Retrospective analysis of patients with severe combined immune deficiency: A 20-year Single center experience

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Abstract

Severe combined immune deficiency (SCID) is a primary immunodeficiency characterized by impairment in the development and function of lymphocytes and could be a fatal disease if not treated with hematopoietic stem cell transplant in the first 2 years of life. There are differences in SCID diagnostic criteria between different primary immunodeficiency societies. This study aimed to retrospectively evaluate clinical and laboratory findings of the patients followed up with the diagnosis of 59 SCID at our clinic over the past 20 years to develop an algorithm to help diagnosis of SCID for the countries which high ratio of consanguineous marriage and haven't started TREC assay in their newborn screening program. The mean age at diagnosis was 5.80 ± 4.90 months, delay in diagnosis was 3.29 ± 3.99 months. The most common complaint and physical examination findings were cough and eczematous rash (63%)/organomegaly (61%), respectively. ADA, Artemis, RAG1/2 deficiency were the most common genetic defects. Lymphopenia (87.5%) was the most frequent abnormal laboratory finding and below 3000/mm³ in 95% of the patients. CD3+ T cell count was 300/mm3and below in 83% of the patients. Although the diagnostic criterion for SCID is specified as a CD3+ T lymphocyte count below 300/mm3 by IUIS and lower total lymphocyte counts (under 3000/mm3) together with determination of genetic defects leading to SCID by ESID, profound lymphopenia might not occur in some genetic defects. Combination of ESID and IUIS criteria for diagnosis of SCID would be safety for the countries with high ratio of consanguineous marriage. Physicians should consider diagnosis of SCID in the patient under 2 years with severe infections together with lymphocyte count under of 3000/mm3.

Introduction

Severe combined immune deficiency (SCID) is the most serious form of T-cell deficiencies which is characterized by severe impairment in the development or function of lymphocytes due to various factors (1). Unless these patients receive hematopoietic stem cell transplant (HSCT) within the first two years of life, the disease results with death. Other types of T-cell deficiencies result with a partial T-cell deficiency due to mutation in T-cell signaling pathways or rearrangement of T-cell receptor genes or thymic dysfunction and called as combined immune deficiencies (CID). Average age at onset of symptoms is higher, and lymphopenia was milder in such patients. Although milder clinical and laboratory findings in CIDs, clinical symptoms and laboratory abnormalities may start in any age including newborn period. Thus, the patients may present with severe clinical pictures and recurrent infections within the first two years of life. This causes to variable presentation age of CID with different clinical and laboratory results depending on the underlying genetic defect, modified genes and epigenetic factors (2).

European Society for Immunodeficiencies (ESID) and International Union of Immunological Societies (IUIS) provide different definitions and classifications for severe combined immune deficiency and T-cell deficiencies. IUIS defines SCID as CD3+ T cell count as 300/mm^3 and below, while classifying other T-cell deficiencies as combined immune deficiencies (CIDs). ESID, on the other hand, specified the following criteria for the diagnosis of SCID: a) presence of maternal T lymphocytes b) an absolute lymphocyte count below 3000/mm^3 along with CD3+T cell count lower than 20% at under 2 years of age and c) presence of accompanying genetic mutations that cause to SCID. If the genetic mutation is unknown, ESID accepts the patients as probable SCID and recommends that they should be treated accordingly until a definitive diagnosis has been established, thus avoiding any scenarios where such cases go unnoticed. However, there is no diagnostic criteria for other T-cell deficiencies in ESID, which may lead to delay diagnosis and treatment of such patients (3-20).

In last 2 years, 55 new and totally 485 genetic defects leading to primary immunodeficiency have been described. (4, 5). Further, more than 19 genetic defects have been reported to cause SCID up to date (3, 5).The inheritance pattern in SCID can be autosomal recessive (AR), autosomal dominant (AD), or X-linked

inheritance (6, 7). Such mutations impair lymphocyte development and function by inhibiting the differentiation and proliferation of T lymphocytes, B lymphocytes, and natural killer (NK) cells. SCIDs are classified by the IUIS according to the involvement of B and NK cells together with T cells (8, 9). Given that genetic testing requires a considerable amount of time to yield reliable results, this type of classification is important because of offers some insight into the underlying genetic defect (9).

