



SIRP α Mismatch Is Associated With Relapse Protection and Chronic Graft-Versus-Host Disease After Related Hematopoietic Stem Cell Transplantation for Lymphoid Malignancies

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*Correspondence:

Jun Zou
jzou@mdanderson.org
Richard E. Champlin
rchampj@mdanderson.org

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Rima M. Saliba¹, Samer A. Srour¹, Uri Greenbaum^{2,3}, Qing Ma⁴, Yudith Carmazzi⁵, Michael Moller⁶, Janet Wood⁷, Stefan O. Ciurea⁸, Piyanuch Kongtim^{8,9}, Gabriela Rondon¹, Dan Li⁴, Supawee Saengboon¹, Amin M. Alousi¹, Katayoun Rezvani¹, Elizabeth J. Shpall¹, Kai Cao⁵, Richard E. Champlin^{1*} and Jun Zou^{5*}

¹ Department of Stem Cell Transplantation and Cellular Therapy, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, ² Department of Hematology, Soroka University Medical Center, Beer Sheva, Israel, ³ Faculty of Health Sciences, Ben Gurion University of the Negev, Beer Sheva, Israel, ⁴ Department of Hematopoietic Biology and Malignancy, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, ⁵ Department of Laboratory Medicine, Division of Pathology/Laboratory Medicine, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, ⁶ School of Health Professions, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, ⁷ Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, TX, United States, ⁸ Division of Hematology/Oncology, Department of Medicine, Chao Family Comprehensive Cancer Center, University of California, Irvine, CA, United States, ⁹ Center of Excellence in Applied Epidemiology, Faculty of Medicine, Thammasat University, Pathumthani, Thailand

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapy for hematologic malignancies. Alloreactivity after HSCT is known to be mediated by adaptive immune cells expressing rearranging receptors. Recent studies demonstrated that the innate immune system could likewise sense the non-self signals and subsequently enhance the alloimmune response. We recently demonstrated that the donor/recipient mismatch of signal regulatory protein α (SIRP α), an immunoglobulin receptor exclusively expressed on innate cells, is associated with a higher risk of cGVHD and relapse protection in a cohort of acute myeloid leukemia patients who underwent allo-HSCT. Whether these effects also occur in other hematologic malignancies remains unclear. In the present study, we compared outcomes by SIRP α match status in a cohort of 310 patients who received allo-HSCT from an HLA matched-related donor for the treatment of lymphoid malignancies. Multivariable analysis showed that SIRP α mismatch was associated with a significantly higher rate of cGVHD (hazard ratio [HR] 1.8, P = .002), cGVHD requiring systemic immunosuppressive therapy (HR 1.9, P = .005), a lower rate of disease progression (HR 0.5, P = .003) and improved progression-free survival (HR 0.5, P = .001). Notably, the effects of SIRP α mismatch

were observed only in the patients who achieved >95% of donor T-cell chimerism. The mismatch in SIRP α is associated with favorable relapse protection and concurrently increased risk of cGVHD in patients who undergo allo-HSCT for lymphoid malignancies, and the optimal donor could be selected based on the finding of the study to mitigate the risk of GVHD and relapse.

Keywords: signal regulatory protein alpha, mismatch, relapse protection, cGVHD, HSCT, lymphoid malignancies, innate immunity

INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is curative for several high-risk hematologic malignancies. Despite the remarkable advances made over the past two decades with notable improvement in overall survival (OS), relapse and graft-versus-host disease (GVHD) remain frequent causes of failure and death after transplant. It has been long known that the success of allo-HSCT is largely based on achieving a balance between graft-versus-tumor (GVT) and graft-versus-host effects. Hence, regulating the alloimmune response to reduce relapse without increasing GVHD remains critical to improving disease control without increasing non-relapse mortality (NRM). Additionally, a considerable rate of GVHD persists in allo-HSCT recipients with human leukocyte antigen (HLA)-matched related donors (1), indicating that alloreactivity derived from non-HLA genetic variation might play a role in regulating alloimmunity in allo-HSCT recipients.

Signal regulatory protein α (SIRP α) is a polymorphic transmembrane protein with three immunoglobulin domains. SIRP α is exclusively expressed on innate immune cells, including monocytes, macrophages, and myeloid cells, whereas its ligand CD47, is expressed ubiquitously. The interaction of SIRP α and CD47 elicits an inhibitory signal and suppresses macrophage phagocytic function (2). A study using a murine model with marrow transplantation showed that a mismatched SIRP α between donor and recipient was associated with increased allorecognition response followed by enhanced monocyte activation and dendritic cell transformation. The alloreactive response was likely elicited by the non-self signaling that occurs when the SIRP α variant introduced with the allograft binds to CD47 with a different affinity (3). Additionally, Jardine et al. showed that human GVHD lesions are predominately infiltrated with donor monocyte-derived macrophages, which enhanced the proliferation and activation of allogeneic T cells. Although its role in GVHD pathogenesis needs to be further clarified, SIRP α was shown to be significantly upregulated in GVHD macrophages (4). Several specific variations in human SIRP α have been identified, the prevalence and clinical effects of donor/recipient SIRP α variant mismatch on HSCT, as well as the underlying cellular mechanisms of these effects, need to be further investigated.

In a recent study of patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS) who underwent HSCT from HLA-matched related donors, we found that SIRP α variant mismatch between donor and recipient pairs was

relatively common, and SIRP α mismatch was associated with a significantly higher risk of chronic GVHD (cGVHD) and lower risk of relapse (5). SIRP α variant mismatch was associated not only with a higher rate of cGVHD and *de novo* cGVHD but also increased severity of cGVHD, indicated by the incidence of cGVHD requiring therapy (5). It is plausible that SIRP α mismatch in allo-HSCT elicits non-self recognition and monocyte activation due to the different SIRP α -CD47 binding between the donor and the recipient. This enhanced innate immunity could further promote adaptive immunity and subsequently lead to a higher risk of cGVHD, accompanied by a lower risk of relapse. It is also unclear whether the observed clinical effects of SIRP α variant mismatch extend to populations beyond those receiving allo-HSCT for AML/MDS. In the present study, we examined the effects of SIRP α variant mismatch on clinical outcomes in patients receiving allo-HSCT from HLA-matched related donors for lymphoid malignancies.

