

Breastfeeding and acute lymphoblastic leukaemia: potential leukemogenesis in children in developing countries

Ameer Kakaje (✉ ameer.kakaje@hotmail.com)

Damascus University Faculty of Medicine <https://orcid.org/0000-0002-3949-6109>

Mohammad Marwan Alhalabi

Damascus University Faculty of Medicine

Ayham Ghareeb

Damascus University Faculty of Medicine

Bahjat Karam

Damascus University Faculty of Medicine

Aya Hamid

Damascus University Faculty of Medicine

Bassam Mansour

Damascus University Faculty of Medicine

Bayan Zahra

Damascus University Faculty of Medicine

Othman Hamdan

Children's university hospital, Damascus, Syria

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Abstract

Background:

Breastfeeding (BF) in infancy is associated with a decreased risk of acute lymphoblastic leukaemia (ALL). However, most of the studies were conducted in developed countries, neglecting developing countries where mothers might be exposed to different carcinogenic substances which could be transferred through breastmilk.

Methods:

This is a case-control study which was conducted in the major paediatric cancer centre in Syria. Data of case and control groups were obtained from the hospital's records. Only patients with no hereditary or chromosomal syndrome and aged 4 years and younger were included. The case group included ALL patients and control group contained hospital patients who visited its various clinics. The patients were categorised into 3 groups depending on their feeding habits before the age of 6 months.

Results:

Our sample contained 70 patients in the case group with 42 (60%) being males and 82 patients in the control group with 52 (55.3%) being males. Sixty (85.7%) cases and 59 (72%) controls were exclusively breastfed. We found a statistically significant difference when comparing cases and controls in BF patterns ($P < 0.05$) as cases were exclusively breastfed more frequently. Exclusive breastfeeding was found more frequently in the case group compared to other patterns of infancy feeding $P = 0.04$ (OR, 2.339; CI, 1.025 -5.336). In case group, parents of a low educational level breastfed their children more frequently ($P < 0.05$). Number of siblings was not associated with ALL or any of its variables. Furthermore, infancy feeding pattern correlation with gender, being born with no complications, consanguinity, CD10, FAB classification, ALL-subtype, risk, and family history were insignificant.

Conclusion:

There are certain practices among the Syrian people, especially among parents of a low educational level that has possibly exposed their children to carcinogenic substances which were possibly transferred through BF, causing this association between ALL and BF. We speculate certain substances and behaviours being responsible. However, BF had minor effects on the prognosis and subtype of ALL, and number of siblings had no effect on ALL.

Background

Breastfeeding (BF) is considered one of the best sources of nutrition for infants. Ideally, children should rely on exclusive breastfeeding (EBF) in the first six months of life [1]. However, in some cases when BF is unattainable, it is substituted with infant formula to meet the infant's nutritional needs. The World Health Organization (WHO) has warned that unmodified cow's milk should never be used in infants. Infant

formula that mimics breast milk cannot be produced. Therefore, infant formula is mostly made with cow's milk or soymilk with certain modifications on proteins and fatty acids. Iron and vitamins are also added to approximate human breastmilk. Nevertheless, quantities of such supplement ingredients are advised to be carefully monitored for the safety and wellbeing of the infant, and thus manufacturing is strictly regulated to meet the designated quality criteria [2, 3].

The most common cancer in children younger than 15 years is leukaemia which can reach up to 30% of malignancies. There are two main types of childhood leukaemia; acute myeloid leukaemia and acute lymphoblastic leukaemia (ALL) that resembles 78% of paediatric leukaemia, and has a peak age of onset around three and four years [4, 5]. Despite childhood leukaemia being widely researched in the past half century, the aetiology and risk factors are still uncertain. Infections, environmental factors, and genetic syndromes such as Down's syndrome are only linked to a small percentage of cases [5].

BF has been proven to boost the newborn's immune system and protect the newborns from early infections such as gastrointestinal infections, and its benefits may continue beyond infancy [6, 7]. Greaves et al. suggested an association between early infections and subtypes of ALL [8]. Furthermore, multiple meta-analyses have showed that short or long term BF reduced the risk of childhood leukaemia [9, 10]. However, most studies were not conducted in developing countries which may have different factors such as environment exposure and daily practices that may have a different outcome. Although BF benefits on the immune system can help against many infections and medical conditions, BF can also transfer harmful and oncogenic substances that the mother might have been exposed to. In this study, we are going to discuss BF and ALL in Syria, a developing country, and discuss different factors that could have led to these findings.

