Supplementary APPENDIX: The Association Between Underlying Conditions and Severe COVID-19: Secondary Immunosuppression from B-Cell-Depleting Therapy

Centers for Disease Control and Prevention (CDC)
National Center for Immunization and Respiratory Diseases (NCIRD)

Brief Summary of Findings on the Association Between Secondary Immunosuppression from B-Cell-Depleting Therapy and Severe COVID-19 Outcomes

Three cohort studies[1-3] reported on the association of secondary immunosuppression from B-cell depleting therapy and severe COVID-19 outcomes and were included in this analysis. The data is inconsistent and inconclusive on the hazard of mortality among patients on B-cell depleting therapy with COVID-19 mortality[1,2]. Limited data from only one study is insufficient to determine if there is an association between secondary immunosuppression from B-cell depleting therapy and invasive mechanical ventilation[2] and hospitalization[1]. Limited data from only one study is insufficient to determine if there is an association between secondary immunosuppression from monoclonal antibody therapy, steroid therapy, and CAR-T cell therapy[3] and COVID-19 mortality.

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A. Methods

The primary aim of this review was to identify and synthesize the best available evidence to answer the question "What is the association between hematologic malignancy or hematopoietic stem cell transplant/hematopoietic cell transplant and severe COVID-19 outcomes" Due to variable reporting across studies on the use of B-cell-depleting therapies for treatment, as well as concurrent reporting on the use of B-cell-depleting therapies for other non-hematologic conditions, the appendix was separated in 2 to include studies reporting the following exposures:

1. Hematologic malignancies / hematologic stem cell transplant (with B-cell depleting therapy unspecified).
2. Treatment with B-cell-depleting medications (for example, rituximab, cyclophosphamide, and dexamethasone) for any underlying condition.

This supplementary appendix is dedicated to the secondary aim of this study. It seeks to answer the question: "What is the association between secondary immunosuppression from B-cell-depleting therapies and severe COVID-19 outcomes?"

This effort is used to update the Centers for Disease Control and Prevention (CDC) website on underlying conditions and enable the creation of a provider-specific website with more rigorous information. The methods for all underlying conditions and risk factors are outlined in the webpage, https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/systematic-review-process.html.
These methods were established in May 2021 and are standard for all conditions and risk factors on the CDC COVID-19 response underlying medical conditions page.

A.1. Literature Search

A list of search terms was developed to identify the literature most relevant to the population, exposure, comparator, and outcome (PECO) question above. Subject matter experts and library scientists were consulted to develop a robust list of search terms. These terms were then incorporated into search strategies, and these searches were performed in OVID using the COVID-19 filter for all articles from the beginning of each data base until December 1, 2021. The detailed search strategies for identifying primary literature and the search results are provided in the *Appendix*. References were included if retrieved by the literature search and reported exposures and outcomes relevant to this review.

A.2. Study Selection

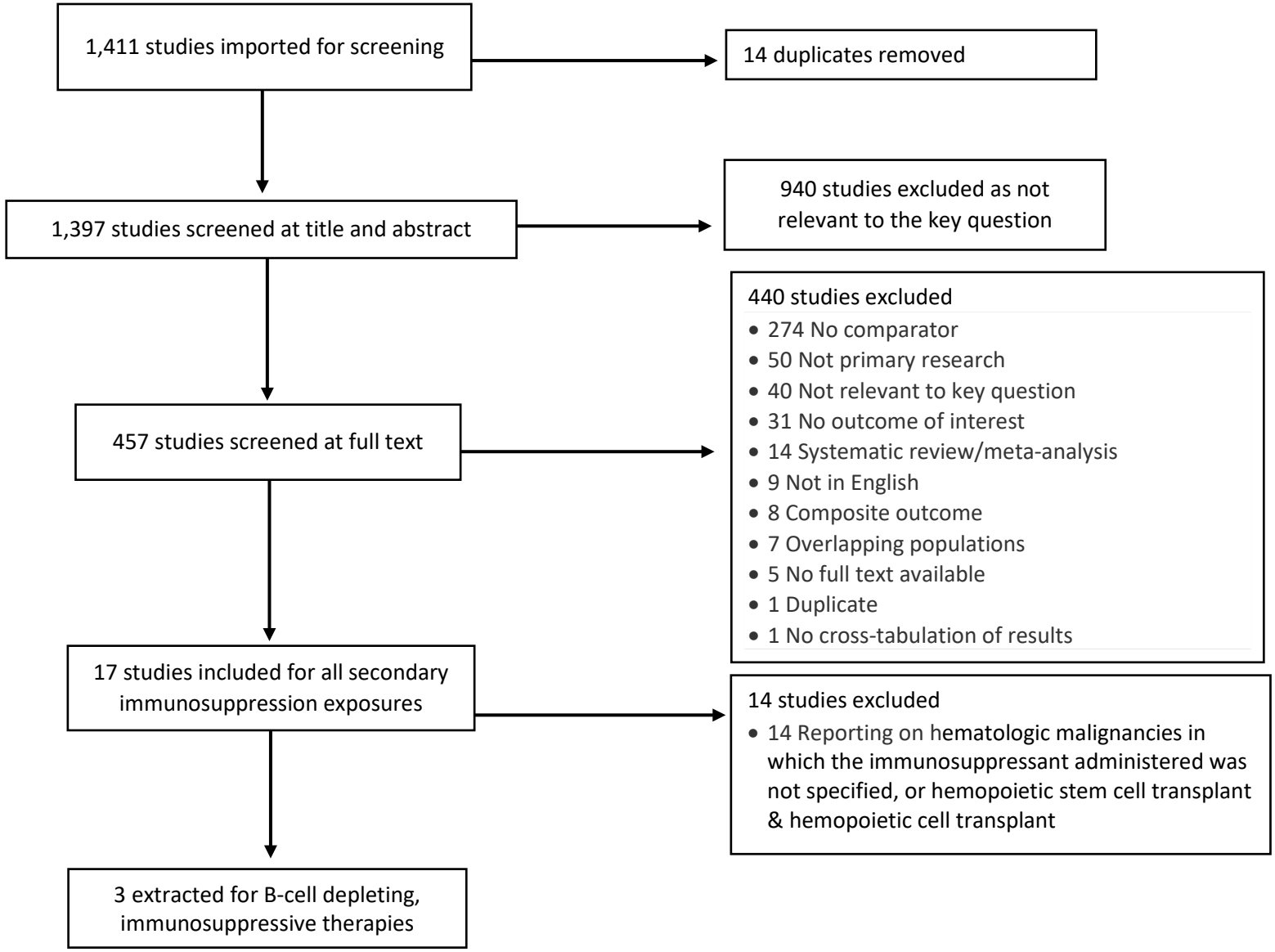
Titles and abstracts from references were screened by dual review (M.M., A.H., D.O.S., E.C.S, C.N.S., J.H., M.W., M.C., or J.K.). Full-text articles were retrieved if they were:

