Demographic, Clinical, and Immunological Features in Combined Immunodeficiency Patients with and Without Pulmonary Complications: A Retrospective Multicenter Study from Iran

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Abstract

Purpose:

Combined immunodeficiency (CID) is characterized by profound defects in the development and function of both B and T cells. We aimed to investigate clinical and immunological phenotype in CID patients with and without pulmonary complications.

Methods:

This retrospective study was performed on patients with established diagnosis of CID registered between 2009 and 2020. Patients were divided into two groups based on the development of pulmonary complications, and their demographic, clinical, and laboratory characteristics were compared. All data were analyzed by SPSS software, and a P-value <0.05 was considered as a significant difference.

Results:

146 patients [56.8% male and 43.2% females] were enrolled in the study and divided into two groups of patients with (n=88) and without (n=58) pulmonary complications. In patients with pulmonary complications, oral candidiasis, failure to thrive, and otitis media, while in the other group, anemia, autoimmunity, rheumatologic disorders, and skin lesions had higher frequency, although not significant. Thoracic high resolution computed tomographies (HRCTs), available in 54.5% of patients with pulmonary complications, were compatible with pneumonia (39.8%), bronchiectasis (12.5%), pulmonary nodules (3.4%), atelectasis (1.1%), interstitial lung disease (1.1%), and pneumothorax (1.1%). Patients with pulmonary complications had lower number of T CD4+ but higher levels of CD8+ cells compared to patients without pulmonary complications ($p=0.012$ and $p=0.005$, respectively). The mortality rate was higher in patients with pulmonary complications compared to the other group (11.4% vs. 6.9%, $p=0.597$).

Conclusion:

Respiratory disorders in CID are common and require early periodic monitoring by respiratory tests and HRCT to avoid irreversible injuries.

I. Introduction

Combined immunodeficiency (CID) is a heterogeneous group of inborn errors of immunity (IEIs), characterized by profound defects in the development and function of both B and T cells. The CID incidence rate is reported to be 1:5000 to 1:100.000 amongst live births [1–3], which may be underestimated due to the high mortality rate before establishing an accurate diagnosis. Moreover, due to the autosomal recessive pattern in most of the CIDs and higher consanguinity rate among Middle East countries, including Iran, a higher incidence rate is expected in these areas compared to western countries [4, 5].
Patients with the severe form of CID, known as severe combined immunodeficiency (SCID), experience a broad spectrum of clinical manifestations, including diarrhea, failure to thrive (FTT), severe infections with opportunistic infections, skin lesions, and so on [6]. Most CID patients are also lymphopenic and/or neutropenic and B and T cell defect predispose affected patients to opportunistic infections, particularly in the respiratory tract, resulting in high morbidity and mortality [7, 8]. However, due to the residual function of T cells (more functional than the severe form), the clinical manifestations are usually less severe. In some CID patients, genetic mutation affects the stimulatory function of T cells, resulting in impaired isotype switching of B lymphocytes and dendritic cell signaling disruption, which increases the susceptibility to bacterial and intracellular pathogens. These patients usually show signs of lower and upper respiratory tract infection in infancy or early childhood.

The non-infectious complications and immunologic profile in patients with CID may help identify patients who are more prone to the development of respiratory complications and therefore require periodic pulmonary evaluations for risk assessment purposes.

Since there is not enough information regarding the pulmonary complications in CID patients, this study aimed to investigate clinical and immunological phenotype in CID patients with pulmonary symptoms and patients who did not develop any respiratory complications.

II. Patients And Methods

II.A. Study Population

This retrospective study was performed on 146 CID patients referred to either Mofid Children's Hospital of Shahid Beheshti Medical University or Pediatric Center of Excellence of Tehran University of Medical Sciences, Tehran, Iran, between 2009 and 2020. The diagnosis of CID was established by clinical immunologists according to the standard criteria of the European Societies for Immunodeficiencies (ESID) and Pan-American Group for Immunodeficiency (http://esid.org/Working-Parties/Registry/Diagnosis-criteria, Table S1). Secondary causes of immunodeficiency and other types of IEIs were considered as the exclusion criteria of this study.

