Original Article

Quality and consistency of clinical practice guidelines for treating children with COVID-19

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Background: The Coronavirus Disease 2019 (COVID-19) pandemic negatively affects children's health. Many guidelines have been developed for treating children with COVID-19. The quality of the existing guidelines and the consistency of recommendations remains unknown. Therefore, we aim to review the clinical practice guidelines (CPGs) for children with COVID-19 systematically.

Methods: We systematically searched Medline, Embase, guideline-related websites, and Google. The Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool and Reporting Items for practice Guidelines in HealThcare (RIGHT) checklist were used to evaluate the methodological and reporting quality of the included guidelines, respectively. The consistency of recommendations across the guidelines and their supporting evidence were analyzed.

Results: Twenty guidelines were included in this study. The mean AGREE II score and mean RIGHT reporting rate of the included guidelines were 37% (range, 22–62%) and 52% (range, 31–89%), respectively. As for methodological quality, no guideline was classified as high, one guideline (5%) moderate, and 19 (95%) low. In terms of reporting quality, one guideline (5%) was rated as high, 12 guidelines (60%) moderate, and seven (35%) low. Among included guidelines, recommendations varied greatly in the use of remdesivir (recommend: 25%, not recommend: 45%, not report: 30%), interferon (recommend: 15%, not recommend: 50%, not report: 35%), glucocorticoids (recommend: 50%, not recommend: 20%, not report: 30%), and intravenous immune globulin (recommend: 35%, not recommend: 30%, not report: 35%). None of the guidelines cited clinical trials from children with COVID-19.

Conclusions: The methodological and reporting quality of guidelines for treating children with COVID-19 was not high. Recommendations were inconsistent across different guidelines. The supporting evidence from children with COVID-19 was very limited.

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Keywords: Clinical practice guidelines (CPGs); quality appraisal; consistency analysis; Coronavirus Disease 2019 (COVID-19); children

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Introduction

Coronavirus Disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a worldwide pandemic (1). Up to October 4, 2020, there have been 34,804,348 confirmed cases and 1,030,738 deaths reported to the World Health Organization (WHO) (2), and the numbers keep increasing. The disease seems to be milder in children compared with adults (3). Most cases of COVID-19 in children were thought to be asymptomatic or have mild clinical manifestations (3). However, the situation appears to be changing, infants and young children present more severe illness (4). Until recently, an unanticipated inflammatory syndrome related to COVID-19 rapidly emerged in children. These children showed features similar to atypical Kawasaki disease (KD). Critical cases may have coronary artery aneurysms (CAA), cardiac insufficiency, toxic shock, and even death (5). Management is mainly supportive care. Some studies suggested antiviral drugs, glucocorticoids, intravenous immunoglobulin (IVIG), and biologics for treating severe and critically ill cases (5,6). Few clinical trials have performed in children with COVID-19, as most clinical trials have focused on adult patients. Therefore, whether these drugs could be used in children remains controversial. The treatment strategies varied in different medical institutions. Therefore, it is important to standardize the treatment of children with COVID-19.

Evidence-based clinical practice guidelines (CPGs) can improve the quality of health care and the prognosis of patients (7). Therefore, CPGs for treating children with COVID-19 are required. National and international organizations are increasingly developing their CPGs. Despite the increasing number, the quality of the existing guidelines, the consistency of recommendations, and their supporting evidence remain unknown. Low-quality and inconsistent recommendations may puzzle the pediatricians and cause incorrect decision making. Hence, we conducted this study to systematically evaluate the methodological and reporting quality of CPGs on the treatment of children with COVID-19, to analyze the consistency of recommendations and their supporting evidence across these CPGs, and to provide a reference for appropriate treatment and future guideline development.

We present this article in accordance with the PRISMA reporting checklist (available at http://dx.doi.org/10.21037/atm-20-7000) (8).

Methods

Data sources and search strategy

We systematically searched Medline and Embase in cooperation with information retrieval experts (9). A manual search in guideline-related websites and Google was also performed. We limited the search to CPGs published from 1 January 2020 until 30 August 2020. The detailed search strategy was presented in Appendix 1.

Eligibility criteria

We included CPGs providing recommendations for treating children with COVID-19 and published in English. We excluded draft guidelines that were under development or not finalized, previous guidelines replaced by updated versions from the same organization, and guidelines for children with underlying diseases.

Study selection

Search results were imported into the specific bibliographic software EndNote and duplicates identified. Before the formal screening, a pilot of 50 random sample citations (from outside of the sample) was conducted to improve consistency. Then two reviewers (QL, ZW) independently screened all searched documents. The formal selection process consisted of three stages: (I) we used the predefined criteria to screen all titles and abstracts of studies and determined whether they were relevant to the research question; (II) once titles and abstracts were screened, the full text should be retrieved and screened to definitely decide whether the study fitted the eligibility criteria; (III)

disagreements were resolved by discussion, or solved with a third reviewer (QZ), if needed.

Data extraction

To improve the agreements among reviewers, extraction of the guidelines was pre-piloted to ensure the comprehensiveness and scientificity of this process, and the standardized form has been modified and improved after the pilot. The following data were extracted using a standardized form: (I) basic information: developing organization, publication year, country, number of recommendations, systematic literature retrieval, evidence quality grading system, recommendation formulation method, funding body, and conflicts of interest; (II) recommendations for treatment and their supporting evidence. Data were extracted by two reviewers (QL, QS). Disagreements were discussed or solved with a third reviewers (QZ).

Quality appraisal of guidelines

The Appraisal of Guidelines for Research and Evaluation II (AGREE II) tool (10-13) was used to evaluate the methodological quality of the included guidelines. It consisted of 23 items grouped into six domains (scope and purpose, stakeholder involvement, rigor of development, clarify and presentation, applicability, and editorial independence). Each item was given a score from 1 (strongly disagree) to 7 (strongly agree). The overall quality scores ranged from 0% to 100%, and guidelines were classified as "high quality" if the AGREE II score was >80%, "moderate quality" if it was 50–80%, and "low quality" if <50% (14). Before the formal evaluation, all reviewers completed an online training tutorial to ensure standardization (10-13). Two rounds of pilot appraisals with four guidelines were conducted to achieve better consistency. The intraclass correlation coefficient (ICC) was used to test inter-rater reliability. Two reviewers (QL, HL) independently assessed each guideline. Table S1 presented the results of the AGREE II evaluation. Appendix 2 presented the formula used to calculate the AGREE II score.

The Reporting Items for practice Guidelines in HealThcare (RIGHT) checklist was used to analyze the reporting quality of the included guidelines (15). It contained 22 items (35 sub-items) grouped into seven domains (information, background, evidence, recommendations, review and quality assurance, funding and conflict-of-interest statements and management, and other information of the guideline). Each item was rated either as "reported" or "not reported". The "reported" option was used when the relevant information was provided in the guideline, whereas "not reported" indicated that the relevant information could not be found or was unclear. The guidelines were classified as "well-reported" if the reporting rate was >80%, "moderate-reported" if it was 50–80%, and "low-reported" if <50% (14). Two rounds of pilot assessment of four guidelines were completed and the ICC value was calculated. Two reviewers (QL and YX) independently assessed the adherence of the guidelines to the RIGHT checklist. Disagreements were discussed or solved with a third reviewers (QZ). Table S2 presented the results of the RIGHT checklist evaluation. Appendix 2 presented the formula used to calculate the RIGHT reporting rates.

Comparison of recommendations

We compared the following recommendations and their supporting evidence: the use of antivirus drugs, glucocorticoids, IVIG, biologics, antiplatelet and anticoagulation, antibiotics, noninvasive ventilation, convalescent plasma therapy, blood purification, extracorporeal membrane oxygenation (ECMO) therapy, and psychotherapy. We further analyzed the treatment type, indication, dosing regimen, course of treatment, numbers, and types of supporting evidence.

Statistical analysis

The categorical variables were presented as frequency and percentage, and the continuous variables were presented as mean ± standard deviation (SD). RevMan 5.3 software was used to compare the differences between different subgroups, and the effect size of continuous variables was presented with a weighted mean difference (WMD) and its 95% confidence interval (CI). SPSS 25.0 software was used to calculate ICC values to test inter-rater reliability. ICC <0.4 indicated low reliability, ICC >0.75 indicated high reliability (16).

Results

Basic information

The ICC values for the pilot test using the AGREE II tool and the RIGHT checklist were 0.96 (95% CI: 0.94–0.98)

