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Haploidentical, Unmanipulated Granulocyte Colony-Stimulating Factor (G-CSF)-Primed Peripheral Blood Stem Cell Transplants for Acute Myeloid Leukemia (AML) in Remission: A Single Center Experience

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Background: Data about application of related haploidentical allogeneic hematopoietic stem cell transplantation (haplo-HSCT) on patients with high-risk or intermediate-risk acute myeloid leukemia (AML) in the first complete remission (CR1) are lacking. In this study, we report the outcomes of using unmanipulated haploidentical allogeneic peripheral blood stem cell transplantation (haplo-PBSCT) as post-remission therapy for patients with high-risk or intermediate-risk AML in CR1.

Material/Methods: From January 2008 to July 2016, 33 patients diagnosed as high-risk or intermediate-risk AML in CR1 undergoing haplo-PBSCT in our institution were enrolled for analysis. The cumulative incidence of platelet and neutrophil recovery, the occurrence of acute graft-versus-host-disease (GVHD) and chronic GVHD, relapse and non-relapse mortality were assessed. Patients' survival rates were estimated using the Kaplan-Meier method.

Results: The cumulative incidence of grade 2-4 acute GVHD, overall and extensive chronic GVHD was 18.2%, 9.1%, and 6.1%, respectively. 2-year probability of relapse was 9.1%. Disease-free survival and overall survival at 2 years were 72.7% and 75.8%, respectively.

Conclusions: Our results showed that unmanipulated haploidentical transplantation with G-CSF primed PBSC alone as a graft source could be an acceptable alternative post-remission treatment for high-risk or intermediate-risk AML patients in CR1 lacking a matched donor.


MeSH Keywords: Bone Marrow Transplantation • Haploidy • Leukemia, Myeloid, Acute

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Background

Acute myeloid leukemia (AML) is one of the most common hematologic malignancies. Even though the majority of AML patients could enter remission upon induction chemotherapy, the risk of relapse is considerable, and the risk varies according to patient age and genetic profiles [1]. Allogeneic hematopoietic cell transplantation (allo-HSCT) has been widely used for many years as a potentially post-remission strategy after first remission with induction chemotherapy for high-risk or intermediate-risk AML patients [1]. Although allo-HSCT from a matched sibling donor or HLA-matched unrelated donor (MUT) have been proved to be 2 of the best choices to cure AML, both have their own shortcomings. There are less than 30% of patients who could get a matched sibling donor allo-HSCT [2,3]. The large variability of HLA polymorphisms and the prolonged time to find a suitable donor limit the use of MUT transplantation, especially for recipients who are in a stage of high-risk of disease progression [2]. In recent years, the progress in HLA-mismatched haploidentical transplantations provide an applicable alternative for patients without an HLA-identical donor [3,4]. Researchers report that unmanipulated haploidentical transplantation with G-CSF primed bone marrow or peripheral blood stem cells as stem cell resource is viable treatment option for high-risk hematologic malignancies [2,5,6]. However, there are few works focusing on the study of patients with AML. The graft sources for allo-HSCT include bone marrow (BM), G-CSF primed PBSCs (G-PB), G-CSF primed BM (G-BM), or the combination of G-BM and G-PB. However, which one is optimal for unmanipulated haplo-identical HSCT under myeloablative conditioning regimen is still unknown. A study by Huang et al. found that as post-remission therapy, haploidentical HSCT has a significant survival advantage over chemotherapy alone [6] and in another study, haploidentical HSCT had a similar outcome compared with sibling-identical transplant for patients with high-risk or intermediate-risk AML in first complete remission (CR1) [7]. In these studies, the source of stem cell grafts was a combination of G-PB and G-BM. Other studies with G-PB as the source for haploidentical HSCT analyzed the short-term safety and efficacy for recipients with hematologic malignancies [8–10]. Recently, our group reported outcomes of unmanipulated haplo-PBSCT in high-risk hematologic malignancies [11]. However, the long-term outcomes of unmanipulated haploidentical transplantation for AML in CR1 by using G-CSF primed peripheral blood as a graft have not been determined. In this study, to evaluate the effect of haplo-PBSCT for the specific high-risk or intermediate-risk AML in CR1, the outcomes of 33 adult patients with high-risk or intermediate-risk AML in CR1 undergoing T cell replete haplo-PBSCT were analyzed.

