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COVID-19 vaccine-related pathologies: cardiac and neurological side effects and Long-term COVID-19

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ABSTRACT: Soon after the commencement of the mass immunization programs, the safety of the COVID-19 vaccines became a top issue. An increase is noticed in the literature in complaints and complications among the public due to a variety of adverse reactions, ranging from the most minor ones like fever, local pain, and myalgias to several potentially serious cardiac and neurological complications like blood clotting, Bell's palsy, myocarditis, hypertensive crisis, pericarditis, and other serious cardiovascular events. Transverse myelitis, cerebral venous thrombosis, and acute inflammatory demyelinating polyneuropathy were only a few among many more conditions. Most of COVID-19 vaccines function through expressing spike protein. They accomplish this either by transfecting the cells with a spike mRNA or by infecting them with an adenovirus containing a spike gene. When spike is expressed, the immune system recognizes it as a foreign antigen and mounts an attack on the protein and consequently on SARS-CoV-2 in case of any contagion. However, the spike protein is the virus's primary mechanism for infection and is accountable for the majority of the complications that COVID 19 brought. When it exists or is produced in sufficient quantities in the body, it can mimic partially a COVID-19 pathological picture, including a cytokine storm, particularly following vaccinations of infected people. In order to know the long-term safety of any new COVID-19 vaccine as any new type of pharmaceutical product, clinical data should be continuously collected for long-term adverse reactions using the country's effective pharmacovigilance systems and questioning the vaccination effect during the diagnosis in hospitals.

KEYWORDS: COVID-19 vaccine; neurological adverse reactions; side effects of mRNA vaccination; Long-term COVID-19, myocarditis, thrombosis.

1. INTRODUCTION

Numerous vaccine candidates have been created using a range of techniques to combat COVID-19 disease, including some based on viral vectors (non-replicating and replicating viral), recombinant peptide/protein subunit/virus-like particles (VLPs), nucleic acid (RNA and DNA), and whole virus (inactivated or attenuated) (Figure 1) [1].

Some of the vaccines developed are BNT162b2 (Biontech), mRNA-1273 (Moderna), GamCOVID-Vac (Sputnik V), Ad26.COV2.S (Janssen/Johnson & Johnson), ChAdOx1 nCoV-19 /AZD1222 (University of Oxford, AstraZeneca and Serum Institute of India), NVXCoV2373, NVX-CoV2373 (Novavax). This vaccine used Matrix-M as an adjuvant; this adjuvant enhances the immune response of the vaccine. Turkovac is based on VLPs which carry non-complete protein fragments from different parts of the virus as the antigenic structures.

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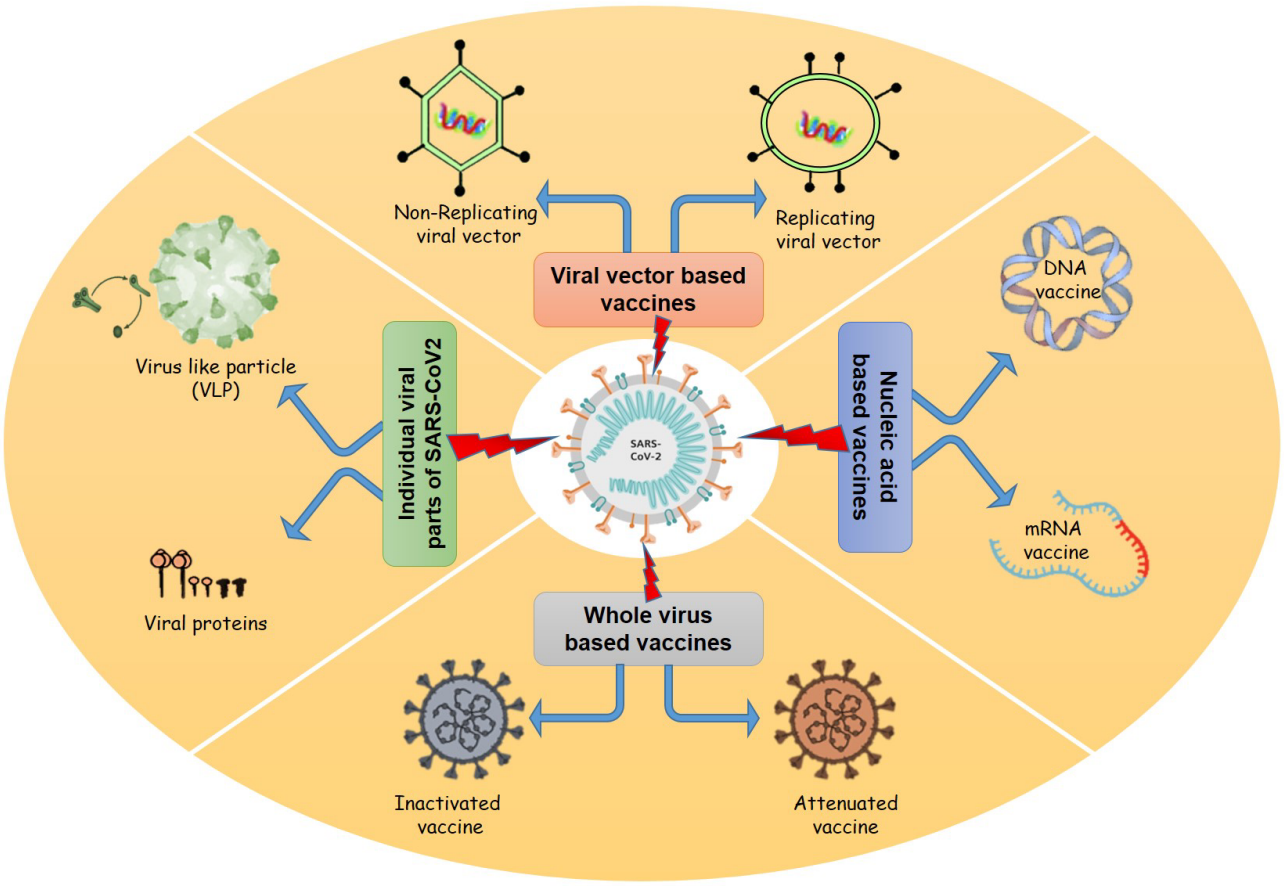

Figure 1. Different vaccination platforms are used to reduce the COVID-19 pandemic. Major vaccination platforms include: nucleic acid vaccines based on DNA and mRNA; vaccines based on recombinant proteins/subunits/VLPs viruslike particles; vaccines based on inactivated or attenuated viruses and vaccines with non-replicating and replicating viral vectors.

The public's worry about the safety of COVID-19 vaccines grew as more stories of severe cardiac and neurological adverse effects appear. More than 130 million doses has been given out in France as of February 2022. 128,766 adverse events (AE) were reported in the first year following vaccination. Prior to the pandemic period, 40,000 AE were recorded annually for all medications [2]. These vaccines were developed in a few months, which seems surprisingly quickly, while the trials for assessing the efficacy and safety were run in parallel, for a relatively short period, which led to the vaccine's emergency approval in a few months.

These vaccines were created in a astonishingly short time (only a few months), while the efficacy and safety tests were conducted concurrently, receiving emergency approval immediately [3]. Both the Moderna vaccine (mRNA-1273, Spikevax) and the Pfizer-BioNTech vaccine (BNT162b2, Comirnaty) use a lipid nanoparticle (LNP) platform to deliver the genetic information (mRNA) necessary to direct the production of the spike protein were among the first vaccines (2020 December) for immediate use. The vaccine's safety profile becomes crucial, especially when taking into account the requirement for frequent booster shots due to the short duration of immunity. These vaccination types also showed negative side effects, such as myocarditis, pericarditis, hypertensive crisis, and other major cardiovascular events, as well as neurological, dermatological, and immunological reactions. There have been recent reports of an upsurge in the frequency of often extremely rare kinds of thromboses linked to thrombocytopenia. Safety profiling of the vaccine becomes pivotal, especially when considering the need for frequent boosting because of immunity waning in only a few months. Particularly in relation to the adenoviral vector vaccine ChAdOx1 nCoV-19 from Astra Zeneca, a rise in the reports of previously extremely uncommon kinds of thromboses linked to thrombocytopenia have occured [4]. Coagulopathies—including thromboses, thrombocytopenia, and other related side effects—are linked to interactions of the vaccine's two components (the spike antigen and the

adenoviral vector) with the innate and immune systems, which, as encountered in some vaccinees, can mimic the pathology of a specific COVID-19 subtype.

The virus's primary mechanism of infection, spike protein, is also the primary target of immune response to vaccines [3]. The majority of COVID-19 vaccines on the market, including all four approved in the U.S. and the EU, function through expressing spike protein in the cells of the host [5]. They accomplish this either by transfecting the cells with a spike-producing mRNA load stabilized on nanoparticles (Pfizer and Moderna vaccines) or by infecting the cells with an adenovirus carrying a spike gene (AstraZeneca and Janssen vaccines). Spike protein functions as the antigen that is taken in, translated in the cell. As a result, the immunological reactions start. Additionally, a synthetic mRNA vaccine technique known as self-amplifying messenger RNA (SAM) has recently been created employing a self-amplifying mRNA produced from an alphavirus genome. Besides the traditional mRNA vaccines, SAM can produce multiple copies of the mRNA in the target cell, resulting in high and extended antigen expression as well as strengthened adjuvanticity in innate immune reaction [6], actually which is quite risky especially in the long term.

4 mechanisms are suggested in COVID-19 pathology: Direct damage by the virus activity; downregulation of the renin-angiotensin-aldosterone system (RAAS) since the blockage of ACE2 blocks the angiotensin II (AngII) cleavage to angiotensin 1-7 (Ang1-7), which leads to suppression of Ang1-7-mediated vasodilation and accumulation of AngII that aggravates pulmonary vasoconstriction and induction of tissue factor (TF) and plasminogen activator inhibitor 1 (PAI-1) expression, inhibiting fibrinolysis and forming thrombosis; endothelial cell damage and immunothrombosis or thromboinflammation; suppression of interferon signaling which lead to downregulation of the immune response leading to hyperinflammation, T cell lymphodepletion, and cytokine storm [5,7]. The course of the disease in SARS-CoV-2-infected people is frequently accompanied with acute respiratory distress syndrome, which includes severe lung injury, coagulopathy, and thrombosis in the alveolar capillaries [8]. It's interesting that issues connected with the presence of spike protein or the translation of spike protein as a result of vaccination have begun to appear among the side effects of various COVID-19 vaccines. The relationship between the side effects and the spike protein following vaccinations can better be understood when the targeted and untargeted actions of spike protein are assessed.

The angiotensin converting enzyme 2 (ACE2), which is found on the membrane of many different cell types, aids in the attachment of the envelope spike (S) glycoprotein to the cell. Two non-covalently bound subunits (S1 and S2) make up the spike protein [3]. ACE2 is found in many organs, such as the lung, kidney, mast cells, brain, testicles, prostate, and uterus, as well as the mucosa of the upper respiratory and gastrointestinal tracts, the endothelium, the platelets, salivary glands, enterocytes, cholangiocytes of the liver, and oral mucosa, bound to the membrane [3,9]. This may be the cause of the multi-organ damages in SARS-CoV-2 infection or circulating in soluble form in the plasma after vaccination. When spike protein binds to ACE2, vasoconstrictor angiotensin II cannot be transformed into peptides with vasodilator properties causing hypertension. After binding, the S2′ is cleaved and later processed by cathepsin or TMPRSS2. Spike proteins are shown to be cleaved by proteases as TMPRSS11A in cell-culture studies. To functionalize the fusion peptide (FP), a second cleavage at the S2′ site is necessary, mediated either by TMPRSS2 on the cell surface or by cathepsins in the endosome [10]. As well as TMPRSS2, other TTSPs or metalloproteases are found to activate spike proteins too. In vitro studies confirmed that furin cleaved at the S1/S2 boundary while TMPRSS2 cleaved at the S2′ site and S2′ binds to the membrane. Once inside the host cell membrane, it is split once more by a protease enzyme at a single arginine or lysine residue that is situated right upstream of the fusion protein. This allows the virus to enter the cell and fuse its membrane with the luminal side of the endosomal membrane. This is the endocytosis pathway. In the non-endocytosis pathway; S2′ creates a central helical bundle with the heptanucleotide repeat 1 (HR1) and repeat 2 (HR2), which are necessary for the fusion of the membranes, before the 6HB is formed by the folding back of HR2 to HR1 and bringing the viral and cell membranes close together, forming a fusion pore through which the viral RNA passes to the other cell. This process requires energy. These two processes are defined in Figure 2.

