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OPEN PEER REVIEW

Evaluation of Risk Factors for Children with Severe Adenovirus Respiratory Infection: Retrospective Study

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 28 Jul 2023

Neda Alijani Reviewer

REJECT 28 Jul 2023

-This article has no novelty, and there are many articles on the correlation between the severity of viral disease and liver enzymes.

-The subject of the article is “Association between aspartate aminotransferase levels and disease severity in children with human adenovirus respiratory infection: retrospective study”; however, the text of the article discusses predicting adenovirus disease severity using various laboratory tests, so I think the title of the article should be “Adenovirus severity prediction with laboratory results” (for example).

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Editor,

It is with excitement that I resubmit to you a revised version of manuscript "Evaluation of risk factors for children with severe adenovirus respiratory infection: retrospective study [Manuscript ID: 134296]" for the "Iranian Journal of Pediatrics". Thank you very much for giving us the opportunity to revise our manuscript. We appreciate the constructive criticisms of the reviewers, and we have carefully taken the comments into consideration in preparing our revision, which has resulted in a paper that is more clear and compelling. The point-by-point responses are attached after this letter. At meanwhile, all changes made to the revised manuscript are in red so that they may be easily identified.

The manuscript has not been published previously, in any language, in whole or in part, and is not currently under consideration elsewhere. None of the authors have any competing financial interest to report.

Thank you for considering our manuscript for publication in your esteemed journal.

Best wishes,

Yours sincerely,

Yiyi Ding

Corresponding author:
Name: Yiyi Ding

Reviewer #1 Comments:
Major Comments:

Comment 1: This article has not novelty , and there are many articles on the correlation of severity of viral disease with liver enzymes.
Author Response 1: Thank you for carefully reviewing our manuscript. HAdv infecion were often accompanied by abnormal liver anzymes, most of all AST. The serum AST level corresponds to the severity of adenoviral RI compared with the other indicators of liver injury during hospitalization. However, there is no report on the independent role and predictive value of AST as an indicator. Hence, we performed a retrospective review further evaluated the relationship between the AST level and the severity of the disease in children.

Comment 2: The subject of the article is; Association between aspartate aminotransferase levels and disease severity in children with human adenovirus respiratory infection: retrospective study; but in the text of the article, it is written about the prediction of various laboratory test with adenovirus disease, so I think the title of the article should be ;Adenovirus severity prediction with laboratory results(for example)
Author Response 2: Thank you very much for your feedback. We have updated the title to "Evaluation of risk factors for children with severe adenovirus respiratory infection: retrospective study".

Reviewer #2 Comments:
Major Comments:

Comment 1: Abstract: State the number of mild vs severe cases in the cohort. Currently the abstract mentions the proportion of URI, bronchiolitis, mild pneumonia, and severe pneumonia but not the total mild vs severe groups.
Author Response 1: Thank you for your careful review of our articles.Lines 97 to 99 of our original manuscript have been added: "The 665 patients in the cohort were divided into a mild group (n=477 cases，71.73%) and a severe group (n=188 cases，28.27%)."

Comment 2: Introduction:The introduction provides good background on adenovirus respiratory infections in children, though the focus on aspartate aminotransferase (AST) could be strengthened. Consider adding 1-2 sentences on what is known about AST levels in adenovirus infections or other respiratory infections, and why AST was chosen as the biomarker to study.
Author Response 2: Thank you for your kind instructive comments. We have added: "The AST level has been shown to be related to the severity of diseases like acute pancreatitis, non-alcoholic fatty liver disease, and severe pneumonia. Children with HAdv infection were often accompanied by abnormal liver function. Xingui Tian et al.[14] demonstrated that the serum AST or LDH level corresponds to the severity of adenoviral RI compared with the other indicators of liver injury during hospitalization."

References：

14 Tian X, Li X, Qiu S, et al. Abnormal liver function in children hospitalized with acute respiratory infection of adenoviruses: a retrospective study. Virol Sin. 2023 Oct;38(5):735-740.

Comment 3: Methods:The methods are clearly described overall. A minor suggestion is to mention in the abstract the timeline of data collection (January to December 2019).

