Clinical and genetic characteristics of BCG disease in Chinese children: A retrospective study

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Abstract

Purpose

Summarize the characteristics of the largest cohort of BCG disease and compare differences in clinical characteristics and outcomes among different genotypes and between primary immunodeficiency disease (PID) and non-PID patients.

Methods

We collected information on patients with BCG disease in our center from January 2015 to December 2020 and divided them into four groups: chronic granulomatous disease (CGD), Mendelian susceptibility to mycobacterial disease (MSMD), severe combined immunodeficiency disease (SCID) and unspecified pathogenic group.

Results

A total of 134 patients were reviewed, and most of them had PID. A total of 112 (83.6%) patients had 19 different types of pathogenic gene mutations, most of whom (91.1%) were classified with CGD, MSMD and SCID. *CYBB* was the most common gene mutation (53/112). BCG disease behaves differently in individuals with different PIDs. Significant differences in sex ($P < 0.001$), age at diagnosis ($P = 0.019$), frequency of recurrent fever ($P = 0.003$) and infection severity ($P = 0.038$) were noted among the four groups. The CGD group had the highest rate of males and the oldest age at diagnosis. The MSMD group had the highest probability of disseminated infection (46.4%). The course of anti-tuberculosis treatment and the survival time between PID and non-PID patients were similar.

Conclusion

Greater than 80% of BCG patients have PID; accordingly, gene sequencing should be performed in patients with BCG disease for early diagnosis. BCG disease behaves differently in patients with different types of PID. Non-PID patients had similar outcomes to PID patients, which hints that they may have pathogenic gene mutations that need to be discovered.

Introduction

Bacille Calmette-Guérin (BCG)—a live, attenuated stain of *Mycobacterium bovis*—is the only recommended vaccine by the World Health Organization (WHO) against tuberculosis, and neonates born in areas with high tuberculosis incidences, such as China, should receive this vaccine[1]. BCG is generally safe, helps reduce the risk of severe tuberculosis and prevents transmission[2, 3]; however, some children

tend to suffer from BCG disease with an incidence of approximately 1:10,000–1:1,000,000 or even disseminated BCG disease, which is a rare and serious adverse reaction[4]. In 2015, Aishwarya Venkataraman et al. observed sixty children who presented with adverse reactions and found that two-thirds (65%) presented with BCG lymphadenitis, one-third (30%) presented with injection site complications, and 54% had received anti-tuberculous therapy and/or a procedure[5]. With the increasing use of gene sequencing, some pathogenic genes have been discovered in some BCG diseases[6]. Rina Yue Ling Ong et al. reported that 10 patients likely had underlying PID – four with SCID, three with MSMD, one with anhidrotic ectodermal dysplasia with PID (EDA-ID), one with combined immunodeficiency (CID), and one with a STAT-1 gain-of-function mutation[7]. A previous study enrolled 74 confirmed cases of BCGosis/BCGitis in our center in 2014. Thirty-two patients (43.2%) had definitive PID, and CGD was the most common PID (n = 23, accounting for 71.9% of all PID patients)[6].

However, limited updated clinical data on large-sized samples of BCG disease have been reported, and differences among different genotypes and between PID and non-PID patients have not been described. This study aims to analyze the clinical and genetic characteristics of the largest cohort of BCG disease and compare differences in clinical manifestations, infectious severity and outcomes among different genotypes and between PID and non-PID patients.

Methods

The study was approved by the ethics committee of the Children's Hospital of Fudan University.

Patients

Initially, all patients who were diagnosed with BCG disease were enrolled. We collected data on year of birth, age at onset, age at diagnosis, sex, residence, clinical manifestation, family history, body mass index (BMI), site of BCG disease, pathogen of coinfection, whole exon sequencing (WES) result, treatment and survival time. Patients who met the enrollment criteria were included[8] (Table 1). According to the classification criteria reported previously[9], the infection severity of the enrolled patients was divided into four grades (Table 1). PID was diagnosed based on WES, which was performed at the Molecular Diagnostic Center of our hospital or the Mygenostics company. According to different types of gene mutations, we divided the recruited patients into four groups: the CGD group, MSMD group, SCID group and unspecified pathogenic group.

Statistical Analysis

SPSS 26.0 (SPSS Inc., Chicago, IL) was used to perform data analysis, and GraphPad Prism 5.0 was used to generate figures. The Kolmogorov–Smirnov test was used to test the normality of the data, and numerical data are presented as the mean and SD or median. Categorical variable data are reported as frequencies and percentages. ANOVA and the Mann–Whitney U test were used to compare the numerical variables. The chi-square test and Fisher's exact test were used to compare the categorical variables

depending on applicable conditions. The Kaplan–Meier method was applied to calculate probabilities of survival after treatment among different groups. A two-tailed $P < 0.05$ was considered statistically significant.

