Latent Class Analysis to identify clinical profiles among Indigenous infants with bronchiolitis

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Abstract

Abstract Background and Objectives: Better phenotyping of the heterogenous bronchiolitis syndrome may lead to targeted future interventions. This study aims to identify severe bronchiolitis profiles among hospitalised Australian Indigenous infants, a population at high-risk of bronchiectasis, using Latent Class Analysis (LCA). Methods: We included prospectively collected clinical, viral and nasopharyngeal bacteria data from 164 Indigenous infants hospitalised with bronchiolitis. We undertook multiple correspondence analysis (MCA) followed by LCA. The best-fitting model for LCA was based on adjusted Bayesian information criteria and entropy R2. Results: We identified five clinical profiles. Profile-A's (23.8% of cohort) phenotype was previous preterm (90.7%), low birth-weight (89.2%) and weight-for-length z-score <-1 (82.7% from combining those with z-score between -1 and -2 and those in the z-score of <-2 group) previous respiratory hospitalisation (39.6%) and bronchiectasis on chest high-resolution computed tomography scan (35.4%). Profile-B (25.3%) was characterised by oxygen requirement (100%) and marked accessory muscle use (45.5%). Infants in profile-C (7.0%) had the most severe disease, with oxygen requirement and bronchiectasis in 100%, moderate accessory muscle use (85% vs 0-51.4%) and bacteria detected (93.1% vs 56.7-72.0%). Profile-D (11.6%) was dominated by rhinovirus (49.4%), mild accessory muscle use (73.8%) and weight-for-length z-score <-2 (36.0%). Profile-E (32.2%) included bronchiectasis (13.8%), RSV (44.0%), rhinovirus (26.3%) and any bacteria (72%). Conclusions: Using LCA in Indigenous infants with severe bronchiolitis, we identified 5 clinical profiles with one distinct profile for bronchiectasis. LCA can characterise distinct phenotypes for severe bronchiolitis and infants at risk for future bronchiectasis, which may inform future targeted interventions.

INTRODUCTION

Bronchiolitis, a common acute lower respiratory infections (ALRIs) among infants worldwide[1] causes considerable morbidity and hospitalisations annually (e.g. >3 million hospitalisations)[2]. It is a heterogenous, multi-dimensional disorder from many perspectives, including clinical phenotypes (during acute disease[3] and future outcomes[4-7]), likely pathophysiology[8] and risk factors[9-11].

The importance of improved phenotyping respiratory disorders (e.g. asthma[12] and bronchiectasis[13]) are increasingly appreciated as such data will likely improve targeted interventions. Indeed, to characterise clinical phenotypes (both during the acute disease and future outcomes) of infants with bronchiolitis using a multi-dimensional approach, Dumas and colleagues undertook two important studies[4]. Using latent class analysis (LCA), Dumas and colleagues described 4 phenotypes in a large USA cohort, of which 2 were replicated (with the remaining 2 combined in a single phenotype) in a Finnish cohort[3]. Later, using LCA and they then described a profile (breathing problems/eczema in infancy and non-respiratory syncytial virus [RSV], mostly human rhinoviruses [hRV] infection) associated with increased risk of future asthma phenotype (doctor-diagnosed asthma Hazard Ratio=2.79; 95% confidence interval [CI] 1.78-4.39 by 3-years of age)[4]. These infants also had "higher eosinophil counts, higher cathelicidin levels, and increased proportions of Haemophilus-dominant or Moraxella-dominant microbiota profiles"[4].

These longer-term outcomes of infants hospitalised with bronchiolitis are of considerable interest with associations with asthma[14] and data linking viral agents (particularly RSV and hRV)[15] and/or nasopharyngeal bacteria[5] to future childhood asthma and allergy[16]. However, while asthma and allergy are relevant and important outcomes in mainstream settings, these are inconsistently reported among and across different populations and settings[2,17]. In settings where acute respiratory infections are prevalent and bronchiectasis is relatively common, such as among Indigenous children living in high-income countries[10], bronchiolitis is more common and severe and their non-Indigenous counterparts[11]. In these settings, the long-term outcomes are also likely different. Indeed, Singleton and colleagues found that Alaskan Native children aged <2-years hospitalized for RSV infection had increased risk for chronic productive cough at 5 to 8 years of age and recurrent lower respiratory infections, but not asthma[18]. Further, we found that within 13-months post-hospitalisation for bronchiolitis, Aboriginal and/or Torres Strait Islander (from here referred as Indigenous) infants 19% (30/157) had bronchiectasis on chest high-resolution computed tomography (HRCT) scan[7].

