Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Immunobiology 227 (2022) 152184

Contents lists available at ScienceDirect

Immunobiology

journal homepage: www.elsevier.com/locate/imbio

CCR2 and DPP9 expression in the peripheral blood of COVID-19 patients: Influences of the disease severity and gender

Mohsen Sharif-zak [a,b], Mojtaba Abbasi-jorjandi [b], Gholamreza Asadikaram [b,c,*], Zohreh-al-sadat Ghoreshi [b,d], Mitra Rezazadeh-Jabalbarzi [e], Alireza afsharipur [e], Hamidreza Rashidinejad [f], Fardin Khajepour [g], Abdollah Jafarzadeh [g], Nasir Arefinia [h], Aliasghar Kheyrkhah [e], Moslem Abolhassani [b,i]

[a] Research Center of Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman, Iran
[b] Department of Clinical Biochemistry, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[c] Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
[d] Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
[e] Clinical Research Development Center of Imam Khomeini Hospital, Jiroft University of Medical Sciences, Jiroft, Iran
[f] Department of Cardiology, School of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[g] Department of Medical Immunology, Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[h] Department of Medical Microbiology (Bacteriology & Virology), Afzalipour Faculty of Medicine, Kerman University of Medical Sciences, Kerman, Iran
[i] Physiology Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran

ARTICLE INFO

Keywords:
COVID-19
CCR2
DPP9
Disease severity

ABSTRACT

Introduction: Hyper-inflammatory reactions play a crucial role in the pathogenesis of the severe forms of COVID-19. However, clarification of the molecular basis of the inflammatory-related factors needs more consideration. The aim was to evaluate the gene expression of two fundamental molecules contributing to the induction of inflammatory like CCR2 and DPP9 in cells from peripheral blood samples from patients with various patterns of COVID-19.

Methods: Peripheral blood samples were collected from 470 patients (235 male and 235 female) with RT-qPCR-confirmed COVID-19 test exhibiting moderate, severe, and critical symptoms based on WHO criteria. 100 healthy subjects (50 male and 50 female) were also enrolled in the study as a control group. The gene expression of DPP-9 and CCR-2 was assessed in the blood samples using real-time PCR method.

Results: The COVID-19 patients in severe stage expressed higher levels of CCR2 and DPP9 compared with healthy controls. In male and female patients, the levels of CCR2 and DDP9 expression significantly differed between moderate, severe, and critical patterns ($p < 0.0001$) as well as between each COVID-19 form and control group ($p < 0.0001$). The male patients with severe COVID-19 expressed greater levels of CCR2 and DPP-9 than female with same disease form. The female patients with moderate and critical COVID-19 expressed greater levels of CCR2 and DPP-9 than male patients with same disease stage.

Conclusion: We demonstrated that the expression of DPP-9 and CCR-2 was substantially increased in COVID-19 patients with different forms of disease. Considerable differences were also demonstrated between male and female with different patterns of disease. Therefore, we suggest to consider the gender of patients and disease severity for management of COVID-19.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-related COVID-19 seriously affected more than 212 territories and countries (Cucinotta and Vanelli, 2020; Jafarzadeh et al., 2021). Since the SARS-CoV-2 receptor (ACE2: angiotensin-converting enzyme 2) is expressed by different types of cells and tissues, thus various organs, in particular lungs, intestine, testis, heart, kidneys, esophagus, bladder, brain and liver are invaded by SARS-CoV2 (Jafarzadeh et al., 2021). COVID-19-related clinical manifestations emerge following a latent time

* Corresponding author.**
E-mail addresses: m.sharif@kmu.ac.ir (M. Sharif-zak), Gh_asadi@kmu.ac.ir (G. Asadikaram).

https://doi.org/10.1016/j.imbio.2022.152184
Received 9 December 2021; Received in revised form 7 January 2022; Accepted 27 January 2022
Available online 1 February 2022

of about 5 days with a range of 2–14 days (Jafarzadeh et al., 2021). Based on the World Health Organization (WHO) criteria, SARS-CoV-2-mediated COVID-19 is categorized into several patterns, including mild, moderate, severe, and critical patterns (Organization, 2021). Patients with COVID-19 mostly exhibit mild forms of COVID-19, while, some patients progress to the moderate, severe, and critical forms, which may express several organ dysfunctions, in particular acute respiratory distress syndrome (ARDS) (Mitra et al., 2020).

