ORIGINAL ARTICLE

A Preliminary Study on Breastfeeding as a Protective Factor in Childhood Acute Leukaemia

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ABSTRACT

Introduction: Research has demonstrated that breastfeeding practice, with its antimicrobial and immunomodulating effects, offers numerous benefits to children, including protection against leukaemia. This study aimed to compare breastfeeding practices among mothers of children with leukaemia and healthy children at Hospital Pakar Universiti Sains Malaysia. **Methods:** This retrospective case-control study involved data on children taken from the medical records and telephone interviews with mothers of children with acute leukaemia who received treatment between January 2007 and December 2022. Similar data was taken from a control group involving children admitted to the paediatric wards for acute illness without prior history of cancer. Logistic regression analysis was used to evaluate the association between breastfeeding practice and other factors and the risk of childhood acute leukemia. **Results:** A total of 384 data sets of children were analyzed, involving 96 in the case group and 288 in the control group. The risk of leukaemia was reduced by ever breastfeeding (OR 0.16, 95% CI: 0.03 – 0.79), those who practiced breastfeeding only (OR 0.27, 95% CI: 0.13 – 0.53) and those who practiced mixed breastfeeding (OR 0.28, 95% CI 0.14 – 0.55). Paternal smoking (OR 2.14, 95% CI: 1.24 – 3.71) and positive family history of cancer (OR 2.93, 95% CI: 1.12-7.69) were found to have higher risk for acute leukaemia in children. **Conclusion:** Breastfeeding practice was shown to have protective effects for childhood acute leukaemia.
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Keywords: Breastfeeding, Breastfeeding practice, Breastfeeding duration, Acute lymphocytic leukemia, Acute myeloid leukemia

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INTRODUCTION

Leukaemia is the most common childhood malignancy worldwide. According to the Malaysian National Cancer Registry 2012-2016, a total of 4,273 new cases of leukaemia were registered for the period of 2012-2016 with the majority of the cases being under 14 years of age (1). The incidence has increased over the years and its rise was largely attributed to many factors such as advanced diagnostic capabilities, environmental and genetic factors, and lifestyle changes.

There are two main types of childhood leukemia, acute lymphocytic leukemia (ALL) and acute myeloid leukemia (AML). ALL is more common than AML and it has better survival than AML (2). The aetiologies of most childhood leukaemia involve genetic and environmental interaction. Studies in the paediatric population have identified several genetic syndromes that could predispose to ALL, such as Down syndrome, Fanconi anaemia, Bloom syndrome, ataxia-telangiectasia, and Nijmegen breakdown syndrome. Other predisposing factors include exposure to ionizing radiation, pesticides, certain solvents, or viruses such as Epstein-Barr Virus and Human Immunodeficiency Virus. However, in most cases of childhood leukaemia it appears as a de novo malignancy (spontaneous mutation) in previously healthy individuals. Chromosomal aberrations are the hallmark of ALL, but their presence alone is not sufficient to generate leukaemia. Greaves hypothesis states that the common B cell precursor of acute lymphoblastic leukemia arises because of abnormal responses to common infections in two genetic events. This hypothesis suggests that a lack of exposure to infections during infancy, along with immunological isolation, increases the risk of developing common ALL; in the absence of early exposure, the immune system may remain 'unprogrammed' and unable to respond appropriately later in life (3).

Breastfeeding has been recognized to have anti-

infective and immunomodulating effects on infants. Human milk has long been recognized as providing numerous antimicrobials, anti-inflammatory, and immunomodulating agents (4). Many studies have shown conclusively that breastfeeding protects against acute gastrointestinal infections through transmission of maternal antibodies, macrophages, and lymphocytes (4,5). Maternal breastfeeding may protect against childhood leukemia by modulating the child's immune system early in life to respond effectively during exposure to common infections.

