Effectiveness of Evusheld in Immunocompromised Patients: Propensity Score-Matched Analysis

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Short title: Effectiveness of Evusheld

Abstract

Background: Tixagevimab and Cilgavimab, a combined monoclonal antibody (Evusheld) was granted emergency use authorization for SARS-CoV-2 preexposure prophylaxis in individuals with moderate to severe immunocompromising condition. In this study we used population-based real-world data to evaluate the effectiveness of Evusheld in immunocompromised patients.

Methods: Using the computerized database of the largest healthcare provider in Israel, we identified all adult immunocompromised patients who were eligible to receive Evusheld (the dose used during the study period was 150mg Tixagevimab and 150mg Cilgavimab) on 15-February-2022. Patients with a documentation of a prior SARS-CoV-2 infection were excluded. A total of 703 patients who received Evusheld were propensity score-matched, using a ratio of 1:4, with 2812 patients who have not received Evusheld (control group). Patients were followed through 30-June-2022 for up to 90-days for the first documentation of SARS-CoV-2 infection and COVID-19 related hospitalization.

Results: Overall, 72 patients in the Evusheld group and 377 patients in the control group had SARS-CoV-2 infection, reflecting and incidence rate of 4.18 and 5.64 per 100 person-months, respectively. HR was 0.75(95%CI,0.58-0.96) for SARS-CoV-2 infection, and 0.41(0.19-0.89) for COVID-19 related hospitalization in the Evusheld group compared to the control group. The magnitude of relative risks reduction of each outcome was greater in non-obese patients (P for interaction=0.020 and 0.045, respectively).

Conclusion: This study suggests that Evusheld (150mg Tixagevimab and 150mg Cilgavimab) is effective in reducing the risk of SARS-CoV-2 infection and COVID-19 hospitalization in immunocompromised patients. The effectiveness of this dose appears to be greater in non-obese patients

Key words: COVID-19; effectiveness; Evusheld; SARS-CoV-2; Tixagevimab and Cilgavimab

Introduction

Despite SARS-CoV-2 vaccination, immunocompromised patients remain at increased risk for severe COVID-19 and mortality [1,2], rendering this vulnerable population a high priority for additional strategies for preexposure prophylaxis.

Tixagevimab and cilgavimab are long-acting monoclonal antibodies that are specifically directed against the spike protein of SARS-CoV-2, designed to block the virus' attachment and entry into human cells. Tixagevimab and cilgavimab bind to different, non-overlapping sites on the spike protein of the virus [3]. This combined monoclonal antibody (Evusheld) has been granted emergency use authorization (EUA) by the U.S food and drug administration (FDA) for individuals 12 years and older who have a moderate to severe immunocompromising condition and may not mount an adequate vaccination response [4,5].

PROVENT, a randomized, double-blind, placebo-controlled trial examined the efficacy of Evusheld in preventing symptomatic COVID-19 infection in adults aged ≥60 years or with chronic medical condition or at increased risk of SARS-CoV-2 infection who are unvaccinated and not previously infected with SARS-CoV-2. On the primary analysis, Evusheld showed a relative risk reduction of 76.7% (95% CI, 46.0-90.0) in symptomatic COVID-19 infection, compared to placebo. Extended follow-up at a median of 6 months showed a relative risk reduction of 82.8% (95% CI, 65.8 to 91.4) [6]. Based on results of the PROVENT trial, the FDA issued an EUA for use of Evusheld on December 8,2021 [5].

Evusheld's use in Israel for immunocompromised patients began in mid-February 2022 as the main circulating SARS-CoV-2 variant was the Omicron [7].

In this retrospective cohort study, we aimed to examine the real-life effectiveness of Evusheld in preventing SARS-CoV-2 infection and COVID-19 related hospitalization in the specific population of immunocompromised patients and in the era of Omicron with the main circulating variant, in Israel, being BA.2 **(Figure S1)**.

