ARTICLE

Sequential haplo-identical conditioning transplant regimen for pediatric patients with relapsed or refractory hemophagocytic lymphohistiocytosis

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Allogeneic hematopoietic stem cell transplantation (HSCT) currently stands as the sole remedy for individuals afflicted with hemophagocytic lymphohistiocytosis (HLH). In this study, we retrospectively evaluated how pediatric patients with relapsed or refractory (R/R) HLH responded to our institution's cocktail conditioning regimen. The disease was diagnosed according to criteria applicable to patients with familial/genetic, relapsing, or severe/persistent HLH. All donors were HLA haplo-identical family donors. In our cohort, sixty-five patients (P-HLH), including 28 with familial/genetic HLH, 36 with secondary HLH, and 1 with an unknown cause, underwent haplo-identical family donor HSCT. The conditioning regimen consisted of intravenous administration of etoposide (VP-16), busulfan, fludarabine, rabbit anti-human thymocyte globulin (r-ATG), and cyclophosphamide (Cy). Tacrolimus and mycophenolate mofetil were used for graft-versus-host disease (GvHD) prevention. We observed that the median time for neutrophil recovery was 11 days (range, 8–24), and for platelet counts to exceed 20×10^9/L, it was 14 days (range, 7–130). There were 5 patients (7.7%) who experienced grades III to IV acute GvHD, and 6 patients (9.2%) developed extensive chronic GvHD. The estimated 3- and 5-year overall survival rates were 78.1% (95% CI, 65.8–84.6%) and 74.9% (95% CI, 61.2–84.4%), respectively. The estimated 3- and 5-year event-free survival rates were 73.5% (95% CI, 60.8–82.6%) and 70.3% (95% CI, 56.4–80.5%), respectively. Our findings demonstrate that our innovative conditioning regimen is both effective and safe, offering valuable insights for healthcare professionals evaluating the merits of existing therapies.

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INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a childhood disease characterized by fever, hepatosplenomegaly, and pancytopenia. It is marked by a selective deficiency in cytotoxicity, leading to the hyperactivation of T cells and macrophages [1–3]. This is a severe hyperinflammatory condition that results in the uncontrolled accumulation of macrophages and lymphocytes. HLH primarily affects children, often leading to multi-organ failure and high mortality. HLH can manifest as familial (fHLH) or secondary/acquired (sHLH). In certain cases of sHLH, such as chronic active Epstein-Barr virus (EBV) infection [4], hematopoietic stem cell transplantation (HSCT) is required. In children, primary HLH is the most common form, and the majority of primary cases are familial. In familial HLH (fHLH), genetic defects, especially those related to perforin, impair the activity of natural killer (NK) cells and cytotoxic T lymphocytes (CTL) [5, 6]. Among this group of patients, a range of genetic abnormalities, including perforin and hMUNC13-4 defects (found in 20% to 40% of patients), as well as mutations in SH2D1A/SAP, have been identified. These findings suggest that a deficiency in initiating apoptosis may be responsible for the disease's pathological features [7–9]. All known genes, except for XIAP, are essential for normal granule-mediated cytotoxicity. As these genetic defects result in reduced or absent cytotoxicity, exposure to a viral or other antigenic trigger can lead to inappropriate hyper-inflammatory responses. This results in prolonged activation and overproliferation of T cells, exaggerated cytokine production, and a loss of the usual mechanisms that down-regulate the immune response. The ensuing inflammatory environment leads to damage in host organs, which is ultimately fatal without proper therapy [10].

Despite advances in survival with chemotherapy and immunosuppressive agents, allogeneic HSCT remains the only treatment option for patients with primary HLH and those with sHLH who do not respond to standard therapies. This recommendation is supported by findings from two extensive international studies, the HLH-94 and HLH-2004 protocols [11, 12]. HSCT with myeloablative conditioning (MAC) for conditions associated with excessive inflammation, such as HLH, is linked with early mortality. The pediatric HLH-94 trial reported a 5-year overall survival (OS) of 50% for fHLH, with many patients succumbing before transplantation, while 66% of those who underwent HSCT were still alive after 5 years. Recent studies have reported similar outcomes, with 3–5-year survival rates ranging from 49% to 64% with MAC conditioning approaches, and most deaths occurring in the first 6 months after HSCT. Some studies have also explored the feasibility of umbilical cord transplantation for HLH, with retrospective series reporting 65% to 71% long-term OS [13–15].