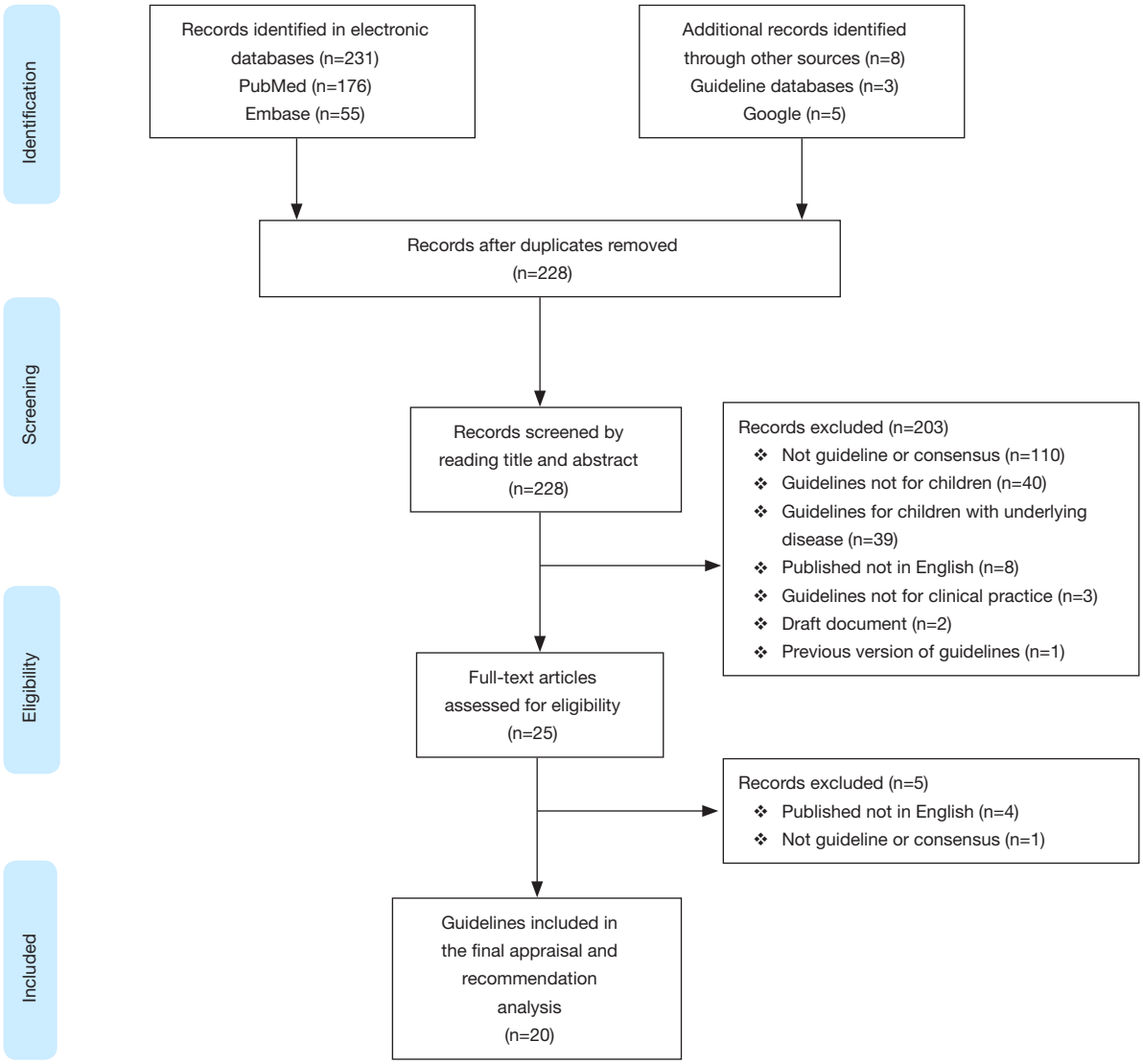

Figure 1 Flow diagram of the search and selection of the guidelines.

and 0.95 (95% CI: 0.92–0.96) respectively, indicating high reliability between all reviewers. A total of 239 references were retrieved by the initial search. Twenty guidelines met our criteria were finally included (17-35). The process of guideline selection was illustrated in *Figure 1*. The characteristics of the included guidelines were presented in *Table 1*.

The methodological and reporting quality of guidelines

Methodological quality

The overall scores of AGREE II for each guideline were presented in *Figure 2*. The mean score of the included guidelines were 37% (range, 22–62%). No guideline was classified as high quality, one guideline (5%) developed by Children's Hospital of Chongqing Medical University was rated as moderate quality with a mean AGREE II score of 62%, and 19 (95%) were rated as low quality. *Figure 3* presented the AGREE II scores of each domain. Domain 1 (scope and purpose) had the highest score (55%) and domain 3 (rigor of development) had the lowest score (19%). The AGREE II scores of guidelines that received funding, conducted systematic literature retrieval, and used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach were significantly higher than those without funding, systematic

Table 1 Characteristics of included guidelines

Guideline	Issuing organization	Publication date (year/month)	Country/region	Number of recommendations	Systematic literature retrieval	Evidence quality grading	Recommendation formulation method	Funding	Declaration of interest
1	Children's Hospital of Zhejiang Medical University	2020/2	China	Unclear	No	No	No	Yes	Yes
2	Children's Hospital of Fudan University	2020/2	China	Unclear	No	No	No	No	Yes
3	Michigan Medicine, University of Michigan	2020/3	United States	Unclear	No	No	No	No	No
4	Children's Hospital of the King's Daughters	2020/3	United States	4	No	No	No	No	No
5	Indian Academy of Pediatrics	2020/3	India	20	Yes	GRADE	No	No	No
6	Saudi Neonatal Society	2020/4	Saudi	Unclear	No	No	No	Yes	Yes
7	Spanish Paediatric Association Working Group	2020/4	Spain	Unclear	No	No	No	No	Yes
8	Royal College of Paediatrics and Child Health	2020/4	United Kingdom	Unclear	No	No	No	No	No
9	Canadian Paediatric Society	2020/4	Canada	Unclear	No	No	No	No	No
10	American Pediatric Infectious Diseases Society	2020/4	United States	12	No	No	No	Yes	Yes
11	Beijing Children's Hospital of Capital Medical University	2020/4	China	Unclear	No	No	No	Yes	Yes
12	Royal College of Pediatrics and Child Health	2020/5	United Kingdom	21	No	No	No	No	No
13	The European Society of Pediatric Radiology	2020/5	International	Unclear	No	No	No	No	Yes
14	Children's Hospital of Chongqing Medical University	2020/5	China	10	Yes	GRADE	Delphi	Yes	Yes

Table 1 (*continued*)

Table 1 (*continued*)

Guideline	Issuing organization	Publication date (year/month)	Country/region	Number of recommendations	Systematic literature retrieval	Evidence quality grading	Recommendation formulation method	Funding	Declaration of interest
15	Buffalo Children's Hospital	2020/5	United States	Unclear	No	No	No	Yes	Yes
16	The Pediatric Difficult Intubation Collaborative	2020/7	International	10	Yes	No	No	Yes	Yes
17	American College of Rheumatology	2020/7	United States	40	Yes	No	RAND/UCLA	Yes	Yes
18	The European Society of Pediatric and Neonatal Intensive Care/The European Society of Pediatric Radiology	2020/7	International	17	No	No	Delphi	No	Yes
19	Vanderbilt University Medical Center	2020/8	United States	13	No	No	No	No	Yes
20	Children's Hospital of Nanjing Medical University	2020/8	China	Unclear	No	No	No	No	Yes

Unclear: recommendations cannot be clearly identified. GRADE, Grading of Recommendations Assessment, Development, and Evaluation; RAND/UCLA, RAND/University of California at Los Angeles Appropriateness Method.

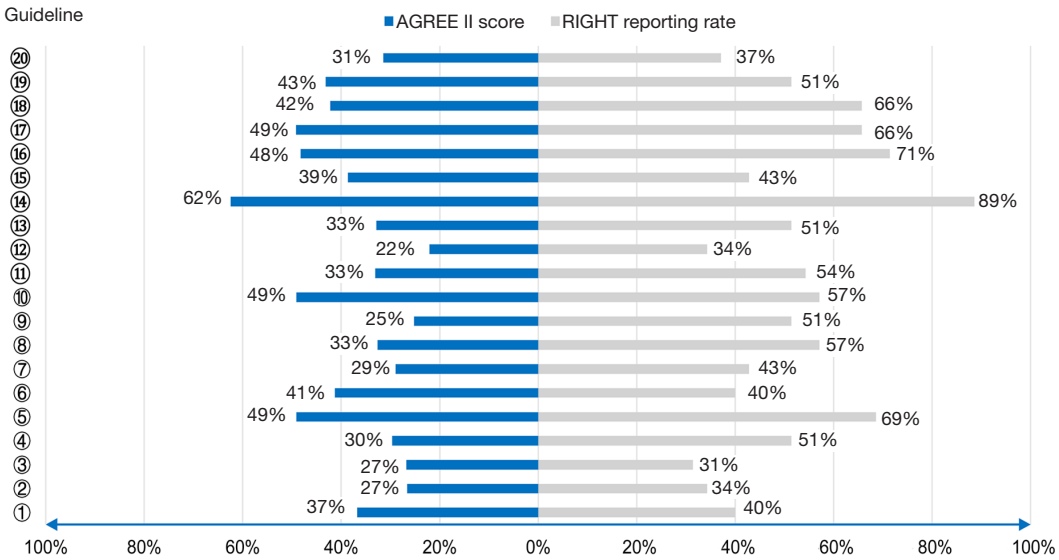

Figure 2 AGREE II mean scores and RIGHT reporting rate of each guideline. ①: Children's Hospital of Zhejiang Medical University; ②: Children's Hospital of Fudan University; ③: Michigan Medicine; University of Michigan; ④: Children's Hospital of the King's Daughters; ⑤: Indian Academy of Pediatrics; ⑥: Saudi Neonatal Society; ⑦: Spanish Paediatric Association Working Group; ⑧: Royal College of Paediatrics and Child Health; ⑨: Canadian Paediatric Society; ⑩: American Pediatric Infectious Diseases Society; ⑪: Beijing Children's Hospital of Capital Medical University; ⑫: Royal College of Paediatrics and Child Health; ⑬: The European Society of Paediatric Radiology; ⑭: Children's Hospital of Chongqing Medical University; ⑮: Buffalo Children's Hospital; ⑯: The Pediatric Difficult Intubation Collaborative; ⑰: American College of Rheumatology; ⑱: The European Society of Paediatric and Neonatal Intensive Care/The European Society of Paediatric Radiology; ⑲: Vanderbilt University Medical Center; ⑳: Children's Hospital of Nanjing Medical University. AGREE II, Appraisal of Guidelines for Research and Evaluation II; RIGHT, Reporting Items for practice Guidelines in HealThcare.

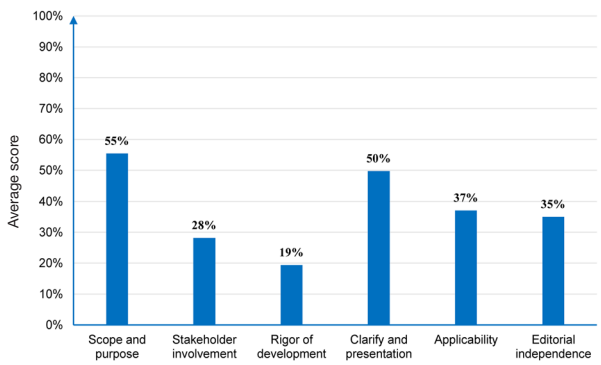

Figure 3 AGREE II mean scores of each domain for all included guidelines.

literature retrieval, and GRADE assessment (P<0.05). No statistical difference was found in AGREE II scores between guidelines with conflicts of interest (COI) and those without COI (P=0.052) (Figure S1). The methodological quality of the included guidelines increased over time generally (Figure S2).

