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Cytokine 153 (2022) 155849

Contents lists available at ScienceDirect

Cytokine

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

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

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ARTICLE INFO

Keywords:
IFNAR1
TYK2
COVID-19
Expression
Biomarker

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 diffrentiate 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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https://doi.org/10.1016/j.cyto.2022.155849
Received 10 December 2021; Received in revised form 28 February 2022; Accepted 1 March 2022
Available online 4 March 2022

Table 1
The sequences of primers.

Gene name	Primer and probe sequence	Primer and probe size	Amplicon size
HPRT1	F: AGCCTAAGATGAGAGTTC R: CACAGAACTAGAACATTGATA FAM -CATCTGGAGTCCTATTGACATCGC-TAMRA	18 21 24	88
TYK2	F: CATCCACATTGCACATAA R: GCGGAAATATAGCATCAG FAM- TGGTATCACTCCTCCTTGCTTCA-TAMRA	18 18 23	142
INFAR1	F: GAAACCACTGACTGTATATTGTGTGAAA R: CAGCGTCACTAAAAACACTGCTTT FAM - CCAGAGCACACACCATGGATGAAAAGC-TAMRA	28 24 27	86

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

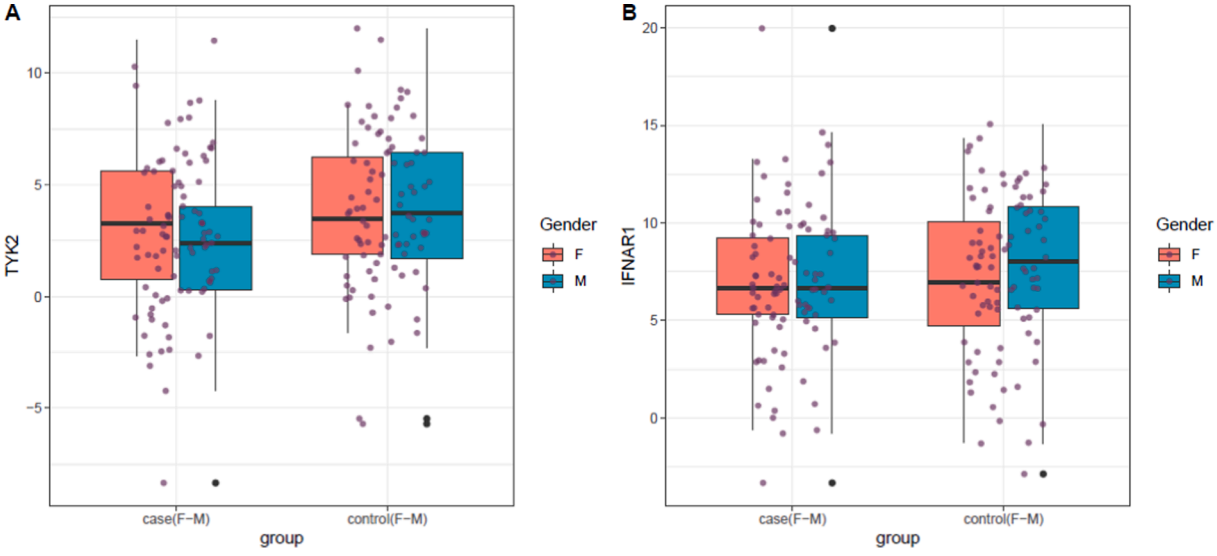

Fig. 1. Expression of *IFNAR1* and *TYK2* transcripts among COVID-19 patients and healthy persons.

