Adults hospitalized with breakthrough COVID-19 have lower mortality than matched unvaccinated adults

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Abstract. Myers LC, Kipnis P, Greene J, Lawson B, Escobar GJ, Fireman BH, et al. Adults hospitalized with breakthrough COVID-19 have lower mortality than matched unvaccinated adults. *J Intern Med.* 2022;**292**:377–384.

Background. Coronavirus disease 2019 (COVID-19) breakthrough infections are common.

Objective. Evaluate in-hospital mortality of patients with COVID-19 by vaccination status using retrospective cohort study.

Methods. We generated propensity scores for receipt of full vaccination in adults requiring supplemental oxygen hospitalized at Kaiser Permanente Northern California (1 April 2021 to 30 November 2021) with positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction tests. Optimal matching of fully vacci-

nated/unvaccinated patients was performed comparing in-hospital mortality.

Results. Of 7305 patients, 1463 (20.0%) were full, 138 (1.9%) were partial, and 5704 (78.1%) were unvaccinated. Fully vaccinated were older than partial or unvaccinated (71.0, 63.0, and 54.0 years, respectively, $p < 0.001$) with more comorbidities (Comorbidity Point Scores 33.0, 22.0, and 10.0, $p < 0.001$) and immunosuppressant (11.5%, 8.7%, and 3.0%, $p < 0.001$) or chemotherapy exposure (2.8%, 0.7%, and 0.4%, $p < 0.001$). Fewer fully vaccinated patients died compared to matched unvaccinated (9.0% vs. 16.3%, $p < 0.0001$).

Conclusion. Fully vaccinated patients are less likely to die compared to matched unvaccinated patients.

Keywords: breakthrough infection, COVID-19, hospitalization, mortality, vaccination

Introduction

Observational studies demonstrate that vaccines currently available in the United States for coronavirus disease 2019 (COVID-19) are effective at preventing hospitalization (68% for adenovirus-based vaccine and 89% for messenger ribonucleic acid–based vaccine) [1, 2–5]. However, there are unprecedented numbers of patients admitted to hospitals for COVID-19, many requiring supplemental oxygen for symptomatic breakthrough infections. Large epidemiologic reports have been published about patients with breakthrough infections [5–7], but the granular characteristics and outcomes of fully vaccinated patients with breakthrough infections severe enough to be hospitalized have not been fully described, such as how their outcomes compare to matched unvaccinated patients. We compare characteristics and outcomes of adults hospitalized for COVID-19 in

Kaiser Permanente Northern California (KPNC) by vaccination status using propensity score matching. We hypothesize that fully vaccinated patients will have lower inpatient mortality than matched unvaccinated patients.

Methods

The KPNC Institutional Review Board approved this retrospective cohort study with a waiver of informed consent. We identified adults (≥18 years) admitted to one of KPNC's 21 hospitals between 1 April 2021 and 30 November 2021 who required supplemental oxygen on the day of admission and had a positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction test during that hospitalization or in the prior 3 weeks. We required that patients receive supplemental oxygen to eliminate patients with incidental positive tests admitted for other reasons (e.g., hip fracture).

Dates were chosen to maximize sample size and encapsulate the period during which (1) Delta was circulating and (2) vaccines were available to the American public. We excluded 199 patients who had another positive test prior to the qualifying hospitalization.

KPNC databases contain vaccine information about patients who receive vaccines in or out of the network. Data from outside the network are transmitted to KPNC from the state of California with minimal time lag. We classified vaccination status on the date of the test: additional dose, fully vaccinated, partially vaccinated, or unvaccinated. We defined "additional dose" as patients who had an additional dose of vaccine beyond the first of a one-dose regimen or second of a two-dose regimen. We defined fully vaccinated as patients with ≥14 days between the final vaccine dose (first of a one-dose regimen, second of a two-dose regimen) and a positive test [8]. Partial vaccination included patients who had received one dose but did not meet the criteria for full vaccination at the time of the positive test. Because there were only 32 patients who had received an additional dose, we combined them into the fully vaccinated group.

