



Original Investigation | Infectious Diseases

CCL5 Levels, Disease Progression, and Mortality in Respiratory Viral Infections

A Systematic Review and Meta-Analysis

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Abstract

IMPORTANCE The role of chemokine C-C motif ligand 5 (CCL5) in respiratory viral infections remains controversial; although essential for viral clearance, it is also implicated in pathogenic hyperinflammation.

OBJECTIVE To quantify associations between CCL5 levels and unfavorable disease progression and mortality in respiratory viral infections.

DATA SOURCES Medline and PubMed, Embase, Scopus, Web of Science, the Cochrane Library, CABI Digital Library, and Global Health (Ovid) were searched from inception to October 1, 2025.

STUDY SELECTION Observational studies evaluating the association of CCL5 levels with clinical severity or survival in patients with confirmed respiratory viral infections.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted data and assessed risk of bias (Newcastle-Ottawa Scale) and certainty of evidence (GRADE). Data were pooled using a random-effects model following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. Data analysis was performed from September 2025 to December 2025.

MAIN OUTCOMES AND MEASURES Unfavorable disease progression (severity) and all-cause mortality.

RESULTS The meta-analysis included 18 studies (2376 patients; median age, 58.2 [range, 0.08-65.0] years; 1278 of 2126 male [60.1%]); 12 studies (67%) were of high methodological quality. Eleven studies (1214 patients) evaluated disease progression and 7 (1162 patients) evaluated mortality. Elevated CCL5 levels were associated with reduced odds of unfavorable disease progression (OR, 0.78; 95% CI, 0.71-0.85; $I^2 = 0\%$) and mortality (OR, 0.65; 95% CI, 0.55-0.76; $I^2 = 23.1\%$). The protective association had significantly larger effect sizes for mortality than for disease progression ($P = .047$ for interaction). Subgroup analyses for disease progression demonstrated consistent protective associations without significant interaction by virus type (coronavirus: OR, 0.80 [95% CI, 0.70-0.90] vs noncoronavirus: OR, 0.74 [95% CI, 0.63-0.87]) or age group (pediatric: OR, 0.79 [95% CI, 0.69-0.90] vs adult: OR, 0.75 [95% CI, 0.63-0.88]). Results remained consistent in sensitivity analyses.

CONCLUSIONS AND RELEVANCE In this systematic review and meta-analysis of 18 observational studies, elevated CCL5 levels were associated with favorable outcomes and survival in respiratory viral infections, reflecting a competent antiviral immune response rather than pathogenic hyperinflammation. These findings suggest that CCL5 may serve as a prognostic biomarker for risk stratification.

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Key Points

Question Are elevated levels of the chemokine C-C motif ligand 5 (CCL5) associated with disease progression and mortality in patients with respiratory viral infections?

Findings In this systematic review and meta-analysis of 18 observational studies including 2376 patients, elevated CCL5 levels were significantly associated with a 35% reduction in the odds of mortality and a 22% reduction in the odds of unfavorable disease progression.

Meaning These findings suggest that elevated CCL5 levels reflect a competent host immune response and may have utility for early risk stratification.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Severe pneumonia and acute respiratory distress syndrome (ARDS) caused by respiratory viruses, including influenza, respiratory syncytial virus (RSV), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), remain leading causes of global mortality.¹⁻⁴ The clinical trajectory of these infections is markedly heterogeneous, ranging from mild symptoms to critical illness. This variability creates a significant challenge for patient management and underscores the urgent need for prognostic biomarkers to identify high-risk patients early and guide therapeutic decision-making.^{5,6}

The host immune response is a determinant of clinical outcome, hinging on the early production of type I interferon (IFN-I).⁷ Within this network, the chemokine C-C motif ligand 5 (CCL5), also known as regulated on activation of normal T cells expressed and secreted (RANTES), has emerged as a key modulator. Unlike other chemokine receptor 5 (CCR5)-binding chemokines implicated in damaging inflammation (eg, CCL3), CCL5-driven responses tend to be protective.⁸ CCL5 acts as a bridge between innate and adaptive immunity by orchestrating the recruitment of effector monocytes, cytotoxic CD8+ T cells, and natural killer cells.⁹⁻¹² Beyond recruitment, CCL5 actively sustains the immune defense by preventing the premature apoptosis of virus-infected alveolar macrophages, a mechanism essential for effective viral clearance.¹³ Furthermore, CCL5 exerts direct antiviral effects by inducing restriction factors and blocking viral entry.^{14,15}

Despite this protective profile, the role of CCL5 in disease severity remains controversial and is often described as a “double-edged sword.” As a canonical interferon-stimulated gene, CCL5 levels serve as a surrogate for the functional competence of the IFN-I pathway.^{16,17} However, sustained or excessive production has been hypothesized to drive immunopathology and collateral lung injury.¹⁸ Clinical evidence is conflicting: some studies associate higher CCL5 levels with mild disease (eg, in SARS-CoV-2 infection),¹⁹ whereas others link elevated levels to exacerbated injury (eg, in severe RSV bronchiolitis).^{20,21} This uncertainty hampers the development of host-directed therapies, as it remains unclear whether clinical strategies should aim to inhibit CCL5 (to limit inflammation) or boost its levels (to enhance viral clearance). Resolving this complexity is critical, as individual observational studies are often underpowered to clarify this issue across different viruses and populations. To address this uncertainty, we conducted a systematic review and meta-analysis to quantify the association between CCL5 levels and key clinical outcomes—unfavorable disease progression and mortality—in patients with respiratory viral infections.

