A Multicentre Preliminary Study of the Effect of Recombinant Human Interferon α1b Treatment of Infants Hospitalized with Lower Respiratory Tract Infection on Subsequent Wheezing

Lihua Yang
Tianjin Medical University
Guocheng Zhang (guochengzhang.tmu@gmail.com)
Tianjin Medical University https://orcid.org/0000-0002-2085-9416
Chengxiu Wang
Chongqing Medical University
Yuanbin Shi
Chongqing Medical University
Xiaoling Ren
Chongqing Medical University
Liao Li
Chongqing Medical University
Hui Shan
Liaoning Cancer Institute and Hospital
Jing Chen
Shenyang Medical College
Yanqi Su
Liaoning Cancer Institute and Hospital
Jianxin Xiong
Changzhou Women and Children's Hospital
Xue Xue
Suzhou Municipal Hospital
Lusheng Huang
taixing people's hospital, Jiangsu
Shaofeng Song
xi'an north hospital, Shaanxi
Li Zhao
Shijiazhuang Medical College
Shuhua An
Hebei Medical University

Haiming Yu
Baoding University
Hong Cao
Yan'an People's Hospital
Lin Zhao
Kunming Medical University
Ming Li
Kunming Medical University
Xiaocui Sheng
Yunnan Cancer Hospital
Yajun Wang
Yunnan Cancer Hospital

Research article

Keywords: wheezing, infant, lower respiratory tract infection, related factors, recombinant human interferon a1b

Posted Date: October 14th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-56752/v1

Abstract

Background: To investigate the impact of recombinant human interferon α1b (rhIFNα1b) treatment of infants hospitalized with lower respiratory tract infections on subsequent wheezing.

Methods: The clinical data of infants in 19 hospitals with viral pneumonia, wheezy bronchitis, or bronchiolitis were retrospectively reviewed from June 2009 to June 2015 (age, gender, diagnosis, the use of rhIFNα1b when in hospital). Age at follow-up, birth weight, gestation age, childhood and family history of allergy, feeding history, family environment, and the number of wheezing episodes within the last year were obtained by telephone and questionnaires. Based on the use of rhIFNα1b in hospital, the subjects were divided into two groups: the rhIFNα1b treatment group (253 cases) and the control group (287 cases). A comparison was made between the two groups in terms of wheezing episodes within the last year. Based on the number of wheezing episodes within the last year, the subjects were divided into two groups, the wheezing group (95 cases) and the non-wheezing group (445 cases). Comparisons were made between the 2 groups in terms of age, diagnosis, the use of rhIFNα1b in hospital, gender, age at follow-up, birth weight, gestation age, childhood and family history of allergy, feeding history, and family environment. If the result of single factor comparison showed that P was <0.05, the indicators were analysed by binary logistic regression. The receiver operator characteristic (ROC) curve was drawn to evaluate the prediction ability of logistic regression models.

Results: (1) Of a total of 813 cases for which follow-up data were available, 273 cases were excluded because of incomplete questionnaires, a dosage of rhIFN a1 b < 1 ug/kg.d or a treatment duration < 3 days, a date in hospital beyond the scope of the follow-up, or because the patient's age when in hospital was > 3 years old. Finally, 540 patients were included in the analysis.(2) A total of 95 (17.6%) out of 540 cases had experienced wheezing episodes within the last year; 35 (13.8%) out of 253 cases that were treated with rhIFN a1 b and 60 cases (20.9%) out of 287 cases without rhIFN a1 b treatment had wheezing episodes within the last year. The difference in wheezing episodes within the last year between the rhIFNα1b treatment group and the control group was statistically significant (P=0.031). (3)The result of single factor regression indicated that the differences between the two groups of wheezing and non-wheezing in terms of age, the use of rhIFNα1b in hospital, a childhood and family history of allergy, housing situation, and feeding history were all statistically significant (all P<0.05). The result of binary logistic regression showed that a childhood history of allergy (OR=2.14, P=0.004), no use of rhIFNα1b therapy (OR=1.70, P=0.028) and living in a crowded house (OR=1.92, P=0.012) were risk factors of subsequent wheezing. Breastfeeding (OR=0.44, P=0.008) and an age of £1year old at the time of hospitalization (OR=0.58, P=0.024) were protective factors. The area under the ROC curve was 0.68, P=0.00, which indicated that the regression model had greater than medium diagnostic accuracy.