Large number of the inflammatory cells (such as monocytes, macrophages, lymphocytes and neutrophils) infiltrate the respiratory system during COVID-19 (Jafarzadeh et al., 2021). Cytokine storm and hyper inflammatory responses perform a crucial role in the Development of COVID-19-related complications (Jafarzadeh et al., 2021; Jafarzadeh et al., 2020). Among the cytokine storm-related factors, chemokines guide the leukocyte infiltration into the inflamed tissues (Jafarzadeh et al., 2020; Jafarzadeh et al., 2019). CC chemokine receptor 2 (CCR2) is mainly expressed by certain cell types, such as monocytes, dendritic cells (DCs), macrophages, NK and T lymphocytes, although it can be induced by other cells under inflammatory situations (Fantuzzi et al., 2019; Wareing et al., 2007). C–C motif chemokine ligand 2 (CCL2), CCL7, CCL8, CCL13, and CCL16 are known as the CCR2 ligands, but CCL2 has been considered as the most potent ligand (Fantuzzi et al., 2019; Palomino and Marti, 2015). Monocytes/macrophages are the major producers of CCL2 (Fantuzzi et al., 2019). MCP-1 interaction with CCR2 play a key role in the induction of inflammation and inflammation-related diseases. Moreover, CCR2 binding by MCP-1 support innate immunity response by recruiting monocytes into inflammatory sites (Bianconi et al., 2018). CCL2/CCR2 pathway is a key player in the trafficking of lymphocytes and monocytes/macrophages have been implicated in the pathogenesis of various diseases, such as viral infections (Fantuzzi et al., 2019). In the infectious diseases process, the expression of CCR2 in peripheral B and T cells strongly elevates and suggests the crucial role of CCR2 in immunomodulation (Hodge et al., 2012). Moreover, it is indicated that by inhibition the pathway of CCR2 interaction in immunity defence in influenza models the levels of cytokine storm mediators including interleukin-6, tumor necrosis factor-α, interferon-γ, and macrophage inflammatory protein 2 was decreased dramatically (Dessing et al., 2007). Such findings highlight the importance of CCR2 in viral diseases such as COVID-19.

Inflammasomes as the amplifiers of the inflammation are also activated by various types of endogenous and exogenous components. Inflammasome activation results in pro-IL-1β and pro-IL-18 maturation into their active forms, and pyroptosis enabling the release of IL-1β and IL-18 which recruit neutrophils, monocytes, and macrophages to the infection sites. Dipeptidyl peptidase 9 (DPP9) blocks the C terminus of NLR Family Pyrin Domain Containing 1 (NLRP1) to prevent inflammasome activation (Hollingsworth et al., 2021). Additionally, NLR Family Pyrin Domain Containing 3 (NLRP3) activates the DPP9 that leads to inflammasome inhibition (Okondo et al., 2017; Okondo et al., 2018; Zhong et al., 2018). DPP9 is extensively expressed in lymphocytes and epithelial cells, but it is up-regulated upon activation of T or B cells (Yu et al., 2009; Abbott et al., 2000; Chowdhury et al., 2013). Although DPP9 is located intracellularly; it is suggested that under certain conditions it may also be translocated on the surface of immune cells (Bank et al., 2011). DPP9 also can act as a MERS-coronavirus receptor (Raj et al., 2013). In addition, it is demonstrated that DPP enzymes family such as DPP9 are crucial immunomodulatory factors, hence, T-lymphocyte proliferation and pro-inflammatory cytokine production could be decreased through reducing the expression or by inhibition of these enzymes (Reinhold et al., 2009; Lankas et al., 2005). Also, it is previously shown that DPP8/9 inactivation leads to T-cell repression and IL-2 release in human in vitro models (Huang et al., 2021). Therefore, these observations emphasize the importance of these enzymes and their role in the immune system as factors that have received less attention in infectious diseases.

Considering the fundamental role of CCR2 and DDP9 in the induction and regulation of the inflammatory responses, this study aimed to evaluate the expression levels of CCR2 and DDP9 in the peripheral blood cells collected from COVID-19 patients, in an attempt to explore the possible association of their expression levels with disease severity and gender of patients.

2. Material and methods

2.1. Subjects

Totally, from 1 to 10 July 2021, 470 subjects (235 male and 235 female; aged 20–80 years) with quantitive real-time PCR (RT-qPCR)-confirmed COVID-19 who were referred to Imam Khomeini hospital of Jiroft (a city located in the southeast of Iran) were enrolled to this case-control study. The patients who had a history of other inflammatory diseases, negative RT-qPCR, or personal dissatisfaction were excluded from the study. According to the WHO guidance concerning the COVID-19-related clinical symptoms and management, the patients were divided into three subgroups including moderate, severe, and critical patients (Table 1). In addition, 100 healthy individuals (50 male and 50 female) without any inflammatory diseases were selected as the control group. A peripheral blood sample was collected from participants for RNA extraction. The Ethics Committee of Kerman University of Medical Sciences evaluated and approved the research protocol that was registered with code: IR.KMU.REC.1400.411.

2.2. RNA extraction and real time-PCR

Commercial kits (Qiagen, Germany) were used to extract total RNA from peripheral blood samples according to the manufacturer's instructions. The absorbance of the extracted RNA samples was measured at 280 nm and 260 nm using a Nanodrop (Thermo Scientific NanoDrop 1000 spectrophotometer) to determine their quantity and purity. The extracted RNA samples were converted to complementary DNA (cDNA) using cDNA synthesis kits (Yekta-Tajhiz, Iran) according to the manufacturer's instructions. A real-time PCR system (BioMolecular Systems, Australia) was utilized to assess the CCR2 and DPP9 gene expression using SYBR green master mix (Yekta-Tajhiz, Iran). Real time-PCR amplifications were set up in triplicate with a 10 μl volume containing 5 μl SYBR green master mix, 1 μl of corresponding cDNA and primers (Table 2). The RT-qPCR was performed at the condition as followed: 94 °C for 15 min, 40 sequential cycles at 95 °C for 10 s and 58 °C for 1 min and the final extension at 72 °C for 10 min. The β-actin gene was also used as an internal control and the levels of the CCR2 and DPP9 expression were calculated by $2^{-\Delta\Delta Ct}$ formula.

