


Advanced Liver Fibrosis Correlates With Impaired Efficacy of Pfizer-BioNTech COVID-19 Vaccine in Medical Employees

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The Pfizer-BioNTech coronavirus disease 2019 (COVID-19) vaccine has been offered to nonallergic ≥ 16 -year-old Israeli adults since December 19, 2020. Data regarding factors associated with vaccine ineffectiveness are limited. The aim of this study is to assess the impact of hepatic fibrosis on the efficacy of the BioNTech vaccine. Serum severe acute respiratory syndrome coronavirus 2 spike immunoglobulins (S IgG) obtained at least 7 days following vaccination completion was correlated with the prevaccine calculated Fibrosis-4 (FIB-4) score among 719 employees in the Hadassah Medical Center, Jerusalem. Positive vaccine response (S IgG levels ≥ 19 AU/mL) was found in 708 of 719 individuals (98.5%). Vaccine failure (S IgG levels < 19) was found in 11 (1.5%); of these, 7 were immunosuppressed. Mean FIB-4 available in 501 of 708 vaccine responders was 1.13 ± 0.66 , mean age 51.4 ± 12.4 years (29.3% males), and mean S IgG titers 239.7 ± 86.1 AU/mL. Similar to the general population, 70.5% had normal FIB-4 (< 1.3), 26.8% undetermined FIB-4 (1.3–2.67), and 2.7% advanced FIB-4 (> 2.67). When divided into response subgroups, 158 of 501 individuals (30.1%) with IgG titers 19–100 AU/mL had a mean FIB-4 of 1.48 ± 0.82 ; 198 (39.5%) with IgG titers 101–200 AU/mL had mean FIB-4 of 1.22 ± 0.76 ; 83 (16.6%) with titers 201–300 AU/mL had mean FIB-4 of 1.04 ± 0.48 ; 38 (7.6%) individuals with IgG titers 301–400 AU/ml had a mean FIB-4 of 1.08 ± 0.63 ; and 121 (24.2%) with IgG titers > 400 AU/mL had mean FIB-4 of 1.18 ± 0.87 . Increased FIB-4, age, and male gender significantly correlated with lower postvaccine IgG titers ($P < 0.001$). FIB-4 results were confirmed using FibroScan data displaying advanced fibrosis impact on weakened COVID-19 vaccine response. **Conclusion:** Immune suppression, older age, male gender, and advanced chronic liver disease are risk factors for lower vaccine response. The FIB-4 provides a simple tool to prioritize candidates for third-dose vaccine booster. (*Hepatology Communications* 2022;6:1278–1288).

Coronavirus disease 2019 (COVID-19) affected over 100 million people globally, with 2,500,000 deaths⁽¹⁾ since it was declared a pandemic by the World Health Organization (WHO) on March 11, 2020.⁽²⁾ Older adults, persons with certain coexisting conditions, and front-line workers are at the highest risk for COVID-19 and its complications. Recent data show increasing rates of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and

COVID-19 in other populations, including younger adults.⁽³⁾ Health organizations, such as the WHO,⁽⁴⁾ emphasized the essential role and need for safe and effective prophylactic vaccines to contain the pandemic. The statement led to the development of 150 vaccination projects.⁽⁵⁾

Several vaccine candidates to protect against SARS-CoV-2 infection or COVID-19 have entered or will soon enter large-scale, phase 3, placebo-controlled

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; COVID-19, coronavirus disease 2019; FIB-4, Fibrosis-4; HMO, Hadassah Medical Organization; IgG, immunoglobulin; S IgG, spike IgG; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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randomized clinical trials.⁽⁶⁾ On December 11, 2020, the U.S. Food and Drug Administration (FDA) issued an Emergency Use Authorization for the Pfizer-BioNTech COVID-19 (BNT162b2) vaccine (Pfizer, Inc., Philadelphia, PA). The vaccine consists of a lipid nanoparticle-formulated, nucleoside-modified messenger RNA (mRNA) vaccine encoding the prefusion-stabilized, membrane-anchored SARS-CoV-2 full-length spike glycoprotein of COVID-19.⁽⁷⁾ Vaccination with the Pfizer-BioNTech COVID-19 vaccine consists of delivering two doses (30 µg, 0.3 mL each) administered intramuscularly, 3 weeks apart. The vaccine has shown high efficacy in clinical and real-world data.⁽⁸⁾ The two-dose regimen of BNT162b2 conferred 95% protection against COVID-19 occurrence in persons 16 years of age or older. Safety over a median of 2 months was similar to that of other viral vaccines.⁽⁹⁾ In Israel, one of the first countries that started a vaccination program,⁽¹⁰⁾ more than 97% of the eligible population (above the age of 16 years; COVID-19-naïve subjects) received at least one dose of the vaccine, and 94% of them completed both doses by the end of May 2021.⁽¹¹⁾ The Israeli nationwide mass vaccination setting suggests that the BNT162b2 mRNA vaccine is effective for a wide range of COVID-19-related outcomes, a finding consistent with that of the randomized trial.⁽¹²⁾