The incidence of genetic defects cause to SCID varies from one country to other. In societies where cousin marriage is quite common, such as our country, we observe a higher number of SCID with AR inheritance (7, 10, 11) . Three recent studies from our country have reported that the most common SCID phenotypes include T- B- and T-B+, among which the most frequent genetic defects with AR inheritance leading to SCID are RAG1/2, JAK3 and ADA enzyme deficiency in our country (12-14). These studies also noted that the median age at admission to the hospital ranged from 3.5 to 5 months, with the most common complaints being oral moniliasis and lung infection, while the most frequently detected laboratory abnormalities were lymphopenia (12-14). In our study, we retrospectively evaluated the clinical and laboratory results of patients diagnosed with SCID at our clinic over the past 20 years and developed an algorithm to help diagnosis of SCID for the countries which high ratio of consanguineous marriage and haven't started TREC assay in their newborn screening program.

Material And Method

We retrospectively reviewed files of SCID patients aged under 2 presenting to Necmettin Erbakan University Meram Medical Faculty, Department of Pediatric Allergy and Immunology between January 2001 and December 2021 by written approval from the ethics committee. Diagnostic criteria for SCID were adopted from IUIS and ESID criterion and compared with the ESID's and IUIS criteria. Briefly, if the patients admitted to hospital with severe life treating infections under 2 years of age and had absolute lymphocyte counts under 3000/mm^3, accepted as SCID. Further if the patients died with severe life treating infection under 2 years of age they also accepted as SCID despite absolute lymphocyte count upper than 3000/mm^3 if they had not checked for presence of maternal T cells. On the other hand, if the patients had molecularly defect or mutation in the genes which classified as CID by IUIS, they accepted as CID even if they admitted with lymphopenia at under 2 years of age (12-14).

A total of 6 patients from the initial 73 were excluded from the study - four were excluded as no data could be found on their pre-HSCT status and two due to clinical and laboratory findings inconsistent with SCID. Eight patients had mutation in the genes which described as CID by IUIS. The remaining 59 patients were accepted as SCID. Both 59 SCID patients and 8 CID patients included in the study to compare their clinical and immunological feature because CID patients were also admitted with severe infections at 2 years of age (Figure 1).

Statistical Analysis

All research data were analyzed on the SPSS 22.0 software package. The study variables were presented as frequency "n", percent "%", arithmetic mean, standard deviation "SD", and median (min-max). Conformity of continuous data to normal distribution was evaluated with q-q plot, skewness and kurtosis, and Shapiro-Wilk test. The research variables failed to meet the normality assumption. The Mann-Whitney U test was used in the analysis of independent pairwise groups. Kruskal Wallis test in more than two independent analyses. The posthoc U test and Bonferroni correction were performed for pairwise comparisons between groups whose Kruskal Wallis test was significant. A p value less than 0.05 ($p<0.05$) was considered statistically significant.

Results

The demographic data of the patients were summarized in Table 1. About 52.5% of the SCID patients were male (n=31) and 47.4% were female (n=28). In CID cases, on the other hand, 62.5% were male (n=5) and 37.5% were female (n=3). Of 59 patients with SCID, 55.9% (n=33) were T-B- and 27.1% (n=16) were T-B+ phenotype. The mean age at diagnosis was 5.99±4.80 months, the median was 5.0 (0 - 24) months, and the mean delay in diagnosis was 3.3 months. The mean age at diagnosis in SCID patients was 5.80 ± 4.90 (1-24) months, delay in diagnosis was 3.29 ± 3.99 months, with a median of 4.5 (0 - 23) months. Six patients were diagnosed as SCID above 1 year of age. Eight patients were diagnosed as CID according to their genetic diagnosis or molecularly defects which detected by flowcytometry including MHC Class II and ZAP70 deficiency. In patients with CIDs, the mean age at diagnosis was 7.38 ± 3.93 (2-12) months, delay in diagnosis was 3.93 ± 3.33, and the median was 6.50 (0-12) months. When we divided the diagnosed patients with SCID 10 years period to understand how awareness changed in last 10 years, no significant difference was observed in terms of delay in diagnosis over the 10-year period ($p<0.554$). Genetic mutation or molecular defect was detected in 27 (45.7%) patients with SCID and in 7 (87.5%) with CIDs. These genetic or molecular defects are presented in Table 2.

