HHS Public Access

Author manuscript

Pediatr Int. Author manuscript; available in PMC 2024 January 01.

Published in final edited form as:

Pediatr Int. 2023 ; 65(1): e15672. doi:10.1111/ped.15672.

Association of surfactant protein A2 with acute respiratory failure in children

Lucy Emery[1,¶], **Elizabeth Kane**[1,¶], **Keenan Anderson-Fears**[2], **Dajiang Liu**[2], **Joanna Floros**[1,3,&], **Chintan K Gandhi**[1,&,*]

[1]Department of Pediatrics, The Pennsylvania State College of Medicine, Hershey, Pennsylvania, United States of America

[2]Department of Public Health Science, The Pennsylvania State College of Medicine, Hershey, Pennsylvania, United States of America

[3]Department of Obstetrics & Gynecology, The Pennsylvania State College of Medicine, Hershey, Pennsylvania, United States of America

Abstract

Background: Interactions among single nucleotide polymorphisms (SNPs) of surfactant protein (SP) are associated with acute respiratory failure (ARF) and its short-term outcome, pulmonary dysfunction at discharge (PDAD) in children. However, genetic association studies using individual SNPs have not been conducted before. We hypothesize that SP genetic variants are associated with pediatric ARF and its short-term complications by themselves.

Methods—We used available genotype and clinical data in the Floros biobank consisting of 248 children aged ≤ 24 months with ARF; 86 developed PDAD. A logistic regression analysis was performed for each of the 14 selected SNPs, SP-A1 and SP-A2 genotypes. A p-value smaller than the Bonferroni correction threshold was considered significant. A likelihood ratio test was done to compare two models (one with demographic data and another with genetic variants).

Results: Before Bonferroni correction, female sex is associated with a decreased risk of ARF. Black race and the rs721917 of the *SFTPD* are associated with increased risk of ARF. After Bonferroni correction, the $1A^0 1A^1$ genotype of *SFTPA2* was associated with decreased risk of ARF. The likelihood ratio test showed that the model of the genotype information with demographic data was a better fit to predict ARF risk. None of the SP SNPs and SP-A1, SP-A2 genotypes were associated with PDAD.

[*]**Corresponding author: Address correspondence to:** Chintan K. Gandhi, Department of Pediatrics, Pennsylvania State University College of Medicine, 500 University Drive, Room C7744, H085, Hershey, PA 17033-0850, USA. Tel # 717 531 8413, Fax # 717 531 0409, cgandhi@pennstatehealth.psu.edu.

[¶]These authors contributed equally to this work.

[&]These authors contributed equally to this work.

Author contribution

C.K.G. and J.F. designed the study; C.K.G., K.A.F. and D.L collected and analyzed data; L.E., E.K., and C.K.G. wrote the manuscript; J.F. gave technical support and conceptual advice. All authors read and approved the final manuscript.

Disclosure

The authors have no relevant financial or non-financial interests to disclose.

Conclusion: Our results indicate that SNPs and genotypes of SPs involved in innate immunity and host defense play an important role in ARF and, in the future, may be used as biomarkers.

Keywords

Pediatric acute respiratory failure; Single nucleotide polymorphism; surfactant protein; surfactant protein genetic variant

Introduction

Acute respiratory failure (ARF) is defined as the inability of the respiratory system to support the metabolic needs of the body (1). Among children, ARF is the most common cause of admission to pediatric intensive care unit (PICU) (1). A recent prospective study of ARF in children showed more than 30% mortality due to severe hypoxemia (2). Although children with pulmonary comorbidities and immunosuppression are the major risk factors for pediatric ARF, it is difficult for clinicians to identify at-risk children for developing ARF and predict short- and/or long-term sequelae among ARF survivors. Pediatric ARF is a multifactorial disease involving complex interactions between genetic and environmental factors. The clinical presentation, progression, and severity of ARF vary significantly and depend on the underlying causes and other host-related factors. Thus, further efforts must be geared towards a better understanding of its complex pathophysiology and the genetic factors that may help clinicians to identify children who are at risk for ARF and its complications.