1. relevant to the PECO question;
2. primary research; and

3. written in English.

The *Appendix* presents the full list of exclusion criteria. The full texts of selected articles were then screened by two independent reviewers, and disagreements were resolved by discussion (M.M., A.H., D.O.S., E.C.S, C.N.S., J.H., M.W., M.C. or J.K.). The results of the study selection process are depicted in Figure 1.

Figure. *Results of the Study Selection Process for Secondary Immunosuppressive Therapy*



A.4. Data Extraction and Synthesis

Methodologic data and results of relevant outcomes from the studies meeting inclusion criteria were extracted into standardized evidence tables. Data and analyses were extracted as presented in the studies. For the purposes of this review statistical significance was defined as $p \leq 0.05$

The internal validity associated with each study was assessed using scales developed by CDC's Division of Healthcare Quality Promotion and scores were recorded in the evidence tables. The *Appendix* includes the dichotomous questions used to assess study execution and risk of bias for each study. In these tables, an answer of yes is indicated by a "1" and an answer of no is indicated by a "0".

A.5. Aggregation of the Evidence

Study results were aggregated in a qualitative method as indicated by the summary statement and the aggregation indices. Aggregation indices include the strength, magnitude, precision, consistency, and applicability of results, and were assessed for all comparators where more than one study is available.

A.6. Reviewing and Finalizing the Systematic Review

Draft findings, aggregation tables, and evidence tables are presented to CDC subject matter experts for review and input.

B. Systematic Literature Review Results

B.1. Search Strategies and Results

Please note, the search strategy presented below includes hematologic malignancy and hematopoietic stem cell transplant. However, articles focusing on these topics which did not specify the immunosuppressant administered are analyzed in a separate appendix. This supplementary appendix only focused on studies that specified the administration of B-cell-depleting therapies for hematologic malignancy / hematopoietic stem cell transplants as well as for other underlying medical conditions (such as rheumatologic diseases, multiple sclerosis, etc).

Table 1 Secondary Immunosuppression / Activity Search Conducted December 1, 2021.

Database	**Strategy**	**Records** 12/01/2021
Medline (OVID) 1946-	hematopoietic cell transplant* OR hematopoietic stem cell transplant* OR haematopoietic cell transplant* OR haematopoietic stem cell transplant* OR HCT OR hematologic malignanc* OR hematologic neoplasm* OR hematological malignanc* OR hematological neoplasm* OR hematopoietic malignanc* OR hematopoietic neoplasm* OR hematologic cancer* OR hematological cancer* OR haematologic malignanc* OR haematologic neoplasm* OR haematological malignanc* OR haematological neoplasm* OR haematopoietic malignanc* OR haematopoietic neoplasm* OR haematologic cancer* OR haematological cancer* OR chimeric antigen receptor* OR chimeric t-cell receptor* OR chimeric immunoreceptor* OR artificial t-cell receptor* OR CAR-T OR CAR-Ts OR bone marrow OR b-cell deplet* OR RTX AND Limit COVID [use validated filter] Limit journal article	992
Embase (OVID) 1988-	(hematopoietic cell transplant* OR hematopoietic stem cell transplant* OR haematopoietic cell transplant* OR haematopoietic stem cell transplant* OR HCT OR hematologic malignanc* OR hematologic neoplasm* OR hematological malignanc* OR hematological neoplasm* OR hematopoietic malignanc* OR hematopoietic neoplasm* OR hematologic cancer* OR hematological cancer* OR haematologic malignanc* OR haematologic neoplasm* OR haematological malignanc* OR haematological neoplasm* OR haematopoietic malignanc* OR haematopoietic neoplasm* OR haematologic cancer* OR haematological cancer* OR chimeric antigen receptor* OR chimeric t cell	877 -680 duplicates =197 unique items

