Iga Vasculitis And COVID-19 In Children: A Systematic Review

Eva Maria Glenn Lecea (eva.glennlecea@nicklaushealth.org)
Nicklaus Children's Hospital
Daniela Aguilar Abisad
Nicklaus Children's Hospital
Ana Paredes
Kidz Nephrology
Arielle Hay
Nicklaus Children's Hospital

Research Article

Keywords: IgA vasculitis, Henoch-Schonlein purpura, SARS-COv2, COVID-19, systematic review, pediatrics.

Posted Date: February 3rd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1043944/v2

Abstract

Background: Immunoglobulin A vasculitis is the most common form of vasculitis in children. The diagnosis is made clinically and patients will present with a rash, together with gastrointestinal, musculoskeletal, and renal system involvement. Progress in the classification of the systemic vasculitides has facilitated better understanding of the pathogenesis underlying these inflammatory conditions. Over the past year, several cases of IgA vasculitis have been reported in both children and adults in association with SARS-CoV2 infection, raising the question of whether there is any causal or even a synergistic association.

Methods: This systematic review was performed following the guidelines of Meta-analysis of Observational Studies in Epidemiology. A literature search was conducted using MEDLINE, SciELO and Google Scholar using the search terms “COVID-19” or “SARS-CoV-2" in combination with “IgA vasculitis”, or “Henoch-Schonlein Purpura”. We considered articles to be eligible for inclusion if they reported a case report or series of cases of IgA vasculitis associated with proven COVID-19 infection. We excluded cases from further review if the case reported was a patient older than 18 years. WHO causality assessment categories were used to standardize case causality.

Results: After reviewing the complete article and applying our exclusion criteria, 12 articles describing 12 cases of COVID-19 associated IgA vasculitis in children were included. In 83% of the cases the diagnosis of COVID-19 was made on presentation of IgA vasculitis symptoms or on presentation to seek medical care. In 17% of cases the SARS Cov-2 test was positive before IgA vasculitis symptoms presentation. The mean age of the patients was 7.3 years of age (SD ±4.8). Male to female ratio was 3:1. Out of the 12 patients, 6 presented 2/4 criteria for IgA vasculitis and 6 presented 3/4 criteria. None presented 4/4 criteria.

Conclusions: During the pandemic, several autoimmune phenomena have been described to co-occur with or following COVID-19. The exact role of COVID-19 in the development of these IgA-related diseases is still being explored. Our review of case series and case reports with standardized causality assessment identified 12 cases of IgA vasculitis associated with and/or in the context of COVID-19 infection in children.

Background

Immunoglobulin A vasculitis (IgAV; formerly Henoch-Schonlein Purpura) is the most common form of vasculitis in children. It can occur in any age and peaks around 4-6 years old. The diagnosis is made clinically and 95% of patients will present with a rash, together with any from a triad of other systems: gastrointestinal, musculoskeletal, and renal (1, 2). Progress in the classification of the systemic vasculitides has facilitated a better understanding of the pathogenesis underlying these inflammatory conditions, which can be mediated by cells, immune complexes, or anti-neutrophil antibodies. Over the past year, several cases of IgA vasculitis have been reported in both children and adults in association

with or in the context of SARS-CoV2 infection, raising the question of whether there is any causal or even a synergistic association, as SARS-CoV-2 has proved to cause endothelial damage via a cytokine mediated inflammatory cascade (3).

The cutaneous manifestations of COVID-19 in children reported in the literature include chilblain-like lesions, erythema multiforme, urticaria, and acute hemorrhagic edema of infancy (4–5). IgA vasculitis associated with and in the context of COVID-19 has been also described in multiple case reports and case series (6–25).

This systematic review's purpose is to answer the question of possible association between IgA vasculitis and COVID-19 in children.

Methods

This systematic review was performed following the guidelines of Meta-analysis of Observational Studies in Epidemiology (26)

Literature Sources

A literature search was conducted using MEDLINE, SciELO and the first 15 pages of Google scholar using the search terms “COVID-19” or “SARS-CoV-2" in combination with “IgA vasculitis”, or “Henoch-Schonlein Purpura” to identify case reports published from January 1st, 2020 until August 30th, 2021. In addition, abstracts from the 2020 conferences of the American Society of Nephrology, the American College of Rheumatology and the American Academy of Pediatrics were reviewed for relevant case reports. Causality criteria of the World Health Organization causality assessment system (27) were applied to each report. Data was subsequently analyzed with descriptive statistics.

