Immune reconstitution and survival of patients with parvovirus B19 related pure red cell aplasia after haplo-PBSCT

Xiao Zhou1,2 · Peiyao Jiang1,2 · Lu Gao1,2 · Jun Yang1,2 · Yu Cai1,2 · Yin Tong1,2 · Huiying Qiu1,2 · Chongmei Huang1,2 · Kun Zhou1,2 · Xiaowei Xu1,2 · Jiahua Niu1,2 · Xinxin Xia1,2 · Ying Zhang1,2 · Chang Shen1,2 · Yu Wei1,2 · Jie Shao1,2 · Xianmin Song1,2 · Liping Wan1,2

Received: 19 November 2021 / Accepted: 29 March 2022 / Published online: 9 April 2022
© The Author(s) 2022

Abstract
Parvovirus B19 (PvB19) infection and PvB19 related pure red cell aplasia (PRCA) in recipients with allogeneic hematopoietic stem cell transplantation have been reported sporadically. However, clinical studies with large sample sizes are lacking, especially in patients undergoing HLA-haploidentical peripheral blood stem cell transplantation (haplo-PBSCT). In addition, clinical features, immune reconstitution, and outcomes of these patients are not clear. We conducted a retrospective analysis of 164 patients who received haplo-PBSCT with low-dose anti-thymocyte globulin (ATG) plus low-dose posttransplant cyclophosphamide (PTCy)-based regimen as graft-versus-host disease (GVHD) prophylaxis. We analyzed the incidence of PvB19 related PRCA and compared the clinical characteristics, immune reconstitution, incidence of GVHD, relapse rate, and survival between patients with and without PvB19 related PRCA. A total of 14 (8.5%) recipients developed PvB19 related PRCA after a median of 5.3 months after haplo-PBSCT. These patients with PvB19 related PRCA had slower immune reconstitution, but similar incidences of GVHD, relapse rate, and overall survival compared with recipients without PvB19 related PRCA. PvB19 related PRCA indicated relative delayed and poor immune reconstitution of the recipients early after haplo-PBSCT. PvB19 related PRCA had no effects on GVHD, relapse, and survival.

Keywords    Parvovirus B19 · Pure red cell aplasia · Immune reconstitution · HLA-haploidentical · Peripheral blood stem cell transplantation

Introduction
Allogeneic hematopoietic stem cell transplantation (allo-HSCT) from HLA-haploidentical family member has been increasingly performed in recent years. Posttransplant virus infections are common complications, which are associated with increased non-relapse mortality (NRM) after allo-HSCT. Human parvovirus B19 (PvB19), a nonenveloped,
single-stranded DNA virus, persists in tonsils, liver, skin, brain, synovial, and testicular tissues as well as bone marrow latently and would reactivate after allo-HSCT [1, 2]. Its seroprevalence among preschool children, young adults, and elderly individuals is estimated to be 15%, 50%, and 85%, respectively [3]. Due to its strong tropism to P antigen of erythroid progenitor cells, the most common clinical manifestations of PbB19 infection in immunocompromised patients are pure red cell aplasia (PRCA), which is characterized as marked reduction or absence of erythroid precursors in bone marrow and severe anemia [4–9].

PbB19 infection and PbB19 related PRCA in recipients of allo-HSCT have been reported sporadically. However, studies on the clinical features, immune reconstitution, and survivals of large-scale patients are lacking, especially in HLA-haploidentical peripheral blood stem cell transplantation (haplo-PBSCT). Therefore, we conducted a retrospective analysis of patients who received haplo-PBSCT, analyzed the incidence of PbB19 related PRCA, and compared the clinical characteristics, immune reconstitution, incidence of graft versus host disease (GVHD), relapse rate, and survival between patients with and without PbB19 related PRCA.

Patients and methods

Patients

A total of 164 consecutive patients of haplo-PBSCT enrolled in the study. All patients received peripheral blood stem cells from their HLA haplo-identical family donors from January 2018 through December 2020 in Shanghai Jiao Tong University Affiliated Shanghai General Hospital. Patients’ refined disease risk index and hematopoietic stem cell transplantation comorbidity index (HCT-CI) were scored according to literatures respectively [10, 11].

Conditioning regimen

Patients with acute myelogenous leukemia (AML) and myelodysplastic syndrome (MDS) received busulfan, fludarabine, and cytarabine-based conditioning regimen. Patients with acute lymphoblastic leukemia (ALL) and non-Hodgkin lymphoma (NHL) received conditioning regimen with total body irradiation (TBI) or busulfan, cyclophosphamide, and etoposide [12].

GVHD prophylaxis

All patients received rabbit anti-thymocyte globulin (Thymoglobulin®, Genzyme Polyclonals S.A.S.) 2.5 mg/kg on day −2 and day −1, cyclophosphamide 50 mg/kg on day +3 (low-dose ATG/PTCy) followed by cyclosporine A 2 mg/kg intravenously from day +4 and mycophenolate mofetil orally 720 mg three times per day from day +4 to day +34 for GVHD prophylaxis [12–14].