Materials and Methods

The study was approved by the institutional review board of Lady Davis Medical Centre and Data Utilization committee of Clalit Health Services (CHS). Owing to the retrospective nature of the study, a waiver of informed consent was granted by the institutional reviewed board. The current study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline

Sources of data

This study is based on data from two sources: CHS database and the Israeli Ministry of Health (MOH) COVID-19 database. CHS provides inclusive health care for more than half of the Israeli population (~4.7 million). CHS maintains a database that receives information from multiple sources including records of primary care physicians, community specialty clinics, hospitalizations, laboratories, and pharmacies. A registry of chronic diseases diagnoses is compiled from these data sources.

The COVID-19 database is maintained by the Israeli Ministry of Health (MOH) and contains data on vaccination, SARS-CoV-2 polymerase chain reaction (PCR) and antigen tests results, and COVID-19 hospitalizations. The collected data are transferred daily to the healthcare providers. Several high quality studies related to COVID-19 have been conducted based on integrated data from these two databases [8,9**]**. A detailed description of the databases is provided in the **Supplementary Appendix**.

Study population

In this retrospective cohort study, we used the computerized database of CHS to identify all adults aged 18 years or older with immunosuppression eligible to receive Evusheld (150 mg Tixagevimab and 150 mg Cilgavimab as the higher dose of 300 mg for each of the components was not approved in Israel during the study period) based on the definition provided by the Israeli MOH upon entrance to the study on 15 February 2022. Immunosuppressed patients who are candidates for pre-exposure prophylaxis with Evusheld were those with at least one comorbidity or condition causing severe immunosuppression (chimeric antigen receptor T-cell therapy (CAR-T), solid organ transplant, autologous or allogenic bone marrow transplant (BMT) in the prior year, hypogammaglobulinemia, active lymphoma, active multiple myeloma, active chronic lymphocytic leukemia (CLL), and B-cell depleting therapies). Unlike the PROVENT study that excluded patients who received any dose of a SARS-CoV-2 vaccine, in this study patients were eligible to be included irrespective of their COVID-19 vaccination status. Exclusion criteria were prior documentation of positive SARS-CoV-2 PCR or antigen test, and the recipient of a COVID-19 vaccine in the prior two weeks before Evusheld treatment.

The propensity-matched study population

We used logistic regression to calculate, in the entire cohort of immunosuppressed patients (n=8260), the predicted probability (propensity score) of being treated with Evusheld given 22 variables, including; demographic variables, baseline comorbidities, and selected medications use, as outlined in Table 1. All confounders included in the multivariable logistic regression model, to estimate the propensity score were

selected based on established prior epidemiologic evidence of their association with the severity of COVID-19 **[10]**. BMI, eGFR and SES had few missing values, to handle this in the analysis, we used a separate category for missing values. Patients in the Evusheld group were matched on calendar date and propensity score to patients in the non-Evusheld group (controls) in a 1:4 ratio using a greedy matching algorithm with a maximum acceptable difference of 0.01 in the propensity score between matched groups (caliper width of 0.01). This matching process yielded 703 patients out of the 732 patients in the Evusheld group and 2812 patients in the control group.

Study outcomes and follow-up

Two outcomes of interest were investigated; first occurrence of SARS-CoV-2 infection based on the documentation of positive SARS-CoV-2 PCR or antigen test, and COVID-19 related hospitalization (defined as a hospitalization that was reported to the Israeli MOH as a hospitalization of a SARS-CoV-2 infected individual).

Follow-up started at the date of Evusheld treatment both for the Evusheld group and matched controls (study start date). Patients were followed from the start date until outcome event, death, follow-up of 90 days or end of the study 30 June 2022, whichever came first.

Study variables

For each patient, we extracted sociodemographic data including age, sex, population sector (Jewish, Arabs), and socioeconomic status (SES) (low, middle, high) that were based on the SES scores of the clinic neighborhood as defined by the Israeli Central Bureau of Statistics. In addition, we extracted COVID-19 vaccination dates and data on comorbidities and conditions associated with study outcome, including body mass index (BMI), diabetes, hypertension, malignancy in the prior year, cardiovascular disease, chronic lung disease, chronic liver disease, chronic kidney disease (eGFR <60 ml/min), neurological disorders, and immunocompromising conditions.