Material and Methods

Patients

Thirty-three patients diagnosed as high-risk or intermediate-risk AML in CR1 undergoing haplo-PBSCT between January 2008 and July 2016 in our center were enrolled in this study. This study was approved by the Institutional Review Board of the Chinese PLA General Hospital. The informed consent materials were read and signed by all the patients and donors.

Conditioning regimens and GVHD prophylaxis

Thirty-three patients were given conditioning therapy with modified busulfan cyclophosphamide (Bu/Cy), which consisted of busulfan (3.2 mg/kg/day; days –10 to –8), cytarabine (4 g/m²/day; days –7 and –6), cyclophosphamide (60 mg/kg/day; days –4 and –3), carmustine (250 mg/m²; day –5), and rabbit anti-thymocyte globulin (ATG) (2.5 mg/kg/day; days –5 to –2). One patient was conditioned with FB regimen, which consisted of fludarabine (30 mg/m²/day; days –7 to –3), busulfan and ATG used in the same way as BuCy regimen. Cyclosporine A (CsA), short-term methotrexate (MTX), and mycophenolate mofetil (MMF) were used for GVHD prophylaxis.

Donor selection and stem cell harvest

Donors were selected based on age, sex, HLA-matched *loci*, and health status. Granulocyte colony-stimulating factor (G-CSF; 5–10 ug/kg/day; filgrastim, Kirin, Tokyo, Japan) were used to mobilize PB for 6 to 7 days. On the fifth and sixth days, PBSCs were collected and infused into the recipient. The target mononuclear cells count and CD34+ cells were >5×10⁸/kg and >2×10⁶/kg of recipient weight, respectively.

Infection prevention and supportive care

All patients were given antibiotic prophylaxis. Oral trimethoprim-sulfamethoxazole was given to prevent *Pneumocystis carinii* infection, fluconazole was used to against *Candida albicans* infection, ganciclovir was administered twice per day for prophylaxis of cytomegalovirus (CMV) infection. After transplantation, recipients were monitored every week by quantitative CMV PCR. Foscarnet or ganciclovir were used for the treatment of CMV antigenemia. All the blood products were irradiated with 2500 cGy. G-CSF (5 ug/kg/day) was given subcutaneously to all patients from day 3 after transplantation until the recovery of myeloid cells.

Monitoring of relapse and treatment

The minimal residual disease (MRD) was monitored at 1, 2, 3, 6, 9, 12, and 24 months after transplantation. Three months

after graft infusion, in MRD-positive patients, the dose of CsA was reduced to discontinuation until the development of GVHD. When a hematologic relapse occurred, CsA was immediately discontinued and the patients received chemotherapy followed by donor lymphocyte infusion (DLI) with the patient's agreement.

Definitions and assessment

The diagnosis of AML was as described previously [12]. Molecular screening was performed for all recipients. CR was diagnosed as BM blasts <5%, absence of extramedullary disease, no blasts with Auer rods, neutrophil count $>1 \times 10^9/L$, platelet (PLT) count $>100 \times 10^9/L$, and without red blood cell transfusion. MRD was defined as described previously [13]. MRD positivity was defined when it was tested to be abnormal in 2 consecutive assessments within 2 weeks. The high-risk group were defined as AML with the following characteristics: 1) AML with the Flt3-ITD mutation, t(9;22) or complex cytogenetic abnormalities (defined as at least 3 unrelated cytogenetic clones); 2) AML during the CR1 after 3 or more cycles of induction, AML in CR1 with positive MRD after 2 cycles of consolidation. Normal cytogenetics with NPM1 mutation in the absent of FLT3-ITD or isolated biallelic CEBPA mutation, and cytogenetic abnormalities t(15;17), t(8;21), t(16;16), or inv(16) were considered as low risk. Patients without low risk or high-risk abnormalities, or without karyotype information, or with KIT mutation were classified as the intermediate-risk group. GVHD and engraftment were evaluated as previously described [14]. Relapse was defined as reappearance of BM blasts >5%, reoccurrence of blasts in blood, or development of extramedullary disease.