Study Selection

We considered articles to be eligible for inclusion if they reported a case report or series of cases of HSP/IgA vasculitis associated with COVID-19 infection. We used the criteria of the Paediatric Rheumatology International Trials Organization and the Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) in 2010 (28), which consists of mandatory and supportive criteria. Mandatory criterion includes palpable purpura in the absence of thrombocytopenia, while the supportive criteria involve at least one or more of the following: acute-onset diffuse abdominal pain, acute-onset arthralgia or arthritis, renal involvement in the form of proteinuria or haematuria, and histopathological evidence of leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant IgA deposits. COVID-19 infection was defined as: Detection of SARS-CoV-2 ribonucleic acid in a respiratory swab or clinical specimen using a diagnostic molecular amplification test or SARS-CoV-2 specific antigen in a clinical specimen (29). We excluded cases from further review if they fulfilled 1 or more of the following criteria: Age older than 18 years, failure to have a positive diagnostic test for COVID-19, missing information that

could not be obtained from the authors or causality criteria of unlikely, conditional/unclassified, or unassessable/ unclassifiable by the WHO-UMC causality assessment.

Data Abstraction

One author (EGL) scanned titles and abstracts for initial selection. Selected articles were reviewed in full and independently assessed for eligibility and causality by two authors (EGL, DAA). Discrepancies were resolved by consensus and involvement of other authors (AP). Data from each included: baseline demographic characteristics (age, gender), comorbid conditions, presenting symptoms and chronological relationship of COVID-19 diagnosis to IgA vasculitis/HSP presentation.

Causality/assessment Criteria

Causality criteria of the World Health Organization-Uppsala Monitoring Center (WHO-UMC) causality assessment system were applied to each report to assess the likelihood of a causal relationship between Covid-19 infection and IgA vasculitis. The WHO-UMC scale is a causality assessment system that is validated and widely accepted in pharmacovigilance that uses pre-specified criteria to categorize the causal link between a drug and an adverse event into 1 of 6 discrete levels of certainty (certain, probable/likely, possible, unlikely, conditional/unclassified, and unassessable/unclassifiable) (27) (Table 1).

Table 1
Causality criteria of the World Health Organization-Uppsala Monitoring Center (WHO-UMC)

CAUSALITY TERM	ASSESSMENT CRITERIA (All points should be reasonably complied with)
CERTAIN	• Event or laboratory test abnormality, with plausible time relationship to drug intake • Cannot be explained by disease or other drugs. • Response to withdrawal plausible (pharmacologically, pathologically) • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon) • Re-challenge satisfactory, if necessary
PROBABLE/ LIKELY	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Unlikely to be attributed to disease or other drugs • Response to withdrawal clinically reasonable • Re-challenge not required
POSSIBLE	• Event or laboratory test abnormality, with reasonable time relationship to drug intake • Could also be explained by disease or other drugs • Information on drug withdrawal may be lacking or unclear
UNLIKELY	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible) • Disease or other drugs provide plausible explanations
CONDITIONAL/ UNCLASSFIED	• Event or laboratory test abnormality • More data for proper assessment needed, or • Additional data under examination
UNASSESSABLE/ UNCLASSIFIABLE	• Report suggesting an adverse reaction • Cannot be judged because information is insufficient or contradictory • Data cannot be supplemented or verified

Statistical Analysis

We used descriptive statistics to compare similarities and differences between cases described. Categorical variables were expressed in percentages. Continuous variables were expressed as a mean with standard deviation.

Result

We identified 22 relevant articles from our literature search, based on titles and abstracts. After reviewing the complete article and applying our exclusion criteria, 12 articles describing 12 cases of COVID-19 associated IgA vasculitis in children were included (Image 1).

