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Original article

Interleukin-17: Could it be a key player in COVID-19 infection severity?

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ABSTRACT

Background: Exaggerated cytokines response with release of proinflammatory cytokines i.e., cytokine storm has been described with COVID-19 infection. This cytokine storm plays an important role in lung injury and development of acute respiratory distress syndrome (ARDS) in severely ill patients. One important cytokine that participates in the cytokine storm is interleukin (IL) -17. **Aim of the study:** Assess serum levels of IL-17 in COVID-19 patients and its correlation with disease severity. **Methods:** Sixty-six COVID-19 infected patients (33 moderate cases and 33 severe cases) and 20 healthy controls (HCs) were included in the study. Serum IL-17 level was assessed by ELISA in patients and HCs. **Results:** IL-17 levels were remarkably higher in patients' groups compared to HCs and also there was statistically significant difference between the patients' subgroups (p<0.0001). IL-17 was correlated with different laboratory and clinical parameters. At a cut-off value of >25 ng/ml, IL-17 was able to differentiate between the patients' groups and HCs with 93.94% sensitivity and 65% specificity. **Conclusion:** Serum IL-17 level correlates to more severe disease courses in COVID 19 patients. Higher levels were associated with devastating outcomes.

Introduction

COVID-19 pandemic disease struck the world at the end of 2019 and is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). First cases were reported in Wuhan, China, then the infection caused a pandemic [1]. Majority of the cases have mild symptoms including fever and cough, which usually subside within 2–3 weeks. Unfortunately, some cases develop more severe course and rapidly develop acute severe respiratory distress syndrome, life-threatening multiorgan dysfunction, metabolic and respiratory acidosis, coagulation disorders, septic shock ending with death [2].

Acute SARS-CoV-2 infection is usually accompanied with immunological responses and variable cytokine patterns to eliminate the virus and investigating these responses is a pivotal step toward treatment strategy for this disease [3]. Following

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SARS-CoV-2 infection, T cells and T helper 17 (Th17) cell are overactivated, leading to a surge of inflammatory cytokines. On the top of the list is IL-17 family, including IL-17A, IL-17B, IL-17C and IL-17D. In response to the cytokine storm and inflammatory cell infiltrations, the alveolar membranes become leaky, allowing shift of water and proteins from intravascular space to the lung interstitium. This ends with uncontrolled pulmonary edema and eventually respiratory failure and death [4].

Considering the pivotal role of IL-17 in inflammation, together with the lack of data about its immunopathological role in COVID-19, we hereby aimed at assessing the potential association of serum IL-17 level and the severity of COVID-19 infection and different clinical and laboratory parameters.

Patients and Methods

Our study is a case control study, conducted at the Quarantine hospitals of Ain Shams University Hospitals on COVID-19 infected patients admitted during the period from 1st of December 2020 till end of June 2021. Twenty healthy subjects were enrolled as a healthy control (HC) group. The study was approved by The Research Ethics Committee, Ain Shams University, Faculty of Medicine (FWA 000017585), and from MASRI (Medical Ain Shams Research Institute) (FMASU R46/2020/2021). A written informed consent was obtained from each patient or patient's guardian.

I- Patients

Patients enrolled in the study were stratified according to Ain Shams clinical guide [5] for COVID-19 into group A: 33 moderate cases of COVID-19 and group B: 33 severe and critical cases of COVID-19. Moderate cases were defined as symptomatic with non-severe pneumonia (e.g., fever, cough, dyspnea), in addition to abnormal laboratory findings. Severe cases cases were diagnosed by chest CT findings of COVID-19 pneumonia and clinical evidence of severe respiratory distress (e.g., respiratory rate > 30 breaths/min; severe respiratory distress; or saturation of peripheral oxygen (SpO_2) 93% or less on room air).

Inclusion criteria

Clinically and radiologically diagnosed COVID-19 patients and confirmed by positive SARS-CoV-2 RT-PCR performed on nasopharyngeal swab or invasive respiratory sample.

Exclusion criteria

Patients with history of chronic lung diseases, history of drugs that affect the immune system e.g.: azathioprine, corticosteroids, methotrexate, interferons, patients with autoimmune disorders, chronic hepatits C and/or B infections or immune deficiency disorders.

II- Methods

Sample collection

Five ml of blood samples were collected from each patient and from HCs in serum separator tube for measuring serum IL-17 level by ELISA.

