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Short Communication

COVID-19 vaccination is associated with reduced non-COVID in-hospital mortality

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ABSTRACT

We retrieved data on a cohort of medical patients at a regional Israeli hospital. The dependent variable was non-COVID-19 hospital mortality; the independent variables were vaccination status, age, and laboratory data. Serum sodium, age, serum creatinine, and COVID-19 vaccination status were the main independent variables associated with non-COVID-19 mortality. The odds ratio for in-hospital deaths of non-vaccinated patients was 2.01 (1.65–2.44) (unadjusted) and 1.61 (1.29–2.03) after adjustment for the independent variables. This "healthy adherer effect" may confound observational assessments of the clinical efficacy of COVID-19 vaccines.

1. Introduction

In 2021, Drs Xu et al. found that the relative risk of non–COVID-19 mortality after the Pfizer-BioNTech vaccine was 0.41 (95% confidence interval [CI] = 0.38–0.44) after dose 1 and 0.34 (CI = 0.33–0.36) after dose 2; and that after the Moderna vaccine was 0.34 (CI = 0.32–0.37) after dose 1 and 0.31 (CI = 0.30–0.33) after dose 2. In other words, they found that a cohort of 4.6 million persons unvaccinated for COVID-19 had an about 3.2 higher non–COVID-19 mortality risk than did 6.4 million demographically similar vaccinees (Xu et al., 2021). The authors acknowledged that their report was limited by its failure to adjust the analyses for the baseline health status of the study populations. This limitation was partly avoided by Bardenheier et al. (Bardenheier et al., 2021) who reported that the 7-day *all-cause mortality* after vaccination for COVID-19 was lower (risk ratio 0.49) than in unvaccinated persons even after adjustment for age, gender, ethnicity, diabetes, chronic pulmonary, kidney, heart disease, hypertension, and physical and cognitive function.

The objective of the present study was to re-examine the association between COVID-19 vaccination and *non-COVID-19* mortality after adjustment for the health status of a cohort of medical Israeli inpatients.

2. Methods

2.1. Patient populations

We analyzed retrospectively a cohort of all 8399 hospitalized adults in January – October 2021 at the internal medicine departments at the Laniado hospital, a 400-bed regional Israeli hospital. Of those, 704 (8.4%) were admitted for COVID-19 (mostly delta). Of the remaining 7695, 62.9% ($n = 4839$) had been vaccinated before hospitalization and 37.1% ($n = 2856$) were not.

2.2. Sources of data

Data were retrieved from the hospital's electronic database that included updated vaccination information from the Ministry of Health. All patients had an antigen test (rapid microfluidic immunofluorescence assay SARS-CoV-2 Ag, LumiraDx, Alloa, UK), and a PCR test (Xpert® Xpress SARS-CoV-2; Allplex™ 2019-nCoV Assay, Seegene Inc., Seoul, Republic of Korea).

2.3. Variables

The dependent variable was in-hospital mortality. The independent variables were those presented in Table 1, as well as vaccination status derived from government registries, and COVID-19 status, as

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Table 1
Scores assigned to age and laboratory variables in hospitalized adult patients at a regional hospital in Israel and their association with nonvaccine status.

Variable	Score				The odds ratio for non-vaccine status
	0	1	2	3	
Age groups (years)	<40	40–59	60–70	≥80	0.84 (0.80–0.89)
Female					1.15 (1.05–1.26)
WBC (10^9/L)	<12	>12–14.9	≥15		1.15 (1.08–1.23)
Neutrophil proportion (%)	≤70	>70	>80	>90	1.09 (1.03–1.14)
Hemoglobin (gm/dL)	≥12.0	10.0–11.9	<10.0		1.12 (1.05–1.20)
MCV (fL/cell)	<100	≥100			1.51 (1.20–1.90)
Platelets (10^9/L)	≥150	100–149	<100		0.81 (0.72–0.91)
BUN (mg/dL)	< 20	20–29	≥ 30		0.97 (0.92–1.03)
Creatinine (mg/dL)	<2	≥2			0.92 (0.79–1.06)
Sodium (meq/L)	<148	≥148			1.17 (0.86–1.60)
Potassium (meq/L)-high	<5.3	≥5.3			1.06 (0.89–1.27)
Potassium (meq/L)-low	≥3.5	<3.5			1.25 (1.03–1.51)
Serum glucose (mg/dL)	<150	150–199	200		1.06 (1.01–1.13)
Albumin (gm/dL)	≥ 3.5	3.0–3.4	< 3.0		1.57 (1.45–1.71)
Alkaline phosphatase	≤140	141–199	≥200		1.25 (1.13–1.37)
SGOT (units/L) *	≤40	>40–99.9	≥100		1.32 (1.20–1.46)
LDH (units/L)	≤400	401–599	≥600		1.20 (1.12–1.28)

* Serum glutamic oxaloacetic transaminase.

determined by PCR.

2.4. Analyses

Bivariate and multiple regression analyses. To determine the association of the secondary variables with non-vaccine status, they were scored (Table 1) and the odds ratios were determined by univariate logistic regression. Next, all variables in Table 1 were entered into the regression model to predict inhospital mortality, and removed if not adding significantly to the model. Then they were added back one at a time and retained if significant.

2.5. Ethical approval

The local Hospital Ethics Committee (0034–20-LND) approved the study without patient informed consent. All local ethics committee decisions are reviewed and approved by the Israeli Ministry of Health.

