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Risk factors for in-hospital mortality in recipients of allogeneic hematopoietic stem cell transplantation with acute respiratory distress syndrome: a retrospective study based on the 2023 new definition of acute respiratory distress syndrome

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Abstract

Introduction ARDS (acute respiratory distress syndrome) is the most severe form of acute hypoxic respiratory failure. Most studies related to ARDS have excluded patients with hematologic diseases, let alone allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients. Numerous patients experiencing severe hypoxic respiratory failure do not meet the Berlin definition due to the limitations of diagnosis and treatment. A new definition of ARDS, remove some diagnosis restrictions, was proposed in 2023. Based on the 2023 new definition of ARDS, we investigated the clinical features of ARDS in allo-HSCT recipients and reported risk factors for in-hospital mortality in allo-HSCT recipients defined by the Berlin definition and the new definition of ARDS respectively.

Methods From Jan 2016 to Dec 2020, 135 allo-HSCT recipients identified with the new definition and 87 identified with the Berlin definition at three teaching hospitals were retrospectively included in this study. Variables (demographic information, characteristics of hematologic disease and ARDS episode, laboratory tests and SOFA score) with $P<0.05$ in univariate logistic regression analysis were included in multivariate stepwise logistic regression analysis. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were reported.

Results Under the new definition, SOFA score (OR = 1.351, 95% CI: 1.146–1.593, $P<0.01$) were found as an independent risk factor for in-hospital mortality in ARDS after allo-HSCT, while SpO2/FiO2 (OR = 0.984, 95% CI: 0.972–0.996, $P<0.01$) was a protective factor. The infusion of peripheral-derived stem cells was found to be a protective factor against in-hospital mortality in post-transplantation ARDS compared with the infusion of bone marrow-derived stem cells (OR = 0.726, 95% CI: 0.164–3.221, $P=0.04$). Under the Berlin definition, PaO2/FiO2 (OR = 0.977, 95% CI: 0.961–0.993,

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$P = 0.01$, lactate (OR = 7.337, 95% CI: 1.313–40.989, $P < 0.01$) and AST (OR = 1.165, 95% CI: 1.072–1.265, $P < 0.01$) were independently associated with in-hospital mortality.

Conclusion These prognostic risk factors we found in allo-HSCT recipients may contribute to closer monitoring and ARDS prevention strategies. These findings require confirmation in prospective, large sample size studies.

Keywords Hematopoietic stem cell transplantation, Hematologic malignancies, Acute respiratory distress syndrome, The New definition of ARDS

Introduction

Since 2000, the number of hematopoietic stem cell transplants (HSCT) performed in China for patients with acute leukemia and severe aplastic anemia has increased dramatically, especially allogeneic hematopoietic stem cell transplantation (allo-HSCT) [1]. With advances in medical technology and concepts, pre- and post-transplant care has been greatly improved, but respiratory failure remains a major obstacle to the overall success of HSCT, and acute respiratory distress syndrome (ARDS) is the most severe form of acute hypoxic respiratory failure [2].

However, most studies related to ARDS have excluded patients with hematologic diseases [3, 4], although the characteristics and management principles of ARDS in the general population may not be applicable to this specific population, especially allo-HSCT recipients. In autologous hematopoietic stem cell transplantation (auto-HSCT), immunodeficiency often improves after successful implantation of the grafts, whereas in allo-HSCT, the introduction of a new immune system results in a more prolonged and complex immune disorder [5]. An epidemiological study involving 2635 HSCT recipients showed a 15.6% incidence of ARDS in allo-HSCT recipients compared to 2.7% in auto-HSCT recipients, with a higher incidence of ARDS in allo-HSCT [6]. Herasevich et al. conducted case–control studies to report the risk factors for the incidence of ARDS in patients with hematologic malignancies before [7] and after HSCT [8]. However, their team did not focus on the allo-HSCT population and the prognostic risk factors for ARDS have not been adequately characterized.

More importantly, previous diagnoses of ARDS were based on the 2012 Berlin definition [9]. However, in clinical practice, numerous patients experiencing severe hypoxic respiratory failure do not meet the Berlin definition due to the limitations of diagnosis, such as difficulties in timely arterial blood gas analysis, and treatment, such as the use of high-flow nasal cannula oxygen (HFNO) and failure to employ the continuous positive airway pressure (CPAP) mode of ventilation. The 2023 New Definition of ARDS considers the aforementioned realities and adjusts the definition and diagnosis of ARDS. PaO2, positive end-expiratory pressure (PEEP), oxygen flow, or specific respiratory support equipment are not necessary for the diagnosis of ARDS when conditions are restricted [10, 11].

Thus, based on the 2023 new definition of ARDS, this study investigated the clinical features of ARDS in allo-HSCT recipients. In addition, Risk factors for in-hospital mortality in allo-HSCT recipients defined by the Berlin definition and the new definition of ARDS were explored respectively.

Method

All protocols in this study have been approved by the ethics committee of the Dushu Lake Hospital Affiliated to Soochow University and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. (The approval number: 220202; approval date: February 8 2022; study title: Prognosis of Acute Respiratory Distress Syndrome in Patients with Allogeneic Hematopoietic Stem Cell Transplant).

Informed consent was obtained from all patients for being included in the study.

Definitions

The Berlin Definition of ARDS [9]

(1) Timing: within one week of new or worsening of existing respiratory symptoms;
(2) Chest imaging: bilateral opacities—not fully explained by effusions, lobar/lung collapse, or nodules.
(3) Source of pulmonary edema: respiratory failure that cannot be explained by cardiac failure or fluid overload; an objective assessment is needed to rule out hydrostatic edema in the absence of risk factors.
(4) Hypoxemia:
Mild, 200 < PaO2/FiO2 ≤ 300 mmHg with PEEP or CPAP ≥ 5 cmH2O;
Moderate, 100 < PaO2/FiO2 ≤ 200 mmHg with PEEP or CPAP ≥ 5 cmH2O;
Severe, 100 < PaO2/FiO2 ≤ 100 mmHg with PEEP/CPAP ≥ 5 H2O.