Image 1. Flow diagram of included studies

Patient Characteristics

The mean age of the patients was 7.3 years of age (SD ±4.8) with a bimodal distribution with the first and larger peak at 3.8 years (SD ±1.24) and the second peak at 13.5 years (SD ±1.5). Out of the 12 patients, there were 9 males and 3 females. In regards to ethnicity, 3 were of Mediterranean origin, 3 were Hispanic, 2 were Caucasian, 1 was black, 1 was Asian and 2 were not specified. Out of the 12 patients, 8 were reportedly healthy, 1 did not specify and 3 had a positive medical history: Atopic dermatitis, Hirschsprung disease, and suprasellar germinoma with secondary panhypopituitarism. (Tables 2 and 3)

Presentation

Per inclusion criteria, all patients included presented palpable purpura. Gastrointestinal manifestations were present in 7 patients, mainly abdominal pain, two of them with hematochezia. Oligoarthritis, defined as swelling and pain in 1-4 joints, was present in seven patients, involving ankles in 5 cases, and both knees in one case. 3 patients presented renal involvement with hematuria/proteinuria. None of the patients had hypertension. Out of the 12 patients, 6 patients met 2 of the criteria for IgA vasculitis, 6 patients met with 3 criteria for IgA vasculitis and none presented the 4 criteria. (Tables 2 and 3)

Laboratory Abnormalities

Six patients had elevation in the CRP level and few of them had other inflammatory markers measured such as D-dimer and ferritin. Elevated IgA in 4, 1 of them had normal IgA levels, the remaining 7 did not have the level measured. One patient’s skin lesion was biopsied. It did not show IgA deposits although the patient did have high serum IgA. (Tables 2 and 3)

Chronology

Chronological relationship between IgA vasculitis symptoms and COVID-19 diagnosis varied. In most cases (83%) the diagnosis of COVID-19 was made on presentation of IgA symptoms or on presentation to seek medical care. In 17% of cases (2/12) the SARS Cov-2 test was positive before IgA vasculitis

symptoms presentation. One of them had a positive PCR SARS Cov2 test 2 days prior to IgA vasculitis symptoms and the other one was 37 days prior. (Tables 2 and 3)

Table 3
Summary of patient characteristics

Demographic	
Age, mean (SD)	**7.3 (±4.8)**
1st peak	**3.8 (±1.24)**
2nd peak	**13.5 (±1.5)**
Male n (%)	**9 (75)**
Ethnicity n (%)	
Hispanic	**3 (25)**
Mediterranean	**3 (25)**
Black	**1 (8)**
Asian	**1 (8)**
Caucasian	**2 (17)**
Not specified	**2 (25)**
Comorbidities n (%)	
Gastrointestinal	**1 (8)**
CNS	**1 (8)**
Dermatologic	**1 (8)**
Presenting symptoms n (%)	
Purpuric rash	**12 (100)**
Arthritis/ Arthralgia	**7 (58)**
Abdominal pain	**7 (58)**
Hematochezia	**2 (17)**
Hematuria/Proteinuria	**3 (25)**
Chronologic relationship	
Simultaneously	**10 (75)**
COVID-19 diagnosis prior to IgA vasculitis symptoms	**2 (17)**

Table 4
Excluded articles

Excluded article	Criteria for exclusion
Allez (2020)	• Age >18 years • Patient's age: 24 years
Barbetta (2021)	• Age >18 years • Patient's age: 62 years
Bracaccia (2021)	• Age >18 years • Patient's age: 59 years
Li (2021)	• Age >18 years • Patient's age: 30 years
Mousavi (2021)	• No objective confirmation of SARS-Cov2 infection. Specimen tested negative for SARS-CoV-2.
Oñate (2021)	3 cases. All 3 patient ages >18 years • Case 1. Patient's age: 84 years • Case 2. Patient's age: 87 years • Case 3. Patient's age: 64 years
Sandhu (2021)	• Age >18 years • Patient's age: 22 years
Serafinelli (2021)	2 cases • Case 1: WHO-UMP causality criteria of unlikely, based on Sars-Cov2 detection weeks after IgA symptoms • Case 2: Failure to detect SARS-CoV2 on PCR. Of note, SARS-CoV2 IgG was positive.
Soleiman (2021)	• Age >18 years • Patient's age: 21 years
Suso (2020)	• Age >18 years • Patient's age: 78 years

Discussion

During the pandemic, several autoimmune phenomena have been described to co-occur with or following COVID-19 (3–4, 30–31) and it seems that the inflammatory response is similar in COVID-19 and autoimmunity. The immunological alterations associated with different stages of COVID-19 have been described since the earliest reports, and include an elevated number of macrophages, hyperactivation of T cells, and the release of increased plasma levels of pro-inflammatory cytokines as well as molecular mimicry, bystander activation and the epitope spreading (32–33).

