Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Risk of COVID-19 breakthrough infection and hospitalization in individuals with comorbidities

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ABSTRACT

Background: The successful development of multiple COVID-19 vaccines has led to a global vaccination effort to reduce severe COVID-19 infection and mortality. However, the effectiveness of the COVID-19 vaccines wane over time leading to breakthrough infections where vaccinated individuals experience a COVID-19 infection. Here we estimate the risks of breakthrough infection and subsequent hospitalization in individuals with common comorbidities who had completed an initial vaccination series.

Methods: Our study population included vaccinated patients between January 1, 2021 to March 31, 2022 who are present in the Truveta patient population. Models were developed to describe 1) time from completing primary vaccination series till breakthrough infection; and 2) if a patient was hospitalized within 14 days of breakthrough infection. We adjusted for age, race, ethnicity, sex, and year-month of vaccination.

Results: Of 1,218,630 patients in the Truveta Platform who had completed an initial vaccination sequence between January 1, 2021 and March 31, 2022, 2.85, 3.42, 2.75, and 2.88 percent of patients with CKD, chronic lung disease, diabetes, or are in an immunocompromised state experienced breakthrough infection, respectively, compared to 1.46 percent of the population without any of these four comorbidities. We found an increased risk of breakthrough infection and subsequent hospitalization in individuals with any of the four comorbidities when compared to individuals without these four comorbidities.

Conclusions: Vaccinated individuals with any of the studied comorbidities experienced an increased risk of breakthrough COVID-19 infection and subsequent hospitalizations compared to the people without any of the studied comorbidities. Individuals with immunocompromising conditions and chronic lung disease were most at risk of breakthrough infection, while people with CKD were most at risk of hospitalization following breakthrough infection. Patients with multiple comorbidities have an even greater risk of breakthrough infection or hospitalization compared to patients with none of the studied comorbidities. Individuals with common comorbidities should remain vigilant against infection even if vaccinated.

1. Introduction

The successful development of multiple COVID-19 vaccines has led to a global vaccination effort with the goal of reducing severe COVID-19 infection and mortality [1,2]. The effectiveness of the COVID-19 vaccines, however, does wane over time and breakthrough infections have been reported since the beginning of the vaccination effort [3–10]. A breakthrough infection is defined here as when an individual experiences a COVID-19 infection despite having completed their initial vaccination sequence (i.e., two doses plus an addition 2 weeks for an mRNA vaccine). This waning vaccine effectiveness, along with vaccine-variant mismatch, are the principal reasons behind the need for individuals to receive one or more booster doses of an mRNA vaccine [3,11–14].

Prior studies of unvaccinated and vaccinated populations have shown more severe outcomes for COVID-19 infection for people with certain high-risk comorbidities such as diabetes, chronic kid-

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ney disease (CKD), lung disease, hypertension, or are immunocompromised (e.g., because of cancer, solid organ transplant, HIV, etc.) among many other conditions when compared to individuals without those conditions [6,15–27]. However, most of the analyses surrounding breakthrough COVID-19 infection, and subsequent hospitalization, in vaccinated populations were not based on people in the United States (though see Embi et al. [24]), and instead focused on large populations in the United Kingdom [9,19,21].

Additionally, explicit interactions between comorbidities have not necessarily been analyzed,as previous work has tended to focus on one or two intrinsically related comorbidities [6,7,19,24,28,29] or are full omnibus analyses which focus on incidence rates of breakthrough and hospitalization [5,9,10,20,21,23,30,31].

In order to better understand the risk of breakthrough infection and severe outcomes in high-risk populations, we used Truveta data [32] to estimate whether vaccinated patients with chronic kidney disease, chronic lung disease, diabetes, or those who have immunocompromising conditions have a greater risk of breakthrough COVID-19 infection and greater odds of hospitalization following breakthrough infection than in those individuals who were vaccinated but did not have any of the studied comorbidities. We chose to study these comorbidities based on their prevalence in the US population, association with impaired immune function, and the previous literature describing risk factors associated with COVID-19 hospitalization in unvaccinated and vaccinated populations [9,11,15,21,33–35].

