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Association of IL10 rs1800896 and IL33 rs10975519 with Severe COVID-19 Case Status in Iraqi Men: An Exploratory Case-Control Study

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ABSTRACT: Host cytokine-gene variation may modify inflammatory responses to SARS-CoV-2, but evidence from Middle Eastern populations remains limited. This exploratory hospital-based case-control study evaluated IL10 rs1800896 and IL33 rs10975519 in 70 Iraqi men with quantitative PCR (qPCR)–confirmed severe COVID-19 and 30 qPCR-negative healthy male controls. Variants were genotyped by high-resolution melting, and ferritin, D-dimer and C-reactive protein (CRP) were measured. The two primary genotype-distribution tests used exact inference with Bonferroni correction; prespecified secondary genotype, inheritance-model and allele contrasts used exact odds ratios (ORs), 95% confidence intervals and false-discovery rate (FDR) adjustment. IL10 rs1800896 differed between groups (exact P = 0.0102; adjusted P = 0.0203; Cramer's V = 0.304). The TC genotype, dominant C-carrier model and C allele met within-variant FDR criteria, although no secondary contrast remained below $q < 0.05$ when all 12 contrasts were adjusted jointly. IL33 rs10975519 showed no statistically supported variant-level association (exact P = 0.1112; Cramer's V = 0.208). Ferritin, D-dimer and CRP were higher in severe cases (all $P < 0.001$). The IL10 finding is therefore a locus-level, hypothesis-generating association with severe-case versus healthy-control status, not evidence of causality or clinical prediction. Replication in larger, sex-balanced cohorts with infected

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non-severe comparison groups, validated genotyping and covariate-adjusted analyses is required.

Keywords: *COVID-19; IL10; IL33; genetic association; biomarkers; Iraq.*

INTRODUCTION

Clinical outcomes after SARS-CoV-2 infection range from asymptomatic infection to severe pneumonia, respiratory failure, thrombo-inflammatory complications and multiorgan injury. Age, comorbidities, vaccination, viral factors and exposure intensity explain part of this heterogeneity; host genetic background may additionally influence immune recognition, cytokine regulation and the balance between antiviral defense and tissue-damaging inflammation [1, 2]. Candidate-gene studies can therefore remain informative in underrepresented populations when variants are selected on biological grounds and findings are interpreted as exploratory rather than deterministic.

Interleukin-10 (IL-10) is a central immunoregulatory cytokine that limits excessive inflammatory signaling and collateral tissue injury. During viral infection, both inadequate and excessive IL-10 activity may be unfavorable: insufficient regulation may promote hyperinflammation, whereas early or sustained immunosuppression may impair viral clearance [3–6]. The promoter variant rs1800896, commonly reported as IL10 -1082 A>G, may influence transcriptional activity. COVID-19 studies have produced positive, null and model-specific findings, with direction and magnitude varying across populations, clinical comparisons, allele orientation and analytic strategy [7–12].

Interleukin-33 (IL-33) is an epithelial- and endothelial-derived alarmin in the IL-1 cytokine family. It is released after tissue injury and may amplify pulmonary inflammation through ST2-dependent pathways. Circulating IL-33 has been associated with lung injury and COVID-19 severity, and experimental evidence indicates that IL-33 signaling can exacerbate pulmonary inflammation under some conditions [13–17]. In contrast to IL10, evidence concerning IL33 germline variants in COVID-19 remains sparse. The rs10975519 variant has been studied in other immune-mediated disorders, but its contribution to severe SARS-CoV-2 disease is uncertain [18–21].

Ferritin, D-dimer and C-reactive protein (CRP) are clinically relevant indicators of systemic inflammation, coagulation activation and disease burden. Meta-analyses and

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cohort studies generally report higher values in severe COVID-19, although prognostic performance depends on sampling time, comorbidity, treatment and outcome definition [22–28]. Integrating genetic and biochemical observations may improve biological interpretation, but valid genotype-biomarker inference requires participant-level data.