II.B. Data Collection

A comprehensive questionnaire was designed to gather data as follows: i) demographical data, including age, sex, consanguinity, date of diagnosis, delay of diagnosis, ii) clinical manifestations, including FTT, Skin lesions, hepatosplenomegaly, malignancy, autoimmunity, etc; iii) imaging and laboratory findings, including thoracic computed tomography (CT), bronchoalveolar lavage (BAL), complete blood count (CBC), serum immunoglobulins, lymphocyte subsets, and lymphocyte transformation test (LTT). Based on the presence of pulmonary manifestations, patients were classified into two groups of patients with and without pulmonary complications. The documented CTs were subsequently re-evaluated by a team of pulmonologists and radiologists.
II.C. Statistical Analysis

Statistical analysis was performed using SPSS software package (SPSS Statistics version 26.0, Chicago, Illinois, USA). Analytic tests including Mann-Whitney, Chi-square, or Fisher exact tests were applied for comparison. A p-value of less than 0.05 was considered statistically significant.

iii. Results

III.A. Demographical Data

A total number of 146 patients [83 (56.8%) male and 63 (43.2%) females] were enrolled in this study and divided into two groups of patients with pulmonary complications (n= 88) and without pulmonary complications (n= 58). Most patients (n=108, 74%) were born to consanguineous parents and a family history of CID was reported in 20 patients (13.7%). 108 out of 146 patients (74%) were alive, 14 patients (9.6%) were deceased, and no information was available about the survival status of 8 (5.5%) patients. The mortality rate was higher in patients with pulmonary complications compared to the other group (11.4% vs. 6.9%), although it was not statistically significant ($p=0.597$). The median (interquartile range (IQR)) age of disease onset was 6 (2-12) months. The median (IQR) age of diagnosis was 15 (6-48) months, and the median (IQR) age of diagnostic delay was estimated at about 6.5 (2-24) months. Patients with pulmonary complications presented the disease's symptoms earlier compared to patients without pulmonary involvement; however, this was not significantly different ($p=0.463$). The detailed demographical data are provided in Table 1.

III.B. Clinical Presentations

The summary of clinical manifestations is provided in Table 2. The most common non-infectious complication among CID patients was anemia (n=101, 69.2%), which was more prevalent in patients without pulmonary complications compared to the other patients (75.9% vs. 64.8%, $p=0.200$).

Failure to thrive (FTT) and weight loss were the second important clinical manifestation among 40.4% and 41.1% of CID patients, respectively. Although most patients with FTT were amongst patients with pulmonary complications group, this was not statistically significant ($p=0.232$).

Hepatomegaly and splenomegaly were reported in 36 (24.7%) and 39 (26.7%) patients. 21 Out of 36 (58.3%) patients with hepatomegaly and 20 out of 39 (51.2%) patients with splenomegaly also suffered from pulmonary complications. Overall, hepatomegaly (25.9% vs. 23.9%) and splenomegaly (32.8% vs. 22.7%) were higher among patients without pulmonary complications compared to the other group, although not statistically significant ($p=0.845$ and $p=0.251$, respectively).

The skin lesion was another prevalent clinical manifestation reported in 58 (39.7%) patients. In the group of patients with pulmonary manifestations, 31 patients (35.2%) and in the group of patients without any respiratory complications, 27 patients (46.6%) were diagnosed with skin lesions in medical examinations. However, these findings were not significantly different between these groups ($p=0.226$).
Nineteen patients (13.0%) were suffered from variable autoimmune disorders with higher frequency in patients without pulmonary complications (17.2% vs. 10.2%, \( p=0.315 \)), including rheumatoid arthritis/juvenile idiopathic arthritis (n=8, 42.1%), Kawasaki disease (n=5, 26.3%), systemic lupus erythematosus (n=4, 21.0%), insulin dependent diabetes mellitus (n=2, 10.5%), autoimmune hemolytic anemia (n=2, 10.5%), scleroderma (n=1, 5.3%), and celiac disease (n=1, 5.3%).

III.C. Imaging and Laboratory Findings

Thoracic CT was available in 48 out of 88 patients (54.5%) with pulmonary complications. Re-evaluation of documented CTs revealed parenchymal disorders (pneumonia (n=35, 39.8%), pulmonary nodules (n=3, 3.4%), atelectasis (n=1, 1.1%), interstitial lung disease (n=1, 1.1%), Figure S1), airway disorder (bronchiectasis (n=11, 12.5%)), and pleural disorder (pneumothorax (n=1, 1.1%)). In four patients, BAL results were available and consisted of fungi (n=2), gram positive cocci (n=1), and resistant Acinetobacter (n=1).

