Association between previous biologic therapy exposure and incidence of life-threatening infections in patients with rheumatoid arthritis and psoriasis. A population-based cohort study.

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1. Abstract

Since the advent of biologic agents targeting key proinflammatory pathways, the treatment of chronic inflammatory and autoimmune diseases has substantially changed. Rheumatoid arthritis and psoriasis are two of the most common conditions for which these agents are administered. Patients taking biologics are more prone to mild infections; however, since most trials conducted have been of short duration, long-term follow-up of these individuals is necessary. Their association with serious infections has not yet been thoroughly analyzed.

In response to the need for further investigation into the long-term effects of biologic therapies, we propose a cohort study of patients with rheumatoid arthritis and/or psoriasis, comparing those exposed to biologic drugs with those who have not been exposed. We aim to analyze the association with potentially severe infections, including influenza, sepsis, pneumonia, and COVID-19.

2. Background and rationale for the study

Since the advent of biologic agents directed at important proinflammatory pathways, the treatment of chronic inflammatory and autoimmune diseases has substantially changed. Biologic agents are a rapidly expanding class of medications accounting for more than 20% of all drugs approved annually by the U.S. Food and Drug Administration (FDA) since 2014 [1]. The introduction at the end of 1990s of biologic disease–modifying management have dramatically changed the outcomes in moderate-to-severe rheumatoid arthritis and psoriasis by the identification of new strategies based on early diagnosis and treatment according to a treat-to-target approach based on disease activity assessment [2-4]. Currently, in Spain, we have more than 50 biosimilar medications corresponding to 16 active ingredients, 4 of which are for immune-mediated rheumatologic, dermatologic, and digestive system diseases: adalimumab, etanercept, infliximab, and rituximab [5]. The first biosimilar medication for this group of diseases was approved in 2015, and it was for infliximab. For biologic agents used to treat rheumatic and immunological disorders, these targets include proinflammatory cytokines, such as different interleukins (IL) and the tumour necrosis factor (TNF). These

newly developed biologic agents include: a) TNF-α inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab; b) IL inhibitors: anakinra (IL-1β), guselkumab (IL-23p19 subunit), ixekizumab (IL-17), risankizumab (IL-23p19 subunit), secukinumab (IL-17), tildrakizumab (IL-23p19 subunit), tocilizumab (IL-6), sarilumab (IL-6), ustekinumab (IL-12/23); c) CD80/86 inhibitor: abatacept; and d) Antibody against the protein CD20: rituximab.

These drugs present an acceptable short- and medium-term safety profile; however, this information is derived mainly from randomized controlled trials, their extensions and reporting of adverse reactions [6,7]. However, clinical trials fall short in their ability to robustly study adverse outcomes: a) Trials are powered to determine efficacy, which generally requires far smaller numbers than would be required to compare safety outcomes; for example, most trials reported observational rates of nasopharyngitis, upper respiratory tract infections and localized mucosal or cutaneous Candida infections – mainly for those taking anti-IL17 biologics – in treatment groups that were higher than placebo [8]; b) Trials are of short duration, typically 12 months or less, which is inadequate for outcomes (such as cancer) that have a lagged exposure risk, posing another limitation that might underestimate the risks associated with their use [9]; and c) Trials self-select for patients who are fit to participate in research, often recruiting a healthier cohort that is not entirely representative of the patient population as a whole; in fact, clinical trial participants are selected using inclusion and exclusion criteria that aim to, among their other goals, avoid risks to participants and these rates may not represent real-world clinical practice [10,11]. In a recent study using big data, Doolan et al. observed in patients receiving biologic treatment that the risk of adverse events was higher for those ineligibles for randomized clinical trials compared to eligible patients [12].

As beforementioned, patients taking biologics are more prone to have mild infectious diseases, but as most of the trials carried out have had short durations, the need to follow up these individuals for a longer period is necessary. Serious infections are defined as infections leading to hospitalization, use of intravenous antibiotics, and sometimes death. Whereas a meta-analysis did not show an increase in the overall frequency of infections in patients treated with abatacept, rituximab or with IL-1, IL-6 or TNF