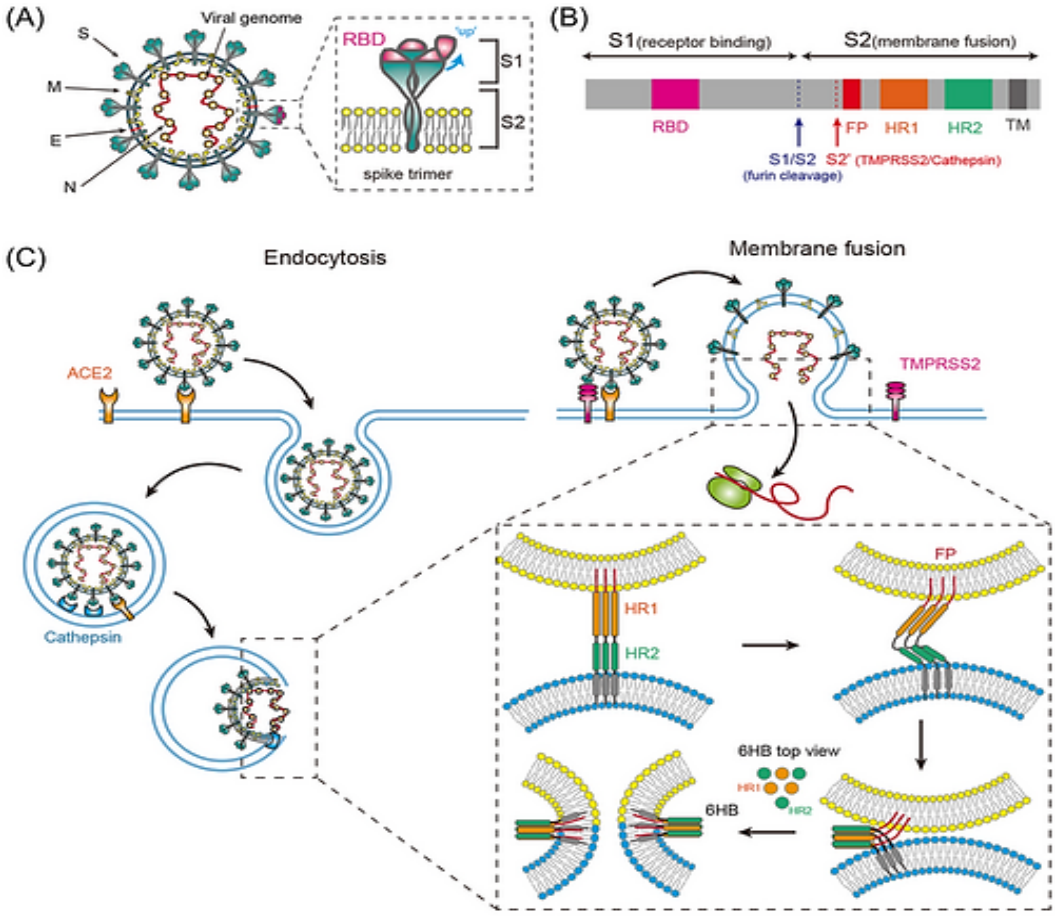

Figure 2. Endocytosis and non-endocytosis pathways of viral RNA passage through cell fusion via the function of spike protein (Reprint from ref. [10]).

As a result of membrane fusion mechanism caused by spike proteins, cell-cell fusion (between similar or different cells) or syncytia formation occurs. Multinucleated cells called syncytia are created when infected cells merge with nearby ones. Syncytia causes the viruses to spread faster, thus may help them to escape from immune system and aids in the pathogenesis of COVID-19 and vaccines.

When human lung microvascular endothelial cells or neutrophils are exposed to spike proteins; transcriptional upregulation of tissue factor (TF), expression and secretion of factor (F)-V, thrombin, and fibrinogen are enhanced; and tissue factor pathway inhibitor (TFPI) regulating blood coagulation extrinsicly, is inhibited [8]. Spike protein activates endothelial cell inflammation through integrin α5β1 signaling [11]. It was demonstrated in vitro and in vivo that the spike protein induces endothelial damage, permeability and leukocyte adhesion to endothelial cells. When spike protein is given intravenously, expression of ICAM1, VCAM1, CD45, TNFα, IL-1β, and IL-6 in the lung, liver, kidney, and eye is stimulated, and when injected in vitreus humor it destroyed retinal capillaries. When spike protein was introduced to the samples, huge, dense abnormal and amyloid aggregates in the whole blood and platelet poor plasma of healthy individuals were observed under scanning electron microscopy (SEM) and fluorescence microscopy [12]. Mass spectrometry also revealed that spike protein S1 interacts with plasma proteins in healthy platelet deficient plasma, making fibrin(ogen), prothrombin, and other coagulation-related proteins significantly more resistant to trypsinization. Blood flow may be hampered by microclots, according to flow analysis research. Thus, it can be concluded that spike protein S1 may be a factor in hypercoagulation and may seriously damage fibrinolysis.

When a virus infects a person, human cells identify the viral RNA as foreign, which sets off defense responses that hinder the translation of the viral RNA into proteins while guiding the destruction of the viral RNA [3]. By switching out uridines for pseudouridines or methyl-pseudouridine, one can prevent the Toll-Like Receptors (TLR) from identifying a foreign mRNA and activating IFN-I. Its translation is stabilized and enhanced by the inclusion of a lengthy poly(A) tail and the 30 untranslated region (UTR) from human globin.

To make it easier for spike protein to enter the cell membrane, a sequence for translation in ribosomes was inserted. Furthermore, while mRNA ratio is 36% in natural SARS-CoV-2, it is 53% in BNT162b2 and 61% in mRNA-1273 vaccines. These could provide an explanation for the various biological and pathological effects in organs located far from the injection site. In humans, the vaccine mRNA's true biodistribution and half-life are yet unclear. Since mRNA is weak and quickly degrades (within a few days), it is attached to the nanoparticles in order to stabilize the molecule [13]. mRNA and spike protein could be detected in axillary lymph nodes even 60 days after vaccination [14] and in the blood of vaccinated individuals after 15 and up to 28 days after the injection of vaccines [15,16]. LNPs (including graphenes in the case of graphene/graphene oxide usage) may fuse with the membrane of any cell they encounter and transmit mRNA [17]. So mRNA may direct the synthesis of the spike protein in all kinds of somatic cells. Transfected cells could free the spike protein and/or its fragments following T cell killing, and S1 (which is cleaved from S1 in Golgi Body) could be spilled to outside of the cell. Supporting this, high amounts of soluble spike proteins have been detected in the circulation of vaccined individuals who developed myocarditis [18]. Both B lymphocytes and antigen-presenting cells can quickly endocytose the soluble spike proteins. Exosomes with the spike proteins on the membrane that are released by the transfected cells can also help to enhance the immune reactions antigen presenting cells in other distant organs [9]. Unpredicted results are encountered with mRNA vaccines, since transfection with mRNA and translation to spike protein can nonspecifically take place in various cells in organs that they reach. The pathways of the spike protein determines which cells will be transfected and the type of the disorder that may occur.

The Novel Coronavirus (SARS-CoV-2) illness can range in severity, causing multi-organ failure and acute respiratory distress syndrome, or it might not show any symptoms [19].Some individuals may show nosymptoms in the post-COVID period. Infected individuals with COVID-19 may feel exhausted for a long time, and their activities of daily life (ADL) performance may be compromised after COVID. Following an activity, there may be an increase in dyspnea, weariness, and muscular fatigue perception. Since a large amount of active mRNA was provided to produce a sufficient level of spike protein that can induce illness, similar symptoms are frequently reported following the immunization. The elderly, children, pregnant women, and unborn children may experience additional side effects if the dose is not modified because all age groups receive the same dosage. Furthermore, the boosters will increase the production of the existing spike proteins and bring forward the risk of autoantibody production which means that the transfected cells will fall prey to the hostility of already generated antibodies or cytotoxic T8 lymphocytes. In this case, worse complications may occur and include many organs to be effected where the spike protein reaches and localizes. CD8+T cells will attack and kill any cell that is generating spike protein and locating it on its membrane. The type, quantity of the effected cells and tissues where the reactions take place will all determine the level of the severity of the pathologies. For instance, the phenomena that myocarditis is more common following the second dose and that it appears after a few days [3,20], show that most probably an auto-immune reaction takes place. To summarize, spike protein triggers not only the immunogenity, but some pathological conditions as well. The spike proteins originated from the vaccines act like virus-derived homologs, and the pathology occurs on the organs in which the spike proteins are generated and disseminated [3]. For example, the same mechanism shown in Figure 3 will probably work fully/or partially, regarding the degree of fusogenity; for the effects on the pathophysiology of the blood and cardiovascular system as a result of the change in the renin-angiotensin system (RAS) equilibrium which is altered by binding spike protein of the virus to the ACE2 receptor**.** The complications given here are also supported also by the increasing number of studies on such AE in the world.

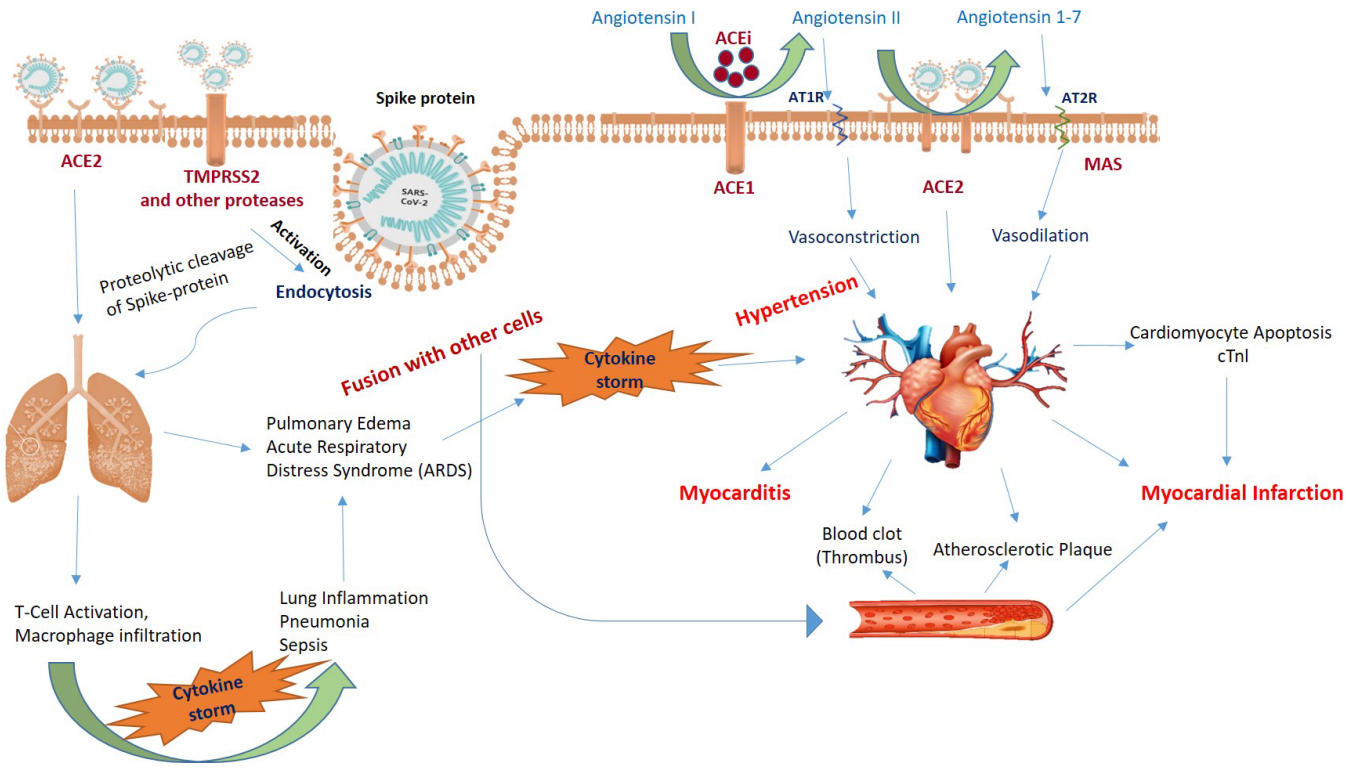

Figure 3. Cardiovascular and pulmonary side effects brought on by the spike protein of the SARS-CoV-2 virus. ACE1, angiotensin I-converting enzyme; ACE2, angiotensin-converting enzyme 2; ACEi, ACE inhibitor; ARBs, angiotensin II type-I receptor blockers; AT1R, angiotensin type 1 receptor; AT2R (Modified from ref. [164]).

mRNA can enter into human liver cells rapidly and reverse transcribed to the DNA in a few hours [21]. If the mRNA message is reverse-transcribed to DNA, which is more stable, it means that the spike proteins will be synthesized and remain in the host for long periods. Two months after immunization, vaccine-originated mRNA and spike protein have been found in the germinal center of secondary lymphoid tissues, indicating ongoing stimulation of spike protein synthesis [14]. Recently, spike proteins were found circulating in the blood of mRNA vacinees hospitalized for myocarditis [18]. Surprisingly, the spike protein content was quantifiable until three weeks after immunization and was substantially higher in symptomatic vaccinees than in asymptomatic ones (mean: 33.9 vs 22.4 pg/mL).

A critical point has been ignored in the development of many vaccines: Encountering the whole virus instructs the immune system thoroughly, thus even if a virus component changes due to gene mutations, the immune memory for the conserved viral components can still start an immune response [3,20]. Moreover, a complex immunologic response that neutralizes the virus can be effectively obtained using different fragments of the virus presented to lymphocytes by antigen presenting cells. At this point it brings to mind that VLP as in Turkovac could be a very safe method of immunization because it carries four parts from each of the virus proteins without any complete action as spike. New variants caused by mutations in the S protein include the B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) lineages (www.who.int, accessed on June 22, 2021). This has led to major concerns about the vaccine's efficacy declining [22]. At this point, vaccines based on VLP brought an advantage of immune responses targeting not only the spike protein (S) but also other viral proteins, including the matrix (M), envelope (E), and nucleocapsid (N). The advantage of VLPs in immune responses that target not only the spike protein (S) but also other viral proteins, such as the matrix (M), envelope (E), and nucleocapsid (N), has been proved by the clinical results of vaccines based on VLP [23,24]. Turkovac, a product made in Turkey based on VLP, uses protein particles made up of 4 separate sections to elicit an immune response in the safest manner. Primary and the booster doses were applied in 15 provinces in Turkiye (February and May 2022) and a cohort study with 29,584 volunteers who had participated in survey. Feedbacks are gathered minimum of 10 days following the vaccination [25]. 0.5% of the participants (142 individuals) reported to experience any allergic reaction. No immediate or anaphylactic

reaction was reported. In another study, two-dose regimens of TURKOVAC 3 µg and 6 µg, had an acceptable safety and tolerability profile and elicited comparable neutralising antibody responses and seroconversion rates exceeding 95% at day 43 and 60 after the first vaccination [26]. The most frequent side effect was pain in the injection site. There were only flu like symptoms (fever, headache, vomiting) and no severe side effects were found no myocarditis except one case who has died during excessive forcing sports at 55 year old.

