# Supplemental Material*

Kip KE, McCreary EK, Collins K, et al. Evolving real-world effectiveness of monoclonal antibodies for treatment of COVID-19. A cohort study. Ann Intern Med. 4 April 2023. [Epub ahead of print]. doi:10.7326/M22-1286

## Contents



* This supplemental material was provided by the authors to give readers further details on their article. The material was not copyedited.

## Supplement Appendix A. COVID-19 Therapeutics Committee Guidelines for Selection of Monoclonal Antibodies

A. Priority Selection for High-Risk Immunocompromised Patients

- Pregnancy (not included in present analysis)
- B-cell therapy (Rituxi-/Ocrelizu-/Ofatumumab)
- Ibrutinib or acalabrutinib therapy
- Chimeric Antigen Receptor T-cell Therapy, CAR-T
- Hematopoietic Cell Transplant
- Graft versus host disease
- Hematological malignancy
- Solid organ transplant
- Severe primary immunodeficiency
- AIDS (CD4 <200 or <15%)
- Age 65 or older and loss of 2 or more ADLs

B. Selection and Implementation of Monoclonal Antibodies

- 12/8/2020: Started bamlanivimab monotherapy
- 3/10/2021: Started casirivimab and imdevimab
- 3/16/2021: Started bamlanivimab and etesevimab
- 3/31/2021: Stopped bamlanivimab monotherapy
- 6/25/2021: Stopped bamlanivimab and etesevimab
- 7/15/2021: Started sotrovimab
- 9/9/2021: Switched casirivimab and imdevimab to subcutaneous administration
- 9/16/2021: Resumed bamlanivimab and etesevimab
- 9/28/2021: Switched system guidelines to only allow monoclonal antibody use in highest risk patients due to drug scarcity (see Part A)
- 12/15/2021 to 12/23/2021: Use of bamlanivimab and etesevimab and casirivimab and imdevimab to conserve sotrovimab supply
- 12/28/2021 to 3/29/2022: Exclusive use of sotrovimab in all settings
- 3/30/2022 to 8/31/2022: Exclusive use of bebtelovimab in all settings

## Supplement Appendix B. Listing of Variables Used in the Primary Propensity Score Model (Table 1) and Method Defined in the Electronic Health Record (EHR)

| Variable | Method Defined in the EHR |
|---|---|
| Age | From patient record at infusion date or COVID-19 test date |
| Female gender | From patient record at infusion date or COVID-19 test date |
| Black race | From patient record at infusion date or COVID-19 test date |
| Body mass index | Based on closest outpatient visit within the last year (supplemented with in-patient visit in the last year, if missing) |
| UPMC health plan member | Insurance/payor status at most recent visit |
| Medicare as primary insurer | Insurance/payor status at most recent visit |
| Medicaid as primary insurer | Insurance/payor status at most recent visit |
| History of obstructive sleep apnea | Active problem or diagnosis at most recent visit within the last year |
| History of diabetes | Any history (must have been seen within the last year) |
| History of hypertension | Any history (must have been seen within the last year) |
| History of valvular heart disease | Any history (must have been seen within the last year) |
| History of atrial fibrillation | Any history (must have been seen within the last year) |
| History of congestive heart failure | Any history (must have been seen within the last year) |
| History of stroke | Any history (must have been seen within the last year) |
| History of dyspnea | Active problem or diagnosis at most recent visit within the last year |
| History of pulmonary hypertension | Any history (must have been seen within the last year) |
| History of COPD | Any history (must have been seen within the last year) |
| History of bronchiectasis | Active problem or diagnosis at most recent visit within the last year |
| History of cancer | Any history (must have been seen within the last year) |
| History of chemotherapy | History of treatment prior to infusion date or COVID-19 test date |
| History of lung cancer | Any history (must have been seen within the last year) |
| History of chronic kidney disease | Any history (must have been seen within the last year) |
| History of fatty liver disease | Active problem or diagnosis at most recent visit within the last year |
| History of cirrhosis | Active problem or diagnosis at most recent visit within the last year |
| History of viral hepatitis | Active problem or diagnosis at most recent visit within the last year |
| History of allergic rhinitis | Active problem or diagnosis at most recent visit within the last year |
| History of rheumatoid arthritis | Any history (must have been seen within the last year) |
| History of sarcoidosis | Active problem or diagnosis at most recent visit within the last year |
| History of lupus | Any history (must have been seen within the last year) |
| History of organ or cell transplant | History of procedure prior to infusion or COVID-19 test date |
| History of immunocompromised | All identified within the last year (sans Lupus, RA, HIV, SLE, IBD which are similar to the variables above that simply require being see within the last year) |
| ACE Inhibitors | Active medication at most recent visit within the last year |
| Angiotensin II receptor blocker | Active medication at most recent visit within the last year |
| Alpha blocker | Active medication at most recent visit within the last year |
| Statins | Active medication at most recent visit within the last year |
| Antidepressants | Active medication at most recent visit within the last year |
| Corticosteroids as a home medication | Active medication at most recent visit within the last year |