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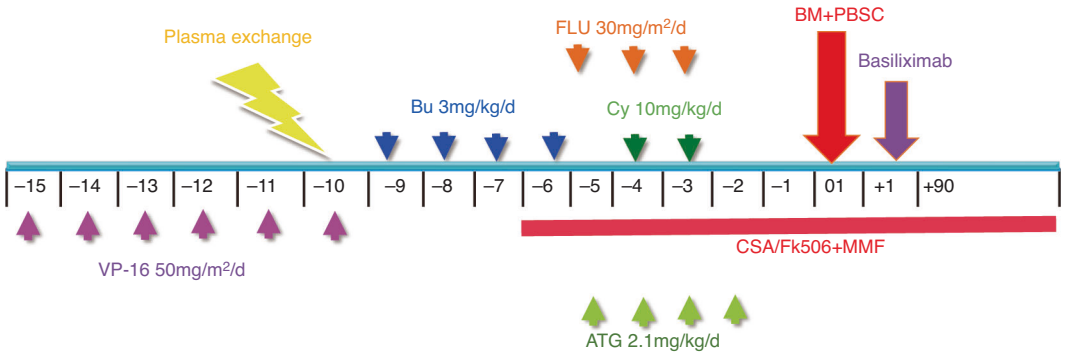

Fig. 1 Cocktail conditioning regimens for patients with p-HLH. HLH hemophagocytic lymphohistiocytosis, p-HLH patients with HLH, Bu Busulfan, ATG rabbit Anti-human thymocyte globulin, BM bone marrow, PBSC peripheral blood stem cell, Flu fludarabine, Cy cyclophosphamide, MMF mycophenolate mofetil, CSA cyclosporine A.

In December 2014, our center introduced a novel conditioning regimen for pediatric patients with HLH (p-HLH), optimizing the dosage of etoposide (VP-16) and cyclophosphamide.

MATERIALS AND METHODS

Patients

In this retrospective investigation, we compiled data from 65 p-HLH who underwent transplantation between July 2015 and June 2022 at the Hospital of Beijing Jingdu Pediatrics. Patients were stratified into three distinct groups based on specific etiologies: (1) the primary HLH group (primary HLH), (2) the Epstein-Barr virus-associated HLH group (EBV-HLH), and (3) patients with HLH of unknown origin. The study received approval from our center's institutional review board, and written informed consent was acquired from the parents or legal guardians of the patients. Patients with relapsed or refractory (R/R) HLH met the following diagnostic criteria: a diagnosis of fHLH, a genetic predisposition to HLH, or clinical HLH without genetic markers, which did not respond to chemoimmunotherapy treatment or recurred after treatment [16, 17]. The data collected encompassed demographic features, laboratory results, treatment outcomes, and mortality. The presence of central nervous system (CNS) involvement was determined if a patient exhibited any of the following characteristics: elevated white blood cell (WBC) count in cerebrospinal fluid (CSF), clinical symptoms consistent with CNS involvement (e.g., seizures or neurological deficits), or magnetic resonance imaging abnormalities consistent with CNS involvement [16].

Pre-HSCT treatment

All patients included in this study were managed in accordance with the HLH-94 or HLH-2004 protocols and had experienced relapses. For patients without achieving remission, the treatment protocol comprised the use of DEP (doxorubicin hydrochloride liposome injection at 25 mg/m^2 on day 1, VP-16 at 100 mg/m^2 once weekly on days 1, 8, and 15, methylprednisolone at 15 mg/kg on days 1–3, 2 mg/kg on days 4–6, with a gradual taper to 0 mg/kg on days 7–21), and ruxolitinib [2.5 mg administered orally twice daily (age <14 years, weight <25 kg); 5 mg administered orally twice daily (age <14 years, weight ≥25 kg); 10 mg administered orally twice daily (age >14 years)] [18].