The present study tested the prespecified hypothesis that genotype distributions of IL10 rs1800896 and IL33 rs10975519 differ between Iraqi men with severe COVID-19 and qPCR-negative healthy male controls. The primary objective was a variant-level comparison of the complete genotype distribution for each locus. Secondary objectives were to estimate prespecified genotype, inheritance-model and allele contrasts and to describe group differences in ferritin, D-dimer and CRP. The interpretation was deliberately hierarchical: primary locus-level tests were distinguished from model-specific secondary signals and from descriptive biomarker findings. Because no infected mild or moderate group was available, the design cannot separate susceptibility to infection from progression to severe disease.

MATERIALS AND METHODS

Study design and participants

This hospital-based case-control study was conducted at Al-Yarmouk Teaching Hospital, Baghdad, Iraq, from October 2022 to June 2023. A total of 100 male participants were enrolled: 70 patients admitted with severe, qPCR-confirmed COVID-19 and 30 qPCR-negative healthy controls recruited during the same study period. Severe disease was operationally defined for the archived cohort by hospitalization, compatible systemic or respiratory manifestations and oxygen saturation below 92%; this was the prespecified hospital definition recorded in the source dataset. Participants were reported to belong to the same ethnic group and to have received a locally available commercial COVID-19 vaccine; however, ancestry-informative markers, vaccine brand, dose number and time since vaccination were unavailable in the archived dataset. Individuals with kidney, heart or chronic lung disease, hypertension, diabetes, obesity, cancer or hepatitis were excluded to reduce major clinical confounding.

Written informed consent was obtained from all participants. The study protocol was approved by the Research Ethics Committee of the University of Baghdad (approval no.

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CSEC/1022/0137). Reporting was revised with reference to the STREGA extension for genetic association studies [29].

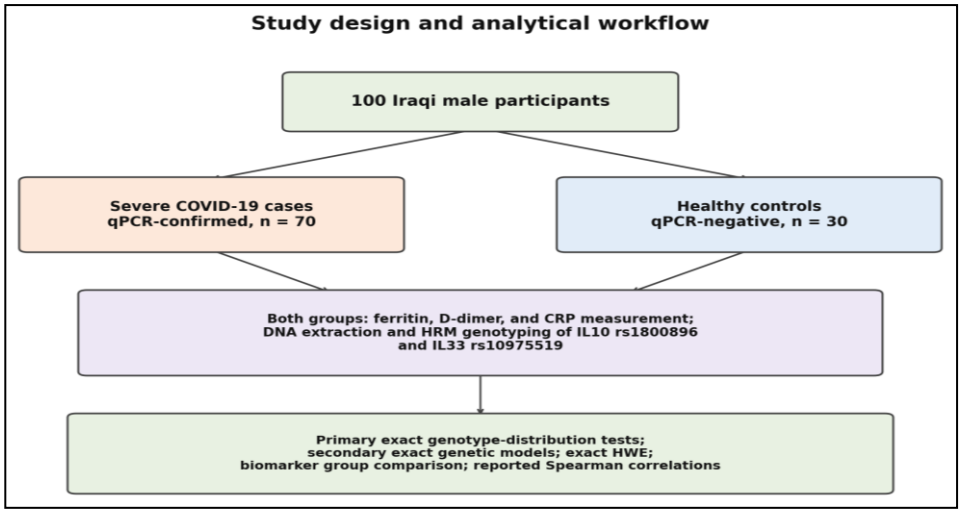

Fig. 1. Study design and analytical workflow. HRM, high-resolution melting; HWE, Hardy-Weinberg equilibrium.