SARS-CoV-2 illness can range in severity causing complications such as multi-organ failure and acute respiratory distress syndrome, or it might be asymptomatic [19]. Some patients may also be asymptomatic in the post-COVID period. Patients with COVID-19 may experience prolonged fatigue, their ADL levels may be affected in the post-COVID period. Dyspnea, fatigue and muscle fatigue may be higher after the exercise. The similar symptoms were experienced after the vaccination since a high amount of active mRNA was given to produce an enough level of spike protein that can cause sickness. Since the same dose is given to all age groups, the elderly and children, as well as pregnant women and unborn children, may have additional consequences if the dose is not adjusted.

Producing an original safe and effective vaccine in a short time brings some challenging consequences challenges [27]. Undesirable immunopotentiation, which frequently occurs following vaccinations with entire virus or whole spike protein vaccines, has been one of the challenges in the early development of SARS coronavirus vaccines. Second, there are growing worries about the negative impacts that vaccinations might have, such as aggravation of existing lung and cardiovascular conditions. During the pandemic, the most vulnerable groups, like the elderly and healthcare workers, were given priority for these vaccination trials; however, the safety of the vaccines should have been thoroughly assessed before these groups were risked. The formulation components, the composition of the LNPs, graphene, etc. and the choice of the vaccine RNA sequence, as well as other factors could also affect the side-effect profile [28].

1.1.Common and rare side effects of COVID-19 vaccines

Many types of side effects were reported by vaccinated individuals. 1,086 participants who received one dose or both doses of any vaccines provided in Jordan were included in a cross-sectional survey. (AstraZeneca, Pfizer, Sinopharm) [29]. 77.2% were not infected before the vaccine application. 40.6% of the participants received Pfizer vaccine, 33.0% with AstraZeneca and 6.4% with Sinopharm vaccine. 89.9% of the participants reported side effects after receiving the first dose of the vaccine (pain at the injection site (78.4%), fatigue (51.8%), myalgia (37.6%), headache (33.1%), chills (32.3%), nausea (15.1%), loss of appetite (9.4%), and diarrhea (6.4%). Side effects are reported merely with AstraZeneca vaccine ($P < 0.001$). Hospitalization was reported in 0.7% of the participants who had the second dose of any of COVID-19 vaccines. In this study, the order of the side effect ratio that the people have experienced was: AstraZeneca > Pfizer > Sinopharm. Besides the mild effects that are encountered more frequently, serious side effects such as anaphylaxis, especially to a vaccine component as polyethylene glycol (PEG), etc are also reported. Palpitation was notably higher among females. In comparison to Sinopharm and Pfizer vaccines, the initial dosage of the AstraZeneca vaccination was related with significantly more reports of bone and muscular pain, flu-like symptoms, gastrointestinal (GI) symptoms, psychological symptoms, cardiac symptoms, and dizziness. Notably, two cross-sectional studies including healthcare personnel who received the Pfizer vaccination experienced localized lymphadenopathy. Females had more tendency to show complications.

In the Czech Republic, injection site pain (89.8%), fatigue (62.2%), headache (45.6%), muscle pain (37.1%), and chills (33.9%) were the most frequently reported side effects [30].The duration of the side effects was 1-3 days. Side effects were more common with two doses. 114 (13%) participants had at minimum one oral complication after immunization with BNT162b2 mRNA vaccine . The most common oral adverse reactions were blisters (36%), halitosis (25.4%), ulcers (14%), bleeding gingiva (11.4%), and white/red plaque (10.5%). Vesicles, blisters, burning gingiva, swollen lips, angular cheilitis, xerostomia, taste disturbance, and tongue tingling were more frequently reported after two doses. Single-dose group had the average number of oral complications. In the quidelines of the Centers for Disease Control and Prevention (CDC), it was declared that individuals with a history of any immediate allergic reaction to vaccines or injectable drugs should be vaccinated with high precaution. Individuals who had experienced severe allergic reactions (as anaphylaxis) after the first shot or allergic to a component of the vaccine such as PEG are not recommended to be vaccinated at this step.

The early complications were reported in a 2021 study that included 321 medical professionals who received the COVID-19 vaccine in Turkey and voluntarily included in the study (%55.6 female, %79.8% under 40, %67.1 nurses, %15.2 physicians, and %17.4% laboratory workers) are given in Table 1 [31].

Table 1. The early complications of the most frequently administered COVID-19 vaccines in Turkey (Modified form ref. [32]).

Adverse Reactions	Sinovac		**Pfizer-** BNT162b2 mRNA vaccine	
Local	**n**	**%**	**n**	**%**
Injection Site Abscess	4	6.0	5	2.0
Injection Site Swelling	12	17.9	33	12.9
Injection Site Redness	19	28.4	66	26.0
Injection Site Heat Increase	22	32.8	78	30.7
Injection Site Pain	31	46.3	141	55.5
Disfunction	3	4.5	12	4.7
Injection Site Itching	10	14.9	26	10.2
Other	8	11.9	24	9.4
Systematic	**n**	**%**	**n**	**%**
Anaphylaxis	3	4.5	25	9.8
Headache	10	14.9	39	15.4
Fever	17	25.4	54	21.3
Urticaria / Skin Rash	13	19.4	54	21.3
Dizziness	1	1.5	5	2.0
Whole body aches	37	55.2	149	58.7
Vomit	3	4.5	14	5.5
Lack of Appetite	1	1.5	12	4.7
Other	3	4.5	25	9.8

In another study, an on-line survey via questionnaire was performed on 803 healthcare workers, where 92.9% had received both doses of the BNT162b2 mRNA vaccine and 7.1% only the first dose during the study. Various symptoms were reported as musculoskeletal (53.3%); gastrointestinal (21.42%); psychological/psychiatric (16.56%); neurological (12.7%); head/ear/eyes/nose/throat (12.08%); endocrine (10.34%); cardiovascular (5.98%); respiratory (2.61%); urinary (1.24%); and allergic (beyond rash) (1.24%). Among these, the most frequent ones were: arthritis/joint pains (16.56%), brain fogging or reduced mental clarity/attention/concentration (5.85%), palopitations were more frequent (4.36%), heat/cold intolerance (3.24%), lymphadenopathy (axillary or regional) (3.36%), numbness (2.86%), vertigo like symptoms (2.49%), rash (2.49%), shortness of breath (1.99%), chest pain (1.12%), heartburn (1.12%), cough (0.87%), blood pressure changes (0.87%), urgent need to urinate (0.75%), decrease in memory (0.75%), hives (0.62%), paralysis/extremity weakness (0.62%), incoordination (0.50%), frequent urination at night (0.37%). 12.83% of the participants experienced trouble to perform regular daily living activities temporarily, 12.33% required transient time off from work and 2.49% required to seek help from outpatient provider.

Researching the effectiveness and adverse effects of various vaccines among various populations is vital because of the genetic variety in distinct communities around the world [32]. Infected patients who were deteriorating displayed more side effects (92.4%) after vaccination, than the group without a history of infection. For both of the AZD-1222 and Covaxin vaccinations, the frequency of adverse effects was higher in overweight vaccinees (BMI>25).

In 2020, simple adverse effects were reported for enrolled 43,252 participants, with variable follow-up time after dose 1; more BNT162b2 recipients than placebo recipients reported any adverse event (27% and 12%, respectively) or a related adverse event (21% and 5%). Simple side events were reported for 43,252 participants who had been enrolled in the study in 2020, with different follow-up times following first shot. BNT162b2 vaccinees reported more adverse event (27% and 12%, respectively), as well as a connected adverse event (21% and 5%), than placebo recipients [33]. Fatigue and headaches were the most often reported systemic side effects at a rate of 39% to 59% after the first dose and 14% to 24% after the second. With the exception of weariness (3.8%) and headaches (2.0%) after the second dosage, the rate of systemic complications were less than 2% after either dose. Another study from 2020 found that vaccinees experienced grade ≥3 (serious) local and systemic side effects (grade 3: interfering with daily activity) more frequently than placebo recipients [34]. The most frequent complications among vaccinees were weariness (4.2%), headaches (2.4%),

muscle pain (1.8%), chills (1.7%), and pain at the injection site (1.4%). In general, grade 3 reactions were less common in older participants than in younger participants and were more frequent after the second dose than after the first dose. Also another 2020 study [35] that used the vaccine in low, moderate, or high doses in three group of participants and a 28-day follow-up period, found that the most often reported systemic adverse responses were fever (46%), fatigue (44%), headache (39%), and muscle discomfort (17%). While specific T-cell response reached maximum at the 14th day post-vaccination, ELISA antibodies and neutralizing antibodies reached maximum at 28th day post-vaccination. These side effects, which manifested quickly, demonstrate the necessity for longer time periods to monitor potential side effects.

In the former studies, vaccine-induced enhanced susceptibility to infection with certain viruses like feline coronavirus, has been shown that antibody-dependent enhancement (ADE) plays an important role [36]. So it should be clearly illustrated with further studies including large populations (comparing vaccinated with unvaccinated with 5 or 6 months observation periods) that if multiple vaccination may increase susceptibility to the risk of COVID-19 infection. Besides contamination due to a possible carelessness while the same vial is used to provide many doses to various people in some centers in the world, longer investigation times revealed some cases of complications and death associated with COVID-19 vaccines [37]. In January 2021, a death from intracranial haemorrhage (56-year-old male) and post-vaccination thrombocytopenia were reported in the United States several weeks after vaccination with BNT162b2, a Pfizer mRNA vaccine [38]. In addition, there are a number of reports of decreased platelets after vaccination in patients with immune thrombocytopenia (ITP) 2-4), and the Japanese Society of Hematology issued a warning in July 2021. Since then, information on the side effects caused by vaccination has been collected in many countries of the world and information based on objective data has been accumulated.

In Saudi Arabia, a cross-sectional quantitative study was conducted to investigate short-term side effects of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines, among the general population with age ≥ 18 years, in Central, Northern, Eastern, Southern, and Western Regions for a period of 6 months (July to December 2021) [39]. Some of the notable complications are (<10%) heaviness, inability to concentrate, fainting, palpitations, blurred vision, sleep disturbance, osteomalacia. Blood clots or thrombosis along with low platelet count was reported for AstraZeneca vaccine by the Saudi-FDA. In Jordan, some vaccinees experienced gastrointestinal side effects (nausea, vomiting, and diarrhea), ear complaints, face pain, drowsiness, diuresis and respiratory side effects (dyspnea) [40]. Common side effects of mRNA vaccine were reported in literature as fatigue, headache, myalgia, chills, and pain at the injection site. Such complications were dose-dependent and were more common after the second immunization. According to EMA, 30 cases of thromboembolic complications were reported for Vaxzevria by March 10th, 2021, regarding ~5 million vaccinees in Europe. Persistent and very severe headaches were reported for 2–3 weeks after vaccination (which brings the need of searching a possibility of cerebral venous thrombosis). The European Medicines Agency (EMA) defined thrombocytopenia as a new frequent adverse reaction on 16 April 2021 (in <1/10 individuals) and thrombosis combined with thrombocytopenia as a new very rare adverse reaction (in <1/10,000 individuals). Two herpes zoster cases (which is a pathology for suppressed immunity) were also declared. The ability of SARS-CoV-2 to induce recurrent opportunistic viral skin and mucous membrane infections have been reported in previous literature. Because of the spike protein pathology shows similarity, it seems that the influence of the vaccine on the immune system should not be underestimated. In another survey study performed in Jordan, a total of 2213 participants were involved in the study after receiving Sinopharm, AstraZeneca, Pfizer-BioNTech, and other vaccines (38.2%, 31%, 27.3%, and 3.5%, in order) and the frequencies of side effects that were noted after receiving COVID-19 vaccines are given in Figure 4 [41].

In a review of research, 45 incidences of thrombosis between 4 and 26 days following the initial dosage of Vaxzevria (Astra Zeneca's viral vector vaccine) were identified [42]. 1/3 of the female patients under 60 years old (who constructed the majority of the participants) had predisposing factors for thrombosis, including hormonal contraception or replacement medication, Hashimoto thyroiditis, hypertension, and a recent pregnancy. Primary sclerosing cholangitis and Von Willebrand disease were also noted as prothrombotic comorbidities. The majority of the patients in this review had previously been healthy, however the case-fatality rate of the 45 cases was 44%.