The median number of white blood cells (WBC) in patients with pulmonary complications was slightly higher compared to patients without pulmonary manifestations (7900 µl vs. 7650 µl); however, this was not significantly different (\( p=0.97 \)). In contrast, the median percentage of lymphocytes was higher in patients who did not show any respiratory manifestations, 43% (27.3%-62.9%) in comparison patients diagnosed with pulmonary complications 38% (26%-52.5%). The median number of CD4 T cells was significantly higher in patients without any respiratory manifestations (30 cell/µl) compared to patients who developed various types of respiratory symptoms (22 cell/µl) (\( p=0.012 \)). Moreover, the median number of CD8 T cells in patients with pulmonary complications was significantly higher than a group of patients without any respiratory symptoms (26.50 cell/µl vs. 19 cell/µl, \( p=0.005 \)).

The median level of IgG was reported to be higher in patients with pulmonary complications (607 md/dL) compared to the group of patients without respiratory manifestation (508.5 mg/dL) (\( p=0.316 \)). On the other hand, the median level of IgA (59 mg/dL vs. 55 mg/dL) and IgM (81 mg/dL vs. 75 mg/dL) was higher in the group of patients who were not diagnosed with any respiratory complications compared to patients with pulmonary symptoms (\( p=0.532 \) vs. \( p=0.805 \)). More details about the laboratory findings are provided in Table 3.

Iv. Discussion

In this study we compared clinical manifestations and immunological profile between CID patients with and without pulmonary complications. Initial presenting manifestations in most of the patients diagnosed with IEIs are infections and lungs are the most commonly affected organ [9]. In a recent study on 16486 documented patients in the ESID registry, 12741 (77%) patients with variable types of IEIs and 37% of CID patients primarily presented with infectious complications [10]. A French prospective study has shown that respiratory tract infection comprises the leading cause of hospital admission [11],
affecting patients’ quality of life. Non-infectious respiratory manifestations such as bronchiectasis, interstitial lung disease, and respiratory benign or malignant lymphoproliferation often develop later in the course of IEIs, following recurrent infections or the CID nature [12]. Identifying CID-related manifestations and immunological features that correlate with the development of pulmonary complications may help early monitoring of high-risk patients and either prevent or decrease associated mortality.

In the present study, according to HRCT and bronchoscopy, 60% of patients (n = 88) were diagnosed with different pulmonary complications, including pneumonia (n = 35, 39.8%), bronchiectasis (n = 11, 12.5%), pulmonary nodules (n = 3, 3.4%), atelectasis (n = 1, 1.1%), interstitial lung disease (n = 1, 1.1%), and pneumothorax (n = 1, 1.1%). In consistent with our findings, Abolhassani et al. reported that 242 out of 969 CID patients were diagnosed with various pulmonary complications [13]. These results suggest that respiratory involvement can be considered as one of the most important complications among IEIs patients, which should always be considered as a clinically important symptom.

Early diagnosis of CID is substantial since the severe forms of the disease require early and immediate intervention and delayed diagnosis impacts the prognosis of the disease [14]. In our study, patients with different pulmonary complications were diagnosed earlier compared to those without any respiratory presentations (14 months vs. 16 months). Early diagnosis of this group is probably due to the fact that patients with various pulmonary complications such as pneumonia and bronchiectasis have undergone more clinical and laboratory evaluations, and an accurate diagnosis has been made earlier.

The development of respiratory complications may affect the mortality rate in CID patients. In this study, patients with respiratory problems had higher mortality rate (n = 10, 11.4%) compared to the other group of patients without any respiratory complications (n = 4, 6.9%). Consistent with our research, among patients diagnosed with predominantly antibody deficiency (PAD), respiratory tract infections (RTIs) are the main causes of morbidity and mortality [15]. Therefore, besides efforts made to increase the knowledge of first-line physicians, major steps are required be taken such as establishing a national neonatal IEI screening program, providing treatment centers and stem cell donation bank for stem cell transplantation in IEI, and reforming the national vaccination program [13].

