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Article

The Frequency and Patterns of Post-COVID-19 Vaccination Syndrome Reveal Initially Mild and Potentially Immunocytopenic Signs in Primarily Young Saudi Women

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Abstract: Vaccination is the most promising approach for ending or containing the SARS-CoV2 pandemic. However, serious post-COVID vaccine reactions including immunocytopenia (ITP) syndrome has been increasingly reported. Several factors cause increased risks including multiple doses, age-dependent heterogeneity in immune-responses, platelet cross-reactions with microbial components, and Long-COVID syndrome. Thus, in the absence of a widely available specific therapeutics, vigilance is important while more studies are imperative. Using a structured questionnaire sent to different regions in Saudi Arabia, we conducted a comprehensive investigation on the frequency, rates, disease patterns, and patient demographics of post-COVID-19 side effects on febrile patients after three major vaccines. Results indicated the majority administered Pfizer BioNtech vaccine (81%, *n*=809); followed by AstraZeneca (16%, *n*=155); and Moderna (3%, *n*=34). In overall 998 participants, 74% (*n*=737) had no serious symptoms; however, 26.2% (*n*=261) revealed typical syndrome. In a focused group of 722, shortness of breath (20%), bruises or bleeding (18%), inattention (18%), GIT symptoms (17.6%), skin irritation (8.6%), and anosmia and ageusia (8%) were the most prominent. The onset time was mostly in 1-3 days in 49% (*n*=128), followed by 4-7 days in 21.8% (*n*=57), 8-14 days in 16.5% (*n*=43), and more than a month in 12.6% (*n*=33). The onsets occurred mostly after the first, second, or both doses 9%, 10%, and 7%, respectively. The frequency of symptoms was significantly higher among after Moderna ® vaccine (*P*-value = 0.00006) and it was significantly lower in participants who received Pfizer (*P*-value 0.00231). We did not find significant difference in symptoms related to differences in regions. Similarly, the region, age, gender, education, and nationality had no influence in the dose and onset timings. The findings of this study have significant clinical implications in disease management strategies, preventive measures, and vaccine development. Future vertical studies would reveal more insights into the mechanisms of post-COVID vaccine syndrome.

Keywords: COVID-19 reactions; ITP syndromes 2; COVID-vaccine women susceptibility

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1. Introduction

The global community is struggling to recover in the aftermath of the most devastating coronavirus pandemic in recent history caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV2). In a matter of a few months, the virus reached every corner on earth dramatically changing human behaviors. As of 12 May 2022, there have Health Organization (WHO); and on the other hand, there have been a total of 11, 655,356,423 vaccine doses administered by 9th May 2022 globally [(available at https://covid19.who.int/) accessed May 13 2022]. This makes it the most rapid and extensive vaccination campaign in history that employed state-of-the-art mRNA vaccine products in human history, the Pfizer Biontech, Moderna, and AstraZeneca, and others. However, as with all vaccines, this did not go without side effects. Despite their high efficacy and safety, cases of potential side effects were reported. One of the most prominent side effects recorded was a condition first appeared in different reports as a prothrombotic syndrome. It has been described differently as vaccine-induced immune thrombotic thrombocytopenia (VITT), thrombosis with thrombocytopenia syndrome (TTS) and vaccine-induced prothrombotic immune thrombocytopenia 2.. Generally, it is an autoimmune disease characterized by isolated platelet count <100×10E9/L, episodes of possible hemorrhage caused by antiplatelet antibodies, furthermore petechiae or purpuric rashes have been reported 3. However, in the absence of exposure it was named VITT. According to American Society of Hematology, VITT is defined as clinical syndrome characterized by positive antibodies against platelet factor 4(PF4) identified by enzyme-linked immunosorbent assay (ELISA) assay. The casual relationship of ITP post COVID-19 vaccine injection has not been well defined 4. Therefore, it is not yet fully clear whether all are vaccine-induced secondary ITP or incidental primary ITP that occurred soon after vaccination 5. As with other countries, reports on incidence of this side effect are limited in the Middle Eastern countries.