Methods

This is a case-control study which was conducted in the Children's University Hospital of Damascus University and covered the period between the 21st of August 2017 and the 21st of August 2018. This hospital is one of two major paediatric centres in Syria, and it is the major centre across the country which provides free healthcare and chemotherapy to its patients. Patients from across the country come to this hospital as it is free, provides the best medical service across Syria, and has clinics and departments that cover all specialties.

We performed a case-control study about childhood ALL to determine the association between BF and childhood ALL. Information from the case and control groups were obtained from the hospital's records and all information were provided by the child's caregiver.

1) Ethical commute approval and consents:

This study was approved by the ethical committee of Damascus University. Informed consent from the caregiver was taken after the examination and diagnosis of the child at the Children's University Hospital. Consent was also obtained to use and publish the data without any indication to the identity of the child.

2) Data collection:

Data were taken from the outpatient clinics by direct interviews with the care givers by the treating physicians. Family history was also taken from the care givers as self-reported family history was found to be a reliable method to determine the risk of being predisposed to cancer of individuals [11]. A caregiver is the legal guardian of the child who is responsible for the care of the child. In the study setting, information were later retrieved from patients' records. These records had information obtained from the caregiver, and any piece of information which was invalid was excluded. Moreover, unreliable and unclear responses were rejected from the study. Data were recorded during time of diagnosis of the child, during the period when the child stayed in the hospital, when the child returned to the hospital clinic for follow-ups, and when procedures were conducted such as a bone marrow aspiration and flow cytometry. Records were later retrieved for the study after obtaining approval from the care giver. As this is the only fully working centre for children in Syria at that time, response rate was excellent and full anonymity was assured. Patients' data were recorded for the study without using names, but only record numbers. ALL was also divided into T-ALL and B-ALL subtypes, and into L1 and L2 classifications.

3) Inclusion and exclusion criteria:

The case group comprised of children with ALL which was diagnosed by bone marrow aspiration and immune phenotyping. We excluded any patient with hereditary haematological, or metabolic disorders, constitutional hereditary diseases, aneuploidy syndromes, and single gene traits. We also excluded any patient who had a medical indication for formula feeding in the first six months of life. We also excluded Burkitt leukaemia (L3) as it has a viral aetiology that might be a confounding factor. Case and control groups were matched according to age and gender only. The children who were included in the control group were hospital patients who visited the general clinics and were referred to other clinics in the hospital as the general clinic role is only to direct children for the appropriate clinic, and they were randomly selected for the study. Patients in control group were randomly selected for the study, and were excluded if they were referred to the haematology clinic or department. Any patient older than 4 years or/and had a medical indication for infant formula was also excluded as patients presenting at an older age than 4 years do not have accurate feeding records in this hospital. We also excluded any patient who had missing or invalid data concerning feeding status in the first six months, gender, or age. Children who required special infant formula that was not based on cow's milk such as soymilk were excluded. Formula feeding was based on cow milk that was modified to meet the quality criteria [2, 3].

Records did not trace feeding habits after 6 months of age. All enrolled patients did not start taking solid food beside milk before the age of 6 months. No more detailed records were available.

4) Covariate measurement:

Demographic data were obtained from the medical records including date of birth, gender, province of origin, number of siblings and whether the child's delivery was complicated or not. History of cancer in the family such as leukaemia was also recorded. Children who only relied on infant formula were children

who stopped BF all together before the age of six months. However, infants who needed a sustained amount of infant formula along with BF before age of six months were categorised into a different group. We considered a parent who was illiterate or only finished primary school education as a parent of a low educational level. We also considered a parent who finished high school as a parent of a medium educational level, and who entered a university or any higher educational institute as a parent of a high educational level. Information about the financial situation could not be obtained as it is not appropriate or acceptable in the Syrian community.