Result

General Features of All Patients

From January 1, 2015 to December 31, 2020, a total of 134 patients who were diagnosed with BCG disease were enrolled. All of the patients had a clear history of BCG inoculation before the onset of the disease, and scars were visible at the vaccination site. Among all of the patients, 101 were male (75.4%). Most patients were from East China (n = 88 65.7%) around Shanghai followed by South China (n = 22 16.4%) and Southwest China (n = 12 9.0%). Almost all patients were lean, and the average BMI was 16.3 ± 1.8 (kg/m^2). The median age at onset of BCG disease of all patients was 3.0 months old (IQR 1.67-4.0). The median age at diagnosis of BCG disease of all patients was 5.5 months old (IQR 4.5–8.6). Thus, a delay in BCG disease diagnosis was noted.

Genotype

Gene sequencing analysis of the 134 patients revealed that 112 cases (83.6%) had pathogenic mutations, whereas 22 cases (16.4%) had no mutations. Among the 112 PID patients, there were 55 cases of CGD (49.1%), including 53 *CYBB* gene mutations and 2 *CYBA* gene mutations; 28 cases of MSMD (25.0%), including 14 *IL12RB1* gene mutations, 8 *IFNGR1* gene mutations, 5 *STAT1* gene mutations, and 1 *IFNGR2* gene mutation; and 19 cases of SCID (17.0%), including 6 *RAG1* gene mutations, 5 *IL2RG* gene mutations, 3 *DCLRE1C* gene mutations, 1 *JAK3* gene mutation, 1 *RAG2* gene mutation and 1 *ADA* gene mutation. There were 4 cases of combined immune deficiency (CID), including 3 *CD40L* gene mutations and 1 *ZAP70* gene mutation. Some rare gene mutations were discovered, including 2 *STAT3* gene mutations, 1 *FADD* gene mutation, 1 *NLRP12* gene mutation, 1 *FLG* gene mutation and 1 *KRAS* gene mutation (Fig. 1). In total, we identified 19 types of gene mutations in 112 cases.

Clinical Manifestation in Different Groups

The number of rare genetic mutations was small and lacked homogeneity; hence, in this study, we did not compare patients with rare mutations with other patients. According to different types of gene mutations, we divided the remaining 124 patients into the CGD group, MSMD group, SCID group and unspecified pathogenic group. The sex composition ratio of the four groups was significantly different ($P < 0.001$). Almost all patients in the CGD group were males. The median ages at onset in the CGD group, MSMD group, SCID group and unspecified pathogenic group were 3.0 months old (IQR 0.6-4.0), 2.5 months old (IQR 1.5-3.0), 3.0 months old (IQR 3.0-3.9) and 3.0 months old (IQR 1.4–4.8), respectively. No significant difference existed among them ($P > 0.05$). The median age at diagnosis of the four groups was 6.8 months old (IQR 5.0-10.3), 4.5 months old (IQR 4.0-8.5), 5.3 months old (IQR 4.5–7.6) and 5.5 months old

(IQR 4.3–6.5). Significant differences were noted among the four groups, and the CGD group had a significantly older age at diagnosis than the other groups ($P = 0.019$) (Table 2). Eighty-two out of 112 PID cases (73.2%) had a positive family history, and 19 out of 22 cases (86.4%) in the unspecified pathogenic group had a positive family history. No significant difference existed between them ($P > 0.05$). Every group experienced an evident delay in the diagnosis of BCG disease, especially the CGD group. Patients in the unspecified pathogenic group may have potential pathogenic gene mutations that require further study.

The most common clinical manifestations of the four groups were recurrent fever, abnormal vaccination site and left axillary lymphadenitis (Fig. 2). Patients also presented with cough, diarrhea, skin abscess, night sweats, abdominal pain, and hematochezia. Symptoms varied among the four groups. The CGD group and SCID group had a significantly higher rate of recurrent fever than the other groups ($P = 0.003$). There was no significant difference in the frequency of abnormal vaccination sites or left axillary lymphadenitis among the four groups ($P > 0.05$). Patients in the MSMD group manifested abnormal gait (2/28), which was due to BCG bone infection (Table 2).

