Brief Summary of Findings on the Association Between Underlying Primary Immunodeficiency and Severe COVID-19 Outcomes

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Seven cohort studies were retrieved that reported data on severe COVID-19 outcomes for people with primary immunodeficiency.

- The available evidence[1-7] indicates an increase in risk for the outcomes of mortality[1-6] and intensive care unit (ICU) admission[4,5,7] for people with underlying primary immunodeficiency.
- Limited evidence suggests no difference in risk of ventilation[3] and an increased risk of hospitalization[4]. However, only one study is insufficient to definitively conclude a change in risk for either of these outcomes and new evidence may change these conclusions.

References

1. Delavari S, Abolhassani H, Abolnezhadian F, et al. Impact of SARS-CoV-2 Pandemic on Patients with Primary Immunodeficiency. *J Clin Immunol*. 02 2021;41(2):345-355. doi:https://dx.doi.org/10.1007/s10875-020-00928-x
2. Karakoc Aydiner E, Bilgic Eltan S, Babayeva R, et al. Adverse COVID-19 outcomes in immune deficiencies: Inequality exists between subclasses. *Allergy*. Jul 27 2021;27:27. doi:https://dx.doi.org/10.1111/all.15025
3. Kharouf F, Ishay Y, Kenig A, Bitan M, Ben-Chetrit E. Incidence and course of COVID-19 hospitalizations among patients with familial Mediterranean fever. *Rheumatology (Oxford)*. Jul 22 2021;22:22. doi:https://dx.doi.org/10.1093/rheumatology/keab577
4. Leon-Abarca J. Obesity and immunodeficiencies are the main pre-existing conditions associated with mild to moderate COVID-19 in children. *Pediatric Obesity*. 2020;15:1-2. doi:10.1111/ijpo.12713
5. Meyts I, Bucciol G, Quinti I, et al. Coronavirus disease 2019 in patients with inborn errors of immunity: An international study. Multicenter Study. *J Allergy Clin Immunol*. Feb 2021;147(2):520-531. doi:https://dx.doi.org/10.1016/j.jaci.2020.09.010
6. Milito C, Lougaris V, Giardino G, et al. Clinical outcome, incidence, and SARS-CoV-2 infection-fatality rates in Italian patients with inborn errors of immunity. *Journal of Allergy and Clinical Immunology: In Practice*. July 2021;9(7):2904-2906.e2. doi:http://dx.doi.org/10.1016/j.jaip.2021.04.017
7. Armann J, Doenhardt M, Hufnagel M, et al. Risk factors for hospitalization, disease severity and mortality in children and adolescents with COVID-19: Results from a nationwide German registry. *medRxiv*. 2021:2021.06.07.21258488. doi:10.1101/2021.06.07.21258488

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A. Methods

The aim of this review is to identify and synthesize the best available evidence on the association between primary immunodeficiency and severe COVID-19 in order 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.

Below are methodologic highlights and additional methods unique to this review. For more information, please visit https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/systematic-review-process.html

A.1. Literature Search

A list of search terms was developed to identify the literature most relevant to the PECO (population, exposure, comparator and outcome) question. Given the diversity of types of primary immunodeficiency, the literature search was developed to find the 10 most prevalent conditions. Clinical 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 October 7, 2021. The detailed search strategies for identifying primary literature and the search results are provided in Part B. References were included if retrieved by the literature search and reported exposures and outcomes relevant to this review.

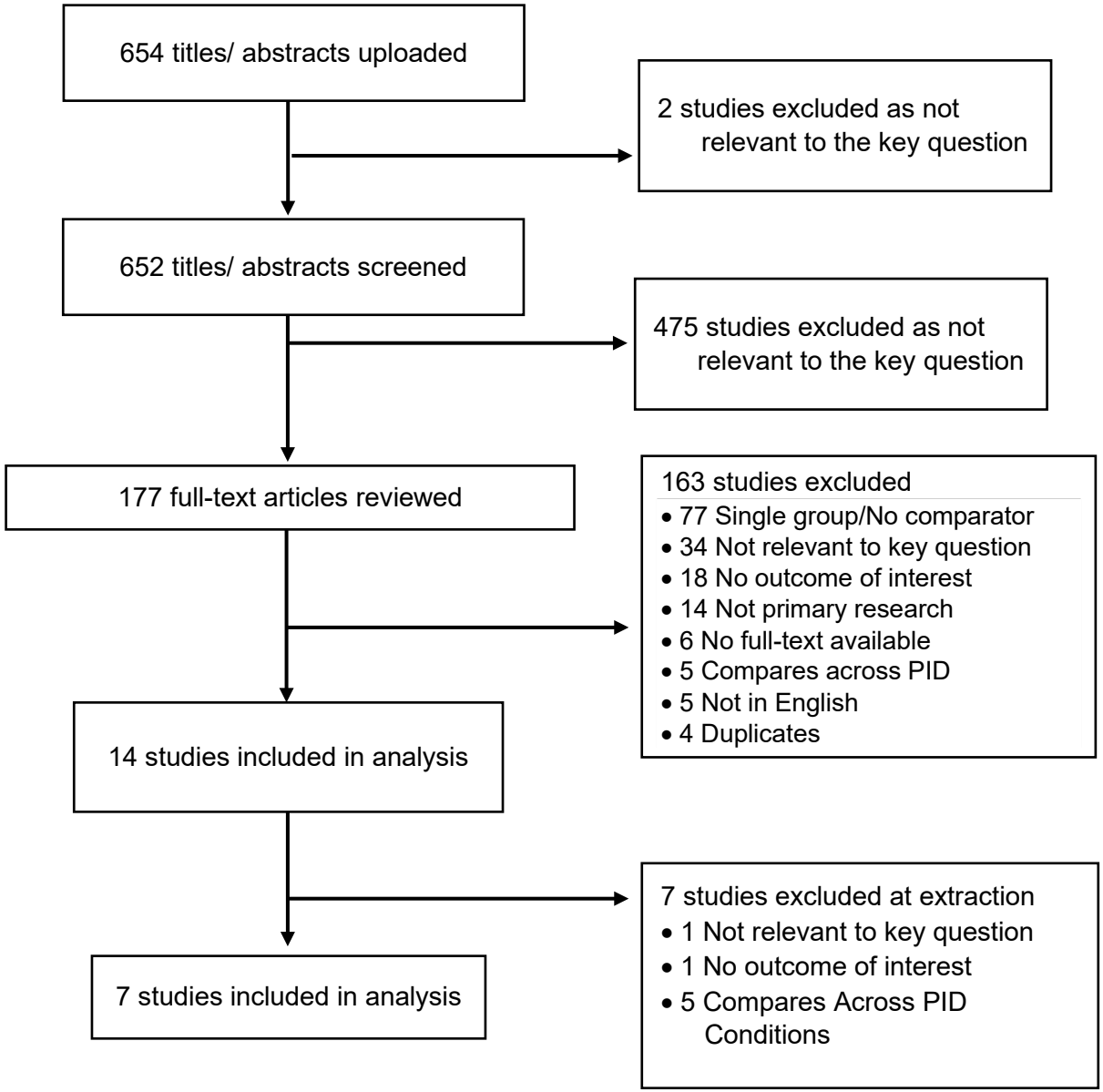
A.2. Study Selection

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

1. Relevant to the PECO question;
2. Primary research; and
3. Written in English.

Part B 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 (A.H., M.M., D.O.S., E.C.S, C.S., J.K., M.W., or T.R.). After the full-text screening was complete, a bibliography of the articles selected for inclusion was vetted with subject matter experts. Additional studies suggested by the subject matter experts were screened for inclusion as described above. The results of the study selection process are depicted in Figure 1.

