Clinical Outcomes in Adults with Severe Immunosuppression and Acute Viral Respiratory Infections: Focus on Respiratory Syncytial Virus

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Non-interventional studIES AND activitIES with minimal risk protocol/ACTIVITY plan	
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1. Abstract

Background: Acute respiratory viral infections, including respiratory syncytial virus (RSV), influenza, and SARS-CoV-2, are associated with substantial morbidity and mortality among adults with severe immunosuppression. Data characterizing the clinical course of these infections in severely immunocompromised hosts — including recipients of hematopoietic stem cell transplantation and solid organ transplantation — remain limited, particularly in Latin America.

Objective: To describe the clinical and epidemiological characteristics and outcomes of severely immunocompromised adults with acute viral respiratory infection due to RSV, influenza, or SARS-CoV-2.

Methods: This is a retrospective cohort study conducted within a reference healthcare network in Buenos Aires, Argentina, including all adults with severe immunosuppression and a laboratory-confirmed diagnosis of RSV, influenza, or SARS-CoV-2 by multiplex PCR, between November 2011 and March 2020, and from May 2022 to August 2025. Data were extracted from the electronic health record using automated, algorithm-based queries, without manual chart review. The primary outcome was clinical status at days 0, 7, and 30, assessed using a validated six-category ordinal scale, and progression from upper respiratory tract infection to lower respiratory tract infection or viral pneumonia. Secondary outcomes included intensive care unit admission, length of hospital stay, and all-cause 30-day mortality. Candidate predictors, including underlying immunosuppression mechanism, neutropenia, lymphopenia, and vaccination status, were assessed using logistic regression. Each virus was analyzed separately, with no formal statistical comparison between viruses.

Relevance: By leveraging a large, retrospective, electronic-health-record-based cohort, this study will provide real-world evidence on the clinical burden of acute respiratory viral infections in severely immunosuppressed adults, informing clinical management and vaccination strategies in this high-risk population.

Keywords: respiratory syncytial virus; SARS-CoV-2; influenza, acute respiratory viral infection; immunocompromised host; severe immunosuppression; viral pneumonia; multiplex PCR; 30-day mortality; intensive care unit admission.

2. Background

Respiratory syncytial virus (RSV) is an enveloped, single-stranded RNA virus that belongs to the Paramyxoviridae family. It is classified into two major subgroups, RSV-A and RSV-B, with RSV-A being the most prevalent; however, the dominant subtype may vary by season. This virus shows a marked tropism for respiratory epithelial cells, which explains its role as a leading cause of respiratory tract infections, particularly in infants, older adults, and immunocompromised individuals [1].

Although traditionally associated with respiratory diseases in young children, RSV poses a significant threat to the adult population, especially in those over 65 years of age and individuals with comorbidities. In adults, symptoms may range from mild manifestations to severe illnesses such as pneumonia, exacerbation of chronic lung diseases, and respiratory failure [2]. The risk of severe disease increases with age and the presence of underlying conditions such as chronic obstructive pulmonary disease (COPD), heart failure, diabetes mellitus, and immunosuppression. This vulnerability is especially pronounced in adults over 75 years of age, residents of long-term care facilities, and transplant recipients [3].

In industrialized countries, the estimated hospitalization rate due to RSV in adults ≥65 years is approximately 157 per 100,000 person-years, with an in-hospital mortality rate close to 6.1% [2]. U.S. data from the 2016–2017 and 2022–2023 seasons reported between 123,000 and 193,000 adult hospitalizations annually, with 24,400–34,900 ICU admissions and 4,680–8,620 hospital deaths each season. The overall hospitalization rate ranged from 49 to 76 per 100,000 adults, reaching up to 245 per 100,000 in those over 75 years. This age group accounted for 45.6% of all RSV-related hospitalizations, 38.6% of ICU admissions, and 58.7% of hospital deaths [4].

In middle-income countries, a disease burden modeling study covering 2010 to 2022 estimated that RSV caused 14,604 hospitalizations and 3,518 deaths annually in adults over 20 years in Argentina, with 79–88% of cases occurring in those ≥65 years. Among adults over 75, hospitalization rates ranged from 256.3 to 294.3 per 100,000, and mortality rates ranged from 33.6 to 112.9 per 100,000 [1].

