Allo-HSCT recipients with invasive fungal disease and ongoing immunosuppression have a high risk for developing tuberculosis

Apeng Yang, Jimin Shi, Yi Luo, Yishan Ye, Yamin Tan, He Huang & Yanmin Zhao

Patients underwent allogeneic hematopoietic stem cell transplantation (allo-HSCT) are at high risk of acquiring tuberculosis (TB) due to a status of immunosuppression. We conducted a nested case control study to investigate the incidence and risk factors for TB after allo-HSCT. Between 2012 and 2017, 730 consecutive allo-HSCT recipients were enrolled, and 14 patients (1.92%) were diagnosed with TB. Relatively, 54 allo-HSCT recipients were selected as control. Patients who suffered TB had a significantly higher 3-year non-relapse mortality rate than the control group (30.36% vs 5.39%, \( p < 0.01 \)). In multivariate analysis, invasive fungal disease (HR 4.87, 95% CI 1.39–17.09), treatment with a relatively high dose of prednisone (HR 10.34, 95% CI 1.12–95.47) and treatment with tacrolimus (HR 4.79, 95% CI 1.18–19.44) were identified independent risk factors for TB occurrence post allo-HSCT (\( P < 0.05 \)). Meanwhile, donor type, dose and type of anti-thymocyte globulin (ATG) administrated, as well as treatment intensity, did not alter the incidence of TB. Therefore, allo-HSCT recipients with unexplained fever, especially those who suffer from invasive fungal disease and ongoing immunosuppression with a relatively high dose of prednisone or tacrolimus, are at a high-risk of developing active TB. Closely Monitoring TB occurrence, making a timely diagnosis and administering the proper treatment may be beneficial to those high-risk patients.

Tuberculosis (TB) remains one of the biggest threats for global public health. More than 2 billion people worldwide are infected with Mycobacterium tuberculosis (M. tuberculosis) and it was responsible for nearly 1.3 million deaths in 2012. China currently has approximately 1,000,000 TB cases, ranking second among all countries in the world. Moreover, patients with immunosuppression are at a higher risk of acquiring TB, leading to significant morbidity and mortality.

For recipients of hematopoietic stem cell transplantation (HSCT), cellular immunity is extremely disrupted by high-dose chemoradiotherapy and subsequent immunosuppressive therapies. Immune reconstitution is delayed after engraftment and will not be completed until 1 to 2 years post-HSCT. Moreover, in the condition of allogeneic HSCT (allo-HSCT), Graft-versus-host disease (GVHD) develops frequently, leading to further deterioration of cellular immunity due to dysregulation and abnormal clonal expansion of T cells. Opportunistic infections caused by bacteria, viruses, and fungi can occur at this time.

Previous observational studies have reported an incidence of 0.80% to 2.84% for TB post-HSCT in the most recent decade. So far, the disease features of TB after allo-HSCT have not been thoroughly described, and the risk factors leading to the occurrence of TB have not been identified. Early diagnosis should be emphasized, and timely treatments should be developed for post-HSCT tuberculosis in order to improve the clinical outcomes. Thus, we conducted a nested case control study to identify the disease features and risk factors for TB after allo-HSCT.
Materials and Methods

Patients. All patients who received allo-HSCT from January 2012 to December 2017 for hematologic diseases were examined. The diagnosis of TB was based on published criteria. Clinical data were collected after the peripheral blood stem cell (PBSC) reinfusion. The protocol was approved by the ethics review committee of the First Affiliated Hospital of Zhejiang University School of Medicine. All participants gave their written informed consent in accordance with the Declaration of Helsinki. Each patient had ongoing follow-up care until either October 31, 2018 or the last visit.

Definition of M. tuberculosis infection. To confirm the diagnosis of active TB, sputum or tissue obtained must be smear-positive or culture positive, and acid-fast organisms and polymerase chain reaction (PCR) results must be positive for Mycobacterium tuberculosis. Miliary TB was diagnosed according to the criteria previously reported. The radiological findings were confirmed by two experienced radiologists. Patients who matched above criteria were considered proven for M. tuberculosis infection. A patient was considered as a possible case when all the following criteria were met: 1. No definite evidence of other infectious. 2. The patient's condition recovered with anti-TB treatment when other antibacterial and antifungal agents were ineffective. 3. Interferon-gamma release assays (IGRA) (such as T-SPOT.TB) positive or a switch from negative to positive. The date of TB diagnosis was defined when all the criteria were met.

