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Serious adverse events following immunization with COVID-19 vaccines in Lebanon: a retrospective analysis of the National Pharmacovigilance Database

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Abstract

Continuous surveillance and risk assessment of inactivated Coronavirus Disease 2019 (COVID-19)) vaccines provide an understanding of their safety profiles, guide vaccination strategy and public health policy. This study aims to analyze the characteristics and prevalence of officially reported serious adverse events following immunization (AEFIs) with inactivated COVID-19 vaccines by System Organ Class (SOC), age, and sex.To achieve this aim, a retrospective observational study was conducted between February 14th, 2021, and June 30th, 2022. Reported AEFIs were evaluated for data completeness. Causality assessment adhered to the World Health Organization guidelines.

Findings revealed that the AEFIs occurrence did not significantly differ between vaccines used (ChAdOx1 vs. BNT162b2), sex, or SOC. The most prevalent AEFIs were vascular disorders (37%), followed by cardiac (25%) and nervous system disorders (14%). The adverse events were predominantly reported post-vaccination with the BNT162b2 vaccine, mainly after the first dose. The mean age was highest for miscellaneous disorders (70 ± 21.7 years) and the lowest for nervous system (46 ± 22 years) and immune system disorders (45 ± 19 years). Age differences were statistically different for vascular disorders ($p = 0.003$) and immune system disorders ($p = 0.012$).

In conclusion, ongoing surveillance and risk assessment of the vaccine's safety profile is crucial for detecting potential safety signals. Active surveillance of the reported serious AEFIs is highly needed to support evidence-based vaccination strategies and maintain public confidence in immunization programs,

Keywords COVID-19 vaccines, Adverse events following immunization, Pharmacovigilance

Background

The Coronavirus Disease 2019 (COVID-19) pandemic, declared by the World Health Organization (WHO) in March 2020, prompted the development of vaccines using various technological platforms. These vaccine platforms encompass RNA-based vaccines, such as Pfizer-BioNTech, adenoviral vaccines by AstraZeneca, and inactivated whole virus vaccines, such as Sinopharm vaccines [1]. On the international level, the WHO granted Pfizer-BioNTech (BNT162b2) and AstraZeneca (ChAdOx1) Emergency Use Authorization (EUA) in January 2021 [2], fostering the widespread implementation

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of mass vaccination campaigns across the globe. As of April 2024, over 40 Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) vaccines have received authorization or approval for use worldwide. When the Omicron variant emerged, pharmaceutical companies attempted to address this variant. Pfizer and Moderna's bivalent vaccines were granted emergency use approval in the United States and the United Kingdom. Chinese and U.S. sponsors have started clinical trials on the Omicron variant COVID-19 vaccine. Asian pharmaceutical companies CNBG (Sinopharm), Sinovac, and Shifa Pharmed have Phase 3 clinical trials under development [3].

On a regional level, the Lebanese Ministry of Public Health (MoPH) initiated a nationwide COVID-19 vaccination campaign on February 14th, 2021 [4]. The first COVID-19 vaccine marketed in Lebanon was the BNT162b2 vaccine, followed by ChAdOx1, Sputnik, Sinopharm, and Moderna COVID-19 vaccines. During the mass campaign, the Lebanese National Pharmacovigilance Program (LNPVP) took unprecedented measures to set up a surveillance system for Adverse Events Following Immunization (AEFIs) and monitor vaccine safety [4, 5]. The program aimed at making timely responses and ensuring the identification (detection), notification, reporting, investigation, data analysis, causality assessment, and feedback of all reported AEFIs with COVID-19 vaccines [6, 7].

An AEFI is any untoward medical event following immunization that does not necessarily have a causal relationship with vaccine use. The adverse event may be any unfavorable or unintended sign, abnormal laboratory finding, symptom, or disease [7]. An AEFI is considered serious if it is life-threatening, meaning it leads to death, hospitalization, or prolonged hospital stay, as well as leads to significant or permanent incapacity/disability or birth defect [7].

In Lebanon, out of 5,427,072 administered doses of COVID-19 vaccines between February 14th, 2021, and June 30th, 2022, 7,029 cases were reported to the LNPVP, including 25,484 AEFIs, of which 514 (7%) were serious [8]. During this period, infodemics fueled and affected vaccine hesitancy. Numerous misinformation circulated and were shared about the reactogenicity of the COVID-19 vaccines [9]. To address this problem, the LNPVP published periodic AEFI reports through the Ministry of Public Health website and took necessary measures to enhance public trust and acceptance of the vaccination programs [5, 10].

To foster transparency, the LNPVP outlines the serious AEFI case reports by System Organ Class (SOC), age groups, and sex. This study addresses a critical knowledge gap by providing a detailed overview of the distribution and characteristics of serious AEFIs, contributing to the ongoing efforts to monitor and improve the safety profile of COVID-19 vaccination programs.

Methods

Reporting system

The LNPVP provided several AEFI reporting methods for the public and healthcare workers. These include:

- A hotline call center (1214) initiated by the MoPH [11]
- The IMPACT Platform, an e-Governance Inter-Ministerial and Municipal Platform for Assessment, Coordination, and Tracking COVID-19, which also allows AEFI reporting [12, 13]
- The Kobo toolbox, an AEFI reporting software for vaccination sites and hospitals
- Direct contact with the LNPVP or other MoPH departments

Data collection

All AEFI cases spontaneously reported to the LNPVP between February 14th, 2021, and June 30th, 2022, were analyzed and included in this study. A case report contains the recipient's name, contact details, age, sex, type of vaccine administered, and the adverse event(s) possibly linked to the COVID-19 vaccine brand. The PV team screened all reported cases for completeness, validity, and reliability.

Handling serious case reports

Serious case reports undergo a five-step process before data entry into VigiFlow, the national web-based Individual Case Safety Report (ICSR) data management system [14–16] :

1. Follow up with the patient/family member/reporter and the treating physician to fill in any missing details.
2. Consult and screen medical records to ensure data completion and consistency. A case narrative is then written, including vaccination date, vaccine type, dose number, AEFI occurrence date, hospital name, hospital admission date, case presentation, history of present illness, relevant laboratory results, radiology results, past medical history, medication history, social history, allergy history, current medications, and follow-up visits.
3. Conduct a literature review to search for case definition, diagnosis, prevalence, risk factors, biological

association with the vaccine (if applicable), and similar reports.

