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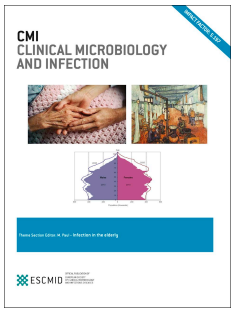

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BNT162b2 vaccine breakthrough: Clinical characteristics of 152 fully-vaccinated hospitalized COVID-19 patients in Israel

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Abstract

Objectives

mRNA COVID-19 vaccines have shown high effectiveness in the prevention of symptomatic COVID-19, hospitalization, severe disease, and death. Nevertheless, a minority of vaccinated individuals might get infected and suffer significant morbidity. Characteristics of vaccine breakthrough infections have not been studied. We sought to portray the population of Israeli patients, who were hospitalized with COVID-19 despite full vaccination.

Methods

A retrospective multicenter cohort study of 17 hospitals included Pfizer/BioNTech's BNT162b2 fully-vaccinated patients who developed COVID-19 more than 7 days after the second vaccine dose and required hospitalization. The risk for poor outcome, defined as a composite of mechanical ventilation or death, was assessed.

Results

152 patients were included, accounting for half of hospitalized fully-vaccinated patients in Israel. Poor outcome was noted in 38 patients and mortality rate reached 22% (34/152). Notable, the cohort was characterized by a high rate of comorbidities predisposing to severe COVID-19, including hypertension (108, 71%), diabetes (73, 48%), CHF (41, 27%), chronic kidney and lung diseases (37, 24% each), dementia (29, 19%), and cancer (36, 24%), and only 6 (%) had no comorbidities. Sixty (40%) of the patients were immunocompromised. Higher SARS-CoV-2 viral-load was associated with a significant risk for poor outcome. Risk also appeared higher in patients receiving anti-CD20 treatment and in patients with low titers of anti-spike IgG, but these differences did not reach statistical significance.

Conclusions

We found that severe COVID-19 infection, associated with a high mortality rate, might develop in a minority of fully-vaccinated individuals with multiple comorbidities. Our patients had a higher rate of comorbidities and immunosuppression compared to previously reported non-vaccinated hospitalized COVID-19 patients. Further characterization of this vulnerable population may help to develop guidance to augment their protection, either by continued social-distancing, or by additional active or passive vaccinations.

Keywords

COVID-19; SARS-CoV-2; BNT162b2; mRNA vaccine; vaccine effectiveness; breakthrough infection; serology; immune compromised

Introduction

The mRNA COVID-19 vaccines, Pfizer/BioNTech's BNT162b2 and Moderna's mRNA-1273 were 94-95% effective in preventing symptomatic COVID-19 in phase III studies, showing similar efficacy in different age groups, including persons older than 75, and persons with comorbidities [1,2]. In Israel 839,162 cumulative COVID-19 cases (9,269/100,000) and 6,396 deaths (70/100,000) were reported due to COVID-19 by 20.5.2021[3]. The Israeli vaccination campaign began on 19.12.2020 and relied exclusively on BNT162b2. By 20.5.2021, more than 5.4 millions received two doses, reaching a coverage of 55% of the population, and about 88% for people older than 50y [3]. The real-life vaccine effectiveness (VE) of BNT162b2 was similar to the efficacy reported in the phase III studies [4,5], and had a significant impact on the local dynamics of COVID-19 [6], with cases declining to 30 new cases/week (0.3/100,000) by May 20th. VE was shown to be somewhat lower in people older than 70 and in those with multiple comorbidities [7]. The VE for the prevention of hospitalization due to COVID-19 was found to be 87% after the second dose in an early case-control study [4], and 96% in a later comparison of person-time incidence rates from a national registry in Israel [5]. Currently, reports from other countries include a US study showing 94% effectiveness after two doses of any mRNA vaccine [8], and two UK studies which measured an 80%-91% effectiveness for prevention of hospitalization of a single dose of BNT162b2 [9,10].

Data is lacking on the nature of breakthrough infections with COVID-19 vaccines. No data was published on the clinical characteristics and serologic correlates of protection of study participants who were hospitalized with COVID-19 after vaccination. Immunocompromised individuals were not included in those pivotal studies. Recent studies measured the immunogenicity of BNT162b2 in immunocompromised patients, showing significantly lower seroconversion rates and lower anti-S-IgG titers in kidney and liver transplant recipients [11,12] and in patients with chronic lymphocytic leukemia [13], and lower antibody titers in hemodialysis patients [14,15].

According to the Israeli Ministry of Health registry, by April 26th 397 fully vaccinated patients were hospitalized in Israel with PCR-proven COVID-19 after their 2nd vaccine dose, 234 of them had severe COVID-19 and 90 died [Dr. Eric Haas, MOH, personal communication]. Using a sample of hospitalized patients, we aimed to characterize vaccinated patients with breakthrough COVID-19 requiring hospitalization and define the main risk factors associated with poor outcomes in this group.