Despite the reported high safety and efficacy of COVID-19 vaccines, some potential side effects remain including autoimmune responses. However, detailed review on all aspects of this condition is limited. For instance, a systematic review on 45 new-onsets of ITP post COVID-19 vaccination showed, after excluding other concomitant factors that can trigger thrombocytopenia in COVID-19, that 75% cases were moderate-to-severe and that the majority of ITP cases (71%) appeared in senior patients (> 50 years), while only three were pediatric cases (7%) 6. In the aforementioned study, 20% of cases of ITP symptoms rose three weeks after onset of COVID-19 symptoms, and no bleedings were reported in 31% cases at diagnosis 6. Appearance of ITP post-COVID-19 vaccine have been reported in different countries worldwide including USA 7, Mexico 8, Italy 9, UK 10. The ITP is known to occur mainly in young adults, particularly young women. This suggests that sex hormones, as in other immune disorders such as systemic lupus, multiple sclerosis, may play a role in the susceptibility to ITP. The condition first appeared in different reports as a prothrombotic syndrome in a small number of individuals after AstraZeneca vaccine administration (University of Oxford, and Serum Institute of India), an adenoviral vector-based vaccine 11. Subsequently, similar findings were observed in a small number of individuals who received the Ad26.COV2.S vaccine (Janssen; Johnson & Johnson), also based on an adenoviral vector 12. Similarly, sporadic cases were reported after Pfizer and Moderna vaccines; however, the rate of ITP was 0.80 per million doses for both vaccines 13. Lee et al.,14 reported a series of cases of very low platelet counts occurring within two weeks of Pfizer and Moderna vaccinations upon review of published data from the USA CDC, the Food and Drug Administration (FDA), agencies of the U.S Department of Health and Human Services (HHS), Vaccine Adverse Events Reporting System (VAERS) 15,16. These included 20 case reports on ITP after vaccination, 17 reports without pre-existing ITP, and 14 with reported bleeding symptoms prior to hospitalization. The aforementioned authors also reported that 19 of 20 hospitalized patients aged 22-73 years (11 females and 8 males) showed petechiae, bruising or mucosal bleeding in 1–23 days post

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Pfizer (9 patients) and Moderna (11 patients) vaccination. Along with platelet counts mostly ≥10 × 109/L (range 1–36 × 109/L; median 2 × 109/L). The vaccine induced ITP could possibly have similar pathogenicity to COVID-19 vaccine induced DIC which highlights the importance of further investigation in agreement with others 17. Recently, a new phenomenon characterized by ITP was reported in multiple patients after vaccination with the ChAdOx1 nCoV-19. The adverse effects in this case remained exceptionally low following the vaccine of more than 400 million people. This new syndrome was quite similar to heparin-induced ITP 18. Detailed studies characterizing the rates, frequencies, and patterns of occurrence, and pathogencity of these cases is limited.

COVID-19 vaccines can trigger a series of unique ITP-related syndromes including skin reactions, shortness of breath, inattention, gastrointestinal (GIT) symptoms, anosmia and ageusia. Molecular mimicry between SARS-CoV-2 spike-protein and human microbial components components may potentially elicit adverse skin and other pathological reactions post vaccinations. For instance, Gambichler et al., reported on most frequent early reactions due to vaccination are known to occur at injection-sites; for instance, Type I, Type IV hypersensitivity reactions including delayed large local skin lesions popularly dubbed as ("COVID arm") can occur 19. In addition, reactions in dermal filler, previous radiation sites or even old BCG scars, and more frequently morbilliform and erythema multiforme-like rashes and different forms of autoimmune-mediated skin conditions post COVID-19 vaccination are likely to occur. Functional angiopathies, pityriasis rosea-like rashes and reactivation of herpes zoster have been also reported after COVID-19 vaccination 20. Similarly, Catala et al., studied 405 reactions from 16 February to 15 May 2021 following vaccination with the BNT162b2 (Pfizer-BioNTech; 40·2%), mRNA-1273 (Moderna; 36·3%) and AZD1222 (AstraZeneca; 23·5%) vaccines. Patient means were 50·7 years male and 80·2% of them were female. Cutaneous reactions were COVID arm', 32·1%, urticaria (14·6%), morbilliform (8·9%), papulovesicular (6·4%), pityriasis rosea-like (4·9%) and purpuric (4%) reactions. Varicella zoster and herpes simplex virus reactivations were reported as 13·8% of reactions. The most frequent reported reactions in each vaccine group were COVID arm (mRNA-1273, Moderna, 61·9%), varicella zoster virus reactivation (BNT162b2, Pfizer-BioNTech, 17·2%) and urticaria (AZD1222, AstraZeneca, 21·1%). The COVID arm was almost exclusive to female (95·4%). Most reactions to the mRNA-1273 (Moderna) vaccine were described in female (90·5%). Eighty reactions (21%) were classified as severe and 81% needed specific treatment 21. Thus, COVID-91 patients with ITP are at an increased risk of mucocutaneous or major bleeding 1. In addition to skin reactions dyspnea and wheezing were identified as the earliest signs of thrombocytopenia syndrome 22. In fact, it has been well established that severe fever, although not easily characterized, has been directly linked to early signs of ITP syndrome in several cases (23–25. In addition, it has also been known that immune ITP is more than a bleeding disorder; cognitive symptoms are commonly reported 26. Furthermore, the cognitive impairments leading to brain fog, a newly emerging COVID-manifestion, has been hypothesized post-mRNA vaccinations27. An association between COVID-19 vaccine (ChAdOx1, AstraZeneca ®) and cerebral vein thrombosis was reported in patients with vaccine-induced immune thrombotic thrombocytopenia. New reports emerged of patients with venous thromboembolism (VTE), or deep vein thrombosis, cerebral, and pulmonary embolism) is associated with mortality and long-term morbidity. The VTE was reported in unusual locations following the ChAdOx1 vaccine, resulting in its suspension in several countries. Consequently, 169 cases of cerebral vein thrombosis (CVT) and 53 cases of splanchnic vein thrombosis were reported to the European Medicines Agency (EMA) among 35 ChAdOx1 million vaccine recipients 28,29. However, a population cohort study in Denmark and Norway reported increased rates of venous CVT among recipients of the ChAdOx1 vaccine with no increase in arterial events 30. These recent data suggested an excess rate of CVT of 2.5 per 100 000 ChAdOx1

