

Expression analysis of *IFNAR1* and *TYK2* transcripts in COVID-19 patients

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ABSTRACT

As a member of JAK family of non-receptor tyrosine kinases, TYK2 has a crucial role in regulation of immune responses. This protein has a crucial role in constant expression of *IFNAR1* on surface of cells and initiation of type I IFN signaling. In the current study, we measured expression of *IFNAR1* and *TYK2* levels in venous blood samples of COVID-19 patients and matched controls. *TYK2* was significantly down-regulated in male patients compared with male controls (RME = 0.34, P value = 0.03). Though, levels of *TYK2* were not different between female cases and female controls, or between ICU-admitted and non-ICU-admitted cases. Expression of *IFNAR1* was not different either between COVID-19 cases and controls or between patients required ICU admission and non-ICU-admitted cases. However, none of these transcripts can properly differentiate COVID-19 cases from controls or separate patients based on disease severity. The current study proposes down-regulation of *TYK2* as a molecular mechanism for incapacity of SARS-CoV-2 in induction of a competent IFN response.

1. Introduction

Tyrosine kinase 2 (TYK2) gene encodes a member of the Janus kinase (JAK) family of non-receptor tyrosine kinases. These kinases have important roles in the regulation of immune response and cell development [1]. This protein has functional association with *IFNAR1* receptor subunit. This association has a positive influence on ligand binding to the receptor complex. In fact, *TYK2* has a crucial role in stable expression of *IFNAR1* on cell surface [2]. Thus, proper activity of *TYK2* is a crucial step for initiation of type I IFN response [3]. IFNs are important antiviral cytokines that diminish the impacts of attacking viruses during early phase of viral infections [4]. Recent studies have

shown inability of COVID-19 infection in induction of a competent IFN response to decrease the severity of the viral infection [4,5]. Although several mechanisms might be involved in this process, an imperfect function of *IRF3* in activation of the *IFN-β* promoter has been suggested as a possible mechanism for incapacity of SARS-CoV-2 in induction of a competent IFN response [4,6]. Another study has revealed the presence of potential inactivating variants in genes related with Toll-like receptors the type I IFN pathway in a proportion of severely affected COVID-19 patients, emphasizing on the importance of these pathways in protection against severe disorder [7]. Consistent with this finding, autoantibodies against type I IFN have been detected in a number of severely affected COVID-19 patients. Notably, most of these

Abbreviations: TYK2, Tyrosine kinase 2; JAK, Janus kinase; AUC, (Area under curve).

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Table 1
The sequences of primers.

Gene name	Primer and probe sequence	Primer and probe size	Amplicon size
<i>HPRT1</i>	F: AGCCTAAGATGAGAGTTC	18	88
	R: CACAGAACTAGAACATTGATA	21	
	FAM- CATCTGGAGTCCTATTGACATCGC-TAMRA	24	
<i>TYK2</i>	F: CATCCACATTGCACATAA	18	142
	R: GCGGAAATATAGCATCAG	18	
	FAM- TGGTATCACTCTCTCTTGTCTCA-TAMRA	23	
<i>IFNAR1</i>	F: GAAACCACTGACTGTATATTGTGTGAAA	28	86
	R: CAGCGTCACTAAAACACTGCTTT	24	
	FAM- CCAGAGCACACCCATGGATGAAAAGC-TAMRA	27	

autoantibodies had neutralising ability in vitro [8].

Although the importance of type I IFN responses has been well established in defence against SARS-CoV-2 and related viral infections, the mechanism of such malfunctioning has not been completely understood. In the current study, we measured expression of *IFNAR1* and *TYK2* levels in venous blood samples of COVID-19 patients and matched controls to unravel their role in determination of the course of COVID-19

2. Materials and methods

2.1. Patients and controls

The current study was performed on 91 COVID-19 cases admitted to Nikan Hospital, Tehran, during 2020. Diagnosis was confirmed through assessment of nasopharyngeal swab samples. Equal numbers of control specimens were obtained from unaffected individuals without history of exposure to COVID-19 cases. The study protocol was approved by ethical committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1400.083). Informed consent was obtained from all patients and controls. Laboratory parameters were gathered from all patients.

2.2. Expression assays

Four milliliters of venous blood were gathered from all cases and healthy individuals. Next, total RNA was retrieved from blood

specimens using the TRIzol reagent. Then, complementary DNA was created from these specimens by using the Smobio cDNA production kit (Taiwan). Transcript quantities of *IFNAR1* and *TYK2* genes were quantified in all samples using the real time PCR Master Mix (Amplicon, Denmark). Primers are summarized in Table 1.

