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# Role of the AB0 blood group in COVID-19 infection and complications: A population-based study

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ABSTRACT

Since the beginning of the COVID-19 pandemic, the ABO blood group has been described as a possible biological marker of susceptibility for the disease. This study evaluates the role of ABO group on the risk of SARS-CoV-2 infection and related complications in a population-based cohort including 87,090 subjects from the Navarre population (Northern Spain) with no history of SARS-CoV-2 infection and with known ABO blood group, after one year of the pandemic (May 2020 – May 2021). The risk of infection, hospitalization, Intensive Care Unit (ICU) admission and death was analyzed using multivariate logistic regression, adjusting for possible confounding variables. A lower risk of infection was observed in group 0 vs non-0 groups [OR 0.94 (95 %CI 0.90−0.99)], a higher risk of infection in group A vs non-A groups [OR 1.09 (95 %CI 1.04−1.15)] and a higher risk of infection in group A vs group 0 [OR 1.08 (95CI 1.03−1.14)] (when the 4 groups are analyzed separately). No association was observed between blood groups and hospitalization, ICU admission, or death in SARS-CoV-2 infected subjects. Regarding the risk of SARS-CoV-2 infection, we observed a protective role of group O and a greater risk in the A group.

## 1. Introduction

Since the WHO declared a pandemic of COVID-19 in March 2020 [1], disease characteristics and factors that could influence SARS-CoV-2 infection and severity have been widely analyzed. Identifying high-risk clinical features and diagnostic predictors of COVID-19 morbidity and mortality remains imperative, as they can aid treatment and lifestyle decisions, improve individual risk prediction, suggest novel treatment targets and enhance the design of new studies. Previous investigations have revealed an association between ABO blood group and host susceptibility to infectious diseases caused by certain viral families, including *Coronaviridae*, *Retroviridae* or *Hepadnaviridae*, and influenza virus, among others [2–4]. Building upon these findings, a possible influence of ABO blood group phenotype in acquisition of COVID-19 infection has been hypothesized.

Recently published systematic reviews that investigated the relationship between the ABO blood group and the occurrence of COVID-19, found that individuals belonging to O blood group type are less susceptible to SARS-CoV-2 infection compared to those non-O group [2,3,5–7]. However, these syntheses were not adjusted and showed high heterogeneity. The studies carried out have diverse designs and quality, and have been conducted in different populations, finding contradictory results. The mechanism underlying the possible association could lie in the presence of IgG anti-A isoagglutinins in O blood group subjects,

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which would prevent the binding of SARS-CoV-2 to its receptor thereby stopping the virus entering the targeted human cells [5]. Thus, in individuals with non-A blood types, specifically O or B, anti-A antibodies may play a protective role in SARS-CoV-2 infection [4]. However, the pathogenic mechanism underlying encompasses several molecular pathways, and therefore additional factors could contribute to the predisposition of acquiring SARS-CoV-2 [4].

COVID-19 disease manifests with a wide spectrum of signs and symptoms, suggesting that severity of the outcomes may be influenced by environmental and host factors. Increasing age, pre-existing comorbidities (e.g., diabetes mellitus, hypertension, and respiratory and cardiovascular diseases), obesity, and immunosuppression, among other factors, have been associated with severe disease and a higher mortality risk [8,9]. The association between ABO blood group and disease severity and mortality has also been investigated. Published systematic reviews have not found an association between group O blood type and severe infection or death [5,6], but a significantly increased risk of COVID-19 severity and mortality has been identified in people belonging to blood group A [3,6].

Distribution of ABO blood group varies among the different geographic regions, race and ethnicity, and studies analyzing the influence of ABO blood group in COVID-19 infection and severity carried out in Spain are scarce [10–14]. Therefore, the objective of the study was to analyze if an association exists between ABO blood group and COVID-19 infection and severity according to data from the Navarre population (Northern Spain).

## 2. Materials and methods

### 2.1. Study design and setting/period studied

A prospective population-based cohort study was performed in Navarre, a Spanish region of around 660,000 inhabitants and an annual birth cohort of 5500 newborns, representing 1.4 % of the Spanish population. The public Navarre Health Service provides health care to 97 % of the population of the region.

Before March 2020, most of the information regarding the contact of the Navarre population with the public health system (including also health care provided at a publicly financed private center in Navarre) were integrated in the BARDENA database (Results Analysis Base of Navarra).

