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COVID-19

Safety of SARS-CoV-2 vaccines in patients with myasthenia gravis: a meta-analysis

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To the Editor:

We read with interest a recent article reported by Trinchillo A. in this journal [1], which found that COVID-19 vaccines were safe in myasthenia gravis (MG) patients. MG is an autoimmune disease affecting the neuromuscular junction, which can involve the ocular, respiratory, and skeletal muscles of the limbs. MG patients are predisposed to develop respiratory diseases in more severe forms due to muscular weakness. The COVID-19 vaccines have been shown to prevent severe COVID-19 in vulnerable patients. However, worsening MG induced by the COVID-19 vaccine has been seen in a few studies [2, 3]. Therefore, a meta-analysis of the safety of COVID-19 vaccination in MG patients is of significant importance.

We searched the EMBASE, Web of Science, and PubMed databases from January 1, 2020, to April 20, 2023, using the following keywords: COVID-19 vaccines, SARS-CoV-2 vaccines, 2019-nCoV vaccine, and myasthenia gravis. We restricted the search language to English. Studies were selected based on the following inclusion criteria: MG patients who received SARS-CoV-2 vaccines and English articles. Exclusion criteria were (1) studies without relevant data and (2) repeated studies.

We used Review Manager 5.3 software for statistical analysis. To evaluate the association between MG patients and the SARS-CoV-2 vaccines, we used single group percentages and corresponding 95% confidence intervals (CIs) and a whole random-effects meta-analysis model to summarize the data. Subgroup analysis was subsequently performed to calculate the percentage of worsening MG and adverse events depending on the vaccine dose. A binary controlled study was used to calculate the worsening MG percentage depending on the gender, antibody positive, and type of MG. In the random-effects meta-analysis model, the odds ratio (OR) and 95% CI were used to evaluate the effect. The I^2 and P values were used to quantify the heterogeneity of the effects in the included studies.

In total, 12 studies involving 1465 patients were included in the final analysis (Table 1) [1–12]. The overall OR for MG worsening after COVID-19 vaccination in MG patients was 0.32 (95% CI, 0.25 to 0.42, $P < 0.001$) based on 12 studies (Fig. 1). The overall OR for MG worsening after COVID-19 vaccination in males vs. females based on eight studies was 0.59 (95% CI, 0.28 to 1.21, $P = 0.15$) (Fig. 2A). The overall OR for

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Table 1 Baseline characteristics of the included studies

Study	Year	Country	Type of study	Total patients	Male/female
Doron A [2]	2022	Israel	Cross-sectional study	160	89/71
Farina A [3]	2022	Italy	Observational study	104	55/49
Gamez J [4]	2022	Spain	Prospective observational study	91	36/55
Ishizuchi K [5]	2022	Japan	Observational study	343	119/224
Li HY [6]	2022	China	Observational study	107	54/53
Lotan I [7]	2022	Israel	Observational study	55	35/20
Lupica A [8]	2022	Italy	Observational study	90	43/47
Pincheira AU [12]	2022	Canada	Observational study	200	103/97
Reyes-Leiva D [9]	2022	Spain	Prospective observational study	100	45/55
Ruan Z [10]	2021	China	A single-center case series	22	16/6
Sansone G [11]	2022	Italy	Retrospective study	80	41/39
Trinchillo, A [1]	2023	Italy	Retrospective study	113	60/53

