

Supplemental Online Content

Pita-Martínez C, Sepúlveda-Crespo D, Bermejo-Martin JF, Martínez I, Resino S. CCL5 Levels, disease progression, and mortality in respiratory viral infections. *JAMA Netw Open*. 2026;9(8):e2628987. doi:10.1001/jamanetworkopen.2026.28987

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

This supplemental material has been provided by the authors to give readers additional information about their work.

Supplemental file 1: Search strategy

Search strategy PubMed

("Chemokine CCL5"[MeSH Terms] OR "(CCL)5" [Title/Abstract] OR "CCL 5" [Title/Abstract] OR "CCL5" [Title/Abstract] OR "CCL-5" [Title/Abstract] OR "D17S136E" [Title/Abstract] OR "eoCP" [Title/Abstract] OR "MGC17164" [Title/Abstract] OR "RANTES" [Title/Abstract] OR "SCYA5" [Title/Abstract] OR "SISd" [Title/Abstract] OR "SIS-Delta" [Title/Abstract] OR "TCP228" [Title/Abstract]) AND ("Adenovirus Infections, Human"[MeSH Terms] OR "Coronavirus Infections"[MeSH Terms] OR "Enterovirus Infections"[MeSH Terms] OR "Metapneumovirus"[MeSH Terms] OR "Orthomyxoviridae Infections"[MeSH Terms] OR "Paramyxoviridae Infections"[MeSH Terms] OR "Respiratory Syncytial Virus Infections"[MeSH Terms] OR "Respiratory Tract Infections"[MeSH Terms] OR "Rhinovirus"[MeSH Terms] OR "2019 nCoV" [Title/Abstract] OR "2019-nCoV" [Title/Abstract] OR "A24 virus*" [Title/Abstract] OR "A9 virus*" [Title/Abstract] OR "adenovirus*" [Title/Abstract] OR "APC virus*" [Title/Abstract] OR "Bornholm Disease Virus" [Title/Abstract] OR "coronavirus*" [Title/Abstract] OR "COVID 19" [Title/Abstract] OR "COVID19" [Title/Abstract] OR "COVID-19" [Title/Abstract] OR "Coxsackie" [Title/Abstract] OR "Coxsackievirus*" [Title/Abstract] OR "D70 virus*" [Title/Abstract] OR "Echo virus*" [Title/Abstract] OR "Echovirus*" [Title/Abstract] OR "EVA71" [Title/Abstract] OR "EV-A71" [Title/Abstract] OR "EVD68" [Title/Abstract] OR "EV-D68" [Title/Abstract] OR "EVD94" [Title/Abstract] OR "EV-D94" [Title/Abstract] OR "Fifth disease" [Title/Abstract] OR "flu" [Title/Abstract] OR "grippe" [Title/Abstract] OR "influenza*" [Title/Abstract] OR "MERS" [Title/Abstract] OR "Metapneumovirus*" [Title/Abstract] OR "Middle East Respiratory Syndrome" [Title/Abstract] OR "parainfluenza" [Title/Abstract] OR "parvovirus B19" [Title/Abstract] OR "Pleurodynia virus*" [Title/Abstract] OR "pneumovirus" [Title/Abstract] OR "Respiratory Infection*" [Title/Abstract] OR "Respiratory Syncytial" [Title/Abstract] OR "Respiratory Tract Infection*" [Title/Abstract] OR "Respiratory Virus*" [Title/Abstract] OR "Rhinovirus*" [Title/Abstract] OR "RSV" [Title/Abstract] OR "SARS CoV 2" [Title/Abstract] OR "SARS-CoV-2" [Title/Abstract] OR "common cold virus" [Title/Abstract] OR "coryza virus*" [Title/Abstract]) AND ("Bronchiolitis"[MeSH Terms] OR "Critical Care"[MeSH Terms] OR "Diagnostic Tests, Routine"[MeSH Terms] OR "Hospitalization"[MeSH Terms] OR "Intensive Care Units"[MeSH Terms] OR "Mortality"[MeSH Terms] OR "Patient Acuity"[MeSH Terms] OR "Pneumonia, Bacterial"[MeSH Terms] OR "Bronchiolitides" [Title/Abstract] OR "Bronchiolitis" [Title/Abstract] OR "CFR" [Title/Abstract] OR "Dead" [Title/Abstract] OR "Death" [Title/Abstract] OR "Die" [Title/Abstract] OR "disease severity" [Title/Abstract] OR "exitus" [Title/Abstract] OR "Fatality" [Title/Abstract] OR "Hospital Admission" [Title/Abstract] OR "ICU" [Title/Abstract] OR "Intensive care" [Title/Abstract] OR "Lower Respiratory Tract Infection" [Title/Abstract] OR "LRTI*" [Title/Abstract] OR "Mortality" [Title/Abstract] OR "Pneumonia*" [Title/Abstract] OR "Preadmission" [Title/Abstract] OR "Routine Admission" [Title/Abstract] OR "RTI" [Title/Abstract]) AND ("humans"[MeSH Terms] OR "persons"[MeSH Terms] OR "adolescent*" [Title/Abstract] OR "adult*" [Title/Abstract] OR "ancient*" [Title/Abstract] OR "baby*" [Title/Abstract] OR "child" [Title/Abstract] OR "children" [Title/Abstract] OR "cohort*" [Title/Abstract] OR "elderly" [Title/Abstract] OR "female*" [Title/Abstract] OR "Homo Sapiens" [Title/Abstract] OR "host*" [Title/Abstract] OR "human*" [Title/Abstract] OR "individual*" [Title/Abstract] OR "infant*" [Title/Abstract] OR "male*" [Title/Abstract] OR "man" [Title/Abstract] OR "men" [Title/Abstract] OR "parents" [Title/Abstract] OR "participant*" [Title/Abstract] OR "patient*" [Title/Abstract] OR "people" [Title/Abstract] OR "person*" [Title/Abstract] OR "player*" [Title/Abstract] OR "population*" [Title/Abstract] OR "student*" [Title/Abstract] OR "subject*" [Title/Abstract] OR "survivor*" [Title/Abstract] OR "volunteer*" [Title/Abstract] OR "woman" [Title/Abstract] OR "women"

[Title/Abstract]) NOT ("review"[Publication Type]) NOT ("meta-analysis"[Publication Type])
NOT ("systematic review"[Publication Type])