2. Methods

2.1. Study population

The study population included a subset of the Truveta patient population who received a complete initial series of an mRNA vaccine for COVID-19 patients present in Truveta between 2021-01-01 and 2022–03-31 [32]. We used the Truveta Studio to access the de-identified medical records used in this study on 2022–10-19. Truveta is a consortium of healthcare systems which have combined their electronic health record (EHR) data to enable medical research. Currently this consortium includes 25 members who provide patient care in over 20,000 clinics and 700 hospitals across 43 states. Updated data is provided daily to Truveta. Similar data fields across systems are mapped though syntactic normalization to a common schema referred to as the Truveta Data Model (TDM). Once organized into common fields, values are then semantically normalized to common ontologies such as ICD-10-CM, SNOMED-CT, LOINC, RxNorm, CVX, etc. These normalization procedures employ an expert-led, artificial intelligence driven process to accomplish high-confidence modeling at scale. The data are then de-identified by expert determination under the HIPAA Privacy Rule. Once de-identified, the data are then made available for analysis using Truveta Studio.

A patient was considered to have completed their primary vaccination series at two weeks after receiving a second mRNA vaccine dose (Moderna or Pfizer) based on the patient's medical records. Patients were excluded from our study population if they were missing sex or age at time of vaccination fields, experienced a COVID-19 infection prior to completing their initial mRNA COVID-19 vaccination sequence (i.e., 14 days post second vaccine dose), were missing their date of being fully vaccinated, or were under 18 years of age at time of first vaccine dose. All vaccination events generally consisted of vaccinations that took place within the health system as well as vaccination records actively pulled from the health system's respective state's Immunization Information System. See the Supplementary Material for a list of CVX codes corresponding to these vaccines.

Our four comorbidities of interest (chronic kidney disease, chronic lung disease, diabetes, and immunocompromised) were defined using Elixhauser comorbidity ICD-10-CM diagnostic codes and related SNOMED-CT diagnostic codes [36], and patients were identified as having one or more of these comorbidities based on the presence of these diagnostic codes in a patient's medical record prior to their completion of a primary COVID-19 vaccination series. Patients who were newly diagnosed with one of the studied comorbidities after completing their initial dose sequence plus 14 days were excluded from analysis.

Our response variables of interest were 1) time from completing a COVID-19 primary vaccination series till breakthrough infection, and 2) if a patient who experienced a breakthrough infection was hospitalized within two-weeks of that infection. SARS-CoV-2 infection was defined as a patient's first diagnosis of COVID-19 using either diagnosis codes or laboratory results.

The code lists associated with all studied conditions were initially based on code lists published to the National Institute of Health's Value Set Authority Center website (https://vsac.nlm.nih.gov/). Our definition of immunocompromised is based on the SNOMED CT-based definition present in Embi et al. [24] combined with a selection ICD-10-CM codes and their descendant codes as determined by the clinical informaticists who are co-authors on this study. The complete lists of ICD-10-CM, SNOMED-CT, CVX, and LOINC codes for each of COVID-19 vaccination, COVID19 diagnosis, COVID-19 test, and all considered comorbidities are presented in the Supplementary Material.

In addition to the four comorbidities stated above, we also included multiple demographic covariates in our models: race (White, Asian, Black or African American, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Unknown), ethnicity (Hispanic or Latino, Not Hispanic or Latino, and Unknown), sex, and person's age in years at time of completing a COVID-19 primary vaccine sequence. In all analyses described below, the effect of age in years was modeled using a natural cubic spline with five degrees of freedom. We also included the year-month when a patient completed their primary vaccine sequence as a categorical covariate. We consider this variable as a proxy for differences associated with COVID-19 variant and transmission "environment" experienced by that patient.

2.2. Time from COVID-19 vaccination to breakthrough infection

We used a Cox proportional hazards model to describe the relationship between the time from completing a COVID-19 primary vaccination series till breakthrough infection and the comorbidities of interest and other covariates listed above. The response variable for our analysis of time from completing a COVID-19 primary vaccination series (i.e., time of second dose plus 14 days) till breakthrough infection was defined as the minimum time among three potential events: time of first COVID-19 infection, time of last encounter in EHR, and 180 days. If a patient did not experience a breakthrough infection they were considered right-censored at either 180 days or the time of their last encounter in the EHR, which ever was first. This censoring scheme assumes all censoring is uninformative and that any censored value less than 180 days indicates that a patient was lost to follow-up as of their last encounter in the EHR.

We hypothesized that, for patients with more than one of these four comorbidities, there may be an interaction effect influencing the chance of breakthrough infection. We developed four models of time till breakthrough infection, each allowing for a different degree of interactions. The base model assumes that the comorbidities have only an additive effect and there is no additional

hazard associated having multiple comorbidities. We also considered all two-way interactions (i.e., any combination of 2 comorbidities), all two- and three- way interactions, and all two-, three-, and four-way interactions between the comorbidities.

We used AIC and AICc to compare the four different models of each outcome and then select the best model for each outcome. When comparing models of the same response, the model with the lowest AIC/AICc indicates which of those models does the best job balancing the complexity of the model and its likelihood [37–40]. This approach was chosen because we did not have a strong hypothesis as to the "correct" number of possible interactions, and we also wanted to balance the complexity of the model with the size of our data set.