Abnormalities in T lymphocytes can predispose CID patients to pulmonary complications. In this study we found that patients with different respiratory complications had lower number of T CD4+ but higher levels of CD8+ cells compared to the other group (p = 0.012 and p = 0.005, respectively). In the same way, HIV patients with lower CD4+ T cells may develop community-acquired respiratory infections more frequent [16]. In a CVID cohort study conducted by Magoline P. et al., bronchiectasis was associated with decreased T CD4+ cell count [17]. Moreover, Weinberger et al. observed higher rate of upper and lower respiratory tract infections in CVID compared to XLA patients and attributed this finding to the more profound T cell defects (both T CD4+ and CD8+) in CVID patients [18]. T cell defects in CID patients may similarly play an important role in the severity of disease and progression of respiratory complications.
However, further studies seem to be required to elucidate the role of T CD4+ and CD8+ cells in the development of respiratory complications.

In the current study, bronchiectasis was documented in 12.5% of CID patients with pulmonary complications. In a cohort of 900 patients with bronchiectasis, IEI was the underlying cause of bronchiectasis in 16% of patients [19]. These results indicate the importance of infection control to prevent irreversible lung injury and bronchiectasis in immunocompromised patients. Various studies have shown that appropriate treatment with antibiotics may slow the progression and change the normal course of the disease toward bronchiectasis. In addition, early treatment reduces the risk of developing chronic lung disease and also decreases the severity of infections, especially opportunistic infections. Diagnostic delay may lead to damage to the lung structures and bronchiectasis. The presence of bronchiectasis at the time of diagnosis in patients with primary immunodeficiency is considered as an indicator of poor prognosis and increased mortality. In our study, the median diagnostic delay was 6.5 months. The sooner the diagnosis is made and the appropriate treatment is started, the better chronic lung disease is prevented or at least less severe lung disease develops, which ultimately increases the quality of life of these patients [20–23].

HRCT imaging is used as a necessary method in the evaluation of respiratory disorders for patients with IEI, due to the very high sensitivity in diagnosing disorders in the anatomical tissues of the respiratory tract. Since the sensitivity of chest X-ray images for early pathological diagnosis in patients is low, in all patients with chronic respiratory problems, HRCT is considered necessary to assess disease progression [24, 12]. In our study, respiratory disorders were mainly evaluated by the HRCT method, which shows the great importance of this method in diagnosing and evaluating patients. Of note, since children are more sensitive to radiations than adults, great care must be implemented and the HRCT protocol should be noted to take the best image quality with lowest radiation dose. Otherwise, radiation-related complications in children, particularly in CID patients might result in several consequences [25].

This research study had some limitations; heterogenous group of patients with variable forms of the CID made it difficult to define a precise correlation between variable kinds of pulmonary complications and the CID subcategory. In addition, we faced problems related to the retrospective design of study such as poor documentation of pulmonary characteristics which are suggested to be addressed in future prospective studies.

**V. Conclusion**

The results of our study showed that respiratory disorders are of great importance in CID patients and require early periodic monitoring by respiratory tests and HRCT imaging to avoid irreversible injuries. With early diagnosis and appropriate treatment of respiratory complications, the disease burden will decline and eventually the quality of life in CID patients will improve.

**Declarations**
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Conflicts of interest/Competing interests: The authors declare that they have no conflict of interest.

Ethics approval:

The present study was conducted according to the principles expressed in the Helsinki Declaration and ethical standards of the Shahid Beheshti University of Medical Sciences committee (IR.SBMU.MSPREC.1399.692).

Consent to participate: Not applicable.

Consent for publication: Not applicable.

Availability of data and material: Figure S1 is provided in the supplementary material.

Code availability: Not applicable.

Authors’ contributions: ZCH, GKH, and MP contributed to the conceptualization, supervision, and writing of the original draft; Data collection and analysis were performed by MJ, SAT, MKH, ASH, SS, SD, ET, SZM, ATB, GE, MF, JE, SHF, and MP. MJ, MM, MSS, NE, NF, MM, and AA reviewed and edited the final manuscript. All authors read and approved the final manuscript.