A study by Gao et al. (2018) concluded that breastfeeding reduces the risk of childhood leukaemia with greater effect if feeding is continued for 7–9 months (6). Another study by Lingappa et al (2018), found that breastfeeding for at least 6 months was associated with reduced risk of acute leukemia among children, and breastfeeding only (in relation to consuming other milk or formula) beyond 6 months showed a statistically significant reduced risk of childhood acute leukemia (7). There were several other studies from around the world that showed breastfeeding as a protective factor in childhood acute leukemia, but not many have been conducted in the local context. In Malaysia, most research looks at other breastfeeding benefits such as protection against gastrointestinal problems or respiratory problems, but not specifically at its protective benefit on childhood leukaemia. There was very limited local research on the link between breastfeeding and childhood leukaemia.
Although Malaysia has one of the highest breastfeeding initiation rates in Southeast Asia, the duration and exclusivity remain suboptimal. National surveys report that while 94.7% of Malaysian mothers initiate breastfeeding, only 47.1% exclusively breastfeed for six months, and fewer than 25% continue beyond one year (8). Despite this, no Malaysian study has specifically examined whether breastfeeding may reduce childhood leukaemia risk, although international evidence suggests a modest protective effect. Thus, the local epidemiological relationship remains unclear. Therefore, this paper aimed to determine the association between breastfeeding practice in mothers with children with leukaemia and healthy children.

MATERIALS AND METHODS

This study employed a retrospective case-control design to investigate the association between breastfeeding practices and childhood acute leukaemia. Cases were defined as children aged six months to 13 years with a confirmed diagnosis of acute leukemia including ALL or AML, based on histopathology and haematology records, admitted to the paediatric oncology ward of Hospital Pakar USM from 1st January 2007 to 31st December 2022. Controls were defined as children of the same age range admitted during the same period for self-limiting acute illnesses such as viral fever, acute gastroenteritis, or respiratory infections, with no past or current diagnosis of any malignancy. 'Acute illnesses' were operationalized as a condition requiring hospital admission for less than fourteen days, not associated with chronic immunological, genetic, or haematological disorders. Exclusion criteria for both groups included congenital immunodeficiency, refusal of telephone consent and mothers who were unable to recall their breastfeeding history. The control group were matched based on their age and gender to the case group. This study involved a ratio of three controls to one case considering the low incidence rate of leukaemia in the community (1).

After identifying eligible candidates for both groups, their case notes were traced from the medical records. The medical record unit used "codEt" or coding expert systems to trace individual case notes. Information was collected based on a standardized checklist consisting of the patients' demographic profile including age between six months to 13 years old (due to the distribution of paediatric patients admitted to the paediatric ward were within this range), ethnicity, gender and risk factors for leukemia which are maternal age at birth, maternal education level, maternal smoking during pregnancy, marital status before diagnosis, paternal age at birth, paternal smoking, household income categories based on the Household Income and Basic Amenities Survey by Department of Statistic (DOSM) which are B40 (below RM 5250), M40 (RM5251 – RM11819) and T20 (above RM11820), immunization status before diagnosis, birthweight, daycare enrolment at five years and below before diagnosis, family history of cancer, and breastfeeding practice among mothers of children (6).

We divided the categories for breastfeeding practice into three groups. The first category was whether the mother ever breastfed (breastfeeding for at least one month or more to avoid recall bias) or never breastfed their child (breastfeeding for less than one month to avoid recall bias). "Ever breastfed" was defined as breastfeeding for one month or more because recall accuracy drops significantly for durations shorter than one month (10). The second category was regarding the duration of breastfeeding and the third category was whether the mother mixed the feeding with formula milk or breastfed only.

Incomplete or unavailable information in the record was completed through a telephone call and interviewing the patient's mother by using a telephone consent script. Telephone interviews may introduce recall bias, particularly for breastfeeding duration in older children. To mitigate this, interviewers used structured, time-anchored questions and memory cues (e.g., maternity leave duration, weaning timing, child milestones) to enhance accuracy. However, residual bias remains possible. This study has received ethical approval from the University Human Research Ethics Committee

(USM/JEPeM/22060392).

Data analysis was performed using IBM SPSS Statistics for Windows, Version 26.0. Descriptive analysis was used for factors such as age, gender, ethnic group, educational status, and family income. Numerical data were presented as mean ± standard deviation (SD) and categorical variables were expressed as frequencies and percentages. The student's t-test and chi-square test were used for quantitative and qualitative data, respectively, to compare the demographic variables between the two groups. Odds ratios for risk factors of leukaemia were calculated using simple logistic regression. Variables with a significant p-value of less than 0.25 were selected and adjusted odds ratios were calculated by multiple logistic regression analysis to exclude confounding factors. Model diagnostics were assessed using goodness-of-fit statistics, inspection for sparse data patterns, and evaluation of collinearity between breastfeeding-related variables. A p-value of less than 0.05 was considered statistically significant.