Methods

This was a multi-center cohort study of patients admitted to any of the seventeen participating hospitals. Included were patients who received two doses of BNT162b2, had a PCR-confirmed diagnosis of SARS-CoV-2 infection and were hospitalized in a COVID-19-dedicated unit. As effectiveness of BNT162b2 was studied in patients more than 7 days after the second dose in most clinical studies [2,4,5], either symptom-onset, the first positive PCR test or the date of admission, whichever happened first, had to be more than seven days following the second dose. Women in labor admitted to maternity wards were excluded.

Clinical data were retrieved from patients' records according to a predefined questionnaire and were entered into a de-identified database. SARS-CoV-2 PCR testing was done using various assays at participating centers, and Cycle threshold (Ct) values were reported according to specific gene-targets but were analyzed together with the lowest Ct value of any gene-target chosen to represent a surrogate for the viral load. Anti-spike antibody tests were performed locally using two available commercial kits: The Liaison SARS-CoV-2-S1/S2-IgG (Diasorin, Saluggia, Italy), with a positive cutoff of >15units/mL; and the Architect AdviseDx SARS-CoV-2-IgG-II (Abbot, Lake Forest, Illinois, USA), with a positive cutoff of >50u/mL. Viral genomic sequencing was done to identify variants of concern (VOC) on available samples, with results categorized as wildtype, B.1.1.7, B.1.351 or other VOC. COVID-19 severity was categorized according to the US National Institute of Health criteria [16].

The primary outcome was a composite of mechanical ventilation or in-hospital death, referred to as poor outcome. Favorable outcome was defined as patients who were either discharged or were still hospitalized and not ventilated at the end of the study.

Statistical analysis: Categorical variables were compared between patients with favorable and poor outcomes using chi-square and Fisher's exact tests, and continuous variables were

compared using independent samples t-test or Mann-Whitney test. NCSS 2021 v21.0.2 software was used for analyses.

The study was approved by the institutional research ethics boards of each participating hospital. Due to the retrospective design, informed consent was not required.

Results

During the study period (18.1.2021-20.4.2021) data was reported for 152 patients from 17 general hospitals across Israel. The epidemic curve of new cases is shown in the online supplement and figure S1. The clinical data of the patients are shown in Table 1. The median time elapsed from the 2nd dose to admission was 39.5 days (range 8-97), and 125/152 (82%) of patients were admitted 21 days or more after vaccination, supporting the assumption that they were not infected before vaccination. The median age was 71.1 (range 22-98), most were males (107, 70%) and 38 (25%) were residents of a long-term care facility (LTCF). Only six patients (4%) had no comorbidity. Immunosuppression was present in 60 patients (40%). Common causes of immunosuppression were chronic corticosteroid treatment, chemotherapy or anti-metabolite treatment, solid organ transplantation and anti-CD20 treatment.

In most cases the source of the patient's infection was unknown. Sixteen patients (12%) were exposed to an infected household member, 15 (11%) were exposed in healthcare settings to another patient (most in LCTF), and 1 (1%) was exposed to an infected healthcare worker.

For most patients, the indication for admission was severe COVID-19 (97, 64%). For 24 (16%) patients the severity of COVID-19 did not necessitate admission, and the patients were admitted to provide means of isolation (e.g., need for dialysis in a COVID-19 patient that could not be arranged outside of the hospital; a resident of a LTCF with no isolation capacity). In 29 patients (19%) there was a medical problem unrelated to COVID-19 that necessitated admission, and in two (1%) there was a late complication of COVID-19 (thromboembolism), with an incidental in-hospital diagnosis of COVID-19.

Most (93, 61%) of the patients in this cohort had severe or critical illness. The mortality rate was 22% (34/152). At the end of the study period, twelve patients were still hospitalized and not ventilated, and were categorized as a favorable outcome. Overall, the primary outcome of mechanical ventilation or death occurred in 38 patients (25%). A comparison of baseline

risk-factors between the groups did not identify any statistically-significant differences. Some nonsignificant differences of-note between favorable and poor outcome included a higher rate of anti-CD20 treatment (13% vs. 4%, *p*=0.12), cancer (32% vs. 22%, *p*=0.23), CHF (34% vs. 25%, *p*=0.25) and dementia (26% vs. 17%, *p*=0.19) in the poor outcome group.

Measurement of anti-S-IgG titers after admission were available for 69 patients, using two different kits. In both, the median titer was lower for patients with a poor outcome: Liaison - 1.5 (IQR 0-8) vs. 30.4 (IQR 0-149); Abbott - 644 (IQR 0-8276) vs. 1,623 (IQR 46.5-15748). In both analyses these differences did not reach statistical significance (*p* values 0.11 and 0.34, respectively). Serology results are shown in Figure 1.

Results of PCR testing including analysis of Ct values appear in the online supplement. Sequencing results of SARS-CoV-2 RNA ware available for 45 patients, with most (40, 89%) found to be B.1.1.7, three (7%) wildtype and two (4%) B.1.351. The distribution of VOC's between the groups showed that both had a majority of B.1.1.7, while the two B.1.351 variants were from patients with a favorable outcome, although one of the B.1.351 patients required HFNC.