Aberrant IgA responses underlie the pathogenesis of IgA vasculitis. The exact role of COVID-19 in the development of these IgA-related diseases is still being explored. Mucosal infections are believed to enhance IL-6 production that stimulates poor glycosylation/galactosylation of IgA1, thus forming Gd-IgA1 and contributing towards the disease process of IgA vasculitis (1, 34-35). COVID-19, being a mucosal infection as well, might cause IgA vasculitis through this pathway.

Our review of case series and case reports with standardized causality assessment identified 12 cases of IgA vasculitis associated with or in context of COVID-19 in children.

As in non-COVID-19-associated childhood IgA vasculitis, our research revealed that childhood IgA vasculitis associated with COVID-19 was more prevalent in early childhood. However, we also identified a second peak during adolescence. COVID-19 associated HSP was more common in males than in females with a ratio of 3:1, in comparison to non-COVID-19 associated IgA vasculitis, in which the ratio is 1.5:1 (1). In a study by Gardner-Medwin et al (36), in which they studied the incidence of childhood IgA vasculitis per ethnicity, there was a predominance of the disease in white and Asian populations. This study did not include Hispanic or Mediterranean population as study subjects. Our study demonstrated more cases of COVID-19-associated IgA vasculitis in both Hispanic and Mediterranean populations.

The disease presentation of the included studies was matched to the known IgA vasculitis presentation (1), with a purpuric rash needed for diagnosis; along with GI symptoms, including blood in stool in around 70% of patients; musculoskeletal involvement developing as arthritis and arthralgia mostly in the lower extremities in around 60% of patients; and renal involvement in 40-50% of patients.

In spite of criteria being met for IgA vasculitis in the context of Covid-19 in these cases, we need to be aware that these findings, including such GI symptoms, hematuria, proteinuria and even arthritis can be present during a viral illness regardless of IgA vasculitis. Moreover, there is evidence that since Covid-19 causes direct damage to capillaries, it can manifest with leucocytoclastic vasculitis (4).

Limitations

We acknowledge that the sample size in our study is small owing to the shortage of published articles related to our research question. Moreover, we were not able to concisely establish the time frame between COVID-19 infection and IgA vasculitis. For these reasons, and in the setting of a pandemic of the magnitude of COVID-19, the possibility of incidental co-disease cannot be excluded. More and larger studies should be done for the purpose of clarifying causality.

Conclusions

Several cases of IgA vasculitis have been described in the literature following, or in the setting of SARS-CoV2 infection. Evidence of a role of IgA in the immune response against COVID-19 is increasing. The exact role of COVID-19 in the development of these IgA-related diseases is still being explored. We hope that the future will bring a better understanding of the pathogenesis, correlation, causality and management of this entity.

Abbreviations

IgAV: Immunoglobulin A vasculitis; HSP: Henoch-Scholein Purpura; WHO-UMC: World Health Organization-Uppsala Monitoring Center

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and material

Data is available upon request

Competing interests

We know of no conflicts of interest associated with this manuscript.

Funding

There has not been significant financial support for this work that could have influenced the outcome

Authors' contributions

EGL and DAA developed the idea of the study, performed a literature search, generated and filled the tables with data, performed data analysis, scored case reports on critical appraisal, and drafted the manuscript. AP and AH also developed the idea of the study, scored case reports on critical appraisal, and reviewed the manuscript. All authors have critically reviewed and approved the final draft.

