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AN INTERPRETATION OF CARDIOVASCULAR COMPLICATIONS IN COVID-19 PATIENTS AND POST-COVID-19-VACCINATION, A PERUSAL

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ABSTRACT: COVID-19, caused by Severe Acute Respiratory Syndrome CoV-2 (SARS CoV-2), has become a global burden. The naïve era of infection prompted early dependence on case reports of insufficient data and conceptual elucidation to explain and anticipate the effect on cardiovascular diseases. Many COVID-19-infected and vaccinated individuals have reported an increased incidence of cardiovascular disorders, leading to higher morbidity and mortality rates. Sometimes COVID can also manifest as a severe coronary artery disease or myocarditis in those with no background in cardiovascular diseases or those with cardiovascular risk factors, which are often misunderstood as a primary cardiovascular disorder. COVID-induced cardiovascular complications like DVT, VTE, MI, and long COVID have been the crux of the matter. To combat the SARS-CoV-2 disease, several countries took the lead in developing COVID-19 vaccines, but only a few were effective against coronavirus, which created a ray of hope in curbing COVID-19 disease. As the thumb rule says, any substance that is foreign to the body, including vaccines, has flaws seen in the forms of adverse effects/adverse events, which has created a great reluctance towards accepting COVID vaccine in society. Despite all this, it is proven that vaccines are effective in managing the COVID-19 situation worldwide, underlining the Darwinian notion.

INTRODUCTION: COVID-19, caused by Severe Acute Respiratory Syndrome CoV-2 (SARS CoV-2), has become a global burden infecting more than 41 million individuals by the end of January 2022 in India [1]. The outbreak of this disease was in Wuhan, China, in December 2019 and was transmitted impulsively throughout the Globe. Since then, researchers have faced a network of provocations with tackling the disease [2].

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The naïve era of infection prompted early dependence on case reports of insufficient data and conceptual elucidation to explicate and anticipate the effect on cardiovascular diseases [3]. COVID-19, an infectious lung disease per se, has engrossed the cardiology loci [3-7]. Patients with cardiovascular disease or risk factors infected with COVID-19 showcase a specific susceptible group of individuals [8].

SARS CoV-2 has predominantly affected many countries' medical and financial status, which led to the union of researchers of different scientific disciplines to discover the diagnostic and therapeutic innovations to eradicate the global pandemic [9]. The principle approach to curb this COVID-19 disease is vaccination [10].

To combat the SARS CoV-2 disease, several countries took the lead in developing COVID-19 vaccines, but only a few were effective against coronavirus. Currently, the following vaccines are available worldwide.

TABLE 1: LIST OF VACCINES ALONG WITH TYPE, MANUFACTURER AND COUNTRY OF ORIGIN [2, 11, 12, 13]

