Note

Data Analytics to Explore the Influence of Nutritional Factors on Adverse Reactions after Vaccination

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ABSTRACT *Background and purpose.* In order to contribute to the elucidation of nutritional approaches to reduce adverse reactions to vaccines, this study examined the influence of nutritional factors on the occurrence of adverse reactions after mRNA-1273 vaccination using a data analysis method based on a free, open-source application that is easy to use in clinical practice. *Methods.* We decided to use a workstation to process a large amount of data, and used MySQL to create a database of data on side effects that occurred after vaccination and nutritional intake, and used R to perform data extraction and statistical analysis. *Results and conclusion.* The results suggest that the intake of some nutrients (ash, VB1, VB2, VB6, VC, and sodium equivalents) over the past month or two, as estimated by the Food Frequency Questionnaire (FFQ), may be somehow related to the development of adverse effects, that thinness may promote the development of adverse effects, and that low physical activity level (PAL) may promote the development of adverse effects. However, it is difficult to rationally understand the mechanism by which nutrients affect the occurrence of adverse effects from this survey alone, and more detailed collection and analysis of large amounts of data using survey techniques that can accurately determine nutrient intake is needed in order to gather clinical knowledge in the future. As a research technique for this purpose, the analysis of large amounts of data using data analytics is expected to become increasingly important in the future.

Key words: mRNA-1273, Adverse Reactions, Nutritional Factors、Food Frequency Questionnaire (FFQ), Data Analytics

INTRODUCTION

Against the backdrop of the rapid development of computer networks, digital transformation has rapidly spread throughout society and has also penetrated the field of academic research.

Digital research technologies such as data science and data analytics are beginning to be introduced into research on diet therapy, nutritional intake, and food safety, which are central themes in nutritional science. Technology for monitoring an individual's physical condition using biometric sensors, smart wearable devices, and mobile applications (1) is already well established, and in the field of nutrition research, some companies are now offering online services (2) that use AI engines to automatically calculate nutritional intake from food image processing. Nutritional research and its clinical applications, which deal with a large number of nutrient intakes, require efforts that make full use of the analysis of vast amounts of data, and it is expected that so-called data science and data analytics methods will be increasingly used. However, in the field of nutrition, the use of data analytics and data science methods has lagged behind, and data analytics techniques that can be easily used in clinical settings have not yet been established. Therefore, this time, we attempted a clinical nutrition research design using data analytical methods, using as an example the analysis of a large amount of data on side effects and nutrition of female students collected during mass vaccination of mRNA-1273 vaccine conducted at Nishikyushu University.

In response to the urgent global need for a safe and effective vaccine to prevent coronavirus infection 2019 (COVID-19), declared a pandemic by the World Health Organization (WHO) on March 11, 2020, and to protect people at high risk of complications, a mRNA vaccine(mRNA-1273 and BNT162b2) was developed. In Japan, a university-led mass vaccination program was implemented from 2021 to 2022 to promote emergency vaccination with these COVID-19 vaccines. This mass vaccination program was also carried out at Nishi-Kyushu University, where the authors work, and used the mRNA-1273 vaccine (3, 4, 5), which is known to be highly effective in preventing infection and severity of COVID-19. This mRNA-1273 vaccine produces a high frequency of mild adverse reactions after vaccination (6), but the adverse

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reactions are, for the most part, mild and temporary (4,7). However, since a certain number of people are hesitant to be vaccinated because of adverse reactions, it is assumed that reducing adverse reactions will be an issue for vaccine dissemination in situations where sufficient vaccine is available. Since adverse reactions are physiological immune responses of the human body, nutritional approaches may be effective in reducing adverse reactions.

Therefore, in this study, in order to help elucidate nutritional approaches to reduce vaccine side effects, this study examined the effects of nutritional factors on the occurrence of adverse reactions after mRNA-1273 vaccination by means of a data analytics approach using a free, open-source application that is easy to use in clinical practice.