Statistics

The cumulative incidence of neutrophil and platelet recovery, acute GVHD, chronic GVHD, relapse and non-relapse mortality were assessed. Patient survival was estimated using the Kaplan-Meier method. Cox proportional hazards model with time-dependent variables were used to calculate the potential risk factors. The date of the last follow-up for all recipients was October 31, 2017. SPSS version 17.0 (SPSS, Chicago, IL, USA) was used for analysis.

Results

Characteristics of patients

Table 1 provides the overview characteristics of the donors and patients.

Thirty-three patients aged 14 to 60 years (median age, 35 years), including 11 females and 22 males, underwent unmanipulated

Table 1. Patient and graft characteristics.

Characteristics	No. of case	%
Age, years, median (range)	35 (14–60)	
Gender, n (%)		
Male	23	(69.7)
Female	10	(30.3)
French-American-British subtype, no. (%)		
M0	0	
M1	0	
M2	15	(45.4)
M4	5	(15.1)
M5	9	(27.3)
M6	1	(3)
M7	0	
Undetermined	3	(9.1)
Risk group		
Intermediate-risk	28	(84.8)
High-risk	5	(15.1)
Donor/recipient relationship, n (%)		
Parent	13	(39.4)
Sibling	13	(39.4)
Child	7	(21.2)
No. of HLA loci mismatched (A/B/C/DRB1/DQB1), n(%)		
0	0	
1	4	(12.1)
2	2	(6.1)
3	5	(15.2)
4	1	(3)
5	21	(63.6)
Graft		
Mononuclear cells ($10^6/kg$)	9.6	(5.4–17.1)
CD34+ ($10^6/kg$)	4.72	(0.83–10.27)

haploidentical allogeneic PBSCT. All patients were diagnosed as high-risk or intermediate-risk AML in CR1, with no appropriate sibling donors or HLA-matched unrelated donors. All donors were HLA mismatched haplo-identical family donors, including

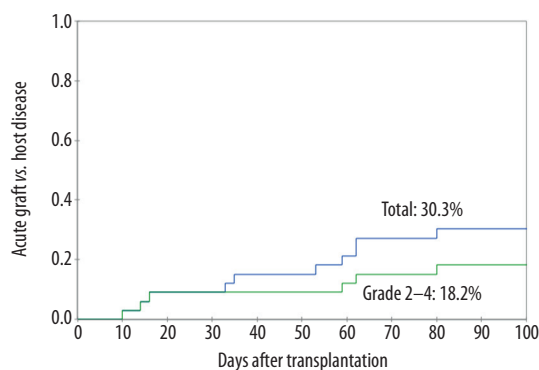


Figure 1. Cumulative incidence of acute and chronic GVHD. Total (blue line) and Grade II–IV (green line) acute GVHD.

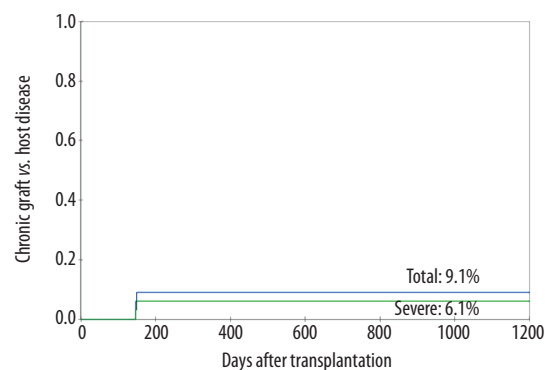


Figure 2. Cumulative incidence of acute and chronic GVHD. Overall (blue line) and extensive (green line) chronic GVHD.

Table 2. Univariate Cox regression analysis for aGVHD in patients (n=33).

Factors	Hazard ratio (95% CI)	P
Gender	0.980 (0.194–4.940)	0.980
Age	0.330 (0.068–1.607)	0.70
FAB subtype	1.035 (0.534–2.007)	0.918
HLA disparity	0.872 (0.496–1.532)	0.633
Donor type	0.355 (0.114–1.08)	0.075
Risk stratification	1.667 (0.233–11.929)	0.611
MNC amount	0.917 (0.208–4.084)	0.909
CD34 amount	0.917 (2.08–4.084)	0.909

aGVHD – acute graft-versus-host disease; MNC – mononuclear cell; CD34 – CD34 positive cell; CI – confidence interval.

fathers, mothers, daughters, sons, sisters, and brothers. HLA-mismatch between donors and recipients were at the allele level for HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQ1. Donor-recipient pairs were mismatched in 1 to 5 *loci*.