Reporting quality

The reporting rates of each guideline were presented in *Figure 2*. The mean reporting rate of the included guidelines was 52% (range, 31–89%). Only one guideline (5%) developed by Children's Hospital of Chongqing Medical University was classified as high quality with a mean reporting rate of 89%, 12 guidelines (60%) were rated as moderate quality, and 7 guidelines (35%) were rated as low quality. Figure S3 presented the reporting rate of each domain. Domain 2 (background) had the highest reporting rate (66%), and domain 5 (review and quality assurance) had the lowest rate (25%). The reporting rates of each item were shown in *Figure 4*. Among the key items (36), the reporting rates of item 11b (systematic reviews identification and assessment) and item 18b (role of funder) were 0%, while the item 14b (resource implication) and item 19a (COI) were 85% and 70%, respectively. The reporting quality of guidelines that conducted systematic literature retrieval and used the GRADE approach was higher than those without systematic literature retrieval and GRADE assessment (P<0.05) (37). Funding (P=0.052) and

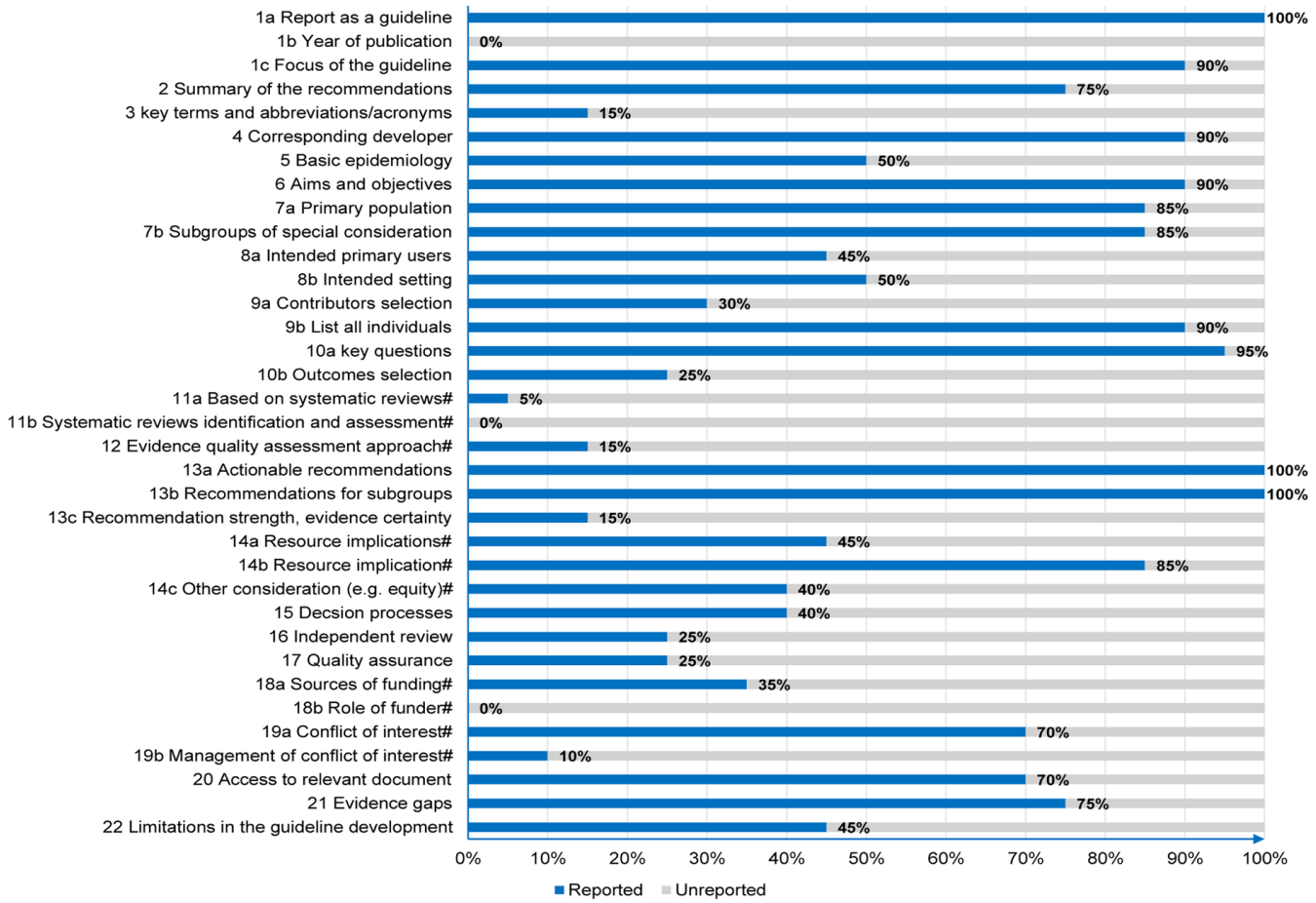

Figure 4 Percentage of reporting items in each item in the RIGHT checklist. #, key items.

COI declaration (P=0.165) had no impact on the reporting quality (Figure S4). The reporting quality of the included guidelines increased over time generally (Figure S2).

Consistency of recommendations

Remdesivir

Among 20 guidelines, five (25%) guidelines recommended remdesivir for children with COVID-19 and nine (45%) guidelines did not recommend the use of remdesivir (*Figure 5*). In the terms of the indication, two guidelines indicated remdesivir should only be used in critically ill patients. All guidelines did not report the timing of initiating remdesivir therapy. The summary of recommendations for the use of remdesivir was presented in Table S3. The supporting evidence regarding the use of remdesivir was very limited. No guidelines cited direct evidence from children with COVID-19. Two guidelines cited a case report from COVID-19 adult patients and one guideline cited a randomized controlled trial (RCT) from COVID-19 adult patients. The summary of supporting evidence for recommendations for remdesivir was shown in Table S4.

Interferon

Among 20 guidelines, three (15%) guidelines recommended interferon for children with COVID-19, and 10 (50%) guidelines did not recommend the use of interferon (*Figure 5*). As for indications of interferon, guidelines recommended interferon-α nebulization for acute respiratory infections in children with COVID-19. All guidelines did not report the timing of initiating interferon therapy. The summary of recommendations for the use of interferon was presented in Table S3. In terms of supporting

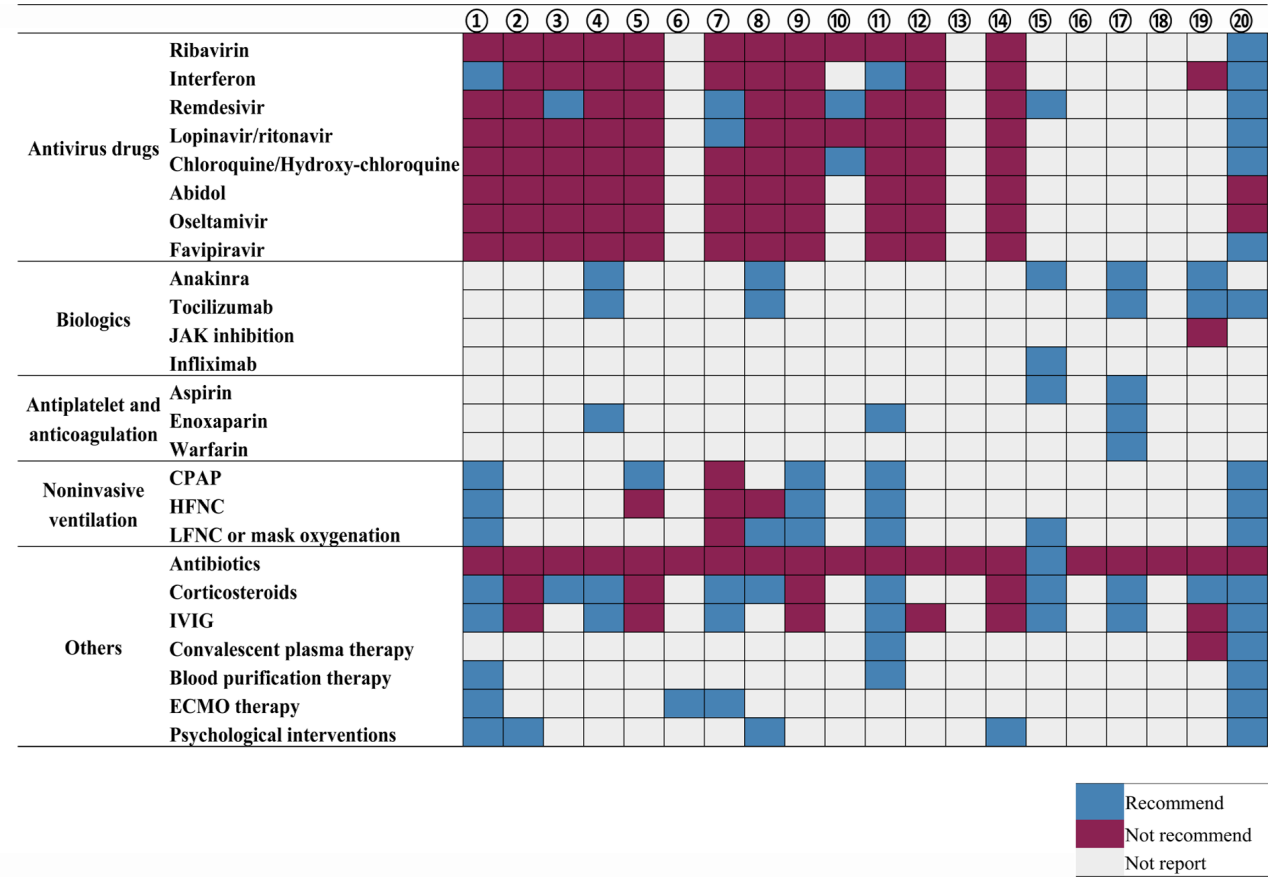

Figure 5 Summary of key recommendations for the treatment of children with COVID-19. ①: Children's Hospital of Zhejiang Medical University; ②: Children's Hospital of Fudan University; ③: Michigan Medicine; University of Michigan; ④: Children's Hospital of the King's Daughters; ⑤: Indian Academy of Pediatrics; ⑥: Saudi Neonatal Society; ⑦: Spanish Paediatric Association Working Group; ⑧: Royal College of Paediatrics and Child Health; ⑨: Canadian Paediatric Society; ⑩: American Pediatric Infectious Diseases Society; ⑪: Beijing Children's Hospital of Capital Medical University; ⑫: Royal College of Paediatrics and Child Health; ⑬: The European Society of Paediatric Radiology; ⑭: Children's Hospital of Chongqing Medical University; ⑮: Buffalo Children's Hospital; ⑯: The Pediatric Difficult Intubation Collaborative; ⑰: American College of Rheumatology; ⑱: The European Society of Paediatric and Neonatal Intensive Care/The European Society of Paediatric Radiology; ⑲: Vanderbilt University Medical Center; ⑳: Children's Hospital of Nanjing Medical University. JAK, Janus-activated kinase; CPAP, continuous positive airway pressure; HFNC, high-flow nasal cannula; LFNC, low-flow nasal cannula; IVIG, intravenous immunoglobulin; ECMO, extracorporeal membrane oxygenation.

evidence, no guidelines cited direct evidence from children with COVID-19. Only one guideline cited evidence from adult patients with COVID-19, while the others cited indirect evidence from other diseases. The summary of supporting evidence for recommendations for interferon was shown in Table S5.