BARDENA is set of multiple, public, population-wide electronic databases for the Navarre Region. BARDENA provides exhaustive longitudinal information including sociodemographic and administrative data (sex, age, nationality, etc.), clinical (diagnoses, procedures, diagnostic tests, etc.), pharmaceutical (drug prescription and dispensing) and healthcare utilization data from hospital care, emergency departments, specialized care (including mental and obstetrics care), primary care and from other public health services. It also includes a set of associated population databases and registries of significant care areas such as cancer, rare diseases, vaccines, microbiology (including all tested positive for SARS-CoV-2 by PCR), blood transfusions and others, and also public health databases from the population screening programs. All the information in the BARDENA databases can be linked at the individual-level through a single pseudonymized personal identification code. The databases were initiated at different moments in time, but all in all BARDENA provides comprehensive individual-level data fed by all the databases from 2012 to date. The information from the different registers is incorporated into BARDENA prospectively on a weekly basis, and every two hours for data related to COVID-19. This database is subjected to quality control procedures before and after data integration, providing a high quality and complete patient-level information.

When the pandemic started, the integration of other sources such as the database maintained by the Blood and Tissue Bank of Navarra (BSTN) was in progress, which includes information regarding donations, blood transfusions and, linked to them, the ABO blood group determination. For this study, data regarding ABO blood group available in the BSTN databank were punctually incorporated in the study database just before the study initiation. Blood Bank of Navarra is the oldest one in Spain (more than 70 years). Navarra classically has one of the highest blood donation rates, apheresis donation rate and fidelity donation. Integral informatic donation-transfusion database exists since before 1990.

Starting in May 2020, we defined a cohort of the Navarre population of both genders and adults ($\geq$ 18 years) with available blood group information (88,990) and with no recorded history of SARS-CoV-2 infection (87,090). The follow-up period ended in May 2021.

The Ethical Committee for Clinical Research of Navarra approved the study protocol (approval code: PI_2021/136; date: 11/19/2021).

### 2.2. Data collection

The following baseline characteristics were taken into account: preventive measures (flu vaccination in 2019); the presence of major chronic conditions or risk factors such as immunodeficiency, coronary artery disease, high blood pressure, diabetes, chronic kidney disease, history of stroke, hyperlipidemia or obesity (BMI $>$ 30 kg/m$^2$); and, gender, age, country of origin (Spain vs other), living in nursing homes, number of cohabitants and degree of dependency as possible socioeconomic and demographics confounding factors.

Two principal endpoints were considered along the follow-up: risk of SARS-CoV-2 infection in the whole susceptible study population (considered when a PCR positive test was registered); and SARS-CoV-2 prognosis: risk of hospitalization, ICU admission or death in those who had been infected.

### 2.3. Statistical analysis

Baseline characteristics, such as demographics, prior health care preventive measures and preexisting risk factors and health conditions, were assessed relative to the SARS-CoV-2 specific risks (infection, hospitalization, ICU admission and death) and presented by ABO blood type.

The population whose blood group was known (blood donors, pregnant women and people who have undergone surgery) may differ from the general population. In order to get insight into its representativeness, the baseline characteristics and relationship with the SARS-CoV-2 infection were contrasted with those of the rest of Navarre population and expressed as standardized differences.

For each study outcome, analyses were carried out for each blood group using O as reference, and results were also successively dichotomized into O, A or B blood group versus all others (reference group). Unadjusted probabilities (percentages and 95 %CIs) of SARS-CoV-2 infection, severity of illness and death were estimated in relation to ABO blood groups. In the bivariate description, the variables measured on an interval scale were contrasted, according to its nature, among ABO groups using Student's t-test, ANOVA or according to the appropriate non-parametric approach, Mann-Whitney U rank test or Kruskall-Wallis test. For categorical or ordinal variables, Chi-square tests were applied. Multivariate logistic regression analyses were used to elucidate the relative effect of the ABO group adjusted by the following variables: flu vaccination status in 2019, immunodeficiency, coronary artery disease, high blood pressure, diabetes, chronic kidney disease, history of stroke, hyperlipidemia, obesity, gender, age, country of origin, living in nursing homes, number of cohabitants and degree of dependency. Results were expressed as adjusted Odds Ratios (OR) with 95 %CI. The hypothesis tests were established with an alpha risk of 0.05 in tests of two tails.

