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Vaccine Effectiveness of BNT162b2 and CoronaVac against SARS-CoV-2 Omicron BA.2 in CKD

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Abstract

Background The ongoing coronavirus disease 2019 (COVID-19) pandemic has posed increased risks of hospitalization and mortality in patients with underlying CKD. Current data on vaccine effectiveness of COVID-19 vaccines are limited to patients with CKD on dialysis and seroconversion in the non-dialysis population.

Methods A case–control study was conducted of adults with CKD using data extracted from the electronic health record database in Hong Kong. Adults with CKD and COVID-19 confirmed by PCR were included in the study. Each case was matched with up to ten controls attending Hospital Authority services without a diagnosis of COVID-19 on the basis of age, sex, and index date (within three calendar days). The vaccine effectiveness of BNT162b2 and CoronaVac in preventing COVID-19 infection, hospitalizations, and all-cause mortality was estimated using conditional logistic regression adjusted by patients' comorbidities and medication history during the outbreak from January to March 2022.

Results A total of 20,570 COVID-19 cases, 6604 COVID-19–related hospitalizations, and 2267 all-cause mortality were matched to 81,092, 62,803, and 21,348 controls, respectively. Compared with the unvaccinated group, three doses of BNT162b2 or CoronaVac were associated with a reduced risk of infection (BNT162b2: 64% [95% confidence interval (CI), 60 to 67], CoronaVac: 42% [95% CI, 38 to 47]), hospitalization (BNT162b2: 82% [95% CI, 77 to 85], CoronaVac: 80% [95% CI, 76 to 84]), and mortality (BNT162b2: 94% [95% CI, 88 to 97], CoronaVac: 93% [95% CI, 88 to 96]). Vaccines were less effective in preventing infection and hospitalization in the eGFR <15 and 15–29 ml/min per 1.73 m^2 subgroups as compared with higher GFR subgroups. However, receipt of vaccine, even for one dose, was effective in preventing all-cause mortality, with estimates similar to the higher eGFR subgroups, as compared with unvaccinated.

Conclusions A dose-response relationship was observed between the number of BNT162b2 or CoronaVac doses and the effectiveness against COVID-19 infection and related comorbidity in the CKD population.

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Introduction

The ongoing coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has posed a serious threat to patients with underlying CKD. These patients are immunocompromised because of a combination of innate and adaptive immune system dysfunction, chronic inflammation, endothelial cell dysfunction, and uremia.[1] In fact, infections have been the leading cause of non-cardiovascular morbidity and mortality in the CKD population.[2] A recent systematic review highlighted the effect of CKD on the outcomes of COVID-19, including increased risk of hospitalization and mortality.[3]

With their relatively immunocompromised status, vaccination becomes crucial for patients with kidney disease. However, the ability of COVID-19 vaccines to mount a sufficient immune response in this population remains questionable because of their lower rates of seroconversion, lower antibody titers, and a less sustained response after immunization compared with healthy controls.[4,5] Previous studies have also demonstrated that patients on hemodialysis and kidney transplant recipients, compared with healthy controls, have a blunted serologic response after vaccination.[6,7]

In the Hong Kong Special Administrative Region, China, a territory-wide vaccination program with mRNA (BNT162b2/Comirnaty, BioNTech/Pfizer/Fosun) and inactivated (CoronaVac, Sinovac Biotech HK Limited) vaccines was commenced in February 2021. Although the effectiveness of both vaccines against severe outcomes has been demonstrated in

the general public in randomized controlled trials and observational studies, current data on efficacy and effectiveness after three doses of COVID-19 vaccines are limited to those with CKD on dialysis and seroconversion in the non-dialysis population.[8–10] Furthermore, with the emergence of the Omicron variant of SARS-CoV-2, vaccine effectiveness seems to be reduced in the general population compared with previous strains of SARS-CoV-2. Therefore, we conducted this population-based, retrospective study to evaluate the vaccine effectiveness during the Omicron BA.2 variant–dominant pandemic wave in the CKD population in Hong Kong.

Methods

Study Design and Population

This was a case–control study among patients with CKD aged 18 years or older. Patients with CKD were identified by the International Classification of Diseases, Ninth Revision, as listed in Supplemental Table 1, or eGFR <60 ml/min per 1.73 m^2 measured in the previous 12 months with at least two taken ≥90 days apart. Those who contracted COVID-19 infection before the index date, had received the fourth dose of the COVID-19 vaccine, or were with a missing date of birth or sex were excluded from the analysis. The fourth dose was available on March 21, 2022, which is very close to our study end date. We, therefore, excluded patients receiving a fourth dose because of the anticipation of a limited sample size. Data were extracted from the electronic health record (EHR) from the Hong Kong Hospital Authority, which records data on patient demographics, diagnoses, prescriptions, and laboratory tests, in addition to real-time data support and monitoring across all clinics and hospitals in the Hospital Authority for routine clinical management. As a statutory administrative organization in Hong Kong, the Hospital Authority provides all public inpatient services and most public outpatient services. The COVID-19 infection and vaccination records were obtained from the Department of Health of the Government of Hong Kong Special Administrative Region, China, which manages and retains all vaccination records in Hong Kong. Datasets provided by the Department of Health were linked to the Hospital Authority database using unique Hong Kong Identity Card Numbers or other personal identification numbers. These databases have previously been applied in several COVID-19 pharmacovigilance studies.[11–18]

Definitions of Vaccine Exposure

In the Hong Kong territory-wide vaccination program, the public have a choice of either BNT16b2 or CoronaVac as their first dose, but the second dose has to be the same vaccine. For the booster dose, they had a choice of either a homologous booster or a heterologous booster. Therefore, the COVID-19 vaccination status could be categorized into nine groups on the basis of the types of vaccines and the number of doses administered as follows: (*1*) unvaccinated, (*2*) one dose of BNT162b2 only, (*3*) one dose of CoronaVac only, (*4*) two doses of BNT162b2 only, (*5*) two doses of CoronaVac only, (*6*) three doses of BNT162b2, (*7*) three doses of CoronaVac, (*8*) two doses of BNT162b2 followed by a CoronaVac booster, and (*9*) two doses of CoronaVac followed by a BNT162b2 booster.

Definitions of COVID-19 Infection and Complications

A positive COVID-19 case was defined as a positive PCR test result obtained from the Department of Health and/or Hospital Authority databases. Patients in the control group who reported positive rapid antigen test results in the voluntary reporting platform online were excluded from the analysis.

The outcomes of this study include (*1*) COVID-19 infection; (*2*) hospitalization within 28 days of COVID-19 infection; and (*3*) post-infection all-cause mortality, defined as all-cause mortality within 28 days after COVID-19 infection. The information on all-cause mortality was provided by the Hong Kong Deaths Registry, which officially records all registered deaths of Hong Kong residents.

