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Disease Risk Comorbidity Index for Patients Receiving Haploidentical Allogeneic Hematopoietic Transplantation

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ABSTRACT

We aimed to develop a disease risk comorbidity index (DRCI) based on disease risk index (DRI) and Hematopoietic Cell Transplantation-Specific Comorbidity Index (HCT-CI) in patients receiving haploidentical hematopoietic stem cell transplantation (haplo-HSCT). We identified the prognostic factors of disease-free survival (DFS) in a training subset (n = 593), then assigned a weighted score using these factors to the remaining patients (validation subset; n = 296). The multivariable model identified two independent predictors of DFS: DRI and HCT-CI before transplantation. In this scoring system, we assigned a weighted score of 2 to very high-risk DRI, and assigned a weighted score of 1 to high-risk DRI and intermediate- and high-risk HCT-CI (i.e., haplo-DRCI). In the validation cohort, the three-year DFS rate was 65.2% (95% confidence interval (CI), 58.2%–72.2%), 55.8% (95% CI, 44.9%–66.7%), and 32.0% (95% CI, 5.8%–58.2%) for the low-, intermediate-, and high-risk group, respectively (P = 0.005). Haplo-DRCI can also predict DFS in disease-specific subgroups, particularly in acute leukemia patients. Increasing score was also significantly predictive of increased relapse, increased non-relapse mortality (NRM), decreased DFS, and decreased overall survival (OS) in an independent historical cohort (n = 526). These data confirmed that haplo-DRCI could effectively risk stratify haplo-HSCT recipients and provide a tool to better predict who will best benefit from haplo-HSCT.

1. Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the most important curative options for patients with hematologic malignances. Allo-HSCT using human leukocyte antigen (HLA)-haploidentical related donor (haplo-HSCT) has become one of the most important options in transplant procedures [1,2] because HLA-identical sibling donors (ISDs) and unrelated donors (URDs) were insufficient [3]. Several protocols, such as *ex vivo* T cell depleted [4,5] and high-dose, post-transplantation cyclophosphamide (PTCY), had been proposed to overcome the HLA disparity [6,7]. Researchers from Peking University established an unmanipulated haplo-HSCT protocol, using antithymocyte globulin (ATG) and granulocyte colony-stimulating factor (G-CSF) to induce immune tolerance (i.e., Beijing Protocol). Beijing Protocol was the most important transplant protocol for haplo-HSCT in China [8–12] and it was also reproduced successfully in other countries [13–15]. Thus, this protocol is universal and has been widely used in haplo-HSCT [16].

However, relapse remains one of the most important causes of transplant failure [17] and identifying patients with a higher risk for relapse is important. We observed that patients with advanced-stage leukemia had a higher risk of relapse after haplo-HSCT [18,19]. Recently, Armand et al. [20,21] developed the disease risk index (DRI), which was a tool to stratify patients according to the disease type and status at the time of transplantation. Several studies reported that DRI can predict the clinical outcomes in patients receiving ISD, URD, and umbilical cord blood transplantation [22–25]. Among haplo-HSCT recipients, McCurdy et al. [26] reported that DRI effectively risk stratified patients of haplo-HSCT with PTCY. However, the efficacy of DRI had not been

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identified in patients of haplo-HSCT receiving Beijing Protocol. In addition, DRI did not address other characteristics besides disease characteristics, and it mainly predicted the risk of disease progression after allo-HSCT.

Comorbidity was another factor which could significantly influence the clinical outcomes of allo-HSCT. Many studies reported that Hematopoietic Cell Transplantation–Specific Comorbidity Index (HCT-CI) could predict the survival and transplant-related mortality of allo-HSCT recipients [27–32]. We also proved the predictive ability of HCT-CI in patients receiving haplo-HSCT with Beijing Protocol [33]. However, HCT-CI does not address characteristics of underlying disease, such as disease type, disease stage, or cytogenetics.