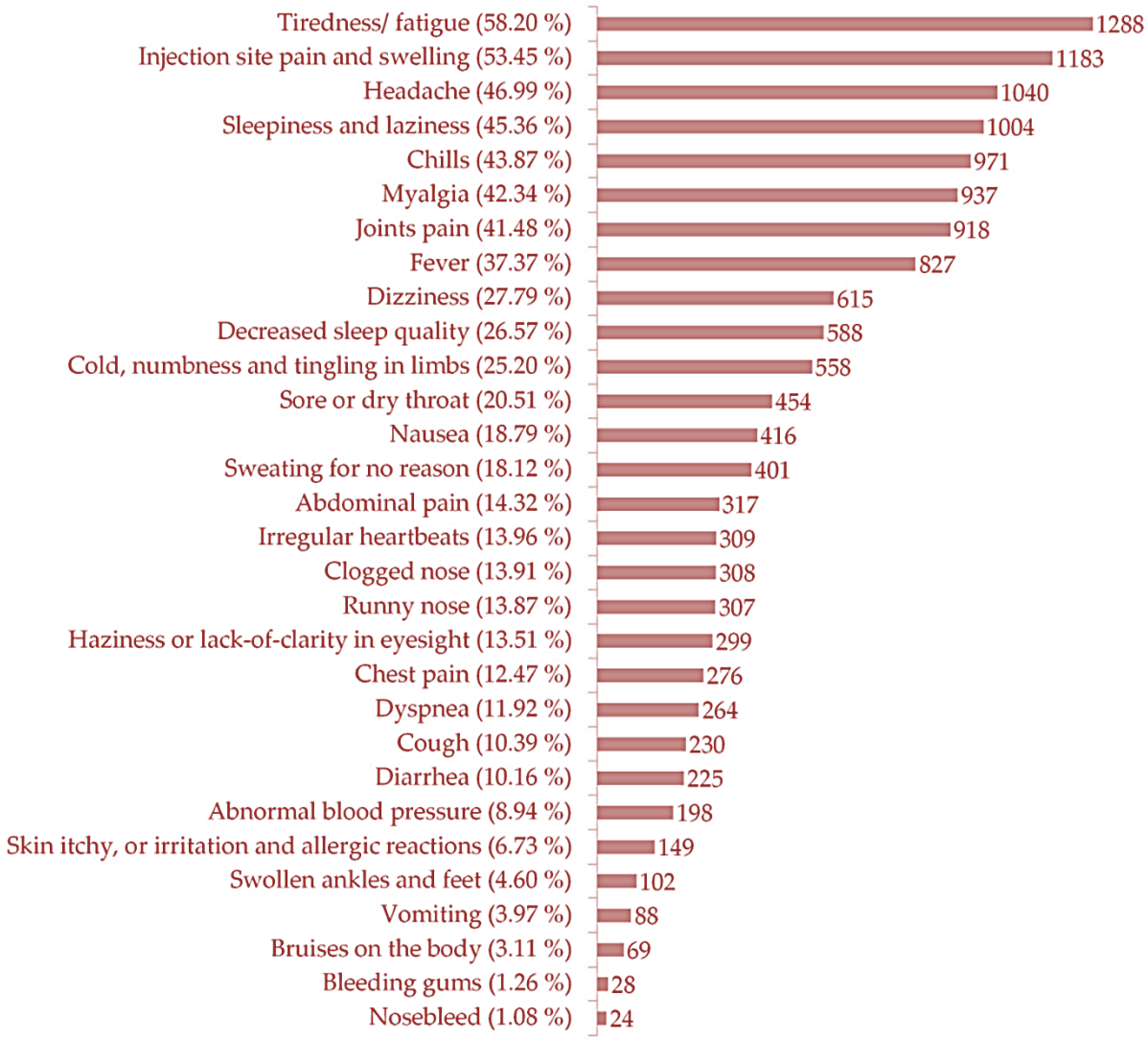

Figure 4. Frequencies of side effects that appeared after receiving COVID-19 vaccines a randomized, cross-sectional study (Reprint from ref. [41]).

A quite long list of serious side effects of COVID-19 vaccines were demonstrated in the literature. It is impossible to investigate each of them under a group. In this review, we have focused on cardiovascular, neurological and immunological complications**.**

1.2.Cardiovascular complications

1.2.1.Myocarditis

According to the CDC, since April 2021, more than 1000 cases of myocarditis and pericarditis have been reported to the Vaccine Adverse Event Reporting System after mRNA COVID-19 vaccination (i.e., Pfizer–BioNTech, Moderna) in the USA [43]. On 25 June 2021, the patient and provider fact sheets of FDA were changed considering the increasing myocarditis and pericarditis risks appearing after vaccination. A total of 23 male patients between 20-51 years old with a median age of 25 (where 22 were in active military duty and 1 was retiree) demonstrated acute onset of marked chest pain within 4 days after mRNA vaccination [44]. All military personnel were previously fit and in good health. 16 of them received the mRNA-1273 immunization whereas seven received the BNT162b2-mRNA vaccine. Twenty individuals in all experienced the onset of symptoms after the second dose of a two-dose series with proper intervals. Heart troponin levels were markedly increased in each case. In the acute stage of their disease, 8 individuals received cardiac magnetic resonance imaging (MRI), and all of the results were consistent with the clinical table of myocarditis.

Additional testing failed to detect alternative causes of myocarditis, such as underlying autoimmune diseases, acute COVID-19 and other infections, ischemia injury, or other etiologies. Myocarditis was discovered in these 23 male patients, 4 days after COVID-19 vaccination.

Following vaccination with mRNA COVID-19 vaccines (ie, Comirnaty and Spikevax), myocarditis and pericarditis can develop within a few days of vaccination, particularly following the second dose [45]. US Vaccine Adverse Event Reporting System received 1226 reports of myocarditis after mRNA vaccinations during December 29th, 2020–June 11th, 2021; with a median symptom onset time of 3 days (range=0–179) following administration (median age: 26 years (range 12–94 years)). 76% occurred after receipt of the second-dose of mRNA vaccine (after both Comirnaty and Spikevax). Myocarditis in 139 adolescents and young adults were also reported from US medical centres. 90.6% of them were male (median symptom onset: 2 days, median age: 15.8 years). Some researchers claim that, the Individual Level Benefit-Risk Analysis Calculations based on per million second doses of mRNA COVID-19 vaccine administered March 27, 2020, [46]: 560 hospitalisations, 11 000 COVID-19 infections, 6 deaths and 138 ICU admissions could be prevented, compared with 39–47 expected cases of myocarditis due to vaccine administration and thus; the benefits (prevention of disease and hospitalisations, ICU admissions, mechanical support of the cardiorespiratory system and deaths from COVID-19) clearly outweigh the risks (expected myocarditis cases due to vaccines). However a question should be asked here: In this one million second-dose vaccinated group, how can we be sure that X cases of COVID is prevented? This calculation can only be done assuming that all unvaccinated healthy people will be infected certainly as in the rate of the previous term and 11.000 decrease from the previous infection number is called prevention. But this is not the case. If decrease is followed, the mutation and the decrease of the virulence of the variant most probably contributes to this decrease. It looses its virulence as the time progresses. It cannot be associated only with mass vaccination, the decrease of virulence and the increase of awareness with social distance and protective measures have certainly a role in that. A pandemic disease as influenza becomes less dangerous and infective after a duration that is represented with a gauss curve Figure 5.

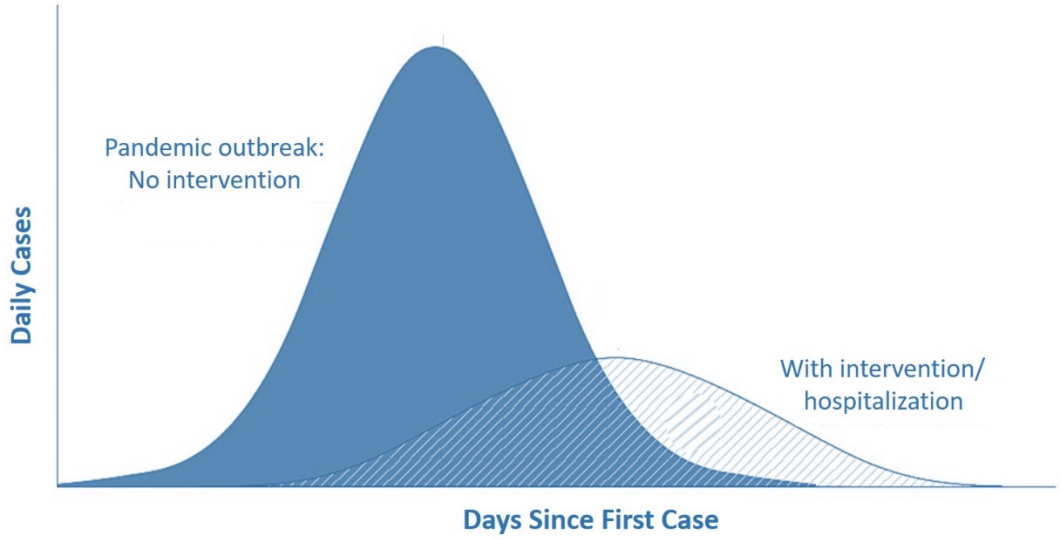

Figure 5. A comparison of the time-lengths and the number of the daily cases of COVID-19 pandemic outbreaks in case of applying interventions and applying no interventions in the U.S. (Modified from ref. [47]).

With interventions, the protective measurements decrease the transmissions, but there is a fact that the normal unintervened period also arrives to a sharp decrease normally. It should be taken into account at which period the vaccination regarding Fig 5, has started when mentioning about the decreases compared to the previous period of time in the pandemic. Furthermore, there are many unvaccinated individuals who have not been infected or infected without application to hospital and for a PCR test. Of course as the hospitals became full, the authorities adviced to the people not to apply to hospital with slight symptoms or simple headaches. So some individuals in the population directed themselves to home therapies. Patients started to heal with the traditional infection treatments. It must not be ignored as a factor in the decrease of

hospitalization. Some remained home along with the on line possibility work activities and isolated while working in their jobs and travelling less. In various papers, the current hypothesis accepts that all the unvaccinated individuals will have COVID-19 and because of this vaccinated individuals are compared only with the COVID infected patients. For the right statistical result, death rates in vaccinated (in the near or far past, with one or more dose) and unvaccinated individuals (including near or far history of COVID infection) should be compared. At that time, the general contributive risk that COVID infection would also be included in the statistics.

In calculation of myocard infarction rates in various papers, COVID infected and vaccinated individuals are compared. The comparison should be performed between vaccinated and unvaccinated. Because if the rates of myocard infarction in vaccinated population is compared with the infected population this would automatically and unsuprisingly give higher rates for infection, from the point of incidence of complications. In the case of Spikevax, the French study showed that in a period of 7 days after the second dose there were about 1.3 extra cases of myocarditis in 12–29 year old males per 10 000 compared with unexposed [48]. A Nordic study reported that there were ≈1.9/10 000 extra cases of myocarditis compared with unexposed, after 28 days following the second dose of Spikevax for males with age of 16–24 years. The study mentions myocarditis as 'very rare' risk, higher among younger males; but concluding that vaccination benefits clearly outweigh the risks (The acceptions here as in various studies are held as all unvaccinated will be infected with COVID-19, so the risk is defined and compared for unvaccinated infected individuals and vaccinated, not for uninfected-unvaccinated). The long- term implications in vaccinated individuals are not yet known.

Young males between the ages of 12 and 29 had the highest relative incidence of myocarditis following the second dosage of the Moderna mRNA vaccine compared to the Pfizer-BioNTech vaccine [49]. Administration of the second dose after 30 days of the first dose, decreased the risk of myocarditis/pericarditis [48,50]. External causes registered in England had a higher proportion of deaths registered in 2021 occurring in 2020 and prior years compared with diseases of the circulatory system (Table 2).

Table 2. Death ratios by year of occurrence of death versus 5 years total deaths registered in England in those aged 15 to 29 years, regarding the selected causes (Modifier from ref. [48]).

Underlying cause of death	Underlying cause of death				
	2021	**2020**	**2019**	**2018**	**2017**
All causes	56,5%	32,3%	8,5%	2,0%	0,7%
Diseases of the circulatory system	**79,3%**	18,3%	2,5%	0,0%	0,0%

By November 2022, 1485 athlete collapses and health issues after vaccination appeared, of which 1014 athlete died after covid vaccination. Most were cardiac arrest, the others were blood clots or thrombosis, stroke, irregular heartbeat, arrhythmia, neuropathy and death [51].

Again the incidence of myocarditis after the first and second doses of the SARS-CoV-2 mRNA vaccine was found to be the highest in young boys aged 16 to 24 years after the second dose in a cohort analysis of 23.1 million individuals across four Nordic countries [20]. Data were compatible for 100 000 individuals who received the second-dose, exhibiting 4-7 excess complications for BNT162b2 and 9-28 for mRNA-1273, in 28 days, in young males. Within 28 days starting from the day of SARS-CoV-2 mRNA vaccinations, rates of myocarditis and pericarditis were found to be higher than in the unvaccinated group. These risks were highest within the first week following first vaccination for mRNA vaccines and increased after the second dose, the risks of myocarditis and pericarditis became more pronounced. Despite this information, the use of mRNA-1273 in people 18 years of age and older and BNT162b2 in people 16 years of age and older, has been fully permitted by the US Food and Drug Administration, with the argument that the risk rates are low and the advantages of immunization outweigh the dangers.

1.2.2.Cell Fusion and Thrombosis

Since the spike protein expressed by viral vectors or by transfection, fuses human cells in the dish [52–54], and that spike protein fuses cells even if expressed in undetectable amounts [52], it is reasonable to extrapolate that spike protein introduced through vaccines does fuse some cells in the injected individuals [5] just as its expression by SARS-CoV-2 and fusing cells in COVID-19 patients [55,56] and this fusion can be pathogenic.