Matching Method

To assess the effectiveness of BNT162b2 and CoronaVac during the Omicron BA.2 outbreak, the inclusion period of each outcome in this study was from January 1, 2022, to March 31, 2022.[19] The matching procedure was applied for each outcome independently. The index date was the date of outcome of interest for the case and the date of hospitalization or attendance at an outpatient clinic for the control. Controls were selected from individuals with CKD who attended any hospital authority service and were not cases. For each case, up to ten matched controls were selected on the basis of age (5-year band), sex, date of attendance (within three calendar days), and Charlson Comorbidity Index (0, 1–2, 3–4, ≥5).[20] The Charlson Comorbidity Index is a morbidity score that reflects mortality risk. A score of zero indicates that no comorbidities were found. The higher the score, the more likely the predicted outcome will result in mortality.[20]

Statistical Analyses

The association between vaccination and each outcome was evaluated using conditional logistic regression, adjusted for chronic comorbidities, including hypertension, cancer, CKD, respiratory disease, coronary heart disease, stroke, heart failure, and dementia, along with the use of chronic medications, including renin-angiotensin system agents, β-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, oral anticoagulants, antiplatelets, and immunosuppressants. Vaccine effectiveness was calculated using the formula: (1−adjusted odds ratio)×100%. Cochran–Armitage test was performed to assess the association between vaccine effectiveness and number of doses of vaccine.

There were three sensitivity analyses in this study. In the first sensitivity analysis, patients who developed infection <14 days after each dose of vaccine were excluded because the time for full vaccine effect is generally regarded as 14 days.[21,22] In the second sensitivity analysis, patients who received their last dose of vaccine more than 180 days before the index date were excluded because waning immunity after vaccination is well recognized after 6 months.[23] In the third sensitivity analysis, a COVID-19 case was defined by either a positive PCR test or a positive

rapid antigen test result. Subgroup analysis stratified by baseline eGFR level (dialysis, <15, 15–29, 30–44, 45–59 ml/min per 1.73 m^2) was conducted.

All statistical tests were two-sided, and a *P* value of <0.05 was considered statistically significant. Statistical analysis was conducted using R version 4.0.3 (www.R-project.org). At least two investigators (V.K.C. Yan, C.I.Y. Chan, B. Wang, and F.W.T. Cheng) conducted the statistical analyses independently for quality assurance.

Post Hoc Analysis

To examine the effects of modification of dose by vaccine type and baseline eGFR category, we conducted *post hoc* analyses stratified by vaccine type with the addition of interaction terms using generalized estimating equations.[24]

Ethical Approval

This study was approved by the Central Institutional Review Board of the Hospital Authority of Hong Kong

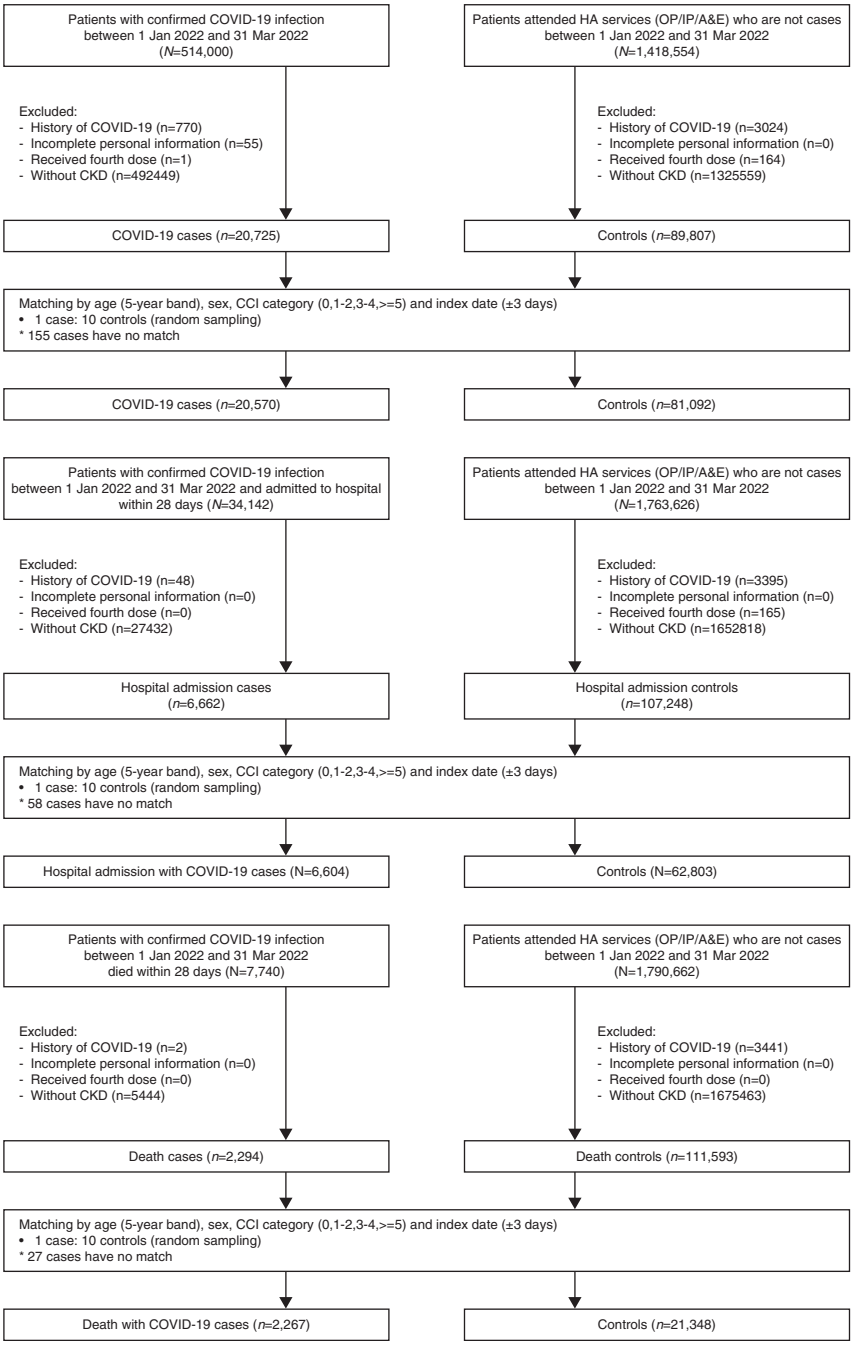

Figure 1. Flowchart of selection of cases and controls. COVID-19, coronavirus disease 2019. A&E, accident and emergency; IP, inpatient; CCI, Charlson Comorbidity Index; OP, Outpatient.

