) & alveolar type II (AT2) cells in the respiratory system. FGFR3, PTGDR2 and NLRP2 were predominately expressed in the epithelial cells of the respiratory system including the airway epithelial cells, alveolar type I (AT1) and alveolar type II (AT2). In contrast, AGTR1 showed predominant expression in the matrix fibroblasts and pericytes compared to other cells.

Figure 6: The mRNA expression levels of different candidate genes in different lung cell populations using Single-cell RNA analysis of LungGENS web-based tool

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Discussion

Since the end of 2019, the novel coronavirus disease (COVID-19) outbreak has become a major public health emergency with a substantial impact [17]. Despite the fact that this disease is characterized by a milder clinical course for the majority of patients compared to other coronavirus infections like SARS-CoV and MERS-CoV [18], patients belonging to specific ethnic and demographic variables as well as patients presented with pre-existing comorbidities showed higher rates of serious adverse outcomes including high mortality rates [5, 8, 19-21]. This heterogenous clinical manifestations highlights the need of more in-depth understanding of the molecular basis of such serious outcomes in those subpopulations.

Indeed, identification of the different risk factors for the critical conditions as well as the identification of pathways and markers involved in their pathogenesis might be an essential step not only to provide the appropriate management plans for each patient [19], but also for the identification of new targets and tools that might be essential for the adoption of more precise targeted therapies.

One of the striking finding related to COVID-19 outbreak is the significant difference in the mortality rates between males and females despite the equal numbers of infection for both sexes [4]. According to the available reports, elderly male patients with comorbidities are more likely to die from COVID-19 compared to females in a ratio reaching to 3:1 [1, 4-6, 22].

The difference observed between both genders were suggested to be associated with some social and behavioural habits including smoking and alcohol consumption and their linked comorbidities [7]. Another reports also suggested a role of the sex-based immunological differences in the variable mortality rates observed between both genders [8, 9].

Despite all these preliminary findings, no in-depth analysis was made to understand the genetic and molecular basis of the difference observed in the mortality rates between both genders. The here presented data shade the light of some possible molecular pathways that might be responsible for this gender difference.

Our results showed downregulation of genes that are involved in the regulation of hydrolase activity including (AGTR1, CHM, DDX3X, FGFR3, and NLRP2) in the lung tissues obtained from males compared to females. Interestingly, group of reports linked the hydrolase activity with antimicrobial effect [23] as well as lung inflammation and immune response [16]. Indeed, alveolar lining fluid (ALF) hydrolases were found to be involved in the regulation of macrophages function and to participate in the host immune response which is essential for infection control [16, 23, 24]. For that reason, the downregulation of genes involved in such pathways might play a role in the different immune responses observed between both genders following COVID-19 infection.

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Another striking finding in this study is the upregulation of the AGTR1 gene also known as AT1 receptor, in the lung tissue obtained from males compared to that obtained from females. This gene is considered as an essential component of the renin-angiotensin system and one of the two G protein-coupled receptors essential for the physiological effects of ANG II [25]. Interestingly, the ACE2, which belong to the same system and considered as an essential component used by the COVID-19 virus to enter the cells was found to show no dependency on age and gender [25]. For that reason, our finding that AGTR1, but not AGTR2 to be upregulated in the lung tissues of males might highlight a possible specific role of AGTR1 in the ACE2 mediated binding of the COVID-19 to the host cells in male patients. Interestingly, recent reports showed that in experimental models, ANG II stimulation of AGTR1 might significantly contributes to lung damage [26]. Moreover, SARS-Coronavirus lung injury experimental model revealed that AGTR1 blockade with losartan might help in reducing the pulmonary edema as well as the severe acute lung injury associated with the disease [27].

For that reason, researchers suggested the use of AGTR1 (AT1R) antagonists like losartan and olmesartan and other angiotensin II receptor blockers (ARBs) as a possible tentative therapeutic option for COVID-19 infection that might protect COVID-19 patients from the severe symptoms and reduce their mortality rate [26, 28].

Those finding might help in improving our understanding of the role of different members of the renin-angiotensin system in COVID-19 infection pathogenesis and their impact on different patient's subpopulation including different sexes. In addition, it might pave the way for the adoption of early treatment of male patients with AGTR1 (AT1R) antagonists and ARBs, which might help in reducing their lung damage and help to improve their clinical outcome.

Finally, our findings also showed a differential expression of some genes that play a role in the immune response including the NLRP2, which is involved in the suppression of the NF-$_K$B signaling pathway leading to the modulation of the inflammatory response [29]. In addition, it is also considered as an important component of the inflammasome, which is a multiprotein intracellular complex, essential for the detection of the pathogenic microorganisms and activation of the pro-inflammatory cytokines including interleukin-1β (IL-1β) and IL-18 [30, 31]. Similarly, PTGDR2, which we also found to be differentially expressed between both genders, is believed to be essential for the pro-inflammatory cytokines induction and found to play a role in asthma pathogenesis [32]. That finding goes with the previous annotations that some of the variations observed in the mortality rates between both genders might be attributed to sex-based immunological differences [8, 9].

Taken together, our results shade the light into some of the molecular mechanisms and pathways that might play a role in the poor outcome and high mortality rates for male patients during the COVID-19 outbreak. Better understanding of such mechanisms might be essential for more precise and appropriate health care response based on the different clinical and epidemiological characteristics. Moreover, it might also help in the discovery

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of new therapeutic approaches based on targeting those specific pathways, which might help in improving the outcome of patients with different epidemiological backgrounds.

Conflict of Interest

- The authors declare no conflict of interest

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