Six patients had no comorbidities. Their average age was 60 years (range 42-85), and none were LTCF residents. Three of them presented with severe COVID-19 but had a good outcome after treatment with oxygen and corticosteroids. Two were admitted due to vestibular neuritis, and one due to chest pain. Viral sequencing was performed on 5 of them, with B.1.1.7 detected.

A repeat comparative analysis between favorable and poor outcome groups including only patients that were admitted with severe COVID-19, excluding other reasons for hospitalization, yielded similar findings (Table 1).

Discussion

This study includes a detailed description of 152 mRNA COVID-19-vaccinated individuals who presented with a significant breakthrough infection leading to hospitalization. All these patients had their disease onset 8 days or more after their 2nd vaccine dose, and in most much later, with a median time to admission exceeding one month.

The clinical profile of the patients is typical of other COVID-19 hospitalized patients, being elderly males and having high rates of comorbidities linked to COVID-19 severity.

Nevertheless, comorbidities were more common in patients with vaccine breakthrough infections compared to large case-series on unvaccinated hospitalized patients (see Table 2), including diabetes (48% vs. 27.9-34.7%), hypertension (71% vs. 43.5-62%), heart failure (28% vs. 5.8-12.8%), chronic lung diseases (24% vs. 7.4-16.5%), chronic kidney disease (32% vs. 12.7-22.8%), and cancer (24% vs. 4.8-10.8%) [17–19]. Furthermore, 96% of the patients had at least one comorbidity. Of six patients with no comorbidity, only three had severe COVID-19, with a favorable outcome. The high rate of comorbidities might be explained by a lower VE in patients with comorbidities, by the risk of comorbidities exacerbation after breakthrough infection, or by both. Immunosuppression in our cohort was common, with 40% of patients having any type, including a corticosteroid, chemotherapy and anti-CD20 treatments, and recipients of organ transplants. This fact is both expected, and in agreement with the lower immunogenicity findings of immunocompromised individuals after vaccination. Immunosuppression was not associated with a worse outcome, except for anti-CD20 treatment, which had a threefold higher odds-ratio to be in the poor outcome group (13% vs. 4%, p=0.12), but the small number of patients could preclude significant comparison of subgroups.

The mortality rate in the cohort was similar to unvaccinated hospitalized COVID-19 patients [20]. We could not find a statistically-significant risk-factor for a poor outcome, defined as mechanical ventilation or in-hospital death, except for a higher upper-respiratory viral load, as represented by a lower Ct value. As our cohort included patients who were admitted due to different reasons, an analysis including only patients whose reason for admission was severe COVID-19 was also performed, with similar findings.

Anti-S-IgG assays were developed and validated for the diagnosis of SARS-CoV-2 infection. They can be used to measure the serological response to vaccination, although no correlate of protection has been identified so far. The two assays used in our cohort have a good correlation with neutralizing antibody titers [21,22]. Results of anti-S-IgG were available for 69 patients, with two assays. These results do not represent titers achieved post-vaccination, as they were measured after SARS-CoV-2 infection, with a median of seven days after symptom onset. Therefore, they might represent the host ability for an early serological response to infection. Overall, results were variable, with titers ranging from below threshold to high titers beyond the assay's upper reporting limit. Patients with poor outcomes had a lower median titer in both assays, but these differences did not reach statistical significance.

BNT162b2, as most COVID-19 vaccines, is based on SARS-CoV-2 spike antigen, and therefore its efficacy might be influenced by antigen change. Mutants with significant changes have emerged around the world, with some exhibiting reduced neutralization by sera from convalescent or immunized individuals [23]. These VOC's, such as B.1.1.7 (20I/501Y.V1), B.1.351 (20H/501Y.V2) and P.1 (20J/501Y.V3), are being monitored in Israel and worldwide. During this study, the dominant circulating strain in Israel was B.1.1.7, with an overwhelming percentage of new infections with this strain beginning in November-December 2020 [17]. The B.1.351 VOC exhibited decreased neutralization and a lower vaccine efficacy for the NVX-CoV2373 vaccine in Novavax's phase III study in South-Africa [23,24]. A recent case-control study from Israel showed a disproportional risk for BNT162b2-vaccinated individuals to be infected with B.1.351, with an odds-ratio of 8:1 compared to unvaccinated individuals, while B.1.1.7 did not seem to have more breakthrough infections in vaccinees [25]. Despite that, the absolute number of B.1.351 variants in that study was low (9 cases overall). The national surveillance in Israel did not identify an emergence of B.1.351 or any other vaccine-escape mutants so far, despite a steady rate of ~1% of all samples found to be B.1.351 [26]. In our cohort only a limited number of isolates were sequenced, with 2/45 (4%) found as B.1.351. While this rate which is above the reported rate of this VOC may support its vaccine-escape capability, the two patients with B.1.351 were reported from the same hospital within a few days and belonged to a community with a high B.1.351 prevalence in unvaccinated individuals. Therefore, this might represent a local outbreak rather than vaccine breakthrough. Most samples were found to be B.1.1.7, as this became the most common strain in Israel.

