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CLINICAL STUDY

Evaluation of interferon gamma release assay to measure t-cell response in COVID-19 patients from intensive care units and inpatient departments

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ABSTRACT
BACKGROUND: Interferon gamma release assay (IGRA) is an *in vitro* blood test to measure interferon gamma (IFN-γ) released from antigen-specific T cells after stimulation with pathogen-specific peptides. In this study, it was aimed to investigate the T-cell response using IGRA and to compare various laboratory values in Coronavirus Disease (COVID-19) patients hospitalized either in hospital inpatient departments or in intensive care units.
METHODS: A total of 100 patients (50+50) who were identified as positive for COVID-19 through the molecular method in Selcuk University Faculty of Medicine Infectious Diseases Service and Reanimation Intensive Care Unit were included in the study. IFN-γ levels in blood samples collected from patients were determined using the QuantiFERON Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2) (QIAGEN, Germany) kit. The patients' gender, age, c-reactive protein (CRP), aspartate aminotransferase (AST), alanine transaminase (ALT), interleukin (IL)-6, lymphocyte count, procalcitonin, and D-dimer results were obtained from the hospital automation system.
RESULTS: Thirty-eight of the IGRA test results were negative, 44 were positive and 18 were inconclusive. The age of patients with negative IGRA test results was significantly higher ($p<0.001$) compared to patients with positive results. There were no significant differences between patients' IGRA test results and gender, prognosis, IL-6, lymphocyte counts, CRP, AST, and ALT values.
Age, death rates, D-dimer, CRP, procalcitonin, AST and ALT values of patients hospitalized in the intensive care unit were significantly higher ($p<0.001$) compared to the those hospitalized in the inpatient department, while conversely, the lymphocyte values were lower ($p<0.001$).
CONCLUSION: The relatively higher IGRA negative results in the elderly, negative and intermediate results in intensive-care patients, and low lymphocyte levels in intensive-care patients indicate that the cellular immune response is diminished and/or absent. The death rates, D-dimer, CRP, procalcitonin, AST and ALT values of the patients hospitalized in the intensive care unit were higher compared to those from the in-patient department, indicating the severity of inflammation and signaling the development of organ failure. In the light of these findings, we suggest that IGRA tests may serve as a guide in immunomodulatory therapy *(Tab. 2, Fig. 2, Ref. 27)*. Text in PDF www.elis.sk
KEY WORDS: COVID-19, interferon gamma release assay test, T cell response.

Introduction

The Coronavirus Disease (COVID-19) pandemic, a global phenomenon, stands as the most significant pandemic of the 21st century thus far. Originating in Wuhan, China, in December 2019, its rapid spread and high mortality rate prompted the World Health Organization (WHO) to declare it a pandemic on March 11, 2020. The declaration was prompted not only by the alarming clinical presentation of the disease but also by the swift dissemination and the reporting of cases and fatalities from 120 countries worldwide (1). Turkey reported its first COVID-19 case on March 11, 2020, marking the beginning of a surge in cases and deaths both domestically and globally (2, 3, 4). While the exact reservoir of Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV-2), the cause of COVID-19, remains unknown, current data suggests an animal origin. Given the virus' capability for person-to-person transmission, COVID-19- positive individuals serve as the primary source of the disease (2).

More than 240 million people have been diagnosed with COVID-19 since cases first emerged, of which nearly 5 million

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have died (https://covid19.who.int/). COVID-19 patients present either as symptom-free (asymptomatic course), or manifest a moderate-to-severe disease requiring hospitalization. Severe pneumonia and acute respiratory distress syndrome (ARDS) are much more common in hospitalized patients than in nonhospitalized individuals (5, 6, 7).

While detailed data on the immunology of asymptomatic or mildly symptomatic individuals not requiring hospitalization remains limited, recent studies on the subject have shed light on immune responses among inpatients. These studies revealed that the adaptive immune responses of T cells in SARS-CoV-2 infection align with those observed in other viral respiratory infections (8, 9, 10, 11). Albeit it remains unclear whether the T-cell responses are beneficial, adequate, dysfunctional or excessive. Studies have shown that resistant T-cell responses may occur after seasonal coronavirus infections, including COVID-19 (12).

Studies have shown that most viral infections in humans activate CD4+T and CD8+T cells, inducing their proliferation, a phenomenon also observed inSARS-CoV-2 infection, thereby suggesting that COVID-19 shares relevant aspects with other viral infections. However, some patients may experience suboptimal T-cell activation or differentiation. Several studies have particularly observed an increase in IL-6, CXCL8, CXCL9 and CXCL10 levels in patients with severe course of COVID-19 (Mudd et al, 2020; Laing et al, 2020; Mathew et al, 2020) along with delayed or defective responses. It has been shown that type-1 interferon responses have been implicated in disrupting T-cell responses (13).