2.3. Data analysis

Data was analyzed using R analyzer software. Transcript quantities of *IFNAR1* and *TYK2* genes were estimated from Ct and efficiency values. *HPRT1* was considered as the normalizer. These figures were log₂ transformed and compared between cases and healthy subjects as well as between those admitted to ICU and non-ICU hospitalized cases. This step was accomplished using *t*-test. Spearman correlation coefficient was calculated to judge about correlation between expression levels of *IFNAR1* and *TYK2* genes as well as their correlation with para-clinical data. Bayesian Generalized Linear Model was used for depicting ROC curves. Youden's J was calculated to identify the optimal threshold. P values < 0.05 were considered as significant.

3. Results

3.1. General paraclinical data

Female/male ratio was 38/53 and 39/52 in cases and controls, respectively. The mean age (\pm standard deviation) of the affected individuals was 57.18 (\pm 16.89) years. A total of 37 cases (40.6%) were admitted in the ICU. Mean (\pm standard deviation) of paraclinical variables of patients were as follow: WBC ($10^9/L$) = 8.12 (\pm 8.5), RBC ($10^{12}/L$) = 4.7 (\pm 0.77), Platelet count ($10^9/L$) = 210.35 (\pm 95.22), Lymphocyte (%) = 21.04 (\pm 11.32), Neutrophil (%) = 69.1 (\pm 13.09), ESR (mm/hr) = 44.13 (\pm 32.7) and CRP (mg/dL) = 73.26 (\pm 69.54).

3.2. Levels of *IFNAR1* and *TYK2* genes

Figs. 1 and 2 illustrate relative transcript levels of *IFNAR1* and *TYK2* in cases and normal controls, and in patients required ICU admission versus those did not require ICU admission, respectively.

TYK2 was significantly down-regulated in male patients compared with male controls (RME = 0.34, P value = 0.03). Nonetheless, expression of *TYK2* was not different between female cases and female controls, or between ICU-admitted and non ICU-admitted cases. Expression of *IFNAR1* was not different either between COVID-19 cases

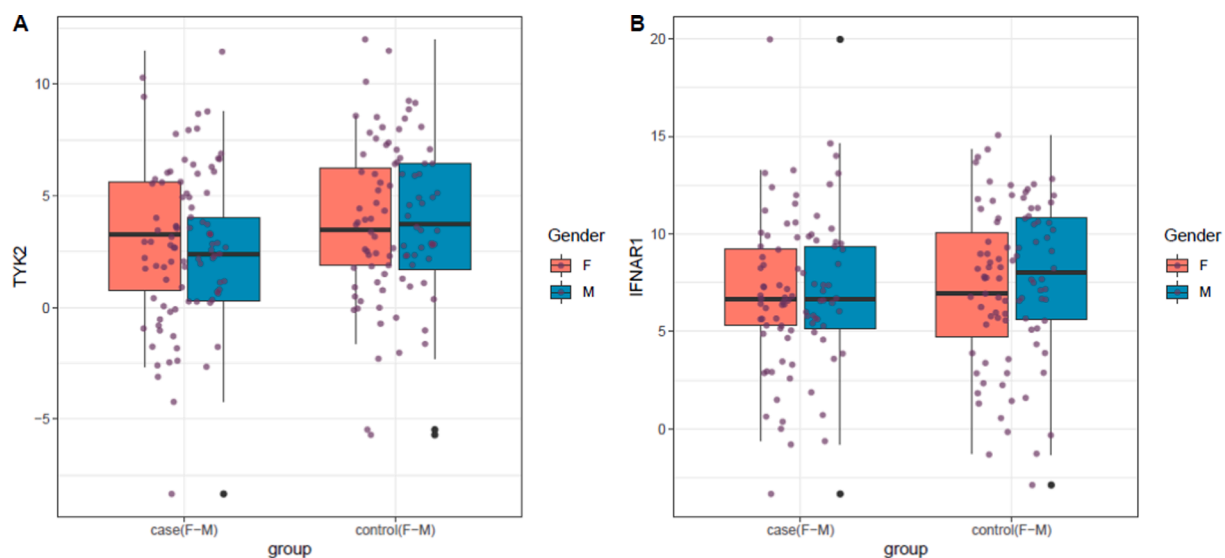


Fig. 1. Expression of *IFNAR1* and *TYK2* transcripts among COVID-19 patients and healthy persons.