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recipients, although laboratory testing has not confirmed that they were due to vaccine- VITT 31. Thus, data on the cognitive effect(s) of COVID-19 is also limited.

Additional hypersensitivity reactions for overexpression of type I interferons, COVID-19 induced coagulopathy, thrombotic microangiopathy and direct viral damage were suggested as side effects. In addition, delayed reactions at injection sites were also observed for the mRNA-1273 vaccine clinical trial (onset after day 8) in 0.8% participants after the first dose and in 0.2% after the second dose.32. In a retrospective analysis of the effects of SARS-CoV-2 vaccination on 109 ITP patients identified with preexisting ITP, approximately 20% experienced an ITP exacerbation following the first dose with 14 of 70 patients having an exacerbation after the second dose. Response to treatment and outcomes were also favorable in the patients with preexisting ITP, and no major bleeds were reported after vaccination. Therefore, the authors concluded that ITP might worsen in some patients with preexisting ITP or may occur de novo post-SARS-CoV-2 vaccination.

Although there is an going risk of ITP after administration of many other vaccines including influenza, measles-mumps-rubella (MMR), hepatitis B, human papilloma virus, varicella, and diphtheria-tetanus-pertussis (DPT) vaccines in children and adolescents [33–35], the COVID-19 reaction carries additional layer of risk due to several factors. Unlike other viral vaccines, the COVID-19 received multiple booster doses. In addition, there risk of age-dependent heterogeneity in SARS-CoV-2-immune responses in senior patients 36. Furthermore, there is a high possibility that initially mild reactions progress into severe prolonged symptoms known as “Long-COVID” leading to multisystem failure and disability. More important, the disseminated intracellular coagulation (DIC) and the consequence of thrombocytopenia has been reported as a major viral mechanism in Covid-19 in contrast to cytokine storm37. Thus, in the absence of a widely available specific therapeutic caution, more post-COVID-19 vaccination studies have become imperative. The aim of this study was to conduct and comprehensive investigation on the frequency, rates, disease patterns, and patient demographics of post-COVID-19 side effects with emphasis on ITP, after administration of different vaccines. Thus, in the absence of a widely available specific therapeutic caution, more post-COVID-19 vaccination studies have become imperative. The aim of this study was to conduct and comprehensive investigation on the frequency, rates, disease patterns, and patient demographics of post-COVID-19 side effects with emphasis on ITP, after administration of different vaccines.

2. Materials and Methods

2.1. Study design:

The current study was conducted as a retrospective cross-sectional survey using a self-administered structured online questionnaire through google platform.

2.2. Study population:

All individuals who have had taken Covid19 vaccines and who agreed to participate in the study, aged ≥18 years, and living in Saudi Arabia were eligible to participate. We posed no restrictions on the gender, nationality, occupation, or socioeconomic level of the participants. However, the emphasis was placed on those with sever fever and fatigue patients.

2.3. Data collection tool

Self-administered computer based multiple choice questionnaire was used. An online link of the web-based survey was developed in google to obtain data regarding side effects of COVID-19, with emphasis on high grade fever and sings of ITP from October to December 2021. On the first screen of the questionnaire, a Plain Language Information Statement (PLIS) and Consent to participate were enclosed. Any details for contact or personal data that identify the participant was not used. Contact details

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of the study investigators were given in the PLIS for transparency. Only the participants with fever and providing consent to participate in the study may move to the next section containing the screening questionnaire to confirm. Only participants who confirm the predefined age-limit were moved to the next pages containing the self-administered survey. The questionnaire consisted of 18 questions; 8 general questions about the respondent, 5 questions related to vaccine, and 5 more related to general history. All responses will be analyzed for significant findings on the prevalence rates in the country. Participants' answers the questions directly related to side effects were will be transferred into a score.

2.4. The questionnaire: development and validation of the questionnaire

In the process of developing the questionnaire, a wide comprehensive review of the available literature about the ITP was performed. Subsequently, a thorough review on the available data, relevancy, vaccine types, and profiles of individuals and disease patterns were studied. A focused discussion was given by experts and first version was produced as draft 1. This was validated for content, criterion, and construct components. For further evaluation, a pilot study of 30 participants was performed, where different reliability measures were also tested: including test-retest reliability/repeatability, consistency, and inter-rater reliability.