Methods

Protocol and Registration

We conducted this systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guideline.^{22,23} We registered the protocol in PROSPERO (CRD420251109172).²⁴ As this study is a systematic review of publicly available data, it was exempt from institutional review board approval and patient informed consent per the institutional policy of the Instituto de Salud Carlos III regarding secondary analyses of anonymized, publicly available datasets. Data analysis was performed from September 2025 to December 2025.

Search Strategy

We searched Medline/PubMed, Embase, Scopus, Web of Science, the Cochrane Library, CABI Digital Library, and Global Health (Ovid) for studies published through October 1, 2025. The search strategy used Boolean operators to combine terms related to chemokine CCL5 (eg, *RANTES*), respiratory viral infections (eg, *coronavirus*, *influenza*), clinical outcomes, and human populations. No language or geographic restrictions were applied. Reference lists of relevant studies were manually screened to

identify additional eligible articles. Detailed search strings are provided in [Supplement 1](#). References were managed using EndNote X9 (Clarivate Analytics) and Excel 2016 (Microsoft Corp).

Selection Criteria

Selection followed the PICOS (Population, Intervention/Exposure, Comparison, Outcomes, Study) framework.²⁵ Inclusion criteria were: (1) observational studies (cohort or case-control); (2) patients with confirmed respiratory viral infection; (3) measurement of CCL5 levels in biological samples (eg, serum, plasma, nasopharyngeal aspirate); and (4) reporting of clinical outcomes (eg, mortality, disease severity) with sufficient data to calculate an effect size (odds ratio [OR], hazard ratio [HR], or relative risk [RR]). We specifically compared patients with elevated CCL5 levels vs those with low or normal levels. We excluded reviews, nonhuman studies, studies lacking a relevant comparison group, and publications without extractable data.

Study Selection and Data Extraction

Two reviewers (C.P.-M. and D.S.-C.) independently screened titles, abstracts, and full-text articles. Discrepancies were resolved by consensus or arbitration by a third reviewer (S.R.). Interviewer agreement was quantified using the Cohen κ coefficient and interpreted according to Landis and Koch's benchmarks.²⁶

We extracted data using a standardized Excel form, capturing study characteristics, patient demographics, CCL5 measurement methods, and clinical outcomes. When key data were missing, we contacted study authors to request additional information; studies were excluded only if essential information remained unavailable after 3 attempts.

Risk of Bias and Quality Assessment

We assessed risk of bias using the Newcastle-Ottawa Scale (NOS),²⁷ classifying studies as high (7 stars or more), moderate (5 or 6 stars), or low (4 stars or less) quality (eAppendix 2 in [Supplement 1](#)). Two reviewers (C.P.-M. and D.S.-C.) independently performed the assessment, with discrepancies resolved by a third reviewer (S.R.). We evaluated the certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.²⁸ Interreviewer reliability was quantified using the intraclass correlation coefficient.^{29,30}

Definition of Clinical Outcomes

To harmonize heterogeneous clinical endpoints, outcomes were aggregated into 2 primary endpoints: (1) unfavorable disease progression and (2) mortality. Unfavorable disease progression was a composite endpoint stratified by severity. Severe progression included indicators of critical illness (eg, intensive care unit [ICU] admission, mechanical ventilation, ARDS) or outcomes explicitly labeled as severe or critical by study authors (eg, severe pneumonia). Moderate progression consisted primarily of hospital admission (for outpatient studies) or outcomes defined as moderate. Mortality encompassed all-cause death (eg, in-hospital, 28-day, or 30-day mortality).