## Supplement Appendix C. Framework of Analytic Decisions to Emulate a Hypothetical Pragmatic Randomized Trial

| Randomized Clinical Trial | Observational Analysis |
|---|---|
| **Eligibility/Exclusion Criteria** | |
| ■ SARS-CoV-2 + test result in the UPMC system from December 8, 2020 to August 31, 2022 | ■ Same |
| ■ Age 12+ | ■ Same |
| ■ Not pregnant | ■ Same |
| ■ Outpatient with mild to moderate COVID (not hospitalized or in the emergency department) but deemed to be at high risk for progression to severe COVID-19, including hospitalization or death, and for whom alternative COVID-19 treatment options approved or authorized by the FDA are not accessible or clinically appropriate | ■ Same |
| ■ No prior receipt of Evusheld for post-exposure (pre-COVID) prophylaxis and not expected to receive Evusheld within 28 days of date of SARS-CoV-2 + test result | ■ Same<br>■ Have at least one health record in the UPMC EHR in the past year (for collection of covariate data) |
| **Treatment Strategies** | |
| ■ "Early" treatment with mAb infusion administered within 1-2 days after SARS-CoV-2 + test result vs. no "early" treatment with mAb infusion. | ■ Same |
| **Assignment Procedures** | |
| ■ Random assignment of "early" mAb infusion to be administered within 1-2 days after SARS-CoV-2 + versus random assignment to no mAb treatment within 1-2 days after SARS-CoV-2 + test. Participants are not blinded to treatment assignment. Those assigned to the no-treatment group may "crossover" and receive "delayed" mAb therapy within 3-10 days after the date of SARS-CoV-2 + test. | ■ Patients will be classified as either "treated" or "non-treated" based on their previous history of receipt of mAb therapy. Patients who received mAb therapy within 1-2 days of SARS-CoV-2 + test result will be classified in the treated group (early treatment). Patients who never received mAb therapy or received mAb therapy within 3-10 days of SARS-CoV-2 + test result (delayed treatment) will be classified in the non-treated group.<br>■ In the absence of true randomization, it is assumed that the assignment of treatment is random within levels of the covariates listed in Table 1 of the manuscript. |
| **Follow-up Period** | |
| ■ 28 days after the date of SARS-CoV-2 + test | ■ Same |

| **Outcome(s)** | |
|---|---|
| ■ Primary: Risk of composite outcome of hospitalization or death at 28-day follow-up<br>■ Secondary: 28-day risk of hospitalization, death, emergency department (ED) visit without hospitalization, and the composite outcome ED visit/hospitalization. | ■ Same<br>■ Same |
| **Causal Contrasts of Interest** | |
| ■ Intention to treat effect<br>■ Per protocol effect | ■ N/A<br>■ Observational analog of the per protocol effect |
| **Analysis Plan** | |
| ■ Intention to treat estimation of risk ratio of hospitalization or death over 28-day follow-up<br>■ Intention to treat Kaplan-Meier survival plot of freedom from hospitalization or death over 28-day follow-up<br>■ Per protocol estimation of risk ratio of hospitalization or death over 28-day follow-up<br>■ Per protocol Kaplan-Meier survival plot of freedom from hospitalization or death over 28-day follow-up | ■ N/A<br>■ N/A<br>■ Same*<br>■ Same* |
| ***A Priori* Subgroups to be Examined** | |
| ■ Individual mAb product<br>■ Presumed SARS-CoV-2 variant<br>■ Patient immunocompromised status | ■ Same<br>■ Same<br>■ Same |
| **Sensitivity Analyses** | |
| ■ Subset of patients with non-missing covariate data<br>■ Subset of patients with known vaccination status | ■ Subset of patients with non-missing BMI<br>■ Subset of patients with EHR documentation of COVID-19 vaccination status<br>■ Modification of the “early” 2-day treatment grace period to either 1-day or 3-days.<br>■ Modified propensity score model that includes vaccination status as a covariate with an imputed value of 0 for unknown vaccination status |

*Propensity-score methodology will be used with a 1:2 ratio to match patients in the treated group to control subjects in the non-treated group. Covariates used in the propensity score (to control for confounding) were documented as close to the COVID+ test date in the EHR to mimic time of enrollment (at baseline).

