Rates and trends of childhood acute lymphoblastic leukaemia: an epidemiology study

Ameer Kakaje1✉, Mohammad Marwan Alhalabi1, Ayham Ghareeb1, Bahjat Karam1, Bassam Mansour1, Bayan Zahra1 & Othman Hamdan2

Acute lymphoblastic leukaemia (ALL) is the most common childhood cancer and has a high survival rate when properly managed. Prognosis is correlated with many factors such as age, gender, white blood cell (WBC) count, CD10, French-American-British (FAB) classification, and many others. Many of these factors are included in this study as they play a major role in establishing the best treatment protocol. This study aims to demonstrate clinical and laboratory features of childhood ALL in Syria. They were treated at Children’s University Hospital, the only working major cancer centre in Syria at the time of the study. Data of 203 patients who aged 0–14 years were obtained for this study. Most patients (48.8%) aged (5–9) years with a male predominance (60.9%). The major features for ALL included lymphadenopathy (82.9%), presenting with systemic symptoms (74.9%), T-ALL subclass (20.2%), L2 FAB classification (36.1%), low educational levels for fathers (53%) and mothers (56.2%), having a high risk (48.4%), and having a duration of symptoms before evaluation for more than 4 weeks (42.6%). Only three (1.5%) patients had normal full blood counts (FBC) and only one (0.5%) patient had an isolated high WBC count at time of presentation. Most patients had either abnormal platelet count (89.3%) or low haemoglobin level (88.8%) when presenting with only (2.0%) having normal levels for both. This suggests that having normal haemoglobin and platelet count can be used for quick screening in crisis time like in Syria for prioritising patients. Many prognostic factors were significantly different from medical literature which emphasises the importance of local studies in the developing countries. This study included a high prevalence of T-all, L2 FAB classification, high-risk and other variables which require further studies to evaluate the aetiology of these features, especially that treatment protocols may have a higher mortality in developing countries when not adjusted to local variables.

Acute lymphoblastic leukaemia (ALL) is the most common cancer in childhood, with a prevalence up to 25% of cancers in children who are under the age of 15 years1. Although ALL is curable, many parts of the world may not have access to modern treatment. Approximately eight to nine of every ten children that have ALL are considered long-term survivors and cured in developed countries, but these results markedly differ in developing countries2,3. These positive outcomes are due to having access to top treatments at the most advanced institutions2. Although the five-year survival rate is 93.5% when using the newest protocols and top chemotherapy, some cases of relapse still occur4. Nevertheless, top treatment cannot be accessed by all countries as many factors may get involved such as resource scarcity5. Few studies were concerned with paediatric ALL in the Middle East6. Little is known about childhood ALL in the Middle East and further studies are needed to establish standard data for future regional collaborative research as it provides a baseline for future protocols in ALL as they needed to be adjusted to the local variables. This raises a challenge as it is not easy to conduct medical research such as medical trials in developing countries due to the unavailability of proper funding and institutions which makes this quite challenging. In this article, the epidemiology and characteristics of ALL patients along with ALL variables such as prognostic risk and subtype are studied. Our study aims to define the risk factors and features associated with ALL in Syria.

1Faculty of medicine, Damascus University, Damascus, Syria. 2Haematology department, Children’s University Hospital, Damascus University, Damascus, Syria. ✉e-mail: ameer.kakaje@hotmail.com
Materials and methods

Study design. Our cross-sectional study was conducted in the Children’s University Hospital of Damascus University. The data was collected from patients’ records and covered the period between 21st August 2017 and 21st August 2018. This hospital is the major paediatric cancer center among two centres in Syria and provides free healthcare to patients. The other centre was in Aleppo and was not working properly in the study period due to the conflict in Aleppo, resulting in most of leukaemia cases to be referred to Damascus.

Sampling and data collecting. This study included children with ALL who aged 0 to 14 years. ALL was diagnosed before initiating chemotherapy by bone marrow aspiration and immune phenotyping. Information was obtained from the hospital’s records which were taken by the physicians at time of diagnosis and information was provided by the child’s caregiver.

Demographics and family history. Data about general characteristics of patients such as age, gender, and province of origin was recorded (Table 1). Caregivers were asked by hospital physicians to determine the history of cancer and leukaemia in the family. Family history was obtained based on the family of the affected child having malignancies in their direct family.

French-American-British (FAB) classification. A skilled professor in haematology was involved in determining FAB classification for each ALL patient whether it was L1, L2 or L3. As FAB does not have independent prognostic significance and it is subjective, it is no longer recommended. FAB classification was the first classification for ALL, and it is based on morphology and cytochemical staining. However, it remains effective despite cytogenetic tests as it can add diagnostic accuracy in some cases. Furthermore, using FAB system is convenient in developing countries as it is easy to conduct in regular labs and does not require much resources. It is also used when there is no alternative which is why it is used in Syria.

Risk determination. Berlin-Frankfurt-Münster (BFM) risk groups determination was used. However, in this study standard and intermediate risk groups were merged into one group that has both characteristics and treated as intermediate risk. This change is more convenient due to lack of resources to determine the genes and it is easier for management and application. In addition, long-term treatment response was beyond this study scope.

Patient’s prognostic risk was defined as standard or high. Poorer prognosis is correlated with age of younger than 1 year and older than 10 years, white blood cell (WBC) count higher than 50 × 10^9 cells/L at time of diagnosis, extramedullary disease, biologic and cytogenetic changes such as having Philadelphia chromosome, T-ALL, positive cerebrospinal fluid (CSF) and testicular involvement, inability to tolerate standard chemotherapy, slow-rate response to initial therapy, the speed and how low leukemia cell count drops after initial therapy, minimal residual disease (MRD) and bone marrow aspiration and FAB determination in the beginning of treatment; these were all considered in the determination of each patient’s prognosis to conduct the correct chemotherapy protocol. MRD was determined by a blood smear on day 8 and steroid response.