The hazard ratio associated for individual comorbidities with no interaction terms is normally calculated as the exponentiated regression coefficients from the Cox regression model. However, as we are interested in the hazard ratios associated with a patient having one or more comorbidities in combination versus a patient with no comorbidities, we used the emmeans R package to calculate these hazard ratios [41].

2.3. Odds of hospitalization following breakthrough infection

We used a logistic regression model to describe the relationship between hospitalization following breakthrough COVID-19 infection and the comorbidities and other covariates listed above. Hospitalization following a breakthrough COVID-19 infection was defined as an inpatient encounter where the patient was hospitalized within 14 days of a positive SARS-CoV-2 test. We choose to analyze this outcome because we were specifically interested in the conversion probability from "infected with COVID-19″ to "hospitalized" and not the time from vaccination till hospitalization nor time from breakthrough infection till hospitalization. This is a binary scenario describing a transition probability within the infected population for which this method is appropriate as we believe this analysis captures our research question well [42].

As with our analysis of time till breakthrough infection, we hypothesized that, for patients with more than one of these four comorbidities, there may be an interaction effect influencing the odds of hospitalization following breakthrough infection. We developed four models of hospitalization following breakthrough infection, each allowing for a different degree of interactions. The base model assumes that the comorbidities have only an additive effect and there is no additional hazard associated having multiple comorbidities. We also developed models which consisted of all two-way interactions (i.e., any combination of 2 comorbidities), all two- and three- way interactions, and all two-, three-, and four-way interactions. And as with the models of time till breakthrough infection, we used AIC and AICc to compare these models and select the best one among that group.

The odds ratio associated for individual comorbidities with no interaction terms is normally calculated as the exponentiated regression coefficients from the logistic regression model [42]. However, as we are interested in the odds ratios associated with a patient having one or more comorbidities in combination versus a patient with no comorbidities, we used the emmeans R package to calculate these odds ratios [41].

Analysis was done using the R programming language (4.1.1) [43] along with the following packages: arrow [44], broom [45], dplyr [46], emmeans [41], ggplot2 [47], janitor [48], purrr [49], rlang [50], stringr [51], survival [52], Table 1 [53], tibble [54], and tidyr [55].

The R code used to run the analyses presented in this study is available at https://github.com/Truveta/smits_et_al_covid_breakthrough_comorbidities.

3. Results

3.1. Study population

1,218,630 patients on Truveta met the study inclusion and exclusion criteria of having completed a primary vaccination sequence between 2021-01-01 and 2022–03-31. Of the patients in our study, 68,896 had chronic kidney disease, 140,435 had chronic lung disease, 135,915 had diabetes, 158,016 were considered immunocompromised, and 862,335 had none of these four studied comorbidities (Table 1). Note that patients can have more than one comorbidity, and thus the sum of patients with each comorbidity will exceed the total of patients with comorbidities.

3.2. Time from COVID-19 vaccination to breakthrough infection

The model of time from COVID-19 primary sequence till breakthrough infection with a maximum of four-way interactions between the comorbidities was considered "best" among the candidate models (Table 2). This means that specific interaction effects (e.g., changes to hazard ratios associated with specific combinations of comorbidities) are estimated up to the maximum possible four-way interaction among the comorbidities. This result means that we have found evidence that while patients with one of these four comorbidities had an increased risk of breakthrough COVID-19 infection compared to individuals without any of the studied comorbidities, patients with two or more of the comorbidities have further increased risk than would be expected by the independent effects of the comorbidities on odds of breakthrough infection.

Presented here (Fig. 1, Table 3) are the hazard ratios of breakthrough COVID-19 infection for a patient having one or more comorbidities versus a patient with none of the studied comorbidities. Our selected model included up to four-way interactions between comorbidities.

We find that persons with any of the studied comorbidities, in any combination, were associated with a greater risk of breakthrough COVID-19 infection than those persons without any of the studied comorbidities after adjustment (Fig. 1; CKD HR 1.83 [CI 1.52, 2.21]; immunocompromised HR 1.81 [CI 1.67, 1.97]; diabetes HR 1.69 [CI 1.53, 1.86]; chronic lung disease HR 2.00 [CI 1.85, 2.16]). See Supplementary Material for a full table of the selected model's parameter estimates.