Site and Severity of BCG Disease in Different Groups

The common BCG infection sites were the left axillary lymph node (104/134), BCG vaccination site (53/134) and lymph nodes except the left axillary lymph node (21/134), lung (13/134), skin (11/134), bone (10/134), digestive tract (6/134), blood (6/134), abdominal cavity (4/132), ear (3/134), spleen (2/134), liver (1/134) and thoracic cavity (1/134) (Fig. 3). Among all the patients, 15 cases (11.2%) were classified as local infections, 69 cases (51.5%) were regional infections, 19 cases (14.2%) were distant infections and 31 cases (23.1%) were disseminated infections.

In the CGD group, 7/55 (12.7%) patients had local infections, 28/55 (50.9%) had regional infections, 11/55 (20.0%) had distant infections and 9/55 (16.4%) had disseminated infections. In the MSMD group, 1/28 (3.6%) had local infections, 11/28 (39.3%) had regional infections, 3/28 (10.7%) had distant infections and 13/28 (46.4%) had disseminated infections. In the SCID group, 5/19 (26.3%) had local infections, 9/19 (47.4%) had regional infections, 1/19 (5.3%) had distant infections and 4/19 (21.1%) had disseminated infections. In the unspecified pathogenic group, none of the patients had local infections, 13/22 (59.1%) had regional infections, 4/22 (18.2%) had distant infections and 5/22 (22.7%) had disseminated infections. A significant difference in infection severity was noted among the four groups ($P = 0.038$). The MSMD group had a higher probability of disseminated infection than the other groups (13/28 [46.4%]). In the other three groups, regional infection was the most common type, accounting for 50.9%, 47.4% and 59.1% of patients in the CGD group, SCID group and unspecified pathogenic group, respectively. It is worth noting that the probability of developing disseminated infection in the unspecified pathogenic group was second only to that in the MSMD group (Table 3).

Coinfections in Different Groups

Apart from BCG infection, these patients often experienced recurrent infections caused by various pathogens, even in patients without PID. Tested samples were obtained from nasal mucosa, sputum, bronchoalveolar lavage fluid (BALF), pus of skin, stool, urine, gastric juice, blood steam and marrow. The common coinfections included fungi (43.5%); viruses, such as *Cytomegalovirus* (17.7%), *Rotavirus* (11.3%), human parainfluenza virus (10.5%), and Epstein—Barr virus (7.3%); bacteria, such as *Klebsiella* (16.1%), *Staphylococcus* (6.5%), *Enterococcus* (5.6%), and *Streptococcus* (4.8%); and other pathogens, such as *Mycoplasma* (14.5%), *Pneumocystis carinii* (6.5%), parasites (1.6%) and *Mycobacterium tuberculosis* (1.6%). Fungal infections were very common in the four groups. The patients in the CGD and MSMD groups were mostly accompanied by bacterial infection, and the patients in the SCID and unspecified pathogenic groups were mostly accompanied by viral infection (Table 5).

Treatment and Prognosis in Different Groups

The median course of anti-tuberculosis treatment for all children was 7.0 months old (IQR 0.6–15). The MSMD group had the longest anti-tuberculosis treatment course at 34.5 months (IQR 9.8–51). The CGD group, SCID group and unspecified pathogenic group had treatment course durations of 7.0 months old (IQR 0.0–15.0), 5.5 months old (IQR 0.0–11.0) and 3.5 months old (IQR 3.0-7.8), respectively. No significant difference in anti-tuberculosis treatment courses was noted among the four groups (P = 0.130). Seventeen cases in the CGD group had completed hematopoietic stem cell transplantation (HSCT), of which 1 case was lost to follow-up, 13 cases were successfully transplanted (76.5%), 3 cases were unsuccessful. In addition, 13 cases in the SCID group had completed HSCT, and 11 cases were successfully transplanted (84.6%). There was no significant difference in the success rate of transplantation between the two groups (P = 1.000) (Table 2). At the end of follow-up, 80.7% of patients in the CGD group survived, 100% in the MSMD group, 88.5% in the SCID group and 89.5% in the unspecified pathogenic group. The median survival times in the four groups were 36.0 months (IQR 18.0–57), 26.5 months (IQR 7.8–35.0), 12.0 months (IQR 7.0-20.9) and 16.7 months (IQR 8.8–23.1) in the CGD group, MSMD group, SCID group and unspecified pathogenic group, respectively. No significant difference in survival time was noted among the four groups (P = 0.292). We wanted to know whether BCG disease severity affects prognosis, so we compared the patients in different severity grades in the CGD group. The results showed that there was no significant difference in survival time among patients with different infection severities in the CGD group (P = 0.925) (Fig. 4).

