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Author contributions:

Aydın Guclu O contributed to the conception and design of the study. Aydın Guclu O, Sezen Goktas S, Erol HA, Karacay ND and Kaya Sel U contributed to the assembly, analysis, and interpretation of data. Aydın Guclu O and Gorek Dilektasli A performed the statistical analysis. Acet Ozturk NA, Demirdogen E, Coskun F, Ediger D, Ursavas A, Uzaslan E and Karadag M participated in the drafting of the article.

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Abstract:

Background: Laboratory biomarkers to estimate the severity of COVID-19 are crucial during the pandemic, since resource allocation must be carefully planned.

Aim: In the present study, we aim to evaluate the effects of basal serum total immunoglobulin E (IgE) levels and changes in inflammatory parameters on the clinical progression of patients hospitalized with COVID-19.

Methods: Patients hospitalized with confirmed COVID-19 were included in the study. Laboratory data and total IgE levels were measured upon admission. Lymphocyte, eosinophil, ferritin, d-dimer and CRP parameters were recorded on the baseline and on the 3rd and 14th days of hospitalization.

Results: The study enrolled 202 patients, of which 102(50.5%) were males. The average age was 50.17 ± 19.68. Of the COVID-19 patients, 41 (20.3%) showed clinical progression. Serum total IgE concentrations were markedly higher (172.90 [0-2124] vs 38.70 [0-912], $p<0.001$) and serum eosinophil levels were significantly lower (0.015 [0-1.200] vs 0.040 [0-1.360], $p=0.002$) in clinically worsened COVID-19 patients when compared to stable patients. The optimal cut-off for predicting clinical worsening was 105.2 ng/L; with 61% sensitivity, 82% specificity, 46.3% positive predictive value and 89.2% negative predictive value (area under the curve=0.729). Multivariable analysis to define risk factors for disease progression identified higher total IgE and CRP levels as independent predictors.

Conclusions: Our single-center pilot study determined that total IgE levels may be a negative prognostic factor for clinical progression in patients hospitalized due to COVID-19 infection. Future studies are required to determine the impact of individuals' underlying immune predispositions on outcomes of COVID-19 infections.

Keywords: COVID-19; total IgE; eosinophil; clinical progression; pilot study

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Introduction:

Coronavirus disease 2019 (COVID-19) caused by SARS-CoV-2, first reported in Wuhan, China, quickly spread to other countries and led to the current pandemic worldwide (1). The first case in Turkey was detected on March 11, 2020 (2). While most patients with COVID-19 have a mild, flu-like illness or may be asymptomatic, a small percentage develops severe pneumonia, acute respiratory distress syndrome (ARDS), multiple organ failure, and may even die (1). Although the reason why some individuals become critically ill while others do not is still unresolved, comorbidities and laboratory markers are recommended for risk stratification (3, 4). Evidence of hyperinflammatory features of elevated serum C-reactive protein (CRP), procalcitonin (PCT), D-dimer, and hyperferritinemia has been reported in critically ill patients. These findings suggest that a cytokine storm likely plays a critical role in the pathophysiology of COVID-19 (4).

Allergic people with eosinophilia have been reported to be less affected by COVID-19 (5). In contrast, eosinopenia was frequently reported in patients who had died from COVID-19 and is considered a predictor of disease progression. (6). Eosinophils are known to be involved in the immune response that enables cytokine secretion and the recruitment of CD8 + T cells during respiratory virus infections. Besides, eosinophil-derived enzymes can also neutralize the virus (7). Using mouse models, it has been shown that eosinophils in the lungs of mice with allergic asthma are activated by the influenza virus, increasing piecemeal degranulation and upregulating APC markers. Eosinophils were able to migrate to draining lymph nodes and present viral antigens to CD8+ T cells, resulting in the activation and proliferation of these cells (8). Decreased eosinophil count is associated with CD8 + T cell depletion and eosinopenia has

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been associated with excessive consumption of eosinophils due to high viral load (6). Severe systemic stress and/or excessive microbial inoculation causes immune system to shift to type 2 response to an infection normally controlled by type 1 immunity. Th2 cells secrete IL-4, IL-5, IL-9, IL-10 and IL-13. These cytokines are responsible for B cell proliferation, antibody production, IgE class-switching, mast cell stimulation and mast cell degranulation. Type-2 inflammation is characterized with tissue infiltration by eosinophils and basophil, extensive mast cell degranulation (9). Mast cell activation has been reported to have a negative effect on the pathogenesis and disease progression of COVID-19 (10). Considering the important role of IgE in severe viral infections, examining IgE's role in COVID-19 is of great importance.