Although vaccine efficacy is defined as protection from COVID-19 occurrence and not serologic response, it is commonly accepted that failure cases do not achieve a serologic response. Estimating vaccine efficacy by measuring serum antibody levels has been used in many historic non-COVID-19 vaccines.⁽¹³⁾ Furthermore, the serologic assessment was validated in SARS-CoV-2 vaccines.⁽¹⁴⁾ In a large medical center study in Israel, hospital workers who were vaccinated and had a breakthrough infection had lower serum antibody levels than

matched controls who were not infected.⁽¹⁵⁾ Hence, serologic evaluation in a high-risk population for vaccine failure might serve as a biomarker for a future strategy. Serologic failures should keep strict protection against SARS-CoV-2; in this case, a boost of the same vaccine, or an alternative vaccine, should be considered. Thus, it is imperative to define the high-risk population to establish a future strategy of postvaccine serologic surveillance.

Studies regarding other historical vaccines have shown that several factors are associated with vaccine effectiveness.⁽¹⁶⁾ These include intrinsic host factors (e.g., age, gender, comorbidities) and extrinsic factors (e.g., preexisting immunity, microbiota, infections, antibiotics, genetics). Patients with severe liver disease have a lower response rate to vaccines.⁽¹⁷⁾ For example, patients with liver disease or chronic hepatitis C were shown to have less seroconversion following one dose of the hepatitis A vaccine than healthy controls.⁽¹⁸⁾ Furthermore, patients who suffer from chronic hepatitis B had lower geometric mean titers than healthy controls 24 weeks after a hepatitis A vaccine.⁽¹⁹⁾ This study aims to allocate possible hepatic risk factors, as liver health is widely correlated with COVID-19 infection and severity, and on the other hand, correlated with historical vaccine failure. The Fibrosis-4 (FIB-4) score correlated with liver fibrosis and was endorsed by different organizations as a biomarker for decision-making processes.⁽²⁰⁾ In addition, the FibroScan-AST score has been shown to identify liver steatosis and fibrosis effectively.⁽²¹⁾ In the current study, we analyzed in a population of hospital employees the association between vaccine ineffectiveness, as measured by low antibody titers, and liver fibrosis using the FIB-4 score. In addition, data collected from patients with nonalcoholic fatty liver (NAFLD) underwent FibroScan and vaccinated twice for BNT162b2 vaccine. Association between liver injury by FibroScan and anti-S serum levels were evaluated.

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Patients and Methods

This study is a retrospective, single-center study of Hadassah Medical Organization (HMO) employees. HMO is the largest hospital in the Jerusalem area. HMO's personnel receive medical care and are entitled to do all of their blood tests and medical procedures in the hospital.

The Pfizer-BioNTech COVID-19 vaccine program started in Israel free of charge on December 19, 2020. Those who completed both vaccine shots got a "Green Pass" certificate via a smartphone application that belongs to the health ministry. However, serologic efficacy, determined by measuring the SARS-CoV-2 spike immunoglobulins (S IgG), was not recommended and was even blocked for routine use by reimbursed services due to cost-benefit considerations. As part of the national vaccine program, HMO workers started receiving the Pfizer-BioNTech COVID-19 vaccine on December 20, 2020. The HMO administration actively encouraged all employees to get the vaccine, and most of them were vaccinated in the HMO or other public channels. By the end of April 2021, almost 99% of the approximate 6,000 HMO employees were vaccinated. As the S IgG test was offered free of charge to HMO employees, some underwent the evaluation after vaccination off-protocol.

The HMO Information Technology System retrieved data regarding HMO workers who received the vaccine and later tested for SARS-CoV-2 S IgG. S IgG was measured using the DiaSorin's LIAISON kit.⁽²²⁾ In this kit, serum S IgG levels of ≥ 19 AU/mL are considered positive for past exposure to SARS-CoV-2 or positive vaccine response. Conversely, serum S IgG levels of < 12 AU/mL are considered negative for past SARS-CoV-2 exposure and vaccine failure; equivocal response refers to serum S IgG levels ≥ 12 and < 19 AU/mL. The S IgG DiaSorin's LIAISON kit ranged from undetectability and increasing titers up to 400 AU/mL, then > 400 AU/mL. Because the routine hospital service did not perform dilutions, each > 400 AU/mL result was recorded as 401 AU/mL.

The HMO Information Technology System retrieved data including the employee's age, gender, and prevaccine blood tests, including aspartate aminotransferase (AST), alanine transaminase (ALT), and platelet count.

All HMO Information Technology System data documented the exact timing (date, hour, and minutes) of all vaccine doses and blood tests (S IgG, ALT, AST, and platelet count). This high-resolution documentation enabled exact calculations, particularly the intervals between the second vaccine dose and the S IgG test. Employee data were anonymous and were not known to the researchers.

To confirm our results, a retrospective FibroScan pilot was completed within available 76 vaccinated patients with known fatty liver disease and postvaccine S IgG assessment. The association of elastography readings with serum anti-S antibody levels was analyzed.