Discussion

BCG is used to prevent severe tuberculosis, and the WHO recommends that newborns born in areas with high tuberculosis incidence should be vaccinated[10–12]. The incidence of severe tuberculosis has been reduced after BCG vaccination, but BCG disease still occurs occasionally[6] and can even be fatal[13–15]. In recent years, there have been few large-sample updated clinical data about BCG disease, and no studies have focused on differences in BCG disease in different types of PID and between PID and non-PID patients.

This retrospective study presents and statistically analyzes the clinical and genetic features from the largest BCG disease cohort to date. We divided the recruited patients into the four groups because CGD, MSMD and SCID accounted for the most patients and were representative. We wanted to determine whether patients without PID had similar characteristics and prognoses to patients without PID. The number of rare genetic mutations was small and lacked homogeneity. Thus, we did not compare these patients with other patients in our study.

We reported a total of 134 cases of BCG disease in our center between January 2015 and December 2020. A total of 112 (83.6%) of them were found to have 19 different types of pathogenic gene mutations, 91.1% of which were classified as CGD, MSMD and SCID. Significant differences in sex ($P < 0.001$), age at diagnosis ($P = 0.019$), frequency of recurrent fever ($P = 0.003$) and severity of infection ($P = 0.038$) were noted among the four groups. The rate of positive family history, the survival time, and the course of anti-tuberculosis treatment between PID and non-PID patients were similar.

According to previous reports, patients suffering from BCG disease often have PIDs, such as SCID, MSMD, CID and CGD[16–18]. In Iranian in 2017, 64.0% of patients with disseminated disease also had PID[18]. Of these patients, 62.5% were classified as CGD, 25.0% were SCID and 12.5% were MSMD. A 15-year retrospective review in Singapore showed that all disseminated BCG diseases had PID, including SCID, MSMD, anhidrotic ectodermal dysplasia with PID (EDA-ID) and CID[7]. Among the 134 patients in our study, 83.6% had pathogenic genes, among which CGD, MSMD and SCID were the main diseases, accounting for 91.1% of all PIDs. Among them, CGD was the most common (49.1%) PID. CGD is a PID of phagocyte function due to defective NADPH oxidase. SCID is a prenatal disorder of T lymphocyte development. MSMD is a rare congenital condition characterized by a selective predisposition to infections caused by weakly virulent mycobacteria and other types of intramacrophagic pathogens, which are caused by inborn errors of IFN-γ immunity. Compared with the report from our center in 2014, 43.2% of BCG disease patients were identified with PID, and the level of PID diagnosis had been significantly improved [16] which is related to the gradual popularization of gene sequencing technology in recent years. It also suggested that if patients can be screened for these diseases before BCG inoculation, a large proportion of serious BCG disease will be prevented. Apart from these, we also found some rare genes, such as *NLRP12*, *FADD*, *FLG* and *KRAS*, which should be noted.

The median age at onset was reported previously as 3.8 months old in Singapore[7]. In 2014, our center reported that the median age at onset of BCG disease was 3.6 months old[6]. In this study, the value was 3.0 months old, which is relatively earlier than previously reported values. This finding may be attributed to the fact that the study in 2014 mostly recruited CGD patients, and we recruited more MSMD and SCID patients. However, there was still a delay in diagnosis, especially in the CGD group. The median age at diagnosis was 6.8 months old in the CDG group, which was significantly later than that of the other group. Physicians should further raise awareness of this issue. A previous study showed that no case had only local infection, 49.4% of patients had a regional infection, 26.6% of patients had a distant infection and 17.7% of patients had a disseminated infection [2]. Most of the patients in the study had

regional infections, which was similar to previous results. The MSMD group had the highest probability of disseminated infection, suggesting that we may adopt more aggressive anti-tuberculosis treatment for MSMD patients.

Previous reports have shown that left axillary lymphadenitis is the most common clinical manifestation [1]. In total, 85%-90% of patients have regional lymphadenitis, and 10.2% of patients have BCG-related osteomyelitis. This study found that recurrent fever, left axillary lymphadenitis and abnormal vaccination sites were the main clinical manifestations in each group, which was consistent with previous reports. If patients have the above three manifestations, they should be alert to BCG disease. More patients in the MSMD group showed abnormal gait, which was caused by BCG infection of lower extremity bones and bone destruction, compared with the other groups. For MSMD patients, comprehensive bone testing should be performed.

It is worth noting that 86.4% of patients in the unspecified pathogenic group had a positive family history, and this value was even higher than that noted in patients diagnosed with PID. Moreover, the survival time of this group was not significantly different from that of the other groups, and this group had a high probability of disseminated infection. We hypothesize that there may be undiscovered gene mutations in these patients, which is worth further research.