Glucocorticoids

Among 20 guidelines, 10 (50%) guidelines recommended glucocorticoids for children with COVID-19 and four (20%) guidelines did not recommend the use of glucocorticoids (*Figure 5*). As for the indication of glucocorticoids, guidelines recommended glucocorticoids only be used in severe or critical patients with acute respiratory distress syndrome (ARDS), septic shock, a multisystem inflammatory syndrome in children (MIS-C), and other serious complications. As for the usage of glucocorticoids, doses and types of glucocorticoids varied in different guidelines. All guidelines did not report the timing of initiating glucocorticoids therapy. The summary

of recommendations for the use of glucocorticoids was presented in Table S6. The supporting evidence concerning the use of glucocorticoids in COVID-19 patients was rare. Only one guideline cited a cohort study from children with COVID-19. Three guidelines cited clinical studies from adults with COVID-19. The other guidelines cited indirect evidence from other diseases. The summary of supporting evidence for recommendations for glucocorticoid was shown in Table S7.

IVIG

Among 20 guidelines, seven (35%) guidelines recommended IVIG for children with COVID-19 and six (30%) guidelines did not recommend the use of IVIG (*Figure 5*). As for the indication of IVIG, four guidelines recommended it for severe or critical COVID-19 and three guidelines recommended it for MIS-C. In terms of dosing regimen, three guidelines recommended giving IVIG 1 g/kg/day for 2 days, or 400 mg/kg/day for 5 days for severe or critical COVID-19. Three guidelines recommended giving IVIG 1–2 g/kg for MIS-C. All guidelines did not report the timing of initiating IVIG. The summary of recommendations for the use of IVIG was presented in Table S8. The supporting evidence concerning the use of IVIG in COVID-19 patients was also very limited. No direct evidence from children with COVID-19 was cited. Only two guidelines cited case reports from adults with COVID-19. The summary of supporting evidence for recommendations for IVIG was shown in Table S9.

Biologics

Three guidelines recommended anakinra and one guideline recommended infliximab for the treatment of MIS-C refractory to IVIG and glucocorticoids. Five guidelines recommended tocilizumab and two guidelines recommended anakinra for the treatment of severe or critical cases with evidence of hyperinflammation. The recommended dosing for tocilizumab is 12 mg/kg IV for children weighting <30 kg, and 8 mg/kg IV for children weighting ≥30 kg (max dose 800 mg). The dosing regimen of anakinra varied across guidelines. None of the guidelines cited any supporting evidence from COVID-19 children. The summary of recommendations for the use of biologic was presented in Table S10.

Antiplatelet and anticoagulation drugs

There were significant differences in the indications and usages across different guidelines. Concerning the use of aspirin, one guideline recommended 80–100 mg/kg/day for patients with excessive inflammation. The other guideline recommended 3–5 mg/kg/day for MIS-C patients with CAA and a maximal Z-score >2.5 and/or thrombocytosis. As for the use of enoxaparin, one guideline recommended it for patients with increased D-dimer and at high risk of thrombosis. The other guideline recommended it for MIS-C patients with CAAs and a Z-score ≥10. No specific dosing regimen for enoxaparin was provided. None of the guidelines cited any supporting evidence from COVID-19 children. The summary of recommendations for the use of antiplatelet and anticoagulation drugs was presented in Table S11.

Other treatments

Among the 20 guidelines, 19 (95%) guidelines recommended against empirical use of antibiotics for children with COVID-19. Only one (5%) guideline recommended the broad-spectrum antibiotics for patients with MIS-C. Six (30%) guidelines recommended non-invasive ventilation for children with dyspnea at early stage, while one guideline (5%) suggested an early intubation. Five (25%) guidelines recommended psychotherapy for children with no specific measures provided. Convalescent plasma therapy, blood purification, and ECMO therapy were recommended for severe COVID-19 patients in two (10%), three (15%), and four (20%) guidelines, respectively (*Figure 5*).

Discussion

Of the 20 guidelines included in this study, the overall methodological and reporting quality was not high. Recommendations varied greatly in the use of antiviral drugs, glucocorticoids, and IVIG. There was a lack of recommendations for the use of biologics, antiplatelet and anticoagulation drugs, non-invasive ventilation, psychotherapy, convalescent plasma therapy, blood purification, and ECMO therapy. Due to the lack of clinical trials for children with COVID-19, most guidelines did not cite direct evidence from children with COVID-19, but indirect evidence from adults with COVID-19 and other diseases.

The consistency of recommendations on the use of remdesivir was generally low. Five guidelines recommended remdesivir. Their reasons were as follows. Remdesivir can effectively inhibit SARS-CoV-2 *in vitro* (38). Besides, adult patients treated with remdesivir showed improvement in symptoms and level of respiratory support (39). Nine

guidelines did not recommend remdesivir. They indicated that no clinical studies have investigated its efficacy on children with COVID-19. Further, the efficacy of remdesivir for adults with COVID-19 remained uncertain (40,41). The efficacy of remdesivir may depend on the timing of its use. Some clinical trials found remdesivir was effective when administered in the first 5 days of symptoms, when the viral load was high (39,40). It may have low efficacy when it is prescribed in advanced stage, with low viral load. More clinical studies are needed to investigate the proper time of remdesivir use and its efficacy for children with COVID-19.

Recommendations were inconsistent in the use of interferon for children with COVID-19. Three guidelines recommended the use of interferon and their reason was that interferon-α can reduce viral load. However, none of the guidelines cited any evidence from COVID-19 patients. Nine guidelines recommended against the use of interferon and their reasons were the following. First, no clinical studies demonstrated that interferon was effective in treating children with COVID-19. Moreover, the efficacy of interferon in treatment of adult with COVID-19 was unclear. Although several RCTs with small sample size showed interferon beta was effective in treatment of adults with COVID-19 (42,43), a living systematic review and network meta-analysis showed it had no effects (44). Second, therapy with interferon was associated with a variety of adverse effects, including fatigue, anorexia, nausea, diarrhea, depression, neutropenia, and anemia (45,46). Given the above concerns, interferon may not be used for treating children with COVID-19.

Recommendations on the use of glucocorticoids varied across guidelines. Four guidelines did not recommend the use of glucocorticoids. Their reasons were that evidence showed that systemic glucocorticoids may have no benefit in severe cases of SARS-CoV-2 and SARS infection (47). Besides severe side effects such as femoral head necrosis and immunosuppression may occur after high dose administrations (48). Ten guidelines recommended the use of glucocorticoids and their reasons were as follows. First, a meta-analysis demonstrated the benefits of glucocorticoids in moderate or severe adult patients with COVID-19 (49), and WHO recommended systemic corticosteroids rather than no systemic corticosteroids for the treatment of patients with severe and critical COVID-19 (50). Second, in settings where monoclonal antibody shortages, glucocorticoids may be the only option for immunomodulatory therapy for critical cases. Third, the cost of glucocorticoids was cheap. Whether glucocorticoids can be used for children with COVID-19 remains unclear. High-quality clinical studies are required to explore the efficacy, safety, dosing, and timing of glucocorticoids therapy for children with COVID-19.

After the emerge of MIS-C, IVIG is the most commonly used immunomodulatory medications in MIS-C patients (51). Some guidelines recommended IVIG for treatment of MIS-C. However, their supporting evidence was mainly based on IVIG use in KD and fulminant myocarditis, two conditions that resembled MIS-C in some aspects (52,53). Although recent case reports found MIS-C patients receiving IVIG resolved rapidly, improvement in clinical status was also observed in mild cases without IVIG treatment (51,54). Data on the efficacy of IVIG to treat MIS-C and indications for the use of IVIG is still limited. And there is few study to compare the efficacy of IVIG and glucocorticoids in MIS-C or to determine if these treatments should be provided alone or in combination. Therefore, more high-quality clinical trials are needed to explore the above problems.

Biological agents may be promising treatments for COVID-19 patients with high inflammatory response syndrome (55,56). A RCT found tocilizumab may reduce the likelihood of mechanical ventilation or death in adult patients with COVID-19 (55). Targeting the inflammatory cascade with anakinra in moderate to severe COVID-19 adults showed good clinical outcomes (56). The included guidelines suggested biologics could be used for pediatric COVID-19. However, recent living systematic reviews and network meta-analyses found tocilizumab did not reduce short-term mortality (44,57). Moreover, there is little evidence from pediatric COVID-19 to support the use of biological agents. Therefore, more clinical studies are needed to investigate the therapeutic effects of biologics on COVID-19 children with high inflammatory response, especially severe and refractory MIS-C.

The advantages of this study were as follows. First, we summarized all key recommendations and compared and visualized the inconsistencies among guidelines related to children with COVID-19. Our findings may provide objective guidance for pediatricians selecting the appropriate treatment. Second, we performed a systematic literature search, and comprehensively explored both methodological and reporting quality of the guidelines. Our findings provided an informative overview of guideline quality for methodologists and may contribute to future guideline development and updates. Third, this

is to our knowledge the first study that comprehensively evaluated the supporting evidence. We proposed the existing research gaps, providing a reference for medical researchers to conduct clinical trials in the future. However, our study had some limitations. First, we restricted our search to guidelines published in English and excluded the guidelines in other languages. Second, we only analyzed recommendations regarding treatment, and recommendations concerning diagnosis, isolation, and prevention were not evaluated. Third, we did not include guidelines after September 2020. Therefore, we were unable to analyze the guidelines published after that time.