Statistical Analysis

All statistical analyses were performed using Stata/SE version 18.0 (StataCorp). Statistical significance was defined as a 2-sided $P < .05$ for all primary pooled effect estimates. For tests of heterogeneity and publication bias, a threshold of $P < .10$ was used to account for the low statistical power of these tests.³¹

The primary effect size measure was the OR. HRs and RRs reported in primary studies for rare outcomes were treated as approximations of the OR for pooling purposes. The OR and its corresponding 95% CI extracted from each study were log-transformed to calculate the standard error, and pooled estimates were computed using a DerSimonian-Laird random-effects model.³² Statistical heterogeneity was assessed using Cochran Q test and quantified with the Higgins I^2 statistic. I^2 values of 25%, 50%, and 75% were interpreted as low, moderate, and high heterogeneity.

respectively.^{33,34} Subgroup differences were evaluated using a χ^2 test for interaction (with significance defined as $P \leq .05$). Furthermore, univariable meta-regression assessed the influence of study-level covariates (publication year, country income status, and sample size) using a restricted maximum likelihood (REML) estimator with the Knapp-Hartung adjustment to provide robust estimates.³⁵

Publication bias was assessed via funnel plots, the Egger test,³⁶ and Begg rank correlation test³⁷ ($P < .10$). To further evaluate the robustness of the pooled results, 2 sensitivity analyses were performed: a nonparametric “trim and fill” method³⁸ and a leave-one-out influence analysis.³⁹

Results

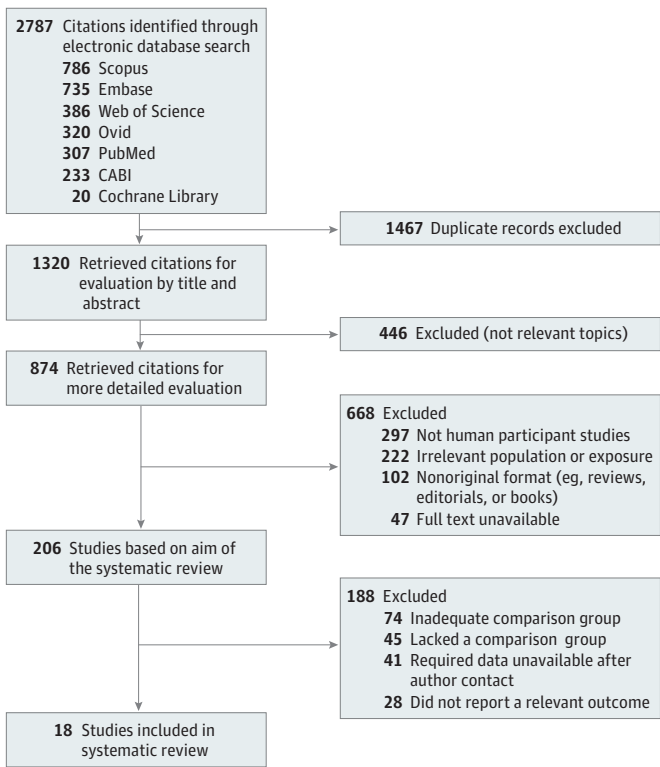
Search Results and Study Selection

The literature search identified 2787 records (Figure 1). After duplicate removal, 1320 records were screened by title and abstract, and 874 full-text articles were assessed for eligibility. Of these, 856 were excluded. Initial full-text screening excluded 668 articles due to irrelevant populations or non-human participants (519 articles), nonoriginal formats (102 articles), or unavailable full texts (47 articles). A subsequent detailed evaluation of 206 articles excluded an additional 188 due to lack of an adequate comparison group or relevant outcome (147 articles), or unavailable data after author contact (41 articles). This process resulted in a final selection of 18 studies^{20,40-56} for inclusion in the quantitative synthesis. Interrater agreement was substantial for screening ($\kappa = 0.77$) and almost perfect for full-text review ($\kappa = 0.92$).

Article Characteristics

The 18 included studies, published between 2012 and 2024,^{20,40-56} comprised 2376 patients (median study age, 58.2 [range, 0.08-65.0] years; 1278 of 2126 patients [60.1%] with available data

Figure 1. PRISMA 2020 Flow Diagram of the Study Selection Process



PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

were male) (Table 1). Most studies (15 [83%]) were conducted in high-income countries, with 3 in low- and middle-income countries.⁴²⁻⁴⁴

Eleven studies evaluated unfavorable disease progression,^{20,40-49} comprising pediatric (7 studies)^{20,40,41,44,47-49} and adult (4 studies)^{42,43,45,46} cohorts. Viral etiologies included SARS-CoV-2 (5 studies),⁴²⁻⁴⁶ RSV (3 studies),^{20,48,49} influenza A virus subtype H1N1 (1 study),⁴⁰ a mix of RSV and rhinovirus (1 study),⁴¹ and a nonspecific viral lower respiratory tract infection (1 study).⁴⁷ Seven studies assessed mortality⁵⁰⁻⁵⁶; all involved adult populations with coronavirus infections (6 SARS-CoV-2^{50-53,55,56} and 1 MERS-CoV⁵⁴).