3.3. Odds of hospitalization following breakthrough infection

The model of hospitalization following breakthrough COVID-19 infection with no interaction terms between the comorbidities was considered "best" among the candidate models (Table 4). While we are able to calculate the odds ratio for an arbitrary number of interactions, our model included no interaction effects among the comorbidities so the presented values are based on additive effects alone. While individuals with multiple of the comorbidities have an increased risk of hospitalization following breakthrough infection, our model selection results are consistent with the comorbidities having independent additive effects on the odds of hospitalization.

Presented here (Fig. 2, Table 5) are the odds ratio of hospitalization following a breakthrough COVID-19 infection for a patient having one or more comorbidities versus a patient with none of the studied comorbidities. Our selected model does not include any interaction effects among the comorbidities, though we can calculate these odds ratios for any combination of comorbidities.

Table 1
Overall summary statistics of our analyzed population of patients who have completed their primary COVID-19 vaccination sequence.

	Chronic kidney disease	Chronic lung disease	Diabetes	Immunocompromised	None of the studied comorbidities	Overall
	(N = 68896)	(N = 140435)	(N = 135915)	(N = 158016)	(N = 862335)	(N = 1218630)
Sex						
Female	36,626 (53.2 %)	90,915 (64.7 %)	70,883 (52.2 %)	98,047 (62.0 %)	530,797 (61.6 %)	742,950 (61.0 %)
Male	32,270 (46.8 %)	49,520 (35.3 %)	65,032 (47.8 %)	59,969 (38.0 %)	331,538 (38.4 %)	475,680 (39.0 %)
Race						
White	52,668 (76.4 %)	110,317 (78.6 %)	95,658 (70.4 %)	128,964 (81.6 %)	600,231 (69.6 %)	873,934 (71.7 %)
Unknown	2841 (4.1 %)	8321 (5.9 %)	10,637 (7.8 %)	8815 (5.6 %)	136,361 (15.8 %)	160,155 (13.1 %)
Black or African American	11,103 (16.1 %)	16,713 (11.9 %)	21,446 (15.8 %)	14,630 (9.3 %)	68,329 (7.9 %)	111,002 (9.1 %)
Asian	1974 (2.9 %)	3999 (2.8 %)	7062 (5.2 %)	4730 (3.0 %)	52,471 (6.1 %)	66,198 (5.4 %)
American Indian or Alaska Native	176 (0.3 %)	750 (0.5 %)	602 (0.4 %)	581 (0.4 %)	2717 (0.3 %)	4184 (0.3 %)
Native Hawaiian or Other Pacific Islander	134 (0.2 %)	335 (0.2 %)	510 (0.4 %)	296 (0.2 %)	2226 (0.3 %)	3157 (0.3 %)
Ethnicity						
Not Hispanic or Latino	64,238 (93.2 %)	128,631 (91.6 %)	119,543 (88.0 %)	146,001 (92.4 %)	696,936 (80.8 %)	1,018,823 (83.6 %)
Hispanic or Latino	3285 (4.8 %)	8476 (6.0 %)	12,789 (9.4 %)	8234 (5.2 %)	92,728 (10.8 %)	117,664 (9.7 %)
Unknown	1373 (2.0 %)	3328 (2.4 %)	3583 (2.6 %)	3781 (2.4 %)	72,671 (8.4 %)	82,143 (6.7 %)
Age (years)						
Mean (SD)	72.2 (12.6)	59.3 (18.0)	64.6 (13.7)	64.6 (15.1)	49.9 (17.7)	53.5 (18.1)
Median [Min, Max]	73.7 [18.2, 99.0]	62.3 [18.1, 99.0]	66.1 [18.1, 98.7]	66.9 [18.1, 98.9]	49.9 [18.1, 98.9]	54.8 [18.1, 99.0]
Age bracket						
[18,20)	25 (0.0 %)	1875 (1.3 %)	158 (0.1 %)	497 (0.3 %)	19,013 (2.2 %)	21,407 (1.8 %)
[20,25)	107 (0.2 %)	4960 (3.5 %)	677 (0.5 %)	1671 (1.1 %)	54,740 (6.3 %)	61,586 (5.1 %)
[25,30)	232 (0.3 %)	5160 (3.7 %)	1199 (0.9 %)	2286 (1.4 %)	64,594 (7.5 %)	72,565 (6.0 %)
[30,35)	423 (0.6 %)	6100 (4.3 %)	1996 (1.5 %)	3427 (2.2 %)	73,725 (8.5 %)	84,258 (6.9 %)
[35,45)	1681 (2.4 %)	14,133 (10.1 %)	8213 (6.0 %)	10,751 (6.8 %)	148,226 (17.2 %)	177,581 (14.6 %)
[45,55)	4122 (6.0 %)	18,884 (13.4 %)	18,320 (13.5 %)	18,920 (12.0 %)	148,768 (17.3 %)	196,359 (16.1 %)
[55,65)	9988 (14.5 %)	27,308 (19.4 %)	32,655 (24.0 %)	32,910 (20.8 %)	151,766 (17.6 %)	227,478 (18.7 %)
[65,75)	21,325 (31.0 %)	33,873 (24.1 %)	41,599 (30.6 %)	47,302 (29.9 %)	132,786 (15.4 %)	229,930 (18.9 %)
[75,85)	21,206 (30.8 %)	21,246 (15.1 %)	24,571 (18.1 %)	30,678 (19.4 %)	54,429 (6.3 %)	114,080 (9.4 %)
[85,Inf)	9787 (14.2 %)	6896 (4.9 %)	6527 (4.8 %)	9574 (6.1 %)	14,288 (1.7 %)	33,386 (2.7 %)
Breakthrough COVID-19 infection						
Breakthrough COVID	1965 (2.9 %)	4800 (3.4 %)	3740 (2.8 %)	4553 (2.9 %)	12,594 (1.5 %)	22,459 (1.8 %)
No breakthrough	66,931 (97.1 %)	135,635 (96.6 %)	132,175 (97.2 %)	153,463 (97.1 %)	849,741 (98.5 %)	1,196,171 (98.2 %)
Hospitalization following breakthrough						
Hospitalized	863 (1.3 %)	1248 (0.9 %)	1065 (0.8 %)	1274 (0.8 %)	1018 (0.1 %)	3352 (0.3 %)
Not hospitalized	68,033 (98.7 %)	139,187 (99.1 %)	134,850 (99.2 %)	156,742 (99.2 %)	861,317 (99.9 %)	1,215,278 (99.7 %)