Infection prevention and monitoring

Valaciclovir and Posaconazole were given to all patients for prevention of herpes virus and fungus infection [15]. Compound sulfamethoxazole was used for pneumocystis jiroveci pneumonia prophylaxis after hematopoietic recovery posttransplant. Quantitative real-time polymerase chain reaction (PCR) assays for cytomegalovirus (CMV)-DNA and Epstein-bar virus (EBV)-DNA in peripheral blood were performed once or twice per week. The cutoff value was 1 × 10^3 copies/mL for both viruses.

Chimerism studies

Quantitative chimerism monitoring was performed by PCR of short-tandem repeats for sorted CD3+ T and CD19+ B lymphocytes of bone marrow every month after transplant within the first 6 months [16]. The AmpFlSTR Profiler Plus Kit (Applied Biosystems, USA) and ABI PRISM 3130 genetic analyzer were used for amplifications and analyzed, respectively [16].

Detection of anti PbB19-IgM and PbB19-DNA

According to published criteria and consensus, for patients with PRCA after transplant, their peripheral blood samples were tested for PbB19-DNA and/or anti-PbB19 IgM [9, 17, 18]. PbB19 DNA was detected by using quantitative real-time PCR (Human Parvovirus Real Time PCR Kit, Shanghai Zhi Jiang Biotechnology Company Limited, China). The cutoff value was 1 × 10^3 copies/mL according to manufacturer. Anti-PbB19 IgM was detected by using Gold Immunofiltration Assay (GIFA, Shandong Kanghua Bio-medical Technology Company Limited, China).

Statistical analysis

SPSS 25.0 was used for data analysis. Baseline characteristics were summarized using descriptive statistics. Fisher exact and chi-square tests were used to compare categorical variables, and the Wilcoxon rank-sum test was used to compare continuous variables. Lymphocyte counts were analyzed with unpaired t test. Overall survival (OS), relapse free survival (RFS), GVHD, and relapse free survival (GRFS) were estimated with Kaplan–Meier and compared by the log-rank test. Risk factors for PbB19 related PRCA were examined in Cox proportional hazards models, and factors with P value < 0.200 were included into multivariate
analysis. A 2-sided $P$ value $< 0.050$ indicated statistical significance.

Results

The patients’ characteristics were shown in Table 1. There were 105 male and 59 female patients. Their median age was 39 (6–64) years old. There were 87 (53.0%) patients diagnosed with AML, 37 (25.0%) patients with ALL, 23 (14.0%) patients with MDS, and 17 (10.4%) patients with NHL.

Engraftment

Out of the 164 patients, 158 (96.3%) patients had successful engraftment; 6 patients died within 28 days. Four of them died of severe pulmonary infection; another 2 patients died of grade IV aGVHD and heart failure, respectively. No patients had primary graft failure. The median time to the engraftment of neutrophil and platelet was 13 (10–21) and 15 (12–26) days, respectively. Of the 158 patients, 150 (94.9%) recipients achieved full donor chimerism within 28 days after transplantation.

PvB19 related PRCA

A total of 14 (8.5%) recipients were diagnosed with PvB19 related PRCA after a median of 5.3 (1.1–34.5) months posttransplant based on their clinical manifestations and serum PvB19-DNA viral loads. One patient had systemic PvB19 infection including PRCA and pneumonia. There were 6 recipients with viral loads $\leq 1 \times 10^8$ copies/mL and 8 recipients $> 1 \times 10^8$ copies/mL. Only 4 patients’ peripheral blood samples were tested for anti-PvB19 IgM, including 1 positive and 3 negatives. ABO blood group incompatible related PRCA were excluded from these patients. All of the patients achieved complete donor chimerism. The median hemoglobin and reticulocyte count were 45 (25–69) g/L and 0.17 (0.09–0.38) $\times 10^9$/L. All patients received high dose intravenous immunoglobulin (IVIG, 400 mg/kg/d × 5 d) therapy. Twelve (85.7%) patients had obvious improvement of hemoglobin level ($\geq 30$ g/L increase) within 1 month after treatment, including 6 patients with viral load $\leq 1 \times 10^8$ copies/mL and 6 patients $> 1 \times 10^8$ copies/mL. One patient with viral load $> 1 \times 10^8$ copies/mL had no response until 3 months after IVIG treatment. Only the patient with systemic PvB19 infection had no response and died 42 days after IVIG treatment. After 1-year follow-up, 11 patients had complete remission of PRCA; however, another 2 (14.3%) patients with PvB19 DNA above $1 \times 10^8$ copies/mL had recurrence of PvB19 related PRCA 3.5 months and 4.3 months after the first episode, respectively, but they also had complete remission of PRCA again within 2 months after repeated IVIG.

Risk factors of PvB19 related PRCA

We compared clinical characteristics between patients with and without PvB19 related PRCA (Table 1). The primary diagnosis of patients with and without PvB19 related PRCA was different ($P < 0.001$). The proportion of B-cell acute lymphoblastic leukemia (B-ALL) in patients with PvB19 related PRCA was significantly higher than patients without PvB19 related PRCA (64.3% vs. 14.0%, $P < 0.001$).