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the local HMO Ethics Committee (Trial registration number: 1000-20-HMO). The local ethical committee waived informed consent, as the vaccine administered was standard-of-care practice. All authors had access to the study coded data (without personal details) and reviewed and approved the final manuscript.

STATISTICAL ANALYSIS

For descriptive analysis, we used counts and percentages for categorical variables. Continuous variables were summarized as means and SDs. A t-test was used to compare means of continuous variables. FIB-4 score was calculated using the following formula: $\text{age (years)} \times \text{AST [U/L]} / (\text{platelets [109/L]} \times \sqrt{\text{ALT [U/L]}})$. Linear regression models were constructed to analyze the correlation of FIB-4 scores and S IgG levels and FibroScan elastography scores with serum anti-S IgG levels. Statistical analysis was performed using R software (R Development Core Team, 2018, PBC, Boston, MA). A *P* value of less than 0.05 was considered statistically significant in all analyses.

Results

From the approximate 6,000 vaccinated HMO employees, postvaccination SARS-CoV-2 S IgG was tested off-protocol in 1,490 individuals in the HMO laboratories. Sixty-five were excluded, as only one dose was documented in the HMO systems.

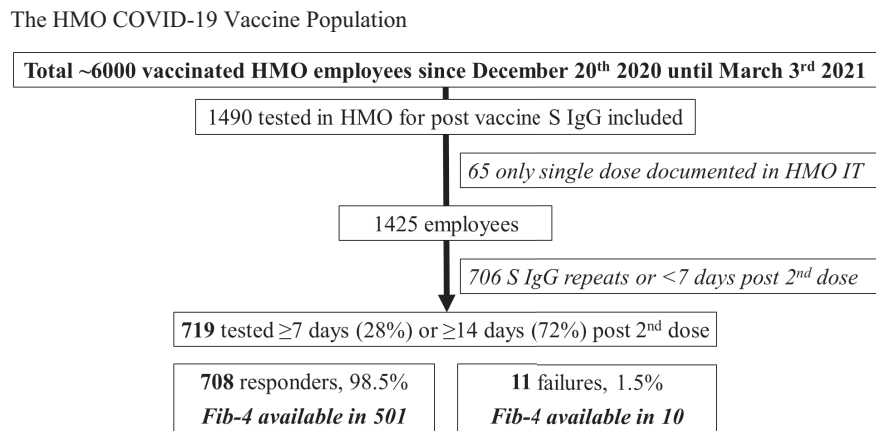


FIG. 1. Flowchart of the study cohorts of HMO workers vaccinated with Pfizer-BioNTech COVID-19 vaccine.

Of the remaining 1,425 employees, 706 cases were excluded because they were tested for S IgG repeatedly or earlier than the recommended 7 days after the second vaccination. After these exclusions, 719 employees were tested for S IgG at least 7-14 days (28% of the cases) or >14 days (72.4%) after completion of both vaccination doses (Fig. 1). The average interval between the second vaccine dose and the S IgG test was 19.77 ± 8.67 days, ranging between 7 and 51 days. The average interval between both vaccine doses was 21.08 ± 0.73 days, ranging from 20.53 to 28.14 days. The average age was 46.8 ± 14 years, with S IgG mean serum levels of 380.6 ± 14 AU/mL.

Vaccine response, defined as serum S IgG levels ≥ 19 AU/mL, was found in 708 of 719 individuals (98.5%). Combination of vaccine failure and equivocal response defined as S IgG levels < 19 AU/mL was observed in 11 (1.5%) cases (Fig. 2A,B). Of the 11 subjects, 7 were immunosuppressed: Two cases were after kidney transplantation (one of them experienced severe COVID-19 infection 6 weeks after vaccine completion), two cases had an active lymphoma undergoing chemotherapy treatment, two individuals had rheumatoid arthritis, and one had multiple sclerosis and was treated with steroids and biologic therapies. Furthermore, 4 of 11 cases had an advanced metabolic syndrome. The average FIB-4 among the nonresponders was 1.43 ± 0.5 .

Simultaneous data of ALT and AST serum levels and platelet count that enable FIB-4 calculation were available in 511 of 719 vaccine responders (71%). The