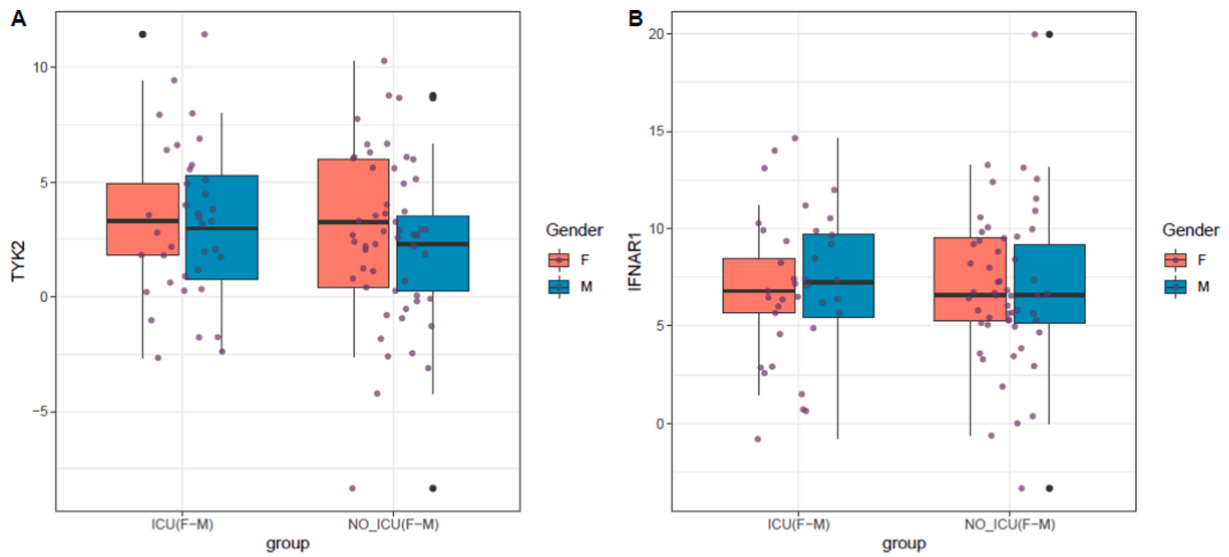


Fig. 2. Expression of *IFNAR1* and *TYK2* transcripts among ICU-admitted COVID-19 patients and non-ICU-admitted cases.