METHODS

Patient Population

This retrospective analysis included adult patients who underwent allo-HSCT for the treatment of lymphoid malignancies at The University of Texas MD Anderson Cancer Center (UTMDACC) between January 2008 and December 2018. Lymphoid malignancies included acute lymphoblastic leukemia (ALL), chronic lymphoblastic leukemia (CLL), Hodgkin's disease (HD), and non-Hodgkin's lymphoma (NHL). All patients included received peripheral blood stem cells from an HLA-matched adult sibling donor, and had donor and patient DNA samples available for SIRP α testing. We excluded patients who failed to engraft as well as those who received post-HSCT cyclophosphamide as GVHD prophylaxis, which has a profound effect on GVHD outcomes compared with conventional GVHD-prevention regimens. All patients provided written informed consent for HSCT according to the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the UTMDACC.

SIRP α Variant Typing and Identification of Mismatch

SIRP α typing was performed as previously described (5). Briefly, we used three sets of SIRP α -specific targeting primers, and each 20- μ L polymerase chain reaction included 2 μ L of tested DNA (20 ng/ μ L),

4 μ L of primer mix, 13.9 μ L of LABType Primer Set Dmix (LTPDMX-B; One Lambda, Canoga Park, CA), and 0.1 μ L of Tag polymerase. The polymerase chain reaction was conducted at 96°C for 2 minutes, at 10 \times (96°C for 10 seconds, 63°C for 1 minute) and 20 \times (96°C for 10 seconds, 59°C for 50 seconds, 72°C for 30 seconds). A total of 20 μ L of the product was run on a 2% agarose gel by electrophoresis, along with controls. Typing was determined by the presence or absence of specific amplicons along with positive and negative controls. Similar to the previous study (5), SIRP α variants were identified and separated into two categories with different CD47 binding interfaces. The SIRP α VI category included SIRP α v1, v4, v5, v6, and v9, and the SIRP α VII category included SIRP α v2, v3, v7, v8, and v10 (5–7). The proportion of donors and recipients in each genotype category (VI/VI, VI/VII, VII/VII) are summarized in **Supplementary Table 1**. The matching or mismatching status on either single alleles or both alleles was determined by the donor and recipient typing results. The direction of mismatch was classified by the presence of “non-self” SIRP VII in the host or donor genotype. Therefore, the donor mismatch group included three types of mismatch (donor versus host): VI/VII \rightarrow VI/VI, VII/VII \rightarrow VI/VI, and VII/VII \rightarrow VI/VII, and the host mismatch group included three other types of mismatch (donor versus host): VI/VI \rightarrow VII/VII, VI/VII \rightarrow VII/VII, and VI/VI \rightarrow VI/VII.

Clinical Endpoints

The primary outcomes were the incidence of grade 2–4 acute GVHD (aGVHD), cGVHD, and cGVHD requiring systemic immunosuppressive therapy (T-cGVHD). Secondary outcomes were grade 3–4 aGVHD, OS, incidence of disease progression, NRM, and progression-free survival (PFS). Time to neutrophil engraftment was also compared according to SIRP α mismatch. If GVHD with strictly aGVHD features was observed after day 100 after HSCT, this was considered late aGVHD, not cGVHD. OS was defined as the time from HSCT to death from any cause. PFS was defined as the time from HSCT to disease progression or death from any cause. NRM was defined as death without evidence of persistence or progression of malignancy. Surviving patients were censored at the time of the last follow-up. Disease progression was defined as evidence of recurrence or progression of malignancy. Time to neutrophil engraftment was defined as the first of 3 consecutive days with an absolute neutrophil count $>500/\mu$ L. Myeloablative and nonmyeloablative HSCT conditioning regimens were defined according to the Center for International Blood and Marrow Transplant Research operational guidelines (8). T cell chimerism testing was performed as previously described (9).

Statistical Methods

Patient-, disease-, and HSCT-related baseline factors were compared using the chi-square or Fisher’s exact test, as appropriate, for categorical variables; the Wilcoxon rank-sum test was used to compare continuous variables. The main effect evaluated in association with outcomes was donor/recipient SIRP α variant match or mismatch status. The cumulative incidences of GVHD, disease progression, and NRM was estimated accounting for competing risks which included death

or disease relapse for GVHD, death of any cause before progression for disease progression, and disease progression or disease-related death for NRM. In addition, a diagnosis of grade 1–4 aGVHD was considered a competing risk for *de novo* cGVHD. PFS and OS were estimated using the Kaplan-Meier method.

Predictors of outcomes were evaluated in univariable and multivariable analyses using competing risk regression for GVHD, disease progression, and NRM, and Cox proportional hazards regression was used to evaluate predictors of PFS and OS. SIRP α variant match or mismatch status was forced in all multivariable models, irrespective of statistical significance in the univariable analysis. All other predictors that were significant in the univariable analysis were included in the multivariable analysis. Backward elimination was used to develop multivariable prognostic models. First-degree interaction effects between SIRP α variant match or mismatch status and predictors that were found to be significant in the univariable analysis were evaluated and accounted for when indicated. The only significant interaction effect we identified was for diagnosis and disease progression and progression-free survival. For these outcomes, the impact of SIRP α mismatch was seen in subgroup analyses for each of the lymphoid malignancies included in the study, except for NHL. We adjusted for this interaction effect in multivariate analysis. Notably, we did not identify significant interaction effects between SIRP α mismatch and diagnosis for survival or GVHD outcomes. The proportional hazards assumption was evaluated and was not found to have been violated. In addition to SIRP α variant matching status, the following factors were evaluated for their association with outcomes: donor-recipient sex, recipient age, HSCT-specific comorbidity index (HCT-CI), diagnosis, disease status at HSCT (chemo-sensitive or chemo-resistant), conditioning regimen (myeloablative or nonmyeloablative), donor-recipient ABO match status and cytomegalovirus (CMV) status. Statistical significance was defined as $P < 0.05$, and statistical analyses were performed using primarily STATA 14.0 (StataCorp, College Station, TX).