Laboratory biomarkers that predict the severity of COVID-19 are crucial during the pandemic for careful planning of resource allocation, which is essential, especially in terms of readiness for respiratory support. The purpose of this study is to ascertain whether basal serum total IgE levels and the changes in eosinophil, lymphocyte, ferritin, CRP and d-dimer levels are associated with increased likelihood of clinical progression, in patients hospitalized with COVID-19.

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Materials and Methods:

Study design and participants:

Every patient that tested positive for and hospitalized with COVID-19, between March 18 and August 04 of 2020, at the Boyabat 75th Year State Hospital in Sinop, Turkey, were enrolled in this observational study. Patients hospitalized with COVID-19, confirmed by a positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test, were included in the study, while those with atopic dermatitis (n=2), urticaria (n=1), and allergic contact dermatitis (n=1) were excluded. Type I hypersensitivity, also known as an immediate reaction, results in the immunoglobulin E (IgE)-mediated release of antibodies to the soluble antigen, followed by mast cell degranulation and release of heparin, histamine, and other inflammatory mediators. Because we could not differentiate between type-1 hypersensitivity reaction and the shift to type-2 response, we excluded patients with known allergies.

Written informed consent was obtained from every participant before their inclusion in the study, which was approved by the Local Ethical Committee (Approval No: OMU KAEK 2020/543) and the Ministry of Health Ethical Committee and conducted in accordance with the principles of the Helsinki Declaration.

Data collection:

Data consisting of demographic information, clinical presentation, comorbidities, chest computed tomography (CT) images, laboratory results, treatments and results were obtained from the hospital's electronic medical records system. Lymphocyte, eosinophil, ferritin, d-dimer, and CRP parameters were recorded on the 3rd and 14th days of hospitalization. Days from

symptoms onset to hospitalization, duration of hospitalization, days from hospitalization to death were also calculated. Secondary infection rates of patients receiving tocilizumab were recorded while they were in the hospital.

Total Immunoglobulin E Measurements:

Approximately 5 mL of peripheral venous blood was collected by venipuncture from study participants at admission to the hospital. Blood samples were centrifuged at 3000 × g for 15-20 min. Obtained serum samples were stored at -80°C until analyzed. Examination of total IgE was quantitatively conducted in vitro, using ADVIA Centaur instruments (Siemens, ADVIA Centaur XP system). The reference standard value for serum total IgE is 0 – 378 IU/mL.

Definitions:

COVID-19 is defined as SARS-CoV-2-induced coronavirus disease. Possible COVID-19 cases were diagnosed according to the Turkish Ministry of Health's national guidelines. Upon admission nasopharyngeal swabs were collected, to be tested by real-time reverse transcriptase-polymerase chain reaction (RT-PCR). The gold standard for diagnosis of COVID-19 is a positive RT-PCR test for SARS-CoV-2. Admission chest x-rays were reviewed, and chest CT patterns and distributions typical of COVID-19 infection were carefully defined according to the expert consensus statement of the Radiological Society of North America (RSNA) (11), which proposes four categories for standardized COVID-19 reporting. These categories include "typical appearance", "indeterminate appearance", "atypical appearance" and "negative for pneumonia". In our study, chest CT of each suspected COVID-19 patient was evaluated by a chest radiologist and an experienced pulmonologist.

The primary outcome was clinical worsening, defined by an ordinal clinical improvement scale. Scores on the scale were defined as follows: (1) = discharged or ready for discharge; (2) = in (or ready for) a non-ICU hospital ward and not receiving supplemental oxygen; (3) = in (or ready for) a non- ICU hospital ward and receiving supplemental oxygen; (4) = in the ICU or a

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non-ICU hospital ward and receiving non-invasive ventilation or high-flow oxygen; (5) = in the ICU, intubated and receiving mechanical ventilation; (6) = in the ICU and receiving extracorporeal membrane oxygenation or mechanical ventilation, and additional organ support; and (7) = death. Worsening was defined as an increase of the score, by at least 1 point for patients receiving supplemental oxygen at baseline, and by at least 2 points for those not receiving supplemental oxygen at baseline (12).

Hospital care and treatment of patients:

From hospital admissions to treatment protocols, all clinical decisions adhered to the national guidelines published by the Turkish Ministry of Health (2). Patients with clinical worsening and hypoxemia received favipiravir (1600 mg twice daily as a loading dose, followed by 600 mg twice daily as a maintenance dose). Given the influenza season, patients were administered oseltamivir (75 mg twice daily) and empirical antibiotics were also applied as initial therapy against the possibility of a bacterial etiology.