Table 1
Classification of patients according to their COVID-19 patterns.

Gender	Moderate	Severe	Critical
Symptoms	**Pneumonia with fever, cough, dyspnoea, fast breathing) and SpO2 ≥ 90%**	**Severe pneumonia with fever, cough, dyspnoea, fast breathing), respiratory rate >30 breaths/min; severe respiratory distress; or SpO2 < 90%**	**Acute respiratory distress syndrome (ARDS), Chest imaging with bilateral opacities, lobar or lung collapse, or nodules, and Oxygenation impairment**
Male (n = 235)	106	96	33
Female (n = 235)	130	70	35
Total (n = 470)	236	166	68

Table 2
Used primers for RT-qPCR.

Gene name	Sense 5′ to 3′	Anti-sense 5′ to 3′
DPP-9	5′-CGAGGTGGAGGTCATTCA-3′	5′-GGATTCTTGCTGCCTGTC-3′
CCR-2	5′-CCTGAGACAAGCCACAAG-3′	5′-GGAGCATAATCATAATCA-3′
Beta-actin (endogenous control)	5′-GCACCACACCTTCTACAATG-3′	5′-TGCTTGCTGATCCACATCTG-3′

2.3. Statistical analysis

All statistical analysis was carried out using SPSS software version 21 (Chicago, IL). Data were analyzed by one-way ANOVA test following Tukey post hoc test. The P values <0.05 were considerd significant.

3. Results

3.1. CCR-2 gene expression alteration in COVID-19 patients

The fold change expression of CCR2 mRNA in the peripheral blood samples from all COVID-19 patients was sugnificantly higher than that in the healthy control group ($p < 0.0001$) (Fig. 1).

The fold change expression of CCR2 mRNA in the peripheral blood samples from male and female patients with COVID-19 according to their disease severity was indicated in the Fig. 2. In male and female patients with COVID-19, the levels of CCR2 expression significantly differed between moderate, severe, and critical patterns ($p < 0.0001$) as well as between whole patients and control group ($p < 0.0001$). Female patients with severe, critical, and moderate forms of COVID-19 expressed higher levels of CCR2 mRNA in comparison with the control group ($p < 0.0001$) (Fig. 2A). Similarly, male patients with severe, critical, and moderate forms of COVID-19 expressed higher levels of CCR2 mRNA than that in the control group ($p < 0.0001$) (Fig. 2B).

The fold change expression of CCR2 mRNA in the peripheral blood samples from patients with different patterns of COVID-19 according to their gender was indicated in the Fig. 3. The female with moderate and critical forms of COVID-19 expressed greater levels of CCR2 than nale patients with same disease forms ($p < 0.0001$). However, the male patients with severe COVID-19 expressed greater levels of CCR2 than female with same disease form ($p < 0.0001$) (Fig. 3).

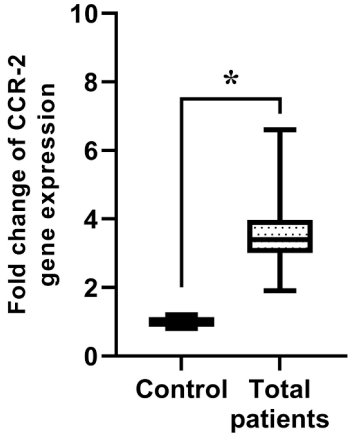

Fig. 1. Comparison of the expression of CCR2 in the peripheral blood samples between total patients and healthy control group. * Significant difference in different groups ($p < 0.0001$). Data are presented as fold change.

3.2. DPP9 gene expression alteration in COVID-19 patients:

The fold change expression of DPP9 mRNA in the peripheral blood samples from all COVID-19 patients was remarkbaly higher compared to healthy control group ($p < 0.0001$) (Fig. 4).

The fold change expression of DPP9 mRNA in the peripheral blood samples from male and female patients with COVID-19 according to their disease severity was indicated in the Fig. 5. In male and female patients with COVID-19, the expression levels of DPP9 significantly differed between moderate, severe, and critical patterns ($p < 0.0001$) as well as between whole patients and control group ($p < 0.0001$). Female patients with severe, critical, and moderate forms of COVID-19 expressed higher levels of DPP9 mRNA in comparison with the control group ($p < 0.0001$) (Fig. 5A). Similarly, male patients with severe, critical, and moderate forms of COVID-19 expressed higher levels of DPP9 mRNA than that in the control group ($p < 0.0001$) (Fig. 5B). male and female patients with critical form of COVID-19 expressed significantly higher levels of DPP-9 compared to male and female with severe and moderate COVID-19, respectively ($p < 0.0001$).