Table 2
Comparison between four candidate models of time till breakthrough COVID-19 infection each with varying degrees of interaction between comorbidities.

Model complexity	AIC	ΔAIC	AICc	ΔAICc
Four-way	613721.79	0.00	613722.11	0.00
Three-way	613721.82	0.03	613722.12	0.02
Two-way	613726.78	5.00	613727.03	4.93
Base	613838.73	116.95	613838.91	116.80

We find that all of the comorbidities were associated with an increased risk of hospitalization following breakthrough COVID-19 infection when compared to patients without any of the studied comorbidities after adjustment (Fig. 2; CKD OR 2.36 [CI 1.93, 2.88]; immunocompromised OR 1.78 [CI 1.53, 2.09]; diabetes OR 1.66 [CI 1.41, 1.97]; chronic lung disease OR 1.79 [CI 1.54, 2.08]). See Supplementary Material for a full table of the selected model's parameter estimates.

4. Discussion

Here we found that the risk of SARS-CoV-2 breakthrough infection and odds of subsequent hospitalization following breakthrough infection were greater among vaccinated patients with diabetes, chronic lung disease, CKD, and with immunocompromising conditions when compared to the vaccinated individuals without these conditions after adjusting for age, sex, race, ethnicity, and

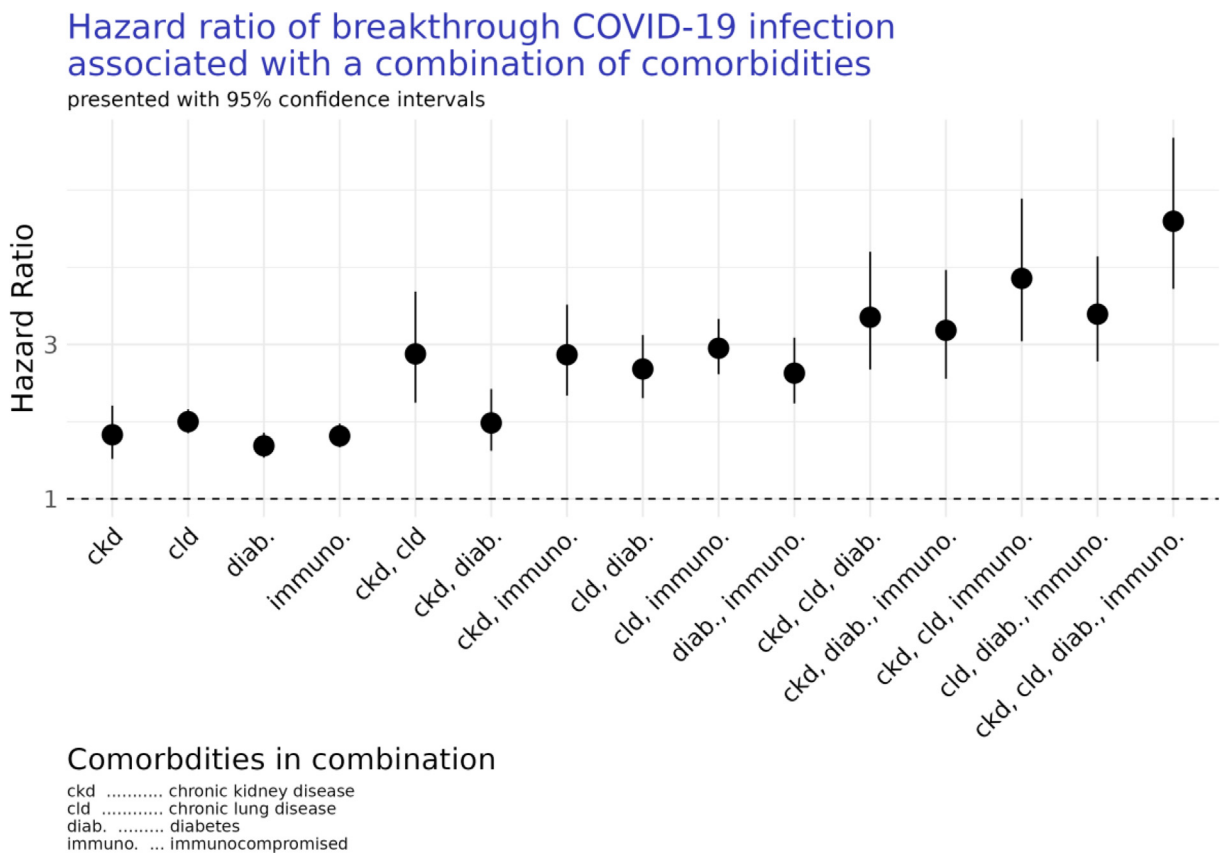

Fig. 1. Estimated hazards ratios of breakthrough COVID-19 infection associated with one or more comorbidity versus having none of the studied comorbidities. Hazards ratios are estimated from a model which considers up to four-way interactions between comorbidities. See Table 3 for the hazard ratio estimates shown here.

Table 3
Estimated hazard ratios of breakthrough infection associated patients having one or more of the studied comorbidities copmared to patients who have none of the studied comorbidities. CKD: chronic kidney disease, CLD: chronic lung disease, Diab.: diabetes, Immuno.. immunocompromised.

Comorbidities	Hazard Ratio [95 % CI]