The 2023 New definition of ARDS [10, 12]

(1) Timing: within one week of new or worsening of existing respiratory symptoms;
(2) Risk factors: such as pneumonia, non-pulmonary infections, trauma, blood transfusions, aspiration, or shock.
(3) Pulmonary edema is not exclusively or primarily attributable to cardiac failure or fluid overload. Impairments in gas exchange are not primarily attributable to atelectasis. If causative factors for ARDS are present, ARDS can be diagnosed in the presence of these conditions.
(4) Chest imaging: Bilateral opacities on chest radiograph and CT, or bilateral B lines and/or consolidations by ultrasound Findings not fully explained by effusions, atelectasis, or nodules/masses
(5) Criteria Applicable to Specific Categories of ARDS:

    1) Nonintubated ARDS: When the HFNO is ≥30 L/min or the noninvasive mechanical ventilation (NIV)/CPAP ≥5 cmH2O end-expiratory pressure, PaO2 /FiO2 ≤ 300 mmHg or SpO2 /FiO2 ≤ 315;
    2) Intubated ARDS: Mild, 200 < PaO2 /FiO2 ≤ 300 mmHg or 235 < SpO2 /FiO2 ≤ 315. Moderate, 100 < PaO2 /FiO2 ≤ 200 mmHg or 148 < SpO2 / FiO2 ≤ 235. Severe, PaO2 /FiO2 ≤ 100 mmHg or SpO2 /FiO2 ≤ 148
    3) Resource-Limited Settings: SpO2 /FiO2 ≤ 315, and the diagnosis of ARDS does not require PEEP, oxygen flow, or specific respiratory support devices.

Sepsis is defined based on the Sepsis-3 definition [13]. Assessment of organ dysfunction was carried out in accordance with the criteria of Sequential Organ Failure Assessment (SOFA).

Acute graft versus host disease (GVHD) was classified according to the modified Glucksberg grading system [14, 15] and grouped as 0-I or II-IV depending on the treatment requirement [16].

Study population

From January 2016 to December 2020, the First Affiliated Hospital of Soochow University, Suzhou Hongci Hematological Disease Hospital, and Dushu Lake Hospital Affiliated to Soochow University admitted 977 patients with hematological diseases who also underwent oxygen therapy. Two physicians from the Department of Respiratory and Critical Care Medicine at the First Affiliated Hospital of Soochow University conducted a review of medical records for all patients. Of the patients, 351 met the Berlin diagnostic criteria for ARDS, while 533 met the new definition of ARDS. After excluding patients who died within 24 h of admission, those who did not undergo allo-HSCT, those who underwent HSCT multiple times, and those diagnosed with ARDS 1 year after allo-HSCT,135 allo-HSCT recipients fulfilled the new definition of ARDS, and 87 patients met the Berlin criteria were final included. (Fig. 1).

Data collection

Clinical data for all these patients were abstained through the electronic medical record system.

(1) Demographic information: gender, age, underlying disease (hypertension, diabetes), length of hospitalization (days).
(2) Characteristics of hematologic disease: diagnosis of hematologic diseases, hematologic malignancy status (remission/relapse), and types of donors (HLA-identical sibling donors, SIB; HLA-matched unrelated donors, MUD; haploidentical related donors, haplo-RD). Source of stem cells (bone marrow/peripheral/bone marrow + peripheral), transplantation characteristics (donor-recipient gender, ABO blood type), the grade of acute GVHD, interval from HSCT to ARDS (days), history of fungal infection, leucocyte deficiency with white blood cell (WBC) < 1 × 109/L at the time of ARDS diagnosis.
(3) Characterization of ARDS episode: risk factors for ARDS (pneumonia, sepsis, and shock),, and oxygenation status (PaO2/FiO2 or SpO2/FiO2, PaCO2, PH, lactate). The highest level of respiratory support used within 48 h of ARDS diagnosis were also recorded.
(4) SOFA scores were recorded within 24 h of ARDS diagnosis, as well as the laboratory tests: procalcitonin (PCT), C-reactive protein (CRP), albumin, pre-albumin, alanine transaminase (ALT), aspartate aminotransferase (AST), creatinine (Cr), hemoglobin (Hb), WBC, platelet (PLT), Lymphocyte, Neutrophil.
(5) Clinical outcome: the occurrence of death during hospitalization for this ARDS episode.

Statistical analysis

We utilized SPSS version 23.0 to both manage data and perform statistical analysis on patients who underwent allo-HSCT and also met the new definition of ARDS. We considered statistical significance if a two-tailed *P* value was less than 0.05. No imputation was applied to missing values.

Figures were plotted based on the new definition and the Berlin definition, respectively. Bar graphs were

