COVID-19 Vaccination Associated With Reduced Postoperative SARS-CoV-2 Infection and Morbidity

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Objective: The purpose of this study was to determine the effect of COVID-19 vaccination on postoperative mortality, pulmonary and thrombotic complications, readmissions and hospital lengths of stay among patients undergoing surgery in the United States.

Background: While vaccination prevents COVID-19, little is known about its impact on postoperative complications.

Methods: This is a nationwide observational cohort study of all 1,255 Veterans Affairs facilities nationwide. We compared patients undergoing surgery at least 2 weeks after their second dose of the Pfizer BioNTech or Moderna vaccines, to contemporary propensity score matched controls. Primary endpoints were 30-day mortality and postoperative COVID-19 infection. Secondary endpoints were pulmonary or thrombotic complications, readmissions, and hospital lengths of stay.

Results: 30,681 patients met inclusion criteria. After matching, there were 3,104 in the vaccination group (1,903 received the Pfizer BioNTech, and 1,201 received the Moderna vaccine) and 7,438 controls. Full COVID-19 vaccination was associated with lower rates of postoperative 30-day COVID-19 infection (Incidence Rate Ratio and 95% confidence intervals, 0.09 [0.01,0.44]), pulmonary complications (0.54 [0.39, 0.72]), thrombotic complications (0.68 [0.46, 0.99]) and decreased hospital lengths of stay (0.78 [0.69, 0.89]). Complications were also low in vaccinated patients who tested COVID-19 positive before surgery but events were too few to detect a significant difference compared to controls.

Conclusion: COVID-19 vaccination is associated with lower rates of postoperative morbidity. The benefit is most pronounced among individuals who have never had a COVID-19 infection before surgery.

Keywords: COVID-19, postoperative complications, vaccines

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The sequencing of SARS-CoV-2 RNA, completion of phase-3 clinical trials for the Pfizer BioNTech and Moderna vaccines, and their delivery commencing in December 2020, is a triumph of medical science.[1,2] Of necessity, the focus of vaccine-related studies has been on the determination of their safety and efficacy in preventing primary COVID-19 infection.[1–6] Little is known about their potential to prevent the postoperative complications known to be associated with COVID-19.[7,8]

The decision to place a moratorium on non-emergency surgical procedures early in the pandemic was based on reports from China and Italy showing high rates of postoperative mortality and pulmonary complications when operating on COVID-19 positive patients.[9,10] The moratorium also preserved hospital resources for COVID-19 infection related admissions.[11] Over the course of time, there has been a gradual resumption of elective surgery. The resumption was undertaken with preoperative COVID-19 screening and delaying procedures on patients found to be COVID-19 positive, and in the setting of the beginning of SARS-CoV-2 immunization. Despite an increasing number of individuals receiving vaccinations against COVID-19, there are limited data on the impact of vaccines on postoperative complications. The Veterans Health Administration (VA) provides care to more than nine million individuals throughout the United States.[12] We analyzed information from patients receiving care at all 1255 VA facilities nationwide to assess the impact of COVID-19 vaccination on postoperative complications.

METHODS

Participants and Study Design

We conducted a multicenter retrospective study of patients who underwent a surgical procedure at any VA facility nationwide. We compared outcome measures in patients who received two doses of a COVID-19 vaccine at least two weeks before surgery, to patients who did not receive any immunization before surgery. Patients in this analysis may, or may not, have had COVID-19 before surgery. The second analysis, designed to determine if not having had the opportunity to gain natural immunity to COVID-19 affected postoperative outcomes in response to the vaccine, included only those patients who had no history of having had COVID-19 before surgery. The third analysis, designed to determine if having had the opportunity to gain natural immunity to COVID-19 affected the response to vaccine, included only those patients who had a history of having had COVID-19 before surgery. To ensure balance between comparison groups, for all three analyses, patients in the respective vaccinated groups were propensity-score matched to control patients who were not vaccinated but undergoing identical surgical procedures. We compared the following outcome measures between the two groups: 30-day mortality, postoperative COVID-19 infection, pulmonary complications, thrombotic complications, hospital readmissions, and hospital lengths of stay. The University of Maryland Institutional Review Board and the Baltimore VA Research and Development Committee reviewed and approved the study and waived the requirement for informed consent.