Method of delivery was also recorded and divided into two groups: the uncomplicated delivery group which included normal delivery and caesarean delivery that both went without any complications, and the complicated delivery group which included having complications such as hypoxia. Flow cytometry for each patient was also recorded to determine the subtype of ALL whether it was B-ALL or T-ALL, and to identify if CD10 was positive. An experienced professor in haematology was involved in determining FAB classification [12] for each ALL patient whether it was L1 or L2. FAB classification is based on morphology and cytochemical staining, remains effective despite cytogenetics, and potentially adds diagnostic accuracy in some cases [13].

Patient's prognostic risk was categorised into low, intermediate, or high risk. It was assessed based on age, white blood cell count at time of diagnosis, biologic and cytogenetic changes such as having Philadelphia chromosome, medical comorbidities, cerebrospinal fluid (CSF) analysis, testicular involvement, inability to tolerate standard chemotherapy, response to initial therapy, predicted outcome, and organomegaly and lymphadenopathy on examination or chest x-ray; these were all considered in the determination of each patient's prognosis to conduct a correct chemotherapy protocol [14]. However, low and intermediate risk groups were combined as it would be easier for comparisons.

5) Statistical analysis:

Data were processed using IBM SPSS software version 25 for Windows (SPSS Inc, IL, USA). Chi-square, Fisher's exact, independent t-test, and one-way ANOVA were performed to determine the statistical significance. We calculated odds ratios (ORs) and the 95% confidence intervals for the groups using Mantel-Haenszel test by using the same software. Values of less than 0.05 for the two-tailed P values were considered statistically significant. Fisher's exact test was used when one or more cells had a value of less than five in 2*2 tables. As there were no similar studies, we could not determine sample size. All patients who met inclusion criteria for the case group were included, so we could only increase the sample size of the control group to increase the power. To set power of the study to 0.90, participants in control group were enrolled until the power reached 0.916 between case and control groups and feeding patterns with Cramer's V value being 0.258 for approximate significance of 0.006. This was achievable with a sample size of 70 in the case group and 82 in the control group.

Results

1. General characteristics

Study sample included 70 cases of ALL with 42 males (60%) and 82 controls with 52 males (55.3%). Gender and province of origin of case and control groups are demonstrated in **(Table 1)**. Sixty cases (85.7%) and 59 (72%) controls were exclusively breastfed, eight (11.4%) cases and seven (8.5%) controls were breastfed with extra infant formula, and two (2.9%) cases and 16 (19.5%) controls only relied on infant formula.

Sixty (85.7%) cases were exclusively breastfed until 6 months of age, eight (11.4%) cases needed additional infant formula with BF, and two (2.9%) only relied on infant formula. In comparison, 59 (72.0%) controls were exclusively breastfed, seven (8.5%) required additional formula feeding with BF, and 16 (10.5%) only relied on infant formula **(Figure 1)**. Infancy feeding patterns among cases according to ALL subtype and classification is demonstrated on **(Figure 2)**.

2. Breastfeeding exposure

A. Case-control groups:

It was found that more children in the control group only relied on formula compared to the case group ($P=0.006$). Moreover, when comparing EBF among case and control groups with other patterns of feeding, EBF was found more frequently in the case group $P=0.04$ (OR, 2.339; CI, 1.025 -5.336). Differences in BF patterns between case and control groups were demonstrated in **(Table 2)**. Moreover, it was found that EBF and requiring infant formula with BF were more common among case groups compared to control groups which had more children who only relied on formula $P=0.002$ (OR, 8.24; 95% CI, 1.82-37.26). No significant differences found when comparing case and control groups with educational levels of parents $P>0.05$.

B. Case Groups:

In summary, we found that gender, having consanguineous parents, being born with complications, having positive CD10, ALL type, FAB classification, prognostic risk, and having a family history for malignancies are significantly correlated with infancy feeding patterns ($P>0.05$). Characteristics of ALL in case group according to infancy feeding patterns are demonstrated in **(Table 3)**. A lower parental educational levels may be correlated with BF. Moreover, we found a higher incidence of positive family history in subjects with mothers of a low educational level when compared to medium educational level mothers ($P=0.029$). However, we found no statistically significant difference when comparing having a positive family history with infancy feeding patterns overall.