COVID-19 vaccination status was classified into two categories: adequate versus non-adequate vaccination status, determined based on the timing of the last vaccine dose before study entry. Patients receiving only the first vaccine dose were considered non-adequately vaccinated. For the second vaccine dose and subsequent doses given more than 180 days apart, a patient was considered to be adequately vaccinated if he/she received the last dose in the prior 8-180 days before study entry. If the gap between the last two doses was less than 180 days, a patient was considered adequately vaccinated starting from the date of the last vaccine dose up to 180 days after.

Data analysis

Continuous variables were summarized with means and standard deviations (SD), and categorical variables were summarized with counts and proportions. The annualized incidence rates of the outcomes of interest were estimated by dividing the number of incident events by the total follow up time and were expressed as number per 100 person-months of observation.

To assess the balance of baseline characteristics, between the Evusheld group and matched controls we used the standardized mean difference (SMD), a measure not influenced by sample size. A standardized mean difference of 0.1 or less indicates a negligible difference in the measured variables between groups [11].

Kaplan-Meier curves were used to depict the distribution of time to events in the Evusheld and control groups. Cox proportional hazard regression models were used to estimate the hazard ratio (HR), along with 95% confidence interval (95% CI), for study outcomes in the Evusheld group compared to the control group. To account for matching, we stratified the analysis by matched sets. An interaction factor was examined between Evusheld and demographic variables, COVID-19 vaccination status, and selected underlying comorbidities. The number needed to treat (NNT) for each outcome was calculated using estimates of 90 days cumulative incidence from the Kaplan Meier curves. Statistical analyses were performed using IBM SPSS Statistics 28.0 (IBM, New York, NY), and SAS version 9.3 software (Cary, NC).

Results

Overall, 8260 immunocompromised patients were identified, of them 732 patients received Evusheld by 30 June 2022. A total of 703 patients who received Evusheld were propensity score matched to 2812 patients who did not receive Evusheld (controls).

Comparison of baseline characteristics between the Evusheld and the control groups is presented separately before and after matching **(Table 1)**. Before matching, patients in the Evusheld group were older, were more likely to be Jewish and to belong to higher socioeconomic status. In addition, patients in the Evusheld group had higher frequency of bone marrow transplant (BMT), lymphomas, and chronic lung disease. They were also more likely to have adequate COVID-19 vaccination status, and more likely to have been treated with B-cell depleting therapies. All differences between the Evusheld and control groups were balanced after matching with standardized mean difference less than 0.1 **(Table 1)**. The distribution of the propensity score, after matching, in the control and Evusheld group is depicted in **Figure S2**.

SARS-CoV-2 infection

Of 703 patients in the Evusheld group 72 patients had SARS-CoV-2 infection, reflecting and incidence rate 4.18 per 100 person-months. Of the 2812 patients in the control group 377 patients had SARS-CoV-2 infection, reflecting and incidence rate 5.64 per 100 person-months **(Table 2)**. The cumulative incidence of SARS-CoV-2 infection was lower in the Evusheld group compared to the control group with NNT of 26 **(Figure 1)**.

The HR for SARS-CoV-2 infection was 0.75 (95% CI, 0.58-0.96) in the Evusheld group compared to the control group **(Table 2)**. Subgroup analysis showed that effectiveness of Evusheld in reducing SARS-CoV-2 infection appears to be greater in non-obese patients (P for interaction = 0.020) **(Figure 2)**

COVID-19 hospitalization

The incidence rate **(Table 2)** as well as the cumulative incidence of COVID-19 related hospitalization **(Figure 3)** was lower in the Evusheld group compared to the control group with NNT of 59.

The HRs for COVID-19 hospitalization was 0.41 (0.19-0.89) in the Evusheld group compared to the control group **(Table 2)**. Subgroup analysis showed that effectiveness of Evusheld in reducing COVID-19 hospitalization appears to be greater in non-obese patients (P for interaction = 0.045) **(Figure S3)**

Discussion

This propensity score-matched analysis of the real-world effectiveness of Evusheld in immunocompromised patients shows a reduced risk for SARS-CoV-2 infection and COVID-19 related hospitalization with HR of 0.75 and 0.41, respectively. Evusheld appears to have more incremental benefit for those who are non-obese, in those who are obese it appears to add less benefit.