Pulmonary surfactant is composed of 90% lipids and 10% proteins and is found in the fluid lining the alveolar surface of the lungs. There are two major categories of surfactant proteins (SPs) - hydrophobic (SP-B and SP-C) and hydrophilic (SP-A and SP-D). Hydrophobic SPs reduce surface tension, whereas hydrophilic surfactant SPs play a role in host defense and innate immunity-related functions (3, 4). SP-B, SP-C, and SP-D are each encoded by a single gene, *SFTPB*, *SFTPC*, and *SFTPD*, respectively (5). The human SP-A is encoded by two functional genes, *SFTPA1* and *SFTPA2* (3). Multiple single-nucleotide polymorphisms (SNPs) have been identified for each of these genes (4–6). These SNPs have been shown to associate with various acute and chronic pulmonary diseases, such as cystic fibrosis (7), acute respiratory distress syndrome (8), neonatal respiratory distress syndrome (RDS) (9), hypersensitivity pneumonitis (10), interstitial pulmonary fibrosis (11), the severity of respiratory syncytial virus (RSV) (12) and tuberculosis (TB) (13). We showed that SNP-SNP interactions among SP genes are associated with pediatric ARF and its short- (14) and long-term outcomes (15). However, these interactions do not provide any information about the contribution of individual SNPs in the given interaction. Some SNPs might have a large influence on the disease risk, while others have a very small contribution. It is therefore beneficial to study association of individual SNPs with disease risk so that they can be used to predict disease outcomes.

For the current study, we utilized a preexisting dataset to investigate the association of single SP SNPs with pediatric ARF and its short-term outcome using logistic regression analysis. We hypothesize that natural SP genetic variants are associated with pediatric ARF and its

short-term complications and can be used as a biomarker to predict disease severity. This genetic information, along with demographic information, may help to identify children who are at risk of pediatric ARF and its short-term outcomes.

Methods

The study was approved by the institutional review board of the Pennsylvania State University College of Medicine and participating sites. Written informed consent was obtained from the parents.

Cases:

We used securely stored genotype and clinical data in the Floros biobank at the Institute of Personized Medicine at the Pennsylvania State University College of Medicine. The study cohort is described in detail elsewhere (14). Briefly, 250 previously healthy children aged 0–24 months admitted with a diagnosis of ARF in the PICUs were enrolled. ARF was defined as the presence of at least one of the following: (1) clinical findings consistent with lower respiratory tract illness, (2) focal or diffuse infiltrative pulmonary process on chest radiograph, or (3) radiographic evidence of air trapping (14). To mitigate the contribution of preexisting comorbidities on the development of ARF, we excluded children with preexisting neurologic, neuromuscular, or cardiac diseases as well as those with a history of (1) prematurity (<35 weeks of gestation), (2) chronic oxygen and/or mechanical ventilation (MV) dependency, (3) bronchodilators, inhaled and/or systemic corticosteroids use prior to the current illness, (4) previous PICU admission and/or MV course other than for surgical procedure, and (5) receipt of exogenous surfactant (14). We also excluded two children who subsequently got diagnosed with cystic fibrosis resulting in a total of 248 subjects.

The short-term outcome of ARF, pulmonary dysfunction at discharge (PDAD), was defined as a need of at least one of the following at 28 days of admission or hospital discharge, whichever comes first: MV, supplemental oxygen, bronchodilators or steroids (inhaled and/or systemic).

Controls:

We used a cohort of 468 randomly selected unrelated term newborns delivered at Penn State Children’s hospital as controls to compare with 248 subjects with ARF. For assessing the short-term sequalae, children without PDAD among ARF survivors served as control to those who did develop PDAD.

DNA Isolation and selection of genetic variants

Genomic DNA was extracted from collected blood using the QIAamp Blood kit (Qiagen, Valencia, CA USA) following the manufacturer’s instructions. A total of 14 targeted SNPs of SP genes, *SFTPA1, SFTPA2, SFTPB, SFTPC,* and *SFTPD* were selected. Details of the selected SNPs are given in supplementary table 1. These SNPs were selected because of their associations with several acute and chronic pulmonary diseases (7, 9–11, 14, 15).

The SP-A1 (6A, $6A^m$, m=0–13) and SP-A2 (1A, $1A^n$, n=0–15) genotypes were assigned as described (6).

Genotype Analysis

Polymerase chain reaction-restriction fragment length polymorphism was used to analyze *SFTPA1*, *SFTPA2*, *SFTPD* (6, 8), *SFTPB* (8), and *SFTPC* (7) gene polymorphisms. The detailed method is described elsewhere (7). To minimize bias in assigning genotypes, samples were processed together and those assigning genotypes were unaware of the clinical status.