Measurement of serum IL-17 level

Blood samples were left for 20 minutes at room temperature to clot followed by centrifugation for 10 minutes at 3000 rpm. Serum was aspirated and preserved at -80^0 C till analysis by using human IL-17 ELISA kit (Bioassay Technology Laboratory, Shanghai, China), as described by the manufacturer. Optical densities were measured by a micro-plate reader (CLARIOstar®, BMG Labtech., Germany) within 10 min from adding the stop solution at 450 nm (primary filter) and 630 nm (secondary filter).

Results

Regarding the demographic data of the groups involved, the study was conducted on 86 subjects: (20 HCs , 33 moderate cases of COVID-19 and 33 severe and critical cases of COVID-1). Regarding the HCs , numbers of males and females were 11 (55%) and 9 (45%) respectively. Their age ranged from 21 to 74 with mean age of 34.90 ± 11.85 SD. The patient groups were 39 (59.1%) males and 27 (40.9%) females with age ranging from 20 to 77 with mean age of 59.21± 17.79 SD. Sixty six percent of patients were above 60 years old.

Serum IL-17 level in patients' groups and HCs

Serum IL-17 level was significantly higher (p<0.0001) in patients in comparison to HCs. When comparing IL-17 level among moderate and severe cases (ranging from 30/165 ng/ml), there was high statistically significant difference (p<0.0001) as shown in table (1). The range values of serum IL-17 levels among patients' groups and HCs are illustrated in **table (1)**.

Correlation of serum IL-17 level with different demographic and clinical parameters among patients ' group

As illustrated in **table (2)**, there was no significant difference in serum IL-17 in patients above and

below 60 years old. Serum IL-17 level was comparable as regards gender and history of comorbid conditions including; diabetes, hypertension, cardiovascular disease, chronic kidney diseases, and chronic respiratory conditions. Concerning the patients' presenting symptoms, serum IL-17 was significantly higher in patients presented with fever, acute kidney injury and patients requiring oxygen (*p* value= 0.01, 0.002, & 0.005 respectively). However, there was no significant difference between patients presenting with GIT manifestations or tachypnoea. Moreover, serum IL-17 was comparable as regards chest CT scan , patients' treatment, and patients' outcome.

Correlation of serum IL-17 level with different laboratory parameters and hospital stay

IL-17 level was positively correlated with absolute lymphocytes counts (p value = 0.002) and significantly positively correlated to serum creatinine level and the number of days of hospital stay (*p*= 0.014 and 0.013 respectively). On the contrary, serum IL-17 was not correlated to LDH, CRP, or serum ferritin level.

Cut-off value of serum IL-17 level as a predictor between patients and control group

From the receiver operating characteristic (ROC) curve, a cut-off value of >25 ng/ml for serum IL-17 level had the ability to differentiate between patients group and HCs with sensitivity of 93.94%, specificity of 65%, positive predictive value (PPV) of 89.9% and negative predictive value (NPV) of 76.5% **(Figure 1, Table 4).**

Table 1. Serum IL-17 level in patients' groups and HCs.

IL17 ng/ml	**Moderate group**	**Severe group**	**Control group**	**Test value**	***p*-value‡**	**Sig.**
	No. = 33	**No. = 33**	**No. = 20**			
Median (IQR)	50 (45 – 56)	55 (50 – 115)	25 (12 – 49)	32.325	0.000	HS
Range	25 – 115	30 – 165	10 – 50			
Post Hoc analysis by Mann Whitney test						
P1		**P2**		**P3**		
0.004		**0.000**		**0.000**		

p-value >0.05: Non significant (NS); *p*-value <0.05: Significant (S); *p*-value< 0.01: highly significant (HS), P1: Moderate Vs severe group, P2: Moderate Vs control group, P3: Severe Vs control group, ‡: Kruskal Wallis test.

Table 2. Correlation of serum IL-17 level with different demographic and clinical parameters.