The magnitude of SARS-CoV-2 infection risk reduction associated with Evusheld is lower in our study compared to the PROVENT trial with HR of 0.75 and 0.17, respectively. These differences derive from many factors. While the PROVENT included a low percentage of immunosuppressed patients (<5%), and study population included among others healthy individuals who are at risk of SARS-CoV-2 exposure, and only unvaccinated patients, our study included solely immunocompromised patients regardless of their vaccination status. Also, the outcome investigated in the PROVENT study was symptomatic COVID-19 infection while our study investigated the outcome of a laboratory confirmed COVID-19 infection regardless of symptoms. Last, the PROVENT study was conducted when the alpha, beta and delta were still the circulating variants while our study was conducted when the prevailing variant in Israel was the Omicron [6,7].

Kertes et al used real-world data to evaluate the effectiveness of Evusheld in immunocompromised patients aged 12 and above regardless of their vaccination status and previous COVID-19 infections. Their results showed an OR of 0.51 (95% CI 0.30-0.84) for SARS-CoV-2 infection, and 0.08 (95% CI 0.01-0.54) for the composite of COVID-19 related hospitalization or all-cause mortality [12]. Unlike this study, our study included patients aged 18 years or older without previous infection with SARS-CoV-2. In addition, some of the differences in the results between our study and Kertes et al study might be related to difference in study design and analytic approach. To account for confounding, we performed propensity score-matching based on 22 variables and used Cox proportional hazard regression analysis to compare between groups. Whereas Kertes et al used standard multivariable logistic regression albeit the different follow-up time between participants. In addition, it is not enough clear which confounders were included in the multivariable model.

Notably, this study was conducted while the main circulating variant in Israel was Omicron with the subvariant of BA.2 being the prevailing one throughout the majority of the study period (Figure S1). Other subvariants like BA.1, BA.4, BA.5 and BA.2.12.1 were still circulating in a lesser extent [7]. Recent studies showed different neutralizing susceptibility against different subvariants of Omicron with overall reduced susceptibility of all Omicron subvariants compared to Alpha, Beta, Gamma and Delta subvariants [13]. Despite the reduced susceptibility of Omicron variants to Evusheld, our study shows a benefit in preventing SARS-CoV-2 infection and related hospitalization, although the parallel course of the Kaplan Meier curves for SARS-CoV-2 infection might suggest a waning effect over time. Considering the rarity of major side effects of Evusheld **[6],** and the estimated NNT, it is suggested that the benefit appears to outweigh the risk. However, the effectiveness of Evusheld may vary depending on the susceptibility of the circulating variants.

Our study suggests that Evusheld might be more effective in non-obese patients which raises a question about the dosing of Evusheld. The FDA revised their recommendation on Evusheld's dosing based on nonclinical data and pharmacokinetic modeling of the activity of Evusheld against subvariants of Omicron and recommends a dose of 300 mg of tixagevimab and 300 mg of cilgavimab [14,15]. These recommendations were not adopted in Israel during the study period and patients received the 150 mg dosing of each component. These findings suggest that weight adjusted dosing approach might be reasonable, but further studies are needed to address this specific issue.

Limitations

This study has several limitations. As with any retrospective cohort study that is based on data from clinical and administrative database, a possible limitation may be related to the quality of the data.

Despite that, information about study outcomes and the administration of COVID-19 vaccines, collected prospectively as part of the Israeli MOH COVID-19 database, are considered complete. Information about Evusheld is also closely monitored by CHS and is considered complete. In addition, this retrospective cohort study is observational in nature, hence albeit using propensity score-matched analysis to adjust for confounders, residual confounding remains of concern. Furthermore, undocumented positive home antigen tests and prior asymptomatic SARS-CoV-2 infection is still a concern. However, we assume this might have happened in a minority of immunocompromised patients, a population with a high awareness of their vulnerable health status, and since COVID-19 follow-up services and eligibility for COVID-19 treatments, which might be crucial for these patients, required a documented test. Moreover, SARS-CoV-2 PCR and institutional antigen tests (performed by a healthcare worker and documented) were highly available and free of charge throughout the country. Finally, the outcome measured in the study was laboratory confirmed COVID-19 infection by means of positive PCR or antigen test regardless of symptoms.