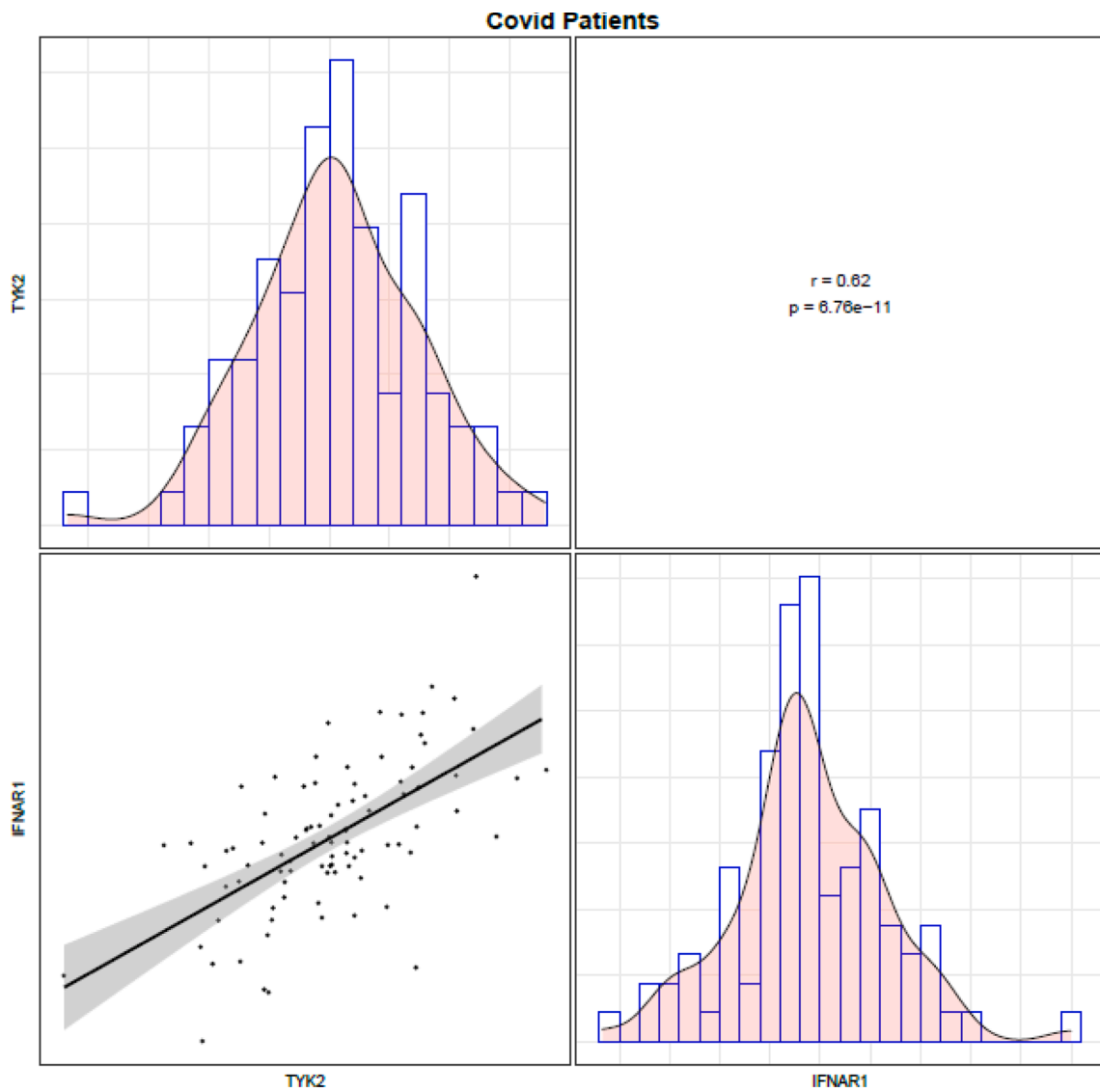


Fig. 3. Correlation between *IFNAR1* and *TYK2* transcripts among COVID-19 patients.

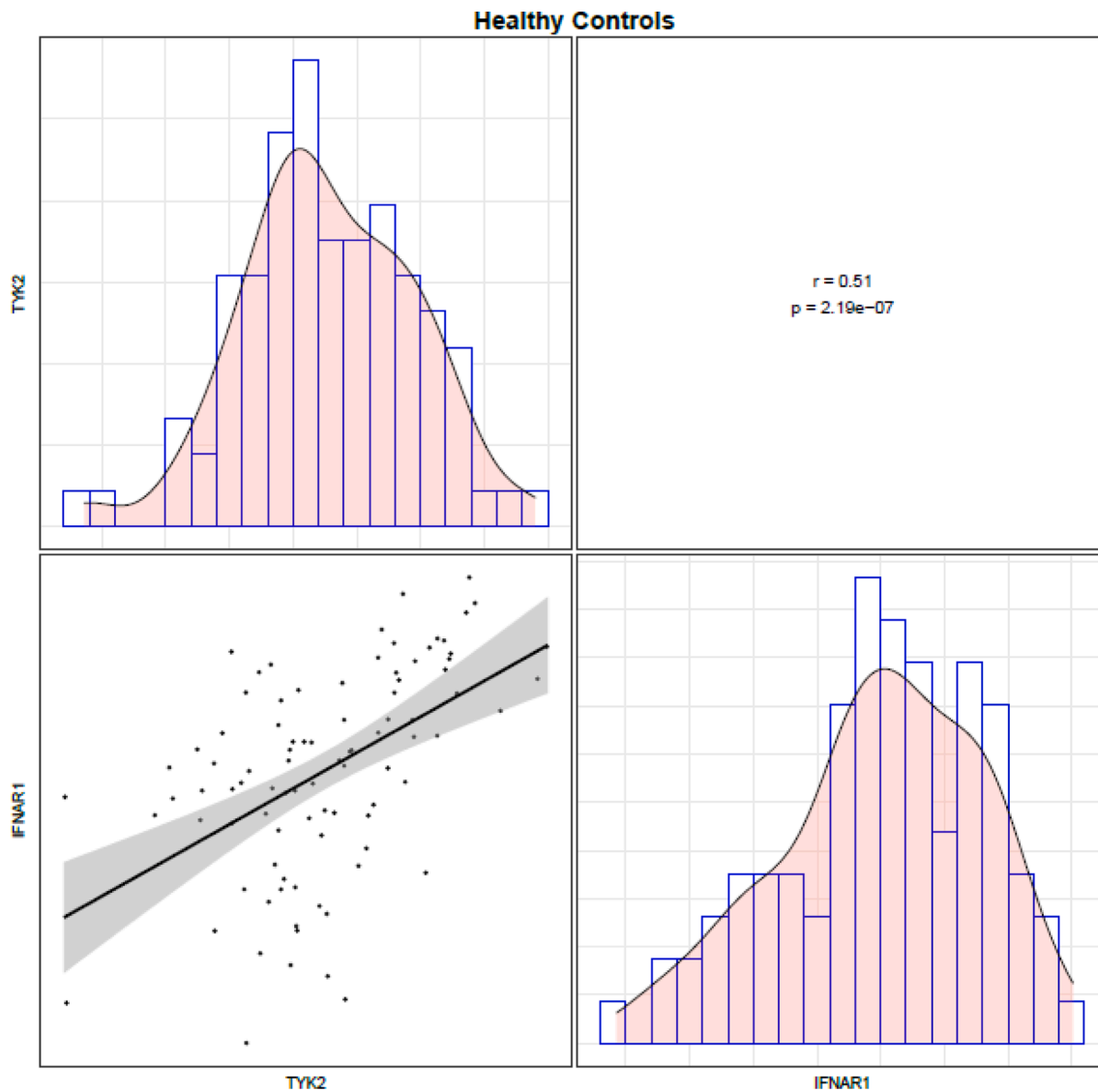


Fig. 4. Correlation between *IFNAR1* and *TYK2* transcripts among healthy controls.