MATERIALS AND METHODS

In this mass vaccination program, known as the university-based vaccination program, vaccinations were administered to students, faculty, staff, and residents of the surrounding area at vaccination sites set up on the university campus. The subjects of this study were 1452 female university students who received two doses of mRNA-1273 vaccine through Nishikyushu University's university-based vaccination program.. After the first vaccination, a second vaccination was administered 28 days apart. In this study, we conducted a questionnaire survey to examine the frequency of adverse reactions and nutritional intake among students who had completed the second vaccination of the mRNA-1273 vaccine. The questionnaire was anonymous, and responses were requested online using Microsoft Forms (Microsoft Co. Ltd.). The questionnaire was conducted two weeks after the second vaccination day. The survey on adverse effects used the same items as the "Survey on Health Status after Ingestion of the New Corona Vaccine (Cohort Survey)" conducted by Juntendo University (8). There are 8 questions, and if there are symptoms of adverse reactions, the answer method is to select the details of the symptoms and the period during which the symptoms were observed from the drop-down list. The survey on nutritional status was conducted by means of the Food Frequency Questionnaire (FFQ), which estimates energy and nutrient intakes over the past month or two based on 30 food groups and 10 cooking methods. The FFQ response results were analyzed using FFQ analysis application software (FFQg Ver. 6, Kenpakusha Co. Ltd.), and nutritional intake was calculated.

Data from 690 university students who responded to both a survey on adverse reactions and a survey on nutritional status were confirmed, and data from 459 students whose responses were all deemed valid was analyzed using a series of data analytics methods. We attempted analysis using several laptops and personal computers so that they could be easily operated in clinical settings, but none of them had the processing power to handle the large amount of data we had, so we decided to use a workstation (Processor ; Intel Core i9-3.00GHz 64bit, RAM: 256 GB, SSD: 20TB) was purchased and used for analysis. The results of adverse reactions and dietary records were cleansed, personal data were divided into separate tables, and each data was stored in a database with ID as the primary key. MySQL 8.0.33 was used as the relational database management system (RDBMS). Information on the presence or absence of adverse reactions and nutritional intake status was extracted from the database, and statistical analysis was performed using R Ver 4.3.1 (9). Fisher's exact test (Fisher's exact probability test) and Welch's t-test (difference of means test) were used for statistical analysis.

This study was conducted in accordance with the Declaration of Helsinki (1964) (Tokyo revision (1975) and Venice revision (1983)) and with the approval of the Ethics Committee of the University of Western Kyushu (No. 21YBP04).

RESULTS

The frequency of occurrence of adverse reactions after the first and second vaccination with mRNA-1273 vaccine is shown in Table 1. The frequency of systemic side effects increased 1.8-fold from 39% after the first vaccination to 72% after the second vaccination. In particular, those who complained of fever after the second vaccination increased 2.5 times more than after the first vaccination. The frequency of adverse reactions at the vaccination site was high, 77% after the first vaccination and 75% after the second vaccination, with no significant difference between the first and second vaccinations. A particularly high number of people complained of pain after both the first and second vaccinations, reaching around 70%. Next, about half of the respondents complained of a warm sensation, and redness and swelling were reported by about 30%.

The relationship between the occurrence of adverse effects after the first and second doses of mRNA-1273 vaccine and nutrient intake during the past month or two, as estimated by the FFQ, is shown in Table 2. After the first vaccination, there was no clear difference in nutrient intake between those who developed systemic or vaccination site adverse reactions and those who did not (Table 2-a). Furthermore, even after the second vaccination, no difference in nutrient intake was observed between those who developed systemic adverse reactions and those who did not. However, there was a statistically significant difference of around 10% in the intake of many nutrients such as ash, VB1, VB2, VB6, VC, and Sodium Equivalent between those who developed adverse effects at the intake site and those who did not (Table 2-b).

