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Pretransplant Minimal Pleural and Peritoneal Effusion Is a Potential Poor Prognostic Indicator in Allogeneic Hematopoietic Stem Cell Transplantation

Takashi Oyama[1] | Akira Honda[1] | Yasutaka Masuda[1] | Ken Morita[1] | Hiroaki Maki[1] | Yosuke Masamoto[1,2] | Mineo Kurokawa[1,2]

[1]Department of Hematology and Oncology, Graduate School of Medicine, The University of Tokyo, Bunkyo-Ku, Tokyo, Japan | [2]Department of Cell Therapy and Transplantation Medicine, The University of Tokyo Hospital, Bunkyo-Ku, Tokyo, Japan

Correspondence: Mineo Kurokawa (kurokawa@m.u-tokyo.ac.jp)

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ABSTRACT

Background: Pleural effusion and ascites developing after allogeneic hematopoietic stem cell transplantation (allo-SCT) are generally associated with inferior overall survival (OS); however, the prognostic value of pretransplant effusion on transplant outcomes remained unclear.

Methods: We retrospectively evaluated minimal pleural effusion and ascites detected by computed tomography in 248 consecutive adult patients who underwent their first allo-SCT from January 2007 to December 2022.

Results: Forty-eight patients demonstrated minimal pleural effusion or ascites within 100 days before transplantation (Effusion group) and the other 200 had no effusion (No effusion group). Serum albumin level was significantly lower in the Effusion group than in the No effusion group (median 3.8 vs. 3.4 g/dL, $p < 0.001$). Performance status (PS) was significantly inferior and refined disease risk index tended to be higher in the Effusion group. The 2-year OS rate after transplantation was significantly worse in the Effusion group (57.1% vs. 36.7%, $p < 0.001$). The Effusion group had a significantly lower cumulative incidence of neutrophil and platelet engraftment and higher hepatic veno-occlusive disease. Moreover, a tendency toward higher cumulative incidence of relapse and non-relapse mortality was shown in the Effusion group. In multivariate analysis, the Effusion group had a significantly inferior OS with a hazard ratio of 1.848 (95% confidence interval 1.231–2.774), even after adjustment for disease risk, serum albumin level, PS, and Hematopoietic Cell Transplant-Comorbidity Index points.

Conclusion: Reflecting high disease activity and impaired general condition, pretransplant effusion can be a complementary indicator for poor prognosis in allo-SCT.

1 | Introduction

Allogeneic hematopoietic stem cell transplantation (allo-SCT) has been acknowledged as a promising curative option for refractory and relapsed hematological malignancies. Despite a reduction in transplantation risk in recent years, morbidity and mortality remain high [1], thus emphasizing the importance of a comprehensive risk assessment for allo-SCT in guiding the decision to transplant and the appropriate posttransplant management [2]. Risk score models, such as the European Group for Blood and Marrow Transplantation (EBMT) risk score [3] and the Hematopoietic Cell Transplant-Comorbidity Index (HCT-CI) [4], have been accepted and validated for mortality prediction. However, these models have been established based on information gathered from large databases, potentially neglecting certain crucial prognostic factors in practical clinical situations.

The ubiquitous utilization of computed tomography (CT) in pretransplant evaluation has generally been directed at uncovering focuses of infection [5–8], and recently, several studies have highlighted the ability of pretransplant CT to evaluate muscle mass [9] and spleen size [10, 11] for prognostic predictions in allo-SCT recipients. These studies suggest the usefulness of CT to serve as an objective, minimally invasive examination for evaluation of recipients' pretransplant status.

Fluid retentions, such as pleural effusion and ascites, encountered in the treatment of hematological malignancies, are often resultant of infectious complications, tumor invasion, cardiac dysfunction, or medication, and possibly correlate to poor prognosis. [12, 13]. Several studies indicate patients with pleural or peritoneal effusions after allo-SCT generally have inferior overall survival (OS) and an increased incidence of hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) [14, 15]. To our knowledge, however, few studies have investigated the prognostic value of pretransplant fluid retention on transplant outcomes.

Pretransplant pleural effusion and ascites have been reported in 4%–7% of recipients with abnormalities in chest CT [5, 6] and 6.8% of recipients with posttransplant ascites [14], respectively, although the exact etiology of a small amount of fluid retention often remained inconclusive. We hypothesized that effusion in the body cavity may be associated with transplant outcomes reflecting the poor general condition of recipients or potential activity of tumor and infection, even if it is small in volume and no diagnosis of malignant effusion has been made. In this study, we retrospectively analyzed the prognostic impact of the CT-identified, pretransplant small amount of effusion on transplant outcomes.

2 | Methods

2.1 | Patients Data Collection

The clinical data of adult patients (aged 16 or over) with hematological malignancy who underwent their first allo-SCT between January 2007 and December 2022 at The University of Tokyo Hospital, Japan were collected from electronic medical records. Patients with a history of previous autologous SCT were included. We excluded patients lacking chest or abdominal CT within 100 days before allo-SCT and those with massive or diagnosed malignant pleural or peritoneal effusion. In this study, minimal pleural effusion was defined as a crescent-shaped fluid collection in the thorax with a maximum 10-mm depth, and a depth exceeding 10-mm was defined as massive [16]. Minimal peritoneal effusion (ascites) was classified as an estimated ascites volume of less than 50 mL, confined to the rectovesical pouch; other cases were defined as massive [14]. Evaluation of pleural and peritoneal effusion was performed by a radiologist and confirmed by physician researchers. Patients with minimal pleural or peritoneal effusion detected in the latest CT taken before the start of the conditioning regimen for transplantation were categorized into the Effusion group, and those without pleural nor peritoneal effusion were the No effusion group. The study was approved by the Ethics Committee of The University of Tokyo Hospital. Informed consent was obtained from all participants.

2.2 | Variables Related to Patient Characteristics

The previously reported definition of the refined disease risk index (R-DRI) was employed in the present study [17]. Myeloablative conditioning (MAC) was defined as regimens that included either total body irradiation (TBI) >8 Gy, busulfan >9 mg/kg, or melphalan >140 mg/m^2, and all other regimens were considered reduced intensity conditioning (RIC). The donor group was classified according to the number of mismatched alleles of human leucocyte antigen (HLA) loci (HLA-A, -B, -C, and -DR) for the graft-versus-host direction. The following categories of HCT-CI were evaluated based on the criteria by Sorror et al. [4]: total points, renal dysfunction, cardiac complications, hepatic disease, and infections requiring antibiotic treatment at transplantation. A course of chemotherapy was defined as a series of chemotherapies from the start of treatment until response or relapse, and the number of courses of chemotherapy before transplantation (not including conditioning regimen) was counted on each patient. Serum albumin level on the day of the last CT before transplantation was collected.