Thirteen clinical factors were taken into univariate analysis for PvB19 related PRCA. Factors with $P$ value $< 0.020$ were included in multivariable analysis. Among them, lymphoid hematological malignancies (RR = 4.292, $P = 0.006$) and HCT-CI $\geq 3$ (RR = 9.010, $P = 0.007$) were independent risk factors for PvB19 related PRCA (Table 2).

Immune reconstitution

We compared lymphocyte subset counts of patients with and without PvB19 related PRCA on the 3rd, 5th, and 12th months after haplo-PBSCT. On the 3rd month and 5th month posttransplant, patients with PvB19 related PRCA had significantly lower total lymphocytes ($P = 0.018$ and 0.002), CD3 $+$ ($P = 0.022$ and 0.003), CD4$^+$ ($P = 0.045$ and 0.020), and CD8$^+$ ($P = 0.033$ and 0.006) lymphocyte counts (Fig. 1A and Table 3). Moreover, on the 5th month posttransplant, patients with PvB19 related PRCA also had less CD19$^+$ ($P = 0.059$), CD4$^+$CD25$^+$ ($P < 0.001$), CD4$^+$CD45RO$^+$ ($P = 0.044$), and CD8$^+$CD45RO$^+$ ($P = 0.035$) lymphocyte counts (Table 3). However, on the 12th month posttransplant, the total and lymphocyte subset counts in patients with and without PvB19 related PRCA were similar (Fig. 1B). Other than that, serum levels of IgG, IgM, and IgA in patients with PvB19 related PRCA were relatively lower than those in patients without PvB19 related PRCA on the 5th month after transplantation, but no significant difference was found. Additional, the serum levels of IgG, IgM, IgA were similar between patients with and without PvB19 related PRCA on the 1st month and 12th month posttransplant (Fig. 2).

GVHD

A total of 25 (15.2%) patients developed grade II–IV aGVHD within 100 days. The median onset time of aGVHD was 18 (9–95) days posttransplant. In patients with PvB19 related PRCA, 2 (14.3%) patients developed grade II–IV aGVHD within 100 days (Table 4). Both of the patients had intensified GVHD therapy when they were diagnosed with PvB19 related PRCA. In terms of
| Variables                          | All patients (N=164) | Patients with PvB19 related PRCA (N=14) | Patients without PvB19 related PRCA (N=150) | P value |
|-----------------------------------|----------------------|------------------------------------------|---------------------------------------------|---------|
| Recipient age, yr, n (%)          |                      |                                          |                                             | 0.085   |
| < 39                              | 81 (49.4)            | 10 (6.1)                                 | 71 (43.3)                                   |         |
| ≥ 39                              | 83 (50.6)            | 4 (2.4)                                  | 79 (48.2)                                   |         |
| Recipient sex, n (%)              |                      |                                          |                                             | 0.546   |
| Male                              | 105 (64.1)           | 10 (6.1)                                 | 95 (58.0)                                   |         |
| Female                            | 59 (35.9)            | 4 (2.4)                                  | 55 (33.5)                                   |         |
| Diagnosis, n (%)                  |                      |                                          |                                             | <0.001  |
| AML                               | 87 (53.0)            | 3 (1.8)                                  | 84 (51.2)                                   |         |
| B-ALL                             | 30 (18.3)            | 9 (5.5)                                  | 21 (12.8)                                   |         |
| T-ALL                             | 7 (4.3)              | 0                                        | 7 (4.3)                                     |         |
| MDS                               | 23 (14.0)            | 2 (1.2)                                  | 21 (12.8)                                   |         |
| NHL                               | 17 (10.4)            | 0                                        | 17 (10.4)                                   |         |
| R-DRI, n (%)                      |                      |                                          |                                             | 0.158   |
| Low                               | 13 (7.9)             | 3 (1.8)                                  | 10 (6.1)                                    |         |
| Intermediate                      | 126 (76.9)           | 8 (4.9)                                  | 118 (72.0)                                  |         |
| High                              | 25 (15.2)            | 3 (1.8)                                  | 22 (13.4)                                   |         |
| Very high                         | 0                    | 0                                        | 0                                            |         |
| Disease status, n (%)             |                      |                                          |                                             | 0.540   |
| CR                                | 111 (67.7)           | 11 (6.7)                                 | 100 (61.0)                                  |         |
| NR                                | 53 (32.3)            | 3 (1.8)                                  | 50 (30.5)                                   |         |
| HCT-CI, n (%)                     |                      |                                          |                                             | 0.899   |
| < 3                               | 148 (90.2)           | 12 (7.3)                                 | 136 (82.9)                                  |         |
| ≥ 3                               | 16 (9.8)             | 2 (1.2)                                  | 14 (8.6)                                    |         |
| Donor age, yr, n (%)              |                      |                                          |                                             | 1.000   |
| < 40                              | 116 (70.7)           | 10 (6.1)                                 | 106 (64.6)                                  |         |
| ≥ 40                              | 48 (29.3)            | 4 (2.5)                                  | 44 (26.8)                                   |         |
| Donor-recipient sex match, n (%)  |                      |                                          |                                             | 0.773   |
| Female to male                    | 36 (21.9)            | 4 (2.4)                                  | 32 (19.5)                                   |         |
| Others                            | 128 (78.1)           | 10 (6.1)                                 | 118 (72.0)                                  |         |
| Donor, n (%)                      |                      |                                          |                                             | 0.822   |
| Parents                           | 45 (27.4)            | 4 (2.4)                                  | 41 (25.0)                                   |         |
| Sibling                           | 33 (20.1)            | 3 (1.8)                                  | 30 (18.3)                                   |         |
| Offspring                         | 81 (49.4)            | 7 (4.3)                                  | 74 (45.1)                                   |         |
| Cousin                            | 5 (3.1)              | 0                                        | 5 (3.1)                                     |         |
| ABO blood type, n (%)             |                      |                                          |                                             | 0.221   |
| Compatible                        | 83 (50.6)            | 6 (3.7)                                  | 77 (46.9)                                   |         |
| Minor incompatible                | 39 (23.8)            | 6 (3.7)                                  | 33 (20.1)                                   |         |
| Major or bidirectional incompatible| 42 (25.6)            | 2 (1.2)                                  | 40 (24.4)                                   |         |
| Conditioning regimen, n (%)       |                      |                                          |                                             | 0.580   |
| MAC                               | 140 (85.4)           | 13 (7.9)                                 | 127 (77.5)                                  |         |
| RIC                               | 24 (14.6)            | 1 (0.6)                                  | 23 (14.0)                                   |         |
| CD34+ cells in graft, n (%)       |                      |                                          |                                             | 0.831   |
| < 8 × 10^6/kg                     | 45 (27.4)            | 3 (1.8)                                  | 42 (25.6)                                   |         |
| ≥ 8 × 10^6/kg                     | 119 (72.6)           | 11 (6.7)                                 | 108 (65.9)                                  |         |
| Umbilical cord blood, n (%)       |                      |                                          |                                             | 0.962   |
| Yes                               | 83 (50.6)            | 7 (4.3)                                  | 76 (46.3)                                   |         |
| No                                | 81 (49.4)            | 7 (4.3)                                  | 74 (45.1)                                   |         |