(CIRB-2021-005-4) and the Department of Health Ethics Committee (LM171/2021).

Results

The selection of cases and controls for COVID-19 infection and complications are shown in Figure 1. A total of 20,570 COVID-19 cases, 6604 cases of COVID-19–related hospitalization, and 2267 all-cause mortality were matched to 81,092, 62,803, and 21,348 controls, respectively.

The characteristics of cases and controls are summarized in Table 1. For COVID-19 infection, there was no noticeable difference between groups in most of the medical and medication history, except for the use of diuretics (case 6459 [31%]; control: 17,474 [22%]). As for COVID-19–related hospitalization, there was a higher proportion of case patients on diuretics (2805 [42%] versus 14,874 [24%]) and antiplatelets (3069 [46%] versus 23,698 [38%]), with fewer case patients on lipid-lowering agents (4073 [62%] versus 45,123 [72%]) and anti-diabetic drugs (2547 [39%] versus 30,365 [48%]). A similar pattern was observed for all-cause mortality, with more case patients on diuretics (1207 [53%] versus 5471 [26%]), antiplatelets (1188 [52%] versus 8806 [41%]), immunosuppressants (166 [7%] versus 216 [1%]), and insulin (1007 [44%] versus 3171 [15%]) but fewer patients with hypertension (1548 [68%] versus 16,443 [77%]) and diabetes mellitus (1228 [54%] versus 13,602 [64%]) prescribed with renin-angiotensin system agents (1028 [45%] versus 12,286 [58%]), lipid-lowering agents (1308 [58%] versus 14,949 [70%]), and anti-diabetic drugs (788 [35%] versus 9849 [46%]).

Table 1. Baseline characteristics of cases and controls

Baseline Characteristics	COVID-19 Infection		COVID-19–Related Hospitalization		All-Cause Mortality	
	Case	Control	Case	Control	Case	Control
N	20,570	81,092	6604	62,803	2267	21,348
Age, yr	75 (14)	75 (14)	79 (14)	79 (13)	84 (11)	84 (10)
Sex, male	12,006 (58)	47,464 (59)	3852 (58)	36,998 (59)	1410 (62)	13,425 (63)
Charlson Comorbidity Index	5.01 (2.23)	4.93 (2.13)	5.72 (2.11)[a]	5.56 (1.98)[a]	6.53 (2.15)[a]	6.29 (1.93)[a]
Hypertension	13,348 (65)	54,607 (67)	4345 (66)[a]	45,532 (72)[a]	1548 (68)[a]	16,443 (77)[a]
Cancer	1383 (7)	4314 (5)	511 (8)	4226 (7)	189 (8)	1823 (9)
Diabetes mellitus	11,625 (57)	49,404 (61)	3629 (55)[a]	39,669 (63)[a]	1228 (54)[a]	13,602 (64)[a]
Respiratory disease	1280 (6)	3986 (5)	573 (9)	3972 (6)	245 (11)	2039 (10)
Coronary heart disease	3487 (17)	11,625 (14)	1373 (21)[a]	10,379 (17)[a]	612 (27)[a]	4117 (19)[a]
Stroke	3250 (16)	11,705 (14)	1371 (21)	11,301 (18)	643 (28)[a]	4818 (23)[a]
Heart failure	2739 (13)[a]	7754 (10)[a]	1295 (20)[a]	7722 (12)[a]	572 (25)[a]	3666 (17)[a]
Dementia	505 (2)	1002 (1)	309 (5)[a]	1211 (2)[a]	144 (6)[a]	628 (3)[a]
eGFR						
Dialysis	768 (4)[a]	87 (0)[a]	656 (10)[a]	69 (0)[a]	121 (5)[a]	16 (0)[a]
<15 ml/min per 1.73 m^2	2158 (11)[a]	5756 (7)[a]	1303 (20)[a]	4028 (7)[a]	466 (21)[a]	1144 (5)[a]
15–29 ml/min per 1.73 m^2	2891 (14)	10,707 (13)	1210 (18)[a]	8921 (14)[a]	568 (25)[a]	3408 (16)[a]
30–44 ml/min per 1.73 m^2	5591 (27)	23,130 (29)	1682 (26)[a]	19,283 (31)[a]	575 (25)[a]	7336 (35)[a]
45–59 ml/min per 1.73 m^2	6143 (30)[a]	29,274 (36)[a]	1272 (19)[a]	22,327 (36)[a]	388 (17)[a]	7267 (34)[a]
≥60 ml/min per 1.73 m^2	2872 (14)	11,744 (15)	467 (7)[a]	7801 (13)[a]	166 (7)	2011 (10)
Renin-angiotensin system agents	12,111 (59)	50,365 (62)	3471 (53)[a]	38,018 (61)[a]	1028 (45)[a]	12,286 (58)[a]
β-blockers	8541 (42)	32,422 (40)	2880 (44)[a]	24,258 (39)[a]	943 (42)	7885 (37)
Calcium channel blockers	13,191 (64)	52,879 (65)	4218 (64)	41,333 (66)	1431 (63)	13,968 (65)
Diuretics	6459 (31)[a]	17,474 (22)[a]	2805 (42)[a]	14,874 (24)[a]	1207 (53)[a]	5471 (26)[a]
Nitrates	3147 (15)[a]	8597 (11)[a]	1304 (20)[a]	7667 (12)[a]	537 (24)[a]	3067 (14)[a]
Lipid-lowering agents	13,614 (66)[a]	57,662 (71)[a]	4073 (62)[a]	45,123 (72)[a]	1308 (58)[a]	14,939 (70)[a]
Oral anticoagulants	1813 (9)	5909 (7)	705 (11)	5366 (9)	260 (11)	2127 (10)
Antiplatelets	7846 (38)	27,935 (34)	3069 (46)[a]	23,698 (38)[a]	1188 (52)[a]	8806 (41)[a]
Immunosuppressants	810 (4)	2866 (4)	225 (3)	1335 (2)	166 (7)[a]	216 (1)[a]
Insulin	4242 (21)[a]	12,954 (16)[a]	1623 (25)[a]	9951 (16)[a]	1007 (44)[a]	3171 (15)[a]
Anti-diabetic drugs	8962 (44)[a]	39,359 (49)[a]	2547 (39)[a]	30,365 (48)[a]	788 (35)[a]	9849 (46)[a]
Vaccination status						
Unvaccinated	7932 (39)[a]	23,776 (29)[a]	3600 (55)[a]	20,614 (33)[a]	1552 (68)[a]	7632 (36)[a]
One dose of BNT162b2	695 (3)	3508 (4)	216 (3)	2566 (4)	45 (2)	700 (3)
One dose of CoronaVac	3745 (18)	12,869 (16)	1315 (20)	11,093 (18)	392 (17)	4148 (19)
Two doses of BNT162b2	2174 (11)	10,209 (13)	389 (6)[a]	6854 (11)[a]	52 (2)[a]	1877 (9)[a]
Two doses of CoronaVac	4158 (20)	18,377 (23)	846 (13)[a]	14,234 (23)[a]	204 (9)[a]	4731 (22)[a]
Three doses of BNT162b2	591 (3)[a]	4908 (6)[a]	89 (1)[a]	2765 (4)[a]	7 (0.3)[a]	775 (4)[a]
Three doses of CoronaVac	1013 (5)	5590 (7)	115 (2)[a]	3702 (6)[a]	13 (0.6)[a]	1226 (6)[a]
B-B-C	6 (0.0)	57 (0.0)	0 (0.0)	29 (0.0)	0 (0.0)	5 (0.0)
C-C-B	256 (1)	1798 (2.2)	34 (0.5)	946 (2)	2 (0.0)[a]	254 (1)[a]
Time from vaccination, d	66.0 (70.7)[a]	58.4 (66.2)[a]	51.1 (61.3)	54.1 (62.8)	54.3 (63.2)[a]	47.6 (57.0)[a]