Conclusions

The methodological and reporting quality of guidelines for treating children with COVID-19 was not high. There was a wide discrepancy between the guidelines in recommendations on the use of antiviral drugs, glucocorticoids, and IVIG. Clinical researches on the pediatric COVID-19 treatment were rare. High-quality guidelines and clinical studies are warranted to improve the treatment of children with COVID-19.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

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Supplementary

Appendix 1 Search strategy

Search in Medline

#1 “COVID-19” [Supplementary Concept]
#2 “Severe Acute Respiratory Syndrome Coronavirus 2” [Supplementary Concept]
#3 “COVID-19” [Title/Abstract]
#4 "SARS-COV-2" [Title/Abstract]
#5 “Novel coronavirus” [Title/Abstract]
#6 “2019-novel coronavirus” [Title/Abstract]
#7 “coronavirus disease-19” [Title/Abstract]
#8 “coronavirus disease 2019” [Title/Abstract]
#9 “COVID 19” [Title/Abstract]
#10 “Novel CoV” [Title/Abstract]
#11 “2019-nCoV” [Title/Abstract]
#12 “2019-CoV” [Title/Abstract]
#13 #1-#12/ OR
#14 "Adolescent" [Mesh]
#15 "Infant" [Mesh]
#16 "Child" [Mesh]
#17 "Pediatrics" [Mesh]
#18 "pediatric* " [Title/Abstract]
#19 "paediatric*" [Title/Abstract]
#20 "child* " [Title/Abstract]
#21 "infant*" [Title/Abstract]
#22 "adolescent*" [Title/Abstract]
#23 "neonat* " [Title/Abstract]
#24 "newborn*" [Title/Abstract]
#25 "teenager*" [Title/Abstract]
#26 #14-#25/ OR
#27 "Practice Guideline" [Publication Type]
#28 "Guidelines as Topic"[Mesh]
#29 "guideline*" [Title]
#30 "recommendation*" [Title]
#31 "guidance* " [Title]
#32 "statement*" [Title]
#33 "consensus*" [Title]
#34 #27-#33/ OR
#35 #13 AND #26 AND #34

Search in Embase

#1 'coronavirus disease 2019'/exp
#2 'severe acute respiratory syndrome coronavirus 2'/exp
#3 'COVID-19': ab,ti
#4 'SARS-COV-2': ab,ti
#5 'novel coronavirus': ab,ti
#6 '2019-novel coronavirus': ab,ti
#7 'coronavirus disease-19': ab,ti

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#8 'coronavirus disease 2019': ab,ti
#9 'COVID 19': ab,ti
#10 'novel cov': ab,ti
#11 '2019-ncov': ab,ti
#12 '2019-cov': ab,ti
#13 #1-#12/ OR
#14 'child'/exp
#15 'child*': ab,ti
#16 'pediatric*': ab,ti
#17 'paediatric*': ab,ti
#18 'adolescent*': ab,ti
#19 'infant*': ab,ti
#20 'neonat*': ab,ti
#21 'newborn*': ab,ti
#22 'teenager*': ab,ti
#23 #14-#22/ OR
#24 'practice guideline'/exp
#25 'guideline*':ti
#26 'recommendation*':ti
#27 'guidance*':ti
#28 ' statement*':ti
#29 ' consensus*':ti
#30 #24-#29/ OR
#31 #13 AND #23 AND #30
#32 [medline]/lim in #31
#33 #31 NOT #32

Search in guideline databases

Website links

Guidelines International Network (G-I-N): www.g-i-n.net
National Institute for Health and Clinical Excellence (NICE): www.nice.org.uk
Scottish Intercollegiate Guidelines Network (SIGN): www.sign.ac.uk/our-guidelines.html
World Health Organization (WHO): https://www.who.int/emergencies/diseases/novel-coronavirus-2019
COVID-19 page on the International Pediatric Association website: https://ipa-world.org/covid-19-news-and-updates. php
European Centres for Disease Control: https://www.ecdc.europa.eu/en/coronavirus
US Centers for Disease Control and Prevention: https://www.cdc.gov/coronavirus/2019-nCoV/index.html
Canadian Paediatric Society: https://www.cps.ca/en/tools-outils/covid-19-information-and-resources-for-paediatricians
American Academy of Paediatrics: https://services.aap.org/en/pages/2019-novel-coronavirus-covid-19-infections
Indian Academy of Paediatrics: www.iapindia.org
UK Royal College of Paediatrics and Child Health guidance for paediatric services: https://www.rcpch.ac.uk/key-topics/covid-19

Search strategy

Combinations of the following key words were searched: 'COVID-19','child','guideline'.

Search in Google website

A search was conducted via the Google engine using the following terms: 'COVID-19'AND 'child'AND '(guideline or guidance or consensus or recommendation)' in English. We screened the first 100 records.

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Table S1 AGREE II scores for each item in each guideline

Guideline			1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Domain1	Item1	Appraiser1	5	5	5	5	5	6	5	4	5	5	5	4	6	6	3	4	6	5	5	5
		Appraiser2	5	5	4	4	5	6	5	5	5	5	5	4	5	6	4	5	5	6	5	5
	Item2	Appraiser1	3	4	3	3	3	3	3	4	3	4	3	3	4	5	3	5	5	5	5	5
		Appraiser2	4	5	3	3	5	4	3	4	3	5	4	3	4	6	4	5	4	5	5	5
	Item3	Appraiser1	4	4	4	4	4	4	4	4	4	4	4	3	2	4	4	4	4	4	5	4
		Appraiser2	5	4	5	4	3	4	3	5	4	4	5	4	2	5	4	5	3	5	5	4
Domain2	Item4	Appraiser1	3	3	1	2	6	4	5	2	2	4	4	2	4	4	4	4	5	5	4	4
		Appraiser2	2	2	1	3	5	5	5	2	3	5	5	2	5	4	4	4	5	6	4	4
	Item5	Appraiser1	1	1	1	1	6	1	1	1	1	1	1	1	1	4	1	1	1	1	1	1
		Appraiser2	1	1	1	1	5	1	1	1	1	1	1	1	1	4	1	1	1	1	1	1
	Item6	Appraiser1	2	2	2	3	5	4	2	3	3	2	3	3	2	5	2	1	4	4	4	1
		Appraiser2	2	2	3	4	4	4	2	4	4	3	4	4	2	5	3	1	3	4	4	1
Domain3	Item7	Appraiser1	1	2	1	1	6	1	1	1	1	1	1	1	1	6	1	5	3	1	2	1
		Appraiser2	1	2	1	1	5	1	1	1	1	1	1	1	1	6	1	6	3	1	2	1
	Item8	Appraiser1	1	1	1	1	2	1	1	1	1	1	1	1	1	6	1	2	1	1	1	1
		Appraiser2	1	1	1	1	2	1	1	1	1	2	1	1	1	6	1	4	1	1	1	1
	Item9	Appraiser1	1	1	1	1	6	1	1	1	1	4	1	1	1	6	1	1	1	1	1	1
		Appraiser2	1	1	1	1	5	1	1	1	1	5	1	1	1	5	1	1	1	1	1	1
	Item10	Appraiser1	1	1	1	1	1	1	1	1	1	4	1	1	1	6	1	2	6	7	2	1
		Appraiser2	1	1	1	1	1	1	1	1	1	5	1	1	1	6	1	2	6	7	2	1
	Item11	Appraiser1	2	2	5	3	5	2	2	4	2	5	2	1	5	6	2	4	6	5	6	2
		Appraiser2	3	3	4	4	4	3	3	5	3	5	3	1	5	5	2	3	4	6	6	2
	Item12	Appraiser1	2	2	2	4	5	2	2	5	2	5	2	1	6	5	2	4	5	5	6	2
		Appraiser2	2	2	3	4	4	3	3	5	2	5	2	1	4	6	2	5	4	5	6	2
	Item13	Appraiser1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	1	1	1
		Appraiser2	1	1	1	1	1	1	1	1	1	1	1	1	1	3	1	1	1	1	1	1
	Item14	Appraiser1	1	1	1	2	5	5	1	4	5	2	1	1	1	4	1	3	3	1	1	1
		Appraiser2	1	1	1	3	4	5	1	2	4	3	1	1	1	3	1	3	2	1	1	1
Domain4	Item15	Appraiser1	3	3	4	4	6	3	3	4	2	6	3	3	4	6	3	5	6	5	5	5
		Appraiser2	2	2	5	5	5	2	2	5	2	5	2	3	4	6	3	5	4	5	6	5
	Item16	Appraiser1	4	3	4	4	6	3	3	5	4	6	4	5	3	6	5	4	6	5	5	5
		Appraiser2	5	4	5	5	5	4	4	5	5	5	5	5	5	4	5	4	4	5	6	5
	Item17	Appraiser1	2	2	4	4	6	2	2	5	2	5	2	3	4	5	1	5	6	4	6	2
		Appraiser2	2	2	5	5	6	3	2	6	3	6	2	3	3	6	1	5	5	5	6	3
Domain5	Item18	Appraiser1	3	3	3	3	3	3	3	4	3	3	3	3	4	4	3	4	4	4	4	2
		Appraiser2	3	3	3	3	4	3	3	5	3	3	3	3	4	5	4	5	5	4	3	2
	Item19	Appraiser1	1	1	5	5	5	4	4	5	5	5	1	4	5	5	4	5	5	5	5	1
		Appraiser2	1	1	4	5	5	4	4	4	4	4	1	5	5	5	5	5	4	5	5	1
	Item20	Appraiser1	3	1	1	1	3	1	1	2	1	3	1	2	3	3	1	2	2	2	4	1
		Appraiser2	4	1	1	1	4	1	1	2	1	4	1	2	1	4	1	4	2	2	4	1
	Item21	Appraiser1	4	4	4	4	5	2	4	4	4	5	2	1	4	2	5	4	5	5	1	5
		Appraiser2	3	3	3	3	4	2	3	5	3	4	2	1	4	2	5	5	4	6	1	5
Domain6	Item22	Appraiser1	7	1	1	1	1	7	1	1	1	3	7	1	1	3	7	6	3	1	1	1
		Appraiser2	7	1	1	1	1	7	1	1	1	3	1	1	1	3	7	5	3	1	1	1
	Item23	Appraiser1	5	5	1	1	1	5	5	1	1	5	5	1	4	6	5	5	5	3	3	5
		Appraiser2	5	5	1	1	1	5	5	1	1	5	5	1	5	6	5	6	5	2	3	5

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Appendix 2 Formulas

1. The overall AGREE II scores of each guideline, each domain, and each item were calculated as follows:

$$AGREE\ II\ \ score\ of\ each\ guideline = \frac{Total\ AGREE\ II\ scores\ of\ domains\ in\ each\ guildeline}{Toal\ number\ of\ domains}$$

$$AGREE\ II\ \ score\ of\ each\ \ domain = \frac{Total\ AGREE\ II\ scores\ of\ \ guidelines\ in\ each\ domain}{Total\ number\ of\ \ guidelines}$$

2. The RIGHT reporting rates of each guideline, each domain, and each item were calculated as follows:

$$RIGHT\ reporting\ rate\ of\ each\ guideline = \frac{Total\ number\ of\ "reported"\ \ in\ each\ guideline}{Total\ number\ of\ "reported"\ and\ "unreported"\ in\ each\ guideline} * 100\%$$

$$RIGHT\ reporting\ rate\ of\ each\ domain = \frac{Total\ number\ of\ \ "reported"\ \ in\ each\ domain}{Total\ number\ of\ "reported"\ and\ "unreported"\ in\ each\ domain} * 100\%$$

$$RIGHT\ reporting\ rate\ of\ each\ item = \frac{Total\ number\ of\ "reported"\ \ in\ each\ item}{Total\ number\ of\ "reported"\ and\ "unreported"\ in\ each\ item} * 100\%$$