This study has some limitations. This cohort of 152 patients from 17 of 26 public general hospitals in Israel represent about half of fully vaccinated patients with COVID-19 requiring hospitalization in the country. As patients admitted to long-term geriatric hospitals were not included, the data is representative of patients admitted to general hospitals. A third of the patients did not have severe COVID-19, and therefore might not truly represent the failure of the vaccine to prevent significant morbidity and mortality, although many had another significant medical indication for admission that might be related to SARS-CoV-2 infection, such as thromboembolism, neurological problems, and exacerbation of their underlying comorbidities. The study was not designed to estimate risk factors for vaccine failure, as patients were identified after hospitalization and were not compared to uninfected controls. Specifically, our findings concerning anti-S-antibody titers do not necessarily represent titers achieved by vaccination or before infection and cannot be used to estimate any correlate of

protection. The number of patients in the cohort was too small for some of the comparisons between favorable and poor outcomes, specifically for some risk factors that seemed to be more common in patients with poor outcome such as different comorbidities, types of immunosuppression and antibody titers. In view of the impact of the successful Israeli vaccination campaign, it is not expected that a significant additional number of vaccinated patients with similar severe breakthrough infection will be available for analysis soon. More data from countries with ongoing COVID-19 might be needed.

Conclusions

A small minority of fully-vaccinated BNT162b2 recipients might still develop severe SARS-CoV-2 infection despite the vaccine's high effectiveness, with need for in-patient care. This representative cohort of hospitalized patients is characterized by older age, high rate of comorbidities predisposing for progression to severe COVID-19, and a high rate of immunosuppression. The outcome of these patients was similar to that of non-vaccinated hospitalized COVID-19 patients. Additional prospective longitudinal studies are urgently needed to identify predictors for vaccine breakthrough infection and simple correlates of vaccine protection, to enable identification of individuals at higher risk, who would require continued strict precautions, and possibly repeated active vaccination or other prophylactic measures, such as passive vaccination. Furthermore, indirect protection of vulnerable individuals is best achieved by mass vaccination leading to herd immunity.

References

[1] Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384:403–16. doi:10.1056/nejmoa2035389.

[2] Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. N Engl J Med 2020;383:2603–15. doi:10.1056/nejmoa2034577.

[3] Ministry of Health. COVID-19 dashboard 2021. https://datadashboard.health.gov.il/COVID-19/general.

[4] Dagan N, Barda N, Kepten E, Miron O, Perchik S, Katz MA, et al. BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med 2021;384:1412–23. doi:10.1056/nejmoa2101765.

[5] Haas E, Angulo A, McLaughlin J, Anis E, Singer S, FK K, et al. Nationwide vaccination campaign with BNT162b2 in Israel demonstrates high vaccine effectiveness and marked declines in incidence of SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths. Lancet 2021;preprint.

[6] Rossman H, Shilo S, Meir T, Gorfine M, Shalit U, Segal E. COVID-19 dynamics after a national immunization program in Israel. Nat Med 2021. doi:10.1038/s41591-021-01337-2.

[7] Barda N, Dagan N, Balicer R. Correspondence: BNT162b2 mRNA Covid-19 Vaccine in a Nationwide Mass Vaccination Setting. N Engl J Med 2021. doi:10.1056/NEJMc2104281.

[8] Tenforde MW, Olson SM, Self WH, Talbot HK, Lindsell C, Steingrub J, et al. Effectiveness of Pfizer-BioNTech and Moderna Vaccines Against COVID-19 Among Hospitalized Adults Aged ≥ 65 Years - United States, January-March 2021. MMWR Morb Mortal Wkly Rep 2021;70. doi:http://dx.doi.org/10.15585/mmwr.mm7018e1.

[9] Vasileiou E, Simpson CR, Shi T, Kerr S, Agrawal U, Akbari A, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. Lancet 2021;397:1646–57. doi:10.1016/S0140-6736(21)00677-2.

[10] Bernal JL, Andrews N, Gower C, Stowe J, Robertson C, Tessier E, et al. Early

effectiveness of COVID-19 vaccination with BNT162b2 mRNA vaccine and ChAdOx1 adenovirus vector vaccine on symptomatic disease, hospitalisations and mortality in older adults in England. MedRxiv 2021:2021.03.01.21252652.

[11] Grupper A, Rabinowich L, Schwartz D, Schwartz IF, Ben-Yehoyada M, Shashar M, et al. Reduced humoral response to mRNA SARS-Cov-2 BNT162b2 vaccine in kidney transplant recipients without prior exposure to the virus. Am J Transplant 2021. doi:10.1111/ajt.16615.

[12] Rabinowich L, Grupper A, Baruch R, Ben-Yehoyada M, Halperin T, Turner D, et al. Low immunogenicity to SARS-CoV-2 vaccination among liver transplant recipients. J Hepatol 2021. doi:10.1016/j.jhep.2021.04.020.