Engraftment

The median number of mononuclear cells (MNCs) and CD34+ cells infused at transplantation was $9.6 (5.4–17.1) \times 10^8/\text{kg}$ and $4.72 (0.8–10.3) \times 10^6/\text{kg}$, respectively. Thirty-two patients (97%) achieved sustained myeloid engraftment with full donor chimerism at a median of 14 days (10–28 days). Thirty-one patients (94%) achieved platelet engraftment at a median of 16 days (10–77 days); the other 2 patients failed to achieve platelets recovery after transplantation.

Table 3. Transplant related complications.

Complications	No. of patients	%
CMV infection	15	(45.4)
Pneumonia	6	(18.2)
Hemorrhage cystitis	6	(18.2)
Central nervous system	1	(3.0)
CMV related eye infection	1	(3.0)

GVHD development and severity

Ten patients experienced acute GVHD after transplantation. Four with Grade I acute GVHD, 4 with Grade II acute GVHD, 2 with Grade III acute GVHD. The cumulative incidence of grades I–IV and grades II–IV acute GVHD on Day 100 was $30.3 \pm 8\%$ and $18.2 \pm 6.7\%$, respectively (Figure 1). Cox regression showed that gender, age, FAB subtype, HLA disparity, donor type, risk stratification, MNC amount, and CD34 amount were not independent risk factors of acute GVHD (Table 2). Thirty-one patients who survived more than 100 days after transplantation were evaluated for chronic GVHD. Three of these patients developed chronic GVHD (1 limited, 2 extensive). The 2-year cumulative incidence of chronic GVHD was $9.1 \pm 5\%$, and the 2-year cumulative incidence of severe chronic GVHD was $6.1 \pm 4.2\%$ (Figure 2).

Transplantation-related complications

Fifteen patients (45.4%) had cytomegalovirus infection. Six patients (18.2%) had pneumonia, 6 patients (18.2%) had hemorrhagic cystitis, 1 patient (3%) had central nervous system infection, and 1 patient (3%) had CMV related eye infection (Table 3).

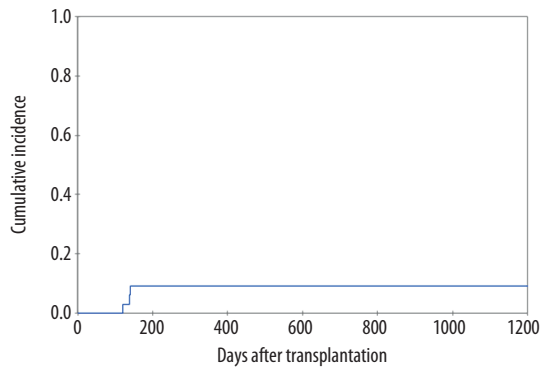


Figure 3. Cumulative incidence of relapse and non-relapse mortality. The 2-year cumulative incidence of relapse was $9.1 \pm 5\%$.

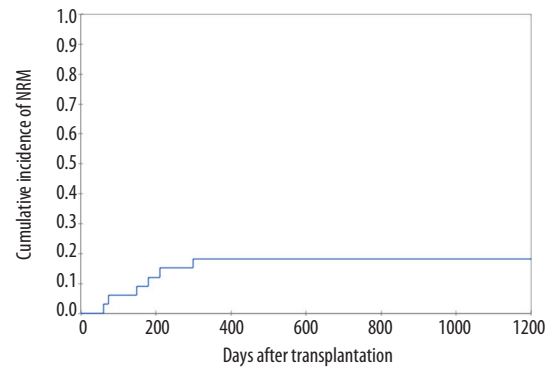


Figure 5. Cumulative incidence of relapse and non-relapse mortality (NRM). The 2-year cumulative incidence of NRM was $18.2 \pm 6.7\%$.