Database	Strategy	Records 12/01/2021
	receptor* OR chimeric immunoreceptor* OR artificial t cell receptor* OR CAR-T OR CAR-Ts OR bone marrow OR b-cell deplet* OR RTX).ti,ab,kw. AND Limit COVID [use validated filter] Limit to journal article; not pubmed/medline	
Global Health	hematopoietic cell transplant* OR hematopoietic stem cell transplant* OR haematopoietic cell transplant* OR haematopoietic stem cell transplant* OR HCT OR hematologic malignanc* OR hematologic neoplasm* OR hematological malignanc* OR hematological neoplasm* OR hematopoietic malignanc* OR hematopoietic neoplasm* OR hematologic cancer* OR hematological cancer* OR haematologic malignanc* OR haematologic neoplasm* OR haematological malignanc* OR haematological neoplasm* OR haematopoietic malignanc* OR haematopoietic neoplasm* OR haematologic cancer* OR haematological cancer* OR chimeric antigen receptor* OR chimeric t cell receptor* OR chimeric immunoreceptor* OR artificial t cell receptor* OR CAR-T OR CAR-Ts OR bone marrow OR b-cell deplet* OR RTX AND (coronavir* OR corona virus* OR corona pandemic* OR betacoronavir* OR covid19 OR covid OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars2 OR 2019nCoV OR wuhan virus* OR NCOV19) Limit to journal article	250 -206 duplicates =44 unique items
Cochrane Library	("hematopoietic cell transplant*" OR "hematopoietic stem cell transplant*" OR "haematopoietic cell transplant*" OR "haematopoietic stem cell transplant*" OR HCT OR "hematologic malignanc*" OR "hematologic neoplasm*" OR "hematological malignanc*" OR "hematological neoplasm*" OR "hematopoietic malignanc*" OR "hematopoietic neoplasm*" OR "hematologic cancer*" OR "hematological cancer*" OR "haematologic malignanc*" OR "haematologic neoplasm*" OR "haematological malignanc*" OR "haematological neoplasm*" OR "haematopoietic malignanc*" OR "haematopoietic neoplasm*" OR "haematologic cancer*" OR "haematological cancer*" OR "chimeric antigen receptor*" OR "chimeric t cell receptor*" OR "chimeric immunoreceptor*" OR "artificial t-cell receptor*" OR CAR-T OR CAR-Ts OR "bone marrow" OR "b-cell deplet*" OR RTX):ti,ab AND (coronavir* OR "corona virus*" OR "corona pandemic*" OR betacoronavir* OR covid19 OR covid OR nCoV OR "novel CoV" OR "CoV 2" OR CoV2 OR sarscov2 OR sars2 OR 2019nCoV OR "wuhan virus*" OR NCOV19):ti,ab	68 -7 duplicates =61 unique items

Database	Strategy	**Records** 12/01/2021
CINAHL (EbscoHost)	("hematopoietic cell transplant*" OR "hematopoietic stem cell transplant*" OR "haematopoietic cell transplant*" OR "haematopoietic stem cell transplant*" OR HCT OR "hematologic malignanc*" OR "hematologic neoplasm*" OR "hematological malignanc*" OR "hematological neoplasm*" OR "hematopoietic malignanc*" OR "hematopoietic neoplasm*" OR "hematologic cancer*" OR "hematological cancer*" OR "haematologic malignanc*" OR "haematologic neoplasm*" OR "haematological malignanc*" OR "haematological neoplasm*" OR "haematopoietic malignanc*" OR "haematopoietic neoplasm*" OR "haematologic cancer*" OR "haematological cancer*" OR "chimeric antigen receptor*" OR "chimeric t cell receptor*" OR "chimeric immunoreceptor*" OR "artificial t-cell receptor*" OR CAR-T OR CAR-Ts OR "bone marrow" OR "b-cell deplet*" OR RTX) AND (coronavir* OR "corona virus*" OR "corona pandemic*" OR betacoronavir* OR covid19 OR covid OR nCoV OR "novel CoV" OR "CoV 2" OR CoV2 OR sarscov2 OR sars2 OR 2019nCoV OR "wuhan virus*" OR NCOV19) Exclude Medline Records	171 -84 duplicates =87 unique items
Scopus	TITLE-ABS-KEY("hematopoietic cell transplant*" OR "hematopoietic stem cell transplant*" OR "haematopoietic cell transplant*" OR "haematopoietic stem cell transplant*" OR HCT OR "hematologic malignanc*" OR "hematologic neoplasm*" OR "hematological malignanc*" OR "hematological neoplasm*" OR "hematopoietic malignanc*" OR "hematopoietic neoplasm*" OR "hematologic cancer*" OR "hematological cancer*" OR "haematologic malignanc*" OR "haematologic neoplasm*" OR "haematological malignanc*" OR "haematological neoplasm*" OR "haematopoietic malignanc*" OR "haematopoietic neoplasm*" OR "haematologic cancer*" OR "haematological cancer*" OR "chimeric antigen receptor*" OR "chimeric t cell receptor*" OR "chimeric immunoreceptor*" OR "artificial t-cell receptor*" OR CAR-T OR CAR-Ts OR "bone marrow" OR "b-cell deplet*" OR RTX) AND TITLE-ABS-KEY(coronavir* OR "corona virus*" OR "corona pandemic*" OR betacoronavir* OR covid19 OR covid OR nCoV OR "novel CoV" OR "CoV 2" OR CoV2 OR sarscov2 OR sars2 OR 2019nCoV OR "wuhan virus*" OR NCOV19) AND NOT INDEX(medline) AND NOT INDEX(embase)	55 -25 duplicates =30 unique items

Notes: Duplicates were identified using EndNote automated “find duplicates” function with preference set to match on title, author, and year. There will likely be additional duplicates found that EndNote was unable to detect.

B.2. Study Inclusion and Exclusion Criteria

Inclusion Criteria: Studies that were extracted for the primary analysis were included in this review if they:

- were relevant to the key question "What is the association between secondary immunosuppression from B-cell depleting therapies and severe COVID-19?";
    - immunosuppressive therapy exposures*:* therapies that deplete B-cell counts including: rituximab (RTX)*,* cyclophosphamide (CP), dexamethasone (DXM), tacrolimus (TAC), vincristine (VCR), Chimeric antigen receptor t-cell therapy (CAR-T), and steroids, including glucocorticoids, corticosteroids, prednisone (PRED), and prednisolone (PRDL);
    - condition exposures: multiple sclerosis (MS), rheumatologic conditions, and hematologic malignancy (HM) where the immunosuppressant administered was specified; long-term immunosuppression including patients starting rheumatologic drugs, antimetabolite drugs, or cancer drugs at least 14 days before the date of admission and either continued during admission or actively stopped on or after the date of admission.
    - outcomes: mortality, ICU admission, intubation or ECMO, ventilation (non-invasive ventilation, invasive mechanical ventilation), hospitalization, and re-admission;
- were primary research;
- were written in English (can be seen as [language] in title);
- examined humans only.