Patients with hereditary risk factors such as Down syndrome, neurofibromatosis, Bloom syndrome, Fanconi anemia, ataxia telangiectasia, Li-Fraumeni syndrome, and constitutional mismatch repair deficiency were excluded from this study.

Definitions. Systemic symptoms were defined as having fever, anorexia, weight loss, or fatigue. Chest x-ray (CXR) was considered positive when it had a mediastinal enlargement or hilar lymphadenopathy. WBC count of (1.5–11.5 × 10^9 cells/L), haemoglobin level of (11–16 g/dL), and platelet count of (150–400 × 10^9 cells/L) were considered normal. A positive family history is when a direct family member has a history of malignancy, regardless of type of cancer or age of presentation.

We defined having a positive CD10 as having 21% or higher CD10 on flow cytometry. Educational levels were divided into 3 groups as in Syria these three groups tend to significantly differ; low education level is for a parent whose higher degree is elementary or lower, medium educational level is when the highest degree is the ninth or 12th grade, and finally high educational level is when having a university degree or higher.

Genetic testing. No routine genetic testing was conducted due to unavailability of resources and other countries boycott the high-tech materials and medications which made them very expensive for the government to obtain for this centre. However, genetic testing was conducted when a hereditary syndrome was highly suspected and therefore these patients could be excluded from this study, but genes prevalence such as Philadelphia gene is not valid to use in this study as genetic testing is not routinely done, and therefore the data was not retrieved.

Consent and ethical approval. Informed written consent was taken before using and publishing the data. It was taken from the parent and/or the legal guardian of the child. The study was approved by the ethics committee of Damascus University. We confirm that all research was performed in accordance with relevant guidelines/regulations.

Data analysis. Data was processed by the software IBM SPSS version 26 for Windows (SPSS Inc, IL, USA). The statistical analysis used was non-parametric as the data was not normally distributed. The statistical analysis used was Chi-square test for determination of statistical significant differences within the groups. We measured odds ratios (ORs) and the 95% confidence intervals when comparing groups by using Mantel–Haenszel test by using the same software. When two-tailed P value was less than 0.05, the results were considered to be statistically significant.
Results

Characteristics of the sample. Our study was conducted on 203 ALL patients who aged (0–14) years. The peak age in our study was (5–9) years comprising 48.5% of the cases with a male predominance (60.9%). Characteristics of ALL children in Syria, including gender, age, geographic distribution, parents' educational level, main presenting symptom, hepato-splenomegaly, lymphadenopathy, ALL-subtype, haemoglobin, WBC and platelet count when diagnosed, CXR, CD10, FAB classification and prognostic risk are demonstrated in (Table 1). Patients distribution in Syrian provinces is shown in (Fig. 1) according to the province of origin.

| Characteristic | Count | Percentage (CI 95%) | Characteristic | Count | Percentage (CI 95%) |
|----------------|-------|---------------------|----------------|-------|---------------------|
| **Gender**     |       |                     | **Characteristics when diagnosed (cells/L)** |       |                     |
| Male           | 123   | 60.9 (54.6–67.8)    | B ALL         | 158   | 79.8 (73.8–85.4)    |
| Female         | 79    | 39.1 (32.2–46)      | T ALL         | 40    | 20.2 (14.6–26.2)    |
| **Age (years)**|       |                     | **WBC when diagnosed (cells/L)** |       |                     |
| 0–4            | 74    | 36.6 (29.7–43.1)    | 1.5×10⁹ and less | 5     | 2.5                 |
| 5–9            | 98    | 48.5 (42.1–55.9)    | (1.5–11.5)×10⁹ | 91    | 45.7                |
| 10–14          | 30    | 14.9 (9.9–20.3)     | 11.5×10⁹ and above | 103  | 51.8                |
| **Place of living** |       |                     | **Hemoglobin levels when diagnosed (g/dl)** |       |                     |
| Damascus       | 15    | 7.7                 | 11–16         | 24    | 12                  |
| Rif-Dimashq    | 36    | 18.5                | 11–7          | 106   | 53                  |
| Aleppo        | 11    | 5.6                 | 7 and less    | 70    | 35                  |
| Homs           | 20    | 10.3                |               |       |                     |
| Hama           | 22    | 11.3                |               |       |                     |
| Deir ex-Zur    | 17    | 8.7                 |               |       |                     |
| Ar Raqqah      | 11    | 5.6                 |               |       |                     |
| Al Hasakah     | 24    | 12.3                |               |       |                     |
| Daraa          | 10    | 5.1                 |               |       |                     |
| As Suwayda     | 8     | 4.1                 | More than 400×10⁹ | 4     | 2                   |
| Quneitra       | 1     | 0.5                 | (150 to 400)×10⁹ | 21    | 10.6                |
| Latakia        | 4     | 2.1                 | (150 to 50)×10⁹ | 63    | 31.8                |
| Tartus         | 4     | 2.1                 | (50 to 20)×10⁹ | 60    | 30.3                |
| Idlib          | 12    | 6.2                 | Less than 20×10⁹ | 50    | 25.3                |
| **Mother education level*** |       |                     | **CXR** |       |                     |
| Low            | 91    | 56.2                | Mediastinal enlargement or lymphadenopathies | 32   | 18.4                |
| Medium         | 55    | 34                  | Negative      | 142   | 81.6                |
| High           | 16    | 9.9                 |               |       |                     |
| **Father education level*** |       |                     | **CD 10** |       |                     |
| Low            | 88    | 53                  | 81% and more  | 104   | 58.1                |
| Medium         | 51    | 30.7                | 21–80%        | 36    | 20.1                |
| High           | 27    | 16.3                | 20% and less  | 39    | 21.8                |
| **Main presenting symptom:** |       |                     | **FAB classification** |       |                     |
| Systemic symptoms | 140 | 74.9                | L1            | 93    | 58.9 (51.3–65.8)    |
| Lymphadenopathy | 20   | 10.7                | L2            | 57    | 36.1 (28.5–44.3)    |
| Hepato-splenomegaly | 5   | 2.7                 | L3            | 8     | 5.1 (1.9–8.9)      |
| Bruising       | 16    | 8.6                 |               |       |                     |
| Accidental     | 6     | 3.2                 |               |       |                     |
| **Hepato-splenomegaly:** |       |                     | **Prognostic risk** |       |                     |
| Positive       | 139   | 73.2                | Standard      | 96    | 51.8 (44.6–58.6)    |
| Negative       | 51    | 26.8                | High          | 90    | 48.4 (41.4–55.4)    |
| **Lymphadenopathy** |       |                     | **Duration of symptoms before evaluation (weeks)** |       |                     |
| Positive       | 165   | 82.9                | 0–2           |       |                     |
| Negative       | 34    | 17.1                | 2–4           | 51    | 25.9                |
|               |       |                     | 4+            | 62    | 31.5                |
|               |       |                     |               | 84    | 42.6                |
| **Family history** |       |                     |               |       |                     |
| Positive       | 20    | 10.6 (6.3–15.9)     |               |       |                     |
| Negative       | 169   | 89.4 (84.1–93.7)    |               |       |                     |