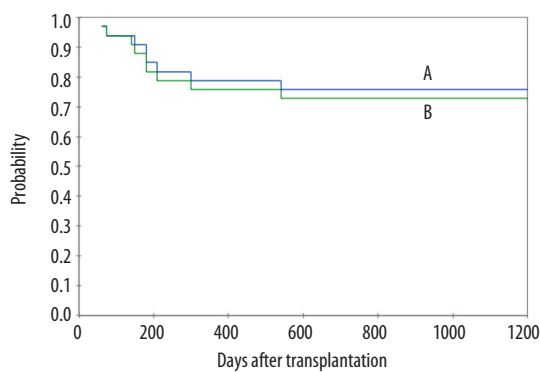


Figure 4. Kaplan-Meier estimates of OS and DFS after unmanipulated haploidentical PBSCT. The 2-year probability of OS and DFS were $75.8 \pm 7.5\%$ A) and $72.7 \pm 7.8\%$ B), respectively.

Relapse

By October 31, 2017, 3 patients had relapsed (2 with hematologic relapse, 1 with extramedullary relapse) at a median of 138 days (range, 120–140 days) after transplantation. The 2-year probability of relapse was $9.1 \pm 5\%$ (Figure 3). One hematologic relapse patient denied receiving any treatment and died after 2 months. The other hematologic relapse patient received chemotherapy with discontinuation of CsA, followed by DLI, and died after 13 months. The extramedullary relapse patient achieved remission after radiotherapy and discontinuation of CsA, and survived for 6 years after relapse. Overall, 2 patients died of disease recurrence.

Table 4. Univariate Cox regression analysis for overall survival in patients (n=33).

Factors	Hazard ratio (95% CI)	P
Gender	0.654 (0.132–3.243)	0.603
Age	3.724 (0.749–18.523)	0.108
FAB subtype	0.843 (0.440–1.614)	0.606
HLA disparity	0.923 (0.504–1.693)	0.796
Donor type	1.516 (0.624–3.679)	0.358
Risk stratification	0.659 (0.081–5.360)	0.696
MNC amount	0.592 (0.141–2.497)	0.476
CD34 amount	0.581 (0.138–2.436)	0.458

MNC – mononuclear cell; CD34 – CD34 positive cell; CI – confidence interval.

Survival

Until the last follow-up in October 31, 2017, 25 patients were still alive. Eight patients died (2 patients for relapse, 6 patients for transplantation-related complications). Among the 6 patients who died due to transplantation-related complications, 5 patients died from pneumonia and 1 patient died from hepatitis. The 2-year probabilities of overall survival (OS) and disease-free survival (DFS) were $75.8 \pm 7.5\%$ and $72.7 \pm 7.8\%$, respectively (Figure 4). The 2-year cumulative incidence of non-relapse mortality was 18.2% (Figure 5). Factors such as gender, age, FAB subtype, HLA disparity, donor type, risk stratification, MNC amount, and CD34 amount had no effect on OS (Table 4).

Discussion

Unmanipulated haploidentical HSCT has become more popular in recent years; encouraging results have been reported for the treatment of hematologic malignancies from several different centers, while the outcome of unmanipulated haplo-HSCT in a disease-specific population of patients with high-risk or intermediate-risk AML in CR1 is very limited. Recently, a group from Peking University compared haploidentical with identical-sibling transplantation for AML in CR1; the stem cell source they used were the combination of G-BM and PBSCs. However, in our retrospective study, we used PBSCs alone as a graft source for unmanipulated haplo-HSCT, and analyzed the clinical outcomes of this type of HSCT for treatment of high-risk or intermediate-risk AML in CR1. A PubMed search revealed that our work is the first study specifically investigating unmanipulated haploidentical G-CSF-primed PBSCs for AML in CR1 in China.