Exclusion Criteria: Studies were excluded at full text review if they:

- were not available as full-text;
- were a conference abstract, poster, or reply letter;
- were narrative, mapping or scoping review;
- were systematic reviews & meta-analyses at full-text review;
- were not written in English;
- reported only autopsy results;

Studies were further excluded at extraction if they:

- were not relevant to the key question "What is the association between long-term conditions treated with b-cell depletion therapies and severe COVID-19 outcomes"
- did not have data available for an analysis of interest, had no primary comparison reported, or reported no comparator;
- did not report a comparator without the underlying conditions of interest;

- were duplicates of an included study;
- were not primary research;
- reported on a population that overlapped with a larger study using the same data set;
- reported only composite outcome measures for "severe COVID-19";
- reported outcomes that were not separated by exposures of interest (no cross-tabulation of exposures of interest);
- reported immunosuppressive therapy as a composite measure;
- reported results examining less than 10 participants; and
- reported hematologic malignancies but did not specify the immunosuppressant administered.

B.3. Evidence Review: Conditions on Secondary Immunosuppression and Severe COVID-19[a]

B.3.a. Strength & Direction of Evidence

Table 2 The Association Between B-Cell Depleting Therapy and Severe COVID-19 Outcomes: People with Any Condition Receiving B-Cell Depleting Therapy Compared to People Not Requiring Use of B-cell-Depleting Therapy

Outcome	Results
Mortality	Evidence from 2 studies[1,2] (N = 288,119) is inconsistent and inconclusive on the hazard of mortality among patients on B-cell depleting therapy with COVID-19. Both studies[1,2] were found to have a low threat to internal validity. • Strength of Association: One study reported multiple matched, unadjusted measures of association, ranging from hazard ratio (HR): 0.92 to HR: 1.72. • Precision of Association: One study reported confidence intervals for multiple comparators, all three were wide, and two crossed the null. • Consistency of Association: The evidence is inconsistent. • Applicability of Association: Settings and populations were applicable. Summary of Evidence: • Two cohort studies[1,2] (N = 288,119) which included 12,865 patients with long-term immunosuppression or on B-cell depleting therapy with COVID-19 reported inconsistent results between mortality and SI among people on rituximab (RTX)[1,2], but no difference in mortality among people with rheumatologic conditions treated with glucocorticoids[1].

[a] studies published since Dec 2020 were not included in the review or analysis

Outcome	Results
	▪ This cohort study[1] (N = 222,575) of adult patients with COVID-19 reported an increase in the hazard of mortality among 132 patients with rheumatologic conditions treated with RTX compared to propensity score matched patients without long-term immunosuppression [mHR: 1.72 (95% CI: 1.10 – 2.69), e = 2.83]. However, the study reported no difference in the hazard of mortality among 4,281 patients with rheumatological conditions treated with glucocorticoids and compared to propensity score matched patients without long-term immunosuppression [glucocorticoid mHR: 0.96 (95% CI: 0.86 – 1.07), e = NS].The propensity score was calculated using a multivariable logistic regression model that included the week of admission, contributing data site, age, sex as recorded in the electronic health record, self-reported race and ethnicity, smoking history, body-mass index, days between COVID-19 diagnosis and hospital admission, medication use for chronic conditions, and relevant comorbidities to predict the probability of being on immunosuppressive medications at the time of admission. ▪ This cohort study[2] (N = 65,544) of people with COVID-19 reported no difference in the proportion of mortality among 24 people with multiple sclerosis treated with RTX compared to people without MS [0.0% (0/24) vs 1.4% (922/65,520), p = 1.0]. The study reported a small proportion of people with multiple sclerosis (n = 24) in the study population, and no mortality among people with multiple sclerosis on RTX, decreasing confidence in the findings. In the study, RTX was administered to patients every 12 months and immunosuppressed patients were advised to isolate, possibly contributing to no deaths in this small population.
Invasive Mechanical Ventilation (IMV)	Limited data from only one study[1] are insufficient to determine an association between B-cell depleting therapy and invasive mechanical ventilation among adult patients with COVID-19. This study reported inconsistent directionality of results among propensity score matched patients across classes of IST. The study was found to have a low threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One cohort study[1] (N = 222,575) which included 12,841 matched patients with long-term immunosuppression (definition in extraction Table 8) reported inconsistent data on the association between IMV and B-cell depleting therapy among patients with COVID-19. ▪ This cohort study[1] (N = 222,575) of adult patients with COVID-19 reported an increase in the hazard of invasive mechanical ventilation among 132 patients with rheumatologic conditions treated with RTX compared to propensity score matched patients with no long-term immunosuppression [mHR: 1.50 (95% CI: 0.85 – 2.64), e = NS]. The study also reported a decrease in the hazard of IMV among 4,281 patients with rheumatological conditions treated with glucocorticoids compared to patients with no long-term immunosuppression [mHR: 0.85 (95% CI: 0.75 – 0.97), e = 1.63]. The propensity score was calculated using a multivariable logistic regression model that included the week of admission, contributing data site, age, sex as recorded in the electronic health record, self-reported race and ethnicity, smoking history, body-mass index, days between COVID-19 diagnosis and hospital admission, medication use for chronic conditions, and relevant comorbidities to predict the probability of being on immunosuppressive medications

Outcome	Results
	at the time of admission. The study reported a wide CI that crossed the null for RTX, decreasing confidence in the findings.
Hospitalization	Limited data from only one study[2] are insufficient to determine an association between B-cell depleting therapy and hospitalization. The study was found to have a low threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One cohort study among adults with COVID-19[2] (N = 65,544) which included 24 people with multiple sclerosis on B-cell depleting therapy reported data suggesting an increase in hospitalization among people with multiple sclerosis treated with RTX compared with people without MS. ▪ This cohort study[2] (N = 65,544) of people with COVID-19 reported a higher proportion of hospitalization among 24 people with multiple sclerosis treated with RTX compared to people with no MS [33.3% (8/24) vs 5.8% (3,799/65,520), p < 0.01]. The study reported a small proportion of people with multiple sclerosis in the study population, decreasing confidence in the findings.