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Inclusion and Exclusion Criteria

Our exposure was the receipt of two doses of either the Pfizer BioNTech or Moderna vaccine at least 14 days before undergoing a surgical procedure. Centers for Disease Control and Prevention guidelines state that maximum protection against COVID-19 infection occurs 2 weeks post-vaccination.[13] Study enrollment began January 25, 2021, the date that the first patient fulfilled criteria for maximum vaccine protection and continued until March 25, 2021. Patients who did not receive the vaccine during the study period were enrolled into the control groups.

Data Collection

Information was obtained from the VA Corporate Data Warehouse which stores all data entered into the VA's electronic medical record.[14] The VA updates and continuously checks the data for accuracy in near real time. Data describing patient age, sex, race (White, Black, and other), ethnicity (Hispanic or Latino), body mass index, smoking status (current, former, or never), and the American Society of Anesthesiologists (ASA) physical status classification (I through VI) were obtained.[15] Medical comorbidities were determined by reviewing International Classification of Disease system-10 (ICD-10) codes. The pre-surgical burden of comorbidity was obtained from the Charlson Comorbidity Index (CCI), a composite score of 17 comorbidities existing during the two years before the date of surgery.[16] The five-digit Current Procedural Terminology (CPT) code describing the procedure in its entirety, case urgency (elective, urgent, or emergency), and type of anesthesia used (general or other, a composite of sedation, spinal, epidural and local) for each procedure were obtained. The organ system undergoing surgery was recorded based on the first two digits of the CPT code. Data on the presence of a positive SARS-CoV-2 PCR test in the medical record at any time point was used to determine time from first positive test to date of surgery.

Outcome Measures

Patients were followed for 30 days after the index procedure. Our co-primary outcome measures were all-cause mortality and a new positive COVID-19 RNA PCR or antigen test after surgery. Secondary outcome measures included composite pulmonary complications (pneumonia, mechanical ventilation, acute respiratory distress syndrome, or acute respiratory failure), composite thrombotic complications (deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and arterial thrombosis), hospital readmissions, and in-hospital lengths of stay. The secondary outcomes were identified by using ICD10 codes and admission, discharge, outpatient, and transfer records. ICD-10 and CPT codes were used to identify mechanical ventilation.

Statistical Analysis

We compared the demographic, clinical and procedural characteristics of the vaccination and control groups using frequencies and percentages, means and standard deviations, or medians and interquartile ranges (IQR). Comparisons of categorical data were performed using Pearson χ^2 test or Fisher Exact test when cell sizes were 5 or less. Student *t*-test was used to compare normally distributed continuous data between study groups, and the Mann-Whitney-*U* test was used for non-normally distributed continuous data.

The primary analysis compared all completely vaccinated patients undergoing surgery to all unvaccinated patients undergoing surgery; two separate secondary analyses compared vaccinated to unvaccinated patients who tested positive for COVID-19 before surgery, and who had no history of having had COVID-19 before surgery respectively. For all three analyses, we used a combination of exact and propensity score matching (propensity to have received vaccination) to create control groups that closely matched their respective vaccination groups. A separate match was performed for each of the three analyses. Patients in the control group were matched 3:1 to the vaccination group with an exact match on all five digits of the CPT code (fully defining the procedure). A greedy nearest neighbor match was performed on race, ethnicity, CCI, ASA class, smoking status, case urgency, and anesthesia type using a caliper of 0.25. The matching minimizes the standardized mean differences in propensity scores between the two groups.[7] The unadjusted primary and secondary outcome events and rates were computed for each group. Multivariable Poisson regression models adjusting for factors that were not balanced after propensity score matching in each analysis were used to determine the effect of vaccination on rates of mortality, pulmonary and thrombotic complications, readmissions and length of stay. An incidence rate ratio (IRR) with 95% confidence intervals (CI) was computed that compared each outcome measure between the groups. A two-sided α of ≤ 0.05 was considered statistically significant.