References

1. Oni L, Sampath S. Childhood iga vasculitis (Henoch Schonlein purpura)-advances and knowledge gaps [Internet]. Frontiers in pediatrics. U.S. National Library of Medicine; 2019 [cited 2022Jan5]. Available from: https://pubmed.ncbi.nlm.nih.gov/31316952/
2. Guillevin L, Dörner T. Vasculitis: Mechanisms involved and clinical manifestations. Arthritis Research & Therapy. 2007Aug15;9(Suppl 2).
3. Mohseni Afshar Z, Babazadeh A, Hasanpour A, Barary M, Sayad B, Janbakhsh A, et al. Dermatological manifestations associated with covid-19: A comprehensive review of the current knowledge [Internet]. Journal of medical virology. U.S. National Library of Medicine; 2021 [cited 2022Jan5]. Available from: https://pubmed.ncbi.nlm.nih.gov/34241899/
4. Mohseni Afshar Z, Babazadeh A, Hasanpour A, Barary M, Sayad B, Janbakhsh A, et al. Dermatological manifestations associated with covid-19: A comprehensive review of the current knowledge [Internet]. Journal of medical virology. U.S. National Library of Medicine; 2021 [cited 2022Jan5]. Available from: https://pubmed.ncbi.nlm.nih.gov/34241899/
5. Andina D, Belloni-Fortina A, Bodemer C, Bonifazi E, Chiriac A, Colmenero I, et al. Skin manifestations of Covid-19 in children: Part 2. Clinical and Experimental Dermatology. 2020;46(3):451–61.
6. AlGhoozi DA, AlKhayyat HM. A child with Henoch-Schonlein purpura secondary to a COVID-19 infection. BMJ Case Reports. 2021Jan6;14(1).
7. Al Haji, M. O., migdadi, m. M. S., aldebei, m. A. H., & jarrar, m. B. F. (2021). A case of henoch-schonlein purpura in a covid-19 patient. *European journal of biomedical*, *8*(6), 161–164.
8. Bekhit OE, Alfatani AA, Eid MHR, Mohamed SA. Childhood immunoglobulin a vasculitis associated with COVID-19: A case report. Journal of Child Science. 2021Aug11;11(01).
9. Borocco C, Lafay C, Plantard I, Gottlieb J, Koné-Paut I, Galeotti C. SARS-COV-2-associated Henoch–Schönlein purpura in a 13-year-old girl. Archives de Pédiatrie. 2021Jul9;28(7):573–5.
10. El Hasbani G, Taher AT, Jawad AS, Uthman I. Henoch-Schönlein purpura: Another Covid-19 complication. Pediatric Dermatology. 2021Jul16;38(5):1359–60.
11. Gogeascoechea G PD, Aparicio V LA. Iga vasculitis associated with covid-19 infection in a pediatric patient, a case report. Revista Paraguaya de Reumatología. 2021Jul30;7(1):27–31.
12. Hoskins B, Keeven N, Dang M, Keller E, Nagpal R. A child with covid-19 and immunoglobulin a vasculitis. Pediatric Annals. 2021Jan1;50(1).
13. Jacobi M, Lancrei HM, Brosh-Nissimov T, Yeshayahu Y. Purpurona: A novel report of covid-19-related Henoch-Schonlein purpura in a child. Pediatric Infectious Disease Journal. 2020;40(2).
14. Kumar G, Pillai S, Norwick P, Bukulmez H. Leucocytoclastic vasculitis secondary to COVID-19 infection in a young child. BMJ Case Reports. 2021Apr7;14(4).
15. Nakandakari Gomez MD, Marín Macedo H, Seminario Vilca R. Iga (Henoch Schönlein purpura) vasculitis in a pediatric patient with COVID-19 and strongyloidiasis. Revista de la Facultad de Medicina Humana. 2021;21(1):184–90.