Blood collection and biomarker assessment

Peripheral venous blood was collected from patients on the second day of hospitalization and from healthy controls at enrollment. Serum from serum-separator gel tubes was used for CRP measurement. Sodium-citrate plasma was used for D-dimer and ferritin assessment with the AFIAS D-Dimer and AFIAS Ferritin kits (Boditech Med Inc., Chuncheon, Republic of Korea; supplied locally by United Medical Company). EDTA-anticoagulated blood was used for genomic DNA extraction with the EasyPure Genomic DNA Kit (TransGen Biotech Co., Ltd., Beijing, China) according to the manufacturer's instructions.

qPCR confirmation of SARS-CoV-2

Viral RNA was extracted from nasopharyngeal swabs using the Viral Nucleic Acid Extraction Kit (Zybio Inc., Chongqing, China). Ten microliters of extracted RNA were added to each reaction. SARS-CoV-2 RNA was detected using the Zybio SARS-CoV-2 Assay Kit on a Rotor-Gene platform (QIAGEN, Hilden, Germany), targeting conserved regions of the N, RdRP and S genes. The thermal protocol is summarized in Table 1A.

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Genomic DNA extraction and primer design

Extracted genomic DNA was stored at -20 °C until analysis. DNA integrity was checked by agarose gel electrophoresis, and concentration was measured using a NanoDrop spectrophotometer. Primers were designed from reference sequences using Primer3Plus. Primer sequences and assay-strand allele notation are listed in Table 1B. For IL10 rs1800896, assay-strand T>C is complementary to the commonly reported -1082 A>G orientation.

Table 1. Laboratory assay conditions and primer sequences.

A. qPCR cycling conditions used for SARS-CoV-2 detection

PCR step	Temperature	Time	Cycles
UNG reaction	37 °C	1 min	1
Reverse transcription	50 °C	5 min	1
Initial denaturation	95 °C	2 min	1
Denaturation	95 °C	5 s	45
Annealing/fluorescence	60 °C	30 s	45

B. Primer sequences used for high-resolution melting genotyping

Variant	Assay orientation	Primer	Sequence (5′–3′)
IL33 rs10975519	C>T	Forward	ATGCATTCTCTTTCAGATAAGGTG
IL33 rs10975519	C>T	Reverse	CCTGATTCATTTGAGGGGTGT
IL10 rs1800896	T>C*	Forward	GGAGGTCCCTTACTTTCCTCTT
IL10 rs1800896	T>C*	Reverse	CACACACAAATCCAAGACAACA

High-resolution melting genotyping

IL10 rs1800896 and IL33 rs10975519 were genotyped by PCR followed by high-resolution melting on a Rotor-Gene Q real-time PCR system (QIAGEN, Hilden, Germany). Each 20-µL reaction contained 10 µL of 2× TransStart Tip Green qPCR SuperMix, 4 µL of nuclease-free water, 1 µL of each primer and 4 µL of DNA template. The HRM step was performed from 55 °C to 95 °C in 0.2 °C increments. Normalized melting and difference curves were interpreted using Rotor-Gene HRM software. Representative curve files and sequencing-confirmation records were not available in the aggregate archive used for the present reanalysis; this constraint is addressed in the limitations.

Study outcomes and statistical analysis

The two primary analyses were the 2×3 genotype-distribution comparisons for IL10 rs1800896 and IL33 rs10975519. Secondary analyses comprised prespecified individual-

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genotype, dominant, recessive, overdominant and allele contrasts, exact Hardy-Weinberg equilibrium (HWE) assessments and group comparisons of ferritin, D-dimer and CRP; biomarker correlations were treated as descriptive. Genotype and allele count used for the present statistical reanalysis were reconstructed from the archived aggregate frequencies reported in the study. The reconstructed counts reproduced the group totals and the reported percentages to two decimal places. Primary variant-level distributions were assessed using two-sided Fisher-Freeman-Halton exact tests, with Pearson chi-square statistics reported for comparability. Cramer's V was calculated from the Pearson chi-square statistics, total sample size and contingency-table dimensions to describe the standardized magnitude of each genotype-distribution difference independently of statistical significance. Bonferroni correction was applied across the two primary tests.

Secondary genetic contrasts were evaluated using two-sided Fisher exact tests. Conditional maximum-likelihood ORs and exact 95% CIs were calculated. Benjamini-Hochberg FDR adjustment was applied separately to the six secondary contrasts for each variant, preserving the prespecified variant-specific interpretation. As a conservative multiplicity sensitivity analysis, the same procedure was also applied jointly across all 12 secondary contrasts. Exact HWE tests were applied separately to cases and controls using the probability-based exact method described by Wigginton et al. [30]. Because IL10 and IL33 are located on different chromosomes, interlocus linkage disequilibrium and conventional haplotype analysis were not performed.