4. Fill in the WHO investigation form, which includes basic details, patient information, details of the first examination, vaccines provided at the site, linked to AEFI on a corresponding day, immunization practice at the vaccination site, cold chain and transport, community investigation (similar events within the same period), and other findings/observations or comments.
5. Perform a causality assessment using the WHO AEFI causality assessment tool. AEFI [17] causality assessment is a systematic review of reported cases to determine the likelihood of a causal association between events and vaccines.

Causality assessment

The AEFI must satisfy the minimum criteria for causality assessment eligibility. These include the vaccine, a valid diagnosis, and an appropriate case definition. As shown in Fig. 1, it is a stepwise guided approach. Causality assessment assists in categorizing the AEFI relationship with the administered COVID-19 vaccine as coincidental, indeterminate, or consistent (Fig. 1).

The AEFI must satisfy minimum criteria for causality assessment eligibility. These criteria include: (Fig. 1).

- The vaccine administered
- A valid diagnosis
- An appropriate case definition

As shown in Fig. 1, the process follows a stepwise guided approach. Causality assessment assists in categorizing the AEFI relationship with the administered COVID-19 vaccine as:

- Coincidental
- Indeterminate
- Consistent

The LNPVP shares the causality assessment decision with officially assigned experts from the Serious AEFI special committee (Ministerial Decision #603/1), providing them with all relevant documents. In case of an inconsistent decision, the AEFI report is examined by a second expert.

Classification of AEFIs using MedDRA® terms

The Medical Dictionary for Regulatory Activities (MedDRA®) is used for categorizing adverse events associated with medical product use. The AEFIs are outlined according to MedDRA® terms and classified into a hierarchy of System Organ Class (SOC).

The variables included in the study were recipients' age, sex, vaccine used, number of doses, date of vaccination, date of AEFI onset, time to onset of indicated AEFI, type of AEFI, SOC, and case reports causality assessment decision.

Statistical analysis

Statistical analyses were conducted using SPSS software (Version 25). Data were disaggregated by age (more or less than 65 years old) and sex. Fisher's exact test was applied to compare percentages, and Student's t-tests were used to compare means between groups. A p-value < 0.05 was considered significant.

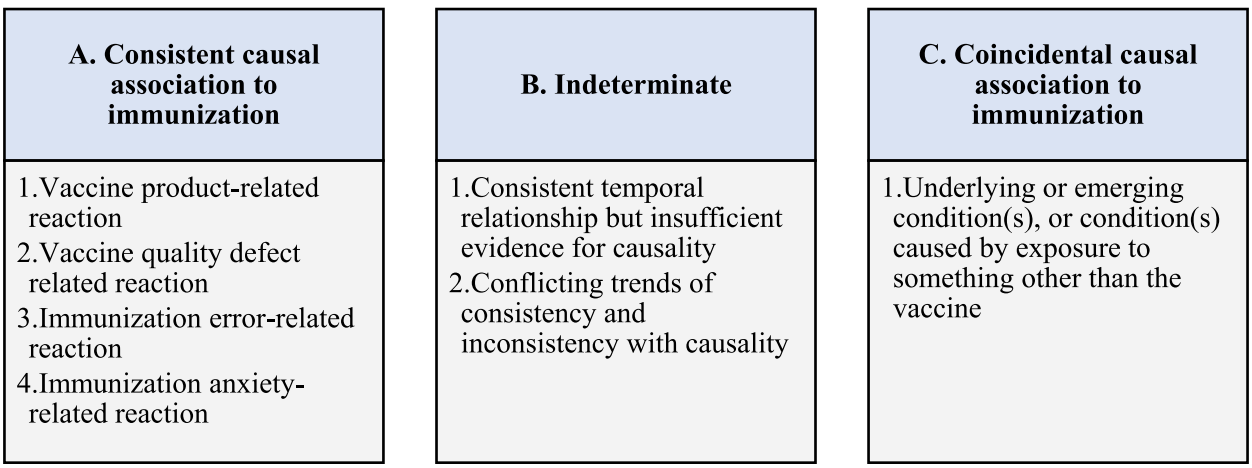

Fig. 1 Causality assessment classification. *Retrieved from reference #14*

Results

Table 1 outlines the occurrence of AEFIs by SOC. The predominant adverse events included primarily Vascular disorders (37%), followed by cardiac (25%) and nervous system (14%) disorders (Table 1).

Table 2 shows no significant differences in the occurrence of serious AEFIs by SOC, although females made-up 75% of miscellaneous disorders and higher occurrence of cardiac (58%) and vascular disorders (54%). In cardiac disorders, there was a significantly higher fatal outcome (55%) compared with other disorders ($p < 0.001$). The majority of adverse events were reported post-vaccination with the BNT162b2 vaccine, mainly after the first dose and occurred after the first dose, however, the differences were not statistically significant. The mean age was highest for miscellaneous disorders (70 ± 21.7 years) and the lowest for nervous system (46 ± 22 years) and immune system disorders (45 ± 19 years). Age differences were statistically different in the occurrence of vascular disorders ($p = 0.003$) and immune system disorders ($p = 0.012$). The mean Time To Onset (TTO) ranged between 2 days for infection and infestations disorders and 18 days for nervous system disorders with no significant statistical differences (Table 2).

Table 3 reports serious AEFIs occurring in vascular disorders ($p < 0.03$) and immune system disorders ($p < 0.042$) are significantly different between elderly (≥ 65 years) and younger vaccine recipients. No difference in the occurrence and types of serious AEFIs is detected between sex-disaggregated data.

In males less than 65 years old, the serious AEFIs exclusively reported were: myocardial infarction (MI), myocarditis and non-ST-elevation MI, functional neurological disorders, anaphylaxis, auto-immune hemolytic anemia, atypical pneumonia, vaccine-induced thrombotic thrombocytopenia (VITT) and febrile neutropenia.

