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ORIGINAL ARTICLE

Changes in T lymphocyte Subsets Following COVID-19 Infection and Vaccination

Walid Mohamed Attiah[1], Neveen George El Antouny [1], Heba Shafeak Abd El Khalik[1], Rania Mohammad Abdullah[2], Ahmed Abdulsaboor Mohammed[2*]

[1] Internal Medicine Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.
[2] Clinical Pathology Department, Faculty of Medicine, Zagazig University, Zagazig, Egypt.

***Corresponding author**: Ahmed Abdulsaboor

Email a.abdulsaboor@gmail.com

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ABSTRACT

Background: Several SARS-CoV-2 vaccines have been developed, and understanding their impact on immune system is of paramount importance. This study aimed to investigate changes in T Lymphocyte subsets following Covid-19 vaccination vs in covid-19 patients.

Methods: This prospective cohort study was conducted on 82 individuals divided into two equal groups of covid patients and healthy recipients of covid vaccines. Patients were subjected to detailed history taking, clinical examination, routine lab and measurement of CD-4 cells, CD-8 cells.

Results: TLC, D. dimer, ferritin, CRP, ESR, LDH, and IL-6 were significantly higher among infected group compared to vaccinated group. Total lymphocytes count, and CD4+ and CD8+ subsets of T cells were significantly lower among infected group compared to vaccinated group ($p<0.001$).

Conclusions: Lymphocyte subsets changes is different in covid patients compared to post-vaccination, indicating different mechanisms of alteration. Lymphocyte counts could be monitored in COVID-19 patients to guide proper healthcare and vaccination programs.

Keywords:
Covid-19; Vaccination; Lymphocyte; CD4+; CD8+

INTRODUCTION

In the last decade, humanity witnessed one of the most violent pandemics in modern history: Covid-19. The aftermath of the pandemic was huge at several levels, not only in healthcare. The range of clinical manifestations in covid patients was broad, with lack of understanding of the underlying pathognomonic and immunologic mechanisms [1].

The potential clinical signs and symptoms included fever, fatigue, muscle aches, diarrhea, and pneumonia. The latter could be fatal in severe cases. Prognosis was worse with older age and in patients with co-morbidities, such as diabetes, and hypertension. Several lab parameters were routinely used to support healthcare providers, especially where diagnostic PCR testing was lacking, such as procalcitonin, lactate dehydrogenase (LDH), D-dimer, C-reactive protein (CRP), total and differential leucocytic counts, and interleukin-6 (IL-6). Lymphopenia and thrombocytopenia were associated with poor outcomes [2].

The exact pathologic mechanisms underlying disease progress remain largely unknown. However, it was believed that exaggerated immune response, cytokine storm, tissue infiltration with immune cells were common phenomena in most severe cases [3]. What made the situation worse was that researchers were struggling to elucidate the disease enigma, given the enormous pool of potential immunological markers that could be studied and the limited resources and expertise at both proteomic and genomic levels. Safety constraints needed for staff and researchers' protection was an additional barrier [4].

From a clinical point of view, more questions were there than the answers. Healthcare providers as well as researchers needed to know which parts of

the immune systems were more important in disease response, humoral or cell mediated. The differences in immune response to infection vs vaccination, and the protective magnitude and duration of vaccines were other hot areas of investigation [5].

Most COVID-19 patients encounter a decrease in lymphocytic count; it has been closely linked to the severity of the case. It has been also linked to the increasing ratios of neutrophils-to-lymphocyte, monocyte-to-lymphocyte and rising cytokine levels [6]. More work is needed to elucidate this phenomenon.

METHODS

This study was a prospective cohort study. It was conducted on vaccinated population in Zagazig, Sharkia, Egypt, and the patients in the isolation sector of Zagazig University Hospitals. Study activities took place in the period from June 2022 to June 2023.

This study included 82 adults, divided into two equal groups: group 1, confirmed cases of COVID-19 infection (infected), and group 2: healthy individuals who received COVID-19 vaccine (vaccinated).

We excluded patients with comorbidities affecting the blood count as hematological conditions, hepatic diseases, on chemotherapy, on radiotherapy and autoimmune diseases. Written informed consent was obtained from all participants or their guardians, and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University **(IRB approval number 9245-23-1-2022)**. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Patients were subjected to detailed history taking including risk factors such as obesity, smoking, and comorbidities. Clinical examination was carried out to evaluate different signs and symptoms. Blood samples were drawn from vaccinated subjects on the 7^{th} day after vaccination, and from COVID-19 patients upon hospitalization.

