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SHORT REPORT

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COVID-19 infection and complications according to ABO blood group in the elderly: A population-based subcohort and meta-analysis

Leire Leache[1,2] | Marta Gutiérrez-Valencia[1,2] | Mónica Enguita-Germán[2,3,4,5,6] | Julián Librero[2,3,4,5,6] | Javier Gorricho[7] | Carlos Jericó[8] | Jose Antonio García-Erce[9,10,11]

[1]Unit of Innovation and Organization, Navarre Health Service, Pamplona, Spain

[2]Navarra Institute for Health Research (IdiSNA), Pamplona, Spain

[3]Unit of Methodology, Navarrabiomed, Pamplona, Spain

[4]University Hospital of Navarra (HUN), Pamplona, Spain

[5]Public University of Navarre (UPNA), Pamplona, Spain

[6]Red de Investigación en Cronicidad, Atención Primaria y Promoción de la Salud (RICAPPS), Madrid, Spain

[7]Service of Evaluation and Dissemination of Results, Navarre Health Service, Pamplona, Spain

[8]Department of Internal Medicine, Hospital Sant Joan Despí-Moisès Broggi, Consorci Sanitari Integral, Barcelona, Spain

[9]Blood and Tissue Bank of Navarre, Navarre Health Service, Pamplona, Spain

[10]Grupo Español de Rehabilitación Multimodal (GERM), Aragon Health Sciences Institute (IACS), Zaragoza, Spain

[11]PBM Group, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, Spain

Correspondence
Jose Antonio García-Erce, Blood and Tissue Bank of Navarre, Calle Irunlarrea 3. 31003, Pamplona, Spain.
Email: jgarcier@navarra.es

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Abstract

Background and Objectives: It is reported that ABO antibodies have a role in COVID-19 infection and severity; however, ABO antibody titres vary with advanced age. The aim was to analyse the association between ABO blood group and risk of COVID-19 infection and complications in elderly patients, and to contrast this data with findings in the overall adult population.

Materials and Methods: A prospective cohort study of the Navarre (Spain) population aged ≥60 years and a meta-analysis of published studies including participants of ≥60 years were carried out.

Results: In the Navarre elderly population, a higher risk of COVID-19 infection was identified in the A versus non-A and O group and lower risk in O versus non-O, with no significant association between hospitalization, intensive care unit admission or mortality and any of the blood groups, results that coincide with those of the overall Navarre adult population. The meta-analyses using studies that included participants of ≥60 years demonstrated a higher risk of hospitalization and mortality in A versus non-A and a lower mortality risk with B versus non-B. Similar mortality results were found in the meta-analyses of the overall adult population.

Marta Gutiérrez-Valencia and Leire Leache contributed equally to this work.

Conclusion: There are no relevant differences between the overall adult population and population aged ≥60 years in the risk of COVID-19 infection and severity according to ABO blood groups, suggesting that age-related changes in ABO would be of limited clinical significance.

KEYWORDS
ABO, blood groups, cohort, COVID-19, meta-analysis

Highlights

- A higher risk of COVID-19 infection was identified in the Navarre, Spain, elderly population with blood group A and lower risk with blood group O.
- There were no significant differences between blood groups in hospitalization, intensive care unit admission or mortality in the Navarre elderly population.
- No relevant differences were found between adults of any age and the elderly population in the risk of COVID-19 infection or severity according to the ABO blood group, suggesting that age-related changes in ABO would be of limited clinical significance.

INTRODUCTION

The COVID-19 infection presents with a considerable spectrum of severity, and host factors may have an impact [1]. As for genetic factors, it has been proposed that anti-A and B antibodies serve as viral neutralizing antibodies for SARS-CoV-2, which could explain in part the differences in risk of infection and complications between ABO groups [2]. However, antibody titres may vary with increasing age, and the clinical significance of these changes is unknown [3–5].

Therefore, the aim was to determine the association between the ABO blood group and the risk of COVID-19 infection and complications (hospitalization, admission to intensive care unit [ICU] and mortality) in elderly patients and to analyse whether these findings differ from those observed in the adult population of any age.