2.5. Statistical analysis

Data were analyzed using IBM SPSS for Windows version 26 statistical software (Statistical Package for Social Sciences (SPSS) software version 26 (SPSS Inc., Chicago, IL, USA). Categorical data was reported as frequency/percentage and continuous data as mean/standard deviation. Data was normalized using tests of normality (Kolmogorov–Smirnov, and Shapiro–Wilk tests). The Chi2 test (or Fisher's exact test, as appropriate) and independent t-test (or the Mann–Whitney U test as appropriate) could be used for testing the difference based on the participants' gender. Moreover, univariate linear regression useful to identify the possible predictors for the awareness and knowledge of symptoms described. The analysis was descriptive and stratified; we present absolute numbers, proportions, and graphical distributions. We conducted exact statistical tests for proportions and show p-values where appropriate (a p-value < 0.05 was considered statistically significant)

3. Results

Since response to vaccine is a multifactorial issue affected by numerous factors, we carefully examined several host, vaccine, and ecological factors including nationality, region of residence, educational level, vaccine type, dose, onset time, previous history and age and gender differences. Respondents included fatigue and high febrile participants with sings of ITP. However, in 998 participants, 74% (n=737) had no bruises or bleeding ITP symptoms; these typically appeared in 26.2% of highly febrile participants (n=261) as explained below. We did not find significant difference in the frequency of bruises and bleeding ITP symptoms related to differences in regions of Saudi Arabia. Similarly, no significant differences were found between regions, age and genders, in the onset timings as well as in the dose numbers after which typical syndrome appeared. The findings of this study have significant clinical implications in disease management strategies, preventive measures, and vaccine development.

In this study, education, nationality, and age and gender differences in response to different vaccines administered at different regions in Saudi Arabia were as shown below. Among the 998 participants, the overwhelming majority administered the Pfizer BioNTech vaccine followed by AstraZeneca and Moderna vaccines (81%, n=809; 16%, n=155; and 3%, n=34, respectively) (Table 1). These participants were primarily young (19-29 years old 53.1%, n= 530), educated (71%, n=711), Saudi (95%, n=953), females (78.7%, n=785) (Figure1a, b, c, d, e, f). The rates of different age groups among

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participants were as followed: 12-18 years old 8.6% (n=86), 19-29 years old 53.1% (n= 530), 30-40 years old 21.1% (n=211), 40-60 years old 14.7% (n=147), and seniors 60 year or more were 2.4% (n=24). However, respondents' estimates based on region showed that most were from the Northern and Central regions (34.4%, n=343; 30.3%, n=302, respectively) followed by similar rates found in Eastern (15.5%, n=155) and Western regions (15.4%, n=154); whereas, the Southern region had the least responders with 4.4% (n=44) (Figure1f). Furthermore, respondents based on educational levels showed that among the 998 participants, 71.2% (n=711) had university degree, while 19.1% (n=191) were secondary school certificate holders, 6.0% (n=60) had postgraduate degrees, 2.8% (n=28) had school certificates, and 0.8%(n= 8) had no formal education (Figure 1d).

We monitored the frequency of visible syndromes in response to different vaccine including ITP symptoms which was highly significant. In 998 participants, 74% (n=737) had no bruises or bleeding ITP symptoms albeit they had other common manifestations. However, typical bruises or bleeding ITP symptoms associated with high fever appeared in 26.2% of participants (n=261) as shown in Figure 2a. For those in whom typical symptoms appeared, the onset of symptoms times ranged from 1-3 days in 49% (n=128), 4-7 days in 21.8% (n=57), 8-14 days in 16.5% (n=43), and in 12.6% (n=33) of participants the onset was within more than a month (Figure 2a,b, and Table 2). This indicate that the risk of ITP was more within the first three days. Based on the doses-dependent symptoms, the signs appeared in 9%, 10%, and 7% after the first, second, and both doses, respectively (Figure 2c). Finally, the frequency of bruises and ITP symptoms was significantly higher among participants who received Moderna ® (p value = 0.00006) and it was significantly lower in participants who received Pfizer (p value 0.00231)(Figure 2d). However, there was no significant difference in the frequency of bruises and bleeding ITP symptoms between different regions of Saudi Arabia. Similarly, no significant differences were associated to differences in regions, genders, and age groups in the onset times (in days) as well as in the doses after which and bleeding ITP symptoms occurred.

After removal of common symptoms such as transient low-grade fevers and headache and focusing on questions from respondents about direct ITP related symptoms associated with sever fever, 722 out of 998 cases were analyzed. In this group, although the overall rates for side effects were acceptably low, the following reactions were reported: shortness of breath (19.88), bruises or bleeding (18), inattention (18), GIT symptoms (17.6), skin irritation (8.6), and anosmia and ageusia (8) were the most prominent among respondents (Figure 2e).