Other analyses:

The mean number of siblings for all patients was 3.85 (SD \pm 2.24), with 3.81 (SD \pm 2.278) for cases and 3.88 (SD \pm 2.23) for controls. Using one-way ANOVA and independent t-test, there was no statistically significant difference in number of siblings among case and control groups, infancy feeding patterns, risk,

subtype, and classification of ALL ($P>0.05$). No statistical difference was found when comparing cases and controls by gender, educational level of parents, and city of origin ($P>0.05$).

When excluding patients who had a mother of a low educational level or who had both parents of a low educational level, there was no statistically significant differences between case and control groups and infancy feeding patterns ($P>0.05$). This was the same when excluding patients who had a father of a low educational level, but $P=0.055$.

Discussion

Overall, this study found that BF in the first 6 months of life was positively correlated with a higher incidence of ALL in the first four years of life, and relying on formula can lower the incidence. This study also found that relying on formula is associated with a decreased percentage of high-risk patients of ALL from 40% to 30% but this result was statistically insignificant ($P>0.05$). However, having a mother or father with a lower educational level may be associated with BF. Moreover, when excluding parents of a low educational level, we found no statistically significant difference between cases and control groups with infancy feeding patterns which suggest that this positive correlation between BF and ALL might only be among low educational parents, and was not as significant with medium educational level parents or higher where it might only have cancelled the protective role of BF against ALL.

This study did not find any correlation between ALL or BF and number of siblings although a study found that having four or more siblings was correlated with a much higher risk for ALL when compared to not having any sibling [15]. Another study found that ALL risk was inversely correlated with birth order [16].

Although pre-labour caesarean delivery may be associated with childhood leukaemia [17], we found no such an association between case and control groups or between different feeding groups.

Patients in our study differed from other studies which found that mothers with a high socioeconomic status (SES) breastfed their children more frequently as low SES mothers more frequently used infant formula [18, 19]. Our findings also contradicted many studies that found an association between BF and a decreased risk of ALL [9, 10]. One meta-analysis that included multiple meta-analyses in developed countries found that children who were fed with infant formula beyond the first 6 months of life had a greater risk for ALL [20]. The potential risk for leukaemia, especially ALL, was negatively correlated with BF in more than one study, mainly in developed countries. This suggests that there might be additional factors in Syria that have contributed to our findings, especially that ALL in Syria has different patterns than most of the other countries [21], and that Syria has unique factors that can be from war or the unique environment [22]. This leads to several hypotheses which can explain additional underlying factors for our findings in developing countries.

Potential factors

Tobacco and diet:

Studies on the effect of tobacco and cigarette smoking in both mothers and fathers during various stages of pregnancy had various results. Their findings were inconclusive for mothers, but paternal smoking was found to be associated with a significant increased risk for childhood ALL [23, 24]. Hookah, which is also known as shisha or water pipe, exposure by either smoking or attending hookah social events is also linked to benzene exposure which is a risk factor for leukaemia [25].

Dietary options such as high consumption of coffee, and consumption of any quantity of cola were also associated with a higher risk for ALL, but tea was found to be a protective factor [26]. Furthermore, mothers with a healthy diet were found to have a lower risk of having a child with ALL [27]. A higher risk was found in mothers who had an increased food intake that contained N-nitroso precursors such as hotdogs [28]. Mate is a traditional South American, caffeine-rich infused drink. Although mate is traditionally consumed in South America, it is very popular in Syria. Mate was found to contain N-nitroso, polycyclic aromatic hydrocarbons (PAH), and other substances which are carcinogenic substances [29].

PAH was found to raise the risk for childhood leukaemia. PAH exposure can be from parental exposure to vehicle exhaust [30], paternal smoking [23, 24], and hookah which was found to have 16 components of PAH [31]. Furthermore, nitrosamine compounds which feature a nitroso group were found in cigarettes, in the urine of hookah smokers, in children who were exposed to its smoke [32], and in fertilisers that are commonly used in Syria [33]. Moreover, hookah has many other carcinogenic substances that were discussed in literature reviews and meta-analyses [34]. PAH and other polluting substances can also be found in drinking water. This was documented in Iran, a neighbouring country to Syria [35].