PvB19 parvovirus B19, PRCA pure red cell aplasia, AML acute myeloid leukemia, B-ALL B-cell acute lymphoblastic leukemia, T-ALL T-cell acute lymphoblastic leukemia, MDS myelodysplastic syndrome, NHL non-Hodgkin’s lymphoma, R-DRI refined-disease risk index, CR complete remission, NR non-remission, HCT-CI hematopoietic cell transplantation comorbidity index, PBSC peripheral blood stem cell, MAC myeloablative conditioning, RIC reduced-intensity conditioning
the incidences of grade II–IV and III–IV aGVHD, 1-year cGVHD and moderate to severe cGVHD, there were no significant differences between patients with and without PvB19 related PRCA (14.3% vs. 15.3%, \( P = 0.916 \); 7.1% vs. 4.0%, \( P = 0.607 \); 14.3% vs. 21.2%, \( P = 0.781 \) and 7.1% vs. 15.3%, \( P = 0.664 \); respectively) (Table 4).

### CMV, EBV, and BKV infection

The incidences of CMV, EBV, and BK virus (BKV) infection were similar between patients with and without PvB19 related PRCA within 5 months posttransplant (42.9% vs. 39.3%, \( P = 0.797 \); 28.6% vs. 28.7%, \( P = 0.994 \); 21.4% vs. 12.7%, \( P = 0.610 \) (Table 5).

### Relapse

After a median of 13.9 (0.4 – 41.8) months follow-up, 29 patients relapsed. The median time to relapse was 7.6 (2.5 – 22.6) months. In patients with PvB19 related PRCA, 5/14 (35.7%) patients relapsed. Three of them had PvB19 related PRCA, and diseases relapse simultaneously. The other two patients had disease relapse within 2 months after the diagnosis of PvB19 related PRCA. Compared with patients without PvB19 related PRCA, the 1-year relapse rate in patients with PvB19 related PRCA was relatively higher; however, there were no significant differences (21.4% vs. 13.3%, \( P = 0.074 \) (Fig. 3A).
Survival

By the end of follow-up, 49 patients died; 39 (79.6%) of them died within 1 year. In patients with PvB19 related PRCA, 8/14 (57.1%) patients died, 5 of them died of infection (including one patient died of disseminated PvB19 infection), and 3 of them died of disease relapse. In patients without PvB19 related PRCA, 41/150 (27.3%) patients died. Eighteen of them died of disease relapse, 16 died of infection, 2 died of cerebral hemorrhage, 2 died of graft rejection, 1 died of heart failure, 1 died of grade IV aGVHD, and 1 of severe cGVHD. The 1-year NRM, OS, RFS, and GRFS were

