BNT162b2 vaccine effectiveness in chronic kidney disease patients—an observational study

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ABSTRACT

Background. Chronic kidney disease (CKD) is a risk factor for severe coronavirus disease 2019 (COVID-19). We aimed to evaluate the real-life effectiveness of the BNT162b2 messenger RNA vaccine for a range of outcomes in patients with CKD compared with matched controls.

Methods. Data from Israel’s largest healthcare organization were retrospectively used. Vaccinated CKD (estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m²) and maintenance dialysis patients were matched to vaccinated controls without CKD (eGFR ≥ 60 ml/min/1.73 m²) according to demographic and clinical characteristics. Study outcomes included documented infection with severe acute respiratory syndrome coronavirus 2, symptomatic infection, COVID-19-related hospitalization, severe disease and death. Vaccine effectiveness was estimated as the risk ratio (RR) at days 7–28 following the second vaccine dose, using the Kaplan–Meier estimator. Effectiveness measures were also evaluated separately for various stages of CKD.

Results. There were 67861 CKD patients not treated with dialysis, 2606 hemodialysis (HD) patients and 70467 matched controls. The risk of severe disease [RR 1.84 [95% confidence interval (CI) 0.95–2.67]] and death [RR 2.00 (95% CI 0.99–5.20)] was increased in nondialysis CKD patients compared with controls without CKD following vaccination. For the subgroup of patients with eGFR < 30 ml/min/1.73 m², the risk of severe disease and death was increased compared with controls [RR 6.42 (95% CI 1.85–17.51) and RR 8.81 (95% CI 1.63–13.81), respectively]. The risks for all study outcomes were increased in HD patients compared with controls.

Conclusion. Two doses of the BNT162b2 vaccine were found to be less efficient for patients with eGFR < 30 ml/min/1.73 m². Risk in HD patients is increased for all outcomes. These results suggest prioritizing patients with eGFR < 30 ml/min/1.73 m² for booster shots, pre- and post-exposure prophylaxis and early COVID-19 therapy.
INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in December 2019 as the cause of coronavirus disease 2019 (COVID-19) [1]. Initial evidence suggested a higher incidence of severe COVID-19 in people with chronic illnesses, including chronic kidney disease (CKD) [2–4]. The incidence of severe COVID-19 in maintenance dialysis was even higher compared with nondialysis CKD (ndCKD) patients [5].

Various reports documented an attenuated response of CKD and dialysis patients to the BNT162b2 messenger RNA (mRNA) vaccine [6, 7]. Dialysis patients had reduced antibody response to the first and second doses of the mRNA vaccine BNT162b2 [8]. The majority (82%) of dialysis patients developed neutralizing antibodies and T-cell response after the second dose, but at significantly lower titers compared with healthy controls [8]. Furthermore, the humoral response was delayed by 3–4 weeks following the third (booster) dose [9]. However, these studies did not address clinical outcomes following the vaccine.

It has become a matter of great importance and urgency to identify the degree of protection afforded to people with kidney disease by two doses of SARS-CoV-2 mRNA vaccines, as it may affect decisions on additional vaccine doses or the use of other treatments and preventive measures [10, 11]. In this study we sought to evaluate the real-life effectiveness of BNT162b2 mRNA vaccine in a nationwide setting for a wide range of outcomes in CKD and dialysis patients compared with vaccinated individuals without kidney disease.

MATERIALS AND METHODS

Study population

Data from Clalit Health Services (CHS), the largest healthcare provider in Israel, were retrospectively analyzed. A detailed description of the data repositories used for data extraction is provided elsewhere [9].

Study design

We designed this observational study to estimate the risk of COVID-19 outcomes in CKD patients following two doses of BNT162b2 vaccine compared with the general vaccinated population. Eligibility criteria included age ≥18 years, vaccination with two doses of BNT162b2 according to the manufacturer’s recommendations, not having a previously documented positive SARS-CoV-2 polymerase chain reaction (PCR) test and being a member of the healthcare organization during the previous 12 months. Vaccination status was validated using the strictly confirmed nationwide database. We excluded kidney transplant patients entirely from the analysis. In addition, we excluded patients for whom the probability of exposure was highly variable (e.g. healthcare workers or individuals for whom data on place of residence were missing).
RESULTS

Overall, 3 247 611 people ≥18 years of age were insured by CHS at the beginning of the study period and 2 203 686 of them met the inclusion criteria. A total of 70 467 individuals had impaired kidney function with available matched preserved kidney function controls. Of these, 67 861 had ndCKD and 2606 were dialysis patients (Fig. 1). The median age for CKD was 76 years [interquartile range (IQR) 71–83] and 48% were males. The mean eGFR for CKD patients was 44.76 ± 11 ml/min/1.73 m² compared with 74.01 ± 14 ml/min/1.73 m² in the control group. Of the study group, 37 428 (55%) had CKD stage 3A, 22 341 (33%) had CKD stage 3B and 8092 (12%) had CKD stage 4 or 5. The median age among the dialysis group was 71 years [IQR 63–77]. The characteristics of the study groups and the control groups are presented in Table 1.