In immunocompromised patients, RSV infection may progress from an upper respiratory tract infection (URTI) to a lower respiratory tract infection (LRTI), with reported progression rates ranging from 19% to 36% [5], depending on the degree of immunosuppression, presence of lymphopenia, and associated comorbidities. In recipients of allogeneic hematopoietic stem cell transplantation (HSCT), RSV-related LRTI mortality can range from 10% to 40%, particularly in those with graft-versus-host disease (GVHD) and prolonged neutropenia [6]. Although early detection and treatment strategies, including ribavirin use, have been implemented, clinical outcomes remain poor. Among solid organ transplant (SOT) recipients, complications are less frequent; however, high-risk subgroups include lung transplant recipients and those with acute rejection episodes or graft dysfunction [7].

Compared to influenza, one study found that RSV-infected patients were older and more frequently presented with congestive heart failure and COPD. Moreover, RSV infection was associated with a higher risk of prolonged hospitalization (≥7 days), pneumonia, ICU admission, and increased one-year post-discharge mortality [8]. Another study, which also included SARS-CoV-2 cases, reported similar findings: patients hospitalized with RSV were more likely to require standard-flow oxygen therapy, high-flow nasal cannula, or non-invasive

ventilation, as well as ICU admission, compared to those hospitalized for COVID-19 or influenza [9].

To date, there is no specific antiviral treatment approved for RSV in adults, and the therapeutic approach remains primarily supportive and symptomatic. However, in 2023, the first vaccines aimed at preventing lower respiratory tract disease due to RSV in adults over 60 years and for individuals aged 18 to 59 years with immunosuppression, were approved. Understanding the disease burden in this population is essential to guide vaccination policies, optimize healthcare resources, and raise awareness about the impact of RSV in adults among healthcare professionals and the general public.

3. Research Question

What is the clinical course and outcomes of respiratory syncytial virus (RSV) infection in severely immunosuppressed adult patients in the context of other respiratory viral pathogens?

4. Objectives

4.1. Primary objectives

To describe the clinical and epidemiological characteristics and outcomes of severely immunocompromised adult patients (≥18 years) with acute respiratory infection (ARI) due to RSV, seeking care within a reference healthcare network in Argentina between 2011 and 2025.

4.2. Secondary objectives

Within a reference healthcare network, among severely immunocompromised adults diagnosed with ARI due to RSV, Covid-19 or influenza

1. Describe the demographic and clinical characteristics in hospitalized severely immunosuppressed patients with acute respiratory infections caused by RSV, COVID-19 & influenza,
2. Describe the demographic and clinical characteristics of ambulatory severely immunosuppressed patients with acute respiratory infections caused by RSV, COVID-19 & influenza
3. Describe course of illness such as hospitalization, re-admission, number of ED visits within 30 days after discharge, in severely immunosuppressed patients with acute respiratory infections caused by RSV, COVID-19 & influenza,
4. Describe ICU admission, use of ventilation support, LOS, status at discharge (at day 0 – 7 and 30 days) in severely immunosuppressed patients with acute respiratory infections caused by RSV, COVID-19 & influenza,
5. Identify risk factors for severe disease outcomes, within each respiratory disease diagnosis, focusing on factors such as age, comorbidities, vaccination status, in severely immunosuppressed adult patients with acute respiratory infections caused by RSV, COVID-19 & influenza,
6. Stratify clinical outcomes and HCRU by baseline condition, immunosuppression treatment, time since diagnosis, disease stage.

4.2.1. Exploratory Objectives

1. To describe the proportion of patients with ARI due to RSV, COVID-19, influenza, presenting also major cardiovascular events (acute coronary syndrome (ACS) or cerebrovascular accident (CVA)]) up to 12 months of the ARI diagnosis.
2. Describe the potential interference of the ARI episode in baseline treatment such as delay in chemotherapy administration implementation, transplant indication or surgeries.
3. Describe mortality due to COVID-19, influenza, RSV, at discharge and 30 days after the diagnosis.
4. Describe all cause mortality up to 12 months after ARI diagnosis.