Sl. no.	Vaccine	Type of Vaccine	Manufacturer	Country of origin
1	Comirnaty (BNT162b2)	mRNA virus	Pfizer-BioNTech	Germany
2	Moderna COVID-19 Vaccine/Spikevax (mRNA-1273)	mRNA Virus	ModernaTX, Inc	US
3	COVID-19 Vaccine AstraZeneca/Covishield (AZD1222)	Adenovirus	Oxford University and AstraZeneca In India, Serum Institute of India Pvt. Ltd	UK
4	Sputnik V	Adenovirus	Gamaleya Research Institute of Epidemiology and microbiology	Russia
5	COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	Adenovirus	Janssen Biotech Inc., a Janssen Pharmaceutical Company of Johnson & Johnson	US
6	CoronaVac/ Sinovac	Inactivated	Sinovac Biotech	China
7	BBIBP-CorV	Inactivated	Beijing Bio-Institute of Biological Products	China
8	EpiVacCorona/ Aurora-CoV	Peptide-based	VektorState Research Center of Virology and Biotechnology	Russia
9	Convidicea (Ad5-nCoV)	Adenovirus	CanSinoBio Biologics Inc	China
10	Covaxin	Inactivated	Bharat Biotech in collaboration with ICMR and NIV	India
11	CoviVac	Inactivated	Chumakov Centre	Russia
12	ZF2001/Zifivax (China)	Protein based	Anhui ZhifeiLongcom and Institute of Microbiology, Chinese Academy of Sciences	China
13	WIBP-CorV	Inactivated	Sinopharm	China
14	QazVac(QazCovid-in)	Inactivated	Research Institute for Biological Safety Problems in Kazakhstan	Kazakhstan
15	COVIranBarekat	Inactivated	Shifa Pharmed Industrial Group	Iran
16	Abdala (CIGB 66)	Protein subunit type	Centre for Genetic Engineering and Biotechnology (CIGB)	Cuba
17	Soberana 02/Soberana plus/ FINLAY-FR-2	Recombinant RBD conjugated to tetanus toxoid)	Finlay Institute	Cuba
18	MVC-COV1901/Medigen	Protein subunit	Medigen Vaccine Biologics Corporation	China
19	ZyCoV-D/ Zydus Cadila vaccine	DNA plasmid virus	Cadila Healthcare	India
20	Spikogen (COVAX-19)	Protein based	Vaxine Pty Ltd	Australia
21	FAKHRAVAC (MIVAC)	Inactivated	Organization of Defensive Innovation and Research, Iran Ministry of Defence	Iran
22	NVX-CoV2373 (Nuvaxovid/Covovax)	Protein based	Serum Institute of India	India
23	Turkovac (ERUCOVVAC)	Inactivated	Health institute of Turkey	Turkey
24	Corbevax	Protein subunit	Biological E. Limited (BioE)	India
25	VLA2001	Inactivated	Valneva SE and Dynavax Technologies	France and Austria
26	COVLP/Covifenz	Virus-Like Particle vaccine grown in an Australian weed	Medicago in Canada and GlaxoSmithKline (GSK)	Canada
27	Noora	Protein subunit	Baqiyatallah University of Medical Sciences	Iran

After the COVID-19 vaccination, there is no established database for adverse effects, which raises concerns about the safety of vaccines from the perspective of Health Care Practitioners [2, 14, 15]. Additional reports of adverse effects caused by vaccination have led to vaccine aversion in society, thus setting an obstacle in preventing the COVID-19 outbreaks [9]. Many of the COVID-19-infected and vaccinated individuals have reported an increased incidence of cardiovascular disorders, leading to higher morbidity and mortality rates; thus, our article reviews cardiovascular complications in COVID-19-infected patients and Adverse Events after COVID-19 immunization.

Section I: Covid-19 Disease and Cardiovascular Complications: COVID-19, majorly affecting the lungs and resulting in hypoxia will lead to a slew of cardiovascular complications. It can also manifest as a severe coronary artery disease or myocarditis in those with no background in cardiovascular diseases or those with cardiovascular risk factors, which are often misunderstood as a primary cardiovascular disorder [4]. To rule out cardiovascular problems and analyze the treatment, it is critical to understand the presentation of preliminary symptoms of COVID-19 disease.

