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The *FCGR2A* rs1801274 polymorphism was associated with the risk of death among COVID-19 patients

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ABSTRACT

Polymorphisms of Fcγ receptors have been associated with variable responses to infections. We determined the association of functional polymorphisms rs1801274 in the *FCGR2A* and rs396991 in the *FCGR3A* with COVID-19 severity. This study involved 453 patients with severe COVID-19, in which the *FCGR2A* rs1801274 G-allele (131-Arg) was significantly associated with death ($p = 0.02$, OR = 1.47). This effect was independent of age and increased IL6 and D-Dimer levels. This study suggests that the *FCGR2A* gene might be associated with the risk of death among COVID-19 patients. Our study has several limitations, mainly the limited number of patients and the inclusion of a single population. It is thus necessary to confirm this result in larger cohorts from different populations.

1. Introduction

The Fcγ-receptors (FCGR) recognise the constant fraction of immunoglobulin G (IgG) mainly triggering processes like antibody-dependent cellular cytotoxicity (ADCC), phagocytosis or production of reactive oxygen species (ROS) [1]. There are six different receptors which are expressed in several immune cells, with variable affinity to IgG and effectors functions [2]. Several FCGR gene variants have been described with consequences in their functionality that can lead to increased susceptibility to diseases [1,2]. Therefore, FCGR2A would be a candidate to modulate the severity of symptoms after SARS-CoV-2 infection. In a model system for COVID-19 inflammation using fluorescent latex beads coated with recombinant SARS-CoV-2 spike (S) proteins (that mimics the SARS-CoV-2 viral particles), antibodies from plasma of convalescent COVID-19 patients were able to facilitate the phagocytosis of the beads by neutrophils (HL60 cell line) [3]. The internalization of the latex beads – anti-S Immunoglobulin complexes was mediated by FCGR2A, which was highly expressed in human neutrophils and HL60 neutrophil-like cells. In this model, the internalization of the Ig-coated particles was accompanied by an increased expression of proinflammatory molecules, and the addition of several immunomodulatory compounds resulted in a decreased bead uptake of SARS-CoV-2-like particles opsonized with plasma from COVID-19 patients and reduced expression of inflammatory markers.

Two Single-nucleotide polymorphisms (SNPs) located in the EC2 domain of *FCGR2A-CD32a* (rs1801274, c.497G > A, p.Arg131His) and *FCGR3A* (rs396991, c.526 T > G, p.Phe158Val) would be directly implicated in IgG-affinity binding. Compared to the FcγRIIA-Arg, the His isoform has a higher binding affinity for IgG1 and especially IgG2, while the binding to IgG3 and IgG4 is similar for both variants [4]. The capacity of binding to IgG immuno-complexes should thus be higher among individuals with the His/His genotype. These polymorphisms have been associated with the risk of developing autoimmune diseases and variable response to infections [5–7]. They might also be of

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pharmacogenetic importance by affecting the response to therapeutic antibodies [8]. SARS-CoV-2 infection triggers a multisystem inflammatory syndrome in children (MIS-C) resembling Kawasaki disease (KD), a paediatric inflammatory condition that has been linked to viral infections [9]. The *FCGR2A* rs1801274 Arg has been associated with the susceptibility to KD by some authors [10].

Bilateral pneumonia due to an exacerbated inflammatory response is characteristic of severe COVID-19, and many patients require respiratory support in the Intensive Care Unit (ICU). These patients are at increased risk of thromboembolitic events and death [11]. Thrombotic thrombocytopenia has been observed in patients with severe COVID-19 or after vaccination with adenoviral vaccines [12–14]. Thrombotic thrombocytopenia resembles heparin-induced thrombocytopenia (HIT), a condition caused by IgG antibodies against heparin-PF4 complexes. The resulting immune-complexes activate platelets via FCGR2A that leads to thrombocytopenia and thrombotic episodes [14,15]. In agreement with the pivotal role of the FCGR2A in HIT, the rs1801274 (p. Arg131His) has been associated with the risk of developing HIT [16–21]. These studies pointed to an increased risk among carriers of the Arg (reduced IgG2-affinity isoform) variant.

In this work we evaluated the role of *FCGR2A* and *FCGR3A* polymorphisms in the risk of developing severe COVID-19 and their impact on mortality among these patients.