antagonists, a substantial increase in the number of serious infections was reported [13]. By contrast, another meta-analysis did not show an increased risk of serious infections after rituximab or abatacept treatment of patients with rheumatoid arthritis, although an increased risk of serious infections was associated with high doses of anakinra [14]. Although the frequency of serious infections varies with the use of different biologic agents, upper respiratory tract infections are the most common, and septicaemia, septic arthritis and osteomyelitis, as well as skin, gastrointestinal and urinary tract infections also occur. In patients treated with TNF antagonists, the overall results are conflicting; some studies concluded that the risk of serious infection was not increased and was even decreased, whereas the results of other studies, including a meta-analysis, suggested an increased risk of serious infection [15,16]. The question arises of whether or not the rate of serious infections is mainly associated with the first few months of anti-TNF therapy. With a careful analysis of a cohort of more than 5,000 individuals, Strangfeld et al. identified a biphasic evolution, an increased risk of serious infections during the first 12 months of treatment, followed by a decline in the risk. A high-risk profile was defined as an age of >60 years, chronic lung and kidney disease, impaired lung function, use of steroids and TNF antagonists, or a previous history of serious infection [17].

We hypothesize that previous biologic use among patients diagnosed of rheumatoid arthritis and/or psoriasis is associated with an increased incidence of life-threatening infections, including COVID-19, influenza infection, pneumonia and/or septicaemia Additionally, we propose that this risk is greatest in patients with significant antibiotic exposure, recent biologic exposure (within the past two months), or a baseline immunosuppressive state. We will utilize routinely collected primary care data to study the association between biologic exposure (from 2014 to 2024, or the most recent update) and disease incidence in patients diagnosed with rheumatoid arthritis and/or psoriasis in the general population of Catalonia.

2.1. References

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3. Hypothesis and objectives

3.1. Hypothesis

We hypothesize that prior biologic use among patients diagnosed with rheumatoid arthritis and/or psoriasis is associated with an increased incidence of life-threatening infections, including COVID-19, influenza, pneumonia, and/or septicaemia. Additionally, this association may change depending on the different biologics used and the patient's baseline immunosuppressive status. We further hypothesize that the risk is greatest in patients with higher antibiotic exposure compared to lower drug exposure and recent biologic exposure (within the past two months).

3.2. General objective

This study aims to evaluate the association between biologic exposure and the incidence of serious infections, including COVID-19, influenza, pneumonia, and/or septicaemia, in patients diagnosed with rheumatoid arthritis and/or psoriasis in the general population of Catalonia.

3.3. Specific objectives

- To describe the sociodemographic and clinical characteristics of patients with rheumatoid arthritis and/or psoriasis, including their comorbidities, pharmacological treatments in use, and the prevalence of serious infections in this population.
- To evaluate the association between different biologics and the incidence of life-threating infections in patients diagnosed with rheumatoid arthritis and/or psoriasis.
- To evaluate the association between the duration of biologic exposure and the incidence of these infections in the same patient population.
- To assess the impact of recent biologic exposure (within the last two months) on the incidence of these infections in the same patient population.
- To evaluate the impact of comorbidities on the associations between biologic therapy and the incidence of infections in the same patient population.
- To determine the influence of concurrent immunosuppressive therapies on biologic exposure and their relationship with the incidence of infections in the same patient population.

4. Methods

4.1. Design

Population-based cohort study.

4.2. Study period

A ten-years period, from January 1, 2014, to June 2024, or the most recent update available of SIDIAP database.

4.3. Population

Adult patients diagnosed with rheumatoid arthritis and/or psoriasis treated with biologic and non-biologic therapies will be identified in the primary healthcare records in Catalonia (ECAP), and they will be categorized into different cohorts based on their prior exposure to biologic treatments.

4.3.1. Inclusion criteria

Adult patients (over 18 years of age) who meet the following criteria:

- Diagnosis of rheumatoid arthritis (M05.* and M06.*) and/or psoriasis (L40.*) in ECAP during the study period.

4.3.2. Exclusion criteria

Patients who are residents in nursing homes (long-term facilities)

4.4. Data sources

The study data source will be the Information System for Research in Primary Care (Sistema de Información para el Desarrollo de la Investigación en Atención Primaria, SIDIAP; www.sidiap.org) database [18], which contains pseudonymized clinical information from 329 primary care healthcare centres of the Catalan Health Institute (ICS), which serve a population of approximately 5.8 million people (around 80% of the Catalan population).

