



RESEARCH ARTICLE

REVISED Adverse drug reactions to the three doses of the severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) mRNA-1273 vaccine in a cohort of cancer patients under active treatment of a tertiary hospital in Madrid, Spain
[version 2; peer review: 2 approved]

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines efficacy and safety have been tested in phase 3 studies in which cancer patients were not included or were underrepresented.

Methods: The objective of this study is to evaluate the safety profile of the mRNA-1273 vaccine across cancer patients and its relationship to patients' demographics. We selected from our records all 18-years or older solid cancer patients under active treatment vaccinated with the complete three-dose schedule mRNA-1273 vaccine whose adverse drug reactions (ADRs) after each dose were recorded. Medical records were reviewed retrospectively to collect data between April 19, 2021, and December 31, 2021. Patients with documented previous infection by SARS-Cov-2 were excluded.

Results: A total of 93 patients met the inclusion criteria. Local ADRs were reported more frequently after the first and second dose than

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version 2 (revision) 26 Jul 2022	 view	 view
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after the third (41.9%, 43% and 31.1% of the patients respectively), while systemic ADRs followed the opposite pattern (16.1%, 34.4% and 52.6% of the patients respectively). We found a statistically significant association between sex and systemic adverse reactions after the third dose, $p < 0.001$ and between systemic adverse reactions after the second dose and systemic adverse reactions after the third dose, $p = 0.001$. A significant linear trend, $p = 0.012$, with a higher Eastern Cooperative Oncology Group (ECOG) score associated with a lower proportion of patients suffering from systemic side effects was found. Women had 5.79 times higher odds to exhibit systemic ADRs after the third dose ($p=0.01$) compared to males. Increasing age was associated with a decreased likelihood of exhibiting ADRs ($p=0.016$).

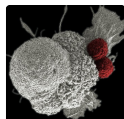
Conclusion: The mRNA-1273 vaccine shows a tolerable safety profile. The likelihood of ADRs appears to be associated with gender and age. Its association with ECOG scores is less evident. Further studies are needed to elucidate this data in cancer patients.

Keywords

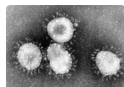
COVID-19, mRNA-1273 Vaccine, SARS-CoV-2, Safety, Cancer, Oncology




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Any reports and responses or comments on the article can be found at the end of the article.

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REVISED Amendments from Version 1

In the second version, we have improved the methodology and results sections of the abstract. "Adverse reactions" has been added to the keywords list. The introduction has been changed to remove redundant or non-necessary sections and more references have been added. Ethical considerations have been moved to the end of the methods section. The Period under investigation has been further clarified. The term "heavily treated" has been defined. The statistical analysis section has been clarified both in the methods and results sections. Subheadings have been written in the results section. More references have been provided for the discussion section. Tables have been changed erasing redundant or non-necessary information.

Any further responses from the reviewers can be found at the end of the article

Introduction

In December 2019 a previously unknown betacoronavirus causing pneumonia was isolated from human epithelial cells, it was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the disease it causes coronavirus disease 2019 (COVID-19). In January 2020 the World Health Organization (WHO) declared an international emergency and on 11th March the WHO declared COVID-19 a pandemic.¹⁻³

COVID-19 has shown a wide variety of symptoms and a broad spectrum of severity being associated with worse clinical outcomes in patients with cancer, with an estimated mortality of 30% in hospitalized cancer patients and 60% in cancer patients admitted to the Intensive Care Unit.⁴⁻⁷ Patient care in this population was disrupted during the pandemic due to the emergency situation with delays in surgeries and cancer medical treatments to prevent cancer patients from getting the infection.⁸

Due to the emergency generated by the pandemic several research projects involving vaccines against SARS-CoV-2 were started. In December 2020 the **Food and Drug Administration (FDA) issued the first Emergency Use Authorization** for the BNT162b2 vaccine after it was found to be safe and efficient in preventing COVID-19 in the general population, followed shortly by the mRNA-1273 vaccine.^{9,10} Patients receiving systemic immunosuppressants or immune modifying drugs within six months of screening were excluded from the clinical trials,^{9,11} thus leaving cancer patients behind in the research for a vaccine against SARS-CoV-2. However, despite the lack of evidence of efficacy and safety in this population, cancer patients were prioritized for the administration of the SARS-CoV-2 vaccine,¹² and **in Spain this population started vaccination in April 2021.**

To our knowledge the scarce evidence regarding safety of the mRNA vaccines mostly comes from studies with the two-dose schedule mRNA vaccine,¹³⁻¹⁵ with only one considering the third dose, in this case of the BNT162b2 vaccine 16. These studies show a low incidence of severe adverse drug reactions (ADRs) most of them being pain at the site of injection, fatigue, myalgia and fever.¹³⁻¹⁶

In this study we describe and analyse the safety profile of the three-dose schedule mRNA-1273 vaccine in a cohort of solid cancer patients under active cancer treatment in a tertiary hospital in Madrid, Spain.