MATERIALS AND METHODS

Two approaches have been used to address the objectives: (1) a cohort study in Navarre (Spain) population aged ≥60 years and (2) a meta-analysis of studies including participants of this age range. This strategy allowed us to contrast the results generated locally with the

TABLE 1 Baseline sociodemographic and clinical characteristics of the cohort of Navarre population of ≥60 years by ABO blood group[a]

Variable	O	A	AB	B	Total	*p* value
N (%)	20,530 (47.9)	18,602 (43.4)	1061 (2.5)	2697 (6.3)	42,890	—
Age, mean (SD)	75.1 (9.6)	75.1 (9.5)	74.7 (9.5)	74.6 (9.3)	75.1 (9.6)	**0.045**
Males, *n* (%)	10,994 (53.6)	9973 (53.6)	554 (52.2)	1418 (52.6)	22,939 (53.5)	0.628
Inmigrants, *n* (%)	519 (2.5)	379 (2.0)	41 (3.9)	128 (4.7)	1067 (2.5)	**<0.001**
Nursing home, *n* (%)	991 (4.8)	845 (4.5)	37 (3.5)	127 (4.7)	2000 (4.7)	0.160
Dependency, *n* (%)	2331 (11.4)	2138 (11.5)	123 (11.6)	290 (10.8)	4882 (11.4)	0.717
Cohabitants, mean (SD)	2.7 (1.7)	2.7 (1.7)	2.6 (1.6)	2.7 (1.7)	2.7 (1.7)	0.446
Dementia, *n* (%)	1116 (5.4)	1026 (5.5)	64 (6.0)	144 (5.3)	2350 (5.5)	0.838
Diabetes, *n* (%)	4677 (22.8)	4467 (24.0)	263 (24.8)	670 (24.8)	10,077 (23.5)	**0.006**
Autoimmune disease, *n* (%)	1521 (7.4)	1371 (7.4)	80 (7.5)	196 (7.3)	3168 (7.4)	0.990
CHD, *n* (%)	6203 (30.2)	5824 (31.3)	304 (28.7)	795 (29.5)	13,126 (30.6)	**0.025**
CKD, *n* (%)	3567 (17.4)	3310 (17.8)	182 (17.2)	477 (17.7)	7536 (17.6)	0.720
COPD, *n* (%)	1583 (7.7)	1539 (8.3)	95 (9.0)	227 (8.4)	3444 (8.0)	0.107
Hyperlipidaemia, *n* (%)	11,837 (57.7)	11,494 (61.8)	625 (58.9)	1607 (59.6)	25,563 (59.6)	**<0.001**
Hypertension, *n* (%)	11,866 (57.8)	10,646 (57.2)	605 (57.0)	1541 (57.1)	24,658 (57.5)	0.672
Stroke, *n* (%)	1985 (9.7)	1856 (10.0)	102 (9.6)	253 (9.4)	4196 (9.8)	0.653
Obesity, *n* (%)	6133 (29.9)	5548 (29.8)	338 (31.9)	849 (31.5)	12,868 (30.0)	0.173
Vaccinated against flu in 2019, *n* (%)	13,490 (65.7)	12,325 (66.3)	696 (65.6)	1759 (65.2)	28,270 (65.9)	0.577

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; *N*, number of subjects; SD, standard deviation.

[a]Statistically significant differences are indicated in bold type.

findings from previous evidence generated both at the national and international levels.

Population-based cohort study in Navarre (Spain)

A prospective cohort of the Navarre population ≥18 years with no previous SARS-CoV-2 infection and with known blood group was established in May 2020, and followed up until May 2021, the findings of which have been published elsewhere [6]. For this study, the subcohort of people ≥60 years was selected.

Data for the study were obtained from the BARDENA (Results Analysis Database of Navarre) database, which includes 97% of the Navarre population, and from the Blood and Tissue Bank of Navarre.