Thus, developing a comprehensive pre-HSCT prognostic system which accounts for both patient- and disease-related risk factors would be of great clinical value for haplo-HSCT recipients. Bejanyan et al. [34] tested the prognostic capability of a composite scoring system including the DRI and HCT-CI (i.e., disease risk comorbidity index, DRCI) in patients receiving peripheral blood (PB) or bone marrow (BM) from ISD, URD, or umbilical cord blood. The DRCI score categorized patients into six risk groups, with two-year overall survival (OS) ranging between 74% for the very low-risk DRCI group and 34% for the very high-risk DRCI group. It is suggested that DRCI can predict outcomes after allo-HSCT. However, this study did not enroll the haplo-HCST recipients. How to develop an appropriate DRCI for haplo-HSCT recipients was still unknown.

Thus, in this study, we aimed to validate the efficacy of DRI in a large cohort of haplo-HSCT recipients with Beijing Protocol. What's more, we aimed to develop a DRCI (i.e., haplo-DRCI) which was appropriate for patients receiving haplo-HSCT.

2. Materials and methods

2.1. Patients

A total of 889 patients with hematologic malignancies receiving haplo-HSCT between January 2015 and December 2016 at the Peking University Institute of Hematology were enrolled. The final follow-up visits for endpoint analysis were conducted on December 31, 2018. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the ethics committee of Peking University People's Hospital.

2.2. Transplant regimens

The major preconditioning treatment consisted of cytarabine, busulfan, cyclophosphamide, and semustine, along with rabbit ATG [8–10,18,19,35]. Twenty-five patients received total body irradiation (TBI)-based regimen. Patients who had relapsed/refractory leukemia and without graft-versus-host disease (GVHD) or severe infection after hematopoietic stem cell transplantation (HSCT) can received prophylactic G-CSF-primed donor leukocyte infusion at 45–60 days after haplo-HSCT (Supplementary methods in Appendix A).

2.3. Donor selection

The methods for donor selection were showed in Supplementary methods [36,37].

2.4. Definitions and assessments

DRI was reported according to the criteria of Armand et al. [21]. For cytogenetic risk in *de novo* acute myeloid leukemia (AML), t(8;21), inv(16), or t(15;17) is considered favorable in the absence of a complex karyotype, complex karyotype ($\geq$4 abnormalities) is adverse, normal or other cytogenetic abnormality is intermediate. For cytogenetic risk in myelodysplastic syndrome (MDS), adverse risk refers to abnormalities in chromosome 7 or complex karyotype ($\geq$4 changes), intermediate risk refers to normal cytogenetics or any other chromosomal abnormalities. Particularly, for cytogenetic risk in AML arising out of MDS, MDS cytogenetic risk criteria were used. Advanced stage is defined as induction failure or relapse before transplantation, including stable disease and untreated relapse. Patients were categorized into low-, intermediate-, high-, and very high-risk groups. The comorbidities of HCT-CI were reported according to the criteria of Sorror et al. [27].

Relapse was defined as recurrence of bone marrow blasts > 5%, reappearance of blasts in the blood, development of extramedullary disease, or by the recurrence and sustained presence of pre-transplantation chromosomal abnormalities. Non-relapse mortality (NRM) was defined as death without disease recurrence. Disease-free survival (DFS) was defined as survival in continuous complete remission. OS was defined as the time from transplantation to mortality.

2.5. Statistical analysis

In the present study, the primary endpoint was DFS, and the secondary endpoints included OS, relapse, and NRM. Patients without death or relapse were censored at last follow-up. A total of 889 patients were randomly assigned to a training data set and a validation data set, comprising 67% (n = 593) and 33% of the cohort (n = 296), respectively. We used training cohort to develop the haplo-DRCI, and the validation cohort to assess the efficacy of haplo-DRCI. Hazard ratios (HRs) for DFS were estimated from univariate and multivariate Cox regression analyses. Based on the magnitude of the HRs associated with variables, a weighted score was assigned to factors which could predict DFS in the training cohort and created the haplo-DRCI scoring system. Then haplo-DRCI scoring system was further validated in the validation cohort and in an independent historic cohort which had been reported by Mo et al. (n = 526) [33].

The probabilities of survival were calculated using the Kaplan–Meier estimator. Competing risk analysis was used to calculate the cumulative incidence of relapse and NRM [38]. P values were two-sided. The SPSS Statistics 20 (IBM, USA) and the R software package (version 2.6.1; http://www.r-project.org) were used for data analysis.