---

**Table 3** Comparison of lymphocytes subset counts of patients with and without PvB19 related PRCA on the 5th months posttransplant

| Lymphocyte subsets | Patients with PvB19 related PRCA (N=10) | Patients without PvB19 related PRCA (N=54) | t value | P value |
|--------------------|-----------------------------------------|---------------------------------------------|--------|--------|
| Total lymphocyte (10⁹/L) | 1.03±0.18 (0.65~1.42) | 2.22±0.18 (1.86~2.57) | 3.30 | 0.002 |
| CD3⁺ (10⁹/L) | 0.72±0.14 (0.41~1.0) | 1.69±0.16 (1.37~2.00) | 3.05 | 0.003 |
| CD3⁺CD4⁺CD8⁻ (10⁹/L) | 0.14±0.05 (0.04~0.24) | 0.24±0.02 (0.20~0.27) | 2.38 | 0.020 |
| CD3⁺CD4⁺CD8⁺ (10⁹/L) | 0.53±0.10 (0.31~0.74) | 1.33±0.14 (1.05~1.61) | 2.85 | 0.006 |
| CD4/CD8 | 0.28±0.05 (0.16~0.39) | 0.26±0.03 (0.20~0.32) | 0.33 | 0.743 |
| CD4⁺CD25⁺ (10⁶/L) | 2.09±0.78 (0.41~3.77) | 13.30±1.37 (10.54~16.05) | 4.09 | <0.001 |
| CD8⁺CD25⁺ (10⁶/L) | 1.38±0.64 (−0.01~2.76) | 1.77±0.20 (1.36~2.18) | 0.77 | 0.445 |
| CD₃⁺CD6₉⁺ (10⁶/L) | 32.14±10.78 (8.86~55.42) | 64.98±25.00 (14.85~115.10) | 0.66 | 0.511 |
| CD₃⁺HLA-DR⁺ (10⁹/L) | 87.58±18.88 (46.78~128.40) | 198.40±21.76 (154.80~242.10) | 2.52 | 0.014 |
| CD₄⁺CD₄₅RA⁺ (10⁹/L) | 2.65±0.75 (1.03~4.27) | 10.64±1.56 (7.51~13.76) | 2.58 | 0.012 |
| CD₄⁺CD₄₅RO⁺ (10⁹/L) | 134.50±46.08 (34.98~234.10) | 217.20±16.78 (183.60~1250.90) | 2.05 | 0.044 |
| CD₈⁺CD₄₅RA⁺ (10⁹/L) | 101.00±47.50 (1.67~203.60) | 342.90±43.11 (256.40~429.40) | 2.74 | 0.008 |
| CD₈⁺CD₄₅RO⁺ (10⁹/L) | 411.40±83.99 (229.90~592.90) | 888.70±110.30 (667.40~1110.00) | 2.15 | 0.035 |
| CD₄⁺CD₉₂⁺ (10⁹/L) | 109.60±34.80 (34.40~184.80) | 194.80±18.79 (157.10~232.50) | 2.08 | 0.041 |
| CD₈⁺CD₂₈⁺ (10⁹/L) | 118.50±34.81 (43.26~193.60) | 215.00±17.97 (179.00~251.10) | 2.45 | 0.017 |
| CD₁₉⁺ (10⁶/L) | 0.06±0.02 (0.02~0.09) | 0.12±0.02 (0.09~0.16) | 1.92 | 0.059 |
| CD₁₆⁺CD₅₆⁺ (10⁶/L) | 0.24±0.07 (0.09~0.38) | 0.38±0.05 (0.28~0.48) | 1.41 | 0.164 |

PvB19 parvovirus B19, PRCA pure red cell aplasia, M mean, SEM standard error of mean

**Fig. 2** Levels of IgG, IgM, and IgA on the 1st, 5th, and 12th months after transplantation
In this study, we analyzed data of 164 recipients of haplo-PBSCT with low-dose ATG/PTCy followed by CSA/MMF for GVHD prophylaxis. Fourteen (8.5%) recipients developed PvB19 related PRCA posttransplant after a median of 5.3 months. Patients with lymphoid hematological malignancies especially B-ALL or HCT-CI ≥ 3 had higher risk for PvB19 related PRCA. Compared with patients without PvB19 related PRCA, patients with PvB19 related PRCA had slower immune reconstitution, similar incidences of acute and chronic GVHD, relapse rate, OS, RFS, and GRFS.

There were some case reports of PvB19 related PRCA after allo-HSCT sporadically; however, the incidence and clinical outcomes in recipients of allo-HSCT especially haplo-PBSCT were lacking. Nevertheless, there were many studies on the incidence of PvB19 related PRCA in solid organ transplantation. It was reported that the incidences of PvB19 related PRCA in adult and pediatric liver transplant recipients were about 2.3% [19, 20] and 9.3% respectively [21]. In renal transplant recipients, a meta-analysis showed the prevalence was 7.6% [22]. The incidence was similar between patients with and without PRCA (14.2% vs. 14.0%, $P = 0.078$; 78.6% vs. 75.4%, $P = 0.159$; 63.5% vs. 71.2%, $P = 0.050$; 48.9% vs. 62.8%, $P = 0.145$; respectively) (Figs. 3B, 4A, B, and C).