Other potential causes

Mothers who had lower education, worked in agriculture, or were exposed to pesticide had a child with childhood leukaemia more frequently [19]. BF might have a protective role against asthma and eczema especially in developing countries. It was also found that IgE-mediated asthma and allergic disorders are correlated with a reverse risk of childhood ALL [38]. BF might also have a protective role against asthma and eczema especially in developing countries [36]. Moreover, higher rates of asthma, atopic and allergic medical conditions were found to accompany cow's milk allergy [37] [36] which is more common with using formula in first months of life. The high rates of allergic conditions in Syria that reached around half of the population might explain this sophisticated association between BF and ALL [22].

Speculations

Tobacco and diet:

The study authors speculate that common factors could cause the correlation between BF and ALL in Syria. Most of the discussed risk factors are more common in parents of a low educational level which was correlated with a higher frequency of BF. Cigarette and hookah smoking, and second-hand smoking from attending hookah social events are very common in Syria [39]. Moreover, we hypothesise that

consuming large quantities of coffee and mate which are very common in Syria, mainly in low educational level populations caused these differences among cases and controls.

Pesticide:

In Syria, 75.8% of land is used for agriculture [40]. We speculate that using pesticide without adequate protection and working in agriculture are among the risk factors for our findings as they are common in Syria, particularly among populations of a low educational level. Although developed countries use high quantities of pesticide as well, old cheaper types of pesticides are commonly used in Syria without appropriate equipment for protection in order to lower expenses as 82.5% of the population is below poverty line [40]. Many people only use hand-made masks when spraying pesticide which is very common, especially among the less educated population.

As a result, BF in these populations could impose a risk as harmful elements could be transferred to the infant through BF.

Limitations

This study only included patients younger than five years as treating physicians tend not to ask about feeding patterns in the first six months if the presenting child was older than that age. We did not anticipate these findings and thus we could not eliminate potential confounding and determine sample size before conducting the study, especially that there were no similar studies. Adjustment for confounding factors could not be achieved, and the risk factors mentioned in the article could not be measured. It was a one-centre study as Syria did not have other working hospital at that time for children with leukaemia as the one centre in Aleppo was not fully functioning due to war at that time. It might also not represent the general population as it is a hospital-based study. Information were not always taken from the mother who can give the most reliable information for breastfeeding. However, any unreliable or invalid information about breastfeeding was rejected for the study, and this confounding factor equally affected both groups of case and control groups. This hospital is a public hospital and deals with many children from across Syria and thus those with a high SES might prefer to go to a nearby country to seek treatment for leukaemia. Finally, we could not determine from the records if the delivery had been pre- or post-term, the birth weight, and the severity of birth complications.

Conclusion

In conclusion, more studies are required in developing countries to confirm these findings and to determine which factors could be the causative agents. Smoking, parental occupation, diet, tea, coffee, mate, and hookah were speculated to be potential causes of these findings. High rates of allergies may also be a contributing factor. Number of siblings was not significantly correlated with ALL or any of its variables. Other studies are needed to determine if infant formula can reduce the risk for leukaemia in

cases when the mother is exposed to leukemogens, and if BF imposes a risk for ALL in some circumstances as it can transfer carcinogenic substances and facilitates malignant transformation.

Declarations

Ethics approval and consent to participate:

This study was approved by faculty of medicine, Damascus University. A written consent from caregivers was taken before admitting and commencing treatment.

Consent for publication:

A written consent was taken when admitting to the hospital for using and publishing their data with full anonymity and that their data can be freely available and be published for research purposes.

Availability of data and materials:

Data and materials can be made available upon request.

Competing interests:

There is no conflict of interest to declare.

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Authors' contribution:

All Authors read and approved the manuscript.

AK: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; original draft; Writing - review & editing.

MMA: Data curation; Formal analysis; Software; original draft; Writing - review & editing.

AG: Software; Methodology; Conceptualization; Validation; Writing editing; investigation.

BK: Software; Methodology; Conceptualization; investigation.