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**Tables**

**Table 1. Demographic data of CID patients with and without pulmonary complications**
| Parameter                              | Total patients (n=146) | With Pulmonary Complication (n=88) | Without Pulmonary Complication (n=58) | p-value |
|----------------------------------------|------------------------|-----------------------------------|---------------------------------------|---------|
| Age at the study time, m, median (IQR) | 96 (58-192)            | 96 (60-162)                       | 96 (48-192)                          | 0.993   |
| Age of onset, m, median (IQR)          | 6 (2-12)               | 5 (2-12)                          | 6 (2-13)                             | 0.463   |
| Age of diagnosis, m, median (IQR)      | 15 (6-48)              | 14 (6-48)                         | 16 (6.5-39)                          | 0.886   |
| Delay diagnosis, m, median (IQR)       | 6.5 (2-24)             | 7 (2-24)                          | 6 (3-24)                             | 0.649   |
| Sex, N (%)                             |                        |                                   |                                       | 0.609   |
| Male                                   | 83 (56.8)              | 52 (59.1)                         | 31 (53.4)                            |         |
| Female                                 | 63 (43.2)              | 36 (40.9)                         | 27 (46.6)                            |         |
| Consanguinity, N (%)                   | 108 (74)               | 67 (76.1)                         | 41 (70.7)                            | 0.564   |
| Family history, N (%)                  | 20 (13.7)              | 11 (12.5)                         | 9 (15.5)                             | 0.633   |
| Mortality, N (%)                       |                        |                                   |                                       | 0.597   |
| Alive                                  | 108 (74)               | 60 (68.2)                         | 48 (82.8)                            |         |
| Dead                                   | 14 (9.6)               | 10 (11.4)                         | 4 (6.9)                              |         |
| Unknown                                | 8 (5.5)                | 5 (5.7)                           | 3 (5.2)                              |         |

Abbreviations: m; month. Note. For quantities data, the median is shown [with IQR, 25th, and 75th percentiles]. N, Count.

*p-value <0.05 has been regarded as significant.

Table 2. Clinical manifestations and organ involvements of CID patients with and without pulmonary complications
| Parameter                              | Total patients (n=146) | With Pulmonary Complication (n=88) | Without Pulmonary Complication (n=58) | p-value |
|---------------------------------------|------------------------|------------------------------------|--------------------------------------|---------|
| Anemia, N (%)                         | 101 (69.2)             | 57 (64.8)                          | 44 (75.9)                           | 0.200   |
| Loss of weight, N (%)                 | 60 (41.1)              | 39 (44.3)                          | 21 (36.2)                           | 0.391   |
| FTT, N (%)                            | 59 (40.4)              | 39 (44.3)                          | 20 (34.5)                           | 0.232   |
| Skin lesions, N (%)                   | 58 (39.7)              | 31 (35.2)                          | 27 (46.6)                           | 0.226   |
| Rheumatoid presentation, N (%)        | 42 (28.8)              | 24 (27.3)                          | 18 (31.0)                           | 0.709   |
| Splenomegaly, N (%)                   | 39 (26.7)              | 20 (22.7)                          | 19 (32.8)                           | 0.251   |
| Oral candidiasis, N (%)               | 37 (25.3)              | 24 (27.3)                          | 13 (22.4)                           | 0.564   |
| Hepatomegaly, N (%)                   | 36 (24.7)              | 21 (23.9)                          | 15 (25.9)                           | 0.845   |
| Lymphadenopathy, N (%)                | 31 (21.2)              | 18 (20.5)                          | 13 (22.4)                           | 0.837   |
| Otitis, N (%)                         | 24 (16.4)              | 16 (18.2)                          | 8 (13.8)                            | 0.649   |
| Autoimmunity, N (%)                   | 19 (13.0)              | 9 (10.2)                           | 10 (17.2)                           | 0.315   |
| Arthritis, N (%)                      | 15 (10.3)              | 8 (9.1)                            | 7 (12.1)                            | 0.587   |
| Alopecia, N (%)                       | 5 (3.4)                | 2 (2.3)                            | 3 (5.2)                             | 0.386   |
| Vasculitis, N (%)                     | 4 (2.7)                | 1 (1.1)                            | 3 (5.2)                             | 0.301   |
| Skeletal dysplasia, N (%)             | 4 (2.7)                | 1 (1.1)                            | 3 (5.2)                             | 0.301   |
| Heart involvement, N (%)              | 3 (2.1)                | 1 (1.1)                            | 2 (3.4)                             | 0.563   |
| PNS involvement, N (%)                | 3 (2.1)                | 1 (1.1)                            | 2 (3.4)                             | 0.564   |
| Malignancy, N (%)                     | 1 (0.7)                | 0 (0)                              | 1 (1.7)                             | 0.397   |

Abbreviations: FTT; failure to thrive, PNS; paranasal sinuses.

Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N, Count.

*p-value <0.05 has been regarded as significant.
Table 3. Laboratory data of CID patients with and without infectious complications
| Parameter                      | Total patients (n=146) | With Pulmonary Complication (n=88) | Without Pulmonary Complication (n=56) | p-value |
|-------------------------------|------------------------|------------------------------------|---------------------------------------|---------|
| **WBC × 1000/µL, median (IQR)** | 7725 (4900-12165)      | 7900 (4835-11700)                  | 7650 (4900-13817)                     | 0.913   |
| **Neutrophil, % of total WBC, median (IQR)** | 48 (29.25-64.75)      | 50 (30-64)                          | 42.80 (26-68)                         | 0.493   |
| **Lymphocyte, % of total WBC, median (IQR)** | 40.35 (26-56)         | 38 (26-52.45)                       | 43 (27.25-62.90)                      | 0.140   |
| **Hb, g/dl, median (IQR)**    | 10.65 (9-12.02)        | 10.70 (9.25-12.20)                  | 10 (8.70-12)                          | 0.144   |
| **Platelet, cell/µL, median (IQR)** | 285500(203000-399250) | 289500(203500-456750)               | 277000(202500-365250)                 | 0.314   |
| **IgG, mg/dl, median (IQR)**  | 600 (309.25-919)       | 607 (263.25-890.25)                 | 582.50 (346-971.50)                   | 0.316   |
| **IgA, mg/dl, median (IQR)**  | 58 (21-122.25)         | 55 (22-124.50)                      | 59 (20-104.25)                        | 0.532   |
| **IgM, mg/dl, median (IQR)**  | 75 (28-138)            | 75 (26.50-139)                      | 81 (30-138)                           | 0.805   |
| **IgE, IU/ml, median (IQR)**  | 10 (2-60.50)           | 10 (2-52)                           | 10 (2-100)                            | 0.990   |
| **CD3⁺ lymphocytes, cell/µL, median (IQR)** | 57 (43-70.47)         | 57.20 (43-70.30)                    | 55 (43-73)                            | 0.851   |
| **CD4⁺ lymphocytes, cell/µL, median (IQR)** | 24 (17-36.50)         | 22 (16-30.35)                       | 30 (18-46)                            | 0.012*  |
| **CD8⁺ lymphocytes, cell/µL, median (IQR)** | 24 (16-40)            | 26.50 (17.75-47.12)                 | 19 (12.85-29)                         | 0.005*  |
| **CD16⁺ lymphocytes, cell/µL, median (IQR)** | 7.62 (3.92-14.70)     | 9.11 (4-15)                         | 7 (2-13.10)                           | 0.153   |
| **CD19⁺ lymphocytes, cell/µL, median (IQR)** | 17.8 (6.30-28.25)     | 14 (6.30-24.50)                     | 20 (8-32)                             | 0.121   |
| **CD20⁺ lymphocytes, cell/µL, median (IQR)** | 18.5 (6.87-29)        | 12 (5-25)                           | 20 (13-29)                            | 0.162   |
| **LTT**                       | PHA                    | 3.75 (3-4.50)                       | 3.60 (2.90-4.50)                      | 3.90 (3-4.55) | 0.818 |
|                              | BCG                    | 2.05 (1.40-3.02)                    | 1.75 (1.20-3)                         | 2.25 (1.57-3.30) | 0.207 |
|                              | Candida                | 1.50 (1-1.87)                       | 1.30 (1-1.70)                         | 1.50 (1-2) | 0.352 |
Abbreviations: WBC; white blood cells, Hb; Hemoglobin, Ig; Immunoglobulins, CD; Cluster of Differentiation, LTT; lymphocyte transformation test, PHA; phytohemagglutinin, BCG; Bacillus Calmette Guerin.

Note. For quantities data the median is shown [with IQR, 25th and 75th percentiles]. N, Count.

*p*-value <0.05 has been regarded as significant.

**Supplementary**

Supplementary Table S1 is not available with this version

**Supplementary Files**

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- FigureS1.docx