Biomarker group comparisons were retained from the original Mann-Whitney U analyses, and the reported Spearman coefficients were summarized descriptively. Participant-level observations were unavailable; therefore, biomarker interquartile ranges, genotype-stratified biomarker analyses and covariate-adjusted logistic regression could not be reconstructed. All tests were two-sided. Unadjusted $P < 0.05$ was considered nominally significant, while corrected P or Q values are reported where applicable.

RESULTS

Study groups

The analysis included 70 male patients with severe COVID-19 and 30 healthy male controls. All cases were qPCR-confirmed, and controls were qPCR-negative at enrollment. Complete aggregate genotype and biomarker summaries were available for both groups.

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Participant-level age, anthropometric, vaccination, treatment and symptom-duration data were not available; adjusted regression and effect-modification analyses therefore could not be performed.

IL10 rs1800896 and severe COVID-19 case status

The overall IL10 rs1800896 genotype distribution differed between severe cases and controls (Fisher-Freeman-Halton exact P = 0.0102; Pearson chi-square=9.25, df=2, P = 0.0098; Cramer's V = 0.304). The result remained below 0.05 after Bonferroni correction for the two primary variant-level tests (adjusted P = 0.0203). The TC genotype occurred in 67.14% of cases and 43.33% of controls, whereas TT occurred in 22.86% and 53.33%, respectively (Fig. 2).

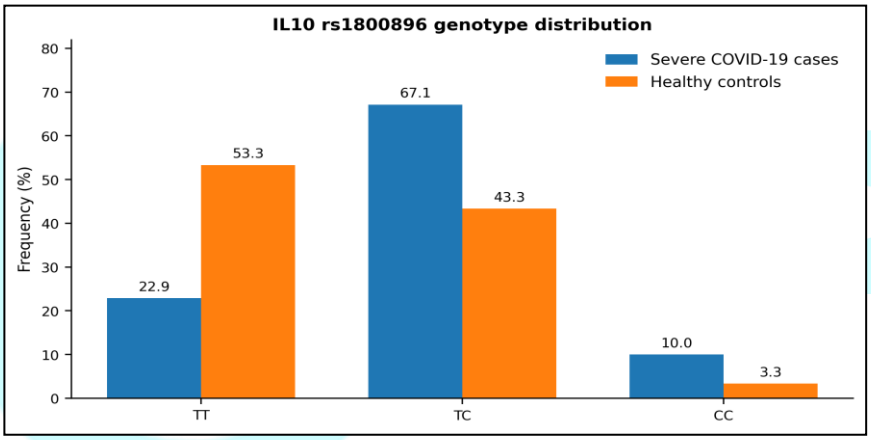

Fig. 2. IL10 rs1800896 genotype frequencies in severe COVID-19 cases and healthy controls.

Relative to TT, TC was associated with higher odds of severe COVID-19 case status (conditional OR = 3.56, exact 95% CI 1.30-10.10; Fisher P = 0.0089; within-variant FDR q = 0.0268). The dominant C-carrier model yielded OR = 3.80 (95% CI 1.41-10.54; P = 0.0046; q = 0.0268), and the C allele yielded OR = 2.31 (95% CI 1.14-4.89; P = 0.0168; q = 0.0336). The CC comparison remained imprecise because only one control carried this genotype (Table 2). These model-specific findings are interpreted together with the joint 12-contrast FDR sensitivity analysis reported below.

Table 2. Exact association estimates for IL10 rs1800896.