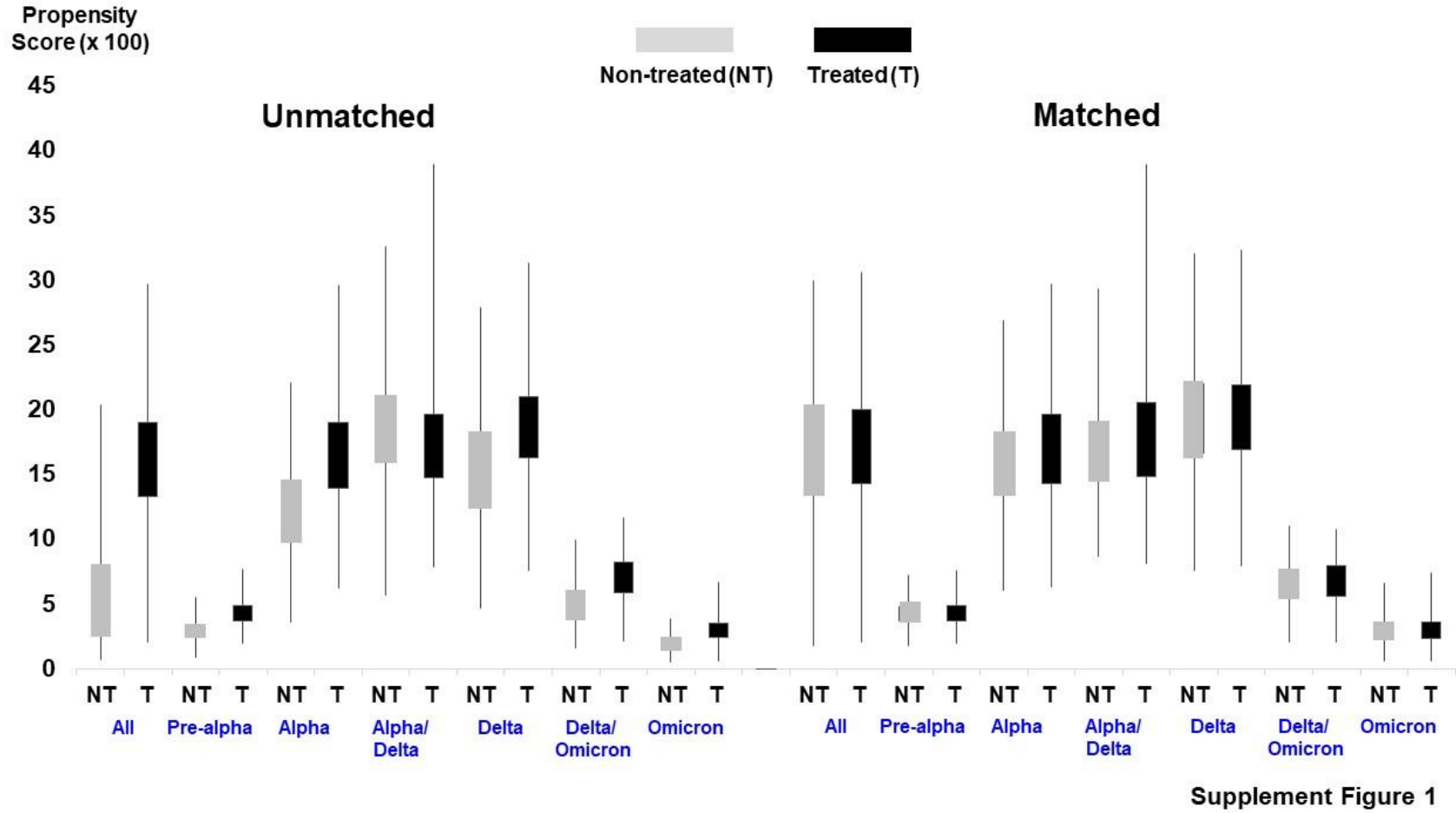
## Supplement Appendix D. Conditions Used to Define Patients as Immunocompromised

All based on within 1 year of mAb treatment for treated patients and within 1 year plus 2 days of COVID test positive date for control subjects.

- Radiation oncology charge
- Cancer diagnosis (heme malignancies, leukemia, lymphoma, myeloma, breast cancer, bone cancer, solid organ cancers, Myelodysplastic syndromes, myeloproliferative disorders, *chronic lymphocytic leukemia*, acute myeloid leukemia, diffuse large B cell lymphoma, follicular lymphoma)
- Any Car T therapy
- Systemic lupus erythematosus
- Actively being on biologics
- Rheumatoid arthritis
- Inflammatory bowel disease
- HIV
- Cell death protein 1 (PD-1) therapy
- B Cell Depleting Therapy medications
- Any transplant including stem cell transplant
- Diagnosis of graft versus host disease
- Other conditions (e.g. sarcoidosis) (ICD codes: D84.81, D84.821, D84.822, D84.89, D84.9, D86, D86.0, D86.1, D86.2, D86.3, D86.8, D86.81, D86.82, D86.83, D86.84, D86.85, D86.86, D86.87, D86.89, D86.9, D89, D89.0, D89.1, D89.2, D89.3, D89.4, D89.40, D89.41, D89.42, D89.43, D89.44, D89.49, D89.8, D89.81, D89.82, D89.831, D89.832, D89.833, D89.834, D89.835, D89.839, D89.89, D89.9, E06.5, K75.4, M30, M30.0, M30.1, M30.2, M30.3, M30.8, M31, M31.0, M31.1, M31.10, M31.11, M31.19, M31.2, M31.3, M31.30, M31.31, M31.4, M31.5, M31.6, M31.7, M31.8, M31.9, M32, M32.0, M32.1, M32.10, M32.11, M32.12, M32.13, M32.14, M32.15, M32.19, M32.8, M32.9, M33, M33.0, M33.00, M33.01, M33.02, M33.03, M33.09. M33.1, M33.10. M33.11, M33.12. M33.13, M33.19, M33.2, M33.20, M33.21, M33.22, M33.29, M33.9, M33.90, M33.91, M33.92, M33.93, M33.99, M34, M34.0, M34.1. M34.2, M34.8, M34.81, M34.82, M34.83, M34.89, M34.9, M35, M35.0, M35.00, M35.01, M35.02, M35.03, M35.04, M35.05, M35.06, M35.07, M35.08, M35.09, M35.0A, M35.0B, M35.0C, M35.1, M35.2, M35.3, M35.4, M35.5, M35.6, M35.7, M35.8, M35.81, M35.89, M35.9, Z92.21, Z92.22, Z92.241, Z92.25, Z92.3)

