

Red cell distribution width as a new prognostic biomarker in refractory chronic graft-versus-host disease

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Supplementary Table S1: Characteristics of the patients and univariate and multivariable associations with RDW $\geq 13.4\%$.

Characteristic	N missing	All patients	RDW <13.4%	RDW $\geq 13.4\%$	P	Multiple logistic model	P [^]
	Absolute count (%)	Absolute count (%), or median [IQR]	Absolute count (%), or median [IQR]	Absolute count (%), or median [IQR]		OR (95%CI)	
All patients	0 (0)	404 (100)	101 (25)	303 (75)			
Age Years	0 (0)	404 (100) 47.2 [31.7-56.9]	101 (25) 47.4 [35.2-56.3]	303 (75) 47.2 [31.0-56.8]	0.82*		
Sex Male Female	0 (0)	404 (100) 231 (57.2) 173 (42.8)	101 (25) 55 (54.5) 46 (45.5)	303 (75) 176 (58.1) 127 (41.9)	0.56 [#]		
Race Black Hispanic Other White Unknown	0 (0)	404 (100) 16 (4.0) 11 (2.7) 12 (3.0) 351 (86.9) 14 (3.5)	101 (25) 4 (4.0) 0 3 (3.0) 90 (89.1) 4 (4.0)	303 (75) 12 (4.0) 11 (3.6) 9 (3.0) 261 (86.1) 10 (3.3)	0.37 [‡]		
Body mass index (kg/m²) <18.0 18.0-24.9 25.0-29.9 ≥ 30.0 Median	25 (6.2)	379 (93.8) 48 (12.7) 180 (47.5) 106 (28.0) 45 (11.9) 23.9 [20.5-27.2]	101 (25) 14 (14.9) 41 (43.6) 28 (29.8) 11 (11.7) 23.7 [20.5- 27.1]	303 (75) 34 (11.9) 139 (48.8) 78 (27.4) 34 (11.9) 24.0 [20.6-27.2]	0.92 [◊] 0.95*		
Karnofsky performance status (%) 90-100 80 <80	10 (2.5)	394 (97.5) 130 (33.0) 131 (33.3) 133 (33.8)	101 (25) 44 (44.4) 36 (36.4) 19 (19.2)	303 (75) 86 (29.2) 95 (32.2) 114 (38.6)	0.0003 [◊]		
Disease AML, ALL, MDS MPN including CML CLL Lymphoma Other	3 (0.7)	401 (99.3) 203 (50.6) 46 (11.5) 22 (5.5) 84 (21.0) 46 (11.5)	101 (25) 45 (45) 19 (19) 4 (4) 17 (17) 15 (15)	303 (75) 158 (52.5) 27 (9.0) 18 (6.0) 67 (22.3) 31 (10.3)	0.0426 [‡]		

Donor relationship	6 (1.5)	398 (98.5)				
Related		225 (56.5)	57 (57.0)	168 (56.4)		
Unrelated		173 (43.5)	43 (43.0)	130 (43.6)	1.00 [#]	
Donor stem cell source	3 (0.7)	401 (99.3)				
Peripheral blood		311 (77.6)	70 (70.0)	241 (80.1)		
Bone marrow		78 (19.5)	28 (28.0)	50 (16.6)		
Cord blood		12 (3.0)	2 (2.0)	10 (3.3)	0.0460 [‡]	
Conditioning	7 (1.7)	397 (98.3)				
Myeloablative		168 (42.3)	39 (39.0)	129 (43.4)		
Non-myeloablative		229 (57.7)	61 (61.0)	168 (56.6)	0.48 [#]	
HLA match	14 (3.5)	390 (96.5)				
Yes		329 (84.4)	78 (78.8)	251 (86.3)		
No		61 (15.6)	21 (21.2)	40 (13.8)	0.08 [#]	
Recipient CMV status	138 (34.2)	266 (65.8)				
Negative		142 (53.4)	40 (58.0)	102 (51.8)		
Positive		124 (46.6)	29 (42.0)	95 (48.2)	0.4 [#]	
Time (months)	0 (0)					
Time from HCT to CGVHD diagnosis		7.6 [4.7-12.3]	8.28 [5.2-12.8]	7.5 [4.6-12.0]	0.21 [*]	
Time from CGVHD diagnosis to study consent		24.5 [12.1-49.1]	26.35 [13.4-54.7]	24.2 [11.3-46.6]	0.32 [*]	
Time from HCT to study consent		35.6 [22.6-58.6]	38.21 [23.2-67.8]	35.1 [22.2-56.7]	0.19 [*]	
History of prior acute GVHD grade II-IV	4 (1)	400 (99.0)				
No		121 (30.3)	30 (30.0)	91 (30.3)		
Yes		279 (69.8)	70 (70.0)	209 (69.7)	1.00 [#]	
NIH global score	6 (1.5)	398 (98.5)				
Mild		8 (2.0)	3 (3.0)	5 (1.7)		
Moderate		102 (25.6)	36 (37.9)	66 (22.4)		
Severe		288 (72.4)	59 (62.1)	229 (77.6)	0.0008 [◊]	
NIH organ involvement						
<i>Ocular</i>	5 (1.2)	399 (98.8)				
None		90 (22.6)	26 (26)	64 (21.4)		
Mild		124 (31.1)	32 (32)	92 (30.8)		
Moderate		122 (30.6)	25 (25)	97 (32.4)		
Severe		63 (15.8)	17 (17)	46 (15.9)	0.4473 [◊]	
<i>Skin</i>	6 (1.5)	398 (98.5)				
None		86 (21.6)	30 (30.6)	56 (18.7)		

