HUMAN VACCINES & IMMUNOTHERAPEUTICS
2022, VOL. 18, NO. 6, e2136435 (5 pages)
https://doi.org/10.1080/21645515.2022.2136435

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RESEARCH ARTICLE

Adverse reactions to inactivated COVID-19 vaccination in patients with chronic liver disease: The effect of anxiety

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ABSTRACT

Studies have shown that patients with chronic liver disease are at a higher risk of contracting novel coronavirus pneumonia than healthy individuals, and many guidelines state that patients with chronic liver disease should be prioritized for COVID-19 vaccination, but there are a few studies on its safety in CLD patients. We aimed to evaluate the safety of the inactivated COVID-19 vaccine in patients with chronic liver disease, and the effect of anxiety on adverse reactions. A questionnaire survey for self-administered post-vaccination adverse reaction monitoring was conducted from June 17, 2021, to August 11, 2021, in patients with chronic liver disease attending a tertiary care hospital in Taizhou, China. We analyzed the data from of a total of 160 participants who scanned the QR code on social media to respond to the questionnaire. The overall incidence of adverse reactions after COVID-19 vaccination in patients with chronic liver disease was 44.4% (71/160), and the most common adverse reaction was local injection site reaction, accounting for 80.3% of adverse reactions (57/71). No serious adverse reactions were reported. Approximately 53.1% of the patients had anxiety about vaccination, and 51.8% of those who felt anxious reported adverse reactions. The safety of COVID-19 vaccination in patients with chronic liver disease is good, and there is a strong association between adverse reactions and vaccine anxiety. Pre-vaccination education for patients with vaccine anxiety and psychological counseling may reduce reports of adverse reactions and improve patients' confidence in the vaccine.

ARTICLE HISTORY
Received 5 August 2022
Revised 4 October 2022
Accepted 10 October 2022

KEYWORDS
Adverse drug reaction; anxiety; liver diseases; COVID-19; vaccines

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), is a novel coronavirus that causes Coronavirus Disease 2019 (COVID-19).[1] The latest data published by the World Health Organization (WHO) shows that as of December 22, 2021, more than 275 million confirmed cases of COVID-19 have been diagnosed worldwide, and more than 5.36 million patients have died from COVID-19.

Chronic liver disease is a high-risk factor for SARS-CoV-2 pneumonia infection,[2] and patients with chronic liver disease have a higher mortality rate than healthy individuals when infected with SARS-CoV-2.[3]

COVID-19 vaccination is an important method for effective prevention of SARS-CoV-2 infection, pneumonia, hospitalization, and death, and for reducing the risk of transmission, and is particularly recommended for patients with chronic disease.[4]

There are a few safety studies related to the COVID-19 vaccine in patients with chronic liver disease,[5,6] and some studies suggest that the COVID-19 vaccine is safe and effective in patients with nonalcoholic fatty liver disease.[7] The rates of infection, as well as post-infection mortality rates, were also reduced after COVID-19 vaccination was administered to patients with cirrhosis.[8]

Through this study, we aimed to discuss the adverse effects of inactivated COVID-19 vaccine in patients with CLD and the effect of anxiety on the adverse effects.

Methods

We conducted an anonymous cross-sectional survey using the WeChat-incorporated Wen-Juan-Xing (Ranxing Information Technology Co., Ltd., Changsha, Hunan, China), the largest online survey platform in China. Our target population was patients with liver disease who were already vaccinated with inactivated COVID-19 vaccine, who presented to a tertiary care hospital in Taizhou, China. We included patients with chronic liver disease combined with certain other diseases (hypertension, hyperlipidemia, diabetes, etc.), but we excluded cancer patients. When patients visited the liver disease clinic from June 17, 2021, to August 11, 2021, they scanned a QR code and answered a self-administered questionnaire about COVID-19 vaccinations. In the questionnaire, we

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The authors have no proprietary interest in any aspect of this study.There was no additional financial support from public or private sources.

first investigated their knowledge, attitudes, and behaviors; then, all those who had had COVID-19 vaccinations recalled whether they experienced any local or systemic adverse reactions after vaccination.