All analyses were performed using R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria; http://www.R-project.org/). For the whole process, different packages of the R statistical program were used (tidyverse, lubridate, Publish, tab, stringr, gmodels, kableExtra,

psych, finalfit, descr, Rmisc, xlsx, tableone and readxl).

## 3. Results

Among 533,890 adult people who made up the Navarre population integrated into BARDENA in May 2020 (99 % of total population), the 87,090 (16.3 %) people who had not been previously infected with SARS-CoV-2 and had an ABO blood group test before that date constituted the study population. The Table S1 shows the comparison between the Navarre population with known and unknown ABO group.

Table 1 shows the ABO distribution in the study population and the baseline variables among the subpopulations defined by each blood group. The predominant blood groups were A and 0. Some variables with a known relationship to the infection or prognosis differed slightly between them. People from groups B and AB were younger, were females and immigrants in a greater proportion, and had a higher prevalence of obesity or diabetes. On the other hand, people from the A group presented more heart or kidney chronic diseases.

In Table 2, the number of infected people (diagnosed by PCR) for the different ABO blood groups and its odds ratio with different aggregation and reference categories (0, non-0, non-A, non-B) is shown. Dichotomized contrasts show a 4% reduction in the risk of infection in 0 group (5% if adjusted by baseline covariables), and an increase of 5% in A group (8% adjusted), and no differences in the risk of population with B blood group.

The poor prognosis of infected people, defined in terms of hospitalization or death, is shown in Table 3 and the risk of ICU admission in Table S2. No significant effect was found in any of the analyses.

## 4. Discussion

The findings of this study suggest a lower risk of SARS-CoV-2 infection in O blood group compared to non-O, with an absolute risk reduction of around 6%. The A blood group would constitute a risk factor, with an increased infection risk of 9%. When analyzing the risk of hospitalization, ICU admission or death among infected subjects, no significant association was found.

Some reviews have previously assessed the risk of SARS-CoV-2 infection and mortality. In general, they coincide in showing an increased risk of infection in A group (versus non-A) and a decreased risk in O group (versus non-O) [2,3,5,6,15].

Mechanisms underlying the relationship between some blood groups and risk of SARS-CoV-2 infection are still unclear, but numerous hypotheses have been raised. The lower susceptibility of people with O blood group to get infected by SARS-CoV or by SARS-CoV-2 has been reported by Cheng et al. in 2005 [16] and Barnkob in 2020 [17], respectively. Another study suggested that the adhesion of S protein and ACE2 could be inhibited by anti-A natural antibody for SARS-CoV [18]. ACE2 has been also suggested to be the receptor for SARS-CoV-2, so the anti-A and anti-B natural antibodies produced in individuals with blood group O could potentially block viral adhesion to cells. Additionally, the expression of the non-prenylated version of OAS1 gene, a component of the antiviral interferon (IFN) system, is associated with a higher risk of developing a severe Covid-19 disease [19].

Regarding disease severity and mortality, we found no association with ABO blood groups. Bhattacharjee et al. [20] failed to find a relationship between people with and without anti-A antibodies and SARS-CoV-2 severe outcomes or death. Fernandez-Botran et al. [21] and Pourali et al. [15] found no association of any of the ABO group with disease severity and mortality, respectively. Liu et al. [3] showed an increased risk of death in A group compared to non A, while Wu et al. [6] found a lower risk in group B. This latter group is more often of Asian origin, and is very rare in Europe and America. It represents 6.6 % of our study population and 449 infected people. With this small sample size, it is possible that the study does not have enough statistical power, but the point estimate suggests a reduction in the adjusted risk of death (B group