Table 1. Characteristics of Children with ALL in Syria. CI: Confidence interval.
Date of the full blood count (FBC) of 197 patients was recorded; only three (1.5%) patients had normal FBC (normal haemoglobin, WBC count and platelet counts) when diagnosed and only one (0.5%) patient had an isolated high WBC count with normal haemoglobin and platelet counts. However, only 21 (10.7%) patients had normal platelet counts, only 22 (11.2%) patients had normal haemoglobin, and only four (2.0%) of the patients having normal haemoglobin and platelet counts when diagnosed.

Having systemic symptoms (74.9%), anaemia (88%) with 35% having severe anaemia, low platelet count (87.4%) with 25.3% having platelet count lower than \((20 \times 10^9\text{ cells/L})\), lymphadenopathy (82.9%), and hepatosplenomegaly (73.9%) were the most frequent observations in our study.

**Variables according to gender.** Comparison between males and females with ALL characteristics is demonstrated in Table 2. T-ALL was more frequently correlated with male gender \(P = 0.0019\) (OR, 3.750; 95% CI 1.565–8.986). Lymphadenopathies were less common in females comparing to males \(P = 0.0286\) (OR, 0.439; 95% CI 0.208–0.928) and males had a longer duration of symptoms before evaluation (more than 4 weeks) when compared to females \(P = 0.0145\) (OR, 2.054; 95% CI 1.149–3.671). No statistically significant difference was found when comparing gender with having family history, parents’ educational levels, hepatosplenomegaly, haemoglobin, WBC and platelet count, CXR, CD10 positivity, prognostic risk and FAB classification \((P > 0.05)\). Classification and ALL subtype according to province of origin are demonstrated in Fig. 2.

**Variables according to age groups.** Comparison between age groups with characteristics of ALL is demonstrated in Table 3. T-ALL was found more frequently than B-ALL in the oldest age group (10–14) when compared with the age group (5–9) \(P = 0.0030\) (OR, 3.690; 95% CI 1.529–8.929) or with the age group (0–9) \(P = 0.0001\) (OR, 4.975; 95% CI 2.160–11.494). The prognostic risk was found to be higher in older patients (10–14) than the younger patients (5–9) \(P = 0.0001\) (OR, 7.500; 95% CI 2.405–23.386) and the youngest patients (0–9) \(P < 0.0001\) (OR, 8.492; 95% CI 2.812–25.643). CD10 was found to be negative more frequently in the age group (0–9) when compared with (10–14) age group \(P = 0.0146\) (OR, 0.352; 95% CI 0.149, 0.833).

L2 was found more frequently than L1 in (10–14) age group when compared with (5–9) age group \(P = 0.0488\) (OR, 2.567; 95% CI 0.991–6.649) or with (0–9) age group \(P = 0.0252\) (OR, 2.702; 95% CI 1.108–6.588). Less hepatosplenomegaly was found in the older age group (10–14) when compared with the younger age group (5–9).
P = 0.0090 (OR, 0.324; 95% CI 0.136–0.771) or with the age group (0–9) P = 0.0076 (OR, 0.344; 95% CI 0.154–0.770). However, no statistically significant difference was found when comparing gender, duration of symptoms before evaluation, haemoglobin, WBC and platelet count, CXR, parents' educational level, lymphadenopathy, or family history with any age group (P > 0.05).