In males 65 years old and above, reports of extensive portal vein thrombosis, pulmonary embolism, transient ischemic attack, Kounis syndrome, amyotrophic lateral sclerosis exacerbation (ALS), aspiration pneumonia, and sepsis were noted.

Exclusively, females less than 65 years old, serious AEFIs were pericarditis, deep vein thrombosis, hemorrhagic cerebrovascular accident, acute disseminated encephalomyelitis, optic neuritis, Hyperstimulation of the Immune System (HIS), urticaria, cutaneous reaction, acute bronchitis, actinomycosis (lung infection), and post-surgical bleeding.

Females older than 65 years reported unstable angina, Hyperstimulation of the Immune System, community-acquired pneumonia, hypoxia, and pulmonary edema (Table 3).

Table 1 Types of serious reported adverse events following immunization by system organ class

Serious AEFI	*N* (%)	
Cardiac disorders	**19 (25)**	
Cardiac arrest	10 (53)	
Myocardial infarction	2 (11)	
Myocarditis	2 (11)	
NSTEMI[a]	1 (5)	
Pericarditis	1 (5)	
STEMI[b]	2 (10)	
Unstable angina	1 (5)	
Vascular disorders	**28 (37)**	
Deep Vein Thrombosis	2 (7)	
Extensive Portal Vein Thrombosis	1 (4)	
Hemorrhagic Cerebrovascular Accident	2 (7)	
Ischemic Cerebrovascular Accident	18 (64)	
Left Axillary Artery Thrombosis	1 (4)	
Pulmonary Embolism	1 (4)	
Transient ischemic attack	3 (11)	
Nervous system disorders	**11 (14)**	
Acute Disseminated Encephalomyelitis	1 (9)	
Amyotrophic lateral sclerosis exacerbation (ALS)	1 (9)	
Cerebral Hemorrhage	1 (9)	
Epileptic Seizure	2 (18)	
Functional Neurological Disorders	1 (9)	
Guillain-Barre Syndrome	4 (36)	
Optic Neuritis	1 (9)	
Immune system disorders	**7 (9)**	
Anaphylaxis	1 (14)	
Auto-Immune Hemolytic Anemia	1 (14)	
Cutaneous reaction	1 (14)	
Hyperstimulation of the Immune System	1 (14)	
Kounis syndrome	1 (14)	
Urticaria	1 (14)	
Vaccine-Induced Immune Thrombotic Thrombocytopenia	1 (14)	
Infections and infestations	**8 (10)**	
Acute Bronchitis	1 (12)	
Aspiration pneumonia	1 (12)	
Atypical Pneumonia	1 (12)	
Community Acquired Pneumonia	2 (26)	
Lung infection (Actinomycosis)	1 (12)	
Sepsis	2 (26)	26%
Miscellaneous	**4 (5)**	
Blood and lymphatic system disorders		
Febrile neutropenia	1 (25)	
Respiratory, thoracic, and mediastinal disorders		
Hypoxia	1 (25)	
Pulmonary edema	1 (25)	
Surgical and medical products		
Post-surgical bleeding (Leep Intervention)	1 (25)	

[a] Non-ST-segment Elevation Myocardial Infarction (NSTEMI)

[b] ST-segment Elevation Myocardial Infarction (STEMI)

Table 2 Characteristics of serious reported adverse events following immunization by system organ class

	Cardiac disorders		Vascular disorders		Nervous system disorders		Immune system disorders		Infections and infestations		Miscellaneous	
N(%)												
Sex												
Male	12 (40)		13 (46)		6 (54)		4(50)		3 (43)		1 (25)	25%
Females	18 (60)		15 (54)		5 (54)		4(50)		4		3 (75)	75%
F/M ratio	1.5		1.15		0.83		0.75		1			
P value		0.219		0.407		0.5		1		1	0.615	
Vaccine used												
ChAdOx1	2 (10)		6 (21)		2 (18)		1 (13)		1(14)		3 (75)	75%
BNT162b2	18(90)		22(79)		9 (82)		7 (87)		6 (86)		1 (25)	25%
		0.496		0.294	0.586			0.601		0.670		0.525
R Dose												
First dose	11 (58)		18 (64)		7 (64)		4 (57)		2 (25)	%	3	75%
Second dose	6 (32)		9 (32)		2 (18)		3 (43)		5 (62)		1	25%
Third dose	2 (10)		1 (4)		2 (18)		0		1 (13)		0	0%
	0.573		0.350			0.453		0.90		0.715	0.707	
Seriousness												
Fatal	11 (55)		2 (7)		1(10)	18%	0		0		0	0%
Hospitalization	9 (45)		26 (93)		10(90)		8(100)		7(100)		4(100)	
P value	<0.001*		0.055		0.678		0.338		0.340		1	
Mean ±SD												
Age (years)	64 ± 22		71 ±17		46 ± 22		45 ± 19		65 ±14		70.75 ± 21.70	
P value	0.726		0.003*		0.004*		0.012*		0.671		0.483	
TTO (days)	8 ± 10		9 ± 8		18 ± 28		5.5± 6.4		2 ± 1		10 ±12	
P value	0.697		0.977		0.263		0.405		0.115		0.931	

*$p < 0.005$

Table 4 classifies half of the reported serious AEFIs as coincidental (51%). Consistent cases include pericarditis, cerebral hemorrhage, functional neurological disorders, anaphylaxis, auto-immune hemolytic anemia, Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT), and cutaneous reactions (Table 4).

Discussion

Serious AEFIS reported to the LNPVP between February 2021 and June 2022 were predominantly vascular disorders, followed by cardiac and nervous systems disorders, infections and infestations, immune disorders, and other disorders. Other disorders include blood and lymphatic, respiratory, thoracic, and mediastinal disorders, and surgical and medical disorders. Sex-disaggregated (males versus females) and vaccine-disaggregated AEFIs (BNT162b2 versus ChAdOx1) did not significantly differ between groups. Age-disaggregated AEFIs showed a significant difference between vascular disorders predominantly reported in elderly recipients (68%) and immune system disorders reported mainly in younger individuals (86%).