Figure 1. Results of the Study Selection Process



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 $p \leq 0.05$, and
- studies with denominators smaller than 50% of the median denominator for this review (N = 94) were considered to have a small sample size (N < 47).

A.5. Internal Validity Assessment

The internal validity associated with each study was assessed using scales developed by the Division of Healthcare Quality Promotion and scores were recorded in the evidence tables. Part B includes the questions used to assess the quality of each study design. The strength, magnitude, precision, consistency, and applicability of results were assessed for all comparators. The overall confidence in the evidence base is reported in the aggregation tables in Part B.

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. Following further revisions, the summary will be published on the CDC website.

B. Systematic Literature Review Results

B.1. Search Strategies and Results

Table 1 Primary Immunodeficiency Search Conducted October 7, 2021.

Database	Strategy	Run Date	Records
Medline (OVID) 1946-	(CVID OR common variable immun* OR acquired hypogammaglobulinemia* OR late-onset immunoglobulin deficienc* OR common variable hypogammaglobulinemia* OR XLA OR x-linked agammaglobulinemia OR Bruton* Agammaglobulinemia OR Congenital Agammaglobulinemia OR FMF OR familial Mediterranean fever OR benign paroxysmal peritoniti* OR familial paroxysmal polyserositi* OR periodic disease* OR periodic peritoniti* OR recurrent polyserositi* OR CID OR combined immunodeficienc* OR combined immunologic deficienc* OR combined immune deficienc* OR hereditary angioedema* OR c1 esterase inhibitor deficienc* OR c1 inhibitor deficienc* OR hereditary angioedema* OR hereditary angioneurotic edema* OR SCID OR bare lymphocyte syndrome* OR familial reticuloendothelios* OR omenn* syndrome* OR CGD OR chronic granulomatous disease* OR cytochrome b-negative granulomatous disease* OR cytochrome b-positive granulomatous disease* OR Selective IgA deficienc* OR Selective immunoglobulin A deficienc* OR SIgAD OR selective IgM deficienc* OR selective immunoglobulin M deficienc* OR SIgMD OR IgG* subclass deficienc* OR immunoglobulin g subclass deficienc* OR IgGsd OR hypogammaglobinemia OR primary immunodeficienc* OR primary deficienc* OR primary immune deficienc* OR primary immunodeficiency) AND Limit COVID [use validated filter]	10/08/2021	198

Embase (OVID) 1988-	(CVID OR common variable immun* OR acquired hypogammaglobulinemia* OR late-onset immunoglobulin deficienc* OR common variable hypogammaglobulinemia* OR XLA OR x-linked agammaglobulinemia OR Bruton* Agammaglobulinemia OR Congenital Agammaglobulinemia OR FMF OR familial Mediterranean fever OR benign paroxysmal peritoniti* OR familial paroxysmal polyserositi* OR periodic disease* OR periodic peritoniti* OR recurrent polyserositi* OR CID OR combined immunodeficienc* OR combined immunologic deficienc* OR combined immune deficienc* OR hereditary angioedema* OR c1 esterase inhibitor deficienc* OR c1 inhibitor deficienc* OR hereditary angioedema* OR hereditary angioneurotic edema* OR SCID OR bare lymphocyte syndrome* OR familial reticuloendothelios* OR omenn* syndrome* OR CGD OR chronic granulomatous disease* OR cytochrome b-negative granulomatous disease* OR cytochrome b-positive granulomatous disease* OR Selective IgA deficienc* OR Selective immunoglobulin A deficienc* OR SIgAD OR selective IgM deficienc* OR selective immunoglobulin M deficienc* OR SIgMD OR IgG* subclass deficienc* OR immunoglobulin g subclass deficienc* OR IgGsd OR hypogammaglobinemia OR primary immunodeficienc* OR primary deficienc* OR primary immune deficienc* OR primary immunodeficiency) AND Limit COVID [use validated filter]	10/08/2021	303 -152 duplicates =151 unique items
Global Health	(CVID OR common variable immun* OR acquired hypogammaglobulinemia* OR late-onset immunoglobulin deficienc* OR common variable hypogammaglobulinemia* OR XLA OR x-linked agammaglobulinemia OR Bruton* Agammaglobulinemia OR Congenital Agammaglobulinemia OR FMF OR familial Mediterranean fever OR benign paroxysmal peritoniti* OR familial paroxysmal polyserositi* OR periodic disease* OR periodic peritoniti* OR recurrent polyserositi* OR CID OR combined immunodeficienc* OR combined immunologic deficienc* OR combined immune deficienc* OR hereditary angioedema* OR c1 esterase inhibitor deficienc* OR c1 inhibitor deficienc* OR hereditary angioedema* OR hereditary angioneurotic edema* OR SCID OR bare lymphocyte syndrome* OR familial reticuloendothelios* OR omenn* syndrome* OR	10/08/2021	58 -49 duplicates =9 unique items

	CGD OR chronic granulomatous disease* OR cytochrome b-negative granulomatous disease* OR cytochrome b-positive granulomatous disease* OR Selective IgA deficienc* OR Selective immunoglobulin A deficienc* OR SIgAD OR selective IgM deficienc* OR selective immunoglobulin M deficienc* OR SIgMD OR IgG* subclass deficienc* OR immunoglobulin g subclass deficienc* OR IgGsd OR hypogammaglobinemia OR primary immunodeficienc* OR primary deficienc* OR primary immune deficienc* OR primary immunodeficiency) 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)		
Cochrane Library	(CVID OR "common variable immun*" OR "acquired hypogammaglobulinemia*" OR "late-onset immunoglobulin deficienc*" OR "common variable hypogammaglobulinemia*" OR XLA OR "x-linked agammaglobulinemia" OR "Bruton* Agammaglobulinemia" OR "Congenital Agammaglobulinemia" OR FMF OR "familial Mediterranean fever" OR "benign paroxysmal peritoniti*" OR "familial paroxysmal polyserositi*" OR "periodic disease*" OR "periodic peritoniti*" OR "recurrent polyserositi*" OR CID OR "combined immunodeficienc*" OR "combined immunologic deficienc*" OR "combined immune deficienc*" OR "hereditary angioedema*" OR "c1 esterase inhibitor deficienc*" OR "c1 inhibitor deficienc*" OR "hereditary angioedema*" OR "hereditary angioneurotic edema*" OR SCID OR "bare lymphocyte syndrome*" OR "familial reticuloendothelios*" OR "omenn* syndrome*" OR CGD OR "chronic granulomatous disease*" OR "cytochrome b-negative granulomatous disease*" OR "cytochrome b-positive granulomatous disease*" OR "Selective IgA deficienc*" OR "Selective immunoglobulin A deficienc*" OR SIgAD OR "selective IgM deficienc*" OR "selective immunoglobulin M deficienc*" OR SIgMD OR "IgG* subclass deficienc*" OR "immunoglobulin g subclass deficienc*" OR IgGsd OR hypogammaglobinemia OR "primary immunodeficienc*" OR "primary deficienc*" OR "primary immune deficienc*" OR "primary immunodeficiency")	10/08/2021	34 -2 duplicates =32 unique items

