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THE SIGNIFICANCE OF VACCINE-INDUCED PROTECTION FROM COAGULATION DISORDERS REPORTED IN COVID-19 PATIENTS WITH A REVIEW OF SEVERITY OF THEIR CLINICAL PRESENTATION

ZNAČAJ VAKCINACIJE U ZAŠTITI OD POREMEĆAJA KOAGULABILNOSTI KOD COVID 19 PACIJENATA SA OSVRTOM NA TEŽINU KLINIČKE SLIKE

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Summary

Introduction. The production and distribution of preventive SARS-CoV-2 vaccines are among the greatest advances that offers protection against severe forms of the disease, including also fatal outcomes. The purpose of our research is to establish the degree to which vaccination contributes to providing protection against coagulation disorder (one of the leading COVID-19 infection complications). Vaccinated patients with COVID-19 breakthrough infections rarely manifest severe clinical presentation with the occurrence of pneumonia. However, the question is whether they are protected against thromboembolic complications irrespective of the occurrence of pneumonia. **Material and Methods.** 132 respondents were divided into 4 groups based on their immunization status (vaccinated V+; unvaccinated V-) and severity of their clinical presentation, the main criterion of which was pneumonia (with pneumonia P+; without pneumonia P-): group 1: V+, P+; group 2: V+, P-; group 3: V-, P+; group 4: V-, P-. All of them tested positive for SARS-CoV-2. The mean values of D-dimer levels were compared to their reference values (0.5 mcg/ml). **Results.** The results indicated elevated D-dimer levels in patients with SARS-CoV-2 pneumonia irrespective of their vaccination status. This refers to both the mean and reference values. The results demonstrated that V+ and P+ had elevated D-dimer levels when compared to V+ and P-, which was not the case with the unvaccinated patients, i.e., V- and P+ had no more significantly higher D-dimer levels when compared to V- and P-. **Conclusion.** Our conclusion is that vaccination has no role in protecting against coagulation disorders irrespective of the occurrence of pneumonia.

Key words: Blood Coagulation Disorders; Thromboembolism; COVID-19 Vaccines; SARS-CoV-2; Fibrin Fibrinogen Degradation Products; Pneumonia; Immunization

Sažetak

Uvod. Najveći napredak do sada u borbi protiv SARS COV-2 pandemije je rana proizvodnja i distribucija vakcina protiv SARS-CoV-2 virusa koje deluju prvenstveno preventivno, a ako i dođe do obolevanja sprečavaju teške forme bolesti i smrtni ishod. Cilj našeg istraživanja jeste da utvrdimo koliko vakcinacija doprinosi zaštiti od poremećaja koagulacije, što je jedna od vodećih komplikacija kod COVID-19 infekcije. Iako se zna da vakcinisani pacijenti ređe obolevaju od teške kliničke slike sa pojavom pneumonije, postavlja se pitanje da li su zaštićeni i od komplikacija u vidu tromboze nezavisno od pojave pneumonije. **Materijal i metode.** U istraživanje su uključena 132 ispitanika, koji su podeljeni u četiri grupe na osnovu statusa imunizacije (vakcinisani V+; nevakcinisani V-) i težine kliničke slike, gde je glavni kriterijum postojanje upale pluća (sa pneumonijom P+; bez pneumonije P-): 1. grupa: V+, P+; 2. grupa: V+, P- ; 3. grupa V-, P+; 4. grupa V-, P-. Svi su imali pozitivan test na SARS-CoV-2 virus. Statistički su poređene prosečne vrednosti D-dimera i vrednosti D-dimera u odnosu na referentne (0,5 mmol/ml) među ovim grupama. **Rezultati.** Rezultati su pokazali da pacijenti sa pneumonijom imaju značajno povišene vrednosti D-dimera bez obzira na status imunizacije. Ovo se odnosi i na prosečne i na referentne vrednosti. Drugi deo rezultata je pokazao da V+, P+ imaju značajno više prosečne vrednosti D-dimera u odnosu na V+, P-, što se nije odnosilo na nevakcinisane, tj. V-, P+, nisu imali značajno više nivoe D-dimera u odnosu na V-, P-. **Zaključak.** Zaključak istraživanja je da vakcinacija nema protektivnu ulogu u zaštiti od poremećaja koagulacije nezavisno od pojave pneumonije.