Table 2

Complete parameters of expression of *IFNAR1* and *TYK2* transcripts in COVID-19 patients and controls (RME: Ratios of mean expressions).

Samples	<i>TYK2</i>					<i>IFNAR1</i>					
	Standard error	RME	P value	95% confidence interval		Standard error	RME	P value	95% confidence interval		
COVID-19 patients/ Healthy controls											
Total	91/91	0.50	0.46	0.03	-2.10	-0.10	0.57	0.70	0.37	-1.64	0.61
Females	38/39	0.71	0.69	0.46	-1.94	0.89	0.77	0.67	0.46	-2.11	0.98
Males	53/52	0.70	0.34	0.03	-2.92	-0.11	0.81	0.71	0.55	-2.10	1.13
ICU admitted/ Non_ICU admitted											
Total	37/54	0.72	1.53	0.39	-0.82	2.05	0.80	1.16	0.78	-1.37	1.82
Females	13/25	1.22	1.28	0.76	-2.18	2.91	1.06	0.97	0.96	-2.22	2.13
Males	24/29	0.92	1.98	0.29	-0.87	2.85	1.15	1.22	0.80	-2.02	2.61

Expression levels of *IFNAR1* and *TYK2* were significantly correlated with each other both among COVID-19 cases ($r = 0.62$, P value = $6.7e-11$) and controls ($r = 0.51$, P value = $2.19e-7$) (Figs. 3 and 4, respectively).

and controls or between patients required ICU admission and those did not require ICU admission (Table 2).

Then, we assessed correlation between expression levels of *IFNAR1* and *TYK2* and a number of demographic and clinical data. Based on the calculated P values, expression of *TYK2* was correlated with gender (P value = $1.51e-01$), ESR (P value = $2.93e-01$), CRP (P value = $5.65e-02$) and age (P value = $1.11e-01$) (Fig. 5).

We also performed a multivariate analysis using linear regression model to assess correlations between expressions of *TYK2* and *IFNAR1* and clinical variables (Table 3). *IFNAR1* expression levels were significantly correlated with MCHC. Thus, the multivariate analysis showed that that the bivariate correlations presented in Fig. 5 are not real.

Finally, we depicted ROC curves to assess diagnostic power of *IFNAR1* and *TYK2* genes in separation of COVID-19 cases from controls

Table 3

Multiple variable analyses using linear regression model showing correlations between *TYK2* and *IFNAR1* expression levels and clinical variables.

Dependent Variables	Independent variables	P value	Regression coefficient (B)	95% CI		
				Lower Bound	Upper Bound	
TYK2	age	0.89	-0.004	-0.068	0.06018	
	WBC	0.28	-6.338e-005	-0.00017	5.293e-005	
	RBC	0.77	-1.97	-15.83	11.88	
	HB	0.16	-4.29	-10.35	1.759	
	HCT	0.21	1.63	-0.9773	4.249	
	MCV	0.36	-0.40	-1.294	0.4759	
	MCH	0.63	0.80	-2.601	4.219	
	MCHC	0.74	0.33	-1.667	2.330	
	PLT	0.72	-1.860e-006	-1.233e-005	8.614e-006	
	LYM	0.85	0.015	-0.160	0.1922	
	NEUT	0.39	0.06	-0.087	0.2217	
	ESR	0.52	0.012	-0.026	0.05203	
	CRP	0.92	0.0008	-0.0164	0.01813	
	IFNAR1	age	0.40	50.28	-68.28	168.8
		WBC	0.48	-0.019	-0.076	0.03630
		RBC	0.96	-2.198e-006	-0.0001	9.873e-005
HB		0.34	6.390	-6.913	19.69	
HCT		0.32	-3.28	-9.901	3.338	
MCV		0.80	0.29	-2.054	2.647	
MCH		0.1092	-0.912	-2.034	0.2087	
MCHC		0.01*	4.196	0.7835	7.609	
PLT		0.15	-2.47	-5.881	0.9249	
LYM		0.26	5.172e-006	-3.962e-006	1.431e-005	
NEUT		0.56	-0.044	-0.1974	0.1089	
ESR		0.70	0.025	-0.1089	0.1606	
CRP		0.19	-0.02	-0.05646	0.01200	

as well as patients required ICU admission and those not required ICU admission (Fig. 6A and B, respectively).

AUC values *IFNAR1* and *TYK2* genes in differentiating COVID-19 patients from healthy subjects were 0.53 and 0.58, respectively. AUC values of these genes in separation of ICU-admitted cases from those did not require ICU admission were 0.59 and 0.49, respectively (Table 4).

