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Peer Review File

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Reviewer Comments

Major point

Comment 1: Are all the patients analyzed confirmed only by adenovirus? Were there any potentially related pathogens identified during the study period? In the study of adenovirus infection or adenovirus pneumonia, there is much controversy as to whether the true pathogen of infection or pneumonia is an adenovirus. Please clarify this concern at the introduction or method section.

Reply 1: Thank you very much for your advice and this comment is valuable. We agree with the point that respiratory virus mixed infection makes the interpretation of positive results more challenging. Previous studies (1)have also shown that 55%-63% of patients have mixed infection including adenovirus. Our patients completed etiological tests of blood and respiratory secretions within 24 hours after admission, including influenza type A and B, respiratory syncytial virus, coxsackie group B virus, adenovirus, mycoplasma pneumoniae, chlamydia pneumoniae and germiculture. Our study also chose the patients have only evidence of adenovirus infection at the beginning of admission. Because mixed infection of adenovirus pneumonia often occurs after 7 days of onse(2), so we repeated the above pathogenic examination for patients who have not improved after 1 week of hospitalization or who have fever again after improvement. Mixed infection is defined as the evidence of other pathogens than adenovirus at this moment. It can be one or more. Although there are still some pathogens in the latent period. We try our best to avoid the interference with other potential pathogens in this way. In addition to etiology, the diagnosis of adenovirus pneumonia still needs to be combined with clinical manifestations and laboratory examination results (white blood cell count, PCT, C-reactive protein, ESR, chest imaging, etc.), we will also comprehensively analyze

them from a clinical perspective when select cases. In view of the reviewer`s comment, the statement has been evaluated and added to revised manuscript in the introduction or method section. We have described it in detail in the text as suggesting.

Reference

(1)Song E, Wang H, Kajon AE, Salamon D, Dong S, Ramilo O, Leber A, Jaggi P. Diagnosis of Pediatric Acute Adenovirus Infections: Is a Positive PCR Sufficient? Pediatr Infect Dis J. 2016 Aug;35(8):827-34. doi: 10.1097/INF.0000000000001119. PMID: 26974888; PMCID: PMC5292826.

(2)National Health Commission of the People's Republic of China,State Administration of Traditional Chinese Medicine.Guideline for diagnosis and treatment of adenovirus pneumonia in children (2019 version).Chin J of Clin Infect Dis,2019 Jun;12(3):161-166.Chinese.

Changes in the text: page 5 line 7-8/ page 6, line 18-22/ page 7, line 1-4

Comment 2: Authors introduced that inclusion criteria were nasopharyngeal swab virus antigen-positive, nasopharyngeal swab adenovirus nucleic acid positive, serum adenovirus-specific IgM antibody positive, and detect adenovirus nucleic acid sequences in bronchoalveolar lavage fluid (BALF) and metagenomics next generation sequencing (mNGS). I think respiratory tract infection and pneumonia are different meanings. The true pathogen of pneumonia has a diagnostic significance when they are samples obtained from the lower respiratory tract.

Reply 2: Thank you so much for your comment. We agree with the reviewer's comment and respiratory infection is different from pneumonia. Specimens from the lower respiratory tract are more representative of the real pathogen of pneumonia. Due to the high sensitivity of nucleic acid detection, and clinical commonly used upper respiratory tract samples instead of lower respiratory tract samples to detect the pathogen of pneumonia, the detected virus is not the pathogen of pneumonia necessary. Previous studies (1)have shown that the adenovirus positive rate of healthy asymptomatic children detected by PCR method is 11%, while the virus isolation rate is only 0.6%. Therefore, it is necessary to make a

reasonable clinical interpretation of the upper respiratory tract etiology positive. Generally, the basic principles and key points of clinical interpretation are combined with the clinical analysis of patients, including whether there is viral pneumonia in clinic, whether the changes of imaging and laboratory examination are consistent with the characteristics of adenovirus pneumonia, whether the time of viral pneumonia and pathogen detection is consistent, and so on. The case we selected in our study accord with the above points. Some scholars (2) have proposed that when using PCR to detect adenovirus. It is best to quantify the viral load and identify the serotype at the same time, which can help to evaluate the clinical significance of PCR positive results. Owing to the limitations of laboratory conditions, our research cannot be achieved for the time being, which is the content that needs to be further improved. Corrections have been made in the revised manuscript.