[13] Herishanu Y, Avivi I, Aharon A, Shefer G, Levi S, Bronstein Y, et al. Efficacy of the BNT162b2 mRNA COVID-19 Vaccine in Patients with Chronic Lymphocytic Leukemia. Blood 2021. doi:10.1182/blood.2021011568.

[14] Agur T, Ben-Dor N, Goldman S, Lichtenberg S, Herman-Edelstein M, Yahav D, et al. Antibody response to mRNA SARS-CoV-2 vaccine among dialysis patients - a prospectivecohort study. Nephrol Dial Transplant 2021. doi:10.1093/ndt/gfab155.

[15] Grupper A, Sharon N, Finn T, Cohen R, Israel M, Agbaria A, et al. Humoral Response to the Pfizer BNT162b2 Vaccine in Patients Undergoing Maintenance Hemodialysis. Clin J Am Soc Nephrol 2021;16:CJN.03500321. doi:10.2215/cjn.03500321.

[16] NIH. COVID-19 treatment guidelines: Clinical Spectrum of SARS-CoV-2 Infection 2021. https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/ (accessed April 30, 2021).

[17] Karagiannidis C, Mostert C, Hentschker C, Voshaar T, Malzahn J, Schillinger G, et al. Case characteristics, resource use, and outcomes of 10 021 patients with COVID-19 admitted to 920 German hospitals: an observational study. Lancet Respir Med 2020;8:853–62. doi:10.1016/S2213-2600(20)30316-7.

[18] Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. JAMA 2020;323:2195–8. doi:10.1001/jama.2020.7202.

[19] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with

coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966. doi:10.1136/bmj.m1966.

[20] Petrilli CM, Jones SA, Yang J, Rajagopalan H, O'Donnell L, Chernyak Y, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966. doi:10.1136/bmj.m1966.

[21] Diasorin. LIAISON ® SARS-CoV-2 S1/S2 IgG Factsheet n.d. https://www.diasorin.com/sites/default/files/allegati/liaisonr_sars-cov-2_s1s2_igg_brochure.pdf.pdf.

[22] Ng DL, Goldgof GM, Shy BR, Levine AG, Balcerek J, Bapat SP, et al. SARS-CoV-2 seroprevalence and neutralizing activity in donor and patient blood from the San Francisco Bay Area. MedRxiv 2020. doi:10.1101/2020.05.19.20107482.

[23] Gómez CE, Perdiguero B, Esteban M. Emerging sars-cov-2 variants and impact in global vaccination programs against sars-cov-2/covid-19. Vaccines 2021;9:1–13. doi:10.3390/vaccines9030243.

[24] Novavax. Novavax COVID-19 Vaccine Demonstrates 89.3% Efficacy in UK Phase 3 Trial 2021:3. https://ir.novavax.com/news-releases/news-release-details/novavax-covid-19-vaccine-demonstrates-893-efficacy-uk-phase-3 (accessed April 27, 2021).

[25] Kustin T, Harel N, Finkel U, Perchik S, Harari S, Tahor M, et al. Evidence for increased breakthrough rates of SARS-CoV-2 variants of concern in BNT162b2 mRNA vaccinated individuals. MedRxiv 2021:2021.04.06.21254882. doi:10.1101/2021.04.06.21254882.

[26] Health M of. South African Variant Found in About 1% of All Positive Tests 2021. https://www.gov.il/en/departments/news/22022021-01 (accessed April 27, 2021).

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This study received no funding.

Conflict of Interests

TBN reports a contract with the Israeli Institute of Biological Research (IIBR) for the conduction of a clinical trial on a novel COVID-19 vaccine. GR reports consulting fees from

MSD and Gilead, travel fees from MSD, and honoraria from Pfizer, MSD and Astellas, none related to vaccine products.

The other authors report no conflicts of interests.

Contribution of individual authors

TBN conceived the study, analyzed the data, and prepared the manuscript. EO, MC, ME, LN, MS, YM, RC, KH, MW, OZ, BC, RN, HZ, GR and YWW collected patient data and made significant contributions to the manuscript. All authors approved the manuscript for publication.

Figure 1: Violin charts of results of anti-S-IgG testing for patients with favorable (good) and poor outcomes: (a) Diasorin's Liaison SARS-CoV-2 S1/S2 IgG (cutoff for positivity of >15u/mL). One result was omitted from the chart as an outlier, of a patient with a favorable outcome, whose antibody titer was estimated to be 2650u/mL using dilutions, as the upper limit of reporting for the assay is 400u/mL. (b) Abbott's Architect AdviseDx SARS-CoV-2 IgG II, (cutoff for positivity of 50u/mL).

For both charts the horizontal line and box represent the median and the interquartile range, respectively. The width of the curved shape represents the proportion of patients.