In both male and female groups, an ascending expression of DPP9 mRNA was observed from moderate to severe and critical patterns, indicating a positive association between the expression levels of DPP9 mRNA and disease severity.

The fold change expression of DPP9 mRNA in the peripheral blood samples from patients with different patterns of COVID-19 according to their gender was indicated in the Fig. 6. The female patients with moderate and critical forms of COVID-19 expressed greater levels of DPP9 mRNA than male patients with same disease forms ($p < 0.0001$). However, the male patients with severe COVID-19 expressed greater levels of CCR2 mRNA than female with same disease form ($p < 0.0001$) (Fig. 6).

4. Discussion

Aberrant production of chemokines and impaired activation of inflammasomes play a fundamental role in the pathogenesis of COVID-19. Here, the increased mRNA expression of CCR2 and DPP9 was observed in the peripheral blood samples from all COVID-19 patients compared to the healthy control group. CCR2 acts as a receptor for several chemokines, especially MCP-1. Previous studies have demonstrated that COVID-19 is associated with dynamic changes in CCR2 and DPP9 gene expression (Schmiedel et al., 2020; Pairo-Castineira et al., 2021; Singh et al., 2021). MCP-1/CCR2 axis can participate induction of anti-virus immune responses and promotion of deleterious hyper-inflammatory responses during COVID-19. Epithelial cell derived-MCP-1 can recruit CCR2 expressing cells (such as NK cells, monocytes, macrophages and DCs) into the SARS-CoV-2-infected respiratory system (Jafarzadeh et al., 2021). The recruited immune cells can limit the viral infection through several mechanisms, for instance interferon production (Vanderheiden et al., 2021). In a mouse model of SARS-CoV-2 infection, it was found that early CCR2 signaling restricts the viral burden in the lung. CCR2 signaling promotes the infiltration of classical monocytes into the lung and the expansion of monocyte-derived cells. Mice lacking CCR2 showed higher viral loads in the lungs and increased lung viral dissemination (Wang et al., 2020).

Elevated levels of MCP-1 (a CCR2 ligand) was reported in COVID-19 patients, especially in the critical form, promoting inflammatory responses through binding to CCR2 (Jafarzadeh et al., 2021). Indeed, MCP-1 is a chemokine among cytokine storm-related chemokines contributing to the tissue inflammation and even organ failure (Jafarzadeh et al., 2020). Thus, targeting the MCP-1/CCR2 axis can attenuate the unwanted inflammatory responses. The selective inhibition of the MCP-1/CCR2 pathway using various antagonist agents has been reported in different clinical trials with inconsistent results (Bianconi et al., 2018). Severe COVID-19 patients displayed greater expression of CCR2 compared to moderate patients, while the expression levels of

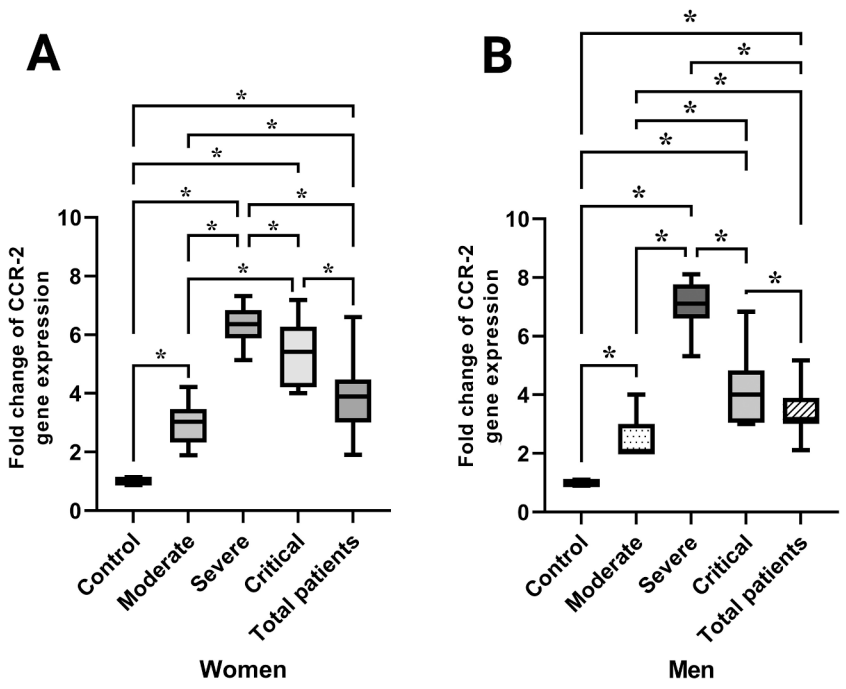

Fig. 2. The expression of CCR2 in female patients (A) and men patients with COVID-19 (B) according to disease severity. * Indicate significant difference between specified groups ($p < 0.0001$).