Methods**Study design, eligibility, and study procedures**

This observational retrospective study included patients with solid tumours receiving anticancer treatment at the outpatient facility of the Hospital Clínico San Carlos Medical Oncology service in Madrid, Spain. We included all the patients vaccinated with the complete three-dose schedule mRNA-1273 vaccine that were on active anticancer therapy and had complete available information about the date of each vaccination dose and side effects for each of the three doses in electronic medical records. Patient electronic medical records were reviewed retrospectively to collect the data from April 19, 2021 to December 31, 2021.

We selected the patients vaccinated with the complete three-dose schedule mRNA-1273 vaccine from the Preventive Medicine and Public Health Department database. This database was linked with the Medical Oncology Department patient database selecting all oncology patients under active treatment who were in the previous database. From these subjects we selected the ones that had information about the appearance or absence of ADRs after each dose of the vaccine available in electronic medical records. Patients who had a documented SARS-CoV-2 infection or a positive SARS-CoV-2 serology test collected during routine clinical practice in the 7 days prior to the first mRNA-1273 vaccine dose were excluded.

Additional clinical information was abstracted from the electronic medical records, including age, sex, performance status (using Eastern Cooperative Oncology Group (ECOG) performance status score),¹⁷ cancer type, cancer stage and

cancer therapy. Authors belonging to Medical Oncology Department had complete access to all electronic medical records available from the patients.

ECOG performance status score describes the level of functioning in terms of the ability to self-care, daily activity, and physical ability of the patients. ECOG 0 patients are fully active. ECOG 1 patients are not able to perform physically demanding activity but are ambulant and able to perform occupations of light nature. ECOG 2 patients are ambulant, up for more than 50% of waking hours, and capable of all personal care, but are unable to perform any work activities. ECOG 3 patients can perform only limited self-care and are bedridden or confined to a chair for more than half of waking hours. ECOG 4 patients are completely incapacitated, unable to perform any self-care and totally confined to a bed or chair. ECOG 5 patients are dead.¹⁷

Cancer type was divided in seven groups: thoracic malignancies, breast cancer, head and neck cancer, gastrointestinal malignancies, gynaecological malignancies, and others (malignancies that did not belong to any of the previous groups).

Cancer stage was divided in metastatic, patients with malignant lesions in locations organs distant from where the primary tumour is, and the rest, defined as localized.

Cancer therapy was divided in chemotherapy, targeted therapy, immunotherapy and combined therapy (any combination of the previous treatments).

Data analysis

The primary end point of this study was ADRs after each dose of mRNA-1273 vaccine. ADRs were categorized as local adverse reactions which included pain, swelling, rash and itchiness at the site of infection and systemic adverse reactions. Systemic adverse reactions reported by patients were fever (defined as body temperature equal or above 38°C), headache, myalgia, malaise, nausea, arthralgia, chills, adenopathies, urticaria, asthenia and cough.

Data was analysed with **IBM SPSS** v.25. For descriptive purposes, categorical variables were represented by absolute and relative frequencies and quantitative variables were represented by central and dispersion measures. In order to ascertain the relationship between nominal independent variables (sex, heavily treated status defined as 3 or more lines of previous treatment and past story of systemic adverse drug reactions) we performed a chi-squared test (all expected cell frequencies were greater than five) followed by a Cramér's V test. For ordinal variables (ECOG performance status score)¹⁷ we performed a Cochran-Armitage test of trend. Significance was tested with an alpha value of 0.05. No multiplicity correction was applied. To test the value as predictors of true baseline variables (age, sex and ECOG performance status) we fitted a binomial logistic regression to ascertain the effects of age, sex and ECOG score on the likelihood that participants have systemic adverse events after the third dose (hereinabove described). We used a Box-Tidwell procedure to evaluate the linear relationship between the logit of the outcome and continuous variables. Following a Bonferroni correction, statistical significance was accepted when $p < 0.0071$. Age was included as a continuous variable, sex as a dichotomous variable, being male considered as reference, and ECOG scores were included as categorical variables, with a score of 0 considered the reference.