Reference

(1)Kalu SU, Loeffelholz M, Beck E, Patel JA, Revai K, Fan J, Henrickson KJ, Chonmaitree T. Persistence of adenovirus nucleic acids in nasopharyngeal secretions: a diagnostic conundrum. Pediatr Infect Dis J. 2010 Aug;29(8):746-50. doi: 10.1097/INF.0b013e3181d743c8. PMID: 20308936; PMCID: PMC3206289.

(2)Song E, Wang H, Kajon AE, Salamon D, Dong S, Ramilo O, Leber A, Jaggi P. Diagnosis of Pediatric Acute Adenovirus Infections: Is a Positive PCR Sufficient? Pediatr Infect Dis J. 2016 Aug;35(8):827-34. doi: 10.1097/INF.0000000000001119. PMID: 26974888; PMCID: PMC5292826.

Changes in the text: page 5, line 6-7

Comment 3: Please explain why you set the patient ratio of training set and data set at the design of the study and patient selection section.

Reply 3: Thank you very much for your advice. The subjects of this study are the clinical data of children with adenovirus infection pneumonia from January 2019 to December 2019. The purpose of our study was to develop and evaluate nomogram for severe adenovirus pneumonia in children. At present, TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis) is a guideline to guide the standardized reporting of prediction model

research in the world, which helps researchers to improve the reporting quality and reproducibility of clinical prediction model (1,2). The modeling scheme uses Type 2a mentioned by TRIPOD to randomly divide the original data set into training dataset and validation datasets according to the proportion of 7:3. We builds the prediction model by using training datasets. the validation dataset was used to be evaluated the model. Additionally, we visualize the model through a nomogram. The characteristics of patients in the training dataset and validation dataset are described in Table 1. Our study strictly complies with the TRIPOD statement and aims to enhance the quality of the report and the repeatability of the results. We have revised our manuscript as advising.

Reference

(1) Moons KG, Altman DG, Reitsma JB, Ioannidis JP, Macaskill P, Steyerberg EW, Vickers AJ, Ransohoff DF, Collins GS. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. Ann Intern Med. 2015 Jan 6;162(1):W1-73. doi: 10.7326/M14-0698. PMID: 25560730.

(2) Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. BMJ. 2015 Jan 7;350:g7594. doi: 10.1136/bmj.g7594. PMID: 25569120.

Changes in the text: page 5, line 20/ page 6, line 1-2, line 4

Minor point

Comment 4: Please clarify the fever definition in the study predictor section.

Reply 4: Thank you very much for your comment. Fever was defined as an axillary temperature of ≥37.3 °C. Corrections have been made in the revised manuscript.

Changes in the text: page 6, line 15-16

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Comment 5: There are several flaws in language quality, although the intended contents remain understandable. Nevertheless, prior to publication, thorough language proofreading by a native speaker should either be arranged by the author.

- page 5, line 2-6
- page 9, line 5-7, line 15-17
- page 10, line 3-7
- page 11, line 2-3, line 6-8

Reply 5: Thank you very much for your suggestion. We pay special attention to language issues. In order to meet the publication requirements, the manuscript has been polished by native speaker and corrections have been made in the revised manuscript.

Changes in the text: page 6, line 9-14/ page 10, line 22/ page 11, line 1-3, line 10-12, line 19-22/ page 12, line 1-5, line 20-22/ page 13, line 2-6

Comment 6: It should be “experiment” instead of “experimen” on page 10, line 18.

Reply 6: Thank you very much for your comment. We have modified our text as advised.

Changes in the text: page 11, line 15