		IL-17 ng/ml		**Test value**	***p*-value**	**Sig.**
		Median (IQR)	**Range**			
Age (years)	Above 60	55 (45 – 90)	25 – 165	-1.407‡	0.159	NS
	Below 60	50 (45 – 56)	25 – 135			
Sex	Male	53 (45 – 90)	25 – 165	-0.138‡	0.891	NS
	Female	55 (45 – 115)	25 – 135			
O_2 or room air	On room air	47 (45 – 55)	25 – 115	12.769‡‡	0.005	HS
	Nasal	60 (50 – 125)	25 – 135			
	Non rebreather mask or Venturi mask	80 (55 – 90)	53 – 90			
	Ventilator	48 (43 – 108)	40 – 165			
Fever presentation	No	80 (45 – 135)	30 – 165	-2.651‡	0.010	S
	Yes	50 (45 – 56)	25 – 115			
Respiratory presentation	Normal	55 (50 – 90)	30 – 165	-0.777‡	0.437	NS
	Tachypnea	53 (45 – 80)	25 – 135			
Acute kidney injury presentation	No	50 (45 – 80)	25 – 135	-3.106‡	0.002	HS
	Yes	115 (60 – 165)	60 – 165			
GIT presentation	No	53 (45 – 70)	25 – 165	-1.323‡	0.186	NS
	Yes	55 (45 – 115)	45 – 135			
CT scan chest	Normal	45 (30 – 80)	30 – 80	1.809‡	0.405	NS

	High probability ground glass appearance	55 (45 – 90)	25 – 165			
	Query	60 (50 – 60)	50 – 60			
Past history of diabetes mellitus	No	53 (45 – 90)	30 – 135	-0.503‡	0.615	NS
	Yes	54 (43 – 80)	25 – 165			
Past history of hypertension	No	50 (45 – 60)	25 – 115	-1.538‡	0.124	NS
	Yes	55 (50 – 115)	25 – 165			
Past history of cardiovascular disease	No	50 (45 – 60)	25 – 135	-1.570‡	0.117	NS
	Yes	55 (50 – 113)	25 – 165			
Past history of chest disease	No	53 (4580)	25 – 165	-0.596‡	0.551	NS
	Yes	115 (40 – 115)	40 – 115			
Past history of renal disease	No	53 (45 – 90)	25 – 135	-1.023‡	0.306	NS
	Yes	60 (50 – 60)	45 – 165			
Treatment	Basic	47 (45 – 115)	30 – 165	5.387‡‡	0.146	NS
	Basic+steroids	55 (50 – 80)	25 – 135			
	Basic+steroids+anti-IL-6	55 (50 – 90)	50 – 90			
	Basic+steroids+ remedisvir	27 (27 – 27)	27 – 27			
Outcome	Died	50 (50 – 90)	40 – 165	3.563‡	0.168	NS
	Improved	53 (45 – 80)	25 – 135			

p-value >0.05: Non significant (NS); *p*-value <0.05: Significant (S); *p*-value< 0.01: highly significant (HS), ‡: Mann Whitney test; ‡‡: Kruskal Wallis test.

Table 3. Correlation of serum IL-17 level with different laboratory parameters and hospital stay.

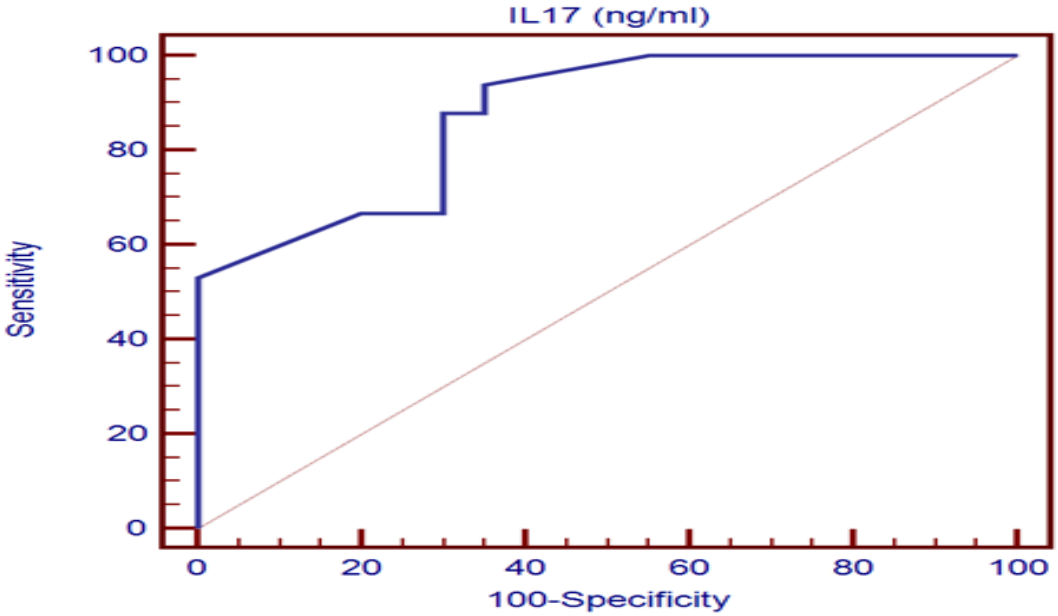
	IL-17 ng/ml	
	r	***p*-value**
Total WBCs	0.119	0.340
percentage lymphocytes	0.112	0.369
Absolute lymphocytes	0.381**	0.002
CRP	-0.131	0.293
Ferritin	-0.061	0.629
LDH	-0.045	0.720
D-dimer	0.123	0.324
Serum creatinine level	0.301*	0.014
ALT	-0.105	0.402
AST	-0.034	0.788
Hospital stay	0.302*	0.013