Consistent with numerous published studies and global official pharmacovigilance reports, serious AEFIs were limited to 514 (7%) case reports [9]. To ensure vaccine safety, the LNPVP closely monitored their reactogenicity. Data about serious and non-serious adverse events following inactivated COVID-19 vaccination were publicly available through the Ministry of Public Health website. Throughout the mass vaccination campaign, the Lebanese National Pharmacovigilance Program (LNPVP) disseminated periodic updates to enhance transparency and mitigate vaccine hesitancy by providing evidence-based information. This systematic approach fosters public trust and promotes informed decision-making regarding COVID-19 vaccination. COVID-19 vaccines are considered safe, but continuous surveillance and risk assessment are crucial to ensure long-term safety and safety detection signals.

In this study, the LNPVP provides a detailed description of the serious AEFIs post-COVID-19 vaccination. They are presented below by SOC as follows:

Table 3 Sex- and age-disaggregated serious adverse events following immunization

	Sex-disaggregated data					Age-disaggregated data				
	Male		Female		*p*-value	< 65 years		≥ 65 years		*p*-value
	n = 39	51%	*n* = 38	49%		37 (48%)		40 (52%)		
Cardiac disorders	**11**	**58%**	**8**	**42%**	**0.322**	**9**	**47%**	**10**	**53%**	**0.578**
Cardiac arrest	5	50%	5	50%		1	10%	9	90%	
Myocardial infarction	2	100%	0	0%		2	100%	0	0%	
Myocarditis	2	100%	0	0%		2	100%	0	0%	
NSTEMI	1	100%	0	0%		1	100%	0	0%	
Pericarditis	0	0%	1	100%		1	100%	0	0%	
STEMI	1	50%	1	50%		2	100%	0	0%	
Unstable angina	0	0%	1	100%		0	0%	1	100%	
Vascular disorders	**13**	**46%**	**15**	**54%**	**0.373**	**9**	**32%**	**19**	**68%**	**0.030***
Deep Vein Thrombosis	0	0%	2	100%		2	100%	0	0%	
Extensive Portal Vein Thrombosis	1	100%	0	0%		0	0%	1	100%	
Hemorrhagic Cerebrovascular Accident	0	0%	2	100%		2	100%	0	0%	
Ischemic Cerebrovascular Accident	8	44%	10	56%		3	17%	15	83%	
Left Axillary Artery Thrombosis	0	0%	1	100%		0	0%	1	100%	
Pulmonary Embolism	1	100%	0	0%		0	0%	1	100%	
Transient ischemic attack	3	100%	0	0%		2	67%	1	33%	
Nervous system disorders	**5**	**55%**	**5**	**45%**	**0.519**	**7**	**64%**	**4**	**36%**	**0.215**
Acute Disseminated Encephalomyelitis	0	0%	1	100%		1	100%	0	0%	
Amyotrophic lateral sclerosis exacerbation (ALS)	1	100%	0	0%		0	0%	1	100%	
Cerebral Hemorrhage	0	0%	1	100%		1	100%	0	0%	
Epileptic Seizure	1	50%	1	50%		2	100%	0	0%	
Functional Neurological Disorders	1	100%	0	0%		1	100%	0	0%	
Guillain-Barre Syndrome	3	75%	1	25%		1	25%	3	75%	
Optic Neuritis	0	0%	1	100%		1	100%	0	0%	
Immune system disorders	**4**	**57%**	**3**	**43%**	**0.629**	**6**	**86%**	**1**	**14%**	**0.043***
Anaphylaxis	1	100%	0	0%		1	100%	0	0%	
Auto-Immune Hemolytic Anemia	1	100%	0	0%		1	100%	0	0%	
Cutaneous reaction	0	0%	1	100%		1	100%	0	0%	
Hyperstimulation of the Immune System	0	0%	1	100%		1	100%	0	0%	
Kounis syndrome	1	100%	0	0%		0	0%	1	100%	
Urticaria	0	0%	1	100%		1	100%	0	0%	
Vaccine-Induced Immune Thrombotic Thrombocytopenia	1	100%	0	0%		1	100%	0	0%	
Infections and infestations	**4**	**50.0%**	**4**	**50.0%**	**0.629**	**5**	**50%**	**4**	**50%**	**0.599**
Acute Bronchitis	0	0.0%	1	100.0%		1	100%	0	0%	
Aspiration pneumonia	1	100.0%	0	0.0%		0	0%	1	100%	
Atypical Pneumonia	1	100.0%	0	0.0%		1	100%	0	0%	
Community Acquired Pneumonia	0	0.0%	2	100.0%		0	0%	2	100%	
Lung infection (Actinomycosis)	0	0.0%	1	100.0%		1	100%	0	0%	
Sepsis	2	100.0%	0	0.0%		1	50%	1	50%	
Miscellaneous	**1**	**25%**	**3**	**75%**	**0.298**	**2**	**50%**	**2**	**50%**	**0.662**
Blood and lymphatic system disorders										
Febrile neutropenia	1	100.0%	0	0.0%		1	100%	0	0%	
Respiratory, thoracic, and mediastinal disorders										
Hypoxia	0	0.0%	1	100.0%		0	0%	1	100%	
Pulmonary Edema	0	0.0%	1	100.0%		0	0%	1	100%	
Surgical and medical products										
Post-surgical bleeding (Leep Intervention)	0	0.0%	1	100.0%		1	100%	0	0%	

*$p < 0.005$

Cardiac disorders

Acute coronary syndrome

Six cases of Acute Coronary Syndrome (ACS) were reported in both sexes to the LNPVP, mainly post-vaccination with the BNT162b2 vaccine. A literature review shows that ACS occurred in male and female patients after the first, second, and third doses of COVID-19 vaccines. It is compatible with our reported cases [18–22]. The American Heart Association (AHA) states that mRNA vaccines numerically increase inflammatory markers, resulting in endothelium inflammation and T-cell infiltration of cardiac muscle [23].