Search strategy Embase

#1 'chemokine ccl5'/exp OR '(ccl)5':ti,ab,kw OR 'ccl 5':ti,ab,kw OR 'ccl5':ti,ab,kw OR 'ccl-5':ti,ab,kw OR 'd17s136e':ti,ab,kw OR 'eocp':ti,ab,kw OR 'mgc17164':ti,ab,kw OR 'rantes':ti,ab,kw OR 'scya5':ti,ab,kw OR 'sisd':ti,ab,kw OR 'sis-delta':ti,ab,kw OR 'tcp228':ti,ab,kw

#2 'adenovirus infections, human'/exp OR 'coronavirus infections'/exp OR 'enterovirus infections'/exp OR 'metapneumovirus'/exp OR 'orthomyxoviridae infections'/exp OR 'paramyxoviridae infections'/exp OR 'respiratory syncytial virus infections'/exp OR 'respiratory tract infections'/exp OR 'rhinovirus'/exp OR '2019 ncov':ti,ab,kw OR '2019-ncov':ti,ab,kw OR 'a24 virus*':ti,ab,kw OR 'a9 virus*':ti,ab,kw OR 'adenovirus*':ti,ab,kw OR 'apc virus*':ti,ab,kw OR 'bornholm disease virus':ti,ab,kw OR 'coronavirus*':ti,ab,kw OR 'covid 19':ti,ab,kw OR 'covid19':ti,ab,kw OR 'covid-19':ti,ab,kw OR 'coxsackie':ti,ab,kw OR 'coxsackievirus*':ti,ab,kw OR 'd70 virus*':ti,ab,kw OR 'echo virus*':ti,ab,kw OR 'echovirus*':ti,ab,kw OR 'eva71':ti,ab,kw OR 'ev-a71':ti,ab,kw OR 'evd68':ti,ab,kw OR 'ev-d68':ti,ab,kw OR 'evd94':ti,ab,kw OR 'ev-d94':ti,ab,kw OR 'fifth disease':ti,ab,kw OR 'flu':ti,ab,kw OR 'grippe':ti,ab,kw OR 'influenza*':ti,ab,kw OR 'mers':ti,ab,kw OR 'metapneumovirus*':ti,ab,kw OR 'middle east respiratory syndrome':ti,ab,kw OR 'parainfluenza':ti,ab,kw OR 'parvovirus b19':ti,ab,kw OR 'pleurodynia virus*':ti,ab,kw OR 'pneumovirus':ti,ab,kw OR 'respiratory infection*':ti,ab,kw OR 'respiratory syncytial':ti,ab,kw OR 'respiratory tract infection*':ti,ab,kw OR 'respiratory virus*':ti,ab,kw OR 'rhinovirus*':ti,ab,kw OR 'rsv':ti,ab,kw OR 'sars cov 2':ti,ab,kw OR 'sars-cov-2':ti,ab,kw OR 'common cold virus':ti,ab,kw OR 'coryza virus*':ti,ab,kw

#3 'bronchiolitis'/exp OR 'critical care'/exp OR 'diagnostic tests, routine'/exp OR 'hospitalization'/exp OR 'intensive care units'/exp OR 'mortality'/exp OR 'patient acuity'/exp OR 'pneumonia, bacterial'/exp OR 'bronchiolitides':ti,ab,kw OR 'bronchiolitis':ti,ab,kw OR 'cfr':ti,ab,kw OR 'dead':ti,ab,kw OR 'death':ti,ab,kw OR 'die':ti,ab,kw OR 'disease severity':ti,ab,kw OR 'exitus':ti,ab,kw OR 'fatality':ti,ab,kw OR 'hospital admission':ti,ab,kw OR 'icu':ti,ab,kw OR 'intensive care':ti,ab,kw OR 'lower respiratory tract infection':ti,ab,kw OR 'lrti*':ti,ab,kw OR 'mortality':ti,ab,kw OR 'pneumonia*':ti,ab,kw OR 'preadmission':ti,ab,kw OR 'routine admission':ti,ab,kw OR 'rti':ti,ab,kw

#4 'humans'/exp OR 'persons'/exp OR 'adolescent*':ti,ab,kw OR 'adult*':ti,ab,kw OR 'ancient*':ti,ab,kw OR 'baby*':ti,ab,kw OR 'child':ti,ab,kw OR 'children':ti,ab,kw OR 'cohort*':ti,ab,kw OR 'elderly':ti,ab,kw OR 'female*':ti,ab,kw OR 'homo sapiens':ti,ab,kw OR 'host*':ti,ab,kw OR 'human*':ti,ab,kw OR 'individual*':ti,ab,kw OR 'infant*':ti,ab,kw OR 'male*':ti,ab,kw OR 'man':ti,ab,kw OR 'men':ti,ab,kw OR 'parents':ti,ab,kw OR 'participant*':ti,ab,kw OR 'patient*':ti,ab,kw OR 'people':ti,ab,kw OR 'person*':ti,ab,kw OR 'player*':ti,ab,kw OR 'population*':ti,ab,kw OR 'student*':ti,ab,kw OR 'subject*':ti,ab,kw OR 'survivor*':ti,ab,kw OR 'volunteer*':ti,ab,kw OR 'woman':ti,ab,kw OR 'women':ti,ab,kw

#5 #1 AND #2 AND #3 AND #4

#6 #5 AND ('Article'/it OR 'Article in Press'/it)

Search strategy Web of Knowledge (WoS)

```
#1: ((((((((((((((((((((((((((TS=(chemokine ccl5)) OR TI=((ccl)5)) OR TI=(ccl 5)) OR TI=(ccl5))
OR TI=(ccl-5)) OR TI=(d17s136e)) OR TI=(eocp)) OR TI=(mgc17164)) OR TI=(rantes)) OR
TI=(scya5)) OR TI=(sisd)) OR TI=(sis-delta)) OR TI=(tcp228)) OR AB=((ccl)5)) OR AB=(ccl 5))
OR AB=(ccl5)) OR AB=(ccl-5)) OR AB=(d17s136e)) OR AB=(eocp)) OR AB=(mgc17164)) OR
AB=(rantes)) OR AB=(scya5)) OR AB=(sisd)) OR AB=(sis-delta)) OR AB=(tcp228)
```

#2:

(((((TS=(adenovirus infections, human)) OR TS=(coronavirus infections)) OR TS=(enterovirus infections)) OR TS=(metapneumovirus)) OR TS=(orthomyxoviridae infections)) OR TS=(paramyxoviridae infections)) OR TS=(respiratory syncytial virus infections)) OR TS=(respiratory tract infections)) OR TS=(rhinovirus) OR TI=(2019 ncov)) OR TI=(2019-ncov)) OR TI=(a24 virus)) OR TI=(a9 virus)) OR TI=(adenovirus)) OR TI=(apc virus)) OR TI=(bornholm disease virus)) OR TI=(coronavirus)) OR TI=(covid 19)) OR TI=(covid19)) OR TI=(covid-19)) OR TI=(coxsackie)) OR TI=(coxsackievirus)) OR TI=(d70 virus)) OR TI=(echo virus)) OR TI=(echovirus)) OR TI=(eva71)) OR TI=(ev-a71)) OR TI=(evd68)) OR TI=(ev-d68)) OR TI=(evd94)) OR TI=(ev-d94)) OR TI=(fifth disease)) OR TI=(flu)) OR TI=(grippe)) OR TI=(influenza)) OR TI=(mers)) OR TI=(metapneumovirus)) OR TI=(middle east respiratory syndrome)) OR TI=(parainfluenza)) OR TI=(parvovirus b19)) OR TI=(pleurodynia virus)) OR TI=(pneumovirus)) OR TI=(respiratory infection)) OR TI=(respiratory syncytial)) OR TI=(respiratory tract infection)) OR TI=(respiratory virus)) OR TI=(rhinovirus)) OR TI=(rsv)) OR TI=(sars cov 2)) OR TI=(sars-cov-2)) OR TI=(common cold virus)) OR TI=(coryza virus)) OR AB=(2019-ncov)) OR AB=(a24 virus)) OR AB=(a9 virus)) OR AB=(adenovirus)) OR AB=(apc virus)) OR AB=(bornholm disease virus)) OR AB=(coronavirus)) OR AB=(covid 19)) OR AB=(covid19)) OR AB=(covid-19)) OR AB=(coxsackie)) OR AB=(coxsackievirus)) OR AB=(d70 virus)) OR AB=(echo virus)) OR AB=(echovirus)) OR AB=(eva71)) OR AB=(ev-a71)) OR AB=(evd68)) OR AB=(ev-d68)) OR AB=(evd94)) OR AB=(ev-d94)) OR AB=(fifth disease)) OR AB=(flu)) OR AB=(grippe)) OR AB=(influenza)) OR AB=(mers)) OR AB=(metapneumovirus)) OR AB=(middle east respiratory syndrome)) OR AB=(parainfluenza)) OR AB=(parvovirus b19)) OR AB=(pleurodynia virus)) OR AB=(pneumovirus)) OR AB=(respiratory infection)) OR AB=(respiratory syncytial)) OR AB=(respiratory tract infection)) OR AB=(respiratory virus)) OR AB=(rhinovirus)) OR AB=(rsv)) OR AB=(sars cov 2)) OR AB=(sars-cov-2)) OR AB=(common cold virus)) OR AB=(coryza virus))

#3: ((TS=(bronchiolitis)) OR TS=(critical care)) OR TS=(diagnostic tests, routine)) OR TS=(hospitalization)) OR TS=(intensive care units)) OR TS=(mortality)) OR TS=(patient acuity)) OR TS=(pneumonia, bacterial) OR TI=(bronchiolitides)) OR TI=(bronchiolitis)) OR TI=(cfr)) OR TI=(dead)) OR TI=(death)) OR TI=(die)) OR TI=(disease severity)) OR TI=(exitus)) OR TI=(fatality)) OR TI=(hospital admission)) OR TI=(icu)) OR TI=(intensive care)) OR TI=(lower respiratory tract infection)) OR TI=(lrti)) OR TI=(mortality)) OR TI=(pneumonia)) OR TI=(preadmission)) OR TI=(routine admission)) OR TI=(rti) OR AB=(bronchiolitides)) OR AB=(bronchiolitis)) OR AB=(cfr)) OR AB=(dead)) OR AB=(death)) OR AB=(die)) OR AB=(disease severity)) OR AB=(exitus)) OR AB=(fatality)) OR AB=(hospital admission)) OR AB=(icu)) OR AB=(intensive care)) OR AB=(lower respiratory tract infection)) OR AB=(lrti)) OR AB=(mortality)) OR AB=(pneumonia)) OR AB=(preadmission)) OR AB=(routine admission)) OR AB=(rti)#4:

(((TS=(humans)) OR TS=(persons)) OR
TI=(adolescent)) OR TI=(adult)) OR TI=(ancient)) OR TI=(baby)) OR TI=(child)) OR
TI=(children)) OR TI=(cohort)) OR TI=(elderly)) OR TI=(female)) OR TI=(homo sapiens)) OR
TI=(host)) OR TI=(human)) OR TI=(individual)) OR TI=(infant)) OR TI=(male)) OR TI=(man))

OR TI=(men)) OR TI=(parents)) OR TI=(participant)) OR TI=(patient)) OR TI=(people)) OR TI=(person)) OR TI=(player)) OR TI=(population)) OR TI=(student)) OR TI=(subject)) OR TI=(survivor)) OR TI=(volunteer)) OR TI=(woman)) OR TI=(women) OR TI=(adolescent)) OR TI=(adult)) OR TI=(ancient)) OR TI=(baby)) OR TI=(child)) OR TI=(children)) OR TI=(cohort)) OR TI=(elderly)) OR TI=(female)) OR TI=(homo sapiens)) OR TI=(host)) OR TI=(human)) OR TI=(individual)) OR TI=(infant)) OR TI=(male)) OR TI=(man)) OR TI=(men)) OR TI=(parents)) OR TI=(participant)) OR TI=(patient)) OR TI=(people)) OR TI=(person)) OR TI=(player)) OR TI=(population)) OR TI=(student)) OR TI=(subject)) OR TI=(survivor)) OR TI=(volunteer)) OR TI=(woman)) OR TI=(women)

#5: #4 AND #3 AND #2 AND #1

#6: #5 and Article (Document Types)

Search strategy

We conducted a comprehensive literature search to identify all relevant studies published up to October 1, 2025. Searches were conducted across multiple electronic databases, including Medline/PubMed, Embase, Scopus, Web of Science, the Cochrane Library, Global Health (CABI), and Ovid HealthSTAR. The search strategy utilized Boolean operators (AND, OR, NOT) to combine terms related to (i) chemokine CCL5 (e.g., "CCL5", "RANTES"), (ii) human respiratory and viral infections (e.g., "coronavirus", "influenza"), (iii) clinical outcomes (e.g., "mortality", "disease severity"), and (iv) human study populations (e.g., "humans", "patients"). No language or geographic restrictions were applied. Reference lists of relevant studies were manually screened to identify additional eligible articles. All retrieved references were managed with EndNote X9 (Clarivate Analytics) and exported to Microsoft Excel 2016 (Microsoft Corporation) for further processing.