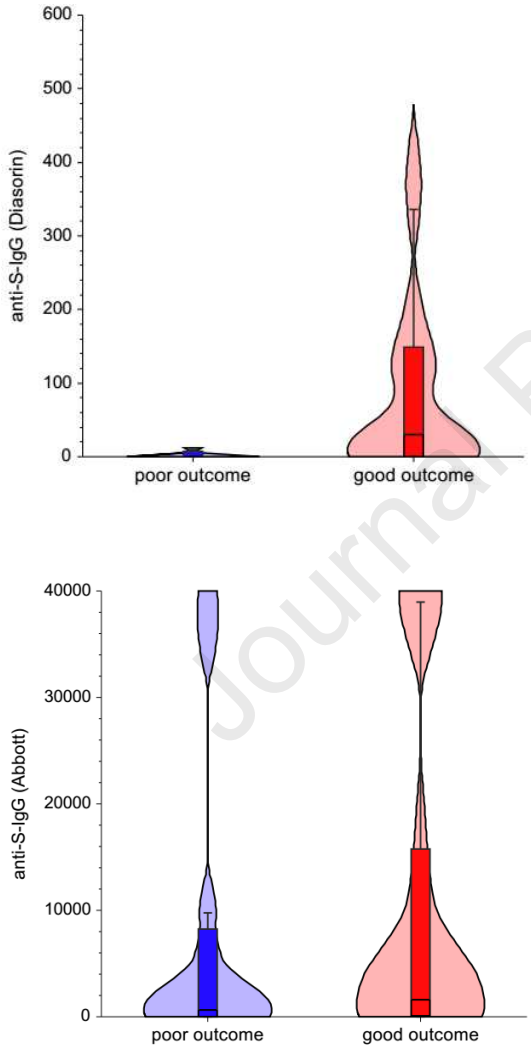


Table 1: Demographic, clinical and laboratory characteristics of hospitalized patients with COVID-19 after BNT162b2 vaccination

Table 2: Comparison of the clinical characteristics of fully-vaccinated and non-vaccinated hospitalized COVID-19 patients cohorts.

	Fully-vaccinated cohort	Non-vaccinated COVID-19 patients cohorts		
		Karagiannidis et al. [17]	Myers et al. [18]	Petrilli et al. [19]
Number of patients	**152**	10,021	377	2,741
Number of hospitals	**17**	920	21	4
Time period	**January-April 2021**	February-April 2020	March 2020	March-April 2020
Country	**Israel**	Germany	California, USA	New York, USA
Inclusion	**All fully-vaccinated patients with a PCR-confirmed COVID-19 and admitted to hospital**	All patients with a PCR-confirmed COVID-19 and admitted to hospital	All patients with a PCR-confirmed COVID-19 and admitted to hospital	All patients with a PCR-confirmed COVID-19 and admitted to hospital
Age - mean±SD or median [IQR]	**71±14.3**	Mean 68±17.3	Median 61 [50-73]	Median 63 [51-74]
Hypertension	**71%**	55.6%	43.5	62%
Diabetes mellitus	**48%**	27.9%	31.3	34.7%
Heart failure	**32%**	19.6%	5.8	12.8%
Chronic lung disease	**24%**	13.6%	7.4	16.5%
Chronic kidney disease	**27%**	22.8%	12.7	21.2%
BMI>30	**32%**	5.9%	NR	39.5%
Cancer	**24%**	NR	4.8	10.8%

Abbreviations: BMI, body mass index; IQR, interquartile range; NR, not reported; SD, standard deviation.

Table 1: Demographic, clinical and laboratory characteristics of hospitalized patients with COVID-19 after BNT162b2 vaccination