Author Response 3: We greatly value your valuable opinion and suggestions.Methods Lines 9 of our original manuscript have been added: "January and December 2019".

Comment 4: Provide more details on the statistical analysis plan - which tests were used for which comparisons, how variables were entered into logistic regression models, etc. This will strengthen the validity of the analysis.

Author Response 4: Thank you for your kind comments. We have provided the details of the statistical analysis: "All analyses were conducted with SPSS 25.0 (IBM Corp., Armonk, NY, USA). Rate comparison was done with the $\chi 2$ test. Inter-group comparisons were done with t-test, for data with normal distribution, and with nonparametric Wilcoxon rank-sum test for data with abnormal distribution. All variables that showed independent association with HAdV RI in univariate analysis were analyzed further using multivariable analysis. The predictability of the risk factors in determining between mild and severe adenoviral RIs cases was examined using a receiver operating characteristic (ROC) analysis and area under the curve (AUC). A P-value of < 0.05 was set as the significance threshold".

Comment 5: Results: Strengthening the results section will greatly improve the impact and clarity of this manuscript.The results section logically presents the main findings. I would suggest adding 95% confidence intervals to the odds ratios in Tables 3 and 4 to better judge the precision of the estimates.For the multivariate analysis, again present the adjusted odds ratios and 95% CIs in table format.

Author Response 5: Thank you for your kind comments. Table 3 and 4 has undergone significant revisions for better judge the precision of the estimates.

Table3 Univariate analyses of influencing factors in children related to severity of HAdV infection

Variable	OR (95%CI)	*P*-value
Age(years)	0.637(0.569-0.714)	0.000*
Gender (male)	1.264(0.889-1.797)	0.192
WBC count(10^9/L)	1.030(0.993-1.068)	0.118
HGB(g/L)	0.957(0.941-0.972)	0.000*
PLT (10^9/L)	1.001(1.001-1.003)	0.048*
CRP（mg/L）	0.990(0.991-1.004)	0.461
Serum ALB(g/L)	0.840(0.796-0.886)	0.000*
ALT（U/L）	1.010(1.004-1.017)	0.002*
AST（U/L）	1.032(1.024-1.040)	0.000*
CK (U/L)	1.001(1.001-1.002)	0.001*
CK-MB (U/L)	1.048(1.035-1.062)	0.000*
LDH (U/L)	1.009(1.007-1.011)	0.000*

Continuous variables were presented as median (range); the categorical variable was presented as absolute and relative frequencies. WBC=White blood cell; HGB=Hemoglobin; PLT=Platelets; CRP=C-reactive protein; ALB=Albumin; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; LDH=lactic acid dehydrogenase; CK=creatine kinase; CK-MB=creatine kinase isoenzyme; *$P < 0.05$

Table4 Multivariate logistic regression analysis of influencing factors in children related to severity of HAdV infection

Variable	OR[a](95%CI)	*P*-value
Age(years)	0.639(0.570-0.716)	0.000*
HGB(g/L)	0.957(0.941-0.972)	0.001*
PLT count(10^9/L)	1.001(1.001-1.003)	0.048*
Serum ALB(g/L)	0.840(0.796-0.886)	0.001*
ALT（U/L）	1.010(1.003-1.017)	0.003*
AST（U/L）	1.032(1.024-1.040)	0.000*
CK（U/L）	1.001(1.001-1.002)	0.001*
CK-MB（U/L）	1.041(1.027-1.055)	0.000*
LDH（U/L）	1.008(1.007-1.010)	0.000*

[a]Adjusted gender; HGB=Hemoglobin; PLT=Platelets; ALB=Albumin; ALT=Alanine aminotransferase; AST=Aspartate aminotransferase; *$P < 0.05$

Comment 6: In describing the ROC analysis, give the 95% CI for the AUC, and numerical values for sensitivity and specificity at the cut-off, rather than just saying "specificity was 83.4%".Add a statement on the Hosmer-Lemeshow goodness-of-fit test to assess how well the model fits the data.
Author Response 6: Thank you for your kind instructive comments and suggestions. Lines (165-169) of our original manuscript have been deleted: "To verify the diagnostic efficacy of AST in assessing disease severity, ROC curve analysis was performed to assess the predictability of AST as an indicator of disease severity. The area under the AST ROC was 0.782 with a sensitivity of 0.606 and a specificity of 0.834. The threshold for the serum AST level was 52.5 U/L for severe HAdV RI

Comment 7: Present the ROC curve for AST in a Figure, as this will nicely illustrate the result.Adding numeric results into tables and figures will strengthen the presentation of the key findings.
Author Response 7: We appreciate your thoughtful suggestions. Figures 2 has undergone significant revisions for clarity.