RESULTS

Patient Population and Allo-HSCT Characteristics

A total of 310 patients met the inclusion criteria. The median age of recipients was 51 years (range 18–72) and one-fourth (24%) had an HCT-CI score >3 at the time of allo-HSCT. Most patients received allo-HSCT for the treatment of ALL (37%) or NHL (37%), and 83% had the chemo-sensitive disease at the time of transplantation. A non-myeloablative conditioning regimen was used in 48% of patients, and the graft source was peripheral blood from a 10/10 HLA-matched related donor for all patients. All patients underwent GVHD prophylaxis with tacrolimus and methotrexate. The median transplant year was 2011 (range: 2008–18). These characteristics were similar between patients with ($n=130$) and without ($n=180$) SIRP α variant mismatch with their donors (**Table 1**).

TABLE 1 | Characteristics of the study population overall and according to donor/recipient SIRP α matching.

	Overall n = 310	Donor/recipient SIRP α		P
		Matched n = 180	Mismatched n = 130	
Recipient age, years				0.8
Median (range)	51 (18-72)	51 (19-72)	52 (18-70)	
HCT-CI, n (%)				0.7
≤3	235 (76)	138 (77)	97 (75)	
>3	75 (24)	42 (23)	33 (25)	
Donor/Recipient gender, n (%)				0.3
Male/Male	116 (37)	68 (38)	48 (37)	
Female/Female	61 (20)	32 (18)	29 (22)	
Male/Female	49 (16)	25 (14)	24 (18)	
Female/Male	84 (27)	55 (31)	29 (22)	
Donor/Recipient CMV status, n (%)				
NR/NR	32 (10)	19 (11)	13 (10)	
R/R	169 (55)	98 (55)	71 (55)	
NR/R	80 (26)	40 (23)	40 (31)	
R/NR	26 (8)	20 (11)	6 (5)	0.04
Donor/Recipient ABO, n (%)				0.7
Matched	208 (67)	125 (69)	83 (64)	
Minor mismatch	44 (14)	24 (13)	20 (15)	
Major mismatch	16 (5)	10 (6)	6 (5)	
Bidirectional	41 (13)	21 (12)	20 (15)	
Diagnosis, n (%)				0.6
Acute lymphoblastic leukemia	115 (37)	63 (35)	52 (40)	
Chronic lymphoblastic leukemia	59 (19)	33 (18)	26 (20)	
Non-Hodgkin's lymphoma	114 (37)	72 (40)	42 (32)	
Hodgkin's lymphoma	22 (7)	12 (7)	10 (8)	
Response prior to transplant, n (%)				0.2
Chemo-sensitive	259 (83)	146 (81)	113 (87)	
Chemo-refractory	51 (16)	34 (19)	17 (13)	
Conditioning intensity, (%)				0.8
Non-myeloablative	150 (48)	86 (48)	64 (49)	
Not non-myeloablative	160 (52)	94 (52)	66 (51)	
% Donor T cell chimerism at day +30				0.07
≤95	86 (33)	56 (37)	30 (27)	
>95	176 (67)	94 (63)	82 (73)	
% Donor T cell chimerism at day +100				0.1
≤95	43 (22)	28 (27)	15 (17)	
>95	148 (77)	77 (73)	71 (83)	
Year of transplant				0.4
Median (range)	2011 (2008-18)	2011 (2008-18)	2012 (2008-18)	
Follow-up in surviving patients, months				N/A
Median (range)	74 (3-124)	73 (3-124)	74 (4-124)	

HCT-CI, HSCT-specific comorbidity index; CMV, cytomegalovirus; NR, non-reactive; R, reactive; allo-HSCT, allogeneic hematopoietic stem cell transplantation; N/A, not applicable. Totals may vary because of missing data.

The median follow-up time in surviving patients was 74 months (range 3-124 months), and most of the events occurred within 3 years after allo-HSCT. At 3-years, the OS rate was 61% (95% confidence interval [CI] 55-66%) and PFS 46% (95 CI 41-52%). The 3-years cumulative incidence of disease progression, NRM, and T-cGVHD was 35% (95 CI 30-41%), 17% (95 CI 13-22%), and 29% (95 CI 24-35%), respectively. At 6 months, the cumulative incidence of grade 2-4 and grade 3-4 aGVHD was 32% (95 CI 27-38%) and 9% (95 CI 7-13%), respectively. Outcomes according to SIRP α variant match or mismatch status are summarized in **Supplementary Table 2**. The impact of the SIRP α mismatch direction between the donor and the host did not differ significantly for any of the outcomes, a mismatch in either direction was therefore counted as a mismatch in our analysis.

Time to neutrophil engraftment was not associated with SIRP α match or mismatch status (hazard ratio [HR] 1.1, P= .6).

aGVHD

In the univariate analysis (**Table 2**), SIRP α mismatch was not associated with the rate of grade 2-4 (HR 1.2, P= .3) or grade 3-4 (HR, 0.5; P= .3) aGVHD at 6-months. Multivariable analysis confirmed the lack of association (HR 1.3, P= .2) between SIRP α variant mismatch and grade 2-4 aGVHD (**Figure 1A**). Female to male HSCT (HR 1.6, P= .03) and the use of a myeloablative conditioning regimen (HR 1.8, P= .004) were the only significant predictors of grade 2-4 aGVHD (**Table 3**). Predictors of grade 3-4 aGVHD were not evaluated in the multivariable analysis given the small number of events.

TABLE 2 | Univariable analysis evaluating predictors of grade 2-4 acute GVHD, chronic GVHD and chronic GVHD requiring immunosuppressive therapy.