5. Methodology

5.1. Study design

Retrospective cohort study including all adults with severe immunosuppression and a confirmed diagnosis of acute respiratory infection caused by RSV, influenza A/B, or SARS-CoV-2 during two study periods: November 1, 2011–March 20, 2020, and May 1, 2022–August 10, 2025, within a Buenos Aires hospital network.
*The COVID period is excluded because emergency services were restructured, telemedicine was increased and the total number of consultations and the proportion of low-complexity consultations decrease. The recommendations of the infection control committee restricted common practices in the initial approach to a patient with respiratory infections, such as the decision of whether or not to perform an invasive respiratory sample collection procedure.

5.2. Setting

HIBA is an integrated healthcare network composed of two hospitals: the main site and the San Justo branch. It is a high-complexity university hospital located in the Autonomous City of Buenos Aires. HIBA has 789 beds, including 246 for critical care, approximately 2.5 million outpatient visits per year, 41,000 discharges, and performs about 45,000 surgical procedures annually across its 57 operating rooms [10]. It also operates a prepaid health plan ("Plan de Salud") with approximately 184,000 members.
All patient care within the network is documented in a single unified electronic health record (EHR) system. This clinical data repository includes both administrative information (e.g., appointments, hospital admissions, medication usage) and clinical information (e.g., medical problems, diagnoses, clinical notes, test results). All patient comorbidities and health conditions are automatically coded using a terminology server that maps the information to the controlled vocabulary SNOMED [11].
A positive test result for RSV was required for inclusion. Institutional guidelines recommended testing in patients with respiratory symptoms and severe immunosuppression—as defined by the CDC—with special emphasis on those with neutropenia or requiring ICU admission due to respiratory infection. Viral diagnosis could be performed using nasopharyngeal swabs or bronchoalveolar lavage samples.
The diagnostic techniques used over the study period included:

-In-house multiplex PCR with capillary electrophoresis, validated in November 2011, capable of detecting Influenza A, B, and C, Parainfluenza 1–4, Human Metapneumovirus, Adenovirus, RSV, Rhinovirus, Coronavirus HKU1, and SARS.
-Fast Track Diagnostics (FTD) Respiratory Pathogens 21 commercial PCR panel, used from March to December 2019.
-BIOFIRE® FILMARRAY® Respiratory 2.1 (RP2.1) Panel, implemented from January 2020 onwards.

5.3. Population

5.3.1. Inclusion Criteria	**1.- Presence of severe immunosuppression.** as defined in Appendix 1, is required for study eligibility. **2.- Suspected acute viral respiratory infection.** A suspected event was defined as any patient in whom a respiratory viral PCR panel was ordered. Among these, an acute viral respiratory infection was defined according to the European Conference on Infections in Leukemia (ECIL) [12] as meeting all three of the following: 1. Clinical suspicion recorded in the electronic health record (EHR) 2. Positive multiplex PCR for RSV, SARS-COV-2 or influenza 3. Fulfillment of criteria for either upper (URTI) or lower respiratory tract infection (LRTI) For patients diagnosed with URTI without chest imaging within 48 hours but with clinical follow-up data and a clearly recorded final diagnosis in the EHR, the event was considered valid. **URTI criteria:** Presence of at least two of the following: rhinorrhea, nasal or sinus congestion, otitis media, pharyngitis, or dry cough (typical of the common cold or laryngopharyngitis) [13]; and normal chest X-ray or CT scan. **LRTI or new pneumonia criteria:** Cough accompanied by at least one of the following: dyspnea, rhonchi, crackles, wheezing, tachypnea, or hypoxemia; and a new pulmonary infiltrate on chest X-ray or CT scan [14].
5.3.2. Exclusion Criteria	1.- Patients under palliative care or with a life expectancy of less than 24–48 hours Lack of nursing NEWS assessment or medical order stating “Do not resuscitate” or “Do not follow NEWS protocol” 2.- Patients vaccinated with an RSV vaccine prior to the acute respiratory infection episode (applicable to the late study period only).

5.4. Variables

5.4.1. Exposures

Epidemiology: Age, sex.