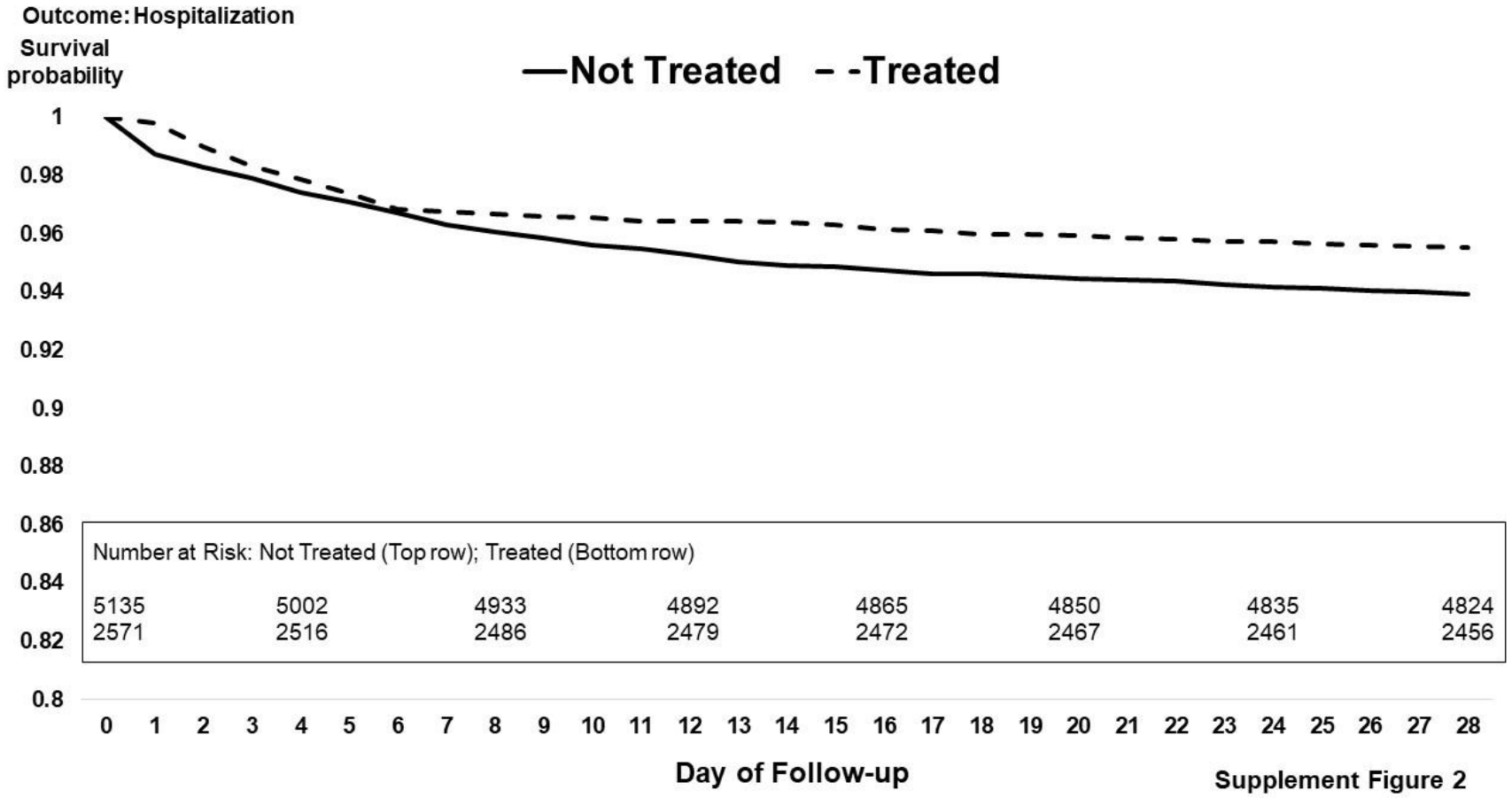
**Potential Explanations for Which Patients Eligible for mAb Therapy did not Receive mAb Therapy**: There are multiple reasons why patients may have met EUA criteria per electronic health record review yet ultimately did not receive monoclonal antibody therapy. First, symptom severity cannot be ascertained through the electronic health record review, and therefore patients may either be asymptomatic or have symptoms too severe for treatment (e.g., require oxygen above baseline needs). Second, after referral (prescription) for monoclonal antibody, treatment was received from the prescriber, the UPMC infusion centers would call the patient to schedule an infusion appointment. At this step, some patients would not answer the phone or subsequently decline therapy. Finally, patients may have been eligible for monoclonal antibody treatment yet did not seek care for various reasons (e.g. personal, religious, etc.).