**Table 1**
Baseline characteristics of the cohort by ABO blood group.

| Variable | levels | O | A | AB | B | p value |
|---|---|---|---|---|---|---|
| N (%) | | 41905 (48.1) | 37209 (42.7) | 2234 (2.6) | 5742 (6.6) | |
| Age, mean (SD) | | 58.9 (18.8) | 59.4 (18.7) | 58.5 (18.4) | 58.1 (18.5) | <0.001 |
| Age group | 0−19 years | 207 (0.5) | 172 (0.5) | 12 (0.5) | 32 (0.6) | <0.001 |
| | 20−39 years | 6778 (16.2) | 5696 (15.3) | 361 (16.2) | 953 (16.6) | |
| | 40−59 years | 14390 (34.3) | 12739 (34.2) | 800 (35.8) | 2060 (35.9) | |
| | 60−79 years | 13702 (32.7) | 12426 (33.4) | 718 (32.1) | 1869 (32.5) | |
| | ≥80 years | 6828 (16.3) | 6176 (16.6) | 343 (15.4) | 828 (14.4) | |
| Gender, n (%) | Male | 21415 (51.1) | 19218 (51.6) | 1102 (49.3) | 2844 (49.5) | 0.005 |
| | Female | 20490 (48.9) | 17991 (48.4) | 1132 (50.7) | 2898 (50.5) | |
| Nursing home, n (%) | No | 40808 (97.4) | 36282 (97.5) | 2188 (97.9) | 5598 (97.5) | 0.322 |
| | Yes | 1097 (2.6) | 927 (2.5) | 46 (2.1) | 144 (2.5) | |
| Immigrant, n (%) | No | 38802 (92.6) | 35411 (95.2) | 2017 (90.3) | 5029 (87.6) | <0.001 |
| | Yes | 3103 (7.4) | 1798 (4.8) | 217 (9.7) | 713 (12.4) | |
| Dependency, n (%) | No | 39401 (94.0) | 34916 (93.8) | 2097 (93.9) | 5433 (94.6) | 0.129 |
| | Yes | 2504 (6.0) | 2293 (6.2) | 137 (6.1) | 309 (5.4) | |
| Convivial unit | Mean (SD) | 3.0 (1.7) | 3.0 (1.6) | 3.0 (1.6) | 3.1 (1.7) | <0.001 |
| Dementia, n (%) | No | 40775 (97.3) | 36170 (97.2) | 2167 (97.0) | 5595 (97.4) | 0.586 |
| | Yes | 1130 (2.7) | 1039 (2.8) | 67 (3.0) | 147 (2.6) | |
| Diabetes, n (%) | No | 36523 (87.2) | 32037 (86.1) | 1920 (85.9) | 4931 (85.9) | <0.001 |
| | Yes | 5382 (12.8) | 5172 (13.9) | 314 (14.1) | 811 (14.1) | |
| Autoimmune Disease, n (%) | No | 39318 (93.8) | 34844 (93.6) | 2094 (93.7) | 5388 (93.8) | 0.753 |
| | Yes | 2587 (6.2) | 2365 (6.4) | 140 (6.3) | 354 (6.2) | |
| CHD, n (%) | No | 34862 (83.2) | 30520 (82.0) | 1874 (83.9) | 4809 (83.8) | <0.001 |
| | Yes | 7043 (16.8) | 6689 (18.0) | 360 (16.1) | 933 (16.2) | |
| CKD, n (%) | No | 37996 (90.7) | 33582 (90.3) | 2033 (91.0) | 5200 (90.6) | 0.190 |
| | Yes | 3909 (9.3) | 3627 (9.7) | 201 (9.0) | 542 (9.4) | |
| COPD, n (%) | No | 40150 (95.8) | 35476 (95.3) | 2124 (95.1) | 5486 (95.5) | 0.009 |
| | Yes | 1755 (4.2) | 1733 (4.7) | 110 (4.9) | 256 (4.5) | |
| Hyperlipemia, n (%) | No | 25375 (60.6) | 21211 (57.0) | 1336 (59.8) | 3426 (59.7) | <0.001 |
| | Yes | 16530 (39.4) | 15998 (43.0) | 898 (40.2) | 2316 (40.3) | |
| HTA, n (%) | No | 28118 (67.1) | 24875 (66.9) | 1511 (67.6) | 3887 (67.7) | 0.546 |
| | Yes | 13787 (32.9) | 12334 (33.1) | 723 (32.4) | 1855 (32.3) | |
| Stroke, n (%) | No | 39698 (94.7) | 35146 (94.5) | 2116 (94.7) | 5461 (95.1) | 0.127 |
| | Yes | 2207 (5.3) | 2063 (5.5) | 118 (5.3) | 281 (4.9) | |
| Obesity, n (%) | No | 33081 (78.9) | 29233 (78.6) | 1734 (77.6) | 4442 (77.4) | 0.024 |
| | Yes | 8824 (21.1) | 7976 (21.4) | 500 (22.4) | 1300 (22.6) | |
| Flu vaccination in 2019, n (%) | No | 26197 (62.5) | 22913 (61.6) | 1402 (62.8) | 3653 (63.6) | 0.004 |
| | Yes | 15708 (37.5) | 14296 (38.4) | 832 (37.2) | 2089 (36.4) | |

CHD: Coronary heart disease. CKD: Chronic kidney disease; COPD: Chronic obstrucive pulmonary disease; HTA: Hypertension.