Conclusions

This study suggests that Evusheld is effective in reducing COVID-19 infections and related hospitalizations in immunocompromised adult patients regardless of their vaccination status. Adjusted weight dosing approach is suggested but needs to be further studied.

Contributors:

RN-D, and WS conceived the study, and edited the final manuscript. WS and NS conducted the analysis. All authors contributed to study design, revising the manuscript for important intellectual content, were responsible for the decision to submit for publication, and approved the final submitted version of the manuscript. All authors had full access to the deidentified data in the study. RN-D, NS and WS accessed and verified the data underlying the study and take responsibility for the data.

Availability of data

Individual level data cannot be publicly available due to legal restrictions.

All data relevant to this analysis were presented in the paper.

Conflict of interest

All authors report no potential conflicts of interest.

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Figures legend

Figure 1: Kaplan-Meier curves depicting the distribution of time to first SARS-CoV-2 infection

Figure 2: The effectiveness of Evusheld in reducing the risk of SARS-CoV-2 infection by subgroups of selected sociodemographic and clinical variables.

Figure 3: Kaplan-Meier curves depicting the distribution of time to COVID-19 related hospitalization

Table 1: Baseline demographic and clinical characteristics before and after propensity score matching

	Before matching			After matching		
Variable	**Evusheld** (n = 732)	**Controls** (n = 7528)	**SMD†**	**Evusheld** (n = 703)	**Controls** (n = 2812)	**SMD†**
Age (years) Mean ± SD	66.3 ± 13.6	61.4 ± 17.2	0.314	66.2 ± 13.7	66.4 ± 14.7	0.017
Female sex	310 (42.3%)	3374 (44.8%)	0.050	301 (42.8%)	1253 (44.6%)	0.036
Population sector						
Arabs	40 (5.5%)	1399 (18.6%)	0.410	40 (5.7%)	155 (5.5%)	0.009
Jewish	692 (94.5%)	6129 (81.4%)		663 (94.3%)	2657 (94.5%)	
SES[a]						
Low	122 (16.7%)	2468 (32.8%)	0.380	121 (17.2%)	473 (16.8%)	0.011
Middle	342 (46.7%)	3154 (41.9%)	0.097	328 (46.7%)	1297 (46.1%)	0.012
High	268 (36.6%)	1898 (25.2%)	0.250	254 (36.1%)	1042 (37.1%)	0.021
Adequate COVID-19 vaccination	546 (74.6%)	4960 (65.9%)	0.191	552 (74.3%)	2096 (74.5%)	0.004
Immunosuppression variables						
CAR-T	7 (0.95%)	59 (0.78%)	0.018	6 (0.85%)	17 (0.60%)	0.029
Solid organ transplant	246 (33.6%)	2842 (37.8%)	0.088	245 (34.9%)	966 (34.4%)	0.010
BMT in the prior year	34 (4.6%)	156 (2.1%)	0.139	23 (3.3%)	88 (3.1%)	0.011
Hypogammaglobulinemia	26 (3.6%)	488 (6.5%)	0.133	26 (3.7%)	101 (3.6%)	0.033
Lymphoma	190 (26.0%)	1387 (18.4%)	0.184	175 (24.9%)	668 (23.8%)	0.026
Multiple myeloma	96 (13.1%)	812 (10.8%)	0.071	87 (12.4%)	380 (13.5%)	0.033
CLL	100 (13.7%)	1081 (14.4%)	0.020	90 (12.8%)	353 (12.6%)	0.006
B-cell depleting therapy	273 (37.3%)	1825 (24.2%)	0.287	252 (35.8%)	985 (35.0%)	0.017
Risk factors for severe COVID-19						
Obesity[a] (BMI ≥ 30 Kg/m^2)	170 (23.2%)	1745 (23.2%)	0.000	164 (23.3%)	684 (24.3%)	0.023
Diabetes	257 (35.1%)	2399 (31.9%)	0.068	245 (34.9%)	977 (34.7%)	0.004
Hypertension	441 (60.2%)	4265 (56.7%)	0.071	426 (60.6%)	1725 (61.3%)	0.014
Cardiovascular disease	221 (30.2%)	2317 (30.8%)	0.013	213 (30.3%)	831 (29.6%)	0.015
Chronic liver disease	34 (4.6%)	527 (7.0%)	0.103	34 (4.8%)	145 (5.2%)	0.018
Chronic lung disease	99 (13.5%)	721 (9.6)	0.122	93 (13.2%)	337 (12.0%)	0.035
CKD[a] (eGFR <60 ml/min)	224 (30.6%)	2337 (31.0%)	0.009	221 (31.4%)	870 (30.9%)	0.011
Neurological disease	73 (10.0%)	725 (9.6%)	0.013	71 (10.1%)	302 (10.7%)	0.020
Malignancy in the prior year	103 (14.1%)	836 (11.1%)	0.090	91 (12.9%)	353 (12.6%)	0.009