3. Results

3.1. Patients

Table 1 showed the patients' characteristics. The median follow-up of the total patients was 865 days (range, 18–1498 days), and was 865 days (range, 18–1498 days) and 875 days (range, 24–1456 days) in training and validation cohorts, respectively. The cumulative incidence of relapse (CIR) and NRM at three years after haplo-HSCT was 15.6% (95% confidence interval (CI), 13.1%–18.1%) and 20.5% (95% CI, 17.8%–23.2%), respectively. The probabilities of DFS and OS at three years after haplo-HSCT were 64.0% (95% CI, 60.7%–67.3%) and 66.8% (95% CI, 63.6%–70.0%), respectively. The clinical outcomes were all comparable between the training and validation cohort (Table S1 in Appendix A).

3.2. Validation of DRI in haplo-HSCT recipients

The clinical outcomes were comparable between low- and intermediate-risk DRI patients. The CIR, DFS, and OS rates of

Table 1
Characteristics between training and validation cohorts.

Characteristics	Training cohort (n = 593)	Validation cohort (n = 296)	P value
Age at HSCT, n (proportion)			0.610
< 16 years	129 (21.8%)	60 (20.3%)	
≥ 16 years	464 (78.2%)	236 (79.7%)	
Male sex, n (proportion)	360 (60.7%)	189 (63.9%)	0.363
Time from diagnosis to HSCT, n (proportion)			0.364
< 12 months	482 (81.3%)	233 (78.7%)	
≥ 12 months	111 (18.7%)	63 (21.3%)	
KPS at HSCT, n (proportion)			0.571
90–100	536 (90.4%)	271 (91.6%)	
< 90	57 (9.6%)	25 (8.4%)	
Underlying disease, n (proportion)			0.085
Acute leukemia	497 (83.8%)	240 (81.1%)	
Myelodysplastic syndrome	54 (9.1%)	30 (10.1%)	
Myeloproliferative neoplasms	17 (2.9%)	15 (5.1%)	
Non-Hodgkin lymphoma	19 (3.2%)	4 (1.3%)	
Plasma cell disease	6 (1.0%)	7 (2.4%)	
HCT-CI scores before HSCT, n (proportion)			0.897
0 (low risk)	425 (71.7%)	210 (70.9%)	
1–2 (intermediate risk)	121 (20.4%)	64 (21.6%)	
≥ 3 (high risk)	47 (7.9%)	22 (7.4%)	
DRI before HSCT, n (proportion)			0.111
Low risk	41 (6.9%)	29 (9.8%)	
Intermediate risk	464 (78.2%)	233 (78.7%)	
High risk	73 (12.3%)	32 (10.8%)	
Very high risk	15 (2.5%)	2 (0.7%)	
Donor–recipient relationship, n (proportion)			0.162
Father–child	285 (48.1%)	132 (44.6%)	
Mother–child	30 (5.1%)	22 (7.4%)	
Sibling–sibling	156 (26.3%)	65 (22.0%)	
Child–parent	110 (18.5%)	70 (23.6%)	
Collateral related donor	12 (2.0%)	7 (2.4%)	
Donor–recipient sex matched, n (proportion)			0.385
Male–male	276 (46.5%)	151 (51.0%)	
Male–female	183 (30.9%)	76 (25.7%)	
Female–male	91 (15.3%)	44 (14.9%)	
Female–female	43 (7.3%)	25 (8.4%)	
Number of HLA-A, HLA-B, HLA-DR mismatches, n (proportion)			0.496
0–2	107 (18.0%)	59 (19.9%)	
3	486 (82.0%)	237 (80.1%)	
Donor–recipient blood type matched, n (proportion)[a]			0.599
Matched	297 (50.1%)	161 (54.4%)	
Major mismatched	122 (20.6%)	60 (20.3%)	
Minor mismatched	143 (24.1%)	61 (20.6%)	
Major–minor mismatched	31 (5.2%)	14 (4.7%)	
Conditioning regimen, n (proportion)			0.889
Chemotherapy based regimen	576 (97.1%)	288 (97.3%)	
TBI based regimen	17 (2.9%)	8 (2.7%)	