We describe demographic and clinical characteristics by vaccination status, including comorbidity burden and individual comorbidities. We reported Comorbidity Point Score, Version 2 (COPS2), which is an externally validated comorbidity index employing *International Classification of Disease* diagnosis codes in the previous year (range 0–1010) [9]. We also reported Laboratory Acute Physiology Score, Version 2 (LAPS2), which is a severity of illness score employing 16 vital signs and laboratory variables (range 0–414) [9]. We identified patients who had been on immunosuppressant medications in the 1 year prior, which included oral/intravenous steroid, rituximab, etanercept, infliximab, abatacept, ocrelizumab, anakinra, tacrolimus, everolimus, cyclosporine, methotrexate, mycophenolate mofetil, leflunomide, and azathioprine. We also identified patients who had chemotherapy in the 1 year prior. The highest level of respiratory support was defined in mutually exclusive, hierarchical categories (nasal cannula/face mask, high flow oxygen, noninvasive ventilation, invasive ventilation). We reported the final code status during the hospitalization where "not full code" was any limitation of life-sustaining therapy, such as "do not intubate."

We performed logistic regression for receipt of full vaccination to obtain a propensity score for each patient adjusting for age, sex, comorbidity burden (COPS2), and the binary comorbidities of hypertension and diabetes. These comorbidities were chosen because they are two of the most common and have been shown in the literature to increase the risk of poor outcome in COVID-19 [10]. Then we performed optimal matching [11] of fully vaccinated patients (including those who received an additional dose) and unvaccinated patients (ratio 1:1). We compared standardized differences by the vaccination status of the patient characteristics used to generate the propensity score. We estimated the effect of the primary outcome of inpatient death using generalized estimating equations to account for matching. We report secondary outcomes of hospice referral within 30 days in order to capture as many anticipated deaths as possible in this contemporaneous cohort [12]. We also report the highest level of respiratory support, need for intensive care unit admission, and hospital length of stay.

We performed the following sensitivity analyses: (1) including the 199 patients who had had positive tests prior to the qualifying hospitalization, (2) excluding the 32 patients who had received an additional dose of vaccine from the fully vaccinated group, and (3) 1:2 matching.

Results

Of 7305 hospitalized patients with COVID-19 requiring supplemental oxygen, 1463 (20.0%) were fully vaccinated or had received an additional dose beyond the initial one- or two-dose vaccine regimens, 138 (1.9%) were partially vaccinated, and 5704 (78.1%) were unvaccinated (Table 1). Fully vaccinated patients were older than partially vaccinated or unvaccinated patients (71.0, 63.0, and 54.0 years, respectively, $p < 0.001$) with higher comorbidity burden (COPS2 33.0, 22.0, and 10.0, $p < 0.001$). Fully vaccinated patients were more likely to have common individual comorbidities compared to partially vaccinated and unvaccinated patients: diabetes (48.5%, 46.4%, and 27.8%, respectively, $p < 0.001$), congestive heart failure (26.2%, 17.5%, and 7.2%, $p < 0.001$), and cancer (12.8%, 9.5%, and 3.4%, $p < 001$). Fully vaccinated patients were more likely to have exposure to immunosuppressants compared to partially vaccinated or unvaccinated patients (11.5%, 8.7%, and 3.0%, respectively, $p < 0.001$)

Table 1. *Characteristics and outcomes of adults hospitalized with coronavirus disease 2019 by vaccination status*