The most frequent complaints for hospital admission in the patients with SCID and CID were cough (50% vs 62.5%), fever (32.8% vs 25%), diarrhea-vomiting (32.8% vs 25%), oral moniliasis (19% vs 25%) and eczematous rash (17.2% vs 25%). More than one pathological finding was detected in the physical examination of the patients at admission. Most frequent detected pathological examination findings in the SCID were organomegaly (61%), eczematous rash (63%), oral moniliasis (58.9%) and tonsillar tissue hypoplasia (66.7%). On the other hand, oral moniliasis (87.5%), organomegaly (37.5%) and eczematous rash (25%) were most frequent detected abnormal physical exam findings for CID patients. When patients were evaluated in terms of infections, we found that SCID patients most commonly suffered sepsis (30.5%), pneumonia (27.1%) and CMV infection (22%), whereas those with CIDs had sepsis (62.5%), pneumonia (12.5%) and CMV infection (37.5%). The vaccination data of the patients revealed that 38 patients (70.4%) had received BCG vaccine. Apart from tuberculous lymphadenitis in a patient during admission, another case of tuberculous lymphadenitis was detected during follow-up.

In complete blood counts, lymphocyte values below 3000/mm^3 were accepted as the threshold for lymphopenia under 2 years of age (ESID criteria for SCID). Lymphopenia was present in 94.9% (n=56) of the patients with SCID, with a median of 876/mm^3 (100-5860), and it was the most common abnormal finding as expected. Pancytopenia was observed in 14.9% (n=10) of the patients with SCID. On the other hand, lymphopenia was observed in 62.5% (n=5) of patients with CIDs, while pancytopenia was present in 12.5% (n=1) of them. In lymphocyte subset analysis, $CD3^+$ T cells for SCID patients was 139.50/mm^3 (0-5612). When peripheric lymphocyte subset values were compared in patients with SCID and CIDs (Table 3), absolute lymphocyte counts, total T ($CD3^+T$) and helper T ($CD3^+4^+$) cell ratio values were higher in the patients with CIDs than in those with SCID, as expected. Recent thymic emigrant cell ratio was measured in 11 patients, nine of whom were diagnosed with SCID. While the percentage of recent thymic emigrants (RTEs) was lower in all SCID patients, this rate was low in only one of the two CID patients in whom RTE value was evaluated (FCHO1 deficiency).

Trimethoprim-sulfamethoxazole, intravenous immunoglobulin (IVIG) and fluconazole prophylaxis were started in 89.6% of the patients with SCID and 100% of the patients with CID. Acyclovir prophylaxis was started in 18.6% of patients with SCID and 37.5% of patients with CID. Because of CMV DNA test positivity, 23.7% of patients with SCID and 25% of patients with CID were treated with ganciclovir. The mean duration of IVIG replacement therapy in the all patients was 38.48±44.97, and the median was 12.0 (1-156) months. In 35 patients who received HSCT, the mean time to receive IVIG after transplantation was 28.33±43.86 months, with a median of 0.0 (1-156) months.

Of our 59 patients diagnosed as SCID, 49 (83%) patients met definitive SCID criteria according to IUIS and 18 (30.5%) according to ESID, whereas 38 (64%) met diagnostic criteria for probable SCID. However, all but one patient presented with severe infection, and 47 died with severe infections under the age of two. Absolute lymphocyte count (ALC) was below 3000/mm^3 in all 67 patients except for 6 patients (in the 3 patients from SCID and 3 patients in CID group). The presence of maternal engraftment had not evaluated in any of the six patients. 18 of 27 SCID patients with known genetic diagnosis met the definitive SCID diagnostic criteria according to ESID. The other 9 patients with known genetic mutations, either their CD3+T cell ratio or absolute lymphocyte count (ALC) was above the specified criteria. Five of the 9 patients had high ratio of CD45RA+T cells (probable maternal engraftment). Of the remaining 32 patients with unknown genetic defect, 20 met probable SCID criteria according to ESID, but the other 12 did not fully meet the SCID diagnostic criteria because of high ratio of CD3+T cell or absolute lymphocyte count.