RESULTS

There were 384 subjects enrolled in the study involving 96 cases and 288 controls. A total of 288 controls were selected and matched to the case group based on age and gender, following a ratio of three controls for every one case, as illustrated in Figure 1. Table I demonstrated the socio-demographic profile retrieved from the participants. The mean age at diagnosis for cases was 5.29 years + 3.67 years, whereas that for controls was 5.59 + 3.69 years. There was no significant age difference between both groups (t=0.771, p=0.82). In terms of ethnic groups, for the case group, 93 (96.9%) were Malay, one (1.0%) was Chinese, and two (2.1%) were Siamese. For the control group, 284 (98.6%) were Malay, three (1.0%) were Chinese and one (0.3%) was

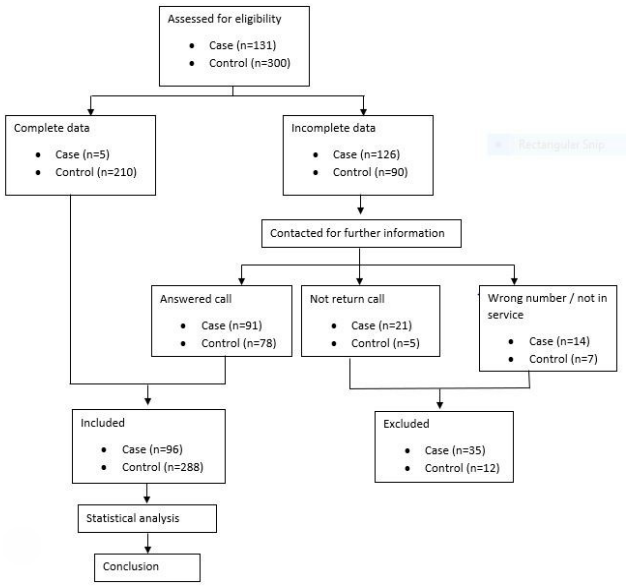

Figure 1: Screening and recruitment of subjects

Table I: Sociodemographic characteristics of study participants

Demographic data	Case group n (%)	Control group n (%)	X^2 [b]	P value
Age (in years)				
Mean ± SD	5.29 ± 3.67	5.39 ± 3.69	t=0.771[a]	0.823
Gender				
Male	56 (58.3%)	182 (63.2%)	0.722	0.395
Female	40 (41.7%)	106 (36.8%)		
Ethnicity				
Malay	93 (96.9%)	284 (98.6%)	2.800	0.247
Chinese	1 (1.0%)	3 (1.0%)		
Indian	-	-		
Others	2 (2.1%)	1 (0.3%)		
Birth weight (in grams)				
<2500g	4 (4.2%)	10 (3.5%)	0.468	0.791
2500g – 3500g	76 (79.2%)	237 (82.3%)		
>3500g	16 (16.7%)	41 (14.2%)		
Gestation				
Term	94 (97.9%)	285 (99.0%)	0.608	0.436
Preterm	2 (2.1%)	3 (1.0%)		
Mode of delivery				
Normal delivery	77 (80.2%)	237 (82.3%)	0.210	0.647
Caesarian section	19 (19.8%)	51 (17.7%)		
Maternal age at birth (in years)				
Mean (SD)	30.35 (5.72)	29.56 (4.84)		
<25	12 (12.5%)	38 (13.2%)	0.370	0.946
25 – 29	39 (40.6%)	114 (39.6%)		
30 – 34	27 (28.1%)	88 (30.6%)		
>=35	18 (18.8%)	48 (16.7%)		
Maternal education level				
Primary school	1 (1.0%)	7 (2.4%)	6.135	0.189
Secondary school	53 (55.2%)	186 (64.6%)		
College	22 (22.9%)	39 (13.5%)		
University	17 (17.7%)	44 (15.3%)		
Postgraduate	3 (3.1%)	12 (4.2%)		
Paternal age at birth (in years)				
Mean (SD)	32.88 (6.21)	32.1 (5.78)		
<25	5 (5.2%)	22 (7.6%)	2.231	0.693
25 – 29	26 (27.1%)	72 (25.0%)		
30 – 34	32 (33.3%)	110 (38.2%)		
35 - 39	18 (18.8%)	51 (17.7%)		
>=40	15 (15.6%)	33 (11.5%)		
Monthly household income				
<RM5250	86 (89.6%)	249 (86.5%)	0.922	0.631
RM5251 – RM11819	8 (8.3%)	34 (11.8%)		
>=RM11820	2 (2.1%)	5 (1.7%)		
House area				
Urban	29 (30.2%)	102 (35.4%)	0.869	0.351
Rural	67 (69.8%)	186 (64.6%)		