Table 2. Comparing males and females with ALL in children in Syria. CI: Confidence interval. *when comparing duration of symptoms before evaluation of 4 weeks and more with less than 4 weeks, P = 0.0145. bP value was only calculated between L1 and L2.
Variables according to ALL subtype. Comparison between T-ALL and B-ALL with characteristics of ALL is demonstrated in Table 4. WBC count was found to be less frequently higher than normal (higher than $11 \times 10^9$ cells/L) in B-ALL $P < 0.0001$ (OR, 0.200; 95% CI 0.083–0.482). However, haemoglobin was found to be more frequently low in B-ALL patients $P = 0.0012$ (OR, 4.421; 95% CI 1.723–11.345). CXR was found to be less positive in B-ALL $P < 0.0001$ (OR, 0.109; 95% CI 0.046–0.259). CD10 was found to be more frequently positive in B-ALL patients $P = 0.0001$ (OR, 32.500; 95% CI 12.462–84.755) and prognostic risk to be lower in B-ALL patients $P < 0.0001$ (OR, 0.016; 95% CI 0.002–0.122). L1 was found less frequently in T-ALL patients $P = 0.0401$ (OR, 0.432; 95% CI 0.192–0.974). No statistically significant difference was found between T-ALL and B-ALL when compared with family history, parents’ educational level, hepatospleno-megaly, time until diagnosis, and platelet count $P > 0.05$.

Variables according to risk group. Comparison between high risk and low risk patients with characteristics of ALL is demonstrated in Table 5. Positive family history was found more frequently in patients with standard risk $P = 0.0438$ (OR, 2.916; 95% CI 0.992–8.570). However, CD10 was found less frequently in patients with high risk $P = 0.0001$ (OR, 0.129; 95% CI 0.050–0.331) and L2 was found more frequently in patients with high risk $P = 0.0227$ (OR, 3.422; 95% CI 1.114–10.690). No statistically significant difference when comparing patient risk with their parents’ educational level ($P > 0.05$).

Variables according to FAB classification. Comparison between L1 and L2 patients with characteristics of ALL is demonstrated in Table 5. CD10 was found less frequently positive in L2 patients $P = 0.0143$ (OR, 0.361; 95% CI 0.157–0.829) and L2 patients had a higher probability of having a father with high educational level $P = 0.0307$ (OR, 3.422; 95% CI 1.096–10.690). However, no statistically significant difference was found when comparing L1 and L2 with haemoglobin, WBC and platelet count, mother educational level and family history.

Other variables. Having hepatospleno-megaly was more frequently correlated with high WBC count $P = 0.0055$ or with abnormal WBC count $P = 0.0057$, and with higher rate of low platelets $P = 0.0095$ or abnormal platelet $P = 0.0079$ compared with normal platelets. Lymphadenopathy was found to be correlated with high WBC count $P = 0.0123$ or abnormal WBC count $P = 0.0144$, and with higher prognostic risk $P = 0.0418$. In patients with low platelets (less than $150 \times 10^9$ cells/L), having hepatospleno-megaly was found to be more frequently correlated with even lower platelet count (less than $20 \times 10^9$ cells/L) $P = 0.0452$.