Model / comparison	Cases n/N	Controls n/N	Exact OR	Exact 95% CI	P	FDR q
TC vs TT	47/63	13/29	3.56	1.30–10.10	0.0089	0.0268
CC vs TT	7/23	1/17	6.71	0.72–334.78	0.1074	0.1289
Dominant: TC+CC vs TT	54/70	14/30	3.80	1.41–10.54	0.0046	0.0268
Recessive: CC vs TT+TC	7/70	1/30	3.19	0.38–150.15	0.4294	0.4294

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Overdominant: TC vs TT+CC	47/70	13/30	2.64	1.02–7.07	0.0439	0.0659
Allele: C vs T	61/140	15/60	2.31	1.14–4.89	0.0168	0.0336

Note: ORs are unadjusted conditional maximum-likelihood estimates with exact 95% CIs. q values are Benjamini-Hochberg adjusted across the six prespecifiedIL10 contrasts. Cases, n = 70; controls, n = 30.

IL33 rs10975519 and severe COVID-19 case status

The overall IL33 rs10975519 genotype distribution did not differ significantly between groups (Fisher-Freeman-Halton exact P = 0.1112; Pearson chi-square=4.34, df=2, P = 0.1141; Cramer's V = 0.208; Bonferroni-adjusted P = 0.2224). The CT genotype was more frequent in severe cases than controls (51.43% vs 30.00%), whereas CC was less frequent (35.71% vs 56.67%) (Fig. 3). The standardized difference was not trivial, but the present sample did not provide sufficiently precise evidence to distinguish a true association from sampling variation.

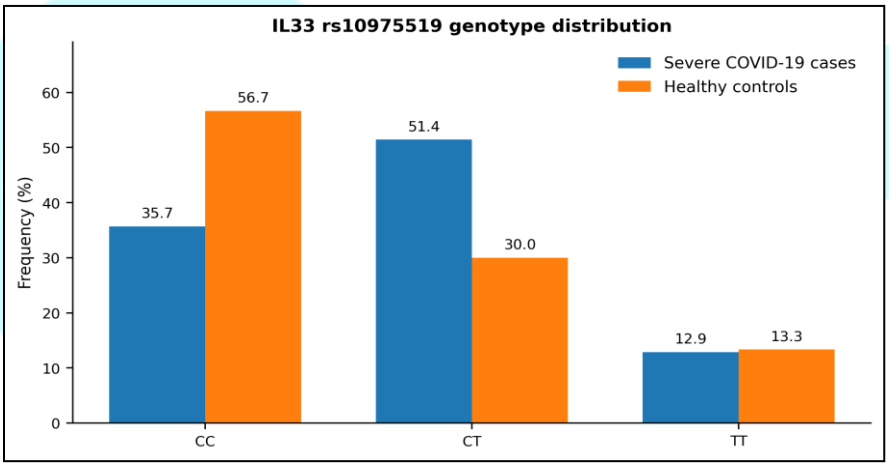

Fig. 3.IL33 rs10975519 genotype frequencies in severe COVID-19 cases and healthy controls.

Compared with CC, the CT estimate was elevated but borderline (conditional OR = 2.69, exact 95% CI 0.95-8.04; Fisher P = 0.0598; within-variant FDR q = 0.1525). Neither the dominant model nor the T-allele comparison reached nominal or FDR-adjusted significance (Table 3).

Table 3. Exact association estimates for IL33 rs10975519.

Model / comparison	Cases n/N	Controls n/N	Exact OR	Exact 95% CI	P	FDR q
CT vs CC	36/61	9/26	2.69	0.95–8.04	0.0598	0.1525
TT vs CC	9/34	4/21	1.52	0.35–7.87	0.7454	0.8945
Dominant: CT+TT vs CC	45/70	13/30	2.33	0.90–6.19	0.0763	0.1525
Recessive: TT vs CC+CT	9/70	4/30	0.96	0.24–4.65	1.0000	1.0000
Overdominant: CT vs CC+TT	36/70	9/30	2.45	0.92–6.98	0.0528	0.1525
Allele: T vs C	54/140	17/60	1.58	0.79–3.28	0.1980	0.2970

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Multiplicity sensitivity analysis: When the Benjamini-Hochberg procedure was applied jointly across all 12 secondary genetic contrasts, no contrast retained $q < 0.05$. The smallest joint-FDR q value was 0.0537 for both IL10 TC versus TT and the IL10 dominant C-carrier model; the IL10 C-allele comparison yielded $q = 0.0672$. Thus, the primary variant-level IL10 result remained significant after it prespecified Bonferroni correction, whereas the secondary model-specific signals were sensitive to the chosen FDR family.