mean serum ALT levels were 22.23 ± 14.05 U/L, ranging from 5 to 125 U/L; elevated levels (reference 10-49 U/L) were found in 4.1% of vaccine responders. The mean serum AST levels were 23.20 ± 10.92 U/L, ranging from 7 to 94 U/L; elevated levels (reference 0-34 U/L) were seen in 9.4% of cases. Mean serum platelet counts were 252.13 ± 63.78 per μL , ranging from 111 to 515 per μL . Elevated levels above 445 per μL were observed in 1.2%, and levels below 150 per cubic milliliter in 2.7%. Of the 511 cases with available data for FIB-4 analysis, serological vaccine response was found in 501 and failure in 10 cases. The mean calculated FIB-4 was 1.13 ± 0.66 , mean age 51.5 ± 12.4 years (29.7% males, mean S IgG titers 235.2 ± 91.1 AU/mL). FIB-4 analyses (Fig. 2C, Table 1) revealed that 70.5% of the study population ($n = 360$, 26.9% males) had a normal FIB-4 score (< 1.3) (mean age 48 ± 11.3 years, and mean S IgG 245.2 ± 85.3 AU/mL). Undetermined FIB-4 score (1.3-2.67) score was found in 26.8% ($n = 137$, 36.5% males, mean age 59.6 ± 10.4 years, and mean S IgG 209.7 ± 97.5 AU/mL). However, only 2.7% ($n = 14$, 35.7% males) had an elevated FIB-4 score (> 2.67) (mean age 63.5 ± 13.9 years and mean S IgG of 227.2 ± 124.1 AU/mL). Individuals with abnormal FIB-4 score (≥ 1.3) were older ($P < 0.0001$), with male predominance ($P = 0.02$), and had lower mean S IgG ($P < 0.0001$) levels when compared with the FIB-4 score in the healthy population (< 1.3) (Table 1).

When dividing 501 responders into subgroups according to S IgG titers (Table 2), 158 of 501 individuals (30.1%) had S IgG titers of 19-100 AU/mL

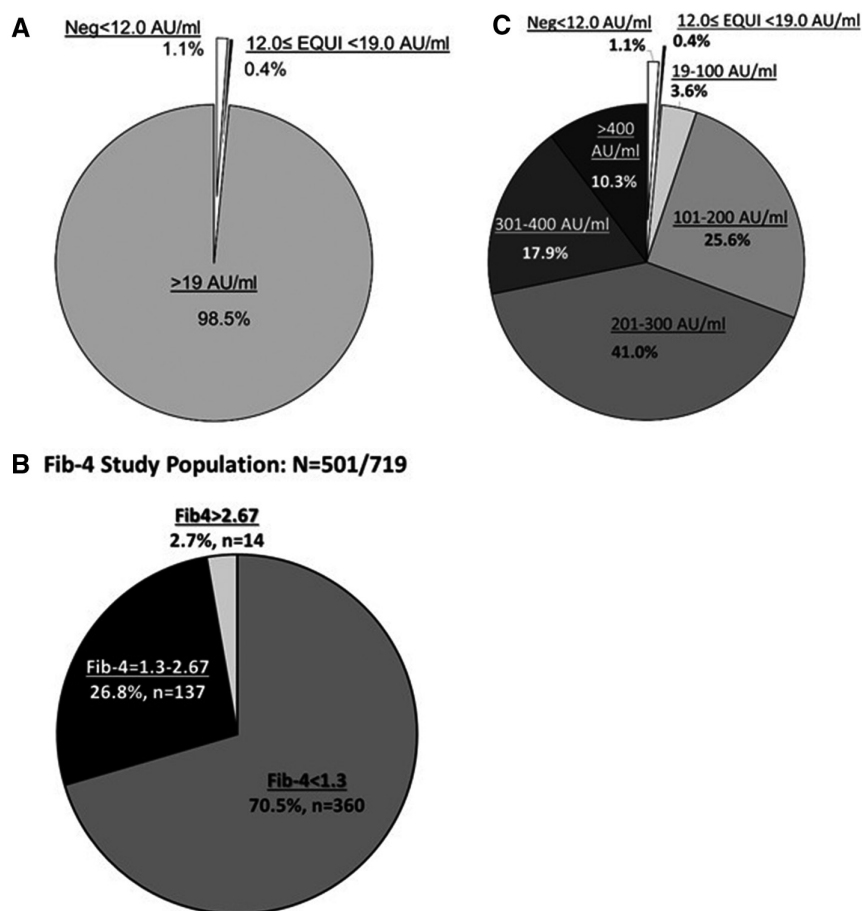


FIG. 2. Distribution of S IgG serum titers. (A) Proportion of serum S IgG. Levels ≥ 19 AU/mL are considered vaccine success; levels < 19 AU/mL are vaccine failure, although levels 12-19 AU/mL are defined by the kit as Equivocal (EQUI). (B) Pie chart distribution of proportion of serum S IgG levels. (C) FIB-4 score distribution among 501 hospital employees who had previous laboratory results (to calculate FIB-4 score).

(age 61 ± 10.4 years, 50% males, and mean FIB-4 of 1.48 ± 0.82); 198 individuals (39.5%) had titers of 101-200 AU/mL (age 54 ± 12.6 years, 32.9% males, and a mean FIB-4 of 1.22 ± 0.76); 83 individuals (16.6%) had titers of 201-300 AU/mL (age 50.2 ± 11.6 years, 32.8% males, and a mean FIB-4 of 1.04 ± 0.48); 38 individuals (7.6%) had S IgG titers of 301-400 AU/mL (age 48.7 ± 11.8 years, 13.3% males, and mean FIB-4 1.08 ± 0.63); 121 individuals (24.2%) had titers > 400 AU/mL (age 46.3 ± 12.5 years, 18.4% males, and mean FIB-4 1.18 ± 0.87). **Figures 3** and **4** show that lower vaccine titers are significantly correlated with male predominance ($P < 0.05$; **Fig. 3**), increased age ($P < 0.001$; **Fig. 4**), and increased FIB-4 ($P < 0.05$; **Fig. 5A-C**). **Figure 5C** shows the statistically significant linear correlation between

high FIB-4 scores and low S IgG serum titers (P value = 0.004).