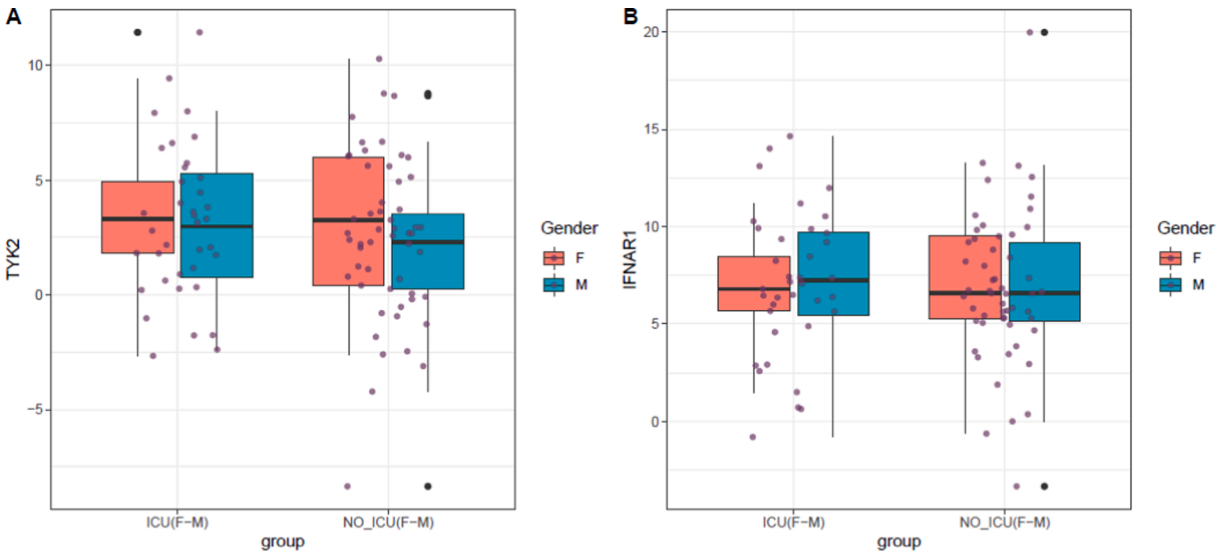

Fig. 2. Expression of *IFNAR1* and *TYK2* transcripts among ICU-admitted COVID-19 patients and non-ICU-admitted cases.