We performed two subgroup analyses. First we compared outcomes among those who tested COVID-19 positive after surgery with those who did not, in vaccinated and unvaccinated patients. Second we compared outcomes for cardiovascular, respiratory, and gastrointestinal procedures, as defined by the first two digits of CPT code in vaccinated and unvaccinated patients. In the second subgroup analysis we followed the same rubric for propensity score matching as the primary analysis and calculated the relative complication rate of vaccinated to unvaccinated controls after adjusting for age and CCI.

All statistical analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria) with the following packages- gtsummary, tableone, dplyr, and matchit.

RESULTS

A total of 30,681 patients underwent a surgical procedure during the study period of January 25 to March 25, 2021 (Fig. 1). For the primary analysis, after excluding those with missing data (n = 1,100), 3,924 patients met criteria for inclusion in the vaccination group and 25,657 met criteria for the control group. After propensity score matching, there were 3,104 patients in the vaccination group (1903 received the Pfizer BioNTech vaccine and 1,201 received the Moderna Vaccine) and 7,438 patients in the control group. Patients were well matched on sex, race and ethnicity, body mass index, smoking status, case urgency, ASA class and organ system undergoing surgery (Table 1). Vaccinated patients were older ($P < 0.001$) and had a higher CCI ($P < 0.001$) compared to controls.

In unadjusted analyses, the vaccination group had a lower rate of 30-day postoperative COVID-19 infection (0.0% vs. 0.3%) but a similar all-cause mortality rate (0.4% vs. 0.6%) compared to non-vaccinated controls (Table 2). The vaccination group had fewer pulmonary complications (1.7% vs. 3.0%), thrombotic complications (1.1% vs 1.5%) and shorter hospital lengths of stay [median (interquartile range), 2 (1, 5) vs. 2(1,6)], but similar rates of readmissions compared to controls. Multivariable models adjusted for age and CCI (Table 2) showed that the vaccination group had a lower incidence rate ratio (95% confidence intervals) of 30-day postoperative COVID-19 infection [0.09, (0.01,0.44)], pulmonary complications [0.54, (0.39–0.72)], thrombotic complications [0.68, (0.46–0.99)] and shorter hospital lengths of stay [0.78 (0.69,0.89)] compared to the control group.

The second analysis compared vaccinated and control patients who never tested COVID-19 positive before surgery. The exact CPT matching followed by propensity score matching resulted in two groups (vaccine group, n = 2876 and control group n = 6971) that were not different with respect to demographics, clinical or procedural characteristics except for age [median 72 (IQR 67,76) vs 71 (65,75), $P < 0.001$] and CCI [2 (1,4) vs 2 (1,4), $P < 0.001$] being