Statistical Analysis

For the genetic analysis within the ARF dataset, we used a total of five dummy variables to represent the six ancestral covariates, i.e. Black, Asian, Mixed, Pacific Islander, Latino, and European, with the European being used as baseline (0,0,0,0,0). Using these encodings, we performed logistic regression analysis for each of the 14 SNPs using PLINK 2.0 following our previously established methods (12). For each model, we report odds ratios (ORs) for each SNP with 95% confidence interval. For the final model containing all SNPs, we perform likelihood ratio tests comparing the full model with all SNPs and non-genetic covariates against the null model containing only non-genetic covariates. To analyze the effects of SP-A1 and SP-A2 genotype distributions for each of the surfactant protein encoding regions, in line with previous methods (16), we combined lower counts of genotypes into a single group. As mentioned above, we compared the full model with genotype information against a null model of the non-genetic covariates only, using a likelihood ratio test. For all tests both each SNP and SP-A genotypes, we considered results to be statistically significant if their p-values are smaller than the Bonferroni correction threshold accounting for all tests performed for each set.

For the genetic analysis in the PDAD dataset, we used a total of four dummy variables to represent the five self-reported ancestry groups, i.e. Black, Asian, Mixed, Latino and European, with European being used as the baseline (0,0,0,0). We followed the same analyses as in ARF by using these encodings along with the additional covariates that are significantly different between the two groups, i.e., age, weight, duration of ventilation and bacterial Infection. We performed the same analysis as ARF dataset to test association with PDAD for each SNP and the collapsed SP-A1 and SP-A2 genotypes separately using similar Bonferroni correction as before. We used *PLINK – 1.9 & 2.0* and *R (stats package included) – 4.0.2* software for analysis.

Results

1. Clinical Characteristics of the Study Cohort

Figure 1 outlines the study layout and cohorts that were compared. Table 1 shows characteristics of the study population. In summary, the majority of participants were non-Hispanic White (~80%), males (~60%). Out of the 248 children, 86 developed PDAD. Those who developed PDAD were more likely to have a positive bacterial culture, required longer duration of ventilator and oxygen support. Those who did not develop PDAD were younger.

2. Comparison between ARF (n=248) Vs. Newborn controls (n=468)

Supplementary tables 2 and 3 show genotype frequencies of SP SNPs in newborn controls and ARF cohort (cases), respectively. The frequency distributions of all SNPs were in Hardy-Weinberg equilibrium (data not shown).

Table 2 shows association of demographic and genetic variables with the development of ARF before Bonferroni correction. Based on OR, female sex is associated with a decreased risk of ARF. Whereas, black race and the C allele of rs721917 of the *SFTPD* (in its heterozygous (CT) and homozygous (CC) forms), are associated with increased risk of ARF. However, after Bonferroni correction, those variables lost statistical significance.

After Bonferroni correction—After Bonferroni correction, the $1A^0 1A^1$ genotype of *SFTPA2* was associated with decreased risk of ARF, OR (95% confidence interval) = 0.17 (0.07 – 0.41), p= 8.33e-05. We calculated the estimated absolute risk of ARF in individuals with the $1A^0 1A^1$ based on ARF incidence of 3.8% among all PICU admissions (17) along with odds ratio of 0.17, individuals with the $1A^0 1A^1$ have an absolute risk reduction to 0.65% for developing ARF compared to general population during their PICU stay. We performed a likelihood ratio test to evaluate the overall addition of genotype information to demographic data. The model with the genotype information along with demographic data was a better fit to predict ARF risk compared to demographic data alone (p = 0.0003 and Chi square of 32.45).

3. Comparison between PDAD (n=86) Vs. No PDAD (n=162) among ARF Survivors

Supplementary tables 4 and 5 show genotype frequencies of SP SNPs in those who did not develop PDAD (controls) and those who developed PDAD (cases), respectively, among ARF survivors. The frequency distributions of all SNPs were in Hardy-Weinberg equilibrium (data not shown). The rs721917_CT of the *SFTPD* was associated with decreased risk of PDAD, however, did not remain significant after Bonferroni correction. None of the other SP genetic polymorphisms, and SP-A1 and SP-A2 genotypes were associated with PDAD. The likelihood ratio test did not show significant difference between two models (one with clinical and demographic data alone and another that included genetic variants as well) in predicting PDAD risk among ARF survivors, (p=0.3 and Chi square of 11.65).