Study designs included prospective (6 studies),^{43,44,47,48,50,56} retrospective (6 studies),^{20,40,45,51,53,55} cross-sectional (4 studies),^{41,46,49,54} and case-control (2 studies)^{42,52} designs. CCL5 was measured in systemic samples (serum and plasma^{40,42-45,47,50,52,54,56} or whole blood^{48,49,51,55}) in 14 studies and respiratory specimens (nasopharyngeal aspirate) in 4.^{20,41,46,53} Quantification methods included protein-based assays (Luminex bead array,^{41,42,44,45,47,50-52,54-56} cytometric bead array,^{40,43} electrochemiluminescence²⁰) in 14 studies and gene expression analysis (quantitative polymerase chain reaction) in 4.^{46,48,49,53}

Association Between CCL5 Levels and Clinical Outcomes

Figure 2 presents the forest plot of the association between CCL5 levels and clinical evolution. Higher CCL5 levels were associated with a 22% reduction in the odds of unfavorable disease progression (11 studies [1214 participants]; pooled OR, 0.78; 95% CI, 0.71-0.85) with no evidence of heterogeneity ($I^2 = 0\%$; $P = .48$).^{20,40-49} For mortality (7 studies [1162 participants]), elevated levels were associated with a 35% reduction in odds (pooled OR, 0.65; 95% CI, 0.55-0.76) with low heterogeneity ($I^2 = 23.1\%$; $P = .23$).⁵⁰⁻⁵⁶ Crucially, the test for subgroup differences confirmed that the protective association had higher effect sizes for mortality than for disease progression (P for between-group heterogeneity [ie, interaction] = .047).

Exploration of Heterogeneity

Subgroup analyses for unfavorable disease progression demonstrated consistent associations without significant interaction across virus types (noncoronavirus: OR, 0.74 [95% CI, 0.63-0.87] vs coronavirus: OR, 0.80 [95% CI, 0.70-0.90]; $P = .47$ for interaction) and age groups (pediatric: OR, 0.79 [95% CI, 0.69-0.90] vs adult: OR, 0.75 [95% CI, 0.63-0.88]; $P = .66$ for interaction) (Table 2). Subgroup analyses for mortality were precluded because all studies involved adult patients with coronavirus infections.

In univariable meta-regression for unfavorable disease progression, none of the tested covariates modified the association: publication year (coefficient, -0.015; 95% CI, -0.049 to 0.019; $P = .35$), country income status (coefficient, 0.011; 95% CI, -0.403 to 0.425; $P = .95$), or sample size (coefficient, -0.0006; 95% CI, -0.0028 to 0.0016; $P = .57$). Similarly, for mortality, no significant association was found with publication year (coefficient, -0.102; 95% CI, -0.240 to 0.037; $P = .12$) or sample size (coefficient, -0.0006; 95% CI, -0.0018 to 0.0007; $P = .30$).

Sensitivity Analyses and Publication Bias

For unfavorable disease progression, visual inspection of the funnel plot suggested no asymmetry, a finding supported by the Begg test ($z = -1.56$; $P = .16$) and Egger test ($z = -1.53$; $P = .13$) (Figure 3A). The trim-and-fill method imputed zero missing studies, yielding no change in the pooled estimate. Leave-one-out analysis indicated that results were not driven by any single study (Figure 3B). Similarly, for mortality, funnel plots, Begg tests ($z = 0.30$; $P = .76$), and Egger tests ($z = 0.30$; $P = .76$) indicated no asymmetry (Figure 3C). No missing studies were imputed by the trim-and-fill method, and leave-one-out analysis showed consistent pooled estimates (Figure 3D).

To address the methodological heterogeneity of pooling different measures of association, we conducted sensitivity analyses restricting the primary analysis to a single effect measure (ORs) by excluding studies reporting hazard ratios (Mondell et al⁴⁷ and Alhethel et al⁵⁴). As supported by the

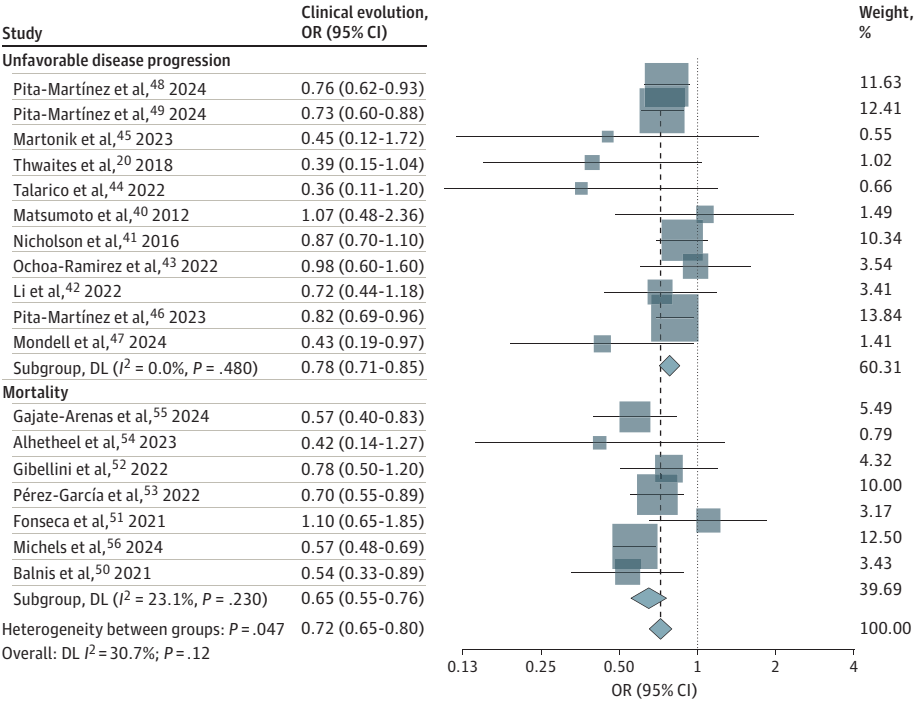
Table 1. Characteristics of Studies Included in the Meta-Analysis on the Association Between CCL5 Chemokine (RANTES) Levels and Key Clinical Outcomes in Patients With Respiratory Virus Infections