The interferon gamma (IFN-γ) release test also known as interferon gamma release assay (IGRA), is an *in vitro* blood test that measures the level of IFN-γ released from antigen-specific T cells after stimulation with specific peptides. In our study, we aimed to determine the T-cell response in COVID-19 patients hospitalized in inpatient departments or intensive care units.

Material and methods

Study groups

A total of 100 patients with COVID-19 PCR-positive test results (50+50) who were hospitalized in inpatient departments or intensive care units of Selcuk University Faculty of Medicine, were included in the study. Inclusion criteria encompass age over 18 years, polymerase chain reaction (PCR) positive for COVID-19, hospitalization in inpatient department or intensive care unit.

A total of 100 patients with COVID-19 PCR-positive test results (50+50) hospitalized in inpatient departments or intensive care units of Selcuk University Faculty of Medicine, were included in the study.

Procedure

In this study, the blood was collected using two types of antigen tubes, SARS-CoV-2 Ag1 and Ag2. Plasma obtained from stimulated samples could be used to detect interferon gamma. Blood from the COVID-19 positive patients was collected in lithium heparin tubes. The IFN-γ Enzyme-Linked ImmunoSorbent Assay (ELISA) was conducted using the QuantiFERON SARSCoV-2 Starter Set Blood Collection Tubes (QIAGEN, Germany) kit according to the manufacturer's instructions. The software program provided by the manufacturer was used to evaluate the results. After completing the ELISA study, the samples were transferred to Eppendorf tubes and stored in a deep freezer at –80°C.

Statistical analysis

All statistical analyzes were conducted using R version 3.6.0 (The R Foundation for Statistical Computing, Vienna, Austria; https://www.r-project.org). Prior to the analysis, the normality of the data was checked through Shapiro–Wilk's normality test and Q-Q charts, and the homogeneity of the group variances was checked utilizing the Levene homogeneity of variances test.

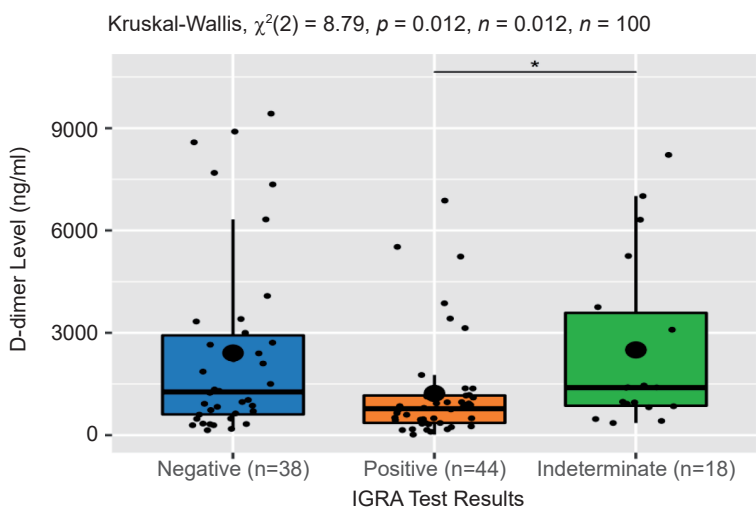

Fig. 1. Box-plot comparison of D-dimer levels according to IGRA test results.

Results

A total of 100 COVID-19-positive patients were included in the study, comprising 50 from inpatient departments and 50 from intensive care units. Their ages ranged from 19 to 89 years (54.13±20.73), with 51 being male (51%) and 49 female (49%). According to the IGRA test result, 38 (38%) of the patients were tested negative for COVID-19 infection (38%), 44 tested positive (44%) while 18 (18%) had indeterminate results.

The distribution of demographic characteristics and laboratory findings of the patients across the IGRA test results are presented in (Table 1). Patients with negative IGRA test results were significantly older than those with positive results (66 [24–88] vs 45 [19–86]; Bonferroni-adjusted p-value<0.001), while the age difference between those with nega-

Tab. 1. Comparison of demographic characteristics and laboratory findings of patients.