Discussion

Age and gender. The mean age group of our study is slightly older than the (3–6) years reported by the Multi-Institutional International Collaborative Study (CALLME1) by the Middle East Childhood Cancer Alliance (MECCA) in which they comprised 33.8%6, older than what was found in the US of (1–4) years comprising (42.9%)11,12, and one international study that covered 184 countries which found the peak age to be (0–4)
|                      | 4 years and below | Percentage (CI 95%) | 5–9 years | Percentage (CI 95%) | P valuea | 10–14 years | Percentage (CI 95%) | P valueb | 0–9 years | P valuec |
|----------------------|-------------------|---------------------|-----------|---------------------|----------|-------------|---------------------|----------|-----------|----------|
| Gender               |                   |                     |           |                     |          |             |                     |          |           |          |
| Male                 | 45                | 60.8 (48.6–71.6)    | 59        | 60.2 (51.0–68.4)    | NS       | 19          | 63.3 (46.7–80.0)    | NS       | 104       | NS       |
| Female               | 29                | 39.2 (28.4–51.4)    | 39        | 39.8 (31.6–49.0)    | 11       | 36.7 (20.0–53.3) | 68       | 0.0001    | <0.0001  |
| Subtype              |                   |                     |           |                     |          |             |                     |          |           |          |
| B-cell ALL           | 66                | 89.2 (81.1–95.9)    | 76        | 80.9 (72.3–89.4)    | NS       | 16          | 53.3 (36.7–70.0)    | 0.003    | 142       | 0.0001   |
| T-cell ALL           | 8                 | 10.8 (4.1–18.9)     | 18        | 19.1 (18.6–27.7)    | 14       | 46.7 (30.0–63.3) | 26       | 0.0001    | <0.0001  |
| Risk category        |                   |                     |           |                     |          |             |                     |          |           |          |
| Standard             | 42                | 61.8 (50.0–72.1)    | 50        | 55.6 (45.6–65.6)    | NS       | 4           | 14.3 (3.6–28.6)     | 0.0001   | 92        |          |
| High                 | 26                | 38.2 (27.9–50.0)    | 40        | 44.4 (34.4–54.4)    | 24       | 85.7 (71.4–96.4) | 66       | 0.0001    | <0.0001  |
| Duration of symptoms before evaluation (weeks) | | | | | | | | | | |
| 0–2                  | 20                | 27.4                | 23        | 24.5                | NS       | 8           | 26.7                | NS       | 43        | NS       |
| 2–4                  | 25                | 34.2                | 29        | 30.9                | NS       | 8           | 26.7                | NS       | 54        | NS       |
| 4+                   | 28                | 38.4                | 42        | 44.7                | 14       | 46.7        | 70                   |          |           |          |
| WBC (cells/L)        |                   |                     |           |                     |          |             |                     |          |           |          |
| 1.5×10⁹ and less     | 1                 | 1.4                 | 4         | 4.1                 | NS       | 14          | 48.3                | NS       | 77        | NS       |
| (1.5–11.5)×10⁹       | 31                | 42.5                | 46        | 47.4                | NS       | 15          | 51.7                | NS       | 88        | NS       |
| 11.5×10⁹ and above   | 41                | 56.2                | 47        | 48.5                | NS       | 7           | 23.3                | NS       | 17        | NS6      |
| Haemoglobin (g/dl)   |                   |                     |           |                     |          |             |                     |          |           |          |
| 11+                  | 6                 | 8.2                 | 11        | 11.3                | NS       | 17          | 56.7                | NS       | 64        | NS5      |
| 11–7                 | 36                | 49.3                | 53        | 54.6                | NS       | 6           | 20                   | NS       |           |          |
| Under 7              | 31                | 42.5                | 33        | 34                  | 2        | 7.1         | 2                   |          | 2         |          |
| Platelets count (cells/L) |               |                     |           |                     |          |             |                     |          |           |          |
| 400 + × 10⁹          | 0                 | 0                   | 2         | 2.1                 | NS       | 4           | 14.3                | NS       | 17        | NS       |
| (150–400) × 10⁹      | 10                | 13.7                | 7         | 7.2                 | NS       | 22          | 78.6                | NS       | 151       | NS       |
| 150 × 10⁹ and less   | 63                | 86.3                | 88        | 90.7                |         |             |                     |          |           |          |
| CXR                  |                   |                     |           |                     |          |             |                     |          |           |          |
| Normal               | 53                | 84.1                | 70        | 81.4                | NS       | 19          | 76                   | NS       | 123       | NS       |
| Abnormal             | 10                | 15.9                | 16        | 18.6                | 6        | 24          | 26                   |          |           |          |
| Mother education level |                 |                     |           |                     |          |             |                     |          |           |          |
| Low                  | 25                | 41.7                | 53        | 67.9                | 0.0018   | 13          | 54.2                | NS       | 78        | NS       |
| Medium               | 29                | 48.3                | 19        | 24.4                | NS       | 7           | 29.2                | NS       | 48        | NS       |
| High                 | 6                 | 10                  | 6         | 7.7                 | 4        | 16.7        | 12                   |          |           |          |
| Father education level |               |                     |           |                     |          |             |                     |          |           |          |
| Low                  | 28                | 47.5                | 48        | 58.5                | NS       | 12          | 48                   | NS       | 45        | NS       |
| Medium               | 24                | 40.7                | 21        | 25.6                | 6        | 24          | 20                   |          |           |          |
| High                 | 7                 | 11.9                | 13        | 15.9                | 7        | 28          | 28                   |          |           |          |
| CD 10                |                   |                     |           |                     |          |             |                     |          |           |          |
| Negative             | 10                | 15.2                | 18        | 21.2                | NS       | 11          | 39.3                | 0.0571   | 123       | 0.0146   |
| 21% and above        | 56                | 84.8                | 67        | 78.8                | 17       | 60.7        |                     |          |           |          |
| FAB classification   |                   |                     |           |                     |          |             |                     |          |           |          |
| L1                   | 39                | 66.1 (54.2–78.0)    | 44        | 59.5 (47.3–70.3)    | NS6      | 10          | 40.0 (20.0–60.0)    | 0.0488e  | 83        | 0.0252e  |
| L2                   | 19                | 32.2 (20.3–44.1)    | 24        | 32.4 (21.6–43.2)    | 14       | 56.0 (36.0–76.0) | 43       |          |          |
| L3                   | 1                 | 1.7 (0.0–5.1)       | 6         | 8.1 (2.7–14.9)      | 1        | 4.0 (0.0–12.0)  | 7        | 0.0009    | 0.0076   |
| Hepato-splenomegaly  |                   |                     |           |                     |          |             |                     |          |           |          |
| Negative             | 16                | 24.6                | 21        | 22.1                | NS       | 14          | 46.7                | 0.009    | 37        | 0.0076   |
| Positive             | 49                | 75.4                | 74        | 77.9                | 16       | 53.3        | 123                  |          |           |          |
| Lymphadenopathy      |                   |                     |           |                     |          |             |                     |          |           |          |
| Negative             | 14                | 19.7                | 13        | 13.3                | NS       | 23          | 76.7                | NS       | 142       | NS       |
| Continued            |                   |                     |           |                     |          |             |                     |          |           |          |
years\textsuperscript{13}, but was close to the age reported in the Tehran study with a mean age of 5.5 years\textsuperscript{14} and a Brazilian study which had the average age of diagnosis of 6.3 ± 0.5 years\textsuperscript{15}. Gender ratio of M/F in our study was (1.56:1) which was slightly higher than the CALLME1 study (1.4:1), the US study (1.35:1), the international study (1.4:1), and the Tehran study (1.32:1), but lower than what was found in the Brazilian study (1.9:1) but there was no significant difference (P > 0.05) when comparing our study with all previous studies.

### Symptoms, FBC and organomegaly.
Most patients presented with systemic symptoms (74.9%) similar to the Tehran study in which the patients had fever (51.2%), organomegaly (31.4%) and pallor (19.2%) and to the Brazilian study which found that hepatomegaly, splenomegaly, fever and lymphadenopathy were the most common clinical features. Most patients (42.6%) in our study required more than 4 weeks to get diagnosed which was similar to the CALLME1 study which found that the mean time before evaluation to be 1.35 months. However, in our study (25.9%) of patients needed less than 2 weeks to get evaluated.