2.3 | Endpoints

The primary endpoint of this study was to compare the 2-year OS rate between the No effusion and Effusion groups. Other endpoints included the cumulative incidence of neutrophil and platelet engraftment, infectious complications, VOD/SOS, grade II-IV acute GVHD (aGVHD), chronic GVHD (cGVHD), relapse, relapse mortality, and non-relapse mortality (NRM). Neutrophil and platelet engraftment were defined as an absolute neutrophil count $> 5 \times 10^9$/L for 3 consecutive days and as an absolute platelet count $> 20 \times 10^9$/L without platelet transfusion, respectively. Disease relapse was defined as acute leukemia, myelodysplastic syndrome, or myeloproliferative neoplasms with more than 5% bone marrow blasts, chronic myeloid leukemia in blastic crisis, or lymphoma, myeloma, and other leukemia with progressive disease. When complete remission was not achieved after transplantation in cases with a pretransplantation disease status of not in remission, the day of relapse was defined as day +0.1. Infectious complications included episodes of severe bacterial, invasive fungal infections, and cytomegalovirus (CMV) until day +100 posttransplantation. Severe bacterial infections were defined as sepsis, bacterial pneumonia [18], or septic shock with positive blood or tissue culture. Invasive fungal infections were defined by histopathology/cytopathology evidence or positive culture of an infected organ and/or radiologic signs consistent with fungal infection according to previous criteria [19]. CMV infection was defined as >2 CMV-positive cells per two slides (CMV pp65 antigenemia C10/C11) [20]. The physicians who performed the transplantations diagnosed and graded VOD/SOS, aGVHD, and cGVHD according to the traditional criteria [21, 22].

2.4 | Statistical Analysis

Comparisons between groups were performed with Fisher's exact test for categorical variables and the Mann–Whitney U test for continuous variables. The probability of OS was estimated according to the Kaplan–Meier method, and the groups were compared using the log-rank test. Log-rank test with Holm–Bonferroni

correction was applied for the comparisons among more than two groups. The Cox proportional hazards model was used for multivariate analyses for OS. The Gray test was used for comparison of cumulative incidence. Relapse death, non-relapse death, and death without the event were defined as a competing event for NRM, relapse mortality, and other endpoints, respectively. The Fine–Gray proportional hazards model was used for multivariate analyses of cumulative incidence. Factors used in the univariate analysis included patient age, diagnosis category, R-DRI, HCT-CI, Eastern Cooperative Oncology Group Performance Status Scale (ECOG PS) [23], graft source, HLA match, donor-to-recipient sex, conditioning regimen, GVHD prophylaxis, and the effusion status. Factors other than the effusion status that showed significant differences ($p < 0.05$) in univariate analyses were included in the multivariate analyses. To avoid multicollinearity between graft source and HLA match, the factor of graft source was applied in the multivariate analysis of engraftment and infection, while that of HLA match was in GVHD. Subgroup analyses by each covariate factor were performed for the comparison of the OS rate. All tests were two-sided, and $p < 0.05$ was considered statistically significant. All statistical analyses were performed with EZR [24], which is a graphical user interface for R version 4.3-1 (R Foundation for Statistical Computing, Vienna, Austria).

3 | Results

3.1 | Patient Characteristics

From January 2007 to December 2022, 292 patients with hematological malignancies underwent their first allo-SCT at our institute. Of these, 41 and 3 patients were excluded due to lack of chest or abdominal CT within 100 days before transplantation and massive or diagnosed malignant pleural effusion or ascites, respectively. We analyzed a total of 248 patients, 48 patients of whom demonstrated minimal pleural or peritoneal effusion detected within 100 days before transplantation (the Effusion group). Table 1a outlines the baseline characteristics of the No effusion and Effusion group. Both groups were comparable on multiple parameters, such as age at allo-SCT, sex, number of courses of chemotherapies, HCT-CI, transplantation period, HLA matching, conditioning regimen, and GVHD prophylaxis. Days from CT-imaging to transplantation did not differ between the two groups (median 16 vs. 18.5 days, $p = 0.695$). Notably, lymphoma was significantly more common in the No effusion group (22% vs. 2.1%, $p < 0.001$) and adult T-cell leukemia-lymphoma was significantly more common in the Effusion group (1.5% vs. 8.3%, $p = 0.028$), and the proportion of high or very high R-DRI tended to be more prevalent in the Effusion group (29% vs. 44%, $p = 0.058$). In the Effusion group, serum albumin level on the day of CT-imaging was significantly lower (median 3.8 vs. 3.4 g/dL, $p < 0.001$), and the proportion of ECOG PS ≥ 1 was significantly higher (33% vs. 50%, $p = 0.031$). The proportion of peripheral blood stem cell transplantation and female donor to male recipient transplantation tended to be more prevalent in the No effusion group (29% vs. 10%, $p = 0.053$ and 25% vs. 13%, $p = 0.083$, respectively).

Table 1b shows the specific sites and etiology of effusion. Among the 48 patients with pleural effusion or ascites, 33 had only ascites, 12 had only pleural effusion, and 3 had both ascites and pleural effusion. According to the etiology of effusion, 18 patients had a history of documented preceding infection, including pneumonia, gastrointestinal (GI) infections, cholecystitis/cholangitis, and pancreatitis, and 4 patients had experienced tyrosine kinase inhibitor (TKI, including imatinib, dasatinib, and ponatinib)—associated pleural effusion. Effusion of 17 patients accompanied paraneoplastic fever, splenomegaly, or lymphadenopathy in non-complete remission (non-CR) status, which was considered as tumor-associated effusion. The etiology of other nine patients was unclear, but four of them were young female with ascites, which was supposed as physiologic menstruation-related ascites.