	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)		
CINAHL (EbscoHost)	(CVID OR "common variable immun*" OR "acquired hypogammaglobulinemia*" OR "late-onset immunoglobulin deficienc*" OR "common variable hypogammaglobulinemia*" OR XLA OR "x-linked agammaglobulinemia" OR "Bruton* Agammaglobulinemia" OR "Congenital Agammaglobulinemia" OR FMF OR "familial Mediterranean fever" OR "benign paroxysmal peritoniti*" OR "familial paroxysmal polyserositi*" OR "periodic disease*" OR "periodic peritoniti*" OR "recurrent polyserositi*" OR CID OR "combined immunodeficienc*" OR "combined immunologic deficienc*" OR "combined immune deficienc*" OR "hereditary angioedema*" OR "c1 esterase inhibitor deficienc*" OR "c1 inhibitor deficienc*" OR "hereditary angioedema*" OR "hereditary angioneurotic edema*" OR SCID OR "bare lymphocyte syndrome*" OR "familial reticuloendothelios*" OR "omenn* syndrome*" OR CGD OR "chronic granulomatous disease*" OR "cytochrome b-negative granulomatous disease*" OR "cytochrome b-positive granulomatous disease*" OR "Selective IgA deficienc*" OR "Selective immunoglobulin A deficienc*" OR SIgAD OR "selective IgM deficienc*" OR "selective immunoglobulin M deficienc*" OR SIgMD OR "IgG* subclass deficienc*" OR "immunoglobulin g subclass deficienc*" OR IgGsd OR hypogammaglobinemia OR "primary immunodeficienc*" OR "primary deficienc*" OR "primary immune deficienc*" OR "primary immunodeficiency") 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)	10/08/2021	27 -13 duplicates =14 unique items

	Exclude Medline Records		
Scopus	TITLE-ABS-KEY(CVID OR "common variable immun*" OR "acquired hypogammaglobulinemia*" OR "late-onset immunoglobulin deficienc*" OR "common variable hypogammaglobulinemia*" OR XLA OR "x-linked agammaglobulinemia" OR "Bruton* Agammaglobulinemia" OR "Congenital Agammaglobulinemia" OR FMF OR "familial Mediterranean fever" OR "benign paroxysmal peritoniti*" OR "familial paroxysmal polyserositi*" OR "periodic disease*" OR "periodic peritoniti*" OR "recurrent polyserositi*" OR CID OR "combined immunodeficienc*" OR "combined immunologic deficienc*" OR "combined immune deficienc*" OR "hereditary angioedema*" OR "c1 esterase inhibitor deficienc*" OR "c1 inhibitor deficienc*" OR "hereditary angioedema*" OR "hereditary angioneurotic edema*" OR SCID OR "bare lymphocyte syndrome*" OR "familial reticuloendothelios*" OR "omenn* syndrome*" OR CGD OR "chronic granulomatous disease*" OR "cytochrome b-negative granulomatous disease*" OR "cytochrome b-positive granulomatous disease*" OR "Selective IgA deficienc*" OR "Selective immunoglobulin A deficienc*" OR SIgAD OR "selective IgM deficienc*" OR "selective immunoglobulin M deficienc*" OR SIgMD OR "IgG* subclass deficienc*" OR "immunoglobulin g subclass deficienc*" OR IgGsd OR hypogammaglobinemia OR "primary immunodeficienc*" OR "primary deficienc*" OR "primary immune deficienc*" OR "primary immunodeficiency") 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)	10/08/2021	70 -53 duplicates =17 unique items

WHO COVID Literature Database	CVID OR "common variable immunodeficiency" OR "common variable immunodeficiencies" OR "common variable immune deficiency" OR "common variable immune deficiencies" OR "acquired hypogammaglobulinemia" OR "late-onset immunoglobulin deficiency" OR "late-onset immunoglobulin deficiencies" OR "common variable hypogammaglobulinemia" OR XLA OR "x-linked agammaglobulinemia" OR "Bruton Agammaglobulinemia" OR "Bruton's Agammaglobulinemia" OR "Congenital Agammaglobulinemia" OR FMF OR "familial Mediterranean fever" OR "benign paroxysmal peritonitides" OR "benign paroxysmal peritonitis" OR "familial paroxysmal polyserositides" OR "familial paroxysmal polyserositis" OR "periodic disease" OR "periodic diseases" OR "periodic peritonitis" OR "periodic peritonitides" OR "recurrent polyserositis" OR "recurrent polyserositides" OR CID OR "combined immunodeficiency" OR "combined immunodeficiencies" OR "combined immunologic deficiency" OR "combined immunologic deficiencies" OR "combined immune deficiency" OR "combined immune deficiencies" OR "c1 esterase inhibitor deficiency" OR "c1 esterase inhibitor deficiencies" OR "c1 inhibitor deficiency" OR "c1 inhibitor deficiencies" OR "hereditary angioedema" OR "hereditary angioneurotic edema" OR SCID OR "bare lymphocyte syndrome" OR "familial reticuloendotheliosis" OR "omenn syndrome" OR CGD OR "chronic granulomatous disease" OR "chronic granulomatous diseases" OR "cytochrome b-negative granulomatous disease" OR "cytochrome b-negative granulomatous diseases" OR "cytochrome b-positive granulomatous disease" OR "cytochrome b-positive granulomatous diseases" OR "Selective IgA deficiency" OR "Selective IgA deficiencies" OR "Selective immunoglobulin A deficiency" OR "Selective immunoglobulin A deficiencies" OR SIgAD OR "selective IgM deficiency" OR "selective IgM deficiencies" OR "selective immunoglobulin M deficiency" OR "selective immunoglobulin M deficiencies" OR SIgMD OR "IgG* subclass deficiency" OR "IgG* subclass deficiencies" OR "immunoglobulin g subclass deficiency" OR "immunoglobulin g subclass deficiencies" OR IgGsd OR hypogammaglobinemia OR "primary immunodeficiency" OR "primary immunodeficiencies" OR "primary deficiency" OR "primary deficiencies" OR "primary immune deficiency" OR "primary immune deficiencies" OR "primary immunodeficiency"	10/08/2021	448 -215 duplicates =233 unique items

B.2. Study Inclusion and Exclusion Criteria

Inclusion Criteria: Studies were included at the title and abstract screen if they:

- were relevant to the key question "What is the association between primary immunodeficiency (PID) and severe COVID-19?";
    - Exposures: Primary immunodeficiency (PID), CVID (common variable immunodeficiency), XLA (x-linked agammaglobulinemia), FMF (familial Mediterranean fever), CID (combined immunodeficiency), hereditary angioedema, SCID (severe combined immunodeficiency), CGD (chronic granulomatous disease), Selective IgA deficiency or selective IgM deficiency, IgG subclass deficiency with IgA deficiency or Isolated IgG subclass deficiency, hypogammaglobinemia
    - Outcomes: mortality, ICU admission, intubation ventilation (non-invasive ventilation or invasive ventilation, ECMO), hospitalization, and re-admission
    - This may include studies reporting on examining characteristics, factors, conditions, comorbidities, general population descriptions, etc.
- were primary research;
- were written in English (can be seen as [language] in title); and
- examined humans only.

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

- were not available as full-text;
- were duplicates;
- were single group studies;
- reported no comparator;
- reported across PID conditions;
- were a conference abstract, poster, or reply letter;
- reported autopsy results; and
- reported only composite outcome measures for "severe COVID-19".

B.3. Evidence Review: Primary Immunodeficiency and Severe COVID-19

B.3.a. Strength & Direction of Evidence

Table 2 The Association Between All Primary Immunodeficiency Conditions Including Composite Categories and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Evidence from 6 studies[1-6] (N = 21,475) indicates that primary immunodeficiency and composite categories are associated with an increase in mortality in COVID-19 patients. Four studies[2-4,6] were found to have a moderate threat to internal validity, and 2 studies[1,5]had a high threat to internal validity. • Strength of Association: One study reported an adjusted measure of association adjusted prevalence ratio (aPR)of 14.44. • Precision of Association: One study reported a wide confidence interval that crossed the null. • Consistency of Association: The evidence is consistent. • Applicability of Association: The settings were applicable. Two studies[3,6] were conducted in high income countries (HIC) , 3[1,2,4] in low to middle income countries (LMIC) , and one[5] across country income settings . Summary of Evidence: • Six cohort studies[1-6] (N = 21,475) indicated that primary immunodeficiency is associated with an increase in mortality among people with COVID-19. The largest study[4] included 808 people with primary immunodeficiency and reported an adjusted effect measure indicating a high risk of mortality for patients with primary immune suppression [aPR: 14.44 (95% CI: 0.99 - 29.86), p = NR]. Five additional cohort studies reported mortality rates[1,2,6] or proportions[3,5] suggesting that primary immunodeficiency is associated with an increase in mortality among people with COVID-19. ▪ Two studies[2,3] reported a low prevalence of primary immunodeficiency, one study[4] did not report the number of COVID-19 positive patients, two reported a small sample size[1,5] , and one study[4] reported wide confidence intervals that span the null, and two[3,5] did not conduct a statistical analysis, decreasing confidence in results.