KPS: Karnofsky performance status.
[a]Minor ABO mismatched indicated that donor possessed isohemagglutinins against recipient red cells, including the following blood group combinations: O (donor) into A, B, or AB (recipient), and A or B (donor) into AB (recipient). Major ABO mismatched indicated that recipient possessed isohemagglutinins against donor red cells, including the following blood group combinations: A, B, or AB (donor) into O (recipient), and AB (donor) into A or B (recipient). Major–minor mismatched indicated that both donor and recipient possessed isohemagglutinins to each other: A into B and vice versa.

high-risk DRI patients were significantly poorer than those of low-risk DRI patients. All the clinical outcomes of very high-risk DRI patients were significantly poorer than those of low-risk DRI patients (Table S2 in Appendix A). Thus, low-risk and intermediate-risk DRI groups were combined in the following analysis.

3.3. HCT-CI in haplo-HSCT recipients

The probabilities of DFS at three years after haplo-HSCT were comparable between intermediate- and high-risk HCT-CI groups (P = 0.438), which were both significantly poorer than those of low-risk patients (high-risk vs low-risk: P = 0.009; intermediate-risk vs low-risk: P = 0.017) (Fig. S1(a) in Appendix A). The probabilities of OS at three years after haplo-HSCT were comparable between intermediate- and high-risk HCT-CI groups (P = 0.203), which were both significantly poorer than those of low-risk HCT-CI patients (high-risk vs low-risk: P = 0.003; intermediate-risk vs low-risk: P = 0.033) (Fig. S1(b) in Appendix A). Thus, intermediate- and high-risk HCT-CI groups were combined in the following analysis.

3.4. Development and validation of haplo-DRCI scoring system

We constructed a Cox proportional hazards model using the training cohort. The following variables were included: patient age at HSCT (< 16 years vs ≥ 16 years), gender, Karnofsky performance status at transplantation (90–100 vs < 90), DRI before transplantation (low- and intermediate-risk vs high-risk vs very high-risk), HCT-CI before transplantation (low-risk vs intermediate- and high-risk), time from diagnosis to transplantation (≥ 12 months vs < 12 months), donor–recipient sex

combination (female–male vs others), donor–recipients relation (mother–child vs others), donor–recipient blood type matched (major mismatched or major–minor mismatched vs matched or minor mismatched), and HLA disparity (≤2 loci vs 3 loci).

Gender, DRI, and HCT-CI at transplantation could predict the DFS in the univariate analysis (Table S3 in Appendix A), which were included in the multivariate analysis. The multivariate model identified two independent predictors of DFS: DRI and HCT-CI at transplantation (Table 2). Thus, we assigned a weighted score of 2 to very high-risk DRI, and a weighted score of 1 to high-risk DRI and intermediate- and high-risk HCT-CI (Table S4 in Appendix A). Then we created the haplo-DRCI scoring system: low risk (score = 0, n = 370), intermediate risk (score = 1, n = 179), and high risk (score ≥ 2, n = 44). The HR for relapse or death (i.e., treatment failure as defined by DFS) was 1.76 (95% CI, 1.30–2.39) for the intermediate-risk group and 4.22 (95% CI, 2.80–6.36) for the high-risk group (using the low-risk group as reference, overall P < 0.001, Table S5 in Appendix A).

Table 2
Multivariable analysis of factors associated with DFS in the training cohort.

Outcome	HR (95% CI)	P value
Disease risk index before HSCT		
Low and intermediate risk	1 (reference)	
High risk	2.48 (1.75–3.53)	<0.001
Very high risk	4.98 (2.82–8.81)	<0.001
HCT-CI before HSCT		
0 (low risk)	1 (reference)	
≥1 (intermediate and high risk)	1.45 (1.08–1.94)	0.013

In the validation cohort, the probabilities of DFS at 3 years after haplo-HSCT were 65.2% (95% CI, 58.2%–72.2%), 55.8% (95% CI, 44.9%–66.7%), and 32.0% (95% CI, 5.8%–58.2%) for the low-, intermediate-, and high-risk group, respectively (overall P = 0.005). The HR for relapse or death (i.e., treatment failure as defined by DFS) was 1.40 (95% CI, 0.94–2.09) for the intermediate-risk group and 2.75 (95% CI, 1.41–5.37) for the high-risk group (using the low-risk group as reference, overall P = 0.007, Table S5).