**Table 2**
Association between ABO blood groups and risk of COVID-19 infection.

| ABO group | N/n | OR [95 %CI] | p value | adjusted OR [95 %CI] | p value |
|---|---|---|---|---|---|
| O | 41905/3186 | Ref | | Ref | |
| A | 37209/2981 | 1.06 [1.00−1.11] | 0.032 | 1.08[1.03−1.14] | 0.003 |
| AB | 2234/166 | 0.98 [0.83−1.15] | 0.765 | 0.96[0.82−1.13] | 0.654 |
| B | 5742/438 | 1.00 [0.90−1.11] | 0.946 | 0.97[0.87−1.07] | 0.515 |
| O | 41905/3186 | Ref | | Ref | |
| A | 37209/2981 | 1.06 [1.00−1.11] | 0.032 | 1.08[1.03−1.14] | 0.003 |
| AB + B | 7976/604 | 1.00 [0.91−1.09] | 0.926 | 0.97[0.88−1.06] | 0.446 |
| Non_O | 45185/3585 | Ref | | Ref | |
| O | 41905/3186 | 0.95 [0.91−1.00] | 0.068 | 0.94[0.90−0.99] | 0.019 |
| Non_A | 49881/3790 | Ref | | Ref | |
| A | 37209/2981 | 1.06 [1.01−1.11] | 0.024 | 1.09[1.04−1.15] | 0.001 |
| Non_B | 81348/6333 | Ref | | Ref | |
| B | 5742/438 | 0.98 [0.88−1.08] | 0.667 | 0.93[0.84−1.03] | 0.176 |

0.77, AB + B groups 0.68).

It is worth mentioning that, in Navarre, Covid-19 vaccination started in the elderly two months before the end of our study. At the end of the study, about 99 % of the population older than 70 had the complete vaccination schedule, so vaccination coverage almost reached 100 % in our setting (reducing the possibility of different coverages among the different ABO groups). Besides, the highest protection against Covid-19 complications is reached some weeks after the administration of the complete schedule (depending on the vaccine), and the rate of vaccination is assumed to be homogeneous according to ABO blood group, so we do not expect that vaccination have had a great impact on our results.

Our study has several strengths to highlight, providing information of interest to the question under study. Given its population nature, we have complete data on almost the entire population of Navarre. The database from which both the results and the possible baseline confounding variables are extracted is obtained from a solid electronic registry derived from the healthcare activity, which has shown good accuracy in previous validation analysis for some comorbidity, such as diabetes [22]. In addition, it incorporates analyses adjusted for confounding factors that may be important sources of bias, such as country of origin, which have not been taken into account in other studies.

Our study presents some limitations. First, we excluded SARS−COV-2 subjects that were detected during the first wave of the pandemic (from February to April 2020) because in that period diagnosis tests were carried out only to suspected subjects with severe symptoms or healthcare workers. Assuming that past infection provides immunity to new infection, our study could have underestimated the risk of infection from May 2020 (overestimated population susceptibility) as it includes mild or asymptomatic individuals infected in this first wave and not detected in the surveillance system. However, it can be assumed that this underestimation has a uniform distribution between ABO groups. Second, in our study it has been assumed that all people without a positive test for COVID-19 were not infected, including those who did not undergone diagnostic testing. Among them, there may have been some asymptomatic infected people who were not tested, but it should be noted that Navarre had a powerful SARS−COV-2 surveillance and contact tracing system in place during the study period, which could have greatly reduced this limitation. On the other hand, due to the various circumstances, that link the study population to the blood registry (blood donors, pregnancy, elective surgery, and blood transfusions); the cohort is not completely representative of the Navarre population as a whole, as reflected in supplementary table S1. However, given the proportion of the population included and the heterogeneity of the subjects from which the data are obtained, no marked bias towards the selection of vulnerable subjects is expected.