Outcome	Results
ICU admission	Evidence from 3 studies[4,5,7] (N = 22,756) indicates that primary immunodeficiency is associated with an increase in ICU admissions in COVID-19 patients. Two studies[4,7] were found to have a moderate threat to internal validity, and one study[5] had a high threat to internal validity. • Strength of Association: Two studies reported measures of association ranging from aPR 0.91 to relative risk (RR) 5.06. • Precision of Association: Two studies reported wide confidence intervals, one of which crossed the null. • Consistency of Association: Overall, the evidence is consistent. Two studies reported an increased risk of ICU admission, and one reported no association. • Applicability of Association: The settings were applicable. One study[7] was conducted in a HIC , one[4] was conducted in a LMIC , and one[5] was conducted across country income levels). Summary of Evidence: • Two cohort studies[5,7] (n = 1,595) of patients of all ages[5] and pediatric patients up to 19 years old[7] reported adjusted and unadjusted effect measures and proportions that indicate an increased risk of ICU admission in COVID-19 patients with primary immunodeficiency compared to patients without primary immunodeficiency ([RR: 5.06 (95% CI: 2.27 - 11.30)] to [adjusted relative risk (aRR): 2.68 (95% CI: 1.15 - 6.24), p = NR]). ▪ One cohort study[7] (N = 1,501) of pediatric patients up to 19 years old reported effect measures indicating an increased risk of ICU admission among COVID-19 patients with primary immunodeficiency [aRR: 2.68 (95% CI: 1.15 - 6.24), p = NR]. This study reported low prevalence of underlying primary immunodeficiency in the study population and a low number of ICU admissions, decreasing confidence in the results. ▪ One cohort study[5] (N = 94) of patients of all ages reported a higher proportion of ICU admissions among COVID-19 patients with primary immunodeficiency compared to an average mortality rate from four countries [20.0% (20/94) vs. 2.3% (n/N =NR); p = NR)]. The study did not conduct a statistical analysis, decreasing confidence in the results. • One cohort study[4] (n = 21,161) of pediatric patients reported an adjusted effect measure suggesting no difference in the odds of ICU admission in COVID-19 patients with primary immunodeficiency ([aPR: 0.91 (95% CI: 0.3 - 2.13), p = NR]). ▪ One cohort study[4] (N = 21,161) of pediatric patients reported no difference in the odds of ICU admission in COVID-19 patients with primary immunodeficiency [aPR 0.91 (95% CI: -0.3 to 2.13); p = NR]. The

Outcome	Results
	confidence interval crosses the null and did not report the number of COVID-19 positive patients, decreasing confidence in the results.
Ventilation	Limited data from only one study[3] is insufficient to determine an association between primary immunodeficiency and ventilation in COVID-19 patients. 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 case-control study[3] (N = 36) reported proportions suggesting no difference in ventilation among patients with or without the primary immunodeficiency Familial Mediterranean Fever (FMF). ▪ One case-control study[3] (N = 36) reported ventilation among patients with and without primary immunodeficiency [8.3% (1/12) vs. 0% (0/24); p = NR]. However, the study only reported on one ventilated patient, decreasing confidence in results. While the study reports the number of patients with primary immunodeficiency, it does not report that number of patients that are COVID-19 positive. The study also reported a low number of ventilation events and a small sample size, further decreasing confidence in the results.
Hospitalization	Limited data from only one study[4] is insufficient to determine an association between common variable immunodeficiency (CVID)and mortality in COVID-19 patients. 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[4] (N = 21,161) reported effect measures suggesting primary immunodeficiency is associated with an increase in hospitalization among COVID-19 patients. ▪ One cohort study[4] (N = 21,161) of patients under the age of 18 indicated an increase in hospitalization among 808 COVID-19 patients with primary immunodeficiency compared to those without primary immunodeficiency. [aPR 8.77 (95% CI: 6.01 - 11.49), p = NR]. The study did not report the number of COVID-19 positive patients, de creasing confidence in the results.

Table 3 The Association Between Underlying Primary Immunodeficiency (PID) and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Overall, the evidence from two studies[1,5] (N = 113) indicates that PID is associated with an increase in mortality in COVID-19 patients. • Strength of Association: No studies reported measures of association. • Precision of Association: No studies reported confidence intervals. • Consistency of Association: Overall, the evidence is consistent. Two studies reported an increased risk of mortality.

Outcome	Results
	• Applicability of Association: The settings were applicable. One study[1] was conducted in a LMIC and one[5] across country income settings . Summary of Evidence: • Two cohort studies[1,5] (N = 113) reported and proportions that indicate an increased risk of mortality in COVID-19 patients with PID compared to patients without PID. ▪ One cohort study[1] (N = 19) PID: 0.003, General population: 0.0003, p < 0.001; PID patients present a 10-fold higher mortality rate compared to the population in patients mainly with combined immunodeficiency and immune dysregulation. ▪ One cohort study[5] (N = 94) reported a higher proportion of mortality among COVID-19 patients with primary immunodeficiency and inborn errors of immunity compared to the general population 20.0% (20/94) vs. 2.3%. The study was a global web-based survey with a small sample size, decreasing confidence in the results.
ICU Admission	Overall, the evidence from two studies[5,7] (N = 1,595) indicates that primary immunodeficiency is associated with an increase in ICU admission in COVID-19 patients. • Strength of Association: Two studies reported measures of association, aPR= 0.91 and relative risk (RR)= 5.06. • Precision of Association: Two studies reported wide confidence intervals, and one reported confidence intervals that crossed the null. • Consistency of Association: Overall, the evidence is consistent. Two studies reported an increased risk of ICU admission. • Applicability of Association: One[7] study was conducted in a HIC, and one[5] across country income settings . Summary of Evidence: • Two cohort studies[5,7] (N = 1,595) reported effect measures and proportions indicating an increased risk of ICU admission in adults[5] and pediatric[7] COVID-19 patients with PID compared to patients without PID. ▪ One cohort study[7] (N = 1,501) reported effect measures indicating that primary immunodeficiency is associated with increased ICU admission among pediatric COVID-19 patients when compared to patients without primary immunodeficiency [aRR: 2.68 (95% CI: 1.15 - 6.24), p = NR]. This study reported low prevalence of underlying primary immunodeficiency in the study population, low number of ICU admissions, and a wide confidence interval, decreasing confidence in the results. ▪ One cohort study[5] (N = 94) reported a higher proportion of ICU admissions among COVID-19 patients with primary immunodeficiency and inborn errors of immunity compared to the general population 20.0%

Outcome	Results
	(20/94) vs. 2.3%. The study was a global web-based survey with a small sample size, decreasing confidence in the results.