Conclusions: Early use of rhIFNα1b treatment for infants hospitalized with lower respiratory tract infections and breastfeeding could prevent subsequent wheezing. An atopic constitution and living in a crowded house could promote subsequent wheezing.

1. Background

Infants and young children, especially children under 2 years of age, often develop lower respiratory tract infections such as pneumonia, wheezy bronchitis, and bronchiolitis, and the main pathogens of lower respiratory tract infections are viruses (1, 2). At the same time, a large number of studies have shown that viral infections during infancy or early childhood influence T lymphocyte subsets and related factors in infants and young children, leading to recurrent wheezing and asthma in later childhood (3–5). So far, only the influenza virus and cytomegalovirus have targeted drug therapy; treatments for other viral infections are still largely supportive and symptomatic. Interferon is an important cytokine produced by the body after viral infection. It has dual effects of anti-virus and immune regulation (6, 7). Recombinant human interferon alpha 1b (rhIFN a 1b, Hapgen®) is a type of genetic engineering interferon developed in China (8), and rhIFNα1b has been used for the treatment of chronic viral hepatitis B, hand, foot and mouth disease and Epstein-Barr virus (EBV) infection (9–11). In this study, we investigated the effects of rhIFNα1b and other factors on subsequent wheezing in infants diagnosed with viral pneumonia, wheezy bronchitis, and bronchiolitis.

2. Methods

2.1 Patients

In 19 hospitals, infants younger than 3 years of age who were hospitalized and had been diagnosed with viral pneumonia, wheezy bronchitis, or bronchiolitis during the period from June 2009 to June 2015 were enrolled in the study.

2.2 Study Design

Questionnaires were based on the literature on wheezing and the asthma epidemiology questionnaire (12). Hospital medical records were retrieved and age, gender, diagnosis (viral pneumonia, bronchiolitis and wheezy bronchitis), the use of rhIFNα1b (a dose of at least 1 ug/kg.d and treatment for at least 3 days) in hospital, age at follow-up, birth weight, gestation age, childhood and family history of allergy, feeding history (breast feeding, mixed feeding, milk powder feeding), family environment (smokers in the home, pets and housing situation), and wheezing episodes within the last year were obtained by telephone and from questionnaires.

Based on the use of rhIFNα1b when in hospital, the subjects were divided into two groups: the rhIFNα1b treatment group and the control group. Comparisons were made between the two groups in terms of wheezing episodes within the last year. Based on the occurrence of wheezing episodes within the last year, the subjects were divided into two groups, the wheezing group and the non-wheezing group, and related factors of wheezing were studied.

2.3 Statistical Methods

SPSS 17.0 software was used for statistical analyses. The quantitative variables were tested by Kolmogorov-Smirnov test for normality, and two-tailed Student's t-tests were used after the data fulfilled the criteria of normal distribution and equal variance; otherwise, Mann–Whitney U-tests were used. The chi square test or Fisher's exact test for categorical variables were also used. Demographics and baseline characteristics were compared between the wheezing group and the non-wheezing group. If the result of single factor comparison showed that P was < 0.05, the indicators were analysed via binary logistic regression (the method of selecting independent variables is forward LR). The receiver operator characteristic (ROC) curve was drawn to evaluate the prediction ability of the logistic regression model.

3. Results

3.1 General information

A total of 273 cases were excluded from among 813 cases with available follow-up data because of incomplete questionnaires, a dosage of rhIFNa1 b < 1 ug/kg.d or a treatment duration < 3 days, a date in hospital beyond the scope of the follow-up, or because the age at the time of hospitalization was > 3 years old Finally, 540 patients were included in the analysis, including 312 cases (57.8%) of pneumonia, 132 cases (24.4%) of wheezy bronchitis, and 96 cases (17.8%) of bronchiolitis. A total of 253 cases were treated with conventional therapy and rhIFN α1b; 287 cases were treated with only conventional therapy, without rhIFNα1b.