COVID-19, coronavirus disease 2019.
[a]Indicate a standardized mean difference >0.1 between cases and controls. All parameters are expressed in either frequency (percentage) or mean (SD).

Table 2. Vaccine effectiveness for preventing coronavirus disease 2019 infection and related morbidity by vaccine type

Outcomes	Unvaccinated	BNT162b2				CoronaVac			
		One Dose Only	Two Doses Only	Three Doses	*P* Value for Trend	One Dose Only	Two Doses Only	Three Doses	*P* Value for Trend
COVID-19 infection									
Case (%)	7932 (36)	695 (3)	2174 (11)	591 (3)	<0.001	3745 (18)	4158 (20)	1013 (5)	<0.001
Control (%)	23,776 (29)	3508 (4)	10,209 (13)	4908 (6)		12,869 (16)	18,377 (23)	5590 (7)	
Vaccine effectiveness %	REF	42	35	64		7	29	42	
(95% CI)		(37 to 47)	(31 to 39)	(60 to 67)		(3 to 11)	(26 to 32)	(38 to 47)	
COVID-19–related hospitalization									
Case (%)	3600 (55)	216 (3)	389 (6)	89 (2)	<0.001	1315 (20)	846 (13)	115 (2)	<0.001
Control (%)	20,614 (33)	2566 (4)	6854 (11)	2765 (6)		11,093 (18)	14,234 (23)	3702 (6)	
Vaccine effectiveness %	REF	54	66	82		25	63	80	
(95% CI)		(46 to 60)	(62 to 80)	(77 to 85)		(19 to 30)	(60 to 66)	(76 to 84)	
All-cause mortality									
Case (%)	1552 (68)	45 (2)	52 (2)	7 (0)	<0.001	392 (17)	204 (9)	13 (1)	<0.001
Control (%)	7632 (36)	700 (3)	1877 (9)	775 (4)		4148 (19)	4731 (22)	1226 (6)	
Vaccine effectiveness, %	REF	67	85	94		45	77	93	
(95% CI)		(53 to 76)	(80 to 89)	(88 to 97)		(37 to 51)	(73 to 81)	(88 to 96)	

Vaccine effectiveness=(1−adjusted odds ratio)×100%, adjusted for chronic comorbidities, including hypertension, cancer, CKD, respiratory disease, coronary heart disease, stroke, heart failure, and dementia, along with the use of renin-angiotensin system agents, β-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, oral anticoagulants, antiplatelets, and immunosuppressants. CI, confidence interval; COVID-19, coronavirus disease 2019.
P value for trend indicates the statistical significance of the change in vaccine effectiveness with respect to the number of doses of vaccines.

A positive dose-response relationship of vaccine effectiveness between the number of BNT162b2 or CoronaVac doses received is summarized in Table 2. Vaccine effectiveness among patients with CKD against COVID-19 infection after the first dose of BNT162b2 and CoronaVac were 42% (95% confidence interval [CI], 37% to 47%) and 7% (3% to 11%), respectively. Much higher effectiveness was shown in vaccine recipients who received three doses of BNT162b2 (64% [95% CI, 60% to 67%]) or CoronaVac (42% [95% CI, 38% to 47%]). A similar dose-response relationship was observed, with more doses of vaccine administered associated with higher vaccine effectiveness in preventing hospitalization and all-cause mortality after COVID-19 infection. Vaccine effectiveness against hospitalization and all-cause mortality after COVID-19 infection were 82% (95% CI, 77% to 85%) and 94% (95% CI, 88% to 97%) after three doses of BNT162b2 and 80% (95% CI, 76% to 84%) and 93% (95% CI, 88% to 96%) after three doses of CoronaVac, respectively. Compared with three doses of CoronaVac, patients who received two doses of CoronaVac with BNT162b2 as a booster had higher vaccine effectiveness against COVID-19 infection (57% [95% CI, 50% to 62%]) but had similar vaccine effectiveness against hospitalization and all-cause mortality. Owing to the small number of people who received CoronaVac after two doses of BNT162b2 (n=63), the vaccine effectiveness against different outcomes could not be compared. The adjusted and unadjusted odds ratios of COVID-19 infection and related morbidity are presented in Supplemental Table 2.

The results of three sensitivity analyses are summarized in Supplemental Tables 3–5. The positive dose-response relationship findings are consistent with the main analysis. As for the subgroup analysis, much higher effectiveness was shown in vaccine recipients with eGFR ≥30 ml/min per 1.73 m^2 who received three doses of BNT162b2 and CoronaVac, compared with two-dose and one-dose recipients. These positive dose-response relationships for COVID-19 infection and COVID-19–related hospitalization were less clear in patients with eGFR <15 ml/min per 1.73 m^2 (Figure 2 and Supplemental Table 6).

The *post hoc* analyses illustrated that interactions were significant between the number of doses and types of vaccines for COVID-19–related hospitalization. A higher boost in vaccine effectiveness was observed with additional doses of CoronaVac as compared with additional doses of BNT162b2. The increase in vaccine effectiveness in preventing COVID-19 infection was also smaller for the second dose versus first dose of BNT162b2, as compared with second dose versus first of CoronaVac (Table 3). Interactions were also significant for the number of doses and eGFR level. The boost in vaccine effectiveness with a second and third dose as compared with one dose in preventing COVID-19–related hospitalization was smaller among individuals with eGFR <15 ml/min per 1.73 m^2 for both BNT162b2 and CoronaVac (Supplemental Table 7).