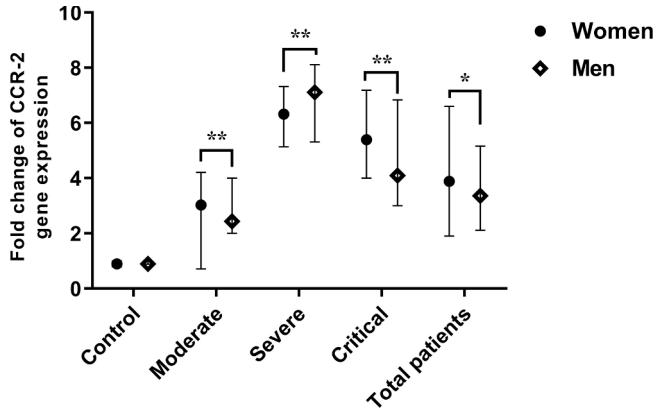

Fig. 3. Comparison of CCR-2 gene expression between female and men patients with various forms of COVID-19. Significant difference in different groups (**$p < 0.0001$ and *$p < 0.05$). Data are presented as fold change.

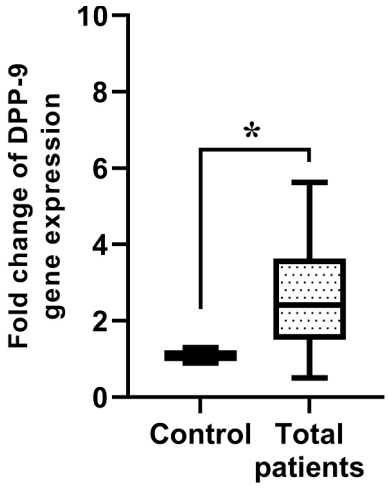

Fig. 4. Comparison of the expression of DDP9 in the peripheral blood samples between total patients and healthy control group. * Indicate Significant difference in different groups ($p < 0.0001$). Data are presented as fold change.

CCR2 was reduced in the critical patients compared to severe COVID-19 patients. The reason for these observations remains to be explained in future studies. Perhaps, the greater tissue leukocytes infiltration in critical COVID-19 could be an account for reduced expression of CCR2 in the peripheral blood.

DPP9 acts as an inhibitor of inflammasome (Okondo et al., 2017; Okondo et al., 2018; Zhong et al., 2018). In agreement with our findings, Wang et al. also reported the elevated DPP9 expression in peripheral blood from COVID-19 patients compared to healthy individual and bacterial-infected patients. They have reported that the DPP9 expression increased from day 0 compared to 7 days and 14 days (Brandi, 2021). After that the severity of COVID-19-related symptoms were dramatically improved (Brandi, 2021). Here, we observed an ascending expression of DPP9 mRNA from moderate to severe and critical patterns. It can be speculated that elevated expression of the DPP9 in more serious forms of COVID-19 may be a homeostatic response to modulate deleterious inflammatory responses.

The results of the present study indicate that female patients with moderate and critical forms of COVID-19 expressed greater levels of CCR2 and DPP9 mRNA than male with same disease forms. However, the male patients with severe COVID-19 expressed greater levels of CCR2 and DPP9 mRNA than female with same disease form. It has been reported that COVID-19-related mortality and morbidity are greater in male patients compared to female (Rehman et al., 2021; Chen et al., 2020). Moreover, profound differences have been indicated between male and female concerning the immunologic and inflammatory responses (Rehman et al., 2021). Whether these differences can influence chemokine responses (such as MCP-1/CCR2 pathway) and regulatory mechanisms (such as DPP9) need to be described in future investigations.

Our study may have several limitations: Firstly, in order to elucidate the role of CCR2/MCP-1 pathway, it was necessary to measure the levels of MCP-1 in sera/plasma samples from patients. Previously, MCP-1 has

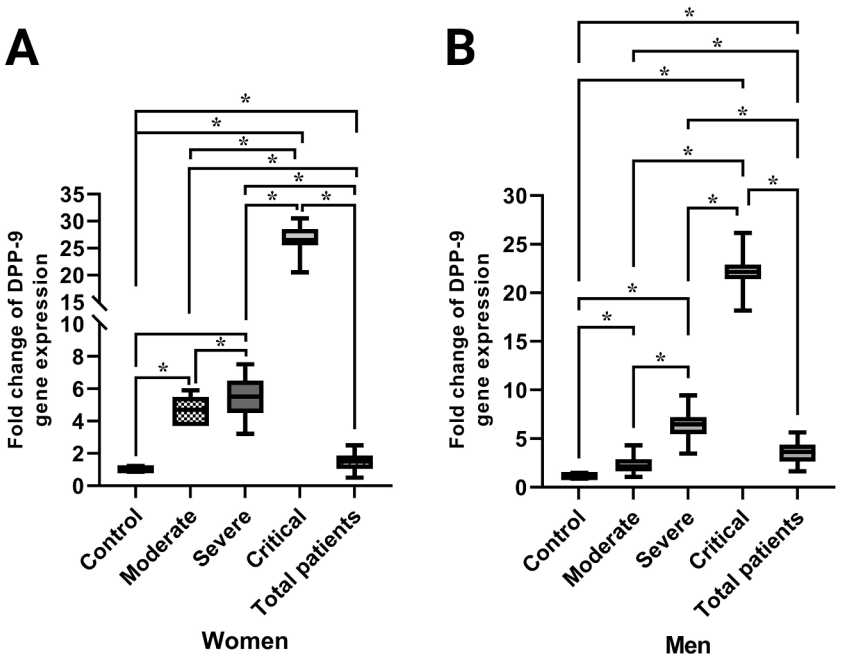

Fig. 5. The expression of DPP-9 in female patients (A) and men patients with COVID-19 (B) according to disease severity. * Indicate significant difference between specified groups ($p < 0.0001$). Data are presented as fold change.