This information is pseudonymized, and originates from different data sources: a) ECAP (electronic health records in primary care of the Catalan Health Institute); including socio-demographic characteristics, comorbidities registered as the International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes [19], specialist referrals, clinical parameters, toxic habits, vaccinations, work incapacity, sickness leave, date of death, laboratory test data, and drug prescriptions issued in primary healthcare and their corresponding ICS pharmacy invoice data (ATC codes) [20]; b) data on diagnoses from the minimum basic data set for acute hospital discharges (CMBD-HA) will also be obtained [21]. The CMBD is a population register that collects

information on the pathology treated in healthcare centres in Catalonia, including healthcare activity and morbidity. It includes data from acute hospital discharges (CMBD-HA) and emergency visits (CMBD-UR). c) The database on medicines prescribed in hospital outpatients visits and dispensed in hospital pharmacies (*medicació hospitalària de dispensació ambulatòria* [MHDA]), where biologics are dispensed.

The SIDIAP database has been extensively used for national and international epidemiologic and pharmacoepidemiologic studies and has been validated in primary care [22,23].

4.5. Sample size

All adults with one of the two diagnoses of interest (or both) and who receive treatment with biological drugs will be included. Given that we cannot know the sample size without requesting for SIDIAP data on diagnoses and MHDA, the following data will be considered:

- Rheumatoid arthritis: the prevalence in Spain is 0.5-0.8%. Of these, approximately 20-25% receive treatment with biological drugs. An approximate calculation in Catalonia would give us a range of between 8,000 and 16,000 patients.

- Psoriasis: the estimated prevalence is 1.4-2.3%. Of these, around 4-5% receive treatment with biological drugs. An approximate calculation in Catalonia would give us a range of between 4,400 and 9,200 patients.

4.6. Variables

4.6.1. Baseline characteristics of the study population

The variables to be collected will include sociodemographic characteristics, socioeconomic and environmental disparities, as quantified by the MEDEA socioeconomic deprivation score, which includes five discrete values [24]; clinical variables, relevant comorbidities, and concomitant use of treatments, with particular emphasis on corticosteroids and other immunosuppressants agents (classified under ATC code L04).

Diagnoses: rheumatoid arthritis, psoriasis.

Sociodemographic variables: sex, age, MEDEA index, healthcare region.

Clinical variables: weight, height, body mass index (BMI), toxic habits (smoking and alcohol consumption).

Comorbidities considered as available diagnoses in ECAP: hypertension, dyslipidaemia (DLP), diabetes mellitus (DM1 and DM2), obesity, anaemia, other cardiovascular diseases (atrial fibrillation, acute myocardial infarction, heart failure, etc.), chronic kidney disease, dialysis and kidney transplant, neoplasms (including solid organ neoplasms, lymphoma, leukemia, multiple myeloma, etc.), stroke, chronic obstructive pulmonary disease, cystic fibrosis, vascular arteriosclerosis, COVID-19, tuberculosis, HIV/AIDS infection, autoimmune diseases (systemic lupus erythematosus, inflammatory bowel disease, etc.), primary immunodeficiencies, etc.

4.6.2. Exposure to drugs

Patients will be classified as exposed to biologic agents if they have received at least one treatment episode during the study period, prior to the diagnosis of serious infection that required hospital admission. They will then be grouped into exposed or non-exposed based on their treatment history. In patients exposed to biologic agents, the duration of exposure will be analysed according to tertiles based on the total exposure time. Recent exposure will be defined as treatment received less than two months prior to any of the infection diagnoses.

Biologic products:

- TNF Inhibitors (Tumour Necrosis Factor): adalimumab, certolizumab pegol, etanercept, golimumab and infliximab
- IL-1 Inhibitors: anakinra
- IL-6 Inhibitors: sarilumab and tocilizumab
- IL-12/IL-23 Inhibitors: ustekinumab
- IL-17 Inhibitors: ixekizumab and secukinumab
- IL-23 Inhibitors: guselkumab, risankizumab and tildrakizumab

- Others: abatacept (T-cell co-stimulation inhibitor) and rituximab (monoclonal antibody targeting CD20)

4.6.3. Infection-related variables

The infections will be classified as potentially severe if they are associated with hospitalization or mortality. The severity will be hierarchically categorized as follows: mortality > hospitalization. The risk of these events will be analysed comparing patients exposed to different types of biologic agent with those non-exposed, as well as according to the duration and recent of biologic exposure. Additionally, subanaly**s**es will be conducted based on the treatment indication (rheumatoid arthritis and/or psoriasis) and gender to explore their influence on infection outcomes. We assume that in individuals with no record of any of the variables of interest, there are no existing severity endpoints, health problems, drug exposure or smoking habits.