### Discussion

In this study, we analyzed data of 164 recipients of haplo-PBSCT with low-dose ATG/PTCy followed by CSA/MMF for GVHD prophylaxis. Fourteen (8.5%) recipients developed PvB19 related PRCA posttransplant after a median of 5.3 months. Patients with lymphoid hematological malignancies especially B-ALL or HCT-CI ≥ 3 had higher risk for PvB19 related PRCA. Compared with patients without PvB19 related PRCA, patients with PvB19 related PRCA had slower immune reconstitution, similar incidences of acute and chronic GVHD, relapse rate, OS, RFS, and GRFS.

There were some case reports of PvB19 related PRCA after allo-HSCT sporadically; however, the incidence and clinical outcomes in recipients of allo-HSCT especially haplo-PBSCT were lacking. Nevertheless, there were many studies on the incidence of PvB19 related PRCA in solid organ transplantation. It was reported that the incidences of PvB19 related PRCA in adult and pediatric liver transplant recipients were about 2.3% [19, 20] and 9.3% respectively [21]. In renal transplant recipients, a meta-analysis showed the prevalence was 7.6% [22]. The incidence was

| GVHD, n (%) | All patients ($n=164$) | Patients with PvB19 related PRCA ($n=14$) | Patients without PvB19 related PRCA ($n=150$) | $P$ value |
|-------------|------------------------|------------------------------------------|---------------------------------------------|----------|
| II–IV aGVHD | 25 (15.2)              | 2 (14.3)                                 | 23 (15.3)                                   | 0.916    |
| III–IV aGVHD| 8 (4.3)                | 1 (7.1)                                  | 6 (4.0)                                     | 0.607    |
| 1 year-cGVHD| 34 (20.6)              | 2 (14.3)                                 | 32 (21.2)                                   | 0.781    |
| 1 year-moderate to severe cGVHD | 24 (14.6) | 1 (7.1) | 23 (15.3) | 0.664 |

GVHD graft-versus-host disease, PvB19 parvovirus B19, PRCA pure red cell aplasia

| Viremia, n (%) | All patients ($n=164$) | Patients with PvB19 related PRCA ($n=14$) | Patients without PvB19 related PRCA ($n=150$) | $P$ value |
|---------------|------------------------|------------------------------------------|---------------------------------------------|----------|
| CMV           | 65 (39.6)              | 6 (42.9)                                 | 59 (39.3)                                   | 0.797    |
| EBV           | 47 (28.7)              | 4 (28.6)                                 | 43 (28.7)                                   | 0.994    |
| BKV           | 22 (13.4)              | 3 (21.4)                                 | 19 (12.7)                                   | 0.610    |

PvB19 parvovirus B19, PRCA pure red cell aplasia, CMV cytomegalovirus, EBV Epstein-bar virus, BKV BK virus

Fig. 3 Cumulative incidences of relapse and non-relapse mortality (NRM) of patients with and without parvovirus B19 related pure red cell aplasia. A: Cumulative incidence of relapse; B: Cumulative incidence of NRM
similar between our study and reported data in liver and renal transplantation.

We found patients with lymphoid hematological malignancies especially B-ALL or HCT-CI ≥ 3 had higher risk for PvB19 related PRCA. The reason might be the lymphodepleting regimen for B-ALL with cyclophosphamide and fludarabine in our study, which resulted in severe immune deficiency after transplant. Previous study found higher HCT-CI score was closely related to increased risk of viral infection [23]; our study was in accordance with it. Since there was no specific antiviral agent for PvB19, present treatments for PvB19 related PRCA included tapering of immunosuppression and high dose IVIG [24, 25]. In a retrospective study on 10 immunocompromised patients, Crabol et al. reported 90% patients had improvement of hemoglobin levels after one course of IVIG treatment. However, about 30% patients had recurrence of PvB19 related PRCA within a median of 4 months [25]. Our study showed similar response rate and relatively lower recurrent rate based on larger case data.

In our study, patients with PvB19 related PRCA had significantly lower counts of CD3+, CD4+, CD8+, CD4+CD45RO+, and CD8+CD45RO+ T lymphocyte and CD19+ B lymphocyte on the 5th month posttransplant. McCuedy et al. reported that the median counts of CD4+, CD8+ T lymphocytes, and CD19+ B lymphocytes were 0.2×10^9/L, 0.4×10^9/L, and 0.1×10^9/L on the 6th month after haplo-PBSCT [26]. In the present study, the median counts of lymphocyte subsets in patients without PvB19 related PRCA were consistent with the report above, whereas patients with PvB19 related PRCA had significantly less lymphocytes subset posttransplant. It was reported that recipients after solid organ transplantation or allo-HSCT with significantly lower counts of CD3+, CD4+, and CD8+ T cell were prone to PvB19 infection, and about 99% of immunocompromised patients with PvB19 infection would develop PRCA due to reduction of antiviral T cells and lack of diversity of T cell receptor [6, 27]. Vassiliki et al. also found virus infection was negatively associated with the number of CD4+ (P = 0.030), CD8+ cells (P = 0.030), CD4+CD45RO+ cells (P = 0.030), and CD8+CD45RO+cells (P = 0.050) after umbilical cord blood transplantation [28]. In addition, previous study showed insufficient quantity and quality of B cell after transplantation were also responsible for the persistence and recurrence of PvB19 infection [29]. These patients could not produce sufficient immunoglobulin, which leads to chronic and long-term infection of PvB19 [30].