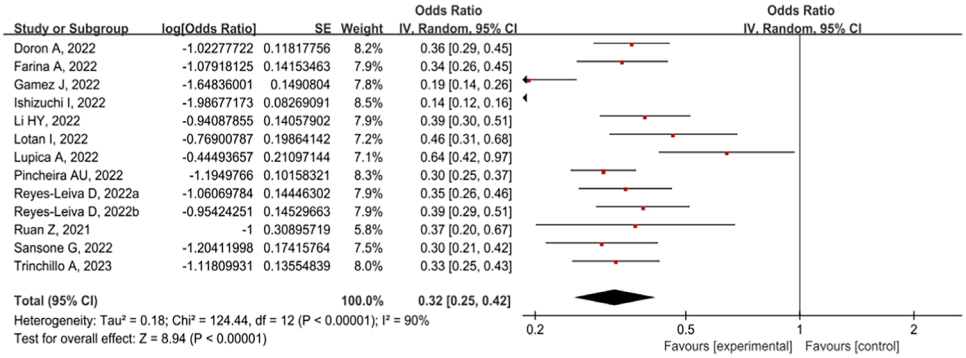

Fig. 1 Worsening MG after SARS-CoV-2 vaccination in MG patients

MG worsening after COVID-19 vaccination in AchR$^+$ vs. MuSK$^+$ groups based on six studies was 0.29 (95% CI, 0.10 to 0.69, $P < 0.05$) (Fig. 2B). The overall OR for MG worsening after COVID-19 vaccination based on eight studies was 0.29 (95% CI, 0.25 to 0.33, $P < 0.001$) (Fig. 2C). The OR for the first dose of the vaccine was 0.27 (95% CI, 0.20 to 0.38, $P < 0.001$), the second dose was 0.29 (95% CI, 0.25 to 0.34, $P < 0.001$), and the third dose was 0.30 (95% CI, 0.25 to 0.35, $P < 0.001$). These results suggested that a small number of MG patients who received the COVID-19 vaccine had a transient worsening MG. The MG worsening rate in MG patients with MuSK$^+$ was significantly higher than in MG patients with AchR$^+$. There was no significant difference in the MG worsening rate after COVID-19 vaccination between genders and different doses of vaccine.

The results from seven studies showed that the overall OR for adverse events after COVID-19 vaccination in MG patients was 0.67 (95% CI, 0.56 to 0.79, $P < 0.001$). The OR of the first dose vaccine was 0.65 (95% CI, 0.47 to 0.91, $P = 0.01$), the second dose vaccine was 0.71 (95% CI, 0.56 to 0.91, $P = 0.007$), and the third dose vaccine was 0.58 (95% CI, 0.47 to 0.72, $P < 0.001$) (Fig. 3). The