Overall, we reviewed the largest cohort of BCG disease and found that greater than 80% of patients with BCG disease had PID. Thus, gene sequencing should be performed in patients with BCG disease to facilitate early diagnosis, which will help us distinguish most patients with PID. BCG disease behaves differently in patients with different types of PID, and this information could help us manage patients more carefully. Patients without PID may have pathogenic gene mutations that deserve further study.

Declarations

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Disclosure of Conflict of Interest

The authors declare that they have no competing interests.

Availability of data and material

Regarding data and privacy protection, the dataset supporting the conclusions of the article is available upon individual request directed to the corresponding author.

Authorship Contributions

S.J.Q., W.X.C., Z.Y.Y., and Y.W.J. designed the study. S.J.Q., W.X.C., H.J., Y.W.J., W.W.J., S.B.J. L.L.Y, H.X.Y., G.Y and S.X.Y diagnosed, treated, and followed up these patients. Z.Y.Y. and Y.W.J abstracted the information from the electronic medical chart and follow-up material. Z.Y.Y. wrote the first draft. S.J.Q., W.X.C., Y.W.J, Z.Y.Y and L.L.Y. reviewed and revised the manuscript. S.J.Q. and W.X.C. supervised the whole process of the study.

Ethics approval

The study was approved by the Ethics Committee of the Children's Hospital of Fudan University.

Consent to participate

The patient and his parents provided written informed consent for enrollment in this study.

Consent for publication

Not applicable.

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tables

Tables 1 to 5 are available in the Supplementary Files section.