A latent tuberculosis infection (LTBI) was defined as a state of persistent immune response to stimulation by Mycobacterium tuberculosis antigens with no evidence of clinically manifest active TB. Either IGRA or tuberculin skin test (TST) could be applied to detect LTBI. There weren't any signs or symptoms of TB in the vast majority of infected people but they were at risk of suffering active TB.

Definition of a relatively high dose of prednisone. The relatively high dose of prednisone was defined as: (1) A dose that started at 1–2 mg/kg/day without dose tapering for at least two weeks; or (2) A dose that started at 1–2 mg/kg/day and then tapered to no less than 0.5 mg/kg/day for more than 6 weeks.

GVHD. All patients received GVHD prophylaxis consisting of cyclosporin A (CSA) and short-term methotrexate (MTX) either with or without a low-dose mycophenolate mofetil (MMF). Tacrolimus (FK 506) was not routinely used in our department, while it may be added as a precautionary measure in case of CSA intolerance. Diagnosis and grading of acute GVHD (aGVHD) was based on the consensus criteria and the definition of chronic GVHD was based on the revised Seattle classification.

Control selection. For each patient diagnosed with TB, 4 allo-HSCT recipients of the same gender and aged ±5 years were selected as control.

Study end points. We compared the patients who developed TB with the control to investigate the risk factors for TB after allo-HSCT. The study end points were 3-year overall survival (OS), non-relapse mortality and TB-related mortality.

Statistical analysis. Since the median time between transplant and TB occurrence was 193.5 days in our cohort, we chose all the clinical and laboratory signs, as well as transplantation complications, that presented within 193 days in the control group or before TB occurrence in the TB group as potential risk factors.

Medians and ranges were used to present continuous variables. For univariate analysis, Pearson's Chi-square test, Chi-square test with continuity correction, and Fisher's exacts were used to compare categorical variables under different circumstances. Variables with p < 0.1 in the univariate analysis were introduced as risk factors and candidates for multivariate analysis. For multivariate analysis, we used conditional logistic regression with a backward likelihood ratio method, and variables were retained if p ≤ 0.05. The 3-year OS was generated using the Kaplan-Meier method. The 3-year NRM and TB-related mortality cumulative incidence curve was computed using Gray's competing risk method, with relapse and death without TB as competing failure mechanisms. R statistical software (version 3.5.0) and SPSS (Version 22.0) were used for statistical analysis.

Results

Patient characteristics. The patient characteristics and risk factors for TB are shown in Table 1. Between January 2012 and December 2017, a total of 730 patients with acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), myelodysplastic syndrome (MDS), aggressive lymphoma or other hematologic diseases underwent allo-HSCT. The median follow-up duration of the survivors was 23.59 (range 3.89–88.21) months. During the studying period, 14 patients (1.92%) were diagnosed with active TB and 56 allo-HSCT recipients were selected as control. No significant difference was observed between the two groups concerning age, gender, underlying disease, donor type, with/without ATG administration or the conditioning intensity.

Clinical characteristics of TB patients. All the evaluated subjects underwent CT screening before transplantation to exclude pretransplant tuberculosis. Having a positive T-SPOT or a transfer from negative to positive was indicative of the possible presence of tuberculosis. To distinguish de novo and recurrent TB after allo-HSCT, we excluded all the patients who were shown positive for the T-SPOT assay before the transplantation. Of the 14 patients with TB after allo-HSCT, 10 were confirmed and 4 were possible cases. The median interval from allo-HSCT to TB diagnosis was 193.5 (43 to 909) days. 12 of the 14 cases were pulmonary TB (85.71%), while the other 2 were extrapulmonary TB (14.29%). 4 patients suffered miliary TB. Unexplained fever (85.71%) and cough (71.43%) uncontrollable by conventional antibiotics were common in these patients. The T-SPOT positive
rate was significantly higher in patients with TB than those without (HR = 6.29, 95% CI, 3.09–12.77; P = 0.000) (Figure 1).