Mild		76 (19.1)	21 (21.4)	55 (18.3)		
Moderate		63 (15.8)	16 (16.3)	47 (15.7)		
Severe		173 (43.5)	31 (31.6)	142 (47.3)	0.0023 [◊]	
<i>Lung</i>	7 (1.7)	397 (98.3)				
None		111 (28.0)	35 (35)	76 (25.6)		
Mild		151 (38.0)	39 (39)	112 (37.7)		
Moderate		94 (23.7)	17 (17)	77 (25.9)		
Severe		41 (10.3)	9 (9)	32 (10.8)	0.0463 [◊]	
<i>Oral</i>	5 (1.2)	399 (98.8)				1.77 (1.20-2.60)
None		138 (34.6)	46 (46)	92 (30.8)		Reference
Mild		202(50.6)	44 (44)	158 (52.8)		
Moderate		45 (11.3)	9 (9)	36 (12.0)		
Severe		14 (3.5)	1 (1)	13 (4.4)	0.0043 [◊]	
<i>Joints and fascia</i>	5 (1.2)	399 (98.8)				
None		154 (38.6)	44 (44.4)	110 (36.7)		
Mild		92 (23.1)	23 (23.2)	69 (23.0)		
Moderate		99 (24.8)	23 (23.2)	76 (25.3)		
Severe		54 (13.5)	9 (9.1)	45 (15.0)	0.0819 [◊]	
<i>Liver</i>	7 (1.7)	397 (98.3)				
None		205 (51.6)	53 (53.5)	152 (51.0)		
Mild		126 (31.7)	33 (33.3)	93 (31.2)		
Moderate		59 (14.9)	12 (12.1)	47 (15.8)		
Severe		7 (1.8)	1 (1.0)	6 (2.0)	0.3721 [◊]	
<i>Gastrointestinal tract</i>	5 (1.2)	399 (98.8)				
None		227 (56.9)	57 (57)	170 (56.9)		
Mild		127 (31.8)	36 (36)	91 (30.4)		
Moderate		25 (6.3)	6 (6)	19 (6.4)		
Severe		20 (5.0)	1 (1)	19 (6.4)	0.2349 [◊]	
<i>Genitals (females only)</i>	0 (0)	173 (100)				
None		81 (46.8)	19 (41.3)	62 (48.8)		
Mild		34 (19.7)	8 (17.4)	26 (20.5)		
Moderate		26 (15.0)	8 (17.4)	18 (14.2)		
Severe		32 (18.5)	11 (23.9)	21 (16.5)	0.2033 [◊]	
Immunosuppressive drugs at evaluation	15 (3.7)	389 (96.3)				
Number of prior lines of CGVHD therapy		4 [2-5]	3 [2-5]	4 [3-5]	0.0047*	