Figures

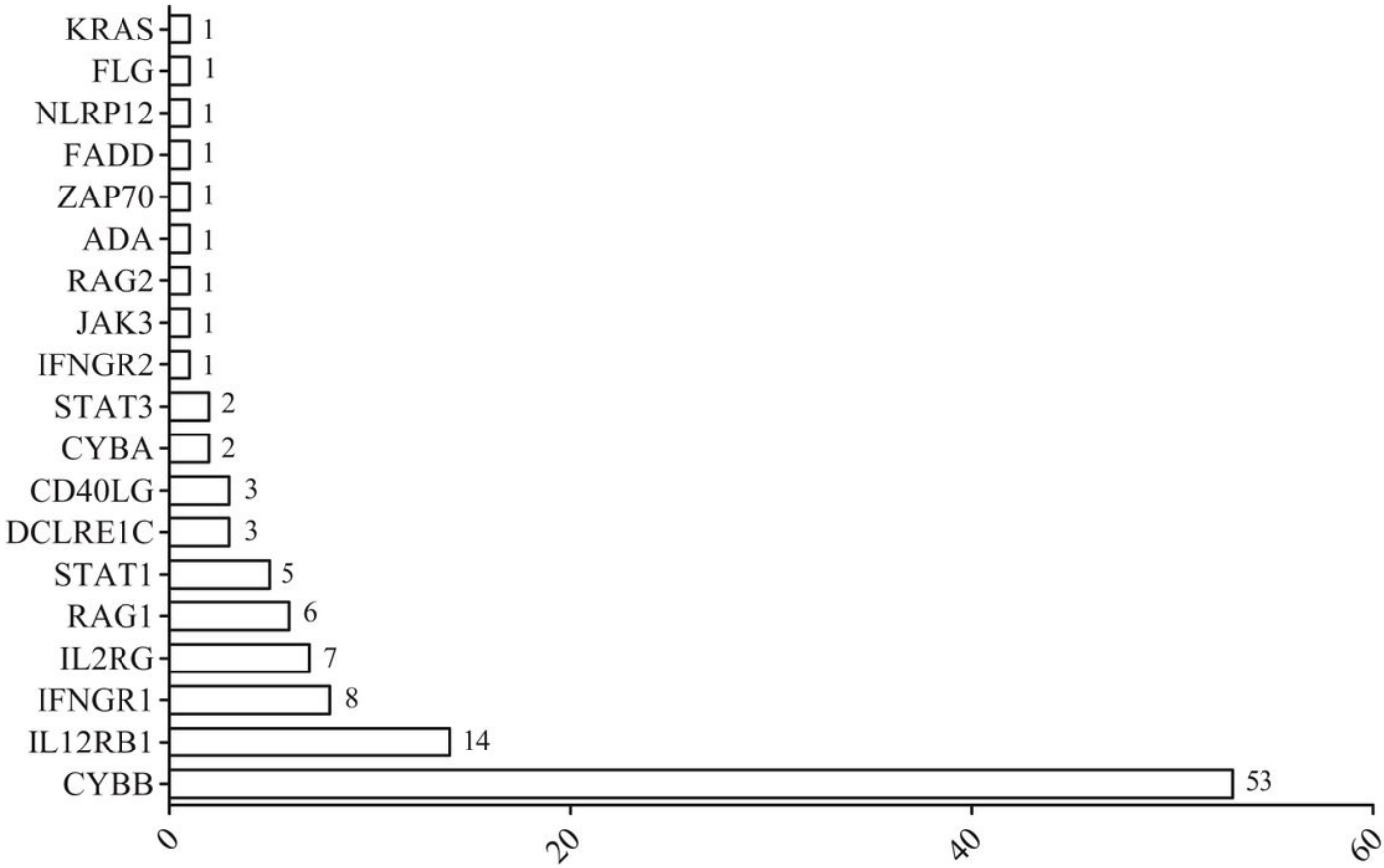

Figure 1

Genotype of all PID patients and classification of PID according to the genotype.

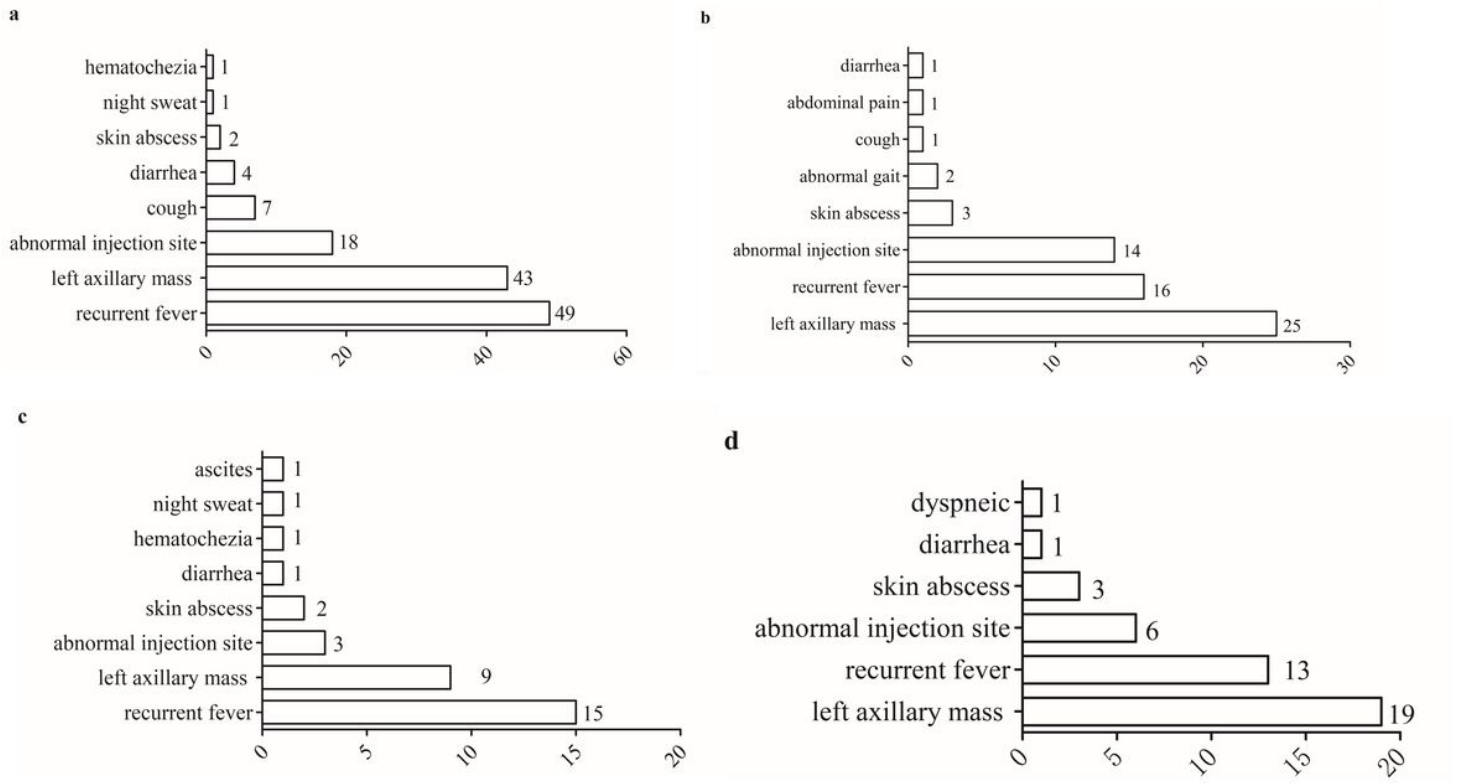

Figure 2

Clinical manifestations related to BCG disease of different groups. Fig.2a indicates clinical manifestations of CGD group. Fig.2b indicates clinical manifestations of MSMD group. Fig.2c indicates clinical manifestations of SCID group. Fig.2d indicates clinical manifestations of unspecified pathogenic group. The most common in the four groups were recurrent fever, abnormal vaccination site and left axillary lymphadenitis.