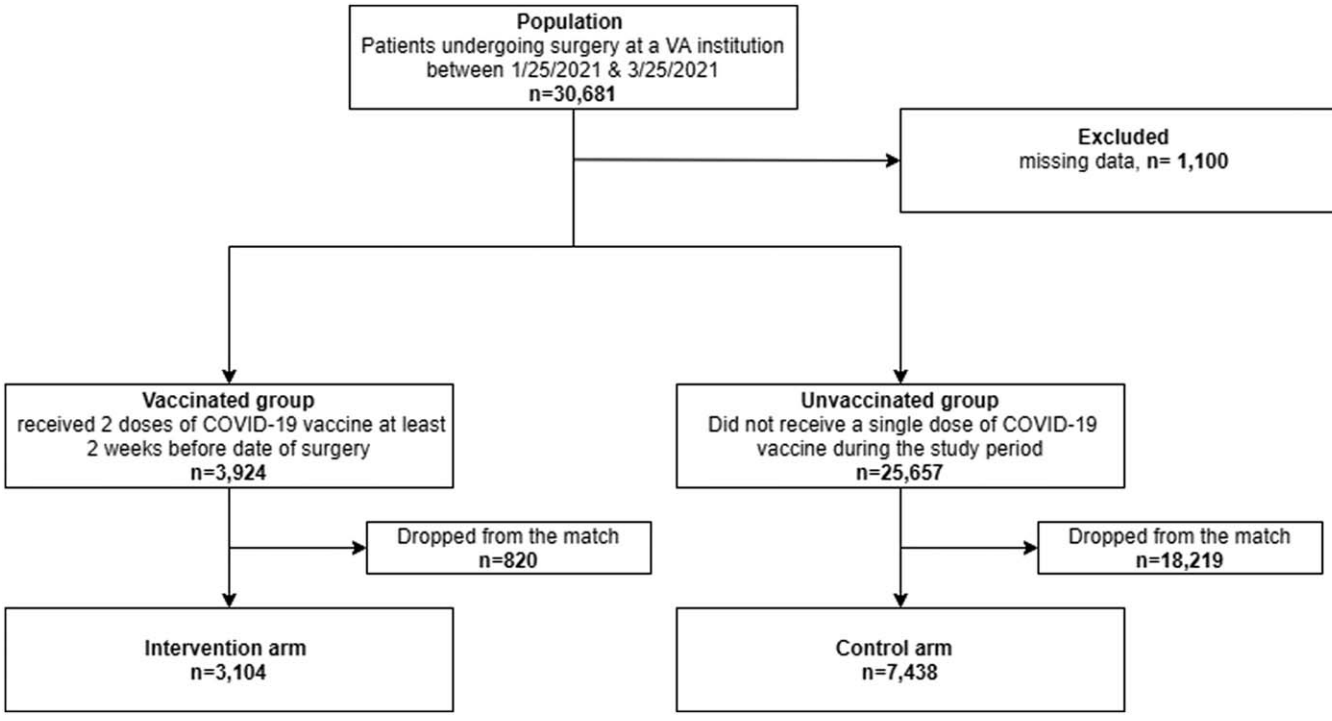

FIGURE 1. Flowchart of patients at veterans affairs hospitals undergoing surgery from January 25 to March 25 2021.

higher, and general anesthesia being used more frequently (42.6% vs 40.3%, p = 0.04) in the vaccination group compared to controls (Supplementary material, http://links.lww.com/SLA/D404). In the unadjusted analysis, vaccination was associated with fewer 30-day postoperative COVID-19 infections (0.0 vs 0.4%), pulmonary complications (1.7% vs. 2.7%) and hospital lengths of stay (median 2 [1,5] vs 2 [1,6]) (Supplementary material, http://links.lww.com/SLA/D404). In a multivariable model that adjusted for age, CCI, and anesthesia type, vaccination was associated with lower rates of postoperative COVID-19 (incidence rate ratio 0.09, 95% CI 0.00–0.40), pulmonary complications (0.57, 95% CI 0.42–0.78) and hospital lengths of stay (0.8 (0.71, 0.91)) compared to controls (Supplementary material, http://links.lww.com/SLA/D404). (vaccine group, n = 2876 and control group n = 6971)

The third analysis examined the effect of vaccine in subjects who had the opportunity to gain natural immunity to COVID-19 due to an infection with SARS-COV-2 before surgery. The exact CPT matching followed by propensity score matching resulted in two well-matched groups that demonstrated no significant differences with respect to demographics, clinical or procedural characteristics (vaccine group, n = 116 and control group n = 269, Supplementary material, http://links.lww.com/SLA/D404). The vaccination group had no deaths (n = 1 in the control group), 2 patients had pulmonary complications (n = 10 in the control group), 1 had a thrombotic complication (n = 2 in the control group) and 2 patients were readmitted (n = 11 in the control group). The median [IQR] hospital length of stay was 2 [1, 4] in the vaccinated group vs 2 [1, 4.25] in controls (Supplementary material, http://links.lww.com/SLA/D404). The event rates were too low in either group to perform reliable comparisons.