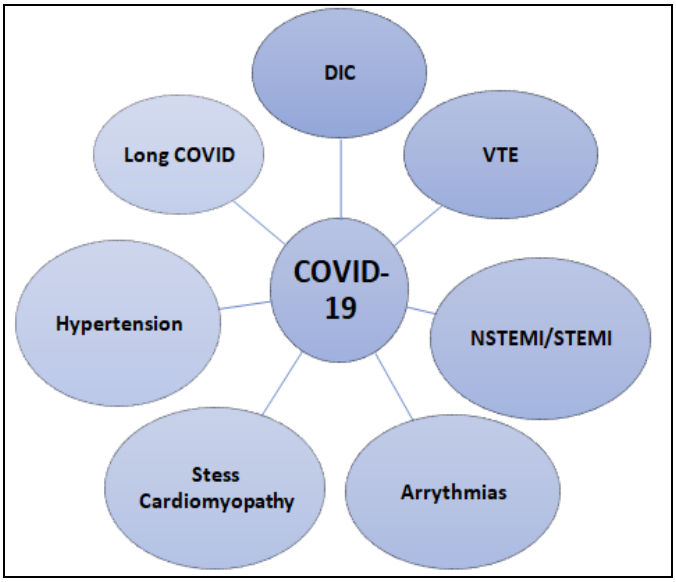

FIG. 1: OVERVIEW OF COVID-19 ASSOCIATED CARDIOVASCULAR COMPLICATIONS

[COVID-19: Corona Virus Disease – 2019, DIC: Disseminated Intravascular Coagulopathy, VTE: Venous Thromboembolism, NSTEMI/STEMI: Non-ST-Elevated Myocardial Injury/ST-Elevated Myocardial Injury].

Many of the study findings have considered the possibility of cardiovascular problems. The following are the most prevalent ones:

Thromboembolic Events: Hyper-coagulation is commonly seen in COVID-19 patients. The patient's profile exhibits thrombocytopenia, elevated D-dimer, prolonged prothrombin time, INR, and short activated partial thromboplastin time, leading to thromboembolic events [4, 16]. In eminence to the above-stated abnormalities, imbalance in the haemostasis is clinically evident in severely infected COVID-19 patients, which manifests as the isolated thrombotic disease of the lungs and thromboembolic events arising from lower extremities [8].

The increased incidence of thrombosis will aggravate the risk of disseminated intravascular coagulopathy (DIC), venous thromboembolism (VTE), and multi-organ failure, which could be fatal [16]. In accordance with the Padua model, one of the studies showed an increased risk of VTE in 40% of COVID-19 hospitalized patients [17,] and among deceased COVID-19 patients, 71.4% had reported DIC having elevated D-dimer [18, 19].

As the site of thromboembolic events is atypical, it is advisable to closely monitor the coagulation protein parameters to avoid further complications of thromboembolic events [16]. As thromboembolic events are life-threatening to COVID-19 patients, treating the same is of paramount importance. Hence, anticoagulants like 'fondaparinux and Low Molecular Weight Heparin (LMWH)' has been recommended and are in use today [8, 20]. Besides all these, metabolic interaction among antiviral, anticoagulant, and antiplatelet medications is another concern that must be considered [19].

Myocardial Injury (MI): SARS-CoV2 or Novel coronavirus can produce robust inflammatory responses that concurrently affect the heart. Myocardial injury can demonstrate ACS, Myocarditis, Heart failure, Stress cardiomyopathy, and Shock [16]. During a viral load, myocardial damage can be surmised using specific biomarkers, distinctive electrocardiographic changes, or contemporary visualizing techniques of the injured heart, which helps assess the damage's depth [7]. Based on hearsay, patients with short-term

myocardial injury are distinguished by high troponin levels (cTnI and cTnT), ST-segment elevation, or fall in ECG and angiography without any cardiac lesions [21, 22]. The incidence of acute myocardial injury in COVID-19 patients more likely to have marked elevations in cardiac troponin I is approximately 8-12 percent [23, 24].

The elevation of cTn-I accompanying other inflammatory mediators, including LDH, D-dimer, and IL-6, contemplates cytokine storm, which causes plaque instability and other mechanisms, including pro-thrombotic state and hypoxemia due to acute respiratory failure caused by SARS-CoV2 may damage myocardial cells [4, 25]. For some of the corona-viruses, Angiotensin-Converting Enzyme 2 (ACE2) has been an access checkpoint into the host cell, through the S-protein of the virus, which is predominantly expressed in the lungs and cardiovascular system. Hence, the ACE2-associated signalling mechanism also plays a pivot role in myocardial injury [25]. Myocardial injury can present itself in various ways, making it difficult to assess periodically, especially when the patients are asymptomatic. Some of the most serious myocardial injuries are discussed hereafter.