3.2 | Overall Survival and Other Transplant Outcomes Between the No Effusion and Effusion Group

The comparison of the OS and cumulative incidence of transplant outcomes between the No effusion and Effusion groups is shown in Table 2a. As a primary endpoint, the 2-year OS rate was significantly lower in the Effusion group than in the No effusion group (57.1% vs. 36.7%, $p < 0.001$, Figure 1a). The cumulative incidence of neutrophil engraftment at day +28 and platelet engraftment at day +100 was significantly lower in the Effusion group (76.0% vs. 56.2%, $p = 0.017$, Figure 1b, and 71.5% vs. 56.2%, $p = 0.013$, Figure 1c). The cumulative incidence of severe bacterial and fungal infections until day +100 tended to be higher in the Effusion group but not significant (24.5% vs. 39.6%, $p = 0.065$ and 7.0% vs. 14.7%, $p = 0.117$, respectively). The cumulative incidence of VOD/SOS at day +100 was significantly higher in the Effusion group (3.5% vs. 14.6%, $p = 0.003$, Figure 1d): only a few patients had a history of inotuzumab ozogamicin or gemtuzumab ozogamicin before transplantation, and the proportion of busulfan or TBI containing conditioning regimen was not different between the two groups (Table 1a). There was no significant difference in the cumulative incidence rate of grade II-IV aGVHD and cGVHD between the two groups. The cumulative relapse at 2 years after transplantation was documented in 32.8% and 41.2% of the No effusion and Effusion groups, respectively, and this difference was not significant ($p = 0.222$, Figure 1e). The 2-year NRM was relatively higher in the Effusion group without significant difference (19.2% vs. 28.8%, $p = 0.180$, Figure 1f), while the 2-year relapse mortality and mortality rate after relapse (95% confidence interval [95% CI]) was significantly higher in the Effusion group (23.7% [17.8–30.1] vs. 34.4% [20.5–48.7], $p = 0.021$ and 29.7% [15.9–45] vs. 7.2% [0.5–27.8], $p = 0.013$, respectively, Figure S1a, b). The main reason for death between the No effusion and Effusion groups is shown in Table 2b; although infections tended to be slightly more common in the Effusion group, no obvious difference was confirmed. Infection and disease relapse were common causes of death in patients with effusion due to infections and tumor-associated, respectively.

We compared the 2-year OS rate according to the sites of effusions (Figure 2a). The 2-year OS (95% CI) in the No effusion group ($N = 200$), patients with only ascites ($N = 33$), patients with only pleural effusion ($N = 12$), and patients with both ascites and pleural effusion ($N = 3$) was 57.1% (49.6–63.9), 43.7% (24.5–61.4), 45.0% (13.9–27.4), and not reached, respectively. Patients with only ascites and those with both effusions showed significantly

TABLE 1a | Baseline characteristics of patients before allo-SCT.

	No effusion		Effusion		*p* value	
Number of patients	200		48		–	
Background characteristics						
Age (year), median (range)	49	(16–69)	50.5	(17–70)	0.356	
Age < 60	163	(82%)	35	(73%)	0.228	
Age ≥ 60	37	(19%)	13	(27%)		
Sex						
Female	70	(35%)	22	(46%)	0.184	
Male	130	(65%)	26	(54%)		
Diagnosis and disease status at transplantation						
Myeloid neoplasms	112	(56%)	32	(67%)	0.196	
Lymphoid and ambiguous lineage neoplasms	88	(44%)	16	(33%)		
Non-CR disease despite chemotherapies at transplantation	82	(41%)	22	(46%)	0.618	
Details of diagnosis						
AML	76	(38%)	20	(42%)	0.742	
CR1/CR2	43		7		–	
NR, ≥2 relapses, and/or adverse cytogenetics	33		13		–	
CML	9	(4.5%)	1	(2.1%)	0.692	
CP	7		1		–	
AP/BC	2		0		–	
MDS/MPN	23	(12%)	9	(19%)	0.228	
MDS without excess blast nor adverse cytogenetics	4		1		–	
MDS with excess blast or adverse cytogenetics	14		8		–	
MPN or MF	6		0		–	
ALL	40	(20%)	11	(23%)	0.696	
CR1/CR2	38		9		–	
NR and/or ≥ 2 relapses	2		2		–	
Lymphoma	44	(22%)	1	(2.1%)	<0.001	*
CR	12		1		–	
PR	20		0		–	
SD/PD	12		0		–	
ATL	3	(1.5%)	4	(8.3%)	0.028	*
Others	5	(2.5%)	2	(4.1%)	0.624	
Refined disease risk index at transplantation						
Low/intermediate	142	(71%)	27	(56%)	0.058	
High/very high	58	(29%)	21	(44%)		
Number of courses of chemotherapies before transplantation						
0	18	(9.0%)	8	(17%)	0.272	
1	127	(64%)	32	(67%)		
2	43	(22%)	7	(15%)		
≥3	12	(6.0%)	1	(2.1%)		
History of inotuzumab ozogamicin	2	(1.0%)	1	(2.1%)	0.477	
History of gemtuzumab ozogamicin	1	(0.5%)	0	(0%)	1.000	

(Continues)

TABLE 1a | (Continued)

	No effusion		Effusion		*p* value	
HCT-CI						
Total points: 0	116	(58%)	26	(54%)	0.471	
Total points: 1	34	(17%)	6	(13%)		
Total points: ≥2	50	(25%)	16	(33%)		
Cardiac complication	21	(11%)	4	(8.3%)	0.794	
Renal dysfunction	2	(1%)	0	(0%)	1.000	
Hepatic disease	25	(12.5%)	10	(21%)	0.157	
Infectious complication requiring antibiotics at transplantation	10	(5.3%)	6	(13%)	0.092	
ECOG PS						
0	134	(67%)	24	(50%)	0.031	*
≥ 1	66	(33%)	24	(50%)		
Serum albumin (g/dL), median (range)	3.8	(2.2–4.8)	3.4	(2.1–4.5)	<0.001	*
Above the median (≥3.8)	89	(45%)	15	(31%)	0.105	
Below the median (<3.8)	111	(56%)	33	(69%)		
Transplantation period						
2007–2014	93	(47%)	23	(48%)	0.873	
2015–2022	107	(54%)	25	(52%)		
Days from last CT to transplantation, median (range)	16	(6–92)	18.5	(6–97)	0.695	
Conditions around transplantation						
Graft source						
BM	105	(53%)	32	(67%)	0.053	
PB	52	(26%)	5	(10%)		
CB	43	(22%)	11	(23%)		
HLA matched or mismatched						
MRD/MUD	111	(56%)	25	(52%)	0.908	
MMRD/MMUD	46	(23%)	12	(25%)		
CB	43	(22%)	11	(23%)		
Donor-to-recipient sex						
Not female to male	150	(75%)	42	(88%)	0.083	
Female to male	50	(25%)	6	(13%)		
Conditioning regimen						
MAC	141	(71%)	31	(65%)	0.486	
RIC	59	(30%)	17	(35%)		
Busulfan containing regimen	13	(6.5%)	5	(10%)	0.356	
TBI containing regimen	178	(89%)	46	(96%)	0.183	
GVHD prophylaxis						
CNI + MTX	177	(89%)	40	(83%)	0.228	
Others	22	(11%)	9	(19%)		