Abbreviations: BMT = bone marrow transplant; CAR-T = chimeric antigen receptor T-cell therapy); CKD = chronic kidney disease; CLL = chronic lymphocytic leukemia; SES = socioeconomic status; SMD = standardized mean difference

[a]The following variables has missing values: BMI, 5 patients; eGFR, 112 patients in the cohort after matching and SES, 8 patients; BMI, 17 patients; eGFR, 332 patients in the cohort before matching

†An SMD of ≤ 0.1 indicates a negligible difference in the measured variables between groups.

Table 2: Association between Evusheld treatment and study outcome

Study outcome*	**Study group**	**No. of events**	**Follow-up duration** (person-months)	**Incidence Rate (95% CI)** (per 100 person-month)	**HR (95% CI)**	**P value**
SARS-CoV-2 infection	Evusheld Control	72 377	1724 6680	4.18 (3.27-5.26) 5.64 (5.09-6.24)	0.75 (0.58-0.96) Reference	0.023
COVID-19 hospitalization	Evusheld Control	7 67	1815 7171	0.39 (0.15-0.79) 0.93 (0.72-1.19)	0.41 (0.19-0.89) Reference	0.025

* All study outcomes refer to events appearing within 90-days

FIGURE 1

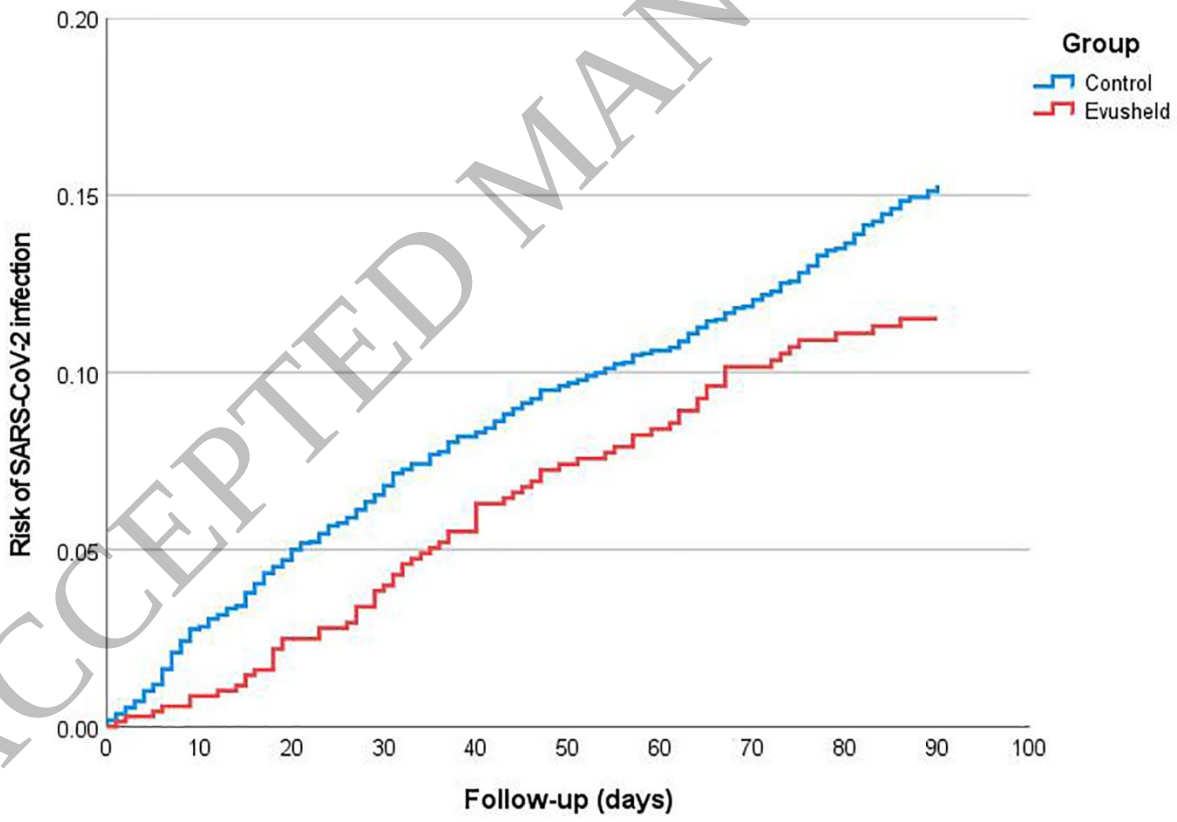

Figure 1
200x150 mm (x DPI)