This study was exempted from informed consent and was approved by the Ethics Committee of Taizhou Hospital, Zhejiang Province, China (approval number: k20210217). All procedures were performed in accordance with the guidelines of our institutional ethics committee and adhered to the principles of the Declaration of Helsinki. All participants' personal information was provided anonymously.

We designed our questionnaire based on the instruction manuals of the inactivated COVID-19 vaccines manufactured by Sinovac after consulting preventive experts about gathering valid feedback on adverse reactions after vaccination. The content of the questionnaire was as follows: (1) basic information such as age, sex, education level, occupation, and place of residence; (2) Any anxiety about COVID-19 vaccination; We asked about their level of anxiety about vaccination and defined anxiety as very anxious, anxious, not anxious, very not anxious; (3) history of vaccination, such as the history of vaccine allergy; (4) the type of chronic liver disease (such as hepatitis B, fatty liver, and cirrhosis), treatment status, and whether other chronic diseases, such as hypertension and diabetes, were comorbid; (5) local and systemic adverse reactions (including Pain, Inflammation, Redness, Swelling, or Itch, Fatigue, dizziness, dizziness, muscle pain, or fever) after COVID-19 vaccination and their extent; According to the grading criteria for adverse events of vaccine issued by the State Drug Administration of China, we define Grade 1 as mild adverse reactions that can resolve on their own; Grade 2 and 3 as moderate adverse reactions that require outpatient medical attention; and Grade 4 as serious adverse reactions that require inpatient treatment.

The primary objective of the investigation was to determine any self-reported adverse reactions to the COVID-19 vaccine experienced by these patients, and whether these reactions were correlated with vaccine anxiety. Our vaccine safety assessment included all patients with chronic liver disease who had received the COVID-19 vaccine and was indicated by the severity and number of reported local or systemic adverse reactions to COVID-19 vaccination.

Responses to questions such as those regarding the participants' basic information, and knowledge attitudes toward the vaccine, were categorized and expressed as counts and percentages. Factors potentially affecting adverse reactions to the COVID-19 vaccine, such as sex, age, work, knowledge, anxiety, and attitude, were tested using chi-square tests. To further analyze whether groups of people who developed adverse reactions after vaccination were significantly influenced by anxiety, we stratified the different groups and analyzed the effect of anxiety on adverse reactions using chi-square tests.

In univariate analysis, variables with $P < .05$, were included in the model. All data were analyzed using IBM SPSS Statistics software (version 26.0; SPSS Inc., Chicago, IL, USA). We identified a P-value < .05, as a statistically significant difference in the study population.

Results

We collected a total of 325 questionnaires, and after excluding oncology patients and incomplete questionnaires, 160 questionnaires were included in the analysis. The response rate was 49.2%. The response data for sex, age, occupation category, place of residence, Anxiety about vaccination, and type of chronic liver disease are shown in Table 1.

In our study, we described the nature, incidence and severity of adverse reactions reported by the survey participants. Most adverse reactions were mild and self-limiting. Of the 71 patients that reported the adverse reactions, 70 were mild. Only one patient presented to the outpatient clinic for management. No serious adverse reactions were observed.

It is shown in the Table 2 that patients who had anxiety ($\chi2 = 4.012$, $p = .045$) reported significantly more adverse reactions after inactivated SARS-CoV-2 vaccination and the type and status of a patient's liver disease, age, and the presence of other comorbid chronic diseases, had no significant effect on the reporting of adverse reactions.

Table 3 shows the relationship between adverse reactions and anxiety in the survey participants. The following groups were more likely to have adverse reactions due to anxiety: males ($\chi2 = 4.226$, $p = .040$), education level of senior

Table 1. Baseline characteristics of patients with chronic liver disease and cardinal analysis of factors associated with adverse effects, N = 160.