3.2 Wheezing episodes within the last year

A total of 95 cases (17.6%) out of 540 cases included wheezing episodes within the last year; 35 (13.8%) out of 253 cases treated with rhIFN a1 b and 60 (20.9%) out of 287 cases without rhIFN a1 b treatment had wheezing episodes within the last year. The difference in wheezing episodes within the last year between the rhIFNα1b treatment group and the control group was statistically significant ($X^2 = 4.64$, P = 0.031).

3.3 Analysis of related factors of wheezing

3.3.1 Comparison of demographics and baseline characteristics between the wheezing and non-wheezing groups

There were 540 cases, including 95 cases in the wheezing group and 445 cases in the non-wheezing group. Age at the time of hospitalization, birth weight and age at follow-up were compared between two groups via the Mann-Whitney test and other factors were compared by chi square test. The result of single factor regression indicated that the differences between the wheezing and non-wheezing groups in the age at the time of hospitalization, the use of rhIFNα1b in hospital, childhood and family history of allergy, housing situation, and feeding history, a total of 6 factors, were all statistically significant (P < 0.05; see Table 1).

Table 1
Comparison of demographics and baseline characteristics of the wheezing and non-wheezing groups

	Wheezing group	Non-wheezing group	X2/Z	P
Male / female	67/28	282/163	1.75	0.19
Term / preterm birth	91/4	408/37	1.88	0.17
Age at the time of hospitalization, years (median)	1.3	1.0	-3.55	0.00
Birth weight, kg (median)	3.0	3.0	-1.04	0.30
Breast feeding/ mixed feeding/ milk powder feeding	33/37/25	229/149/67	11.02	0.004
Child history of allergy (yes/no)	29/66	76/369	9.04	0.003
Family history of allergy (yes/no)	21/74	56/389	5.81	0.016
Smokers in home (yes/no)	51/44	256/189	0.47	0.49
Pets in home (yes/no)	11/84	37/408	1.03	0.31
rhIFNα1b treatment (yes/no)	35/60	218/227	4.64	0.031
Viral pneumonia / bronchiolitis / wheezy bronchitis	50/22/23	262/74/109	2.41	0.3
Housing situation (spacious/crowded)	25/70	179/266	6.44	0.011
Age at follow-up, years (median)	3.4	3.3	-0.064	0.95

3.3.2 A binary logistic regression analysis of factors related to wheezing.

The factors that were significantly different in the univariate analysis ($P < 0.05$) were assigned (see Table 2). Binary logistic regression analysis showed that: a childhood history of allergy, feeding history, the use of rhIFNα1b in hospital, age at the time of hospitalization, and the housing situation entered into the final regression equation. A childhood history of allergy, no rhIFNα1b treatment, and crowded housing were risk factors; breastfeeding and age ≤1 year old at the time of hospitalization were protective factors. Results are shown in Table 3.

Table 2
Related factors and the assignment of wheezing within the last year

Factors	Assignment
Age at the time of hospitalization	≤1 year old = 1 ; >1 year old = 0
Childhood history of allergy	yes = 1 ; no = 0
Housing situation	crowded = 1 ; spacious = 0
The use of rhIFNα1b	no = 1 ; yes = 0
Feeding history	Breast feeding = 1 ; mixed feeding = 2 ; milk powder feeding = 3
Wheezing episodes within the last year	wheezing = 1 ; non-wheezing = 0

Table 3
Logistic regression analysis of related factors of wheezing within the last year

	B	SE	Wald	P	OR	95%CI
rhIFNα1b	0.53	0.24	4.83	0.028	1.70	1.06 ~ 2.74
Age at the time of hospitalization	-0.54	0.24	5.08	0.024	0.58	0.37 ~ 0.93
Childhood history of allergy	0.76	0.27	8.21	0.004	2.14	1.27 ~ 3.59
Feeding history			7.07	0.03		
Breast feeding	-0.82	0.31	7.02	0.008	0.44	0.24 ~ 0.81
Mixed feeding	-0.44	0.31	2.08	0.15	0.64	0.35 ~ 1.17
Housing situation	0.65	0.26	6.26	0.012	1.92	1.15 ~ 3.21

3.3.3 ROC curve analysis

The ROC curve was drawn by using the predicted values of the model, and the area under the curve was 0.68, 95% CI (0.62 ~ 0.74), P = 0.00, which showed that the regression model had greater than medium diagnostic accuracy (see Fig. 1).