Table 3 The Association Between RTX and Severe COVID-19 Outcomes[b]

Outcome	Results
Mortality	Evidence from 2 studies[1,2] (N = 288,119) is inconsistent and inconclusive on the hazard of mortality among patients with COVID-19 who are treated with RTX. Both studies[1,2] were found to have a low threat to internal validity. • Strength of Association: One study reported a matched, unadjusted measure of association, HR: 1.72. • Precision of Association: One study reported a confidence interval, which was wide. • Consistency of Association: The evidence is inconsistent. • Applicability of Association: Settings and populations were applicable. Summary of Evidence: • One cohort study[1] (N = 288,119) which included 12,841 matched patients with long-term immunosuppression (definition in extraction Table 8) reported data suggesting RTX is associated with an increase in mortality among patients with rheumatologic conditions and COVID-19.

[b] RTX sub-analysis of table 2

Outcome	Results
	▪ This cohort study[1] (N = 222,575) of adult patients with COVID-19 reported an increase in the hazard of mortality among 132 patients with rheumatologic conditions treated with RTX compared to propensity score matched patients without long-term immunosuppression [mHR: 1.72 (95% CI: 1.10 – 2.69), e = 2.83]. The propensity score was calculated using a multivariable logistic regression model that included the week of admission, contributing data site, age, sex as recorded in the electronic health record, self-reported race and ethnicity, smoking history, body mass index, days between COVID-19 diagnosis and hospital admission, medication use for chronic conditions, and relevant comorbidities to predict the probability of being on immunosuppressive medications at the time of admission. • One cohort study among people with COVID-19[2] (N = 65,544) which included 24 people with multiple sclerosis treated with RTX reported data suggesting no difference in mortality among people with multiple sclerosis treated with RTX compared to people without MS. ▪ This cohort study[2] (N = 65,544) of people with COVID-19 reported no difference in the proportion of mortality among 24 people with multiple sclerosis treated with RTX compared to people without MS [0.0% (0/24) vs 1.4% (922/65,520), p = 1.0]. The study reported a small proportion of people with multiple sclerosis in the study population, and no mortality among people with multiple sclerosis on RTX, decreasing confidence in the findings. In the study, RTX was administered to patients every 12 months and immunosuppressed patients were advised to isolate, possibly contributing to no deaths in this small population.
Invasive Mechanical Ventilation (IMV)	Limited data from only one study[1] are insufficient to determine an association between RTX and invasive mechanical ventilation. The study was found to have a low threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One cohort study[1] (N = 288,119) which included 12,841 matched patients with long-term immunosuppression (definition in extraction Table 8) reported data suggesting that RTX is associated with an increase in IMV among patients with rheumatologic conditions and COVID-19. ▪ This cohort study[1] (N = 222,575) of adult patients with COVID-19 reported an increase in the hazard of invasive mechanical ventilation among 132 patients with rheumatologic conditions treated with RTX compared to propensity score matched patients without long-term immunosuppression [mHR: 1.50 (95% CI: 0.85 – 2.64), e = NS]. The propensity score was calculated using a multivariable logistic regression model that included the week of admission, contributing data site, age, sex as recorded in the electronic health record, self-reported race and ethnicity, smoking history, body-mass index, days between COVID-19 diagnosis and hospital admission, medication use for chronic conditions, and relevant comorbidities to predict the probability of being on immunosuppressive medications at the time of admission. The study reported a wide confidence interval that crossed the null, decreasing confidence in the findings.

Outcome	Results
Hospitalization	Limited data from only one study[2] is insufficient to determine an association between RTX and hospitalization. The study was found to have a low threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One cohort study[2] (N = 65,544) which included 24 people with multiple sclerosis on B-cell depleting therapy reported data suggesting an increase in hospitalization among people with multiple sclerosis treated with RTX and with COVID-19. ▪ This cohort study[2] (N = 65,544) of people with COVID-19 reported a higher proportion of hospitalization among 24 people with multiple sclerosis treated with RTX compared to people with no MS [33.3% (8/24) vs 5.8% (3,799/65,520), p < 0.01]. The study reported a small proportion of people with multiple sclerosis in the study population, decreasing confidence in the findings.

Table 4 The Association Between Steroids and Severe COVID-19 Outcomes[c]

Outcome	Results
Mortality	Evidence from 2 studies[1,3] (N = 222,667) is inconsistent and inconclusive on the hazard of mortality among patients treated with steroids with COVID-19. One study[1] was found to have a low threat to internal validity and one study[3] was found to have a moderate threat to internal validity. • Strength of Association: One study reported a matched measure of association, HR: 0.96. • Precision of Association: One study reported a confidence interval, which was wide and crossed the null. • Consistency of Association: The evidence is inconsistent. • Applicability of Association: Settings and populations were applicable. Summary of Evidence: • One cohort study[1] (N = 222,575) which included 12,841 matched patients with long-term immunosuppression (definition in extraction Table 8) reported data suggesting no association between mortality and glucocorticoids among patients with rheumatologic conditions and COVID-19. ▪ This cohort study[1] (N = 222,575) of adult patients with COVID-19 reported no difference in the hazard of mortality among 4,281 patients with rheumatologic conditions treated with glucocorticoids compared to propensity score matched patients without long-term immunosuppression [mHR: 0.96 (95% CI: 0.86 – 1.07), e =