To further confirm our FIB-4 results, we conducted a FibroScan pilot within 76 random patients with NAFLD vaccinated with the same vaccine. The study group included 31 patients who achieved anti-S levels < 200 AU/mL versus 45 cases with anti-S ≥ 200 AU/mL. The mean age was 56.7 ± 13.4 years (58.1 ± 12.7 vs. 50.9 ± 14.6 in both response groups, respectively; $P = 0.001$); mean BMI was 30.5 ± 5.2 (30 ± 5.6 vs. 30.8 ± 5.1 ; $P = 0.2$); 48.7% were males (48.4 vs. 48.9; $P = 0.4$); 51.3% were Jewish (64.5% vs. 42.2%; $P = 0.029$); 54.4% had type 2 diabetes or impaired fasting glucose (55.6% vs. 53.1; $P = 0.4$); 56.7% had hypertension (59.3% vs. 54.5%; $P = 0.36$); 18.2% were smokers (16% vs. 20%; $P = 0.3$); white blood counts

TABLE 1. MEAN AGE AND S IgG LEVELS DISTRIBUTED BY FIB-4 SCORE

	Age (years) \pm SD	Males (%)	S IgG (AU/mL) \pm SD
Total group (n = 511)	51.5 \pm 12.4	29.7%	235.2 \pm 91.1
FIB-4 < 1.3 (n = 360)	48.0 \pm 11.3	26.9%	245.2 \pm 85.3
FIB-4 = 1.3-2.67 (n = 137)	59.6 \pm 10.4	36.5%	209.7 \pm 97.5
FIB-4 > 2.67 (n = 14)	63.5 \pm 13.9	35.7%	227.2 \pm 124.1
FIB-4 \geq 1.3 (n = 151)	60.0 \pm 10.8	36.4%	211.3 \pm 99.9
<i>P</i> (normal vs. abnormal FIB-4)	0.0000	0.0162	0.0001

TABLE 2. MEAN AGE, SEX, AND MEAN FIB-4 SCORE DISTRIBUTED BY S IgG LEVELS

S IgG (AU/mL) in 501 Responders	Age (years) \pm SD	Male (%)	FIB-4 \pm SD
19-100 (n = 158, 30.1%)	61 \pm 10.4	50%	1.48 \pm 0.82
101-200 (n = 198, 39.5%)	54 \pm 12.6	32.9%	1.22 \pm 0.76
201-300 (n = 83, 16.6%)	50.2 \pm 11.6	32.8%	1.04 \pm 0.48
301-400 (n = 38, 7.6%)	48.7 \pm 11.8	13.3%	1.08 \pm 0.63
>400 (n = 121, 24.2%)	46.3 \pm 12.5	18.4%	1.18 \pm 0.87
<i>P</i> (low vs. high titers)	<0.001	<0.001	<0.001

were 6.5 ± 2 K/uL (6.2 ± 1.7 vs. 6.8 ± 2.2 ; $P = 0.1$); hemoglobin level was 13.6 ± 1.7 g/dL (13.8 ± 1.6 vs. 13.5 ± 1.7 ; $P = 0.2$); platelet count was $215.2 \pm 100.2 \times 10^9/L$ (205.5 ± 94.5 vs. 222.4 ± 104.9 ; $P = 0.2$); international normalized ratio was 1.1 ± 0.2 (1.1 ± 0.1 vs. 1.1 ± 0.2 ; $P = 0.3$); and ALT level was 45.8 ± 30.9 U/L (52.1 ± 38.3 vs. 41.1 ± 23.2 ; $P = 0.07$). Serum AST, gamma-glutamyltransferase, alkaline phosphatase, and bilirubin were similar.

Figure 6 shows the percentage of cases with either anti-S levels < 200 AU/mL (black bars) or with anti-S \geq 200 AU/mL according to different elastography thresholds shown in x-axis. *P* value shown below each elastography threshold indicates that significant differences started from the threshold >6 kPa and above. In those high fibrosis ranges, the proportion of strong response significantly decreased.