	Total $n = 7305$	Fully vaccinated (including additional dose) $n = 1463$	Partially vaccinated $n = 138$	Unvaccinated $n = 5704$	*P*-value
Age at admission	57.0 (44.0, 70.0)	71.0 (60.0, 81.0)	63.0 (54.0, 73.8)	54.0 (41.0, 65.0)	<0.001
Age 65+	2481 (34.0)	967 (66.1)	60 (43.5)	1454 (25.5)	<0.001
Female	3412 (46.7)	631 (43.1)	66 (47.8)	2715 (47.6)	0.009
Comorbidities					
COPS2 at admission	10.0 (10.0, 26.0)	33.0 (13.0, 66.0)	22.0 (10.0, 49.5)	10.0 (10.0, 21.0)	<0.001
Diabetes	2359 (32.3)	709 (48.5)	64 (46.4)	1586 (27.8)	<0.001
Chronic pulmonary disease	1910 (26.6)	562 (38.8)	59 (43.1)	1289 (23.0)	<0.001
Congestive heart failure	809 (11.3)	380 (26.2)	24 (17.5)	405 (7.2)	<0.001
Renal failure	789 (11.0)	358 (24.7)	28 (20.4)	403 (7.2)	<0.001
Hypertension	1068 (14.6)	146 (10.0)	32 (23.2)	890 (15.6)	<0.001
Liver disease	688 (9.6)	167 (11.5)	21 (15.3)	500 (8.9)	0.001
Solid tumor without metastasis	280 (3.9)	131 (9.0)	10 (7.3)	139 (2.5)	<0.001
Metastatic cancer	110 (1.5)	55 (3.8)	3 (2.2)	52 (0.9)	<0.001
Acquired immune deficiency syndrome	12 (0.2)	<5	<5	7 (0.1)	0.12
Immunosuppressant medication in the last 12 months	350 (4.8)	168 (11.5)	12 (8.7)	170 (3.0)	<0.001
Chemotherapy in the last 12 months	67 (0.9)	41 (2.8)	<5	25 (0.4)	<0.001
None of the above conditions/treatments	3913 (53.6)	441 (30.1)	39 (28.3)	3433 (60.2)	<0.001
Body mass index	31.8 (27.4, 37.5)	30.3 (26.1, 36.4)	32.2 (27.0, 38.0)	32.0 (27.8, 37.8)	<0.001
Days since vaccine	158.0 (111.0–196.0)	162.0 (124.0–199.0)	32.0 (21.0–89.0)	Not applicable	<.0001
Days between positive test and admission	1.0 (0.0, 5.0)	1.0 (0.0, 4.0)	0.5 (0.0, 2.0)	1.0 (0.0, 6.0)	<0.001
Laboratory values					
White cell count ref.: 3.7–11.1 K/ul	6.7 (5.0, 9.0)	7.6 (5.6, 10.3)	7.7 (5.5, 11.3)	6.5 (4.9, 8.6)	<0.001
Creatinine ref.: ≤1.11 mg/dl	0.9 (0.8, 1.2)	1.1 (0.8, 1.6)	1.0 (0.8, 1.5)	0.9 (0.7, 1.2)	<0.001
Lactate ref.: 0.5–1.9 mmol/L	1.4 (1.1, 1.9)	1.5 (1.1, 2.0)	1.5 (1.0, 2.1)	1.4 (1.1, 1.9)	0.63
D-dimer ref.: ≤0.49 ug/ml	1.0 (0.7, 1.6)	1.0 (0.6, 1.8)	1.0 (0.7, 1.8)	1.0 (0.7, 1.6)	0.54
Highest level of respiratory support					
Nasal cannula/face mask	4126 (56.5)	930 (63.6)	90 (65.2)	3106 (54.5)	<0.001
High flow oxygen	712 (9.7)	78 (5.3)	8 (5.8)	626 (11.0)	
Noninvasive ventilation	1596 (21.8)	325 (22.2)	26 (18.8)	1245 (21.8)	
Invasive ventilation	871 (11.9)	130 (8.9)	14 (10.1)	727 (12.7)	

(*Continued*)