	N	Grade 2-4 acute GVHD D180		Chronic GVHD 3 yrs		Chronic GVHD requiring IS therapy 3 yrs	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
SIRPα							
Matched	180	1.0		1.0		1.0	
G mismatch	66	1.2 (0.8-2)	0.4	1.6 (0.9-2.5)	0.05	1.7 (0.9-2.8)	0.05
H mismatch	64	1.2 (0.8-2)	0.4	1.7(1.1-2.7)	0.01	1.7 (1.02-2.9)	0.04
G/H Mismatched vs matched	130	1.2 (0.8-1.8)	0.3	1.6 (1.1-2.4)	0.008	1.7 (1.1-2.6)	0.01
Recipient age, years							
≤50	143	1.0		1.0		1.0	
>50	167	0.8 (0.6-1.2)	0.3	1.02 (0.7-1.5)	0.9	0.9 (0.6-1.5)	0.9
HCT-CI, n (%)							
≤3	235	1.0		1.0		1.0	
>3	75	1.1 (0.7-1.6)	0.8	0.8 (0.5-1.3)	0.4	0.7 (0.4-1.2)	0.2
Donor / Recipient gender							
Male / Male	116	1.0		1.0		1.0	
Female / Female	61	0.8 (0.5-1.5)	0.6	1.04 (0.6-1.8)	0.9	0.96 (0.5-1.8)	0.9
Male / Female	49	0.9 (0.5-1.7)	0.8	1.2 (0.7-2.2)	0.5	0.9 (0.4-1.9)	0.7
Female / Male	84	1.5 (0.9-2.4)	0.08	1.9 (1.2-2.9)	0.005	1.8 (1.1-2.9)	0.02
Donor / Recipient CMV status							
NR/NR	32	1.0		1.0		1.0	
R/R	169	1.3 (0.6-2.8)	0.5	0.7 (0.4-1.3)	0.3	0.9 (0.4-1.9)	0.8
NR/R	80	1.3 (0.6-3.1)	0.4	1.1 (0.6-2.1)	0.7	1.3 (0.6-2.9)	0.4
R/NR	26	0.9 (0.3-2.6)	0.8	1.5 (0.7-2.9)	0.3	1.7 (0.7-3.9)	0.2
Donor/Recipient ABO							
Matched	208	1.0		1.0		1.0	
Minor mismatch	44	1.05(0.6-1.8)	0.9	1.3 (0.8-2.3)	0.3	1.4 (0.7-2.5)	0.3
Major mismatch	16	0.3 (0.1-1.4)	0.1	(0.4-2.1)	0.8	1.2 (0.5-3)	0.6
Bidirectional	41	1.05 (0.6-1.8)	0.8	1.6 (0.9-2.6)	0.06	1.6 (0.9-2.8)	0.09
Diagnosis							
ALL	115	1.8(1.1-2.9)	0.02	0.8 (0.5-1.2)	0.3	1.1 (0.6-1.8)	0.8
CLL	59	2.0 (1.1-3.5)	0.01	1.2 (0.8-2)	0.4	1.4 (0.8-2.5)	0.2
NHL	114	1.0		1.0		1.0	
HD	22	1.2 (0.5-3.1)	0.5	1.6 (0.8-3.1)	0.2	1.7 (0.8-3.8)	0.2
Response prior to transplant							
Chemo-sensitive	259	1.0		1.0		1.0	
Chemo-refractory	51	1.3 (0.8-2.2)	0.3	0.9 (0.5-1.5)	0.7	1.1 (0.7-2)	0.6
Conditioning intensity							
Non-myeloablative	150	1.0		1.0		1.0	
Myeloablative	160	1.8 (1.2-2.8)	0.003	0.7 (0.5-1.0)	0.06	0.8 (0.5-1.2)	0.3

GVHD, graft-versus-host disease; IS, immunosuppressive; HR, hazard ratio; CI, confidence interval; ALL, Acute lymphoblastic leukemia; CLL, Chronic lymphoblastic leukemia; NHL, Non-Hodgkin's lymphoma; HD, Hodgkin's disease; HCT-CI, HSCT-specific comorbidity index; CMV, cytomegalovirus; NR, non-reactive; R, reactive; allo-HSCT, allogeneic hematopoietic stem cell transplantation. Totals may vary because of missing data.

cGVHD

In the univariate analysis (**Table 2**), SIRP α variant mismatch was associated with a significantly higher rate of cGVHD (HR 1.6, $P = .008$) and T-cGVHD (HR 1.7, $P = .01$) at 3 years, and these effects persisted in the multivariable analysis (**Figures 1B, C**). Female-to-male HSCT was also independently associated with a higher rate of cGVHD (HR 1.9, $P = .001$) and T-cGVHD (HR 2.03, $P = .002$) at 3 years. In addition, the use of a myeloablative conditioning regimen (HR 0.7, $P = .04$) was associated with a lower rate of cGVHD (**Table 3**).

Disease Progression and NRM

In the univariate analysis (**Table 4**), SIRP α mismatch was protective against disease progression (HR 0.7, $P = .05$) and this effect persisted in multivariate analysis (HR 0.5, $P = .003$) (**Table 5** and **Figure 2A**). We further performed subgroup analysis and found that the protective effect of SIRP α mismatch perseveres in each of the lymphoid malignancies included in the study, except for NHL.

Our data did not show any effect of SIRP α mismatch on disease progression (HR 1.2, $P = .5$) for patients with NHL. Stratified analyses showed the median time to relapse in the NHL group was 95 days, which is significantly shorter than that observed for the rest of the cohort (**Supplementary Table 3**). None of the remaining factors evaluated were associated with the rate of disease progression. SIRP α mismatch was not associated with the 3-years NRM rate (**Figure 2B**) in univariable (HR 0.7, $P = .3$) or multivariable analysis (HR 0.7, $P = .2$). Recipient age >50 years (HR 1.8, $P = .04$) and HCT-CI>3 (HR 2.2, $P = .007$) were the only significant predictors of NRM in the multivariate analysis (**Table 5**).