13 patients (92.86%) received first-line anti-TB treatment (INH, rifampicin, ethambutol, and pyrazinamide) and 1 patient received second-line therapy because of INH and rifampicin resistance. 5 cases were susceptible to anti-TB medication, 4 cases were still under treatment at the end of the study period, and 5 cases did not respond to anti-TB treatment. 6 patients died within the study period, with 4 with respiratory failure, 1 with engraftment failure/multiorgan failure, and 1 with primary disease relapse while receiving anti-TB treatment. The clinical characteristics and diagnosis/treatment of the TB patients are summarized in Table S1.

### Risk factors for TB occurrence

In univariate analysis, we identified grades 2 to 4 aGVHD (HR = 3.98, 95% CI, 1.33–11.88; P = 0.013), moderate to severe cGVHD (HR = 3.95, 95% CI, 1.11–14.03; P = 0.033), Epstein Barr virus viremia (HR = 9.21; 95% CI, 1.20–70.45; P = 0.032), invasive fungal disease (HR = 3.91, 95% CI, 1.35–11.32; P = 0.012), treatment with etanercept (HR = 3.93, 95% CI, 1.38–11.22; P = 0.011), a relatively high dose of prednisone (HR = 17.83, 95% CI, 2.33–136.48, P = 0.006), and tacrolimus (HR = 4.34, 95% CI, 1.45–12.97, P = 0.009) as risk factors for the occurrence of TB. It is necessary to note that a possible diagnosis of cGVHD was

| 70 Allo-HSCT recipients | Subjects with TB (n = 14) | Subjects without TB (n = 56) | P value |
|-------------------------|--------------------------|-------------------------------|---------|
| Demographic characteristics |                         |                               |         |
| Age                     | 27.5                     | 9–60                          |         |
| Sex                     |                          |                               | 0.988   |
| Male                    | 9                        | 64.29%                        | 36      | 64.29%                     | 0.923 |
| Female                  | 5                        | 35.71%                        | 20      | 35.71%                     |
| Underlying disease      |                          |                               |         |
| Acute lymphoblastic leukaemia | 3          | 21.43%                        | 24      | 42.86%                     | 0.983 |
| Acute myeloblastic leukaemia | 8          | 57.14%                        | 20      | 35.71%                     |
| hybrid acute leukemia    | 1                        | 7.14%                         | 1       | 1.79%                      |
| Myelodysplastic syndrome | 0                        | 0.00%                         | 6       | 10.71%                     |
| Chronic myeloid leukaemia | 1                      | 7.14%                         | 2       | 3.57%                      |
| Aggressive lymphoma      | 1                        | 7.14%                         | 2       | 3.57%                      |
| myelofibrosis            | 0                        | 0.00%                         | 1       | 1.79%                      |
| Donor type               |                          |                               |         |
| Unrelated donor         | 3                        | 21.43%                        | 9       | 16.07%                     | 0.437 |
| Haploidentical-related donor | 8                     | 57.14%                        | 31      | 55.36%                     |
| Matched sibling donors   | 3                        | 21.43%                        | 16      | 28.57%                     |
| ATG given as conditioning | 12                       | 85.71%                        | 41      | 73.21%                     | 0.305 |
| Conditioning intensity   |                          |                               |         |
| MAC                     | 13                       | 92.86%                        | 52      | 92.86%                     |
| RIC                     | 1                        | 7.14%                         | 4       | 7.14%                      |
| GVHD prophylaxis         |                          |                               |         |
| CSA based               | 5                        | 35.71%                        | 42      | 75.00%                     | 0.344 |
| FK 506 based            | 9                        | 64.29%                        | 14      | 25.00%                     | 0.009 |
| TB occurrence (months after HSCT) | 6.95 | 1.54–32.46 | N/A |
| 3-year overall survival after HSCT | 57.14% | 43 | 76.79% | 0.102 |
| NRM at 3 years after HSCT | 30.36 ± 13.55% | 3 | 5.39 ± 3.06% | 0.002 |
| aGVHD (%)                |                          |                               |         |
| Grades0–1               | 5                        | 35.71%                        | 41      | 73.21%                     | 0.013 |
| Grades2–4               | 9                        | 64.29%                        | 15      | 26.79%                     | 0.033 |
| cGVHD (%) group after HSCT ≥100d |              |                               |         |
| none-mild               | 4                        | 40%                           | 32      | 80%                        |
| moderate-severe         | 6                        | 60%                           | 8       | 20%                        |
| Cytomegalovirus viremia  | 11                       | 78.57%                        | 30      | 53.57%                     | 0.123 |
| Epstein Barr virus viremia | 13              | 92.86%                        | 30      | 53.57%                     | 0.032 |
| Invasive fungal disease  | 11                       | 78.57%                        | 13      | 23.21%                     | 0.012 |
| Follow-up duration, median months (range) | 18.27 | 3.93–88.21 | 27.14 | 3.89–87.93 | 0.219 |
| Patients who died(range) | 12.05 | 3.93–39.79 | 13.93 | 3.89–51.86 |
| Patients alive at last follow-up(range) | 42.02 | 13.43–88.21 | 43.07 | 11.04–87.93 |