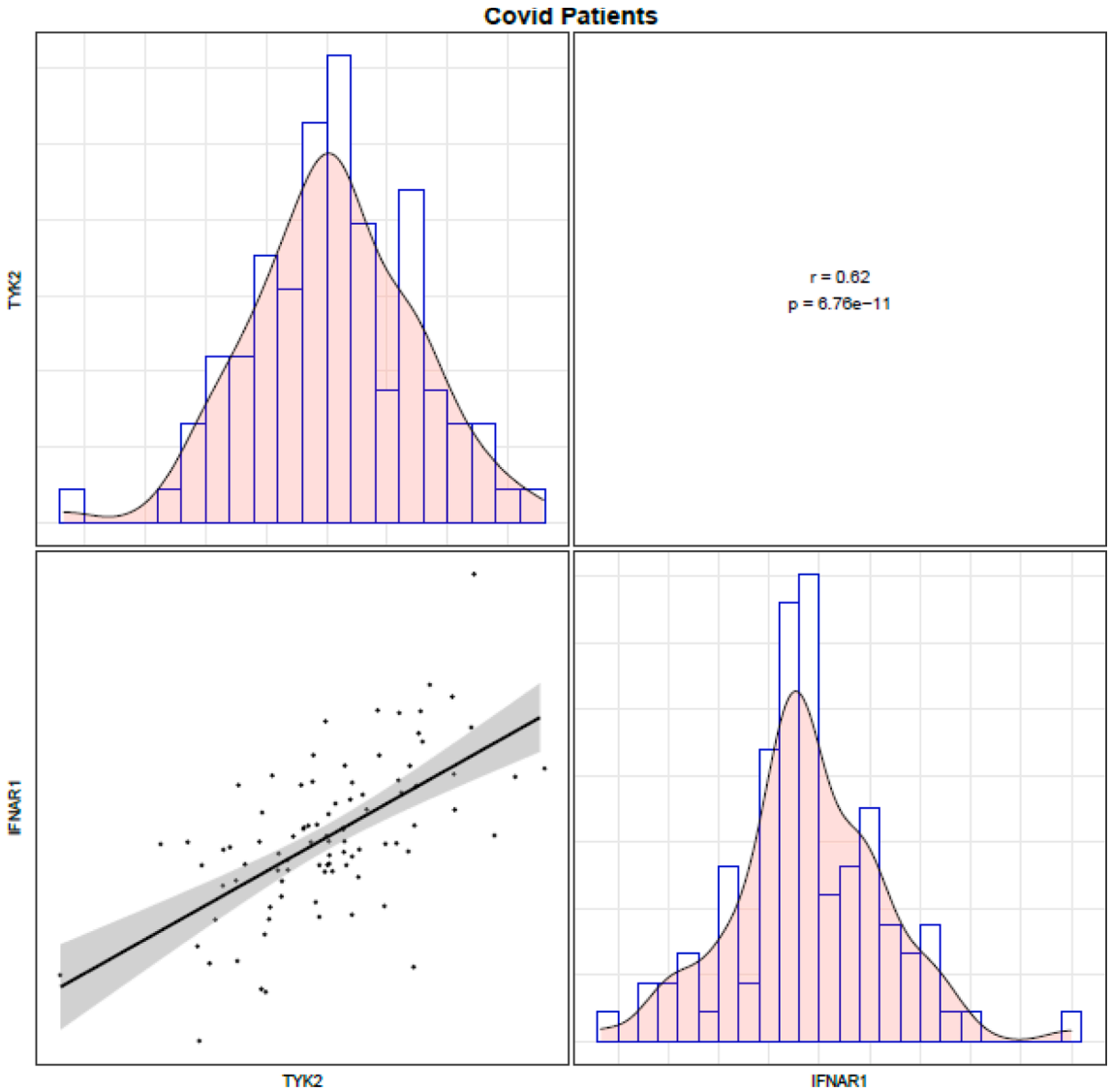

Fig. 3. Correlation between *IFNAR1* and *TYK2* transcripts among COVID-19 patients.

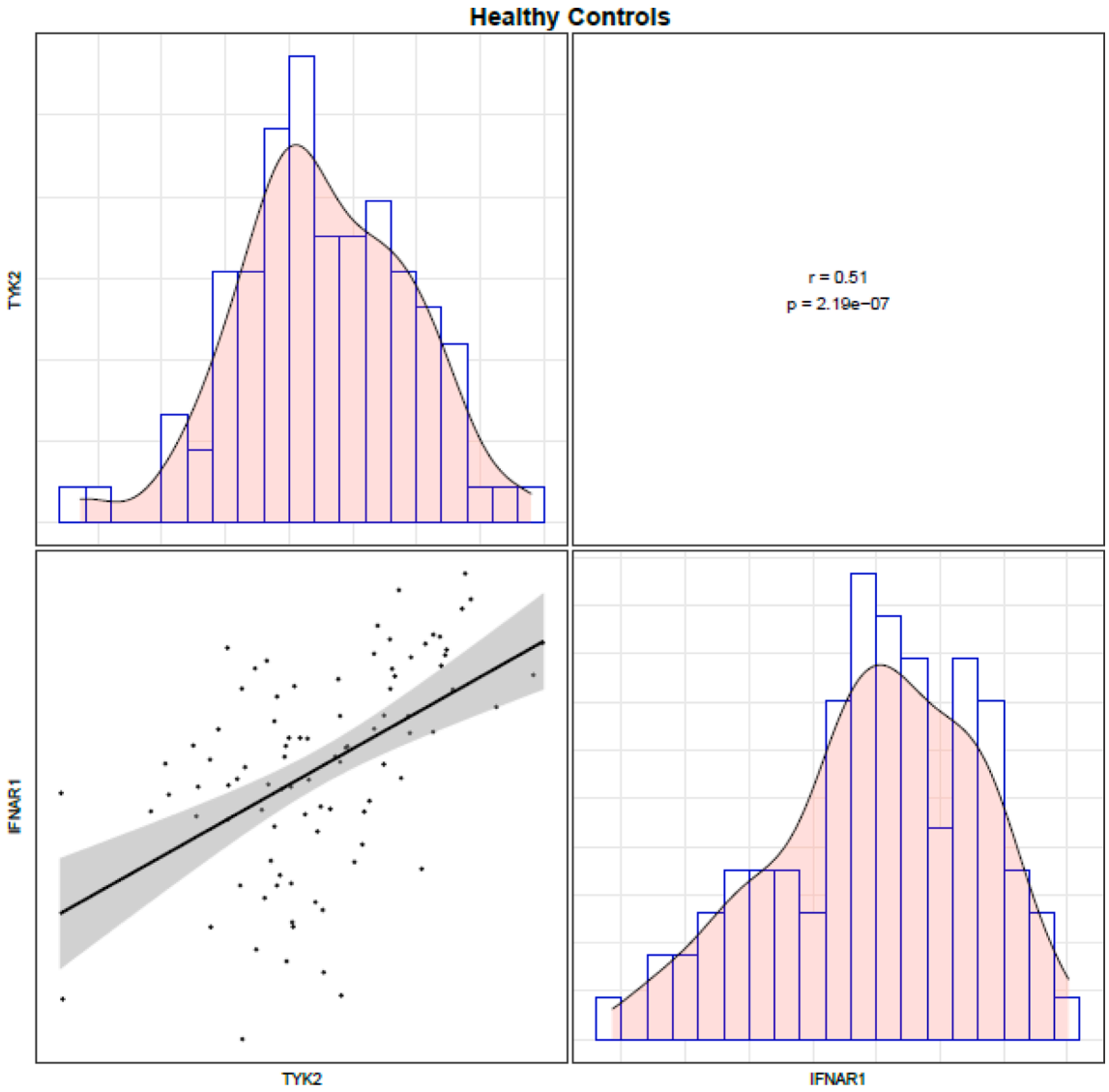

Fig. 4. Correlation between *IFNAR1* and *TYK2* transcripts among healthy controls.