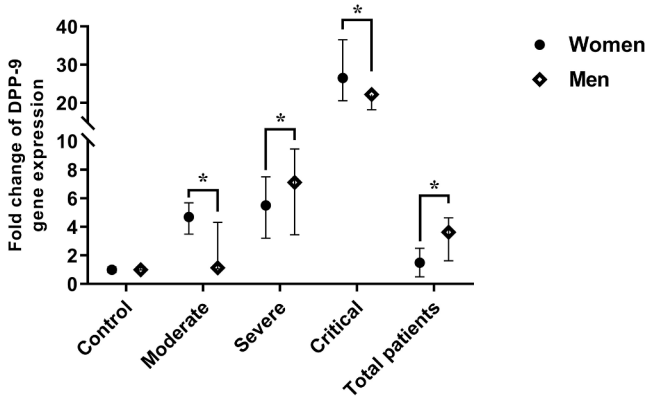

Fig. 6. Comparison of CCR-2 gene expression between female and men patients with various forms of COVID-19. * Indicate significant difference in different groups ($p < 0.0001$). Data are presented as fold change.

been introduced as a biomarker of COVID-19 severity, so that the highest levels of MCP-1 were observed in the patients with critically form promoting inflammatory responses via binding to CCR2 (Jafarzadeh et al., 2021; Cabaro et al., 2021). Secondly, in order to elucidate the role of DPP9-related pathway, it was necessary to measure the expression levels of DPP9-related molecules in samples from patients. As mentioned NLRP3 inflammasome can acts an activator of the DPP9, which in turn can inhibit the activity of inflammasome (Okondo et al., 2017; Okondo et al., 2018; Zhong et al., 2018). It has been indicated that SARS-CoV-2 activates NLRP3 inflammasome through induction of P2RX7, releasing of various types of DAMPs from dead cells, and raising in angiotensin II levels (Jafarzadeh et al., 2021). However, inability of DPP9 to control inflammasome may partly contribute to progression of inflammatory responses. Thirdly, evaluation of the influence of the gene polymorphisms on the expression of CCR2 and DPP9 was not a part of our study. As the polymorphisms within the CCR2 and DPP9 can influence their expression, the association of CCR2 and DPP9 gene polymorphisms with the expression levels of these factors and with COVID-19 severity remains to be elucidated in future studies.

5. Conclusion

In summary, our study shows that the expression of DPP9 and CCR2 was substantially increased in COVID-19 patients with moderate, severe, and critical forms of disease. The expression of both CCR2 and DDP9 was also influenced by the COVID-19 pattern, so that the greatest expression levels of DPP9 and CCR2 was observed in severe forms of disease. Considerable differences were also observed between male and female patients with different disease pattern, concerning the DPP9 and CCR2. Therefore, we further suggest to consider the gender of patients and disease severity in management of COVID-19.

Acknowledgment

The authors acknowledge the patients' participation and specimen donation in this study. This research was financially supported by Kerman University of Medical Sciences, Kerman, Iran. This research was part of a Ph.D. thesis (Ethics code: IR.KMU.REC.1400.411).

References

Abbott, C.A., Yu, D.M., Woollatt, E., Sutherland, G.R., McCaughan, G.W., Gorrell, M.D., 2000. Cloning, expression and chromosomal localization of a novel human dipeptidyl peptidase (DPP) IV homolog, DPP8. Eur. J. Biochem. 267 (20), 6140–6150.

Bank U, Heimburg A, Wohlfarth A, Koch G, Nordhoff K, Julius H, et al. Outside or inside: role of the subcellular localization of DP4-like enzymes for substrate conversion and inhibitor effects. 2011.

Bianconi, V., Sahebkar, A., Atkin, S.L., Pirro, M., 2018. The regulation and importance of monocyte chemoattractant protein-1. Curr. Opin. Hematol. 25 (1), 44–51.

Brandi, M.L., 2021. Are sex hormones promising candidates to explain sex disparities in the COVID-19 pandemic? Rev. Endocr. Metab. Disorders 1–13.

Cabaro, S., D'Esposito, V., Di Matola, T., Sale, S., Cennamo, M., Terracciano, D., Parisi, V., Oriente, F., Portella, G., Beguinot, F., Atripaldi, L., Sansone, M., Formisano, P., 2021. Cytokine signature and COVID-19 prediction models in the two waves of pandemics. Sci. Rep. 11 (1) https://doi.org/10.1038/s41598-021-00190-0.

Chen, Y., Wang, J., Liu, C., Su, L., Zhang, D., Fan, J., Yang, Y., Xiao, M., Xie, J., Xu, Y., Li, Y., Zhang, S., 2020. IP-10 and MCP-1 as biomarkers associated with disease severity of COVID-19. Mol. Med. 26 (1) https://doi.org/10.1186/s10020-020-00230-x.