FIGURE 2

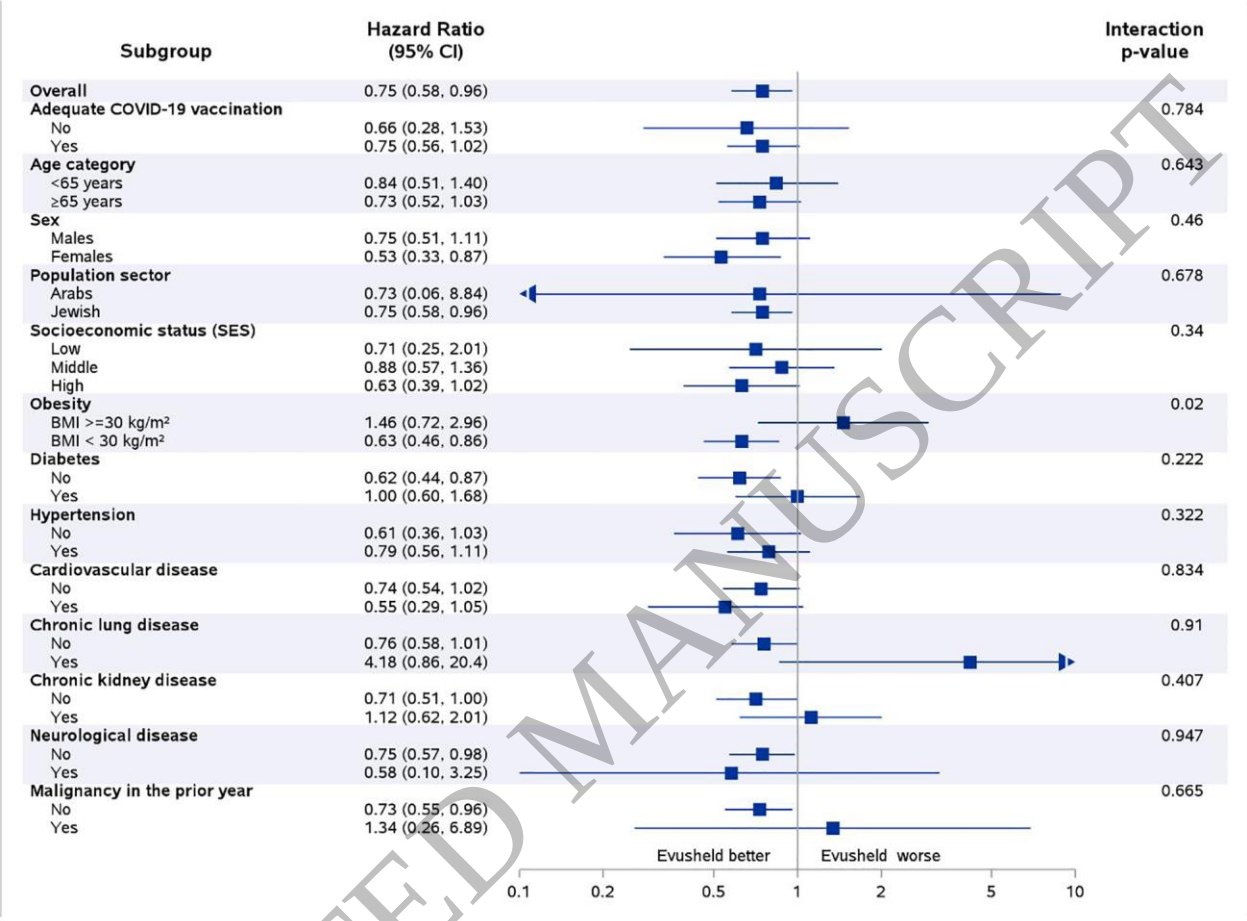

Figure 2
165x138 mm (x DPI)