Cardiac arrest

Our data shows that 10 cases of cardiac arrest reported mainly in patients 75 years and above were associated with fatal outcomes. AstraZeneca Vaccine Case Series Analysis Print reported 200 cardiac arrests, of which 43 resulted in a fatal outcome [24]. Based on the WHO Database, Kaur (2021) reported cardiac arrest and circulatory collapse occurring with COVID-19 vaccines. It includes ChAdOx1 and BNT162b2s in patients 75 years and above [25]. Sadiq (2022) described a case of a cardiopulmonary arrest occurring the same day of vaccination with mRNA COVID-19 vaccine [26]. This finding aligns with the three cardiac arrests occurring a few minutes to hours after BNT162b2 vaccine administration.

Causality assessment showed that the patient in our database has underlying health conditions and at least one risk factor, such as male gender, older age, HTN, DM, DLP, obesity, and arrhythmias (including Atrial Fibrillation) [27, 28]. Other factors may be due to the lack of adherence to medications [29] and potential drug shortage.

Myocarditis and pericarditis

The reported cases of myocarditis and pericarditis occurred after receiving the BNT162b2 vaccine. Myocarditis presented with gastrointestinal symptoms, unlike the reported literature, whereby chest pain was the most common presenting symptom [30–32].

Heymans and Cooper (2022) suggest that the immune system may identify mRNA vaccines as antigens. Leading to activation of immunological pathways and pro-inflammatory cascades in the heart [33]. Another plausible explanation might be the molecular mimicry between cardiac self-antigens and the spike protein of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [33].

A cohort study found that myocarditis incidence was 1.7 per 100,000 vaccinated persons within 28 days of any mRNA COVID-19 vaccine [34]. Another Canadian report showed that 1192 out of 1,886 cases of myocarditis and pericarditis were associated with BNT162b2 use [35]. Several published case reports have also suggested a possible relationship between myocarditis and mRNA COVID-19 vaccines [30].

A retrospective cohort study by Wong et al. (2022) documented a higher risk of pericarditis or myocarditis in men aged 18 to 25 following the second dose of mRNA vaccines [36]. In addition, Witberg (2021) reported that male vaccine recipients between 16 and 29 years have the highest incidence of myocarditis. The estimate is at 10.7 cases per 100,000 [37].

Our data findings confirm the occurrence of myocarditis in 24- and 25-year-old male patients. Das (2021) described 10% of 29 cases of myocarditis and pericarditis occur after the first dose [38]. LNPVP reported cases showed that the onset of myocarditis and pericarditis was within 19 to 39 days after receiving their vaccine. In contrast, 1,081 (90%) out of 1,199 cases reviewed in the US had myocarditis within seven days of their mRNA COVID-19 vaccine [39].

Vascular disorders

Cerebrovascular accidents

Of the reported Cerebrovascular Accidents (CVAs), 18 were ischemic, two were hemorrhagic, and three were transient ischemic strokes. Five reported cases of stroke post-ChAdOx1s vaccination occurred in patients between 32 and 55 years within five to 32 days post-vaccination.

Ischemic CVA cases occurred following BNT162b2 vaccination (78%), where two hospitalizations and the rest had a fatal outcome. Half of the hospitalized patients were 75 years old and above. Tabagi (2022) found that out of 17,014 hospitalized patients 75 years and above with ischemic stroke, 54% received at least one dose of the BNT162b2, and 38% received two doses [40]. In contrast, two cases of ischemic CVA occurred after the ChAdOx1 in two males aged 52 and 48 years old, which aligns with an ischemic stroke report of a 43-year-old male in Saudi Arabia [41]. CVAs post influenza and varicella vaccination were documented in the literature. A possible hypothesis suggested that similar to the nature of the disease, such vaccines may induce angiopathy of the brain, resulting in constriction and eventually blockage of cerebral vessels, causing ischemic infarctions [42]. Concerns about similar potential unknown mechanisms of the ChAdOx1 vaccine causing a hypercoagulable state resulting in thrombotic events were raised [41].

Hemorrhagic stroke was reported to the LNPVP post-vaccination with the ChAdOx1 vaccine. The reported cases of hemorrhagic stroke in Lebanon occurred in two previously healthy women five days following the same type of COVID-19 vaccine. The reported cases in

Table 4 Classification of serious adverse events following immunization by causality

	Indeterminate		Coincidental		Consistent	
	n	**%**	***n***	**%**	***n***	**%**
	26	**34%**	**39**	**51%**	**12**	**15%**
Cardiac disorders	**6**	**32%**	**10**	**53%**	**3**	**15%**
Cardiac arrest	4	40%	6	60%	0	0%
Myocardial infarction	0	0%	1	50%	1	50%
Myocarditis	1	50%	0	0%	1	50%
NSTEMI	0	0%	1	100%	0	0%
Pericarditis	0	0%	0	0%	1	100%
STEMI	1	50%	1	50%	0	0%
Unstable angina	0	0%	1	100%	0	0%
Vascular disorders	**12**	**43%**	**15**	**54%**	**1**	**3%**
Deep Vein Thrombosis	1	50%	1	50%	0	0%
Extensive Portal Vein Thrombosis	0	0%	1	100%	0	0%
Hemorrhagic Cerebrovascular Accident	1	50%	1	50%	0	0%
Ischemic Cerebrovascular Accident	7	39%	10	56%	1	6%
Pulmonary Embolism	1	100%	0	0%	0	0%
Transient ischemic attack	2	67%	1	33%	0	0%
Nervous system disorders	**6**	**55%**	**1**	**9%**	**4**	**36%**
Acute Disseminated Encephalomyelitis	1	100%	0	0%	0	0%
Amyotrophic lateral sclerosis exacerbation (ALS)	1	100%	0	0%	0	0%
Cerebral Hemorrhage	0	0%	0	0%	1	100%
Epileptic Seizure	1	50%	1	50%	0	0%
Functional Neurological Disorders	0	0%	0	0%	1	100%
Guillain-Barre Syndrome	2	50%	0	0%	2	50%
Optic Neuritis	1	100%	0	0%	0	0%
Immune system disorders	**1**	**14%**	**2**	**29%**	**4**	**57%**
Anaphylaxis	0	0%	0	0%	1	100%
Auto-Immune Hemolytic Anemia	0	0%	0	0%	1	100%
Cutaneous reaction	0	0%	0	0%	1	100%
Hyperstimulation of the Immune System	0	0%	1	100%	0	0%
Kounis syndrome	1	100%	0	0%	0	0%
Urticaria	0	0%	1	100%	0	0%
Vaccine-Induced Immune Thrombotic Thrombocytopenia	0	0%	0	0%	1	100%
Infections and infestations	**0**	**0%**	**8**	**100%**	**0**	**0%**
Acute Bronchitis	0	0%	1	100%	0	0%
Aspiration pneumonia	0	0%	1	100%	0	0%
Atypical Pneumonia	0	0%	1	100%	0	0%
Community Acquired Pneumonia	0	0%	2	100%	0	0%
Lung infection (Actinomycosis)	0	0%	1	100%	0	0%
Sepsis	0	0%	2	100%	0	0%
Miscellaneous	**1**	**25%**	**3**	**75%**	**0**	**0%**
Blood and lymphatic system disorders						
Febrile neutropenia	0	0%	1	100%	0	0%
Respiratory, thoracic, and mediastinal disorders						
Hypoxia	0	0%	1	100%	0	0%
Pulmonary Edema	1	100%	0	0%	0	0%
Surgical and medical products						
Post-surgical bleeding (Leep Intervention)	0	0%	1	100%	0	0%