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Table S2 RIGHT reporting quality for each item in each guideline

Guideline		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Domain1	1a	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
	1b	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR
	1c	R	R	R	R	R	R	R	R	R	R	R	UR	R	R	UR	R	R	R	R	R
	2	UR	R	R	R	R	UR	R	R	R	R	UR	R	R	UR	UR	R	R	R	R	R
	3	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	R	R	R	UR	UR	UR	UR
	4	R	R	UR	UR	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
Domain2	5	R	UR	UR	R	R	UR	R	UR	UR	R	R	UR	R	R	UR	UR	UR	R	R	UR
	6	R	R	R	R	R	R	R	R	R	R	R	R	R	R	UR	R	R	R	R	UR
	7a	UR	UR	UR	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
	7b	UR	UR	UR	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
	8a	UR	UR	UR	UR	UR	R	UR	R	R	UR	R	R	UR	R	UR	R	R	UR	R	UR
	8b	R	UR	R	R	R	UR	UR	R	R	UR	R	UR	UR	R	UR	UR	R	R	UR	UR
	9a	UR	UR	UR	R	R	UR	UR	UR	UR	UR	R	UR	UR	R	UR	R	R	UR	UR	UR
	9b	R	R	UR	R	R	R	R	R	R	R	R	UR	R	R	R	R	R	R	R	R
Domain3	10a	R	R	R	R	R	UR	R	R	R	R	R	R	R	R	R	R	R	R	R	R
	10b	UR	UR	UR	UR	R	UR	UR	UR	R	R	UR	UR	UR	R	UR	R	UR	UR	UR	UR
	11a	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	R	UR	UR	UR	UR	UR	UR
	11b	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR
	12	UR	UR	UR	UR	R	UR	UR	UR	UR	R	UR	UR	UR	R	UR	UR	UR	UR	UR	UR
Domain4	13a	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
	13b	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R	R
	13c	UR	UR	UR	UR	R	UR	UR	UR	UR	UR	UR	UR	UR	R	UR	UR	R	UR	UR	UR
	14a	UR	UR	UR	UR	R	UR	UR	R	UR	UR	UR	R	R	R	R	R	UR	R	UR	R
	14b	R	R	UR	R	R	R	UR	R	R	R	UR	R	R	R	R	R	R	R	R	R
	14c	R	UR	R	UR	R	UR	UR	R	UR	UR	R	UR	UR	R	UR	R	UR	R	UR	UR
	15	UR	UR	UR	UR	R	UR	UR	R	UR	R	UR	UR	UR	R	UR	R	R	R	R	UR
Domain5	16	UR	UR	UR	R	UR	UR	UR	UR	R	UR	UR	UR	UR	R	UR	UR	R	R	UR	UR
	17	UR	UR	UR	R	UR	UR	UR	UR	UR	UR	R	UR	UR	R	UR	UR	R	R	UR	UR
Domain6	18a	R	UR	UR	UR	UR	R	UR	UR	UR	R	R	UR	UR	R	R	R	UR	UR	UR	UR
	18b	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR
	19a	R	R	UR	UR	UR	R	R	UR	UR	R	R	UR	R	R	R	R	R	R	R	R
	19b	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	UR	R	UR	R	UR	UR	UR	UR
Domain7	20	UR	R	R	UR	R	R	R	R	R	UR	UR	UR	R	R	R	R	R	R	R	UR
	21	UR	UR	R	R	R	UR	R	R	R	R	R	UR	R	R	R	R	R	R	R	UR
	22	UR	UR	UR	R	R	UR	UR	R	UR	R	UR	UR	R	R	UR	R	R	R	UR	UR

R, reported; UR, unreported

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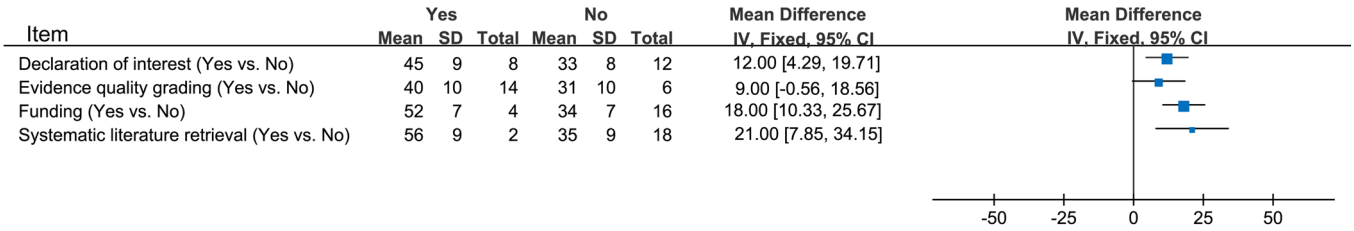

Figure S1 Weight mean difference (WMD) of AGREE II score between groups.

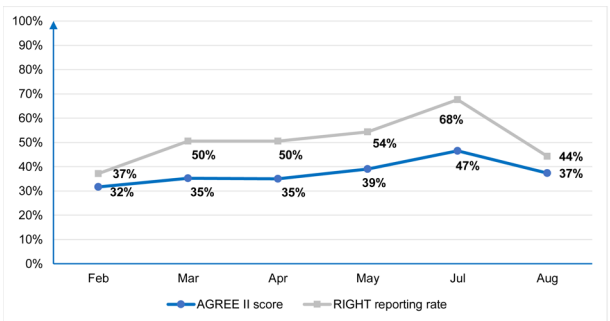

Figure S2 AGREE II score and reporting rate in the RIGHT checklist reported by month.

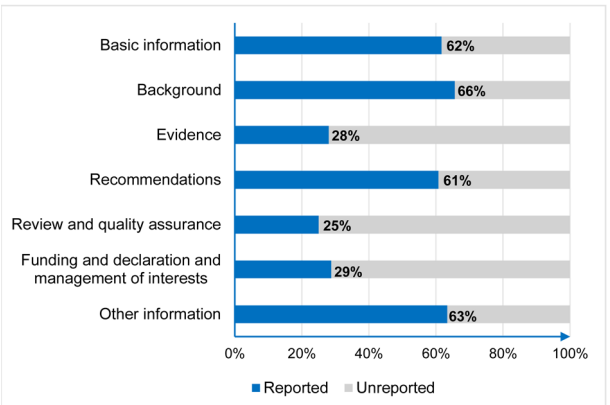

Figure S3 Percentage of reporting items in each domain in the RIGHT checklist.

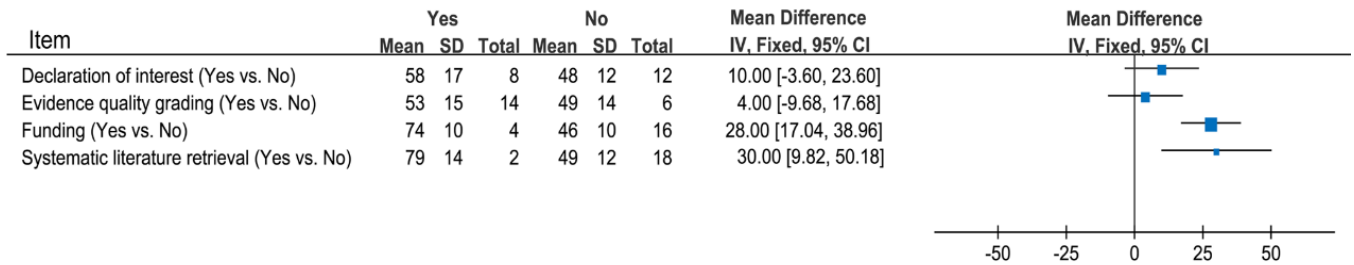

Figure S4 Difference of reporting rates in the RIGHT checklist between groups.

http://dx.doi.org/10.21037/atm-20-7000

Table S3 Summary of recommendations for antivirus drugs by included guidelines

Guideline	Ribavirin	Interferon	Remdesivir	Lopinavir/ritonavir	Chloroquine/Hydroxy-chloroquine	Abidol	Oseltamivir	Favipiravir
1	Not recommend	Recommend Dosing regimen: Interferon- α 2b nebulization: 100,000–200,000 IU/kg for mild cases, and 200,000–400,000 IU/kg for severe cases, two times/day for 5–7 days	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
2	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
3	Not recommend	Not recommend	Recommend Dosing regimen: <40 kg: 5 mg/kg IV loading dose on day 1; followed by 2.5 mg/kg IV q24h >40 kg: 200 mg IV loading dose on day 1; followed by 100 mg IV q24h	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
4	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
5	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
7	Not recommend	Not recommend	Recommend for severe case	Recommend Dosing regimen: Age >6 months and <18 years 7–15 kg: 12/3 mg/kg, 15-40 kg: 10/2.5 mg/kg, >40 kg: 400 mg/100 mg; every 12 h Age 2 weeks to 6 months 16/4 mg/kg (equivalent to 0.2 mL/kg), given twice daily with food	Not recommend	Not recommend	Not recommend	Not recommend
8	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
9	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
10	Not recommend	Not report	Recommend for critical case Dosing regimen: <40 kg: 5 mg/kg IV loading dose on day 1; followed by 2.5 mg/kg IV q24h >40 kg: 200 mg IV loading dose on day 1; followed by 100 mg IV q24h Recommended duration: Up to 10 days, with 5-day duration favored for fast responders	Not recommend	Recommend Dosing regimen: 13 mg/kg (maximum: 800 mg) PO followed by 6.5 mg/kg (maximum: 400 mg) PO at 6, 24, and 48 hours after initial dose (duration could be extended for up to 5 days on a case-by-case basis) OR 6.5 mg/kg/dose (maximum: 400 mg/dose) PO bid on day 1, followed by 3.25 mg/kg/dose (maximum: 200 mg/dose) PO bid for up to 5 days Neonates: dosing not established; consider use on a case-by-case basis Recommended duration: No more than 5 days. The duration studied for acute malaria is 3 days.	Not report	Not report	Not report
11	Not recommend	Recommend Dosing regimen: IFN- α spray: 1–2 sprays on each side of the nasal cavity, 8–10 sprays to the oropharynx for 8–10 times/day, with a treatment course of 5–7 days for high-risk children who had close contact with suspected patients or those with upper respiratory tract symptoms in the early stage of virus infection. IFN- α nebulization: 200,000–400,000 IU/kg or 2–4 μg/kg, 2 times/day, at a treatment course of 5–7 days.	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
12	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
14	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend	Not recommend
15	Not report	Not report	Recommend Dosing regimen: 5 mg/kg load IV once (max dose 200 mg) on day 1, then 2.5 mg/kg (100 mg max dose) IV daily for 9 days.	Not report	Not report	Not report	Not report	Not report
19	Not report	Not recommend	Not report	Not report	Not report	Not report	Not report	Not report
20	Recommend Dosing regimen: 10 mg/kg/time, via intravenous infusion, 2 to 3 times daily	Recommend Dosing regimen: 200,000 to 400,000 IU/kg in 2 mL sterile water, with nebulization two times per day for 5–7 days	Recommend	Recommend Dosing regimen: Weight 7–15 kg, 12 mg/3 mg/kg; weight 15–40 kg, 400 mg/100 mg as adult each time, twice a day for 1–2 weeks	Recommend Dosing regimen: 3–5 mg/kg/day (max dose 400 mg), twice daily for 5 days	Not recommend	Not recommend	Recommend