Discussion

ARF is a multifactorial disease with significant morbidity and mortality (2). Surfactant dysfunction and/or inactivation are central to the pathophysiologic mechanisms of various pulmonary diseases, including ARF in the pediatric population (14). We studied associations of SP genetic variants with pediatric ARF and its short-term outcome, PDAD. We observed that the $1A^0/1A^1$ genotype of *SFTPA2* is associated with decreased risk of ARF. The likelihood ratio test showed that the model with the SP genetic information along with demographic data is a better fit to predict ARF risk compared to demographic data alone. Although not statistically significant after Bonferroni correction, female sex is associated with decreased risk of ARF, whereas, black race, and the rs721917 of *SFTPD* in its heterozygous (CT) and homozygous (CC) form are associated with increased risk of ARF.

We did not observe significant association of studied SP SNPs and SP-A1, SP-A2 genotypes with PDAD among ARF survivors.

Our findings point toward a role of *SFTPA2* genotypes, particularly the $1A^0/1A^1$, in pediatric ARF. The rationale for such an association may be due to a higher activity of SP-A2 (encoded by *SFTPA2)* in innate host defense/inflammatory processes compared to SP-A1 (encoded by *SFTPA1)* (3, 4). Both in vitro and in vivo studies have shown that the $1A^1$ and $1A^0$ variants were more efficient in enhancing bacterial phagocytosis by alveolar macrophages compared to other variants (4). Of note, the major cause of ARF in our cohort was infection (~85%), most notably due to RSV (~50%). Therefore, association of *SFTPA2* genotypes with decreasing risk of ARF is not surprising. Moreover, the potential role of the carbohydrate recognition domain of SP-A2 variants, which could enable binding to a broader range of sugars on pathogen surfaces compared to SP-A1 variants (18), could be a contributing factor. Further research is required to ascertain the precise mechanisms driving these associations.

Previously, the same SP-A2 genotypes have been studied in various other infectious pulmonary diseases such as RSV (12, 16), influenzae (19), community acquired pneumoniae (20), and TB (13). Those studies have shown varying associations of *SFTPA2* genotypes based on etiology of pulmonary diseases and patient population used in the particular study. For example, recently we observed an increased risk of severe RSV with the $1A^0$ genotype, in its homozygous ($1A^0/1A^0$) and in its heterozygous ($1A^0/1A^3$) form (12). In contrast, another similarly performed study found a decreased risk of severe RSV with the $1A^0/1A^0$ genotype (16). Although ~50% of patients in our cohort were diagnosed with RSV bronchiolitis, we observed a decreased risk of ARF with the $1A^0/1A^1$, but no significant association was observed with the $1A^0/1A^0$ or $1A^0/1A^3$ genotypes. The difference between the study findings is likely due to impact of other infectious and non-infectious etiologies of ARF. The other possibility could be due to differences in study population and design.

We also observed association of decreased and increased risk of ARF with female sex and black race, respectively. Sex is one of the main determinants of pulmonary health and disease (21). Our findings are in line with previous human epidemiological and animal studies showing better outcomes for females compared to males after pulmonary infections (22, 23). Black race has been associated with poorer outcomes after acute lung injury in adults (24), however, the role of race in pediatric ARF studies remains inconclusive, possibly due to a limited sample size (2). Nonetheless, our findings need to be replicated in a larger cohort of children with ARF.

We observed an association of increased risk of ARF with the rs721917 of *SFTPD* in its heterozygous (CT) and homozygous (CC) form before the Bonferroni correction. Of note, the rs721917 has been associated with increased risk of other infections pulmonary diseases, such as RSV (25) and TB (13). The rs721917 polymorphism results in a change in amino acid from methionine to threonine at position 11 and this change is shown to reduce the multimeric and trimeric assembly of the mature SP-D (26) and the binding of SP-D to Mycobacterium tuberculosis (27). It remains to be determined whether the rs721917 has

functional consequences such as reduced levels of SP-D and/or deficient antiviral properties against RSV and other childhood viruses that are commonly responsible of ARF in children.