Acute Coronary Syndrome (ACS)–NSTEMI and STEMI: Due to physiological and pathological changes in the thoracic cavity of COVID-19-infected patients, blood circulation to the heart is majorly affected which manifests as ACS. ACS is characterized by sinus dysfunction, dyspnoea, and chest pain which concomitantly occurs with COVID-19 expression making it hard to identify [19]. To diagnose myocardial infarction, a leap and/or sink-in cTn-I is not adequate; also, clinical judgement, signs and symptoms, ECG variations, and imaging data should be authenticated [26]. As reported by the European Association of Cardiovascular Imaging (EACVI) and the American College of Cardiology (ACC), a rise in cardiac enzymes is likely to be subsidiary to a non-specific elevation during COVID-19 infection [27, 28]. The likelihood of MI in respiratory infectious diseases outstretches the apex at the outset of the illness and is pro-rata to the intensity of the infection [29]. A primary coronary artery event such as Type 1 MI attributing to acute plaque rupture and events occurring secondary to an acute imbalance in myocardial oxygen supply and demand such as Type 2 MI can ensue in COVID-19 infection, [5, 7] as Type 2 MI manifests similar to COVID-19 symptoms such as dyspnoea, chest pain *etc*., it is challenging to identify/diagnose the same and patients may present with a high prevalence of comorbidities which may obscure ischemia and localized wall abnormalities which are mysterious [30]. Sepsis and other infections are now associated with substantial cardiovascular consequences, including ACS, leading us to assume that COVID-19 may potentially be the primary cause of ACS [29, 31]. In censorious patients, the frequency of MI will go unfamous [32] and autopsy examination showed that the prevalence of undetected acute MI was traversing from 5-25% in patients who demised from acute respiratory failure [33, 34]. Hence, it is preeminent to closely monitor COVID-19 patients for MI which may go undetected and could be a cause of death.

For patients presenting to the Emergency department with ACS and COVID-19 infections, the utmost importance is to prioritize the treatment. One of the hurdles in managing COVID-19 patients is a defence against the infection, i.e., using Personal Protection Equipment (PPE). According to European and American guidelines, Primary Percutaneous Coronary Intervention (PCI) is an effective therapy for acute myocardial infarction over thrombolysis therapy [35]. In China, Sichuan Provincial People's Hospital and Peking Union Medical College Hospital have come up with an adjuration that COVID-19 patients with STEMI should be managed with thrombolytic therapy aloft PCI, whilst for NSTEMI/Unstable Angina, the preference was to rule out SARS-CoV2 infection primarily, since hands of a clock to STEMI patients is downplay [35, 36]. STEMI is unpredictable and unexpected, and the patient's fear of COVID-19 infection and hospitalization causes delays in reaching the hospital, resulting in mortality before admission.

Arrhythmias: It is known that at the molecular level, COVID-19 infection triggers inflammatory mediators that damage host cells, including myocardial cells, leading to altered heart electrophysiology, thereby resulting in arrhythmias. A Chinese study depicting clinical outline in 138 COVID-19-confirmed patients revealed a 16.7% incidence of arrhythmias [37].

In contrast, the incidence was higher in COVID-19 patients, with 44.4% of those requiring ICU hospitalization differing from those who did not [23]. The systemic inflammation in COVID-19 down-regulates the translational alteration of myocardial ion channels leading to signal dys-conduction and arrhythmia. In addition, electrolyte imbalances activated Protein kinase C (PKC), active respiratory infections, or oxidized CaMKII (Ca2+/calmodulin-dependent protein kinase II) can also contribute to triggering arrhythmias [38]. Initially, when COVID had a major effect on the public, effective treatment was not established. Researchers have thought Chloroquine and Hydroxychloroquine would be a potential drugs to fight the infection and usage of Chloroquine (CQ) and hydroxychloroquine (HCQ) caused arrhythmia in the COVID-19 patients by affecting action potential firing rate and the funny current (If) which causes a delay in depolarization [39].

In the COVID-19 setting, patients exhibited abnormal ECG changes for tachycardia, which is substantially self-limiting with an incidence of 72%; in contrast, bradycardia was microscopically ranging from 2-15%; besides these, atrial fibrillation, premature beats, QT prolongation or even sudden cardiac deaths were noted in SARS patients [40-45]. Hence, both tachy- and bradycardias are seen in COVID-19-infected patients. In clinical practice, all types of arrhythmias in COVID-19 patients are generally managed based on treating the causing factors, which include correction of electrolyte imbalances, managing degree of body fluid levels, ceasing medications causing arrhythmias or subsiding catecholamine rush [46-48] and specifically in stable arrhythmias, beta-blockers are most preferred drugs [49].