[c] Steroid sub-analysis of table 2

Outcome	Results
	NS]. The propensity score was calculated using a multivariable logistic regression model that included the week of admission, contributing data site, age, sex as recorded in the electronic health record, self-reported race and ethnicity, smoking history, body-mass index, days between COVID-19 diagnosis and hospital admission, medication use for chronic conditions, and relevant comorbidities to predict the probability of being on immunosuppressive medications at the time of admission. • One cohort study of people with COVID-19[3] (N = 92) which included 39 people with HM on immunosuppressive therapy reported data suggesting an increase in mortality among patients treated with steroids. ▪ This cohort study[3] (N = 92) of people with COVID-19 reported a higher proportion of mortality among 12 people with HM treated with steroids compared to people with no HM or SI [33.3% (4/12) vs 13.2% (7/53)]. No statistical analysis was conducted for this comparison and the study reported a small sample size, decreasing confidence in the findings.
Invasive Mechanical Ventilation	Limited data from only one study[1] are insufficient to determine an association between steroids and IMV. The study was found to have a low threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One cohort study[1] (N = 222,575) which included 12,841 matched patients with long-term immunosuppression (definition in extraction Table 8) reported data suggesting glucocorticoids are associated with a decrease in IMV among patients with rheumatologic conditions and COVID-19. ▪ This cohort study[1] (N = 222,575) of adult patients with COVID-19 reported a decrease in the hazard of invasive mechanical ventilation among 4,281 patients with rheumatologic conditions treated with glucocorticoids compared to propensity score matched patients without long-term immunosuppression [mHR: 0.85 (95% CI: 0.75 – 0.97), e = 1.63]. The propensity score was calculated using a multivariable logistic regression model that included the week of admission, contributing data site, age, sex as recorded in the electronic health record, self-reported race and ethnicity, smoking history, body-mass index, days between COVID-19 diagnosis and hospital admission, medication use for chronic conditions, and relevant comorbidities to predict the probability of being on immunosuppressive medications at the time of admission. Therapy-specific analyses were conducted in the propensity score matched cohort, with doubly robust adjustments for any remaining covariate imbalances after matching.

Table 5 The Association Between Monoclonal Antibody Therapy and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Limited data from only one study[3] are insufficient to determine an association between monoclonal antibody therapy and mortality among people with COVID-19. The study was found to have a moderate threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One cohort study[3] (N = 92) which included 39 people with HM on immunosuppressive therapy reported data suggesting an increase in mortality among patients treated with monoclonal antibodies with COVID-19. ▪ This cohort study[3] (N = 92) of people with COVID-19 reported a higher proportion of mortality among five people with HM treated with monoclonal antibodies compared to people with no HM or SI [20% (1/5) vs 13.2% (7/53)]. The study reported a small sample size, a small number of people treated with monoclonal antibody therapy in the study population, and no statistical analysis was conducted for this comparison, decreasing confidence in the findings.

Table 6 The Association Between Chimeric Antigen Receptor (CAR) T-Cell Therapy and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Limited data from only one study[3] is insufficient to determine an association between CAR-T cell therapy and mortality among people with COVID-19. The study was found to have a moderate threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One cohort study[3] (N = 92) which included 39 people with HM on immunosuppressive therapy reported limited data suggesting no difference in mortality among people treated with CAR-T cell therapy with COVID-19. ▪ This cohort study[3] (N = 92) of people with COVID-19 reported a lower proportion of mortality among five people with HM on CAR-T cell therapy/transplantation and one person with CD19 CAR-T cell therapy within the last year compared to people with no HM or SI [CAR-T cell therapy: 0% (0/5) vs 13.2% (7/53); CD19 CAR-T: 0% (0/1) vs 13.2% (7/53)]. The study reported a small sample size, a small number of people on CAR-T cell therapy

Outcome	Results
	in the study population, and no statistical analysis was conducted for this comparison, decreasing confidence in the findings.

B.3.b. Extracted Evidence

Table 7 Extracted Studies Reporting on the Association Between Immunosuppressive Therapy and Severe COVID-19 Outcomes

Study	Population and Setting	Exposure	Definitions	Results
Author: Andersen[1] **Year:** 2021 **Data Extractor:** MM **Reviewer:** AH **Study Design:** Cohort **Study Objective:** To evaluate whether individuals taking long-term immunosuppressive medications have worse outcomes when hospitalized with COVID-19 compared with non-immunosuppressed individuals whether the	**Population:** N = 222,575 with COVID-19 **Setting:** 42 clinical sites **Data Source:** Electronic health record repository **Location:** USA **Study Dates:** January 1, 2020—June 11, 2021 **Inclusion Criteria:** Individuals with complete hospitalization episodes, documented by either discharge or death. **Exclusion Criteria:** Individuals with missing data for age or sex, those younger	**Medical Condition, n/N (%):** Long-term immunosuppression • Entire cohort: 16,494/222,575 (7.0%) • Matched cohort: 12,841/42,227 (30.4%) Rheumatologic drugs: 5,366/16,494 (33.0%) • Glucocorticoid with rheumatological condition: 4,281/16,494 (26.0%) • RTX with rheumatological condition: 132/16,494 (1.0%) **Control/Comparison Group, n/N (%):** Non-immunosuppressed • Entire cohort: 206,081/222,575 (92.6%) • Matched cohort: 29,386/42,227 (69.6%)	**Medical Condition(s):** *Long-term immunosuppression:* patients using one or more immunosuppressive drug with immunosuppression to be started at least 14 days before the date of admission, and either continued during admission or actively stopped on or after the date of admission. This includes patients on rheumatologic drugs (Glucocorticoid, RTX, and others), Cancer therapies (Cyclophosphamide, Targeted, RTX, and others) *Rheumatologic drugs*: glucocorticoid, RTX *Glucocorticoids with solid organ transplant*: ND Non-immunosuppressed: patients without use of any of the immunosuppressive drugs on the date of admission. **Severity Measure(s):** NR	**Severe COVID-19:** Matched hazard ratio (mHR); *The propensity score was calculated using a multivariable logistic regression model that included week of admission, contributing data site, age, sex as recorded in the electronic health record, self-reported race and ethnicity, smoking history, body-mass index, days between COVID-19 diagnosis and hospital admission, medication use for chronic conditions, and relevant comorbidities to predict the probability of being on immunosuppressive medications at the time of admission.* e-value*: used for strength of association between immunosuppressive medication classes and clinical outcomes in COVID; the study reported an overall e-value of 1.50 for mortality and 1.21 for IMV* *Mortality:* Rheumatologic drugs: Glucocorticoid with rheumatological condition • mHR: 0.96 (95% CI: 0.86 – 1.07), e = 1.25 (NS) RTX with rheumatological condition • mHR: 1.72 (95% CI: 1.10 – 2.69), e = 2.83