We did not observe any associations between single SP SNPs and the development of PDAD among ARF survivors. The lack of significant associations could be due to a small sample size in subgroups, only 86 of the 248 ARF patients developed PDAD. Moreover, we did not observe significant associations of the hydrophobic SPs (*SFTPB* and *SFTPC*) SNPs with ARF and its short-term outcome, PDAD. Considering the limited role of *SFTPB* and *SFTPC* in antiviral, anti-inflammatory and host defense functions compared to the hydrophilic SPs (*SFTPA* and *SFTPD*), our findings are not surprising. In addition, it may explain why exogenous surfactant therapy that contains only SP-B and SP-C, but not SP-A, fails to show improvement in survival after ARF in pediatric (28) and adult patients (29).

A likelihood ratio test showed that the model with genetic information along with demographic data is superior in predicting ARF risk compared to the model without genetic information. In the future, physicians could use this genetic variant information, either alone or with other genetic variants, to predict ARF risk early for high-risk children, offering thus personalized treatment to improve outcomes.

Our study has several strengths. First, it is a multicenter prospective study that enrolled only previously healthy children with detailed sociodemographic information. Therefore, we were able to nullify the impact of preexisting comorbid conditions on ARF risk and its sequalae. Second, we used a robust Bonferroni correction to decrease spurious associations. However, our study has a few limitations. First, we used newborns as controls instead of age-matched children to study association of SP genetic variants with ARF risk. It is important to note that ARF is rare in previously healthy children. More importantly, the mean age of our cohort is ~3 months. Hence, the use of newborn controls is justified in our study. Third, enrollment of homogenous patients (~85% were white) in our study limits generalizability of our findings. Finally, the small number of subjects especially after the ARF cohort was divided into those who developed PDAD vs no PDAD could miss significant associations. Therefore, additional studies with larger sample sizes and heterogenous patients should be conducted to confirm and/or refute our findings.

Conclusion

We demonstrated associations of hydrophilic SP SNPs and SP-A2 genotypes, but not of hydrophobic SP SNPs, with the pediatric ARF in previously healthy children. More importantly, including genetic information to clinical data may help clinicians to identify children who are at higher risk of developing ARF after viral infections. In the future, exogenous surfactant that contains SP-A should be considered an additional treatment option for children with ARF.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by NIH HL34788 to JF. The authors thank the parents and study participants.