Variables	Category	*N*	(%)
Total		160	100.0%
Sex	Male	102	63.8%
	Female	58	36.3%
Age (years)	≤60	139	86.9%
	>60	21	13.1%
Residence	Rural	106	66.3%
	City	54	33.8%
Occupation	Farmer	58	36.3%
	Non-Farmer	102	63.8%
Education level	Junior Secondary and below	78	48.8%
	Senior Secondary	30	18.8%
	Junior College and above	52	32.5%
Anxiety	Yes	85	53.1%
	No	75	46.9%
Hepatitis B	Yes	102	63.8%
	No	58	36.3%
Nonalcoholic fatty liver disease	Yes	57	35.6%
	No	103	64.4%
Other Liver Diseases	Yes	34	21.3%
	No	126	78.8%
Liver cirrhosis	No	142	88.8%
	Yes	18	11.3%
Comorbidity	No comorbidity	96	60.0%
	One comorbidity	40	25.0%
	More than one comorbidity	24	15.0%
Hypertension	Yes	30	18.8%
	No	130	81.3%
Hyperlipidemia	Yes	25	15.6%
	No	135	84.4%
Diabetes	Yes	16	10.0%
	No	144	90.0%
Hyperuricemia	Yes	9	5.6%
	No	151	94.4%
Respiratory diseases	Yes	5	8.0%
	No	152	95.0%
Kidney disease	Yes	2	1.3%
	No	158	98.8%
Treatment	Yes	82	51.3%
	No	78	48.8%
Allergic reaction	No	146	91.3%
	Yes	14	8.8%

Table 2. Univariate analysis of factors associated with adverse reactions of COVID-19 vaccine. N = 160.

		No adverse reactions		Incidence of adverse reactions			
Variables	Category	n	(%)	n	(%)	χ2	P
Total		**89**	**55.6%**	**71**	**44.4%**		
Sex	Male	58	56.9%	44	43.1%	0.175	0.676
	Female	31	53.4%	27	46.6%		
Age (years)	≤60	76	54.7%	63	45.3%	0.386	0.534
	>60	13	61.9%	8	38.1%		
Residence	Rural	61	57.5%	45	42.5%	0.47	0.493
	City	28	51.9%	26	48.1%		
Occupation	Farmer	38	65.5%	20	34.5%	3.607	0.058
	Non-Farmer	51	50.0%	51	50.0%		
Education level	Junior Secondary and below	49	62.8%	29	37.2%	3.59	0.166
	Senior Secondary	16	53.3%	14	46.7%		
	Junior College and above	24	46.2%	28	53.8%		
Anxiety	Yes	41	48.2%	44	51.8%	4.012	**0.045**
	No	48	64.0%	27	36.0%		
Hepatitis B	Yes	55	53.9%	47	46.1%	0.331	0.565
	No	34	58.6%	24	41.4%		
Nonalcoholic fatty liver disease	Yes	36	63.2%	21	36.8%	2.036	0.154
	No	53	51.5%	50	48.5%		
Other Liver Diseases	Yes	17	50.0%	17	50.0%	0.553	0.126
	No	72	57.1%	54	42.9%		
Liver cirrhosis	No	81	57.0%	61	43.0%	1.027	0.311
	Yes	8	44.4%	10	55.6%		
Comorbidity	No comorbidity	50	52.1%	46	47.9%	4.769	0.092
	One comorbidity	28	70.0%	12	30.0%		
	More than one comorbidity	11	45.8%	13	54.2%		
Treatment	Yes	50	61.0%	32	39.0%	1.951	0.162
	No	39	50.0%	39	50.0%		
Allergic reaction	No	82	56.2%	64	43.8%	0.197	0.657
	Yes	7	50.0%	7	50.0%		

Table 3. Relationship between adverse reactions to inactivated COVID-19 vaccine and anxiety in different populations, N = 160.