The risk of SARS-CoV-2 infection (established by a polymerase chain reaction [PCR]-positive test) was analysed in the whole study population, and the risk of complications in those who were infected. Parametric or non-parametric methods were used to compare continuous variables among blood groups and the chi-square test for categorical variables. Results adjusted by baseline characteristics were estimated using multivariate logistic regression models.

The study protocol was approved by the Ethical Committee for Clinical Research of Navarra (PI_2021/136), which waived the requirement for participant consent.

Systematic review and meta-analysis

On the basis of a previously published systematic review that analysed the risk of COVID-19 infection and severity in adults ≥18 years according to ABO blood groups [7], we selected the individual studies whose population had a mean/median age of ≥60 years or if ≥50% of the population was ≥60 years old.

The meta-analyses of each of the analysed outcome variables (COVID-19 infection, hospitalization, admission to ICU and mortality) were performed based on the identified studies that provided data for the corresponding variable and blood group comparison. The Mantel–Haenszel method and a random-effects model were used. Heterogeneity was analysed using I^2 statistic test, and in cases of substantial heterogeneity ($I^2 > 65\%$), sensitivity analyses were carried out restricting to low risk of bias studies. The risk of bias was analysed using the Newcastle-Ottawa Scale [8].

RESULTS

Results of the population-based cohort study of the Navarre population aged ≥60 years

The cohort included 42,890 people ≥60 years, with a mean age of 75 years. Table 1 shows the baseline characteristics. Results for the association between ABO blood groups and COVID-19 infection and severity are presented in Table 2. A significantly higher risk of

TABLE 2 Association between ABO blood group and risk of COVID-19 infection and severity in the Navarre population of ≥60 years[a]

	COVID-19 infection		Hospitalization		Admission to ICU		Mortality	
	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)	OR (95% CI)	aOR (95% CI)
A versus O	**1.11 (1.02–1.20)**	**1.12 (1.03–1.21)**	1.04 (0.87–1.23)	1.04 (0.86–1.24)	0.97 (0.59–1.60)	0.98 (0.59–1.64)	0.98 (0.78–1.23)	0.93 (0.73–1.20)
B versus O	1.09 (0.93–1.28)	1.07 (0.91–1.26)	1.18 (0.84–1.65)	1.14 (0.80–1.62)	1.56 (0.68–3.59)	1.71 (0.73–4.00)	0.95 (0.60–1.51)	0.80 (0.48–1.31)
AB versus O	**0.69 (0.51–0.93)**	**0.70 (0.52–0.94)**	0.67 (0.32–1.39)	0.58 (0.27–1.25)	1.74 (0.41–7.51)	2.00 (0.45–8.87)	0.59 (0.21–1.66)	0.43 (0.14–1.31)
O versus non-O	**0.92 (0.85–0.99)**	**0.92 (0.85–0.99)**	0.96 (0.81–1.14)	0.97 (0.81–1.16)	0.94 (0.59–1.50)	0.91 (0.56–1.47)	1.03 (0.83–1.29)	1.12 (0.88–1.42)
A versus non-A	**1.11 (1.03–1.20)**	**1.12 (1.04–1.21)**	1.03 (0.87–1.21)	1.03 (0.87–1.23)	0.89 (0.56–1.43)	0.89 (0.55–1.44)	1.00 (0.81–1.25)	0.98 (0.77–1.25)
B versus non-B	1.04 (0.89–1.22)	1.03 (0.88–1.20)	1.16 (0.84–1.62)	1.13 (0.80–1.59)	1.56 (0.71–3.46)	1.70 (0.76–3.81)	0.97 (0.62–1.51)	0.84 (0.51–1.36)

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval; ICU, intensive care unit; OR, odds ratio.
[a]Statistically significant differences are indicated in bold type.