Abbreviations: ALL, acute lymphoblastic leukemia; allo-SCT, allogeneic hematopoietic stem cell transplantation; AML, acute myeloid leukemia; AP, accelerated phase; ATL, adult T-cell leukemia-lymphoma; BC, blastic crisis; BM, bone marrow; CB, cord blood; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CMMoL, chronic myelomonocytic leukemia; CNI, calcineurin inhibitor; CR, complete remission; CP, chronic phase; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HCT-CI, hematopoietic cell transplant-comorbidity index; MAC, myeloablative conditioning; MDS, myelodysplastic syndrome; MF, myelofibrosis; MMRD, HLA-mismatched related donor; MMUD, HLA-mismatched unrelated donor; MPN, myeloproliferative neoplasm; MRD, HLA-matched related donor; MTX, methotrexate; MUD, HLA-matched unrelated donor; NR, non-remission; PB, peripheral blood; PD, progressive disease; PR, partial remission; RIC, reduced intensity conditioning; SD, stable disease; TBI, total body irradiation.

TABLE 1b | Characteristics of sites and supposed etiology of effusion in the Effusion group.

Number of patients (Effusion group)	**48**	
Sites of effusion		
Only ascites	33	(69%)
Only pleural effusion	12	(25%)
Both ascites and pleural effusion	3	(6.3%)
Supposed etiology		
Infections	18	(38%)
Preceding pneumonia	8	(17%)
Preceding gastrointestinal infection, cholecystitis/cholangitis, or pancreatitis	10	(21%)
Preceding TKI (imatinib, dasatinib, or ponatinib) treatment	4	(8.3%)
Tumor associated – paraneoplastic fever, splenomegaly or lymphadenopathy in non-CR patients	17	(35%)
Others	9	(19%)
Female age < 45, supposed as physiological	4	(8.3%)
Not explained	5	(10%)

Abbreviation: TKI, tyrosine kinase inhibitor.

TABLE 2a | Comparison of the OS and cumulative incidence of transplant outcomes between the No effusion and Effusion groups.

	No effusion		**Effusion**		***p* value**	
Number of patients	**200**		**48**		**—**	
Engraftment						
Neutrophil engraftment at day +28 (95% CI)	0.760	(0.694–0.814)	0.562	(0.409–0.690)	0.017	*
Platelet engraftment at day +100 (95% CI)	0.715	(0.647–0.773)	0.562	(0.408–0.691)	0.013	*
Infections						
Severe bacterial infection at day +100 (95% CI)	0.245	(0.188–0.307)	0.396	(0.257–0.531)	0.065	
Fungal infection at day +100 (95% CI)	0.070	(0.040–0.111)	0.147	(0.064–0.263)	0.117	
CMV infection at day +100 (95% CI)	0.065	(0.036–0.105)	0.021	(0.002–0.097)	0.236	
Complications						
VOD/SOS at day +100 (95% CI)	0.035	(0.016–0.067)	0.146	(0.063–0.261)	0.003	*
Grade ≥ 2 acute GVHD at day +100 (95% CI)	0.245	(0.188–0.307)	0.271	(0.154–0.402)	0.886	
Chronic GVHD at 2-year posttransplant (95% CI)	0.178	(0.127–0.235)	0.092	(0.029–0.202)	0.130	
Relapse and NRM						
Relapse at 2-year posttransplant (95% CI)	0.328	(0.262–0.394)	0.412	(0.267–0.552)	0.222	
2-year NRM (95% CI)	0.192	(0.139–0.252)	0.288	(0.163–0.427)	0.180	
Survival						
2-year OS (95% CI)	0.571	(0.496–0.639)	0.367	(0.226–0.509)	<0.001	*

Abbreviations: CI, confidence interval; CMV, cytomegalovirus; GVHD, graft-versus-host disease; NRM, non-relapse mortality; OS, overall survival; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

TABLE 2b | Main reasons for death in the No effusion and Effusion groups.

					Effusion group								
					Etiology of effusion at transplantation								
	No effusion group		Total		Infections		TKI		Tumor associated		Others		
Number of patients	200		48		18		4		17		9		
Dead patients	95		33		14		1		13		5		
Main death reason (%)													
Infection	25	(26%)	12	(36%)	7	(50%)	0	(0%)	4	(31%)	1	(20%)	
Relapse	23	(24%)	7	(21%)	3	(21%)	0	(0%)	4	(31%)	0	(0%)	
GVHD	13	(14%)	3	(9.1%)	1	(7.1%)	0	(0%)	1	(7.7%)	1	(20%)	
Noninfectious pulmonary disease	11	(12%)	4	(12%)	1	(7.1%)	0	(0%)	2	(15%)	1	(20%)	
VOD/SOS	4	(4.2%)	2	(6.1%)	0	(0%)	1	(100%)	1	(7.7%)	0	(0%)	
Hemorrhage	6	(6.3%)	2	(6.1%)	1	(7.1%)	0	(0%)	0	(0%)	1	(20%)	
Cardiac dysfunction	5	(5.3%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	0	(0%)	
Others or unknown	8	(8.4%)	3	(9.1%)	1	(7.1%)	0	(0%)	1	(7.7%)	1	(20%)	

Abbreviations: GVHD, graft-versus-host disease; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

worse 2-year OS compared to the No effusion group ($p = 0.030$ and $p < 0.001$, respectively).

According to the etiology of effusion in the Effusion group, the 2-year OS (95% CI) was 36.1% (15.0–57.9), 75.0% (12.8–96.1), 15.5% (2.7–38.4), and 62.5% (22.9–86.1) by the etiology of infections, TKI, tumor-associated, and others, respectively (Figure 2b). No significant difference was observed ($p = 0.090$), but infection or tumor-associated effusion had a tendency of poor outcome.

3.3 | Univariate and Multivariate Analysis Including Covariate Factors

Factors associated with neutrophil and platelet engraftment, infectious complications, VOD/SOS, acute and chronic GVHD, relapse, NRM, and OS in the univariate and multivariate analyses are listed in Table S1 and Tables 3a, 3b, respectively. After adjustment by covariate factors, no significant difference in neutrophil and platelet engraftment was shown between the No effusion and Effusion groups, with hazard ratios (HRs) of 0.823 (95% CI, 0.564–1.203) and 0.730 (95% CI, 0.468–1.148), respectively. As in the univariate analysis, there were no significant differences between the No effusion and Effusion groups after multivariate adjustment in the cumulative incidence of bacterial infection, acute and chronic GVHD, relapse, and NRM. According to the analysis of VOD/SOS, because the cumulative number of cases of VOD/SOS was as small as 14, the factor of HCT-CI score, which showed the smallest p value in the factors analyzed in univariate analyses, was solely included in the multivariate analysis in addition to the No effusion and Effusion groups. The Effusion group had a significantly higher rate of VOD/SOS even after adjustment by HCT-CI with HRs of 4.036 (95% CI 1.407–11.58).