Statistical analysis:

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 22.0 software program (IBM Corp., Armonk, NY, USA). Variables were investigated using the Kolmogorov-Smirnov/Shapiro-Wilk's test to determine distribution. Continuous data are presented as the mean ± standard deviation if normally distributed or median (min-max) if non-normally distributed. Categorical characteristics are presented as numbers (%). When comparing continuous outcome variables between groups, two-sample t-test was used for normally distributed and Mann–Whitney U-test was used for non-normally distributed data. Categorical variables were compared with the Pearson Chi-square test. Friedman tests were employed to identify if in the lymphocyte, eosinophil, ferritin, d-dimer and CRP variables a significant change was observed due to incorrect parametric test assumptions (non-normal distribution). The Wilcoxon test was performed to assess the significance of pairwise

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differences, using Bonferroni correction to adjust for multiple comparisons. Receiver-operating-characteristics (ROC) analysis was performed using MedCalc software (version 20.026; MedCalc). The ability of serum total IgE level to distinguish COVID-19 stable patients from patients with clinical worsening was evaluated by using ROC curve analysis. For this purpose, the Youden index was used to maximize the sum of sensitivity and specificity. Optimal cut-off maximizing sensitivity and specificity was selected. Possible risk factors were evaluated by logistic regression analysis to determine independent predictors of patient clinical outcome. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. An overall %5 type-1 error level was used to infer statistical significance.

Results:

The study enrolled 202 patients, of which 102 (50.5%) were male. Ranging from 18 to 87 years old, patients' mean age was 50.17 ± 19.68. Most common comorbid diseases among the participants were hypertension (n=61), diabetes mellitus (n=33), cardiovascular disease (n=21), chronic obstructive pulmonary disease (COPD) (n=15) and asthma (n=10). Median length of hospital stay was 10 [0-57] days and the median virus clearance time was 11 [3-50] days. Chest CT scans of the cases were evaluated as 35.6% typical, 19.8% indeterminate, 9.9% atypical, and 34.7% negative. Among the COVID-19 patients, 41 (20.3%) showed clinical progression. Clinical worsening was observed on day 7 [4-10]. During follow up 20.3% (n=41) of the patients needed supplemental oxygen, 3.5% (n=7) required intensive care, 3% (n=6) were intubated, 2% (n=4) died. The median time from admission to death was 13.5 [10-28] days.

Patients with clinical worsening had lower lymphocyte counts (1.190 [0.420-3.510] vs 1.600 [0.320-10.400], p=0.002) and higher levels of d-dimer (0.63 [0.19-6.09] vs 0.38 [0.17-10.90], p<0.001), AST (34 [15-104] vs 25.5 [12-155], p=0.014), creatinine (1 [0.63-2.40] vs 0.78 [0.43-7.62], p<0.001), ferritin (191.30 [17-1650] vs 79.60 [3.20-1180], p<0.001), and CRP (36.30 [0.20-345] vs 4.60 [0.20-192.50], p<0.001). When compared to stable patients, clinically

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worsened COVID-19 patients had markedly higher serum total IgE concentrations (172.90 [0-2124] vs 38.70 [0-912], p<0.001) (Fig 1) and significantly lower serum eosinophil levels (0.015 [0-1.200] vs 0.040 [0-1.360], p=0.002). Comparisons of the demographic, clinical, radiological and laboratory features of COVID-19 patients between the stable and clinically worsening groups are summarized in Table-1. No correlation was found between age and total IgE levels (r=-0.031, p=0.666).

ROC curve analysis was employed to evaluate the performance of total IgE as a predictor of clinical worsening. The optimal cut-off for prediction of clinical worsening was 105.2 ng/L with a 61% sensitivity, 82% specificity, 46.3% positive predictive value (PPV), and 89.2% negative predictive value (NPV) (area under the curve=0.729) (Fig.2a). A separate ROC curve analysis was performed to evaluate the diagnostic value of lymphocyte, eosinophil, d-dimer, ferritin, and CRP levels in distinguishing deteriorating patients from patients who did not show disease progression (Fig.2b).

There were statistically significant differences in lymphocyte, eosinophil, ferritin, d-dimer and CRP levels at baseline, and on the 3rd and 14th days. Post-hoc analysis with Wilcoxon signed-rank tests was conducted with a Bonferroni correction applied, resulting in a significance level set at $p < 0.017$. The course of parameters on the baseline, and on the third and 14th days of hospitalization and the post-hoc analysis results are summarized in Table-2.