3.5. Application of haplo-DRCI in total population

We applied the haplo-DRCI in the total population for analysis of secondary endpoints. We observed that haplo-DRCI was associated with relapse (overall P < 0.001), NRM (overall P < 0.001), DFS (overall P < 0.001), and OS (overall P < 0.001) in total population (Figs. 1(a)–(d)). In addition, haplo-DRCI could predict DFS in children (< 16 years, overall P = 0.010) and adults (≥ 16 years, overall P < 0.001, Figs. S2(a) and (b) in Appendix A). Haplo-DRCI could also predict DFS in AML (overall P < 0.001), acute lymphoblastic leukemia (ALL, overall P < 0.001), MDS/myeloproliferative neoplasms (overall P = 0.021), and non-Hodgkin lymphoma (NHL)/plasma cell disease (overall P = 0.001) (Figs. S3(a)–(d) in Appendix A).

3.6. Validation of haplo-DRCI in an independent historical cohort

We also validated the haplo-DRCI in an independent historical cohort (n = 526). The burdens of comorbidities in the historical

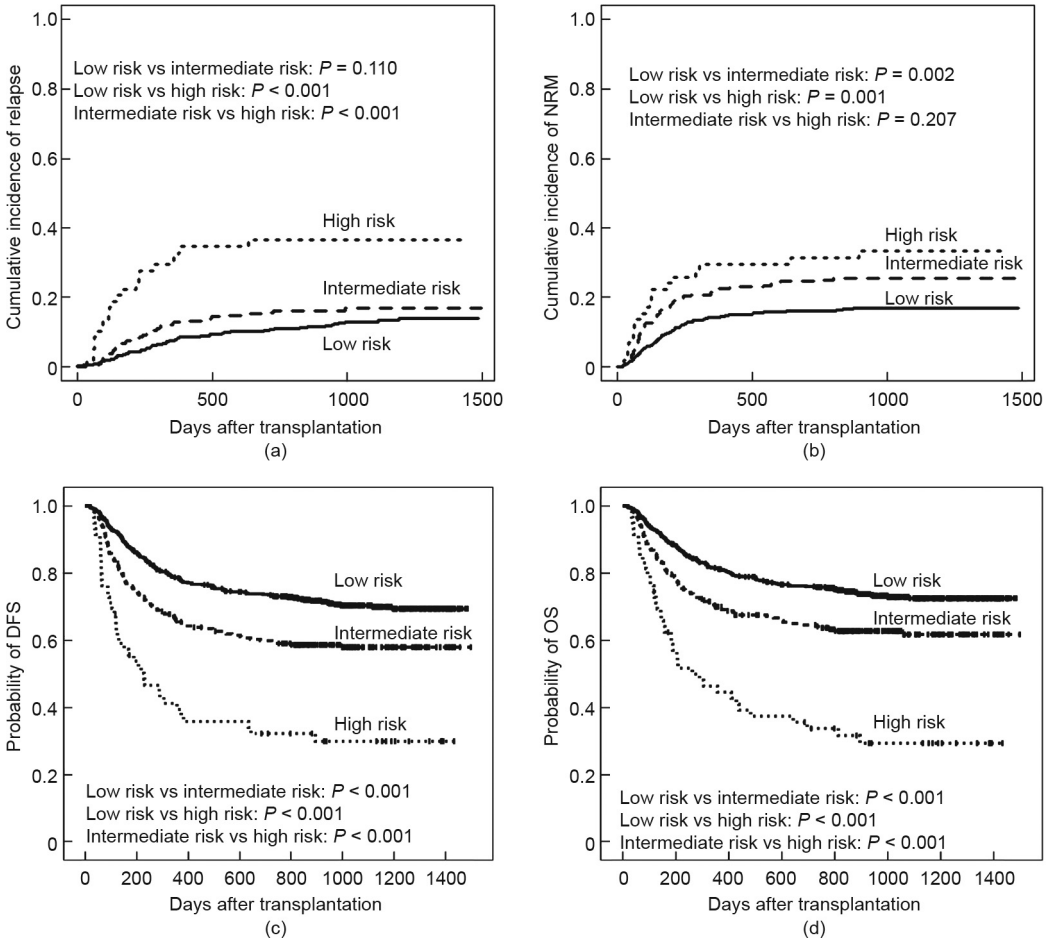

Fig. 1. Clinical outcomes after haplo-HSCT according to haplo-DRCI in current cohort: (a) relapse, (b) NRM, (c) DFS, and (d) OS.