Five of 8 patients diagnosed with CIDs according to IUIS criteria had a lymphocyte count below 3000/mm^3, and two patients had high ratio of CD45RO+ T cell (probable maternal engraftment). Although these patients met probable SCID diagnostic criteria according to ESID, one of them was diagnosed with ZAP70 deficiency due to very low CD8+T cell ratio. In the other patient, the genetic mutation was unknown. Table 4 presents findings on several variables including age at admission, delay in diagnosis, lymphocyte count at admission, and abnormal laboratory findings according to genetic defects. When we compared cases by presence of lymphopenia, we found that lymphopenia was more severe in ADA deficiency, ligase 4 deficiency and Artemis defect. Statistically, the median value of ALC in patients with RAG1/2 mutation was found to be significantly higher than those with Artemis gene defect (p=0.021).

HSCT was performed in 35 patients under the age of one, including 30 (50.8%) patients with SCID and 5 (62.5%) patients with CIDs. The vital information of 6 patients out of 32 patients who did not have transplants could not be obtained. All of the remaining 26 patients died as a result of severe infections. Mean survival time was 59.47±46.53 months, with a median of 60.00 (0-156) months in patients with SCID, and 20.33±24.58 months in the patients with CIDs, with a median of 12.00 (1-48). Of the 35 patients receiving HSCT, 15 patients died after transplantation (13 SCID and 2 CID). Unfortunately, no data was found to specify how long two of these deceased patients survived after the transplantation. In the other 13 patients, the mean survival time for those with SCID was 15.82±36.16 months, with a median of 2.00 (0-168) months, and for those with CIDs 5.75±5.18 months, with a median of 5.00 (1.0- 12.0) months. Causes of death in these patients were reported as infection. The mean survival time of all surviving patients was 53.60±45.75 months, with a median of 48 (0-156) months.

Discussion

SCID is defined as a type of inborn error of immunity, which could be fatal if not diagnosed and treated in the first 2 years of life. It is the most severe disease among all IEIs, and HSCT is the only curative treatment option in most countries. When a patient receives HSCT within the first 3 months, the chance of success rises to 95% (1, 13). However, there are differences in SCID diagnostic criteria between different primary immunodeficiency societies (3, 20). In our 20-year follow-up, 49 (83%) of our 59 patients diagnosed with SCID according to the IUIS criteria and 18 (30.5%) according to the ESID criteria met the diagnostic criteria for definitive SCID and 20 (34%) for probable SCID. However, all of the patients, except one, presented with severe infection, and all those not receiving a transplant died before age 2 with severe infection, which means these cases were clinically consistent with SCID. Therefore, we believe that patients aged 2 or below presenting with severe clinical infection should be approached as SCID cases until the diagnosis of SCID is excluded. In our cohort, lymphocyte count was below 3000/mm^3 in 56 (95%) of the SCID patients and in 5 (63%) of 8 CID patients according to the ESID criteria. Thus, it would be safety to accept lower threshold for lymphopenia as 3000/mm^3 for children in the first two years of life in the countries with high ratio of consanguineous marriage, such as our country. If patients present with a severe infection under two years of age, even if the lymphocyte

count is above 3000/mm^3, they should be approached the cases as SCID until a definitive diagnosis. Thus, we suggest to use our algorithm to approach to the children under 2 years of age who presents with severe infections (Fig. 2).

In our study, the mean age at diagnosis was 5.99 ± 4.80 months, the median was 5.0 (0–24) months, and the mean delay in diagnosis was 3.3 months. In the study of Aluri et al. from India, the mean time to onset of symptoms was 2 months, and the mean age of diagnosis was 5 months (15). In another study conducted in China, the mean age at diagnosis was 7.10 ± 7.96 months and the mean age of onset of symptoms was 3.56 ± 3.91 months (16). Including of T-cell Receptor Excision Circle (TREC) test in newborn screening program in the USA, the patients were diagnosed at much earlier age like a month (earliest: 0 - latest: 304 days) (17). When we evaluated our cohort 10-year period, there was increase in patients' numbers, however no significant difference was observed in the age at diagnosis. This suggests that the awareness of SCID is still not at desired levels in our country and the TREC test should be included among the newborn screening tests as soon as possible.