Multivariable analysis to define risk factors for disease progression identified higher total IgE and CRP levels as independent predictors. Odds ratio for serum total IgE concentrations ≥ 105.2 pg/mL was 9.893 (95% CI: 3.907-25.049, p<0.001) and odds ratio for being COPD was 5.887 (95% CI: 1.345-25.762, p=0.019) (Table-3).

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Discussion:

The goal of this study was to ascertain whether basal serum total IgE levels and changes in eosinophil, lymphocyte, ferritin, CRP and d-dimer levels are associated with increased likelihood of clinical progression in patients hospitalized with COVID-19. During the ongoing worldwide pandemic, in aiding clinical decision-making, laboratory medicine has turned its focus mainly to predicting prognosis and accelerating risk stratification.

In our study population, 41 (20.3%) patients showed clinical progression. During follow up, 3.5% (n=7) of the patients required intensive care, 3% (n=6) were intubated, and 2% (n=4) died. Despite sharing similar demographic features with earlier studies of COVID-19, the mortality rate in our study was lower than previously reported (1, 13-15). A possible explanation for the conflicting findings of our study might be the changes made to the criteria for hospital admissions, since the beginning of the pandemic.

We have found serum total IgE concentrations to be markedly higher and serum eosinophil levels to be significantly lower in clinically worsened COVID-19 patients, when compared to stable patients. Even though it was predominantly the elderly patients among our study population that exhibited clinical worsening, age was not considered as a possible confounder

since no significant correlation was found between IgE levels and age. Our study has found that to predict clinical progression during COVID-19 infection, a cut-off value of 105.2 ng/L for total IgE had 61% sensitivity, 82% specificity, 46.3% positive predictive value (PPV) and 89.2% negative predictive value (NPV). Lucas et al. have also found that patients with severe disease had higher levels of type 2 antibody isotype IgE, which continued to increase during the course of the disease (16).

Chronic allergic disease is associated with the tissue remodeling process and persistent inflammation can weaken patient's immune system, inducing susceptibility to infection (17). Type 2 inflammatory cytokines, such as IL-13, mediate host cell entry of SARS-CoV-2 in asthma and atopic airway cells by inducing the expression of angiotensin-converting enzyme 2 (ACE2) to decrease and the expression of transmembrane serine protease 2 (TMPRSS2) expression to increase significantly (18). In individuals with allergies, the secretion of innate interferons such as Type 1 and Type 3 in mononuclear cells and airway epithelial cells is impaired, resulting in increased susceptibility to viral infections (19).

The relationship between allergic disease and serious clinical outcomes in COVID-19 has not been demonstrated and is controversial (13, 20). In a study conducted in Wuhan (21), a relationship was found between an history of allergy and COVID-19 risk, while another study reported that asthma is associated with COVID-19 (22). In a cohort study, presence of asthma and allergic rhinitis were found to be associated with increased SARS-CoV-2 test positivity and poor clinical outcomes; it was also determined that there was a higher risk of COVID-19 positivity and worse clinical outcomes in non-allergic asthma cases (23).

Multivariable analysis to define risk factors for disease progression identified having COPD and higher total IgE and CRP levels as independent predictors. A meta-analysis showed that pre-existing COPD is likely to worsen the progression and prognosis of COVID-19 (24).

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Respiratory viruses trigger local inflammatory cascades that enter the upper and lower respiratory tract bronchial epithelium and cause disruption of the bronchial defense system. The virus activates the T helper 2 pathway by inducing cytokines such as IL-25 and IL-33 in epithelial cells and causes eosinophilia, an increase in proinflammatory cytokines such as IL-4, IL-5, IL-13, and an increase in the amount of mucin (25). It was reported that IgE levels were related to the antiviral response in human RSV, with asthmatic subjects displaying higher levels than non-asthmatics (26). It has been shown that specific IgE can be produced against respiratory viruses such as RSV, and that these virus specific IgE play an essential role in increasing Th2 inflammation in the lungs and causing excessive responsiveness in the airways (25). Antiviral IgE can induce an incompatible immune response against respiratory viruses, which bypasses the classic viral immune protective responses with a possible incitement of widespread viral infection in the airways (25, 27). Conversely, it has been proven that certain viral infections can automatically induce the activation of immunological mechanisms and morphological changes such as tissue remodeling, which may contribute to the initiation or exacerbation of atopic diseases. (28, 29). It is thought that SARS-CoV-2 itself could potentially aggravate allergies and facilitate viral infections, leading to the more devastating consequences of COVID-19 (23).