**Supplement Figure 1. Distribution of propensity scores (x 100) before and after matching of treated and non-treated patients overall and by presumed SARS-CoV-2 variant.**

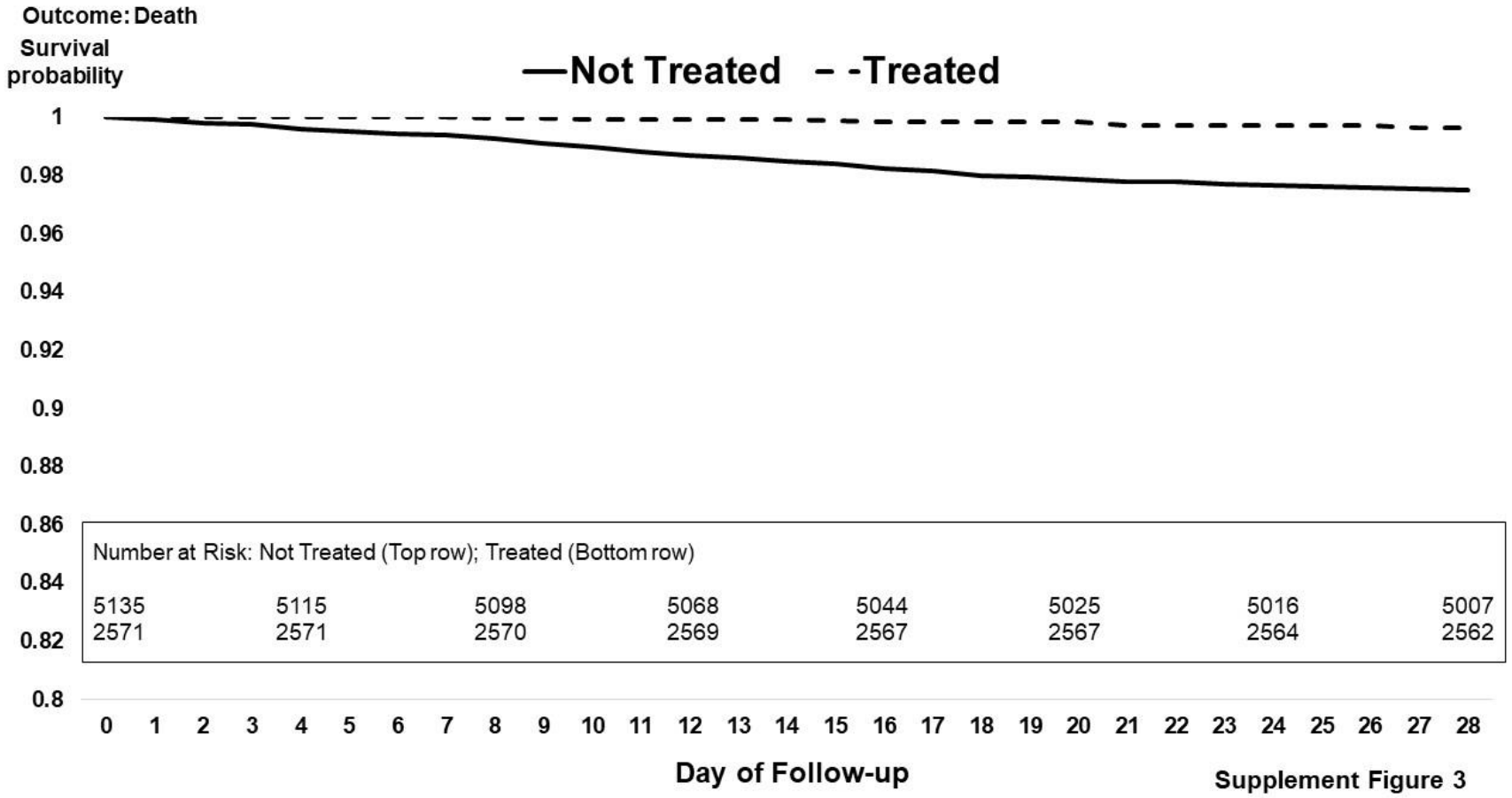



NT: Non-treated. T: Treated.