Figure 1.

4. Discussion

The main pathogens of lower respiratory tract infections during infancy or early childhood are viruses (1, 2), and many studies have suggested that early viral infections in infants and young children are

associated with subsequent wheezing or asthma (13–17). In order to study the effect of rhIFNα1b and other related factors on subsequent wheezing in infants hospitalized with lower respiratory tract infection, this study investigated 13 possible related factors. The results show that rhIFNα1b treatment, age at the time of hospitalization, a childhood history of allergy, feeding history and housing situation are associated with subsequent wheezing in 540 infants hospitalized with lower respiratory tract infection.

This study shows that, compared with infants aged 2 and 3 years old, infants who are less than or equal to 1 year old who have a lower respiratory tract infection are not prone to wheezing (OR = 0.58, P = 0.024). Further studies are needed to confirm this phenomenon. However, Feldman et al. (18) recently studied the relationship between the aetiology and timing of early childhood respiratory wheezing illnesses during the first 3 years of life and the development of asthma in children at the age of 6, and found that there was no correlation between childhood respiratory syncytial virus (RSV) infection at the age of 1 and 2 and the diagnosis of asthma at age 6, but wheezing RSV illnesses that occurred at the age of 3 were associated with a nearly 14-fold increase in asthma risk at 6 years of age. Therefore, although a number of studies have shown that early viral infection in infants and young children is associated with recurrent wheezing episodes, this issue is controversial (18, 19). Therefore, the identification of the risk and protective factors between early viral infection and recurrent wheezing in infants and young children is the most effective strategy for the prevention of wheezing in children.

A childhood history of allergy is a risk factor for wheezing (OR = 2.21, P = 0.004). Compared with milk powder feeding, breastfeeding protects infants with lower respiratory tract infection from subsequent wheezing (OR = 0.44, P = 0.008). Studies have shown that early childhood sensitization to food and inhalant allergens may be the beginning of the “atopic march” and may promote other allergic diseases, such as respiratory allergies (20, 21). Breast milk contains IgA, cytokines, and long-chain fatty acids that stimulate the development of the infants' immune system (22). Breastfeeding also activates the intestinal microflora in infants, which in turn activates T cells and enhances immune function (23). Therefore, breastfeeding and the extension of exclusive breastfeeding time will reduce the risk of subsequent wheezing in infants and young children (24). Living in a crowded house (P = 0.012 OR = 1.92) increases the chance of respiratory infection and the chance of exposure to allergens in the home and contributes to wheezing episodes.

Interferon (IFN) is a type of antiviral low molecular weight protein in the normal human body that can play antiviral and immunomodulatory roles in a variety of ways. According to the specificity of the receptor, IFN can be divided into type I IFNs, type II IFNs and type III IFNs. Type I IFNs include IFN-α, IFN-β, etc. Different subtypes of IFN play different immunomodulatory roles (25). This study shows that the application of rhIFNα1b treatment for infants with lower respiratory tract infection has a protective effect on subsequent wheezing (without rhIFNα1b treatment OR 1.70, P = 0.028), probably because exogenous rhIFNα1b can elevate the level of IFN, and IFNs are important modulators of the immune response, particularly in the inhibition of viral replication within host cells, the activation of natural killer cells and macrophages, the increase in antigen presentation to lymphocytes, the induction of the resistance of host cells to viral infection, and the weakening of the damage of the virus to lung tissue (6, 7, 26). On the other

hand, it may be related to the immunomodulatory functions of type I interferons on T lymphocyte subsets (27).

5. Conclusion

The outstanding characteristic of this study is that it demonstrated that the early application of rhIFNα1b therapy for infants with lower respiratory tract infection can protect infants from subsequent wheezing.

Abbreviations

Recombinant human interferon α1b (rhIFNα1b); Epstein-Barr virus (EBV); Receiver operator characteristic (ROC); Respiratory syncytial virus (RSV); Interferon (IFN).