Ključne reči: poremećaji koagulacije; tromboembolije; COVID-19 vakcine; SARS-CoV-2; D-dimer; pneumonija; imunizacija

Introduction

The COVID-19 pandemic has been a significant global, health, social and economic issue ever since the occurrence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in December 2019. Globally, several different types of COVID-19 vaccines have been administered, with various de-

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Abbreviations

SARS-CoV-2	– severe acute respiratory syndrome coronavirus 2
V+	– vaccinated
V-	– unvaccinated
P+	– with pneumonia
P-	– without pneumonia
DD	– D-dimer
DIC	– disseminated intravascular coagulation
CT	– computirized tomography
RT-PCR	– real time polymerase chain reaction
EHRs	– electronic health records

grees of efficiency. However, each one of the vaccines significantly reduces the risk of occurrence of severe clinical presentation and fatal outcomes [1–5].

Health risks are primarily associated with respiratory problems and the incidence of severe viral pneumonia, coupled with coagulopathy which eventually leads to thrombosis and embolization of the whole body, disseminated intravascular coagulation (DIC) [6, 7]. Post-Covid patients can suffer from severe complications, such as heart problems, neurological system disorders, problems with the liver, kidneys, skin, etc. [8–10].

The diagnosis of COVID-19 pneumonia is confirmed based on the positive SARS-CoV-2 virus test, clinical symptoms, signs, and objective medical examination, and is verified by the use of diagnostic imaging methods, such as computed tomography (CT) scans and chest X-rays [11]. On the other hand, an elevated D-dimer level is shown to be a sensitive (but not entirely specific) test for detecting coagulopathy [12]. A few sources confirm the correlation between the severity of the clinical presentation and elevation of D-dimer levels, though it is also possible to detect thrombosis in patients with mild upper respiratory tract symptoms [13].

Vaccination primarily focuses on prevention. Furthermore, it reduces the severity of clinical presentation, development of the most severe forms of illness, and fatal outcome as well [14]. No single vaccine can provide full (100%) protection against the SARS-CoV2 virus and that a certain percentage of vaccinated people can also develop viral pneumonia [15]. Pre-existing chronic diseases are the established risk factors for COVID-19 outcomes [16, 17].

As thrombosis is one of the most common causes of death from coronavirus infection, the question is whether vaccination can help reduce the risk of coagulation disorders incidence irrespective of the incidence of pneumonia [18]? Actually, the real question is whether vaccinated patients with pneumonia are less likely to develop coagulation disorder compared to unvaccinated patients with confirmed pneumonia?

Some sources confirm the correlation between the severity of clinical presentation and elevation of D-dimer levels, suggesting that this particular analysis could be used as a predictive factor for the development of severe clinical presentation and adverse course of the disease, but there are reports of COVID-19 cases where patients with mild upper respiratory tract symptoms developed thrombosis, which is a dangerous and potentially fatal condition. The second question is whether correlation between the severity of clinical presentation and elevation of D-dimer levels could be considered statistically significant?

The aim of the research was to show whether there was any difference between the coagulability levels in vaccinated and in unvaccinated patients with pneumonia, taking into account the fact that thrombosis was associated with the severity of clinical presentation that also depends on the vaccination status of the above patients.

Material and Methods

Our research was conducted as a retrospective cohort study that included 132 participants divided into four separate groups. The main variable, which was measured for each participant, referred to the D-dimer levels.

All the participants tested positive for the SARS-CoV-2 virus in the period between April 1, 2021, and June 15, 2021. They were treated (primarily) at the Outpatient Clinic for Respiratory Diseases and Febrile Conditions, Kragujevac Health Center, Kragujevac.