ckd	1.83 [1.52, 2.21]
cld	2 [1.85, 2.16]
diab.	1.69 [1.53, 1.86]
immuno.	1.81 [1.67, 1.97]
ckd, cld	2.88 [2.25, 3.69]
ckd, diab.	1.98 [1.62, 2.42]
ckd, immuno.	2.87 [2.34, 3.52]
cld, diab.	2.68 [2.3, 3.12]
cld, immuno.	2.95 [2.61, 3.33]
diab., immuno.	2.63 [2.24, 3.09]
ckd, cld, diab.	3.35 [2.68, 4.2]
ckd, diab., immuno.	3.18 [2.56, 3.97]
ckd, cld, immuno.	3.86 [3.04, 4.89]
cld, diab., immuno.	3.39 [2.78, 4.14]
ckd, cld, diab., immuno.	4.6 [3.72, 5.68]

yearmonth of vaccination (Fig. 1). This is consistent with studies in unvaccinated and vaccinated people showing higher risk of infection and hospitalization in people with any of these comorbidities or similar high-risk conditions [5–7,9,10,19–21,23,24,26,28–31]. We also found that while patients with one of these four comorbities had an increased risk of breakthrough COVID-19 infection compared to individuals without any of the studied comorbidities, patients with two or more of the comorbidities have further increased risk than would be expected by the independent effects of the comorbidities on odds of breakthrough infection (Fig. 1, Table 2). In contrast, while individuals with multiple of the comorbidities have an increased risk of hospitalization following breakthrough infection, our model selection results are consistent with the comorbidities having independent effects on odds of hospitalization (Fig. 2, Table 4).

We identified chronic kidney disease as the highest risk individual comorbidity for hospitalization after adjustment for age and other demographic factors (Fig. 2). This result is consistent with previous work examining differences in COVID-19 breakthrough infection incident rates in the United Kingdom [19,21]. These stud-

Table 4
Comparison between four candidate models of probability of hospitalization following breakthrough COVID-19 infection each with varying degrees of interaction between comorbidities.