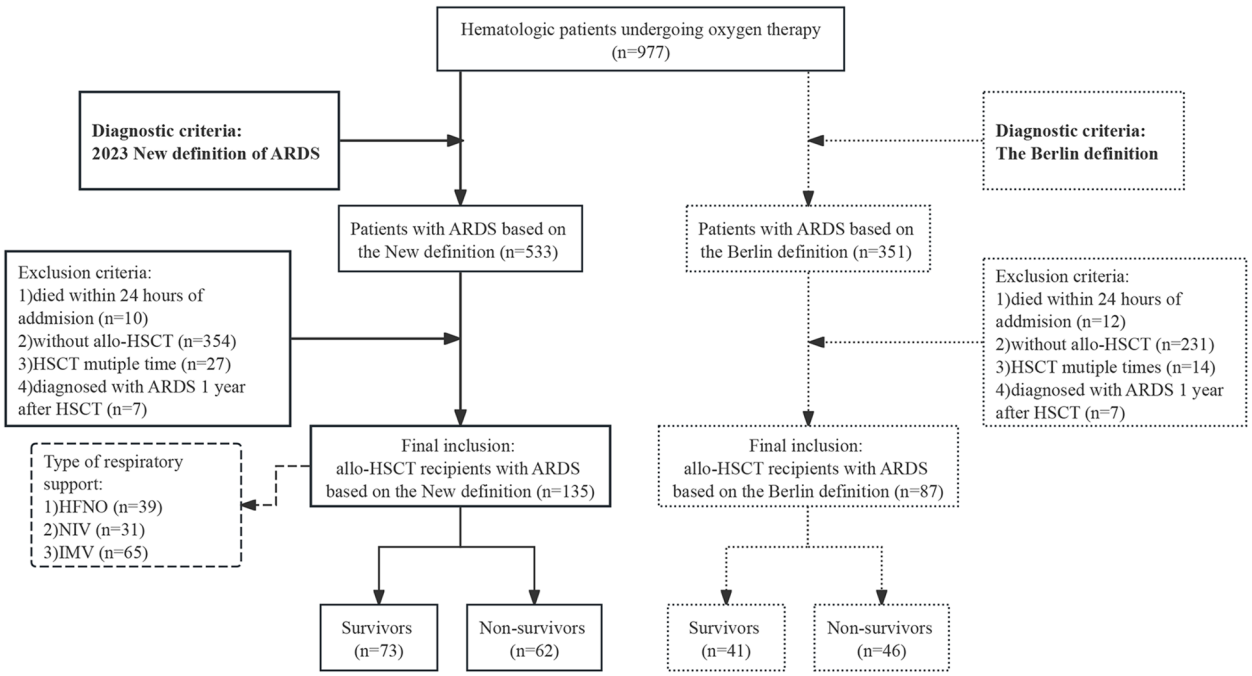

Fig. 1 The study cohort. From January 2016 to December 2020, allo-HSCT recipients diagnosed with ARDS at three teaching hospitals were included in this study. Types of Respiratory Support: The highest level of respiratory support used within 48 h of ARDS diagnosis were recorded. Abbreviations: ARDS, acute respiratory distress syndrome; allo-HSCT, allogeneic hematopoietic stem cell transplantation; HFNO, high-flow nasal cannula oxygen; NIV, noninvasive mechanical ventilation; IMV, invasive mechanical ventilation

constructed based on the interval from HSCT to the diagnosis of ARDS (from month 1 to month 12) in order to illustrate the number of patients diagnosed with ARDS at specific time points post-transplant. Furthermore, line graphs were employed to illustrate the in-hospital mortality for each bucket.

Kaplan–Meier survival curves were employed to characterize patient survival 180 days following the diagnosis of ARDS in allo-HSCT recipients with the new definition and the Berlin definition.

The normality of continuous variables was initially evaluated using the Shapiro–Wilk and Kolmogorov–Smirnov tests. If the variables were not normally distributed, they were presented as medians and quartiles and compared using the Mann–Whitney U test. Conversely, if the variables were normally distributed, they were expressed as mean and standard deviation (SD) and compared using the t-test. In addition, we expressed categorical variables as component ratios and compared them using the chi-square test.

Analysis of independent risk factors for in-hospital mortality in allo-HSCT recipients combined ARDS identified with the new definition ($n=135$): Univariate logistic regression analysis was performed with in-hospital mortality as the dependent variable and the demographic information, characteristics of hematologic disease and ARDS episode, laboratory tests and SOFA scores as independent variables. Variables with $P<0.05$ in univariate logistic regression analysis were included in multivariate stepwise logistic regression analysis (backward: conditional) with probabilities of 0.05 and 0.10 for stepwise entry and exclusion, respectively. Adjusted odds ratios (ORs) and 95% confidence intervals (95% CIs) were then reported with forest plot. The same analysis was applied in allo-HSCT recipients combined ARDS identified with the Berlin definition ($n=87$).

Results

Baseline characteristics of patients

Under the new definition, Origin on the X-axis was referred to the day-of-infusion and groups were organized according to the time of ARDS diagnosis. The peak incidence of ARDS was 1–4 months after allo-HSCT, and 77 patients were diagnosed during this period. The in-hospital mortality was described for each group respectively, and the overall trend showed that the longer the ARDS onset from HSCT, the lower the in-hospital mortality. For example, 24 allo-HSCT recipients developed ARDS in the 1st month after HSCT, with the in-hospital mortality of 58%, but 14 patients developed ARDS in the 12nd month, with the in-hospital mortality of 20%. (Fig. 2A).