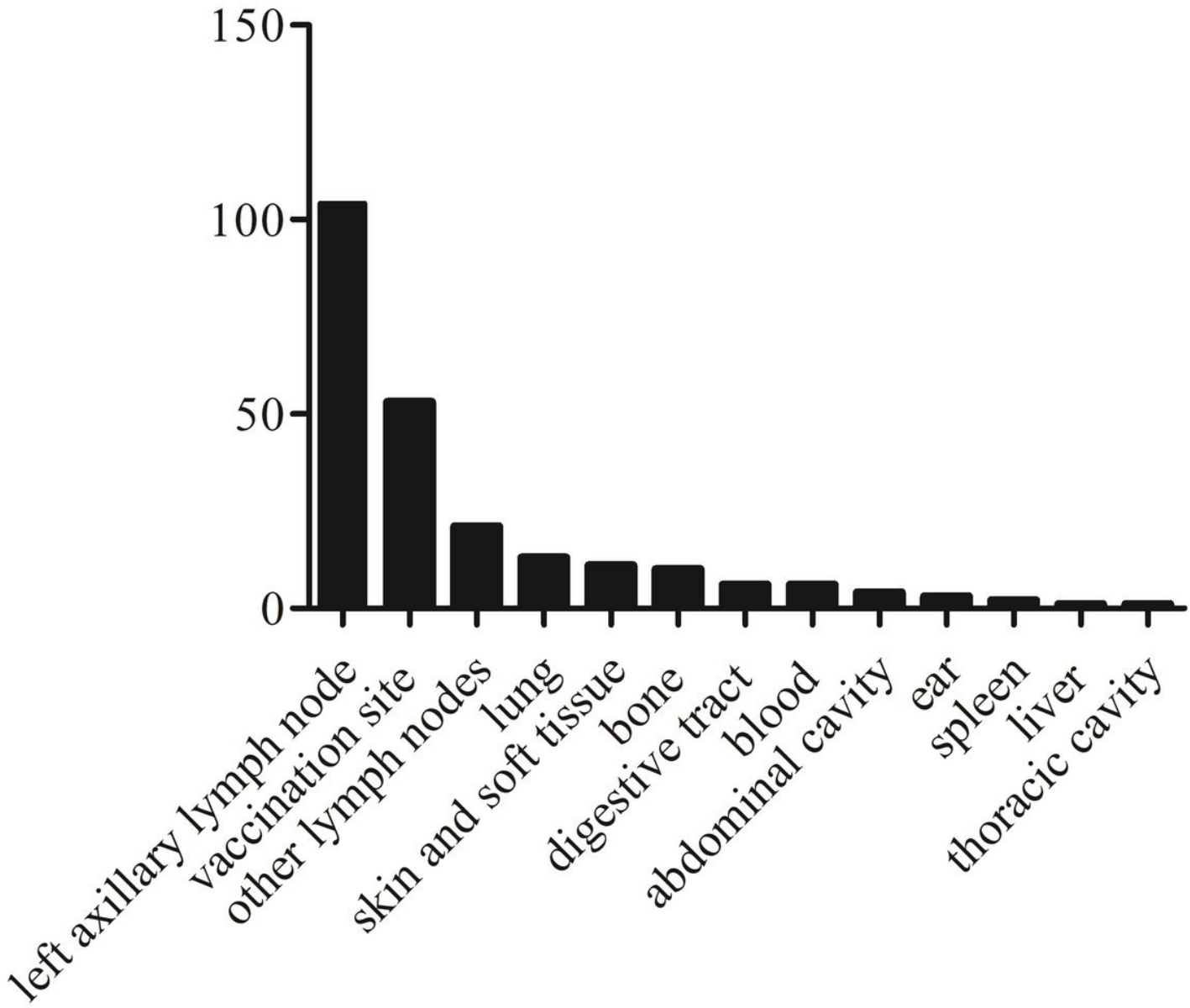

Figure 3

Localization of infection in 134 cases. The common BCG infection sites were theleft axillary lymph node (104/134), BCG vaccination site (53/134) and lymph nodes except the left axillary lymph node (21/134), lung (13/134), skin (11/134), bone (10/134), digestive tract (6/134), blood (6/134), abdominal cavity (4/132), ear (3/134), spleen (2/134), liver (1/134) and thoracic cavity (1/134).