Discussion

On December 12, 2020, the Advisory Committee on Immunization Practices issued an interim recommendation for using the Pfizer-BioNTech COVID-19 vaccine in persons aged ≥ 16 years to prevent COVID-19.⁽²³⁾ Regulatory approval of a SARS-CoV-2 vaccine requires demonstration of safety and clinical benefit in a placebo-controlled efficacy trial. The FDA guidance indicates that acceptable primary endpoints for approval could include SARS-CoV-2 infection, symptomatic COVID-19 disease, severe COVID-19,⁽²⁴⁾ or some combination of these. From a public health perspective and an individual perspective, prevention of severe COVID-19 is perhaps the most crucial clinical benefit expected from an effective vaccine. Many vaccines have greater efficacy against severe disease than against a milder disease (such as for dengue, influenza, pertussis, pneumococcal bacteremia, rotavirus, and varicella).⁽²⁵⁾ However, serologic assays have been developed and validated to accurately detect anti-SARS-CoV-2 nucleocapsid antibodies, which would be elicited by naturally acquired infection but not by a SARS-CoV-2 spike protein-based vaccination.⁽²⁶⁾ Letizia et al.⁽²⁷⁾ showed that subjects with higher serum following disease S IgG titers were less likely to have a subsequent infection. In addition, Bergwerk et al.⁽¹⁵⁾ showed a similar phenomenon among vaccinated individuals. Thus, a serology-based assay is a reliable surrogate for the evaluation of vaccine efficacy.

The high efficacy of the Pfizer-BioNTech vaccine has been demonstrated in a controlled study and big real-world data.^(8,9) However, studies that attempt to find risk factors for vaccine ineffectiveness are scarce. For instance, several studies linked serum IgG levels in elderly persons with B-cell immune senescence⁽²⁸⁾ but did not relate the study to vaccine effects. Multiple factors may also contribute to these immune activity changes. T cells have been shown to participate in immune senescence. However, the role of B cells in this respect remains unclear. Recent findings illustrate conspicuous shifts in B-cell subsets in the elderly, suggesting that age-related changes in B cells may contribute to immune senescence.^(28,29) The discovery of a subset of B cells, termed age-associated B cells, has drawn significant attention in recent years. Moreover, steroids such as Prednisone treatment inhibit the differentiation of B lymphocytes into plasma cells in a

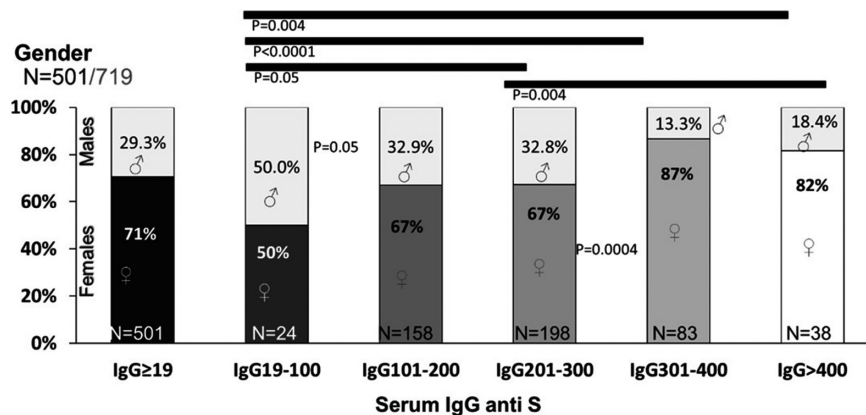


FIG. 3. Proportion of gender in groups divided by serum S IgG levels.

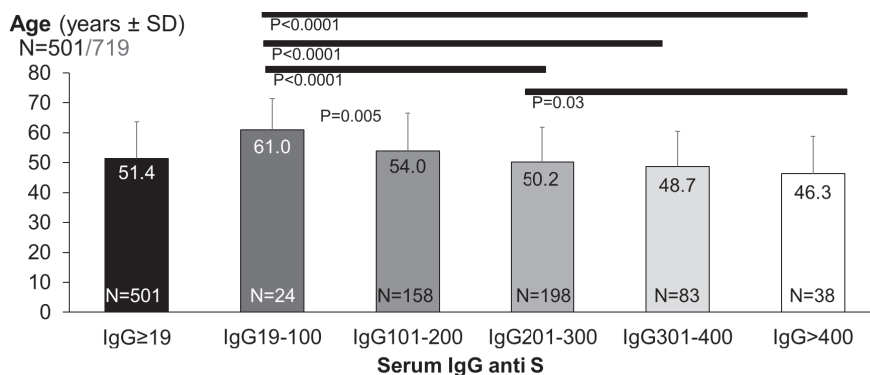


FIG. 4. Mean age in groups divided by serum S IgG levels.

mice model of autoimmune disease.⁽³⁰⁾ While the gold standard for vaccine ineffectiveness becomes evident when a patient vaccinated gets infected with SARS-CoV-2, antibody titers can be a good marker for patients with lower vaccine response. As the postvaccine screening for antibody titers is not cost-effective, identifying populations for high-risk vaccine failure will make the postvaccine surveillance for antibody titers more cost-effective.