Table 4 The Association Between Common Variable Immunodeficiency (CVID) and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Limited data from only one study[6] is insufficient to determine an association between CVID and mortality in COVID-19 patients. 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[6] (N = 131) reported infection fatality rates suggesting that CVID is associated with an increase in mortality among COVID-19 patients. ▪ One study[6] reported a higher infection fatality rate among 74 adult and pediatric patients with CVID compared to the general Italian population [4.05% vs 3.28%; p = NR]. CVID was diagnosed according to the European Society for Primary Immune Deficiencies criteria and patients were diagnosed as SARS-CoV-2 positive by Polymerase Chain Reaction (PCR).

Table 5 The Association Between X-linked Agammaglobulinemia (XLA) and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Overall, limited data from only one study[6] is insufficient to determine an association between XLA and mortality in COVID-19 patients. 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[6] (N = 131) reported no deaths among XLA patients suggesting no association between that XLA and mortality among COVID-19 patients. ▪ One study[6] (N = 131) reported zero deaths among the 13 patients with XLA and COVID-19. This limited data is less than the infection fatality rate of 3.28 found in the general Italian population with COVID-19 (N = 3,123,368). This study reported a small study population and no deaths, decreasing confidence in the findings.

Table 6 The Association Between Familial Mediterranean Fever (FMF) and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Limited data from only one study[3] is insufficient to determine an association between FMF and mortality in COVID-19 patients. 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 case-control study[3] (N = 36) reported limited data on mortality in patients with FMF. ▪ One study[3] reported one death among the 12 COVID-19 patients with FMF compared to no deaths among COVID-19 patients without FMF [8.3% (1/12) vs. 0% (0/24); p = NR]. The study reported a small overall sample size, decreasing confidence in the results.
Ventilation	Limited data from only one study[3] is insufficient to determine an association between FMF and ventilation in COVID-19 patients. 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 case-control study[3] (N = 36) reported proportions suggesting that FMF is associated with an increase in ventilation among COVID-19 patients. ▪ One case-control study[3] reported one case of ventilation among COVID-19 patients with FMF compared to no ventilations in COVID-19 patients without FMF [8.3% (1/12) vs. 0% (0/24); p = NR]. The study reports a low number of PID patients that are COVID-19 positive and a small overall sample size, decreasing confidence in the results.

Table 7 The Association Between Combined Immunodeficiency (CID) and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Limited data from only one study[1] is insufficient to determine an association between CID and mortality in pediatric COVID-19 patients. The study was found to have a high threat to internal validity. Aggregation indices are not assessed for outcomes reported by only one study. • One cohort study[1] (N = 19) reported mortality rates suggesting that CID is associated with an increase in mortality among COVID-19 patients.

Outcome	Results
	▪ One study[1] (N = 19) reported that COVID-19 patients with CID had a higher mortality rate than the mortality rate of the general Iranian population [0.01 vs. 0.00; p = NR]. The study had small sample size, decreasing confidence in the results.

Table 8 The Association Between Severe Combined Immunodeficiency (SCID) and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Evidence from one study[1] (N = 19) is insufficient to determine an association between SCID and mortality in pediatric COVID-19 patients. 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[1] (N = 19) reported mortality rates suggesting that SCID is associated with an increase in mortality among COVID-19 patients. ▪ One cohort[1] (N = 19) reported that COVID-19 patients with SCID had a higher mortality rate than patients without SCID [0.04 vs. 0.00; p = NR]. PID patients overall presented a 10-fold higher mortality rate compared to the population in patients with combined immunodeficiency and immune dysregulation. The study reported a small sample size, decreasing confidence in the results.

Table 9 The Association Between Selective IgA Deficiency (SIgAD) and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Limited data from only one study[6] is insufficient to determine an association between SIgAD and mortality in COVID-19 patients. 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[6] (N = 131) reported case-fatality rates suggesting that SIgAD is associated with an increase in mortality among COVID-19 patients. ▪ One study[6] reported a lower case-fatality rate among 7 patients with SIgAD and COVID-19 compared to the general Italian population with COVID-19 and without SIgAD [0% (n/N = NR) vs 3.28% (n/N = NR; p =

Outcome	Results
	NR)]. SIgAD patients were diagnosed according to the European Society for Primary Immune Deficiencies criteria.

Table 10 The Association Between Inborn Errors of Immunity (IEI) and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Overall, the evidence from three studies[2,5,6] (N = 259) suggests that IEI is associated with an increase in mortality in COVID-19 patients. Two[2,6] were found to have a moderate threat to internal validity and one[5] was found to have high threat to internal validity. • Strength of Association: None of the studies reported measures of association. • Precision of Association: No studies reported confidence intervals. • Consistency of Association: Overall, the evidence is consistent. Three cohorts report an increase in risk of mortality. • Applicability of Association: The settings were applicable. Two[2,6] studies were conducted in HIC , and one[5] across country income settings. Summary of Evidence: • Three cohort studies[2,5,6] (N = 259) reported rates suggesting that IEI is associated with an increase in mortality. ▪ One cohort study[2] (N = 34) reported that Turkish patients with IEI and COVID-19 had a mortality rate of 23.5%, which is ten times higher than the global population and 23.5 times higher than the general Turkish population [p = NR]. The study had a low sample size, decreasing confidence in the results. ▪ One cohort study[6] (N = 131) reported a higher infection fatality rate among COVID-19 patients with IEI's compared to patients without IEI [3.81% (n/N = NR) vs 3.28% (n/N = NR); p = 0.61]. This study reported a small sample size decreasing confidence in the results. ▪ One cohort study[5] (N = 94) reported a higher proportion of hospitalized COVID-19 patients with primary immunodeficiency and IEI compared to the general population [9.6% (9/94) vs. 5.40%]. The study was found to have a high threat to internal validity and reports on a small sample size for the worldwide population, decreasing confidence in the results.

Table 11 The Association Between Inborn Errors of Immunity, Risk Factors (Age), and Severe COVID-19 Outcomes

Outcome	Results
Mortality	Overall, limited data from only one study[6] is insufficient to determine an association between age, IEI, and mortality in COVID-19 patients. 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[6] (N = 131) reported proportions suggesting that IEI and age are associated with an increase in mortality among COVID-19 patients. ▪ The study[6] reported that adult COVID-19 patients with IEI had a increased infection fatality rate compared to children in the Italian population with COVID-19 and without IEI's (N = 3,123,368) [3.81% (n/N = NR) vs 3.28% (n/N = NR); p = 0.61].

B.3.b. Extracted Evidence

Table 12 Extracted Studies Reporting the Association between the top ten primary immunodeficiency disorders and Severe COVID-19 Outcomes

Study	Population and Setting	Exposure	Definitions	Results
Author: Armann[7] **Publication:** 2021 **Data Extractor:** MW **Reviewer:** DOS **Study Design:** Cohort	**Population:** N =1,501 **Setting:** 169 hospitals **Data Source:** Electronic case reports **Location:** Germany & Austria	**Medical Condition, n/N (%):** Primary immunodeficiency: 11/1,501 (0.7%) **Control/Comparison Group, n/N (%):** No primary immunodeficiency: 1,490/1,501 (99.3%)	**Medical Condition(s):** *Primary immunodeficiency:* ND **Severity Measure(s):** NR **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* NR *ICU admission:* severe disease defined by requirement of	**Severe COVID-19:** *aRR: adjusted relative risk, model included all considered risk factors simultaneously* *RR: relative risk, bivariate model* *ICU admission, n/N (%)* Primary immunodeficiency: • aRR: 2.68 (95% CI: 1.15 - 6.24) • RR: 5.06 (95% CI: 2.27 - 11.30) • ICU: 4/111 (3.6%) • Non-ICU: 7/1,390 (0.5%)