Source	Country	LMIC	Virus	Sample size	Age, y	Male, %	Age group	Study design	Assays	Sample	Outcome
Unfavorable disease progression											
Matsumoto et al, ⁴⁰ 2012	Japan	No	H1N1	47	7	63.8	Pediatric	Retrospective	CBA	Serum	Severe
Nicholson et al, ⁴¹ 2016	US	No	RSV/RV	109	NA	57.7	Pediatric	Cross-sectional	LBA	NPA	Moderate/severe
Thwaites et al, ²⁰ 2018	England	No	RSV	20	NA	NA	Pediatric	NA	MSD-ECL	NPA	Severe
Li et al, ⁴² 2022	China	Yes	SARS-CoV-2	143	NA	NA	Adult	Case-control	LBA	Plasma	Moderate/severe
Ochoa-Ramirez et al, ⁴³ 2022	Mexico	Yes	SARS-CoV-2	148	54	62.8	Adult	Prospective	CBA	Serum	Severe
Talarico et al, ⁴⁴ 2022	Argentina	Yes	SARS-CoV-2	51	6.5	43.1	Pediatric	Prospective	LBA	Serum	Moderate/severe
Martoni et al, ⁴⁵ 2023	Poland	No	SARS-CoV-2	44	63	72.7	Adult	Retrospective	LBA	Serum	Severe
Pita-Martínez et al, ⁴⁶ 2023	Spain	No	SARS-CoV-2	223	60.5	61	Adult	Cross-sectional	qPCR	NPA	Severe
Mondell et al, ⁴⁷ 2024	US	No	Unidentified	191	NA	52.9	Pediatric	Prospective	LBA	Plasma	Severe
Pita-Martínez et al, ⁴⁸ 2024	Spain	No	RSV	117	0.17	57.3	Pediatric	Prospective	qPCR	Blood	Moderate/severe
Pita-Martínez et al, ⁴⁹ 2024	Spain	No	RSV	121	0.17	55.4	Pediatric	Cross-sectional	qPCR	Blood	Severe
Survival											
Balnis et al, ⁵⁰ 2021	US	No	SARS-CoV-2	41	59.9	68.3	Adult	Prospective	LBA	Plasma	Mortality
Fonseca et al, ⁵¹ 2021	US	No	SARS-CoV-2	87	NA	NA	Adult	Retrospective	LBA	Blood	Mortality
Gibellini et al, ⁵² 2022	Italy	No	SARS-CoV-2	80	65	76.2	Adult	Case-control	LBA	Plasma	Mortality
Pérez-García et al, ⁵³ 2022	Spain	No	SARS-CoV-2	255	63.8	60	Adult	Retrospective	qPCR	NPA	Mortality
Altheheel et al, ⁵⁴ 2023	Saudi Arabia	No	MERS-CoV	100	50.9	73	Adult	Cross-sectional	LBA	Plasma	Mortality
Gajate-Arenas et al, ⁵⁵ 2024	Spain	No	SARS-CoV-2	160	58.2	63.1	Adult	Retrospective	LBA	Blood	Mortality
Michels et al, ⁵⁶ 2024	Netherlands	No	SARS-CoV-2	439	62.2	57.1	Adult	Prospective	LBA	Plasma	Mortality