Search strategy SCOPUS

(TITLE-ABS-KEY ({CCL}5 }) OR TITLE-ABS-KEY ({CCL 5}) OR TITLE-ABS-KEY ({CCL5}) OR TITLE-ABS-KEY ({CCL-5}) OR TITLE-ABS-KEY ({D17S136E}) OR TITLE-ABS-KEY ({eoCP}) OR TITLE-ABS-KEY ({MGC17164}) OR TITLE-ABS-KEY ({RANTES}) OR TITLE-ABS-KEY ({SCYA5}) OR TITLE-ABS-KEY ({SISd}) OR TITLE-ABS-KEY ({SIS-Delta}) OR TITLE-ABS-KEY ({TCP228}) AND TITLE-ABS-KEY ({2019 nCOV}) OR TITLE-ABS-KEY ({2019-nCOV}) OR TITLE-ABS-KEY ("A24 virus*") OR TITLE-ABS-KEY ("A9 virus*") OR TITLE-ABS-KEY ("adenovirus*") OR TITLE-ABS-KEY ("APC virus*") OR TITLE-ABS-KEY ({ Bornholm Disease Virus }) OR TITLE-ABS-KEY ("coronavirus*") OR TITLE-ABS-KEY ({ COVID 19 }) OR TITLE-ABS-KEY ({ COVID19 }) OR TITLE-ABS-KEY ({ COVID-19 }) OR TITLE-ABS-KEY ({ Cocksackie }) OR TITLE-ABS-KEY ("Cocksackievirus*") OR TITLE-ABS-KEY ("D70 virus*") OR TITLE-ABS-KEY ("Echo virus*") OR TITLE-ABS-KEY ("Echovirus*") OR TITLE-ABS-KEY ({ EVA71 }) OR TITLE-ABS-KEY ({ EV-A71 }) OR TITLE-ABS-KEY ({ EVD68 }) OR TITLE-ABS-KEY ({ EV-D68 }) OR TITLE-ABS-KEY ({ EVD94 }) OR TITLE-ABS-KEY ({ EV-D94 }) OR TITLE-ABS-KEY ({ Fifth disease }) OR TITLE-ABS-KEY ({ flu }) OR TITLE-ABS-KEY ({ gripe }) OR TITLE-ABS-KEY ({ influenza* }) OR TITLE-ABS-KEY ({ MERS }) OR TITLE-ABS-KEY ("Metapneumovirus*") OR TITLE-ABS-KEY ({ Middle East Respiratory Syndrome }) OR TITLE-ABS-KEY ({ parainfluenza }) OR TITLE-ABS-KEY ({ parvovirus B19 }) OR TITLE-ABS-KEY ("Pleurodynia virus*") OR TITLE-ABS-KEY ({ pneumovirus }) OR TITLE-ABS-KEY ("Respiratory Infection*") OR TITLE-ABS-KEY ({ Respiratory Syncytial }) OR TITLE-ABS-KEY ("Respiratory Tract Infection*") OR TITLE-ABS-KEY ("Respiratory Virus*") OR TITLE-ABS-KEY ("Rhinovirus*") OR TITLE-ABS-KEY ({ RSV }) OR TITLE-ABS-KEY ({ SARS CoV 2 }) OR TITLE-ABS-KEY ({ SARS-CoV-2 }) OR TITLE-ABS-KEY ({ common cold virus }) OR TITLE-ABS-KEY ("coryza virus*") AND TITLE-ABS-KEY ({ Bronchiolitides }) OR TITLE-ABS-KEY ({ Bronchiolitis }) OR TITLE-ABS-KEY ({ CFR }) OR TITLE-ABS-KEY ({ Dead }) OR TITLE-ABS-KEY ({ Death }) OR TITLE-ABS-KEY ({ Die }) OR TITLE-ABS-KEY ({ disease severity }) OR TITLE-ABS-KEY ({ exitus }) OR TITLE-ABS-KEY ({ Fatality }) OR TITLE-ABS-KEY ({ Hospital Admission }) OR TITLE-ABS-KEY ({ ICU }) OR TITLE-ABS-KEY ({ Intensive care }) OR TITLE-ABS-KEY ({ Lower Respiratory Tract Infection }) OR TITLE-ABS-KEY ({ LRTI* }) OR TITLE-ABS-KEY ({ Mortality }) OR TITLE-ABS-KEY ("Pneumonia*") OR TITLE-ABS-KEY ({ Preadmission }) OR TITLE-ABS-KEY ({ Routine Admission }) OR TITLE-ABS-KEY ({ RTI }) AND TITLE-ABS-KEY ("adolescent*") OR TITLE-ABS-KEY ({adult*}) OR TITLE-ABS-KEY ({ancient*}) OR TITLE-ABS-KEY ("baby*") OR TITLE-ABS-KEY ({ child }) OR TITLE-ABS-KEY ({ children }) OR TITLE-ABS-KEY ({cohort*}) OR TITLE-ABS-KEY ({ elderly }) OR TITLE-ABS-KEY ("female*") OR TITLE-ABS-KEY ({ Homo Sapiens }) OR TITLE-ABS-KEY ({ host* }) OR TITLE-ABS-KEY ("human*") OR TITLE-ABS-KEY ("individual*") OR TITLE-ABS-KEY ("infant*") OR TITLE-ABS-KEY ("male*") OR TITLE-ABS-KEY ({ man }) OR TITLE-ABS-KEY ({ men }) OR TITLE-ABS-KEY ({ parents }) OR TITLE-ABS-KEY ("participant*") OR TITLE-ABS-KEY ("patient*") OR TITLE-ABS-KEY ({ people }) OR TITLE-ABS-KEY ("person*") OR TITLE-ABS-KEY ("player*") OR TITLE-ABS-KEY ("population*") OR TITLE-ABS-KEY ("student*") OR TITLE-ABS-KEY ("subject*") OR TITLE-ABS-KEY ("survivor*") OR TITLE-ABS-KEY ("volunteer*") OR TITLE-ABS-KEY ({ woman }) OR TITLE-ABS-KEY ({ women })) AND (EXCLUDE (DOCTYPE , "tb") OR EXCLUDE (DOCTYPE , "er") OR EXCLUDE (DOCTYPE , "no") OR EXCLUDE (DOCTYPE , "ch") OR EXCLUDE (DOCTYPE , "sh") OR EXCLUDE (DOCTYPE , "cp") OR EXCLUDE (DOCTYPE , "ed") OR EXCLUDE (DOCTYPE , "le") OR EXCLUDE (DOCTYPE , "re"))