We calculated the risk ratio (RR) of patients with ndCKD versus controls for COVID-19 infection [RR 0.98 (95% CI 0.76–1.30)], symptomatic COVID-19 infection [RR 0.96 (95% CI 0.68–1.34)], COVID-19-related hospital admission [RR 1.34 (95% CI 0.81–2.33)], severe COVID-19 (RR 1.84 (95% CI 0.95–2.67)) and COVID-19-related death [RR 2.0 (95% CI 0.99–5.2)] (Table 2).

Outcomes according to CKD stage

A total of 26% of the patients in stage 3A had a CDC risk score of ≥4, compared with 44% of the patients in stage 3B and 61% of the patients in stage 4 and 5. This difference was largely due to a higher prevalence of diabetes mellitus and heart disease with more severe CKD (Supplementary Table S2).

Patients with CKD stages 3A and 3B had similar risks for all outcomes compared with those without CKD (Fig. 2, Supplementary Fig. S2 and Table S2). Patients with stage 4 and 5 ndCKD had increased risk of COVID-19-related hospital admissions [RR 2.98 (95% CI 0.96–12.74)], severe COVID-19 [RR 6.48 (95% CI 1.85–17.51)], and COVID-19 related mortality [RR 8.81 (95% CI 1.63–13.81)] compared with vaccinated matched controls without CKD. The results of CKD patients according to CKD stages are presented in Fig. 2, Supplementary Fig. S1 and Table S2. The summary results for all CKD patients (with all stages collapsed) compared with controls without CKD are presented in Fig. 4 and Supplementary Fig. 2.

Outcomes in dialysis patients

Baseline characteristics of dialysis patients and matched controls are presented in Table 1. Risk for COVID-19 infection and symptomatic disease was higher for dialysis patients compared with controls [RR 3.75 (95% CI 1.5–15.20), and RR 3.88 (95% CI 2.35–8.03) respectively]. In the dialysis group there were 10 events of COVID-19-related hospital admissions, 8 events of severe COVID-19 and 5 events of COVID-19-related deaths compared with no events for these outcomes in the control group (Fig. 3).

DISCUSSION

We evaluated the effectiveness of two doses of BNT162b2 vaccine in a nationwide cohort of 67 861 people with ndCKD and 2606 dialysis patients compared with vaccinated matched controls without CKD. The risk of severe disease [RR 1.84 (95% CI 0.95–2.67)] and COVID-19-related death [RR 2 (95% CI 0.99–5.20)] for ndCKD were increased compared with matched controls. However, this presentation blunts the heterogeneity of outcomes in CKD patients. Subgrouping according to the different stages of CKD revealed two different groups of patients. Among patients with ndCKD stage 4–5 (eGFR <30 ml/min/1.73 m²), the risks of severe COVID-19 infection and death were higher compared with controls (RRs of 6.48 and 8.8, respectively). In contrast, outcomes were similar in individuals with stage 3 CKD compared with controls without CKD.
Dialysis patients exhibited uniformly increased vulnerability with qualitatively increased risks compared with controls for all outcomes. Although the number of events was small, risks of documented, symptomatic and severe infection, as well as hospitalization and death rates were numerically higher for dialysis patients compared with matched controls. Our finding of a threshold of eGFR $<30$ ml/min/1.73 m$^2$ as a risk factor for severe disease and death among CKD patients differs from the frequently used cutoff for risk exposure of $<60$ ml/min/1.73 m$^2$ [13] and suggest that the severity of CKD and not just its presence or absence is a critical determinant of risk.

One explanation for the increased risk in dialysis and CKD stage 4–5 patients may be diminished immunogenicity in response to vaccination as GFR declines. The literature regarding clinical response of CKD patients to the SARS-CoV-2 vaccine is scarce. Inclusion of patients with kidney disease in completed and ongoing COVID-19 vaccine studies remains low, with most trials explicitly excluding individuals with ‘severe’ or ‘chronic’ kidney disease.