Conditioning regimen and GvHD prophylaxis

The conditioning regimen administered to the 65 patients ($n = 65$) was as follows: VP-16 (300 mg/m^2), distributed over six days from day −15 to −10; Bu (a total of 12 mg/kg), divided into four days from day −9 to −6; Cy (10 mg/kg/day for four days) from day −4 to −3; Flu (30 mg/m^2/day for three days) from day −5 to −3; and rabbit anti-human thymocyte immunoglobulin (ATG: 7.5–8.5 mg/kg), divided into four days, from day −5 to −2, served as graft-versus-host disease (GvHD) prophylaxis. All these medications were administered intravenously. Cytokine clearance was performed through plasma exchange on day −10 following etoposide treatment. Tacrolimus (0.01 to 0.05 mg/kg/day, maintaining serum levels between 4–6 ng/ml) or cyclosporine (3 mg/kg/day, maintaining serum levels between 100–150 ng/ml) was initiated on day −6 and gradually tapered off by day +90 if no GvHD was observed. All patients received intravenous mycophenolate mofetil (MMF) on day −6, which was discontinued on day +28. Basiliximab was used for GvHD prophylaxis, with a dose of 20 mg once daily for patients weighing over 20 kg, and 10 mg for those weighing under 20 kg. Further details are provided in Fig. 1.

The presence of donor-specific antibodies (DSA) has recently been recognized as a significant impediment to the successful engraftment of donor cells, potentially affecting transplant survival. Patients who tested positive for DSA were managed with rituximab, immunoglobulin (Ig), or plasma exchange, following the consensus recommendations from the European Society for Blood and Marrow Transplant Group [19]. Chimerism was assessed by PCR analysis of variable numbers of nucleotide tandem repeats unique to donors or recipients in total peripheral blood and isolated CD3+ T cells. Chimerism testing was conducted at the 1-month, 3-month, 6-month, 9-month, and 12-month milestones following HSCT.

Definition and criteria

The pre-HSCT patient status was defined based on the following criteria: Complete response (CR): normalization of all diagnostic clinical and laboratory abnormalities associated with HLH. Partial response (PR): sustained normalization of three or more of the previously validated diagnostic parameters with no apparent progression of other parameters. Nonresponse: normalization of two or fewer diagnostic parameters or clear progression of other aspects of HLH disease. Post-HSCT, disease relapse or activation (DA) was defined as the recurrence of typical HLH symptoms with the re-establishment of recipient hematopoiesis. Reactivation of CNS HLH was determined by pleocytosis in cerebrospinal fluid or magnetic resonance imaging findings consistent with CNS inflammation unrelated to other causes. CR and PR for p-HLH patients receiving treatment were adopted with reference to a prior publication [20]. Engraftment criteria required an absolute neutrophil count exceeding 0.5×10^9/L for three consecutive days if WBC count successfully engrafted, and a platelet count exceeding 20×10^9/L for seven consecutive days without the need for platelet transfusion if platelet engraftment was successful. Mixed chimerism was defined as the presence of at least 10% recipient-derived cells. Secondary graft failure was characterized by engraftment followed by a decline of donor cells to less than 5% [21, 22]. Acute GvHD (aGvHD) and chronic GvHD (cGvHD) were graded using standard criteria [23, 24]. Lymphocyte subset analysis, Ig levels, and NK cell function were assessed through clinical assays. Patients' performance status was determined using age-appropriate scales (Lansky, for individuals below 18; Karnofsky, for those 18 and older). The cGvHD-free survival (GFS) event was the first occurrence among cGvHD, relapse, secondary malignancy, or death from any other cause. Event-free survival (EFS) was defined as the time from transplantation until relapse, secondary malignancy, death, or the last follow-up. OS was calculated from the transplantation date until the date of death due to any reason or the last contact with the patient. The last follow-up date was July 21, 2023.

Supportive therapy

All patients received prophylaxis against bacterial, viral, and fungal infections. G-CSF (granulocyte colony-stimulating factor) at a dose of 5 μg/kg (lenograstim or filgrastim) was initiated on day four. Continuous infusion of low-dose heparin, alprostadil injections, and ursodeoxycholic acid capsules were administered from the start of the preparative regimen until post-transplantation day 28 to prevent veno-occlusive disease (VOD), in accordance with our center's protocols. Adequate hydration and urine

alkalization were maintained for all patients until post-transplant day 28 to prevent hemorrhagic cystitis.

Statistical analysis

Statistical analysis was conducted using GraphPad Prism software version 5.01 or SPSS version 19.0. Survival analysis was carried out using the Kaplan–Meier method.