Life-threatening infections: any infection that requires hospitalization or is associated with mortality, including pneumonia, influenza, septicaemia, and COVID-19.

4.6.4. Potential confounding variables

Age, sex, years since the diagnosis of rheumatoid arthritis and psoriasis, socioeconomic status, smoking status, body mass index, comorbidities of interest, concomitant medication.

4.7. Data analysis

The study population will be described overall and stratified by exposure status (exposed vs. unexposed individuals). Quantitative variables will be summarized using means with standard deviations (SD) or medians with interquartile ranges (IQR), depending on the distribution of the variable. Categorical variables will be presented as absolute and relative frequencies. Bivariate comparisons between groups will be conducted using Student's t-tests, Wilcoxon rank-sum tests, or Chi-square tests, as appropriate.

For the primary outcome, marginal structural models (MSMs) will be employed to estimate the risk of treatment exposure while addressing confounding. Inverse probability of treatment weights (IPTWs) will be derived from propensity scores

calculated using age, sex, socioeconomic deprivation score, previous life-threatening infections, and other relevant clinical factors. If necessary, weights will be truncated at the 1st percentile to stabilize estimates. Covariate balance before and after weighting will be evaluated using the standardized mean difference (SMD). Variables with SMD > 0.1 after weighting will be included in the MSM as additional covariates to achieve double robustness.

IPTWs will then be applied in logistic regression models to estimate risk ratios (RRs) with 95% confidence intervals (CIs), using robust standard errors (SEs) to account for variability. Statistical significance will be determined using the Wald test at a 0.05 level. When assessing the association between prior biologic exposure and severity outcomes, patients will be assigned to the worst outcome observed (all-cause death > hospitalization > disease presence) to ensure a mutually exclusive classification.

All analyses will be performed using R software (v4.2 or above).

4.8. Difficulties and limitations

This study presents several limitations inherent to its observational design, which restricts the ability to establish causal relationships between exposure to biologic treatments and infection outcomes. However, the evaluation of these results is conducted under standard clinical practice conditions, utilizing data from electronic primary care records through the SIDIAP database, which has demonstrated validity and representativeness of the population in numerous previous studies.

Additionally, the quality of the data in the database may be affected by underreporting, resulting in an underestimation of both treatment exposure and infection incidence, which limits the precision of the information available for analysis. There are also challenges in accurately measuring the duration and adherence to biological treatment, which could influence the interpretation of the results. Furthermore, the absence of data on the severity of the diseases of interest may affect the comparability of outcomes. The evolution of biological therapies over time represents another significant limitation, as changes in clinical practices and treatment options could affect the applicability of the findings in the future. Lastly, we could incur in a selection bias if the population included

differ systematically from the population of interest leading to a systematic error in an association or outcome. This bias might be mitigated at the design stage with the population selection.

5. Pharmacovigilance

Adverse events/reactions will not be collected or analysed as part of this evaluation. The non-interventional nature of this feasibility assessment, using secondary data, does not meet the criteria for the reporting of adverse events, according to module VI, VI.C.1.2.1.2 of Good Pharmacovigilance Practices.

6. Ethical and data confidentiality aspects

The protocol will be submitted for evaluation by the Ethics Committee of the Primary Care Research Institute (IDIAP) Jordi Gol, a reference institution for Primary Care research at the ICS, considering national and international regulations.

The study will be conducted following guidelines on ethical aspects and Good Research Practices and in accordance with the principles of the Declaration of Helsinki, as well as Royal Decree 957/2020, of November 3, which regulates observational studies with human-use medicines (EOm). Data processing will comply with Regulation (EU) 2016/679 of the European Parliament and Council of April 27, 2016, concerning the protection of natural persons regarding the processing of personal data and the free movement of such data, as well as Law 3/2018, of December 5, on the Protection of Personal Data and the guarantee of digital rights. The study will not interfere with routine clinical practice in primary care consultations.

The necessary variables for carrying out the study have been obtained in accordance with Articles 6.e) and 9.2.j) of the GDPR, as well as Additional Provision 17.2.d of the LOPD-GDD. The data collected will refer to sociodemographic, clinical, and analytical issues, diagnoses of comorbidities, and pharmacological treatments (specify according to the study). These data will be obtained from the SIDIAP (Information System for the Development of Research in Primary Care) database and pseudonymized by assigning an

internal code that prevents the identification of the participants. In cases of cross-referencing between SIDIAP and other databases, a "trusted third party" will be used, which will not have access to clinical information but only to codes and identifiers, thus ensuring compliance with data confidentiality.