Hence, arrhythmias are life-threatening to the patient with COVID-19; they should be given with prime attention and treated effectively and should be balanced between the anticipatory benefit of therapy and administered under supervision.

Stress Cardiomyopathy: Stress cardiomyopathy, commonly known as Takotsubo cardiomyopathy or shattered heart syndrome, is a consequence of COVID-19 and multi-organ system failure [50]. Patients infected with severe COVID-19 with widespread inflammation experience anxiety, and present as stress cardiomyopathy, which is produced by cytokine storm, mental and physical stress on the cardiac myocardium [51]. Also the cumulative effect of catecholamine tide and vascular damage in COVID-19 patients may result in dyskinesia of left ventricular apex and effluent stretch eventuating in stress cardiomyopathy [16].

Many researchers are concerned about stress cardiomyopathy and have conducted several studies to understand the presentations of stress cardiomyopathy better. For example, in one study, an 84-year-old male with diabetes and arterial hypertension who was on high-flow nasal cannula exhibited worsening dyspnoea and chest pain due to hypertensive crisis, which was managed by IV metoprolol, the hs-cTn was high at 70ng/ml, and ECG showed typical stress cardiomyopathy with left ventricular ejection fraction (LVEF) as 53%, who was treated with aspirin, fondaparinux sc, and nitroglycerine iv and discharged successfully [52]. Although a minor illness, stress cardiomyopathy can cause significant changes in a person's lifestyle; hence it is crucial to managing the issue.

Hypertension: As previously stated, the S-protein of COVID-19 binds to ACE2, predominantly expressed in pulmonary cells, and facilitates the entrance into the host cell leading to the deregulation of ACE2, causing vasoconstriction which may worsen hypertension using epithelial damage and oxidative stress [16].

The prevalence of hypertension in non-critically ill patients is about 4.5% and in older patients is >30% [53]. A retrospective multi-center study by P. Zhang and others included 1128 hypertensive patients with COVID-19. It indicated that inpatient use of Angiotensin Converting Enzyme inhibitors/ Angiotensin receptor blockers (ACEI/ARB) was associated with a low mortality rate in contrast to ACEI/ARB non-users, after adjustment of dose for age, comorbidity, and gender [54]. Hence, ACEI/ARB are the best choices of drugs in the management of Hypertension in COVID-19 patients. Hypertension is a well-known common condition in society. It is managed by various methods including Pharmacologic and Non-Pharmacologic therapies (lifestyle modifications). Still, in the COVID-19 scenario, the patients are already under stress, which creates anxiety and may cause fluctuation in

BP, which can result in the patient's untimely death. Therefore, it is of greater importance to constantly monitor BP and other vital signs throughout the infection, especially in critically infected patients.

Long COVID: Even when the viral load is low, many patients report persisting symptoms after an acute COVID infection. Post-acute COVID syndrome (PACS) is the persistence of COVID-19 symptoms after three weeks of acute COVID infection and twelve weeks of chronic COVID infection [55]. The reported symptoms ranged widely from cardiopulmonary and neurologic complaints, including fatigue, palpitations, chest pain, breathlessness, brain fog, and dysautonomia [55-60]. Regarding cardio symptoms, approximately 20% of individuals complained of chest pain, and 14% reported palpitations in 60 days [61, 62].

Persistent symptoms indicate damage to the affected organs; the appropriate examination is required to evaluate the extent of damage and intervene accordingly to minimize the complications and death of a COVID-19-infected individual. Knowing the risks and complications of COVID-19 infection on the cardiovascular system, it is important to be alert to notice the changes in the infected individual and take necessary precautions and measures to improve the quality of life and reduce the patient's suffering, which contributes to better patient care.