RESULTS

Patient characteristics

A total of 65 patients were enrolled in this study, comprising 33 males and 32 females. The median age at the time of HSCT transplantation was three years, ranging from 0.5 to 14.5 years. At the time of diagnosis, four patients (6.2% of the overall population) had CNS involvement. Among the 65 patients, genetic mutations associated with fHLH were identified in 28 patients (43.1%). One patient had an unknown cause for HLH, while 36 patients (55.4%) were diagnosed with EBV-associated HLH. The disease status was categorized as follows: 22 patients (33.8%) achieved a CR, 30 patients exhibited a PR, and 13 patients (20.0%) experienced DA. All donors were HLA haplo-identical family donors, including 37 patients (56.9%) who received grafts from 5/10 HLA-compatibility donors, 11 patients (16.9%) from 6/10 HLA-compatibility donors, 12 patients (18.5%) from 7/10 HLA-compatibility donors, and 5 patients (7.7%) from 8/10 HLA-compatibility donors. All grafts consisted of a combination of bone marrow (BM) and peripheral blood stem cells (PBSC). The median dose of mononuclear cells (MNC) was 9.26×10^8/kg for both BM and PBSC grafts, with a range from 3.89 to 9.95. The mean dose of CD34+ cells was 5.86×10^6/kg, ranging from 3.16 to 9.93. Patient and HSCT characteristics are summarized in Table 1.

Table 1. Characteristics of 65 pediatric patients with HLH before transplantation.

Patient characteristic	*n* (%) or median (range)
Number of patients	65
Sex	
Male	33 (50.8%)
Female	32 (49.2%)
Diagnosis, HLH type	
fHLH	28 (43.1%) (PRF1: $n = 10$, UNC13D: $n = 5$, STX11: $n = 6$, Lyst: $n = 7$)
EBV-HLH	36 (55.4%) (EBV-DNA < 500 copies/ml: $n = 20{,}500$ copies/ml ≤EBV-DNA ≤ 10,000 copies/ml: $n = 11$)
HLH-Unknown	1 (1.5%)
Median age at diagnosis (years)	4 (0.9–10)
Median age at transplantation (years)	6.5 (0.5–14.5)
Median time from diagnosis to transplantation (years)	0.5 (0.1–6.4)
Disease statue before transplantation	
CR	22 (33.8%)
PR	30 (46.2%)
DA	13 (20.0%)
CNS involvement	4 (6.2%)
CNS normal	61 (93.8%)
HLA-compatibility (Family donor)	
5/10	37(56.9%)
6/10	11 (16.9%)
7/10	12 (18.5%)
8/10	5 (7.7%)
Cell dose (BM + PBSC)	
MNC ($\times 10^8$ /kg)	9.26 (3.89–9.95)
CD34+ ($\times 10^6$ /kg)	5.86 (3.16–9.93)

HLH hemophagocytic lymphohistiocytosis, *fHLH* familial HLH, *EBV* Epstein-Barr virus, *CR* complete response, *PR* partial response, *DA* disease activation, *CNS* central nervous system, *BM* bone marrow, *PBSC* peripheral blood stem cell, *MNC* mononuclear cells.

Engraftment, Chimerism, and GvHD occurrence

Neutrophil engraftment after the first HSCT was achieved in 62 out of 65 patients (95.4%) at a median time of 11 days, with a range from 8 to 24 days. Platelet engraftment after the first HSCT was achieved in 63 out of 65 patients (95.4%) at a median duration of 14 days, ranging from 7 to 130 days. Stable full donor chimerism was maintained in 62 patients (95.4%), while three patients experienced primary graft failure and subsequently underwent a second transplantation. Only 5 patients (7.7%) developed grades III-IV aGvHD and received treatment with methylprednisolone (1-2 mg/kg/day) or second-line treatments such as ruxolitinib. One patient responded well to the treatment and survived. Six patients (9.2%) developed extensive cGvHD and were treated with ruxolitinib and low doses of MTX or Cy, resulting in symptom relief for all of them. Nine patients developed thrombotic microangiopathy (TMA). Among the patients, 20 (30.1%) experienced reactivation of cytomegalovirus (CMV) after transplantation, while 10 (15.4%) had EBV activity. Out of these, six patients with EBV-driven secondary HLH and four patients with familial HLH. For patients with activated EBV and CMV, immunosuppressant use was reduced, and foscarnet was employed. Further details are presented in Table 1.