[a]Independent t-test was performed, [b]Pearson's Chi-Square test was performed, *Significant difference (p< 0.05)
Case group were children aged 6 months–13 years with confirmed ALL/AML
Control group were age- and sex-matched children admitted for self-limiting acute illnesses with no prior cancer history.

Siamese. There was no significant difference of ethnicity in both groups (X^2 = 2.800, p=0.25). There were 56 (58.3%) males and 40 (41.7%) females in the case group, while there were 182 (63.2%) males and 106 (36.8%) females in the control group. Both groups have similar gender distribution (X2 = 0.72, p=0.40). In terms of maternal age at birth, for the case group, 12 (12.5%) were below 25 years old, 39 (40.6%) were between 25 to 29 years old, 27 (28.1%) were between 30 to 34 years old, and 18 (18.8%) were 35 years old and above. For the control group, 38 (13.2%) were below 25 years old, 114 (39.6%) were between 25 to 29 years old, 88 (30.6%) were between 30 to 34 years old and 48 (16.7%) were 35 years old and above. In terms of the mother's education level, for the case group, one (1.0%) studied until primary school, 53 (55.2%) studied until secondary school, 22 (22.9%) studied until college, 17 (17.7%) studied until university and three (3.1%) studied until postgraduate. For the control group, seven (2.4%) studied until primary school, 186 (64.6%) studied until secondary school, 39 (13.5%) studied until college, 44 (15.3%) studied until university and 12 (4.2%) studied until postgraduate. For paternal age at birth, for the case group, 5 (5.2%) were below 25 years old, 26 (27.1%) were 25-29 years old, 32 (33.3%) were 30-34 years old, 18 (18.8%) were 35-39 years old and 15 (15.6%) were 40 years old and above. For the control group, 22 (7.6%) were below 25 years old, 72 (25.0%) were 25-29 years old, 32 (33.3%) were 30-34 years old, 18 (18.8%) were 35-39 years old and 15 (15.6%) were 40 years old and above. In terms of household income, for the case group, 86 (89.6%) were from B40, eight (8.9%) were from M40 and two (2.1%) were from T20. For control group, 249 (86.5%) were from B40, 34 (11.8%) were from M40 and five (1.7%) were from T20. In terms of birth weight, for the case group, four (4.2%) have a birth weight less than 2500grams, 76 (79.2%) have a birth weight between 2500 grams and 3500 grams, and 16 (16.7%) have a birth weight more than 3500 grams. For the control group, 10 (3.5%) have a birth weight less than 2500 grams, 237 (82.3%) have a birth weight between 2500 grams and 3500 grams, and 41 (14.2%) have a birth weight more than 3500 grams.

Table II showed the crude odds ratio for acute leukaemia with socio-demographic factors, family background and breastfeeding practice. It was found that there was a significant difference between case and control groups in ever breastfeeding (OR 0.25, 95% CI 0.15 – 0.44, p <0.001), breastfeeding only (OR 0.10, 95% CI: 0.05 – 0.21, p <0.001), mixed breastfeeding (OR 0.52, 95% CI: 0.29-0.93, p= 0.027), breastfeeding duration of one to 11 months (OR 0.46, 95% CI: 0.22 – 0.96, p=0.039), breastfeeding duration of 12-24months (OR 0.23, 95% CI: 0.13-0.41, p <0.001) and breastfeeding duration more than 25 months (OR 0.09, 95% CI: 0.02 – 0.39, p=0.002) between the two groups.