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therapeutic class of immunosuppressive medications alters the risk of invasive mechanical ventilation or death. **IVA Score:** 27 (Low)	than 18 years, those transferred to the N3C data partner already on a ventilator, and individuals with implausible information, such as a COVID-19 diagnosis in 2018 or a date of death predating their date of admission. Six clinical sites were further excluded that did not meet N3C standards of data quality.		**Clinical Marker:** NR **Outcome Definitions:** *Mortality:* COVID-19-related mortality *ICU admission:* NR *Intubation:* NR *Ventilation:* invasive mechanical ventilation *Hospitalization:* first inpatient visits up to 21 days after the date of confirmed or suspected SARS-CoV-2 infection *Non-elective readmissions*: NR **Comments:** None The propensity matched cohort was calculated among 12,841 immunosuppressed and 29,386 non-immunosuppressed patients.	*Invasive mechanical ventilation:* Rheumatologic drugs: Glucocorticoid with rheumatological condition • mHR: 0.85 (95% CI: 0.75 – 0.97), e = 1.63 RTX with rheumatological condition • mHR: 1.50 (95% CI: 0.85 – 2.64), e = 2.37 (NS) **Severity of Condition:** NR **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** Non-elective readmissions: NR
Author: Langer-Gould[2] **Year:** 2021 **Data Extractor:** AH **Reviewer:** MM **Study Design:** Cohort **Study Objective:** To determine whether RTX-treated persons with multiple sclerosis (pwMS) were at higher	**Population:** N = 65,544 COVID-19+ **Setting:** Community **Data Source:** Kaiser Permanente of Southern California (KPSC) **Location:** California, USA **Study Dates:** January 1—September 30, 2020 **Inclusion Criteria:** patients with positive antibody tests	**Medical Condition, n/N (%):** people with multiple sclerosis on RTX-: 24/65,544 (0.04%) **Control/Comparison Group, n/N (%):** No MS: 65,520/65,544 (99.96%)	**Medical Condition(s):** *RTX – multiple sclerosis (RTX-MS)*: RTX treated individuals with multiple sclerosis **Severity Measure(s):** NR **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* death due to COVID-19, severe COVID-19 *ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* hospitalization due to COVID-19, moderate COVID-19 *Non-elective readmissions*: NR	**Severe COVID-19:** *Mortality, n/N (%):* • RTX-MS: 0/24 (0%) • No MS: 922/65,520 (1.4%) • p = 1.0 *Invasive Ventilation, n/N (%):* • RTX-MS: 0/24 (0) • No MS: NR, but stated not at increased risk *Non-invasive Ventilation, n/N (%):* • RTX-MS: 0/24 (0) • No MS: NR, but stated not at increased risk *Hospitalization, n/N (%):* • RTX-MS: 8/24 (33.3%) • No MS: 3,799/65,520 (5.8%) • p < 0.0001

Study	Population and Setting	Exposure	Definitions	Results
risk of more severe COVID-19 infection compared to the general population, and whether this risk is best explained by known risk factors for moderate-to-severe COVID-19, MS-related disability, or RTX treatment characteristics. **IVA Score:** 26 (Low)	(available starting in June) without prior PCR testing and RTX-treated people with multiple sclerosis. **Exclusion Criteria:** NR		**Comments:** Author's note: We think the absence of severe COVID-19 cases and slightly lower infection rate among rituximab-treated people with multiple sclerosis compared to the general population are probably best explained by how rituximab is used in our practice. We recommended extending rituximab dosing intervals to 12 months or more and have advised rituximab-treated people with multiple sclerosis to consider themselves at high risk of severe COVID-19 since March of 2020 due to the lack of information and the biological plausibility that impaired antiviral antibody production could contribute to a more severe COVID-19 disease course Time since last infusion in months (adjusted OR = 0.32, 95% CI = 0.15–0.69, p = 0.0033) and receiving 1000 mg compared to a lower dose at last infusion (adjusted OR = 6.28, 95% CI = 1.38–28.54, p = 0.0173) were independent predictors of COVID-19 severity but cumulative lifetime dose was not (adjusted OR = 1.003, 95% CI = 0.92–1.09, p = 0.9514 per 1000 mg). Hispanic ethnicity was no longer significant after adjustment for RTX-treatment characteristics (OR = 2.70, 95% CI = 0.61–11.96, p = 0.1903).	**Severity of Condition:** NR **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** Non-elective readmissions: NR