COVID-19 patients were diagnosed by real time PCR of viral RNA in nasopharyngeal swab samples, using COVID-19 Genesig® Real-Time PCR kits (Primerdesign Ltd, UK). Real time PCR was done on "Stratagene Mx3005P" platform (Agilent Technologies, USA). CD4 and CD8 were measure by immunophenotyping on peripheral blood samples, taken on EDTA vacutainers. Analysis was performed using BD FACS Canto II flowcytometer (Becton Dickinson, USA) using monoclonal reagents supplied by manufacturer.

STATISTICAL ANALYSIS

All data were collected, tabulated and statistically analyzed using SPSS 24.0 for windows (SPSS Inc., Chicago, IL, USA).

Data were tested for normal distribution using the Shapiro Walk test. Qualitative data were represented as frequencies and relative percentages. Chi square test ($\chi 2$) and Fisher exact was used to calculate difference between qualitative variables as indicated. Quantitative data were expressed as mean ± SD (Standard deviation) for parametric and median and range for non-parametric data. Independent-T test and Mann Whitney test were used to calculate difference between quantitative variables in two groups for parametric and non-parametric variables respectively.

All statistical comparisons were two tailed with significance Level of P-value ≤ 0.05 indicates significant, $p < 0.001$ indicates highly significant difference while, $P > 0.05$ indicates non-significant difference.

RESULTS

There was no significant difference between the two study groups in demographic data. There was a significant difference between infected and vaccinated groups regarding vital signs (**Table 1)**.

Table 2 shows that TLC, D. dimer, ferritin, CRP, ESR, LDH, and IL-6 were significantly higher among infected group compared to vaccinated group. Relative lymphocytes count, absolute CD4+ and absolute CD8+ counts were significantly lower among infected group compared to vaccinated group.

In addition, we found that 41.5% of the patients showed post COVID-19 infection complications; Chronic lung fibrosis in (22%), DM in (12.2%), and nasal mucormycosis in (4.9%). Moreover, 2 patients died one of them was secondary to thrombosis. Meanwhile, side effects of COVID-19 vaccination included flu symptoms in almost 30% of the patients and local pain or irritation in 5% of the patients **(Table 3)**.

Table 1. Demographic and clinical characteristics of study population

	Infected (n=41)	**Vaccinated** (n=41)	**P**
Age (years)	43.73 ± 5.91	41.88 ± 7.54	.220
BMI (kg/m^2)	27.12 ± 2.84	26.53 ± 2.37	.310
Gender			
Female	15 (36.6%)	19 (46.3%)	.370
Male	26 (63.4%)	22 (53.7%)	
Comorbidities			
Smoking	19 (46.3%)	14 (34.1%)	.261
DM	17 (41.5%)	10 (24.4%)	.100
HTN	15 (36.6%)	18 (43.9%)	.499
HR (beat/min)	90.45 ± 2.87	86.1 ± 5.76	**<0.001***
Temperature (°C)	37.59 ± 0.214	37.3 ± 0.358	**<0.001***
RR (cycle/min)	21.75 ± 5.45	18.92 ± 3.47	**.007***
SBP (mmHg)	129.74 ± 9.46	125.1 ± 8.35	**.021***
DBP (mmHg)	79.22 ± 6.19	77.52 ± 4.81	.169

BMI, body mass index; DM, Diabetes mellitus; HTN, hypertension; HR, Heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, Diastolic blood pressure. Quantitative data were expressed as mean ± SD, Qualitative data were represented as frequencies and relative percentages.