Table 2
Complete parameters of expression of *IFNAR1* and *TYK2* transcripts in COVID-19 patients and controls (RME: Ratios of mean expressions).

Samples		*TYK2*					*IFNAR1*				
		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.

DependentVariables	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-κB-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-1β-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 foe 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 mulativariate analyses. A previous study has demonstrtaed 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 diffrentiate 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

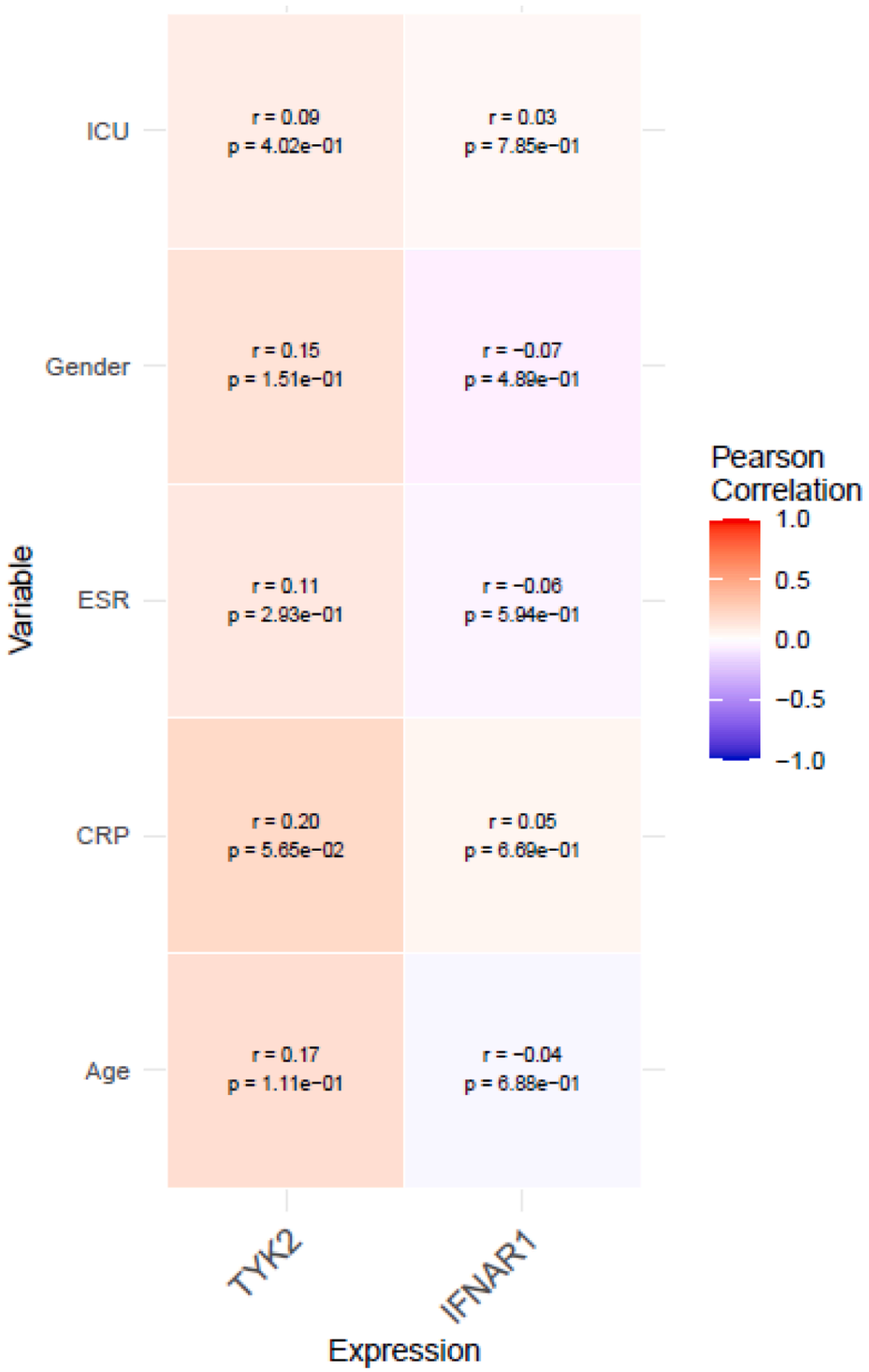

Fig. 5. Correlation between expressions of *IFNAR1* and *TYK2* genes and clinical variables.