Table II: Simple logistic regression analysis for selected risk factors

Variables	Cases	Control	Crude OR	95% CI	p-value
Breastfeeding					
No	34 (35.4%)	35 (12.2%)	1		
Yes	62 (64.6%)	253 (88.5%)	0.25	0.15 – 0.44	<0.001*
Feeding type					
Formula milk	34 (35.4%)	35 (12.2%)	1		
Breastfeeding only	16 (16.7%)	161 (55.9%)	0.10	0.05 – 0.20	<0.001*
Mixed	46 (47.9%)	92 (31.9%)	0.52	0.29 – 0.93	0.027*
Breastfeeding duration					
<1month	34 (35.4%)	35 (12.2%)	1		
1 – 11 months	18 (18.8%)	40 (13.9%)	0.46	0.22 – 0.96	0.039*
12 – 24 months	42 (43.8%)	189 (65.6%)	0.23	0.13 – 0.41	<0.001*
>25 months	2 (2.1%)	24 (8.3%)	0.09	0.02 – 0.39	0.002*
Birth weight (in grams)					
<2500g	4 (4.2%)	10 (3.5%)	1		0.792
2500g – 3500g	76 (79.2%)	237 (82.3%)	0.80	0.24 – 2.63	0.715
>3500g	16 (16.7%)	41 (14.2%)	0.98	0.27 – 3.56	0.970
Gestation					
Term	94 (97.9%)	285 (99.0%)	2.02	0.33 – 12.28	0.445
Preterm	2 (2.1%)	3 (1.0%)			
Mode of delivery					
Normal delivery	77 (80.2%)	237 (82.3%)	1.15	0.64 – 2.06	0.647
Caesarian section	19 (19.8%)	51 (17.7%)			
Immunization					
Complete	90 (93.8%)	286 (99.3%)	1		
Incomplete	6 (6.3%)	2 (0.7%)	9.53	1.89 – 48.06	0.006*
Daycare enrolment at 5 years old and below					
No	76 (79.2%)	252 (87.5%)			
Yes	20 (20.8%)	36 (12.5%)	1.842	1.01 – 3.37	0.047*
Maternal age at birth (in years)					
Mean (SD)	30.35 (5.72)	29.56 (4.84)			
<25	12 (12.5%)	38 (13.2%)	1		0.946
25 – 29	39 (40.6%)	114 (39.6%)	1.08	0.52 – 2.28	0.833
30 – 34	27 (28.1%)	88 (30.6%)	0.97	0.45 – 2.12	0.942
>=35	18 (18.8%)	48 (16.7%)	1.19	0.51 – 2.77	0.690
Mother smoked during pregnancy					
No	94 (97.9%)	287 (99.7%)	6.11	0.55 – 68.11	0.141
Yes	2 (2.1%)	1 (0.3%)			
Mother's marital status					
Married	92 (95.8%)	287 (99.7%)	5.93	1.14 – 30.76	1.00
Unmarried	-	1 (0.3%)			
Divorced	4 (4.2%)	-			

CONTINUE

Table II: Simple logistic regression analysis for selected risk factors (continued)