Discussion

This study stemmed from our previous study to specifically evaluate the dose-response effectiveness of an mRNA (BNT162b2) and an inactivated virus (CoronaVac) COVID-19 vaccine against the Omicron BA.2 variant in the CKD population.[11] A clear dose-response relationship between the number of vaccine doses and the magnitude of vaccine effectiveness against COVID-19 infection, hospitalization, and all-cause mortality was demonstrated in

		Cases (%)	Controls (%)	Vaccine Effectiveness % (95% CI)
	COVID-19 infection			
eGFR <15	Unvaccinated	1125 (52)	2289 (40)	REF
	1-dose BNT162b2	90 (4)	346 (6)	24.6 (-30.3 - 56.4)
	2-dose BNT162b2	201 (9)	750 (13)	35.2 (7.1 - 54.8)*
	3-dose BNT162b2	55 (3)	333 (6)	63.6 (34.0 - 80.0)*
eGFR 15-29	Unvaccinated	1390 (48)	4260 (40)	REF
	1-dose BNT162b2	79 (3)	417 (4)	51.8 (19.1 - 71.3)*
	2-dose BNT162b2	207 (7)	954 (9)	40.7 (18.3 - 57.0)*
	3-dose BNT162b2	42 (1)	341 (3)	69.9 (41.1 - 84.7)*
eGFR 30-44	Unvaccinated	2321 (42)	7246 (31)	REF
	1-dose BNT162b2	154 (3)	1009 (4)	58.6 (46.7 - 67.9)*
	2-dose BNT162b2	488 (9)	2606 (11)	46.1 (36.9 - 54.0)*
	3-dose BNT162b2	102 (2)	1088 (5)	76.5 (68.6 - 82.5)*
eGFR 45-59	Unvaccinated	1981 (32)	7397 (25)	REF
	1-dose BNT162b2	195 (3)	1202 (4)	38.6 (24.8 - 49.8)*
	2-dose BNT162b2	659 (11)	3720 (13)	27.5 (17.7 - 36.1)*
	3-dose BNT162b2	218 (4)	1959 (7)	57.0 (48.1 - 64.4)*
	COVID-19–related hospitalization			
eGFR <15	Unvaccinated	739 (57)	1776 (44)	REF
	1-dose BNT162b2	46 (4)	252 (6)	68.8 (45.2 - 82.2)*
	2-dose BNT162b2	98 (8)	450 (11)	43.5 (16.8 - 61.7)*
	3-dose BNT162b2	32 (3)	157 (4)	46.5 (3.6 - 70.3)*
eGFR 15-29	Unvaccinated	710 (59)	3840 (43)	REF
	1-dose BNT162b2	27 (2)	300 (3)	56.7 (20.3 - 76.5)*
	2-dose BNT162b2	36 (3)	707 (8)	63.8 (41.3 - 77.7)*
	3-dose BNT162b2	7 (1)	160 (2)	80.9 (48.0 - 93.0)*
eGFR 30-44	Unvaccinated	962 (57)	6592 (34)	REF
	1-dose BNT162b2	35 (2)	789 (4)	70.7 (56.6 - 80.3)*
	2-dose BNT162b2	74 (4)	1823 (9)	76.1 (67.9 - 82.2)*
	3-dose BNT162b2	5 (0)	633 (3)	94.6 (86.5 - 97.8)*
eGFR 45-59	Unvaccinated	675 (53)	6352 (28)	REF
	1-dose BNT162b2	40 (3)	878 (4)	54.8 (33.7 - 69.2)*
	2-dose BNT162b2	50 (4)	2719 (12)	78.5 (70.2 - 84.5)*
	3-dose BNT162b2	5 (0)	1169 (5)	96.3 (89.9 - 98.7)*
	COVID-19–related mortality			
eGFR <15	Unvaccinated	352 (76)	507 (44)	REF
	1-dose BNT162b2	10 (2)	59 (5)	79.9 (7.9 - 95.6)*
	2-dose BNT162b2	10 (2)	95 (8)	95.2 (75.7 - 99.0)*
	3-dose BNT162b2	1 (0)	27 (2)	88.8 (-12.2 - 98.9)*
eGFR 15-29	Unvaccinated	396 (70)	1488 (44)	REF
	1-dose BNT162b2	6 (1)	93 (3)	81.1 (31.2 - 94.8)*
	2-dose BNT162b2	9 (2)	227 (7)	82.8 (56.6 - 93.2)*
	3-dose BNT162b2	0 (0)	42 (1)	NA
eGFR 30-44	Unvaccinated	386 (67)	2645 (36)	REF
	1-dose BNT162b2	8 (1)	247 (3)	78.5 (45.8 - 91.5)*
	2-dose BNT162b2	10 (2)	587 (8)	87.0 (69.9 - 94.4)*
	3-dose BNT162b2	1 (0)	242 (3)	96.8 (66.1 - 99.7)*
eGFR 45-59	Unvaccinated	261 (67)	2327 (32)	REF
	1-dose BNT162b2	9 (2)	230 (3)	63.1 (4.3 - 85.8)*
	2-dose BNT162b2	7 (2)	749 (10)	91.9 (80.3 - 96.7)*
	3-dose BNT162b2	2 (1)	329 (5)	93.9 (70.1 - 98.8)*