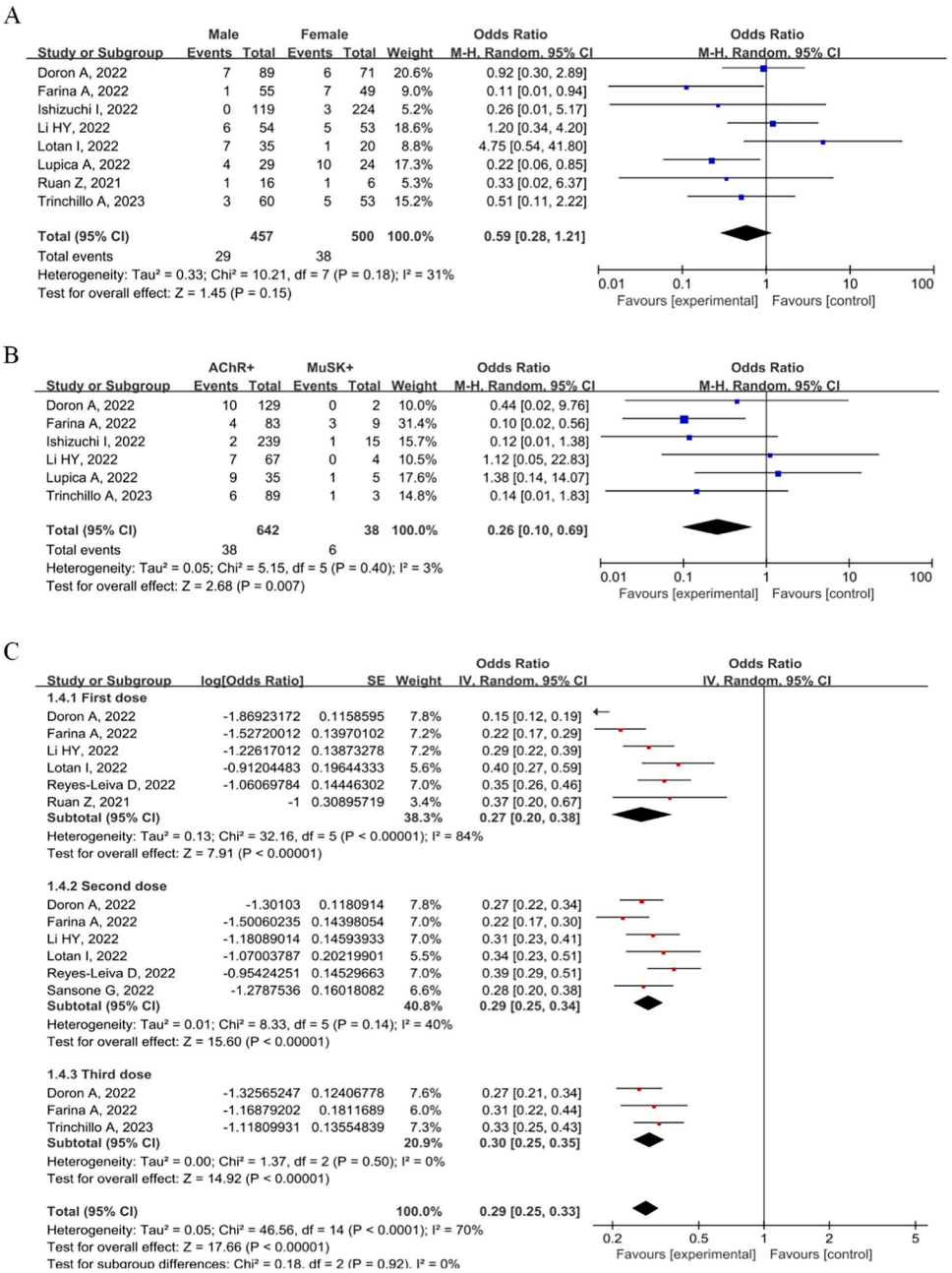

Fig. 2 Worsening MG after SARS-CoV-2 vaccination in MG patients subtyped for gender (**A**), antibody positive (**B**), and dose of vaccine (**C**)

subgroup analysis did not show any significant differences within subgroups based on the dose of vaccine.

In conclusion, the results of our meta-analysis showed that few MG patients who received the SARS-CoV-2 vaccines experienced a transient worsening MG. The worsening MG rate in MG patients with MuSK$^+$ was significantly higher than in MG patients with AchR$^+$. Anti-MuSK-ab positivity is an independent risk factor for disease deterioration and is associated with poor outcome of myasthenic crisis [13]. In addition, the MuSK-MG subtype

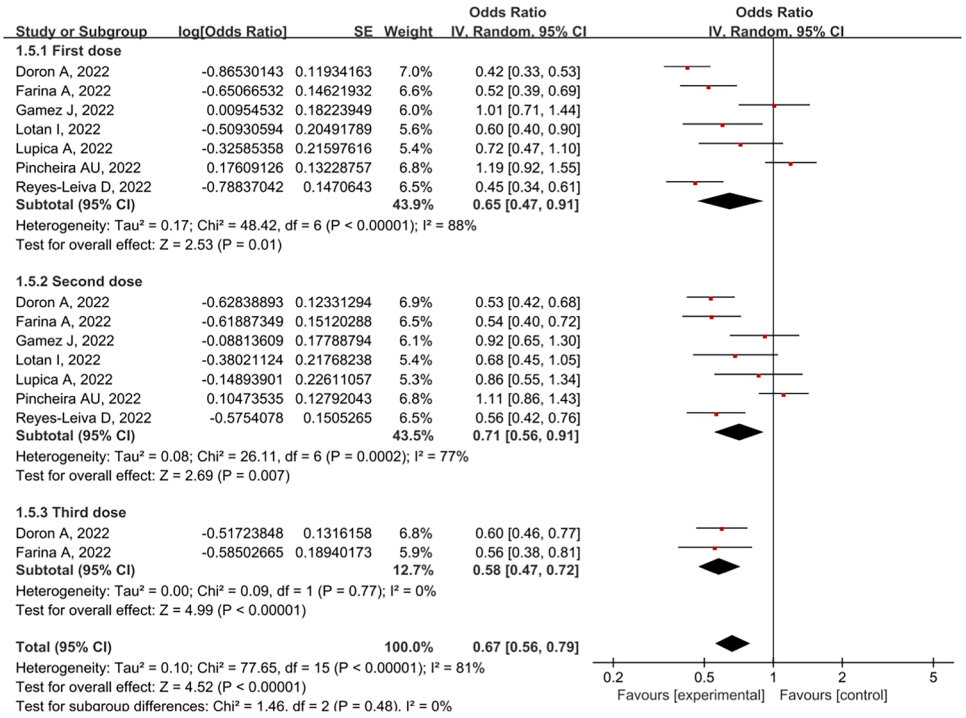

Fig. 3 Adverse events after SARS-CoV-2 vaccination in MG patients subtyped for dose of vaccine

is deficient in both central and peripheral B-cell tolerance checkpoints, where the major role appears to be played by plasmablasts [14]. The COVID-19 vaccine could stimulate circulating autoreactive B cells and make MuSK-MG patients more susceptible. The SARS-CoV-2 vaccines are relatively safe for MG patients. Therefore, we encouraged patients with well-controlled MG vaccinated SARS-CoV-2 vaccine, unless there was a specific contraindication.

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Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval and Informed consent None.

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