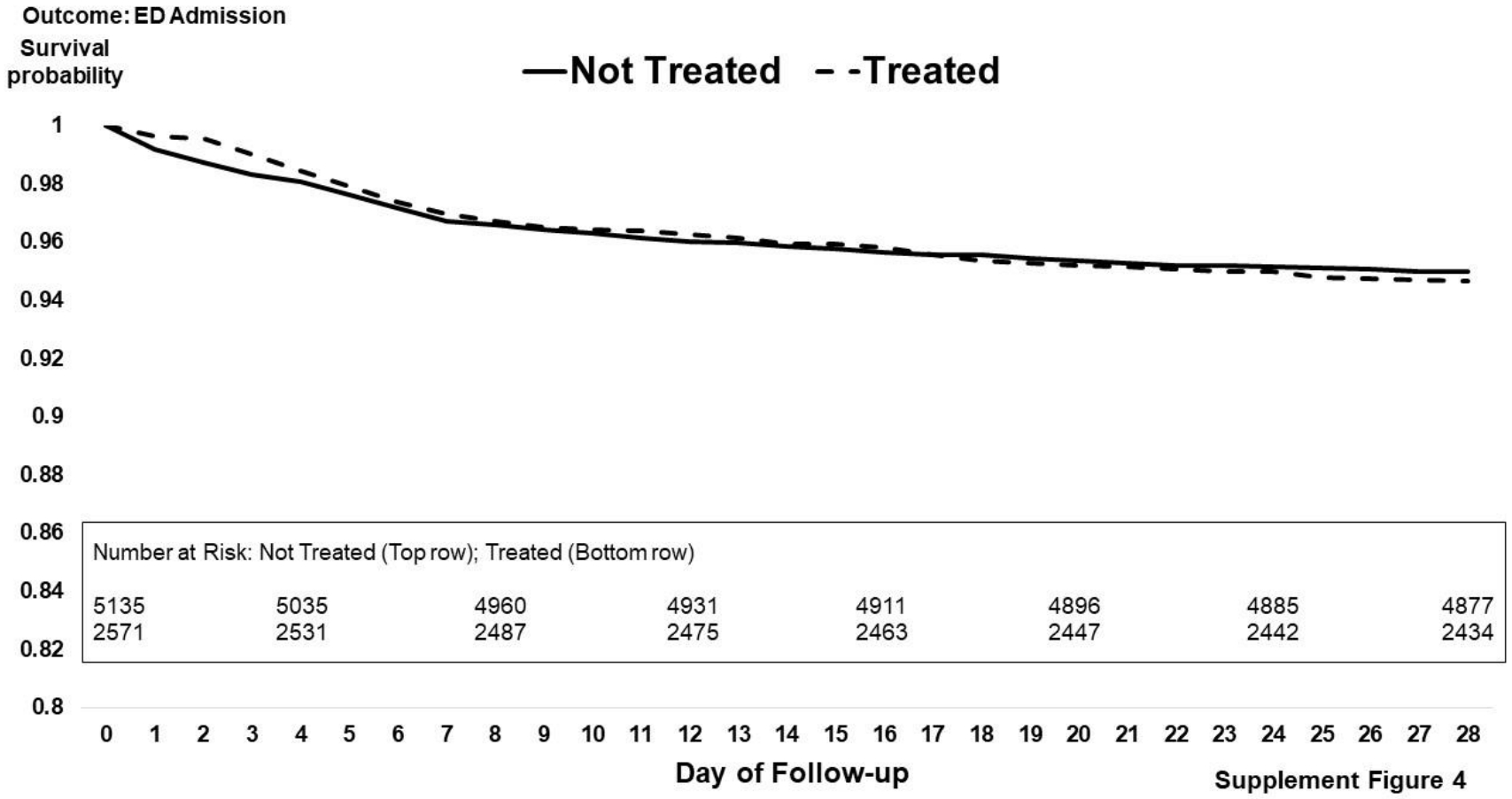
**Supplement Figure 2. Kaplan-Meier plot of the probability of freedom from hospitalization over 28-day follow-up for treated patients (*dashed line*) and non-treated matched controls (*solid line*).**



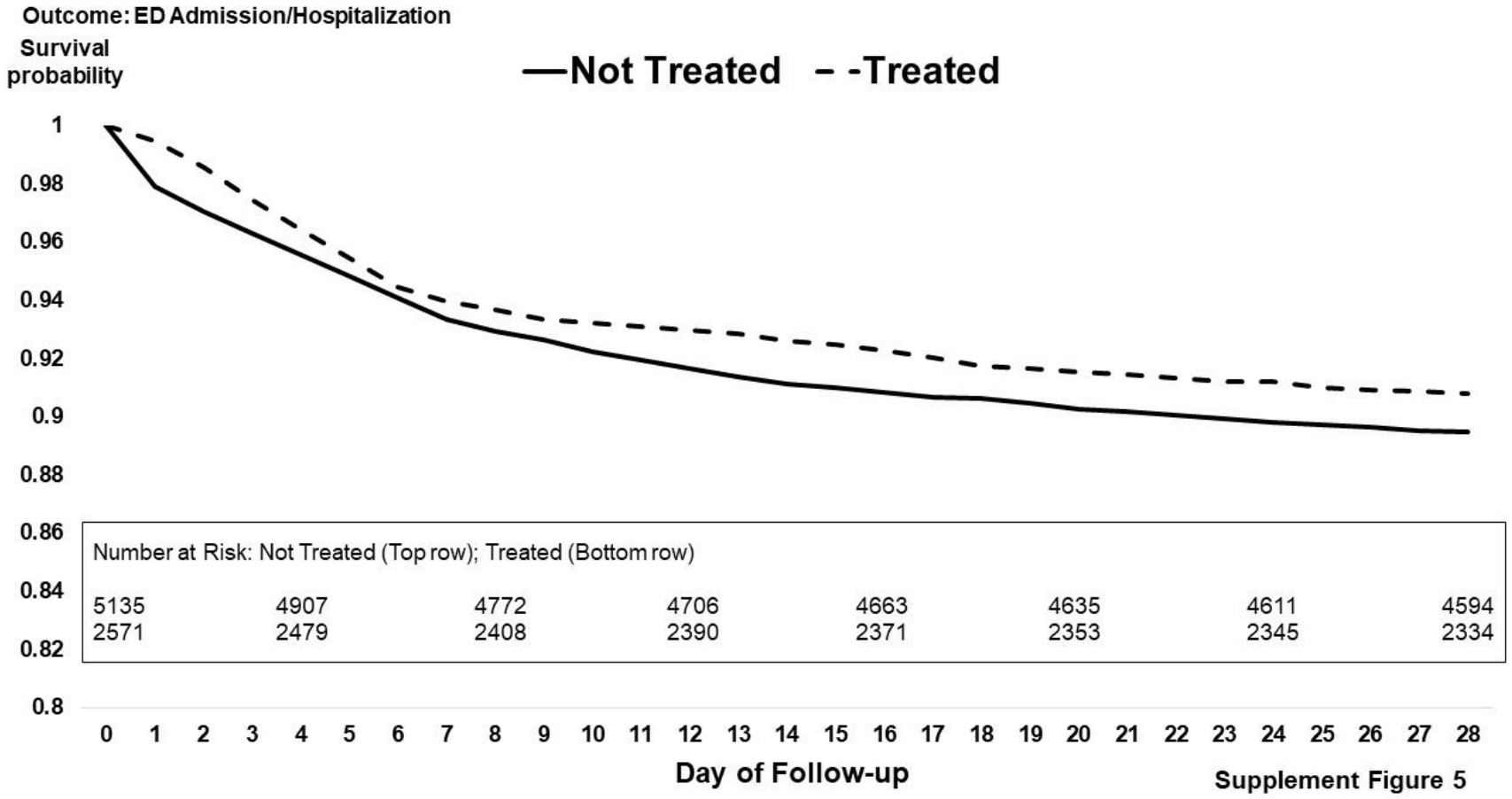
**Supplement Figure 3. Kaplan-Meier plot of the probability of freedom from death over 28-day follow-up for treated patients (*dashed line*) and non-treated matched controls (*solid line*).**