Then, we evaluated diagnostic power of these genes in differentiation of male cases from male controls (Fig. 7). *TYK2* could differentiate these two subgroups with AUC value of 0.63, sensitivity of 0.71 and specificity of 0.52 (P value = 0.03).

4. Discussion

SARS-CoV-2 infection is linked with low IFN I responses, while high levels of numerous chemokines and IL-6 [9]. Another study has demonstrated impairment IFN I response in patients with severe or critical COVID-19. This study has reported down-regulation of IFN-I and ISGs in peripheral blood of these patients, in spite of high levels of TNF and IL-6 and augmented NF- κ B-associated inflammatory reactions [10]. Contrary with these studies, a recent immune landscape investigation has shown the impact of IFN I response in the evolution of severe COVID-19 [11]. The latter study has shown presence of a hyperinflammatory signature in all immune cells of patients with COVID-19 which was illustrated by significant over-expression of TNF/IL-1 β -associated immune responses. Authors have also demonstrated coexistence of type I IFN response in classical monocytes of patients who experienced severe course of COVID-19. Based on these results authors have suggested that type I IFN responses contribute in intensifying inflammatory responses in severe COVID-19 cases [11]. Thus, the impact of type I IFN responses in determination of COVID-19 course is a matter of conflict.

We examined expression levels of two genes related with type I IFN responses in blood of COVID-19 patients and controls. *TYK2* was significantly down-regulated in male patients compared with male controls. However, expression of *TYK2* was not different between female cases and female controls, or between ICU-admitted and non ICU-admitted cases. A previous study has demonstrated down-regulation of *TYK2* in multiple sclerosis patients treated with interferon-beta [12]. Moreover, experiments in Tyk-2(-/-) asthmatic mice have shown induction of peribronchial collagen deposition as well as stimulation of IRF4 and hyperproliferative lung Th2 CD4 + effector T cells and a variety of other T cells, suggesting SOCS3-mediated impact of Tyk-2 on various groups of T helper cells [13]. It is worth mentioning that *STAT* genes-associated regulation of *SOCS* genes has a central impact in the pathogenesis of COVID-19 [14]. Moreover, *SOCS1* and *SOCS3* have been shown to function as virus stimulated intrinsic virulence factors in a variety of viral infections including SARS-CoV-2. In fact, *SOCS* binds to the activation loop of *TYK2* via the *SOCS* kinase inhibitory region, which suppresses *STAT* induction by the kinases [15].

Expression of *IFNAR1* was not different either between COVID-19 cases and controls or between those required ICU admission and non ICU-admitted cases. A recent study has shown that SARS-CoV-2 has a tendency toward the proximal JAK-*STAT* pathway components. This effect of SARS-CoV-2 leads to destabilization of *IFNAR1* via ubiquitination, inducing resistance to type I IFN in the infected cells [16]. The inconsistency between our results and the results of the mentioned study can be explained by the source of expression assays i.e. peripheral blood versus human cell lines derived from lung, intestine, heart, kidney, liver, and brain. Alternatively, the technique used for expression assays (transcriptomic versus proteomics techniques) might affect the results.

Although bivariate analyses showed correlation between expression of *TYK2* and gender, ESR, CRP and age, these correlations were not conformed by multivariate analyses. A previous study has demonstrated the role of IFN- α in suppression of CRP promoter activity and CRP release in the context of systemic lupus erythematosus [17]. However, data regarding the influence of *TYK2* on CRP and ESR levels are scarce. *TYK2* has been shown to prevent accumulation of *IFNAR1* at intracellular compartment and induce its stabilization at the cell surface [2]. However, there are some other routes of stabilization of *IFNAR1* which are independent from *TYK2*. For instance, RNA-binding protein RBM47 can stabilize *IFNAR1* transcripts [18].

In spite of abnormal expression of *TYK2* in COVID-19 cases, neither *TYK2* nor *IFNAR1* transcripts can properly differentiate COVID-19 cases from controls or separate patients based on disease severity. The current study proposes down-regulation of *TYK2* as a possible mechanism for incapacity of SARS-CoV-2 in induction of a competent IFN response. However, this gene is not involved in the determination of severity of COVID-19, as its expression levels were not different between patients