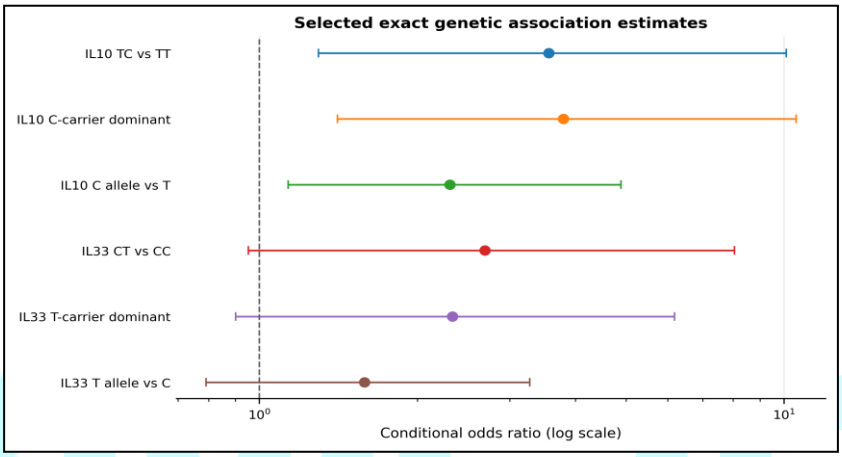

Fig. 4. Selected exact unadjusted genetic association estimates on a logarithmic odds-ratio scale. The dashed vertical line indicates OR = 1. Horizontal bars show exact 95% confidence intervals.

Hardy-Weinberg equilibrium

IL10 rs1800896 deviated from HWE among severe cases (exact P = 0.0035) but not controls (exact P = 0.6404). IL33 rs10975519 was compatible with HWE in both groups (Table 4). Because HWE is principally used in controls as a quality-control indicator, the compatible control result is reassuring. Nevertheless, the case-group deviation may reflect disease enrichment, population structure, selection, chance or genotype misclassification and increases the importance of independent genotyping validation and replication.

Table 4. Exact Hardy-Weinberg equilibrium analysis.

Variant	**Group**	**Observed genotypes**	**Expected genotypes**	**Exact HWE P**	**Interpretation**
IL10 rs1800896	Cases	16 / 47 / 7	22.29 / 34.42 / 13.29	0.0035	Deviation
IL10 rs1800896	Controls	16 / 13 / 1	16.88 / 11.25 / 1.88	0.6404	Compatible
IL33 rs10975519	Cases	25 / 36 / 9	26.41 / 33.17 / 10.41	0.6152	Compatible
IL33 rs10975519	Controls	17 / 9 / 4	15.41 / 12.18 / 2.41	0.1786	Compatible

Ferritin, D-dimer and CRP

Ferritin, D-dimer and CRP were substantially higher in severe COVID-19 cases than healthy controls. The original non-parametric analyses reported P = 0.0001 for each

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comparison; these are presented as P < 0.001. The source archive labelled the central values as medians while also providing SDs. Because participant-level observations were unavailable, IQRs and the underlying distributions could not be verified. Table 5 therefore reproduces both measures exactly as reported; SD should not be interpreted as dispersion around a median.

Table 5. Aggregate biomarker summaries.

Biomarker	Group	Reported central value	Reported SD	Mean rank	Mann-Whitney U	P
Ferritin (ng/mL)	Cases	390.90	428.37	62.16	233.50	<0.001
Ferritin (ng/mL)	Controls	61.50	24.60	23.28		
D-dimer (µg/mL)	Cases	1.44	4.20	62.74	193.00	<0.001
D-dimer (µg/mL)	Controls	0.21	0.11	21.93		
CRP (mg/L)	Cases	19.70	38.74	63.61	132.00	<0.001
CRP (mg/L)	Controls	0.20	0.09	19.90		

Descriptive biomarker correlations

The reported Spearman coefficients were positive for ferritin with D-dimer (ρ = 0.627), ferritin with CRP (ρ = 0.792) and D-dimer with CRP (ρ = 0.784); all reported P values were <0.001 (Table 6). The analytic sample used for these correlations was not documented, so the coefficients are presented descriptively and are not interpreted as evidence of genotype-biomarker coupling.