Seasonality: Categorical ordinal variable; the proportion of viruses diagnosed in each month, the proportion in each season of the year (Southern Hemisphere), and the period of time in which 75% of diagnoses are concentrated will be described.

Vaccination status:

- Pneumococcal vaccination status: ordinal categorical variable, classified as complete (received both conjugate and polysaccharide vaccines), incomplete (received only one of the two), or unvaccinated.
- Influenza vaccination status: ordinal categorical variable, classified as complete (received the current year's seasonal vaccine from April 1 onward), incomplete (received previous year), or unvaccinated.
- RSV vaccination status (added in this version): binary categorical variable (vaccinated/unvaccinated), based on documented receipt of an RSV vaccine prior to the acute respiratory infection episode. Applicable only to the later study period (May 2022–August 2025), coinciding with RSV vaccine availability in Argentina. Patients vaccinated with an RSV vaccine prior to the ARI episode are excluded from the cohort (see Exclusion Criteria); this variable is tracked to enable transparent reporting of exclusions and sensitivity analyses.

Comorbidities: Binary categorical variable indicating presence or absence of: chronic kidney disease, dialysis, arrhythmia, heart disease, inflammatory bowel disease, diabetes, cerebrovascular disease, psychiatric illness, mild liver disease, obesity, prior infection, moderate lung disease, rheumatologic disease, peptic ulcer, prior malignancy, valvular heart disease, severe pulmonary disease, and severe liver disease.

Underlying condition leading to severe immunosuppression: Categorized according to the primary disease or therapeutic mechanism responsible for immunosuppression at the time of ARI diagnosis, as detailed in Appendix 1.

Clinical presentation: URTI or LRTI, as described in the inclusion criteria.

Laboratory findings: Cytopenias, defined by the presence or absence of leukopenia, neutropenia, severe neutropenia, renal failure, and hypogammaglobulinemia (serum IgG levels less than 0.6 g/dL).

Chest imaging: Chest X-ray and/or CT scan performed at or within 48 hours of the diagnostic test; pathologic image defined as the presence of any consolidative or interstitial infiltrate or pleural effusion; type of pathologic image (unilateral vs. bilateral; consolidative vs. interstitial; presence of pleural effusion).

Respiratory virus identified by multiplex PCR: Respiratory Syncytial Virus (RSV); Influenza A/B; SARS-CoV-2.

5.4.2. Outcomes - primary

Clinical status at days 0, 7, and 30, as defined by Davey et al., a validated ordinal scale for assessing clinical course and survival in influenza studies. This variable includes six mutually exclusive categories describing disease severity over time:

- Discharged with full recovery
- Discharged but not back to normal activities
- Hospitalized without oxygen requirement
- Hospitalized with oxygen requirement
- ICU admission

- Death

Progression from URTI to LRTI: in patients initially meeting criteria for URTI (compatible symptoms and normal chest imaging), progression is defined as the development, within 48 hours to 30 days of diagnosis, of new lower respiratory symptoms plus radiologic evidence of new pulmonary lesions not previously present.

5.4.3. Outcomes - secondary

- ICU admission: admission to an intensive care unit within 30 days after diagnosis.
- Hospitalization within 30 days: for patients initially managed as outpatients, hospitalization is considered an outcome if it occurs within 30 days of the positive PCR test.
- Length of hospital stay: among hospitalized patients, total number of days between hospital admission and discharge (which may include transfer, discharge, or death).
- ICU length of stay: number of days from ICU admission to discharge from the hospital (transfer to general ward, discharge, transfer to another center, or death).
- Number of emergency department (ED) visits within 30 days, with a chief complaint related to the infection or decompensation of a related underlying condition.
- Number of outpatient visits within 30 days, with a visit reason related to the infection or worsening of a related comorbidity.
- Major cardiovascular events: occurrence of acute coronary syndrome (ACS) or cerebrovascular accident (CVA) within 366 days of diagnosis.
- All-cause 30-day mortality: death within 30 days of the positive PCR result. This is a time-to-event outcome; date of death will be recorded.