AH: Conceptualization; original draft; Writing - review

BM: Software; Project administration; Conceptualization; Writing editing; investigation

BZ: Software; Project administration; investigation

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Abbreviations

ALL	Acute lymphoblastic leukaemia
BF	breastfeeding
CI	Confidence interval
EBF	Exclusive breastfeeding
Group A	children who were exclusively breastfed
Group B	children who regularly took infant formula with breastmilk
Group C	children who ceased breastfeeding altogether
OR	Odds ratio
PAH	polycyclic aromatic hydrocarbons
SES	Socioeconomic status
SPSS Inc	Statistical Package for the Social Sciences incorporated

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Tables

Characteristic	Cases (%)	Controls (%)
Gender		
Male	42 (60%)	94 (62.3%)
Female	28 (40%)	57 (37.7%)
Place of living		
Damascus, Rif-Dimashq, and Aleppo	23 (34.3%)	59 (39.9%)
Homs and Hama	17 (25.4%)	31 (20.9%)
Al-Jazira region	13 (19.4%)	32 (21.6%)
Southern Syria	8 (11.9%)	17 (11.5%)
Syrian coast	3 (4.5%)	4 (2.7%)
Idlib	3 (4.5%)	5 (3.4%)

	Cases (%)	Controls (%)	P value	OR (Lower-Upper)
EBF	60 (85.7%)	59 (72.0%)	0.006*	-
BF with IF	8 (11.4%)	7 (8.5%)		
Only IF	2 (2.9%)	16 (10.5%)		
EBF	60 (85.7%)	59 (72.0%)	0.040*	2.339 (1.03 - 5.34)
BF with IF and only IF	10 (14.3%)	23 (28.0%)		
EBF and BF with IF	68 (97.1%)	66 (80.5%)	0.002	8.242 (1.82 - 37.26)
Only IF	2 (2.9%)	16 (19.5%)		
EBF	60 (88.2%)	41 (87.2%)	0.872*	1.098 (0.35 - 3.40)
BF with IF	8 (11.8%)	6 (12.8%)		
BF with IF	8 (80.0%)	6 (31.6%)	0.021	8.667 (1.40 - 53.85)
Only IF	2 (20.0%)	13 (68.4%)		

ALL: acute lymphoblastic leukemia; EBF: exclusively breastfed; BF: Breastfed; IF: infant formula; OR: odds ratio.
Chi-square test was used for the variable with asterisk while Fischer exact test was used in the other variables.

TABLE 3: Comparison of Characteristics of patients in the case group between Breastfed children and relying on Infant formula

	EBF (Group A)	BF with IF + Only IF (Group B+C)	P value	OR (Lower - Upper)
Delivery			0.130	-
No complication	60 (100.0%)	8 (88.9%)		
Complicated	0 (0.0%)	1 (11.1%)		
Mother education level			0.031	8.800 (1.01 - 76.71)
Low	22 (45.8%)	1 (11.1%)	0.297	-
Medium	20 (41.7%)	8 (88.9%)		
High	6 (12.5%)	0 (0%)		
Father education level			0.117	4.688 (0.84 - 26.15)
Low	25 (53.2%)	2 (22.2%)	0.646	0.444 (0.04 - 4.50)
Medium	16 (34%)	6 (66.7%)		
High	6 (12.8%)	1 (11.1%)		
CD 10			1.0	-
0-20%	8 (15.1%)	1 (11.1%)		
20% and above	45 (84.9%)	8 (88.9%)		
FAB classification			0.461	-
L1	31 (68.9%)	5 (55.6%)		
L2	14 (31.1%)	4 (44.4%)		
Types			1.0	-
B ALL	54 (90.0%)	9 (90.0%)		
T ALL	6 (10.0%)	1 (1)		
Risk			0.729	-
Intermediate	33 (60.0%)	7 (70.0%)		
High	22 (40.0%)	3 (30.0%)		

ALL: acute lymphoblastic leukemia; **EBF:** exclusively breastfed; **BF:** Breastfed; **IF:** infant formula; **NS:** not significant; **FAB:** French-American-British classification. **Group A:** being EBF; **Group B:** being BF with requiring additional IF; **Group C:** being dependent on only IF.