Variables	Cases	Control	Crude OR	95% CI	p-value
Maternal education level					
Primary school	1 (1.0%)	7 (2.4%)	1		
Secondary school	53 (55.2%)	186 (64.6%)	2.00	0.24 – 16.57	0.523
College	22 (22.9%)	39 (13.5%)	3.95	0.46 – 34.22	0.213
University	17 (17.7%)	44 (15.3%)	2.71	0.31 – 23.06	0.369
Postgraduate	3 (3.1%)	12 (4.2%)	1.75	0.15 – 20.23	0.659
Paternal age at birth (in years)					
Mean (SD)	32.88 (6.21)	32.1 (5.78)			
<25	5 (5.2%)	22 (7.6%)	1		0.697
25 – 29	26 (27.1%)	72 (25.0%)	1.59	0.55 – 4.63	0.396
30 – 34	32 (33.3%)	110 (38.2%)	1.28	0.45 – 3.65	0.644
35 - 39	18 (18.8%)	51 (17.7%)	1.55	0.51 – 4.71	0.437
>=40	15 (15.6%)	33 (11.5%)	2.00	0.64 – 5.30	0.236
Father smoker					
No	47 (49.0%)	79 (27.4%)	1		
Yes	49 (51.0%)	209 (72.6%)	2.54	1.58 – 4.09	<0.001*
Family history of malignancy					
No	84 (87.5%)	276 (95.8%)	1		
Yes	12 (12.5%)	12 (4.2%)	3.29	1.42 – 7.59	0.005*
Monthly household income					
<RM5250	86 (89.6%)	249 (86.5%)	1		0.634
RM5251 – RM11819	8 (8.3%)	34 (11.8%)	0.68	0.30 – 1.53	0.352
>=RM11820	2 (2.1%)	5 (1.7%)	1.16	0.22 – 6.08	0.862
House area					
Urban	29 (30.2%)	102 (35.4%)	1.27	0.77 – 2.09	0.352
Rural	67 (69.8%)	186 (64.6%)			

Crude odds ratios (ORs) and 95% confidence intervals (CIs) are presented. *Significant difference (p< 0.25)
Reference categories were selected based on epidemiological relevance
Variables with small cell counts are interpreted with caution due to sparse data bias.

Some other crude associations reached statistical significance but warrant cautious interpretation due to small cell sizes. Incomplete immunization had a significant difference (OR 9.53, 95% CI 1.89 – 48.11, p=0.006) and children with daycare enrolment at five years and below (OR 1.84, 95%CI: 1.01 – 3.37, p=0.047) also had a significant difference. Paternal smoking was also found to have significant difference (OR2.54, 95% CI 1.58 – 4.09, p <0.001) as well as a positive family history of malignancy (OR 3.286 95% CI 1.42-7.59, p <0.001). There was no significant difference in birth weight, maternal and paternal age at birth, marital status, maternal smoking during pregnancy, maternal education level, household income and household area. Variables meeting the pre-specified threshold (p<0.25) in simple logistic regression were included in the multivariable model. Adjusted odds ratios are shown in Table III. There was a significant difference seen in ever breastfeeding (OR 0.16, 95% CI: 0.03 – 0.79, p=0.025), those who practiced breastfeeding only (OR 0.27, 95% CI: 0.13 – 0.53, p <0.001) and those who practiced mixed breastfeeding (OR 0.28, 95% CI 0.142 – 0.551, p=<0.001). There was no significant difference found in the duration of breastfeeding after multivariable adjustment.

Regarding other covariates, it was found that paternal smoking had a significant difference (OR 2.14, 95% CI: 1.24 – 3.71, p=0.007), and a positive family history of cancer was also significantly different (OR 2.93, 95% CI: 1.12-7.69, p=0.029). Daycare enrolment at five years and below and incomplete immunization, which were significant in crude analyses, did not remain statistically significant after adjustment with other variables (incomplete immunization: OR 6.09, 95% CI 0.94 – 39.53, p = 0.058; daycare enrolment: adj. OR 1.80, 95% CI 0.92–3.53, p = 0.086), likely reflecting sparse data and imprecision for these categories.

Model diagnostics raised two important considerations. First, a number of exposure categories contained small counts, producing wide confidence intervals and potential sparse-data bias. Second, feeding-type variables (ever breastfed, duration, and feeding type) are highly related; therefore, collinearity checks were performed and the final adjusted model accounted for this by retaining breastfeeding indicators that best represented exposure while avoiding redundant variables. Overall, the adjusted analyses support a protective association between breastfeeding and childhood acute leukaemia, and identify paternal smoking and family history as independent risk factors in this cohort.

DISCUSSION

This study found that the majority of children with acute leukemia were Malays followed by Chinese and others (Siamese) and none were Indian, which was consistent with the Malaysia Nasional Cancer Registry Report (MNCR) 2012–2016 which stated the age-standardized incidence rate (ASR) per 100,000 of childhood acute leukemia was highest in Malays (3.9 males, 2.9 females) followed by Chinese (3.8 males, 2.9 females) and Indians (2.8 males, 2.6 females) (1). This was probably related to the ethnic distribution in the population of Kelantan, which has the highest Malay community (95%) followed by Chinese 3.8%, others 0.9% and Indian 0.3% (9).