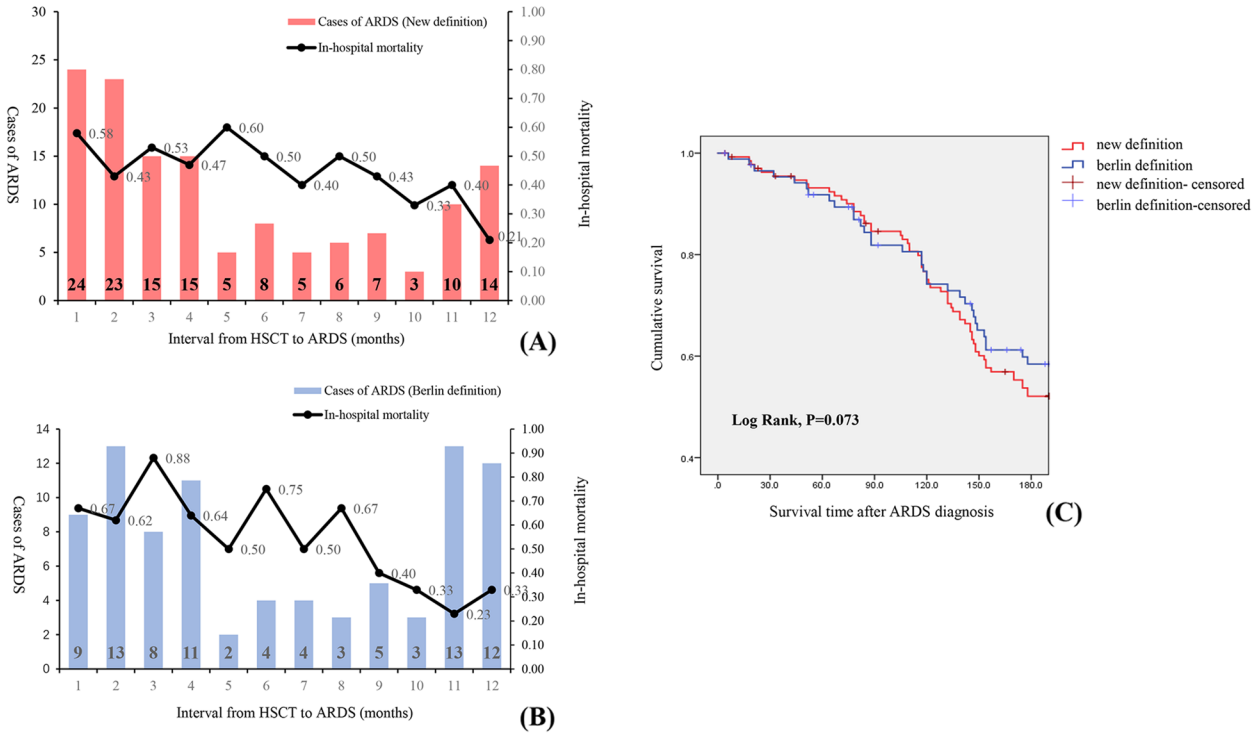

Fig. 2 General characteristics of the occurrence and survival of allo-HSCT recipients with ARDS according to the Berlin criteria and the new global definition. **A** Under the new definition, Origin on the X-axis was referred to the day-of-infusion and groups were organized according to the time of ARDS diagnosis. The in-hospital mortality was described for each group respectively. For example, 24 allo-HSCT recipients developed ARDS in the 1st month (30 days) after HSCT, and the in-hospital mortality for this group was 58%. **B** Under the Berlin definition, Origin on the X-axis was referred to the day-of-infusion and groups were organized according to the time of ARDS diagnosis. The in-hospital mortality was described for each group respectively. For example, 9 allo-HSCT recipients developed ARDS in the 1st month (30 days) after HSCT, and the in-hospital mortality for this group was 67%. **C** Kaplan–Meier curves were constructed for allo-HSCT recipients diagnosed with ARDS based on the new and Berlin definitions. Origin on the X-axis was referred to the day when allo-HSCT was diagnosed of ARDS diagnosis. The results demonstrated that there was no statistically significant difference in 180-day cumulative survival after ARDS diagnosis between the two groups ($P=0.073$)

Under the Berlin definition, the peak incidence of ARDS was 1–4 months after allo-HSCT, and 77 patients were diagnosed during this period. The overall trend of in-hospital mortality was similar with Fig. 2A. For example, 9 allo-HSCT recipients developed ARDS in the 1st month of HSCT, and the in-hospital mortality for this group was 67%, and 12 patients developed ARDS in the 12nd month, with the in-hospital mortality of 33%. (Fig. 2B).

Kaplan–Meier curves (Fig. 2C) were constructed for allo-HSCT recipients diagnosed with ARDS based on the new and Berlin definitions. Origin on the X-axis was referred to the day when allo-HSCT was diagnosed of ARDS diagnosis. The results demonstrated that there was no statistically significant difference in 180-day cumulative survival after ARDS diagnosis between the two groups ($P=0.073$). The allo-HSCT recipients with ARDS identified with the new definition were 53.5% males and 46.7% females, while patients identified with the Berlin definition were 56.3% males and 43.7% females ($P=0.66$). The highest number of diagnoses about hematologic diseases in allo-HSCT recipients based on the new definition was acute myeloid leukemia, followed by acute lymphoblastic leukemia, myelodysplastic syndromes, lymphomas, and aplastic anemia. Patients with Berlin definitional diagnosis-based diagnoses exhibited similar distributions ($P=0.98$). Furthermore, no statistically significant differences were observed in median age (37.5 years versus 37.0 years), underlying diseases, or other factors, including the status of hematologic tumors, source of stem cells, and donors. However, patients identified with the new definition exhibited a higher percentage of donor-recipient gender concordance (60.0% versus 46.0%, $P=0.04$). Moreover, the median interval from HSCT to ARDS onset was longer in the Berlin definition group (135.0 days) compared with the new definition group (116.0 days), with a statistically significant difference, $P=0.02$ (Table 1). A greater proportion of patients identified using the Berlin definition had acute GVHD (59.8% versus 45.2%), and a higher prevalence of patients

Table 1 Characteristics of allo-HSCT recipients with ARDS diagnosed by the Berlin definition versus those diagnosed by the new definition

Characteristic	New definition (*n*=135)	Berlin definition (*n*=87)	*P* value
Gender			0.66
Male	72 (53.3%)	49 (56.3%)	
Female	63 (46.7%)	38 (43.7%)	
Age	37.5 (28.0-50.0)	37.0 (27.0, 50.0)	0.59
Underlying diseases			
Hypertension	9 (6.7%)	5 (5.7%)	0.78
Diabetes	11 (8.1%)	8 (9.2%)	0.79
Diagnosis			0.98
Acute myeloid leukemia	51 (37.8%)	31 (35.6%)	
Acute lymphoblastic leukemia	33 (24.4%)	21 (24.1%)	
Acute mixed phenotype leukemia	7 (5.2%)	7 (8.0%)	
Lymphoma	12 (8.9%)	9 (10.3%)	
Myelodysplastic syndrome	13 (9.6%)	8 (9.2%)	
Multiple myeloma	3 (2.2%)	2 (2.3%)	
Myelofibrosis	1 (0.7%)	1 (0.8%)	
Aplastic anemia	12 (8.9%)	7 (9.2%)	
Chronic lymphocytic leukemia	1 (0.7%)	1 (1.1%)	
Chronic granulocytic leukemia	2 (1.5%)	0	
Status (hematological malignancy)			0.61
Complete remission	85 (69.1%)	58 (72.5%)	
Active disease	38 (30.9%)	22 (27.5%)	
Donors			0.53
haplo-RD	84 (62.2%)	48 (55.2%)	
MUD	31 (23.0%)	22 (15.8%)	
SIB	20 (14.8%)	17 (19.5%)	
Source of stem cells			0.89
Bone marrow	25 (18.5%)	16 (18.4%)	
Peripheral	75 (55.6%)	47 (54.0%)	
Bone marrow + peripheral	35 (25.9%)	24 (27.6%)	
Donors and Recipients			
Matched gender	81 (60.0%)	40 (46.0%)	0.04
Matched ABO blood type	65 (48.1%)	47 (54.0%)	0.39
Acute GVHD			< 0.01
Without	74 (54.8%)	35 (40.2%)	
I	32(23.7%)	11 (12.6%)	
II	8 (5.9%)	22 (25.3%)	
III	10 (7.4%)	11 (12.6%)	
IV	11 (8.1%)	7 (8.0%)	
Interval from HSCT to ARDS (days)	116.0 (51.0-272.8)	135.0 (58.5, 360)	0.02

Abbreviations: *ARDS* acute respiratory distress syndrome, *GVHD* graft-versus-host disease, *HSCT* hematopoietic stem cell transplantation, *haplo-RD* haploidentical related donors, *MUD* HLA-matched unrelated donors, *SIB* HLA-identical sibling donors

with grade II-IV GVHD was observed compared to those identified with the new definition, $P<0.01$. In addition, the in-hospital mortality rate was 45.9% in allo-HSCT recipients identified with new definition, while 52.9% of those identified with the Berlin definition (Fig. 1).