Consanguineous marriage ratio is high in our country and it causes increased frequency of OR-hereditary diseases. While the incidence of consanguineous marriage was 50% in the study of Metin et al, it was reported to be 76% by Ikinciogullari et al (13, 18). In our study, however, this rate was calculated as 90.9%. The most common SCID phenotype was T-B- (41–63%) in the studies from our country (12, 13, 18). Similar to these studies, we also found that the most common SCID phenotype was T-B- (55.9%). In the study by Fırtına et al., the most frequent detected mutations were RAG1/2 (29.1%), ADA enzyme deficiency (12.5%) and IL2RG mutation (12.5%) in patients with T-B- SCID, while JAK3 mutation (16.6%) in those with T-B + SCID(12). Metin et al., reported, the most frequent mutations in their series including 34 patients, were ADA deficiency (17.6%), RAG1/2 mutation (14.7%) and Artemis gene defect (14.7%) (18). Likewise, in the study of İkincioguları et al., which included a larger cohort, RAG1/2(15.4%) and Artemis mutation (5.6%) were found to be the most common among T-B- SCID patients, while JAK3 mutation (6.8%) was the most common in T-B + SCID cases (13). In our study, genetic mutations were detected in 27 patients, and the most common genetic defects were ADA enzyme deficiency, RAG1/2 and Artemis deficiency in T-B-phenotype, and JAK3 deficiency was found most frequently in T-B + phenotype.

Recurrent or life-threatening infections is the most common reason for hospital admission in SCID cases. Infections due to both bacterial and viral agents and even opportunistic agents can be observed in these patients. Our patients were also admitted with recurrent infections including complaints of cough (29.05%), diarrhea (18.8%) and fever (18.8%). Patients with SCID may also present to hospitals with signs and symptoms other than infection. In a study conducted in Brazil, organomegaly was found in 34.4% of the patients, and growth retardation was found in 35.9% (19).In the study of Yao et al., 50% organomegaly and 38.64% growth retardation were found on physical examination at admission (16). Consistent with such studies, organomegaly, eczematous rash, oral moniliasis and tonsillar tissue hypoplasia were the most common findings at physical examination in our study. Growth retardation was other detected abnormal physical examination findings in the majority of our patients. For this reason, we think that SCID should be kept in mind in the patients younger than 2 years old with severe infection and growth retardation. In addition, when investigating the cause of organomegaly and eczematous rash in patients under 2 years of age, especially if lymphopenia is accompanied, SCID should definitely be taken into account.

The most common abnormal laboratory finding in SCID is lymphopenia, and some immunodeficiency foundation take into account the absolute lymphocyte count while others look at the absolute CD3 + T cell ratio as a diagnostic criterion for SCID. However, flow cytometric analysis may not be performed in every hospital, which shows to need multicenter studies to develop an algorithm including clinical and simple laboratory test to early diagnosis of these patients. In our study, lymphocyte count was found to be below 3000/mm³ in all, but three of 59 patients diagnosed with SCID according to ESID criteria. The mean lymphocyte count in all patients was 1489/mm^3 (100–9200/mm^3). While the

mean lymphocyte count of the patients who were admitted under the age of one (n = 58) was 1505/mm^3 (100–9200/mm^3), it was 1378/mm^3 (200–3400/mm^3) in patients admitted between the ages of 1–2 (n = 9). For this reason, we believe that in countries with high ratio of consanguineous marriage, where increased frequency of AR inherited IEIs are common, we can minimize the number of patients going unnoticed by accepting the lymphocyte lower limit of 3000/mm^3 until the age of 2.

Currently, HSCT stands out as the only curative therapy in most of SCID, and it should perform the earlier stage to achieve the higher the chance of success. Our cohort showed that out of 32 patients who could not undergo HSCT, all 26 patients with available data died, and 20 of 35 (60.6%) patients receiving transplantation survived. The mean survival time after HSCT was 38.46 ± 52.20 months, with a median of 12.00 (0-168) months. Bayram et al. reported that HSCT was performed in 61 of 72 their patients and that only 12 of them died, with an overall survival rate of 80.3% (14). In a cohort study conducted by İkincioguları et al, the overall survival rate was 65.7%, similar to our findings, and this rate was found to be 54% for the first 10 years and 69% for the second 10 years (13).