Only the personal data necessary to achieve the objectives of the study will be included, limited to the methodology determined in the project.

ICS will act as the data controller in the context of this study. The information will be stored on ICS servers, and the institution's program tools will be used. The data retention period will correspond to the project's duration, estimated at 5 years, after which the data will be destroyed.

The appropriate security measures will be established to ensure data accessibility only by the study's research team while preventing access by unauthorized external parties. No international data transfer procedures are anticipated, nor are there considered to be high-risk situations for the data subjects' rights and freedoms that would require an impact assessment. The project also does not consider the use of cloud storage systems, wearable devices, or apps. The study's researchers declare no conflicts of interest.

7. Work plan

- Development of the study protocol: October-December 2024
- Evaluation of the amendment by the SIDIAP Scientific Committee and the CEIm of IDIAPJGol: January 2025
- Registration of the project protocol in the EMA-HMA Catalogue: February 2025
- Operationalization of the variables for extraction from SIDIAP: February-March 2025.
- Data extraction: March 2025
- Data analysis: April-July 2025
- Interpretation of results and preparation of the report/scientific publications: July-December 2025.

8. Experience of the research team on the proposed topic

Some of the members of the research team conducted a similar study two years ago, aimed at evaluating the association between the intensity of antibiotic courses and the incidence, severity, and mortality of COVID-19 [25].

Different members of this team are part of the CIBER Enfermedades Infecciosas and the Instituto de Salud Carlos III.

Different members of this team are part of the research group EMAP, accredited by AGAUR.

All members of the research team are actively publishing studies based on SIDIAP in national and international journals.

Suyvan Esther Mata Ley will conduct her doctoral thesis with this project. The thesis directors will be: Rosa Morros Pedrós, Lina Camacho Arteaga and Maria Giner-Soriano.

9. Resources available for the project's execution

This project will be carried out at IDIAPJGol, which has the appropriate infrastructure to ensure the smooth development of the study and has extensive experience in conducting research projects in the field of primary healthcare. The UEM team has vast experience in conducting pharmacoepidemiologic studies using data from SIDIAP.

The data necessary for the project will be extracted from the SIDIAP database. The SIDIAP staff has the technical capacity and necessary experience in managing databases, along with the required servers to handle data from various sources.

10. Justification for funding and requested budget

The project is funded by CIBER Enfermedades Infecciosas and the Instituto de Salud Carlos III in Madrid and is considered a non-profit clinical research study that complies with the conditions set forth in paragraph e) of article 2.2 of Royal Decree 1090/2015, of December 4.

11. **Annex. Diagnostic and Drug Codes**

This annex details the diagnostic codes according to the International Classification of Diseases, 10th Revision, Clinical Modification (ICD-10-CM), and the drug codes according to the Anatomical Therapeutic Chemical (ATC) classification system, corresponding to the study variables.

11.1. Diagnoses (ECAP)

- Rheumatoid arthritis: M05.* and M06.*
- Psoriasis: L40.*

11.2. Potentially severe infections (ECAP and CMBD-HA)

- Pneumonia: J12, J12.0, J12.1, J12.2, J12.3, J12.8, j12.89, 12.9, J13.*, J14.*, J15.*, J16.*, J17.* and J18.*
- COVID-19: U07.1, J12.81 and J12.82
- Influenza: J09.*, J10. and J11.*
- Septicaemia: A40.* and A41.*
- Other infections: A00-B99

11.3. Drug (ATC codes)

11.3.1. Biologic products (MHDA)

- TNF Inhibitors
  - Adalimumab: L04AB04
  - Certolizumab pegol: L04AB05
  - Etanercept: L04AB01
  - Golimumab: L04AB06
  - Infliximab: L04AB02

- IL-1 Inhibitors
  - Anakinra: L04AC03

- IL-6 Inhibitors
  - Sarilumab: L04AC14
  - Tocilizumab: L04AC07

- IL-12/IL-23 Inhibitors
  - Ustekinumab: L04AC05

- IL-17 Inhibitors
  - Ixekizumab: L04AC13
  - Secukinumab: L04AC10

- IL-23 Inhibitors
  - Guselkumab: L04AC16
  - Risankizumab: L04AC18
  - Tildrakizumab: L04AC17

- Others
  - Abatacept (T-cell co-stimulation inhibitor): L04AA24
  - Rituximab (monoclonal antibody targeting CD20): L01FA01