5.4.4. Key covariates

- Demographics: age, sex.
- Vaccination status (influenza, pneumococcal, RSV): yes/no.
- Comorbidities (cardiovascular, pulmonary, renal, metabolic, oncologic, etc.).
- Underlying condition and mechanism leading to severe immunosuppression, classified into mutually exclusive categories based on the dominant cause of immunosuppression at the time of diagnosis, using a predefined hierarchical algorithm that prioritizes conditions associated with profound cellular immune dysfunction (e.g., recent allo-HSCT, CAR-T therapy) over laboratory abnormalities or maintenance therapies. Laboratory abnormalities such as neutropenia, lymphopenia, and hypogammaglobulinemia will be analyzed as immunological phenotypes reflecting the functional consequences of the underlying immunosuppressive condition, and not as mutually exclusive categories of immunosuppression.
- Radiologic findings (chest X-ray and CT scan characteristics).

- Seasonality of infection.

5.5. Data sources

Data will be obtained from the integrated electronic health record (EHR) system of the Hospital Italiano de Buenos Aires (HIBA).
All data extraction will be performed using automated, algorithm-based queries developed by the Department of Health Informatics, without manual chart review.

The dataset will include structured clinical, laboratory, imaging, and administrative data.
All records will be fully anonymized prior to analysis, and no re-identification will be possible.

5.6. Study sice

This study will include all consecutive adult patients meeting inclusion criteria during the predefined study periods (November 1st, 2011 – March 20th, 2020 and May 1st, 2022 – August 10th, 2025).

No formal sample size calculation was performed, as this is an exhaustive retrospective cohort based on secondary data. The final sample size will be determined by the number of eligible cases identified in the EHR.

5.7. Data Analysis

Descriptive statistics will be used to summarize baseline characteristics.

- Continuous variables: median and interquartile range (IQR)/ mean and standard deviation (SD).
- Categorical variables: absolute and relative frequencies.

Associations between predictors and outcomes (URTI-to-LRTI progression, ICU admission, 30-day mortality) will be assessed using bivariable logistic regression models, reporting odds ratios (ORs) with 95% confidence intervals.
Ordinal logistic regression models will be used to analyze the association between predictors and the ordinal clinical status at days 0, 7, and 30.
The proportional odds assumption will be evaluated using standard statistical tests.
Each virus will be analyzed with a separate model and no formal comparison will be made.
All analyses will be performed using STATA v16 MP (StataCorp, USA).
Statistical significance will be defined as $p < 0.05$.

5.8. Ethical Considerations

This study involves the secondary analysis of fully de-identified data extracted from the electronic health record, with no patient contact and no manual chart review, and is therefore considered minimal risk.

Ethics committee approval. The protocol was approved by the Hospital Italiano de Buenos Aires Research Ethics Committee (Comité de Ética en Protocolos de Investigación, CEPI; approval No. **7738**, PRIISA expediente 18297). Prospective approval was obtained prior to study initiation, and all IRB/EC correspondence and approval documents are retained and available to Pfizer as required.

Waiver of informed consent. Given the retrospective, secondary-data nature of the study, the absence of patient contact, and the use of fully anonymized data with no possibility of re-identification, informed consent was waived by the CEPI, consistent with CIOMS 2019 Guideline 10 on modifications and waivers of informed consent.

Data protection. All data are extracted from the institutional EHR using automated, algorithm-based queries, without manual chart abstraction, and are fully de-identified prior to analysis. The resulting dataset is stored on a password-protected computer accessible only to the study's principal investigator and will be permanently deleted upon completion of the statistical analysis. Data handling complies with Argentine data protection law (Law 25.326, Habeas Data).

Regulatory framework. The study is conducted in accordance with Argentine Ministry of Health Resolution 1480/2011, Law 3301/09 of the City of Buenos Aires, the Declaration of Helsinki, and the ICH E6 Good Clinical Practice guidelines.

Adverse event reporting. As the study involves only existing structured EHR data without manual validation, it is not possible to establish a causal link between any Pfizer product and a specific adverse event in an identifiable individual. The minimum criteria for adverse event reporting (identifiable patient, reporter, suspect product, and event) therefore cannot be met, and no adverse event reporting is expected from this study.