Number of concurrent CGVHD treating agents		2 [1-3]	1 [0-2]	2 [1-3]	<0.0001*		
<i>Steroids at evaluation</i>	15 (3.7)	389 (96.3)					
No		140 (36.0)	53 (53.5)	87 (30)			
Yes		249 (64.0)	46 (46.6)	203 (70)	<0.0001#		
Dose (mg/kg/day prednisone equivalent)		0.10 [0-0.31]	0 [0-0.14]	0.14 [0-0.35]	<0.0001*		
<i>Calcineurin inhibitor</i>	15 (3.7)	389 (96.3)					
No		205 (52.7)	51 (51.5)	154 (53.1)			
Yes		184 (47.3)	48 (48.5)	136 (46.9)	0.8162#		
<i>Mycophenolate mofetil</i>	15 (3.7)	389 (96.3)					
No		285 (73.3)	76 [76.8]	209 [72.1]			
Yes		104 (26.7)	23 [23.2]	81 [27.9]	0.4303#		
<i>mTOR inhibitor</i>	15 (3.7)	389 (96.3)					
No		313 (80.5)	92 (92.9)	221 (76.2)		Reference	
Yes		76 (19.5)	7 (7.1)	69 (23.8)	0.0002#	3.49 (1.47-8.29)	0.0047
<i>Tyrosine kinase inhibitor</i>	15 (3.7)	389 (96.3)					
No		371 (95.4)	98 (99.0)	273 (94.1)			
Yes		18 (4.7)	1 (1.0)	17 (5.9)	0.0523#		
Extracorporeal photopheresis at evaluation	15 (3.7)	389 (96.3)					
No		315 (81.0)	89 (89.9)	226 (77.9)	0.0077#		
Yes		74 (19.0)	10 (10.1)	64 (22.1)			
Blood cell indices							
White blood cell count, absolute (x10 ⁹ /L)	3 (0.7)	7.5 [5.5-9.8]	6.4 [5.0-9.1]	7.8 [5.8-10.0]	0.0022*		
Neutrophils, absolute (x10 ⁹ /L)	4 (1)	4.7 [3.4-6.7]	3.7 [2.7-5.5]	5.2 [3.7-7.0]	<0.0001*	1.21 (1.07-1.36)	0.0016
Lymphocytes, absolute (x10 ⁹ /L)	4 (1)	1.2 [0.6-2.2]	1.6 [1.1-2.4]	1.1 [0.6-2.1]	0.0002*		
Eosinophils, absolute (x10 ⁹ /L)	3 (0.7)	0.07 [0.02-0.16]	0.11 [0.06-0.16]	0.06 [0.01-0.16]	<0.0001*		
Hemoglobin (g/dL)	2 (0.5)	12.5 [11.2-13.8]	13.3 [12.5-14.1]	12.2 [10.8-13.5]	<0.0001*	0.68 (0.57-0.80)	<0.0001
Mean corpuscular volume (fL)	0 (0)	95.4 [89.4-100.5]	96.4 [92.7-100.8]	95.0 [88.7-100.4]	0.022*		
RDW (%)	N/A	14.5 [13.4-16.0]	12.7 [12.3-13.0]	15.2 [14.2-16.7]	N/A		
Reticulocytes (%)	14 (3.5)	1.6 [1.2-2.5]	1.4 [1.1-2.0]	1.8 [1.2-2.6]	0.0012*		
Platelets (x10 ⁹ /L)	2 (0.5)	248 [186-317]	245 [195-316]	251 [183-317]	0.82*		
Inflammation							
C-reactive protein (mg/L)	8 (2)	2 [0.6-7.6]	0.8 [0.4-2.7]	3.1 [0.8-8.9]	<0.0001*		
Interleukin 6 (pg/mL)	297 (74)	11.4 [6.3-22.7]	10.30 [4.8-18.4]	14.60 [6.9-25.4]	0.10*		
Erythrocyte sedimentation rate (mm/h)	19 (4.7)	16 [8-34]	13.0 [6.0-24.5]	18.0 [8.0-36.0]	0.0012*		
Ferritin (ng/mL)	4 (1)	373.5 [89.3-1321.5]	450.0 [115.0-1217.5]	337.5 [80.5-1413.3]	0.33*		

C3 (mg/dL)	9 (2.2)	134 [118.0-151.5]	124.0 [112.0-144.0]	136.0 [122.7-156.0]	0.0002*		
C4 (mg/dL)	9 (2.2)	27.9 [22.2-33.0]	24.8 [20.0-29.8]	28.9 [23.0-35.0]	<0.0001*		
Other organ functions							
Lactate dehydrogenase (U/L)	12 (3)	220.0 (179.0-288.0)	184.5 [150.0-212.5]	237 [192.0-304.3]	<0.0001*	1.01 (1.01-1.02)	<0.0001
Bilirubin (mg/dL)	5 (1.2)	0.5 [0.3-0.6]	0.6 [0.4-0.7]	0.4 [0.3-0.6]	<0.0001*		
eGFR (mL/min/1.73m ²)	2 (0.5)	95.6 [69.2-116.1]	90.1 [65.6-109.2]	97.3 [71.2-117.1]	0.12*		
Albumin (g/dL)	3 (0.7)	3.8 [3.5-4.1]	3.9 [3.6-4.1]	3.7 [3.4-4.1]	0.013*		
Immunoglobulin G (g/L)	9 (2.2)	6.3 [4.4-9.8]	6.9 [5.4-10.9]	5.9 [4.0-9.1]	0.0031*		

ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; CGVHD: chronic graft-versus-host disease; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; CMV: cytomegalovirus; eGFR: estimated glomerular filtration rate according to Chronic Kidney Disease Epidemiology Collaboration 2021; IQR: interquartile range; MDS: myelodysplastic neoplasms; MPN: myeloproliferative neoplasm; mTOR: mammalian target of rapamycin; OR: odds ratio; RDW: red cell distribution width.