Indications of reduced effectiveness of the SARS-CoV-2 vaccine came from studies measuring serologic response following COVID-19 infection in dialysis patients. The immunoglobulin G (IgG) level decreased gradually within 3 months following COVID infection, and such serologic changes might predict less efficacy of vaccination [18]. Antibody titer was also lower among dialysis patients compared with healthy controls [19, 20]. Seroconversion rates induced by mRNA-1273 compared with BNT162b2 vaccine were 97% and 88%, respectively, in dialysis patients and specific IgG directed against the spike protein were significantly higher in dialysis patients vaccinated by mRNA-1273 (95%) compared with BNT162b2 [21, 22]. Vaccine efficacy may be hampered by alteration of innate immunity in the uremic milieu, older age and deficiency of vitamin D and erythropoietin [23]. The uremic milieu, for example, reduces expression of costimulatory molecules such as CD80/CD86 on antigen-presenting cells and dendritic cells, reducing recognition of pathogen by the immune systems of CKD patients [24]. In addition, expression of the Toll-like receptor is decreased on monocytes and hence proinflammatory cytokine release is reduced in CKD [25]. These conditions also decrease antibody production by B lymphocytes and increase apoptosis of memory T cells [23, 26]. In fact, patients can exhibit lymphopenia and defects in B cell differentiation, therefore the generation of antibodies might be influenced [27, 28]. The efficacy of the influenza vaccine, for example, was negatively associated with age and CKD status [29]. Other factors that might influence vaccine efficacy in dialysis patients are erythropoietin titer [30] and low vitamin D, which were associated with lower seroconversion rates in the case of hepatitis B virus vaccine [31]. Additionally, it is possible that dialysis patients might experience near-continuous and inevitable exposure to COVID-19 during regular visits to the dialysis unit. This might have contributed, at least in part, to the increased infection rate in this population.

To summarize, two doses of BNT162b2 mRNA vaccine appear to be less effective in preventing severe infection, admissions
FIGURE 2: Cumulative incidence of severe infection and death related to COVID-19 in ndCKD patients according to CKD stage. Patients (red) were grouped according to eGFR and are shown compared with matched controls (blue). (A, B) Patients with CKD3A (eGFR 45 to <60 ml/min/1.73 m²), (C, D) CKD 3B (eGFR 30–<45 ml/min/1.73 m²), (E, F) patients with CKD 4–5 (eGFR 0–<30 ml/min/1.73 m²). (A, C, E) severe COVID-19 infection, (B, D, F) death related to COVID-19.
Table 1. Characteristics of CKD patients and matched controls

| Parameter                                      | CKD patients | Controls | Dialysis patients | Controls |
|------------------------------------------------|--------------|----------|-------------------|----------|
| N                                              | 67861        | 67861    | 2606              | 2606     |
| Age (years), median, (IQR)                     | 76 (71–83)   | 77 (71–83)| 71 (63–77)        | 71 (63–77)|
| Female, n (%)                                  | 35485 (52)   | 35485 (52)| 1032 (40)         | 1032 (40)|
| Influenza vaccine in the past 5 years, n (%)   | 66343 (98)   | 66342 (98)| 2524 (97)         | 2524 (97)|
| CDC ‘certain’ risk criteria, n (%)             | 3854 (5.7)   | 4224 (6.2)| 18 (0.6)          | 16 (0.6)|
| CDC ‘possible’ risk criteria, n (%)            | 72876 (41)   | 30672 (45)| 1463 (56)         | 1480 (57)|

COPD, chronic obstructive pulmonary disease; BMI, body mass index; CDC, Centers for Disease Control.

Table 2. Analysis in CKD subgroups

| Patients' subgroup | COVID-19-related events | CKD, n | Control, n | RR (95% CI) |
|--------------------|------------------------|--------|------------|-------------|
| All CKD eGFR <60 ml/min/1.73 m² (N = 67861) | Documented Infections | 126    | 128        | 0.98 (0.76–1.30) |
|                    | Symptomatic infections | 80     | 81         | 0.96 (0.68–1.34) |
|                    | Severe infections      | 43     | 26         | 1.84 (0.95–2.67) |
|                    | Admissions             | 41     | 34         | 1.34 (0.81–2.33) |
| COVID-19-related death | 21            | 14     | 2.00 (0.99–5.20) |
| CKD 3A eGFR 45–<60 ml/min/1.73 m² (N = 37428) | Documented Infections | 56     | 60         | 0.98 (0.61–1.56) |
|                    | Symptomatic infections | 34     | 38         | 0.82 (0.47–1.39) |
|                    | Severe infections      | 14     | 9          | 1.43 (0.57–4.31) |
| COVID-19-related death | 9              | 5      | 1.41 (0.45–7.35) |
| CKD 3B eGFR 30–<45 ml/min/1.73 m² (N = 22341) | Documented Infections | 49     | 52         | 0.96 (0.63–1.42) |
|                    | Symptomatic infections | 30     | 35         | 0.87 (0.51–1.42) |
|                    | Severe infections      | 14     | 15         | 0.89 (0.39–1.88) |
| COVID-19-related death | 15             | 18     | 0.83 (0.39–1.75) |
| CKD 4–5 eGFR 0–<30 ml/min/1.73 m² (N = 8092) | Documented Infections | 21     | 16         | 1.19 (0.60–2.33) |
|                    | Symptomatic infections | 16     | 8          | 1.84 (0.74–5.68) |
|                    | Severe infections      | 15     | 2          | 6.42 (1.85–17.51) |
| Admissions         | 10                   | 4       | 2.98 (0.96–12.74) |
| COVID-19-related death | 9              | 1      | 8.81 (1.63–13.81) |

RR, risk ratio.