Table 1. Demographic characteristics of the 70 Allo-HSCT recipients and risk factors for TB occurrence. MAC: myeloablative conditioning. RIC: reduced intensity conditioning. ATG: anti-thymocyte globulin. CSA: Cyclosporine A. FK 506: tacrolimus.
investigated in patients diagnosed with TB 100 days post-transplantation and in controls who survived over 100 days after allo-HSCT. Therefore, 10 TB patients and 40 controls were studied for cGVHD.

Multivariate analysis (Table 2) revealed that invasive fungal disease (HR 4.87, 95% CI 1.39–17.09), treatment with a relatively high dose of prednisone (HR 10.34, 95% CI 1.12–95.47) and tacrolimus (HR 4.79, 95% CI 1.18–19.44) were independent risk factors for TB occurrence (P < 0.05). Figure 2A–C shows the correlation of these risk factors with TB incidence after HSCT.

Disease outcome. The median survival of patients with TB was 18.27 (range 3.93–88.21) months post-HSCT. The causes of death were TB/engraftment failure and multiorgan failure (n = 1), TB/primary disease relapse (n = 1), and TB/death due to respiratory failure (n = 4). Figure 3A shows the comparative 3-year OS rates. With the median follow-up of 18.27 (range 3.93–88.21) months for TB patients and 27.14 (range 3.89–87.93) months for patients without TB, the 3-year OS rates were 57.14% and 76.79%, respectively (P = 0.102). Figure 3B shows the 3-year NRM cumulative incidence curve, which shows that the 3-year NRM was significantly higher in TB patients than patients without TB (30.36% ± 13.55% vs 5.39% ± 3.06%, P = 0.002).

Discussion
Post-transplantation TB infections are rare, but they carry significant morbidity and mortality. TB screening for recipients before allo-HSCT should be emphasized because active TB can either occur via reactivation of latent disease within the immunosuppressed recipient or via acquisition of new infections22. However, TB screening of donors is not recommended by the American Society of Blood and Marrow Transplantation (ASBMT) as donor-derived TB has not been reported in the HSCT setting23. In solid organ transplantation, however, donors with a TB infection should be excluded, as active tuberculosis could be transmitted from the donor’s infected organs (e.g. lung or liver) to the recipient24–26.

China has the second largest population of TB patients worldwide. The incidence of TB among allo-HSCT recipients is reported to be 2–40 times higher than that of the general population9,12,27–29. In our department, active TB occurred in 1.92% of patients underwent allo-HSCT, which is lower than that reported in other parts of Asia such as India, Pakistan and Taiwan, regardless of the fact that study periods and cohorts varied17–20. The lower incidence might be related to the single-agent INH prophylaxis for those recipients with positive T-SPOT.
before allo-HSCT. However, the true incidence of TB in the present study might be underestimated, because
the TB diagnosis may be difficult given the nonspecific presentations of the disease, and a useful diagnostic
approach—molecular testing for mycobacterial DNA (such as GeneXpert MTB/RIF) hasn’t been performed in
our center.