WBCs: white blood cells, CRP: C reactive protein, LDH: lactate dehydrogenase enzymes, ALT: alanine transaminase, AST: aspartate aminotransferase.

Table 4. Cut-off value of serum IL-17 level as a predictor between patients and control.

Parameter	**AUC**	**Cut of Point**	**Sensitivity**	**Specificity**	**PPV**	**NPV**
IL-17 ng/ml	0.874	>25	93.94	65.0	89.9	76.5

Figure 1. ROC curve of serum IL-17 as a predictor of COVID 19 severity.



Discussion

Our immune system battles against viral infections. Viral infections may cause devastating outcomes through acute and chronic pathological responses, depending on the nature of the invading virus as well as the affected body organ [6]. When viruses invade the host, the innate immune system recruits many cells to the site of infection such as macrophage cells, dendritic cells and granulocytes and subsequently specific adaptive immune response mediated by lymphocytes (B and T cells) is activated. The immune system has to respond vigorously, but at the same time, the severity of inflammation has to be firmly controlled to avoid tissue destruction and adverse outcomes [7].

IL-17 is a remarkably pleiotropic cytokine that plays a specific role in host immune response. A wide range of immune cell populations, such as Th17 cells , neutrophils, natural killer (NK) cells, mast cells, natural killer T (NKT) cells, CD8+ T cells and group 3 innate lymphoid cells produce IL-17 [7-10]. IL-17 has a crucial role in the preservation of tissue integrity and initiation of protective immune responses to infectious microorganisms, mostly at epithelial barrier sites [11].

A novel coronavirus - SARS-CoV-2 was first reported in Wuhan, China and consequently the virus has spread around the world [1]. The WHO declared COVID-19 a global crisis. A lot of patients developed ARDS, which ended in pulmonary edema and lung failure, liver, heart, and kidney injuries [12]**.** This cytokine storm is accompanied with elevated serum levels of Interferon (IFN) γ, tumor necrosis factor (TNF) α, Interferon-inducible protein (IP)-10, monocyte chemoattractant protein (MCP) -1, macrophage inflammatory protein (MIP)-1A, MIP-1B, IL-1β, IL-2, IL-7, IL-8, IL-9, IL-10 and IL-17 [13].

Our study population included 66 patients diagnosed as COVID 19 admitted to Ain Shams isolation hospital and 20 HCs controls. The patient groups were 39 (59.1%) males and 27 (40.9%) females with age ranging from 20 to 77 with mean age of 59.21± 17.79 SD. Sixty six percent of patients were above 60 years old.

Yauhen and his co-workers [14], reported that men were much more affected than females and older patients ran more severe course in their study This signifies that sex hormones may be play a role in COVID-19 infection. Oestrogen hormone triggers active cellular and humoral immune responses which results in instant elimination of pathogens and resilience to infections among the female population . Also, oestrogen hormones contract the expression of SARS-CoV- receptor, angiotensin-converting enzyme-2 [15]**;** limiting the virus invasion. On the contrary, testosterone has a noxious effect on the immune system. The decline in testosterone level with the ageing is always accompanied with a rise in the antibody levels, inflammatory cytokines, CD4/CD8 ratios, natural killer cells and a decrease in regulatory T cells levels [16-18]**.** This may explain that 66% of the patients in our study were above 6o and 59% were males.

Failure of adequate progression from innate to adaptive immune response is a characteristic feature of ageing, accompanied with hyperinflammation, cytokines torms and uncontrolled coagulation leading to devastating multiorgan failure if an elderly patient acquired COVID-19 infection. Moreover, elderly people usually have associated chronic diseases, such as diabetes, renal affection, cardiovascular or lung diseases. This state of sustained activation of the immune system, makes elderly not only more prone to have a complicated disease course, but also at a higher risk of death if they get infected[12,19]**.**

In concordance to our results, **Fouad and his coworkers** [12] identified age as a highly significant variable (p=0.000), OR 1.06 (CI 1.04–1.08) in their work to stratify patients at higher risk for ICU admission with COVID-19 infection. The patients required ICU admission were in a higher age group (57.9 ± 16y) compared to (44 ± 15.3y) in the non-ICU admitted population.