Table 1　Frequency of occurrence of adverse reactions after first and second vaccination with mRNA-1273 vaccine in female university students

Number of female university students who received mRNA-1273 vaccine: n=459			
		Number (percentage) of who complained of adverse reactions after vaccination	
		After the 1st vaccination	After the 2nd vaccination
Persons who complained of systemic symptoms		179 (39.0%)	330 (71.9%)
	Fever	125 (27.2%)	312 (68.0%)
	Headache	111 (24.2%)	248 (54.0%)
	Fatigue	150 (32.7%)	297 (64.7%)
	Snot	5 (1.1%)	22 (4.8%)
Persons who complained of injection site symptoms		352 (76.7%)	344 (74.9%)
	Redness	119 (25.9%)	121 (26.4%)
	Swelling	133 (29.0%)	148 (32.2%)
	Induration	52 (11.3%)	56 (12.2%)
	Pain	335 (73.0%)	316 (68.8%)
	Warmth	179 (39.0%)	287 (62.5%)
	Itch	106 (23.1%)	107 (23.3%)

Table 2 Relationship between incidence of adverse reactions and nutritional intake after the first and second doses of mRNA-1273 vaccine (n=459)

(a) After the 1st vaccination

	Systemic symptoms					Injection site symptoms				
	With symptoms		No symptoms		p value	With symptoms		No symptoms		p value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Energy (kcal)	1731	688	1674	676	0.375	1710	702	1652	606	0.411
Protein (g)	58.7	24.2	56.9	24.7	0.435	58.0	24.9	56.2	23.1	0.502
Fat (g)	60.9	29.3	59.0	27.4	0.472	60.7	29.2	56.5	24.2	0.132
Carbohydrate (g)	229	90.6	221	90.8	0.381	225	92.8	222	84.0	0.778
cholesterol (mg)	297	131	282	151	0.264	290	147	278	132	0.425
ash (g)	13.0	5.5	12.6	5.5	0.446	13.0	5.80	12.0	4.4	0.069
RAE #	359	174	346	187	0.434	356	187	333	166	0.211
VD (μg)	3.9	2.5	3.6	2.4	0.125	3.6	2.4	3.9	2.5	0.394
VB_1 (mg)	0.92	0.42	0.89	0.39	0.464	0.91	0.41	0.87	0.38	0.332
VB_2 (mg)	0.99	0.40	0.95	0.41	0.351	0.98	0.42	0.92	0.36	0.190
Niacin (mg)	12.7	6.4	12.3	6.3	0.463	12.5	6.4	12.3	6.1	0.735
Niacin Equivalent (mg)	24.5	11.1	23.7	11.1	0.463	24.2	11.3	23.5	10.6	0.534
VB_6 (mg)	0.91	0.41	0.88	0.42	0.497	0.90	0.42	0.86	0.38	0.301
VB_{12} (μg)	4.05	2.53	3.79	2.55	0.277	3.87	2.56	3.95	2.51	0.766
VC (mg)	56	31	54	29	0.398	56	31	51	26	0.134
Sodium Equivalent (g)	7.4	3.4	7.2	3.4	0.434	7.4	3.6	6.9	2.8	0.144

(b) After the 2nd vaccination

	Systemic symptoms					Injection site symptoms				
	With symptoms		No symptoms		p value	With symptoms		No symptoms		p value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Energy (kcal)	1687	629	1720	801	0.678	1715	707	1638	593	0.246
Protein (g)	57.3	22.5	58.2	28.9	0.763	58.5	25.2	54.9	21.9	0.141
Fat (g)	59.8	26.4	59.6	32.3	0.970	61.0	29.2	56.1	24.5	0.081
Carbohydrate (g)	222	84.3	229	106	0.483	225	94.1	221	80.1	0.595
cholesterol (mg)	288	135	286	164	0.919	293	147	272	131	0.162
ash (g)	12.6	4.8	13.1	7.0	0.455	13.0	5.80	11.8	4.35	0.018 ※
RAE #	353	172	346	205	0.735	360	189	325	159	0.056
VD (μg)	3.6	2.2	3.9	3.0	0.235	3.7	2.5	3.7	2.3	0.870
VB_1 (mg)	0.90	0.38	0.91	0.45	0.933	0.99	0.42	0.91	0.35	0.042 ※
VB_2 (mg)	0.97	0.38	0.97	0.47	0.949	0.91	0.43	0.83	0.34	0.047 ※
Niacin (mg)	12.3	5.8	12.8	7.5	0.533	12.6	6.5	11.9	5.6	0.247
Niacin Equivalent (mg)	23.9	10.2	24.5	13.2	0.646	24.4	11.5	22.9	9.8	0.154
VB_6 (mg)	0.89	0.38	0.90	0.50	0.778	0.91	0.43	0.83	0.34	0.047 ※
VB_{12} (μg)	3.81	2.22	4.09	3.23	0.368	3.93	2.63	3.75	2.29	0.473
VC (mg)	55	27	54	37	0.961	56	32	50	24	0.017 ※
Sodium Equivalent (g)	7.1	3.0	7.6	4.3	0.258	7.4	2.6	6.8	2.8	0.045 ※