Fortunately, spike proteins used in the other three vaccines has been modified to decrease fusogenicity while improving spike's antigenic properties. In some vaccines; the structure was stabilized via two mutations that supress the conformational change due to binding to ACE2, thus inhibits cell fusion in tissue culture assay by several fold [5,57]. To change the location that furin recognizes (which is a protease that aids the activation of spike protein by cleaving it into two subunits), two more mutations were added to the Janssen vaccine substantially reduced this incidence. It is unknown if these additional mutations continue to function as well in the human body, because other proteases can take the place of furin and this cleavage site maybe different changing the incidence or location of some pathologies [5]. The S2' site whose cleavage is important to activate the fusion peptide, was not modified by any of the vaccine manufacturers. Vaccines that use spike fragments or derivatives that are not fusogenic, are expected to exhibit less side effects. Vaccines that use inactivated virus (e.g. Sinovac) have an intermediate incidence of side effects [58,59], because spike proteins introduced via inactivated viruses can still fuse cells, the incidence of syncytia is limited by the number of injected viral particles, however much more data is needed to be compiled via pharmacovigilance systems.

The fusion of endothelial cells to each other or others carrying a spike receptor in the blood may cause thrombosis, while the fusion of neurons may cause neurological pathologies (Figure 6). Some side effects arising from cell fusion may be specific to a certain vaccine or to COVID-19 since the action paths regarding SARS-CoV-2, mRNA-carrying lipid particles or adenoviral vectors are close but not exactly the same [5] as in the AstraZeneca vaccine sample which has the highest rate of adverse effect reports among the four most used vaccines (Figure 7).

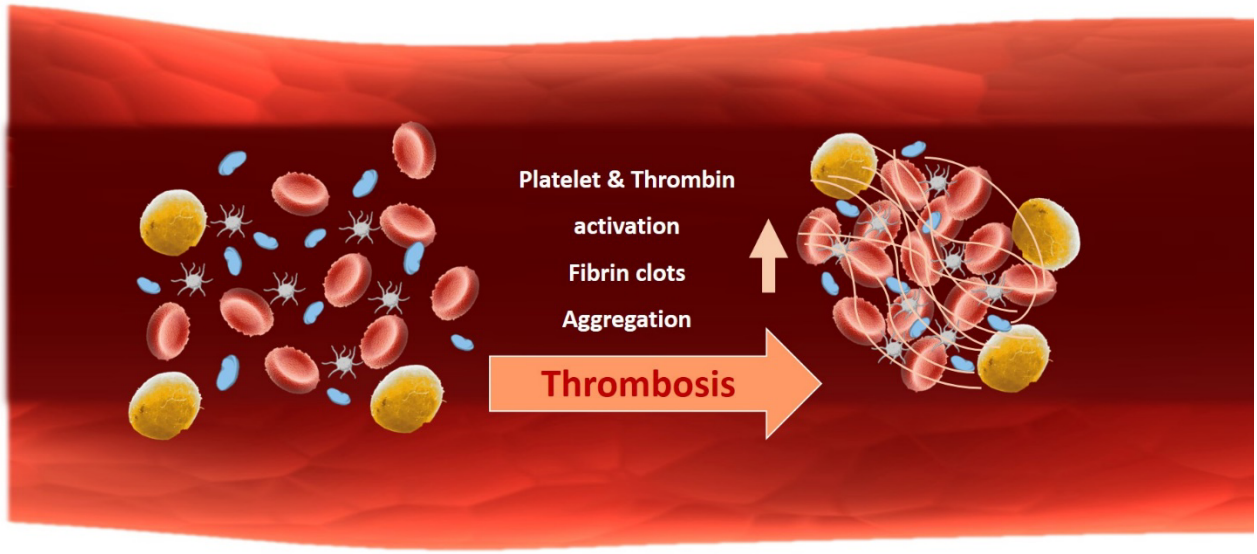

Figure 6. Thrombosis as a result of fusion of cells carrying a spike receptor, inside the blood.

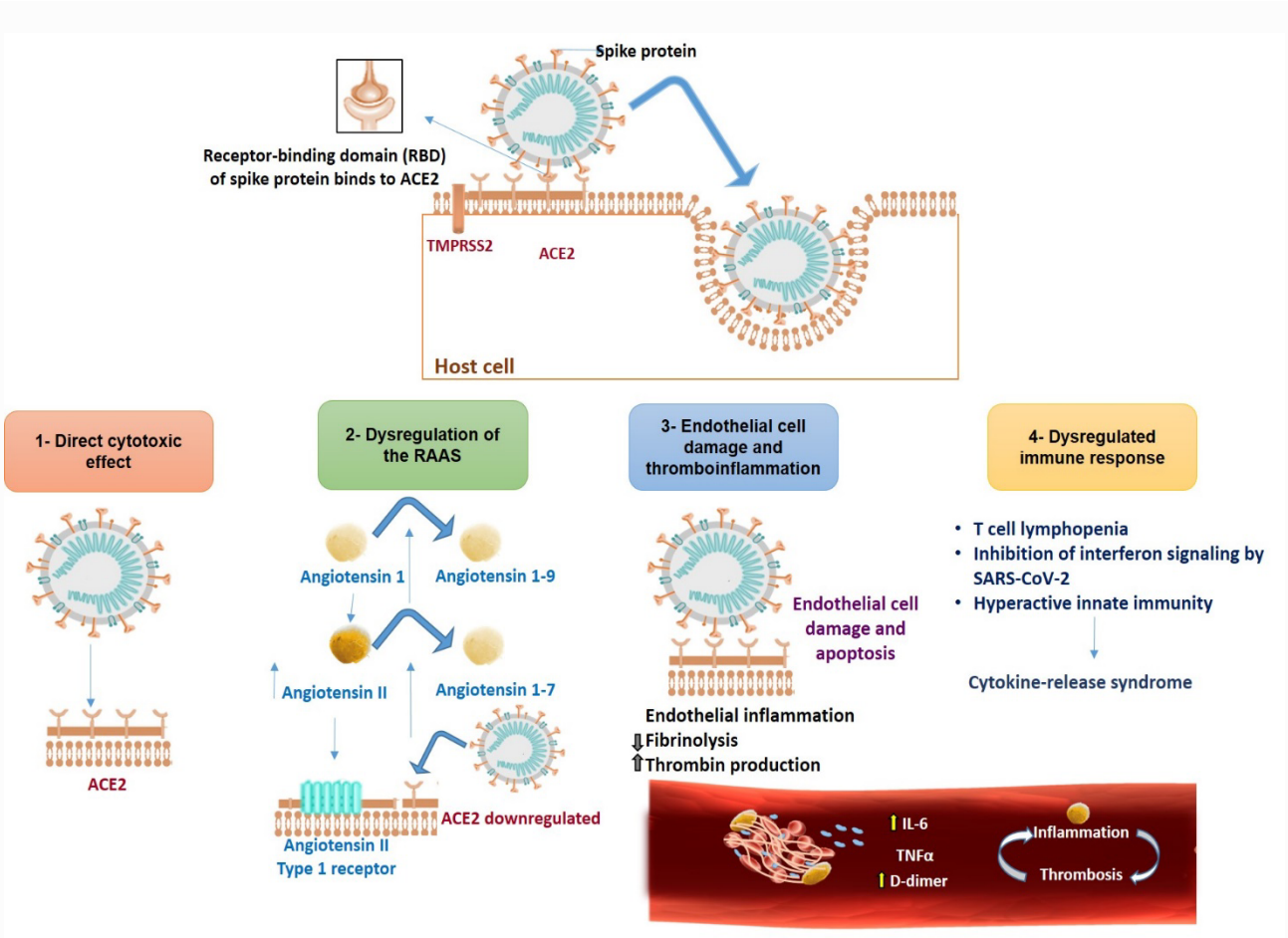

Figure 7. A summary of biochemical mechanisms of different pathological effects of spike protein (Modified from ref. [5]).

Vaccine-induced immune thrombotic thrombocytopenia (VITT) and thrombocytopenia-associated thrombocytopenia are also observed side effects profiles [38,60]. According to data from the US Vaccine Adverse Event Reporting System (VAERS), 77 cases of new-onset immune thrombocytopenia (ITP) have been reported after vaccination through March 2021. A half of the vaccines used were BNT162b2 and half were mRNA-1273, and the median time from vaccination to the onset of Immune Thrombocytopenia ITP was 8 (0-38) days. 77% developed symptoms after the first dose, 23% developed symptoms after the second dose, and 32% had a history of autoimmune disease. As a mechanism by which COVID-19 vaccination causes ITP, mechanisms such as the production of antibodies that cross-react between viral proteins and platelets) have been proposed. The causal relationship between the novel coronavirus vaccine and the onset of ITP is expected to become clear in the future as vaccine-related AE accumulate. Based on current information: ITP exacerbations may occur in approximately 10% to 20% of patients and careful monitoring of platelet count and bleeding symptoms after vaccination is considered necessary.

In March 2021, several European countries, banned the use of AZD1222 vaccine due to case reports of unusual and complicated thromboembolism with thrombocytopenia [61]. In a study performed including Norway, Finland and Denmark; more than 5.3 million people were vaccinated with either 1 or 2 doses, 4 265 343 (80%) with BNT162b2, 635 039 (12%) with AZD1222. In particular, AZD1222 has been associated with an increased incidence of hospital visits for thromboembolic disorders, in particular for thrombocytopenia and an increased risk of cerebrovascular disease, especially cerebral vein thrombosis. Also significant increases in the risk of hospital contacts have been reported for thrombocytopenic and thromboembolic events after BNT162b2 and mRNA-1273. An incidence of 20.25 (95% CI, 8.14-17.0) was found for CVT and 3.02 (95% CI, 1.76-4.83) for thrombocytopenia related to AZD1222 vaccination among individuals between 18 and 65 years. It was also reported that subarachnoid and intracerebral hemorrhage (SAH) which can be primary or secondary to venous thrombosis may arise following COVID-19 vaccine administration [62].

As vaccinations are widespread, catastrophic cases of thrombosis started to emerge along with thrombocytopenia and antibodies against PF4 (platelet factor 4) [63]. This is called vaccine-induced immune thrombotic thrombocytopenia (VITT). Ischemic stroke can be one of the symptoms of VITT. The most frequent cases were encountered after ChAdOx1 nCoV-19 vaccine, especially with accompanying middle cerebral artery (MCA). Most of the patients were<60 year-old females. Cerebral Venous Sinus Thrombosis (CVST), secondary ischemic or hemorrhagic stroke, and VITT were among the complications [64–67]. Headache is the most frequent symptom of CVST. The clinical table of CVST due to vaccines may demonstrate more severe symptoms than classical CVST due to reasons other than vaccines. Urgent evaluation of the ongoing or exceptional neurological symptoms after vaccination with neuroimaging techniques as well as laboratory tests must be carried out to recognize a possible VITT.

A study in 2021 compared Sinopharm, AstraZeneca-Oxford and Pfizer-BioNTech vaccines available in Iraq [68]. D-dimer elevation was demonstrated on 6 women among 220 tested individuals. D-dimer test has high reliability for thromboembolism. AstraZeneca vaccine and female gender in vaccination were significant risk factors in D-dimer elevation. AstraZeneca vaccine was reported to be associated with rare blood-clotting conditions in > 20 countries mostly among women (≤55 years) Several reports exist also for mRNA vaccines. A case series identified through the Vaccine Adverse Event Reporting System (VAERS) (as of April 21, 2021), a national vaccine safety surveillance program of the Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA), regarding CVST associated with Ad26.COV2.S (Janssen/Johnson & Johnson) vaccine, was also demonstrated in the literature [69]. In 12 vaccinees (18-59 years old) symptoms appeared in 6-15 days following injections, accompanied by decreases in platelet amounts, severe CVST in 12 vaccinees and non-CVST thrombosis in 8 of them. 10 of the 12 vaccinees needed intensive care, 7 had intracerebral hemorrhage additionally and 3 have died. In Europe, it was demonstrated that cases emerged after ChAdOx1 nCov-19 vaccine, have the same clinical and laboratory table with autoimmune heparin-induced thrombocytopenia. Although there was no heparin exposure before, 11 patients with accessible ELISA-based testing for the antibody ratio to platelet factor 4 (PF4) in complex with polyanions had obviously positive results. Based on these findings, there may be a connection between the immunological response to the vaccine and the clotting condition due to the development of antibodies.

1.3. Long-term COVID-19

Coronavirus vaccinations can occasionally result in symptoms similar to Long-term COVID-19. After COVID or after immunization, patients with mild or even asymptomatic cases also started describing other complaints which indicated Long-term COVID symptoms. These included brain fog, shortness of breath, kidney problems, and cardiac abnormalities [70]. Trouble in sleeping, general pain and discomfort, cognitive problems, such as: memory loss, difficulty in concentrating, mental health symptoms, such as: anxiety, depression are also among the Long-term COVID-19 symptoms. Symptoms can be mild or sever, and can sometimes disappear and reappear. Long-term COVID-19 is a disease with multiorgan pathology for most people who experience it [71]. In the literature, the primary factors for long-term symptoms are identified as being the severity of the disease at the beginning, hospital admission, obesity, pre-existing comorbidities (especially asthma), and the requirement for oxygen therapy.

One of the prevailing explanations concerning long-COVID that makes the most sense is that the initial surge in antibody production led to the development of autoantibodies against the body's own proteins. These antibodies target the body and cause cell damage. Another explanation would be the constant creation of spike proteins because RNA is reverse transcribed to DNA. A Long-term COVID-19 can affect every organ in the body and is characterized by a variety of symptoms, the most frequent of which is extreme fatigue [71]. In a prospective cross-sectional study by Blumberg et al. [72], 15 vaccinated volunteers and 28 unvaccinated ones were enrolled. Following acute COVID-19 infection, all of the subjects conducted a symptom-limited cardio-pulmonary exercise test (CPET) to assess aerobic capacity and exercise performance. The peak oxygen consumption percentage, peak work out heart rate, and ventilation values were all lower in the vaccinated group than in the unvaccinated group, indicating a significant difference between the two groups in favour of the unvaccinated.