Table 2 shows the basic clinical features of both survivors and non-survivors based on the new definition. There were no statistically significant differences in the gender, age, underlying diseases (hypertension and diabetes), hematologic diagnosis, disease status, donor-recipient gender and ABO blood concordance, and the grade of acute GVHD between the survivors and non-survivors. The donor types varied between the survivors and non-survivors. The

Table 2 Baseline characteristic for allo-HSCT recipients with ARDS meeting new definition

Characteristic	Survivors ($n=73$)	Non-survivors ($n=62$)	*P* value
Gender			0.47
Male	41 (56.2%)	31 (50.0%)	
Female	32 (43.8%)	31 (40.0%)	
Age	35.0 (27.0–50.0)	40.0 (28.0–50.8)	0.69
Underlying diseases			
Hypertension	5 (6.8%)	4 (6.5%)	0.93
Diabetes	8 (11.0%)	3 (4.8%)	0.20
Diagnosis			0.47
Acute myeloid leukemia	28 (38.4%)	23(37.1%)	
Acute lymphoblastic leukemia	21 (28.8%)	12 (19.4%)	
Acute mixed phenotype leukemia	3 (4.1%)	4 (6.5%)	
Lymphoma	6 (8.2%)	6(9.7%)	
Myelodysplastic syndrome	3 (4.1%)	10 (16.1%)	
Multiple myeloma	2 (2.7%)	1 (1.6%)	
Myelofibrosis	1 (1.4%)	0 (0%)	
Aplastic anemia	7 (9.6%)	5 (8.1%)	
Chronic lymphocytic leukemia	1 (1.4%)	0 (0%)	
Chronic granulocytic leukemia	1 (1.4%)	1 (1.6%)	
Status (hematological malignancy)			0.35
Complete remission	48 (72.7%)	37 (64.9%)	
Active disease	18 (27.3%)	20 (35.1%)	
Donors			< 0.01
haplo-RD	35 (47.9%)	49 (79.0%)	
MUD	23 (31.5%)	8 (12.9%)	
SIB	15 (20.5%)	5 (8.1%)	
Source of stem cells			
Bone marrow	8 (11.0%)	17 (27.4%)	0.03
Peripheral	47 (64.4%)	28 (45.2%)	
Bone marrow + peripheral	18 (24.7%)	17 (27.4%)	
Donors and Recipients			
Matched gender	44 (60.3%)	37 (59.7%)	0.94
Matched ABO blood type	33 (45.2%)	32 (51.6%)	0.46
Acute GVHD			0.07
Without	43 (58.9%)	31 (50.0%)	
I	21 (28.8%)	11 (17.7%)	
II	2 (2.7%)	6 (9.7%)	
III	3 (4.1%)	7 (11.3%)	
IV	4 (5.5%)	7 (11.3%)	
Interval from HSCT to ARDS (days)	161.0 (51.0–326)	80.5 (45.0–174.8)	< 0.01

Abbreviations: *ARDS* Acute respiratory distress syndrome, *GVHD* Graft-versus-host disease, *HSCT* Hematopoietic stem cell transplantation, *haplo-RD* Haploidentical related donors, *MUD* HLA-matched unrelated donors, *SIB* HLA-identical sibling donors

non-survivors had a higher incidence of haplo-HSCT and MUD-HSCT, and a lower incidence of SIB-HSCT as compared to the survivors ($P<0.01$). Concerning the source of hematopoietic stem cells, survivors had fewer sources of bone marrow and more peripheral and peripheral + bone marrow compared to the non-survivors ($P=0.03$). Furthermore, the intervals from HSCT to ARDS was significantly longer in survivors at 161.0 days compared to 80.5 days in non-survivors ($P<0.01$).

Characterization of ARDS episode in survivors and non-survivors based on the new definition were

presented in Table 3. In terms of risk factors for ARDS, a total of 72.6% of allo-HSCT recipients had pneumonia, 38% had sepsis, and 16.3% had comorbid shock, but there was no statistically significant difference between survivors and non-survivors in terms of the risk factors of ARDS. Furthermore, 16.4% of survivors and 24.2% of non-survivors had a history of fungal infection ($P=0.26$). At the time of ARDS diagnosis, 8.2% of survivors and 17.7% of non-survivors were in a leukocyte-deficient status, with no statistically significant difference between the two groups ($P=0.10$). Objective evaluations indicate that survivors displayed higher levels of PaO2, PaO2/FiO2, SpO2, SpO2/FiO2, lymphocytes, Hb, PLT, and pre-albumin compared to non-survivors. Non-survivors exhibited significantly higher levels of lactate, ALT, AST, and SOFA scores compared to survivors (Table 4). Furthermore, non-survivors had a longer hospital stay than survivors (42.5 days vs. 31.0 days); however, the difference was not statistically significant.

Table 3 Characterization of ARDS episode in survivors and non-survivors based on the new definition

Variables	Survivors ($n=73$)	Non-survivors ($n=62$)	*P* value
Risk factors for ARDS			
Pneumonia			0.05
yes	58 (79.5%)	40 (64.5%)	
no	15 (20.5%)	22 (35.5%)	
Sepsis			0.84
yes	25 (34.2%)	26(41.9%)	
no	48 (65.8%)	36(58.1%)	
Shock			0.07
yes	8 (11.0%)	14 (22.6%)	
no	65 (89.0%)	48(77.4%)	
History of fungal infection[a]	12 (16.4%)	15 (24.2%)	0.26
Leucocyte deficiency[b]	6 (8.2%)	11 (17.7%)	0.10
Oxygenation			
PaO_2 (mmHg)[c]	84.2 (72.0, 96.0)	68.0 (59.3, 86.2)	< 0.01
PaO_2/FiO_2 (mmHg)	200.4 ± 45.2	144.0 ± 55.6	< 0.01
SpO_2 (%)	93.0 (92.0, 95.0)	92.0 (87.3, 95.0)	0.03
SpO_2/FiO_2	232.3(193.1, 237.4)	168.2(134.4, 202.1)	< 0.01
$PaCO_2$ (mmHg)	39.7 (34.4, 46.0)	37.9 (33.7, 46.6)	0.86
PH	7.39 (7.40, 7.46)	7.43 (7.40, 7.45)	0.84
Lactate (mmol/L)	1.63 (1.25–1.89)	2.2 (1.4–3.18)	< 0.01
Length of stay (days)	31.0 (24.0, 53.0)	42.5 (20.0, 70.00)	0.39