CKD patients were divided according to stages as defined by KDIGO criteria. RRs were evaluated using the same estimator for the period 7–28 days following the second vaccine dose.

and death at an eGFR <30 ml/min/1.73 m². Furthermore, the vaccine is less effective for all outcomes assessed in patients requiring dialysis.

Thus more data are needed to inform providers and patients with CKD regarding the use of COVID-19 vaccines [32] and it is of great importance to include these patients in clinical trials examining the efficacy of future treatments. With the emergence of booster shot campaigns and the appearance of new SARS-CoV-2 strains, further research is needed to assess the efficacy of the vaccine in these situations. Our data suggest that individuals with eGFR <30 ml/min/1.73 m² should be prioritized for additional vaccine doses, with further research evaluating the optimal type of vaccine and number of doses in this population. Moreover, patients with CKD should not be excluded from trials assessing pre- and postexposure prophylaxis measures or testing treatments for breakthrough infection.

Our study has several limitations. Due to the time-sensitive effectiveness of the vaccine and changes in common viral strains with time, the results represent the vaccine effectiveness as of February 2021, during a time when the Alpha variant was
active in Israel. Further studies are needed to understand how the use of booster doses or the presence of new viral variants might modify vaccine effectiveness. Additionally, the number of patients on dialysis was small. Furthermore, we studied only a single vaccine type. Since only the BNT162b2 mRNA vaccine was utilized in the study, we are unable to assess whether our findings are specific to that particular vaccine or broadly representative of the clinical effectiveness of mRNA vaccines for COVID-19. To wit, at least one analysis has shown that immunologic response to mRNA-1273 vaccine is more robust than response to the BNT162b2 in the setting of dialysis [20, 33]. We acknowledge that due to the small number of events our confidence intervals are quite large and this can result in overestimation.

Finally, we could not match dialysis patients’ exposure to the general population. Since dialysis patients receive treatment three times a week in a setting mandating social interaction, their risk is a combination of biological and social factors that cannot be matched with the general population. That being said, we believe their increased risk is a combination of frequent exposure and decreased ability to develop immunity. Lastly, due to the transient nature of stage 5 ndCKD patients, transitioning rapidly to either dialysis or transplantation, we had a relatively small number of patients and events in this group and hence were unable to assess the specific risk.

In conclusion, after two doses of BNT162b2, patients with advanced CKD and dialysis are less protected against COVID-19 infection and complications compared with a matched population with normal renal function. Additional measures might be considered to improve the protection of CKD patients, including additional vaccine doses (either same or heterologous), pre- and postexposure prophylaxis and therapies for COVID-19. Inclusion of these patients in clinical trials should be encouraged, despite limitations in dosing adjustment.

SUPPLEMENTARY DATA
Supplementary data are available at cj online.

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AUTHORS’ CONTRIBUTIONS
D.B. was responsible for conceptualization, data curation, investigation, methodology, visualization, writing the original draft and review and editing. G.L. was responsible for data curation, formal analysis, investigation, software, validation and review and editing. N.B. was responsible for conceptualization, data curation, investigation, methodology, software, supervision and review and editing. N.D. was responsible for investigation,
methodology, supervision and review and editing. T.S. was responsible for conceptualization, methodology and review and editing. D.Y. was responsible for methodology, supervision and review and editing. D.M.C. was responsible for investigation, methodology, supervision and review and editing. R.B. was responsible for methodology, resources, supervision and review and editing. B.R.Z. was responsible for conceptualization, investigation, methodology, supervision, writing the original draft and review and editing.

DATA AVAILABILITY STATEMENT

Owing to data privacy regulations, the raw data for this study cannot be shared.

CONFLICT OF INTEREST STATEMENT

D.M.C. has received personal fees or fees paid by Janssen Pharmaceuticals to the Baim Institute; consulting fees from Amgen, Eli Lilly, Fresenius, CSL Behring, Gilead, Medtronic/Covidien, Merck, Novo Nordisk, Zoll, AstraZeneca, Merck, PLC Medical and Allena Pharmaceuticals and research support from Medtronic and Amgen. B.R.Z. has received consultation fee from Fresenius, Novartis and Sanofi and speaker fees from AstraZeneca. G.L., N.D. and R.B. report institutional grants to the Clalit Research Institute from Pfizer outside the submitted work and unrelated to COVID-19, with no direct or indirect personal benefits. The other authors have no conflicts of interest.

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