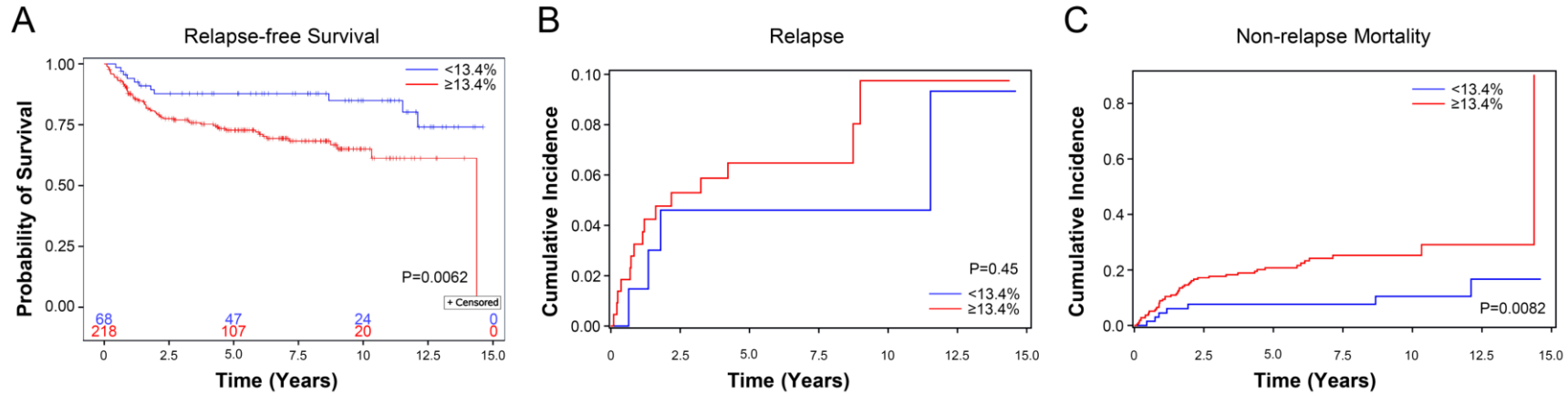
*Wilcoxon rank sum test; #Fisher's exact test; †Mehta's modification to Fisher's exact test; °Cochran-Armitage trend test; ▲Multivariable logistic regression analysis: Only significant p-values of independent factors shown.

Supplementary Figure S1: Relapse-free survival, relapse incidence and non-relapse mortality according to RDW $\geq 13.4\%$.

(A) Relapse-free survival was defined as time from enrollment until relapse or death restricted to patients transplanted for hematological neoplasms.

(B) Cumulative incidence of relapse was defined as time from study enrollment to relapse with non-relapse mortality as a competing risk. (C)

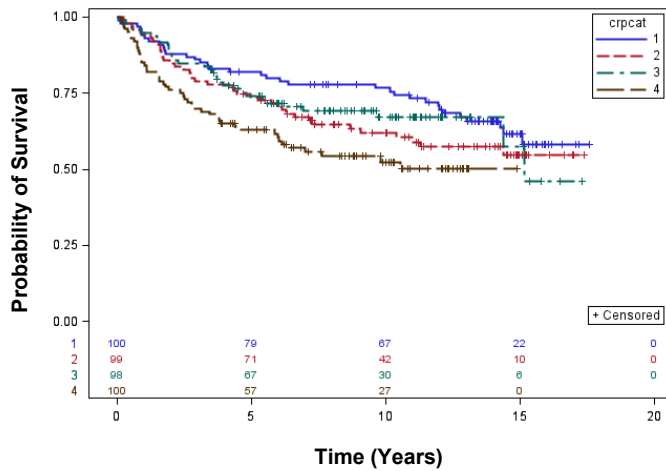
Cumulative incidence of non-relapse mortality was defined as time from study enrollment to death with relapse as a competing risk. P-values correspond to full curve analyses.



Supplementary Figure S2: Overall survival according to CRP.

(A) Quartiles. 1st quartile: <0.63 mg/dL; 2nd quartile: 0.63-2.0 mg/dL; 3rd quartile: 2.01-7.58 mg/dL; 4th quartile: ≥ 7.59 mg/dL. P=0.017. (B) Two groups could be distinguished, separated at 7.6 mg/L which is around the upper limit of normal of most non-high-sensitivity CRP tests (upper limit of normal of the high-sensitivity CRP test at NIH Clinical Center: 5 mg/L). However, CRP ≥ 7.6 mg/L was not independently associated with overall survival in the Cox model (HR=1.147, 95% CI: 0.783-1.679; p=0.4819). The asterisk (*) denotes a p-value that was adjusted for three implicit cut-points that could have been used when dividing the groups into quartiles.

A



B