Study	Population and Setting	Exposure	Definitions	Results
Study Objective: To characterize the clinical features of children and adolescents hospitalized with SARS-CoV-2 infections and to explore predictors for disease severity. **IVA Score:** 24 (Moderate)	**Study Dates:** March 18, 2020 – April 30, 2021 **Inclusion Criteria:** Patients up to 19 years of age who had laboratory confirmed SARS-CoV2-2 by either RT-PCR test or by rapid antigen test and who were hospitalized between the study dates. **Exclusion Criteria:** NR		admission to intensive care unit due to COVID-19 *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** None	**Severity of Condition:** NR **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR
Author: Delavari[1] **Publication:** 2021 **Data Extractor:** MM **Reviewer:** DOS	**Population:** N = 2,754 COVID-19 positive, N = 19 **Setting:** 38 medical centers **Data Source:** Iranian PID registry database **Location:** Iran	**Medical Condition, n/N (%):** Primary immunodeficiency (PID): 19/19(100%) • Combined immunodeficiencies: 10/19 (52.6%) • Severe combined immunodeficiency (SCID): 5/19 (26.3%) **Control/Comparison Group, n/N (%):** General population: NR	**Medical Condition(s):** *PID:* clinical diagnosis was made according to the criteria of the European Society for immunodeficiencies *Combined immunodeficiency:* NR immunodeficiencies *SCID:* ND **Severity Measure(s):** NR **Clinical Marker:** NR	**Severe COVID-19:** *Mortality, rate (n/N (%)):* Primary Immunodeficiency: • PID: 0.003 • General population: 0.0003 • p < 0.001 PID patients present a 10-fold higher mortality rate compared to the population in patients mainly with combined immunodeficiency and immune dysregulation.

Study	Population and Setting	Exposure	Definitions	Results
Study Design: Cohort **Study Objective:** To compare the rate and outcomes of COVID-19 infection between diagnosed cases in the Iranian primary immunodeficiency (PID) registry with population-based data. **IVA Score:** 16 (High)	**Study Dates:** NR - October 4, 2020 **Inclusion Criteria:** Patients enrolled in the Iranian PID Registry from the National PID Network. All cases identified through the 38 medical centers collaborating on registry were sent to referral hospital for a definitive diagnosis. COVID-19 was confirmed with RT-PCR SARS-CoV-2 test. Data on COVID-19 infection in the normal population was used as a comparison. **Exclusion Criteria:** NR		**Outcome Definitions:** *Mortality:* ND *ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** None	Combined immunodeficiencies: • Combined immunodeficiencies: 0.009 (6/10 (60.00%) • General population: 0.0003 • p = NR SCID: • SCID: 0.03 (4/5 (80.00%) • General population: 0.0003 • p = NR **Severity of Condition:** NR **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** Non-elective readmissions: NR
Author: Karakoc Aydiner[2]	**Population:** N = 34	**Medical Condition, n/N (%):** Combined immune deficiencies (CID): 19/34 (26.5%)	**Medical Condition(s):** *IEI:* Deficiencies of the immune system which disable the hosts	**Severe COVID-19:** *Mortality:*

Study	Population and Setting	Exposure	Definitions	Results
Publication: 2021 **Data Extractor:** MM **Reviewer:** MW **Study Design:** Cohort **Study Objective:** To describe a prospective multicenter survey exploring the COVID-19 performance of inborn errors of immunity (IEI) subjects to determine risk factors for severe disease. **IVA Score:** 21 (Moderate)	**Setting:** Six different IEI centers **Data Source:** Prospective Survey **Location:** Turkey **Study Dates:** March, 2020 – December, 2020 **Inclusion Criteria:** Patients with IEI & COVID-19 diagnosis made by RT-PCR or with a radiological score between 4 and 6 assessed by chest computed tomography. **Exclusion Criteria:** NR	Severe combined immune deficiencies (SCID): 3/34 (8.8%) **Control/Comparison Group, n/N (%):** General population: NR Turkey population: NR	defense against pathogens and causes untoward inflammatory responses that disrupt self-tissues **Severity Measure(s):** NR **Clinical Marker:** *Trough IgG:* measured before COVID-19 **Outcome Definitions:** *Mortality, Case fatality rate:* the proportion of deceased patients among all COVID-19 cases regardless of their symptom status *ICU admission:* NR *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** Worldwide & Turkish general population mortality rates cited from the World Health Organization, 2021.	Patients with IEI's had a mortality rate of 23.5%, which is ×10 than the global population and ×23.5 higher than the general Turkish population. **Severity of Condition:** NR **Duration of Condition:** NR **Comorbid Conditions:** NR **Clinical Markers:** *Mortality, Median (IQR):* Trough IgG: • p = 0.011 • Deceased: 662 (340 – 1,160) • Survived: 1095 (775 – 1639) **Risk Markers:** NR **Long-term Sequelae:** Non-elective readmissions: NR

Study	Population and Setting	Exposure	Definitions	Results
Author: Kharouf[3] **Publication:** 2021 **Data Extractor:** DOS **Reviewer:** AH **Study Design:** Cohort **Study Objective:** To study the prevalence and course of COVID-19 among FMF patients who are already treated with colchicine in order to shed light on the real-life interactions between SARS-CoV-2 infection, FMF, and colchicine. **IVA Score:** 23 (Moderate)	**Population:** N = 36 **Setting:** Two large HMOs **Data Source:** EMR **Location:** Israel **Study Dates:** February 1, 2020 – March 10, 2021 **Inclusion Criteria:** Hospitalization data was calculated for patients from two large HMOs at beginning of February 2020. Three additional FMF patients were included from other HMOs. Mortality data was calculated for hospitalized patients with FMF and COVID-19 who were matched as best as possible on age, sex, ethnicity, and major comorbidities to control inpatients diagnosed with COVID-19 but not with FMF.	**Medical Condition, n/N (%):** Familial Mediterranean fever (FMF): 12/36 (33.3%) **Control/Comparison Group, n/N (%):** No FMF: 24/36 (66.7%)	**Medical Condition(s):** *FMF:* patients with active diagnosis of FMF identified via HMO query **Severity Measure(s):** NR **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* NR *Intubation:* NR *Ventilation:* mechanical ventilation *Hospitalization:* hospitalization for COVID-19 *Non-elective readmissions*: NR **Comments:** None	**Severe COVID-19:** *Mortality, n/N (%):* • FMF: 1/12 (8.3%) • No FMF: 0/24 (0%) • p = NR *Ventilation, n/N (%):* • FMF: 1/12 (8.3%) • No FMF: 0/24 (0%) • p = NR **Severity of Condition:** NR **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR **Long-term Sequelae:** NR

Study	Population and Setting	Exposure	Definitions	Results
	Exclusion Criteria: NR			
Author: Leon-Abarca[4] **Publication:** 2020 **Data Extractor:** MM **Reviewer:** DOS **Study Design:** Cohort **Study Objective:** To identify which conditions are associated with SARS-CoV-2 infection and its clinical progression. **IVA Score:** 23 (Moderate)	**Population:** N = 21,161 COVID-19+ clinical suspicion **Setting:** Population **Data Source:** Mexican Open Registry **Location:** Mexico **Study Dates:** NR **Inclusion Criteria:** Patients under 18 years old with symptoms associated with COVID-19 at least one week before presentation to a healthcare facility. **Exclusion Criteria:** NR	**Medical Condition, n/N (%):** Immunodeficiencies: 808/21,161 (3.8%) **Control/Comparison Group, n/N (%):** No immunodeficiency: 20,353/21,161 (96.2%)	**Medical Condition(s):** *Immunodeficiency:* includes the four most commonly diagnosed primary immunodeficiency diseases (PID), transient hypogammaglobinemia, impaired polysaccharide responsiveness, and IgA deficiency *Clinical suspicion*: patient must have had symptoms associated with COVID-19 at least a week before presentation to a healthcare centre **Severity Measure(s):** NR **Clinical Marker:** NR **Outcome Definitions:** *Mortality:* ND *ICU admission:* ND *Intubation:* NR *Ventilation:* NR *Hospitalization:* ND *Non-elective readmissions*: NR	**Severe COVID-19:** *aPR: Adjusted Prevalence Ratio; included model variables: age, sex* *Mortality, n/N (%), or Median (IQR):* • aPR: 14.44 (95% CI: -0.99 -29.86) *ICU admission, n/N (%), or Median (IQR):* • aPR: 0.91 (95% CI: -0.3 - 2.13) *Hospitalization, n/N (%), or Median (IQR):* • aPR: 8.77 (95% CI: 6.01-11.49) **Severity of Condition:** NR **Duration of Condition:** NR **Comorbid Conditions:** NR **Risk Markers:** NR