In our analysis, 32 patients (97%) achieved myeloid engraftment and 31 patients (94%) achieved platelet engraftment after HLA-mismatched/haploidentical PBST. One report by Xu et al. [8] compared the outcomes of haploidentical HSCT with PBSCs alone as a graft source or combination of G-BM and PB as graft source, and the results indicated better engraftment with G-BM/PB. However, in our study, myeloid reconstitution and platelet engraftment were comparable to that with G-BM/PB haplo-identical HSCT results reported by Xu et al. [15] (97% versus 100%, 94% versus 86%). The lower engraftment with PBST in the aforementioned study may relate to the relatively lower stem cell number. The number of CD34+ cells and MNCs are critical for engraftment [16]. In our study, the median numbers of MNC ($9.6 \times 10^8/\text{kg}$) and CD34+ cells ($4.72 \times 10^6/\text{kg}$) are higher than those ($7.14 \times 10^8/\text{kg}$ and $2.54 \times 10^6/\text{kg}$, respectively) reported by Xu et al. In our study, of the 2 patients who experienced graft failure, 1 patient achieved myeloid engraftment but did not achieve platelet engraftment until death, and he died 6 months after transplantation due to infection and failed platelet engraftment; the number of CD34+ and MNCs for this patient were normal. Another patient did not achieve both myeloid and platelet engraftment until death, she died just 2 month after transplantation, due to the graft failure; the number of CD34+ cells ($0.827 \times 10^6/\text{kg}$) in this patient was very low, which was consistent with stem cell number critical for engraftment.

Regarding GVHD, the rates of GVHD observed after HLA-mismatched/haploidentical PBST in our AML CR1 population were lower than those described in Huang et al. report after haploidentical HSCT using a G-BM/PB as a graft source [7]. The cumulative incidences of grade II to IV acute GVHD, chronic GVHD, and extensive chronic GVHD in the Huang et al. report [7] were 36%, 42%, and 12%, respectively. Furthermore, when compared with their report about HLA-identical sibling HSCT [7],

the incidence of GVHD in our study were comparable if not lower. There are also trials showing a significantly higher incidence of acute GVHD and chronic GVHD in PBSC recipients compared with BM recipients in HLA-matched sibling transplantation [17,18]. While a report about unrelated transplants showed that the different incidence of GVHD could be abolished with the use of ATG for GVHD prophylaxis [19]. The lower incidences of acute GVHD and chronic GVHD in our study may be associated with the using of short-term MTX, CsA, and MMF for GVHD prophylaxis, the addition of ATG for conditioning regimen [20], and the infusion of PBSCs mobilized by G-CSF [21]. A large-scale study is still needed to further clarify the differences between using G-PB alone or G-BM/PB as stem cell source for HLA-mismatched/haploidentical transplantation.

Other important limitations to survival benefit of applying HLA-mismatched/haploidentical transplant are relapse and transplantation-related mortality [22]. Even though the use of ATG significantly reduce the occurrence of severe GVHD, the relatively delayed immune reconstitution and higher frequency of infection should be noticed. In our present analysis, the 2-year probability of relapse was only $9.1 \pm 5\%$, lower than those reported by Huang et al. [7]. While it should be noted that the non-relapse mortality was relatively high and the major cause of death in this study was infection, effective infection control needs to be improved. The OS and DFS in our analysis were similar to those AML patients in CR1 undergoing haploidentical donor transplantation in a Huang et al. study report [6] (75% versus 79%, 72% versus 74%).

The major difference between the protocol in Huang group study and our method was the using G-PB alone or in combination with marrow cells as stem cell source. By using G-BM/PB as the graft source, the Huang group demonstrated that in patients with high-risk or intermediate-risk AML in CR1, the HLA-mismatched haplo-identical transplantation had outcomes similar to identical-sibling transplant [7] and superior to chemotherapy alone [6]. Compared with these reports, our retrospective study showed a lower incidence of II to IV acute GVHD and chronic GVHD, a comparable OS and DFS, and in addition, a little bit higher but acceptable non-relapse mortality, although it should be noted that there is deficiency in comparability between different transplantation centers.

Conclusions

Although the effects of identical-sibling HSCT has been well established in patients with AML in CR1 [12,23,24], a lot of patients do not get the appropriate donor in a timely manner because of limited family members and genetic differences, making the case for the application of haploidentical HSCT in AML to be extended [25,26]. Our risk factor analysis for clinical

outcomes indicated that gender, age, FAB subtype, HLA disparity, donor type, risk stratification, MNC amount and CD34 amount had no effect on OS or acute GVHD, and thus would make it easier to consider the application of haploidentical PBSCT in clinical work. Our data support the reliability of considering haploidentical HSCT with G-CSF primed PBSCs as a graft source and a viable alternative choice for patients with high-risk or intermediate-risk AML in CR1 lacking a matched donor.

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Data availability statements

The data that support the findings of this study are available from Chinese PLA General Hospital, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of Chinese PLA General Hospital.

Conflict of interest

None.