3. Results

Bivariate analysis indicated that low serum albumin, high MCV, elevated serum alkaline phosphatase, glutamic oxaloacetic transaminase (SGOT), and lactate dehydrogenase (LDH) were associated with non-vaccine status (Table 1). Regression analysis indicated that serum sodium, age, serum creatinine, and COVID-19 vaccination were independently associated with non-COVID in-hospital mortality. Non-COVID-19 mortality rates were 7.8% (223/2856) in non-vaccinated and 4.1% (196/4839) in vaccinated patients. The odds ratio for in-hospital deaths of non-vaccinated patients was 2.01 (1.65–2.44) (unadjusted) and 1.62 (1.29–2.03) after adjustment for the independent variables (Table 2).

When all variables associated with no-vaccine status were forced into the regression model, the association between no covid-19 vaccination and non-Covid mortality was [1.63 (1.30–2.04) and nearly identical to that presented in Table 2.

Table 2
Multivariate regression analysis of the association of selected independent variables with in-hospital mortality among 7695 non-COVID-19 hospitalized adult patients during January–October 2021.

Variable	Reference**	Odds ratios (95% confidence limits)
Sodium (meq/L)	< 148	1.90 (1.27–2.85)
Creatinine (mg/dL)	< 2	1.73 (1.32–2.29)
Age groups (years)	<60 years old	1.71 (1.43–2.05)
COVID-19 vaccination, two doses, yes/no	yes	1.62 (1.30–2.03)
Albumin (gm/dL)	≥ 3.5	2.57 (1.23–2.96)
LDH (units/L) *	≤400	1.49 (1.28–1.73)
SGOT (units/L) *	≤40	1.48 (1.22–1.80)
WBC (10^9/L)	< 12	1.43 (1.26–1.63)
BUN (mg/dL)	< 20	1.37 (1.16–1.63)
Platelets (10^9/L)	≥ 150	1.29 (1.04–1.59)
Serum glucose (mg/dL)	< 150	1.29 (1.13–1.48)
Alkaline phosphatase	≤140	1.23 (1.04–1.45)

4. Discussion

The main sources of information about COVID-19 vaccine effectiveness are observational studies. Such studies are subject to biases (Dean et al., 2021), and the presented findings highlight one of them, to wit: adherence to vaccination may be an independent surrogate marker for healthy behavior.

This "healthy adherer effect" was first reported in 1980 (Coronary Drug Project Research Group, 1980), and a 2006 meta-analysis confirmed that adherence to placebo accounted for about half of the reduction in mortality (Simpson et al., 2006). In 2006, Jackson et al. (Jackson et al., 2006) studied the effect of the healthy adherer effect on the assessment of the efficacy of vaccination. They found that influenza vaccination was associated with a 41% reduction in the risk of *all-cause* mortality during an influenza season; however, they also found a 61% reduction in this risk in the pre-influenza period, which indicated a healthy vaccinee bias. The authors concluded that, in the absence of randomized trials, the benefits of flu vaccination were lower than those attributed to it.

So far, randomized trials have tested the immunogenicity of COVID-19 vaccines (Pormohammad et al., 2021). We know of no randomized trials of the clinical efficacy of COVID-19 vaccination, and today such trials would not be ethically permissible (Dal-Ré and Caplan, 2021). Certainly, the healthy adherer effect should not affect the current vaccination policy. Yet, this effect was not mentioned in published observational studies suggesting that the Covid-19 vaccine had an effectiveness of 94% (Tenforde, 2021) and 91% (Rosenberg et al., 2022) against hospital admission; 74% against symptomatic disease (Andrews et al., 2022); and 74% (Magen et al., 2022) and 90% (Arbel et al., 2021) against Covid-19–related deaths.

The main strength of the present study is its focus on non-Covid mortality adjusted for the health status of the study populations as reflected in the laboratory data. As such, it adds to the findings by Xu et al. (2021) that were adjusted for demographic data only, and by Bardenheier et al. (2021) that compared the *all-cause mortality* after vaccination for COVID-19 with that in unvaccinated persons after adjustment for age, gender, ethnicity, diabetes, chronic pulmonary, kidney, heart disease, hypertension, and physical and cognitive function. The main limitation of this study is the use of data from a single hospital. Its finding may not apply to larger patient populations. However, we feel that this limitation does not disqualify our conclusion that the reported effectiveness of Covid-19 vaccination may have been partly due to the healthy adherer effect, and therefore, exaggerated.

What is new?

The clinical effectiveness of the COVID-19 vaccine is based on observational studies that compare the mortality of vaccinated and non-vaccinated subjects.

This paper adds to this knowledge by indicating that COVID-19 vaccination reduced in-hospital non-COVID-19 mortality rates after adjustment for age and health status of the study population. This finding highlights the "healthy adherer effect", whereby adherence to vaccination may be an independent surrogate marker for healthy behavior, and suggests that the reported effectiveness of COVID-19 vaccination may have been exaggerated.

Authors' contribution

Drs Froom and Benbassat conceived the study; Drs Shimoni and Froom retrieved and analyzed the data, and all of us organized the findings into a scientific assay.

Declaration of Competing Interest

JB, PF, and ZS declare no competing interests. This study did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors.

Data availability

Data will be made available on request.

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