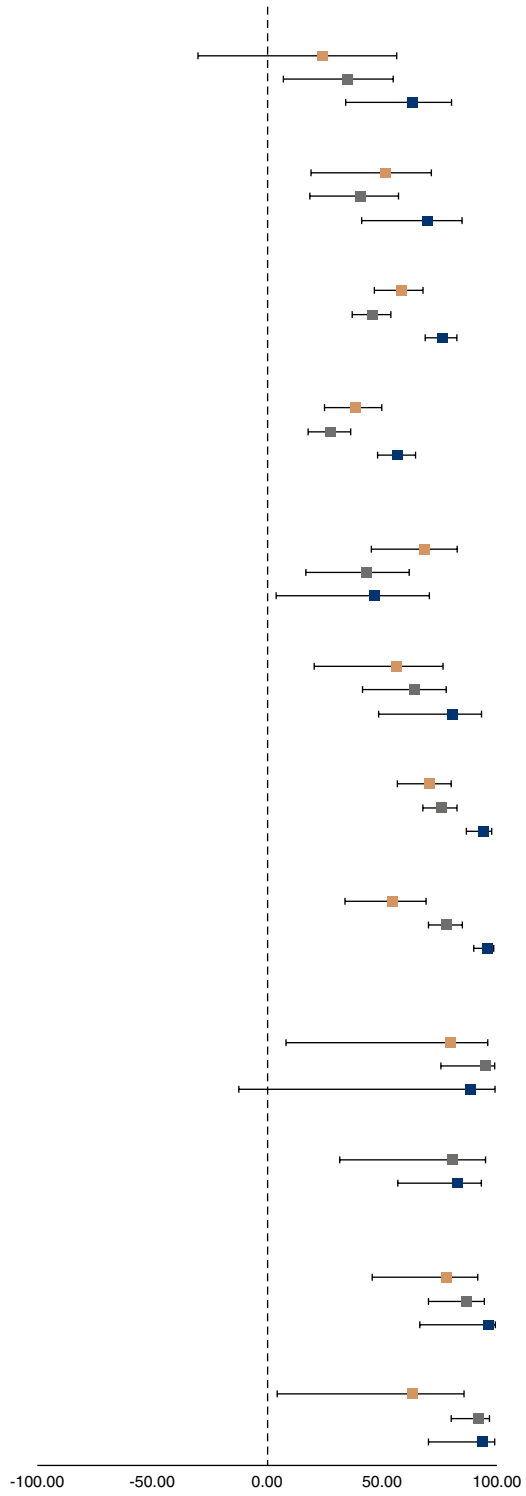

Figure 2. Vaccine effectiveness for preventing COVID-19 infection and related morbidity across eGFR strata, stratified by vaccine type. Using the unvaccinated group as the reference group, vaccine effectiveness was calculated from (1−aOR)×100% among different subgroups stratified by baseline eGFR level. Patients on dialysis were not included in the analysis because of the limited sample size. For instance, the vaccine effectiveness of one dose, two doses, and three doses of BNT162b2 against COVID-19 infection among patients with eGFR <15 ml/min per 1.73 m^2 were 24.6%, 35.2%, and 63.6%, respectively. Vaccine effectiveness with * indicates the result is statistically significant. CI, confidence interval; aOR, adjusted odds ratio. Figure 2 can be viewed in color online at www.cjasn.org.

		Cases (%)	Controls (%)	Vaccine Effectiveness % (95% CI)
		COVID-19 infection		
eGFR <15	Unvaccinated	1125 (52)	2289 (40)	REF
	1-dose CoronaVac	323 (15)	944 (16)	31.2 (6.4 - 49.5)*
	2-dose CoronaVac	283 (13)	859 (15)	26.6 (-3.2 - 47.8)
	3-dose CoronaVac	63 (3)	152 (3)	-12.6 (-119.5 - 42.3)
eGFR 15-29	Unvaccinated	1390 (48)	4260 (40)	REF
	1-dose CoronaVac	574 (20)	1973 (18)	-0.8 (-23.8 - 17.9)
	2-dose CoronaVac	504 (17)	2284 (21)	32.8 (16.2 - 46.2)*
	3-dose CoronaVac	76 (3)	362 (3)	45.3 (4.5 - 68.7)*
eGFR 30-44	Unvaccinated	2321 (42)	7246 (31)	REF
	1-dose CoronaVac	1120 (20)	3992 (17)	16.5 (6.3 - 25.5)*
	2-dose CoronaVac	1128 (20)	5428 (23)	34.3 (26.3 - 41.5)*
	3-dose CoronaVac	227 (4)	1372 (6)	57.5 (47.4 - 65.6)*
eGFR 45-59	Unvaccinated	1981 (32)	7397 (25)	REF
	1-dose CoronaVac	1181 (19)	4482 (15)	4.3 (-6.6 - 14.1)
	2-dose CoronaVac	1464 (24)	6996 (24)	18.4 (9.7 - 26.3)*
	3-dose CoronaVac	356 (6)	2648 (9)	50.2 (41.7 - 57.4)*
		COVID-19–related hospitalization		
eGFR <15	Unvaccinated	739 (57)	1776 (44)	REF
	1-dose CoronaVac	194 (15)	702 (17)	39.8 (16.5 - 56.6)*
	2-dose CoronaVac	155 (12)	524 (13)	30.8 (1.8 - 51.2)*
	3-dose CoronaVac	31 (2)	115 (3)	56.8 (10.5 - 79.1)*
eGFR 15-29	Unvaccinated	710 (59)	3840 (43)	REF
	1-dose CoronaVac	271 (15)	1757 (20)	6.5 (-17.4 - 25.5)*
	2-dose CoronaVac	148 (12)	1825 (21)	51.7 (37.0 - 62.9)*
	3-dose CoronaVac	10 (1)	246 (3)	55.8 (-2.1 - 80.9)*
eGFR 30-44	Unvaccinated	962 (57)	6592 (34)	REF
	1-dose CoronaVac	358 (21)	3701 (19)	34.2 (22.9 - 43.8)*
	2-dose CoronaVac	222 (13)	4591 (24)	65.4 (58.4 - 71.2)*
	3-dose CoronaVac	19 (1)	954 (5)	88.8 (80.8 - 93.4)*
eGFR 45-59	Unvaccinated	675 (53)	6352 (28)	REF
	1-dose CoronaVac	290 (23)	3632 (16)	19.8 (4.0 - 32.9)*
	2-dose CoronaVac	190 (15)	5383 (24)	60.5 (51.7 - 67.7)*
	3-dose CoronaVac	18 (1)	1768 (8)	87.1 (78.7 - 92.1)*
		COVID-19–related mortality		
eGFR <15	Unvaccinated	352 (76)	507 (44)	REF
	1-dose CoronaVac	62 (13)	247 (22)	79.3 (57.1 - 90.0)*
	2-dose CoronaVac	28 (6)	162 (14)	80.5 (54.2 - 91.7)*
	3-dose CoronaVac	3 (1)	38 (3)	97.6 (62.0 - 99.8)*
eGFR 15-29	Unvaccinated	396 (70)	1488 (44)	REF
	1-dose CoronaVac	101 (18)	756 (22)	34.3 (3.2 - 55.4)*
	2-dose CoronaVac	53 (9)	700 (21)	60.4 (35.3 - 75.8)*
	3-dose CoronaVac	3 (1)	83 (2)	97.6 (62.0 - 99.8)*
eGFR 30-44	Unvaccinated	386 (67)	2645 (36)	REF
	1-dose CoronaVac	106 (18)	1453 (20)	38.2 (15.2 - 54.9)*
	2-dose CoronaVac	61 (11)	1705 (23)	64.7 (48.8 - 75.6)*
	3-dose CoronaVac	1 (0)	400 (5)	88.8 (45.6 - 97.7)*
eGFR 45-59	Unvaccinated	261 (67)	2327 (32)	REF
	1-dose CoronaVac	72 (19)	1306 (18)	32.8 (0.2 - 54.7)*
	2-dose CoronaVac	36 (9)	1681 (23)	79.0 (65.4 - 87.3)*
	3-dose CoronaVac	1 (0)	536 (7)	97.0 (77.2 - 99.6)*