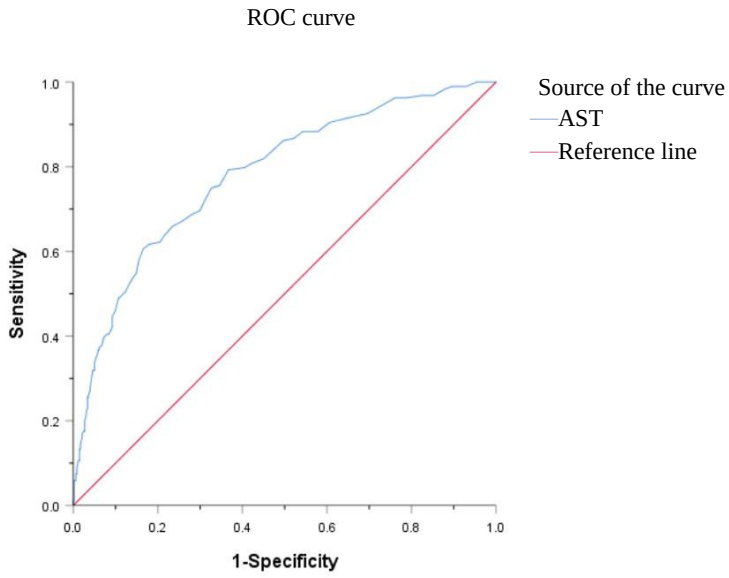


Fig.2 Receiver operating characteristic (ROC) curve of AST to evaluate for the severity of HAdV infection.The area under the AST ROC was 0.782 with a sensitivity of 0.606 and a specificity of 0.834.

Comment 8: Discussion: The discussion could be enhanced by comparing the AUC and cut-off found for AST in this study to other predictive biomarkers of respiratory infection severity reported in the literature. How does AST compare as a severity predictor? Are there studies showing AUCs for CRP, procalcitonin etc in respiratory

infections? This context helps judge the predictive value of AST.

Author Response 8: We appreciate your thoughtful suggestions. We have made the following improvements to the discussion section: "Pei-Qiong Wu et al[29]. found that high serum LDH level(AUC=0.87) and low lymphocyte count (AUC=0.70) could be used as predictors of adenovirus respiratory infection severity in children. The cut-off value for serum LDH level and LYMPH count was 507.5U/L and 0.3910–9/L, respectively. Our results also confirms that severe adenovirus infection is assocciated with LDH, which may be related to the weak immunity of younger children; another possible mechanism is that adenovirus may have triggered a cytokine storm. The levels of AST and LDH in the severe group were significantly higher than those in the mild group, consistent with the findings of Xu N et al.[30] Patients with severe pneumonia may experience both diminished pulmonary ventilation and pulmonary ventilation, which may result in hypoxemia and severe microcirculatory disruptions.[31] Severe HAdV RI focuses primarily on the lungs causing a systemic inflammatory response syndrome. Both pathogenic microorganisms and numerous inflammatory factors produce varying levels of destruction to liver cells and cardiomyocytes, increasing the cell membrane permeability and, in turn, serum AST concentrations[32]. Moreover, according to the report about marker for the early diagnosis of severe adenovirus infection, the area under the ROC curve of WBC, N, and CRP were 0.748, 0.770,and 0.740[33]. Thus, this study showed that the AUC of AST ROC analysis to predict the severity of HAdV pneumonia was 0.782, which was significantly greater than the other inflammatory indicators".