Model complexity	AIC	ΔAIC	AICc	ΔAICc
Four-way	16568.43	10.84	16568.76	10.99
Three-way	16567.03	9.44	16567.35	9.58
Two-way	16562.84	5.25	16563.10	5.33
Base	16557.59	0.00	16557.78	0.00

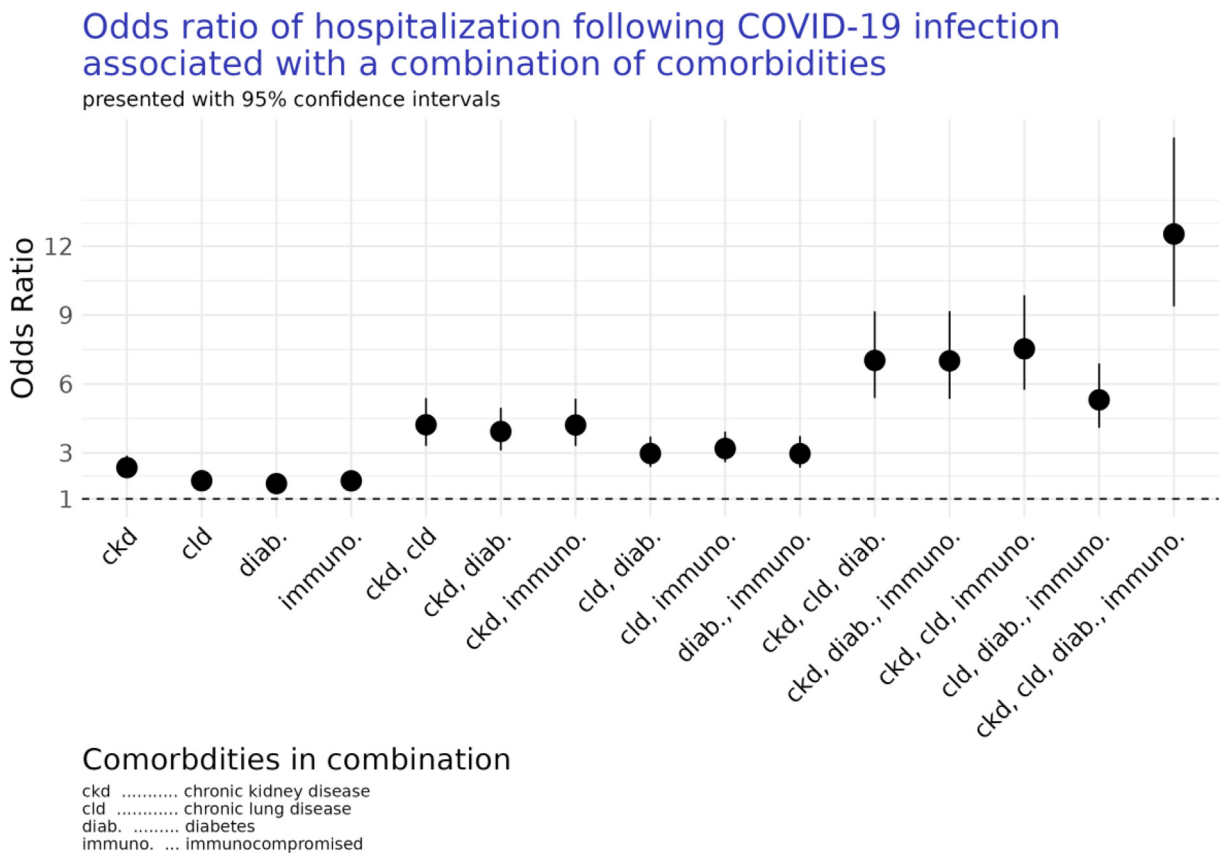

Fig. 2. Estimated odds ratios of breakthrough COVID-19 infection associated with one or more comorbidity versus being comorbidity free. Odds ratios are estimated from a model which considers no interactions between comorbidities, and their combined effects do not reflect any explicit interaction effects between comorbidities. See Table 5 for the odds ratio estimates shown here.

Table 5
Estimated odds ratios of hospitalization associated patients having one or more of the studied comorbidities copmared to patients who have none of the studied comorbidities. CKD: chronic kidney disease, CLD: chronic lung disease, Diab.: diabetes, Immuno.. immunocompromised.