Different total subjects between groups occur as some data is missing.

Fischer exact test was used in this table.

Figures

Stacked Bar Count of Infancy Feeding Patterns by Gender by Case and Control Groups

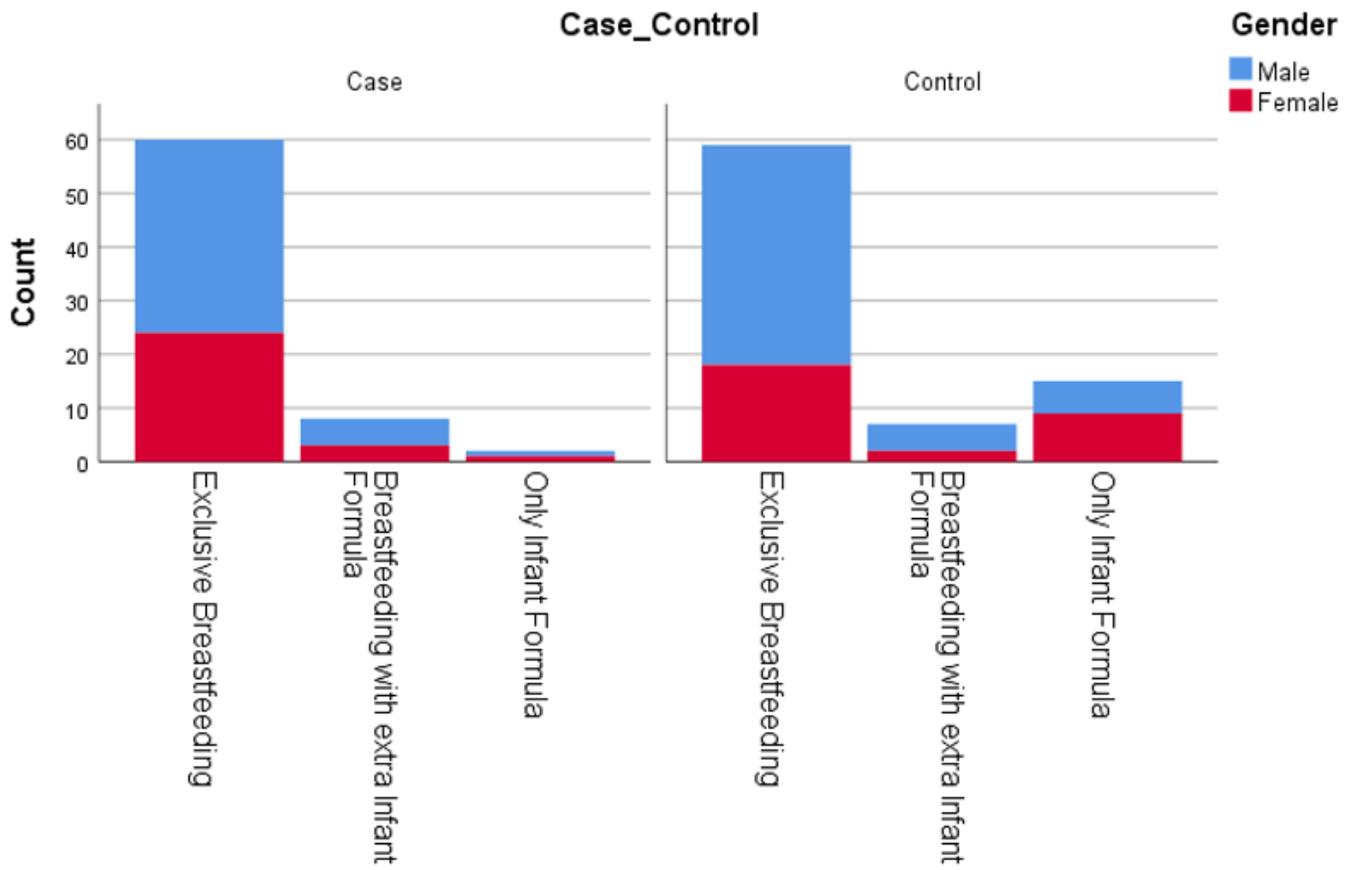


Figure 1

Showing infancy feeding patterns among case and control groups.