Retinol Activity Equivalent (μg)

Table 3 Crosstabulationtable of frequency of adverse reactions and BMI（Body Mass Index） after the first and second rounds of mRNA-1273 vaccination (n=459)

(a) After the 1st vaccination

Number (percentage) of who complained of adverse reactions after vaccination							
	Systemic symptoms			Injection site symptoms			N
	With symptoms	No symptoms	P value	With symptoms	No symptoms	P value	
BMI＜ 18.5 kg /m^2	28 (42.4%)	38 (57.6%)	0.586	54 (81.8%)	12 (18.2%)	0.346	66
18.5 kg /m^2 ≦ BMI	151 (38.4%)	242 (61.6%)		298 (75.8%)	95 (24.2%)		393
Total	179 (39.0%)	280 (61.0%)		352 (76.7%)	107 (23.3%)		459 (100.0%)

(b) After the 2nd vaccination

Number (percentage) of who complained of adverse reactions after vaccination							
	Systemic symptoms			Injection site symptoms			N
	With symptoms	No symptoms	P value	With symptoms	No symptoms	P value	
BMI＜ 18.5 kg /m^2	57 (86.4%)	9 (13.6%)	0.005 ※※	54 (81.8%)	12 (18.2%)	0.219	66
18.5 kg /m^2 ≦ BMI	273 (69.5%)	120 (30.5%)		290 (73.8%)	103 (23.7%)		393
Total	330 (71.9%)	129 (28.1%)		344 (74.9%)	115 (25.1%)		459 (100.0%)

The effect of Body Mass Index (BMI) on the frequency of adverse effects is shown in Table 3. Since only 3 subjects were judged to be obese based on BMI values, the influence of obesity could not be examined. On the other hand, since those judged to be thinness accounted for more than 14% of the total number of subjects, the incidence of adverse reactions was divided into 2 groups: those who were thinness (BMI < 18.5) and those who were not (BMI ≥ 18.5) and compared between the groups. The results showed no clear difference in BMI between those who developed systemic or vaccination site adverse reactions and those who did not after the first vaccination (Table 3-a). There was also no difference in BMI between those who developed adverse reactions at the vaccination site and those who did not, even after the second vaccination. However, there was a suggested effect of BMI between those who developed systemic side effects and those who did not, with those who were thinness having a significantly higher incidence of systemic side effects than those who were not (Table 3-b).

Table 4 Frequency of adverse reactions after the first and second rounds of mRNA-1273 vaccination in relation to physical activity level (PAL) (n=459)

(a) After the 1st vaccination

	Systemic symptoms					Injection site symptoms				
	With symptoms		No symptoms		p value	With symptoms		No symptoms		p value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
PAL #	2.19	0.71	2.21	0.71	0.795	2.18	0.71	2.30	0.69	0.123

(b) After the 2nd vaccination

	Systemic symptoms					Injection site symptoms				
	With symptoms		No symptoms		p value	With symptoms		No symptoms		p value
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
PAL #	2.19	0.71	2.24	0.70	0.550	2.16	0.71	2.35	0.69	0.010 ※

physical activity level

The effect of physical activity level (PAL) on the frequency of adverse effects is shown in Table 4. After the first vaccination, there was no clear difference in PAL between those who developed systemic or vaccination site adverse reactions and those who did not (Table 4-a).