Section II: Covid-19 Vaccination and Cardiovascular Complications:

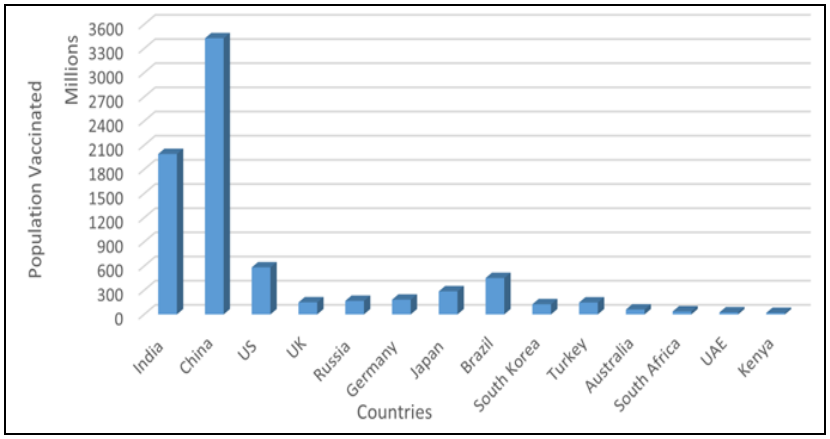

FIG. 2: NUMBER OF COVID-19 VACCINE DOSES ADMINISTERED. The data has been constituted from WHO dashboard [63]

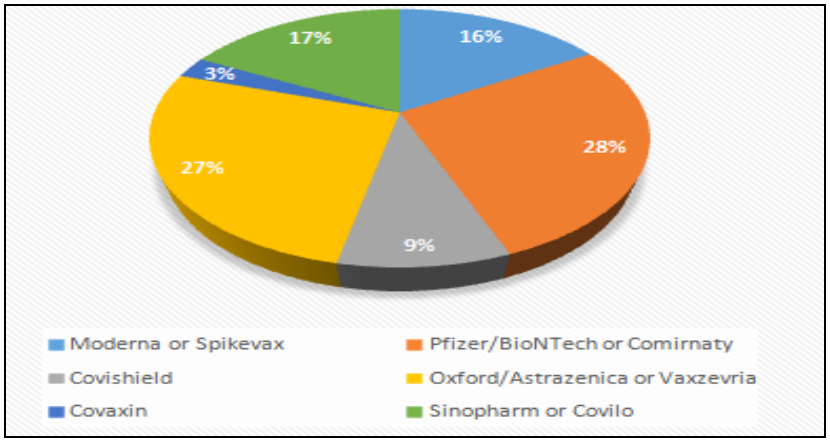

FIG. 3: NUMBER OF COUNTRIES APPROVED FOR USAGE OF COVID-19 VACCINES. The data has been constituted from COVID-19 Vaccine Development and Approvals Tracker [64]

The vaccination drive is surging worldwide with a ray of hope of complete eradication of COVID-19 illness; globally, more than 11.5 billion doses of COVID-19 vaccines have been administered [65]. As the hope created, COVID-19 severity was less seen in the 3rd wave, after COVID vaccination, compared to the 2nd wave, before vaccination worldwide.

As the thumb rule says, any substance that is foreign to the body (xenobiotics, in general) has its flaws, seen in the forms of adverse effects/events. Many adverse events have been reported following COVID-19 vaccination, and there do say that vaccination has its peculiar unintended effects on the heart, which are highlighted hereon. BBC news reports on 5th May 2022 state that 61% of the Indian population are vaccinated [66]. In India, two jabs of COVISHIELD and COVAXIN are available as an "Emergency Use Authorisation" during the COVID-19 pandemic granted by Central Drugs Standard Control Organisation (CDSCO). Later, Sputnik V was added to the list. Initially, the vaccination was rolled out to the frontline healthcare professionals and later extended to 45 years' age group population, and now COVAXIN is available for the 12+ age group population [67, 68].