A better understanding of clinical phenotypes including outcomes in Indigenous settings are important, in the context of (a) Dumas and colleagues'[3,4] likely paradigm-changing findings for future intervention studies; (b) the absence of further studies using LCA to define these bronchiolitis clinical phenotypes; and (c) the differential long-term outcomes in populations at high-risk of bronchiectasis. We used LCA to analyse data from Indigenous infants from Australia who participated in our previous prospective hospitalised bronchiolitis studies[19-21]. We aimed to identify distinct clinical profiles particularly those at-risk of future bronchiectasis.

METHODS

Study population

We used de-identified data sourced from three prospective studies undertaken between June 2008 and September 2013[19-21]. For this study, we included only the 232 Indigenous infants living in the Northern Territory (Australia). Here we briefly describe these studies; two were randomised controlled trials (RCT) where we found neither single or 3-weekly azithromycin (single or 3-weekly) doses, compared to placebo, improved any clinical outcomes for infants hospitalised with bronchiolitis[19,20]. The third was a cohort study to determine the validity and reliability of a bronchiolitis scoring system of infants hospitalised with bronchiolitis[21]. An overview of the studies is further described in the Figure. The local Human Research Ethics Committee approved each original study (HREC 07/60, HREC-2010-1324) and written informed consent obtained from the primary carer. In all studies[19-21], infants were aged [?]24-months hospitalised with a diagnosis of bronchiolitis using a standardised hospital protocol, with the same exclusion criteria (detailed in E-text).

Clinical Data

All clinical data and routine medical investigations during hospitalisation were recorded on standardised data collection forms[3,23,24]. Data for bronchiectasis was based on chest HRCT diagnosis and obtained from a previous study[7]. In this analysis, the most commonly detected co-morbidities were reported and combined as a single variable where appropriate (e.g. any otitis media or any skin infection). Length of stay (LOS) was defined in the original studies as duration from time from admission to "ready for discharge" (oxygen saturation >94% in air for >16-hours) and feeding adequately[19,20]. Accessory muscle use was taken from our modified Tal score[21] and weight-for-length z-score defined using WHO criteria (detailed in E-text).

Virus and bateria

Virus and bacteria data were obtained from nasopharyngeal swabs (NPS) collected at enrolment. NPS were placed into skim milk tryptone glucose glycerol broth (STGGB), stored at -80°C. NPS bacterial pathogens were cultured at our institution[22] and respiratory viruses using PCR undertaken at the Queensland Paediatric Infectious Diseases laboratory in Brisbane, as previously done[19-21]. For this study, we combined any bacteria detected as a single variable and only the two most frequently detected viruses (RSV and HRV) were analysed (so as to allow inclusion of more data). Further methods are detailed in the E-text file.

Statistical analysis

Sample size calculations were not undertaken for this study. Descriptive analyses of patient characteristics are presented as median and interquartile range (IQR: 25^{th}-75^{th}percentile) for continuous variables or frequencies and percentages for categorical variables. Weight-for-length z-score categories were defined using Zanthro software in STATA v14.0. Data were analysed using R package version 3.4.1.

Multiple Correspondence Analysis (MCA)

In the original studies, a total of 104 variables were available for MCA analysis. Firstly, we removed variables if missing data was >15%, then further removed variables if there were less than 20 infants for each categorical result (e.g. present or absent)[23]. We then selected variables based on clinical importance for bronchiolitis severity which included; age (<12-months), preterm (<37-weeks), low birth weight (<2.5kg), weight-for-length z-score, exposure to household smoke or in utero, currently breastfed, lobar collapse/consolidation on chest x-ray, previous respiratory hospitalisation, sex, remote (defined as >100km from hospital with paediatric expertise)[7], any antibiotics during hospital, supplemental oxygen requirement, any co-morbidity, carer-reported cough or breathing difficulty in last 7-days, any NPS bacteria, bronchiectasis on HRCT in addition to including as many variables (RSV, HRV, accessory muscle use and LOS) as Dumas and colleagues included in their study[3]. These variables were then entered into the MCA[23] to identify the most relevant variables for LCA and to decompose the inertia by identifying a small number of mutually independent dimensions that represent the most important deviations from independence[24].