In the multivariate analysis for OS, besides high or very high R-DRI and ≥2 HCT-CI, the Effusion group had a significantly inferior survival rate with HRs of 1.848 (95% CI, 1.231–2.774). ECOG PS, serum albumin, and conditioning regimen were not significant factors after adjustment. The Effusion group showed significantly inferior OS to the No effusion group in most subgroups (Figure 3).

3.4 | Stratification of Mortality Risk by Disease Risk and HCT-CI Score With the Effusion Status

As the R-DRI, HCT-CI score, and the effusion status were significant factors for the OS in multivariate analysis, we aimed to combine the effusion status with the other two factors for more precise stratification of transplantation risk. Combined with R-DRI (Figure 4a), the 2-year OS (95% CI) was 69.3% (60.5–76.5), 59.8% (37.9–76.2), 27.8% (16.7–39.9), and 6.0% (0.4–23.6) among patients with low/intermediate R-DRI and No effusion ($N = 142$), low/intermediate R-DRI and Effusion ($N = 27$), high/very high R-DRI and No effusion ($N = 58$), and high/very R-DRI and Effusion ($N = 21$), respectively. When combined with HCT-CI (Figure 4b), the 2-year OS (95% CI) was 62.3% (53.7–69.8), 46.7% (27.4–63.9), 41.3% (26.8–55.2), and 18.8% (4.6–40.2) among patients with HCT-CI 0–1 and No effusion ($N = 150$), HCT-CI 0–1 and Effusion ($N = 32$), HCT-CI ≥ 2 and No effusion ($N = 50$), and HCT-CI ≥ 2

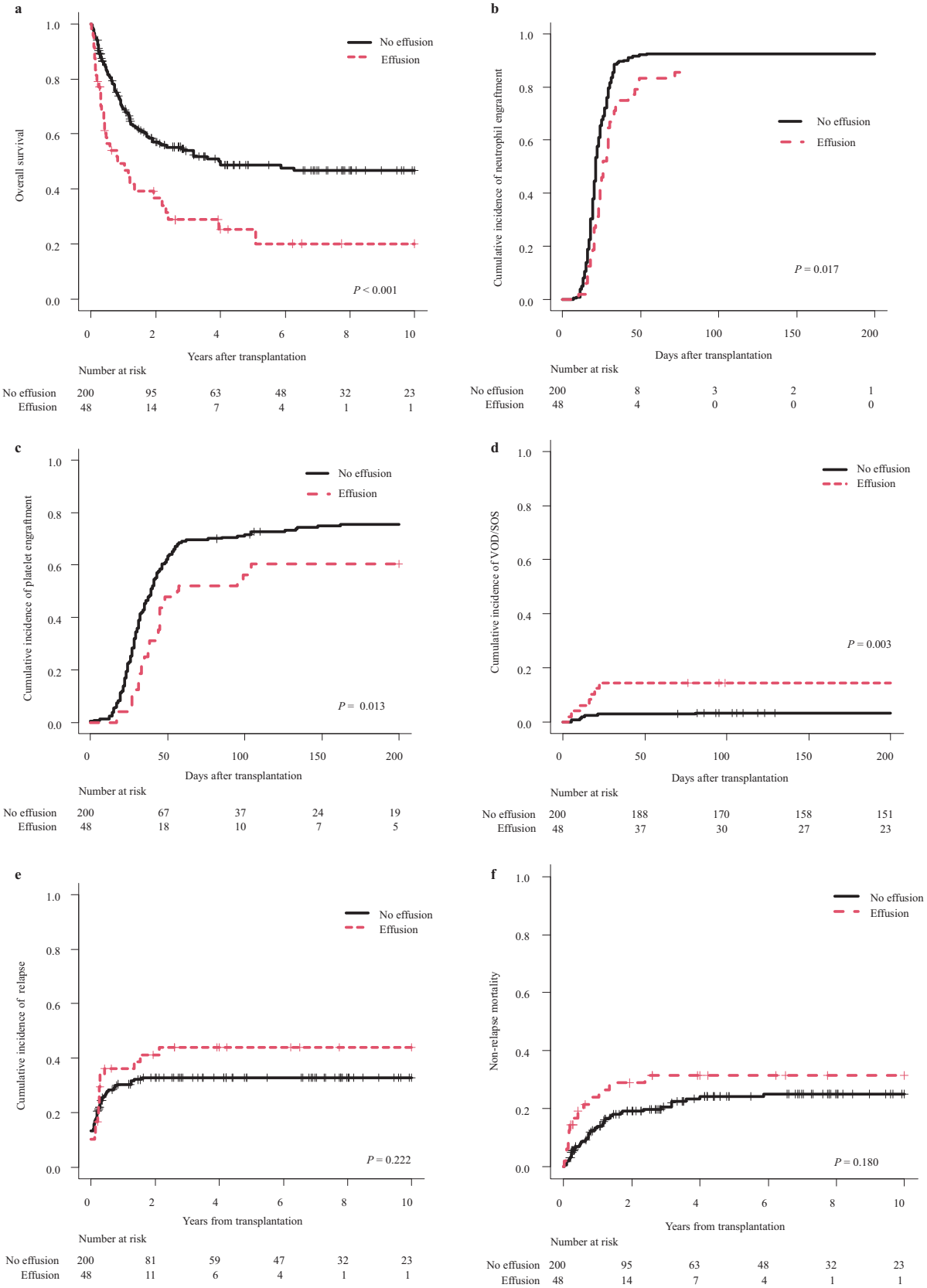

FIGURE 1 | (a) Comparison of the OS between the No effusion or Effusion groups. Cumulative incidences of neutrophil engraftment (b), platelet engraftment (c), VOD/SOS (d), relapse (e), and NRM (f) between the two groups. NRM, non-relapse mortality; OS, overall survival; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