Serum IL-17 level was significantly higher (p<0.0001) in patients in comparison to HCs. When comparing IL-17 levels among moderate and severe cases (ranging from 30/165 ng/ml), there was a statistically significant difference (p<0.0001). Moreover, serum IL-17 was strongly correlated to the presence of fever (p <0.010), acute kidney insult (p< 0.002) and increased oxygen requirements (p< 0.005).

When comparing serum IL-17 levels to laboratory biomarkers in COVID 19 patients, IL-17 level was strongly correlated to absolute lymphocytes counts. On the other hand, it was not correlated to LDH, CRP or serum ferritin level. A cut-off value of >25 ng/ml for serum IL-17 level could differentiate between patients' group and HCs with sensitivity of 93.94%, specificity of 65%, positive predictive value.

Comparable results were observed by **Askari et al**, [20] who reported that plasma and salivary IL-17 remarkably elevated in severe cases with COVID-19 compared to milder or asymptomatic cases. Moreover, serum IL-17 was correlated to many inflammatory markers such as CRP and TNF. Furthermore, the cut off value of >28 ng/ml differentiated between mild cases and healthy controls, which is nearly comparable to our work.

Also **Fadlallah and co-workers** [21] analysed the data from 9 different studies regarding serum IL-17 in 2 groups of patients, 219 patients suffered from moderate disease and 128 patients with severe disease. They concluded that serum IL-17 level was strikingly higher in the group with severe disease compared to the group suffering of moderate disease.

On the contrary to our work**, Ghazavi** and **his co-workers** [22] reported that the mean level of IL-17 was significantly higher in mild cases in comparison to the severe group and control group. This controversy between our study and this study may be attributed to differences between study populations, study designs, and different virus strains.

It is well established that activation of the IL-17 pathway is a marker of severity in respiratory viruses infections such as (MERS-CoV) outbreak in 2012 [22], H1N1 pandemic in 2009 [23], Respiratory syncytial virus infections [24] and recently SARS-CoV [25]**.** IL-17 expression was accompanied with a poor IF production.

In response to viral infections, IL-17 stimulate non immune cells e.g., fibroblasts or epithelial cells to release a surge of proinflammatory cyto-chemokines such as IL-1, IL-6, TNF-α, MIP-2, IL-8, IP-10 to stimulate neutrophils chemotaxis. Excessive neutrophil infiltration can be noxious leading to increased morbidity and mortality[26]. The decline in lymphocyte subpopulations and the rise in Th17 cells and Th17-derived cytokines seen in patients of SARS-Cov, fortify the idea that IL-17 amplifies host immune response leading to severe inflammation and tissue damage. Those findings paved the way to think that IL-17 blockade using already available biological drugs could be a novel therapy for COVID -19 patients with moderate and severe pulmonary inflammation [27,28].

Conclusion

Serum IL-17 may acts as a prognostic factor of severity in COVID-19 patients. IL-17 blockade could be a novel therapy for COVID -19 patients, specially in severe pulmonary inflammation.

Limitation of our study

During peaks of COVID 19 pandemic, matching the age of our healthy controls to our study groups was extremely difficult. Since elderly persons and those with multiple co morbidities were kept at home for their own safety. Only young and healthy individuals were available in our health facilities to be enrolled in our HC population .

Also serum IL-17 in mild cases was not evaluated in our work , since mild cases was managed at out patient clinic or even by telemedicine.

Contributors

All authors have made substantial contributions to the design of the study. Sample collection, clinical examination and clinical diagnosis were performed by **Dr/Marwa Abdelazim abdelgawad** and **Dr Amr Hosny hamza**. The Serological tests were performed by **Dr/Amira E. Abdelhamid** and **Dr/Fatma El zahraa Youssef**. Data analysis and interpretation were contributed to all the authors. Drafting the article was performed by **Dr/Amira E. Abdelhamid**, **Dr/Fatma El zahraa Youssef** and **Dr/Mayada Moneer Mahmoud**. Revising the draft critically for important intellectual and scientific content was carried out by all the authors. All the authors provided final approval of the version to be published.

Conflict of interest

All authors declare no conflict of interest in this work.

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