By evaluating the laboratory values of clinically worsened patients, measured at the beginning and then at the 3rd and the 14th days, it was observed that lymphocyte and eosinophil levels increased during the follow-up, and that both ferritin and CRP levels increased on the 3rd day, with the latter decreasing on the 14th, compared to the baseline. Eosinophils are powerful proinflammatory cells and function as regulatory cells involved in protective immunity, including antiviral responses (30). In a cohort of asthma patients with COVID-19, it was found that eosinophilia was a protective factor for hospital admission and mortality (5). Eosinophilia has also been reported to be associated with a reduced risk of mortality in COVID-19 infection,

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in both asthmatic and non-asthmatic cases (31). In our study, no statistically significant increase in clinical progression was found in asthma cases. There was no significant difference in the follow-up levels of clinically worsened patients in terms of d-dimer change. Patients with clinical worsening had lower lymphocyte count and higher d-dimer, AST, creatinine, ferritin, and CRP levels. A meta-analysis showed that elevated serum CRP, d-dimer, and ferritin could be used as laboratory biomarkers for a poor outcome in COVID-19 (13).

The prediction based on CRP with ROC AUC equal to 0.780 proved to be the most accurate. Previous studies that attempted to predict mortality in sepsis by the presence of an elevated serum CRP were inconsistent. These inconsistencies might be caused by the different cut-off values used. Despite its value in predicting a poor outcome in COVID-19, it should be noted that various factors could affect serum CRP levels, including age, gender, smoking status, weight, lipid levels, blood pressure, and liver injury (32).

With regards to the findings of this study certain limitations should be given consideration: Firstly, total IgE levels have not been followed up during the disease. Secondly, since a notable number of non-serious patients were hospitalized due to their advanced age or concomitant comorbidities at the onset of the pandemic, our study may likely represent less severe COVID-19 patients. Should that be the case, the low positive predictive power of IgE could be a consequence as it affected the prevalence of clinically worsened patients. Another limitation of our study is that patients were not evaluated for bacterial, fungal or other viral etiologies. Lastly, this is a retrospective study that is potentially vulnerable to uncontrolled confounders that we did not identify.

Conclusion:

Our single-center pilot study determined that total IgE levels may be a negative prognostic factor for clinical progression patients in hospitalized with COVID-19 infection. Future studies

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are required to determine the impact of individuals' underlying immune predisposition on outcomes of COVID-19 infection.

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Tables and figures:

Table-1. Comparisons of the demographic, clinical, radiological and laboratory features of COVID-19 patients between stable and clinically worsening groups

Table-2. Comparison of the course of biochemical parameters between stable and clinically worsening groups

Table-3. Results of binary logistic regression analysis of potential predictors of COVID-19 pneumonia with clinical worsening

Fig.1. Comparison of the total IgE levels in stable and clinically worsening groups

Fig.2. ROC curves of total IgE (2a), and comparison of total IgE, eosinophil, lymphocyte, ferritin, d-dimer and CRP levels to predict clinical worsening (2b)

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Tables:

Table-1. Comparisons of the demographic, clinical, radiological and laboratory features of COVID-19 patients between stable and clinically worsening groups

Characteristic	Overall patients (n=202)	Stable Patiens (n=161)	Patients with Clinical Worsening (n=41)	p-value
Age, years	50.17 ± 19.68	47.25 ± 19.45	61.66 ± 16.26	<0.001
Male sex, n (%)	102 (50.5%)	73 (45.3%)	27 (65.9%)	0.019
Comorbidities, n (%)	83 (41.1%)	55 (34.2%)	28 (68.3%)	<0.001
Hypertension	61 (30.2%)	38 (23.6%)	23 (56.1%)	<0.001
Diabetes mellitus	33 (16.3%)	19 (11.8%)	14 (34.1%)	0.001
Cardiovascular disease	21 (10.4%)	17 (10.6%)	4 (9.8%)	0.880
COPD	15 (7.4%)	7 (4.3%)	8 (19.5%)	0.001
Asthma	10 (5%)	6 (3.7%)	4 (9.8%)	0.112
Initial vital signs				