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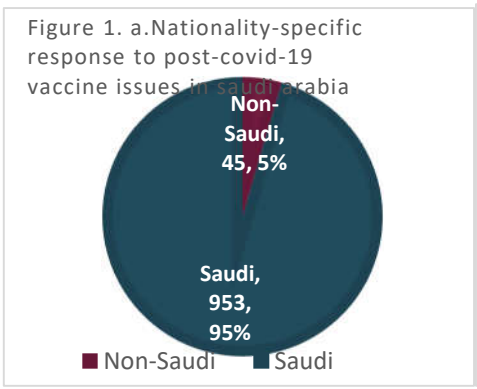

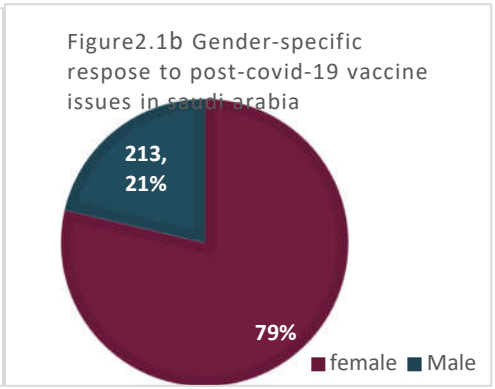

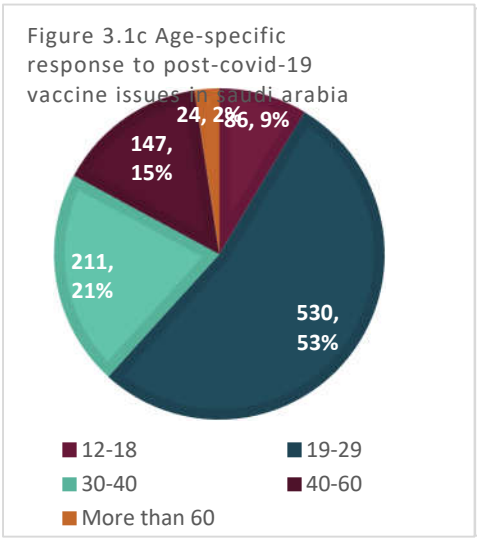

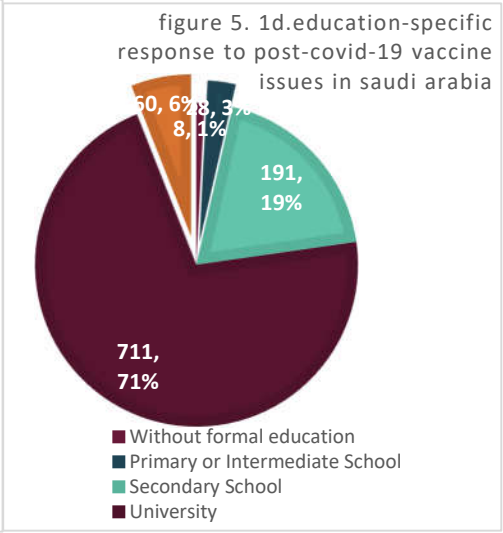

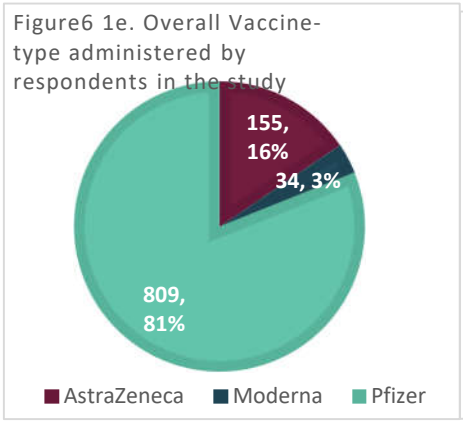

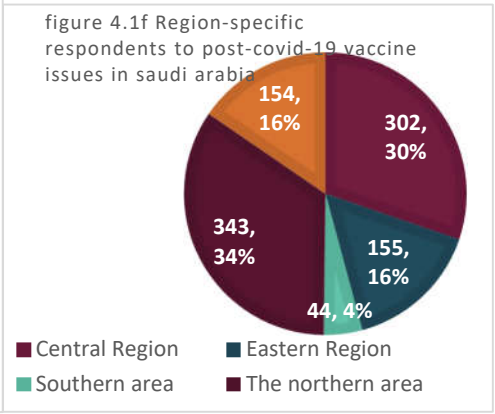

Table 1. Frequency of different types of vaccines administered by respondents in the study.