Immune reconstitution and overall survival

All surviving patients exhibited normal immune recovery with healthy lymphocyte subsets and appropriate responses to both inactivated and live immunizations. No chronic infections or secondary malignancies were reported during the post-transplantation follow-up to date. At the time of the last follow-up, 50 patients were alive and free from the disease, with a median follow-up duration of 3.5 years (ranging from 0.5 to 7.5 years). The 3-year and 5-year EFS rates were 73.5% (95% CI, 60.8–82.6%) and 70.3% (95% CI, 56.4–80.5%), respectively. The 3-year and 5-year OS rates were 78.1% (95% CI, 65.8–84.6%) and 74.9% (95% CI, 61.2–84.4%), respectively. Additionally, the 3-year and 5-year GFS rates were 41.1% (95% CI, 29.1–52.8%) and 38.2% (95% CI, 25.9–50.4%), respectively (as shown in Fig. 2). In contrast, 15 patients passed away within 0.5–24 months after transplantation. The primary causes of death included transplant-associated TMA in six cases, aGvHD in four cases, cGvHD in three cases, CMV infection in two cases, and EBV-driven secondary HLH and familial HLH relapses in two cases (as shown in Table 2).

DISCUSSION

Most studies on allogeneic HSCT in p-HLH have reported the use of matched BM or peripheral blood as graft sources. In our retrospective study, 65 patients (comprising 22 in CR, 30 in PR and 13 with DA) with R/R HLH from our center received a combination of VP-16, BU, and fludarabine along with plasma exchange to improve outcomes, based on recent data reported [25]. All patients received grafts from HLA haplo-identical family donors, which consisted of a combination of BM and peripheral blood stem cells (PBSC). Despite the range of survival rates reported recently, which falls between 50% and 70% for various regimens [26], our results remain promising. However, there is room for improvement in several aspects.

Protection against HLH reactivation in patients with cytotoxic defects necessitates stable donor chimerism exceeding 10–20%.

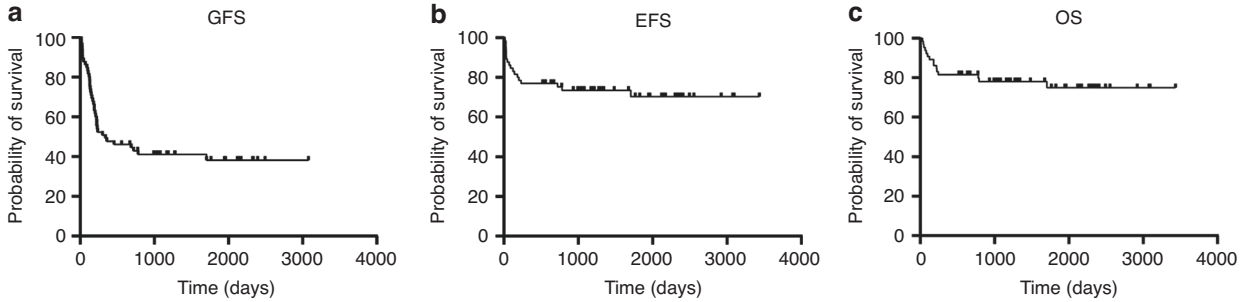

Fig. 2 Survival analysis for patients with p-HLH after HSCT. GFS (**a**), EFS (**b**), and OS (**c**) are shown in survival analysis. After transplantation, 50 out of 65 patients were alive with 3- and 5-year GFS probabilities of 41.1% (95% CI, 29.1–52.8%) and 38.2% (95% CI, 25.9–50.4%), respectively. Additionally, 3- and 5-year EFS probabilities were 73.5% (95% CI, 60.8–82.6%) and 70.3% (95% CI, 56.4–80.5%), respectively. Furthermore, 3- and 5-year OS probability of 78.1% (95% CI, 65.8–84.6%) and 74.9% (95% CI, 61.2–84.4%), respectively. HLH hemophagocytic lymphohistiocytosis, p-HLH patients with HLH, GFS cGvHD-free survival, EFS event-free survival, OS overall survival.

Table 2. HSCT outcomes and complications.