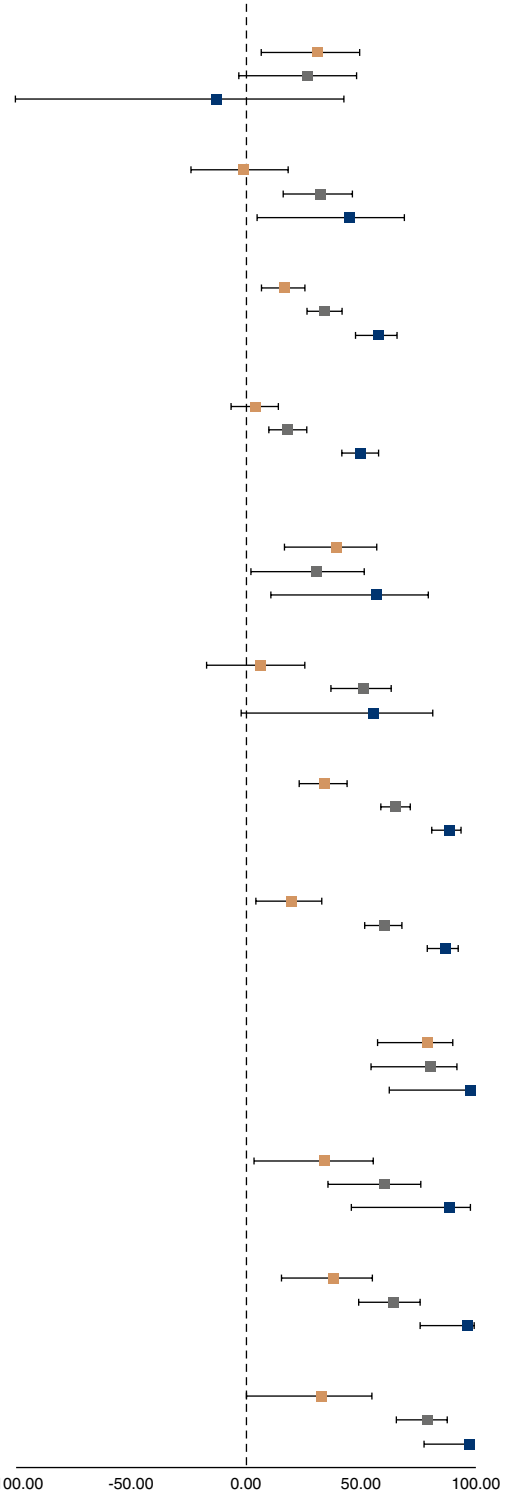

Figure 2. *Continued.*

this study. Compared with BNT162b2, a greater boost in vaccine effectiveness was observed with additional doses of CoronaVac. As a result, both vaccines demonstrated similar vaccine effectiveness after two to three doses of vaccination. Our study also illustrated that a similar level of protection could still be conferred in patients with CKD

Table 3. Relationship of vaccine dose and type with coronavirus disease 2019 infection and related morbidity among patients receiving at least one dose of vaccine

Outcomes	Crude OR (95% CI)	Adjusted OR (95% CI)
COVID-19 infection		
Vaccine type		
CoronaVac	REF	
BNT162b2	0.68 (0.62 to 0.74)	0.66 (0.60 to 0.72)
Vaccine dose		
One dose	REF	
Two doses	0.78 (0.74 to 0.82)	0.81 (0.77 to 0.85)
Three doses	0.62 (0.58 to 0.67)	0.66 (0.61 to 0.72)
BNT162b2: vaccine dose		
BNT162b2: two doses	1.38 (1.24 to 1.54)	1.42 (1.28 to 1.59)
BNT162b2: three doses	0.98 (0.85 to 1.12)	0.98 (0.85 to 1.13)
COVID-19–related hospitalization		
Vaccine type		
CoronaVac	REF	
BNT162b2	0.71 (0.61 to 0.83)	0.63 (0.54 to 0.74)
Vaccine dose		
One dose	REF	
Two doses	0.50 (0.46 to 0.55)	0.56 (0.51 to 0.61)
Three doses	0.26 (0.22 to 0.32)	0.32 (0.26 to 0.39)
BNT162b2: vaccine dose		
BNT162b2: two doses	1.35 (1.11 to 1.63)	1.49 (1.22 to 1.82)
BNT162b2: three doses	1.46 (1.06 to 2.01)	1.47 (1.06 to 2.02)
All-cause mortality		
Vaccine type		
CoronaVac	REF	
BNT162b2	0.68 (0.50 to 0.94)	0.64 (0.46 to 0.90)
Vaccine dose		
One dose	REF	
Two doses	0.46 (0.38 to 0.54)	0.52 (0.43 to 0.63)
Three doses	0.11 (0.06 to 0.20)	0.15 (0.09 to 0.26)
BNT162b2: vaccine dose		
BNT162b2: two doses	0.95 (0.61 to 1.47)	0.91 (0.58 to 1.45)
BNT162b2: three doses	1.25 (0.47 to 3.33)	1.23 (0.45 to 3.35)

Vaccine type refers to the odds ratio comparing BNT162b2 with CoronaVac among those who received one dose of vaccine; vaccine dose refers to the odds ratio comparing three dose and two dose with one dose among those who received CoronaVac; combination of point estimates of vaccine type, vaccine dose, and interaction terms refers to the odds ratio compared with one-dose CoronaVac. For instance, the crude odds ratio of coronavirus disease 2019 infection of one-dose BNT162b2 versus one-dose CoronaVac is 0.68; the crude odds ratio of coronavirus disease 2019 infection of two-dose CoronaVac versus one-dose CoronaVac is 0.78; the crude odds ratio of coronavirus disease 2019 infection of two-dose BNT162b2 versus one-dose CoronaVac is 10^[log(0.68)+log(0.78)+log(1.38)]=0.73. Compared with one-dose CoronaVac, the odds ratios for two-dose CoronaVac, one-dose BNT162b2, and two-dose BNT162b2 are 0.78, 0.68, and 0.73, respectively. *P* value of BNT162b2: two doses indicates that the differential effect between these odds ratios is statistically significant. BNT162b2: vaccine dose, interaction terms for BNT162b2 and vaccine dose (modification of effect of vaccine type by dose); CI, confidence interval; COVID-19, coronavirus disease 2019; OR, odds ratio.
Adjusted for chronic comorbidities, including hypertension, cancer, CKD, respiratory disease, coronary heart disease, stroke, heart failure, and dementia, along with the use of renin-angiotensin system agents, β-blockers, calcium channel blockers, diuretics, nitrates, lipid-lowering agents, oral anticoagulants, antiplatelets, and immunosuppressants.

as in the general public with sufficient doses of vaccination, highlighting the importance of booster dose administration for patients with CKD.