In conclusion, SCID is a pediatric emergency and fatal unless the patients receive the curative treatment of HSCT within the first 2 years of life. Pleasing outcome could be obtained with early diagnosis and treatment. In countries with high ratio of consanguineous marriage, the TREC test should be included in newborn screening as soon as possible for early diagnosis and treatment of SCID. However, physicians should consider SCID in their diagnosis of young patients presenting with severe infection, oral moniliasis, eczematous rash and organomegaly, particularly those aged under 2 with a lymphocyte count below 3000/mm^3, which will prevent many such cases go unnoticed and save lives.

Declarations

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Declarations

There is no conflict of interest of any authors.

Ethical Approval:

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of University Necmettin Erbakan (Date:18.12.2020/No: 2020/2969)

Consent to Participate:

informed consent was obtained from the parents.

Consent to Publish:

The authors affirm that parents of participants provided informed consent for publication.

Author Contribution:

Sevgi Keles supervised the study and, evaluated clinical and immunological results of the patients.

Sevim Busra Korkmaz and Sevgi Keles wrote the paper.

Sevgi Keles, Ismail Reisli, Selma Erol Aytekin, Sukru Guner and Huseyin Tokgoz contributed to the evaluation of the patients

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Tables

Table 1

Demographic and clinical characteristics of the patients

Demographic and clinical data	SCID	CID
	n (%)	n (%)
Gender		
Male	31 (52.5)	5 (62.5)
Female	28 (47.5)	3 (37.5)
The mean age at diagnosis	5.80 ± 4.90	7.38 ± 3.93
Delay in diagnosis	3.29 ± 3.99	3.93 ± 3.33
HSCT status		
Yes	30 (50.8)	5 (62.5)
No	29 (49.2)	3 (37.5)
Last condition		
Survided	20 (43.4)	3 (37.5)
Deceased	26 (56.5)	5 (62.5)
Consanguineous marriage		
Yes	53 (91.3)	7 (87.5)
No	5 (8.6)	1 (12.5)
Family history of IEI		
Yes	14 (26.4)	3 (42.8)
No	16 (30.1)	2 (28.5)
Unkown	22 (41.5)	2 (28.5)
Total	59 (76.1)	8 (11.9)

Table 2

Genetic diagnosis of the patients

Detected genetic mutations	Immune deficiency type	Inheritance type	n (%)
ADA Deficiency	SCID	AR	6 (10)
Artemis Defect	SCID	AR	5 (8.5)
RAG 1/2 Mutation	SCID	AR	5 (8.5)
IL-2 Res Defect	SCID	X-L	4 (6.7)
JAK3 Deletion	SCID	AR	3 (5.1)
Ligase 4 Deficiency	SCID	AR	3 (5.1)
PGM-3 Mutation	SCID	AR	1 (1.7)
MHC Class 2 Deficiency	CIDs	AR	4 (50)
FCHO1 Defect	CIDs	AR	2 (25)
ZAP 70 Deficiency	CIDs	AR	1 (12.5)

IL2R: Interleukin 2 receptor, ADA: Adenosine deaminase, RAG: recombination activating genes, JAK3: Janus Kinase 3, MHC: Major histocompatibility complex, PGM 3: phosphoglucomutase 3, FCHO1: F-BAR domain only protein 1, ZAP70: Zeta-chain-associated protein kinase 70, SCID: severe combined immunodeficiency, CIDs: combined immune deficiencies, AR: Autosomal recessive inheritance, X-L: X-linked inheritance