PFS and OS

In the univariate analysis (**Table 4**), SIRP α variant mismatch was associated with more favorable PFS (HR 0.7, $P = .02$), and this effect persisted (HR 0.5, $P = .001$) in multivariable analysis (**Table 5** and **Figure 3A**). Myeloablative conditioning (HR 1.6, $P = .007$) and

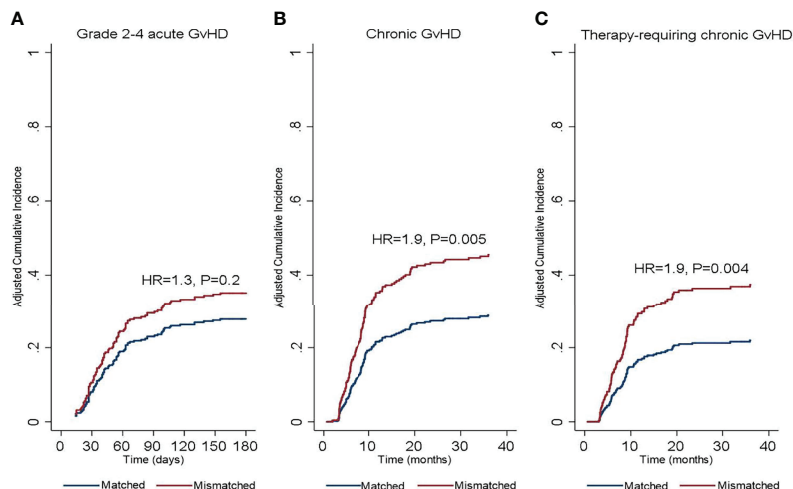


FIGURE 1 | Cumulative incidence of (A) grade 2-4 acute graft-versus-host disease, (B) chronic graft-versus-host disease, and (C) therapy requiring chronic graft-versus-host disease according to donor/recipient SIRP α match or mismatch status. HR, hazard ratio.

HCT-CI>3 (HR 1.7, $P= .003$) was associated with worse PFS in the multivariable analysis. For OS, there was no significant impact for SIRP α mismatch (**Figure 3B**) in univariate (HR 0.9, $P= .9$) but a trend of superior survival in multivariate analysis (HR 0.7, $P= .1$). HCT-CI>3 (HR 1.9, $P<.001$) and an ALL diagnosis (HR 2.2, $P<.001$) were the only two significant predictors of adverse OS in the multivariable analysis (**Table 5**).

Effects of Donor T Cell Chimerism on SIRP α Variant Mismatch

We performed landmark analyses to evaluate the impact of SIRP α mismatch on disease progression and cGVHD depending on donor T cell chimerism. On day 30 (range 21-45) and day 100 (range 70-145) after allo-HSCT, the impact of SIRP α mismatch was limited to the subset of patients who had >95% donor T cell chimerism (**Supplementary Table 4** and **Supplementary Figures 1A, B**). For patients with >95% donor T cell chimerism at day +30 after HSCT, SIRP α mismatch was associated with a significantly lower rate of subsequent disease progression (HR 0.5, $P= .01$) and a higher rate of cGVHD (HR 2.1, $P= .005$). In contrast, for patients with \leq 95% donor T cell chimerism at day +30 after HSCT, SIRP α variant mismatch was not associated with disease progression (HR 0.8, $P= .5$) or cGVHD (HR 0.9, $P= .8$). Consistent

results were observed in the landmark analysis starting at day +100.

DISCUSSION

There remains an unmet need to improve the cure rates for patients with lymphoid malignancies who failed multiple lines of treatment. Except for a subgroup of patients with B-cell lymphoid malignancies who may benefit from chimeric antigen receptor T-cell therapies, allo-HSCT remains the only potentially curative intervention for these high-risk patients. In this large cohort of patients with lymphoid malignancies who underwent allo-HSCT from MRD, we found that SIRP α variant match or mismatch status is predictive of relapse and GVHD after transplant. In line with the previous study in AML/MDS cohort (5), the results of the study suggested that SIRP α variant mismatch in allo-HSCT could elicit non-self recognition and innate immune activation, which further promotes adaptive immunity and subsequently leads to a reduced risk of relapse and a higher risk of cGVHD. Given the high prevalence and significant clinical impact of donor/recipient SIRP α mismatch, the findings of the present study could have practical

TABLE 3 | Multivariable analysis evaluating predictors of grade 2-4 acute GVHD, chronic GVHD and chronic GVHD requiring immunosuppressive therapy

Predictor	Grade 2-4 acute GVHD D180		Chronic GVHD 3 yrs		Chronic GVHD requiring IS therapy 3 yrs	
	HR(95% CI)	P	HR(95% CI)	P	HR(95% CI)	P
SIRPα						
Mismatched	1.3 (0.9-1.9)	0.2	1.8 (1.2-2.6)	0.002	1.9 (1.2-2.9)	0.005
Donor/recipient gender						
Female / Male	1.6 (1.05-2.4)	0.03	1.9 (1.3-2.9)	0.001	2.03 (1.3-3.2)	0.002
Conditioning regimen						
Myeloablative	1.8 (1.2-2.7)	0.004	0.7 (0.5-0.9)	0.04	0.8 (0.5-1.2)	0.2

GVHD: graft-versus-host disease; IS: immunosuppressive.

TABLE 4 | Univariable analysis evaluating predictors of non-relapse mortality, disease progression, progression-free survival and overall survival.