[a] Electronic Medical Records were reviewed from the diagnosis of hematologic disease to this admission to our hospital

[b] Patients with WBC < 1×10^9/L at the time of ARDS diagnosis was identified as Leucocyte deficiency

Table 4 Clinical characteristic for allo-HSCT recipients with ARDS meeting the new definition

Variables	Survivors ($n=73$)	Non-survivors ($n=62$)	*P* value
Laboratory tests			
WBC (10^9/L)	2.9 (2.1–5.3)	3.1 (1.4–5.5)	0.95
Lymphocyte (10^9/L)	0.6 (0.4–1.1)	0.3 (0.1–1.1)	0.02
Neutrophil (10^9/L)	1.85 (1.1–3.0)	2.2 (1.0–3.6)	0.89
Hb (g/L)	86.0 (67.0–105.0)	66.0 (59.0–76.0)	< 0.01
PLT (10^9/L)	37.0 (21.0–112.0)	16.0 (7.3–28.8)	< 0.01
ALT (U/L)	20.0 (11.0–43.0)	38.0 (16.0–98.5)	< 0.01
AST (U/L)	33.0 (16.0–41.0)	37.0 (25.3–74.0)	0.04
Pre-albumin (mg/L)	173.8 (161.8–197.3)	158.4 (140.4–181.0)	< 0.01
Albumin (g/L)	33.6 (31.0–37.8)	32.5 (31.0–36.7)	0.48
Cr (umol/L)	50.2 (45.7–72.8)	57.6 (40.5–84.3)	0.58
PCT (ng/L)	0.47 (0.15–1.34)	0.34 (0.12–1.06)	0.33
CRP (mg/L)	13.4 (8.5–42.3)	13.9 (9.4–28.2)	0.99
SOFA score	5.0 (4.0–8.0)	10.0 (7.0–13.0)	< 0.01

Abbreviations: *ALT* Alanine transaminase, *AST* Aspartate aminotransferase, *Cr* Creatinine, *CRP* C-reactive protein, Hb Hemoglobin, *PCT* Procalcitonin, *PLT* Platelet, *SOFA score* Sequential organ failure assessment score, *WBC* White blood cell

Risk factors for in-hospital mortality in allo-HSCT recipients with ARDS

Allo-HSCT recipients meeting the 2023 new definition of ARDS

The risk factors we examined were the demographic information, characteristics of hematologic disease and ARDS episode, laboratory tests and SOFA scores. The results of univariate logistic regression analysis were listed in the Table S1. The univariate logistic regression analysis revealed that the types of donors, source of stem cells, grade of acute GVHD, interval from HSCT to ARDS, SpO2/FiO2, lactate, pre-albumin, ALT, AST, Hb, PLT, and SOFA score met the significance level of $P<0.05$. These variables were therefore included in the multivariate logistic stepwise regression analysis.

The multivariate logistic stepwise regression analysis indicated that an increase of 1 point in the SOFA score led to a 1.351 times higher in-hospital mortality. The infusion of peripheral-derived stem cells was found to be a protective factor against in-hospital mortality in post-transplantation ARDS compared with the infusion of bone marrow-derived stem cells (OR = 0.244, 95% CI: 0.062–0.963, $P=0.04$). In addition, SpO2/FiO2 was also a protective factor against in-hospital mortality (OR = 0.984, 95% CI: 0.972–0.996, $P<0.01$). (Fig. 3).

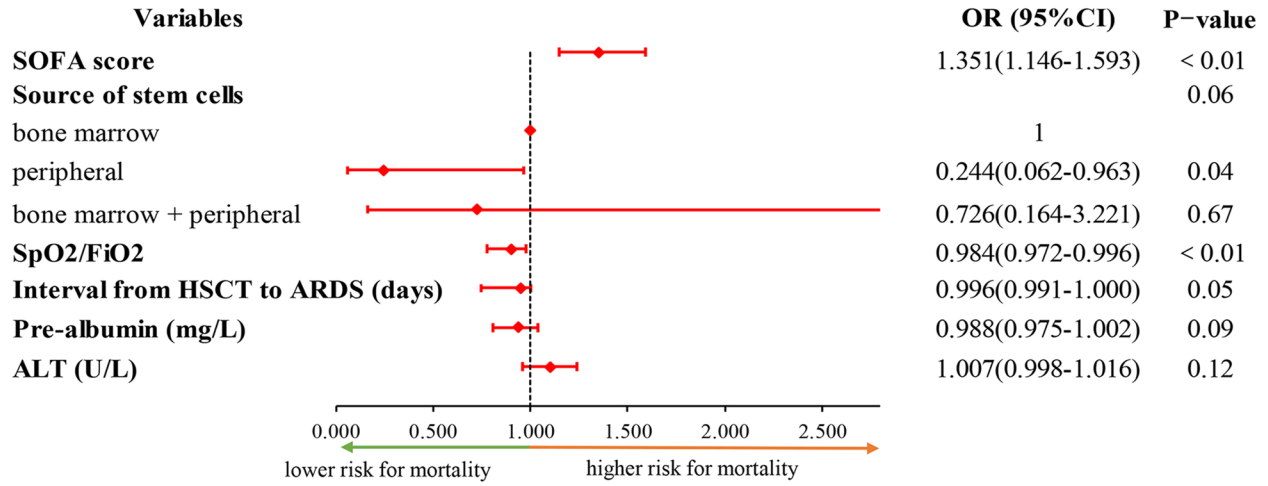

Fig. 3 Risk factors for in-hospital mortality in allo-HSCT recipients combined with ARDS identified with the new definition. The ORs on the X axis were from multivariate analyses. The right side of the reference line (OR > 1) indicated a higher risk of mortality, whereas the left side of the reference line (OR < 1) indicated a lower risk of mortality. Abbreviations: ARDS, acute respiratory distress syndrome; ALT, alanine transaminase; SOFA score, sequential organ failure assessment score; HSCT, hematopoietic stem cell transplantation

Allo-HSCT recipients meeting the Berlin definition of ARDS

Similarly, univariate regression analyses were performed in patients with ARDS who met the Berlin definition. The results of univariate logistic regression analysis were listed in the Table S2. The univariate logistic regression analysis revealed that shock status, the grade of acute GVHD, interval from HSCT to ARDS, PaO2/FiO2, lactate, AST, PLT, and SOFA score met the significance level of $P < 0.05$. These variables were therefore included in the multivariate logistic stepwise regression analysis.