Table 6. Reported Spearman correlation matrix for ferritin, D-dimer and CRP.

Variable	Ferritin	D-dimer	CRP
Ferritin	1.000	0.627a	0.792a
D-dimer	0.627a	1.000	0.784a
CRP	0.792a	0.784a	1.000

a P < 0.001 as reported in the source archive; participant-level data were unavailable for independent verification.

DISCUSSION

Principal's findings

The evidential hierarchy is central to interpretation. The strongest result is the prespecified two-degree-of-freedom IL10 genotype-distribution test, which remained below 0.05 after correction for the two loci and had Cramer's V = 0.304. This supports a locus-level difference between severe cases and healthy controls. By contrast, the TC, dominant and C-allele estimates are model-specific secondary results: they met within-locus FDR criteria but did not remain below q < 0.05 under joint adjustment across all 12 secondary contrasts.

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The appropriate claim is therefore an exploratory IL10 locus-level association, not confirmation of a dominant inheritance mechanism. For IL33, the point estimates and Cramer's V = 0.208 leave room for an effect, but the confidence intervals and corrected tests are inconclusive rather than evidence of absence. None of the estimates is adjusted for demographic or clinical covariates.

Interpretive boundaries and clinical relevance

The reported ORs quantify a contrast between hospitalized severe cases and healthy qPCR-negative controls; they do not estimate infection risk, absolute risk or the probability of progression after infection. A non-severe infected comparison group would be required to address progression more directly. Moreover, a candidate cytokine variant should not be treated as a clinical biomarker merely because an association test is significant. Clinical translation would require independent replication, sequence-validated genotyping, adjustment for ancestry and clinical covariates, and demonstration of incremental discrimination, calibration and clinical utility beyond established risk factors.

Comparison with previous IL10 studies and sex generalizability

Previous COVID-19 studies of IL10 rs1800896 (commonly reported as -1082 A>G; complementary assay orientation T>C in the present study) have produced positive, null and model-specific findings. Signals were reported in selected Egyptian cohorts [7, 9, 10], whereas studies from India, Iran, Cameroon and a small pediatric cohort were largely null for severity or susceptibility [8, 12, 31, 32]. Differences in ancestry, allele orientation, age structure, clinical comparison, control selection, viral and vaccination era and statistical modeling may contribute to the heterogeneity. Several external cohorts included substantial numbers of women, but none reported genotype-by-sex effect estimates; consequently, the present male-only findings cannot be extrapolated to Iraqi women. Table 7 summarizes selected studies most relevant to interpretation of the present results.

Table 7. Selected COVID-19 studies of IL10 rs1800896 relevant to interpretation of the present findings.

Study / population	Clinical comparison	Women	Method	Main rs1800896 finding
Present Iraqi study	70 severe cases; 30 controls	0/100 (0%)	HRM	TC, dominant and allele signals; male-only cohort
Rizvi et al. [31], India, 2022	85 mild; 75 severe	60/160 (37.5%)	PCR-RFLP	No significant severity association

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Azadinejad et al. [8], Iran, 2024	150 mild; 143 severe	133/293 (45.4%)	PCR-RFLP	No significant severity association
Tah et al. [32], Cameroon, 2024	120 cases; 120 controls	118/240 (49.2%)	PCR-RFLP	No significant susceptibility association
Eldesouki et al. [9], Egypt, 2024	110 cases; 110 gender-matched controls	Both sexes; exact total NR	TaqMan	Model- and outcome-specific signals
El-Bendary et al. [7], Egypt, 2024	354 patients; moderate vs severe	NR	Allelic qPCR	C allele more frequent in severe disease

Abbreviations: HRM, high-resolution melting; NR, not reported; PCR-RFLP, PCR-restriction fragment length polymorphism.