FIGURE 3

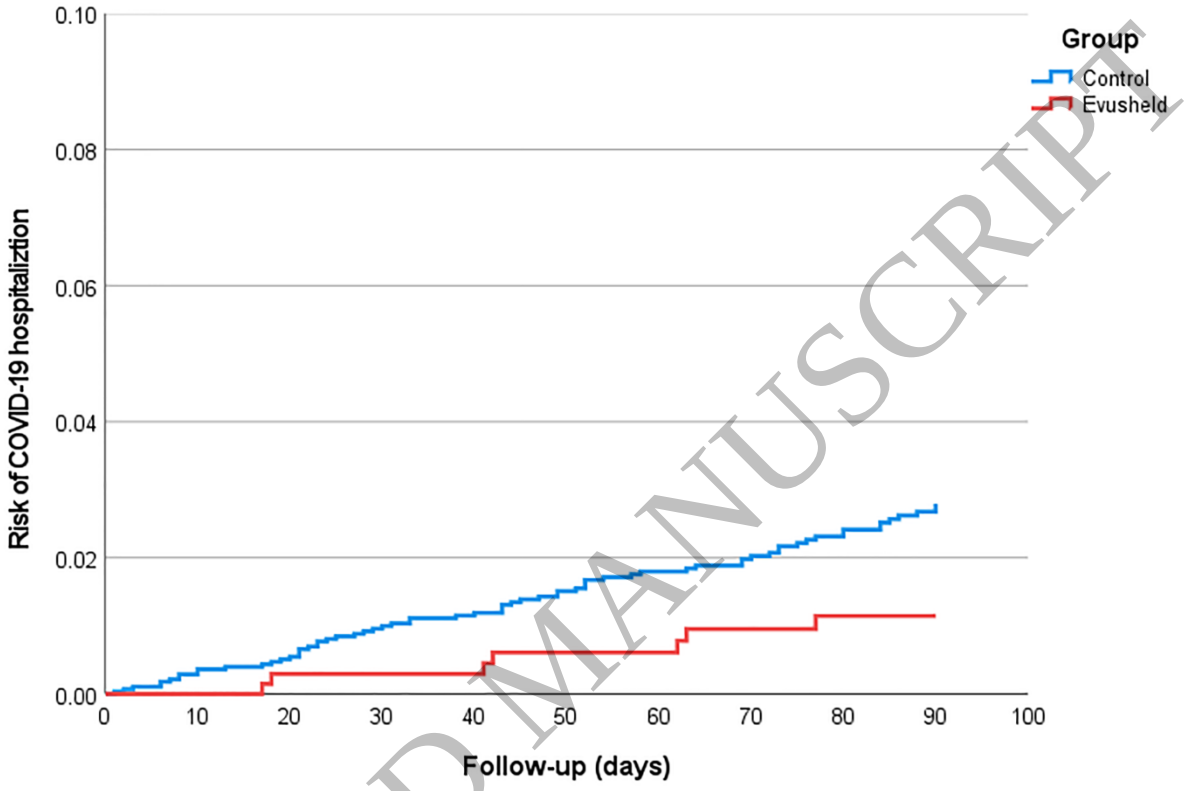

Figure 3
268x210 mm (x DPI)