		Entire cohort				Patients admitted due to severe disease			
		All patients (N=152)	Patients with favorable outcome (N=114)	Patients with poor outcome (N=38)	*p* value	All patients (N=93)	Patients with favorable outcome (N=62)	Patients with poor outcome (N=35)	*p* value
Onset of infection (from 2nd vaccine dose)	to symptom onset - median (IQR)	35 (21-48) N=125	36 (24-50) N=91	31.5 (20-40.25) N=34	0.09	34 (21-47) N=89	36 (24.5-51.5)	31.5 (20-40)	0.095
	to hospital admission - median (IQR)	39.5 (25.5-52)	40.5 (28-53)	35 (22-48)	0.19	40 (28-53)	41.5 (30-59)	34 (21-46)	**0.04**
Age - Mean (±SD)		71.1 (±14.3)	70 (±15.2)	74.7 (±10.5)	0.13	72 (±12)	70.8 (±12.6)	74.2 (±10.5)	0.19
Male gender		107 (70%)	80 (70%)	27 (71%)	0.92	71 (73%)	47 (76%)	24 (69%)	0.44
LTCF residence		38 (25%)	29 (25%)	9 (24%)	0.83	23 (24%)	14 (23%)	9 (26%)	0.73
Comorbidities	Hypertension	108 (71%)	78 (68%)	30 (79%)	0.22	72 (74%)	44 (71%)	28 (80%)	0.33
	Diabetes mellitus	73 (48%)	56 (49%)	17 (45%)	0.64	52 (54%)	35 (56%)	17 (49%)	0.45
	BMI>30	47/149 (32%)	36 (32%)	11 (30%)	0.78	31 (33%)	19 (32%)	12 (34%)	0.79
	Chronic renal failure	48 (32%)	38 (34%)	10 (26%)	0.34	30 (31%)	21 (34%)	9 (26%)	0.40
	Ischemic heart disease	43 (28%)	32 (28%)	11 (29%)	0.92	28 (29%)	18 (29%)	10 (29%)	0.96
	Congestive heart failure	41 (27%)	28 (25%)	13 (34%)	0.25	27 (28%)	14 (23%)	13 (37%)	0.12
	Chronic lung disease	37 (24%)	28 (25%)	9 (24%)	0.91	22 (23%)	15 (24%)	7 (20%)	0.64
	Cancer	36 (24%)	25 (22%)	12 (32%)	0.23	31 (32%)	21 (34%)	10 (29%)	0.59
	Dementia	29 (19%)	19 (17%)	10 (26%)	0.19	18 (19%)	9 (15%)	9 (26%)	0.19
	Chronic liver disease	7 (5%)	6 (5%)	1 (3%)	0.68	4 (4%)	3 (5%)	1 (3%)	1.0
Immunosuppression	Any type	60 (40%)	42 (37%)	18 (47%)	0.25	50 (52%)	32 (52%)	18 (51%)	0.99
	Chemotherapy or anti-metabolite	27 (18%)	20 (18%)	7 (18%)	0.90	23 (24%)	16 (26%)	7 (20%)	0.52
	Corticosteroids	29 (19%)	21 (18%)	8 (21%)	0.72	22 (23%)	14 (23%)	8 (23%)	0.98
	Anti-CD20	10 (7%)	5 (4%)	5 (13%)	0.12	10 (10%)	5 (8%)	5 (14%)	0.49
	Solid organ transplantation	16 (11%)	13 (11%)	3 (8%)	0.76	13 (13%)	10 (16%)	3 (9%)	0.37
Exposure leading to infection	Unknown	95 (73%)	68 (71%)	27 (77%)	**0.03**	68 (81%)	42 (82%)	26 (79%)	0.23
	Household	16 (12%)	14 (14.5%)	2 (5.5%)		9 (11%)	7 (14%)	2 (6%)	
	Nosocomial transmission from another patient	15 (11%)	13 (13.5%)	2 (5.5%)		2 (2%)	1 (2%)	1 (3%)	
	Nosocomial transmission from a HCW	1 (1%)	0 (0%)	1 (3%)		1 (1%)	0 (0%)	1 (3%)	
	Other	4 (3%)	1 (1%)	3 (9%)		4 (5%)	1 (2%)	3 (9%)	
Indication for	Severe COVID-19	97 (64%)	63 (55%)	34 (89%)	**0.00**	97 (100%)			

admission									
	Non-severe COVID-19 necessitating hospital isolation	24 (16%)	23 (20%)	1 (3%)		NA			
	Medical condition unrelated to COVID-19	29 (19%)	26 (23%)	3 (8%)					
	Late complication of COVID-19	2 (1%)	2 (2%)	0%					
Anti-S IgG testing	Liaison - median (IQR) * cutoff >15	9.7 (0-128.5) N=25	30.4 (0-149) N=21	1.5 (0-8) N=4	0.11	9.7 (0-118)	30.4 (2.5-230)	0 (0-7.3)	0.06
	Abbot - Median (IQR) * cutoff >50	947.5 (29-13,129) N=44	1623 (46.5-15,748) N=32	644 (0-8,276) N=12	0.34	526 (1-15,748)	458 (14-39,485)	595 (0-3,861)	0.38
	Positive serology (any assay)	44/69 (64%)	36/53 (68%)	8/16 (50%)	0.19	28/48 (58%)	21/33 (63%)	7/15 (47%)	0.27
	Time from symptom onset to serologic test - median days (IQR)	7 (3-10)	6 (3-10.5)	8 (4.2-9)	0.43	8 (4-10.5)	8 (4-11)	8 (4-9)	0.77
First PCR done on admission	Ct value - mean±SD	22.7±5.9 N=103	23.4±5.8 N=76	20.5±5.8 N=27	**0.02**	22.4±5.5 N=66	23.6±5 N=42	20.4±5.7 N=24	**0.02**
Virus sequencing (N=32)	wildtype	3/45 (7%)	1/36 (3%)	2/9 (22%)	0.13	1/26 (4%)	0 (0%)	1/7 (14%)	0.15
	B.1.1.7	40/45 (89%)	33/36 (91%)	7/9 (78%)		23/26 (88%)	17/19 (89%)	6/7 (86%)	
	B.1.351	2/45 (4%)	2/36 (6%)	0 (0%)		2/26 (8%)	2/19 (11%)	0 (0%)	
Treatment	Oxygen	97 (66%)	62 (56%)	35 (100%)	0.00	89 (96%)			
	HFNC	46 (32%)	21 (19%)	25 (71%)	0.00	46 (52%)			
	Mechanical ventilation	20 (13%)	0 (0%)	20 (53%)	0.00	19 (20%)			
	Inotropic support	18 (12%)	0 (0%)	18 (47%)	0.00	17 (18%)			
	Renal replacement therapy	16 (11%)	12 (11%)	4 (11%)	1.00	8 (8%)			
	Corticosteroids[a]	101 (66%)	65 (58%)	35 (92%)	0.00	92 (95%)			
	Remdesivir	35 (23%)	25 (22%)	10 (26%)	0.58	34 (35%)			
	Convalescent plasma / hyperimmune serum	26 (17%)	17 (15%)	9 (24%)	0.22	25 (26%)			
	Tocilizumab	8 (5%)	3 (3%)	5 (13%)	0.02	7 (7%)			