Ethical considerations

The Comité de Ética del Medicamento e Investigación Clínica (Ethics Committee) of Hospital Clínico San Carlos approved the project with the code: 22/033-E. The Comité de Ética del Medicamento e Investigación Clínica (Ethics Committee) of Hospital Clínico San Carlos deemed the necessary requirements for appropriateness of the protocol in relation to the objectives of the study were met, the informed consent waiver was considered adequate, the procedure foreseen for the handling of personal data was adequate. The ethical precepts formulated in the Declaration of Helsinki of the World Medical Association for medical research on human beings and its subsequent revisions are complied with, as well as those required by the applicable legal regulations according to the characteristics of the study.

Results

Study population

Data was retrieved from electronic medical records on the 31st of December, 2021. In total 93 patients were eligible for the current analysis.¹⁸ Patient demographic, cancer, and therapy characteristics included are summarized in [Table 1](#).

Adverse drug reactions

The number of ADRs categorized as local and systemic after the first, the second and the third vaccine dose are shown in [Figure 1](#). Local ADRs included pain, swelling, rash and itchiness at the site of infection. We can observe that systemic ADRs have a clearly increasing trend while local ADRs have a discrete downward trend.

Table 1. Demographic, cancer, and therapy characteristics of the patients.

Characteristic	N = 93
Age, years (SD)	61 [8]
Sex, No. (%)	
Female	62 (66.6)
Male	31 (33.3)
Cancer type, No. (%)	
Thoracic	11 (11.8)
Breast	32 (34.4)
Head and Neck	9 (9.7)
Gastrointestinal	16 (17.2)
Genitourinary	8 (8.6)
Gynaecological	10 (10.8)
Other	7 (7.5)
Stage, No. (%)	
Localised	31 (33.3)
Metastatic	62 (66.6)
Treatment modality, No. (%)	
Chemotherapy	34 (36.6)
Targeted therapy	21 (22.6)
Immunotherapy	11 (11.8)
Combined therapy (any combination of the previous treatments)	27 (29)
Heavily treated (3 or more lines of previous treatment), No. (%)	
Yes	29 (31.2)
No	64 (68.8)
ECOG, No. (%)	
0	55 (59.1)
1	30 (32.3)
2	8 (8.6)

SD: Standard Deviation; ECOG: East Cooperative Oncology Group Performance Status Scale. ECOG 0: fully active. ECOG 1: not able to perform physically demanding efforts but are ambulant and capable of performing tasks of sedentary nature. ECOG 2: outpatient, fully capable of all personal care but unfit for any working activity. Up for more than half of waking time.

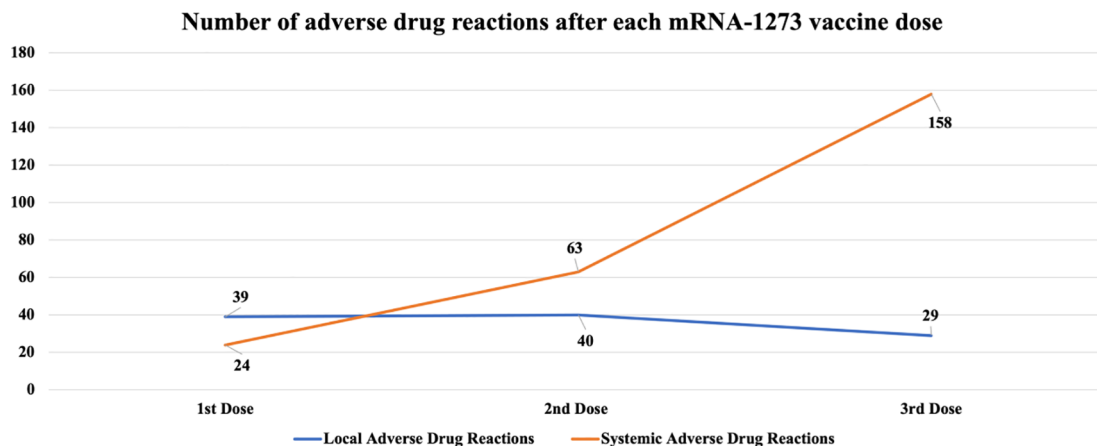


Figure 1. Number of ADRs after each mRNA-1273 vaccine dose.