References：

29 Wu PQ, Zeng SQ, Yin GQ, Huang JJ, Xie ZW, Lu G, Jiang WH. Clinical manifestations and risk factors of adenovirus respiratory infection in hospitalized children in Guangzhou, China during the 2011-2014 period. Medicine (Baltimore). 2020 Jan;99(4):e18584.

30 Xu N, Chen P, Wang Y. Evaluation of Risk Factors for Exacerbations in Children with Adenoviral Pneumonia. Biomed Res Int. 2020 Jul 31;2020:4878635.

31 Giannitti F., Diab S. S., Uzal F. A., et al. Infection with a Hepatozoon sp. closely related to Hepatozoon felis in a wild Pampas gray fox (Lycalopex -Pseudalopex -gymnocercus) co-infected with canine distemper virus. Veterinary Parasitology. 2012;186(3-4):497–502.

32 Hwang S. M., Park D. E., Yang Y. I., et al. Outbreak of febrile respiratory illness caused by adenovirus at a South Korean military training facility: clinical and radiological characteristics of adenovirus pneumonia. Japanese Journal of Infectious Diseases. 2013;66(5):359–365.

33 Liu XY, Zhang XF, Li J, et al. Application of heparin-bingding protein in severe adenovirus pneumonia [J]. Chin J Appl Clin Pediatr ,2021,24(09):1014-1019.

Comment 9: Comment on why AST may be increased in severe infections: is it specific to adenovirus pathology or a general marker of inflammation/tissue damage? Elaborate more on the underlying mechanisms/causes of increased AST in severe infections. Some discussion of the biology behind the observation would be

informative.

Author Response 9: We appreciate you alerting us about this. We have made the following improvements to the discussion section: "Most adenovirus subspecies are coxsackievirus-adenovirus receptor, which is mainly on the cardiac cell membrane. AST is a mitochondrial enzyme that is found in the cytoplasm and mitochondrial matrix of cells. It is expressed in the cells of all major organ systems such as the heart, liver, and kidney. When the human body is infected with adenovirus, under the synergistic action of coxsackievirus-adenovirus receptor, causing cardiomyocyte degeneration, necrosis, lysis, leading to the increase of myocardial enzyme, AST levels[21].

Patients with severe pneumonia may experience both diminished pulmonary ventilation and pulmonary ventilation, which may result in hypoxemia and severe microcirculatory disruptions.[31] Severe HAdV RI focuses primarily on the lungs causing a systemic inflammatory response syndrome. Both pathogenic microorganisms and numerous inflammatory factors produce varying levels of destruction to liver cells and cardiomyocytes, increasing the cell membrane permeability and, in turn, serum AST concentrations[32]."

References：

21 Kawasaki Y, Hosoya M, Katayose M, et al. Correlation between serum interleukin 6 and C-reactive protein concentrations in patients with adenoviral respiratory infection[J]. Pediatr Infect Dis J, 2002, 21(5):370-374 .

31 Giannitti F., Diab S. S., Uzal F. A., et al. Infection with a Hepatozoon sp. closely related to Hepatozoon felis in a wild Pampas gray fox (Lycalopex -Pseudalopex -gymnocercus) co-infected with canine distemper virus. Veterinary Parasitology. 2012;186(3-4):497–502.

32 Hwang S. M., Park D. E., Yang Y. I., et al. Outbreak of febrile respiratory illness caused by adenovirus at a South Korean military training facility: clinical and radiological characteristics of adenovirus pneumonia. Japanese Journal of Infectious Diseases. 2013;66(5):359–365.

Comment 10: Comment on any limitations or caveats of using AST as a biomarker. For example, does it lack specificity since it can be elevated in other conditions? How would you distinguish between a high AST from adenovirus pneumonia vs other causes?

Author Response 10: We appreciate your careful evaluation and positive feedback on our manuscript. Compared with ALT, AST is non-specific injury, and AST level may be increased due to other organs. However, we could not collect relevant literature to distinguish between a high AST from adenovirus pneumonia vs other causes. Therefore, we assume this is one of our study's limitations. The following statement has been added in the revised article: "At present, we haven't collected information on the difference between high AST in severe adenovirus pneumonia and other causes, and we will conduct further research in the future".

2 Revision 1

0 comments

No public comments in this round.