Declarations

Ethics approval and consent to participate: The study design was approved by the Shaanxi University of Chinese medicine (Approval Number: 2019-014).

Consent for publication: This manuscript has not been published and is not under consideration for publication elsewhere in whole or in part. No conflicts of interest exist in the submission of this manuscript, and the manuscript has been approved for publication by all listed authors.

Availability of data and material: The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Authors' contributions: Conceptualization: LY and GZ; methodology: LY and GZ; software: CW and YS; validation: LY, GZ and CW; formal analysis: XR and LH; investigation: LY; resources: LY, GZ, CW, YS, XR, LL, HS, JC, YS, JX, XX, LH, SS, LZ, SA, HY, HC, LZ, ML, XS, YW; data curation: GZ, CW and YS; writing—original draft preparation: LY, SS, LZ and SA; writing—review and editing: GZ, CW and YS; visualization: LY and CW; supervision: GZ and YS; project administration: GZ. All authors have read and approved the manuscript.

Acknowledgements: The authors would like to thank all those who contributed their time and resources to the development of this article.

References

1. Jain S, Williams DJ, Arnold SR, Ampofo K, Bramley AM, Reed C, et al. Community-acquired pneumonia requiring hospitalization among U.S. children. N Engl J Med. 2015 Feb;26(9):835–45.

372(.

2. Rossi GA, Silvestri M, Colin AA. Viral bronchiolitis in children [Internet]. Vol. 374, New England Journal of Medicine. Massachussetts Medical Society; 2016 [cited 2020 Mar 14]. p. 1792–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27144868.
3. Bønnelykke K, Vissing NH, Sevelsted A, Johnston SL, Bisgaard H. Association between respiratory infections in early life and later asthma is independent of virus type. J Allergy Clin Immunol [Internet]. 2015 Jul [cited 2020 Mar 14];136(1):81–86.e4. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25910716.
4. Jackson DJ, Gern JE, Lemanske RF. The contributions of allergic sensitization and respiratory pathogens to asthma inception. Vol. 137, Journal of Allergy and Clinical Immunology. Mosby Inc.; 2016. p. 659–65.
5. Pickles RJ, DeVincenzo JP. Respiratory syncytial virus (RSV) and its propensity for causing bronchiolitis. J Pathol. 2015 Jan 1;235(2):266–76.
6. González-Navajas JM, Lee J, David M, Raz E. Immunomodulatory functions of type I interferons. Nat Rev Immunol [Internet]. 2012 Feb 6 [cited 2020 Mar 14];12(2):125–35. Available from: http://www.nature.com/articles/nri3133.
7. Sadler AJ, Williams BRG. Interferon-inducible antiviral effectors. Vol. 8, Nature Reviews Immunology. NIH Public Access; 2008. p. 559–68.
8. Hou YD, Zhang ZQ, Yang XK, Mu SH, Li YY, Peng JZ, et al. [Cloning of alpha interferon cDNA from human umbilical cord leukocytes and its expression in Escherichia coli]. Zhongguo Yi Xue Ke Xue Yuan Xue Bao [Internet]. 1982 Dec [cited 2020 Mar 14];4(6):327–35. Available from: http://www.ncbi.nlm.nih.gov/pubmed/6221811.
9. Zheng Y, Zhao L, Wu T, Guo S, Chen Y, Zhou T. Efficacy of consensus interferon in treatment of HbeAg-positive chronic hepatitis B: A multicentre, randomized controlled trial. Virol J. 2009;6:99.
10. Huang X, Zhang X, Wang F, Wei H, Ma H, Sui M, et al. Clinical efficacy of therapy with recombinant human interferon α1b in Hand, Foot, and Mouth Disease with enterovirus 71 infection. PLoS One. 2016 Feb 1;11(2).
11. Liu X, Lu J, He M-L, Li Z, Zhang B, Zhou L-H, et al. Antitumor Effects of Interferon-Alpha on Cell Growth and Metastasis in Human Nasopharyngeal Carcinoma. Curr Cancer Drug Targets [Internet]. 2012 May 31 [cited 2020 Mar 14];12(5):561–70. Available from: http://www.ncbi.nlm.nih.gov/pubmed/22414012.
12. Lee S-Y, Kim B-S, Kwon S-O, Oh S-Y, Shin HL, Jung Y-H, et al. Modification of additive effect between vitamins and ETS on childhood asthma risk according to GSTP1 polymorphism: a cross -sectional study. BMC Pulm Med [Internet]. 2015 Dec 22 [cited 2020 Mar 14];15(1):125. Available from: http://bmcpulmmed.biomedcentral.com/articles/10.1186/s12890-015-0093-0.
13. Neuman Å, Bergström A, Gustafsson P, Thunqvist P, Andersson N, Nordvall L, et al. Infant wheeze, comorbidities and school age asthma. Pediatr Allergy Immunol [Internet]. 2014 Jun [cited 2020 Mar 14];25(4):380–6. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24720853.