Adverse drug reactions after 1st dose

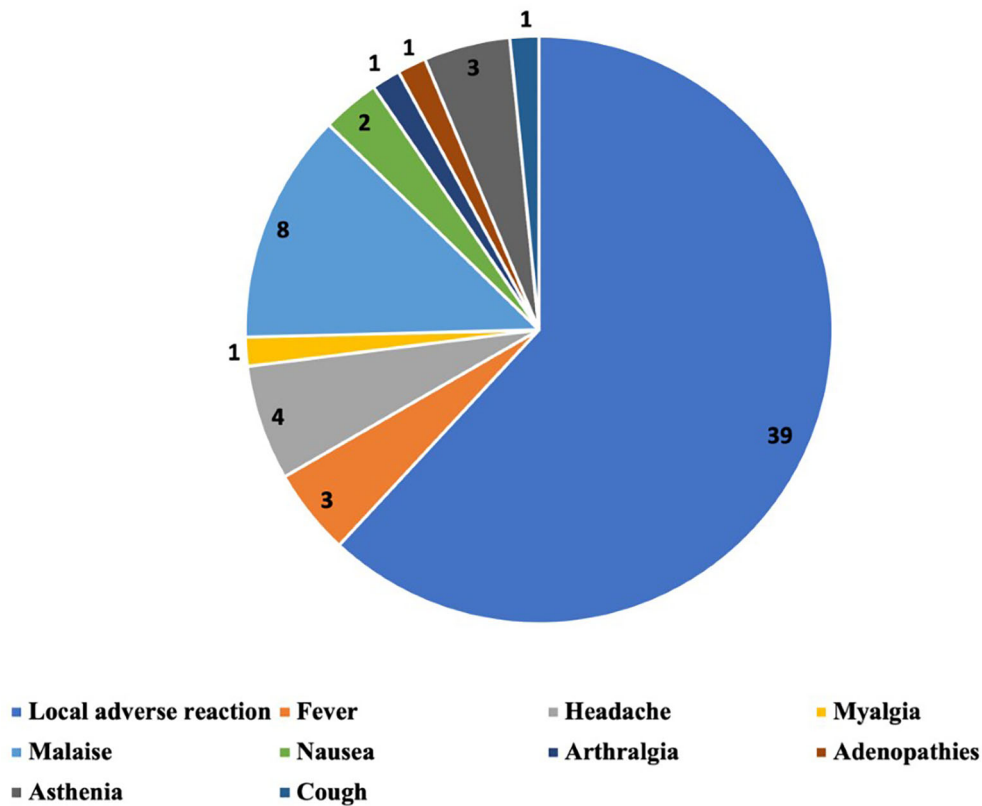


Figure 2. Number and type of adverse drug reactions after 1st dose.

After the first, second and third dose 41.9%, 43% and 31.1% of the patients respectively reported a local ADR, while systemic ADRs were increasingly reported after each dose (16.1%, 34.4% and 52.6% of the patients respectively).

The ADRs occurring after the first, the second and the third vaccine dose are described in Figures 2–4 respectively. The most common ADR after the first dose was local reaction with a marked difference compared with systemic ADRs. After the second dose the most frequent ADR was still local reaction, but systemic were becoming increasingly important. After the third dose we can observe that local ADR is less common and takes second place after fever and that the rest of systemic effects are increasingly frequent.

No severe ADRs requiring hospitalization occurred in this population. No new SARS-CoV-2 infections occurred in this population during the period studied.

Statistical analysis

There was a statistically significant association between sex and systemic adverse reactions after the third dose, $\chi^2(1) = 12.982$, $p < 0.001$. The association was moderate (Cramér's $V = 0.396$). We didn't find a statistically significant association between heavily treated status and systemic adverse reactions after the third dose, $\chi^2(1) = 0.063$, $p = 0.802$. The association was small (Cramér's $V = 0.05$).

Regarding adverse reactions after previous vaccine doses, there was not a statistically significant association between systemic adverse reactions after the first dose and after the third one, $\chi^2(1) = 1.897$, $p = 0.168$, being the association between the variables small, Cramér's $V = 0.172$. On the other hand, we found a statistically significant association between systemic adverse reactions after the second dose and systemic adverse reactions after the third dose, $\chi^2(1) = 11.372$, $p = 0.001$. The association was moderate, Cramér's $V = 0.372$.