2. Methods

The study was approved by the Ethical Research Committee of Asturias. Informed consent was obtained from each patient's next of kin. All the patients were of European ancestry from the region of Asturias (Norther Spain, total population one million, 25% aged >65 years) and were recruited in the period March-2020 to March-2021, were three pandemic waves occurred in Spain. We studied 453 COVID-19 patients (SARS-CoV-2 confirmed by nasopharyngeal PCR) who required hospitalization due to bilateral pneumonia in the Intensive Care Unit (ICU) of Hospital Universitario Central de Asturias. The DNA was obtained from whole blood leukocytes and all the individuals were genotyped for *FCGR2A* rs1801274 A/G and *FCGR3A* rs396991 G/T SNPs using real time PCR and Taqman probes (supplementary file). The quality of the genotyping method was assessed by Sanger sequencing individuals with the three genotypes (supplementary figures). In addition to the demographic values (age, sex), IL6 (pg/mL), D-Dimer (ng/mL) and Ferritin (ug/L) were measured at ICU admission [26]. Data from the patients were collected and logistic regression was used to compare p-values and Odds ratios with 95% confidence intervals. The statistical analysis was performed with the R-free software (www.r-project.org).

3. Results

In Table 1 we summarised the main values in the COVID-19 patients. The risk of death was associated with advanced age ($p < 10^{-7}$), hypertension ($p = 0.025$), hypercholesterolemia ($p = 0.005$), elevated IL6 ($p = 0.03$), and elevated D-dimer ($p = 0.01$). These results were in agreement with several reports that identified higher IL6 and D-dimer values as significant predictors of mortality [22–24].

The *FCGR2A* rs1801274 G allele (131-Arg) was associated with mortality with a dominant effect (GG + AG vs AA, $p = 0.02$, OR = 2–22, 95% 1.20–4.45). The frequency of deaths was 26%, 22%, and 12% among GG, AG and AA patients, respectively. In the multiple logistic regression the genotype (GG + AG) was associated with death independently of the other variables (Fig. 1). The FCGR2A with the risk Arg allele would bind less efficiently to IgG1 and IgG2, thus reducing the capacity of cleaning viral immuno-complexes among Arg-carriers. This could explain the higher risk for adverse outcome among rs1801274 G (Arg) carriers.

The FCGR3A SNP was not associated with the risk of death in our cohort (Table 1).

Table 1
Main values in the COVID-19 ICU patients.

	Death	Survivors	p-value	OR (95%CI)
	N = 95	N = 358		
Male	68 (72%)	260 (73%)	0.84	0.95 (0.58–1.59)
Diabetes	24 (25%)	76 (21%)	0.40	1.25 (0.73–2.10)
Hypercholesterol	57 (60%)	157 (44%)	0.005	1.92 (1.2–3.06)
Hypertension	50 (68%)	143 (53%)	0.02	1.88 (1.10–3.27)
Age mean	70.39 ± 10.81	62.67 ± 11.50	7×10^{-9}	1.08 (1.06–1.11)
Age IQ range	56–71	66–78		
IL6 pg/mL* median	94	67	0.83	1.00 (0.99–1.01)
IL6 IQ range	40–157	21–145		
≤15 pg/mL	6 (6%)	50 (15%)		
15-70 pg/mL	29 (31%)	112 (34%)		
>70 pg/mL	58 (62%)	163 (51%)	0.04	1.65 (1.03–2.64)
D-Dimer ng/mL** median	1486	1001	0.109	1.01 (0.99–1.00)
D-Dimer IQ range	909–2502	590–1656		
<230 ng/mL	0	8 (2%)		
230-500 ng/mL	11 (12%)	45 (16%)		
501-2000 ng/mL	48 (52%)	166 (59%)		
>2000 ng/mL	33 (36%)	64 (23%)	0.01	1.91 (1.55–3.18)
FERRITIN ug/L*** median	1275	1151		
Ferritin IQR	751–1595	804–1590	0.64	1.12 (0.68–1.34)
rs1801274 A/G				
GG	30 (31%)	87 (24%)		
GA	53 (56%)	184 (52%)		
AA	12 (13%)	87 (24%)		
G-Arg-frequency	0.59	0.50	0.02	1.47 (1.01–2.03)
AG + GG vs AA			0.01	2.22 (1.16–4.26)
rs396991 T/G				
TT	45 (47%)	180 (50%)		
TG	42 (44%)	140 (39%)		
GG	8 (9%)	38 (11%)		
T-frequency	0.70	0.70	0.78	1.06 (0.71–1.59)

* IL6 was measured at ICU admission in 94 deceased and 325 survivors.
** D-Dimer was measured at ICU admission in 92 deceased and 283 survivors.
*** Ferritin was measured at ICU admission in 63 deceased and 206 survivors.