TABLE 3 Results of the meta-analysis of studies, including population of ≥60 years[a]

	COVID-19 infection		Hospitalization		Admission to ICU		Mortality	
	Studies (*N*)	OR (95% CI); I^2	Studies (*N*)	OR (95% CI); I^2	Studies (*N*)	OR (95% CI); I^2	Studies (*N*)	OR (95% CI); I^2
A versus O	3 (3776)	1.87 (0.81–4.36); 78%	3 (7579)	1.03 (0.76–1.40); 62%	5 (1147)	1.28 (0.98–1.67); 0%	6 (4660)	**1.20 (1.04–1.37)**; 0%
B versus O	3 (3349)	0.98 (0.72–1.33); 0%	3 (4489)	0.94 (0.80–1.10); 0%	5 (686)	1.45 (0.59–3.54); 69%	6 (3764)	0.89 (0.74–1.07); 0%
AB versus O	3 (2391)	1.12 (0.71–1.78); 0%	3 (3916)	**0.75 (0.58–0.97)**; 0%	5 (620)	0.96 (0.50–1.83); 0%	6 (3045)	1.06 (0.77–1.45); 0%
O versus non-O	3 (5528)	0.67 (0.35–1.28); 68%	3 (8560)	1.01 (0.92–1.12); 0%	6 (1634)	0.85 (0.68–1.07); 0%	6 (5865)	0.93 (0.82–1.05); 0%
A versus non-A	3 (5528)	2.00 (0.84–4.77); 84%	3 (8866)	1.13 (0.78–1.61); 75%	5 (1317)	1.19 (0.82–1.71); 37%	7 (5887)	**1.23 (1.08–1.40)**; 0%
B versus non-B	3 (5528)	0.92 (0.71–1.21); 0%	3 (8866)	0.99 (0.85–1.16); 0%	5 (170)	0.98 (0.46–2.11); 0%	6 (5865)	**0.83 (0.70–0.99)**; 0%

Abbreviations: CI, confidence interval; ICU, intensive care unit; *N*, number of participants; OR, odds ratio.
[a]Statistically significant differences are indicated in bold type.

COVID-19 infection was found for the blood group A compared to O (adjusted odds ratio [OR] 1.12, 95% CI 1.03–1.21), also when compared to non-A (adjusted OR 1.12, 95% CI 1.04–1.21) (Table 2). In contrast, people in the blood group AB showed lower infection risk compared to O (adjusted OR 0.70, 95% CI 0.52–0.94) (Table 2). Also, a slightly lower risk was found for the blood group O when compared to non-O (adjusted OR 0.92, 95% CI 0.85–0.99) (Table 2). There were no significant differences between blood groups in hospitalization, admission to ICU or mortality (Table 2).

Results of the systematic review and meta-analysis

Thirteen studies were identified that met the age criteria (Table S1). Table S2 shows the risk of bias assessment of the included studies. The studies included in the meta-analysis of each of the outcome variables are shown in Table S3, and meta-analysis results for COVID-19 infection and severity are presented in Table 3. No significant association was found between any of the blood groups and COVID-19 infection (Table 3). AB group showed a lower hospitalization risk as compared to O (OR 0.75, 95% CI 0.58–0.97, I^2 0%) (Table 3), and sensitivity analyses yielded a higher hospitalization risk with A versus non-A (OR 1.38, 95% CI 1.04–1.83, I^2 0%) (Table S4). No significant differences were identified in the risk of ICU admission between blood groups (Table 3). Blood group A was associated with a significantly higher mortality risk when compared to O (OR 1.20 95% CI 1.04–1.37, I^2 0%) and non-A (OR 1.23, 95% CI 1.08–1.40, I^2 0%), and a lower risk was found for the blood group B when compared to non-B (OR 0.83, 95% CI 0.70–0.99, I^2 0%) (Table 3). In the study by Apea et al., which provided aggregate data that could not be included in the meta-analysis, showed a significantly lower mortality risk in B group as compared to O (adjusted hazard ratio 0.66, 95% CI 0.47–0.92) [9].

DISCUSSION

To date, the association between ABO blood group and susceptibility to COVID-19 infection and severity in people of advanced age has not yet been specifically addressed, and to our knowledge, this cohort study and meta-analysis are the first to provide evidence on this issue.