**Table 3**
Association between ABO blood groups and risk of hospitalization or death in COVID-19 infected population.

| ABO | N/n | OR [95 %CI] | p value | adjusted OR [95 %CI] | p value |
|---|---|---|---|---|---|
| ***Hospitalization*** | | | | | |
| O | 3186/427 | Ref | | Ref | |
| A | 2981/419 | 1.06 [0.91−1.22] | 0.456 | 1.01 [0.86−1.19] | 0.867 |
| AB | 166/19 | 0.84 [0.51−1.36] | 0.47 | 0.98 [0.57−1.68] | 0.934 |
| B | 438/65 | 1.13 [0.85−1.49] | 0.41 | 1.02 [0.75−1.39] | 0.897 |
| O | 3186/427 | Ref | | Ref | |
| A | 2981/419 | 1.06 [0.91−1.22] | 0.456 | 1.01 [0.86−1.19] | 0.867 |
| AB + B | 604/84 | 1.04 [0.81−1.34] | 0.739 | 1.01 [0.77−1.33] | 0.941 |
| Non_O | 3585/503 | Ref | | Ref | |
| O | 3186/427 | 0.95 [0.83−1.09] | 0.454 | 0.99 [0.85−1.15] | 0.866 |
| Non_A | 3790/511 | Ref | | Ref | |
| A | 2981/419 | 1.05 [0.91−1.21] | 0.497 | 1.01 [0.87−1.18] | 0.878 |
| Non_B | 6333/865 | Ref | | Ref | |
| B | 438/65 | 1.10 [0.84−1.45] | 0.487 | 1.01 [0.75−1.37] | 0.925 |
| ***Death*** | | | | | |
| O | 3186/183 | Ref | | Ref | |
| A | 2981/179 | 1.05 [0.85−1.30] | 0.628 | 0.93 [0.73−1.19] | 0.583 |
| AB | 166/4 | 0.41 [0.15−1.11] | 0.080 | 0.40 [0.13−1.22] | 0.107 |
| B | 438/24 | 0.94 [0.61−1.46] | 0.797 | 0.77 [0.47−1.26] | 0.300 |
| O | 3186/183 | Ref | | Ref | |
| A | 2981/179 | 1.05 [0.85−1.30] | 0.628 | 0.93 [0.73−1.19] | 0.581 |
| AB + B | 604/28 | 0.79 [0.53−1.19] | 0.269 | 0.68 [0.43−1.08] | 0.106 |
| Non_O | 3585/207 | Ref | | Ref | |
| O | 3186/183 | 0.99 [0.81−1.22] | 0.928 | 1.12 [0.89−1.42] | 0.333 |
| Non_A | 3790/211 | Ref | | Ref | |
| A | 2981/179 | 1.09 [0.89−1.34] | 0.410 | 0.99 [0.78−1.25] | 0.928 |
| Non_B | 6333/366 | Ref | | Ref | |
| B | 438/24 | 0.94 [0.61−1.43] | 0.759 | 0.81 [0.50−1.30] | 0.383 |

## 5. Conclusions

In this population-based study, regarding the risk of SARS-CoV-2

infection, we observed a protective role of group O and a greater risk in group A. No association was observed between blood groups and infection-related complications such as hospitalization, ICU admission, or death.

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## Author contributions

Conceptualization, JGE, JGM, JL; methodology, JL,ME; software, ME, JL, LL, MG; validation, ME, JL, LL, MG; formal analysis, ME, JL; investigation, JGE, JL, LL, MG, ME, CJ; resources, JGE, JGM, JL, IT; data curation, ME, IT; writing—original draft preparation ME, JL, LL, MG; writing—review and editing, JGE, JGM, IT, CJ.; visualization, ME, LL, JL, MG; supervision, JGE, JGM, JL All authors have read and agreed to the published version of the manuscript.

## Institutional review board statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Ethical Committee for Clinical Research of Navarra (Ref: PI_2021/136; date: 11/19/2021).

## Informed consent statement

Participant consent was waived because this is a population-base study with a retrospective nature within the Real-World Data framework, and data were irreversibly anonymized prior to transfer to the research team.

## Declaration of Competing Interest

The authors declare no conflict of interest for this study.

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.transci.2022.103357.

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