Chowdhury, S., Chen, Y., Yao, T.-W., Ajami, K., Wang, X.M., Popov, Y., Schuppan, D., Bertolino, P., McCaughan, G.W., Yu, D.MT., Gorrell, M.D., 2013. Regulation of dipeptidyl peptidase 8 and 9 expression in activated lymphocytes and injured liver. World J. Gastroenterol. 19 (19), 2883–2893.

Cucinotta, D., Vanelli, M., 2020. WHO Declares COVID-19 a Pandemic. Acta bio-medica : Atenei Parmensis. 91 (1), 157–160.
Dessing, M.C., van der Sluijs, K.F., Florquin, S., van der Poll, T., 2007. Monocyte chemoattractant protein 1 contributes to an adequate immune response in influenza pneumonia. Clin. Immunol. 125 (3), 328–336.
Fantuzzi, L., Tagliamonte, M., Gauzzi, M.C., Lopalco, L., 2019. Dual CCR5/CCR2 targeting: opportunities for the cure of complex disorders. Cell Mol. Life Sci. 76 (24), 4869–4886.
Hodge, D.L., Reynolds, D., Cerbán, F.M., Correa, S.G., Baez, N.S., Young, H.A., Rodriguez-Galan, M.C., 2012. MCP-1/CCR 2 interactions direct migration of peripheral B and T lymphocytes to the thymus during acute infectious/inflammatory processes. Eur. J. Immunol. 42 (10), 2644–2654.
Hollingsworth, L.R., Sharif, H., Griswold, A.R., Fontana, P., Mintseris, J., Dagbay, K.B., Paulo, J.A., Gygi, S.P., Bachovchin, D.A., Wu, H., 2021. DPP9 sequesters the C terminus of NLRP1 to repress inflammasome activation. Nature 592 (7856), 778–783.
Huang, J., Al Emran, A., Endaya, J., McCaughan, G., Gorrell, M., Zhang, H., 2021. Associations between DPP9 expression, survival and gene expression signature in human hepatocellular carcinoma: Comprehensive in silico analyses. FASEB J. 35 (S1) https://doi.org/10.1096/fsb2.v35.S110.1096/fasebj.2021.35.S1.04490.
Jafarzadeh, A., Nemati, M., Jafarzadeh, S., 2019. The important role played by chemokines influence the clinical outcome of Helicobacter pylori infection. Life Sci. 231, 116688. https://doi.org/10.1016/j.lfs.2019.116688.
Jafarzadeh, A., Chauhan, P., Saha, B., Jafarzadeh, S., Nemati, M., 2020. Contribution of monocytes and macrophages to the local tissue inflammation and cytokine storm in COVID-19: Lessons from SARS and MERS, and potential therapeutic interventions. Life Sci. 257, 118102. https://doi.org/10.1016/j.lfs.2020.118102.
Jafarzadeh, A., Nemati, M., Saha, B., Bansode, Y.D., Jafarzadeh, S., 2021. Protective Potentials of Type III Interferons in COVID-19 Patients: Lessons from Differential Properties of Type I- and III interferons. Viral Immunol. 34 (5), 307–320.
Jafarzadeh, A., Nemati, M., Jafarzadeh, S., 2021. Contribution of STAT3 to the pathogenesis of COVID-19. Microb. Pathog. 154, 104836. https://doi.org/10.1016/j.micpath.2021.104836.
Jafarzadeh, A., Jafarzadeh, S., Nemati, M., 2021. Therapeutic potential of ginger against COVID-19: Is there enough evidence? J. Tradit. Chin. Med. Sci. 8 (4), 267–279.
Lankas GR, Leiting B, Roy RS, Eiermann GJ, Beconi MG, Biftu T, et al. Dipeptidyl peptidase IV inhibition for the treatment of type 2 diabetes: potential importance of selectivity over dipeptidyl peptidases 8 and 9. Diabetes. 2005;54(10):2988-94.
Mitra P, Misra S, Sharma P. COVID-19 pandemic in India: what lies ahead. Springer; 2020.
Okondo, M.C., Johnson, D.C., Sridharan, R., Go, E.B., Chui, A.J., Wang, M.S., Poplawski, S.E., Wu, W., Liu, Y., Lai, J.H., Sanford, D.G., Arciprete, M.O., Golub, T. R., Bachovchin, W.W., Bachovchin, D.A., 2017. DPP8 and DPP9 inhibition induces pro-caspase-1-dependent monocyte and macrophage pyroptosis. Nat. Chem. Biol. 13 (1), 46–53.
Okondo, M.C., Rao, S.D., Taabazuing, C.Y., Chui, A.J., Poplawski, S.E., Johnson, D.C., Bachovchin, D.A., 2018. Inhibition of Dpp8/9 activates the Nlrp1b inflammasome. Cell Chem. Biol. 25 (3), 262–267.e5.
Organization, W.H., 2021. COVID-19 clinical management: living guidance, 25 January 2021. World Health Organization.