References

1. Friedman ML, Nitu ME. Acute respiratory failure in children. Pediatric annals. 2018;47(7):e268–e73. [PubMed: 30001440]
2. Khemani RG, Smith L, Lopez-Fernandez YM, Kwok J, Morzov R, Klein MJ, et al. Paediatric acute respiratory distress syndrome incidence and epidemiology (PARDIE): an international, observational study. Lancet Respir Med. 2019;7(2):115–28. [PubMed: 30361119]
3. Floros J, Tsotakos N. Differential Regulation of Human Surfactant Protein A Genes, SFTPA1 and SFTPA2, and Their Corresponding Variants. Front Immunol. 2021;12:766719.
4. Floros J, Thorenoor N, Tsotakos N, Phelps DS. Human Surfactant Protein SP-A1 and SP-A2 Variants Differentially Affect the Alveolar Microenvironment, Surfactant Structure, Regulation and Function of the Alveolar Macrophage, and Animal and Human Survival Under Various Conditions. Front Immunol. 2021;12:681639.
5. Wert SE, Whitsett JA, Nogee LM. Genetic disorders of surfactant dysfunction. Pediatr Dev Pathol. 2009;12(4):253–74. [PubMed: 19220077]
6. DiAngelo S, Lin Z, Wang G, Phillips S, Ramet M, Luo J, et al. Novel, non-radioactive, simple and multiplex PCR-cRFLP methods for genotyping human SP-A and SP-D marker alleles. Dis Markers. 1999;15(4):269–81. [PubMed: 10689550]
7. Lin Z, Thorenoor N, Wu R, DiAngelo SL, Ye M, Thomas NJ, et al. Genetic Association of Pulmonary Surfactant Protein Genes, SFTPA1, SFTPA2, SFTPB, SFTPC, and SFTPD With Cystic Fibrosis. Front Immunol. 2018;9:2256. [PubMed: 30333828]
8. Lin Z, Pearson C, Chinchilli V, Pietschmann SM, Luo J, Pison U, et al. Polymorphisms of human SP-A, SP-B, and SP-D genes: association of SP-B Thr131Ile with ARDS. Clin Genet. 2000;58(3):181–91. [PubMed: 11076040]
9. Amatya S, Ye M, Yang L, Gandhi CK, Wu R, Nagourney B, et al. Single Nucleotide Polymorphisms Interactions of the Surfactant Protein Genes Associated With Respiratory Distress Syndrome Susceptibility in Preterm Infants. Front Pediatr. 2021;9:682160.
10. Gandhi CK, Chen C, Amatya S, Yang L, Fu C, Zhou S, et al. SNP and Haplotype Interaction Models Reveal Association of Surfactant Protein Gene Polymorphisms With Hypersensitivity Pneumonitis of Mexican Population. Frontiers in Medicine. 2021;7.
11. Abbasi A, Chen C, Gandhi CK, Wu R, Pardo A, Selman M, et al. Single Nucleotide Polymorphisms (SNP) and SNP-SNP Interactions of the Surfactant Protein Genes Are Associated With Idiopathic Pulmonary Fibrosis in a Mexican Study Group; Comparison With Hypersensitivity Pneumonitis. Front Immunol. 2022;13:842745.
12. Depicolzuane LC, Roberts CM, Thomas NJ, Anderson-Fears K, Liu D, Barbosa JPP, et al. Hydrophilic But Not Hydrophobic Surfactant Protein Genetic Variants Are Associated With Severe Acute Respiratory Syncytial Virus Infection in Children. Frontiers in Immunology. 2022;13.
13. Floros J, Lin HM, García A, Salazar MA, Guo X, DiAngelo S, et al. Surfactant protein genetic marker alleles identify a subgroup of tuberculosis in a Mexican population. J Infect Dis. 2000;182(5):1473–8. [PubMed: 11023470]
14. Gandhi CK, Chen C, Wu R, Yang L, Thorenoor N, Thomas NJ, et al. Association of SNP-SNP Interactions of Surfactant Protein Genes with Pediatric Acute Respiratory Failure. J Clin Med. 2020;9(4).
15. Gandhi CK, Thomas NJ, Meixia Y, Spear D, Fu C, Zhou S, et al. SNP-SNP Interactions of Surfactant Protein Genes in Persistent Respiratory Morbidity Susceptibility in Previously Healthy Children. Front Genet. 2022;13:815727.
16. El Saleeby CM, Li R, Somes GW, Dahmer MK, Quasney MW, DeVincenzo JP. Surfactant protein A2 polymorphisms and disease severity in a respiratory syncytial virus-infected population. J Pediatr. 2010;156(3):409–14. [PubMed: 19914637]