The incidences of grade II–IV aGVHD and 1-year moderate-to severe cGVHD were similar in patients with and without PvB19 related PRCA in our study. We supposed it was due to the effective GVHD prophylaxis regimen with low-dose ATG/
PTCy in our study [31]. Besides, patients with PvB19 related PRCA had similar total lymphocytes and subsets counts on the 12th month after transplantation. This might be the major reason for similar incidence of cGVHD in patients with and without PvB19 related PRCA.

Relapse rate and overall survival in patients with and without PvB19 related PRCA were similar in this study. Reports about direct influences of PvB19 related PRCA on relapse and survival after allo-HSC are very rare. In renal transplantation, PvB19 related PRCA has no significant effect on long-term posttransplant survival [32]. PvB19 related PRCA was rarely life-threatening in the majority of cases except for disseminated PvB19 infection [9]. It is a complication closely related to immunocompromised status early posttransplant. In other words, infection with PvB19 indicates relatively delayed and poor immune reconstitution of the recipients early after transplantation, but immunity would gradually restore in the long run. The lymphocytes were lower in the early stage but gradually reconstituted in the later stage in patients with PvB19 related PRCA in our study.

In conclusion, our study showed that 8.5% recipients of haplo-PBSCST developed PvB19 related PRCA after a median of 5.3 months posttransplant, which indicated lower immune status of the recipients early after transplantation, but PvB19 related PRCA had no direct influences on GVHD, relapse, and survival.

Funding This work was supported by the Clinical Research Innovation Plan of Shanghai General Hospital, Shanghai Shen Kang Hospital Development Center under Grant SHDCCR2020CR3028B, SHDCCR2020CR1012B, 16CR1010A and SHDC12018X09, Shanghai General Hospital under Grant CTCCR-2018B02 and CTCCR-2018BP03, Science and Technology Commission of Shanghai Municipality under Grant 18411968400, Shanghai Municipal Health and Family Planning Commission under Grant 201840043, and National Clinical Research Center for Hematologic Disease under Grant 2020ZKPC02.

Declarations

Ethics approval This study was approved by the Clinical Research Ethics Committee of Shanghai, China. All procedures in this study were conducted in accordance with the Shanghai Municipal Clinical Research Ethics Committee approved protocols.

Consent to participate Written informed consent was obtained from the patient(s) for their anonymized information to be published in this article.

Conflict of interest The authors declare no competing interests.

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 licence, and indicate if changes were made. The images or other third party material in this article are included in the article’s Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article’s Creative Commons licence 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 licence, visit http://creativecommons.org/licenses/by/4.0/.