The multivariate logistic stepwise regression analysis indicated that PaO2/FiO2 was a protective factor against in-hospital mortality (OR = 0.977, 95% CI: 0.961–0.993, $P = 0.01$). Furthermore, lactate (OR = 7.337, 95% CI: 1.313–40.989, $P < 0.01$) and AST (OR = 1.165, 95% CI: 1.072–1.265, $P < 0.01$) were found to be risk factors for in-hospital mortality in post-transplantation ARDS. (Fig. 4).

Discussion

From June 2021 to March 2022, a consensus conference of 32 critical care ARDS experts was convened to discuss a new definition of ARDS, which was proposed in 2023 and eventually published in January 2024 in Am J Respir Crit Care Med [11]. This retrospective cohort study attempted to explore the prognostic risk factors for allo-HSCT recipients combined with ARDS, as a preliminary attempt to validate this new definition. Similar analysis among patients meeting Berlin ARDS criteria were also performed. These risk factors we found may contribute to closer monitoring and ARDS prevention strategies.

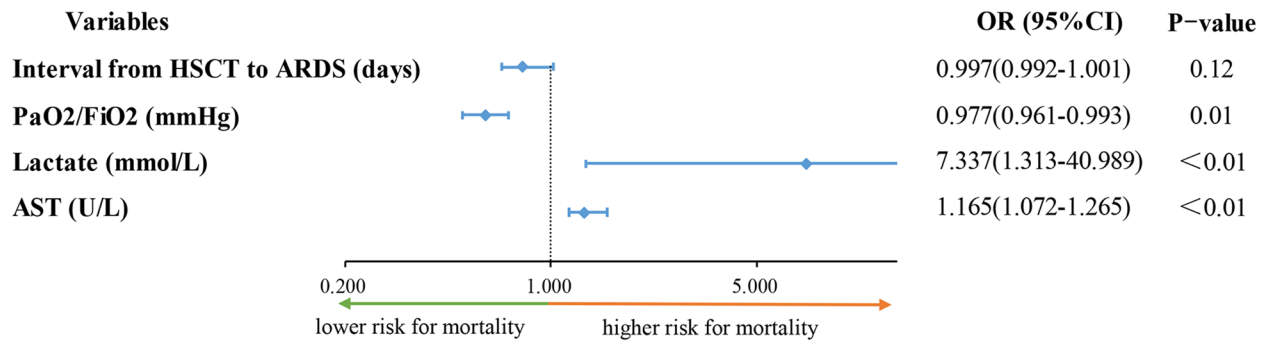

Fig. 4 Risk factors for in-hospital mortality in allo-HSCT recipients combined with ARDS based on Berlin definition. The ORs on the X axis were from multivariate analyses. The right side of the reference line (OR > 1) indicated a higher risk of mortality, whereas the left side of the reference line (OR < 1) indicated a lower risk of mortality. Abbreviations: ARDS, acute respiratory distress syndrome; AST, aspartate aminotransferase; HSCT, hematopoietic stem cell transplantation

As Fig. 2 presented, the peak incidence of ARDS was observed 1–4 months after HSCT under both the new and Berlin definitions. The overall trend of in-hospital mortality indicated that the longer the ARDS onset from allo-HSCT, the lower the in-hospital mortality. Furthermore, in a univariate logistic regression analysis, a longer interval from HSCT to ARDS was identified as a protective factor for in-hospital mortality. An analysis of the LUNG SAFE database showed that pneumonia, sepsis, and non-cardiogenic shock were the most common risk factors for ARDS in immunocompromised patients [17]. Allo-HSCT recipients underwent a process of immunosuppression, with a decrease in the number of natural killer and T cells in the first 100 days after HSCT when the patient was in a state of cellular immunodeficiency and immune insufficiency, which led to a greater possibility of infection [18], which may lead to the development of ARDS. Moreover, allo-HSCT recipients suffered ARDS may benefit from the gradual recovery of immune function as the duration of HSCT increasing.

The in-hospital mortality of allo-HSCT recipients diagnosed with ARDS, according to the Berlin definition, was 52.9%. This mortality rate aligned with previously reported rates for immunosuppressed patients and HSCT patients with combined ARDS [4, 6, 17]. Compared to the Berlin definition, ARDS diagnosed with the new definition resulted in a lower in-hospital mortality rate of 45.9% among allo-HSCT recipients. This could be attributed to the Berlin definition being more stringent, resulting in patients being diagnosed only in the severe stage of the disease.

Under the new definition, higher SOFA scores were found as an independent risk factor for allo-HSCT recipients combined with ARDS, while SpO2/FiO2 was a protective factor against in-hospital mortality. The infusion of peripheral-derived stem cells was found to be a protective factor against in-hospital mortality in post-transplantation ARDS compared with the infusion of bone marrow-derived stem cells. Under the Berlin definition, higher PaO2/FiO2 was found to be a protective factor against in-hospital mortality. Furthermore, higher lactate and higher AST were found to be independent risk factors for in-hospital mortality in post-transplantation ARDS.

In our study, the PaO2/FiO2 and the SpO2/FiO2 were identified as protective factors for mortality in ARDS after allo-HSCT, in accordance with the Berlin definition and the new definition, respectively. PaO2/FiO2 has been identified as an important clinical biomarker of ARDS severity. Previous studies have reported that higher PaO2/FiO2 is associated with in-hospital mortality in patients with ARDS [19–21]. Moreover, SpO2/FiO2 was identified as a prognostic correlate in the context of the new definition. Previous studies employing the Berlin-Kigali modified definition have demonstrated that SpO2/FiO2 is a significant diagnostic and prognostic indicator of ARDS, and the clinical efficacy of the prediction was found to be comparable to that of the PaO2/FiO2 [22]. SpO2/FiO2 may be valuable for rapid, dynamic assessment when blood gases are not available. Nevertheless, the validity of SpO2/FiO2 still requires further confirmation in clinical practice before becoming widely accepted [23]. The SOFA score was a crucial tool for evaluating organ dysfunction and predicting outcomes in critically ill patients [24, 25]. Previous studies have reported that multiorgan failure is an independent risk factor for death in patients with hematologic malignancies and in patients with ARDS [20, 26, 27], and higher SOFA scores were associated with poor intensive care unit (ICU) prognosis in allo-HSCT recipients [28, 29]. The novelty of our study was the the initial exploration in the newly published definition of ARDS and in the study population of allo-HSCT recipients with comorbid ARDS. In addition to common ICU scoring systems such as the SOFA score and APACHE score, a number of new and self-created prognostic scoring systems have emerged. Liang M et al. developed a novel risk score for screening patients with COVID-19 who are at high risk for ARDS [30]. Moreover, Bayraktar UD et al. developed a new predictive scoring system to predict mortality in the ICU based on comorbidities, laboratory markers, and so on. scoring system to predict prognosis of allo-HSCT recipients in the ICU [31, 32]. Future research may focus on the development of more accurate scoring systems.