Having systemic symptoms, anaemia which is usually severe, low platelets, lymphadenopathy, and hepato-splenomegaly were the most frequent observations in most of our patients similar to many studies, but with different prevalence such as the CALLME1 study where the prevalence was for fever (75.5%), pallor (79.2%), lymphadenopathy (62.6%) (P = 0.0001 when compared to our study), hepatomegaly (59.5%), and splenomegaly (60.8%), and the Brazilian study where the prevalence was for anaemia (85%) with (35%) having severe anaemia of HB < 7 g/dL (P > 0.05), low platelet counts of less than (100 × 10^9 cells/L) in (65%) of the patients with (10.5%) having platelet counts less than (20 × 10^9 cells/L) (P = 0.0177), lymphadenopathy (43.4%) (P = 0.0003 when comparing these numbers to our study), hepatomegaly (63%), and splenomegaly (57.8%). Our study had significantly higher prevalence of the aforementioned factors when comparing to these studies.

The most frequent haemoglobin level group in our study was (11–7 g/dL) and platelet count group was (50–150 × 10^9 cells/L). These were within ranges of CALLME1 study where mean haemoglobin level was (7.9 g/dL) and platelet count mean was (66.1 × 10^9 cells/L) and the Brazilian study where mean haemoglobin level was (8.24 g/dL). However, high WBC count was only found in half of our sample which is similar to what was found in the Brazilian study where the average WBC counts at diagnosis was (31.8 × 10^9 cells/L).

ALL has many factors for negative prognosis such as high WBC count when presenting, CD10 negativity, lymphadenopathy and having extra-medullary disease\textsuperscript{1}. Most patients in our study had either abnormal platelet counts or low haemoglobin level when diagnosed with only (2.0%) of the patients having normal levels for both which means that they can be used when patients presenting with ALL is speculated at crisis time such as the war in Syria to prioritise patients; Our findings are similar to what was found in Brazil where (4%) of the patients had normal FBC (P > 0.05 when comparing to this study). Positive findings on CXR were found in (18.4%) in our study which was higher than what was found in the Brazilian study (11.8%) (P > 0.05 when comparing to this study). Other prognostic factors include age, gender, and race\textsuperscript{1}. Patients in the older age group (10–14) were found to have a worse prognostic risk (85.7% of them had high risk). However, most studies showed a good prognosis for the age group (1–9)\textsuperscript{1}.

### Other variables.
Overall, parents’ educational level was low in ALL patients as more than the half of fathers and mothers had low educational level. Positive family history in our study was lower than in the Tehran study (1.32:1), but lower than what was found in the Brazilian study (1.9:1) but there was no significant difference (P > 0.05) when comparing our study with all previous studies.

| 4 years and below | Percentage (CI 95%) | 5–9 years | Percentage (CI 95%) | P value\textsuperscript{a} | 10–14 years | Percentage (CI 95%) | P value\textsuperscript{e} | 0–9 years | P value\textsuperscript{b} |
|---------------------------------|--------------------|---------|--------------------|-----------------|-----------|--------------------|-----------------|---------|-----------------|
| Positive                        | 57                 | 80.3    | 85                 | 86.7            |           |                    |                 |         |                 |
| **Family history**              |                    |         |                    |                 |           |                    |                 |         |                 |
| Negative                        | 62                 | 92.5    | (85.1–98.5)        | 84              | 89.4      | (83.0–94.7)        | NS              | 23      | 82.1           | (64.4–92.9) | NS        | 146    | NS               |
| Positive                        | 5                  | 7.5     | (1.5–14.9)         | 10              | 10.6      | (5.3–17.0)         | 5               | 17.9    | (7.1–35.6)     |           |           | 15     |                 |

Table 3. Comparison of Characteristics of ALL children comparing with age groups. ALL: acute lymphoblastic leukaemia; NS: not significant; FAB: French–American–British classification. Different total count for subjects is due to missing data. a P value is between (0–4) and (5–9) age groups. b P value is between (5–9) and (10–14) age groups. c P value is between (0–9) and (10–14) age groups. d When comparing normal haemoglobin with abnormal haemoglobin between age groups of (0–9) and (10–14) years, P = 0.0383. e P value is calculated between L1 and L2 FAB classification.
with a poorer prognosis. FAB classification in our patients showed a higher rates of L2 and L3 ($P = 0.0001$ when comparing our result with other studies) in comparison with the CALLME1 study where FAB classification was L1 = 77.4%, L2 = 20.4% and L3 = 21%, and with a Brazilian study L1 = 83% and L2 = 17%\(^b\), but L1 incidence in our study was close to what was found in Tehran L1 = 57.6% and L2 + L3 = 42.4% ($P > 0.05$). However, another study found that L1 accounted for (85–89%) of the cases, L2 (14.1%) and L3 (0.8%)\(^b\).