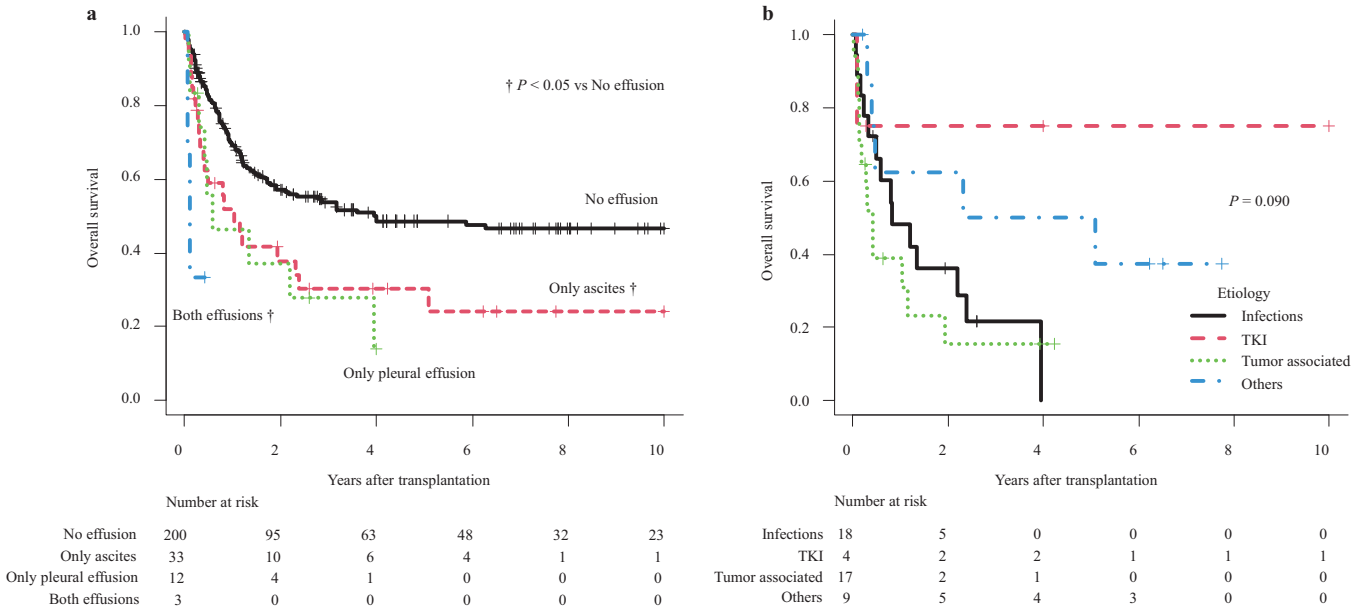

FIGURE 2 | (a) Comparison of the OS according to sites of effusion with Holm–Bonferroni correction. (b) Comparison of the OS according to the etiology of effusion. OS, overall survival.

and Effusion ($N = 16$), respectively. Significant differences were detected in each comparison.

4 | Discussion

In this study, for the first time, we demonstrated that pleural or peritoneal effusion before transplantation adversely affects the OS. This trend was also confirmed after multivariate analysis, including disease risk and HCT-CI, supporting the possibility that the status of pretransplant effusion is a new meaningful prognostic factor in allo-SCT.

Our study revealed that even minimal effusions significantly worsened the OS, suggesting they should not be overlooked in pretransplant evaluation. Massive effusions are generally assumed with poor prognosis due to tumor infiltration, infection, or organ failure and prompt appropriate management [12–15]. However, minimal effusions pose diagnostic challenges partially due to difficulty in paracentesis and tend to be underestimated, especially in the case of minimal ascites, which is often regarded as physiologically insignificant in healthy females with menstruation [25]. We estimated the etiology of effusion by pretransplant clinical conditions: infection, association with tumor activity, TKIs-related, and unknown reasons. Interestingly, tumor-related or infection-related effusions tended to have a worse prognosis than TKIs-related or unexplained effusions. Among patients with the same disease risk or with infection at the time of transplantation, a tendency of worse prognoses existed in the Effusion group (Figure 3 and Figure S1c). We consider that the effusion status might emphasize background illness and prognosis would be different among its etiologies, though identifying accurate causes of pretransplant minimal effusion is usually challenging.

We hypothesize that pretransplant effusion could worsen the OS, primarily by increasing relapse mortality as an indicator of high disease activity, and secondary by partially increasing NRM as a reflection of smoldering infectious complication. Our analysis revealed that there was no significant difference in the rate of pretransplant organ damage and in the number of chemotherapies between patients with or without effusion, implying that the history of treatment before transplantation itself was not a direct contributor for effusion, but tumor activity or severe infection which could yield effusion was a more important risk factor. Significantly lower albumin level and inferior ECOG PS in the Effusion group might be the resultants of potential high disease activity or infections, reflecting increased vascular permeability and systemic inflammation [26, 27]. Moreover, while the increase of cumulative incidence of relapse in the Effusion group was not significant, high relapse mortality and mortality rate after relapse supported the relationship between effusion and high disease activity. The increased incidence rate of VOD/SOS in the Effusion group would be explained similarly, as the effusion might reflect high disease activity and poor ECOG PS, which are known risk factors for VOD/SOS [28]. Additionally, the existence of a lot of infection-related effusion and death by infection in the Effusion group might explain worsened NRM as the expression of high susceptibility to infection, attributing to the poor OS in partial.

We aimed to utilize the status of pleural and peritoneal effusion, which can be objectively and easily identified by CT, for pretransplant risk assessment together with other established criteria. We combined the R-DRI and HCT-CI scores with the status of pretransplant effusion to stratify the OS. Significantly lowered survival was shown under the existence of pretransplant effusions, even with the same R-DRI or HCT-CI score category, which allowed for the meaningful categorization like in Figure 4a, b. Pretransplant effusions have great potential to be a comprehensive indicator reflecting the recipient's overall condition alongside existing risk assessment tools.

TABLE 3a | Multivariate analyses for engraftment, infectious complications, VOD/SOS, and acute and chronic GVHD with the No effusion and Effusion groups added to the model.