Patients were divided into four separate groups based on the following criteria: patients in whom COVID-19 was confirmed by the real-time RT-PCR test or the rapid SARS-CoV-2 antigen detection test and the severity of clinical presentation (a patient with pneumonia J12, J15 and J18 according to the International Classification of Diseases (ICD)/a patient without pneumonia).

Inspecting the electronic medical records for each individual patient, we checked whether the date of diagnosis met the diagnostic criteria given: 1. Diagnostic vaccination; 2. Minimum 15 days after the vaccination, the diagnosis is confirmed based on the positive result of tests for SARS-CoV-2 virus; 3. Diagnosis of pneumonia during the treatment of COVID-19 infection. Additionally, we checked whether the above diagnosis was verified by chest X-rays.

Having gained insight into the current medical records, we selected 132 patients, i.e., each of the four groups comprised of 33 patients for whom the lab data were collected on D-dimer (DD) levels.-

- Group 1: vaccinated, with pneumonia (V+, P+);
- Group 2: unvaccinated, with pneumonia (V-, P+);
- Group 3: vaccinated, without pneumonia (V+, P-);
- Group 4: unvaccinated, without pneumonia (V-, P-).

Statistical data analysis was performed with use of IBM SPSS® Statistics software.

The obtained data were displayed primarily in a descriptive manner using a combination of tabulated description (i.e., tables) and graphic description (i.e., graphs). Continuous variables, i.e., D-dimer values, were shown using the least and greatest value, the mean value and standard deviation, as well as the median values.

The independent-samples t-test was used for the purpose of analyzing the D-dimer values compared to the immunization status and incidence of pneumonia in the study participants. The above test was used

to compare the mean D-dimer levels between the two examined groups of participants. The analysis was made not only for each participant respectively, but for each of the given groups, and compared again according to their immunization status and the incidence of pneumonia. The results of the analysis were presented graphically in a clustered column graphs.

The results were considered to be statistically significant if the level of statistical significance (the p-value) was less than 0.05 (typically ≤ 0.05).

Results

Out of the total of 132 study participants, 66 participants or 50% of participants were vaccinated, i.e., unvaccinated. Compared to their pneumonia status, there were 66 participants, or 50% of participants with and without pneumonia. The D-dimer levels ranged from 0.01 to 6.20. The mean D-dimer value was 0.69 with a standard deviation of 0.90, whereas the median value was 0.37. Compared to the D-dimer values less than 0.5 and greater than 0.5, there were 86 participants, i.e., 65.6% of participants with D-dimer values less than 0.5, and also, there were 45 participants, i.e., 34.4% of participants with the D-dimer values greater than 0.5.

Using the independent samples t-test, we established that there was no statistically significant difference between D-dimer values in vaccinated participants, i.e., unvaccinated participants (p = 0.356). It referred to both patients with pneumonia (p=0.222) and patients without pneumonia (p=0.671) **(Table 1)**.

For all participants

In V+ group, the mean D-dimer value was 0.76 mcg/ ml. In V- participants, the mean D-dimer value was 0.62 mcg/ml.

For participants with pneumonia

In P+, V+ group, the mean D-dimer value was 1.12 mcg/ml. In P+, V- group, the mean value was 0.79 mcg/ml. The results were presented graphically in **Graph 1**.

For participants without pneumonia

In P-, V+ group, the mean D-dimer value was 0.39 mcg/ml. In P-, V- group, the mean value was 0.44 mcg/ml.

For the purpose of analyzing D-dimer values in comparison to the pneumonia status of the participants, we used the independent samples t-test, comparing thus the mean D-dimer values in participants with, i.e., without pneumonia.

The analysis was supposed to be made not only for all the participants, but for the immunized and non-immunized ones as well **(Table 2)**.

For all participants

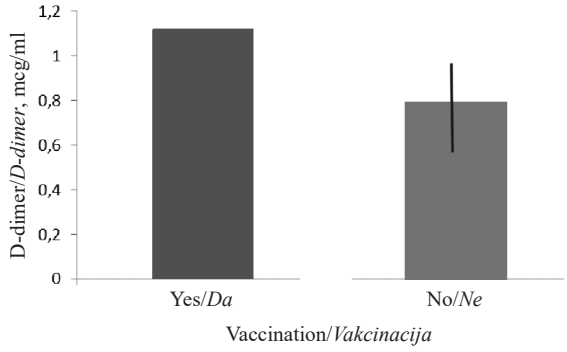
In P+ group, the mean D-dimer value was 0.96 mcg/ml. In P- group, the mean value was 0.41 mcg/ml.