Search strategy Cochrane Library

- #1 MeSH descriptor: [Chemokine CCL5] explode all trees
- #2 ("(CCL)5"):ti,ab,kw
- #3 (CCL 5):ti,ab,kw
- #4 (CCL5):ti,ab,kw
- #5 (CCL-5):ti,ab,kw
- #6 (D17S136E):ti,ab,kw
- #7 (eoCP):ti,ab,kw
- #8 (MGC17164):ti,ab,kw
- #9 (RANTES):ti,ab,kw
- #10 (SCYA5):ti,ab,kw
- #11 (SISd):ti,ab,kw
- #12 (SIS-Delta):ti,ab,kw
- #13 (TCP228):ti,ab,kw
- #14 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
- #15 MeSH descriptor: [Adenovirus Infections, Human] explode all trees
- #16 MeSH descriptor: [Coronavirus Infections] explode all trees
- #17 MeSH descriptor: [Enterovirus Infections] explode all trees
- #18 MeSH descriptor: [Metapneumovirus] explode all trees
- #19 MeSH descriptor: [Orthomyxoviridae Infections] explode all trees
- #20 MeSH descriptor: [Paramyxoviridae Infections] explode all trees
- #21 MeSH descriptor: [Respiratory Syncytial Virus Infections] explode all trees
- #22 MeSH descriptor: [Respiratory Tract Infections] explode all trees
- #23 MeSH descriptor: [Rhinovirus] explode all trees
- #24 (2019 nCoV):ti,ab,kw
- #25 (A24 virus):ti,ab,kw
- #26 (A9 virus):ti,ab,kw
- #27 (adenovirus):ti,ab,kw
- #28 (APC virus):ti,ab,kw
- #29 (Bornholm Disease Virus):ti,ab,kw
- #30 (coronavirus):ti,ab,kw
- #31 (COVID 19):ti,ab,kw
- #32 (COVID19):ti,ab,kw
- #33 (COVID-19):ti,ab,kw
- #34 (Coxsackie):ti,ab,kw
- #35 (Coxsackievirus):ti,ab,kw
- #36 (D70 virus):ti,ab,kw
- #37 (Echo virus):ti,ab,kw
- #38 (Echovirus):ti,ab,kw
- #39 (EVA71):ti,ab,kw
- #40 (EV-A71):ti,ab,kw
- #41 (EVD68):ti,ab,kw
- #42 (EV-D68):ti,ab,kw
- #43 (EVD94):ti,ab,kw
- #44 (EV-D94):ti,ab,kw
- #45 (Fifth disease):ti,ab,kw
- #46 (flu):ti,ab,kw
- #47 (grippe):ti,ab,kw
- #48 (influenza):ti,ab,kw

#49 (MERS):ti,ab,kw
 #50 (Metapneumovirus):ti,ab,kw
 #51 (Middle East Respiratory Syndrome):ti,ab,kw
 #52 (parainfluenza):ti,ab,kw
 #53 (parvovirus B19):ti,ab,kw
 #54 (Pleurodynia virus):ti,ab,kw
 #55 (pneumovirus):ti,ab,kw
 #56 (Respiratory Infection):ti,ab,kw
 #57 (Respiratory Syncytial):ti,ab,kw
 #58 (Respiratory Tract Infection):ti,ab,kw
 #59 (Respiratory Virus):ti,ab,kw
 #60 (Rhinovirus):ti,ab,kw
 #61 (RSV):ti,ab,kw
 #62 (SARS CoV 2):ti,ab,kw
 #63 (SARS-CoV-2):ti,ab,kw
 #64 (common cold virus):ti,ab,kw
 #65 (coryza virus):ti,ab,kw
 #66 #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25
 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR
 #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48
 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR
 #60 OR #61 OR #62 OR #63 OR #64 OR #65
 #67 MeSH descriptor: [Bronchiolitis] explode all trees
 #68 MeSH descriptor: [Critical Care] explode all trees
 #69 MeSH descriptor: [Diagnostic Tests, Routine] explode all trees
 #70 MeSH descriptor: [Hospitalization] explode all trees
 #71 MeSH descriptor: [Intensive Care Units] explode all trees
 #72 MeSH descriptor: [Mortality] explode all trees
 #73 MeSH descriptor: [Patient Acuity] explode all trees
 #74 MeSH descriptor: [Pneumonia, Bacterial] explode all trees
 #75 (Bronchiolitides):ti,ab,kw
 #76 (Bronchiolitis):ti,ab,kw
 #77 (CFR):ti,ab,kw
 #78 (Dead):ti,ab,kw
 #79 (Death):ti,ab,kw
 #80 (Die):ti,ab,kw
 #81 (disease severity):ti,ab,kw
 #82 (exitus):ti,ab,kw
 #83 (Fatality):ti,ab,kw
 #84 (Hospital Admission):ti,ab,kw
 #85 (ICU):ti,ab,kw
 #86 (Intensive care):ti,ab,kw
 #87 (Lower Respiratory Tract Infection):ti,ab,kw
 #88 (LRTI):ti,ab,kw
 #89 (Mortality):ti,ab,kw
 #90 (Pneumonia):ti,ab,kw
 #91 (Preadmission):ti,ab,kw
 #92 (Routine Admission):ti,ab,kw
 #93 (RTI):ti,ab,kw

#94 #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93

#95 MeSH descriptor: [Humans] explode all trees

#96 MeSH descriptor: [Persons] explode all trees

#97 (adolescent):ti,ab,kw

#98 (adult):ti,ab,kw

#99 (ancient):ti,ab,kw

#100 (baby):ti,ab,kw

#101 (child):ti,ab,kw

#102 (children):ti,ab,kw

#103 (cohort):ti,ab,kw

#104 (elderly):ti,ab,kw

#105 (female):ti,ab,kw

#106 (Homo Sapiens):ti,ab,kw

#107 (host):ti,ab,kw

#108 (human):ti,ab,kw

#109 (individual):ti,ab,kw

#110 (infant):ti,ab,kw

#111 (male):ti,ab,kw

#112 (man):ti,ab,kw

#113 (men):ti,ab,kw

#114 (parents):ti,ab,kw

#115 (participant):ti,ab,kw

#116 (patient):ti,ab,kw

#117 (people):ti,ab,kw

#118 (person):ti,ab,kw

#119 (player):ti,ab,kw

#120 (population):ti,ab,kw

#121 (student):ti,ab,kw

#122 (subject):ti,ab,kw

#123 (survivor):ti,ab,kw

#124 (volunteer):ti,ab,kw

#125 (woman):ti,ab,kw

#126 (women):ti,ab,kw

#127 #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126

#128 #14 AND #66 AND #94 AND #127

Search strategy Global Health (CABI)