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	AstraZeneca	155	15.5	15.5	15.5
	Moderna	34	3.4	3.4	18.9
	Pfizer	809	81.1	81.1	100.0
	Total	998	100.0	100.0	

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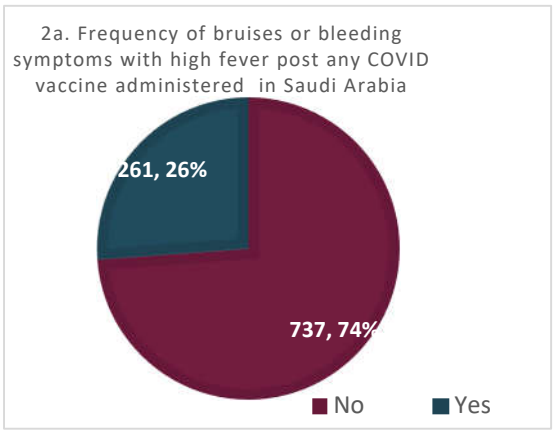

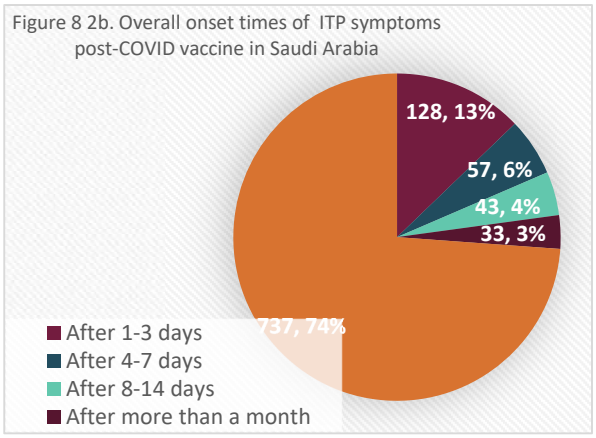

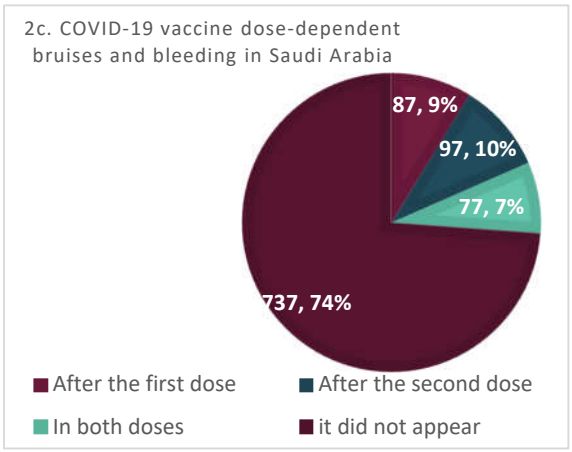

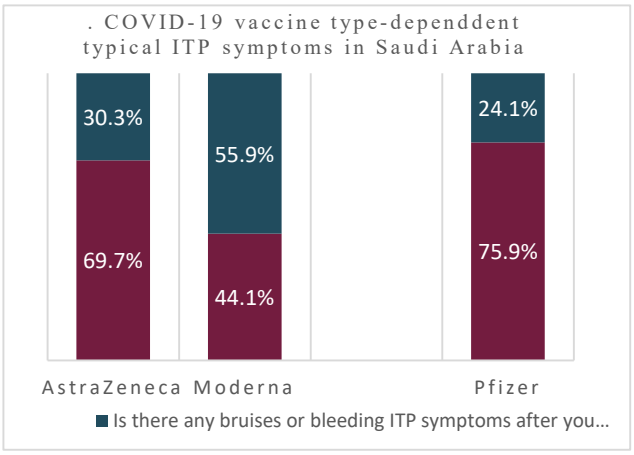

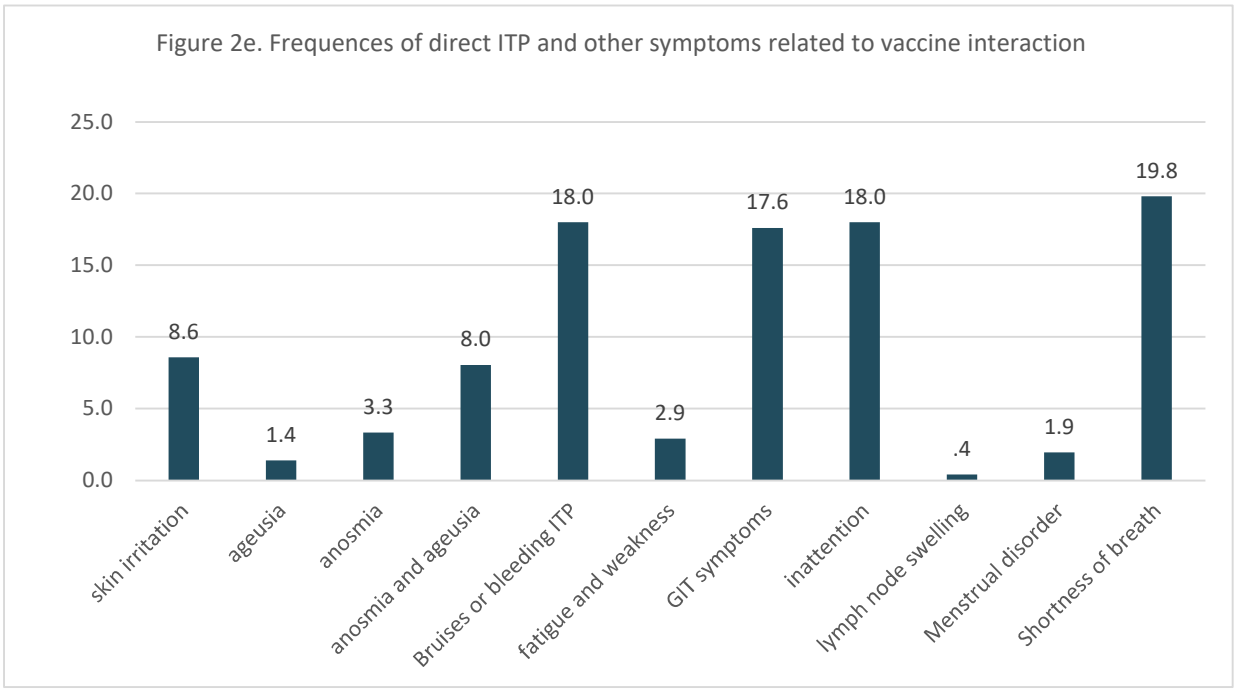

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Table 2. Overall frequency of bruises or bleeding ITP symptoms and onset times after any COVID-19 Vaccine in Saudi Arabia.

Onset times after symptoms						Overall frequency of bruises or bleeding ITP symptoms					
		Frequency	Percent	Valid Percent	Cumulative Percent			Frequency	Percent	Valid Percent	Cumulative Percent
Valid	After 1-3 days	128	12.8	12.8	12.8	Valid					
	After 4-7 days	57	5.7	5.7	18.5						
	After 8-14 days	43	4.3	4.3	22.8		No	737	73.8	73.8	73.8
	After > month	33	3.3	3.3	26.2		Yes	261	26.2	26.2	100.0
	it did not appear	737	73.8	73.8	100.0						
	Total	998	100.0	100.0			Total	998	100.0	100.0	

4. Discussion

The COVID-19 mass vaccination campaign has been one of its kind the 21st century in speed, efficacy, and approach. This campaign employed the first in-silico biologics used directly from bench to arm. The efficacy of the mRNA vaccines was among the highest seen in history albeit their serious side effects made it imperative for safety and efficacy to be revisited. In this comprehensive study, we report on specific post vaccine syndromes with emphasis on direct ITP reactions known to be induced by vaccine component(s). To cover the wide breadth of potential factors that are prone to influence post COVID-19 side effects, we included a variety of questions including nationality, region of residence, educational level, vaccine type, onset time, previous history and age and gender differences. However, in 998 participants, 74% (n=737) had no bruises or bleeding ITP symptoms. Typical bruises or bleeding ITP symptoms appeared in 26.2% of participants (n=261) as shown above. We did not find significant difference in the frequency of symptoms in the different regions of Saudi Arabia. Similarly, no significant differences were found between regions, genders, and age groups, in onset days as well as in the doses after which and bleeding ITP symptoms occurred. The findings of this study have significant clinical implications in disease management preventive measures, and vaccine development strategies,