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Percentage oxygen saturation with room air	98 [61-100]	98 [65-100]	96 [61-99]	<0.001
Systolic blood pressure	120 [90-210]	120 [90-200]	130 [100-210]	0.262
Diastolic blood pressure	80 [50-120]	80 [50-100]	80 [50-120]	0.841
Heart rate	88 [40-139]	88 [60-139]	94 [40-131]	0.251
Time from symptom onset to admission, days	3 [0-30]	3 [0-30]	4 [0-15]	0.001
Symptom, n (%)				
No symptom	161 (79.7%)	39 (24.2%)	2 (4.9%)	0.006
Cough	105 (52%)	78 (48.4%)	27 (65.9%)	0.046
Fatigue	62 (30.7%)	47 (29.2%)	15 (36.6%)	0.360
Short of breath	51 (25.2%)	33 (20.5%)	18 (43.9%)	0.002
Fever	36 (17.8%)	30 (18.6%)	6 (14.6%)	0.550
Myalgia	36 (17.8%)	27 (16.8%)	9 (22%)	0.439
Headache	30 (14.9%)	28 (17.4%)	2 (4.9%)	0.044
Throat ache	18 (8.9%)	13 (8.1%)	5 (12.2%)	0.408
Sputum	12 (5.9%)	8 (5%)	4 (9.8%)	0.247
Vomiting	8 (4%)	5 (3.1%)	3 (7.3%)	0.217

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Diarrhea		7 (3.5%)	6 (3.7%)	1 (2.4%)	0.687
Chest tightness		3 (1.5%)	2 (1.2%)	1 (2.4%)	0.572
Smell and taste dysfunction		2 (1%)	1 (0.6%)	1 (2.4%)	0.294
Chest radiography findings on admission (%)					
None		73 (36.1%)	70 (43.5%)	3 (7.3%)	<0.001
Unilateral infiltrates		27 (20.3%)	24 (25.3%)	3 (8.1%)	
Bilateral infiltrates		102 (79.7%)	68 (74.7%)	34 (91.9%)	
Chest CT images, n (%)					
Typical		72 (35.6%)	45 (28.0%)	27 (65.9%)	<0.001
Indeterminate		40 (19.8%)	32 (19.9%)	8 (19.5%)	
Atypical		20 (9.9%)	17 (10.6%)	3(7.3%)	
Negative		70 (34.7%)	67 (41.6%)	3(7.3%)	
Initial laboratory findings*					
Parameters	*Normal range*				
Leukocyte, per mm^3	(3.500-10.500)	5.600 [2.210-18.980]	5.600 [2.210-14.460]	5.600 [2.600-18.980]	0.159
Lymphocyte, per mm^3	(1.300-3.800)	1.530 [0.320-10.400]	1.600 [0.320-10.400]	1.190 [0.420-3.510]	0.002

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Neutrophil, per mm^3	(2.000-6.900)	3.365 [0.930-3.240]	3.290 [0.930-3.240]	3.890 [1.200-17.500]	0.803
Eosinophil, per mm^3	(0.02-0.5)	0.040 [0-1.360]	0.040 [0-1.360]	0.015 [0-1.200]	0.002
Hemoglobin, g/dL	(11.5-16.5)	13.52 ± 1.81	13.45 ± 1.80	13.77 ± 1.87	0.315
Platelet count, per 10^9/liter	(145-400)	200.5 [74-408]	208 [100-408]	182 [74-397]	0.076
d-dimer, mg/L	(0-0.55)	0.40 [0.17-10.90]	0.38 [0.17-10.90]	0.63 [0.19-6.09]	<0.001
ALT, U/L	(5-34)	20 [6-85]	19 [6-85]	24 [6-83]	0.268
AST, IU/L	(0-55)	27 [12-155]	25.5 [12-155]	34 [15-104]	0.014
Creatinin kinase, U/L	(29-168)	103 [29-1411]	98 [29-820]	118 [11-1411]	0.124
LDH, U/L	(125-220)	211.50 [2.50-567]	208 [3.92-567]	239 [2.50-485]	0.150
Creatinine, mg/dL	(0.57-1.11)	0.79 [0.43-7.62]	0.78 [0.43-7.62]	1 [0.63-2.40]	<0.001
Ferritin, ng/mL	(22-322)	90.45 [3.20-1650]	79.60 [3.20-1180]	191.30 [17-1650]	<0.001
c-reactive protein, mg/L	(0-5)	7.75 [0.20-345]	4.60 [0.20-192.50]	36.30 [0.20-345]	<0.001
Total IgE, IU/mL	(0-378)	50.20 [0-2124]	38.70 [0-912]	172.90 [0-2124]	<0.001
Treatment, n (%)					
	Oseltamivir	81 (%40.1)	67 (%41.6)	14 (16.4%)	0.384
	Favipiravir	25 (%12.4)	4 (%.2.5)	21 (51.2%)	<0.001

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Plaquanil	201 (%99.5)	160 (%99.4)	41 (100%)	0.613
Azitromisin	196 (%97)	157 (%97.5)	39 (95.1%)	0.420
Virus clearance time, day	11 [3-50]	11 [3-28]	11 [6-50]	0.507
Hospital stay, days	10 [0-57]	9 [0-34]	14 [6-57]	<0.001

Data are presented as mean±st.deviation, median (min.: max.) and n(%).