Table 3

Laboratory findings according to genetic defects

		n	Median	Min - Max	p
ALC (cell/mm^3)	SCID	56	876.0	100 - 5860	0.025
	CID	8	2115.0	300 - 9200	
$CD3^+T$ (%)	SCID	58	11.00	0 - 92	<0.001
	CID	8	60.50	24 - 81	
$CD3^+4^+T$ (%)	SCID	58	5.00	0 - 93	0.004
	CID	8	16.00	9 - 79	
$CD3^+8^+T$ (%)	SCID	58	10.45	0 - 78	0.090
	CID	8	28.50	2 -70	
$CD19^+B$ (%)	SCID	57	3.00	0 - 95	0.210
	CID	8	11.80	0 - 57	
CD16-56^+ NK (%)	SCID	57	28.00	0 - 95	0.053
	CID	8	7.00	0 - 14	
$CD4^+CD45RA^+CD31^+T$ (%)	SCID	9	6.40	0 - 22	0.436
	CID	2	32.15	5.9 - 58.4	

Table 4

Comparison of absolute lymphocyte and lymphocyte subsets according to SCID and CID

Genetic defects	ADA*	RAG1/RAG2*	DCLRE1C*	IL2RG*	Ligase 4*	JAK3*	FCHO1*	MHCclass 2*	p
Age at admission (months)	2.5 (1-4)	6.0 (3-33)	5.0 (3-24)	3.5 (3-5)	7.0 (2-11)	2.0 (2 – 8)	31.0 (11 – 51)	6.0 (3-12)	0.09
Delay in diagnosis	1.5 (0-2.5)	3.0 (0-6.0)	3.0 (2-4.5)	1.5 (1-4)	1.0 (0.5-8)	2.8 (1.6-4.0)	8	6.0 (1-7)	0.489
ALS (/mm^3) (months)	208.0 (100-1600)	1700 (1280-1870)	400 (100-930)	1790 (1070 – 5860)	200 (193 – 800)	1115 (400 – 2340)	1300.0 (1100– 1500)	1100 (300-3400)	0.021
$CD3^+$ T cells (%)	0.0 (0 - 830)	210 (0 – 612)	0.0 (0 – 224)	0.0 (0-791.8)	100.0 (81 – 240)	93.6 (0 – 324)	763.5 (627 – 900)	264 (192– 2754)	0.11

IL2RG: interleukin 2 receptor gene defect, ADA: Adenosine deaminase, JAK 3: Janus kinase 3, RAG: recombination activating genes, MHC: Major histocompatibility complex, FCHO1: F-BAR domain only protein 1, CD: Cluster of differentiation, * Median (Min-Max)