Bone marrow, previously the sole source of stem cells, can now be mobilized from healthy donors using granulocyte colony-stimulating factor (G-CSF) to obtain hematopoietic stem cells from their peripheral blood. Our study reported, for the first time, the effect of stem cell source on the development of ARDS after allo-HSCT under the new definition. The infusion of peripheral-derived stem cells was found to be a protective factor against in-hospital mortality in post-transplantation ARDS compared with the infusion of bone marrow-derived stem cells. Notably, no specific mechanism has been elucidated for the relationship between stem cell sources and ARDS pathogenesis, and more in vivo and in vitro studies are required in the future.

Lactate serves as an indicator of tissue hypoxia and organ perfusion insufficiency, and it holds major implications for diagnosis, treatment, and prognosis [33–35]. Previous studies of HSCT recipients admitted to intensive care units have demonstrated a correlation between elevated lactate levels and a poorer prognosis for patients [35, 36]. Moreover, studies on ARDS have demonstrated that elevated lactate levels are also a prognostic risk

factor [37]. Our study found that lactate was one of the risk factors for in-hospital mortality in ARDS (Berlin definition) after allo-HSCT, which is in general agreement with the results of the aforementioned clinical studies.

AST was found to be an independent risk factor for in-hospital mortality in ARDS after allo-HSCT under the Berlin definition, although ALT was not statistically significant in the multivariate analysis under the new definition. An elevated AST may be associated with hepatobiliary disorders, pharmacologic injuries, cardiac disease, and infectious diseases. A study conducted at the Mayo Medical Center has demonstrated a correlation between elevated serum transaminase levels and the subsequent development of ARDS after HSCT [7, 8]. Additionally, Harnisch et al. described ARDS-associated hypoxic injury and cholangiocellular injury, which occurred in the early stages of ARDS [24]. Consequently, it is important to recognize the underlying causes of elevated serum aminotransferases in allo-HSCT recipients with comorbid ARDS in order to prevent the progression of ARDS and its associated poor prognosis.

In this study, pre-albumin was included in the multivariate regression model (the new definition), although the results were not statistically significant. Pre-albumin and albumin were regarded as sensitive indicators of nutrition and immune inflammation. However, albumin was not identified as an independent risk factor in our study. Ayuk FA et al. reported that lower serum albumin levels were associated with a poorer overall survival rate in allo-HSCT recipients combined with acute GVHD [38]. The prevalence of acute GVHD in this study was about 50%, which may have influenced the discovery of albumin as a risk factor.

Limitations

After the update of the 2023 new definition of ARDS, we focused on analyzing the specific population of allo-HSCT as thoroughly as possible. However, our study has some limitations that we need to consider. First, the sample size of this study was relatively limited considering the morbidity of ARDS and the total number of HSCTs. Further research is needed, especially prospective clinical trials with larger samples, to gain a more complete understanding of the risk factors.. Second, we examined only the hospitalization on the occasion of the diagnosis of ARDS, and the history prior to allo-HSCT was not comprehensive. Future research could encompass the complete course of the disease, starting with the identification of hematologic disorders up to HSCT, post-transplantation, and ultimately clinical outcomes. Third, the process we used to include the study population precluded the ability to provide an accurate incidence of ARDS in allo-HSCT recipients. Fourth, the new definition focused exclusively on the severity assessment of intubated ARDS patients, while the criteria for non-intubated patients remain undefined, which made it challenging to differentiate between severity levels.

Conclusion

Under the new definition, SOFA scores were found as an independent risk factor for in-hospital mortality in ARDS after allo-HSCT, while SpO2/FiO2 was a protective factor. The infusion of peripheral-derived stem cells was found to be a protective factor compared with the infusion of bone marrow-derived stem cells. Under the Berlin definition, PaO2/FiO2, lactate and AST were independently associated with in-hospital mortality. These risk factors we found may contribute to closer monitoring and ARDS prevention strategies and these findings require confirmation in prospective, large sample size studies.

Abbreviations

Allo-HSCT	Allogeneic hematopoietic stem cell transplantation
ARDS	Acute respiratory distress syndrome
ALT	Alanine transaminase
AST	Aspartate aminotransferase
Cr	Creatinine
CRP	C-reactive protein
CPAP	Continuous positive airway pressure
GVHD	Graft versus host disease
HFNO	High-flow nasal cannula oxygen
Hb	Hemoglobin; high-flow nasal cannula oxygen
Haplo-RD	Haploidentical related donors
HSCT	Hematopoietic stem cell transplants
MUD	HLA-matched unrelated donors
NIV	Noninvasive mechanical ventilation
PEEP	Positive end-expiratory pressure
PCT	Procalcitonin
PLT	Platelet
SOFA score	Sequential organ failure assessment score
SIB	HLA-identical sibling donors
WBC	White blood cell

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-024-03195-3.

Supplementary Material 1.

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NA.

Authors' contributions

Shiqi Guo, Dan Xie, and Ye Gao equally contributed to write the manuscript, and took responsibility for the content of the manuscript, including data and analysis. Lijuan Yang and Jiahao Chen provided the help with statistical methods. Ying He, Yuanxiao Sun, Siyu He contributed to data collection. Feng Chen helped write the discussion section on blood diseases. Feng Chen directed the writing of the section of the discussion. Qiang Guo and Ying Wang provided research ideas and revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
All protocols in this study have been approved by the ethics committee of the Dushu Lake Hospital Affiliated to Soochow University and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. (The approval number: 220202; approval date: February 8 2022; study title: Prognosis of Acute Respiratory Distress Syndrome in Patients with Allogeneic Hematopoietic Stem Cell Transplant).
Informed consent was obtained from all patients for being included in the study.

Consent for publication
Not applicable

Competing interests
The authors declare no competing interests.

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