Covishield is a widely accepted vaccination that shows an efficacy of 72% against symptomatic SARS CoV2, as revealed by the primary data analysis [69]. Regardless of the inter-dose interval from preceding participants who had two standard doses with an interval range from roughly 4 to 12 weeks, vaccination efficacy was observed to be better when the interval between doses was longer. Covaxin, India's first indigenous COVID-19 vaccine, has its own benefits with the safety and administration in the adolescent age group, which shows the efficacy against COVID-19 of any severity, 14 or more days post-dose 2, was 78% and vaccine efficacy against severe disease is 93% [70].

Safety of COVID Vaccines: The vaccination safety has not been firm to date. But, few of the studies showed that adverse effects after the first dose and second dose of vaccination were reported, such as feeling unwell, headache, fever, fatigue, muscle ache, decreased appetite, dizziness, nausea, myalgia, itching, and runny nose being non-serious and altered sensorium being a serious adverse event [71].

Anaphylaxis Due to Covishield: According to the basic tenet of vaccination, vaccinations are made to have a person's immunity against disease and to build a memory of defense that aids in fighting the virus when it is re-infected. Occasionally, immunizations may cause immunogenic reactions by over-activating the immune system. Likewise, Covishield, one of the vaccines with Emergency Use Authorisation, had an allergic reaction. A government panel, researching the negative consequences of the COVID vaccine noted the first anaphylactic fatality, which occurred on March 8, 2021, involved a 68-year-old male and the person who received the immunization should wait at least 30 minutes at the vaccination facility after receiving it to evaluate any immunogenic reactions [72].

COVID-19 Infection Popping Post-vaccination: The fact that vaccinations only work as a preventative measure and not as a treatment raises doubts about a person's capacity to fight off an infection. Although that vaccination consists of inactivated or destroyed germs, they introduce a fraction of the full pathogen capable of causing an illness. One study from India demonstrated the same outcome, in a group of 123 healthcare workers in New Delhi, 28 were vaccinated with Covaxin, 85 with Covishield, and 19 reported symptomatic COVID-19 infection after any vaccination dose [73]. Regardless of the severity of the infection, it is well-recognized worldwide that the COVID vaccination significantly boosted the COVID-19 infection's survival rate. Given this, it is a source of pride to report that the public, particularly Indians, has accepted the vaccine.

Thromboembolic Events: Thromboembolic events with COVID vaccinations have been commonly documented. DVT following immunization is one of the primary occurrences. According to Refai Showkathali and co-authors' study, there were higher incidences of COVAXIN-induced DVT compared to COVISHELD [74]. In a study conducted in Nepal, two patients, a 24-year-old young Chhetri male, and a 62-year-old female, who received the Covishield vaccine, complained of left calf pain and went to the emergency room, where the first exhibited mild to moderated irradiating pain below the knee that was exacerbated by movements. In contrast, the second, who had reported with severe pain, was diagnosed with superficial vein thrombosis, which can be a possible result of Covishield [75]. It is medically aware that thromboembolic events are managed easily with proper attention and surveillance.

Other Complications: Myocarditis, myoperi-carditis, thrombocytopenia, and hypertension are majorly seen in vaccines like Pfizer and Moderna [9]. In our paper, we mainly focused on Indian scenarios with data from neighbouring countries; all the above-described adverse effects/events are a possibility of post-immunization, which may not necessarily occur in all individuals vaccinated with SARS-CoV2 vaccines. In the general run, Covishield and Covaxin were safe and effective in curbing the COVID-19 pandemic. It is most important to get vaccinated and prevent the spread of infection.

CONCLUSION: COVID-19 caused an issue that impacted everyone both socially and economically. This has taught us a lesson and is a constant reminder that life is precious and that every individual has a purpose. Even though COVID-19 may have been an unintentional outbreak, it proved that danger still exists. We must understand how one prioritizes health over their career. The need to educate ourselves and society on health and cleanliness cannot be overstated. We've all realized that, aside from fleeing a circumstance like COVID, living with COVID is a sweeter piece of cake. Although this epidemic may have affected each and every one of us differently, we all managed to live. This COVID-19 situation highlighted the Darwinian notion of "Survival of the Fittest," with *immunized individuals* being the *fittest*.

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CONFLICTS OF INTEREST: Nil

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