Figures

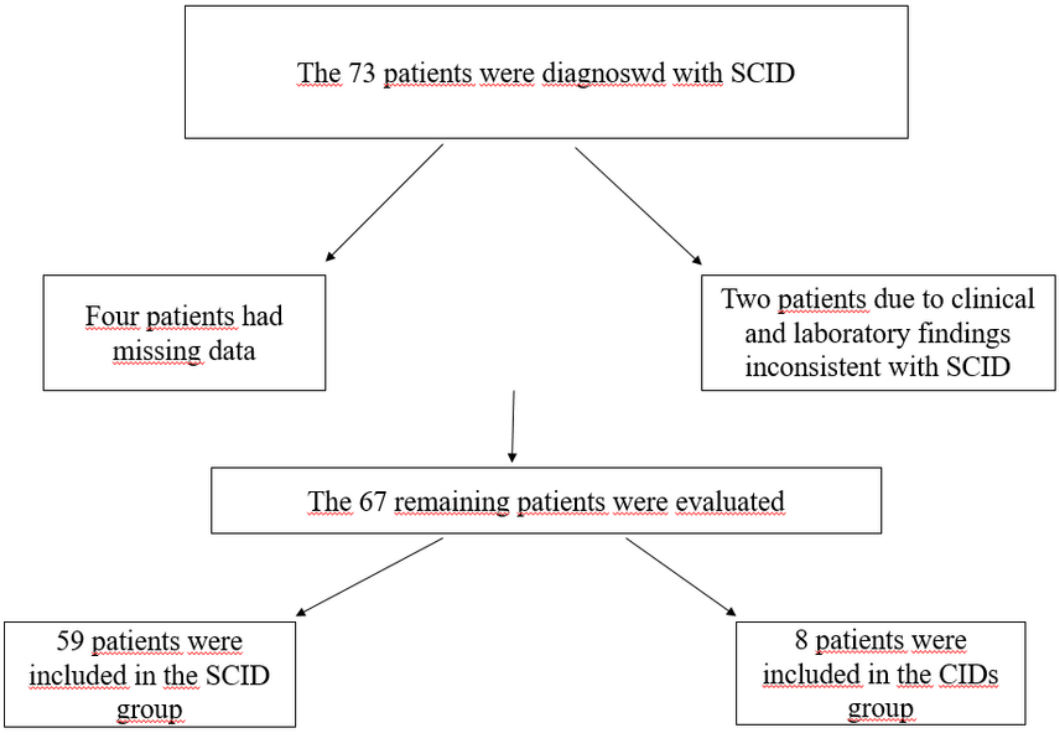

Figure 1

Patient selection flowchart

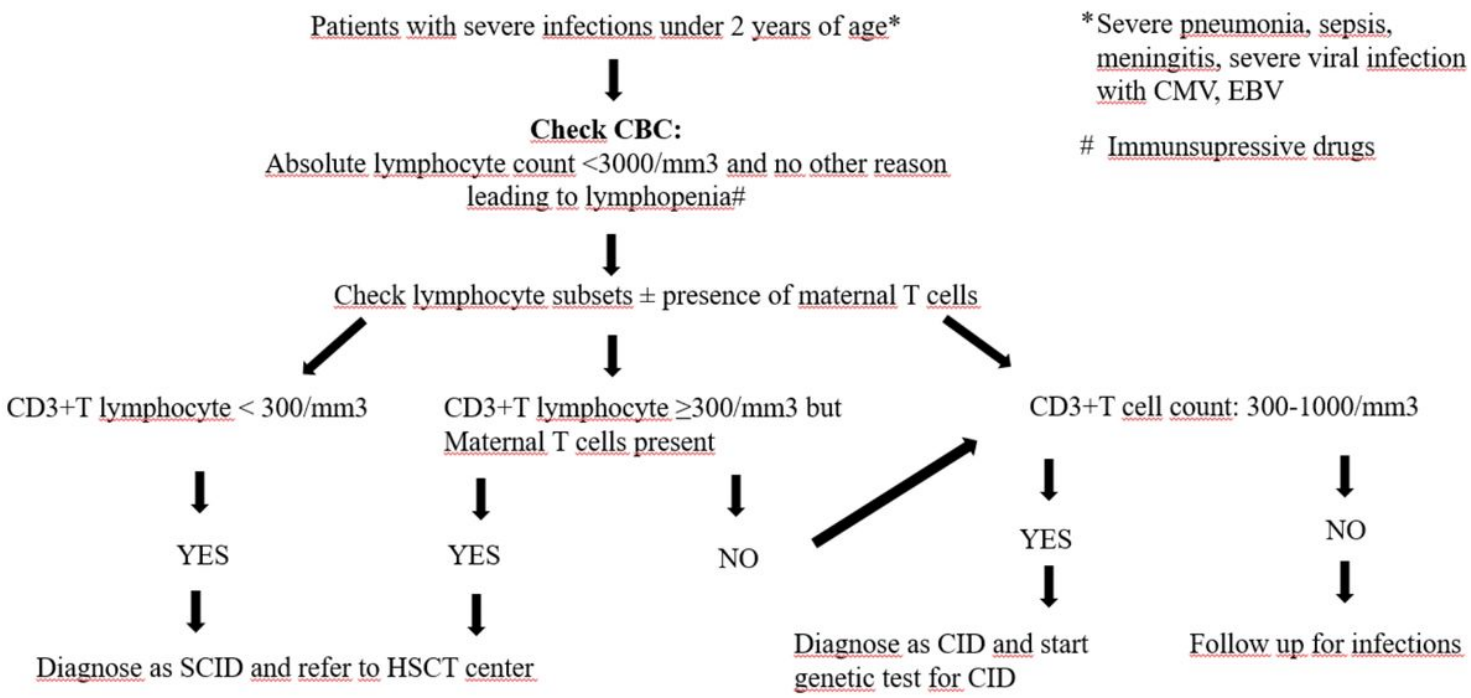

Figure 2

Approach to children under 2 years of age presenting with severe infection