Abbreviations: CBA, cytometric bead array; H1N1, influenza A virus subtype H1N1; ICU, intensive care unit; LBA, luminex bead array; LMIC, low- and middle-income countries; LRTI, low respiratory tract infection; MERS-CoV, Middle East respiratory syndrome coronavirus; MSD-ECL, meso scale discovery-electrochemiluminescence; NA, not available; NPA, nasopharyngeal aspiration; qPCR, quantitative real-time polymerase chain reaction; RV, rhinovirus; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

leave-one-out analysis, restricting the pool to ORs did not significantly alter the protective associations for either disease progression (OR, 0.79; 95% CI, 0.72-0.86) or mortality (OR, 0.66; 95% CI, 0.56-0.78). Furthermore, to address heterogeneity in confounding structures, we stratified the analysis by adjustment status. For unfavorable disease progression, the protective association remained significant in unadjusted models (OR, 0.77; 95% CI, 0.70-0.85) but was not significant when restricted to multivariable-adjusted models (OR, 0.94; 95% CI, 0.63-1.39). For mortality, the protective association persisted in unadjusted models (OR, 0.64; 95% CI, 0.52-0.78) and in the single study reporting a multivariable-adjusted estimate (OR, 0.70; 95% CI, 0.55-0.89).

Figure 2. Forest Plot of the Association Between Elevated CCL5 Levels and Clinical Evolution, Stratified by Outcome



Each square represents the OR for an individual study, with the size of the square being proportional to the weight of that study in the analysis. The horizontal lines indicate the 95% CI for each study's OR. The diamonds represent the pooled OR calculated using a DL random-effects model for each subgroup and for the overall analysis; the width of the diamond corresponds to the 95% CI of the pooled estimate. An OR of less than 1 signifies a protective association, where elevated CCL5 levels are linked to a reduced risk of the adverse outcome. The I^2 statistic quantifies the percentage of heterogeneity between studies. The P value for interaction indicates whether the difference in pooled odds ratios between the two outcome subgroups is statistically significant. DL indicates DerSimonian-Laird; OR, odds ratio.

Table 2. Subgroup Analyses of the Association Between Elevated CCL5 Levels and Clinical Outcomes

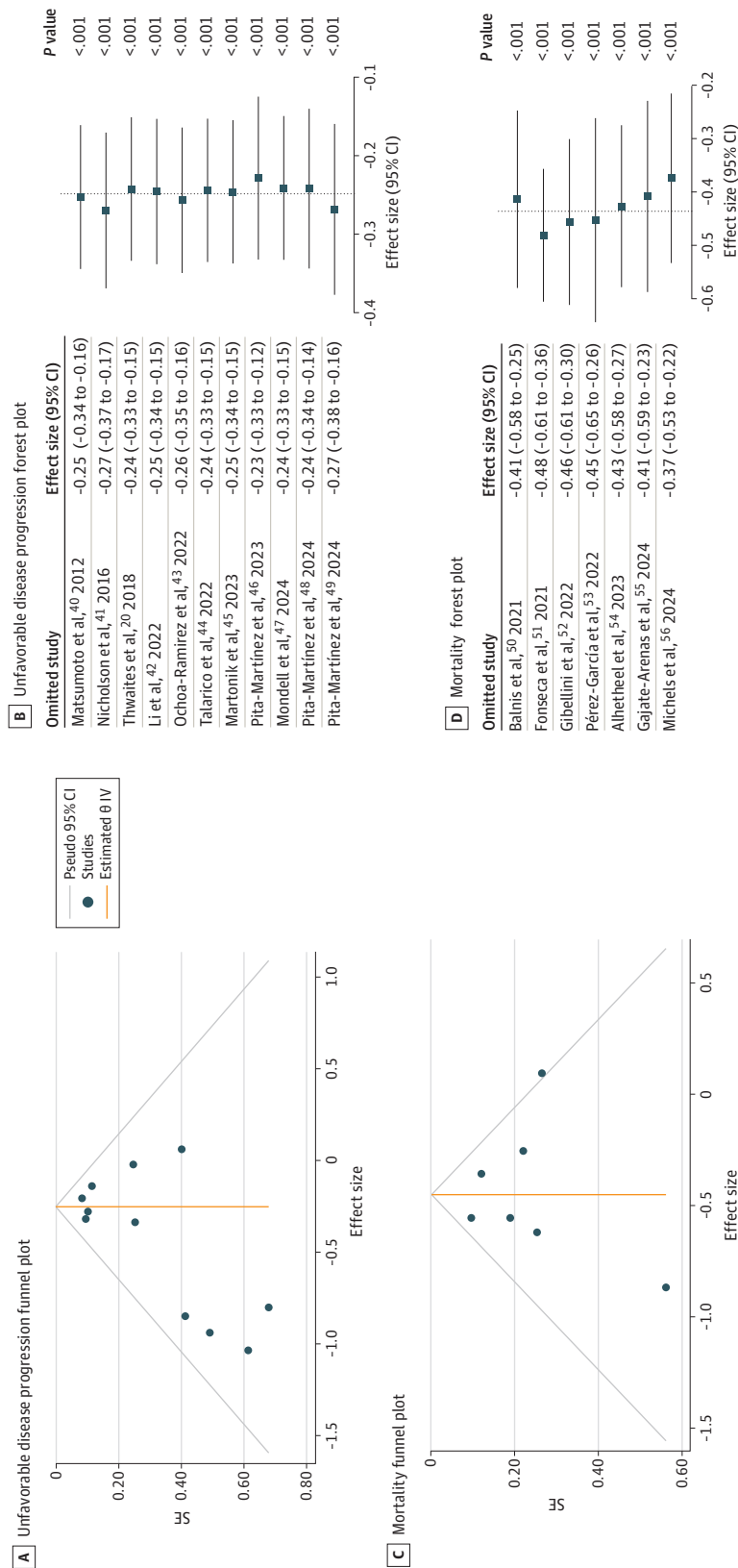
Outcome and subgroup	No. of Studies	No. of patients	<i>I</i> ²		Pooled OR (95% CI)	<i>P</i> value for interaction
			%	<i>P</i> value		
Analysis by virus type						
Unfavorable disease progression						
Noncoronavirus	5	609	0	.52	0.74 (0.63-0.87)	.47
Coronavirus	6	605	11.9	.34	0.80 (0.70-0.90)	
Mortality						
Noncoronavirus	0	0	NA	NA	NA	NA ^a
Coronavirus	7	1162	26.1	.23	0.65 (0.55-0.76)	
Analysis by population age						
Unfavorable disease progression						
Pediatric	7	656	18.5	.29	0.79 (0.69-0.90)	.66
Adult	4	558	0	.61	0.75 (0.63-0.88)	
Mortality						
Adult	7	1162	26.1	.23	0.65 (0.55-0.76)	NA ^b
Pediatric	0	0	NA	NA	NA	