11.3.2. Non-biological drugs for rheumatoid arthritis and psoriasis (MHDA + prescripció + facturació):

- Methotrexate: L01BA01 and L04AX03
- Leflunomide: L04AK01
- Hydroxychloroquine: P01BA02
- Cyclosporine: L04AD01
- Apremilast: L04AA32
- Tofacitinib: L04AF01
- Baricitinib: L04AF02
- Upadacitinib: L04AF03
- Filgotinib: L04AF04
- Glucocorticoids: H02AB*
- Non-steroidal anti-inflammatory: M01A*
- Other inmmunosupressants agents: L04A*

11.4. Other variables

11.4.1. Comorbidities (ECAP):

- Cardiovascular diseases: I10, I11, I11.0, I11.9, I12, I12.0, I12.9, I13, I13.0, I13.1, I13.2, I13.9, I15, I15.0, I15.1, I15.2, I15.8, I15.9, I20, I20.0, I20.1, I20.8, I20.9, I21, I21.0, I21.1, I21.2, I21.3, I21.4, I21.9, I22, I22.0, I22.1, I22.8, I22.9, I23, I23.0, I23.1, I23.2, I23.3, I23.4, I23.5, I23.6, I23.8, I24, I24.0, I24.1, I24.8, I24.9, I25, I25.0, I25.1, I25.2, I25.3, I25.4, I25.5, I25.6, I25.8, I25.9, I26, I26.0, I26.9, I48.*, I49, I49.0, I49.3, I49.5, I49.8, I49.9, I50.*, I51, I51.0, I51.1, I51.2, I51.3, I51.4, I51.5, I51.6, I51.7, I51.8, I51.9, I67.2, I67.3, I67.4, I67.7, I67.8, I67.9, I70.*, I73, I73.0, I73.1, I73.8, I73.9, I74, I74.0, I74.1, I74.2, I74.3, I74.4, I74.5, I74.8, I74.9 and I82.*
- Dyslipidemia: E78.*