Table 1. *Continued*

	Total $n = 7305$	Fully vaccinated (including additional dose) $n = 1463$	Partially vaccinated $n = 138$	Unvaccinated $n = 5704$	*P*-value
LAPS2 at admission	78.0 (62.0–99.0)	84.0 (64.0–109.0)	82.0 (59.0–109.0)	77.0 (62.0–96.0)	<0.0001
Ratio of oxygen saturation–fraction of inhaled oxygen	110.6 (95.0–160.8)	122.5 (99.5–189.0)	97.4 (97.1–97.7)	105.6 (94.3–156.3)	0.11
Ever in the intensive care unit	1310 (17.9)	235 (16.1)	23 (16.7)	1052 (18.4)	0.10
Final recorded code status					
Not full code	548 (8.3)	257 (19.3)	18 (15.0)	273 (5.3)	<0.001
Full code	6054 (91.7)	1074 (80.7)	102 (85.0)	4878 (94.7)	<0.001
Length of hospital stay (days)	5.0 (4.0–9.0)	5.0 (3.0–9.0)	5.0 (3.0–8.0)	5.0 (4.0–9.0)	0.001
Inpatient death	703 (9.6)	132 (9.0)	18 (13.0)	553 (9.7)	0.29
Hospice referral within 30 days of admission	143 (2.0)	64 (4.4)	6 (4.3)	73 (1.3)	<0.001
Hospice referral within 30 days of admission or inpatient death	836 (11.4)	194 (13.3)	24 (17.4)	618 (10.8)	0.003

Note: Continuous variables are reported as median (interquartile range). Categorical variables are reported as number (percent). Patients who received an additional dose of vaccine (either as a third dose to complete the series for an immuno-compromised state or as a booster) are classified under fully vaccinated. *P*-values compare across the three groups (fully vaccinated, partially vaccinated, and unvaccinated).
Abbreviations: COPS2, COmorbidity Point Score, Version 2; LAPS2, Laboratory Acute Physiology Score, Version 2.

and chemotherapy (2.8%, 0.7%, and 0.4%, $p < 0.001$). There were 441 (30.1%) fully vaccinated patients who had none of the nine individual comorbidities listed in Table 1 or exposure to immunosuppressants/chemotherapy.

Median time between the last dose of vaccine and admission was 162.0 days (interquartile range 124.0–199.0) for fully vaccinated patients and 32.0 days (interquartile range 21.0–89.0) for partially vaccinated patients ($p < 0.0001$). Fully vaccinated patients had a higher severity of illness score at the time of admission compared to partially vaccinated or unvaccinated patients (LAPS2 84.0, 82.0, and 77.0, respectively, $p < 0.001$) and were more likely to have limitations of life-sustaining therapies as their final recorded care directive (19.3%, 15.0%, and 5.3%, $p < 0.001$).

After developing propensity scores for receipt of full vaccination, we matched 1463 fully vaccinated patients with 1463 unvaccinated patients (Table 2). Of the variables used to generate the

propensity score, there was adequate balance in all but COPS2, indicating a higher comorbidity burden in fully vaccinated patients (33.0 vs. 23.0, standardized difference 0.27). Despite this difference, fully vaccinated patients were less likely to die inpatient compared to unvaccinated (9.0% vs. 16.3%, $p < 0.0001$, Table 3) and equally likely to receive hospice referral (4.4% vs. 4.5%, $p = 0.86$). A lower proportion of fully vaccinated patients dying in the hospital was consistent in the three sensitivity analyses described above. Fully vaccinated patients were also less likely to require intensive care (16.1% vs. 21.4%, $p = 0.0003$) and had a shorter hospital length of stay (median 5 days, interquartile range 3–9 vs. 6 days, interquartile range 4–11, $p < 0.0001$).