### Table 4. Comparing Characteristics of T-ALL and B-ALL in children in Syria.

| Characteristic                        | T-ALL     | Percentage (CI 95%) | B-ALL     | Percentage (CI 95%) | $P$ value |
|---------------------------------------|-----------|---------------------|-----------|---------------------|-----------|
| Family history                        |           |                     |           |                     |           |
| Negative                              | 33        | 84.6 (74.4–94.9)    | 133       | 90.5 (85.7–95.2)    | NS        |
| Positive                              | 6         | 15.4 (5.1–25.6)     | 14        | 9.5 (4.8–14.5)      |           |
| Mother Education level                |           |                     |           |                     |           |
| Low                                   | 23        | 63.9                | 68        | 55.7                | NS        |
| Medium                                | 10        | 27.8                | 41        | 33.6                | NS        |
| High                                  | 3         | 8.3                 | 13        | 10.7                |           |
| Father Education level                |           |                     |           |                     |           |
| Low                                   | 19        | 54.3                | 68        | 53.5                | NS        |
| Medium                                | 10        | 28.6                | 39        | 30.7                | NS        |
| High                                  | 6         | 17.1                | 20        | 15.7                |           |
| Hepato-splenomegaly                   |           |                     |           |                     |           |
| Negative                              | 9         | 23.7                | 39        | 26.4                | NS        |
| Positive                              | 29        | 76.3                | 109       | 73.6                |           |
| Lymphadenopathy                       |           |                     |           |                     |           |
| Negative                              | 3         | 7.9                 | 31        | 19.7                | 0.0841    |
| Positive                              | 35        | 92.1                | 126       | 80.3                |           |
| Duration of symptoms before evaluation (weeks) |           |                     |           |                     |           |
| 0–2                                   | 16        | 43.2                | 34        | 21.8                | 0.0972    |
| 2–4                                   | 11        | 29.7                | 49        | 31.4                | NS\(^a\) |
| 4+                                    | 10        | 27                  | 73        | 46.8                |           |
| WBC (cells/L)                         |           |                     |           |                     |           |
| 1.5 × 10\(^9\) and less              | 1         | 2.6                 | 3         | 1.9                 | NS        |
| (1.5–11.5) × 10\(^9\)                | 7         | 18.4                | 83        | 52.9                | 0.0001\(^a\) |
| 11.5 × 10\(^9\) and above            | 30        | 78.9                | 71        | 45.2                |           |
| Haemoglobin levels when diagnosed (g/dl) |           |                     |           |                     |           |
| 11–16                                 | 12        | 30.8                | 12        | 7.6                 | 0.0012\(^c\) |
| 11–7                                  | 19        | 48.7                | 84        | 53.5                | NS        |
| 7 and less                            | 8         | 20.5                | 61        | 38.9                |           |
| Platelets count (cells/L)             |           |                     |           |                     |           |
| More than 400 × 10\(^9\)             | 2         | 5.4                 | 2         | 1.3                 | NS        |
| (150 to 400) × 10\(^9\)              | 5         | 13.5                | 16        | 10.2                | NS        |
| 150 × 10\(^9\) and less              | 30        | 81.1                | 139       | 88.5                |           |
| CXR                                   |           |                     |           |                     |           |
| Mediastinal enlargement or lymphadenopathies | 18        | 51.4                | 14        | 10.4                | <0.0001   |
| Normal                                | 17        | 48.6                | 121       | 89.6                |           |
| CD 10                                 |           |                     |           |                     |           |
| 21% and more                          | 9         | 25                  | 130       | 91.5                | <0.0001   |
| Negative                              | 27        | 75                  | 12        | 8.5                 |           |
| Prognostic risk                       |           |                     |           |                     |           |
| Standard                              | 1         | 2.8 (0.0–8.3)       | 95        | 63.8 (55.7–71.1)    | <0.0001   |
| High                                  | 35        | 97.2 (91.7–100.0)   | 54        | 36.2 (28.9–44.3)    |           |
| FAB classification                    |           |                     |           |                     |           |
| L1                                    | 14        | 46.7 (26.8–66.7)    | 79        | 63.2 (55.2–72.0)    | 0.0401\(^d\) |
| L2                                    | 16        | 33.3 (33.3–73.2)    | 39        | 31.2 (23.2–39.2)    |           |
| L3                                    | 0         | 0                   | 7         | 5.6 (1.6–9.6)       |           |
T-ALL prevalence in our study was higher than the CALLME1 study where T-ALL = 14.8% (P = 0.079 when comparing these two studies), and the Brazilian study where T-ALL = 10.5% (P = 0.0867 when comparing these two studies) which reflect multiple factors that could be affecting these findings. Higher risk patients were more frequent in Syria (48.4%) than what was found in the CALLME1 study where high risk patients comprised (36.0%) (P = 0.0108) and what was found in Brazil where high risk patients comprised (46%) (P > 0.05).

Therefore, ALL patients in Syria have more frequently poor prognosis which could be due to other factors being involved in the period of the study such as the war. T-ALL is known for its poorer prognosis\(^1\),\(^2\),\(^9\). This all could explain the very high prevalence of high-risk ALL in Syria as these poor prognostic factors had a higher prevalence when comparing our study with other studies. It is crucial to study all prognostic factors to conduct an adequate treatment plan, so that patients are not under- or overtreated\(^2\),\(^3\). All the prognostic factors should be determined prior to treatment as an intense treatment protocol can eliminate the effect of some of the unfavourable factors and decrease relapse as protocols differ among risk groups\(^2\),\(^3\). T-ALL and L3 (Burkett) incidence can