LCA analysis

To identify the best-fitting model for LCA (i.e. between 1-5 models), we chose the minimum adjusted Bayesian Information Criteria (aBIC)[25,26] as this is known to be more robust with smaller datasets (<400 participants) than Bayesian Information Criterion (BIC)[26,27] and Akaike's Information Criterion (AIC)[26,28]. Entropy R^2 was used as the second criterion to determine the separation between the models using the highest value between models[29].

RESULTS

Participant characteristics

Clinical data of the final 164 infants are summarised in Table-1. During their hospital stay, 57.9% of infants received oxygen supplementation, RSV was detected in 42.1%, HRV in 28.0% and 68.9% had any bacteria detected. LOS varied but most infants (34.8%) were discharged within 48-hours. Bronchiectasis was detected on HRCT in 34 (20.7%) of infants at a later timepoint for clinical reasons.

MCA

Of 22 variables included in MCA (Table-2), the top three dimensions (of a possible 39) were chosen as they represented the largest number of independent variations between each dimension (Table-2). The top 4 variables (total n=12) from each dimension (e.g. LOS, low birth weight, preterm, weight-for-length z-score, supplemental oxygen requirement, accessory muscle use, RSV, HRV, any bacteria, any co-morbidity, bronchiectasis and previous respiratory hospitalisation) were then selected for LCA, including as many variables included in Dumas and colleagues' study[3].

LCA

Of the 232 infants, 68 were excluded due to missing data leaving a total of 164 infants for LCA (Figure). A Class-5 model was identified using LCA (Table-3). Class-5 model had the highest Entropy value and Class-3 model had the lowest aBIC value, however Class-5 model was chosen as the best-fitting model for LCA based on Entropy value and the clinic importance of the models. The five profiles included within the Class-5 model are described below and in Table-4.

Profile-A (23.8% of cohort) had the highest frequency of infants born preterm (90.7% vs 0.0-12.6%); low birth weight (89.2% vs 0.0-15.0% for other profiles), poor growth weight-for-length z-score of <-1 (82.7% from combining those with z-score between -1 and -2 and those in the z-score of <-2 group vs. 0.0-36.0% for

other profiles), and previous respiratory hospitalisations (39.6% vs. 11.1-19.4%). Infants in this profile had the second highest frequency of bronchiectasis (35.4%).

Profile-B (25.3% of cohort) was characterised by highest detection of RSV (48.6%), marked accessory muscle use (45.5% vs. 13.4-26.2%), supplemental oxygen requirement (100% along with Profile C) and LOS [60-96-hrs (48.1 vs. 0.0-30.5%) and >96-hours (34.4% vs. 0.0-31.2%)], but none had bronchiectasis.

Profile-C (7% of cohort) was the smallest group characterised by bronchiectasis in 100% (compared to 0.0-35.4% for other profiles), the highest frequency of moderate accessory muscle use (84.7% vs 0.0-51.4%), presence of 'any bacteria' (93.1% vs 56.7-72.0%), any co-morbidity (75.4% vs. 33.9-68.3%) and supplemental oxygen requirement (100.0%).

Profile-D (11.6% of cohort) had the highest prevalence of hRV (49.4% vs 23.2-32.5%) and mild accessory use (73.8% vs 0.0-54.2%). Weight-for-length z-score <-2 was higher in this group (36.0% vs. 8.2-23.9%) with the least having bronchiectasis (7.0%).

Profile-E (32.2% of cohort) was characterised by RSV detected in 44.0%, HRV in 26.3%, any bacteria in 72.0%. None had low birth weight (0.0%); most had LOS <48-hours (39.8%), low requirement for oxygen supplementation (20.3%) but 13.8% had bronchiectasis.

Clinical profile for future bronchiectasis on LCA

We identified one (100.0%) distinct clinical profile for Indigenous infants at-risk for future bronchiectasis (Table-4) and one without any risk (0.0%) (Profile-B). Infants in Profile-C who all had bronchiectasis also had the highest frequency of markers of severity for bronchiolitis i.e. supplemental oxygen requirement (100.0%), moderate accessory muscle use (84.7%), any co-morbidity (75.4%) and any bacteria (93.1%). Profile-A was the second most severe group with bronchiectasis in 35.4%, preterm birth in 90.7%, low birth weight in 89.2% and previous respiratory hospitalisation in 39.6%. However, many infants in this profile lacked known markers of severity (e.g. prolonged LOS, supplemental oxygen requirement etc).