Funding and sponsor role. The study is conducted under a research agreement with, and is funded by, Pfizer S.R.L. (CUIT 30-50351851-8), under the Acuerdo de Condiciones Particulares de Servicios between Pfizer S.R.L. and the Sociedad Italiana de Beneficencia en Buenos Aires – Hospital Italiano (accepted June 29, 2026; Pfizer **NISAMR tracker ID 2025010848**). This is the first external funding obtained for this line of research; the study team's prior work in this area was conducted without external funding and has previously been approved by the CEPI, with results published in a peer-reviewed journal (PMID 41654383). Pfizer has no access to identifiable patient data, is not involved in patient-level data collection or analysis, and the study continues to be coordinated and executed exclusively by the Hospital Italiano research team.

Amendments. This section reflects Protocol Version 3.0 (July 27, 2026), amended solely to incorporate the funding disclosure described above; no changes were made to the study objectives, design, population, variables, or statistical analysis plan as a result of this amendment.

Amendments and Updates

Version Identifier	Date	Section(s) Changed	Summary of Amendment(s)	Reason
1.0	01/13/2026	—	Original version	Initial protocol submission to CEPI
2.0	02/19/2026	Study Design; Population/Setting; Statistical Considerations; document formatting	Addressed CEPI evaluation comments (Report dated January 15, 2026): corrected verb tense in the Study Design section ("the study period was..."); clarified wording in the Setting/Population section regarding inclusion requirements ("for inclusion, it was required..."); revised statistical considerations paragraphs (previously highlighted in green); added a date to the protocol; and numbered all pages.	CEPI approval
3.0	07/27/2026	Funding	Added a Funding section detailing the financial support obtained from Pfizer S.R.L. (CUIT 30-50351851-8) under the Acuerdo de Condiciones Particulares de Servicios between Pfizer S.R.L. and the Sociedad Italiana de Beneficencia en Buenos Aires – Hospital Italiano, accepted June 29, 2026 (Pfizer NISAMR tracker ID 2025010848), including funding amount, payment schedule, and contracted services. No changes were made to the study objectives, design, population, variables, or statistical analysis; no changes to patient-facing procedures; Pfizer has no access to identifiable patient data.	CEPI amendment approval

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Appendix

Appendix 1. Operational Definition of Severe Immunosuppression

Rationale

Severe immunosuppression was defined using a structured, operational framework developed by the research group, based on prior CDC guidance, IDSA recommendations, and contemporary literature addressing immunocompromised hosts.

Historically, operational definitions of severe immunosuppression were clearly delineated in earlier CDC travel and vaccination guidance (e.g., CDC Yellow Book and immunization best practice guidance). However, more recent CDC and IDSA documents provide general principles but are less explicit in defining specific operational thresholds applicable to retrospective database research. Therefore, to ensure reproducibility, internal consistency, and feasibility for automated electronic health record extraction, the study team developed a predefined operational definition grounded in published literature and international guidance.

Severe Immunosuppression Criteria

Patients were considered to have severe immunosuppression if any of the following were present:

1. Hematologic Conditions

- Acute leukemia during induction or re-induction therapy (AML during induction/re-induction, including intensive consolidation; T-ALL during induction/re-induction).
- Recent hematopoietic stem cell transplantation (HSCT): allogeneic HSCT within 3 months (without ATG), or within 6 months (if ATG used); autologous HSCT within 12 months.
- Active graft-versus-host disease (GVHD).
- CAR-T therapy: within 12 months of infusion, or at any time if persistent cytopenia attributable to CAR-T or ongoing immunomodulatory therapy.

2. Neutropenia — Absolute neutrophil count <500/μL for >7 consecutive days.

3. Prolonged Lymphopenia — Absolute lymphocyte count <1000/μL for ≥14 consecutive days.

4. Solid Organ Transplantation (SOT)

- All SOT recipients within 12 months post-transplant.
- All lung transplant recipients, regardless of time since transplant.
- Other SOT recipients (kidney, liver, heart, pancreas) if treated for acute rejection within 6 months, including high-dose corticosteroid pulses, antithymocyte globulin, alemtuzumab, or significant intensification of maintenance immunosuppression.