The current study demonstrated that breastfeeding was significantly protective against childhood acute leukaemia by ever breastfeeding either breastfeeding only or mixed breastfeeding. Children of mothers who ever breastfed their child had less likelihood of getting acute leukemia compared to those who never breastfed with an odds ratio of 0.16. Other previous studies had reported a statistically significant protective association between breastfeeding and risk of childhood leukemia

Table III: Multiple logistic regression analysis for acute leukaemia in children

Demographic data	Case group n (%)	Control group n (%)	Adj. OR	95% CI	P value
Immunization					
Complete	90 (93.8%)	286 (99.3%)	1		
Incomplete	6 (6.3%)	2 (0.7%)	6.093	0.94 – 39.53	0.058
Daycare enrolment at 5 years old and below					
No	76 (79.2%)	252 (87.5%)	1		
Yes	20 (20.8%)	36 (12.5%)	1.802	0.92 – 3.53	0.086
Father smoker					
No	47 (49.0%)	79 (27.4%)	1		
Yes	49 (51.0%)	209 (72.6%)	2.143	1.23 – 3.74	0.007
Family history of malignancy					
No	84 (87.5%)	276 (95.8%)	1		
Yes	12 (12.5%)	12 (4.2%)	2.93	1.10 – 7.83	0.032
Breastfeeding					
No / <1month	34 (35.4%)	35 (12.2%)	1		
Yes (>1month)	62 (64.6%)	253 (88.5%)	0.16	0.03 – 0.79	0.025
Breastfeeding duration					
<1 month	34 (35.4%)	35 (12.2%)	1		
1 – 11 months	18 (18.8%)	40 (13.9%)			0.215
12 – 24 months	42 (43.8%)	189 (65.6%)	4.12	0.79 – 21.39	0.092
>25 months	2 (2.1%)	24 (8.3%)	2.80	0.59 – 13.26	0.194
Type of feeding					
Formula milk only	34 (35.4%)	35 (12.2%)	1		
Breastfeeding only	16 (16.7%)	161 (55.9%)	0.27	0.13 – 0.53	<0.001
Mixed	46 (47.9%)	92 (31.9%)	0.28	0.14 – 0.55	<0.001

Adjusted odds ratios (ORs) and 95% confidence intervals (Cis) are presented. *Significant difference (p< 0.05)
Adjusted model includes variables meeting purposeful selection criteria (p < 0.25) while accounting for multicollinearity between breastfeeding variables. Wide confidence intervals indicate potential rare-event bias.

(10-11). The ways that breastfeeding might lower the risk of childhood acute leukemia include its ability to fight infections, boost the immune system, and help regulate immune responses (6-7,10-11). The leukocytes, antibodies, and immune-boosting substances in the milk, like lactoferrin, lysozyme, and lactoperoxidase, help strengthen the baby's still-developing immune system (4). Breastfeeding has been found to reduce the risk of enteric infectious diseases, otitis media, and respiratory infections in infants through transmission of maternal antibodies and macrophages and lymphocytes via colostrum and human milk. Breastfeeding also can stimulate or modulate the development of the immune system of infants, with breastfed infants demonstrating enhanced vaccine responses and larger thymus size (3).

Although breastfeeding itself was protective, the adjusted model did not identify a statistically significant linear association with breastfeeding duration. Furthermore, the elevated adjusted odds ratio for the 12–24 month category likely reflects instability due to sparse data and collinearity with the 'breastfeeding >1 month' variable. Multicollinearity can inflate standard errors, obscure true associations, and generate counterintuitive directionality. Future modelling approaches such as Firth penalized regression may better address rare cells and improve estimate stability.

Paternal smoking remained significantly associated with childhood leukaemia, consistent with other studies (12-13) which revealed similar finding. It was found that, genetic variants of the child's enzymes (i.e., CYP1A1) involved in the oxidation activation and subsequent conjugation detoxification of carcinogens when exposed to postnatal smoking exposure and this play a role in susceptibility to leukemogenesis in children (14). In addition, smoking has been associated with DNA damage and increased frequencies of chromosomal abnormalities (15).