cohort were significantly higher than those of the current cohort. In addition, patients with high- and very high-risk DRI were more common in the historical cohort. Patient's age, HLA disparity, and donor–recipient relation were also significantly different between current and historical cohort (Table S6 in Appendix A). However, increasing haplo-DRCI scores were also predictive of increased relapse (overall $P < 0.001$), increased NRM (overall $P = 0.001$), decreased DFS (overall $P < 0.001$), and decreased OS (overall $P < 0.001$) in this independent historical cohort (Figs. 2(a)–(d)).

4. Discussion

In this study, we observed that haplo-DRCI, which combined DRI and HCT-CI together, could significantly predict the relapse, mortality, and survival of haplo-HSCT recipients, particularly for the patients with acute leukemia. Thus, this study firstly developed a comprehensive scoring system which can address the characteristics of both comorbidities and diseases in patients receiving haplo-HSCT.

Although HCT-CI and DRI could predict the survival after haplo-HSCT [26,33] HCT-CI was concerned about comorbidities and DRI was concerned about the disease characteristics, which suggested that using DRI or HCT-CI alone could only partially predict the DFS after haplo-HSCT. Because DRI and HCT-CI were the only two risk factors predicting the DFS in multivariate analysis, we combined them organically and found that haplo-DRCI could effectively distinguish the DFS among low-, intermediate-, and high-risk patients. Thus, haplo-DRCI can help to evaluate patients receiving haplo-HSCT more comprehensively.

In the high-risk haplo-DRCI groups, the relapse and NRM rate was 36.6% and 33.4%, respectively, and DFS rate was only 30.0%. These patients had advanced-stage disease (high- or very high-risk DRI) and/or high comorbidities burden (HCT-CI $\geq$ 1) before haplo-HSCT, which suggested that they had a higher risk of disease progression and may be vulnerable to drug toxicities and transplant complications. Similarly, Bejanyan et al. [34] reported that the survival of patients who had both high-risk DRI and high-risk HCT-CI were the worst. Reducing the intensity of conditioning regimen may help to prevent the chemotherapeutic toxicities; however, the relapse rate of patients receiving nonmyeloablative regimen was higher than that of myeloablative regimen, particularly for those with relapse/refractory leukemia [39,40]. Thus, how to prevent post-HSCT relapse on the basis of controlling the toxicities of conditioning regimen was important to improve the clinical outcomes of the high-risk haplo-DRCI patients.

European Group for Blood and Marrow Transplantation (EBMT) risk score is the most common prognostic scoring systems for predicting clinical outcomes after allo-HSCT. EBMT score was based on an analysis of patients transplanted for chronic myeloid leukaemia (CML) [41] and could predict the survival and mortality in a variety of hematologic malignances [42]. Wang et al. [43] proposed the haplo-EBMT score on the basis of the EBMT score, which included disease stage, patient's age at HSCT, time from diagnosis to HSCT, donor–recipient sex combination, and HLA disparity. Disease stage before HSCT was the most important prognostic factor [18,19,44]; however, the prognostic values of the other four factors were