17. Shein SL, Maddux AB, Klein MJ, Bhalla A, Briassoulis G, Dahmer MK, et al. Epidemiology and Outcomes of Critically Ill Children at Risk for Pediatric Acute Respiratory Distress Syndrome: A Pediatric Acute Respiratory Distress Syndrome Incidence and Epidemiology Study. Crit Care Med. 2022;50(3):363–74. [PubMed: 34582416]
18. Oberley RE, Snyder JM. Recombinant human SP-A1 and SP-A2 proteins have different carbohydrate-binding characteristics. Am J Physiol Lung Cell Mol Physiol. 2003;284(5):L871–81. [PubMed: 12505869]
19. Herrera-Ramos E, López-Rodríguez M, Ruíz-Hernández JJ, Horcajada JP, Borderías L, Lerma E, et al. Surfactant protein A genetic variants associate with severe respiratory insufficiency in pandemic influenza A virus infection. Crit Care. 2014;18(3):R127. [PubMed: 24950659]
20. García-Laorden MI, Rodríguez de Castro F, Solé-Violán J, Rajas O, Blanquer J, Borderías L, et al. Influence of genetic variability at the surfactant proteins A and D in community-acquired pneumonia: a prospective, observational, genetic study. Crit Care. 2011;15(1):R57. [PubMed: 21310059]
21. Silveyra P, Fuentes N, Rodriguez Bauza DE. Sex and Gender Differences in Lung Disease. Adv Exp Med Biol. 2021;1304:227–58. [PubMed: 34019273]
22. Mahmood K, Eldeirawi K, Wahidi MM. Association of gender with outcomes in critically ill patients. Critical Care. 2012;16(3):1–9.
23. Durrani F, Phelps DS, Weisz J, Silveyra P, Hu S, Mikerov AN, et al. Gonadal hormones and oxidative stress interaction differentially affects survival of male and female mice after lung Klebsiella pneumoniae infection. Exp Lung Res. 2012;38(4):165–72. [PubMed: 22394250]
24. Erickson SE, Shlipak MG, Martin GS, Wheeler AP, Ancukiewicz M, Matthay MA, et al. Racial and ethnic disparities in mortality from acute lung injury. Crit Care Med. 2009;37(1):1–6. [PubMed: 19050621]
25. Lahti M, Lofgren J, Marttila R, Renko M, Klaavuniemi T, Haataja R, et al. Surfactant protein D gene polymorphism associated with severe respiratory syncytial virus infection. Pediatr Res. 2002;51(6):696–9. [PubMed: 12032263]
26. Sorensen GL, Hoegh SV, Leth-Larsen R, Thomsen TH, Floridon C, Smith K, et al. Multimeric and trimeric subunit SP-D are interconvertible structures with distinct ligand interaction. Molecular Immunology. 2009;46(15):3060–9. [PubMed: 19577304]
27. Hsieh MH, Ou CY, Hsieh WY, Kao HF, Lee SW, Wang JY, et al. Functional Analysis of Genetic Variations in Surfactant Protein D in Mycobacterial Infection and Their Association With Tuberculosis. Front Immunol. 2018;9:1543. [PubMed: 30013576]
28. Willson DF, Thomas NJ, Markovitz BP, Bauman LA, DiCarlo JV, Pon S, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. Jama. 2005;293(4):470–6. [PubMed: 15671432]
29. Meng S-S, Chang W, Lu Z-H, Xie J-F, Qiu H-B, Yang Y, et al. Effect of surfactant administration on outcomes of adult patients in acute respiratory distress syndrome: a meta-analysis of randomized controlled trials. BMC Pulmonary Medicine. 2019;19(1):9. [PubMed: 30626363]