Table 2. Laboratory parameters in study groups

	Infected (n=41)	**Vaccinated** (n=41)	**P**
Hemoglobin (g/dL)	11.66 ± 1.29	12.41 ± 1.12	**.006***
TLC (x10^3/L)	11.76 ± 5.1	8.74 ± 0.966	**.002***
Lymphocytes (%)	8.02 ± 4.24	28.51 ± 8.67	**<0.001***
PLT (x10^3/L)	260.29 ± 97.67	258.85 ± 40.3	.931
D. dimer (µg/mL)	0.691 ± 0.588	0.23 ± 0.103	**<0.001***
Ferritin (ng/mL)	581.48 ± 243.5	141.61 ± 42.53	**<0.001***
CRP (mg/L)	107.1 ± 62.59	2.92 ± 1.67	**<0.001***

	Infected (n=41)	**Vaccinated** (n=41)	**P**
ESR 1st h (mm/h)	62.27 ± 26.19	7.98 ± 5.87	**<0.001***
LDH (U/L)	475.46 ± 161.1	277.95 ± 34.27	**<0.001***
IL-6 (pg/ml)	16.67 ± 16.12	4.39 ± 1.32	**<0.001***
CD4+ (cell/mm^3)	327.11 ± 81.12	659.1 ± 130.64	**<0.001***
CD8+ (cell/mm^3)	249.51 ± 74.69	538.29 ± 73.1	**<0.001***
CD4+:CD8+ ratio	1.34 ± 0.223	1.23 ± 0.215	**.024**

Quantitative data were expressed as mean ± SD.

Table 3: Complications in study groups

	Infected (n=41)	**Vaccinated** (n=41)
Lung fibrosis	9 (22%)	0 (0%)
2ry DM	5 (12.2%)	0 (0%)
Mucormycosis	2 (4.9%)	0 (0%)
Thrombosis	2 (4.9%)	0 (0%)
Flu symptoms	0 (0%)	12 (29.2%)
Local pain or irritation	0 (0%)	2 (4.9%)

Qualitative data were represented as frequencies and relative percentages.

DISCUSSION

Covid-19 has infected more than 430 million patients globally, with around six million related deaths. Vaccination is a powerful tool to prevent transmission of communicable diseases, therefore developing vaccines for Covid-19 was a priority to control the pandemic [7]. Many markers have been studied for their ability to predict disease progress, but none was perfect. While some excelled in ease of use and costs, others showed better accuracy and adaptability to different settings [8]. Current tools for care and triage of COVID-19 cases are based on a mix of lab, imaging, clinical and demographic data [9, 10].

Accordingly, we documented that there was a significant difference between infected and vaccinated regarding vital signs, but there was no significant difference regarding demographic data and comorbidities.

It has been shown that covid-19 triggers an escalating inflammatory response, especially in severe cases, depleting even the immune modulatory cells [12]. Covid-19 virus receptors are abundantly expressed in a variety of cells and tissues, with potential for direct organ injury. Biomarkers reflecting tissue damage have been studied extensively [8, 11].

In line with the previous reports, we found that total lymphocytes and T cell subsets (CD4+ve and CD8+ve) were significantly lower among infected individuals compared to vaccinated individuals. Inflammatory markers as CRP, ferritin, ESR, LDH, and IL-6, and markers of activation of coagulation cascades as D-dimer, were all significantly higher among infected individuals compared to vaccinated individuals.

Similar low counts of lymphocyte and T cell subsets were reported [13]. Those phenomena were attributed to the cellular migration to sites of infection, or due to the direct effect of covid-19 virus on T cells [2]. In addition, it was reported that T cell count correlates directly with infection protection, and inversely with disease severity. This explains their higher values in vaccinated subjects [14]. However, Sushentseva et. al. [15] reported that specific T cells were equal in vaccinated subjects and patients. It was not clear if that meant lower T cells in vaccinated subjects, or higher T cell counts in patients. Both possibilities meant an altered pathway either in vaccine action, or disease progress. Patients were reported to recover from covid-19. Hence, the situation was inconclusive.

There seems to be a threshold for T cells for patients to survive the disease, but this needs further investigation. A meta-analysis by Lai et al. actually revealed that lymphocyte count is a critical defensive determinant in Covid-19 patients. An extremely lower level of lymphocyte counts below a suggested nadir of $\leq 0.87 \times 10^9$/L implies immune compromise and poorer prognosis [10]. While vaccination boosts lymphocytes, especially T subsets, infection does the opposite. The negative impact of infection seems to escalate with disease severity.

CONCLUSIONS

In this study, total lymphocyte population and T subset counts were differently affected by covid-19 infection and vaccination. While infection had a negative impact, vaccination boosted them. We inferred that lymphocyte counts can be an important biomarker for monitoring covid-19 progress, and the benefits of vaccination. Future studies can investigate exact timings of lymphocytes dynamics, and whether a protective value conferred by vaccination is superior to that acquired after infection in survivors.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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