#1 de:(chemokines OR RANTES) OR ti:("(CCL)5" OR "CCL 5" OR "CCL5" OR "CCL-5" OR "D17S136E" OR "eoCP" OR "MGC17164" OR "RANTES" OR "SCYA5" OR "SISd" OR "SIS-Delta" OR "TCP228") OR ab:("(CCL)5" OR "CCL 5" OR "CCL5" OR "CCL-5" OR "D17S136E" OR "eoCP" OR "MGC17164" OR "RANTES" OR "SCYA5" OR "SISd" OR "SIS-Delta" OR "TCP228")

#2 de:(adenovirus infections OR coronaviridae OR enterovirus OR metapneumovirus OR orthomyxoviridae OR paramyxoviridae OR "respiratory syncytial virus" OR "respiratory tract infections" OR rhinovirus) OR ti:("2019 nCoV" OR "2019-nCoV" OR "A24 virus*" OR "A9 virus*" OR "adenovirus*" OR "APC virus*" OR "Bornholm Disease Virus" OR "coronavirus*" OR "COVID 19" OR "COVID19" OR "COVID-19" OR "Coxsackie" OR "Coxsackievirus*" OR "D70 virus*" OR "Echo virus*" OR "Echovirus*" OR "EVA71" OR "EV-A71" OR "EVD68" OR "EV-D68" OR "EVD94" OR "EV-D94" OR "Fifth disease" OR "flu" OR "grippe" OR "influenza*" OR "MERS" OR "Metapneumovirus*" OR "Middle East Respiratory Syndrome" OR "parainfluenza" OR "parvovirus B19" OR "Pleurodynia virus*" OR "pneumovirus" OR "Respiratory Infection*" OR "Respiratory Syncytial" OR "Respiratory Tract Infection*" OR "Respiratory Virus*" OR "Rhinovirus*" OR "RSV" OR "SARS CoV 2" OR "SARS-CoV-2" OR "common cold virus" OR "coryza virus*") OR ab:("2019 nCoV" OR "2019-nCoV" OR "A24 virus*" OR "A9 virus*" OR "adenovirus*" OR "APC virus*" OR "Bornholm Disease Virus" OR "coronavirus*" OR "COVID 19" OR "COVID19" OR "COVID-19" OR "Coxsackie" OR "Coxsackievirus*" OR "D70 virus*" OR "Echo virus*" OR "Echovirus*" OR "EVA71" OR "EV-A71" OR "EVD68" OR "EV-D68" OR "EVD94" OR "EV-D94" OR "Fifth disease" OR "flu" OR "grippe" OR "influenza*" OR "MERS" OR "Metapneumovirus*" OR "Middle East Respiratory Syndrome" OR "parainfluenza" OR "parvovirus B19" OR "Pleurodynia virus*" OR "pneumovirus" OR "Respiratory Infection*" OR "Respiratory Syncytial" OR "Respiratory Tract Infection*" OR "Respiratory Virus*" OR "Rhinovirus*" OR "RSV" OR "SARS CoV 2" OR "SARS-CoV-2" OR "common cold virus" OR "coryza virus*")

#3 de:(bronchiolitis OR "critical care" OR diagnosis OR hospitalization OR "intensive care" OR mortality OR pneumonia) OR ti:("Bronchiolitides" OR "Bronchiolitis" OR "CFR" OR "Dead" OR "Death" OR "Die" OR "disease severity" OR "exitus" OR "Fatality" OR "Hospital Admission" OR "ICU" OR "Intensive care" OR "Lower Respiratory Tract Infection" OR "LRTI*" OR "Mortality" OR "Pneumonia*" OR "Preadmission" OR "Routine Admission" OR "RTI") OR ab:("Bronchiolitides" OR "Bronchiolitis" OR "CFR" OR "Dead" OR "Death" OR "Die" OR "disease severity" OR "exitus" OR "Fatality" OR "Hospital Admission" OR "ICU" OR "Intensive care" OR "Lower Respiratory Tract Infection" OR "LRTI*" OR "Mortality" OR "Pneumonia*" OR "Preadmission" OR "Routine Admission" OR "RTI")

#4 de:(man) OR ti:("adolescent*" OR "adult*" OR "ancient*" OR "baby*" OR "child" OR "children" OR "cohort*" OR "elderly" OR "female*" OR "Homo Sapiens" OR "host*" OR "human*" OR "individual*" OR "infant*" OR "male*" OR "man" OR "men" OR "parents" OR "participant*" OR "patient*" OR "people" OR "person*" OR "player*" OR "population*" OR "student*" OR "subject*" OR "survivor*" OR "volunteer*" OR "woman" OR "women") OR ab:("adolescent*" OR "adult*" OR "ancient*" OR "baby*" OR "child" OR "children" OR "cohort*" OR "elderly" OR "female*" OR "Homo Sapiens" OR "host*" OR "human*" OR "individual*" OR "infant*" OR "male*" OR "man" OR "men" OR "parents" OR "participant*" OR "patient*" OR "people" OR "person*" OR "player*" OR "population*" OR "student*" OR "subject*" OR "survivor*" OR "volunteer*" OR "woman" OR "women")

Search strategy Ovid HealthSTAR

#1 exp Chemokine CCL5/ or ("CCL)5" or "CCL 5" or "CCL5" or "CCL-5" or "D17S136E" or "eoCP" or "MGC17164" or "RANTES" or "SCYA5" or "SISd" or "SIS-Delta" or "TCP228").ab,ti.