The finding that respondents were primarily young (19-29 years old 53.1%, n= 530), educated (71%, n=711), Saudi (95%, n=953), females (78.7%, n=785) is a significant criterion indicating age- and gender-specific factors in susceptibility to post-COVID vaccine reactions. Our results are consistent with recent studies on similar sample sizes of studies in different continents including Germany, Israel, Africa 38–40. This implies that being female at a young age is a major global risk factor that is constant across different nations with mosaic as well as homogenous population genetic structures. The common global factor widely known is that the ITP occurs mainly in young adults particularly women in their third or fourth decade with an overall female to male ratio of 3-4 to 1. These figures suggest that sex hormones, as in other immune disorders such as systemic lupus, multiple sclerosis, may play a role in the susceptibility to ITP. More importantly, global genetic variability in susceptibility to post vaccine reactions might have no significant role since we obtained similar results in this genetically homogeneous population in Saudi Arabia. Thus, several gaps exist in the pathogenicity, clinical profiles, and preventive measures of SARS-CoV2. Since regional variations in respondents did not alter the common patterns of syndromes seen, it is plausible that larger scale national surveys would potentially reach to the same present conclusions we reported here.

Significant data on post-COVID vaccination syndrome is required. Vigorous profiling of post-vaccine syndrome has become imperative in the absence of a widely available specific therapeutic, the risk of age-dependent heterogeneity in SARS-CoV-

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2-immune responses 36, and the high possibility that initially mild reactions progress into severe prolonged symptoms known as "Long-COVID" leading to multisystem failure and disability. In this study, the overall frequency of side effects was low albeit some were serious. We found 26.2% (n=261) of respondents showed side effects mostly occurring after the firsts dose in 33.3% (n=87) within the first three days and declined afterwards potentially indicating an initial immune trigger in the vaccine. It has been shown that several early immune signatures, including plasma RIG-I levels, early interferon signaling, and related cytokines (CXCL10, MCP1, MCP-2 and MCP-3) associated with subsequent disease progression, control of viral shedding, and the SARS-CoV-2 specific T cell and antibody response measured up to several months after activation 41.