Participants who had a full vaccination before infection with coronavirus indicated that their Long-term COVID-19 symptoms were getting worse, according to Arjun et al. [73]. In their study, Strain et al. found a significant difference in the primary symptoms of fatigue, myalgia, and chest discomfort between those who received the Moderna vaccine and those who received the AstraZeneca/Oxford vaccine [74].

Long-term COVID-19 may occur in 8% to 12% of vaccinated individuals who experience breakthrough infections after vaccinations [75]. Long-term COVID-19 risks were 17% higher among vaccinated

immunocompromised individuals with breakthrough infections compared to previously healthy, vaccinated individuals who experienced breakthrough infections.

1.4.Neurological complications

The main neurological side effects pertaining to mRNA vaccines were body aches, paresthesia, and difficulty walking, erythema migrans lesion, fatigue, myalgia, and pain in the left lateral deltoid region [76]. The main neurological side effects from vector-based vaccinations included difficulty in feeding, difficulty in ambulating, arm pain, fatigue, chills, facial droop, headaches, a generalized epileptic seizure, hemianopia, and mild aphasia, acute transverse myelitis, deep vein thrombosis, acute somnolence, hemiparesis, vigilance disorder and twitching, immobilizing opsoclonus myoclonus syndrome, and encephalitis.

The neurological complications associated with AstraZeneca vaccine included transverse myelitis and cerebral venous sinus thrombosis. Bell's palsy, and Guillain–Barre syndrome cases were reported after mRNA vaccinations. Other complications included temporary and unspecific sign effects, headache, dizziness, muscle pain, and paresthesia. The side effects of Johnson&Johnson COVID-19 vaccination covered venous and cerebral thrombosis. While the frequency is higher with adenovirus-based vaccines, it has been discovered that Guillain-Barré syndrome is linked to all types of COVID-19 vaccines [50,77,78]. Typically, mild and transient neurological side effects following COVID-19 vaccines commonly include headache, fatigue, myalgia, arthralgia, and skin manifestations like swelling, redness, and sorenessAnxiety-related occurrences are common, including feelings of syncope and/or dizzyness. Cerebral venous thrombosis, thrombocytopenia, vasculitis, Guillain-Barre syndrome, allergy, seizures are some of the additional side effects.

Individuals who have had a vaccination and are experiencing headaches should be cautious about CVT. The central nervous system may be severely inflamed and demyelinated by acute disseminated encephalomyelitis (ADEM) after vaccination causing many, distinct T2/FLAIR hyperintense damages in the brain which can be monitored with MRI [76]. With mRNA vaccinations, Bell's palsy frequently developed. The acute transverse myelitis (ATM), a localized and inflammatory spinal cord disorder, is among the reported manisfestations, where sensory changes, rapidly developing motor weakness, and autonomic dysfunction are observed as the symptoms. Even Herpes Zoster (HZ) cases are encountered more in the population recently, as a neurological manifestation following COVID-19 vaccines such as BNT162b2, mRNA-1273, and AZD1222, which may be one of the reasons of facial nerve palsy [79]. An unpublished Herpes Zoster case is also encountered months after immunization with Sinovac in an individual who has not encountered with a liquid from a lesion caused by Varicella Zoster before, which is the condition for contagion for this virus.Three cases of acute transverse myelitis (ATM) were reported by Gustavo C. Román et al. following a booster dose of the COVID-19 vaccine (ChAdOx1 nCoV-19 (AZD1222)) [80]. After first vaccination with ChAdOx1 nCov-19, post-vaccine encephalitis with deep vein thrombosis in the left leg, a vigilance problem and twitching, and a severe immobilizing opsoclonus myoclonus syndrome in the three individuals were reported [81]. ChAdOx1 nCov-19 vaccination was demonstrated to be temporally associated with encephalitis.

After vaccination with BNT162b2, a 82-year-old female exhibited neurological side effects such as Guillain–Barre syndrome [77]. Wolf et al. reported the neurological side effects such as intracranial venous sinus thrombosis, headaches, generalized epileptic seizure, hemianopia, mild aphasia, acute somnolence, and right-hand hemiparesis as well as thrombocytopenia after AstraZeneca vaccines in three individuals [42]. Elevated levels of D-dimers, corona spike protein antibodies, platelet factor 4 antiplatelet antibodies along with thrombocytopenia were observed in vaccinated individuals.

After receiving the Janssen vaccine, Prasad et al. described a case of the unusual bifacial diplegia type of Guillain-Barre syndrome (an immune-mediated demyelinating disorder) [82]. Acute urine retention started in a 41-year-old male, 12 days after vaccination. After 3 days, the patient complained of painful arms, a slight feeling of fatigue, and chills. The left-sided facial paralysis and Bell's palsy were identified on the fifteenth day. On the 21st day, he experienced weakness, paresthesias in extremities, trouble in diet and difficulty in walking due to weakness, and an onset of right facial weakness.

Parsonage-Turner syndrome (neuralgic amyotrophy) generally progresses with acute unilateral shoulder pain with accompanying upper limb and brachial plexus weakness. There are some reports on Parsonage-Turner syndrome observed after vaccine injections among which Pfizer-BioNTech and Moderna (mRNA-1273) vaccines exist [83,84]. In a case, after receiving the Pfizer-BioNTech vaccine, the patient had severe, electric, shooting pain in his left, fatigue, erythema migrans lesion, pain in the muscles, and sudden sharp, cramping pain in the left lateral deltoid region. Three months later, the patient had no lingering pain but had developed more weakness. The motion and power never returned to their initial levels. An interm

ediate enhancement in peripheral neuropathies was also obsereved with Ad26.COV2.S vaccine cohort [76].

After vaccination, some people experienced non-epileptic seizures characterized by bursts of odd hyperkinetic movements without an electrographic correlate, while others experienced fluctuating limb weakness as in a cerebral vascular event [50]. There is also a report of a middle aged man developing respiratory distress, swollen tongue, right hemiparesis, and facial sensory loss after second dose. Some patients experiencing acute neurological symptoms reported exacerbation of these symptoms after vaccination. Though uncommon yet, autoimmune events such as relapses in patients with multiple sclerosis (MS) have been reported after vaccination.

Numerous cases of neuroleptic malignant syndrome, a potentially fatal side effect of many antipsychotic drugs, have been reported in elderly vaccinees who continue taking antipsychotics. This syndrome is characterized by altered sensorium, muscle rigidity, hyperpyrexia, and autonomic dysfunction along with significantly elevated creatine phosphokinase levels and subsequent renal dysfunction caused by myoglobinuria [85,86].

RNA vaccines may set off a series of immunological reactions that result in abnormal stimulation of innate and acquired immunity [87]. Moreover, some adjuvants have the ability to alter the self-reactive T cells, which harms the host's tissue. SARS-CoV-2 adjuvanticity functions as a TLR-7/8 or TLR-9 agonist. Probably this is a brand-new pathogenic mechanism in charge of human immune-mediated illnesses. TLR pathways also control the activation of adaptive immunity regarding vaccinations. These results demonstrate a critical function for TLRs in the vaccination effectiveness besides in the etiology of MS and Neuromyelitis Optica Spectrum Disorder (NMOSD), which is a demyelinating autoimmune condition, as a result of the attack by the immune system to the myelin around nerves. In a case reported by Chen et al., a female patient was diagnosed with NMOSD having bilateral hypothalamus lesions and weakness, 3 days after receiving the first dose of an inactivated COVID-19 vaccine [88]. A case reported by Caliskan et al. exhibited NMOSD the day after the second dose of an mRNA vaccine [89]. At this point, the pre-vaccine titers of the AQP4 antibody should be questioned before vaccination. Because the person may have a high antibody titer before the vaccine and be prone to developing autoimmunity. In another case, a mRNA vaccinated individual with a prior inflammatory background in CNS following COVID-19 vaccine injection developed MS [90]. This subject had underlying conditions as a previous brain lesion, steroid use that should be considered for a possibility of triggered neurological disorders in her CNS after vaccination.

Cases of fatal myositis with rhabdomyolysis and acute kidney injury requiring renal replacement therapy after vaccination with Pfizer and Moderna, have also been presented in the literature [91]. Case reports of possible vaccine-induced rhabdomyolysis with good outcome following prompt treatment were demonstrated [92,93]. Severe rhabdomyolysis is an uncommon clinical syndrome characterized with myoglobinuria, acute kidney injury and high creatinine kinase values (<100U/L[2]). Accumulation of myoglobin in kidney tubules cause the tubules to be obstructed, resulting with renal damage [94]. There are also other studies with rhabdomyolysis cases (two experienced AKI, one worsened due to late presentation to the hospital with concurrent heart failure and died) associated with the Moderna vaccine [91,95–98]. A search of the VAERS (Vaccine Adverse Event Reporting System) mined in November2021 revealed 386 reported cases of COVID-19 vaccine–related rhabdomyolysis [94]. In 2021, 26 cases of Creuzfeldt-Jacob Disease, a rapidly progressive, invariably fatal neurodegenerative disorder, were diagnosed with first symptoms appearing within an average of 11.38 days after a Pfizer, Moderna, or AstraZeneca COVID-19 vaccine injection. By late 2021, 20 had died within 4.76 months. By June 2022, 5 more patients had died, and at the time of the submission of the study, only 1 remained alive.

1.5. Other issues

Besides the kidney injuries reported with COVID-19 vaccines associated with vaccination including many types as glomerulonephritis, vasculitis and interstitial nephritis and which may develop as acute kidney injury [60,94,99–101]; immunological syndromes as ASIA (Autoimmune/inflammatory Syndrome Induced by Adjuvants) with typical clinical symptoms as chronic fatigue, joint and muscle pain, cognitive impairment, and/or (atypical) neurological symptoms caused by adjuvants or environmental immune stimulatory factors that act as an adjuvant (e.g. aluminium hydroxide in vaccines, bioimplants, metal implants), are also reported [102]. Though with low rate, several ocular symptoms associated with vaccination, including lid edema, Tolosa-Hunt Syndrome, uveitis, superior ophthalmic vein thrombosis, choroiditis, retinal necrosis, macular retinopathy, central retinal vein occlusion, and optic neuritis have been demonstrated in literature [50,77,78]. Between July 1st, 2021- May 30th, 2022, a retrospective cohort study on 1.610.719 individuals treated at Veterans Health Administration facilities in different parts of US, who received one booster of any

combination of mRNA-1273 (Moderna), BNT162b2 (Pfizer-BioNTech), and Ad26.COV2.S (Janssen/Johnson & Johnson) in addition to first vaccination, was conducted [61]. Total incidence of hospitalization with COVID-19 or death after vaccination and booster were investigated for high-risk populations. Total rate of hospitalized individuals regarding high-risk populations (aged ≥65 years, with high-risk comorbidities, or with immunocompromising conditions), with pneumonia or death in 24-week was 1/1 000 (95% CI, 9.1-10.1). Incidence of hospitalization with COVID-19 pneumonia or death for only those with immunocompromising conditions was 4/1000 (95% CI, 36.6-42.9). Those with immunocompromising conditions had an additional risk of hospitalization with COVID-19 pneumonia or death at 51 to 150 days after booster, compared with first 50 days period after booster as well as in comparison to those without immunocompromising conditions. For each booster regarding 3 doses of mRNA-1273 and 3 doses of BNT162b2, this trend was identified persistently. In the graph drawn with the results obtained from the use of booster dose of BNT162b2 vaccine in the study; it can be clearly seen that the incidence of hospitalization with COVID-19 or death was dramatically increasing with the time for immunocomprimised group, while also significant increases were noted for individuals with high risk comorbidities and the elderly aged ≥65 years in the same time period. Longer time periods should be investigated to see the long-term effects.

It is a fact that mRNA vaccines strong inducers of IFN-I [103]. Similar to the current COVID-19 vaccinations, IFN-I injection causes a notable pattern of fever, headaches, and exhaustion. Additionally, persistent therapeutic IFN-I administration can cause depression and cognitive impairment, thus closely resemble the chronic fatigue syndrome. IFN-I promotes the production of a wide variety of cytokines and chemokines. It has been suggested that a short exerbation of IFN-I production may also contribute to the COVID-19 vaccine's adverse effects. According to reports, vaccinations can trigger cytokine release syndrome (cytokine storm), especially when given to cancer patients as part of their immunological treatment [104].

Regarding the immuno-histopathological data, mRNA vaccines can exhibit a distribution regardless of target in tissues that are terminally differentiated, resulting in autoimmune reactions [105]. These include the heart and brain, where spike protein may be produced leading to a potent autoimmune inflammatory response. Since the human body is not a rigorously compartmentalized and because every cell that produces non-self antigens is targeted by the immune system, detailed and correct pharmacokinetic/dynamicdynamic studies are required to pinpoint exactly in which tissues can the complications may appear.

mRNA COVID-19 vaccination has also been reported to cause hematological malignancies as diffuse large B-cell non-Hodgkin lymphoma and T/NK-cell lymphoma, diagnosed shortly after the administration of the vaccine [106].

In a review of 17 autopsy reports of vaccinated individuals, 38 cases were investigated (19 female, 19 male) [107]. 22 cases received ChAdOx1 nCov-19 (AstraZeneca), 10 BNT162b2 (Pfizer – BioNTech), 4 mRNA-1273 (Moderna) and 2 Ad26.COV2.S (Janssen COVID-19 vaccine). 22 individuals vaccinated with ChAdOx1 nCov-19 (AstraZeneca) died immediately after administration. It is suggested in the study that, any signs suggestive of VITT, such as intracranial hemorrhage and multiple foci of diffuse microthrombi, is needed to be carefully checked during the autopsies.