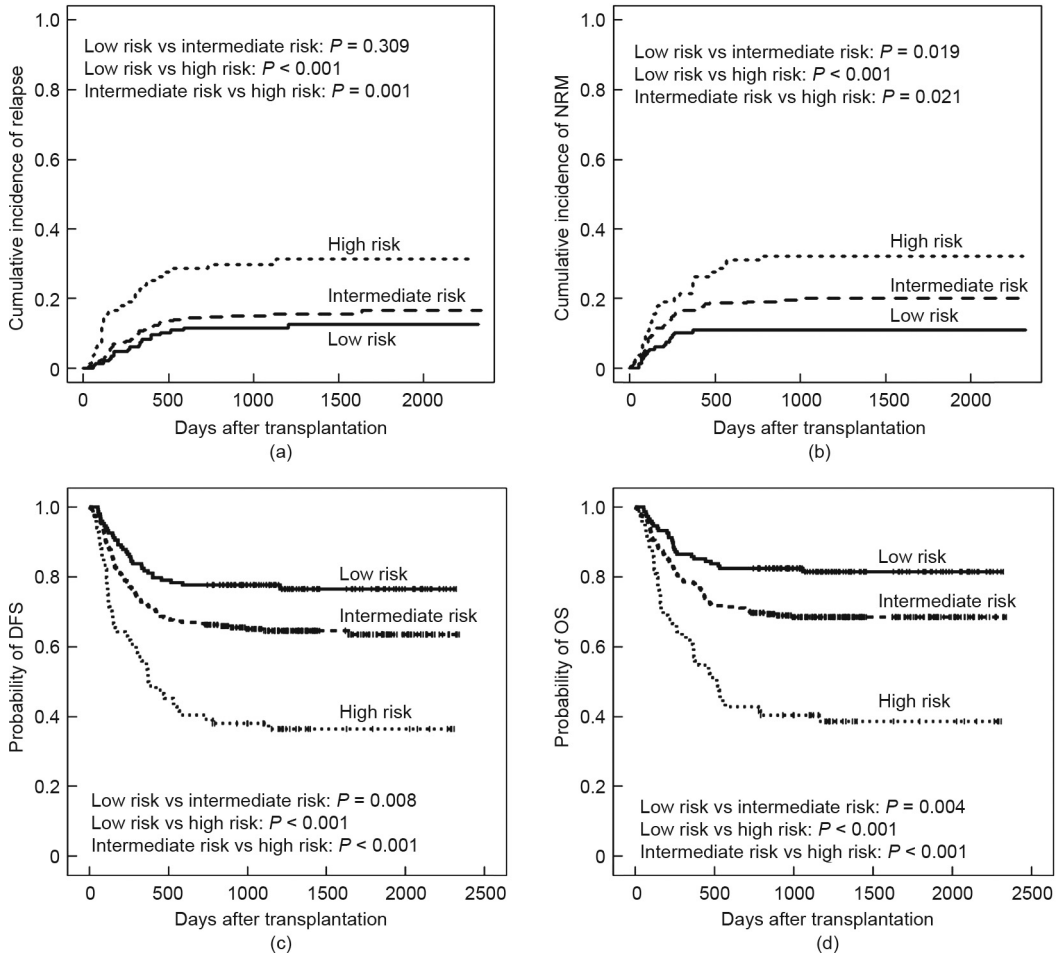

Fig. 2. Clinical outcomes after haplo-HSCT according to haplo-DRCI in historical cohort: (a) relapse, (b) NRM, (c) DFS, and (d) OS.

controversial. Some authors reported that time from diagnosis to transplantation, patient's age, female donor/male recipient, and HLA disparity did not influence the survival after haplo-HSCT [18,45–48] and we did not observe the associations between these four factors and DFS in the present studies. Thus, we suggested that the prognostic effect of haplo-EBMT score may mainly due to the prognostic effect of disease stage. On the other hand, it is suggested that comorbidities and DRI were more important prognostic factors for haplo-HSCT recipients, and most of them were not included in the haplo-EBMT score. Thus, EBMT and haplo-EBMT risk scores may not comprehensively reflect the characteristics of patients receiving haplo-HSCT.

We observed that the relapse, NRM, and survival were all comparable between low- and intermediate-risk DRI groups. In the study of Armand et al. [21], the OS of low-risk DRI group was better than that of intermediate-risk DRI group ($P < 0.001$). However, Beauverd et al. [22] observed that OS for low- and intermediate-risk DRI groups was 63% and 54%, respectively, in patients receiving T-cell-replete HSCT. Törlén et al. [24] reported that clinical outcomes were all comparable between low- and intermediate-risk DRI groups, most of whom had leukemia (337/521) and received ATG-based conditioning regimen (371/521). Paviglianiti et al. [25] reported that OS for low- and intermediate-risk DRI groups was comparable in patients receiving myeloablative conditioning. Thus, the fact that most of the patients had acute leukemia and all of them receiving haplo-HSCT with ATG-based myeloablative conditioning in the present study may contribute to the comparable clinical outcomes between low- and intermediate-risk DRI groups. Although McCurdy et al. [26] observed that the HR of OS was more than two-fold greater in the intermediate-risk group compared with the low-risk DRI group (HR = 2.11; $P = 0.0009$) in a cohort enrolling haplo-HSCT recipients, all of them received non-myeloablative regimen with PTCY and only one third of the patients had leukemia, which were significantly different from the present study.