| Characteristic | High risk | Percentage% | Standard risk | Percentage% | P value |
|----------------|-----------|--------------|---------------|--------------|---------|
| Family history |           |              |               |              |         |
| Negative       | 74        | 85.10%       | 83            | 94.30%       | 0.0438  |
| Positive       | 13        | 14.90%       | 5             | 5.70%        |         |
| Mother Education level | |              |               |              |         |
| Low            | 43        | 55.80%       | 42            | 59.10%       | NS      |
| Medium         | 28        | 36.40%       | 20            | 28.20%       | NS      |
| High           | 6         | 7.80%        | 9             | 12.70%       |         |
| Father Education level | |              |               |              |         |
| Low            | 42        | 53.20%       | 40            | 54.80%       | NS      |
| Medium         | 26        | 32.90%       | 19            | 26.00%       | NS      |
| High           | 11        | 13.90%       | 14            | 19.20%       |         |
| CD 10          |           |              |               |              |         |
| 21% and more   | 51        | 63.70%       | 82            | 93.20%       | <0.0001 |
| Negative       | 29        | 36.30%       | 6             | 6.80%        |         |
| FAB classification | |              |               |              |         |
| L1             | 40        | 55.60%       | 51            | 73.90%       | 0.0227  |
| L2             | 32        | 44.40%       | 18            | 26.10%       |         |
| Characteristic | L1        | Percentage%  | L2            | Percentage%  | P value |
| WBC (cells/L)  |           |              |               |              |         |
| 1.5 × 10\(^9\) and less | 2 | 2.10% | 1 | 1.80% | NS |
| (1.5–11.5) × 10\(^9\) | 37 | 39.80% | 21 | 38.20% | NS |
| 11.5 × 10\(^9\) and above | 54 | 58.10% | 33 | 60.00% |         |
| Hemoglobin levels when diagnosed (g/dl) | | | | | |
| 11–16          | 10        | 10.80%       | 9             | 16.10%       | NS      |
| 11–7           | 43        | 46.20%       | 31            | 55.30%       | NS      |
| 7 and less     | 40        | 43.00%       | 16            | 28.60%       |         |
| Platelets count (cells/L) | | | | | |
| More than 400 × 10\(^9\) | 1 | 1.10% | 2 | 3.70% | NS |
| (150 to 400) × 10\(^9\) | 8 | 8.60% | 5 | 9.30% | NS |
| 150 × 10\(^9\) and less | 84 | 90.30% | 47 | 87.00% |         |
| Mother Education level | | | | | |
| Low            | 40        | 52.60%       | 26            | 56.50%       | NS      |
| Medium         | 30        | 39.50%       | 15            | 32.60%       | NS      |
| High           | 6         | 7.90%        | 5             | 10.90%       |         |
| Father Education level | | | | | |
| Low            | 39        | 51.30%       | 27            | 56.30%       | NS      |
| Medium         | 28        | 36.80%       | 10            | 20.80%       | 0.0307  |
| High           | 9         | 11.90%       | 11            | 22.90%       |         |
| CD 10          |           |              |               |              |         |
| 21% and more   | 70        | 84.30%       | 13            | 66.00%       | 0.0143  |
| Negative       | 13        | 15.70%       | 17            | 34.00%       |         |
| Family history |           |              |               |              |         |
| Negative       | 76        | 87.40%       | 49            | 90.70%       | NS      |
| Positive       | 11        | 12.60%       | 5             | 9.30%        |         |

Table 5. Characteristics of High and standard risk categories patient and L1 and L2 in ALL in Syrian children.
be related to virus exposure. Using FAB system is convenient in developing countries as it is easy to conduct in regular labs and does not require much resources, and it remains effective despite cytogenetic tests as it can add diagnostic accuracy in some cases. L2 was found to have a higher relapse and mortality rate which is similar to our finding of L2 being correlated with higher risk. A weak or negative CD 10 expression is correlated with ZNF384, and KMT2A in blasts which often express high levels of FLT3 rearrangement, t(4;11)(q21;q23) in particular which accompanies a poorer outcome. However, leukemic cells which demonstrate a germline configuration are correlated with positive CD10 expression in precursor-B ALL and have a better outcome. Nevertheless, CD10 prognostic significance independently from KMT2A rearrangement is not clear.

The much higher L2 and high risk prevalence comparing to other studies may reflect an underlying cause, such as from war or environment as many practices in Syria may contain leukemogenesis such as unprotected pesticide usage, mate drinking and hookah smoking, mainly in low educational level population. It is suggested that the protocols that were developed in the advanced centres might increase the rate of death as these protocols are not adjusted to the local conditions of low- and mid-income countries, and therefore more studies are required in developing countries such as Syria for adjustment of protocols that change ALL variables. Although the cost of treatment in Syria is covered, there is data suggesting that families within low SES are correlated with worse prognosis in children as determination of indirect costs is difficult which can explain having lower educational parents was correlated with poorer prognosis in our study.

In conclusion, in this study we have discussed multiple features and risk factors of ALL and compared characteristics of ALL children in Syria in the Middle East with multiple studies from the Middle East and multiple regions across the globe. The data covered most aspects of ALL and its prevalence in addition to factors which are correlated with worse prognosis such as L2 FAB classification, negative CD10, male gender, T-ALL, and low parental educational level. The results suggest high T-ALL, L2, and high risk prevalence which could reflect underlying factors and poor survival rates, especially that treatment protocols may have a higher mortality in developing countries when not adjusted to local variables. The results also suggests that having normal haemoglobin and platelet count can be used for quick screening in crisis time like in Syria for prioritising patients.

This is the first detailed study to demonstrate the epidemiology of ALL in Syria and its relation to other factors. It also suggests common risk factors that might worsen the prognosis while comparing with multiple studies from different countries. This study was also conducted at war-torn Syria which also could be the factor for this phenomenon. It also enforces the significance of FAB classification and its relation to higher risks of ALL. The different findings also enforce the importance of local studies in developing countries as they might have considerably different factors than the developed countries.

Data availability
Data will be available on request from the corresponding author.

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**Author contributions**
A.K. Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Supervision; Validation; original draft; Writing - review & editing. M.A. Data curation; Formal analysis; Software; original draft; Writing - review & editing. A.G. Software; Methodology; Conceptualization; Validation; Writing editing; investigation. B.K. Software; Methodology; Conceptualization; investigation. B.M. Software; Project administration; Conceptualization; Writing editing; investigation. B.Z. Software; Project administration; investigation. O.H. Project administration; Resources; Validation.

**Competing interests**
The authors declare no competing interests.

**Additional information**

**Correspondence** and requests for materials should be addressed to A.K.

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