Complication/outcome	n (%) or median (range)
Neutrophil engraftment, days post-transplant	62 (95.4%), median 11 (8–24)
Keeping platelets counts over 20×10^9/L	62 (95.4%), median 14 (7–130)
Full donor chimerism post-transplant	62 (95.4%)
Patients received DSA treatment	10 (15.4%)
Full donor chimerism	61 (93.8%)
Primary graft failure	4 (6.2%)
aGvHD (grades III-IV), post- transplant	5 (7.7%)
cGvHD (extensive), post-transplant	6 (9.2%)
3-year GFS	41.1% (95% CI, 29.1–52.8%))
5-year GFS	38.2% (95% CI, 25.9–50.4%)
TMA, days post-transplant	9 (13.8%)
CMV reactivation, days post-transplant	20 (30.1%)
EBV reactivation, days post-transplant	10 (15.4%)
Number of patients off immunosuppression and IgG substitution	40 (61.5%)
Follow-up (median 3.5 years)	50 (76.9%) are alive

HSCT hematopoietic stem cell transplantation, *DSA* donor specific antibody, *GvHD* graft-versus-host disease, *aGvHD* acute GvHD, *cGvHD* chronic GvHD, *GFS* cGvHD-free survival, *TMA* thrombotic microangiopathy, *CMV* cytomegalovirus, *EBV* Epstein-Barr virus.

For patients with HLH due to cytotoxicity defects, donor T cells alone may suffice to prevent HLH reactivation. RIC HSCT has been associated with a high incidence of mixed donor and recipient chimerism [10, 15, 27]. The choice between RIC HSCT and traditional myeloablative HSCT should be evaluated on a case-by-case basis, particularly for patients with cord blood as the sole HSCT option. The MAC regimen is anticipated to increase the risk of end-organ damage and infertility. Transplant-related mortality (TRM) is a significant factor in the failure of MAC in this pediatric patient population, which already has significant preexisting comorbidities. High rates of pulmonary, gastrointestinal, and hepatic toxicities, including a high incidence of VOD, have been observed [28]. Felber et al. successfully employed therapeutic drug monitoring for Busulfan in primary HLH patients. In their study, targeted busulfan-based reduced-intensity conditioning, combined with HLA-matched HSCT, effectively cured hemophagocytic lymphohistiocytosis. Their study involved 25 patients across multiple centers, achieving an OS and EFS of 100% and a VOD incidence of 32% [29]. Recent studies have reported that 10 out of 14 pediatric patients (71.4%) who received reduced-intensity conditioning are currently alive and well, with a median age of 11.2 years after transplantation (ranging from 8.5 to 18.25 years) [26]. Unfortunately, in our study, we were unable to perform the cumulative AUC for busulfan. Nevertheless, considering the patients' tolerance, we did not observe organ toxicity after administering VP-16 at a total dose of 300 mg/m^2, divided into six days. The use of the cocktail conditioning regimen in conjunction with plasma exchange to prevent CRS and DSA showed promise in our study. It is possible that the use of both BM and PBSC contributed to achieving stable full donor chimerism in 62 patients (95.4%).

Persistent GvHD is frequently observed in p-HLH post-HSCT due to co-existing EBV reactivation and the heightened "hyperinflammatory" spectrum [30]. In our study, basiliximab was administered on the first day to reduce the incidence of aGvHD. Consequently, only 5 patients (7.7%) developed stages III-IV aGvHD, and only 6 patients (9.2%) developed extensive cGvHD. After transplantation, 20 patients (30.1%) exhibited CMV activity, and 10 patients (15.4%) exhibited EBV activity. Compared to reported results showing the incidence of stage III-IV aGvHD ranging from 11% to 24% [17, 31], our findings indicate a lower incidence of severe complications. This suggests that the use of basiliximab and the limitation of III-IV aGvHD have contributed to these favorable outcomes.

In conclusion, our data demonstrate that in p-HLH, our modified cocktail conditioning HSCT regimen is effective in achieving a cure and restoring a normal immune response against pathogens. These results further support the hypothesis of improved outcomes with RIC compared to MAC. Although our recent study shows encouraging results, the follow-up period was limited, and further investigation is warranted.

DATA AVAILABILITY

Detailed data are available upon request to corresponding author.

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AUTHOR CONTRIBUTIONS

YY, SF and YS designed, wrote and revised the manuscript. YY, ZL, YS, FJ, SF collected data and provided clinical care. YY, JC and JQ analyzed the clinical data. All authors approved the final manuscript for publication.

COMPETING INTERESTS

Author JQ was employed by Acornmed Biotechnology Co., Ltd. The remaining authors declare that the research was conducted without any commercial or financial relationships that could be considered potential conflicts of interest.

ETHICS APPROVAL

Informed consent was obtained from the patients/participants included in the study. All procedures conducted in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee, and they were conducted following the Helsinki Declaration and its later amendments or comparable ethical standards.

ADDITIONAL INFORMATION

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