Study	Population and Setting	Exposure	Definitions	Results
			Comments: None	**Long-term Sequelae:** Non-elective readmissions: NR
Author: Meyts[5] **Publication:** 2021 **Data Extractor:** AH **Reviewer:** DOS **Study Design:** Cohort **Study Objective:** To assess the impact of SARS-CoV-2 infection on patients with IEIs, thereby providing the first comprehensive description on the susceptibility	**Population:** N = 94 **Setting:** Population **Data Source:** Global web-based survey **Location:** Four countries: Spain, Italy, China, & South Korea **Study Dates:** March 16 – June 30, 2020 **Inclusion Criteria:** Physicians were invited to submit data on patients of all ages with an underlying primary immunodeficiency (PID)/inborn errors of immunity (IEI) that were infected by SARS-CoV-2, determined by serology or PCR from all age groups.	**Medical Condition, n/N (%):** Primary immunodeficiency (PID)/Inborn errors of immunity (IEI): 94/94 (100%) **Control/Comparison Group, n/N (%):** General population: 646,358/646,358 (100%)	**Medical Condition(s):** *PID:* ND *Inborn errors of immunity (IEI):* a PID or monogenic inborn error of immunity exhibiting increased susceptibility to pathogen infection. **Severity Measure(s):** *X-linked chronic granulomatous disease (X-CGD):* ND *Hypogammaglobulinemia:* antibody deficiency *Common variable immune deficiency (CVID):* antibody deficiency *IgG deficiency:* antibody deficiency *IgA and IgG_2 deficiency:* antibody deficiency **Clinical Marker:** NR	**Severe COVID-19:** *Mortality, n/N (%):* • PID/IEI: 9/94 (10%) • General population: 5.40% (range: 1% - 20%) • p = NR *ICU admission, n/N (%):* • PID/IEI: 20/94 (20%) • General population: 2.3% • p = NR **Severity of Condition:** *Mortality, n/N (%):* • X-CGD: 1/9 (11.11%) • Hypogammaglobulinemia: 1/9 (11.11%) • CVID: 4/9 (44.44%) • IgG deficiency: 1/9 (11.11%) • IgA and IgG_2 deficiency: 1/9 (11.11%) **Duration of Condition:** NR

Study	Population and Setting	Exposure	Definitions	Results
of an at-risk population of patients to SARS-CoV-2 infection, as well as their COVID-19 clinical course, severity, complications, and outcomes. **IVA Score:** 16 (High)	Physicians from members of various societies (European Society for Immunodeficiencies, Clinical Immunology Society, Latin American Society for Immunodeficiencies, African Society for Immunodeficiencies, Asia Pacific Society for Immunodeficiencies, Australasian Society for Clinical Immunology & Allergy), as well as the International Patient Organization for Primary Immunodeficiencies, the Jeffrey Modell Foundation, and the International Union of Immunological Societies Committee for Inborn Errors of Immunity were invited to participate with the aid of social media alerts. **Exclusion Criteria:** NR		**Outcome Definitions:** *Mortality:* COVID-19 related deaths. *ICU admission:* admitted into ICU for respiratory insufficiency, severe autoimmune haemolytic anaemia, hypotension, or MIS-C and military Mycobacterium avium infection. *Intubation:* NR *Ventilation:* NR *Hospitalization:* NR *Non-elective readmissions*: NR **Comments:** NA	**Comorbid Conditions:** Overall, rates of comorbid conditions such as pre-existing heart, lung, or kidney disease that are associated with severe COVID-19 were similar in patients with PID/IEI to those in the general population. **Risk Markers:** Younger male patients with PID/IEI are more likely to endure severe COVID-19 and require ICU admission than those without IEI. **Long-term Sequelae:** NR

Study	Population and Setting	Exposure	Definitions	Results
Author: Milito[6] **Publication**: 2021 **Data Extractor**: MW **Reviewer**: CS **Study Design**: Cohort **Study Objective**: To evaluate the impact of the pandemic on patients with inborn errors of immunity (IEI) with the aim to assess SARS-CoV-2 incidence and infection-fatality rate in different IEI entities, to quantify the length of time of	**Population**: N = 3,263; N = 131 COVID-19 positive **Setting**: 21 centers **Data Source**: IPINet national registry and Italian National Institute of Health **Location**: Italy **Study Dates**: The early stages of the pandemic – February 2021 **Inclusion Criteria**: Adult and pediatric patients with IEI diagnosed according to the European Society for Primary Immune Deficiencies criteria and diagnosed as SARS-CoV-2 positive by PCR for which exact figure data is available.	**Medical Condition, n/N (%):** Common Variable Immune Deficiency (CVID): 74/131 (56.49%) X-linked agammaglobulinemia (XLA): 13/131 (9.92%) Selective IgA deficiency (SIgAD): 7/131 (5.34%) **Control/Comparison Group, n/N (%):** SARS-CoV-2 positive Italian population: 3,123,368	**Medical Condition(s):** *CVID*: Patients with IEI diagnosed according to the European Society for Primary Immune Deficiencies criteria *XLA*: Patients with IEI diagnosed according to the European Society for Primary Immune Deficiencies criteria *SIgAD*: Patients with IEI diagnosed according to the European Society for Primary Immune Deficiencies criteria **Severity Measure(s)**: NR **Clinical Marker**: NR **Outcome Definitions:** Mortality: Infection-fatality rate ICU admission: NR Intubation: NR Ventilation: NR Hospitalization: NR Non-elective readmissions: NR	**Severe COVID-19**: *Mortality, Infection fatality rate (%)* IEI: • IEI: 3.81 • Italian population: 3.28 • p = 0.61 CVID: • CVID: 4.05 • Italian population: 3.28 XLA: • XLA: 0 • Italian population: 3.28 SIgAD: • SIgAD: 0 • Italian population: 3.28 **Severity of Condition:** NR **Duration of Condition:** NR **Comorbid Conditions**: NR **Risk Markers:**

Study	Population and Setting	Exposure	Definitions	Results
SARS-CoV-2 positivity, and to verify whether a condition of lymphopenia might be a possible predictor of COVID-19 outcome. **IVA Score**: 21 (Moderate)	**Exclusion Criteria**: NR		**Comments**: None	Mortality, Infection fatality rate (%) Age: < 18 y • IEI: 0 • Italian population: 0.005 > 18 y • IEI: 5.10 • Italian population: 3.68 • p= 0.5 **Long-term Sequelae**: NR

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

Table 13 Internal Validity Assessments of Extracted Studies Reporting the Association Between Primary Immunodeficiency and Severe COVID-19 Outcomes