Abbreviations: NA, not applicable; OR, odds ratio.

^aComparison not possible as no studies evaluating mortality in patients with noncoronavirus infections were included in the meta-analysis.

^bComparison not possible as no studies evaluating mortality in pediatric patients were included in the meta-analysis.

Figure 3. Assessment of Publication Bias and Sensitivity Analysis for the Association Between Elevated CCL5 Levels and Clinical Outcomes



Funnel plots of the studies included in the meta-analysis for the outcomes of unfavorable disease progression (A) and mortality (C). The log OR for each study is plotted against its standard error. Each circle represents an individual study. The vertical line indicates the pooled log OR, and the diagonal lines represent the pseudo 95% CIs. Symmetrical distribution of studies around the pooled estimate suggests a low likelihood of publication bias. Leave-one-out sensitivity analyses for the outcomes of unfavorable disease progression (B) and mortality (D). Each line shows the pooled OR and 95% CI after omitting 1 study at a time. This analysis assesses the influence of individual studies on the overall pooled estimate. OR indicates odds ratio.

Study Quality Assessment

Of the 18 included studies, 12 (67%) were rated as high quality (7 stars or more)^{20,41,43,46-49,51-53,55,56} and 6 (33%) as moderate quality (5 or 6 stars)^{40,42,44,45,50,54} (eFigure in Supplement 1). No studies were rated as low quality (4 stars or less).

In the comparability domain (eFigure 1B in Supplement 2), the 6 moderate-quality studies received zero stars because they lacked statistical adjustment for confounders.^{40,42,44,45,50,54} In contrast, all 12 high-quality studies performed multivariable adjustments, strengthening the validity of the findings.^{20,41,43,46-49,51-53,55,56} Regarding representativeness, 9 studies (50%) did not report consecutive recruitment,^{20,40-45,54,55} suggesting potential selection bias. Using the GRADE approach, the certainty of evidence was upgraded from low to moderate for both outcomes due to the large magnitude of the effect and low heterogeneity (eTable in Supplement 2).

Discussion

In this systematic review and meta-analysis of 18 studies comprising 2376 patients, elevated CCL5 levels were associated with reduced risks of unfavorable disease progression and mortality in patients with specific respiratory viral infections (SARS-CoV-2, RSV, influenza, and MERS-CoV). The protective association had higher effect sizes for mortality (35% reduction in odds) than for disease progression (22% reduction). The consistency of these findings, with low statistical heterogeneity, suggests that CCL5 elevation represents a marker of a competent immune response rather than a driver of pathogenic hyperinflammation across these evaluated viral etiologies.