Statistical significance was determined by the two-sample t-test for normally distributed continuous variables, the Mann-Whitney U test for comparison of continuous non-normal data. Categorical variables were compared by the Pearson Chi-square test.

Abbreviations: COPD, chronic obstructive pulmonary disease; CT: computed tomography;

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase

Table2. Comparison of the course of biochemical parameters between stable and clinically worsening groups

Overall patients (n=202) ***Stable patients (n=161)*** ***Patients with clinical worsening (n=41)***	**Baseline-1st day**	**3rd day**	**14th day**	**P value**
Lymphocyte, per mm^3				
Overall patients	1.530 [0.320-3.500]	1.570 [0.440-5.880]	1.785 [0.170-4.890]	0.004
Stable patients	1.600 [0.320-3.500]	1.670 [0.530-5.880] [a]	1.830 [0.540-3.480] [a]	0.057
Patients with clinical worsening	1.190 [0.420-3.510]	1.200 [0.440-3.160] [b]	1.600 [0.170-4.890] [b]	0.048
Eosinophil, per mm^3				
Overall patients	0.040 [0-1.360]	0.070 [0-1.260]	0.140 [0-0.600]	<0.001
Stable patients	0.040 [0-1.360] [c]	0.090 [0-1.260] [c]	0.140 [0-0.560] [c]	<0.001
Patients with clinical worsening	0.015 [0-1.200] [d]	0.020 [0-0.700] [d]	0.135 [0-0.600] [d]	<0.001
Ferritin, ng/mL				
Overall patients	90.45 [3.20-1650]	105 [4.9-1650]	126 [1.9-1650]	<0.001
Stable patients	79.60 [3.20-1180]	80.40 [4.9-1080]	87 [1.9-1608]	0.005
Patients with clinical worsening	191.30 [17-1650] [e]	399 [27-1650] [e]	341 [32-1650]	0.001
D-dimer, mg/L				
Overall patients	0.40 [0.17-10.90]	0.34 [0.03-10.35]	0.37 [0.17-34.00]	0.003
Stable patients	0.38 [0.17-10.90] [f]	0.30 [0.03-10.35] [f]	0.33 [0.17-3.44]	0.002
Patients with clinical worsening	0.63 [0.19-6.09]	0.56 [0.19-10.35]	0.73 [0.17-34.00]	0.094
CRP, mg/L				

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Overall patients	7.75 [0.20-345.00]	4.70 [0.20-330.00]	2.9 [0.30-306.00]	<0.001
Stable patients	4.60 [0.20-192.50]	2.30 [0.20-120.00]	1.80 [0.20-123.00]	0.005
Patients with clinical worsening	36.30 [0.20-345.00] [g]	68.25 [0.80-330.00] [g]	11.10 [0.20-306.00] [g]	<0.001

Data are presented as median (min.: max.).

Overall group comparisons were performed by Friedman Test. The Wilcoxon test was performed to test the significance of pairwise differences using Bonferroni correction to adjust for multiple comparisons.

Abbreviations: CRP, c-reactive protein

a p=0.004: between lymphocyte levels of 3rd day and 14th day in stable patients

b p: 0.007: between lymphocyte levels of 3rd day and 14th day in patients with clinical worsening

c p=0.001: between eosinophil levels of 1st day and 3rd day, p<0.001: between eosinophil levels of 1st day and 14th day, p<0.001: between eosinophil levels of 3rd day and 14th day in stable patients

d p<0.001: between eosinophil levels of 1st day and 14th day, p=0.003: between eosinophil levels of 3rd day and 14th day in patients with clinical worsening

e p<0.001: between ferritin levels of 1st day and 3rd day in patients with clinical worsening

f p=0.006: between d-dimer levels of 1st day and 3rd day in patients with clinical worsening

g p=0.009: between CRP levels of 1st day and 3rd day, p<0.001: between CRP levels of 3rd day and 14th in patients with clinical worsening

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Tablo-3. Results of binary logistic regression analysis of potential predictors of COVID-19 pneumonia with clinical worsening