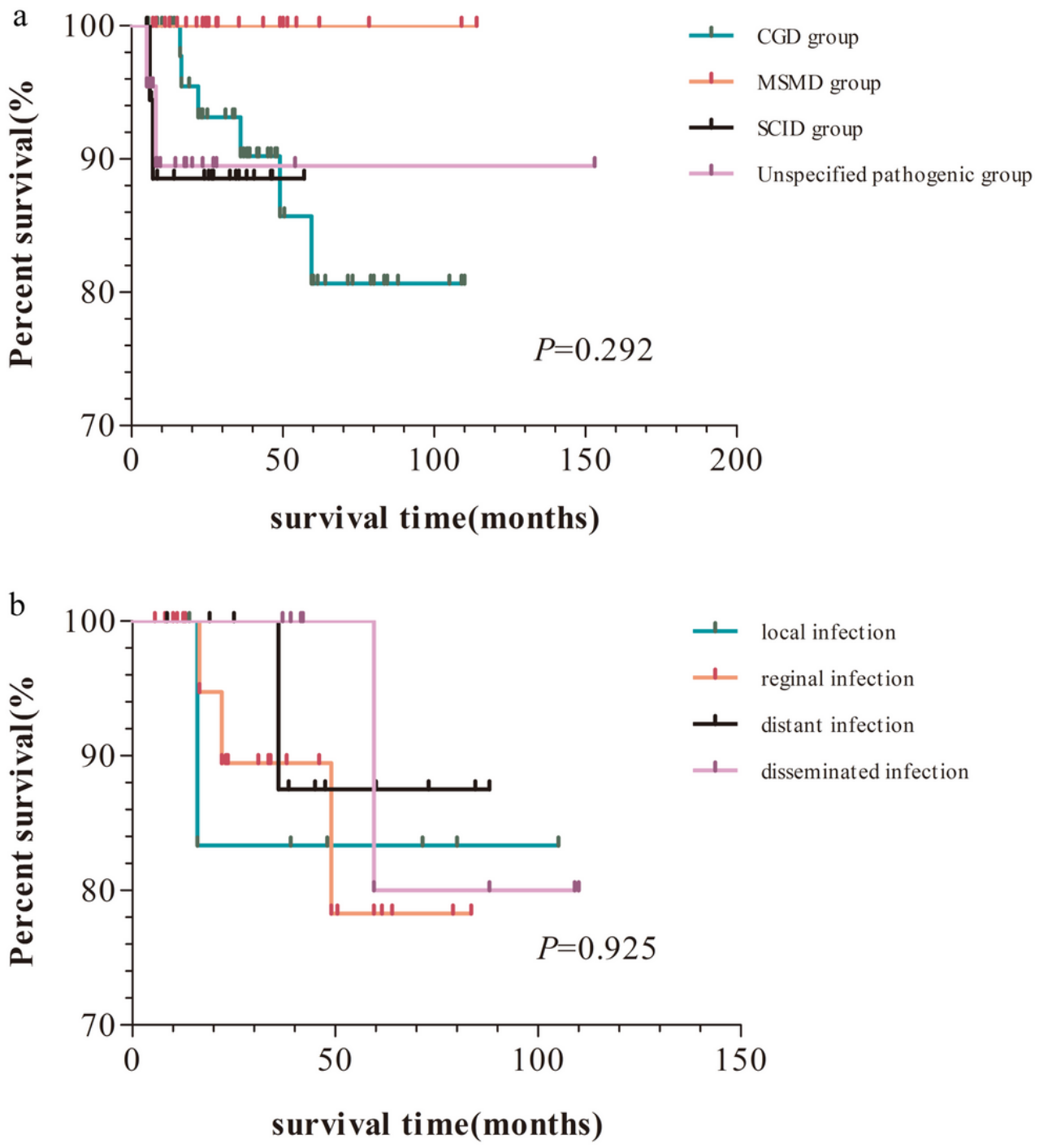

Figure 4

Fig.4a indicates difference in survival time of the groups. Fig.4b indicates difference in survival time of different BCG disease severity in CGD groups.

Supplementary Files

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- Tables.xlsx