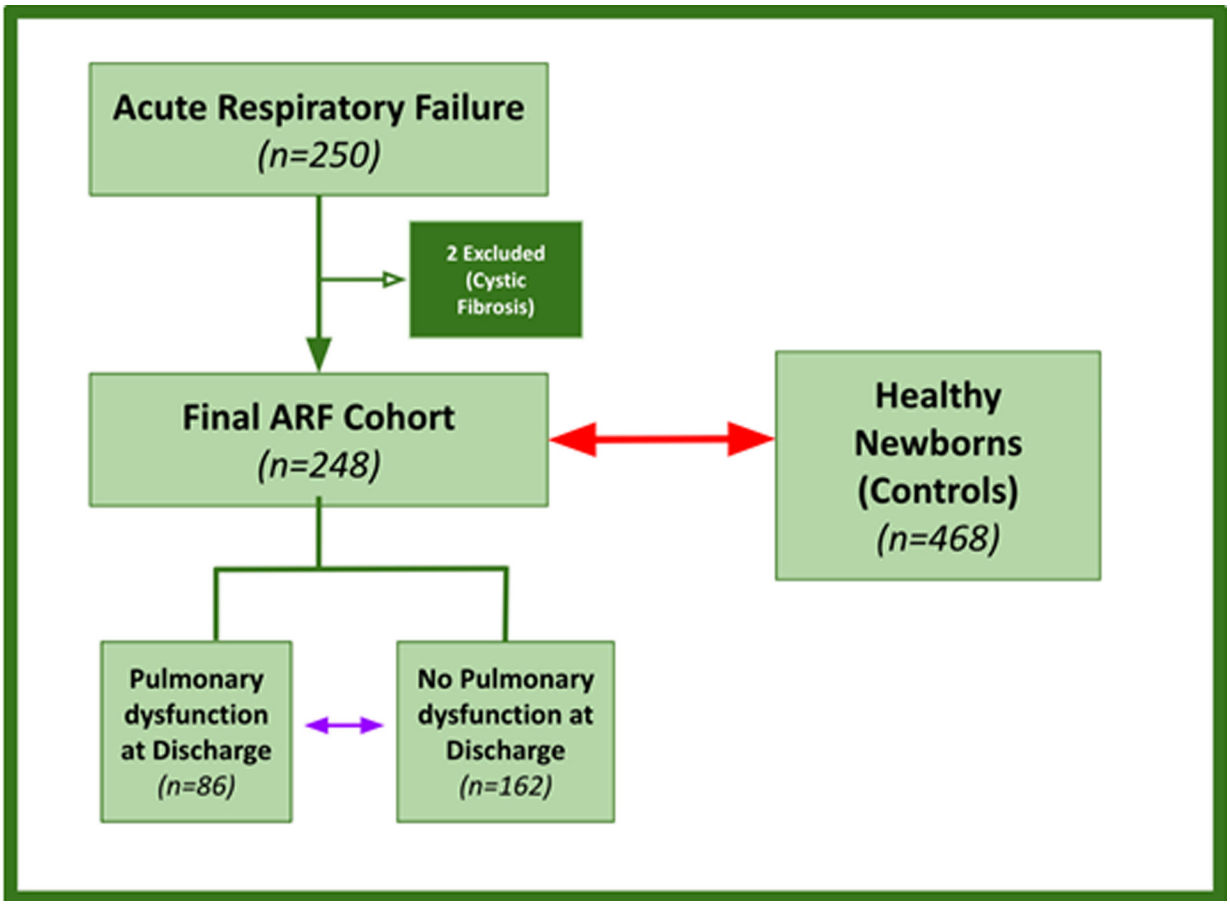

Figure 1. Study design.

Previously healthy children (n=250) who developed acute respiratory failure (ARF) participated in this study. Two participants were excluded from analysis following a diagnosis of cystic fibrosis. Initial analysis was performed between ARF patients (cases) and a control group of healthy newborns (n=468) (as shown with the red arrow). Further analysis was done to compare two subgroups of the ARF survivors, those who developed pulmonary dysfunction at discharge (PDAD, n=86) and those without PDAD (n=162) (as shown with the purple arrow).

Table 1

Characteristics of the study population

Demographics	Whole ARF cohort (n = 248)	No PDAD (n = 162)	PDAD (n = 86)
Age (months)	3.7 ± 4.5	2.8 ± 3.5	5.4 ± 5.6
Female/male (%/%)	99/149 (39/61)	63/99 (39/61)	36/50 (42/58)
Race			
White	197 (79)	128 (79)	69 (80)
Black	42 (17)	27 (17)	15 (17)
Asian	5 (2)	5 (3)	0
Native Hawaiian or Pacific Islanders	1 (1)	1	0
American Indian/Alaska Native	3 (1)	1	2 (3)
Mixed			
Ethnicity			
Hispanic	52 (21)	31 (19)	21 (24)
Non-Hispanic	196 (79)	131 (81)	65 (76)
Admission diagnosis (%)			
RSV bronchiolitis	127 (51)	89 (55)	38 (44)
Nonspecific bronchiolitis	56 (23)	39 (24)	17 (20)
Other pneumonia	30 (12)	13 (8)	17 (20)
Other respiratory failure	29 (12)	17 (10)	12 (14)
Non-pulmonary	6 (2)	4 (2)	2 (2)
Specific virus positive (%) (n = 187)			
RSV	140 (75)	102 (79)	38 (64)
Influenza	4 (2)	3 (2)	1 (1)
Parainfluenza	3 (1)	1 (1)	2 (2)
Adenovirus	2 (1)	1 (1)	2 (3)
Bacterial culture positive (%) (n = 195)	135 (70)	81 (63)	54 (82)
Duration of support			
Ventilator days	7.5 ± 7.9	6.5 ± 4.0	9.5 ± 12.1
Oxygen days	10.9 ± 9.3	10.0 ± 5.1	12.7 ± 14.5
PICU days	9.6 ± 9.0	8.3 ± 4.6	12.1 ± 13.5

ARF – Acute respiratory failure, PDAD – Pulmonary dysfunction at discharge, RSV – Respiratory syncytial virus

Table 2

Association of clinical variables and surfactant protein genetic polymorphisms with ARF before Bonferroni correction

Variables	OR (95% CI)	p value
Female sex	0.35 (0.2 –0.8)	0.01
Black race	5 (1.3–18.6)	0.02
rs721917_CT	2.92 (1.4 –7.5)	0.03
rs721917_CC	5.90 (1.0–34.7)	0.05

OR= Odds ratio, CI = Confidence interval