#2 exp "Adenovirus Infections, Human"/ or exp "Coronavirus Infections"/ or exp "Enterovirus Infections"/ or exp Metapneumovirus/ or exp "Orthomyxoviridae Infections"/ or exp "Paramyxoviridae Infections"/ or exp "Respiratory Syncytial Virus Infections"/ or exp "Respiratory Tract Infections"/ or exp Rhinovirus/ or ("2019 nCoV" or "2019-nCoV" or "A24 virus*" or "A9 virus*" or "adenovirus*" or "APC virus*" or "Bornholm Disease Virus" or "coronavirus*" or "COVID 19" or "COVID19" or "COVID-19" or "Coxsackie" or "Coxsackievirus*" or "D70 virus*" or "Echo virus*" or "Echovirus*" or "EVA71" or "EV-A71" or "EVD68" or "EV-D68" or "EVD94" or "EV-D94" or "Fifth disease" or "flu" or "grippe" or "influenza*" or "MERS" or "Metapneumovirus*" or "Middle East Respiratory Syndrome" or "parainfluenza" or "parvovirus B19" or "Pleurodynia virus*" or "pneumovirus" or "Respiratory Infection*" or "Respiratory Syncytial" or "Respiratory Tract Infection*" or "Respiratory Virus*" or "Rhinovirus*" or "RSV" or "SARS CoV 2" or "SARS-CoV-2" or "common cold virus" or "coryza virus*").ab,ti.

#3 exp Bronchiolitis/ or exp "Critical Care"/ or exp "Diagnostic Tests, Routine"/ or exp Hospitalization/ or exp "Intensive Care Units"/ or exp Mortality/ or exp "Patient Acuity"/ or exp "Pneumonia, Bacterial"/ or ("Bronchiolitides" or "Bronchiolitis" or "CFR" or "Dead" or "Death" or "Die" or "disease severity" or "exitus" or "Fatality" or "Hospital Admission" or "ICU" or "Intensive care" or "Lower Respiratory Tract Infection" or "LRTI*" or "Mortality" or "Pneumonia*" or "Preadmission" or "Routine Admission" or "RTI").ab,ti.

#4 exp humans/ or exp persons/ or ("adolescent*" or "adult*" or "ancient*" or "baby*" or "child" or "children" or "cohort*" or "elderly" or "female*" or "Homo Sapiens" or "host*" or "human*" or "individual*" or "infant*" or "male*" or "man" or "men" or "parents" or "participant*" or "patient*" or "people" or "person*" or "player*" or "population*" or "student*" or "subject*" or "survivor*" or "volunteer*" or "woman" or "women").ab,ti.

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

Detailed description of the guidelines used to assess the methodological quality and risk of bias of the studies included in this systematic review, using the Newcastle-Ottawa Scale (NOS). Specific versions of the scale were applied for case-control and cohort studies. For each item or signaling question, the criteria for awarding a star (★) are defined.

A. NOS adapted for case-control studies

1. Domain 1: Selection (Maximum of ★★★★★)

Q1. Is the case definition adequate? (★)

- Star awarded (★): If the case definition was objective and based on reliable sources, such as standardized diagnostic criteria (e.g., WHO guidelines), hard clinical endpoints (e.g., mortality, ICU admission, need for mechanical ventilation), or independent validation through medical records, laboratory tests, or imaging.
- No star awarded (-): If the case definition was unclear, subjective, or based solely on self-reporting without validation

Q2. Representativeness of the cases? (★)

- Star awarded (★): If the study stated that cases were enrolled consecutively or represented a complete or random sample of all eligible cases from a defined population within a specified timeframe.
- No star awarded (-): If the study used a convenience sample, did not describe the recruitment method, or if the selection process introduced a high potential for selection bias.

Q3. Selection of controls? (★)

- Star awarded (★): If controls were drawn from the same population as the cases (e.g., community controls, hospital controls from the same clinical setting and time period).
- No star awarded (-): If controls were selected from a different population (e.g., healthy blood donors for a study on hospitalized patients) or if their origin was not described.

Q4. Definition of controls? (★)

- Star awarded (★): If the study confirmed that controls did not have the outcome of interest (e.g., severe disease, mortality) and this was verified using objective criteria similar to those for cases.
- No star awarded (-): If the absence of the outcome in controls was not mentioned or verified.

2. Domain 2: Comparability (Maximum of ★★)

Q5. Comparability of cases and controls on the basis of the design or analysis? (★★)

- Two stars awarded (★★): If the study performed a robust multivariable analysis (e.g., logistic regression, Cox regression) to adjust for multiple key confounders (e.g., age, sex, comorbidities, and/or baseline severity).
- One star awarded (★): If the study performed statistical adjustment for at least one key confounding variable (e.g., age or comorbidities).
- No star awarded (-): If the study only described baseline characteristics of the groups without performing a formal statistical adjustment in the analysis of the association.

3. Domain 3: Exposure (Maximum of ★★★)

Q6. Ascertainment of exposure? (★)

- Star awarded (★): If the exposure (CCL5 levels, protein or gene expression) was measured using objective, reliable, and standardized methods (e.g., ELISA, Luminex, RT-PCR from validated records).
- No star awarded (-): If the exposure was based on self-report or unclear/unreliable methods.

Q7. Same method of ascertainment for cases and controls? (★)

- Star awarded (★): If the same method of exposure measurement was used for all study participants, regardless of their case/control status.
- No star awarded (-): If different methods were used or if this information was not stated.

Q8. Non-response rate? (★)

- Star awarded (★): If the rate of participation was complete for all recruited subjects, or if any data loss was minimal and stated to be non-differential between cases and controls.
- No star awarded (-): If there were significant or unexplained losses of participants or samples from the analysis.

B. NOS adapted for cohort studies

1. Domain 1: Selection (Maximum of ★★★)

Q1. Representativeness of the exposed cohort? (★)

- Star awarded (★): If the exposed cohort was drawn from a defined community or clinical population and was either truly representative or somewhat representative of that population.
- No star awarded (-): If the cohort was a highly selected group (e.g., specific ICU patients only) with limited generalizability.

Q2. Selection of the non-exposed cohort? (★)

- Star awarded (★): If the non-exposed cohort was drawn from the same source population as the exposed cohort.
- No star awarded (-): If drawn from a different source population.

Q3. Ascertainment of exposure? (★)

- Star awarded (★): If the exposure (CCL5 levels) was determined from secure and reliable records (e.g., laboratory assays like ELISA, Luminex, RT-PCR).
- No star awarded (-): If based on self-report or methods of unclear reliability.

Q4. Demonstration that outcome of interest was not present at start of study? (★)

- Star awarded (★): If it was confirmed that all participants were free of the outcome (e.g., mortality, unfavorable disease progression) at the time of the exposure measurement.
- No star awarded (-): If this was not confirmed.