The HWE deviation among IL10 cases is an important caution. HWE is principally evaluated in controls to identify genotyping error or population structure, and the control group was compatible with equilibrium. Deviation in a selected disease group can arise from a true association; however, in a small study it may also reflect chance, hidden population stratification, selection or genotype misclassification. Because representative HRM curves and sequencing-confirmation data were unavailable, repeat genotyping of ambiguous curves and sequencing of a prespecified subset would materially improve confidence.

IL33 and biomarker findings

Evidence for IL33 rs10975519 was weaker. The CT genotype was more common in cases and produced an elevated OR, but its exact CI included unity, the variant-level exact test was not significant and all secondary FDR-adjusted results were null. Independent COVID-19 replication of this specific variant is currently lacking; therefore, the observation should be regarded as an unreplicated exploratory pattern rather than a confirmed association. IL-33 remains mechanistically relevant to pulmonary epithelial injury and cytokine amplification [13–17], but cytokine-level evidence cannot substitute for independent replication of the germline variant. Studies in other inflammatory and autoimmune disorders suggest that IL33 effects may be population- and phenotype-specific [18–21].

The biomarker findings were clinically coherent: ferritin, D-dimer and CRP were markedly elevated in severe cases, consistent with systemic inflammation and coagulation activation reported in severe COVID-19 [22–28]. The reported positive correlations also fit a shared

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inflammatory-thrombotic phenotype. However, the aggregate data do not establish that either genotype caused or modified biomarker elevation. A valid genotype-biomarker analysis would require participant-level biomarker values stratified by genotype and adjustment for age, treatment, vaccination, symptom duration and other covariates. The correlation sample must also be clarified because case-control pooling may exaggerate correlation coefficients.

Strengths and limitations

Strengths include qPCR-confirmed cases, biologically selected cytokine variants, concurrent measurement of three clinically relevant biomarkers, exact genetic association analyses and focus on an underrepresented Iraqi population. The statistical framework distinguishes the two primary variant-level tests from prespecified secondary inheritance-model contrasts, uses exact OR intervals and reports multiplicity-adjusted results.

The sample was small and unbalanced, all participants were male, and the study compared severe cases with healthy controls but included no mild or moderate COVID-19 group. The observed associations may therefore reflect susceptibility to infection, progression to severe disease, selection into hospitalization or a combination of these processes. Case-control ORs should not be interpreted as absolute or population-level risks. Participant-level demographic and clinical covariates were unavailable, precluding adjusted regression and effect-modification analyses. Ancestry-informative markers were not available, and vaccination brand, dose number and timing were incompletely documented. Controls were qPCR-negative only at enrollment, and prior infection was not excluded serologically. Biomarker interquartile ranges could not be reconstructed, the sample used for correlation analysis was undocumented, circulating IL-10 and IL-33 were not measured, and HRM calls were not documented as sequence-validated. In addition, the secondary IL10 model-specific findings did not remain below 0.05 under the conservative joint 12-contrast FDR sensitivity analysis. These constraints support interpreting the results as hypothesis-generating and preclude individual-level clinical prediction.

CONCLUSION

In this exploratory Iraqi male cohort, IL10 rs1800896 showed a locus-level association with severe COVID-19 case status versus healthy-control status after correction for the two

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primary loci. Model-specific TC, dominant and C-allele signals were less robust because they did not survive joint adjustment across all secondary contrasts. Evidence for IL33 rs10975519 was inconclusive, not definitively null. Ferritin, D-dimer and CRP were markedly higher in severe cases, but the aggregate dataset could not test genotype-biomarker coupling. These findings are biologically plausible and useful for hypothesis generation, but they are not ready for causal or clinical interpretation. A decisive next study should use multicenter, sex-balanced recruitment; infected controls spanning disease severity; participant-level covariates and cytokine measurements; ancestry control; and sequence-validated genotyping.

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