	IGRA Test Results			
	Negative (n=38)	Positive (n=44)	Indeterminate (n=18)	p
Demographic Properties				
Age (Year)	66 (24–88)[a]	45 (19–86)[b]	55.5 (21–89)	.001[1]
Gender (Male/Female)	20 (52.6)/18 (47.4)	23 (52.3)/21 (47.7)	8 (44.4)/10 (55.6)	.828[2]
Hospitalization Unit (Inpatient Clinics /ICU)	15 (39.5)/23 (60.5)	28 (63.6)/16 (36.4)	7 (38.9)/11 (61.1)	.054[2]
Prognosis (Discharged/Ex)	21 (55.3)/17 (44.7)	31 (70.5)/13 (29.5)	11 (61.1)/7 (38.9)	.358[2]
Laboratory Results				
D-dimer (ng/ml)	1270 (609.5–2926.5)	779 (358.75–1164.75)[a]	1394 (864.75–3587)[b]	.012[1]
IL-6 (pg/ml)	19.65 (8.32–28.40)	14.75 (7.21–30.30)	17.65 (7.27–40.47)	.805[1]
Lymphocyte (k/UI)	0.95 (0.50–1.58)	1.15 (0.60–2.20)	0.80 (0.50–1.28)	.389[1]
CRP (mg/L)	64.25 (22.33–108.50)	56.30 (17.57–98.68)	88.65 (45.35–171.75)	.239[1]
Procalcitonin (ug/L)	0.15 (0.08–0.56)	0.10 (0.05–0.21)[a]	0.28 (0.11–0.79)[b]	.032[1]
AST (U/L)	47.5 (33.5–77.5)	42 (27–63.25)	69 (27–108.5)	.536[1]
ALT (U/L)	45 (27.25–60)	40 (20–61.25)	49.5 (29.75–99)	.337[1]

Data were presented as median (minimum–maximum) for age, median (IQR) for other numerical parameters, and frequency (n) and percentile (%) for categorical variables. Different letters in each line show significant differences between groups as a result of pairwise comparisons. A p<0.05 value was used for statistical significance. [1]Kruskal–Wallis Test, [2]Pearson's Chi-Square test, [3]Fisher–Freeman–Halton test

tive or indeterminate IGRA test results (Bonferroni-adjusted p-value=.130) and those with positive or indeterminate IGRA test results was insignificant (Bonferroni-adjusted p-value>0.999). The gender distribution (p=0.828) and prognosis distribution (p=0.358) across the IGRA test results were similar (Tab. 1). The differences between values of laboratory results for interleukin (IL)-6 (p=0.805), lymphocyte (p=0.389), c-reactive protein (CRP) (p=0.239), aspartate aminotransferase (AST) (p=0.536) and alanine transaminase (ALT) (p=0.337) across IGRA test results were not statistically significant.

On the other hand, the D-dimer levels in those with indeterminate IGRA test results were significantly higher compared to those with conclusively positive results (1394 [IQR, 864.75–3587] vs 779 [358.75–1164.75], Bonferroni-adjusted p-value=.033), while a significant difference in D-dimer levels was observed between those with positive and negative test results (Bonferroni-adjusted p=0.056), as well as between those with indeterminate and negative test results (Bonferroni-adjusted p>0.999) (Fig. 1).

The distribution of demographic characteristics and laboratory findings of the patients across the hospitalization regimen types are presented in Table 2. Age, mortality rates, D-dimer, CRP, procalcitonin, AST and ALT values of the patients hospitalized in the intensive care unit were significantly higher compared to those from inpatient departments. Conversely, lymphocyte levels were significantly lower. The distributions of gender and IL-6 levels across hospitalization regimen types were similar.

Similarly, while the procalcitonin levels of those with indeterminate IGRA test results was significantly higher compared to those with positive test results (0.28 [IQR, 0.11–0.79] vs 0.10 [0.05–0.21], Bonferroni-adjusted p=0.044) there was no significant difference between procalcitonin levels between those with positive and negative test results (Bonferroni-adjusted p-value=.159), nor between those with indeterminate and negative test results (Bonferroni-adjusted p>0.999) (Fig. 2).

Discussion

No specific COVID-19 antiviral therapy has been proven effective worldwide so far, and the treatment of COVID-19 is primarily based on palliative management of comorbidities. Despite the beneficial effect of the palliative protection during the course of the disease, especially in the early stages, the treatment of COVID-19 requires a detailed understanding of immune responses, especially an in-depth comprehension of T cell responses implicated in fatal comorbidities.