Discussion

We found that characteristics among patients hospitalized with COVID-19 varied by vaccination status. The fully vaccinated patients were older with higher comorbidity burden and

Table 2. *Comparison of characteristics of fully vaccinated versus unvaccinated patients hospitalized with COVID-19 matched by propensity to receive full vaccination*

	Matched patients		
	Fully vaccinated, $n = 1463$	Unvaccinated, $n = 1463$	Standardized differences
Characteristics			
Age at admission	71.00 (60.00, 81.00)	71.00 (60.00, 80.00)	0.04
Sex, female	631 (43.1%)	643 (44.0%)	−0.02
COPS2 at admission	33.00 (13.00, 66.00)	23.00 (10.00, 48.00)	0.27
Diabetes	709 (48.5%)	694 (47.4%)	0.02
Hypertension	146 (10.0%)	160 (10.9%)	−0.03

Note: Continuous variables are reported as median (interquartile range). Categorical variables are reported as number (percent). A standardized difference greater than 0.10 or less than −0.10 is considered statistically significant.
Abbreviation: COPS2, COmorbidity Point Score, Version 2.

Table 3. *Comparison of outcomes in fully vaccinated versus unvaccinated patients hospitalized with COVID-19 matched by propensity to receive full vaccination*

	Matched		
Patients	Fully vaccinated, $n = 1463$	Unvaccinated, $n = 1463$	*P*-value
Primary outcome			
Inpatient death	132 (9.0%)	238 (16.3%)	<0.0001
Secondary outcomes			
Highest level of respiratory support			
Nasal cannula/face mask	930 (63.6%)	762 (52.1%)	<0.0001
High flow oxygen	78 (5.3%)	129 (8.8%)	0.0003
Noninvasive ventilation	325 (22.2%)	364 (24.9%)	0.09
Invasive ventilation	130 (8.9%)	208 (14.2%)	<0.0001
Ever in the intensive care unit	235 (16.1%)	313 (21.4%)	0.0003
Length of hospital stay	5.00 (3.00, 9.00)	6.00 (4.00, 11.00)	<0.0001
Hospice referral within 30 days of admission	64 (4.4%)	66 (4.5%)	0.86
Hospice referral within 30 days of admission or inpatient death	194 (13.3%)	299 (20.4%)	<0.0001

Note: Continuous variables are reported as median (interquartile range). Categorical variables are reported as number (percent). *P*-values were produced using generalized estimate equations to account for the fact that this was a matched sample.

likelihood of having received immunosuppressants/chemotherapy. Given that the initial vaccine trials excluded immunocompromised patients [3], understanding how this vulnerable population does after vaccination is clinically important. One previous study reported a higher incidence rate of breakthrough infection by immune condition (solid organ transplant, human immunodeficiency virus, etc.) but did not examine rates by immunosuppressant medication exposure, which may be driving

the susceptibility more than the underlying condition [13]. They also did not examine patients with cancer receiving chemotherapy as a population at risk for breakthrough infection [13]. Therefore, we add insights into the current understanding of patients hospitalized with breakthrough infections.

We found that the median time between the last dose of vaccine and admission in fully vaccinated patients was ~5.5 months, which is consistent

with existing evidence of waning immunity occurring at 4–7 months [14, 15]. Previous studies from Israel revealed higher likelihood of infection, including severe disease, among the vaccinated as more time elapsed from full vaccination [16]. Therefore, our findings make sense as older, more comorbid patients were first to be vaccinated in the United States and would be the first to exhibit waning immunity.

A sizeable percentage (∼30%) of fully vaccinated patients did not have common comorbidities or known exposure to immunosuppressants/chemotherapy. This observation is likely because the majority of the northern California population was vaccinated at the study end date (>80% of eligible adults) and the virus has remained in circulation. We do not think it is explained by immune evasion of viral variants because current evidence indicates that vaccinated patients are protected against severe disease from the Delta variant, which was the predominant strain during the study period [17, 18]. It is critical to note that unvaccinated patients had *double the percentage* without common comorbidities or known exposure to immunosuppressants/chemotherapy. Given that the fully vaccinated patients were at a higher risk of death due to comorbidity burden yet had a lower risk of death, we are likely underestimating the true difference in outcomes. This strengthens the findings of this study and further underscores the benefit of vaccination.