In the first subgroup analysis unvaccinated patients who developed postoperative COVID-19, when compared to vaccinated patients who did not, had higher mortality (2.5% vs. 0.6%), composite pulmonary complications (19.8% vs. 2.2%), composite thrombotic complications (6.2% vs. 1.3%), readmission rates (27.2% vs. 3.4%); and longer lengths of stay (7 vs. 2 days) (Supplementary materials, http://links.lww.com/SLA/D404). In the second subgroup analysis, vaccinated compared to unvaccinated patients undergoing cardiovascular, respiratory, and gastrointestinal procedures had lower pulmonary complication rates (0.37, 95% CI 0.24–0.55) and lower thrombotic complication rates (0.58, 0.32 -0.99) (Supplementary data, http://links.lww.com/SLA/D404).

DISCUSSION

We present the first report demonstrating the perioperative benefits of complete vaccination against COVID-19. In a comparison of two groups undergoing surgery that were matched on demographic features, comorbidities, and procedural characteristics, patients who received COVID-19 vaccination before surgery had fewer postoperative COVID-19 infections [0.0% vs. 0.3%, adjusted IRR (95% CI) 0.09 (0.01, 0.44)], pulmonary complications (1.7% vs. 3.0%, 0.54 (0.39,0.72)), thrombotic complications [1.1% vs. 1.5%, 0.68 (0.46, 0.99)] and shorter hospital lengths of stay [0.78 (0.69,0.89)]. Mortality [0.4% vs 0.6%, 0.63 (0.32, 1.13)] and readmissions [3.1% vs. 3.7%, 0.8 (0.63,1.00)] did not differ between the two groups. Patients who had never had a COVID-19 infection before surgery benefited from vaccination. While patients who tested COVID-19 positive before surgery also showed nominally fewer postoperative complications, the event rates were too low to reliably detect differences. Subgroup analyses confirmed our previous findings of elevated complications associated with postoperative COVID-19 infection[17] and reduction in pulmonary and thrombotic complications associated with vaccination was more pronounced when we restricted the cohort to patients undergoing cardiovascular, pulmonary and gastrointestinal procedures. These results are important for two reasons: 1) they demonstrate the efficacy of COVID-19 vaccine in reducing postoperative SARS-CoV-2 infections in a cohort of older adults with high

TABLE 1. Comparison of Characteristics of Vaccinated Patients Undergoing Surgery Versus Propensity Score Matched Patients Undergoing Surgery Without Prior Vaccination

	Control N = 7438(%)	Vaccine N = 3104(%)	*P*-value
Age, median (IQR), yr	71.00 [66.00, 75.00]	72.00 [67.00, 76.00]	<0.001
Sex (Male)	7007 (94.2)	2937 (94.6)	0.428
Race/ethnicity*			0.577
White	5474 (73.6)	2277 (73.4)	
Black	1470 (19.8)	634 (20.4)	
other	494 (6.6)	193 (6.2)	
Hispanic or Latino	426 (5.7)	172 (5.5)	0.741
Body Mass Index	29.84 (6.01)	29.63 (5.93)	0.103
Smoking status			0.686
Current Smoker	1101 (14.8)	441 (14.2)	
Former Smoker	3983 (53.5)	1663 (53.6)	
Never Smoker	2354 (31.6)	1000 (32.2)	
Charlson comorbidity index(median [IQR])	2.00 [1.00, 4.00]	2.00 [1.00, 4.00]	<0.001
General anesthesia	3004 (40.4)	1312 (42.3)	0.077
Case urgency			0.331
Elective	6206 (83.4)	2555 (82.3)	
Urgent	1134 (15.2)	509 (16.4)	
Emergency	98 (1.3)	40 (1.3)	
ASA Class†			0.183
I	17 (0.2)	6 (0.2)	
II	855 (11.5)	345 (11.1)	
III	5732 (77.1)	2359 (76.0)	
IV	834 (11.2)	394 (12.7)	
Organ System‡			0.084
Cardiovascular	539 (7.2)	275 (8.9)	
Gastrointestinal	1026 (13.8)	432 (13.9)	
Integumentary	353 (4.7)	156 (5.0)	
Musculoskeletal	1176 (15.8)	481 (15.5)	
Neurological	375 (5.0)	166 (5.3)	
Ophthalmological	2265 (30.5)	871 (28.1)	
Respiratory	253 (3.4)	117 (3.8)	
Urology	1318 (17.7)	544 (17.5)	

ASA indicates American Society of Anesthesiologists; CPT, current procedural terminology; FNA, fine-needle aspiration; IQR, interquartile range.