http://dx.doi.org/10.21037/atm-20-7000

Table S4 Summary of supporting evidences for recommendations for remdesivir

Guideline	Recommendation	Reference number	Study type of supporting evidence							
			Guidelines/ Consensuses	SR/meta-analysis	Review	RCT/CCT	Cohort studies	Case-control studies	Case series/ case reports	Animal studies/ *in vivo* studies
1	Not recommend	0	0	0	0	0	0	0	0	0
2	Not recommend	0	0	0	0	0	0	0	0	0
3	Recommend	2	0	0	0	2	0	0	0	0
4	Not recommend	2	0	0	0	1	0	0	0	1
5	Not recommend	1	1	0	0	0	0	0	0	0
7	Recommend	2	0	0	0	0	0	0	1	1
8	Not recommend	1	0	0	0	0	0	0	0	1
9	Not recommend	0	0	0	0	0	0	0	0	0
10	Recommend	13	0	0	0	1	0	0	1	11
11	Not recommend	0	0	0	0	0	0	0	0	0
12	Not recommend	0	0	0	0	0	0	0	0	0
14	Not recommend	0	0	0	0	0	0	0	0	0
15	Recommend	0	0	0	0	0	0	0	0	0
20	Recommend	3	0	0	2	0	0	0	0	1

Guideline	Recommendation	Supporting evidence							
		Evidence source of SR/Meta-analysis				Evidence source of original studies			
		Children with COVID-19	Patient with COVID-19	Other evidence	The proportion of direct evidence	Children with COVID-19	Patient with COVID-19	Other evidence	The proportion of direct evidence
1	Not recommend	0	0	0	NA	0	0	0	NA
2	Not recommend	0	0	0	NA	0	0	0	NA
3	Recommend	0	0	0	NA	0	0	2	0%
4	Not recommend	0	0	0	NA	0	1	1	0%
5	Not recommend	0	0	0	NA	0	0	0	NA
7	Recommend	0	0	0	NA	0	1	1	0%
8	Not recommend	0	0	0	NA	0	0	1	0%
9	Not recommend	0	0	0	NA	0	0	0	NA
10	Recommend	0	0	0	NA	0	1	12	0%
11	Not recommend	0	0	0	NA	0	0	0	NA
12	Not recommend	0	0	0	NA	0	0	0	NA
14	Not recommend	0	0	0	NA	0	0	0	NA
15	Recommend	0	0	0	NA	0	0	0	NA
20	Recommend	0	0	0	NA	0	0	1	0%

Original studies include RCT/CCT, cohort studies, case-control studies, case series/case reports, animal studies and *in vivo* studies. Other evidence includes studies of patients with other diseases, animal studies or *in vivo* studies. The proportion of direct evidence, evidence from children with COVID-19/(evidence from patients with COVID-19 + other evidence). NA, not applicable; CCT, clinical controlled trials; RCT, randomized controlled trials; SR, systematic review.

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Table S5 Summary of supporting evidences for recommendations for interferon

Guideline	Recommendation	Reference number	Study type of supporting evidence							
			Guidelines/ consensuses	SR/meta-analysis	Review	RCT/CCT	Cohort studies	Case-control studies	Case series/case reports	Animal studies/ *in vivo* studies
1	Recommend	0	0	0	0	0	0	0	0	0
2	Not recommend	0	0	0	0	0	0	0	0	0
3	Not recommend	0	0	0	0	0	0	0	0	0
4	Not recommend	0	0	0	0	0	0	0	0	0
5	Not recommend	1	1	0	0	0	0	0	0	0
7	Not recommend	1	0	0	1	0	0	0	0	0
8	Not recommend	1	0	0	1	0	0	0	0	0
9	Not recommend	0	0	0	0	0	0	0	0	0
11	Recommend	11	5	0	1	1	1	0	0	3
12	Not recommend	0	0	0	0	0	0	0	0	0
14	Not recommend	1	0	1	0	0	0	0	0	0
19	Not recommend	21	0	0	6	3	3	1	4	4
20	Recommend	1	1	0	0	0	0	0	0	0

Guideline	Recommendation	Supporting evidence							
		Evidence source of SR/meta-analysis				Evidence source of original studies			
		Children with COVID-19	Patient with COVID-19	Other evidence	The proportion of direct evidence	Children with COVID-19	Patient with COVID-19	Other evidence	The proportion of direct evidence
1	Recommend	0	0	0	NA	0	0	0	NA
2	Not recommend	0	0	0	NA	0	0	0	NA
3	Not recommend	0	0	0	NA	0	0	0	NA
4	Not recommend	0	0	0	NA	0	0	0	NA
5	Not recommend	0	0	0	NA	0	0	0	NA
7	Not recommend	0	0	0	NA	0	0	0	NA
8	Not recommend	0	0	0	NA	0	0	0	NA
9	Not recommend	0	0	0	NA	0	0	0	NA
11	Recommend	0	0	0	NA	0	0	5	0%
12	Not recommend	0	0	0	NA	0	0	0	NA
14	Not recommend	0	0	5	0%	0	0	0	NA
19	Not recommend	0	0	0	NA	0	8	7	0%
20	Recommend	0	0	0	NA	0	0	0	NA

Original studies include RCT/CCT, cohort studies, case-control studies, case series/case reports, animal studies and *in vivo* studies. Other evidence includes studies of patients with other diseases, animal studies or *in vivo* studies. The proportion of direct evidence, evidence from children with COVID-19/(evidence from patients with COVID-19 + other evidence). NA, not applicable; CCT, clinical controlled trials; RCT, randomized controlled trials; SR, systematic review.

http://dx.doi.org/10.21037/atm-20-7000

Table S6 Summary of recommendations for glucocorticoids by included guidelines

Guideline	Recommendation	Indication	Dosing regimen
1	Recommend	1. With rapidly deteriorating chest imaging and occurrence of ARDS. 2. With obvious toxic symptoms, encephalitis, or encephalopathy, hemophagocytic syndrome and other serious complications. 3. With septic shock. 4. With obvious wheezing symptoms.	Intravenous methylprednisolone (1–2 mg/kg/day) Short-duration (3–5 days)
2	Not recommend	Not applicable	Not applicable
3	Recommend	mechanical ventilation, or high levels of oxygen support	Dexamethasone: 0.15 mg/kg/dose IV q24h (max: 6 mg/dose) Duration: maximum 10 days, or until discharge.
4	Recommend	1.Respiratory support: oxygen or invasive mechanical ventilation 2. Continuation for underlying condition requiring chronic steroid treatment 3. Additional diagnosis where steroid therapy is appropriate 4. MIS-C	Preferred: Dexamethasone-0.15 mg/kg once daily (Max: 6 mg) Alternatives: Preterm infant: Corrected GA <40 weeks: Hydrocortisone (0.5 mg/kg q12h × 7 days, 0.5 mg/kg daily × 3 days) Duration: up to 10 days
5	Not recommend	Not applicable	Not applicable
7	Recommend	ARDS, septic shock, encephalitis, hemophagocytic syndrome or with severe bronchospasm associated with wheezing	Intravenous methylprednisolone (1–2 mg/kg/day) Short-duration (3–5 days)
8	Recommend	used if clinically indicated	Not report
9	Not recommend	Not applicable	Not applicable
11	Recommend	Severe COVID-19	Intravenous methylprednisolone (1–2 mg/kg/day) Short-duration (3–5 days)
14	Not recommend	Not applicable	Not applicable
15	Recommend	Patients have presented with severe inflammation with or without KD features consistent with CSS in particular if they are not responding to supportive care or first line treatments	Not report
17	Recommend	MIS-C COVID-19 and hyperinflammation	Low-moderate dose glucocorticoids: MIS-C. High dose, IV pulse glucocorticoids: life-threatening complications, such as shock, and specifically, if a patient requires high dose or multiple inotropes and/or vasopressors
19	Recommend	Pediatric patients with critical COVID-19	Not report
20	Recommend	Fever over 38.5 ℃ for 3 days, CRP ≥30 mg/L, serum ferritin ≥1,000 μg/kg, the rapid progressing of imaging findings, significant hypoxia, patients manifesting the symptoms of ARDS, and obvious wheezing.	Short periods (3–5 days) Methylprednisolone not exceed 1–2 mg/kg/day

ARDS, acute respiratory distress syndrome; MIS-C, multisystem inflammatory syndrome in children; GA, gestational age; KD, Kawasaki disease; CSS, cytokine storm syndrome

http://dx.doi.org/10.21037/atm-20-7000

Table S7 Summary of supporting evidences for recommendations for glucocorticoid

Guideline	Recommendation	Reference number	Study type of supporting evidence							
			Guidelines/ consensuses	SR/meta-analysis	Review	RCT/CCT	Cohort studies	Case-control studies	Case series/ case reports	Animal studies/ *in vivo* studies
1	Recommend	5	3	0	1	0	1	0	0	0
2	Not recommend	0	0	0	0	0	0	0	0	0
3	Recommend	1	0	0	0	1	0	0	0	0
4	Recommend	2	0	0	0	2	0	0	0	0
5	Not recommend	1	1	0	0	0	0	0	0	0
7	Recommend	5	3	0	0	0	2	0	0	0
8	Recommend	0	0	0	0	0	0	0	0	0
9	Not recommend	0	0	0	0	0	0	0	0	0
11	Recommend	0	0	0	0	0	0	0	0	0
14	Not recommend	1	0	1	0	0	0	0	0	0
15	Recommend	0	0	0	0	0	0	0	0	0
17	Recommend	19	0	4	0	10	4	1	0	0
19	Recommend	0	0	0	0	0	0	0	0	0
20	Recommend	3	1	0	2	0	0	0	0	0

Guideline	Recommendation	Supporting evidence							
		Evidence source of SR/meta-analysis				Evidence source of original studies			
		Children with COVID-19	Patient with COVID-19	Other evidence	The proportion of direct evidence	Children with COVID-19	Patient with COVID-19	Other evidence	The proportion of direct evidence
1	Recommend	0	0	0	NA	0	0	1	0%
2	Not recommend	0	0	0	NA	0	0	0	NA
3	Recommend	0	0	0	NA	0	1	0	0%
4	Recommend	0	0	0	NA	0	2	0	0%
5	Not recommend	0	0	0	NA	0	0	0	NA
7	Recommend	0	0	0	NA	0	0	2	0%
8	Recommend	0	0	0	NA	0	0	0	NA
9	Not recommend	0	0	0	NA	0	0	0	NA
11	Recommend	0	0	0	NA	0	0	0	NA
14	Not recommend	0	5	18	0%	0	0	0	NA
15	Recommend	0	0	0	NA	0	0	0	NA
17	Recommend	0	0	65	0%	1	5	9	7%
19	Recommend	0	0	0	NA	0	0	0	NA
20	Recommend	0	0	0	NA	0	0	0	NA

Original studies include RCT/CCT, cohort studies, case-control studies, case series/case reports, animal studies and *in vivo* studies. Other evidence includes studies of patients with other diseases, animal studies or *in vivo* studies. The proportion of direct evidence, evidence from children with COVID-19/(evidence from patients with COVID-19 + other evidence). NA, not applicable; CCT, clinical controlled trials; RCT, randomized controlled trials; SR, systematic review.

http://dx.doi.org/10.21037/atm-20-7000

Table S8 Summary of recommendations for intravenous immunoglobulin by included guidelines.