		Anxious		Not anxious			
		Incidence of adverse reactions					
Population stratification		n	(%)	n	(%)	χ2	P
Sex	Male	28	52.8%	16	32.7%	4.226	**0.040**
	Female	16	50.0%	11	42.3%	0.341	0.559
Age (years)	≤60	71	51.1%	68	48.9%	1.780	0.182
	>60	14	66.7%	7	33.3%	3.387	0.076
Residence	Rural	30	48.4%	15	34.1%	2.153	0.142
	City	14	60.9%	12	38.7%	2.597	0.107
Education level	Junior Secondary and below	20	42.6%	9	29.0%	1.462	0.227
	Senior Secondary and above	24	63.2%	18	40.9%	4.040	**0.044**
Hepatitis B	Yes	29	56.9%	18	35.3%	4.774	**0.029**
Nonalcoholic fatty liver disease	Yes	12	38.7%	9	34.6%	0.102	0.750
Other Liver Diseases	Yes	12	63.2%	5	33.3%	2.982	0.084
Liver cirrhosis	No	37	50.0%	24	35.3%	3.127	0.077
	Yes	7	63.6%	3	42.9%	0.748	0.387
Comorbidity	No	18	45.0%	7	29.2%	1.580	0.209
	Yes	26	57.8%	20	39.2%	3.301	0.069
Treatment	Yes	23	56.1%	9	22.0%	10.045	**0.002**
	No	21	47.7%	18	52.9%	0.209	0.648
Allergic reaction	Yes	5	62.5%	2	33.3%	1.167	0.280
	No	39	50.6%	25	36.2%	3.072	**0.080**

secondary and above (χ2 = 4.040, p = .044), hepatitis B (χ2 = 4.774, p = .029), undergoing treatment (χ2 = 10.045, p = .002), and previous allergic reactions (χ2 = 3.072, p = .080). However, age, residence, presence of other types of liver disease besides hepatitis B, and presence of other comorbidities (P > .05) did not have a significant effect.

It is shown in the Table 4 that We did a multiple logistic regression analysis of factors associated with anxiety and found that no factors had significant effect on anxiety. (p > .05)

Discussion

Many people are concerned about studies of COVID-19 vaccination in patients with chronic liver disease.[9] Previous studies have shown that the safety of COVID-19 vaccination in patients with chronic liver disease is good, with the incidence of minor adverse reactions ranging from 24.9% to 90%. The most common adverse reactions are local injection site reactions, fatigue, headache, exhaustion, and muscle pain, which are usually mild and self-limiting.[7,9–11]

Table 4. Multiple logistic regression analysis of factors associated with anxiety. N = 160.

Variables	Categories	P	OR (95%CI)
Sex	Male vs. Female	0.735	0.579–2.171
Education level	Senior Secondary and above vs. Junior Secondary and below	0.056	0.985–3.554
Hepatitis B	Yes vs. No	0.666	0.445–3.554
Treatment	Yes vs. No	0.805	0.418–3.080
Allergic reaction	Yes vs. No	0.999	0

Table 5. The relationship between adverse reactions to inactivated COVID-19 vaccine and anxiety in different populations.

Author	Study design	Study period	Study sample	Setting	Vaccine	Content	Reference
Anne M.et al.	Cross-sectional study	2021		America	COVID-19	Sixty-four cases of anxiety-related adverse reactions were reported, with dizziness or headache in 36 cases (56%), pallor and excessive sweating in 20 cases (31%), nausea and vomiting in 16 cases (25%), and hypotension in 10 cases (16%)	15
Vincenza et al.	Cross-sectional study	2021	Total: 314664	Italy	COVID-19	Anxiety accounted for 24% of the 1704 adverse reactions (n = 339).	16
Tiffany A. et al.	Review	2017	Total:120	America	HPV. et al	Seven articles reported anxiety-related adverse reactions. The most frequently reported adverse reactions were syncope, dizziness, fatigue, headache, and tic disorder or involuntary movements.	13
Awnish K. et al.	Review	2017	Total:1037	India	JE, DTP et al	Anxiety-related adverse reactions were reported in 175 (17%) articles. Of these, 95 (54%) articles reported anxiety-related reactions to the Japanese encephalitis (JE) vaccine and 56 (32%) articles reported anxiety-related reactions to the measles vaccine.	17

We studied the adverse reactions to COVID-19 vaccination reported by 160 patients with chronic liver disease and found that the overall incidence of adverse reactions in patients with chronic liver disease was 44.4% (71/160), of which 80.3% (57/71) were local injection reactions; that most of the adverse reactions were mild and resolved spontaneously; and that no severe adverse reactions occurred.