Lebanon had different outcomes since one led to death, and the second had a smooth recovery.

De Mélo Silva (2021) reported a case of a previously healthy 57-year-old woman who had a hemorrhagic stroke five days after receiving her first dose of ChAdOx1 in the absence of thrombocytopenia, or coagulation disorder, which led to disability [43].

Two cases of Transient Ischemic Stroke (TIA) were reported to the LNPVP. They occurred in males 47 and 75 years within one to 20 days post-vaccination with BNT162b2. TIA was documented in the literature in a 56-year-old woman eight days after receiving the first dose of BNT162b2 administration [44].

Thrombotic events

The LNPVP received five cases of thrombosis, two post-immunizations with ChAdOx1, and three following BNT162b2 vaccination. The patients were three females and two males aged between 41 and 77 years. The onset of symptoms was between 2 to 16 days after the first dose of the vaccine.

Deep Vein Thrombosis (DVT) occurred in a 64-year-old female four days following immunization with the first dose of the BNT162b2 vaccine. The European Medicines Agency (EMA) outlined similar reports post-vaccination after the ChAdOx1 [45].

A case of pulmonary embolism was documented in Lebanon following the use of the BNT162b2 vaccine. In the literature, Tobaiqy et al. (2021) stated that 3,420 thrombotic adverse events from the Eudra Vigilance database occurred following COVID-19 vaccines, 58.1% after ChAdOx1, and 32% post-BNT162b2 use [46].

A single case of Portal Vein Thrombosis (PVT) was reported in Lebanon in a 65-year-old male within 16 days of the first dose of ChAdOx1. A systemic review by Kheyrandish (2021) reported similar cases [47]. Cases reported by Öcal (2021) were also consistent with our findings by sex, type of vaccine used, and vaccine dose [48].

Nervous system disorders

Guillain-Barré Syndrome (GBS)

Four cases of GBS were reported to the LNPVP after the first dose, following the use of the BNT162b2 vaccine. The mean age was 57 years, and symptoms onset Ranged from 0 to 10 days after BNT162b2 use. None was documented post-immunization with the ChAdOx1 vaccine.

A systematic review conducted in 2021 outlined 39 cases of GBS associated with COVID-19 vaccines [49]. Hanson (2022) found 36 confirmed cases of GBS from the Vaccine Safety Datalink in the US, after predominantly the second dose of mRNA-vaccine administration, including BNT162b2 [50]. Bouattour (2022) described a case of a 67-year-old male hospitalized seven days post-vaccination with the first dose of BNT162b2 for rapidly progressive muscle weakness [51]. This case is consistent with our findings. Kim (2022) presented five cases of GBS post-BNT162b2 with a mean age of 45 years and the onset of symptoms within 11 to 14 days post-vaccination [52].

One cerebral hemorrhage case was documented in Lebanon in a 54-year-old female 17 days following the first dose of the ChAdOx1 vaccine. Similarly, fatal cerebral hemorrhage cases were reported to the Norwegian Medicines Agency following the ChAdOx1. The patient was a previously healthy woman in her thirties who developed intracranial bleeding with severe thrombocytopenia seven days after receiving the ChAdOx1 vaccine [53]. Intracranial bleeding cases post mRNA vaccination are documented in the literature [54, 55].

Only one Acute Disseminated Encephalomyelitis (ADEM) case was reported in Lebanon in a 39-year-old female following the immunization with the first dose of ChAdOx1vaccine [56].

A similar case was described by Nagaratnam (2022) in a 36-year-old female following the first dose of the ChAdOx1 vaccine [6]. Cao and Ren (2022) described a case of ADEM in a 24-year-old female two weeks after the inactivated form of the COVID-19 vaccine, Sinopharm [57]. Kania (2021) reported ADME in a patient two weeks after receiving the first dose of Moderna, an mRNA COVID-19 vaccine [58]. Rinaldi (2022) outlined a case of ADME in a 45-year-old male 12 days after his first dose of ChAdOx1 vaccination [59].

Amyotrophic Lateral Sclerosis (ALS)

A case of rapid deterioration of ALS has been reported to the LNPVP in a 69-year-old male after receiving his second dose of the BNT162b2 vaccine. The patient died due to respiratory failure 93 days post-vaccination.

Patients between 66 and 78 years old with ALS were documented with a rapid functional decline after contracting the COVID-19 infection [60].

Exacerbation of other neurodegenerative disorders, such as multiple sclerosis, was reported in the literature. Khayat-Khoei (2022) reported seven cases of new-onset Multiple Sclerosis (MS) or MS exacerbation in females aged between 24 and 64 years old who received an mRNA COVID-19 vaccine, either BNT162b2 or Moderna [61].

Epileptic seizures and functional neurological disorder

Three cases of seizures (epileptic and non-epileptic) aged between 12 and 32 years for the first time within 20 min to 15 days after receiving the first dose of the BNT162b2 vaccine.