	N	Non-relapse mortality 3 yrs		Disease progression 3 yrs		Disease-free survival 3 yrs		Overall survival 3 yrs	
		HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
SIRPα	310								
Matched	180	1.0		1.0		1.0		1.0	
G mismatch	66	0.6 (0.3-1.4)	0.2	0.6 (0.4-1.1)	0.08	0.6 (0.4-0.9)	0.04	0.8 (0.5-1.3)	0.3
H mismatch	64	0.8 (0.4-1.7)	0.6	0.7 (0.4-1.2)	0.2	0.7 (0.5-1.1)	0.1	0.8 (0.5-1.3)	0.4
G/H Mismatch	130	0.7 (0.4-1.3)	0.3	0.7 (0.4-1.0)	0.05	0.7 (0.5-0.9)	0.02	0.9 (0.5-1.7)	0.9
Recipient age, years									
≤50	143	1.0		1.0		1.0		1.0	
>50	167	1.9 (1.05-3.4)	0.03	0.7 (0.5-1.01)	0.06	1.02 (0.7-1.4)	0.9	1.1 (0.7-1.5)	0.7
HCT-CI, n (%)									
≤3	235	1.0		1.0		1.0		1.0	
>3	75	2.2 (1.3-3.9)	0.01	1.1 (0.7-1.7)	0.6	1.6 (1.1-2.2)	0.008	1.8 (1.2-2.7)	0.002
Donor/Recipient gender									
Male/Male	116	1.0		1.0		1.0		1.0	
Female/Female	61	0.8 (0.4-1.7)	0.6	0.8 (0.5-1.4)	0.4	1.1 (0.7-1.7)	0.5	1.1 (0.7-1.9)	0.6
Male/Female	49	1.0 (0.4-2.6)	0.9	0.6 (0.3-1.2)	0.1	0.8 (0.5-1.4)	0.5	0.8 (0.4-1.5)	0.5
Female/Male	84	1.4 (0.6-2.9)	0.4	0.8 (0.5-1.3)	0.4	1.1 (0.7-1.7)	0.7	1.2 (0.7-2)	0.5
Donor / Recipient CMV									
NR/NR	32	1.0		1.0		1.0		1.0	
R/R	169	1.3 (0.5-3.8)	0.6	1.4 (0.8-2.7)	0.3	1.5 (0.9-2.7)	0.1	2.3 (1.1-5)	0.03
NR/R	80	1.7 (0.6-5)	0.3	0.9 (0.4-1.8)	0.8	1.3 (0.7-2.4)	0.4	2.0 (0.9-4.5)	0.09
R/NR	26	1.2 (0.3-4.9)	0.7	0.7 (0.3-2.1)	0.6	0.9 (0.4-2)	0.8	1.2 (0.4-3.4)	0.7
Donor/Recipient ABO									
Matched	208	1.0		1.0		1.0		1.0	
Minor mismatch	44	1.5 (0.7-3.1)	0.2	0.9 (0.5-1.7)	0.9	1.1 (0.7-1.7)	0.6	1.3 (0.8-2.1)	0.4
Major mismatch	16	0.4 (0.05-2.8)	0.3	1.5 (0.7-3.2)	0.3	1.03 (0.5-2.1)	0.9	1.1 (0.5-2.4)	0.9
Bidirectional	41	1.3 (0.6-2.7)	0.5	1.3 (0.8-2.3)	0.3	1.4 (0.9-2.1)	0.1	1.3 (0.8-2.2)	0.3
Diagnosis									
ALL	115	1.5 (0.8-2.9)	0.2	1.6 (0.9-2.5)	0.06	1.6 (1.1-2.4)	0.009	2.1 (1.4-3.3)	<0.01
CLL	59	1.7 (0.8-3.6)	0.1	1.1 (0.6-1.9)	0.7	1.3 (0.8-2)	0.2	1.2 (0.7-2)	0.5
NHL	114	1.0		1.0		1.0		1.0	
HD	22	0.7 (0.2-3)	0.6	1.2 (0.6-2.7)	0.6	1.01(0.5-2)	0.9	0.8 (0.3-2)	0.7
Response prior									
Chemo-sensitive	259	1.0		1.0		1.0		1.0	
Chemo-refractory	51	1.1 (0.5-2.2)	0.8	1.5 (0.9-2.4)	0.06	1.5 (1.0-2.1)	0.05	1.2 (0.8-1.9)	0.4
Conditioning									
Non-myeloablative	150	1.0		1.0		1.0		1.0	
Myeloablative	160	1.4 (0.8-2.5)	0.2	1.4 (1.02-2.2)	0.04	1.6 (1.2-2.2)	0.002	2 (1.4-2.9)	<0.01

GVHD, graft-versus-host disease; HR, hazard ratio; CI, confidence interval; ALL, Acute lymphoblastic leukemia; CLL, Chronic lymphoblastic leukemia; NHL, Non-Hodgkin's lymphoma; HD, Hodgkin's disease; HCT-CI, HSCT-specific comorbidity index; CMV, cytomegalovirus; NR, non-reactive; R, reactive; allo-HSCT, allogeneic hematopoietic stem cell transplantation.

applications in best donor selection based on disease risk status. For instance, for patients at high risk of relapse, a mismatched SIRP α donor might be preferred despite the increased risk of cGVHD given the overall improvement in PFS. Instead, for patients who are at low risk for relapse, a matched SIRP α is more reasonable to decrease the risk of cGVHD.

In addition to tumor control function, a growing body of evidence has shown that innate immune activation is crucial for the initiation and persistence of cGVHD, and innate responses were upregulated in patients with cGVHD (10–12). In the present study, the SIRP α mismatch was associated with increased incidence and severity of cGVHD, as evidenced by the increased number of patients requiring systematic therapy, but no impact on aGVHD. It is plausible that the allo-response elicited by the innate cells likely occurs several weeks to months after transplant which is responsible for this impact on cGVHD but not aGVHD (13). The association between the relapse protection and the incidence and severity of GVHD has been

reported in several studies of allo-HSCT, but the inverse relationship between GVT and the coupled GVHD is not always consistent among various hematologic malignancies (14, 15). The impact of the SIRP α mismatch on cGVHD observed in the current lymphoid cohort is similar to that seen in the AML/MDS cohort. However, in that study, the relapse protection effect was borderline statistical significant ($P = 0.05$), whereas a significant association was observed between the presence of SIRP α variant mismatch and reduced relapse (HR 0.5, $P = .003$) in the present study, which contributed to the significantly improved PFS (HR 0.5, $P = .001$). These findings indicate that certain lymphoid malignancies may be more sensitive to cGVHD-associated GVT, which could be partially attributable to the innate alloreactivity derived from the SIRP α variant mismatch. In our exploratory subgroup analysis, the trend of increased cGVHD with SIRP α mismatch was seen across all disease subtypes whereas the relapse protection effect was absent in the NHL patients. Of note, the median time to

TABLE 5 | Multivariate analysis evaluating predictors of non-relapse mortality, disease progression, progression-free survival and overall survival.