Abbreviations: BMI, body mass index; HCW, healthcare worker; HFNC, high-flow nasal canula; IQR, interquartile range; LTCF, long term care facility; SD, standard deviation; NA, not applicable.

[a] Corticosteroids were given for treatment of severe COVID-19, as a part of maintenance treatment for patients on chronic steroid treatment, or to treat immunological complications (e.g., vestibular neuritis).

Online supplement

BNT162b2 vaccine breakthrough: Clinical characteristics of 152 fully-vaccinated hospitalized COVID-19 patients in Israel

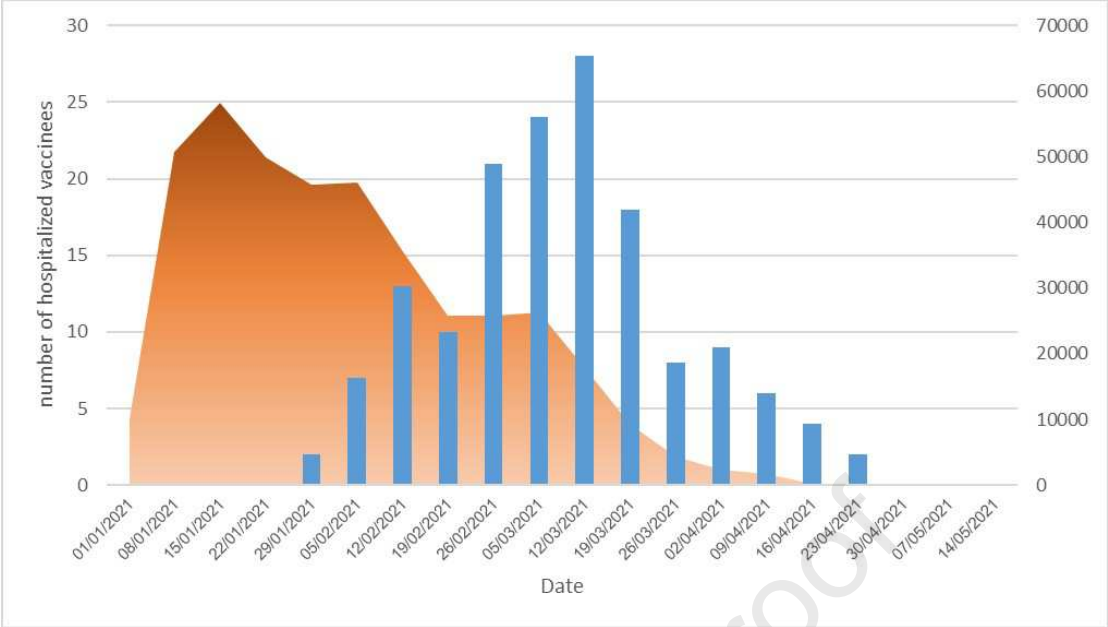
Patients with breakthrough COVID-19 that were not included in this cohort study

Not included in the cohort were patients admitted to non-participating hospitals, patients admitted to LTCF's that are considered as hospitals by the IMOH, and patients hospitalized with COVID-19 without knowledge of their vaccination status at time the of admission.

Epidemic curve of breakthrough infections during the study period

The incidence of new admissions reflected the national epidemic curve for COVID-19 (Figure S1). As the vaccination campaign began in the middle of December 2020, fully-vaccinated individuals increased in numbers from the 3rd week of January 2021, followed by an increase in the number of hospitalized vaccinees. Cases declined with the national decline in incidence.

Fig S1: Weekly incidence of fully-vaccinated hospitalized patients with COVID-19 and the weekly national new COVID-19 cases: The blue bars represent the weekly number of fully-vaccinated patients with COVID-19 that were hospitalized and reported in the study cohort. The orange area represents the weekly number of new PCR-proven COVID-19 patients in Israel, according to the Israeli Ministry of Health registry



Results of SARS-CoV-2 PCR testing

There was a significant difference between the Ct values of the first on-admission PCR, with a mean of 20.5±5.8 vs. 23.4±5.8 for patients with poor and favorable outcomes, respectively, representing a higher upper-respiratory viral load for the former group. Analyzing Ct values for different gene targets yielded similar differences: 21.7±5.5 vs. 24.8±5.8 for N (N=75), 18.6±3.7 vs. 23±6.2 for E (N=35), 21.1±6 vs. 25.2±6.7 for ORF1 (N=32), and 19.3±5.9 vs. 23.9±7 for S (N=27).