We had reported that although HCT-CI could predict the clinical outcomes of haplo-HSCT, the relapse, NRM, and survival rates were all comparable between low- and intermediate-risk HCT-CI groups [33]. However, in the present study, survival rates of intermediate-risk HCT-CI group were worse than those of low-risk HCT-CI group. We observed that the comorbidity burdens were lower in the current cohort compared to those of our historical cohort (Table S6), which may be due to the fact that we strengthened comorbidity screening before HSCT and some patients with high comorbidity burdens did not receive HSCT after our previous study. Whatever, the efficacy of DRCI was also proved in the historical cohort with higher comorbidity burdens.

There were several limitations in this study. First, this is a single center study, and despite enrolling 889 patients and validated in a relatively large independent historical cohort, the sample of very high-risk DRI patients was relatively small, which might influence the validity of the haplo-DRCI for outcome prediction. Second, more than 80% of the patients had acute leukemia, and the sample of patients with other diseases (e.g., myeloproliferative neoplasms, lymphoma, and plasma cell disease) was relatively small. Thus, the efficacy of haplo-DRCI should be further identified in these patients. Lastly, several molecular markers may predict the relapse and survival of acute leukemia patients. It may help to further risk stratify the patients with normal cytogenetics and modify the haplo-DRCI.

5. Conclusion

These data confirmed that haplo-DRCI can effectively risk stratify haplo-HSCT recipients. The scoring system can be calculated quickly, providing the tool to better predict who will best benefit from haplo-HSCT.

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Authors' contribution

Xiao-Dong Mo and Xiao-Jun Huang designed the study. Lan-Ping Xu, Xiao-Hui Zhang, Yu Wang, Chen-Hua Yan, Huan Chen, Yu-Hong Chen, Wei Han, Feng-Rong Wang, Jing-Zhi Wang, and Kai-Yan Liu collected the data. Xiao-Dong Mo and Xiao-Jun Huang analyzed the data and drafted the manuscript. All authors contributed to the data interpretation, manuscript preparation, and approval of the final version.

Compliance with ethics guidelines

Xiao-Dong Mo, Xiao-Hui Zhang, Lan-Ping Xu, Yu Wang, Chen-Hua Yan, Huan Chen, Yu-Hong Chen, Wei Han, Feng-Rong Wang, Jing-Zhi Wang, Kai-Yan Liu, and Xiao-Jun Huang declare that they have no conflict of interest or financial conflicts to disclose.

Nomenclatures

ALL	acute lymphoblastic leukemia
Allo-HSCT	allogeneic hematopoietic stem cell transplantation
AML	acute myeloid leukemia
ATG	antithymocyte globulin
BM	bone marrow
CI	confidence interval
CIR	cumulative incidence of relapse
CML	chronic myeloid leukaemia
DFS	Disease-free survival
DRCI	disease risk comorbidity index
DRI	disease risk index
EBMT	European Group for Blood and Marrow Transplantation
G-CSF	granulocyte colony-stimulating factor
GVHD	graft-versus-host disease
Haplo-HSCT	haploidentical related donor hematopoietic stem cell transplantation
HCT-CI	Hematopoietic Cell Transplantation-Specific Comorbidity Index
HLA	human leukocyte antigen
HSCT	hematopoietic stem cell transplantation
HR	hazard ratio
ISD	identical sibling donor

MDS	myelodysplastic syndrome
NHL	non-Hodgkin lymphoma
NRM	non-relapse mortality
OS	overall survival
PB	peripheral blood
PTCY	post-transplantation cyclophosphamide
TBI	total body irradiation
URD	unrelated donor

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.eng.2020.12.005.

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