The current study is a retrospective real-world experience of the HMO employees. Although our target population was only 511 individuals with available FIB-4 data, the entire group of 719 employees gives us further information regarding vaccine efficacy. We show high serologic efficacy of 98.5% in only 1 of 719 cases (0.01%) of postvaccination COVID-19 infection in a kidney transplant recipient. Although

allergic reactions were observed following the first dose, significant adverse events were not recorded in the excluded 65 subjects who received only one documented dose. These individuals obtained the second vaccination dose via other public channels and submitted their Green Pass certificate to HMO human resources. A serologic vaccine response, defined as serum S IgG levels ≥ 19 AU/mL, was found in 708 of 719 individuals (98.5%). This high efficacy is consistent with published data and supported the 7-day cut-off as an ideal timepoint to assess efficacy. Serological vaccine failure or equivocal response, defined as S IgG levels < 19 AU/mL, was observed in 11 (1.5%) cases, suggesting immunosuppression (in 7 of 11 cases) as the leading cause for failure.

The 2.7% cases with advanced fibrosis (FIB-4 > 2.67) were occult cirrhosis cases. Increased

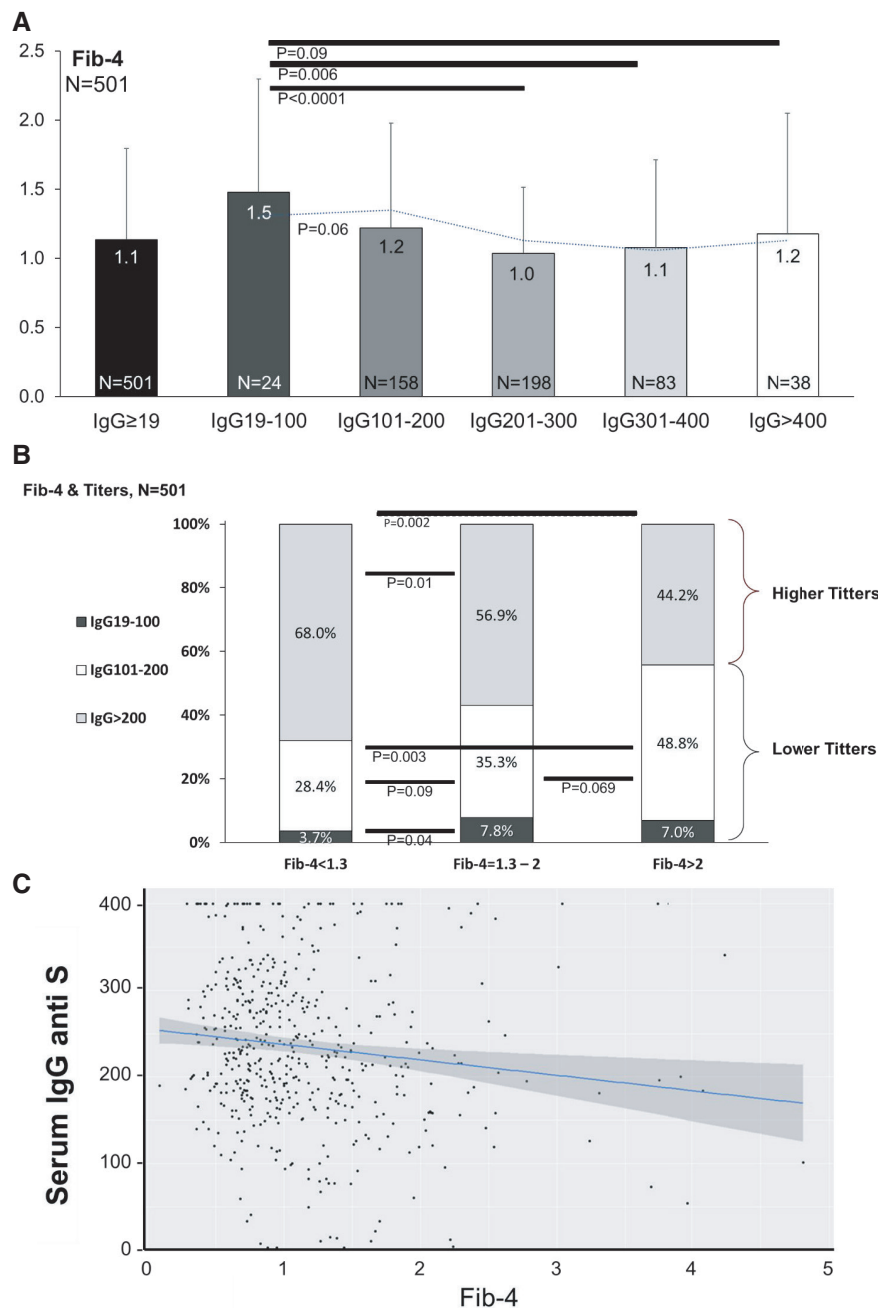


FIG. 5. (A) Mean FIB-4 in each group of serum S IgG levels. (B) Proportion of S IgG levels by FIB-4 score. (C) Linear regression model showing a negative correlation between S IgG levels and FIB-4 score.