For vaccinated participants

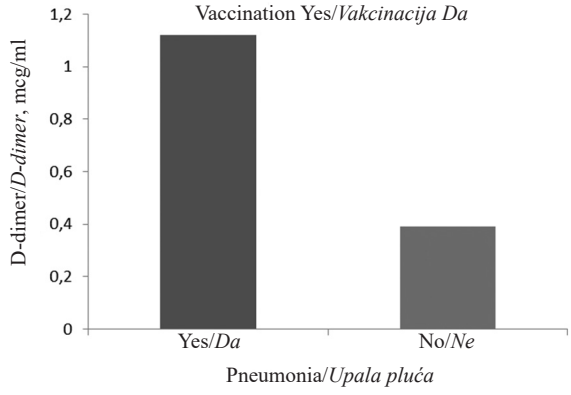
In V+, P- group, the mean value was 0.39 mcg/ml. The results are presented graphically in **Graph 2**. It clearly shows that D-dimer values are signifi-

Table 1. Results of the analysis of D-dimer values compared to the immunization status
Tabela 1. *Rezultati analize vrednosti nivoa D-dimera u odnosu na status imunizacije*

	p/*p*
All participans/*Svi ispitanici*	0.356
Only participans with pneumonia/*Samo ispitanici sa pneumonijom*	0.222
Only participans without pneumonia/*Samo ispitanici bez pneumonije*	0.671



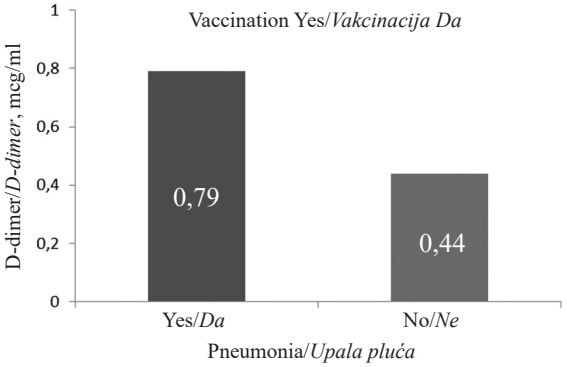
Graph 1. D-dimer values compared to the immunization status of participants with pneumonia
Grafikon 1. *Vrednosti nivoa D-dimera u odnosu na status imunizacije ispitanika koji imaju pneumoniju*



Graph 2. D-dimer values compared to the incidence of pneumonia in immunized participants
Grafikon 2. *Vrednosti nivoa D-dimera u odnosu na prisustvo pneumonije kod imunizovanih ispitanika*

Table 2. The results of the analysis of D-dimer values compared to the incidence of pneumonia
Tabela 2. *Rezultati analize vrednosti nivoa D-dimera u odnosu na prisustvo pneumonije*

	p/*p*
All participants/Svi ispitanici	0.000
Only immunized participants/*Samo imunizovani ispitanici*	0.003
Only non-immunized participants/ *Samo neimunizovani ispitanici*	0.053



Graph 3. D-dimer values compared to the incidence of pneumonia in non-immunized participants
Grafikon 3. *Vrednosti nivoa D-dimera u odnosu na prisustvo pneumonije kod neimunizovanih ispitanika*

cantly higher in the group of immunized participants with pneumonia.

For unvaccinated participants

In V-, P+ group, the mean D-dimer value was 0.79 mcg/ml. In V-, P- group, the mean value was 0.44 mcg/ml. The results are presented graphically in **Graph 3**. D-dimer values in non-immunized patients with pneumonia are not significantly higher than the D-dimer values in non-immunized patients without pneumonia.