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DISCUSSION

In this first study using LCA in a cohort at-risk of bronchiectasis rather than asthma, we identified 5 distinct clinical profiles among the 164 Indigenous infants hospitalised with bronchiolitis. The most striking characteristics were Profile-A phenotype was being preterm (90.7%), low birth-weight (89.2%) and weight-for-length z-score <-1 (82.7%). Profile-B phenotype were characterised by all (100.0%) requiring oxygen supplementation (100%) yet absence of future chronic symptoms necessitating chest CT scan (0.0%) whilst all in Profile-C had future bronchiectasis (100.0%) and at the point of hospitalisation, most (93.0%) had NP bacteria. Profile-D was characterised by the absence of low birth-weight (100.0%) yet low weight for length z-score of <-2 (36.0%) and hRV infection (49.4%) and infants in Profile-E had low concurrent co-morbidity (33.9%).

Use of clinical phenotypes for various diseases have been appreciated increasingly over the last decade in a range of conditions. LCA has been generally used for this and to the best of our knowledge, there are only two such published studies[3,4] involving infants with bronchiolitis. Both these novel studies[3,4] were based in high-income settings where asthma is the outcome of interest. In the absence of any such studies in a setting where infants are at high risk of chronic suppurative lung disease[30], we undertook this study to determine of LCA can identify phenotypes that may inform future interventions relevant to children at high-risk of bronchiectasis.

Uniquely, we identified two main clinical profiles with future bronchiectasis i.e. all in Profile-C had bronchiectasis and the second most common group with bronchiectasis was Profile-A (35.0%). Over a third of infants were included in these profiles which included many known risk factors for severe disease. It was not surprising that these profiles included the greatest number of infants with bacterial carriage and current co-morbidities. In Australia, Indigenous children particularly from remote communities often live in overcrowded homes[30],

are exposed to early and dense acquisition of respiratory bacteria (*Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarrhalis*)[31] which are associated with poorer clinical outcomes (chronic wet cough[18] and bronchiectasis[30]) in our setting. Whilst the above finding need confirmation in a large cohort from multi-centres, our novel findings highlight that LCA could be used for phenotyping children at-risk of future bronchiectasis and subsequently inform targeted interventions for these infants that could possibly prevent future bronchiectasis.

Unsurprising, our phenotypes are very different from that of Dumas and colleagues'[3] for many reasons, of which the most important is the different target population. Further our study was substantially smaller, we excluded infants admitted to the intensive care unit, and did not include all the variables examined by Dumas and colleagues[3]. Nevertheless, we identified 5 distinct clinical profiles by use of LCA. Profile-B was the third largest group with markers of severity (e.g. marked accessory muscle use, oxygen requirement and prolonged LOS). This group is common to that of the USA cohort,[3] whereby Dumas and colleagues[3] reported a severe profile among infants with RSV, moderate to severe accessory muscle use and prolonged LOS (>3-days). The same result however was not replicated in the Finish study[3] where these markers of severity (e.g. retractions and LOS) were distributed across two profiles. However, our Profile-B included oxygen requirement, a factor that was not included in Dumas and colleagues'[3] LCA profile.

The limitations of the original studies whereby this cohort was obtained from, were previously published[19-21]. However, this study has further other important limitations. Firstly, we did not use BIC because our relatively small sample size restricted the use of BIC as cohorts of <400 that BIC underestimate classes[32]. We thus used aBIC, suitable for smaller cohort[26,32]. As aBIC still suggested that the sample is sufficiently large (n[?]200)[32], we thus included entropy as a second information criterion[33] in class-models. Secondly, our data was cross-sectional and weakened by the lack of longer follow-up. Thirdly, our data were limited to Indigenous hospitalised for bronchiolitis with the lack of community-based children and the absence of recurrent wheezing and asthma, important factors in studies from high-income settings[34].

In conclusion, our study is unique as, for the first time, we identified 5 clinical phenotypes in an at-risk population by using LCA. Two profiles were important for future bronchiectasis. Importantly, our data further highlights the heterogeneity of bronchiolitis phenotypes among infants. We now need confirmation of our novel findings in a large multi-centre cohort to determine such phenotypes in children at-risk of future bronchiectasis. Such work could subsequently inform targeted interventions for these infants that could possibly prevent future bronchiectasis, an increasingly recognised condition worldwide of which a significant proportion commences in childhood[13].

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FIGURE LEGEND

Figure. Description of original studies where Indigenous infants were recruited from the Royal Darwin Hospital

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Figure: Description of original studies where Indigenous infants were recruited from the Royal Darwin Hospital