*Other includes Asian, American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander.

†ASA classes V and VI were excluded and the others were grouped due to low proportions.

‡Definition of the organ system is based on the first two digits of the CPT code. The following procedure types were excluded due to low proportions: miscellaneous, mediastinum/diaphragm, operating microscope, lymphatic, gynecological, maternity care, FNA procedures, endocrine, and auditory.

comorbidity burden, and 2) they demonstrate a reduction in COVID-19-related postoperative complications.

Ongoing clinical trials have demonstrated an efficacy of 95% for the Pfizer BioNTech vaccine and 94.1% for the Moderna vaccine for preventing COVID-19 infection.[1,2,18] Recent real-world data confirm the efficacy of the Pfizer and Moderna COVID-19 vaccines in preventing infection and have also shown effectiveness in reducing hospitalizations and mortality.[19,20] However, surgical procedures

TABLE 2. Primary and Secondary Outcomes in Vaccinated Patients Undergoing Surgery Versus Propensity Score Matched Patients Undergoing Surgery Without Prior Vaccination

	Control[a] N = 7438 N (%)	Vaccination[a] N = 3104 N (%)	IRR[b](95% CI)	*P*-value[c]
Mortality	45 (0.6)	13 (0.4)	0.63 (0.32,1.13)	0.14
COVD-19 positive after surgery	25 (0.3)	1 (0.0)	0.09 (0.01,0.44)	0.02
Composite pulmonary complications [d]	222 (3.0)	53 (1.7)	0.54 (0.39,0.72)	<0.001
Composite thrombotic complications [e]	114 (1.5)	35 (1.1)	0.68 (0.46,0.99)	0.05
Readmissions	277 (3.7)	97 (3.1)	0.8 (0.63,1.00)	0.06
Hospital length of stay [median (IQR)]	2.00 [1.00, 6.00]	2.00 [1.00, 5.00]	0.78 (0.69,0.89)	<0.001

CCI indicates Charlson Comorbidity Index; CI, confidence interval; IQR, interquartile range; IRR, incidence rate ratio.

aevent numbers and unadjusted rates.

bincidence rate ratio with Control group as Reference (1.00) in a Poisson regression model adjusting for age and CCI.

cp-value for incidence rate ratio adjusting for age and CCI.

d30-day pulmonary complications: pneumonia, mechanical ventilation, acute respiratory distress syndrome, or acute respiratory failure.

e30-day thrombotic complications: deep vein thrombosis, pulmonary embolism, myocardial infarction, ischemic stroke, and arterial thrombosis.

performed on COVID-positive patients are associated with increased 30-day mortality, postoperative pneumonia and need for unexpected mechanical ventilation.[8] The consequent broad moratorium on elective surgery during the height of the pandemic surge led to widespread disruption in hospital services across the world. Surgery is gradually being reinstated with recommendations for delaying the procedure in those that test COVID-19 positive on preoperative screening. These delays are resulting in large backlogs in elective surgery with potential delays in treatment for time-sensitive diseases such as cancers.[21] Our results demonstrate for the first time, that vaccination for COVID-19 accomplished at least 2 weeks before surgery is associated with lower rates of postoperative COVID-19 infection, pulmonary and thrombotic complications, and shorter hospital length of stay. The fact that that benefit included COVID-19 negative patients has important implications for current guidelines for surgical services. In patients that test negative on preoperative screening and are planned for non-time-sensitive elective surgery, full vaccination will likely yield the best postoperative outcomes. Time-sensitive urgent or emergency surgeries are still best served by proceeding as planned after a negative screening test for COVID-19.