Predictor	Non-relapse mortality		Disease progression		Disease-free survival		Overall survival	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
SIRPα								
Mismatched	0.7 (0.4-1.3)	0.2	0.5* (0.3-0.8)	0.003	0.5* (0.3-0.8)	0.001	0.7 (0.5-1.1)	0.1
HCT-CI								
>3	2.2 (1.2-3.8)	0.007	---	---	1.7 (1.2-2.3)	0.003	1.9 (1.3-2.9)	<0.001
Age, years								
>50	1.8 (1.02-3.3)	0.04	---	---	---	---	---	---
Conditioning regimen								
Myeloablative	---	---	---	---	1.6 (1.1-2.2)	0.007	---	---
Diagnosis								
ALL	---	---	---	---	---	---	2.2 (1.5-3.2)	<0.001

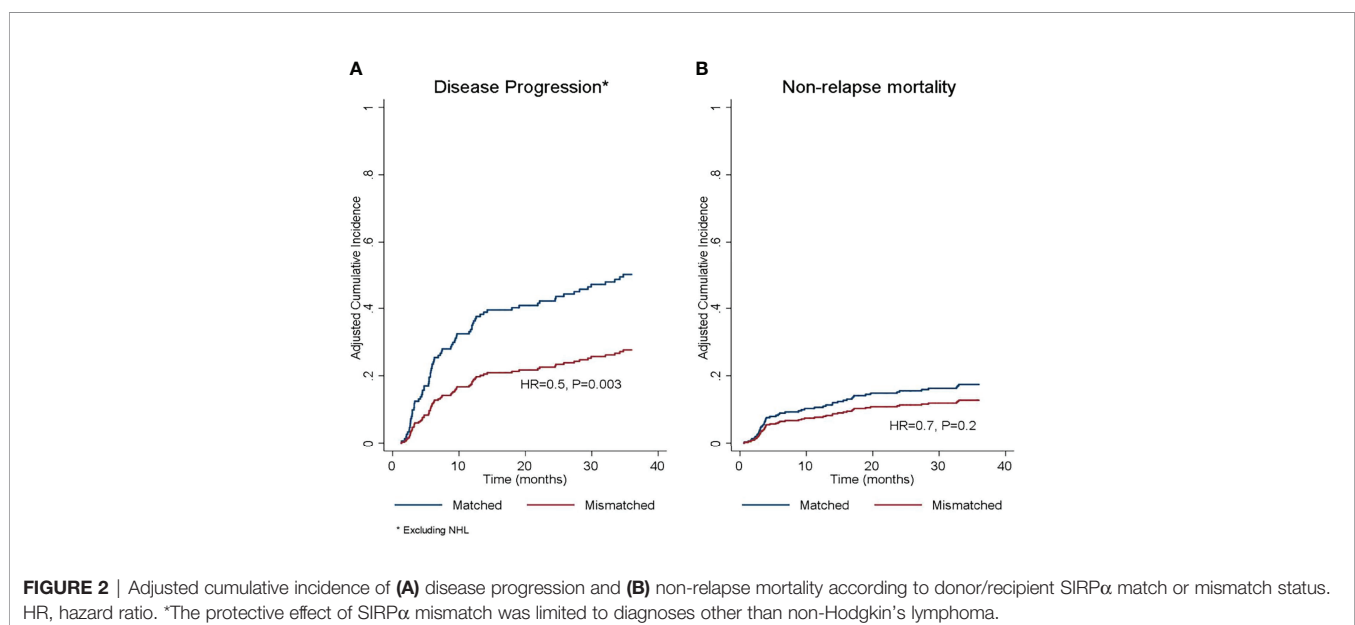
ALL: acute lymphoblastic leukemia* The protective effect of SIRP α mismatch was limited to diagnoses other than non-Hodgkin's lymphoma. SIRP α mismatch did not impact the rate of disease progression (HR=1.2, 95% CI 0.6-2.5, P= .5) or progression-free survival (HR=1.1, 95% CI 0.6-1.9, P= .8) in patients with non-Hodgkin's lymphoma.

relapse for NHL patients was 95 days after transplant compared to 225 days in all other subgroups (**Supplementary Table 3**), indicating the relapses in NHL may precede the alloreactivity enforced by the recovered innate cells.

Recent data from experimental models have shown that the innate immune system could recognize the non-self signals and prime the immunity against allogeneic grafts (16). Unlike allorecognition mediated by T cells that express rearranging receptors, allorecognition by the innate system appears to be independent of major histocompatibility complex (MHC) mismatch and possibly initiated by the mismatching signal from non-MHC genomic loci (17). In the allo-HSCT setting, it is believed that the host antigens, especially antigens from HLA molecules, are processed and presented to donor T cells by either host or donor

Antigen-presenting Cells (APC)s (18), the direction of alloreactivity (GVH or HVG) derived from the HLA mismatch affect the outcomes differently (19). In the present study, all the SIRP α mismatches, regardless of the alloreactive vector or the presence of a specific genotype, are associated with cGVHD and relapse protection. It would be reasonable to postulate that mismatched SIRP α molecules may not be served as an allo-epitope to provoke the adaptive alloimmunity in this scenario, instead, the innate alloresponse activated by the presence of "non-self" SIRP α -CD47 interaction could set up the stage of the subsequent T cell-mediated alloimmunity.