- Diabetes: E10, E10.0, E10.1, E10.2, E10.3, E10.4, E10.5, E10.6, E10.7, E10.8, E10.9, E11, E11.0, E11.1, E11.2, E11.3, E11.4, E11.5, E11.6, E11.7, E11.8, E11.9, E12, E12.0, E12.1, E12.2, E12.3, E12.4, E12.5, E12.6, E12.7, E12.8, E12.9, E13, E13.0, E13.1, E13.2, E13.3, E13.4, E13.5, E13.6, E13.7, E13.8, E13.9, E14, E14.0, E14.1, E14.2, E14.3, E14.4, E14.5, E14.6, E14.7, E14.8 and E14.9
- Obesity: E66.*
- Anemia: D50-D64
- Chronic kidney diseases: N01, N01.0, N01.1, N01.2, N01.3, N01.4, N01.5, N01.6, N01.7, N01.8, N01.9, N03, N03.0, N03.1, N03.2, N03.3, N03.4, N03.5, N03.6, N03.7, N03.8, N03.9, N04, N04.0, N04.1, N04.2, N04.3, N04.4, N04.5, N04.6, N04.7, N04.8, N04.9, N05, N05.0, N05.1, N05.2, N05.3, N05.4, N05.5, N05.6, N05.7, N05.8, N05.9, N07, N07.0, N07.1, N07.2, N07.3, N07.4, N07.5, N07.6, N07.7, N07.8, N07.9, N08, N08.0, N08.1, N08.2, N08.3, N08.4, N08.5, N08.8, N11, N11.0, N11.1, N11.8, N11.9, N12, N14, N14.0, N14.1, N14.2, N14.3, N14.4, N18, N18.0, N18.8, N18.9, N19, Q61, Q61.0, Q61.1, Q61.2, Q61.3, Q61.4, Q61.5, Q61.8 and Q61.9
- Patient on dialysis: Z99.2 or Z49.*
- Kidney transplant: Z94.0
- Malignant neoplasm: C00, C00.0, C00.1, C00.2, C00.3, C00.4, C00.5, C00.6, C00.8, C00.9, C01, C02, C02.0, C02.1, C02.2, C02.3, C02.4, C02.8, C02.9, C03, C03.0, C03.1, C03.9, C04, C04.0, C04.1, C04.8, C04.9, C05, C05.0, C05.1, C05.2, C05.8, C05.9, C06, C06.0, C06.1, C06.2, C06.8, C06.9, C07, C08, C08.0, C08.1, C08.8, C08.9, C09, C09.0, C09.1, C09.8, C09.9, C10, C10.0, C10.1, C10.2, C10.3, C10.4, C10.8, C10.9, C11, C11.0, C11.1, C11.2, C11.3, C11.8, C11.9, C12, C13, C13.0, C13.1, C13.2, C13.8, C13.9, C14, C14.0, C14.2, C14.8, C15, C15.0, C15.1, C15.2, C15.3, C15.4, C15.5, C15.8, C15.9, C16, C16.0, C16.1, C16.2, C16.3, C16.4, C16.5, C16.6, C16.8, C16.9, C17, C17.0, C17.1, C17.2, C17.3, C17.8, C17.9, C18, C18.0, C18.1, C18.2, C18.3, C18.4, C18.5, C18.6, C18.7, C18.8, C18.9, C19, C20, C21, C21.0, C21.1, C21.2, C21.8, C22, C22.0, C22.1, C22.2, C22.3, C22.4, C22.7, C22.9, C23, C24, C24.0, C24.1, C24.8, C24.9, C25, C25.0, C25.1, C25.2, C25.3, C25.4, C25.7, C25.8, C25.9, C26, C26.0, C26.1, C26.8, C26.9, C30, C30.0, C30.1, C31, C31.0, C31.1, C31.2, C31.3, C31.8, C31.9, C32, C32.0, C32.1, C32.2, C32.3, C32.8, C32.9, C33, C34, C34.0, C34.1, C34.2, C34.3, C34.8, C34.9, C37, C38, C38.0, C38.1, C38.2, C38.3, C38.4, C38.8, C39, C39.0, C39.8, C39.9, C40, C40.0, C40.1, C40.2, C40.3, C40.8, C40.9, C41, C41.0, C41.1, C41.2, C41.3, C41.4, C41.8, C41.9, C43, C43.0, C43.1, C43.2, C43.3, C43.4, C43.5, C43.6, C43.7, C43.8, C43.9, C44, C44.0, C44.1, C44.2, C44.3, C44.4, C44.5, C44.6, C44.7, C44.8, C44.9, C45, C45.0, C45.1, C45.2, C45.7, C45.9, C46, C46.0, C46.1, C46.2, C46.3, C46.7, C46.8, C46.9, C47, C47.0, C47.1, C47.2, C47.3, C47.4, C47.5, C47.6, C47.8, C47.9, C48, C48.0, C48.1, C48.2, C48.8, C49, C49.0, C49.1, C49.2, C49.3, C49.4, C49.5, C49.6, C49.8, C49.9, C50, C50.0, C50.1, C50.2, C50.3, C50.4, C50.5, C50.6, C50.8, C50.9, C51, C51.0, C51.1, C51.2, C51.8, C51.9, C52, C53, C53.0, C53.1, C53.8, C53.9, C54, C54.0, C54.1, C54.2, C54.3, C54.8, C54.9, C55, C56, C57, C57.0, C57.1, C57.2, C57.3, C57.4, C57.7, C57.8, C57.9, C60, C60.0, C60.1, C60.2, C60.8, C60.9,