Adverse drug reactions after 2nd dose

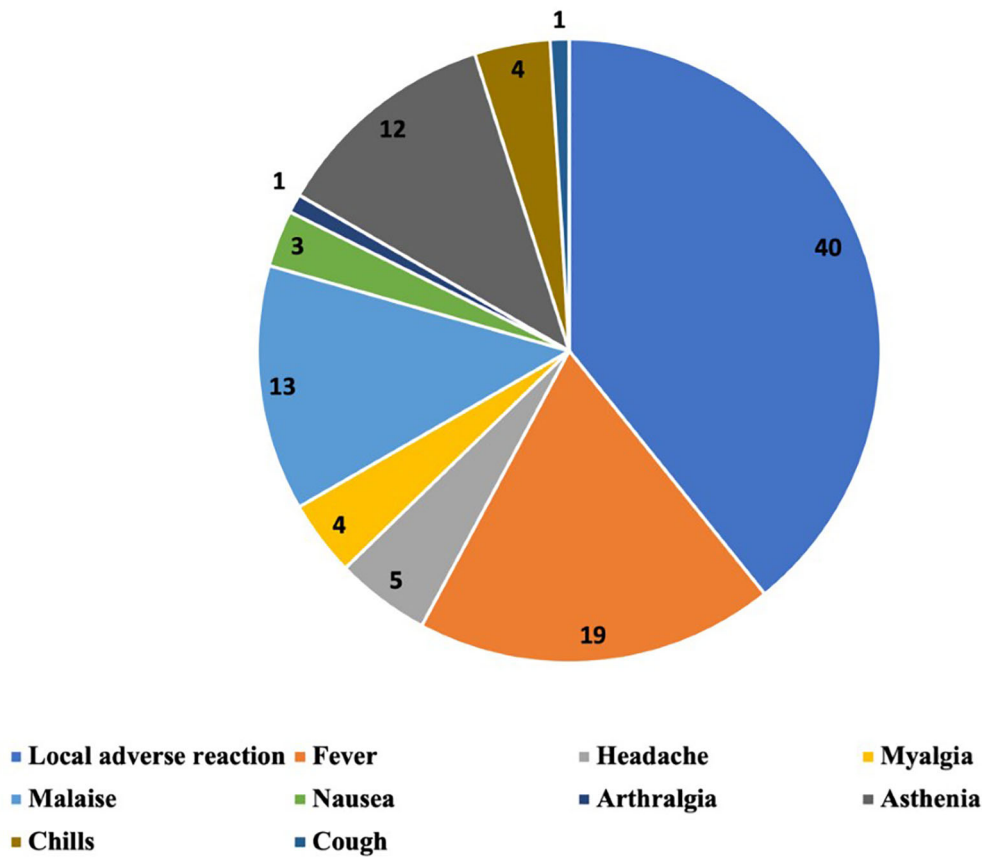


Figure 3. Number and type of adverse drug reactions after 2nd dose.

The Cochran-Armitage test of trend showed a statistically significant linear trend, $p = 0.012$, with a higher ECOG score associated with a lower proportion of patients suffering from systemic side effects. The scores tested were ECOG 0 ($n = 56$), ECOG 1 ($n = 30$), ECOG 2 ($n = 7$), and the proportion of patients suffering a side effect was 0.643, 0.4 and 0.286, respectively.

Concerning the binomial logistic regression model assumptions, age was found to be linearly related to the logit of the dependent variable based on the Box-Tidwell procedure assessment and a Hosmer *et al.* goodness of fit test was not statistically significant ($p = 0.577$).¹⁹ The logistic regression model was statistically significant, $\chi^2(4) = 25.641$, $p < 0.001$, explained 32.2% (Nagelkerke R^2) of the variance in systemic adverse events after the third dose and correctly classified 72.0% of cases. Sensitivity was 82%, specificity was 60.5%, positive predictive value was 70.7% and negative predictive value was 74.3%. The area under the ROC curve was 0.783 (95% CI, 0.688 to 0.878) (Figure 5), which is at the upper level of an acceptable level of discrimination according to Hosmer *et al.*¹⁹

Only two variables were statistically significant: age and sex (as shown in Table 2). Women had 5.79 times higher odds to exhibit systemic adverse events after the third dose compared to males. Increasing age was associated with a decreased likelihood of exhibiting adverse events. ECOG score was not statistically significant but a trend towards a diminished likelihood of systemic adverse reactions with higher ECOG score compared to ECOG 0 was observed.

Discussion

Among completed and ongoing trials of SARS-CoV-2 vaccines there is scarce information regarding safety and efficacy of these vaccines in solid cancer patients. Subjects receiving systemic immunosuppressants or immune modifying drugs within six months of screening were excluded from the major vaccine trials.^{9,11}