14. Sly PD, Kusel M, Holt PG. Do early-life viral infections cause asthma? J Allergy Clin Immunol [Internet]. 2010 Jun [cited 2020 Mar 14];125(6):1202–5. Available from: http://www.ncbi.nlm.nih.gov/pubmed/20304476.
15. Stern DA, Morgan WJ, Halonen M, Wright AL, Martinez FD. Wheezing and bronchial hyper-responsiveness in early childhood as predictors of newly diagnosed asthma in early adulthood: a longitudinal birth-cohort study. Lancet. 2008;372(9643):1058–64.
16. Quah PL, Loo EXL, Lee GNLY, Kuo IC, Gerez I, Llanora GV, et al. Clinical phenotype and allergen sensitization in the first 2 years as predictors of atopic disorders at age 5 years. World Allergy Organ J. 2015 Dec 2;8(1).
17. Loo EXL, Sim JZT, Goh A, Teoh OH, Chan YH, Saw SM, et al. Predictors of allergen sensitization in Singapore children from birth to 3 years. Allergy, Asthma Clin Immunol. 2016 Oct 24;12(1).
18. Feldman AS, He Y, Moore ML, Hershenson MB, Hartert TV. Toward primary prevention of asthma: Reviewing the evidence for early-life respiratory viral infections as modifiable risk factors to prevent childhood asthma. Am J Respir Crit Care Med. 2015 Jan 1;191(1):34–44.
19. Saglani S. Viral infections and the development of asthma in children. Vol. 1, Therapeutic Advances in Infectious Disease. SAGE Publications; 2013. p. 139–50.
20. Wisniewski JA, Agrawal R, Minnicozzi S, Xin W, Patrie J, Heymann PW, et al. Sensitization to food and inhalant allergens in relation to age and wheeze among children with atopic dermatitis. Clin Exp Allergy. 2013 Oct;43(10):1160–70.
21. Nissen SP, Kjær HF, Høst A, Nielsen J, Halken S. The natural course of sensitization and allergic diseases from childhood to adulthood. Pediatr Allergy Immunol [Internet]. 2013 Sep [cited 2020 Mar 14];24(6):549–55. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23902477.
22. Biesbroek G, Bosch AATM, Wang X, Keijser BJF, Veenhoven RH, Sanders EAM, et al. The impact of breastfeeding on nasopharyngeal microbial communities in infants. Am J Respir Crit Care Med [Internet]. 2014 Aug 1 [cited 2020 Mar 14];190(3):298–308. Available from: http://www.ncbi.nlm.nih.gov/pubmed/24921688.
23. Walker WA, Iyengar RS. Breast milk, microbiota, and intestinal immune homeostasis [Internet]. Vol. 77, Pediatric Research. Nature Publishing Group; 2015 [cited 2020 Mar 14]. p. 220–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/25310762.
24. den Dekker HT, Sonnenschein-van der Voort AMM, Jaddoe VWV, Reiss IK, de Jongste JC, Duijts L. Breastfeeding and asthma outcomes at the age of 6 years: The Generation R Study. Pediatr Allergy Immunol [Internet]. 2016 Aug 1 [cited 2020 Mar 14];27(5):486–92. Available from: http://www.ncbi.nlm.nih.gov/pubmed/27062455.
25. Pestka S, Krause CD, Walter MR. Interferons, interferon-like cytokines, and their receptors. Immunol Rev. 2004;Vol. 202:8–32.
26. Ioannidis I, Ye F, McNally B, Willette M, Flano E. Toll-Like Receptor Expression and Induction of Type I and Type III Interferons in Primary Airway Epithelial Cells. J Virol. 2013 Mar;15(6):3261–70. 87(.