The *FCGR2A* rs1801274 SNP is well represented in populations worldwide, with allele frequencies in the range 47%–72% (supplementary figures). The reported frequency among Europeans was G = 0.48, with G = 0.53 for Spanish. This value was almost identical to the observed in our ICU patients (G = 0.52), suggesting that the *FCGR2A* variant was not associated with an increased risk for hospitalization in the ICU at a population scale.

Our patients were recruited during the three first pandemic waves, with peaks of COVID-19 cases in April and november-2020 and February 2021 (suppl. Figure). While the two first waves were characterised by the presence of the original SARS-CoV-2 the third wave was dominated by the alpha variant. We sought to investigate whether these pandemic peaks were characterised by different mortality rates and frequency of the *FCGR2A* variant. The two first waves had significantly higher mean age ($p = 0.01$) and mortality ($p = 0.01$), and non-significantly higher frequency of the G-risk allele (Table 2). The G-frequency was higher among the deceased in the two groups, although the number of patients was too low to reach statistically significant differences.

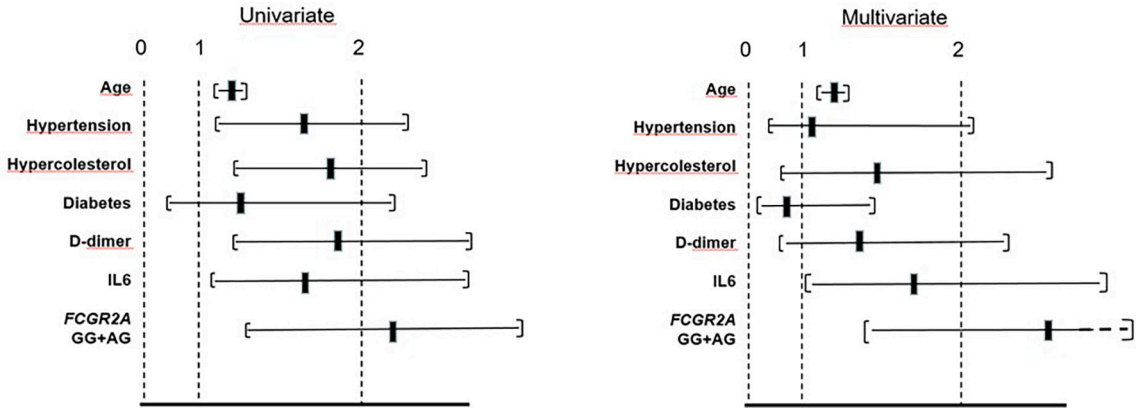

Fig. 1. Odss ratios (ORs) and 95% confidence intervals (CI) for the death vs survivors. The raw data are presented in a supplementary table.
The next variables were correlated with age:
D-Dimer>2000 ng/mL, $p = 0.007$.
Hypercholesterolemia, $p = 1 \times 10^{-5}$.
Diabetes, $p = 5 \times 10^{-4}$.
Hypertension, $p = 4 \times 10^{-9}$.

Table 2
Main values according to the three pandemic waves. The two first waves were characterised by the original SARS-CoV-2 variant and patients were thus grouped, while the third wave was dominated by the alpha variant.

	First/second wave	Third wave	P value
	N = 280	N = 173	
Mean age	65 ± 12	62 ± 12	0.01
Male	199 (71%)	129 (75%)	0.41
Death	69 (25%)	26 (15%)	0.01
FCGR2A			
GG	76 (27%)	41 (24%)	
AG	146 (52%)	91 (52%)	
AA	58 (21%)	41 (24%)	
G	0.53	0.50	0.34
G-deaths	0.59	0.62	
G-survivors	0.51	0.47	
FCGR3A			
TT	142 (51%)	83 (48%)	
TG	108 (39%)	74 (43%)	
GG	30 (10%)	16 (9%)	
T	0.70	0.69	0.84
T-deaths	0.67	0.68	
T-survivors	0.71	0.75	

4. Discussion

In addition to advanced age, Interleukin-6 and D-Dimer values were significantly associated with death among COVID-19 patients. Il-6 has been associated with adverse outcomes in COVID-19 [22–24]. High levels of circulating IL-6 indicate an exacerbated inflammatory state, and promotes the coagulation cascade and thromboembolic events. We measured IL6 plasma levels al hospital admission in 419 patients. According to some authors the normal value of IL6 among apparently healthy adults was <15 pg/mL. Among the non-survivors, who had non-significantly higher mean values of IL6, there was a significantly higher frequency of individuals with plasma values above the normal range (IL6 > 15 pg/mL; p = 0.05) (Table 1). Previous studies showed that a IL6 > 70 was the cut-off predictive value for mortality [22]. In our patients the frequency of IL6 > 70 was significantly higher among the deceased (p = 0.03; 95%CI = 1.05–2.70). In the multiple logistic regression an IL6 > 70 was an independent risk factor for death (Table 2).