The association of a family history of malignancy and acute leukaemia was also statistically significant between the case and control groups. A previous study also reported similar results (6). Some genes have been identified that can be inherited in an autosomal dominant fashion and specifically predispose people to the development of leukemia which are CEPBA, RUNX1, and GATA2 (16). These germline variants predispose to myeloid and lymphoid malignancies through impaired DNA repair and aberrant hematopoiesis. Therefore, genetic susceptibility was important in terms of childhood leukemia etiology.

This study was unable to prove Greaves's hypothesis that diminished exposure to common childhood infection

was associated with increased risk of B-cell precursor ALL. This study found no association between daycare enrolment in children aged five years and below and childhood acute leukaemia. Another study reported a similar finding, indicating no significant association between attendance at specific preschool groups and ALL risk (17). Another study that supported the hypothesis showed that daycare attendance appeared to be associated with a reduced risk of childhood ALL and children who had more total child–hours at a daycare had a significantly reduced risk of ALL (18).

There was no association found between immunization status and childhood leukemia. A similar finding was reported showing no relationship between vaccination and the risk of ALL (19). However, another study has reported a contradictory finding that MMR vaccination is protective for childhood acute leukaemia in children immunised after one year (20).

In the study, there was no association between household income and leukemia. This is contrary to a previous study that reported high levels of family income and parental education have been consistently associated with lower risk of childhood leukemia (21). In this study, there was also no significant association between maternal education and acute leukaemia. This conclusion contradicts a study that found medium and high levels of parental education were associated with a higher risk of acute myeloid leukaemia (AML) in the offspring, mainly driven by children diagnosed at ages 0 to 4 years (22). On the other hand, another study found that parents' higher education can be effective in preventing the development of leukemia in children (23). Parental education may influence various factors, including lifestyle choices, smoking habits, parental occupations, family planning, daycare attendance, and more. This variation in parental education and age could lead to differing findings in the studies. Parental age more or equal to 35 years old was not associated with acute leukemia in this study. This finding is inconsistent with another study that found that children with parents more than or equal to 35 years old have a higher risk of acute leukemia than those with parental ages below 35 years old (12). Another study showed maternal age more or equal to 35 years old to be associated with acute leukaemia in children (24). Advanced maternal age has been linked to several adverse pregnancy outcomes including an increase in the risk of chromosomal abnormalities in the offspring (25). Advanced paternal age has also been associated with single-gene mutation birth defects and chromosomal abnormalities potentially increasing offspring vulnerability to carcinogenesis (26,27).

Furthermore, birth weight was not found to be associated with acute leukemia in this study. The result was inconsistent with other studies which showed increased risk with increased birth weight (24). Another previous study has shown that high birthweight has been linked to acute myeloid leukemia and children diagnosed with cancers under two years (28). Another study identified a biological mechanism involving insulin-like growth factor (IGF-1), which is elevated in larger babies and can stimulate the proliferation of at least a significant subset of leukaemia cells (29). However, this study could not prove the above theory, and further study on the subject may be needed in the future.

Maternal smoking, maternal age, socioeconomic status, and urban/rural residence were not included in the multiple logistic regression model due to non-significant findings from the crude analysis.

A key limitation in this study was the potential recall bias as mothers needed to recall events from many years ago. To reduce recall bias, interviewers were trained to use specific prompts and objective questions during the interview, but sometimes there can still be incorrect information delivered, and this might affect the findings of the study. Other limitations include sparse data for several exposure categories, and a modest number of cases relative to the number of covariates. Wide confidence intervals in multiple estimates suggest possible rare-event bias; therefore, future studies should consider penalized regression, larger sample sizes, and prospective data collection.

CONCLUSION

The study demonstrated the protective effects of breastfeeding practices on childhood acute leukaemia, including continuous breastfeeding, exclusive breastfeeding, and mixed breastfeeding. Paternal smoking and a family history of malignancy were associated with a higher risk of acute leukaemia.
While several variables exhibited wide confidence intervals due to sparse data, the overall findings underscore the importance of early-life exposures in shaping leukaemia risk. Future studies should employ prospective designs, larger sample sizes, and penalized regression techniques to better account for rare events and reduce recall bias.

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