2. Domain 2: Comparability (Maximum of ★★)

Q5. *Identical to the case-control scale*

3. Domain 3: Outcome (Maximum of ★★★)

Q6. Assessment of outcome? (★)

- Star awarded (★): If the outcome was ascertained through independent blind assessment or from reliable medical records (record linkage).
- No star awarded (-): If based on self-report or if the ascertainment method was not described.

Q7. Was follow-up long enough for outcomes to occur? (★)

- Star awarded (★): If the follow-up period was appropriate for the outcome of interest (e.g., duration of hospitalization for disease progression; 28-30 days for acute mortality).
- No star awarded (-): If the follow-up was too short.

Q8. Adequacy of follow up of cohorts? (★)

- Star awarded (★): If follow-up was complete for all subjects, or if losses were minimal and unlikely to introduce bias.
- No star awarded (-): If there were significant losses to follow-up or if the follow-up rate was not described.

Summary of the quality assessment by using NOS

Author (year)	Ref.	Selection (★★★★)	Comparability (★★)	Outcome/Exposure (★★★)	NOS score
Matsumoto et al. (2012)	40	★★★★		★★★★	6
Nicholson et al. (2016)	41	★★★★	★★	★★★★	8
Thwaites et al. (2018)	20	★★★★	★	★★★★	7
Li et al. (2022)	42	★★★★		★★★★	6
Ochoa-Ramirez et al. (2022)	43	★★★★	★	★★★★	7
Talarico et al. (2022)	44	★★★★		★★★★	6
Martonik et al. (2023)	45	★★★★		★★★★	6
Pita-Martínez et al. (2023)	46	★★★★★	★★	★★★★	9
Mondell et al. (2024)	47	★★★★★	★★	★★★★	9
Pita-Martínez et al. (2024)	48	★★★★★	★★	★★★★	9
Pita-Martínez et al. (2024)	49	★★★★★	★★	★★★★	9
Balnis et al. (2021)	50	★★★★		★★★★	6
Fonseca et al. (2021)	51	★★★★	★★	★★★★	8
Gibellini et al. (2022)	52	★★★★	★★	★★★★	8
Pérez-García et al. (2022)	53	★★★★★	★★	★★★★	9
Alhethel et al. (2023)	54	★★★★		★★★★	6
Gajate-Arenas et al. (2024)	55	★★★★	★★	★★★★	8
Michels et al. (2024)	56	★★★★	★★	★★★★	8

In the Selection domain, there are four items, each of which may receive one star (★), for a total maximum of four stars (★★★★). The Comparability domain consists of a single item that may receive up to two stars (★★). In the Outcome/Exposure domain, there are three items, each of which may receive one star (★), for a total maximum of three stars (★★★).

eTable. GRADE summary of findings for the association between elevated CCL5 levels and clinical outcomes. Question: Are elevated CCL5 levels associated with a reduced risk of unfavorable disease progression or mortality in patients with respiratory viral infections?

Outcome	No. of studies (Participants)	Risk of bias ¹	Inconsistency ²	Indirectness ³	Imprecision ⁴	Publications bias ⁵	Other considerations ⁶	Relative effect: Pooled OR; 95% CI	Certainty ⁷	Outcome importance ⁸
Unfavorable disease progression	11 (n=1,241)	Not serious	Not serious	Not serious	Not serious	Not serious	Upgraded (+1)	0.78; 0.71-0.85	Moderate ⊕⊕⊕○	Critical
Mortality	7 (n=1,162)	Not serious	Not serious	Not serious	Not serious	Not serious	Upgraded (+1)	0.65; 0.55-0.76	Moderate ⊕⊕⊕○	Critical

Abbreviations: CI, Confidence Interval; GRADE, Grading of Recommendations Assessment, Development and Evaluation; OR, Odds Ratio.

¹ Risk of bias: We did not downgrade for risk of bias. Although 6 of the 18 included studies were of moderate quality, the majority of the evidence (12/18 studies, 66.7%) was derived from high-quality studies that adequately controlled for key confounding variables.

² Inconsistency: We did not downgrade for inconsistency. Statistical heterogeneity was very low for both unfavorable disease progression (I²=0%) and mortality (I²=23.1%), and the direction of effect was consistent across nearly all studies.

³ Indirectness: We did not downgrade for indirectness. The included studies directly addressed the population, exposure, and outcomes specified in our review question.

⁴ Imprecision: We did not downgrade for imprecision. The total number of participants was large for both outcomes, and the 95% confidence intervals for the pooled estimates were sufficiently narrow and did not cross the line of no effect.

⁵ Publication bias: We did not downgrade for publication bias. Although visual inspection of the funnel plot suggested a potential slight asymmetry for one outcome, formal statistical tests (Begg's and Egger's tests) were non-significant for both outcomes. Sensitivity analyses, including trim-and-fill, confirmed the robustness of the results.

⁶ Other considerations: We upgraded the certainty of evidence by one level by the combination of a large and consistent magnitude of effect (a 22% and 35% reduction in odds, respectively), the low heterogeneity, and the fact that high-quality observational studies predominantly supported this effect.

⁷ GRADE certainty ratings. (i) High: The result is very reliable. Further research is very unlikely to change our confidence in the estimate of the effect; (ii) Moderate: The result is reliable. Further research may impact our confidence in the estimate of the effect and may change the estimate; (iii) Low: The result has limited reliability. Additional research is likely to impact our confidence in the estimate of the effect and is expected to change the estimate; and (iv) Very low: The result is very unreliable. Any estimate of effect is very uncertain. The starting certainty of evidence was low because the analysis is based on observational studies.

⁸ Outcome importance ratings. This classification rates how crucial an outcome is from a patient's perspective for making decisions: (i) Critical: Outcomes that are essential to a patient when making a decision. These typically include life-threatening events like mortality or the need for life support; (ii) Important: Outcomes that are relevant to patients but are not as decisive as critical ones (e.g., length of hospital stay, duration of symptoms), and (iii) Limited importance: Outcomes that most patients would not consider a key factor in their decisions (e.g., minor changes in a laboratory test without direct symptoms).

eFigure. Risk of bias assessment of the included studies. (A) Overall methodological quality of the 18 included studies, assessed with the Newcastle-Ottawa Scale (NOS) and presented as a stacked bar chart categorized by high (≥ 7 stars) or moderate (5–6 stars) quality. (B) Item-by-item breakdown of the NOS assessment, showing the percentage of studies that received stars for each of the eight evaluated questions (Q1–Q8) across the domains of selection, comparability, and exposure/outcome. Abbreviations: NOS, Newcastle-Ottawa Scale.