OUTCOME MEASURE		Armann 2021[7]	Delavari 2021[1]	Karakoc Aydiner 2021[2]	Kharouf 2021[3]
		ICU admission	Mortality	Mortality	Mortality, ventilation, hospitalization
Domain	**Signaling question**				
Study Elements	Design appropriate to research question	1	1	1	1
	Well described population	1	1	1	0
	Well described setting	1	1	1	1
	Well described intervention/ exposure	1	1	1	1
	Well described control/ comparator	1	0	1	1
	Well described outcome	1	1	1	1
	Clear timeline of exposures/ interventions and outcomes	1	1	1	1
Selection Bias: Sampling	Randomization appropriately performed	0	0	0	0
	Allocation adequately concealed	0	0	0	0
	Population sampling appropriate to study design	1	1	1	1
Selection Bias: Attrition	Attrition not significantly different between groups	1	0	1	1
	Attrition <10-15% of population	1	0	1	1
	Attrition appropriately analyzed	1	0	1	1

OUTCOME MEASURE		Armann 2021[7]	Delavari 2021[1]	Karakoc Aydiner 2021[2]	Kharouf 2021[3]
		ICU admission	Mortality	Mortality	Mortality, ventilation, hospitalization
Information Bias: Measurement and Misclassification	Measure of intervention/ exposure is valid	1	1	1	1
	Measure of outcome is valid	1	1	1	1
	Fidelity to intervention is measured	0	0	0	0
	Fidelity to intervention is valid	0	0	0	0
	Prospective study	1	1	1	1
	Adequately powered to detect result	0	0	0	0
Information Bias: Performance & Detection	Outcome assessor blinded	0	0	0	0
	Study participant blinded	0	0	0	0
	Investigator/ data analyst blinded	0	0	0	0
	Data collection methods described in sufficient detail	1	1	1	1
	Data collection methods appropriate	1	1	1	1
	Sufficient follow up to detect outcome	1	1	1	1
Information Bias: Analytic	Appropriate statistical analyses for collected data	1	0	0	1
	Appropriate statistical analyses are conducted correctly	1	0	0	1
	Confidence interval is narrow	0	0	0	0

OUTCOME MEASURE		Armann 2021[7]	Delavari 2021[1]	Karakoc Aydiner 2021[2]	Kharouf 2021[3]
		ICU admission	Mortality	Mortality	Mortality, ventilation, hospitalization
Confounding	Potential confounders identified	1	0	1	1
	Adjustment for confounders in study design phase	0	0	0	1
	Adjustment for confounders in data analysis phase	1	0	0	0
Reporting Bias	All pre-specified outcomes are adequately reported	1	1	1	1
Other Bias	No other sources of bias	1	1	1	1
COI	Funding sources disclosed and no obvious conflict of interest	1	1	1	1
SCORE	Threat to internal validity	24	16	21	23
	Low, Moderate, High	Moderate	High	Moderate	Moderate

OUTCOME MEASURE		Leon-Abarca 2020[4]	Meyts 2021[5]	Milito 2021[6]
		Mortality, ICU admission, hospitalization	Mortality, ICU admission	Mortality
Domain	**Signaling question**			
Study Elements	Design appropriate to research question	1	1	1
	Well described population	1	1	1
	Well described setting	0	1	1
	Well described intervention/ exposure	1	1	1
Study Elements	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	0	1
Selection Bias: Attrition	Attrition not significantly different between groups	1	1	1
	Attrition <10-15% of population	1	1	1
	Attrition appropriately analyzed	1	1	1
	Measure of intervention/ exposure is valid	1	1	1

Information Bias: Measurement and Misclassification	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	0	1
	Adequately powered to detect result	0	0	0
Information Bias: Performance & Detection	Outcome assessor blinded	0	0	0
	Study participant blinded	0	0	0
	Investigator/ data analyst blinded	0	0	0
Information Bias: Performance & Detection	Data collection methods described in sufficient detail	1	1	1
	Data collection methods appropriate	1	0	1
	Sufficient follow up to detect outcome	1	1	1
Information Bias: Analytic	Appropriate statistical analyses for collected data	1	0	0
	Appropriate statistical analyses are conducted correctly	1	0	0
	Confidence interval is narrow	0	0	0
Confounding	Potential confounders identified	1	0	1
	Adjustment for confounders in study design phase	1	0	0
	Adjustment for confounders in data analysis phase	0	0	0
Reporting Bias	All pre-specified outcomes are adequately reported	1	0	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	23	16	21
	Low, Moderate, High	Moderate	High	Moderate

C. References

1. Delavari S, Abolhassani H, Abolnezhadian F, et al. Impact of SARS-CoV-2 Pandemic on Patients with Primary Immunodeficiency. *J Clin Immunol*. 02 2021;41(2):345-355. doi:https://dx.doi.org/10.1007/s10875-020-00928-x
2. Karakoc Aydiner E, Bilgic Eltan S, Babayeva R, et al. Adverse COVID-19 outcomes in immune deficiencies: Inequality exists between subclasses. *Allergy*. Jul 27 2021;27:27. doi:https://dx.doi.org/10.1111/all.15025
3. Kharouf F, Ishay Y, Kenig A, Bitan M, Ben-Chetrit E. Incidence and course of COVID-19 hospitalizations among patients with familial Mediterranean fever. *Rheumatology (Oxford)*. Jul 22 2021;22:22. doi:https://dx.doi.org/10.1093/rheumatology/keab577
4. Leon-Abarca J. Obesity and immunodeficiencies are the main pre-existing conditions associated with mild to moderate COVID-19 in children. *Pediatric Obesity*. 2020;15:1-2. doi:10.1111/ijpo.12713
5. Meyts I, Bucciol G, Quinti I, et al. Coronavirus disease 2019 in patients with inborn errors of immunity: An international study. Multicenter Study. *J Allergy Clin Immunol*. Feb 2021;147(2):520-531. doi:https://dx.doi.org/10.1016/j.jaci.2020.09.010
6. Milito C, Lougaris V, Giardino G, et al. Clinical outcome, incidence, and SARS-CoV-2 infection-fatality rates in Italian patients with inborn errors of immunity. *Journal of Allergy and Clinical Immunology: In Practice*. July 2021;9(7):2904-2906.e2. doi:http://dx.doi.org/10.1016/j.jaip.2021.04.017
7. Armann J, Doenhardt M, Hufnagel M, et al. Risk factors for hospitalization, disease severity and mortality in children and adolescents with COVID-19: Results from a nationwide German registry. *medRxiv*. 2021:2021.06.07.21258488. doi:10.1101/2021.06.07.21258488

D. Abbreviations

Acronym	Definition

95% CI	95% confidence interval
ADJ1	Next to each other, in any order
ADJ2	Next to each other, in any order, up to 1 word in between
ADJ3	Next to each other, in any order, up to 2 words in between
aPR	Adjusted Prevalence Ratio
aRR	Adjusted Relative Risk
CGD	Chronic granulomatous disease
CI	Confidence interval
CID	Combined immunodeficiency
COI	Conflict of interest
CVID	Common variable immunodeficiency
ECMO	Extracorporeal membrane oxygenation
EMR	Electronic medical record
FMF	Familial Mediterranean fever
HIC	High income country
HMO	Health maintenance organization
ICU	Intensive Care Unit
IEI	Inborn errors of immunity
IFR	Infection Fatality Rate
IQR	Interquartile range
IVA	Internal Validity Assessment
LMIC	Low-to-Middle Income Country
NA	Not applicable
ND	Not defined
NR	Not reported
OR	Odds ratio
PCR	Polymerase chain reaction
PECO	Population, evaluation, control, outcome
PID	Primary immunodeficiency

PR	Prevalence ratio
RR	Relative risk
SCID	Severe combined immunodeficiency
SIgAD	Selective IgA deficiency
UK	United Kingdom
US	United States
WHO	World Health Organization
XLA	X-linked agammaglobulinemia