16. Riscassi S, Kalapurackal MA, Battisti L, Eisendle K, Raffeiner B, Mercolini F. Vasculitis in a child with covid-19: A novel presentation of henoch-schönlein purpura. Klinische Pädiatrie. 2021;
17. Ziyara R, Thompson A, Liu B. Henoch-Schönlein purpura in a covid-19-positive child with abdominal pain and pims-ts. Clinical Pediatrics. 2021;61(1):5–8.
18. Allez M, Denis B, Bouaziz JD, Battistella M, Zagdanski AM, Bayart J, et al. Covid-19–related Iga Vasculitis. Arthritis & Rheumatology. 2020;72(11):1952–3.
19. Barbetta L, Filocamo G, Passoni E, Boggio F, Folli C, Monzani V. Henoch-Schönlein purpura with renal and gastrointestinal involvement in course of COVID-19: A case report [Internet]. Clinical and experimental rheumatology. U.S. National Library of Medicine; 2021 [cited 2022Jan6]. Available from: https://pubmed.ncbi.nlm.nih.gov/33769259/
20. Bracaccia ME, De Cicco N, Moioli A, Barberi S, Fofi C, Mene' P. MO240A fatal case of vasculitis after SARS-COV-2 negativization. Nephrology Dialysis Transplantation. 2021;36(Supplement_1).
21. Li NL, Papini AB, Shao T, Girard L. Immunoglobulin-a vasculitis with renal involvement in a patient with COVID-19: A case report and review of acute kidney injury related to SARS-COV-2. Canadian Journal of Kidney Health and Disease. 2021Feb5;8:205435812199168.
22. Oñate I, Ortiz M, Suso A, Mon C, Galindo K, Lentisco C, et al. Vasculitis Iga con nefritis (Púrpura de Schönlein-Henoch) tras covid-19: Una serie de casos Y revisión de la literatura. Nefrología. 2021Aug3;
23. Sandhu S, Chand S, Bhatnagar A, Dabas R, Bhat S, Kumar H, et al. Possible association between iga vasculitis and covid -19. Dermatologic Therapy. 2020Nov25;34(1).
24. Stroup DF. Meta-analysis of observational studies in epidemiology. A proposal for reporting. JAMA. 2000;283(15):2008.
25. World Health Organization. The use of the WHO-UMC system for standardized causality assessment [Internet]. [cited 2021Sep27]. Available from: https://who-umc.org/Graphics/24734.pdf
26. Ozen S, Pistorio A, Iusan SM, Bakkaloglu A, Herlin T, Brik R, et al. Eular/printo/PRES criteria for Henoch-Schonlein purpura, childhood polyarteritis nodosa, childhood wegener granulomatosis and childhood takayasu arteritis: Ankara 2008. part II: Final classification criteria. Annals of the Rheumatic Diseases. 2010May22;69(5):798–806.
27. Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19) 2021 case definition [Internet]. Centers for Disease Control and Prevention. Centers for Disease Control and Prevention; 2021 [cited 2021Sep27]. Available from: https://ndc.services.cdc.gov/case-definitions/coronavirus-disease-2019-2021/
28. Zacharias H, Dubey S, Koduri G, D'Cruz D. Rheumatological complications of covid 19. Autoimmunity Reviews. 2021Sep;20(9):102883.
29. Sacchi MC, Tamiazzo S, Stobbione P, Agatea L, De Gaspari P, Stecca A, et al. SARS-COV-2 infection as a trigger of autoimmune response. Clinical and Translational Science. 2021Jan21;14(3):898–907.
30. Novelli L, Motta F, De Santis M, Ansari AA, Gershwin ME, Selmi C. The janus of chronic inflammatory and autoimmune diseases onset during COVID-19 – A systematic review of the literature. Journal of

Autoimmunity. 2021;117:102592.
31. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. Covid-19: Consider cytokine storm syndromes and immunosuppression. The Lancet. 2020;395(10229):1033–4.
32. Sugino H, Sawada Y, Nakamura M. Iga vasculitis: Etiology, treatment, biomarkers and epigenetic changes. International Journal of Molecular Sciences. 2021;22(14):7538.
33. Heineke MH, Ballering AV, Jamin A, Ben Mkaddem S, Monteiro RC, Van Egmond M. New insights in the pathogenesis of immunoglobulin a vasculitis (Henoch-Schönlein purpura). Autoimmunity Reviews. 2017Oct14;16(12):1246–53.
34. Gardner-Medwin JMM, Dolezalova P, Cummins C, Southwood TR. Incidence of henoch-schonlein purpura, Kawasaki disease, and rare vasculitides in children of different ethnic origins. The Lancet. 2002Oct19;360(9341):1197–201

Table

Table 2 is available in the Supplemental Files section.