There are few studies evaluating the effectiveness of SARS-CoV-2 vaccines in the CKD population, aside from against the Omicron BA.2 variant.[25,26] Andrews *et al.* reported that the vaccine effectiveness of BNT162b2 against symptomatic infection in the general public in England was approximately 45.7%–66.9% after a booster dose.[27] Our results were comparable with the upper bound of their study as we defined both symptomatic and asymptomatic PCR-positive as COVID-19 infection. In a previous study conducted in the general public in Hong Kong during the same period,[28] the vaccine effectiveness against COVID-19–related mortality after two doses of BNT162b2 and CoronaVac ranged from 74.8% to 90.7% across different age groups and further increased to 86.6%–98.4% after three doses of SARS-CoV-2 vaccines, which is comparable with our current findings.

Consistent with other studies,[28] our study also displayed the highest vaccine effectiveness against Omicron BA.2 infection after three doses of BNT162b2 and CoronaVac, supporting the importance of booster dose administration in individuals with CKD. In addition, three doses of BNT162b2 was shown to be more effective than three doses of CoronaVac against any SARS-CoV-2 infection, which is consistent with findings from a serologic study conducted in Turkey[29] and real-world evidence in Hong Kong and Singapore.[30,31] However, our *post hoc* analysis suggested that the effect modification of the number of doses of

vaccine differs by vaccine type, with CoronaVac having a greater boost in efficacy in preventing COVID-19–related hospitalization with additional doses of vaccines compared with BNT162b2.

Despite the fact that a heterologous booster dose of BNT162b2 after two doses of CoronaVac may be as effective as three doses of CoronaVac in our study, this should be interpreted with caution given that a limited number of people received heterologous boosters. As illustrated in our previous study,[11] both vaccines demonstrated excellent safety profiles in patients with CKD, and hence, the risk–benefit calculation leans toward additional doses at relatively low risk of side effects. Therefore, favorable consideration should be given to fourth or fifth doses because both homologous and heterologous boosters were found to be effective in protecting against severe COVID-19 outcomes.

Both BNT162b2 and CoronaVac appeared to be less effective against COVID-19–related hospitalization in individuals with a baseline eGFR <15 ml/min per 1.73 m^2 and between 15 and 29 ml/min per 1.73 m^2 compared with other eGFR categories. The reasons why the effectiveness of vaccines appeared less dose dependent in moderate-to-severe kidney failure remain to be elucidated. Despite the greater rates of infection and hospitalization in these individuals, the risk of all-cause mortality was not higher, suggesting that vaccinations remained effective against mortality despite the higher rates of hospitalization. In addition, there are significant interactions between vaccine doses and baseline eGFR category. Additional doses of vaccines seem to be less effective for both COVID-19 infection and COVID-19–related hospitalization in individuals with baseline eGFR <15 ml/min per 1.73 m^2. The explanation for the reduced vaccine effectiveness in this group of patients could be attributed to their reduced ability to surmount robust immune responses, and further prospective studies on immunization schedules are warranted for patients with kidney failure.[32–34]

This study is one of the first studies to provide real-world evidence on the effectiveness of mRNA (BNT162b2) and inactivated virus (CoronaVac) vaccines against the Omicron BA.2 variant among patients with CKD. Our study was consistent with previous studies and further extended the current evidence beyond the general population to include those with non-dialysis CKD. A key strength of this study is the broad representativeness of the sample as the Hospital Authority EHR covers the entire territory of Hong Kong. Furthermore, data linkage between vaccination and EHR is highly accurate because the Hong Kong Government has the sole responsibility for the distribution of COVID-19 vaccines and documentation of each vaccination.

Nonetheless, several limitations are worthy of mention. First, the limited number of individuals receiving CoronaVac boosters after the primary series of BNT162b2 hindered the estimation of the risk of infection-related complications and mortality in this group of people. Second, only positive PCR and rapid antigen tests are available in the database of the Department of Health of the Hong Kong Government. Hence, a test-negative case–control study design could not be applied using the current dataset. There is a possibility that people with asymptomatic COVID-19 infections could be misclassified as controls, leading to bias in the estimates toward null. However, the surveillance of COVID-19 in Hong Kong is strict, and mandatory tests are required for a wide range of people considered to be at a high risk of infection. Third, the waning of vaccine effectiveness was not adjusted for in our primary analysis, although a sensitivity analysis was conducted by limiting vaccine exposure to at most 180 days from the latest dose. Fourth, it is important to note that the case–control study design can only establish associations, not causation, between the number and type of vaccines administered and COVID-19–related outcomes. Finally, the results from the subgroup and *post hoc* analyses are only hypothesis generating. Further prospective studies on immunization schedules are warranted to examine the vaccine effectiveness among patients with CKD.

To conclude, a dose-response relationship was observed between the number of BNT162b2 or CoronaVac doses administered with effectiveness against COVID-19 infection and severe COVID-19 diseases during the Omicron BA.2 pandemic in the CKD population in comparison with the unvaccinated patients, highlighting the importance of booster dose administration to reduce the risk of COVID-19 infection and the subsequent development of complications. A greater boost in vaccine effectiveness was observed with additional doses of CoronaVac, with both BNT162b2 and CoronaVac demonstrating similar vaccine effectiveness after two to three doses. Further prospective studies on immunization schedules are warranted for patients with kidney failure.

Disclosures

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Data Sharing Statement

Data cannot be shared. Data will not be available for others as the data custodians have not given permission.

Supplemental Material

This article contains the following supplemental material online at http://links.lww.com/CJN/B845.

Supplemental Table 1. Definitions of CKD using ICD-9-CM.

Supplemental Table 2. Unadjusted and adjusted odds ratio of COVID-19 infection and related morbidity by vaccine type.

Supplemental Table 3. Vaccine effectiveness for preventing COVID-19 infection and related morbidity by vaccine type after limiting vaccine exposure to at least 14 days from latest dose.

Supplemental Table 4. Vaccine effectiveness for preventing COVID-19 infection and related morbidity by vaccine type after limiting vaccine exposure to at most 180 days from latest dose.

Supplemental Table 5. Vaccine effectiveness for preventing COVID-19 infection and related morbidity by vaccine type after including rapid antigen test–positive cases.

Supplemental Table 6. Vaccine effectiveness for preventing COVID-19 infection and related morbidity by vaccine type, stratified by baseline eGFR.

Supplemental Table 7. Relationship of vaccine dose and eGFR strata with COVID-19 infection and related morbidity among patients receiving at least one dose of vaccine.

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