Assiri e (2022) described a case of a 58-year-old female admitted for an isolated seizure occurring for the first time 25 days following the first dose of the ChAdOx1 vaccine [44]. Liu (2021) presented two other cases of seizures in an 86-year-old woman and a 73-year-old man, 7 to 21 days after getting their first shot of Moderna (mRNA COVID-19 vaccine) [62]. A cross-sectional study conducted in Kuwait following the BNT162b2 and ChAdOx1s found that 93.9% of patients with epilepsy did not report seizure worsening post-vaccination [63].

Optic Neuritis (ON)

One case of ON was seen in a 52-year-old female after the third dose of BNT162b2. ON has been reported after COVID-19 vaccines in India and Mexico [64, 65]. Jaffry (2022) investigated the association and found no causal relationship between ON and COVID-19 vaccine [66]. The mechanism by which BNT162b2 may cause optic neuritis is unclear since inflammation in any ocular region can occur due to immune responses triggered by COVID-19 vaccines [67].

Immune system disorders

Anaphylaxis

A 50-year-old male had anaphylaxis a few minutes after the first dose of the BNT162b2 vaccine. Sobczak (2022) described cases of anaphylaxis post-immunization predominantly with BNT162b2 and ChAdOx1 vaccines [68].

In the US, 47 cases of anaphylaxis were reported following the use of the BNT162b2 vaccine. Out of which 37 occurred after the first dose [69]. Female recipients had a higher reporting rate of anaphylaxis following the BNT162b2 than males [70]. Polyethylene Glycol (PEG) 2000 in mRNA vaccines was an eligible cause of allergic reactions, including anaphylaxis [71–74].

Urticaria

A 25-year-old female reported a case of urticaria that occurred 15 days after her first dose of BNT162b2 vaccine. The reported case is similar to those found in the literature [75–77]. Triwatcharikorn (2022) reported cases of urticaria that occurred within 5 min to 18 h post-immunization [78].

Kounis syndrome (KS)

KS can be due to multiple causes, including certain types of food, drugs, environmental exposures, and coronary stents [79]. Other vaccines are also potential triggers of KS, including influenza and tetanus vaccine, BNT162b2, ChAdOx1 vaccines, and the inactivated form of the vaccine (CoronaVac) [79–82].

In Lebanon, anaphylaxis-induced stent thrombosis known as KS Type III was reported in a 64-year-old man. He was admitted minutes after receiving the first dose of the BNT162b2. KS was also documented post-immunization with BNT162b2 [83], the inactivated form, CoronaVac, and ChAdOx1 vaccines [81, 84].

KS occurred after the first dose administration of COVID-19 vaccines in males and females aged between 22 and 86 years old, with and without underlying comorbidities. The onset of symptoms was within 15 min to 1.5 h after vaccine administration, except for one case whose symptoms started two days post-immunization [82–85]. Kounis (2021) suspected vaccine excipients to cause an allergic reaction. It is due to the PEG in BNT162b2 and Moderna and polysorbate 80 in ChAdOx1 vaccines [86].

Vaccine-induced immune thrombotic thrombocytopenia

One case of VITT has been reported 14 days after the first dose of ChAdOx1.

Similar findings in terms of dose number [87, 88] and the onset of symptoms [87, 89] were documented in the literature. In the United Kingdom, in 2021, 309 cases of VITT were reported post-immunization with ChAdOx-1vaccine [90].

EMA estimated the incidence of VITT after the use of the CHADOX1 vaccine ranges between 1 in 125,000 and 1 in 1 million [91]. In Lebanon, the estimated incidence is 1.4 in 1 million ChAdOx1 doses administered.

Hyperstimulation of the Immune System (HIS)

In Lebanon, a 31-year-old female known to have Hashimoto's Disease reported HIS after the second dose of BNT162b2.

Jara (2022) considered that autoimmune syndrome occurred after the administration of COVID-19 vaccines, but causality was not established [92]. The occurrence of autoimmune diseases in COVID-19 vaccine recipients may be high in genetically susceptible individuals [93]. This argument is potentially in line with our patient with Hashimoto's disease, an autoimmune disorder that leads to the destruction of thyroid cells via antibody and cell-mediated immune processes [94].

Autoimmune Hemolytic Anemia (AIHA)

A 58-year-old male with thalassemia reported a case of AIHA after the second dose of the BNT162b2.

Similarly, several cases are described in the literature following immunization with mRNA vaccines [95–98]. AIHA was documented following the first dose [99, 100], second dose [98], and third dose [97] of mRNA

COVID-19 vaccines. Although AIHA is prevalent in females, reported cases have been described in males [97, 100], predominantly aged 45 years and above [96–99].

Cutaneous reaction

A 13-year-old girl, previously known to have psoriasis, experienced a skin reaction after the second dose of the BNT162b2 vaccine. Conflicting medical opinions lead to two possible diagnoses: severe atopic dermatitis or exacerbation of cutaneous psoriasis. Blumenthal (2021) documented 12 patients between 31 and 61 years after a median onset of 8 days post-first dose of mRNA-1273 vaccination [101]. COVID-19 vaccines were associated with new-onset and exacerbation of pre-existing psoriasis [102, 103].

Infections and infestations

Lung infection

An 86-year-old female reported pneumonia post third dose of BNT162b vaccine2. Yoshikawa presented similar findings in a 78-year-old female following the first and second dose of BNT162b2 and was diagnosed with pneumonia [104]. May (2022) documented a case of pneumonia in a non-smoker 55-year-old female with the onset of symptoms within seven weeks post the first dose of the ChAdOx1 vaccine [105]. This case is similar to the pulmonary infection reported in Lebanon in a 60-year-old female, known to be a current smoker, with no medical history.

Additional cases reported to the LNPVP were a 50-year-old female who presented with acute bronchitis after her first dose of BNT162b2. An 80-year-old male presented with aspiration pneumonia following his second dose of BNT162b2. It is worth highlighting that several studies in the literature discussed COVID-19 infection as a potential cause of short- and long-term lung infection [106–108].

Sepsis

Two cases of sepsis occurred after receiving the second dose of the BNT162b2 COVID-19 vaccine, whereby one led to a fatality. A similar case was described in the US following the first dose of COVID-19 vaccines (BNT162b2, ChAdOx1, and Moderna) [109], and the second dose of mRNA vaccines (BNT162b2 and Moderna) led to sepsis.