27. Farrar JD, Murphy KM. Type I interferons and T helper development. Immunol Today [Internet]. 2000 Oct [cited 2020 Mar 14];21(10):484–9. Available from: http://www.ncbi.nlm.nih.gov/pubmed/11071526.

Figures

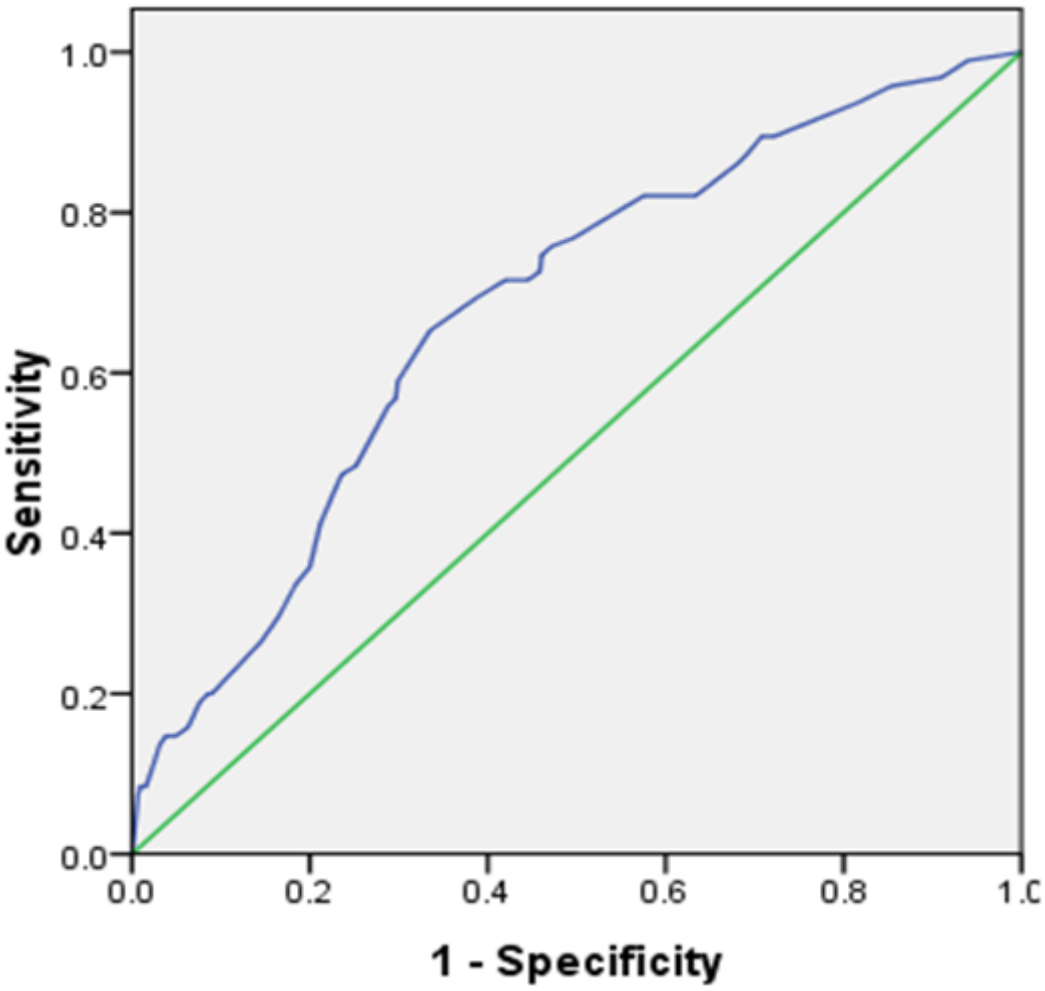

Figure 1

The receiver operator characteristic curve of the model predicting subsequent wheezing of infants hospitalized with lower respiratory tract infection