5. Pharmacologic Immunosuppressive Therapy

- Systemic corticosteroids at doses ≥20 mg/day of prednisone (or equivalent) for ≥14 consecutive days.
- Major immunosuppressive agents including calcineurin inhibitors, antimetabolites, mTOR inhibitors, anti-TNF agents, anti–IL-6 agents, JAK

inhibitors, anti-CD20 agents, or a combination of ≥2 systemic immunosuppressive agents.

6. HIV Infection

- CD4 count <200 cells/mm³.
- Active AIDS-defining opportunistic infection, regardless of CD4 count.

7. Other Causes

- Asplenia.
- Moderate-to-severe combined primary immunodeficiency.
- Advanced liver cirrhosis (Child-Pugh C).
- End-stage renal disease on dialysis plus immunosuppressive therapy.

Mild Immunosuppression *

- Systemic corticosteroids at doses >20 mg/day but ≤50 mg/day of methylprednisolone (or equivalent).
- Monotherapy with immunomodulatory agents with low immunosuppressive impact.
- Stable solid organ transplant recipients without recent rejection (except lung transplant).
- HIV infection with CD4 count ≥200 but <400 cells/mm³ and no active opportunistic infections.
- End-stage renal disease (stage 5 chronic kidney disease) on dialysis.

** Patients meeting criteria for mild immunosuppression will not be included in the study cohort and are described for contextual and classification purposes only.*

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Appendix 2. Variable Operationalization Table (EHR-based automated extraction)

A) Demographics and encounter context

Domain	Variable	Operational definition	Type/Coding	Time window	Data source	Notes
Demographics	Age	Age in years at index date (PCR/sample date)	Continuous (years)	At index date	Patient demographics	—
Demographics	Sex	Sex recorded in EHR	Categorical (F/M/Other/Unknown)	Baseline	Patient demographics	—
Encounter	Care setting at diagnosis	Patient location/encounter type at index date	Binary: inpatient vs. outpatient/ED	Index date	Encounter/ADT tables	If ED visit results in admission, classify as inpatient at diagnosis

B) Comorbidities (binary core)

General rule: comorbidities are captured as presence/absence based on structured diagnoses/problem list. Baseline comorbidities are defined as present if recorded before or on the index date.

Domain	Variable	Operational definition	Coding	Time window
Renal	Chronic kidney disease (CKD)	Any structured diagnosis of CKD	Binary (0/1)	Prior to/on index
Renal	Dialysis	Chronic dialysis recorded	Binary (0/1)	Prior to/on index
Cardiovascular	Arrhythmia	Any structured diagnosis of arrhythmia	Binary (0/1)	Prior to/on index
Cardiovascular	Heart disease	Structured diagnosis of ischemic heart disease or heart failure	Binary (0/1)	Prior to/on index
Cardiovascular	Cerebrovascular disease	Structured diagnosis of stroke/TIA	Binary (0/1)	Prior to/on index
Metabolic	Diabetes	Structured diagnosis of diabetes	Binary (0/1)	Prior to/on index
Metabolic	Obesity	Structured diagnosis of obesity or BMI ≥30	Binary (0/1)	Prior to/on index
Pulmonary	Moderate lung disease	Structured diagnosis of chronic lung disease	Binary (0/1)	Prior to/on index
Pulmonary	Severe pulmonary disease	Structured diagnosis flag for severe lung disease	Binary (0/1)	Prior to/on index
Liver	Mild liver disease	Structured diagnosis consistent with mild chronic liver disease	Binary (0/1)	Prior to/on index
Liver	Severe liver disease	Structured diagnosis consistent with severe liver disease/cirrhosis	Binary (0/1)	Prior to/on index
GI/Immune	Inflammatory bowel disease	Any structured diagnosis of IBD	Binary (0/1)	Prior to/on index
Rheumatology	Rheumatologic disease	Any structured diagnosis of systemic rheumatic disease	Binary (0/1)	Prior to/on index
Psychiatric	Psychiatric illness	Any structured diagnosis	Binary (0/1)	Prior to/on index
GI	Peptic ulcer disease	Any structured diagnosis	Binary (0/1)	Prior to/on index
Oncology	Prior malignancy	Any structured history of malignancy	Binary (0/1)	Prior to/on index