D-dimer is a product of fibrin degradation and is increased in the blood of patients with thrombotic events. In COVID-19 abnormal D-dimer at admission was associated with higher incidence of critical illness, thrombotic events, and death. While a value <230 mg/dL is considered normal, individuals with D-dimer >2000 ng/mL had the highest risk of thrombotic events and death [23,24]. A D-dimer value >2000 ng/mL was associated with the risk of death (p = 0.01; OR = 1.91, 95%CI = 1.14–3.18). In the multivariate logistic regression the D-dimer was not associated with death (Table 2). This variable was correlated with age (p = 0.01) with patients showing >2000 ng/mL showing a higher mean age (67 ± 11 vs. 63 ± 12). This was in agreement with an increased risk of thrombotic events in aged patients. Because rs1801274 (p.Arg131His) might increase the risk of death in patients with thrombotic events, we hypothesised that it could increase the risk of death among those with high D-dimer values. *FCGR2A* G-carriers with D-dimer >2000 were 33% in the deceased and 17% in the survivors (p = 0.002), with an OR = 2.37 (95%CI = 1.38–4.03). This value was higher that the OR of each risk factor separately (Table 2).

Ferritin is an intracellular protein that plays and important role in inflammation. Hyperferritinemic syndromes such as macrophage activation syndrome and septic shock are characterised by high circulating ferritin. Some studies suggested that high ferritin was an independent risk factor for severity and mortality in patients with COVID-19, although others failed to confirm this association [25,26]. In our ICU cohort the ferritin median value was higher among the deceased, without statistical significance.

We found higher frequencies of the *FCGR2A* rs1801274 G allele among deceased in the first pandemic waves that were dominated by different SARS-CoV-2 variants (the original in the two first and alpha in the third). This suggested that the association between *FCGR2A* and mortality was independent of the dominant virus variant. However, we did not determine the specific variant in each patient and we cannot compare the difference between confirmed SARS-CoV-2 variants.

Finally, our work has several limitations. First, it was based on a limited number of patients from a single population, and requires thus validation in larger cohorts from different populations. Also, our patients were not evaluated by imaging techniques (ultrasound, magnetic resonance or others) to determine the presence of pulmonary thrombosis, and the only approach to underlying thromboembolism was the measure of D-Dimer as a surrogate marker. Other markers of inflammation and thrombosis were not measured in a number of patients high enough to stablish an accurate statistical analysis.

If confirmed by others, our findings might have implications for a personalised medicine in COVID-19 patients. The genotyping of the functional variant might help to identify patients at higher risk of adverse events, that could benefit of a more extensive therapeutic

intervention. Also, these gene variants might explain part of the heterogeneous response to therapeutic antibodies and vaccines.

5. Conclusions

In a Spanish cohort of ICU COVID-19 patients the *FCGR2A* rs1801274 G variant (131 Arg) was associated with all-causes mortality independently of age, IL6 and D-Dimer values. The *FCGR2A* rs1801274 G variant was associated with the risk of death independently of IL6 and D-Dimer values, suggesting a functional effect beyond inflammation and thrombosis. These results require validation in larger cohorts, and studies focused on the mechanism that explains the *FCGR2A* role in COVID-19.

Authors contribution

Lead researchers: RLM, EC, GMA, JG. Study design: EC, GMA, JG. Patient assessment: GMA, LAR, MGC. Genetic study: RLM, EC, ECL, JG, DVC, VA. Database: EC, GMA, LAR, ECL. Data filtering and analysis: RLM, EC, JG, DVC. Statistical analysis: RLM, EC, DVC. Analysis of results: RLM, EC, GMA, JG. Drafting of manuscript: RLM, EC. Revision of manuscript: all authors.

All the authors contributed to this work by recruiting the patients and performing the genetic and statistical analysis. E.C. takes full responsibility for the accuracy of the data. All the authors approved the submission of this manuscript.

Data accessibility

To facilitate the revision of the results by other researchers, a file with the patient's data is available as an excel file upon request to the corresponding author.

Declaration of Competing Interest

None of the authors have competing interests related to this work.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clim.2022.108954.

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