Regarding the risk of COVID-19 infection, previously published results from the meta-analyses and from the cohort of Navarre adult population of any age [6, 7] coincide in general terms with those obtained in the subcohort of Navarre population ≥60 years, showing a higher risk of COVID-19 infection with A group and lower risk O. By contrast, the meta-analyses of studies in population aged ≥60 years did not find significant differences in risk of infection with any of the blood groups. These discrepancies between the findings from the cohort study and the results from the meta-analyses may be due to the fact that two of the three studies used to meta-analyse this outcome (which sums up at least 84% of the sample) were conducted in Iran, suggesting a possible contribution of other potential social,

racial and demographic confounding factors, and of differences in COVID-19 detection capacity and prevention measures.

As for hospitalization risk, findings from the cohort and the meta-analyses in the overall adult population [6, 7] were almost maintained when limited to people of advanced age, not showing any significant association according to blood groups, except for AB, in which a lower hospitalization risk was identified in the meta-analysis. Also, when restricted to studies with a low risk of bias, the A group showed a higher hospitalization risk when compared to non-A.

No significant differences were identified in the risk of ICU admission between blood groups in the subcohort of people of ≥60 years or in the meta-analyses, results that coincide with those obtained from the overall adult population [6, 7]. Meta-analyses showed a higher mortality risk in people of advanced age with A versus non-A blood groups, and a lower risk with B versus non-B, observations that were already reported in the meta-analyses of adult population of any age [7].

Although an effect of immunosenescence on agglutinin protection cannot be ruled out, our findings, in general, did not suggest differences with respect to the adult population of any age in the risk of COVID-19 infection and severity according to the ABO blood group. This may support the hypothesis that the significance in real clinical practice of the age-related changes in A and B antibody titres and protection would be of questionable magnitude [5] and may also point out that other mechanisms apart from the role of antibodies may be involved on the variability in risk of COVID-19 according to blood group.

Our cohort study can be considered representative of the Navarre population aged ≥60 years, as it included almost the entire population of this age. Also, the validation process to which the BARDENA database is subjected ensures the quality of the information. Moreover, the results were adjusted by several possible confounding factors, which enhances the robustness of the findings. On the other hand, the meta-analyses carried out enables us to contrast the concordance of results of our cohort study with those from other national and international studies. A rigorous methodology was applied, and the review process was carried out independently by two reviewers, which guarantees their validity.

In conclusion, a higher risk of COVID-19 infection was identified in the Navarre elderly population with A versus non-A and O blood group and a lower risk in O versus non-O, findings that were already observed in the overall adult population [6]. Although no significant differences in severity were identified between blood groups in the Navarre elderly population, meta-analyses results demonstrated a higher risk of hospitalization and mortality in A versus non-A, and lower mortality risk with B versus non-B. Similar results for mortality were found in the meta-analyses of the overall adult population [7]. In general terms, we identify no relevant differences in the risk of COVID-19 infection and severity according to the ABO blood group between the overall adult population and population aged ≥60 years. However, future studies should analyse this relevant matter in greater depth.

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L.L was involved in conceptualization of the study. L.L., M.G.-V., M.E.-G. and J.L. were involved in developing the methodology for the study. L.L., M.G.-V., M.E.-G. and J.L. were involved in formal analysis and software. L.L. and M.G.-V. wrote the original draft. L.L., M.G.-V., M.E.-G., J.L., J.G., C.J. and J.A.G.-E were involved in draft review and editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest for this study.

ORCID

Leire Leache https://orcid.org/0000-0003-2272-7086
Marta Gutiérrez-Valencia https://orcid.org/0000-0002-3229-6614
Mónica Enguita-Germán https://orcid.org/0000-0002-2890-1252
Julián Librero https://orcid.org/0000-0002-4859-9054
Javier Gorricho https://orcid.org/0000-0003-3609-9922
Carlos Jericó https://orcid.org/0000-0003-1049-4027
Jose Antonio García-Erce https://orcid.org/0000-0001-7662-6286

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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