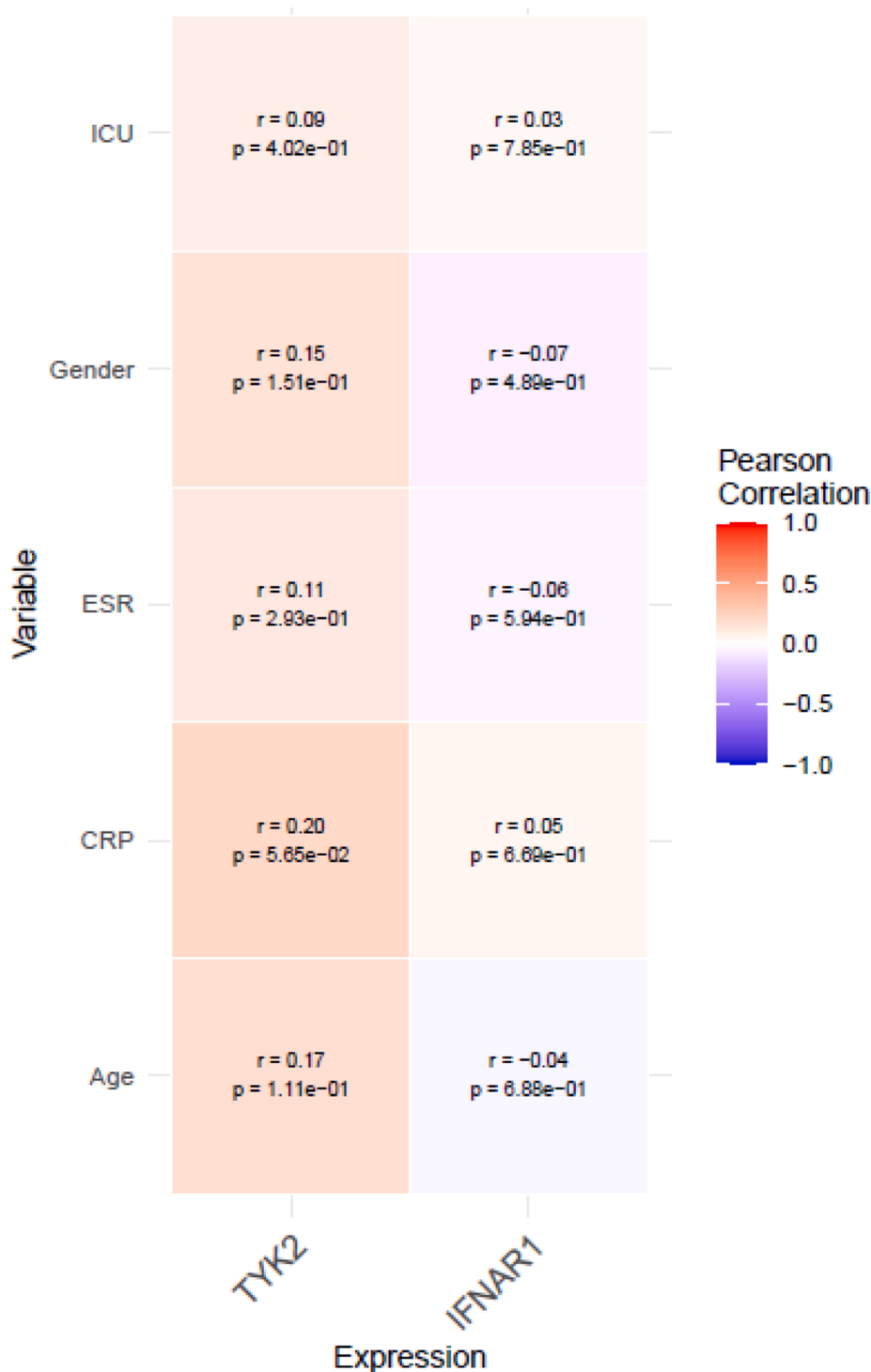


Fig. 5. Correlation between expressions of *IFNAR1* and *TYK2* genes and clinical variables.

required ICU and the the other group of patients.

Our study has a limitation regarding lack of assessment of expression of TYK2 and IFNAR1 at protein level. This type of assay is required to confirm that IFNAR1 levels are not affected by TYK2. The importance of this assessment is highlighted by the previous report by Ragimbeau et al. that demonstrated low TYK2 protein levels are related with low IFNAR1 protein levels. We also emphasize that these results should be verified in further studies.

5. Ethics approval and consent to participant

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent forms were obtained from all study participants. Informed consent forms were obtained from all study participants and from legally authorized representative/next of kin of deceased patients. The study protocol was approved by the ethical committee of Shahid Beheshti University of