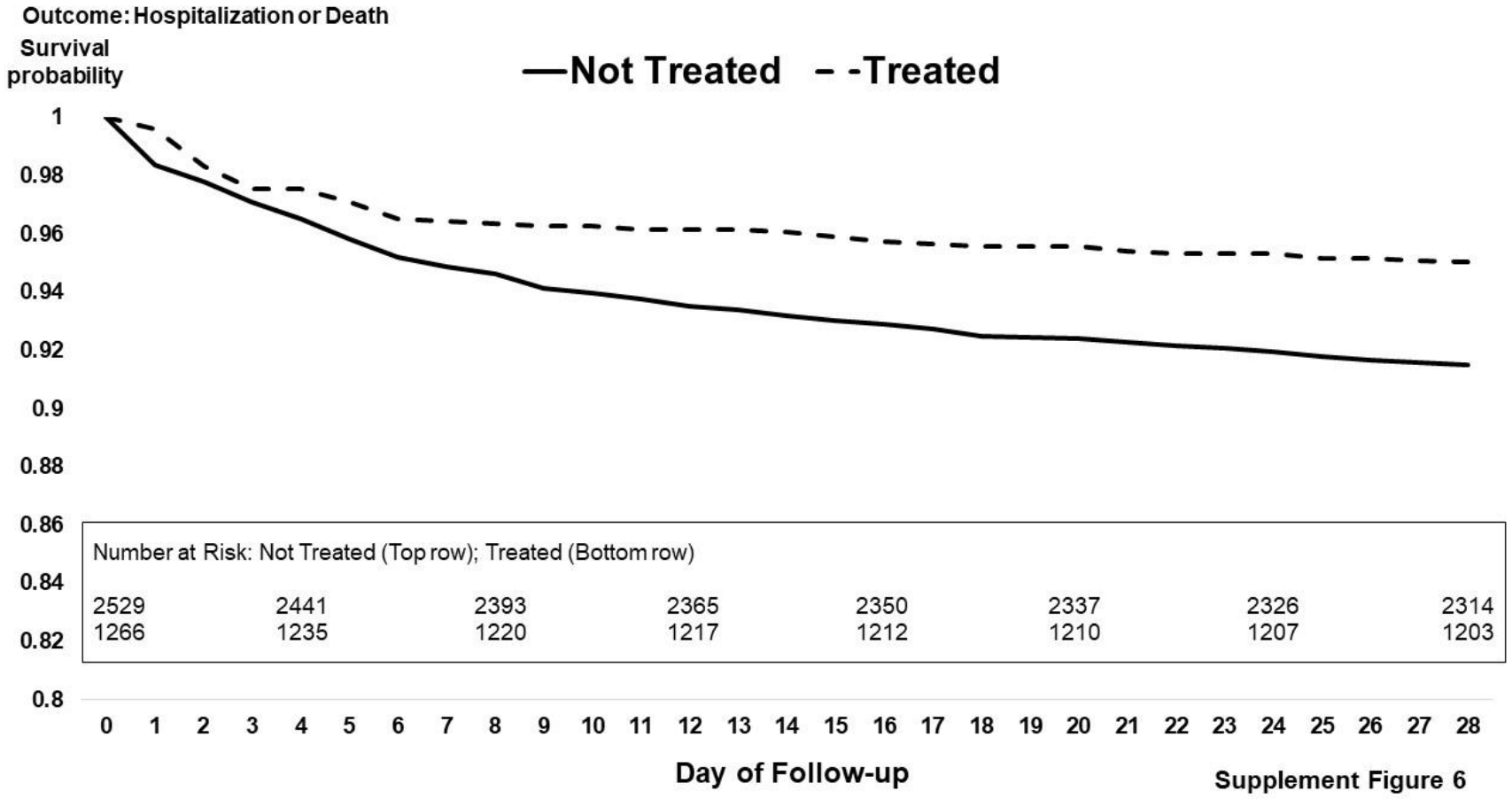
**Supplement Figure 4. Kaplan-Meier plot of the probability of freedom from emergency department admission without hospitalization over 28-day follow-up for treated patients (*dashed line*) and non-treated matched controls (*solid line*).**