Our analysis of factors influencing adverse reactions to COVID-19 vaccination in patients with chronic liver disease suggests that age and anxiety were important factors influencing adverse reaction reports. In our study by chi-square analysis, we found no significant effect of other comorbidities on adverse vaccine reactions in patients with liver disease, which may be related to the sample size as well as population differences. Interestingly, a higher percentage of patients with chronic liver disease had anxiety about the COVID-19 vaccine, compared to other patients with chronic diseases.[12] which in turn was significantly correlated with the rate of adverse reaction reports. Among the patients we surveyed, 53.1% (n = 85/160) had vaccine anxiety. In turn, 51.8% (44/85) of the patients with anxiety reported adverse reactions, which was significantly higher than the 36.0% of patients without anxiety (P = .045). In this study, men, high school education and above, patients with hepatitis B, and those undergoing treatment for liver disease, were more likely to have more reports of adverse reactions due to anxiety. We did a multiple logistic regression analysis of the factors affecting anxiety and found that none of them were significant. Maybe anxiety is inherent in the population, which is independent of other influencing factors.

Anxiety is a common health issue worldwide. Many countries have reported adverse reactions to vaccinations (such as headache, dizziness, and fatigue), as a result of group anxiety, which were confirmed to be unrelated to the vaccine itself in subsequent investigations by medical personnel.[13] The WHO defines these type of adverse reactions as immunization anxiety-related adverse reactions.[9]

A number of studies have observed anxiety-related adverse events after immunization, involving vaccines such as tetanus, tetanus diphtheria, hepatitis B, human papillomavirus, and influenza A vaccine (Table 5) .[14] In a COVID-19 vaccine study, 64 cases of anxiety-related adverse reactions were reported in the United States, mostly presenting with dizziness or headache.[15] Researchers in Italy also reported 339 cases of anxiety-related adverse reactions after COVID-19 vaccination, accounting for 24% of the adverse reactions.[16] In addition, anxiety-related adverse reactions to the Japanese encephalitis vaccine, measles vaccine, and cervical cancer vaccine have all been reported in the literature.[17] In 2015, the WHO Global Advisory Committee on Vaccine Safety convened an expert working group to discuss "Adverse reactions due to immunization anxiety," which was updated to "Immunization stress related reactions."[18] In a slight departure from their working group discussion, we included anxiety about the vaccine as a potential factor in the occurrence of adverse reactions, and found that patient anxiety about the vaccine was associated with reports of adverse effects of the vaccine. It has been shown that we can reduce patients' anxiety about vaccines and reduce vaccine anxiety-related adverse reactions by increasing patient awareness through better education and increasing patients' confidence in vaccines.

Our study has some limitations. First, direct questioning was used to ascertain whether anxiety was present, and no scale was used to assess the degree of anxiety, which may not provide a comprehensive understanding of anxiety. Second, the patients' adverse effects were self-reported and may have been biased. Third, the possibility that the nature of the questionnaire being retrospective could be a limitation. The reason

being, patients recalling previous vaccine adverse reactions, and reporting current feelings of anxiety about the vaccine, could indicate that for some patients, experiencing adverse reactions causes anxiety about the vaccine – and perhaps not the other way around. Fourth, the possibility that the group of patients attending the hospital who chose to complete the questionnaire may have been biased toward those that experienced anxiety toward vaccines, and/or those that had experienced adverse reactions. Fifth, we collected questionnaires in the hospital, lacking blank controls for the healthy population. Last, our study was conducted on patients with chronic liver disease in one hospital, making it difficult to reflect the characteristics of all patients with chronic liver disease.

Conclusion

Our study shows that the COVID-19 vaccine has a good safety profile in patients with chronic liver disease, and that there is a strong correlation between reported adverse reactions and vaccine anxiety. Therefore, it is beneficial to reduce anxiety-induced adverse reactions through education and psychological guidance to increase the confidence of patients with chronic liver disease in the COVID-19 vaccine.

Acknowledgments

We would like to thank the participants for their cooperation and support.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This paper did not receive any funding.

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Author contributions

J.S. Z. and T.H.T. conceived the study. M.X.Z., J.S. Z. and T.H.T. designed the questionnaire. J.S. Z. and H. S. collected the data. X.Q. L. was responsible for coding the analyses. L.L. and X.Q.L. analysed and interpreted the data and wrote the first draft of the paper. Y.C.and H.D.C. searched, sorted, and interpreted the relevant literature. All authors edited and approved the final manuscript.

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