In our study, the 3-year NRM was 4.35 times higher in TB patients than that in subjects without, indicating
that active TB had a pivotal impact on their clinical outcomes. Therefore, TB risk factors should be screened
and TB monitoring should be done soon after HSCT. Several risk factors for post-HSCT TB occurrence have
been reported, including the use of busulfan, cyclophosphamide, corticosteroid therapy, tacrolimus, GVHD, etc.
Herein, we revealed the significant predictive value of Epstein Barr virus viremia, invasive fungal disease, aGVHD
(Grades 2 to 4), cGVHD (moderate-severe), treatment with etanercept, treatment with a relatively high dose of
prednisone and tacrolimus for TB post allo-HSCT. Among them, aGVHD and cGVHD have been reported to be
closely related to posttransplant TB in many studies9,29. However, The immune reactivity to EBV among patients
with active TB has not been explored. Intact cellular immune responses to EBV reflect the general immunological
fitness30. Compromised immune responses to EBV are linked to disease progression in patients with cancer or in
patients posttransplantation30. Progression of latent TB infection to clinical TB disease is associated with aberrant
host immune responses31. EBV antigens reported may represent as one of intrinsic markers for immune fitness
during TB treatment32. Thus, EBV viremia might be a co-infection and co-morbidity that could be associated as
one of TB risk factors. Herein, notably, we identified only three independent risk factors for the development of
post-HSCT TB by a multivariate analysis: 1) the presence of high-risk invasive fungal disease (IFD); 2) treatment
with a relatively high dose of prednisone; and 3) treatment with tacrolimus. It is known that the immunosuppres-
sive activity of FK506 is 10 to 100 times more potent than CSA33. The inhibition of T lymphocyte activation
and additional immunosuppression are frequently seen in cases where there is a long-term use of tacrolimus and
a high dose of glucocorticoid34,35. Comorbid opportunistic infections such as IFD may act as potential risk for
acquiring TB36.

Figure 2. Independent risk factors of TB incidence (A). Curve comparing groups with or without treatment
with a relatively high dose of prednisone (P = 0.000); (B) Curve comparing groups with or without invasive
fungal disease (P = 0.000); (C) Curve comparing groups with or without treatment with tacrolimus (P = 0.004).

Figure 3. (A) Three-year overall survival (OS) rates comparing subjects with and without TB. No statistically
significant difference was found between subjects with and without TB (57.14% vs 76.79%; P = 0.102); (B)
Three-year nonrelapse mortality (NRM) cumulative incidence curve. Grey’s competing risk method revealed a
significantly higher 3-year NRM in subjects with TB compared to that of subjects without TB (30.36% ± 13.55%
vs 5.39% ± 3.06%, P = 0.002).
Early diagnosis of TB is very important for management and control but become a challenge in seriously immunocompromised hosts, such as HSCT recipients, in whom TB may present different clinical manifestation. A definite diagnosis of TB in patients who have received HSCT is usually difficult to establish because immunological deficits may lead to nonspecific clinical features. In addition to the above risk factors, low fever or chronic cough that is uncontrollable with common antibiotics and a positive T-Spot (Fig. 1) were the specific and common manifestations of tuberculosis. HSCT recipients with these signs should be closely monitored for TB.

In conclusion, we propose that invasive fungal disease, treatment with a relatively high dose of prednisone, and tacrolimus were independent risk factors for the development of TB after HSCT. Strict standardized diagnostic standards and monitoring strategies, as well as timely treatment, should be routinely performed in the management and control of TB after HSCT. Our study may help to target high-risk patients for the early-diagnosis and timely treatment making.

References

1. Zumila, A., George, A., Sharma, V. & Herbert, N. Baroness Masham of I. WHO’s 2013 global report auf tuberculosis: successes, threats, and opportunities. Lancet 382, 1765–1767, https://doi.org/10.1016/S0140-6736(13)62078-4 (2013).

2. Dheda, K., Barry, C. E. 3rd & Maartens, G. Tuberculosis. Lancet 387, 1211–1226, https://doi.org/10.1016/S0140-6736(15)00151-8 (2016).

3. Global Tuberculosis Report 2017. World Health Organization. http://www.who.int/tb/publications/global_report/en/ (2017).