There was also no difference in PAL between those who developed systemic adverse reactions and those who did not after the second vaccination. However, there was a slight difference in PAL between those who developed side effects at the ingestion site and those who did not, and a significant difference was observed (Table 4-b).

DISCUSSION

The mRNA-1273 vaccine is a vaccine that introduces mRNA encoding part of the spike protein of the SARS-CoV-2 virus into the body, thereby triggering an immune response against the spike protein synthesized by body cells, producing antibodies and immune cells to strengthen the infection defense response (10). Vaccine injections stimulate skin and muscle tissue, including localized tissue damage, causing a localized inflammatory response. This inflammatory response is well known to activate the immune system, which includes the release of inflammatory cytokines and proliferation of immune cells, and promotes immune processes that generate antibodies and immune cells. When inflammation resolves, immune cells and growth factors that promote tissue repair and recovery are involved, and pain and swelling gradually decrease over a few days.

As shown in Table 1, the frequency of systemic adverse reactions increased 1.8-fold from 39% after the first vaccination to 72% after the second vaccination, while the frequency of adverse reactions at the site of inoculation was nearly 80% both after the first and second vaccinations. This result is almost the same as that of Ali et al. (4), and may indicate a certain degree of reliability of this survey methodology conducted using Microsoft Forms. The relationship between the incidence of adverse reactions after vaccination and nutrient intake is shown in Table 2, where the nutrient intakes indicated represent the nutrient intakes during the past one to two months from the date of the survey, as estimated by a survey using the Food Frequency Questionnaire (FFQ). There was no clear difference in nutritional intake between those who developed systemic or vaccination site side effects after the first vaccination and those who did not, nor was there any difference in nutritional intake between those who developed systemic side effects and those who did not after the second vaccination. On

the other hand, after the second inoculation, there was a statistically significant difference of about 10% in the intake of many nutrients, including ash, VB1, VB2, VB6, VC, and sodium equivalents, between those who developed adverse reactions at the site of intake and those who did not (Table 2-b). There is insufficient information to draw any inference from the results of this study as to how differences in the intake of these nutrients in the month or two prior to vaccination affect the occurrence of adverse reactions at the vaccination site, and no similar studies have been reported, so future research is expected. When the incidence of adverse reactions was compared separately for thinness (BMI <18.5) and not-thinness (BMI ≥18.5) individuals, the incidence of systemic adverse reactions was significantly higher in thinness individuals than in not-thinness individuals after the second vaccination (Table 3-b). This result appears to contradict the short-term nutritional results above, but if thinness is understood as a long-term nutritional deficiency, it could be that the malnourished state promotes adverse reactions by reducing normal resilience to immune responses, but again, it is difficult to infer this solely from the results of this study. The PAL of those who developed intake site side effects after the second vaccination was significantly lower (Table 4-b), which may suggest that balancing nutrient expenditure and nutrient intake at a high level is effective in reducing the incidence of side effects.

CONCLUSION

The results of this study, which indicate that the intake of some nutrients may affect the incidence of adverse reactions by means of an FFQ that estimates nutrient intake over the past month or two, do not contain enough information to infer how individual nutrients may affect the mechanism of adverse reactions, but they do suggest that adequate nutrient intake may have some effect on the immune response elicited by mRNA- 1273 vaccination may have some effect on the immune response elicited by vaccination. However, it is difficult to rationally understand the mechanism by which nutrients affect the occurrence of adverse effects from this survey alone, and more detailed collection and analysis of large amounts of data using survey techniques that can accurately determine nutrient intake is needed in order to gather clinical knowledge in the future. As a research technique for this purpose, the analysis of large amounts of data using data analytics is expected to become increasingly important in the future.

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