We show that the majority of patients hospitalized with COVID-19 were unvaccinated (78%), which is generally consistent with previously reported results (88%) [19]. A case-control study from 21 American hospitals showed that mechanical ventilation and death for COVID-19 was associated with decreased likelihood of vaccination for the subgroup of patients with hypoxemia ($n = 902$, odds ratio 0.30, 95% confidence interval 0.16–0.58) [19]. While this study reported genotype data, they only examined patients who received mRNA-based vaccines, did not assess partial vaccination status, and did not assess hospice referrals. Therefore, we extend existing studies in these three ways. Our starting cohort of patients hospitalized with hypoxemia is also much larger ($n = 7305$) than Tenforde et al.'s subgroup [19], which facilitated us to perform a matched analysis with enough power to detect a difference in mortality despite

higher comorbidity burden remaining in the fully vaccinated group.

Our findings have implications for hospital operations and vaccination/booster guidelines. As more of the population becomes vaccinated, breakthrough infections will become more common. It is reassuring that fully vaccinated patients have lower inpatient mortality than matched unvaccinated patients, which we observed despite the fully vaccinated group having a higher comorbidity burden after matching. Given how safe the current vaccines are [1] and the favorable outcomes of vaccinated patients with breakthrough infections who do require hospitalization, we strongly encourage vaccination for eligible patients. Older, immunocompromised patients may benefit from protections beyond vaccination, such as masking and social distancing.

Several limitations should be considered. First, we do not report genotype data but limited the study period to when Delta was circulating. Research will be necessary on outcomes related to the Omicron surge. Second, more research is needed to understand breakthrough infections by vaccine combinations, previous infection status, and type/severity of the immunocompromised state. Third, some unmeasured confounders could not be adjusted for in the analysis, such as behaviors that are associated with getting vaccinated and mortality. Fourth, there could be variation in outcome by medical center, as previous literature has demonstrated worse outcomes in areas with more cases of COVID-19 [20]. However, matching by medical center was not feasible due to power.

There are several benefits. First, we only examined patients who required supplemental oxygen as a way of identifying patients who were symptomatic. Second, we performed a matched analysis because the patient populations (fully vaccinated and unvaccinated) were different. We benefited from a large enough cohort prior to matching such that we could detect differences in outcomes between matched groups. Third, the variables we report are more granular than previous studies whose data originate from a research consortium or public health reporting, and we are able to report on partial vaccination status and history of receipt of chemotherapy. Fourth, our results are robust in multiple sensitivity analyses.

Conclusion

Hospitalizations for COVID-19 during the Delta surge were predominantly in unvaccinated patients. Breakthrough infections occurred in fully vaccinated patients, who tended to be older with a higher comorbidity burden and rates of immunosuppression. Fully vaccinated patients with COVID-19 had better in-hospital outcomes than matched unvaccinated patients.

Acknowledgments

Conflict of interest

Nicola P. Klein reports research support from Pfizer for COVID vaccine trials and from Pfizer, Merck, Sanofi Pasteur, GlaxoSmithKline, and Protein Science (now Sanofi Pasteur) for unrelated research. Gabriel J. Escobar, Vincent X. Liu, and Laura C. Myers report research support from Astra Zeneca unrelated to vaccine research. The other authors have no conflict of interest.

Author contributions

Laura C. Myers, Gabriel J. Escobar, and Vincent X. Liu developed the cohort. John Greene and Brian Lawson extracted and formatted the data and performed the analyses. Patricia Kipnis advised on how to develop the propensity score and generate statistical comparisons accounting for the matched sample. Laura C. Myers drafted the manuscript. Nicola P. Klein and Bruce H. Fireman contributed to the conception of the manuscript, analytic plan, and result interpretation. Vincent X. Liu supervised the project's execution. All authors critically reviewed the manuscript.

Data availability statement

Laura C. Myers and Vincent X. Liu had full access to the data and take responsibility for the content.

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