4. TB burden estimates. World Health Organization. http://www.who.int/tb/country/data/download/en/ (2016).

5. Marcialis, O. C. & Vogelgang, G. R. Graft-versus-host disease. Crit Care Clin 131, 131–138 (1997).

6. Hoyle, C. & Goldman, J. M. Life-threatening infections occurring more than 3 months after BMT. 18 UK Bone Marrow Transplant Teams. Bone Marrow Transplant 14, 247–252 (1994).

7. Kumar, R. et al. Allogeneic hematopoietic SCT performed in non-HEPA filter rooms: initial experience from a single center in India. Bone Marrow Transplant 43, 115–119, https://doi.org/10.1038/bmt.2008.268 (2009).

8. Moon, S. M. et al. Comparison of the Quantiferon-TB Gold In-Tube test with the tuberculin skin test for detecting latent tuberculosis infection prior to hematopoietic stem cell transplantation. Transpl Infect Dis 15, 104–109, https://doi.org/10.1111/tid.12794 (2013).

9. Fan, W. C. et al. Long-term risk of tuberculosis in haematopoietic stem cell transplant recipients: a 10-year nationwide study. Int J Tuberc Lung Dis 19, 58–64, https://doi.org/10.5588/ijtld.14.0301 (2015).

10. Agrawal, N. et al. Incidence and clinical profile of tuberculosis after allogeneic stem cell transplantation. Transpl Infect Dis 20, https://doi.org/10.1111/tid.12794 (2018).

11. Diagnostic Standards and Classification of Tuberculosis in Adults and Children. This official statement of the American Thoracic Society and the Centers for Disease Control and Prevention was adopted by the ATS Board of Directors, July 1999. This statement was endorsed by the Council of the Infectious Disease Society of America, September 1999. Am J Respir Crit Care Med 161, 1376–1385, https://doi.org/10.1164/ajrccm.161.4.16141 (2000).

12. de la Camara, R. et al. Tuberculosis after hematopoietic stem cell transplantation: incidence, clinical characteristics and outcome. Spanish Group on Infectious Complications in Hematopoietic Transplantation. Bone Marrow Transplant 26, 291–298, https://doi.org/10.1038/sj.bmt.1702506 (2000).

13. Kwon, J. C. et al. Clinical characteristics and the usefulness of the Quantiferon-TB Gold In-Tube test in hematologic patients with hepatic or splenic lesions. Korean J Intern Med 28, 187–196, https://doi.org/10.3904/kijm.2013.28.2.187 (2013).

14. Eom, K. S. et al. Tuberculosis before hematopoietic stem cell transplantation in patients with hematologic diseases: report of a single-center experience. Transpl Infect Dis 17, 73–79, https://doi.org/10.1111/tid.12341 (2015).

15. Pang, A. et al. Evaluation of an Interferon Gamma Release Assay to Detect Tuberculosis Infection in Children in San Diego, California. J Pediatr Infect Dis Soc 1, 74–77, https://doi.org/10.1093/jpids/pjv013 (2012).

16. Qin, L. L. et al. T-Spot.TB for detection of tuberculosis infection among hematological malignancy patients and hematopoietic stem cell transplant recipients. Asian Pac J Cancer Prev 14, 7415–7419 (2013).

17. Zhu, F., Ou, Q. & Zheng, J. Application Values of T-Spot.TB in Clinical Rapid Diagnosis of Tuberculosis. Iran J Public Health 47, 18–23 (2018).

18. Latent, T. B. Infection: Updated and consolidated guidelines for programmatic management, 2018. World Health Organization, http://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/ (2018).

19. Loo, Y. et al. T-cell-replete haploidentical HSCT with low-dose anti-T-lymphocyte globulin compared with matched sibling HSCT and unrelated HSCT. Blood 124, 2735–2743, https://doi.org/10.1182/blood-2014-04-571570 (2014).

20. Przeworska, D. et al. 1994 Consensus Conference on Acute GVHD Grading. Bone Marrow Transplant 15, 825–828 (1995).

21. Jagasia, M. H. et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease. J. The 2014 Diagnosis and Staging Working Group report. Biol Blood Marrow Transplant 21, 389–401 e381, https://doi.org/10.1016/j.bbmt.2014.12.001 (2015).

22. Bumbace, D. et al. The risk of tuberculosis in transplant candidates and recipients: a TBNET consensus statement. Eur Respir J 40, 990–1013, https://doi.org/10.1183/09031936.0000712 (2012).