FIB-4 in those cases derived from older age and low platelet count, suggesting advanced fibrosis. Mimicking the reported distribution in the general population, 70.5% of the study population had normal FIB-4 levels (<1.3) and were younger. Significant differences were observed in the characteristics of abnormal FIB-4 groups as compared with the

average FIB-4 population, including increased mean age ($P < 0.0001$), male predominance ($P = 0.02$), and decrease of mean S IgG ($P < 0.0001$) (Table 1). The FIB-4 score consists of age and three other serum markers. To exclude the effect of age from the association between vaccine response and fibrosis, we correlated vaccine response with a modified FIB-4

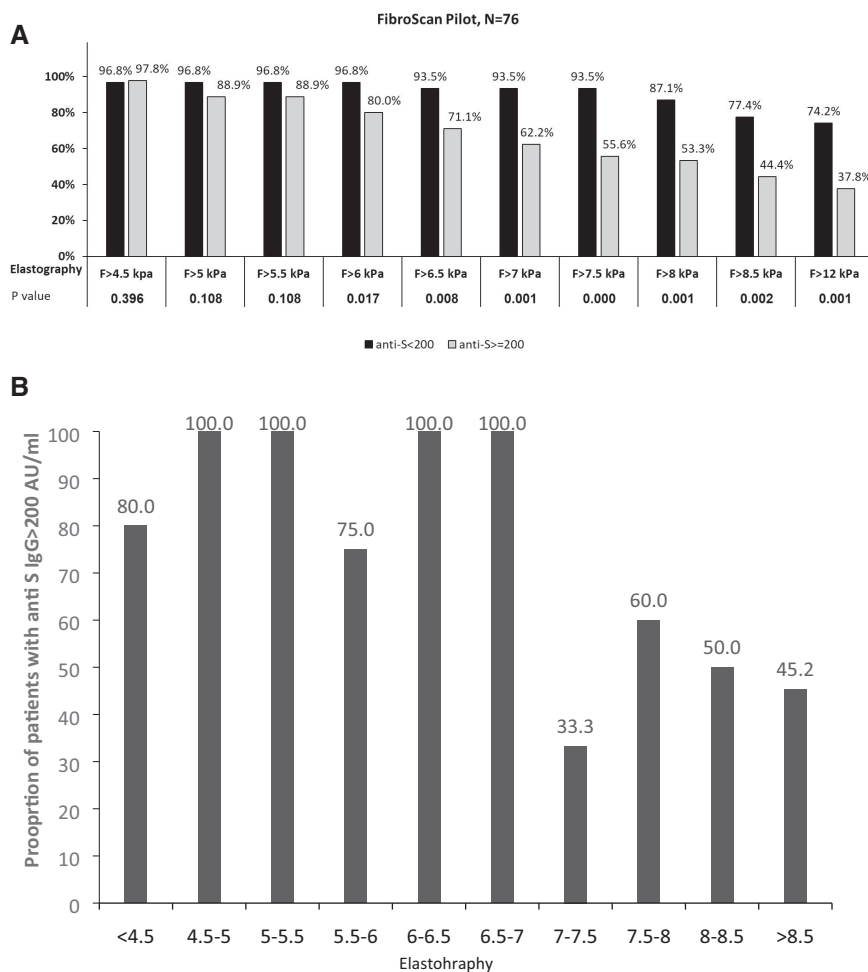


FIG. 6. (A) Patients with serum S IgG levels > 200 AU/mL versus patients with serum S IgG levels < 200 by FibroScan elastography levels. (B) Proportion of patients with serum S IgG > 200 Au/mL by FibroScan elastography levels.

score (AST/PLT * \sqrt{ALT}) that lacks age. Yet, the modified FIB-4 kept in line with the same observation even without the age. The modified FIB-4 strongly tends to be greater (P value = 0.003) in the good response group of IgG > 200 AU/mL (Supporting Fig. S1).

Altogether, the results from this analysis suggest that young females with low fibrosis achieve better serologic responses to the Pfizer-BioNTech vaccine. An S IgG of 200 AU/mL was a statistically significant cutoff for all parameters tested. FIB-4 results were validated by FibroScan to confirm advanced fibrosis as a biomarker for weak vaccine response. Although these levels are high and represent an immune response to the vaccine, it should be noted that only part of these

antibodies are neutralizing antibodies⁽³⁰⁾ and thus can be associated with increased risk of infection.⁽¹⁵⁾ As serum SARS COV-2 antibodies decline over time,⁽³¹⁾ a need for a booster vaccine is warranted.⁽²⁹⁾ Patients with lower vaccine response and advanced fibrosis should prioritize for booster.

However, it should be noted that data from a large health insurer in Israel showed that multiple comorbidities, but not old age, were associated with decreased vaccine effectiveness.⁽¹²⁾ This contradiction may be explained by the differences in the age of the study populations.

Our study has few limitations. We used serum IgG antibodies and not neutralizing antibodies. Neutralizing antibodies are more closely associated

with breakthrough infection for vaccinated persons.⁽¹⁵⁾ In addition, the antibody kits used do not show the exact value when serum IgG is greater than 400 AU/mL. This causes the difference between the two groups to look smaller than it probably really is.

In conclusion, we describe S IgG levels as linearly correlated with advanced fibrosis (assessed with FIB-4), in addition to age and gender. Patients with advanced liver fibrosis should be prioritized toward third dose vaccination.

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