Guideline	Recommendation	Indication	Dosing regimen
1	Recommend	Severe COVID-19	1 g/kg/day for 2 days, or 400 mg/kg/ day for 5 days
2	Not recommend	Not applicable	Not applicable
4	Recommend	MIS-C (KD features and/or coronary artery changes)	2 g/kg (max dose 100g)
5	Not recommend	Not applicable	Not applicable
7	Recommend	Severe COVID-19	1 g/kg/day for 2 days, or 400 mg/kg/day for 5 days
9	Not recommend	Not applicable	Not applicable
11	Recommend	Severe COVID-19	Not report
12	Not recommend	Not applicable	Not applicable
14	Not recommend	Not applicable	Not applicable
15	Recommend	Patients with KD-like illness, evidence of excessive inflammation (ferritin >700 ng/mL, CRP >30 g/dL, or multisystem organ failure), or cardiac involvement.	2 g/kg
17	Recommend	MIS-C	1-2 g/kg
19	Not recommend	Not applicable	Not applicable
20	Recommend	Severe and critical COVID-19	1 g/kg/day for 2 days, or 400 mg/kg/day for 5 days

MIS-C, multisystem inflammatory syndrome in children; KD, Kawasaki disease; COVID-19, coronavirus disease 2019.

http://dx.doi.org/10.21037/atm-20-7000

Table S9 Summary of supporting evidences for recommendations for intravenous immunoglobulin

Guideline	Recommendation	Reference number	Study type of supporting evidence							
			Guidelines/ consensuses	SR/Meta-analysis	Review	RCT/CCT	Cohort studies	Case-control studies	Case series/ Case reports	Animal studies/ *in vivo* studies
1	Recommend	4	4	0	0	0	0	0	0	0
2	Not recommend	0	0	0	0	0	0	0	0	0
4	Recommend	0	0	0	0	0	0	0	0	0
5	Not recommend	1	1	0	0	0	0	0	0	0
7	Recommend	0	0	0	0	0	0	0	0	0
9	Not recommend	0	0	0	0	0	0	0	0	0
11	Recommend	0	0	0	0	0	0	0	0	0
12	Not recommend	0	0	0	0	0	0	0	0	0
14	Not recommend	1	0	1	0	0	0	0	0	0
15	Recommend	0	0	0	0	0	0	0	0	0
17	Recommend	9	3	1	1	3	0	0	1	0
19	Not recommend	6	0	1	2	0	0	0	3	0
20	Recommend	2	2	0	0	0	0	0	0	0

Guideline	Recommendatiodsn	Supporting evidence							
		Evidence source of SR/Meta-analysis				Evidence source of original studies			
		Children with COVID-19	Patient with COVID-19	Other evidence	The proportion of direct evidence	Children with COVID-19	Patient with COVID-19	Other evidence	The proportion of direct evidence
1	Recommend	0	0	0	NA	0	0	0	NA
2	Not recommend	0	0	0	NA	0	0	0	NA
4	Recommend	0	0	0	NA	0	0	0	NA
5	Not recommend	0	0	0	NA	0	0	0	NA
7	Recommend	0	0	0	NA	0	0	0	NA
9	Not recommend	0	0	0	NA	0	0	0	NA
11	Recommend	0	0	0	NA	0	0	0	NA
12	Not recommend	0	0	0	NA	0	0	0	NA
14	Not recommend	0	2	4	0%	0	0	0	NA
15	Recommend	0	0	0	NA	0	0	0	NA
17	Recommend	0	0	13	0%	0	1	4	0%
19	Not recommend	0	9	0	0%	0	2	1	0%
20	Recommend	0	0	0	NA	0	0	0	NA

Original studies include RCT/CCT, cohort studies, case-control studies, case series/case reports, animal studies and *in vivo* studies. Other evidence includes studies of patients with other diseases, animal studies or *in vivo* studies. The proportion of direct evidence, evidence from children with COVID-19/(evidence from patients with COVID-19 + other evidence). NA, not applicable; CCT, clinical controlled trials; RCT, randomized controlled trials; SR, systematic review.

Table S10 Summary of recommendations for biologics by included guidelines

Guideline	Recommendation	Anakinra (IL-1 inhibition)		Tocilizumab (IL-6 inhibition)		JAK inhibition		Infliximab	
		Indication	Dosing regimen	Indication	Dosing regimen	Indication	Dosing regimen	Indication	Dosing regimen
4	Recommend	Fevers >24 hrs post steroids/ IVIG or moderate/severe presentation	2–4 mg/kg/dose (max 100 mg/dose) SQ/IV BID, May ↑ to TID or QID if poor response Continue for 5–7 days	Consider adding to antiviral therapy for patients meeting criteria, criteria for risk high-risk of cytokine storm	<30 kg: 12 mg/kg IV; ≥30 kg: 8 mg/kg IV, max 800 mg (round dose to nearest full vial) Duration: One dose Consider additional dose 8–12 hours after if continued clinical decompensation	Not report	Not report	Not report	Not report
8	Recommend	Severe/critical case with evidence of hyperinflammation (raised CRP, Ferritin, IL6, sCD25)	SC: 2 mg/kg once daily Increase dose by 2 mg/kg per day if unresponsive Maximum dose 8 mg/kg, Stop if no clinical benefit at maximum dose IV: <20 kg 2 mg/kg stat loading dose, followed by a continuous infusion of 0.02 mL/kg/hr (2 mg/kg/day) >20 kg 2 mg/kg stat loading dose, followed by a continuous infusion of 0.01 mL/kg/hr (2 mg/kg/day) Increase by dose by 2 mg/kg/day every 12 hours if unresponsive; Maximum dose 12 mg/kg/day; Maximum dose in 24 hours 400 mg (excluding loading dose)	Severe/critical case with evidence of hyperinflammation (raised CRP, Ferritin, IL6, sCD25)	<30 kg 12 mg/kg, IV >30 kg 8 mg/kg (max dose 800 mg), IV If no improvement at 12 hours, repeat with same dose	Not report	Not report	Not report	Not report
15	Recommend	Patients have presented with severe inflammation with or without KD features consistent with CSS in particular if they are not responding to supportive care or first line treatments	Not report	Not report	Not report	Not report	Not report	If the presentation is most consistent with KD and there is failure of first line treatment	Not report
17	Recommend	MIS-C refractory to IVIG and glucocorticoids or in patients with contraindications to these treatments	>4 mg/kg/day IV or SQ Time: Initiation of anakinra before invasive mechanical ventilation may be beneficial	COVID-19 pneumonia and signs of hyperinflammation	<30 kg: 12 mg/kg IV; ≥30 kg: 8 mg/kg IV, max 800 mg	Not report	Not report	Not report	Not report
19	Recommend	Confirmed critical COVID-19 (SARS-CoV-2 PCR positive) with evidence of hyperinflammation	Not report	Confirmed critical COVID-19 (SARS-CoV-2 PCR positive) with evidence of hyperinflammation	Not report	Not recommend	Not applicable	Not report	Not report
20	Recommend	Not applicable	Not applicable	Recommend	Not report	Not applicable	Not applicable	Not applicable	Not applicable

KD, Kawasaki Disease; SC, subcutaneous; IV, intravenous; CSS, cytokine storm syndrome; MIS-C, Multisystem Inflammatory Syndrome in Children; IVIG, intravenous immunoglobulin; CD-25, cluster of differentiation-25; COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

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Table S11 Summary of recommendations for antiplatelet and anticoagulation drugs by included guidelines

Guideline	Recommendation	Aspirin		Enoxaparin		Warfarin	
		Indication	Dosing regimen	Indication	Dosing regimen	Indication	Dosing regimen
4	Recommend	Not report	Not report	COVID-19 patients unless contraindicated	Not report	Not report	Not report
11	Recommend	Not report	Not report	Increased D-dimer and at high risk of thrombosis	Not report	Not report	Not report
15	Recommend	Patients with KD-like illness, evidence of excessive inflammation (ferritin >700 ng/mL, CRP >30 g/dL, or multisystem organ failure), or cardiac involvement.	20–25 mg/kg/dose every 6 h (80–100 mg/kg/day) IVIG: intravenous immunoglobulin CRP: C-reactive protein CD-25: cluster of differentiation-25 KD: Kawasaki disease CSS: cytokine storm syndrome COVID-19: coronavirus disease 2019	Not report	Not report	Not report	Not report
17	Recommend	MIS-C patients with CAAs and a maximal z-score >2.5 and/or thrombocytosis (platelet count ≥450,000/μL)	3-5 mg/kg/day; max 81 mg/day	MIS-C patients with CAAs and a a z-score ≥10.0 Documented thrombosis or ongoing moderate to severe LV dysfunction	Not report	MIS-C patients with CAAs and a z-score ≥10.0 Documented thrombosis or ongoing moderate to severe LV dysfunction	Not report

IVIG, intravenous immunoglobulin; CRP, C-reactive protein; CD-25, cluster of differentiation-25; KD, Kawasaki disease; CSS, cytokine storm syndrome; COVID-19, coronavirus disease 2019.

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