Variable	Univariable model			Multivariable model		
	OR	%95 CI	P value	OR	%95 CI	P value
Age, *years*	1.042	1.021-1.063	<0.001	-	-	-
Sex, *male*	2.325	1.136-4.758	0.021	-	-	-
COPD	4.136	2.012-8.464	<0.001	5.887	1.345-25.762	0.019
Asthma	2.793	0.750-10.402	0.126	-	-	-
Hypertension	4.136	2.021-8.464	<0.001	-	-	-
Diabetes Mellitus	3.875	1.735-8.656	0.001	-	-	-
Lymphocyte, per mm^3	3.875	1.735-8.656	0.001	0.610	0.330-1.129	0.116
Eosinophil, per mm^3	0.659	0.085-5.093	0.689	-	-	-
Ferritin, ng/mL	1.003	1.002-1.005	<0.001	-	-	-
D-dimer, mg/L	1.438	1.015-2.037	0.041	-	-	-
CRP, mg/L	1.019	1.009-1.028	<0.001	1.012	1.002-1.023	0.025
Total IgE >105.2 IU/mL	1.005	1.002-1.007	<0.001	9.893	3.907-25.049	<0.001

Abbreviations: OR, odds ratio; CI, confidence interval; CRP, c-reactive protein

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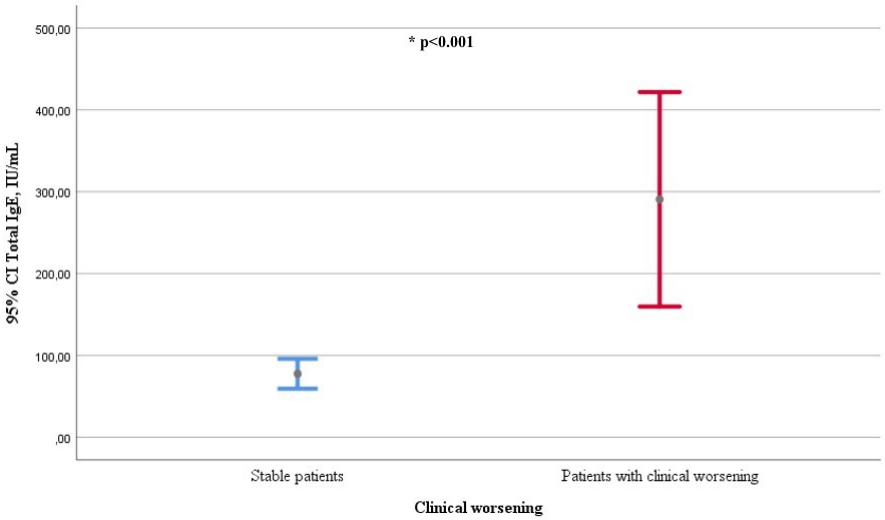

IMJ_15728_Figure 1 IgE Clinical Worsening.jpg

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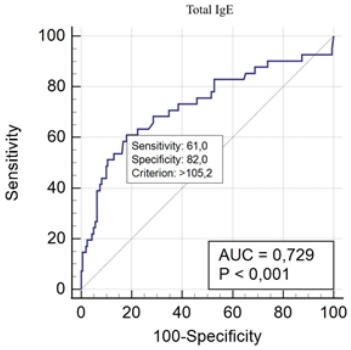

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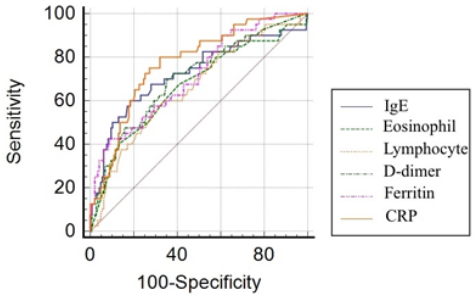

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	Associated criterion	AUC	95% CI	Sensitivity (%)	95% CI	Specificity (%)	95% CI	PPV	NPV	P value
Total IgE, IU/mL	>105.2	0.729	0.662-0.789	61	44.5-75.8	82	75.2-87.6	46.3	89.2	<0,001
Eosinophil, per mm³	≤0.01	0.663	0.593-0.729	40	24.9-56.7	86.7	80.4-91.6	41.7	84.6	0.001
Lymphocyte, per mm³	≤1.380	0.660	0.590-0.725	61	44.5-75.8	62.7	54.8-0.2	30.1	86.6	0.001
Ferritin, ng/mL	>275	0.722	0.654-0.784	43.9	28.5-60.3	90.3	84.5-94.5	45	85.3	<0.001
D-dimer, mg/L	>0.45	0.703	0.632-0.768	70.7	54.5-83.9	64.7	56.6-72.3	34.9	89.2	<0.001
CRP, mg/L	>12.7	0.780	0.706-0.831	80.5	65.1-91.2	69.6	61.8-76.6	40.2	93.3	<0.001