Study	Population and Setting	Exposure	Definitions	Results
Author: Sanchez-Pina[3] **Year:** 2020 **Data Extractor:** AH **Reviewer:** MM **Study Design:** Cohort **Study Objective:** To describe infection in a consecutive series of patients with hematological malignancies who were diagnosed with COVID-19 in the greater Madrid area. **IVA Score:** 24 (Moderate)	**Population:** N = 92 COVID-19+ **Setting:** Community **Data Source:** Medical records **Location:** Spain **Study Dates:** March 7, 2020 – April 7, 2020 **Inclusion Criteria:** For the control group, selected patients were similar to the hematological cases with respect to age and severity index values at admission, but they did not have any history of cancer. **Exclusion Criteria:** NR	**Medical Condition, n/N (%):** Hematological malignancy (HM): 39/92 (42.4%) Treatments: • Monoclonal antibody: 5/38 (13.2%) • Steroids: 12/38 (32.0%) **Control/Comparison Group, n/N (%):** No cancer (matched control): 53/92 (57.6%)	**Medical Condition(s):** *Hematological malignancies (HM):* a heterogeneous group of diseases with a high risk of bacterial, fungal, and viral infections **Severity Measure(s):** *Multiple Myeloma:* ND *Lymphoma:* ND *Chronic Lymphocytic Leukemia:* ND *Acute leukaemia and MDS:* ND *cMPN:* ND *Histiocytosis:* ND **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* Death due to COVID-19 *ICU admission:* ICU admission due to COVID-19 complications *Intubation:* NR *Ventilation:* NR *Hospitalization:* Hospitalized due to COVID-19 *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** *Mortality, n/N (%):* • No HM, no IST: 7/53 (13.2%) *Treatment* • Monoclonal antibody: 1/5 (20.0%) • Steroids: 4/12 (33.3%) • CAR-T cell therapy: 0/5 (0%) • CD19 CAR-T: 0/1 (1%) **Severity of Condition:** **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** Non-elective readmissions: NR

B.3.c. Internal Validity Assessments of Extracted Studies

Table 8 Internal Validity Assessments of Extracted Studies Reporting the Association Between Conditions with SI and Severe COVID-19 Outcomes

	Author & Year	Andersen[1] 2021	Langer-Gould[2] 2021	Sanchez-Pina[3] 2020
OUTCOME MEASURE		mortality, invasive & mechanical ventilation	mortality, hospitalization	mortality
Domain	**Signaling question**			
Study Elements	Design appropriate to research question	1	1	1
	Well described population	1	1	1
	Well described setting	1	1	1
	Well described intervention/ exposure	1	1	1
	Well described control/ comparator	1	1	1
	Well described outcome	1	1	1
	Clear timeline of exposures/ interventions and outcomes	1	1	1
Selection Bias: Sampling	Randomization appropriately performed	0	0	0
	Allocation adequately concealed	0	0	0
	Population sampling appropriate to study design	1	1	1
Selection Bias: Attrition	Attrition not significantly different between groups	1	1	1
	Attrition <10-15% of population	1	1	1

	Author & Year	Andersen[1] 2021	Langer-Gould[2] 2021	Sanchez-Pina[3] 2020
	Attrition appropriately analyzed	1	1	1
Information Bias: Measurement and Misclassification	Measure of intervention/ exposure is valid	1	1	1
	Measure of outcome is valid	1	1	1
	Fidelity to intervention is measured	0	0	0
	Fidelity to intervention is valid	0	0	0
	Prospective study	1	1	1
	Adequately powered to detect result	1	1	1
Information Bias: Performance & Detection	Outcome assessor blinded	0	0	0
	Study participant blinded	0	0	0
	Investigator/ data analyst blinded	0	0	0
	Data collection methods described in sufficient detail	1	1	0
	Data collection methods appropriate	1	1	1
	Sufficient follow up to detect outcome	1	1	1
Information Bias: Analytic	Appropriate statistical analyses for collected data	1	1	0
	Appropriate statistical analyses are conducted correctly	1	1	1
	Confidence interval is narrow	1	0	0
Confounding	Potential confounders identified	1	1	1
	Adjustment for confounders in study design phase	1	1	1

	Author & Year	Andersen[1] 2021	Langer-Gould[2] 2021	Sanchez-Pina[3] 2020
	Adjustment for confounders in data analysis phase	1	1	1
Reporting Bias	All pre-specified outcomes are adequately reported	1	1	1
Other Bias	No other sources of bias	1	1	1
COI	Funding sources disclosed and no obvious conflict of interest	1	1	1
SCORE	Threat to internal validity	27	26	24
	Low, Moderate, High	Low	Low	Moderate

C. Abbreviations

Table 9 Abbreviations

Acronym	Full
95% CI	95% confidence interval
ANOVA	analysis of variance
ARDS	acute respiratory distress syndrome
BADL	basic activities of daily living
BMI	body mass index
CAR	chimeric antigen receptor
CAR-T	chimeric antigen receptor- T-cell
CDC	Centers for Disease Control and Prevention
COI	conflict of interest
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019, a disease caused by the SARS-CoV-2 virus
ED	emergency department
EEG	electroencephalogram

EHR	electronic health records
EMR	electronic medical records
HM	hematologic malignancy
HR	hazard ratio
ICF	intermediate care facility
ICU	intensive care unit
IST	immunosuppressive therapy
IVA	internal validity assessment
mHR	matched hazard ratio
MRI	magnetic resonance imaging
MS	multiple sclerosis
NA	not applicable
ND	not defined
NR	not reported
NY	New York
NYC	New York City
OR	odds ratio
PCR	polymerase chain reaction
PECO	population, exposure, comparator, outcomes
RR	risk ratio
RT	real time
RTX	rituximab
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SI	secondary immunosuppression
SOFA	sequential organ failure assessment
TF	task force
UK	United Kingdom
US	United States
USA	United States of America
WHO	World Health Organization

D. References

1. Andersen KM, Bates BA, Rashidi ES, et al. Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: a retrospective cohort study using data from the National COVID Cohort Collaborative. *Lancet Rheumatol*. Nov 15 2021;15:15. doi:https://dx.doi.org/10.1016/S2665-9913(21)00325-8
2. Langer-Gould A, Smith JB, Li BH, Group KMS. Multiple sclerosis, rituximab, and COVID-19. Research Support, Non-U.S. Gov't. *Ann*. 04 2021;8(4):938-943. doi:https://dx.doi.org/10.1002/acn3.51342
3. Sanchez-Pina JM, Rodriguez Rodriguez M, Castro Quismondo N, et al. Clinical course and risk factors for mortality from COVID-19 in patients with haematological malignancies. *Eur J Haematol*. Nov 2020;105(5):597-607. doi:https://dx.doi.org/10.1111/ejh.13493