Miscellaneous

Hypoxia

An 87-year-old female reported hypoxia post-immunization with the second dose of the BNT162b2 vaccine. In Germany, a short report published in 2022 revealed that oxygen levels in 12 participants have dropped below 94% post-immunization with the BNT162b2 within two to five days after vaccination [110]. Tutak (2021) discussed the case of a 66-year-old male who presented with hypoxia (oxygen saturation ranging from 85 to 90%) and dyspnea 14 days after the second dose of the COVID-19 vaccine [111].

Pulmonary edema

A 90-year-old female known to have Congestive Heart Failure (CHF) had pulmonary edema after the first dose of the BNT162b2 vaccine. Following the second dose of the Moderna vaccine, a case report describes pulmonary edema in a patient with a history of CHF [112].

Post-surgical bleeding

Five days after cervical surgery, a 50-year-old female reported post-surgical bleeding when she received the first dose of the ChAdOx1 vaccine. The Royal Australian College of Surgeons recommends a two-week gap between elective surgeries and the final COVID-19 vaccine dose received [113].

Febrile neutropenia

A 52-year-old male, known to have Squamous Cell Lung Cancer Stage IIIB, reported febrile neutropenia less than 24 h post-vaccination with the BNT162b2 vaccine. A systematic review and results from randomized clinical trials revealed that numerous cases of neutropenia were reported within two weeks of vaccination [114].

Limitations

This study has several limitations to consider when interpreting the results. The retrospective design and reliance on spontaneously reported AEFIs may lead to underreporting and potential underestimation of serious adverse events. The analysis did not adjust for confounding variables such as age, sex, comorbidities, and concomitant medications. The limited number of serious events precluded more sophisticated statistical analyses, such as regression modeling. The absence of an unvaccinated control group prevents the determination of whether the observed adverse events exceeded expected baseline rates. Reporting biases due to increased public awareness of COVID-19 vaccines cannot be ruled out. The findings may have limited generalizability beyond the Lebanese population due to differences in healthcare systems and reporting practices across countries. Lastly, despite the observed temporal associations between vaccination and adverse events, the study design limits the ability to establish definitive causal relationships. Future active surveillance studies, such as prospective cohort or case-control designs, could address many of these limitations and provide more robust evidence on vaccine safety.

Conclusion

This study provides the first comprehensive analysis of official national data on serious adverse events reported to the LNPVP following COVID-19 vaccination in Lebanon. The limited number of serious AEFI cases, relative to the substantial number of vaccine doses administered, confirms the overall safety profile of the vaccination campaign.

The findings contribute significantly to the expanding global pharmacovigilance database on COVID-19 vaccines, evidence-based clinical decision-making, and tailored public health communication strategies. Notably, the observed age- and sex-related differences in certain AEFIs highlight the need for further investigation and the development of a more targeted approach to vaccine administration and post-vaccination monitoring protocols.

While the inherent limitations of passive surveillance systems and the observational nature of this study preclude definitive causal inferences, this research establishes a crucial foundation for future active surveillance initiatives. Prospective cohort studies or case-control analyses could address many current methodological limitations, providing more robust and generalizable evidence on vaccine safety.

This study highlights the indispensable role of robust pharmacovigilance systems in meticulously monitoring vaccine safety and fostering public trust in immunization programs. As global vaccination efforts persist, the importance of ongoing surveillance, timely dissemination of safety data, and in-depth research into the underlying mechanisms of rare adverse events are crucial. These concerted efforts optimize the benefit-risk profile of COVID-19 vaccines and inform evidence-based public health strategies in Lebanon and potentially in other countries with comparable healthcare systems and population demographics.

Furthermore, this research highlights the need for continued international collaboration in vaccine safety monitoring. By sharing data and methodologies across borders, the global scientific community can more effectively identify rare adverse events, understand their mechanisms, and develop strategies to mitigate risks. This collaborative approach is essential for maintaining public confidence in vaccination programs and ensuring the continued success of global immunization efforts against COVID-19 and future pandemic threats.

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Authors' contributions
Conceptualization: R.K. Methodology: A.Z. Formal Analysis and Data Curation: K.I. Writing – Original Draft Preparation: R.K., K.I., M.W. and A.Z. Writing – Review and Editing: R.K. KI, and A.Z. Visualization: R.K. Supervision: A.Z. All authors contributed to the article and approved the final manuscript.

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Data availability
The datasets generated and/or analyzed during the current study are not publicly available. Data are accessible upon specific request to RK.

Declarations

Ethics approval and consent to participate
Study data were obtained by accessing the case reports received at the National Pharmacovigilance Data base i.e VigiFlow. All cases are anonymous, non-reversible, individually coded, centrally assigned before data storage. According to national data ethics regulations, access to health information is then available to accredited institutions for administrative, healthcare planning, or epidemiological purposes, and only after official institutional authorization.
The study was waived by the IRB of the Lebanese International University. This waiver was based on the fact that our study data was obtained by accessing the case reports received at the National Pharmacovigilance Data base i.e. VigiFlow. All cases were anonymous, non-reversible, individually coded, centrally assigned before data storage. According to national data ethics regulations, access to health information is then available to accredited institutions for administrative, healthcare planning, or epidemiological purposes, and only after official institutional authorization. Thus, the need for informed consent to participate was deemed unnecessary, according to both relevant national and international ethical guidelines and regulations. Mainly, the following three factors support the compliance to regulations for this study: nature of the study, data anonymization and no direct patient interaction. Being a retrospective anonymized study in nature, anonymized data was simply analyzed and did not directly involve human subject interventions. As detailed previously, the data was securely processed through a national database to ensure confidentiality and privacy of people involved. No personal identifiable information was disclosed or even used during the data analysis process. Since results obtained from this study were processed from data already available at the National Pharmacovigilance Database, no patient was interacted with for this study. Thus, no direct patient interactions, no interventions nor treatments were administered as part of this study, making any potential risk or harm to participants negligible and even obsolete.

Consent for publication
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Competing interests
The authors declare no competing interests.

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