It is not clear why the frequency of ITP related symptoms was significantly higher among participants who received Moderna® (P-value = 0.00006) but was significantly lower in those who received Pfizer (P- value 0.00231) (Figure 10). This observation occurred even though the overwhelming majority administered the latter vaccine. Rashes and skin reactions to Moderna vaccine related reactions have been report in seniors. For instance, a case of purpuric rash and thrombocytopenia was reported in a 60-year-old comorbid African American male in the USA after the first dose of the m-RNA-1273 vaccine42. Similarly, a 66-years-old obese Guyanese male presented with a bullous rash following receipt of a commercial COVID-19 mRNA vaccine 43. The FDA has granted emergency use authorization for the Pfizer/BioNTech and Moderna COVID-19 vaccines to protect recipients from a SARS-CoV- 2 infection by formation of antibodies and provide immunity against a SARS-CoV-2 infection. However, while both vaccines can cause various adverse effects, they are comparatively more frequent after Moderna COVID-19 vaccine which is stored at lower temperatures for ease of transportation44. Although reactions to post Moderna vaccination are commonly reported in comorbid seniors, we report on this reaction in primarily young (19-29 years old 53.1% (n= 530) females (78.7%, n=785) Saudi (95%, n=953) without underlying causes.

Menstrual bleeding was one of the least prevalent symptoms we report in this study with only 1.9% of women experienced. However, consistent with earlier findings and contrary to unsupported beliefs, bleeding is not generally proportional to the platelet count. Earlier studies in adults ITP cases with a platelet count of less than 50 × 109/L, the presenting symptom was hemorrhage in 12% and purpura in 58% 45 while 28% remained asymptomatic and in other cases more than half of patients remained so with a platelet count of 30 to 50 × 109/L 46. Albeit ITP has been widely known as a bleeding disorder, many findings indicate otherwise. For instance, ITP has been found paradoxically associated with thrombosis; in a 4-year follow up in United Kingdom revealed thromboembolic was about 1.3 times higher in patients with ITP than in matched controls. 47. More important is that ITP is potentially associated, in many cases, to common microbial infections necessitating pre-diagnosis. The antigenic similarity in organisms as Hepatitis C virus, HIV, and H.pylori and platelet glycoproteins, elicits antibody response against platelets leading to thrombocytopenia 48,49. Finally, we report on significant gastrointestinal symptoms post-COVID-19 vaccination; almost 18% of patients revealed GIT signs mostly during the first week. It was not clear whether those were cytokine release syndrome (CRS). The Pfizer-BioNTech mRNA COVID-19 vaccine-in

Patients with stomach and colorectal cancers have been reported to have CRS evidenced by raised inflammatory markers, thrombocytopenia, elevated cytokine levels (IFN-γ/IL-2R/IL-18/IL-16/IL-10) and steroid responsiveness 50. This particularly becomes complicated when patient has infections of Hepatitis C virus, HIV, and H.pylori. Therefore, a great deal of certainty in the diagnosis of cancers, microbial infections, and any potential underlying causes that can aggravate post-COVID-vaccine syndromes has become imperative.

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5. Conclusions

For the first time in the Middle East and perhaps globally, to the best of our knowledge, we report on the COVID-19 vaccine related typical signs on highly febrile and potentially immunocytopenic young, educated, primarily Saudi women 1-3 days after administration of mRNA vaccines. Since several factors aggravate post-vaccine immune reactions including multiple doses, age-dependent heterogeneity in immune-responses, platelet cross-reactivity to pathogen antigens, and Long-COVID syndrome, vigorous screening tests have become imperative before conclusions on any case. Thus, in the absence of a widely available specific therapeutics, vigilance is important while more studies are needed. The findings of this study have significant clinical implications in disease management strategies, preventive measures, and vaccine development. The limitations of this study is that it used online questionnaire.

Supplementary Materials: There is no material anywhere else. The Supplementary Material is attached along with this manuscript.

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Ethical Approval and Institutional Review Board Statement: The standard guidelines were followed during this research according to the IRB protocols. The ethical application for this study was reviewed and (Approved) by the Research Ethics Committee (REC at the University of Ha'il (KSA), dated 22/10/2020 and endorsed by University President letter number Nr. 13675/5/42 dated 08/03/1441 H; for Deanship Project RG20064, REC# H-2020-187, and H-2021-212. The KACST Institutional Review Board (IRB) registration numbers are H-8-L-074 IRB log 2021-11 that also Approved the projects of this study.

Informed Consent Statement: "Informed consent was obtained from all subjects involved in the study."

Data Availability Statement: All data included in the manuscript, additional files are attached along with this submission.

Conflicts of Interest: The authors declare no conflict of interest.

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