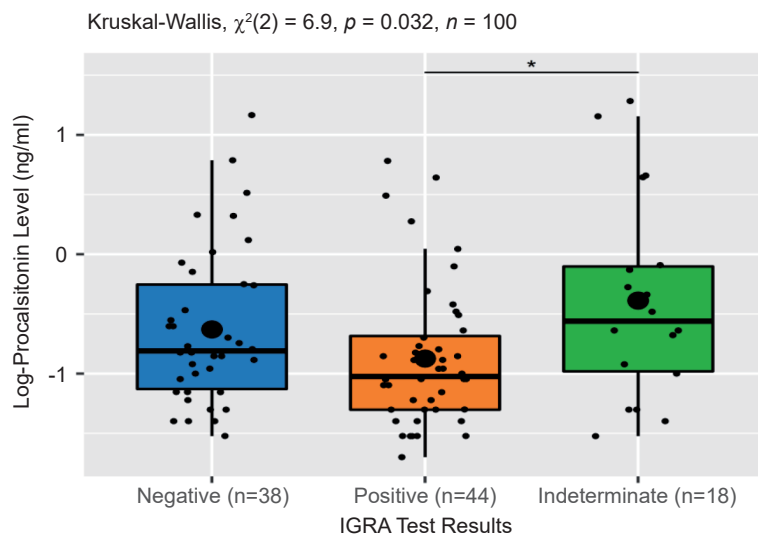

Fig. 2. Box-plot comparison of procalcitonin (natural logarithm) levels across IGRA test results.

Tab. 2. Comparison of demographic characteristics and laboratory findings of patients according to hospitalization unit.

	Hospitalization regimen types		p
	Inpatient departments (n=50)	Intensive care unit (n=50)	
Demographic properties			
Age (year)	35.5 (19–85)	66 (21–89)	<0.001[1]
Gender (male/female)	25 (50)/25(50)	26 (52)/24 (48)	.841[2]
Prognosis (discharged/ex)	45 (90)/5 (10)	18 (36)/32 (64)	<0.001[3]
Laboratory results			
D-dimer (ng/ml)	503 (341.5–966.25)	1400 (923–3997.25)	<0.001[1]
IL-6 (pg/ml)	17.40 (7.23–34.35)	16.45 (8.10–28.40)	.945[1]
Lymphocytes (k/UI)	1.40 (1.02–2.60)	0.50 (0.40–0.90)	<0.001[1]
CRP (mg/L)	47.35 (21.73–75.88)	98.95 (32.95–174.25)	<0.001[1]
Procalcitonin (ug/L)	0.08 (0.05–0.17)	0.24 (0.13–1.09)	<0.001[1]
AST (u/l)	33 (25.25–47.5)	63.5 (47–101.75)	<0.001[1]
ALT (u/l)	29 (19.25–42.75)	54 (40.25–79)	<0.001[1]

Data were presented as median (minimum–maximum) for age, median (IQR) for other numerical parameters, and frequency (n) and percentile (%) for categorical variables. Different letters in each line show significant differences between groups as a result of pairwise comparisons. A $p<0.05$ value was used for statistical significance. [1]Mann–Whitney U test, [2]Pearson chi-square test, [3] Chi-square test with Yates continuity correction

In total, 100 individuals comprising 51 males and 49 females aged between 19 and 89 years were included in the study. The difference between the mean age of the COVID-19 patients hospitalized in the intensive care unit (63.54±18.90 years) and those from inpatient departments (44.72±18.17 years) was significant ($p<0.001$). Studies show that age is a factor directly proportional to the rate of hospitalization in an intensive care unit (14, 15).

In the study by Torre et al (2020), more than one-third (122/335; 36.4%) of patients had indeterminate IGRA results due to inadequate immune response to mitogen control, with 19 individuals testing positive (5.7%) and 194 testing negative (57.9%) (16). In our study, 38 of the patients were tested negative for COVID-19 infection (38%), 44 tested positive (44%) while 18 had indeterminate results (18%). In their study, Ward et al (2021) reported no significant difference in the distribution of IGRA test results between COVID-19 patients treated in the intensive care unit and those from inpatient departments (17). Our study yielded similar findings, however, the numbers of cases with negative or indeterminate results were relatively higher in patients treated in intensive care units compared to those from inpatient departments.

In another study, Imeneo et al (2022) evaluated the results of IGRA using Quantiferon-TB Gold Plus in patients experiencing a severe course of COVID-19 and found that indeterminate results were more common in patients with severe symptoms of the disease. They attributed this phenomenon to an insufficient interferon release upon phytohemagglutinin stimulation (18).

The distributions of gender (p=0.828) and prognosis (p=0.358) across the hospitalization regimen type were found to be similar. In the studies performed by Chen et al (2020) and Ward et al (2021), the authors revealed no significant impact of gender on test results (17).