Adverse drug reactions after 3rd dose

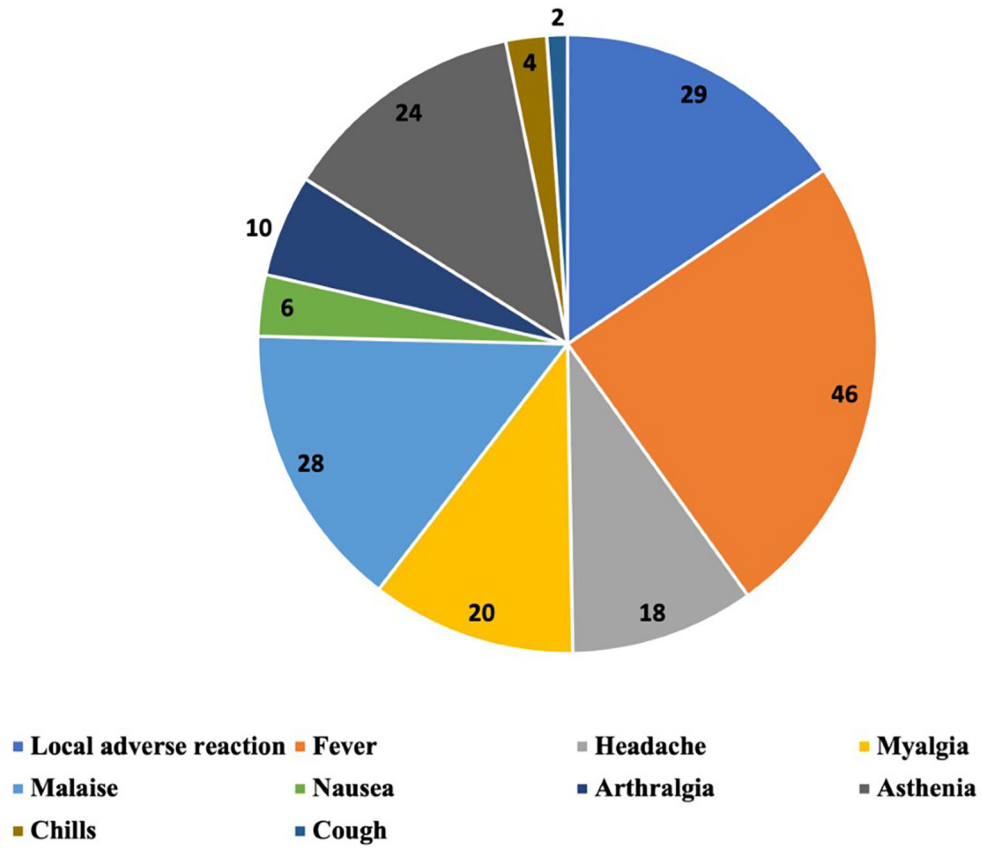


Figure 4. Number and type of adverse drug reactions after 3rd dose.

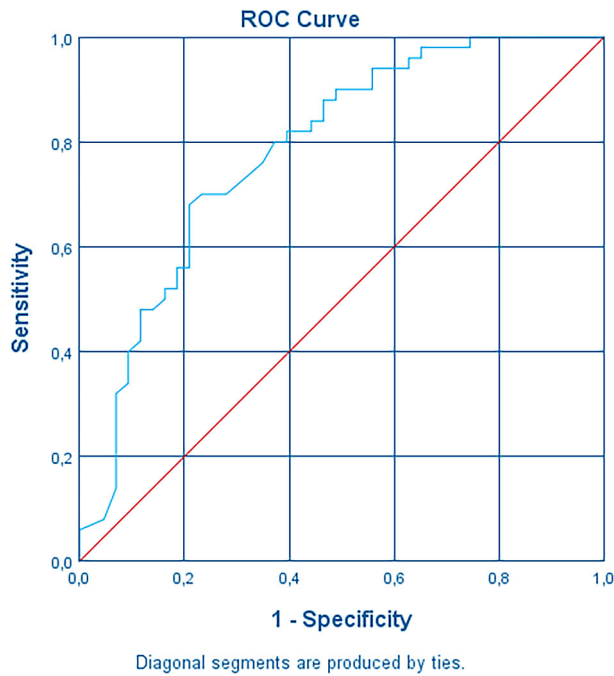


Figure 5. Receiving Operating Characteristic curve (ROC curve).

Table 2. Logistic regression predicting Likelihood of Systemic Adverse Reactions based on Age, Sex and ECOG score.

	B	SE	Wald	df	p	OR	95% CI for OR	
							Lower	Upper
ECOG 1	-,434	,538	,652	1	,420	,648	,226	1,858
ECOG 2	-1,669	,967	2,979	1	,084	,188	,028	1,254
Female Sex	1,756	,533	10,839	1	,001	5,789	2,035	16,468
Age (years)	-,059	,024	5,804	1	,016	,943	,899	,989
Constant	2,846	1,524	3,485	1	,062	17,215		

Abbreviations: B logarithmic regression slope, SE standard error, degrees of freedom, OR odds ratio, CI confidence interval. Regarding the variable Sex, male was considered the reference. Regarding the variable ECOG, ECOG 0 was considered the reference.

In the phase 3 clinical trial of the mRNA-1273 SARS-CoV-2 vaccine, the mRNA-1273 group showed 84.2% of local ADRs after the first dose and 88.6% after the second dose. Systemic ADRs in the mRNA-1273 group occurred in 54.9% of patients after the first dose and 79.4% of patients after the second. Fever, headache, and myalgia were the most common systemic ADRs.¹¹ In our population we observed both less local and systemic ADRs than in the healthy population from this trial.