Defining the effector cells and their contributions following the SIRP α mismatch allorecognition would expand our knowledge on the orchestration of innate and adaptive



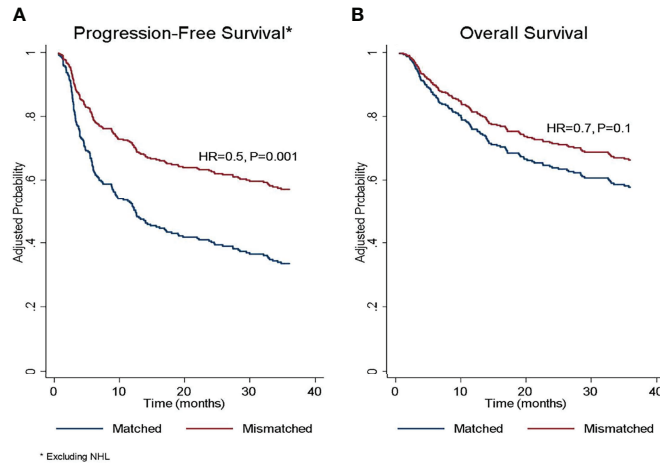


FIGURE 3 | Adjusted probability of (A) progression-free survival and (B) overall survival according to donor/recipient SIRP α match or mismatch status. HR, hazard ratio; NHL, non-Hodgkin lymphoma. *The protective effect of SIRP α mismatch was limited to diagnoses other than non-Hodgkin's lymphoma. *The protective effect of SIRP α mismatch was limited to diagnoses other than non-Hodgkin's lymphoma.

immunity post-HSCT. Consistent with our previous study in AML/MDS, in the present study, the effect of SIRP α mismatch on both cGVHD and relapse protection was observed only in the patients who achieved full (>95%) donor T cell chimerism after allo-HSCT, indicating that enhanced innate immunity may need to activate adaptive immunity first which then leads to a higher risk of cGVHD and a lower risk of relapse. In a mice model that lacked all lymphoid cells, Oberbarnscheidt et al. showed that allograft, but not the syngeneic graft, elicited the differentiation of monocytes into mature DCs, which further stimulated T cell proliferation and IFN- γ production *ex vivo* (16). Studies on the cells influenced by SIRP α -CD47 blockage suggested the tumor control effect is likely attributed to a direct boosting of T cell function and/or an improved APC function [reviewed by Logtenberg et al. (20)]. In the present study, it is possible that donor T cells respond to recipient SIRP α as an alloantigen, and thus create a late-appearing set of T cells enacting both cGVHD and tumor regression. Additionally, other cells expressing SIRP α may also be involved in the alloimmunity mediating cGVHD and relapse protection in our study. Disruption of the SIRP α -CD47 axis significantly enhanced the killing capacity of NK cells, the effect was notably found to be species-specific (21). Moreover, a subset of virus-specific SIRP α ⁺ CD8⁺ T cells remained cytolytic function during chronic exhaustion, and programmed cell death ligand (PD-1) blockage expanded this particular subset (22). Future studies are necessary to generate effector donor T cells *in vitro* and assess their specific effector functions for tumor cells and host tissues.

The antibodies targeting CD47 and SIRP α , either alone or in combination with tumor cell-specific opsonizing antibodies and T-cell checkpoint inhibitors, have shown promise in several trials for various malignancies (23–26). A recent study provided substantial evidence suggesting that blockage SIRP α /CD47 axis could enhance adaptive immunity and prime an anti-tumor cytotoxic T-cell response (20). Using an *in vivo* CRISPR

screening approach, Manguso et al. showed that loss of CD47 significantly improved tumor control in melanoma cells treated with GVAX and anti-PD-1 immunotherapy in a T-cell-dependent process (27). The persistent alloresponse created from the SIRP α mismatch signal after HSCT could behave similarly to that effect derived from SIRP α /CD47 blockade, and this may work synergistically with other antitumor immunotherapy or immune regulator cell infusions. Further studies are warranted to elucidate the underlying mechanisms and to define the specific role of SIRP α mismatch in an allo-HSCT setting.

The present study was limited by its retrospective nature and the relatively small number of patients with heterogeneous lymphoid malignancy subtypes. The use of the National Institutes of Health criteria was not universally adopted for scoring cGVHD during the study period; hence we assessed the cGVHD severity by the rate of cGVHD requiring systematic treatment. This might negatively impact the reproducibility of our findings in future studies. Additionally, minor H antigens are created by mismatched nonsynonymous single-nucleotide polymorphism (nsSNP), and T cell responses against relevant minor H antigens are generally restricted by certain HLA genotypes (28). Our findings may be influenced by certain nsSNP that impact cGVHD and relapse outcomes. However, most of the studies showing an association between minor H antigen disparity and clinical outcome in allo-HSCT are relatively small, and few of the associations were confirmed in a large multi-institutional study (28, 29).

In conclusion, in our analysis of patients who underwent allo-HSCT from MRD for lymphoid malignancies, we found that SIRP α mismatch was commonly detected in donors/recipient pairs and was significantly associated with a lower rate of relapse, improved PFS, and increased risk of cGVHD. Future prospective studies are needed to validate our findings and to investigate the impact of SIRP α in allo-HSCT with other donor sources. The

results of the present study, not only provide valuable information regarding donor choice but also advance our knowledge of allorecognition of the innate immune system in the context of allo-HSCT.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by The Institutional Review Board of The University of Texas MD Anderson Cancer Center. The ethics committee waived the requirement of written informed consent for participation.

AUTHOR CONTRIBUTIONS

RS, SS, RC, and JZ designed the study and contributed to data collection and interpretation and manuscript writing. RS, SSr, UG, and JZ wrote the initial draft of the manuscript. RS designed and performed the statistical analysis, interpreted results, and reviewed and approved the manuscript. SSr, UG, QM, YC, MM, JW, PK, DL, Ssa, and KC contributed to data collection and data

analysis and reviewed and approved the manuscript. MM, and JW performed the SIRP α variation typing and mismatch interpretation. GR contributed to data collection and reviewed and approved the manuscript. SC, PK, and KC contributed to data interpretation and reviewed and approved the manuscript. SSr, UG, AA, KR, ES, and RC contributed to the treatment of patients and reviewed, edited, and approved the final version of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fimmu.2022.904718/full#supplementary-material>

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