There is a moderate positive correlation between D-dimer levels and aging (R=0.265). This result is statistically significant, which means that D-dimer levels increase with age**.**

Discussion

Considering the fact that there has been a rising debate among healthcare workers about the significance of D-dimer levels during the COVID-19 infection, the objective of our research was primarily related to identifying the significance of this particular analysis. The statistical data analysis was made in comparison to mean D-dimer values. The two main research questions were as follows:

1. Are vaccinated patients with COVID-19 pneumonia less likely to show coagulation abnormalities as opposed to unvaccinated patients with confirmed coronavirus pneumonia?

2. Is there a statistically significant correlation between the severity of clinical manifestation and elevation of D-dimer levels considering the existing immunization gap?

The following conclusions were drawn from this particular research:

No statistically significant difference was found between the D-dimer levels in patients with pneumonia compared to the immunization status. Therefore, patients with pneumonia were more frequently reported to have elevated levels of D-dimer, irrespective of whether they were vaccinated or not. In addition, COVID-19 patients without pneumonia were reported to have less mean D-dimer values irrespective of their immunization status. On the basis of our research, it should be emphasized that vaccination had no important role in gaining potentially protective immunity against coagulation abnormalities, irrespective of the lung inflammation occurring during the COVID-19 infection.

Based on the previous experiences not only from clinical practice, but the latest research as well, the increase in D-dimer levels is proportionate to the risk of the development of thrombosis [21]. Our research findings contributed to drawing the three significant conclusions as follows: Firstly, patients with pneumonia had significantly higher D-dimer levels compared to the patients without pneumonia, without considering the vaccination gap (P+: 0.96 mcg/ml compared to P-: 0.41 mcg/ml), which is in accordance with the latest findings of our analysis related to the increase in D-dimer levels during the infection.

However, when all the pneumonia-related findings are examined separately, it can be noted that the results of vaccinated participants contribute significantly to the overall result. This means that vaccinated patients with pneumonia are reported to have significantly higher mean D-dimer values compared to the vaccinated ones without pneumonia (V+, P+: 1.12 mcg/ml compared to V+, P-: 0.39 mcg/ml).

Our previous conclusion confirms the argument on vaccination not being able to offer protection against coagulation abnormalities, irrespective of the incidence of pneumonia.

However, when it comes to the group of unvaccinated patients, our research findings demonstrated that mean D-dimer values do not significantly differ between the patients with mild clinical manifestation without pneumonia and the patients with pneumonia (V-, P-: 0.44 mcg/ml compared to V-, P+: 0.79 mcg/ml).

However, the above levels of D-dimer were lower in comparison to the participants in the vaccinated group, the significance of which lies in the fact that the risk factor for thrombosis development and its growth is proportionate to the increase in D-dimer levels, as mentioned earlier.

Taking into consideration the fact that the study was conducted based on the primary care data ob-

tained from electronic health records (EHRs), there are no data for earlier D-dimer values (if they were checked) based upon which it would have been easy to exclude patients with a previously acquired coagulation disorder.

It should be emphasized that in this particular paper it was not possible to conduct a more thorough and detailed statistical data analysis in regard to the type of vaccines used.

Conclusion

Vaccination offered no protection against coagulation disorder, irrespective of the development of pneumonia. Therefore, regardless of the immunization status, if a more severe clinical presentation involved the development of pneumonia, there would be an increase in the D-dimer levels, which would consequently lead to the increased risk factors for the development of thrombosis.

The vaccinated patients had higher mean D-dimer levels once they developed pneumonia, as opposed to the vaccinated patients with mild clinical manifestation. In the case of unvaccinated patients though, the opposite is true – the mean D-dimer levels of unvaccinated patients with pneumonia are not significantly higher than the levels of unvaccinated patients who showed no evidence of this particular respiratory complication.

Our clinical study is valuable and important to clinical practice as it indicates that the vaccinated patients should receive the same thorough treatment just like the unvaccinated ones. Despite the fact that they rarely develop more severe forms of the disease, they can also develop certain complications that can eventually lead to a lethal outcome.

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