The published literature regarding ADRs in cancer patients after COVID-19 vaccine administration mostly shows an increasing trend of systemic ADRs after the second dose.^{13,20-27} We could only find one study conducted in Thailand in which ADRs after the first and second of AZD1222 vaccine doses were evaluated observing the opposite trend.²⁸

Some articles have also showed an association between gender and the incidence of ADRs after the SARS-CoV-2 vaccines. Female gender was associated with higher risk of experiencing ADRs.^{27,29}

Only a few reports have evaluated the safety profile of the COVID-19 vaccines in cancer patients, fewer have reported data specifically about the mRNA-1273 vaccine safety profile in this population, and none of them have reported data about ADRs after the third dose of this vaccine. Our study is at the moment, the only one evaluating the safety profile of each of the three doses of mRNA-1273 vaccine in cancer patients. It shows an increasing frequency of systemic ADRs after each dose and its association with gender and age. **In a scenario where the start of the administration of the fourth dose in cancer patients is ongoing**, we expect that this article could help predict the trend in the incidence of ADRs after the fourth dose of the vaccine and aid us in anticipating subgroups at greater risk of ADRs.

This study has some important limitations. (1) The retrospective nature of the study makes it more prone to error, making measurements less precise. (2) The small population in this study and its characteristics do not represent the general cancer patient population and makes it difficult to generalize the results, thus external validity can be compromised. (3) The absence of a healthy control group makes it difficult to reach conclusions.

Conclusion

Although based on a small number of patients and limited by the observational nature of the study, the mRNA-1273 vaccine shows a tolerable safety profile in this cohort of cancer patients similar to the non-oncologic population. No severe ADRs requiring hospitalization occurred in this population. The likelihood of ADRs appears to be associated with gender and age. The likelihood of systemic ADRs after the third dose appears to be associated with systemic ADRs after the second dose. There appears to be a trend towards more systemic and less local ADRs with every consecutive dose of the vaccine. Its association with ECOG performance score is less evident. To date this is the first study evaluating the safety profile of the three doses of mRNA-1273 vaccine.

Data availability

Underlying data

Dryad: Adverse drug reactions to the three doses of the SARS-COV-2 mRNA-1273 vaccine in a cohort of cancer patients of a tertiary hospital. <https://doi.org/10.5061/dryad.cnp5hq6d>.¹⁸

This project contains the following underlying data:

- ADRs_mRNA-1273_database_excel.xlsx (database with all the individual anonymized data regarding the parameters analysed in this article)
- README.docx (document with the explanation of the data used in the database)

Data are available under the terms of the [Creative Commons Zero “No rights reserved” data waiver](#) (CC0 1.0 Public domain dedication).

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Version 2

Reviewer Report 05 January 2023

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Durga Neupane 

Department of Surgery, B.P. Koirala Institute of Health Sciences, Dharan, Nepal

First of all, thank you for giving me an opportunity to review this article. The authors have done a good study about the safety and efficacy of COVID vaccine targeted on solid cancer patients. The former reviewer's comments have been addressed properly. I recommend that the article is copy edited. Otherwise, it has added significantly to existing literature. I recommend that it is indexed without any revision.

Thank you.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Neurosurgery; Oncology; Public Health; Neuroscience

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 30 August 2022

<https://doi.org/10.5256/f1000research.136429.r145418>

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Manushak Avagyan 

¹ International Agency for Research on Cancer, Lyon, France

² Hematology Center after Prof. Yeolyan, Yerevan, Armenia

Thank you for improving the manuscript further.

There are no additional remarks.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Childhood cancer, cancer epidemiology, childhood cancer registration, cancer registries.

I confirm that I have read this submission and believe that I have an appropriate level of

expertise to confirm that it is of an acceptable scientific standard.

Version 1

Reviewer Report 03 May 2022

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Manushak Avagyan 

¹ International Agency for Research on Cancer, Lyon, France

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The manuscript presents a detailed assessment of the mRNA-1273 vaccine's safety profile in 93 cancer patients and its link to their demographics.

In view of the paucity of knowledge on data about the safety and efficacy of the vaccines among cancer patients, this is a potentially valuable contribution to knowledge. However, the manuscript needs adjustments to be ready for indexing in F1000Research, as covered in the following specific comments.

Overall, the work might benefit from greater literature support; consider updating with the latest publications concerning vaccination safety in cancer patients.

Title:

- The title is lengthy yet self-explanatory.