Solanich et al (2021) reported no significant differences in serum ferritin, CRP, IL-6 and troponin levels across IGRA test results. Similarly, Ward et al (2021) reported no significant differences in CRP, LDH and total bilirubin levels between surviving patients and deceased COVID-19 patients (19). Elevated CRP levels seem to be unique to COVID-19 patients when compared to other viral infections. In addition, consistent elevations in procalcitonin (PCT) and IL-6 levels, as well as serum urea, creatinine, direct bilirubin, cholinesterase, and cystatin C were detected in those who deceased (20). The differences in our laboratory findings of IL-6 (p=0.805), lymphocyte count (p=0.389), CRP (p=0.239), AST (p=0.536) and ALT (p=0.337) across the IGRA test results,) were not statistically significant.

Solanich et al (2021) reported that the D-dimer level in COVID-19 patients with indeterminate IGRA results was significantly higher than in COVID-19 patients with conclusive IGRA test results (19). In our study, the D-dimer levels in the patients with indeterminate IGRA test results were found to be significantly higher than in those with positive IGRA test results, while no significant difference was found between those with positive and negative test results, nor between those with indeterminate and negative test results.

The study by Liu et al (2020) reported that the procalcitonin level in patients with severe COVID-19 was significantly higher compared to patients with a moderately severe course of COVID-19. Similarly, in our study, the patients with indeterminate IGRA test results had significantly higher procalcitonin levels than those with positive IGRA test results, while no difference was found in procalcitonin levels between those with positive and negative test results, nor between those with indeterminate and negative test results (21).

Our study concluded that the mortality rate in patients treated in the intensive care unit was significantly higher compared to those treated in inpatient departments. The morbidity and mortality rates associated with COVID-19 have been linked to a pathological host response, with two different hypotheses proposed for this condition. The first one is based on the hyperinflammatory cytokine storm, and the other implicates a failure of the host immunity resulting in uncontrolled viral spread and organ damage (22).

Remy et al (2020) determined that the 30-day mortality rate in COVID-19 patients was higher than in patients with sepsis, however, the difference between the groups was not statistically significant. Deaths occurred 2 weeks after the onset of symptoms and at least 6 days post admission to the intensive care unit (22). Other relevant studies observed an increased mortality rate among those treated in the intensive care units (23, 24).

Lu and Wang (2020) reported elevated levels of CRP, AST, ALT, and D-dimer values in COVID-19 patients, with the elevation levels being directly proportional to the severity of the disease (25) Our analysis of the distribution of demographic characteristics and laboratory findings of the patients across hospitalization regimen types revealed that age, mortality rates, and levels of

D-dimer, CRP, procalcitonin, AST and ALT values of the patients hospitalized in the intensive care unit were significantly higher compared to those from inpatient departments. The distributions of gender and IL-6 levels across hospitalization regimen types were similar.

Mukherjee and Pahan (2021) reported that although men and women share a similar clinical picture, men experience a more severe course of the disease compared to women (26). Another study conducted by Echeverría et al (2021) posits that T cell response was positive in 77% of critically ill patients with COVID-19, 100% of asymptomatic patients, and 47% of healthy individuals (27). In the study by Torre et al (2020), more than a third (36.4%) of patients yielded an inconclusive IGRA result due to inadequate immune response to mitogen control, with 19 testing positive (5.7%) and 194 testing negative (57.9%) (16). The same study reported that most patients with lymphocytopenia had indeterminate IGRA results (52.3%). Liu et al (2020) have shown that the rate is even higher in patients with severe lymphocytopenia (63%), while lymphopenia, elevated liver enzymes, elevated lactate dehydrogenase, elevated D-dimer levels in inflammatory markers (CRP, ferritin, etc.), and acute kidney injury were identified as markers of poor prognosis (21). In this study, lower lymphocyte counts (lymphopenia) were found in intensive-care patients compared to those hospitalized in inpatient departments. This shows that the cellular immune response is diminished and/or absent in intensive care patients ($p<0.001$).

In conclusion, the mortality rates, D-dimer, CRP, procalcitonin, AST and ALT values of the patients hospitalized in the intensive care unit are higher compared to patients hospitalized in inpatient departments, indicating that they have the potential of serving as markers of the severity of inflammation and signaling the development of organ failure. Hyperinflammatory cytokine storm and the host's immune response disorder/collapse in COVID-19 patients are shown to be implicated in morbidity and mortality. In the light of these findings, we suggest that IGRA tests can serve as a guide in immunomodulatory treatment.

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