Pairo-Castineira, E., Clohisey, S., Klaric, L., Bretherick, A.D., Rawlik, K., Pasko, D., Walker, S., Parkinson, N., Fourman, M.H., Russell, C.D., Furniss, J., Richmond, A., Gountouna, E., Wrobel, N., Harrison, D., Wang, B.o., Wu, Y., Meynert, A., Griffiths, F., Oosthuyzen, W., Kousathanas, A., Moutsianas, L., Yang, Z., Zhai, R., Zheng, C., Grimes, G., Beale, R., Millar, J., Shih, B., Keating, S., Zechner, M., Haley, C., Porteous, D.J., Hayward, C., Yang, J., Knight, J., Summers, C., Shankar-Hari, M., Klenerman, P., Turtle, L., Ho, A., Moore, S.C., Hinds, C., Horby, P., Nichol, A., Maslove, D., Ling, L., McAuley, D., Montgomery, H., Walsh, T., Pereira, A. C., Renieri, A., Shen, X., Ponting, C.P., Fawkes, A., Tenesa, A., Caulfield, M., Scott, R., Rowan, K., Murphy, L., Openshaw, P.J.M., Semple, M.G., Law, A., Vitart, V., Wilson, J.F., Baillie, J.K., 2021. Genetic mechanisms of critical illness in Covid-19. Nature 591 (7848), 92–98.
Palomino, D.C.T., Marti, L.C., 2015. Chemokines and immunity. Einstein (Sao Paulo) 13 (3), 469–473.
Raj, V.S., Mou, H., Smits, S.L., Dekkers, D.H.W., Müller, M.A., Dijkman, R., Muth, D., Demmers, J.A.A., Zaki, A., Fouchier, R.A.M., Thiel, V., Drosten, C., Rottier, P.J.M., Osterhaus, A.D.M.E., Bosch, B.J., Haagmans, B.L., 2013. Dipeptidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 495 (7440), 251–254.
Rehman, S., Ravinayagam, V., Nahvi, I., Aldossary, H., Al-Shammari, M., Amiri, M.S.A., Kishore, U., Al-Suhaimi, E.A., 2021. Immunity, Sex Hormones, and Environmental Factors as Determinants of COVID-19 Disparity in Women. Front. Immunol. 12 https://doi.org/10.3389/fimmu.2021.680845.
Reinhold D, Goihl A, Wrenger S, Reinhold A, Kühlmann UC, Faust J, et al. Role of dipeptidyl peptidase IV (DP IV)-like enzymes in T lymphocyte activation: investigations in DP IV/CD26-knockout mice. Clinical chemistry and laboratory medicine. 2009;47(3):268-74.
Schmiedel, B.J., Chandra, V., Rocha, J., Gonzalez-Colin, C., Bhattacharyya, S., Madrigal, A., et al., 2020. COVID-19 genetic risk variants are associated with expression of multiple genes in diverse immune cell types. bioRxiv.
Singh, S., Anshita, D., Ravichandiran, V., 2021. MCP-1: Function, regulation, and involvement in disease. Int. Immunopharmacol. 101, 107598. https://doi.org/10.1016/j.intimp.2021.107598.
Vanderheiden, A., Thomas, J., Soung, A.L., Davis-Gardner, M.E., Floyd, K., Jin, F., Cowan, D.A., Pellegrini, K., Shi, P.-Y., Grakoui, A., Klein, R.S., Bosinger, S.E., Kohlmeier, J.E., Menachery, V.D., Suthar, M.S., Schultz-Cherry, S., 2021. CCR2 Signaling Restricts SARS-CoV-2 Infection. mBio. 12 (6) https://doi.org/10.1128/mBio.02749-21.
Wang, L., Balmat, T.J., Antonia, A.L., Constantine, F.J., Henao, R., Burke, T.W., et al., 2020. An atlas connecting shared genetic architecture of human diseases and molecular phenotypes provides insight into COVID-19 susceptibility. medRxiv.
Wareing, M.D., Lyon, A., Inglis, C., Giannoni, F., Charo, I., Sarawar, S.R., 2007. Chemokine regulation of the inflammatory response to a low-dose influenza infection in CCR2–/–mice. J. Leukoc. Biol. 81 (3), 793–801.
Yu, D.M.T., Ajami, K., Gall, M.G., Park, J., Lee, C.S., Evans, K.A., McLaughlin, E.A., Pitman, M.R., Abbott, C.A., McCaughan, G.W., Gorrell, M.D., 2009. The in vivo expression of dipeptidyl peptidases 8 and 9. J. Histochem. Cytochem. 57 (11), 1025–1040.
Zhong, F.L., Robinson, K., Teo, D.E.T., Tan, K.-Y., Lim, C., Harapas, C.R., Yu, C.-H., Xie, W.H., Sobota, R.M., Au, V.B., Hopkins, R., D'Osualdo, A., Reed, J.C., Connolly, J.E., Masters, S.L., Reversade, B., 2018. Human DPP9 represses NLRP1 inflammasome and protects against autoinflammatory diseases via both peptidase activity and FIIND domain binding. J. Biol. Chem. 293 (49), 18864–18878.