Since 2021, many potential side effects including Bell's palsy, lymphadenopathy, autoimmune hepatitis (AIH) were identified during the earliest phase III clinical trials [108]. It is not just the COVID-19 vaccination that can cause vaccine-induced AIH. Following vaccines for diseases like typhoid, polio, diphtheria/tetanus, hepatitis A, measles, mumps, and rubella (MMR), case reports have shown that AIH may occur. Acute symptoms such as stomach discomfort and jaundice were seen in the majority of patients with AIH. Moreover, on the first histologic examinations of several individuals, signs of chronic liver disease were seen. In those who are vulnerable, mRNA vaccines as BioNTech and Moderna vaccines that induce spike protein synthesis and corresponding spike protein-specific antibodies, may result in molecular mimicry and autoimmune tissue damage which could contribute to the emergence of AIH. Acute pancreatitis may also develop after receiving the COVID-19 vaccination [109].

In an on-line cohort study including 19 586 COVID-19 vaccinees [110], allergic reaction or anaphylaxis was reported in 26 (0.3 %) out of 8680 individuals who received 1 dose of BNT162b2 or mRNA-1273 and 27 (0.2%) out of 11 140 participants who received 2 doses of BNT162b2 or mRNA-1273 or 1 dose of JNJ-78436735. Thrombocytopenia was among the reported rare complications, while the severity of these complications varied across vaccine brands. People with prior COVID-19 had greater odds of adverse effects and more severe adverse effects after COVID-19 vaccination. Following full vaccination, those with younger ages, female sex, past COVID-19, Asian racial backgrounds, baseline pregnancies, and marijuana usage were all associated with increased risk of adverse effects regarding the mRNA-1273 vaccine. People who were infected previously with COVID-19, were more likely to experience more severe side effects after vaccination. When participants

receiving different vaccines are compared, the order of odds of reporting adverse effects were as: mRNA-1273> BNT162b2> JNJ-78436735.

2. DISCUSSION

Even though they are regarded as uncommon, since the mechanism of most of the COVID-19 vaccines rely on the use of spike protein as antigen and its production via mRNA introduction; side effects of can include serious clinical manifestations like acute myocardial infarction, cerebral venous sinus thrombosis, Bell's palsy, Guillain-Barré syndrome, rhabdomyolysis, some other neurological pathologies, myocarditis/pericarditis (usually in younger ages), pulmonary embolism, stroke, thrombosis with thrombocytopenia syndrome, autoimmune diseases, acute kidney disease, lymphadenopathy, appendicitis and herpes activation [111]. Besides the clinical investigations, unfortunately, most of the complications have been demonstrated in multicenter, nationwide and international observational studies and case reports. To understand the level of causation, active monitoring by health team and awareness of the population and effective reporting of the complications are necessary [112–114].

Based on medical feedbacks from older Americans, the FDA stated in July 2021 that four potential complications are determined to be associated with COVID-19 vaccines: acute myocardial infarction, immune thrombocytopenia, pulmonary embolism, and disseminated intravascular coagulation. The mRNA vaccines combined were associated with an extra risk of severe side effects of 1 per 800 vaccinated persons, according to an independent report on complications recorded in phase III clinical trials of Pfizer and Moderna [115].

Some side effects (as myocardial infarction, Guillain–Barré syndrome) are reported to increase with age, while others (e.g., myocarditis, anaphylaxis, appendicitis) were encountered more frequently young individuals [116,117]. In a publication regarding the US military personnel as the participants, the number of myocarditis cases in males was more than expected following the first booster [44]. In accordance with that, in other studies the rate of cardiac complications was also found be higher in young male vaccinees, following the first booster [118,119].

There is a proof that mRNA introduced via vaccination, circulates in the bloodstream for at least two weeks after BNT162b2 injection [15,105]. The extended persistence mRNA in the systemic circulation may allow it to reach even distant organs as a result of chemical kinetics and passive diffusion [9]. In accordance, mRNA introduced via vaccines was found in biofluids like breast milk [120]. Also it is found that vaccine originated mRNA can continue to exist in the lymph nodes up to 8 weeks [14]. Similar phenomena exists for spike proteins; forexample free spike protein was detected to remain in the blood samples from children and young adults experiencing myocarditis after vaccination [18]. Exosomes containing spike proteins were found in blood on the 14th day following injection, and their levels increased in blood in the four months after the booster dosage [9].

An ignored topic among the side effects is potential transgenerational effects [121]. There are some examples of transgenerational research on drugs, although they typically concentrate on environmental causes. While the studies on generational transmission of negative effects of drugs are inadequate in the literature, a recent study on chemotherapy-induced late transgenerational effects has generated an alert. There is a concern that: “Was the population ready to take the risk of facing or carrying potentially fatal diseases to future generations for the sake of speed in developing an urgent vaccine skipping necessary long-term and transgenerational safety studies, undertaking the risk of unknown or unexpected exposures to toxicity”. The LNPs that transfer mRNA in vaccines to the cells, also act as exosomes, transferring the genetic code of spike protein to the reproductive organs [122]. So, beyond the Sperm-Mediated Gene Transfer (SMGT), the gonadal attack of the spike protein produced in these organs may negatively effect the fertility [123,124]. A sequence embedded in Human DNA that was almost identical to a sequence in the SARS-CoV-2 genome was discovered, and the integration of the RNA of the virus into human DNA via endogenous reverse transcriptase was demonstrated on Long Interspersed Nuclear Element (LINE)-1 (17% of Human DNA) [125].

In the literature, SARS-CoV-2 RNA sequences were demonstrated to be able to be reverse-transcribed into DNA form and actively integrate into the human genomes via retrotransposons. In some SARS-CoV-2-infected patient specimens, a significant portion of SARS-CoV-2 sequence was proved to be integrated and produce SARS-CoV-2-human chimeric transcripts. Another surprise finding from a study released in 2021 was that Pol may reverse transcribe RNA into DNA [126]. It should be considered that ,this transcription of the integrated sequences might account for PCR-positive tests.

When postinfection and postvaccination autoimmunity is regarded, latency times can range from days to years [121]. It has been demonstrated that vaccine side effects such as inflammatory demyelination of the central nervous system (CNS) and diabetes, start to manifest after 3 years following vaccination. Except for

occasional cases of non-Hodgkin lymphoma, longer-term effects such as cancer, Alzheimer's disease, Parkinson's disease, etc., have not been investigated yet [106]. Moderna began clinical studies 63 days after choosing their sequencing [127]. Before more established methods (such as inactivated and live-attenuated vaccinations) began clinical trials, an unproven nanotechnology formulation known as mRNA vaccines had already entered clinical testing. There are significant worries about the long-term complications in particular, due to this very quick improvement. Furthermore, the issue of the effectiveness and toxicity in the old and fragile population is still unexplored. More data is required about the vaccine's long-term safety, interactions with other vaccines and drugs, use in pregnant or nursing women, immunocompromised patients, and in susceptible population [128].

Underlying and immunocomprimised conditions certainly influence the profile and the severity of the side effects. Patients with cancer are more likely to experience venous thromboembolism (VTE), arterial thromboembolic events and pulmonary embolism [7]. The COVID-19 vaccination is connected to coagulopathy and hemostasis issues as well. It should be taken into account that SARS-CoV-2 infection may increase the risk of thrombosis in cancer patients. If the mRNA attached to the LNPs enter the cardiac myocytes and produce the spike protein; the induced inflammation would probably cause the myocardium to necrose to a level determined by the number of cells involved [129]. According to preclinical findings for some vaccines under investigation, immunological complexes between low-neutralizing antibodies and helper T cells can aggravate the respiratory diseases [130]. Besides all these, it should be kept in consider that vaccination do not induce adequate immunity in all vaccinated individuals.

Some authors dealing with the studies on adverse effects of vaccines claim that myocard injury with COVID-19 infection is more common and severe than those observed with the mRNA vaccination [131]. They declare that; considering the higher risks of disease progression or death during COVID-19, the benefits of the COVID-19 vaccination outweigh the risks among patients with underline medical conditions. A significant number of existing studies suggesting this compare healthy people with sick people. However, it is not certain that everyone will catch COVID-19, however it is certain that mass vaccination has been tried to be applied to everyone without the information of if they would catch COVID. For more realistic statistical results reflecting the population, universe selection should be made between healthy vaccinated and unvaccinated. What about the people who wouldn't catch COVID-19 because of working isolated conditions, but being vaccinated? We cannot comment as if each individual in the population will be infected with COVID-19 and has more risk of developing myocarditis than vaccinated. The universes should be regarded as vaccinated and unvaccinated in statistics, instead of comparing the vaccinated versus infected (with hospital admission and PCR test confirmation) populations. At that time the results will probably reverse.

Accelerated vaccine development is also fraught with ethical questions, especially with the hyper-reduced time spent on phases II and III of clinical trials. In a study, it is recommended for vaccine breakthrough infection that; firstly, the use of the vaccine should be spread as soon as possible and further optimized and its quality should be enhanced [132]. However in the practice, new complications arise in vaccinated individuals after a certain time, as many serious ones started to be reported, through rare but which shouldn't be ignored. The demographically the most risky group for these vaccines is the elderly, who have high rates of comorbid conditions and compromised immune systems. Howeveri, the first applications in the population started from elderly, where this situation shows itself as they are sacrificed for the benefit of young. However, the relatively young and healthy population is also the test demographic population being used for the early clinical trials (as explained below). The current fast testing schedule raises questions about the trial's effectiveness and how these findings could be extrapolated from young, healthy cohorts to aged or vulnerable populations.

Seneff et al. suggest that lethal prion-like fibrils (prion: proteinaceous infectious agents causing untreatable diseases e.g. Creutzfeldt-Jakob disease) can accumulate in neurons as a result of vaccine-induced spike protein production [133]. The spike protein, with its prion-like properties, causes neuroinflammation and neurodegenerative diseases, clotting issues in the vasculature, increased disease risk due to suppressed prion protein regulation in the context of widely prevalent insulin resistance, and other health complications. Evidence that CD16+ monocytes can continue to generate spike protein for months after immunization is particularly alarming. This could be due to prolonged cytosolic mRNA presence or reverse transcription of the mRNA into DNA. The antibodies produced by immunization diminish over time, necessitating repeated booster shots to increase antibody levels and each booster increases the likelihood of developing a later neurodegenerative disease. Thanks to the Omicron variant infection's much diminished prion-like capabilities, which had decreased the need of vaccination and had been identified by some researchers as "the end of COVID-19" pandemic. Seneff et al. have given a scheme of the biochemical pathway of spike protein in the induction of the neurodegenerative diseases as below (Figure 8):

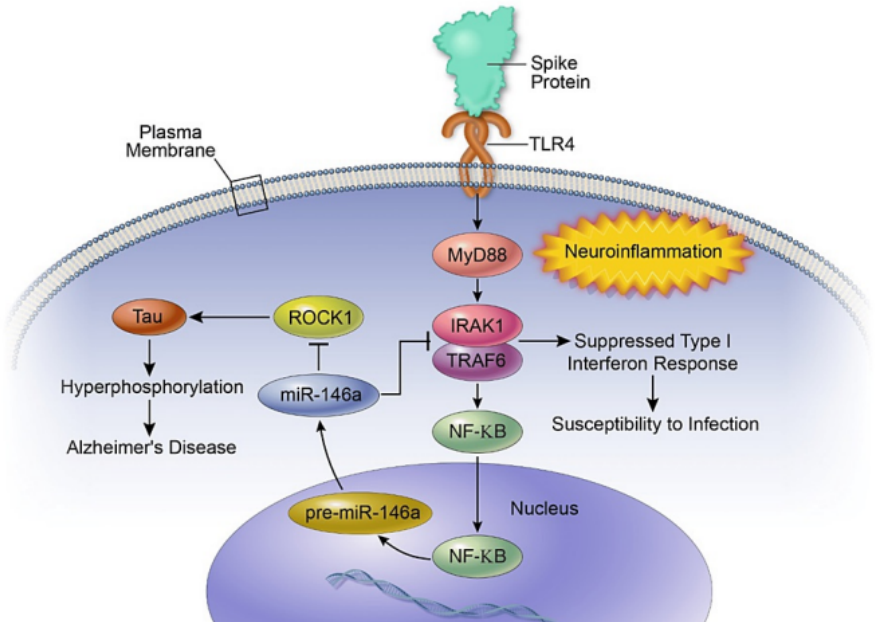

Figure 8. Schematic of pathways and consequences of spike protein binding to the TLR4 receptor in neurons and stimulating the NF-kB signaling response, leading to upregulation of miR-146a and subsequent sequelae (Reprint from ref. [133]).

So, systemic inflammation after vaccinations may induce complications in the brain function [134]. Additionally, reports of delirium in older persons following COVID-19 vaccination include symptoms of memory loss, acute onset and and disrupted sleep-wake cycle.