Variable	HR	(95% CI)	*p* value		Variable	HR	(95% CI)	*p* value	
Neutrophil engraftment					Platelet engraftment				
Disease category					Refined disease risk index				
Myeloid neoplasms	1				Low/intermediate	1			
Lymphoid neoplasms	2.386	(1.764–3.226)	<0.001	*	High/very high	0.795	(0.519–1.218)	0.290	
Refined disease risk index					HCT-CI total points				
Low/intermediate	1				0–1	1			
High/very high	0.624	(0.435–0.896)	0.011	*	≥2	0.558	(0.366–0.852)	0.007	*
HCT-CI total points					ECOG PS				
0–1	1				0	1			
≥2	0.599	(0.421–0.852)	0.004	*	≥1	0.650	(0.450–0.939)	0.022	*
ECOG PS					Serum albumin				
0	1				Above the median	1			
≥1	1.106	(0.797–1.535)	0.550		Below the median	0.727	(0.512–1.031)	0.074	
Serum albumin					Graft source				
Above the median	1				BM	1			
Below the median	0.632	(0.475–0.840)	0.002	*	PB	2.363	(1.460–3.823)	<0.001	*
Graft source					CB	0.744	(0.537–1.030)	0.075	
BM	1				Conditioning regimen				
PB	3.124	(2.141–4.559)	<0.001	*	MAC	1			
CB	0.526	(0.378–0.730)	<0.001	*	RIC	0.665	(0.455–0.972)	0.035	*
Conditioning regimen					Effusion				
MAC	1				No	1			
RIC	0.697	(0.506–0.960)	0.027	*	Yes	0.730	(0.468–1.141)	0.170	
Effusion									
No	1								
Yes	0.823	(0.564–1.203)	0.310						
Bacterial infection					Grade 2–4 acute GVHD				
Graft source					HLA match				
BM	1				MRD/MUD	1			
PB	0.250	(0.097–0.640)	0.004	*	MMRD/MMUD	1.826	(1.087–3.067)	0.023	*
CB	1.241	(0.751–2.050)	0.400		CB	0.331	(0.130–0.842)	0.020	*
Effusion					Effusion				
No	1				No	1			
Yes	1.454	(0.874–2.418)	0.150		Yes	1.027	(0.559–1.889)	0.930	
VOD/SOS					Chronic GVHD				
HCT-CI					Serum albumin				
0–1	1				Above the median	1			
≥2	3.562	(1.236–10.26)	0.019	*	Below the median	0.421	(0.196–0.904)	0.027	*

(Continues)

TABLE 3a | (Continued)

Variable	HR	(95% CI)	*p* value		Variable	HR	(95% CI)	*p* value	
Effusion					HLA match				
No	1				MRD/MUD	1			
Yes	4.036	(1.407–11.58)	0.010	*	MMRD/MMUD	1.394	(0.709–2.738)	0.340	
					CB	0.366	(0.107–1.250)	0.110	
					Effusion				
					No	1			
					Yes	0.5618	(0.201–1.568)	0.270	

Abbreviations: BM, bone marrow; CB, cord blood; CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; GVHD, graft-versus-host disease; HCT-CI, hematopoietic cell transplant-comorbidity index; HR, hazard ratio; MAC, myeloablative conditioning; MMRD, HLA-mismatched related donor; MMUD, HLA-mismatched unrelated donor; MRD, HLA-matched related donor; MUD, HLA-matched unrelated donor; PB, peripheral blood; RIC, reduced intensity conditioning; VOD/SOS, veno-occlusive disease/sinusoidal obstruction syndrome.

TABLE 3b | Multivariate analyses for relapse, NRM, and OS with the No effusion and Effusion groups added to the model.

Variable	HR	(95% CI)	*p* value		Variable	HR	(95% CI)	*p* value	
Relapse					OS				
Refined disease risk index					Refined disease risk index				
Low/intermediate	1				Low/intermediate	1			
High/very high	2.394	(1.552–3.693)	<0.001	*	High/very high	3.276	(2.251–4.767)	<0.001	*
Serum albumin					HCT-CI				
Above the median	1				0–1	1			
Below the median	1.285	(0.832–1.985)	0.260		≥2	1.746	(1.204–2.533)	0.003	*
Effusion					ECOG PS				
No	1				0	1			
Yes	1.101	(0.665–1.823)	0.710		≥1	1.255	(0.870–1.809)	0.225	
NRM					Serum albumin				
Refined disease risk index					Above the median	1			
Low/intermediate	1				Below the median	1.125	(0.782–1.617)	0.526	
High/very high	1.704	(1.015–2.860)	0.044	*	Conditioning regimen				
HCT-CI					MAC	1			
0–1	1				RIC	1.185	(0.817–1.718)	0.372	
≥2	1.480	(0.857–2.556)	0.160		Effusion				
Conditioning regimen					No	1			
MAC	1				Yes	1.848	(1.231–2.774)	0.003	*
RIC	1.949	(1.146–3.313)	0.014	*					
Effusion									
No	1								
Yes	1.335	(0.715–2.495)	0.360						

Abbreviations: CI, confidence interval; ECOG PS, Eastern Cooperative Oncology Group Performance Status; HR, hazard ratio; HCT-CI, hematopoietic cell transplant-comorbidity index; MAC, myeloablative conditioning; NRM, non-relapse mortality; OS, overall survival; RIC, reduced intensity conditioning.