Updated guidelines from the American Society of Anesthesiology recommend that elective surgery be delayed for 4 weeks in most patients with mild COVID-19 disease and up to 10 weeks for immunocompromised patients.[22] This is based on reports that the risk of perioperative complications due to COVID-19 can persist for at least 4 weeks[7] and up to 7 weeks.[23] The implicit assumption is that delaying surgery would prevent COVID-related postoperative complications. Our results did not show a significant reduction in the primary or secondary endpoints among patients with prior COVID-19 infection who underwent surgery thereafter. This is in keeping with reports that COVID infection is typically associated with generation of protective antibodies that can last up to 8 months.[24] At present there is no reliable data on how long immunity lasts after infection, and further work is needed to evaluate the long-term sequelae of COVID-19 infection. One interpretation of our findings may be that once infected and recovered from COVID-19, patients may undergo surgery without vaccination. However, our data also showed nominally fewer pulmonary complications ($n = 2$ vs. $n = 10$) and readmissions ($n = 2$ vs. $n = 11$) among vaccinated patients with prior COVID-19 infection. Our cohort for this analysis included patients who had tested positive for COVID-19 before surgery at any time since the commencement of the pandemic. More studies are needed to determine if this is the beginning of a pattern highlighting a potential for diminished immune protection from remote COVID-19 infection over time. Therefore, vaccination must not be avoided in this group of patients.

Infection with the SARS-CoV-2 virus is associated with pulmonary and extrapulmonary manifestations due to viral entry via the Angiotensin-converting enzyme 2 receptor, a target that is distributed widely throughout the body.[25] Coronaviridae are capable of mutation, producing variants that may elude existing molecular diagnostic tests, depending on the target genes or proteins being evaluated.[26] This is of sufficient concern that the United States Food and Drug Administration released an open letter on January 8, 2021 warning about the potential for false negative tests in the setting of SARS-CoV-2 viral mutation.[27] We noted a reduction in the rate of pulmonary and thrombotic complications among vaccinated individuals that is not sufficiently accounted for by the reduction in rates of postoperative COVID-19 infections alone. These data have two potential explanations. Vaccination was associated with a reduction in pulmonary and thrombotic complications attributable to SARS-CoV-2 infections that were potentially missed by available molecular testing (false negatives). However, a potential pleiotropic effect of the mRNA vaccines cannot be excluded. More experience with the vaccines will clarify these mechanisms.

We acknowledge the limitations of using administrative data combined with information from an electronic medical record. In addition, our cohort consisted of older male Veterans with comorbidity rates higher than in the general population. However, their demographic features and comorbidities represent the population at highest risk for the sequelae of COVID-19 and are therefore an ideal cohort for the analysis. It should also be noted that a large proportion of the procedures performed were outpatient and low operative risk, which may have affected the results. While the beneficial effect of vaccination appears to be consistent, the magnitude of the protective effect remains to be determined in other populations and specific procedures. It is possible that the differences in treatment effect would be smaller in younger, healthier patients. While the study was well-powered for the first two analyses, the sample size for the third analysis (preoperative COVID-positive patients) was small. The retrospective allocation of patients to intervention or control groups may have introduced bias from selection. We do not anticipate the possibility of a randomized study in the near future to test the hypotheses, therefore propensity matching along with exact matching on surgical procedure remains a reliable means of assessment. We acknowledge that the balance on matching was not perfect but were still able to adjust for the imbalance covariates (age and CCI) in a multivariable regression. Finally, the specific cause of death was not available in our dataset, limiting conclusions that can be drawn about differences in mortality rates. Overall, this study represents the first nationwide assessment of the contribution of the COVID-19 vaccines in reducing postoperative complications.

CONCLUSIONS

Complete vaccination for COVID-19 using the Pfizer or Moderna vaccines two weeks before undergoing a surgical procedure is associated with lower postoperative morbidity. This protective effect may extend to patients who have never previously tested COVID-19 positive.

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