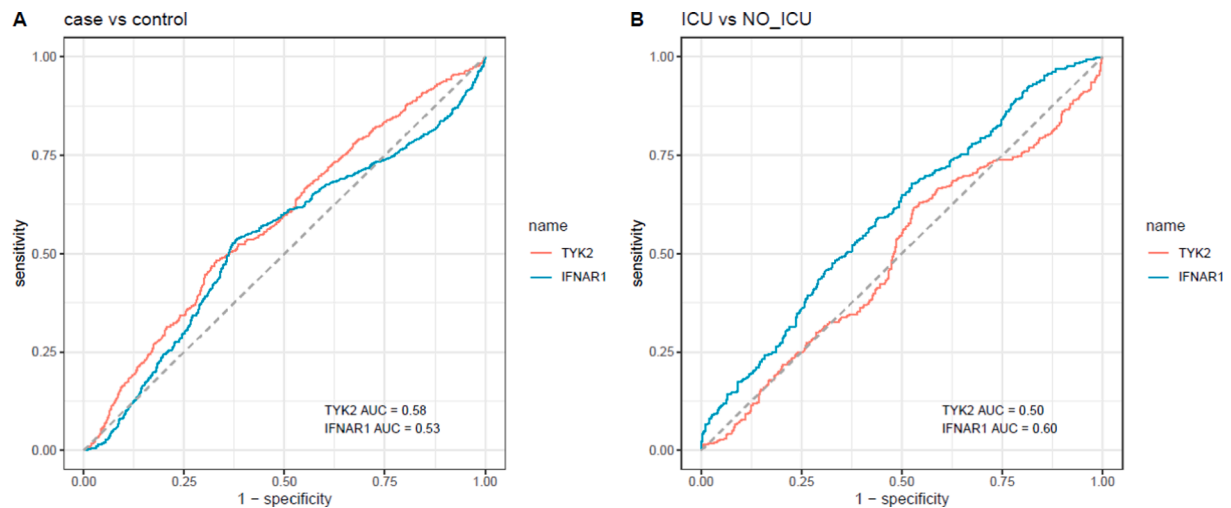


Fig. 6. ROC curves showing the diagnostic power of *IFNAR1* and *TYK2* in separation of COVID-19 cases from normal persons (A) and separation of patients required ICU admission from the other group of patients (B).

Table 4

Detailed statistics of ROC curves for judgment of the diagnostic power of *IFNAR1* and *TYK2* genes in diagnosis of COVID-19 patients from healthy subjects and in separation of patients required ICU admission from those did not require ICU.

Number of Samples	<i>TYK2</i>			<i>IFNAR1</i>			Both genes		
	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity	AUC	Sensitivity	Specificity
COVID-19/ Healthy controls									
Total 91/91	0.58	0.48	0.66	0.53	0.536	0.61	0.57	0.49	0.67
ICU/ Non_ICU									
Total 37/54	0.49	0.61	0.47	0.59	0.677	0.47	0.57	0.23	0.88

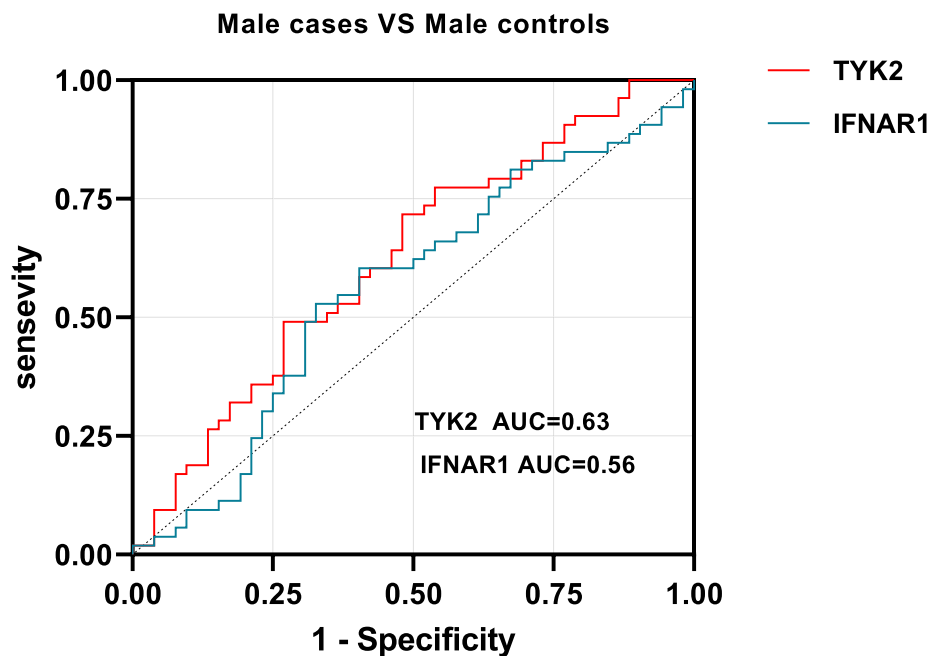


Fig. 7. ROC curves showing the diagnostic power of *IFNAR1* and *TYK2* in separation of male COVID-19 patients from normal male persons.

Medical Sciences (IR.SBMU.RETECH.REC.1399.592). All methods were performed in accordance with the relevant guidelines and regulations

6. Consent of publication

Not applicable

7. Availability of Data and Materials

The analyzed data sets generated during the study are available from the corresponding author on reasonable request.

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9. Authors' contributions

SGF and MT wrote the draft and revised it. MF designed and supervised the study. NS, AT and MF performed the experiment and data collection. AS and MAB analyzed the data. All the authors read and approved the submitted version.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Not applicable

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