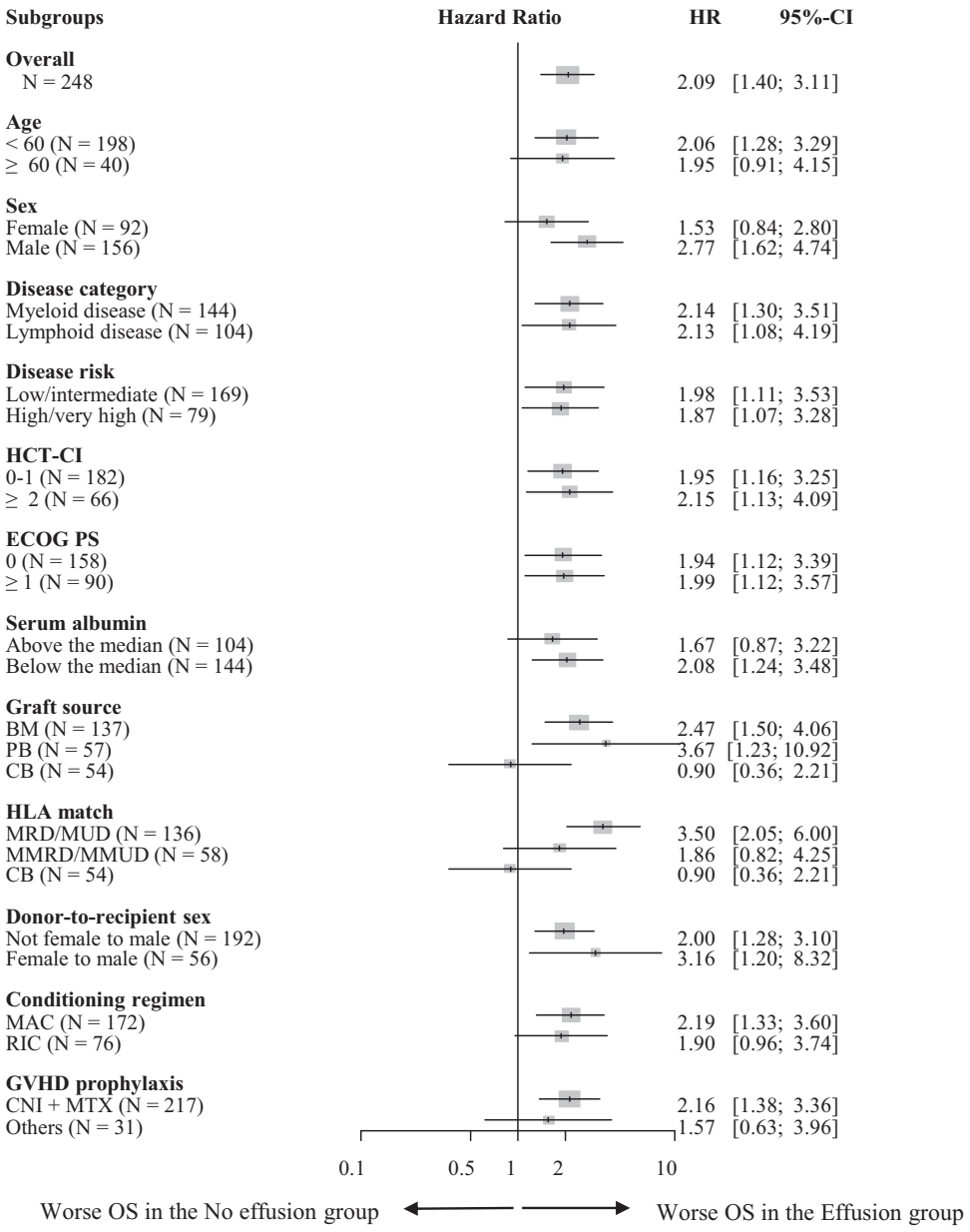

FIGURE 3 | Forest plot of the OS according to subgroups between the No effusion and Effusion groups. OS, overall survival.

As for treatments that could improve prognosis in the Effusion group, our analysis revealed that infectious complication was a common cause of death in patients with effusion due to infections, and disease relapse occupied a larger proportion of death reason in patients with tumor-associated effusion (Table 2b). These suggest that non-CR patients with effusion should require a higher therapeutic intensity than usual, and patients with effusion of infectious origin should undergo adequate prophylaxis against infection, such as empiric antibiotic therapy. Moreover, as the incidence rate of VOD/SOS was significantly high in the Effusion group, enough attention should be paid to its occurrence and early therapeutic intervention would be desirable. However, because no significant difference in the OS between the No effusion and Effusion groups was observed when classified by each subgroup of graft source, HLA match, conditioning regimen, or GVHD prophylaxis, it would be difficult to further investigate the appropriate management of pretransplant minimal effusion in this retrospective, observational study.

This study has several limitations. Firstly, the retrospective single-center design and limited sample size precluded validation of the proposed risk classification combining R-DRI and HCT-CI with pretransplant effusion status in other cohorts. Secondly, adjustment by multivariate covariate was limited to a few representative factors, and unknown factors may serve as confounders for the presence of effusions. Future large-scale or prospective studies are warranted to validate our findings and devise better treatment strategies.

In conclusion, our study suggests that pretransplant effusion, even if it is minimal, can be a comprehensive indicator reflecting high disease activity and insufficient control of infections, and is beneficial for more precise prediction of posttransplant outcomes.

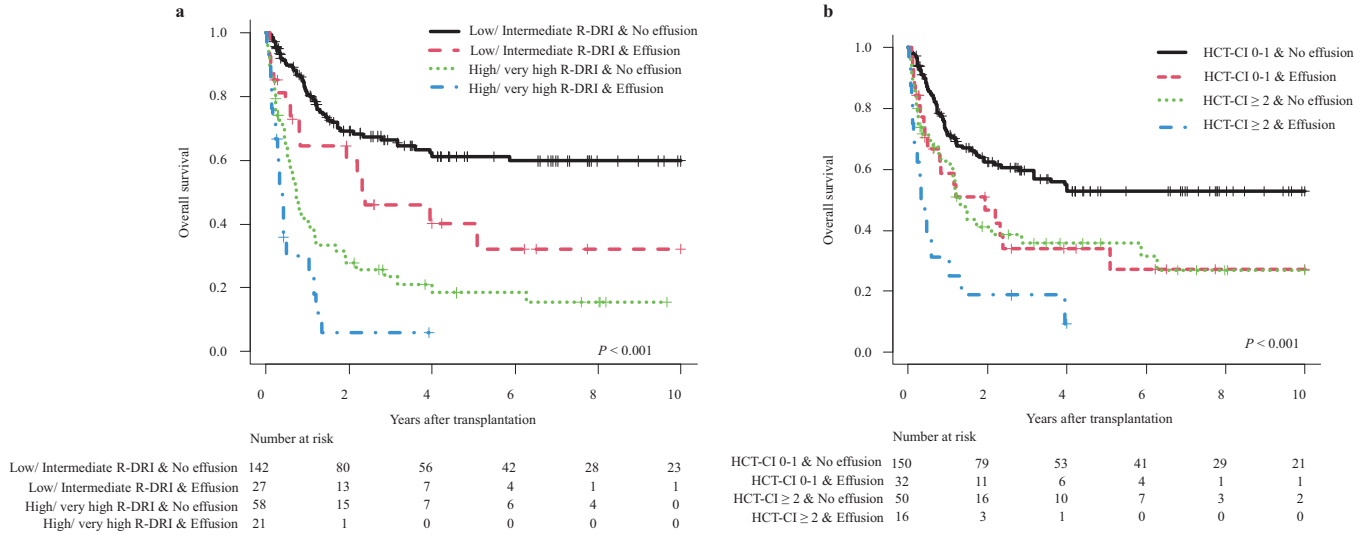

FIGURE 4 | (a) Comparison of the OS among patients with low/ intermediate R-DRI and No effusion, low/intermediate R-DRI and Effusion, high/very high R-DRI and No effusion, and high/very high R-DRI and Effusion. (b) Comparison of the OS among patients with HCT-CI 0–1 and No effusion, HCT-CI 0–1 and Effusion, HCT-CI ≥ 2 and No effusion, and HCT-CI ≥ 2 and Effusion. HCT-CI, Hematopoietic Cell Transplant-Comorbidity Index; OS, overall survival; R-DRI, refined disease risk index.

Author Contributions

Takashi Oyama, Akira Honda, and Yasutaka Masuda were involved in the study design, data collection, analysis, and interpretation. Takashi Oyama drafted the paper. Ken Morita, Hiroaki Maki, Yosuke Masamoto, and Mineo Kurokawa critically revised the report and commented on drafts of the manuscript. All authors approved the final report.

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Ethics Statement

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.