Comorbidities	Odds Ratio [95 % CI]
ckd	2.36 [1.93, 2.88]
cld	1.79 [1.54, 2.08]
diab.	1.66 [1.41, 1.97]
immuno.	1.78 [1.53, 2.09]
ckd, cld	4.22 [3.31, 5.38]
ckd, diab.	3.93 [3.11, 4.96]
ckd, immuno.	4.21 [3.31, 5.36]
cld, diab.	2.98 [2.39, 3.71]
cld, immuno.	3.19 [2.59, 3.93]
diab., immuno.	2.97 [2.36, 3.73]
ckd, cld, diab.	7.02 [5.39, 9.16]
ckd, diab., immuno.	7 [5.35, 9.17]
ckd, cld, immuno.	7.53 [5.75, 9.87]
cld, diab., immuno.	5.31 [4.09, 6.89]
ckd, cld, diab., immuno.	12.53 [9.38, 16.73]

ies found that the effectiveness of the COVID-19 vaccines against breakthrough infection and subsequent hospitalization varied with the severity of chronic kidney disease. In contrast, a large study in male U.S. veterans did not show an elevated risk of severe outcomes in breakthrough infections in patients with diabetes, chronic lung disease, or CKD [27]. This discrepancy was possibly due to differences in study design where patients were matched by comorbidity burden which may reduces differences between health status and demographics between groups and may limit the generalizability between patients in the Veterans Health Administration population and the other sample populations [56]. In contrast our study compared patients with any of the identified comorbidities in any combination as well as with patients who had none of the selected comorbidities, and did not exclude patients with multiple comorbidities.

Like all studies of EHR data, ours is subject to a variety of known limitations [57–62]. We are only able to identify events that are captured by the constituent health care systems that are a part of the Truveta member system. This means we will not capture COVID-19 infections which were reported or diagnosed by a health care system that is not a part of the Truveta. Similarly, we will not capture COVID-19 infections which were never reported to a health care system. This limitation means we patients with a precedent COVID-19 infection may be missed as part of our inclusion and exclusion criteria. Another example limitation is that a patient's COVID-19 vaccination status may not captured in our data because only a limited number of member HCS reconcile their records with state health registries and other locations where many patients may have been vaccinated. Finally, a patients' comorbidity status may be misclassified in our data set because their comorbidity status is captured in a different, non-member HCS or they are classified in the EHR using codes that were not present in our codesets. These are common and well understood limitations associated with using this kind of data. In the context of this study these inherent limitations will most likely lead to an underestimation of the size of the vaccinated population which will most likely lead to an underestimation of the effects of the comorbidities on risk of breakthrough COVID-19 infection and sub-

sequent odds of hospitalization following breakthrough infection, especially in combination.

In addition to the limitations inherent in retrospective analysis of EHR data, there are other limitations associated with our study. For example, we did not include certain risk factors such as hypertension and smoking status due to limitations of the Truveta Platform at the time of analysis. Additionally, we do not consider alternate outcomes or competing risks in our analysis of time from COVID-19 vaccination till breakthrough infection, and instead consider all censoring uninformative. A follow-up analysis should consider a large suite of demographic features and risk factors as well as more varied outcomes and the potential for competing risks.

Future work should also consider the effect of booster doses on time till breakthrough COVID-19 infection and odds of hospitalization following breakthrough infection. The timing of the booster dose would most likely have to be accounted for as a time-varying covariate to account for the variation in time from completion of primary dose sequence till time of a booster dose. However, many individuals in our population were vaccinated well before booster doses were made available, meaning that booster doses may not be captured by the 180-day follow-up period. Similarly, additional subgroup analyses of differences breakthrough infection and hospitalization associated with severity level of CKD is warranted as recent analysis have found substantial differences in COVID-19 outcomes associated with severity of CKD [19,21].

Overall, these findings complement prior studies which have shown worse outcomes following COVID-19 infection in people who are have diabetes, CKD, chronic lung disease, or immunocompromising conditions [5–7,9,10,15–17,19–21,23,24,28–31]. These results add additional support to the recommendation of booster vaccines for those with high-risk conditions given that these groups continue to fare worse than the vaccinated population without any of the studied comorbidities in terms of breakthrough infection and subsequent hospitalization rates. Those with comorbidities will most likely benefit from booster vaccinations to increase and improve their immune response to infection, as has been observed in people with chronic kidney disease [19].

As vaccinated people continue to make decisions about booster vaccinations, they will be looking for information regarding their personal risk of breakthrough COVID-19 infection and severe outcomes like hospitalization. The FDA and CDC have both made recommendations that people belonging to high-risk groups, such as those with immunocompromising conditions, should receive additional doses of the COVID-19 vaccines and at a faster rate than the population without any of these comorbidities. The findings of this study improve the evidence and support recommendations for people with comorbidities such as chronic kidney disease, chronic lung disease, diabetes or who have immunocompromising conditions to receive booster vaccinations.

Data availability

Code is available on referenced GitHub repository. Data is available to all Truveta subscribers.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2023.02.038.

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