**Supplement Figure 5. Kaplan-Meier plot of the probability of freedom from emergency department admission or hospitalization over 28-day follow-up for treated patients (*dashed line*) and non-treated matched controls (*solid line*).**

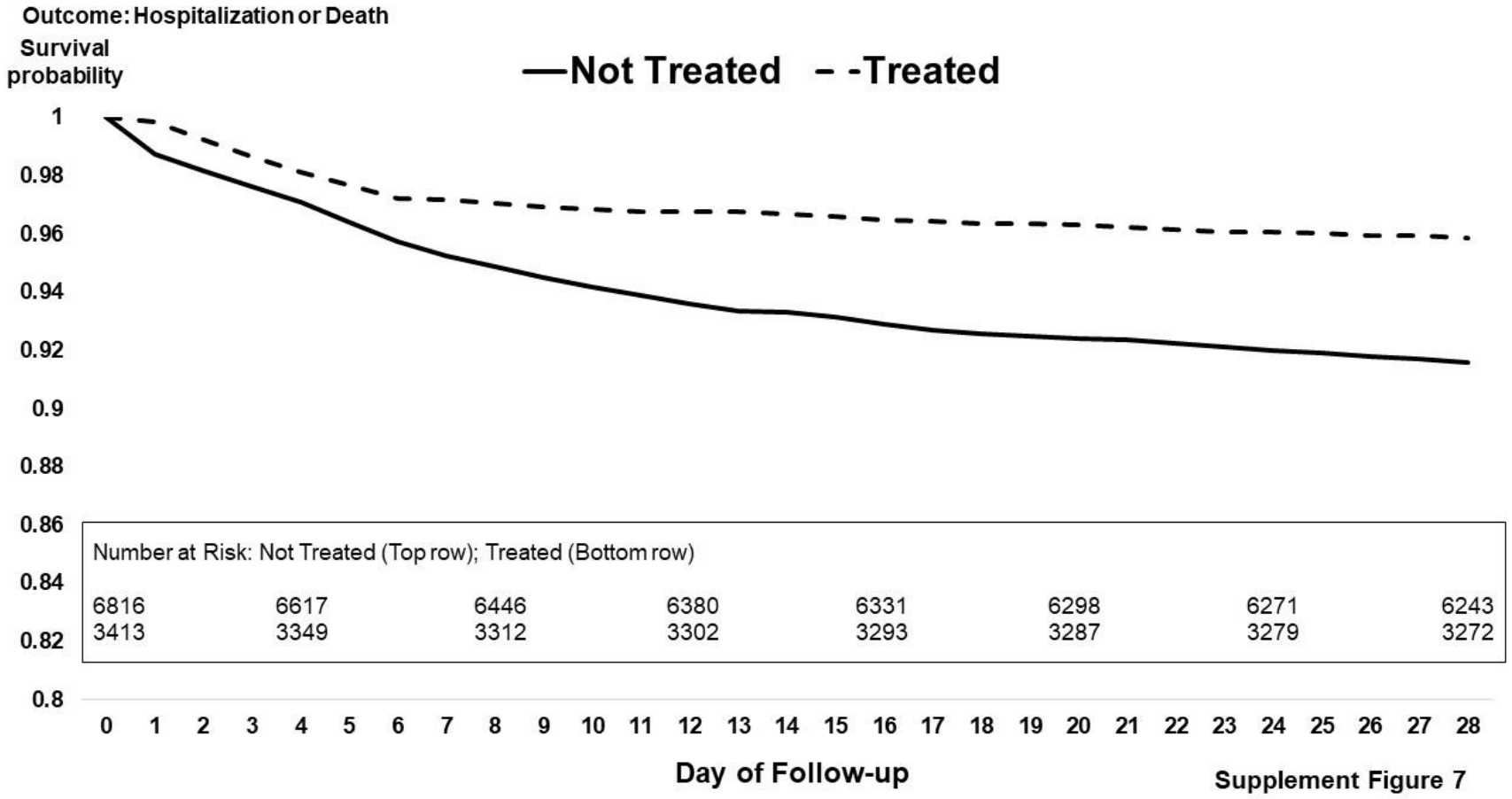


**Supplement Figure 6. Kaplan-Meier plot of the probability of freedom from hospitalization or death over 28-day follow-up for treated patients (dashed line) and non-treated matched controls (solid line): 1-day treatment grace period.**




The analysis reflects a 1-day treatment grace period from date of positive SARS-CoV-2 test to mAb treatment.

**Supplement Figure 7. Kaplan-Meier plot of the probability of freedom from hospitalization or death over 28-day follow-up for treated patients (dashed line) and non-treated matched controls (solid line): 3-day treatment grace period.**




The analysis reflects a 3-day treatment grace period from date of positive SARS-CoV-2 test to mAb treatment.