References

1. Gama BE, Emmel VE, Oliveira-Silva M et al (2017) Parvovirus B19 in the context of hematopoietic stem cell transplantation: evaluating cell donors and recipients. Transplant Direct 3:e217
2. Landry ML (2016) Parvovirus B19. Microbiol Spectr 4
3. Cohen BJ, Buckley MM (1988) The prevalence of antibody to human parvovirus B19 in England and Wales. J Med Microbiol 25:151–153
4. Koda Y, Mori T, Kato J et al (2013) Persistent parvovirus B19 infection resulting in red cell aplasia after allogeneic hematopoietic stem cell transplantation. Transpl Infect Dis 15:E239–242
5. Arnold DM, Neame PB, Meyer RM et al (2005) Autologous peripheral blood progenitor cells are a potential source of parvovirus B19 infection. Transfusion 45:394–398
6. Eid AJ, Brown RA, Patel R, Razonable RR (2006) Parvovirus B19 infection after transplantation: a review of 98 cases. Clin Infect Dis 43:40–48
7. Inazawa N, Hori T, Nojima M et al (2017) Virus reactivation after autologous hematopoietic stem cell transplantation detected by multiplex PCR assay. J Med Virol 89:358–362
8. Shao EX, Wang CSW, Javorský G (2018) Parvovirus B19 induced red cell aplasia in a heart transplant patient diagnosed on pleural fluid. Transplantation 102:e367–e368
9. Means RT Jr (2016) Pure red cell aplasia. Blood 128:2504–2509
10. Fujiwara S, Hattori N, Matsui T et al (2019) Refined disease risk index for hematological malignancies, including rare disorders, after allogeneic stem cell transplantation. Transplant Proc 51:3437–3443
11. Sorror ML, Maris MB, Storb R et al (2005) Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood 106:2912–2919
12. Xu X, Yang J, Cai Y et al (2021) Low dose anti-thymocyte globulin with low dose posttransplant cyclophosphamide (low dose ATG/PTCy) can reduce the risk of graft-versus-host disease as compared with standard-dose anti-thymocyte globulin in haploidentical peripheral hematopoietic stem cell transplantation combined with unrelated cord blood. Bone Marrow Transplant 56:705–708
13. Sun X, Yang J, Cai Y et al (2021) Low-dose antithymocyte globulin plus low-dose posttransplant cyclophosphamide combined with cyclosporine and mycophenolate mofetil for prevention of graft-versus-host disease after HLA-matched unrelated donor peripheral blood stem cell transplantation. Bone Marrow Transplant 56:2423–2431
14. Yang J, Jiang J, Cai Y et al (2019) Low-dose anti-thymocyte globulin plus low-dose posttransplant cyclophosphamide as graft-versus-host disease prophylaxis in haploidentical peripheral blood stem cell transplantation combined with unrelated cord blood for patients with hematologic malignancies: a prospective, phase II study. Bone Marrow Transplant 54:1049–1057
15. Sun X, Yang J, Cai Y et al (2021) Low-dose antithymocyte globulin plus low-dose posttransplant cyclophosphamide combined with cyclosporine and mycophenolate mofetil for prevention of graft-versus-host disease after HLA-matched unrelated donor
peripheral blood stem cell transplantation. Bone Marrow Transplant 56(10):2423–2431
16. Jiang Y, Wan LP, Qin YW et al (2014) Chimerism status is correlated to acute graft-versus-host disease after allogeneic stem cell transplantation. Int J Hematol 99:322–328
17. Red Blood Cell Disease (Anemia) Group CSoH (2020) [Chinese expert consensus on the diagnosis and treatment of acquired pure red cell aplasia (2020)]. Zhonghua Xue Ye Xue Za Zhi 41:177–184
18. Mangla A, Hamad H (2021) Pure red cell aplasia. In StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2021, StatPearls Publishing LLC
19. Zhang M, Zhong X, Zhang W et al (2015) Human parvovirus B19 infection induced pure red cell aplasia in liver transplant recipients. Int J Clin Pract 69(Suppl. 183):29–34
20. Zhang J, Ren B, Hui R et al (2018) Clinical heterogeneity of human parvovirus B19 infection following adult liver transplantation. Medicine (Baltimore) 97:e12074
21. Würdinger M, Modrow S, Plentz A (2017) Impact of parvovirus B19 viremia in liver transplanted children on anemia: a retrospective study. Viruses 9(6):149
22. Thongprayoon C, Khoury NJ, Bathini T et al (2020) Epidemiology of parvovirus B19 and anemia among kidney transplant recipients: a meta-analysis. Urol Ann 12:241–247
23. Friend BD, Broglie L, Logan B et al (2020) Expanded comorbidity definitions improve applicability of the hematopoietic stem cell transplantation-comorbidity index for children, adolescents, and young adults with hematologic malignancies undergoing allogeneic stem cell transplantation. Blood 136:34–35
24. Sackett K, Cohn CS, Fahey-Ahrendt K et al (2018) Successful treatment of pure red cell aplasia because of ABO major mismatched stem cell transplant. J Clin Apher 33:108–112
25. Crabol Y, Terrier B, Rozenberg F et al (2013) Intravenous immunoglobulin therapy for pure red cell aplasia related to human parvovirus B19 infection: a retrospective study of 10 patients and review of the literature. Clin Infect Dis 56:968–977
26. McCurdy SR, Luznik L (2019) Immune reconstitution after T-cell replete HLA-haploidentical transplantation. Semin Hematol 56:221–226
27. Guan J, Sun Y, Fu R et al (2019) A study of immune functionality of newly diagnosed severe aplastic anemia patients with virus infection. Clin Lab 65(6). https://doi.org/10.7754/Clin.Lab.2018.180905
28. Karantanos T, Kim HT, Tijaro-Ovalle NM et al (2019) Reactivation of BK virus after double umbilical cord blood transplantation in adults correlates with impaired reconstitution of CD4(+)+ and CD8(+) T effector memory cells and increase of T regulatory cells. Clin Immunol 207:18–23
29. Young NS, Brown KE (2004) Parvovirus B19. N Engl J Med 350:586–597
30. Obeid KM (2019) Infections with DNA viruses, adenovirus, polyomaviruses, and parvovirus B19 in hematopoietic stem cell transplant recipients and patients with hematologic malignancies. Infect Dis Clin North Am 33:501–521
31. Luznik L, O’Donnell PV, Symons HJ et al (2008) HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide. Biol Blood Marrow Transplant 14:641–650
32. Krishnan P, Ramadas P, Rajendran PP et al (2015) Effects of parvovirus B19 infection in renal transplant recipients: a retrospective review of three cases. Int J Angiol 24:87–92

Publisher’s note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.