C61, C62, C62.0, C62.1, C62.9, C63, C63.0, C63.1, C63.2, C63.7, C63.8, C63.9, C64, C65, C66, C67, C67.0, C67.1, C67.2, C67.3, C67.4, C67.5, C67.6, C67.7, C67.8, C67.9, C68, C68.0, C68.1, C68.8, C68.9, C69, C69.0, C69.1, C69.2, C69.3, C69.4, C69.5, C69.6, C69.8, C69.9, C70, C70.0, C70.1, C70.9, C71, C71.0, C71.1, C71.2, C71.3, C71.4, C71.5, C71.6, C71.7, C71.8, C71.9, C72, C72.0, C72.1, C72.2, C72.3, C72.4, C72.5, C72.8, C72.9, C73, C74, C74.0, C74.1, C74.9, C75, C75.0, C75.1, C75.2, C75.3, C75.4, C75.5, C75.8, C75.9, C76, C76.0, C76.1, C76.2, C76.3, C76.4, C76.5, C76.7, C76.8, C77, C77.0, C77.1, C77.2, C77.3, C77.4, C77.5, C77.8, C77.9, C78, C78.0, C78.1, C78.2, C78.3, C78.4, C78.5, C78.6, C78.7, C78.8, C79, C79.0, C79.1, C79.2, C79.3, C79.4, C79.5, C79.6, C79.7, C79.8, C80, C81, C81.0, C81.1, C81.2, C81.3, C81.7, C81.9, C82, C82.0, C82.1, C82.2, C82.7, C82.9, C83, C83.0, C83.1, C83.2, C83.3, C83.4, C83.5, C83.6, C83.7, C83.8, C83.9, C84, C84.0, C84.1, C84.2, C84.3, C84.4, C84.5, C85, C85.0, C85.1, C85.7, C85.9, C88, C88.0, C88.1, C88.2, C88.3, C88.7, C88.9, C90, C90.0, C90.1, C90.2, C91, C91.0, C91.1, C91.2, C91.3, C91.4, C91.5, C91.7, C91.9, C92, C92.0, C92.1, C92.2, C92.3, C92.4, C92.5, C92.7, C92.9, C93, C93.0, C93.1, C93.2, C93.7, C93.9, C94, C94.0, C94.1, C94.2, C94.3, C94.4, C94.5, C94.7, C95, C95.0, C95.1, C95.2, C95.7, C95.9, C96, C96.0, C96.1, C96.2, C96.3, C96.7, C96.9, C97, D00, D00.0, D00.1, D00.2, D01, D01.0, D01.1, D01.2, D01.3, D01.4, D01.5, D01.7, D01.9, D02, D02.0, D02.1, D02.2, D02.3, D02.4, D03, D03.0, D03.1, D03.2, D03.3, D03.4, D03.5, D03.6, D03.7, D03.8, D03.9, D04, D04.0, D04.1, D04.2, D04.3, D04.4, D04.5, D04.6, D04.7, D04.8, D04.9, D05, D05.0, D05.1, D05.7, D05.9, D06, D06.0, D06.1, D06.7, D06.9, D07, D07.0, D07.1, D07.2, D07.3, D07.4, D07.5, D07.6, D09, D09.0, D09.1, D09.2, D09.3, D09.7, D09.9, D33, D33.0, D33.1, D33.2, D33.3, D33.4, D33.7, D33.9, D37, D37.0, D37.1, D37.2, D37.3, D37.4, D37.5, D37.6, D37.7, D37.9, D38, D38.0, D38.1, D38.2, D38.3, D38.4, D38.5, D38.6, D39, D39.0, D39.1, D39.2, D39.7, D39.9, D40, D40.0, D40.1, D40.7, D40.9, D41, D41.0, D41.1, D41.2, D41.3, D41.4, D41.7, D41.9, D42, D42.0, D42.1, D42.9, D43, D43.0, D43.1, D43.2, D43.3, D43.4, D43.7, D43.9, D44, D44.0, D44.1, D44.2, D44.3, D44.4, D44.5, D44.6, D44.7, D44.8, D44.9, D45, D46, D46.0, D46.1, D46.2, D46.3, D46.4, D46.7, D46.9, D47, D47.0, D47.1, D47.2, D47.3, D47.7, D47.9, D48, D48.0, D48.1, D48.2, D48.3, D48.4, D48.5, D48.6, D48.7, D48.9, D63.0, M36.0, M36.1, M90.6 and M90.7

- Stroke: G46, G46.0, G46.1, G46.2, G46.3, G46.4, G46.5, G46.6, G46.7, I05, I05.0, I05.1, I05.2, I05.8, I05.9, I60, I60.0, I60.1, I60.2, I60.3, I60.4, I60.5, I60.6, I60.7, I60.8, I60.9, I61, I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, I61.9, I62, I62.0, I62.1, I62.9, I63, I63.0, I63.1, I63.2, I63.3, I63.4, I63.5, I63.6, I63.8, I63.9, I64, I65, I65.0, I65.1, I65.2, I65.3, I65.8, I65.9, I66, I66.0, I66.1, I66.2, I66.3, I66.4, I66.8, I66.9, I68.* and I69.*
- Chronic obstructive pulmonary disease: J44.*
- Cystic fibrosis: E84.*
- Tuberculosis: A15-A19
- HIV infection, unspecified: B20
- Systemic lupus erythematosus: M32.*

- Inflammatory bowel disease: K50.*, K51.* and K52.9
- Congenital immunodeficiency: D80-D84

11.4.2. Admission in ICU (CMBD-HA)

If available:

- Days of admission in ICU
- Diagnoses during ICU admission