Abstract:

- The abstract and overarching objectives are clear. The methodology is not thorough and the analysis is not clear from the appropriate section. The main outcomes are clear, and the conclusions are relevant to the aim.

Keywords:

- Please consider including a keyword that addresses adverse reactions in addition to safety.

Introduction:

- The broad description section at the beginning could be improved, particularly the first six sentences, which should be shortened and summarized into 2-3 sentences and present more about the characteristics of oncology patients, as well as a presentation about other vaccine-related information among cancer patients.
- The use of a hyperlink at the end of the introduction does not seem proper by highlighting one sentence.

- There is a need for references for the pre-last phrase concerning a few studies indicating vaccination safety among cancer patients.
- Consider removing the patient count from the final line of the introduction, while describing the aim of the study.

Methods:

- Move the ethical considerations to the end of the methods section.
- Please specify the time period under investigation. The methodology section (it's clearly specified in the abstract) does not specify which dates were verified for recruitment since there are dates in the middle of the paragraph discussing data collecting for additional variables.
- In the methods section, please define the term "heavily treated."
- If you find it feasible, an extra step for the study would be to use a logistic regression model and evaluate the model's fit to the data.

Results:

- The reported findings are based on the analysis mentioned in the methodology section.
- Having subheadings in the results section can improve.
- Consider mentioning the full date in the first sentence of the results section.
- Page 7:
 - a. The second paragraph, which discusses the relationship between various doses and the subsequent systemic response, might be articulated clearly in the first opening phrase.
 - b. The presentation of the findings in the third paragraph might be improved.
 - c. In the fourth paragraph, the first two phrases need clarification.

Discussion:

- In the discussion section, only three new references are provided, and further comparisons and references are needed; this might be updated with new research released in 2022.

Tables:

- In Table 1, the word "SD" appears twice in the second row.
- Table 2 might be improved by deleting unnecessary information generated during analysis and presenting a clearer and more focused table, with the main values being OR, P, and CI, and the rest could be discarded.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

I cannot comment. A qualified statistician is required.

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Childhood cancer, cancer epidemiology, childhood cancer registration, cancer registries.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Author Response 20 Jul 2022

Javier David Benitez Fuentes, Hospital Clinico San Carlos, Madrid, Spain

In the 2nd version, I am submitting the following has been addressed:

Abstract:

- The abstract and overarching objectives are clear. The methodology is not thorough and the analysis is not clear from the appropriate section. The main outcomes are clear, and the conclusions are relevant to the aim.

Response: Methodology and results description has been improved.

Keywords:

- Please consider including a keyword that addresses adverse reactions in addition to safety.

Response: Done

Introduction:

- The broad description section at the beginning could be improved, particularly the first six sentences, which should be shortened and summarized into 2-3 sentences and present more about the characteristics of oncology patients, as well as a presentation about other vaccine-related information among cancer patients.

Response: Done

- The use of a hyperlink at the end of the introduction does not seem proper by highlighting one sentence.

Response: Editors from the journal suggested this format.

- There is a need for references for the pre-last phrase concerning a few studies indicating vaccination safety among cancer patients.

Response: Done

- Consider removing the patient count from the final line of the introduction, while describing the aim of the study.

Response: Done

Methods:

- Move the ethical considerations to the end of the methods section.

Response: Done

- Please specify the time period under investigation. The methodology section (it's clearly specified in the abstract) does not specify which dates were verified for recruitment since there are dates in the middle of the paragraph discussing data collecting for additional variables.

Response: Done

- In the methods section, please define the term "heavily treated."

Response: Done

- If you find it feasible, an extra step for the study would be to use a logistic regression model and evaluate the model's fit to the data.

Response: Clarified by the biostatistician

Results:

- The reported findings are based on the analysis mentioned in the methodology section.
- Having subheadings in the results section can improve.

Response: Done

- Consider mentioning the full date in the first sentence of the results section.

Response: Done

- Page 7:
 - a. The second paragraph, which discusses the relationship between various doses and the subsequent systemic response, might be articulated clearly in the first opening phrase.

Response: Done

- b. The presentation of the findings in the third paragraph might be improved.

Response: Done

- c. In the fourth paragraph, the first two phrases need clarification.

Response: Done

Discussion:

- In the discussion section, only three new references are provided, and further comparisons and references are needed; this might be updated with new research released in 2022.

Response: Done

Tables:

- In Table 1, the word "SD" appears twice in the second row.

Response: Erased

- Table 2 might be improved by deleting unnecessary information generated during analysis and presenting a clearer and more focused table, with the main values being OR, P, and CI, and the rest could be discarded.

Response: Done

Competing Interests: No competing interest

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