Other	Prior infection	Any structured record of selected prior infection history	Binary (0/1)	Prior to/on index
Cardiovascular	Valvular heart disease	Any structured diagnosis	Binary (0/1)	Prior to/on index

C) Granular comorbidity definitions (pre-specified refinements)

Domain	Variable	Operational definition	Coding
Renal	CKD stage	CKD stage from structured problem list/registry (if available)	Ordinal 1–5/Unknown
Cardiovascular	Coronary artery disease (CAD)	Structured CAD/MI diagnosis	Binary (0/1)
Cardiovascular	Heart failure	Structured HF diagnosis	Binary (0/1)
Cardiovascular	Major CVD composite	CAD and/or HF and/or cerebrovascular disease	Binary (0/1)
Pulmonary	COPD	Structured COPD diagnosis	Binary (0/1)
Pulmonary	Asthma	Structured asthma diagnosis	Binary (0/1)
Pulmonary	Interstitial lung disease (ILD)	Structured ILD diagnosis	Binary (0/1)
Pulmonary	Severe chronic lung disease (composite)	COPD or ILD or home O2 or severe lung disease flag	Binary (0/1)
Oncology	Active malignancy	Active cancer therapy or active malignancy status in structured data	Binary (0/1)

D) Immunosuppression variables (eligibility, etiologic classification, phenotypes)

Domain	Variable	Operational definition	Coding	Time window
Eligibility	Severe immunosuppression	Meets ≥1 criterion in Appendix 1	Binary (0/1)	Baseline
Exposure (etiology)	Underlying cause/mechanism of severe immunosuppression	Mutually exclusive category based on dominant cause at index date, using a hierarchical algorithm	Categorical (1…K)	Index date
Phenotype	Neutropenia	ANC <500/µL for >7 consecutive days	Binary (0/1)	Baseline/around diagnosis
Phenotype	Prolonged lymphopenia	ALC <1000/µL for ≥14 consecutive days	Binary (0/1)	Baseline/around diagnosis
Phenotype	Hypogammaglobulinemia	Serum IgG <0.6 g/dL	Binary (0/1)	Closest to index
Treatment	Corticosteroid exposure (high-risk)	Systemic corticosteroids ≥20 mg/day prednisone equivalent for ≥14 consecutive days	Binary (0/1)	Prior to/on index

Note on hierarchy: in patients meeting multiple criteria, the etiologic category is assigned using a pre-defined hierarchy prioritizing profound cellular immune dysfunction (e.g., recent allo-HSCT, CAR-T) over laboratory phenotypes or maintenance therapies.

E) Vaccination status and seasonality

Domain	Variable	Operational definition	Coding	Time window
Vaccination	Pneumococcal vaccination status	Complete/incomplete/unvaccinated based on documented vaccines	Ordinal (3 levels)	Prior to index

Vaccination	Influenza vaccination status	Complete/incomplete/unvaccinated/no data, based on documented vaccines	Ordinal (4 levels)	Prior to index
Vaccination	RSV vaccination status (added)	Vaccinated/unvaccinated based on documented receipt of RSV vaccine prior to index date. Used as exclusion criterion in the later study period only (May 2022–August 2025)	Binary (0/1)	Prior to index
Seasonality	Month of diagnosis	Calendar month of index date	Categorical (Jan–Dec)	Index date
Seasonality	Southern hemisphere season	Summer/Autumn/Winter/Spring based on month	Categorical (4 levels)	Index date
Seasonality	75% concentration window	Shortest contiguous period containing 75% of diagnoses	Derived	Study period

F) Virus diagnosis and clinical syndrome at presentation

Domain	**Variable**	**Operational definition**	**Coding**	**Time window**
Virology	Virus identified	Positive multiplex PCR for RSV / Influenza A/B / SARS-CoV-2	Categorical (RSV/Flu/COVID)	Index
Syndrome	URTI vs. LRTI	Per ECIL-based criteria plus imaging within 48h (or documented final diagnosis when imaging absent)	Binary (URTI/LRTI)	±48h from index