The short-, medium-, and long-term effects of receiving booster doses repeatedly throughout time are not elucidated adequately. The situation of innate immunity should be taken into account when evaluating the safety of repeated booster dosages that stimulate the immune system [3]. It should be considered that because of the "epigenetic" reprogramming of cellular chromatin, innate immunity which is the first line defense, has a long-term memory and can be trained to be more responsive even after inflammation has subsided. This epigenetic reprogramming was linked to an increase in cytokine production and a switch in the metabolic pathway from oxidative phosphorylation to glycolysis in monocytes and macrophages. This can be regarded as a beneficial specific immune response, however this trained immunity can demonstrate "maladaptivity" in some conditions that are characterized by chronic systemic inflammation. Glycolysis is the conversion of glucose to pyruvate or lactate which results in the generation of ATP and has been shown to be abnormal in peripheral cells in Alzheimer's disease, Parkinson's disease, and Amyotrophic Lateral Sclerosis [135], and the expression of glycolytic markers increase in atherosclerotic lesions [136], while, most cancer cells rely on glycolysis to generate ATP, even when oxygen is available [137]. Moreover, some non-immune cells, including fibroblasts and endothelial cells, exhibit trained immunological properties; this has been observed in COVID-19 infection. So the long-term effect of repeated boosters may be the development or escalation of pre-existing atherosclerosis since atherosclerosis is a chronic inflammatory disease of the arterial wall that also involves monocyte-macrophage phagocytic cells. Therefore, boosters repeatedly injected with a few months interval could increase the strength of a particular immunity (antibody or T-cells), but it might also induce a "non-specific function" due to trained immunity of endothelial cells and macrophages. It has been demonstrated that ionizable lipids found in LNPs may also activate Toll-like receptors (TLRs) inducing proinflammatory reactions [138]. In the decision of such mass vaccination programmes, fundamental immunological mechanisms and the potential autoimmune consequences shouldn't be ignored. It is a common fact that even conventional vaccines may provoke the immune system to direct to its own cells inducing an autoimmunization [105].

Unfortunately, yet no accepted treatment protocol exists for COVID-19 vaccine-related pathologies [139]. Although extra treatment methods are needed for cardiovascular, neurological, endocrine, thrombotic, immunological pathologies, protocols directed to degrade the spike protein and antagonize its effects might

be a good strategy, because the spike protein has a principal role in pathophysiology, triggers inflammation, and causes blood clots. Regarding their biological activities [139], the combination of nattokinase, bromelain, and curcumin is recommended for COVID-19 vaccine-related pathologies. Curcumin is known to reduce viral replication through blocking the spike protein binding sites, ACE-2 receptors and TMPRSS-2, thus preventing SARS-CoV-2 entry into cells, in in-silico studies. The processes that curcumin modulates also include tumor cell growth, cell survival, tumor suppressor pathways, cell death, death receptor pathway, protein kinase pathway and mitochondrial pathways [140]. The current studies suggest that curcumin exerts anti-cancer activity not only through influencing various signaling pathways, but also through enhancing the immune system. So that tumor cells are eliminated at early stages and severely growing of the tumors can be inhibited. Also there are studies that show the specific immunomodulatory actions of bromelain as 1) inhibiting NF-kB and cyclooxygenase 2 (COX-2), thus PGE-2 (the proinflammatory prostaglandin); 2) triggering antiinflammatory PGE-1; 3) inciting inflammatory mediators (interferon-g, interleukin 1b, interleukin-6 and tumor necrosis factor-a) and inhibiting inflammatory mediators that produce cytokine storm; 4) in vitro and in vivo modulation of T-cell activities; and 5) inducing T-cell-dependent antigen-specific B-cell antibody activities. When bromelain activity is considered, it shows anticoagulant activity in a dose-dependent manner through reversing the pathyway of PGE-2 and thromboxane A2 (TXA2), thus causing an increase of prostacyclin in platelets, and induction of fibrinolysis and thus inhibiting of platelet aggregation. Bromelain may stimulate the absorption of xenobiotics including chemotherapeutic agents, ACE inhibitors, antibiotics, certain antidepressants, benzodiazepines, barbiturates, etc. Medical supervision is recommended against a possibility that the drugs reach toxic leves or a risk of bleeding. Nattokinase have been found to degrade spike protein and it has a widespread use as an antiatherosclerotic and antithrombotic supplement in Japan, on which safety tests were performed in doses up to 80,000 fibrinolytic units (FU) Daily [141]. It prevents the activity of plasminogen activator inhibitor-1 and enhances fibrinolysis [142], reduces the plasma levels of cytokines, fibrinogen, factor VII and VIII [143]. Considering these effects, McCullough et al., have recently proposed that oral nattokinase, bromelain, and curcumin can be used in combination in targeting the spike protein for proteolytic degradation and against thrombosis to assist in the management of post-vaccine injury syndromes [139]. Although additional treatment methods may be needed for cardiovascular, immunological, neurological, endocrinal, thrombotic syndromes; this base detoxification protocol is suggested for post-acute sequalaes of both COVID-19 infection and vaccination: Nattokinase 2000 FU (100) mg orally twice a day without food+Bromelain 500 mg orally once a day without food+Curcumin 500 mg orally twice a day (nano, liposomal, or with piperine additive suggested) can be applied for ≥3-12 months. Yet no therapeutic allegations can be made since wide-scope, double-blind, prospective, placebo controlled randomized trials have not been performed for this protocol. No such researches are planned or funded currently by authorities or institutions. The primary risks here are allergic reactions and bleeding. Patients should seek medical supervision in case of bleeding. This protocol can be applied besides the use of antiplatelet and antithrombic agents, but the risk of bleeding should be monitored. There is no adequate evidence that nattokinase can be used in lactating women or pregnants or children.

In COVID-19-related pathologies, chronic inflammation and oxidative stress decrease the glycocalyx which is the extracellular matrix that surrounds all cells [144]. Moreover, disturbance of the endothelial function enhances oxidative stress and systemic inflammation, induces a procoagulant and antifibrinolytic state and cause the degradation of glycocalyx. It is worth attention that though most of the population in the world is exposed to SARS-CoV-2, ≥80% of the population had not been infected before the start of the COVID-19 mass-vaccinations, most were asymptomatic, or demonstrated very mild symptoms [145,146], and the ones that experienced severe illness covered a very low percentage [147,148]. du Preez et al. [144], related this phenomena with the degree of glycosaminoglycan sulfation which influences the integrity of the glycocalyx, rather than the expression of ACE receptor. As the sulfation ratio in glycocalyx is attenuated, susceptibility to SARS-CoV-2 infection increases, and the modulation capability of inflammatory and coagulatory responses decreases [149]. ACE2 expression is low in an adequately sulfated glycocalyx [150]. Among the hospitalized COVID-19 patients; 59% of suffered proteinuria, where 22% of nonventilated and 90% of ventilated patients developed acute kidney injury [151]. This shows endothelial glycocalyx degradation in COVID-19 patients and the same phenomena is suggested for patients after vaccination. Since many of the severe symptoms of vaccines exert similarity with COVID-19 disease, protecting the glycocalyx through sulfation support with n-acetyl cysteine and other sulfur donors as inorganic sulfate precursors might be another effective treatment strategy for COVID-19 vaccine-related pathologies [144]. Although n-acetyl cysteine is a precursor of glutathione, it is immediately hydrolysed in the cell and cysteine (a rate-limiting substrate for glutathione) comes out, and this cysteine plays role in the formation of hydrogen sulfide (H_2S), inorganic sulfate, taurine, coenzyme A and albumin. Reduction of glutathione and cysteine in extracellular

fluids is suggested to be a cause and a marker of enhanced risk of COVID-19 infection [144]. H_2S is shown to have antiviral, anti-inflammatory and mucolytic activity; treats the pathologies caused by reactive oxygen species, TNFα, and IL-6 andnitric oxide, pulmonary tissue injury by inducing ACE2 upregulation and procludes the disruption of endothelial function in cardiovascular disorders. H_2S concentrations in non-survivors are lower than in the patients who have healed from COVID-19 [152]. COVID-19 patients with mild symptoms demonstrated higher circulating H_2S concentrations than those with severe pneumonia [153]. Therefore, H_2S donors are suggested as a potential therapy in COVID-19 [154]. This strategy can also be beneficial in COVID-19 vaccine-related pathologies, for the similar symptoms. The anti-inflammatory activity of H_2S seem work through the upregulation of endothelial ACE2 expression [155]. The above information suggests that H_2S levels should be kept in a homeostatic balance so that its protective activity will be utilized, while a possible toxicity in high levels will be prevented. The toxic effect of H_2S on the nervous system has been intensively studied [156]. Cognition and memory deficits, persistent headaches, neurotoxicity, motor and sensory deficits are some of the neurological toxicities of H_2S [157]. However, there are increasing evidences that demonstrate that H_2S acts as a signaling molecule at physiological concentrations, in processes such as neuromodulation in the brain and smooth muscle relaxation in the vascular system, besides modulating insulin release, angiogenesis and inflammation [156]. Its cytoprotective effect (protecting cardiac muscle and neurons from oxidative stress and ischemia-reperfusion injury) has been proven. Total H_2S concentration released from acid-labile sulfur+free H_2S was found to be in the range of 50–160 μM in the brain. Acid-labile sulfur is produced from sulfur atoms in the iron–sulfur center of mitochondria respiratory chain enzymes. Since H_2S may not be released from mitochondrial pH of 7-8, the reported intracellular H_2S levels have been most probably overestimated. So, care should be taken that, the concentration levels should not rise to toxic limits. Some cofactor nutrients as vitamin B6, are important for inorganic sulfate formation from cysteine. When administering n-acetyl cysteine to rise cysteine concentrations, it is also vital to be sure that there is no deficiency of the cofactor nutrients, in order to maintain the necessary metabolic conversions in the sulfur metabolism. Also, methylsulfonylmethane (MSM) supplementation will increase glutahione [158] and inorganic sulfate. MSM was previously demonstrated to reduce paraquat-induced pulmonary and hepatic injury in mice, through decreasing TNFα, myeloperoxidase (MPO) and malondialdehyde (MDA) concentrations and increasing the glutathione, catalase (CAT) and superoxide dismutase (SOD) concentrations in lung and liver tissues. It also inhibits oxidative stress biomarkers (as nitric oxide and PGE-2 in macrophages) induced by lipopolysaccharides, minimizes inflammation [144]. Sulfur-donor supplements as n-acetyl cysteine, can provide a synergistic immune-modulatory activity with the anti-inflammatory drugs which need sulfur for their metabolization so they can be considered to maintain the required sulfur equilibrium if drugs metabolized using sulfur will be used. Cysteine derivatives such as NAC [144], carbocisteine, or erdosteine and MSM as sulfur-donor can be useful for maintaining the necessary cysteine and inorganic sulfate levels. Allicin which is also found in garlic, or marine-derived sulfated polysaccharides can also be considered. MSM can be supplemented in doses up to 4 g to protect from infection and regulate the immune response.

Since mass vaccination was performed, now the serious side effects and long term effects should be monitored in the populations with perfect pharmacovigilance studies. Countries which have the systems to evaluate the side effects retrospectively should take action immediately [159]. Examples of advanced systems include the US Vaccine Safety Datalink and ACCESS (the European COVID-19 vaccine monitoring programme). Although these systems have shown their power to carry out robust evaluations, they are limited with locally used vaccines and the population sizes, and cannot have a high chance to catch and evaluate very rare events such as Guillain–Barre Syndrome. These restrictions can be overcome via global collaboration and adequate investments. Risks and the rates of serious AE should be compared between vaccinated and unvaccinated people.

3. CONCLUSION

Reports on side effects as a result of vaccination are increasing. Especially the results of studies on vaccines that have started to emerge since 2022, brought out some concerns that these vaccines may have serious side effects in the long term, thus started to influence the decision to accept or reject the vaccination.

Unfortunately, none of the current vaccines can prevent or reduce virus infection, and it is reported that they are mostly aimed to decrease the severity of the COVID-19 disease and to reduce hospitalizations [160]. The risk-benefit ratio here is said to be weighted towards benefit. It is also said that when individuals of all ages are fully vaccinated and boosted, they just don't get serious health outcomes related to SARS-CoV-2, and especially with Omicron." However it is started to be seen from the literature that it is not as simple. Firstly, it is not certain or an estimated result that everyone will catch COVID-19 in the pandemic period, however it is

certain that mass vaccination has been tried to be applied to everyone without a certain information of if they were previously or will be infected and get sick with COVID-19. What about the people who wouldn't get infected or sick with COVID-19 because of working in isolated conditions, but they are vaccinated. It should be accepted that unvaccinated who are not or will not be infected will have zero risk for complications of COVID-19 or vaccine, but this was not included to the statistics. We cannot comment as if everyone will get sick or infected with COVID-19 and has more risk of developing myocarditis than vaccinated. So the accurate universes should be regarded in statistics. Vaccinated and unvaccinated. At that time the results will most probably reverse.

Given the available tools, it would be dangerous and unethical to introduce any new vaccination based on results from accelerated clinical trials into a population without a perfectly working safety monitoring. Besides, the public's trust in vaccinations as well as immunization programs in general may be threatened by the deployment of vaccines prior to the successful conclusion of reliable clinical programs. Furthermore, this virus mutates almost weekly, at a rate more than 50% higher thanpreviously thought [161]. Therefore, in fact it is almost impossible to catch all new variants for it with fast vaccination development.

The possible risks of genetic vaccines that cause autoimmune reactions cannot be illuminated without knowing the exact distribution and pharmacokinetics of LNPs and mRNA, thus the spike protein [162]. Therewas not any statistically significant difference in the RT-PCR test density between the vaccinated participants who received booster and who did not receive [163]. A short duration of follow-up does not allow to reach conclusions on the long-term effect of the vaccines and boosters. What happens to long term immunity is still a question. Thus, suspected vaccine-related ADRs should be rapidly, fully and correctly reported via pharmacovigilance systems to support the continuing trials to ensure vaccine safety. Also an integration of regional and national pharmacovigilance systems may construct a reliable global database. Vaccinated individuals should look for urgent medical check if they suffer; shortness of breath, chest pain, leg swelling, persistent abdominal (belly) pain, neurological symptoms such as severe and persistent headaches or blurred vision or tiny blood spots under the skin beyond the site of the injection in weeks after vaccination.

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