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

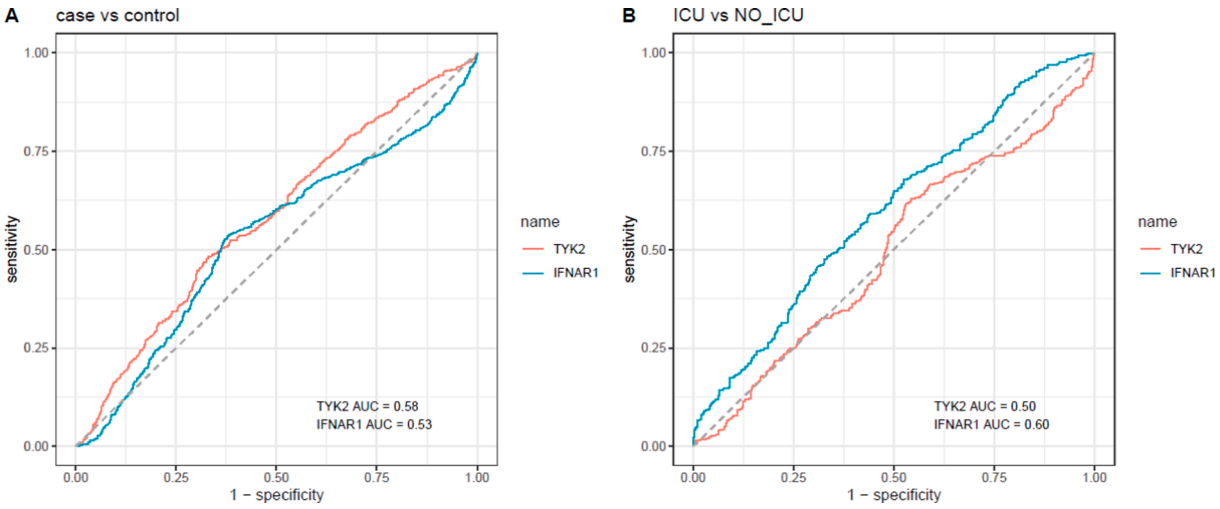

Fig. 6. ROC curves showing the diagnostic power of *IFNAR1* and *TYK2* in separation of COVID-19 cases from normal persons (A) and separation of patients required ICU admission from the other group of patients (B).

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	*TYK2*			*IFNAR1*			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

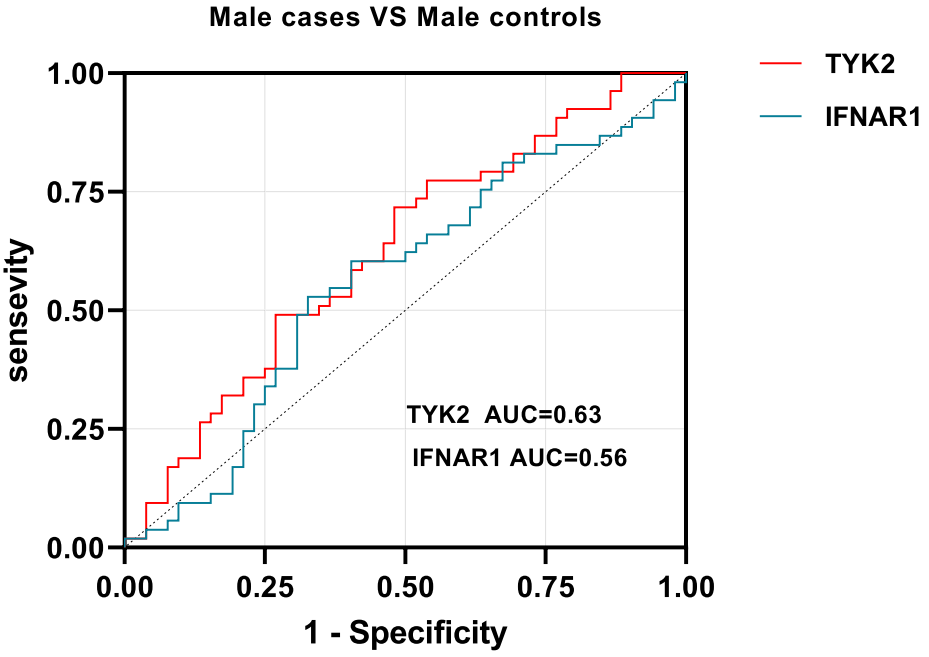

Fig. 7. ROC curves showing the diagnostic power of *IFNAR1* and *TYK2* in separation of male COVID-19 patients from normal male persons.

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.

Funding

This study was financially supported by Shahid Beheshti University of Medical Sciences.

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.

Acknowledgement

Not applicable

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