23. Munoz, L. & Santin, M. Prevention and Management of Tuberculosis in Transplant Recipients: From Guidelines to Clinical Practice. Transplantation 100, 1840–1852, https://doi.org/10.1097/TP.0000000000001224 (2016).

24. Holyo, J. E. & Sista, R. R. Mycobacterium tuberculosis infection in transplant recipients: early diagnosis and treatment of resistant tuberculosis. Curr Opin Organ Transplant 14, 613–618, https://doi.org/10.1097/MOT0b013e3283324dfc (2009).

25. Sidhu, A., Verma, G., Humar, A. & Kumar, D. Outcome of latent tuberculosis infection in solid organ and hematopoietic stem cell transplantation. Clin Chest Med 38, 761–770, https://doi.org/10.1016/j.ccm.2017.07.011 (2017).

26. Arslan, O. et al. Incidence of tuberculosis after bone marrow transplantation in a single center from Turkey. Haematologica (Budap) 29, 59–62 (1998).

27. Kato, S. C. et al. Pulmonary tuberculosis in allogeneic hematopoietic stem cell transplantation. Bone Marrow Transplant 27, 1293–1297 (2001).

28. Lee, H. J. et al. The demanding attention of tuberculosis in allogeneic hematopoietic stem cell transplantation recipients: High incidence compared with general population. PLoS One 12, e0173250, https://doi.org/10.1371/journal.pone.0173250 (2017).

29. Jung, J. & Munz, C. Immune control of oncogenic gamma-herpesviruses. Curr Opin Virol 14, 79–86, https://doi.org/10.1016/j. coviro.2015.08.014 (2015).
31. Zumla, A. et al. Inflammation and tuberculosis: host-directed therapies. *J Intern Med* **277**, 373–387, https://doi.org/10.1111/joim.12256 (2015).
32. Nagu, T. et al. Strong anti-Epstein Barr virus (EBV) or cytomegalovirus (CMV) cellular immune responses predict survival and a favourable response to anti-tuberculosis therapy. *Int J Infect Dis* **56**, 136–139, https://doi.org/10.1016/j.ijid.2017.01.022 (2017).
33. Thomson, A. W. & Starzl, T. E. New immunosuppressive drugs: mechanistic insights and potential therapeutic advances. *Immunol Rev* **136**, 71–98 (1993).
34. Ganetsky, A. et al. Higher tacrolimus concentrations early after transplant reduce the risk of acute GvHD in reduced-intensity allogeneic stem cell transplantation. *Bone Marrow Transplant* **51**, 568–572, https://doi.org/10.1038/bmt.2015.323 (2016).
35. Nygaard, M. et al. Longitudinal follow-up of response status and concomitant immunosuppression in patients treated with extracorporeal photopheresis for chronic graft versus host disease. *Bone Marrow Transplant*, https://doi.org/10.1038/s41409-018-0206-5 (2018).
36. Lee, J. W. et al. Two children with differing outcomes after treatment for pulmonary tuberculosis diagnosed after allogeneic hematopoietic stem cell transplantation. *Transpl Infect Dis* **13**, 520–523, https://doi.org/10.1111/tid.1399-3062.2011.00641.x (2011).

Acknowledgements
The authors sincerely thank the participants for their understanding and willingness to participate in this study. This work was supported by the National Natural Science Foundation of China (81670148 and 81470307) and the Fujian Provincial Health and Family Planning Youth Scientific Research Project (2016-1-54).

Author contributions
A.Y.: study design, data collection, analysis and interpretation of data, drafting the article; J.S., Y.L. and Y.T.: data collection, statistical analysis; Y.Y.: study design, manuscript editing; H.H. provided expert advice; Y.Z: study design, analysis and interpretation of data, manuscript editing and revision. All authors contributed to the final manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary information is available for this paper at https://doi.org/10.1038/s41598-019-56013-w.
Correspondence and requests for materials should be addressed to H.H. or Y.Z.
Reprints and permissions information is available at www.nature.com/reprints.
Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons license, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons license and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this license, visit http://creativecommons.org/licenses/by/4.0/.

© The Author(s) 2019