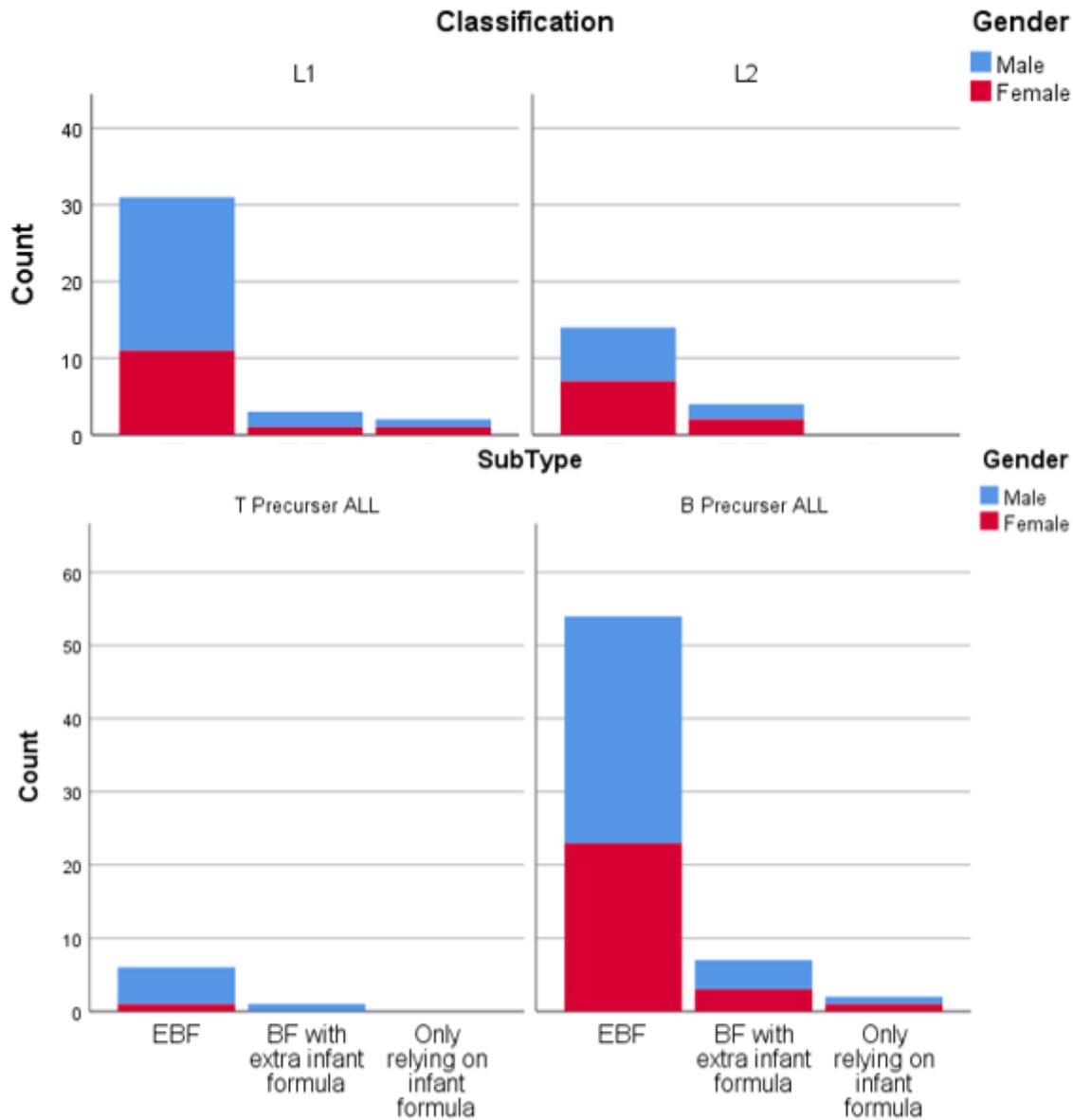


Figure 2

Showing infancy feeding patterns according to FAB classification and ALL subtype.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [STROBEchecklistcasecontrol.doc](#)