Biological Plausibility and Mechanisms

Although some earlier studies suggested that high CCL5 levels contribute to immunopathology,¹⁸ our findings support the hypothesis that CCL5 is a key marker of a favorable clinical course during these specific respiratory viral infections. CCL5 recruits effector cells (including CD8⁺ T cells, natural killer cells, and monocytes) bridging innate and adaptive immunity.⁵⁷ This aligns with the observed functional dichotomy among C-C motif CCR5 ligands: while CCL5 promotes protective antiviral responses, other ligands such as CCL3 (macrophage inflammatory protein 1α) have been linked to excessive inflammation and tissue damage.^{58,59} The protective role of CCL5 is evolutionarily underscored by the fact that successful respiratory pathogens, such as influenza A virus and RSV, have evolved specific virulence factors (eg, NS1 proteins) to actively suppress CCL5 expression, thereby evading host immunity.⁶⁰ These data suggest that the protective association of CCL5 predominates during infections with these specific pathogens, reflecting a competent host defense rather than pathogenic hyperinflammation. Low CCL5 levels may characterize patients with inadequate immune responses, predisposing them to uncontrolled viral replication. For instance, longitudinal profiling in COVID-19 showed that high early-stage CCL5 levels characterized mild disease, whereas low levels preceded progression to severe illness.¹⁹ Similarly, in critical COVID-19 patients, higher plasma CCL5 levels were observed in “elite” viral controllers with improved survival.⁶¹ Thus, elevated CCL5 signifies a coordinated host defense essential for viral clearance.

Differential Association of CCL5 With Mortality vs Progression

The larger effect size observed for the protective association with mortality compared with disease progression is a key finding that may reflect distinct biological roles. While other immune mechanisms might compensate for defective CCL5 responses to prevent progression to severe disease (eg, requirement for oxygen), our results imply that low CCL5 is a central actor in the immunological events determining death, likely by failing to prevent systemic viral dissemination and uncontrolled viremia.^{62,63}

This protective association was consistent across viral etiologies and patient populations. The consistency across age groups is particularly notable given the profound developmental differences

between pediatric and adult immune systems.^{64,65} This suggests that a robust early CCL5 response represents a highly conserved, age-independent host defense mechanism against respiratory viruses.^{66,67} The absence of statistical heterogeneity ($I^2 = 0\%$) further supports the generalizability of this finding across different clinical contexts.

Clinical and Research Implications

These findings support the potential utility of CCL5 as a prognostic biomarker for early risk stratification. Admission CCL5 measurement could identify patients with ineffective host defenses at high risk of deterioration, facilitating biomarker-guided triage and therapeutic decision-making.^{68,69}

Furthermore, our results provide a rationale for a theranostic framework for tailored immunomodulation.⁵⁷ This presents a personalized medicine approach involving 2 distinct strategies: (1) augmenting protective antiviral responses in patients identified as low CCL5 producers at an early stage (eg, with recombinant interferon β)^{70,71} and (2) mitigating immunopathology in established ARDS via CCR5 blockade, but potentially only in those with pathogenic overexpression.^{72,73} Future research should prioritize validation in prospective, multicenter cohorts using standardized assays to establish precise clinical cutoffs.

Strengths and Limitations

Strengths of this study include being, to our knowledge, the first meta-analysis to quantitatively synthesize evidence on the prognostic role of CCL5 across diverse respiratory viruses and clinical settings. The inclusion of a substantial proportion of high-quality studies with multivariable adjustments strengthens the validity of the pooled estimates.

However, this study has limitations. First, the number of studies was small for certain subgroups, particularly for the mortality outcome, precluding detailed stratified analyses. Second, studies varied in CCL5 assay techniques and definitions of disease severity. Specifically, our composite endpoint of disease progression combined diverse clinical outcomes (eg, ICU admission, mechanical ventilation, and acute respiratory distress syndrome); thus, the reported low statistical heterogeneity may reflect overaggregation rather than true clinical homogeneity. Third, pooling heterogeneous measures of association (OR, HR, and RR) derived from different regression models (eg, logistic vs Cox proportional hazards) is a methodological limitation. This approach combines time-to-event and non-time-to-event effects. Furthermore, covariate adjustment varied across studies. Although sensitivity analyses restricting data to a single effect measure and stratifying by adjustment status demonstrated consistent trends, the pooled estimate implicitly assumes comparability across confounding structures, which may not hold. Consequently, the pooled estimate should be interpreted as a broad measure of association rather than a precise, unified target metric. Fourth, although formal tests suggested no asymmetry, publication bias cannot be excluded. Finally, because the analysis was based on observational data, findings are subject to inherent limitations, including residual confounding and the inability to establish causality.

Conclusions

Elevated CCL5 levels were consistently associated with favorable clinical outcomes and survival in patients with respiratory viral infections. These findings suggest that high CCL5 levels reflect a proficient antiviral immune response rather than pathogenic hyperinflammation. CCL5 has potential as a prognostic biomarker for patient stratification, and our results support the investigation of therapeutic strategies to boost CCL5 responses in patients with demonstrated deficiencies in this chemokine.

ARTICLE INFORMATION

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SUPPLEMENT 1.

eAppendix 1. Search strategy

eAppendix 2. Risk of bias assessment adapted from the Newcastle-Ottawa Scale (NOS)

eTable. GRADE summary of findings for the association between elevated CCL5 levels and clinical outcomes

eFigure. Risk of bias assessment of the included studies

SUPPLEMENT 2.

Data Sharing Statement