Figures

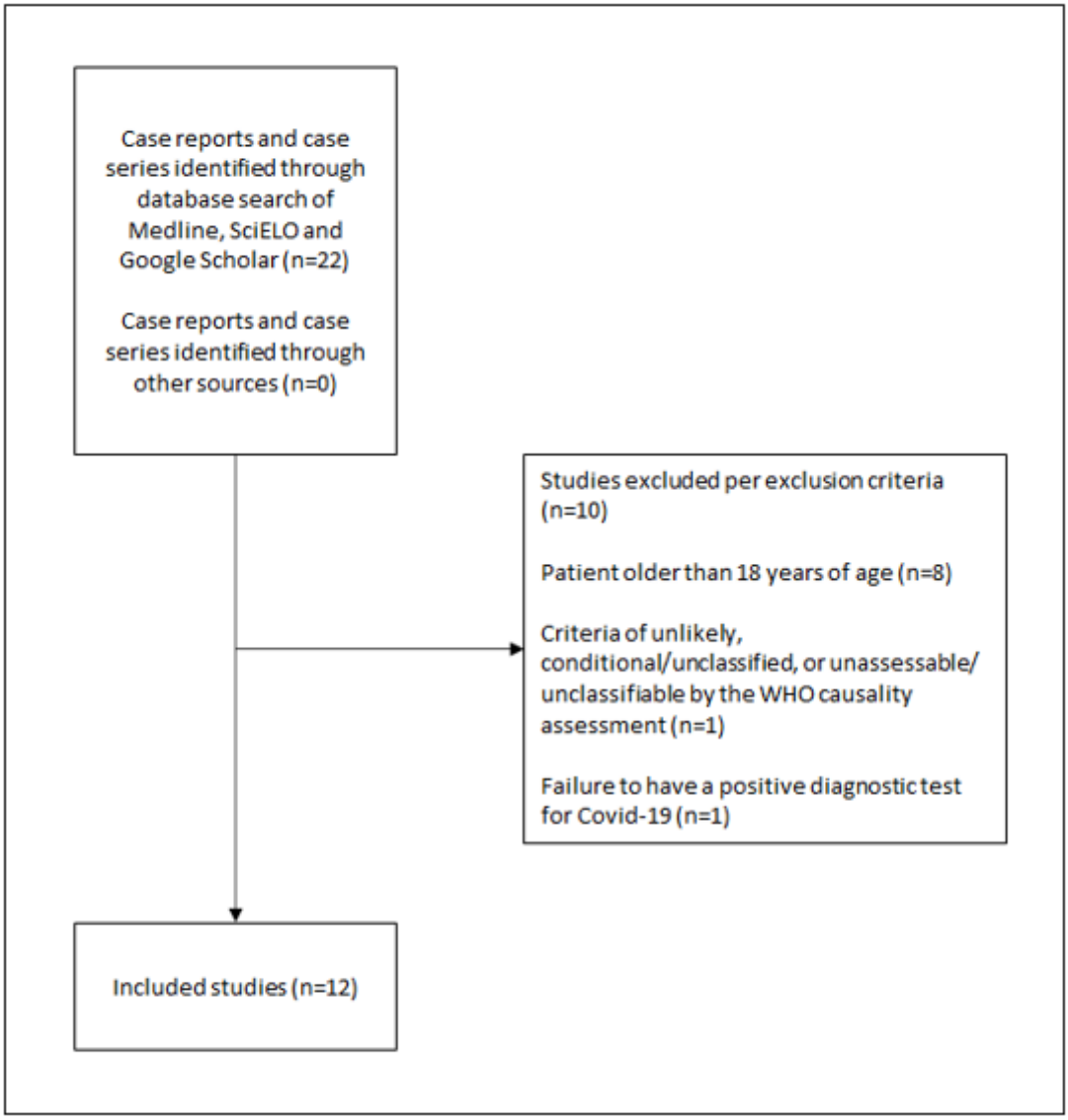

Figure 1

Flow diagram of included studies

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2Casereportdescriptions.docx