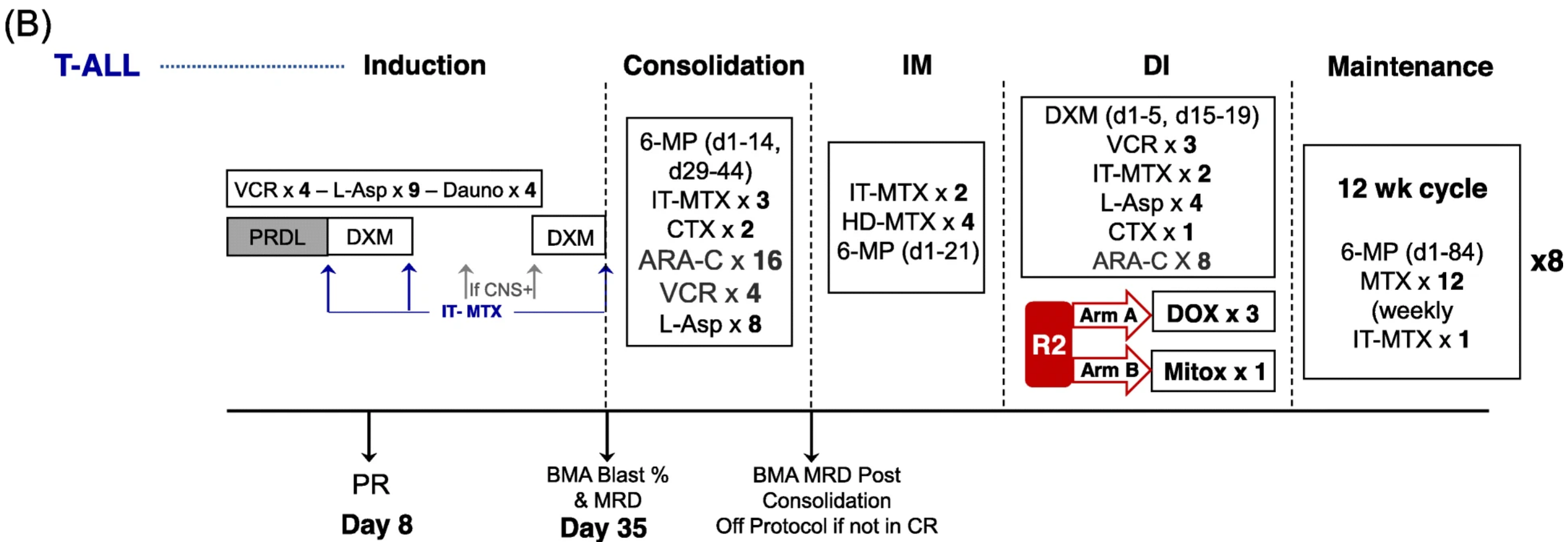
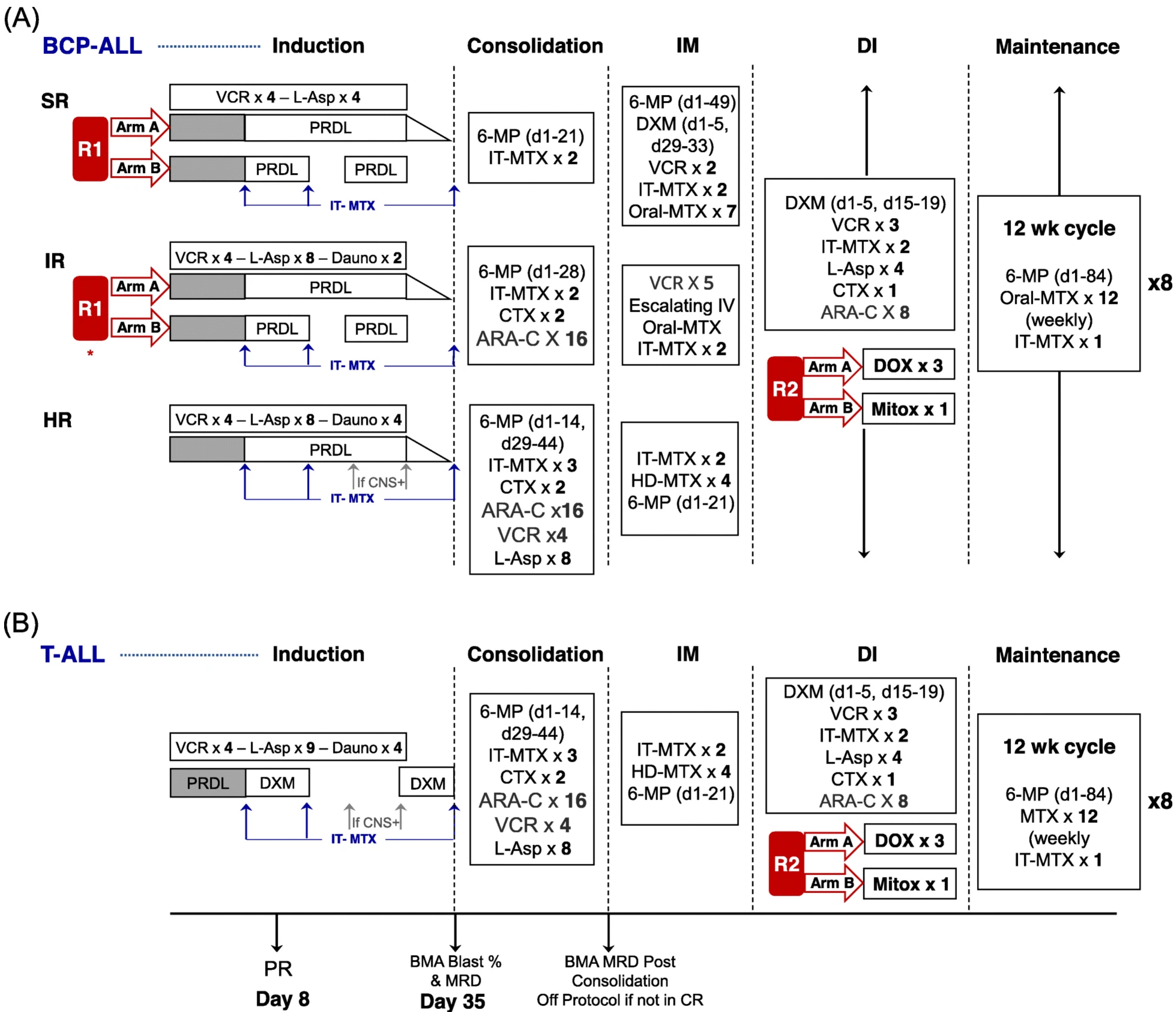
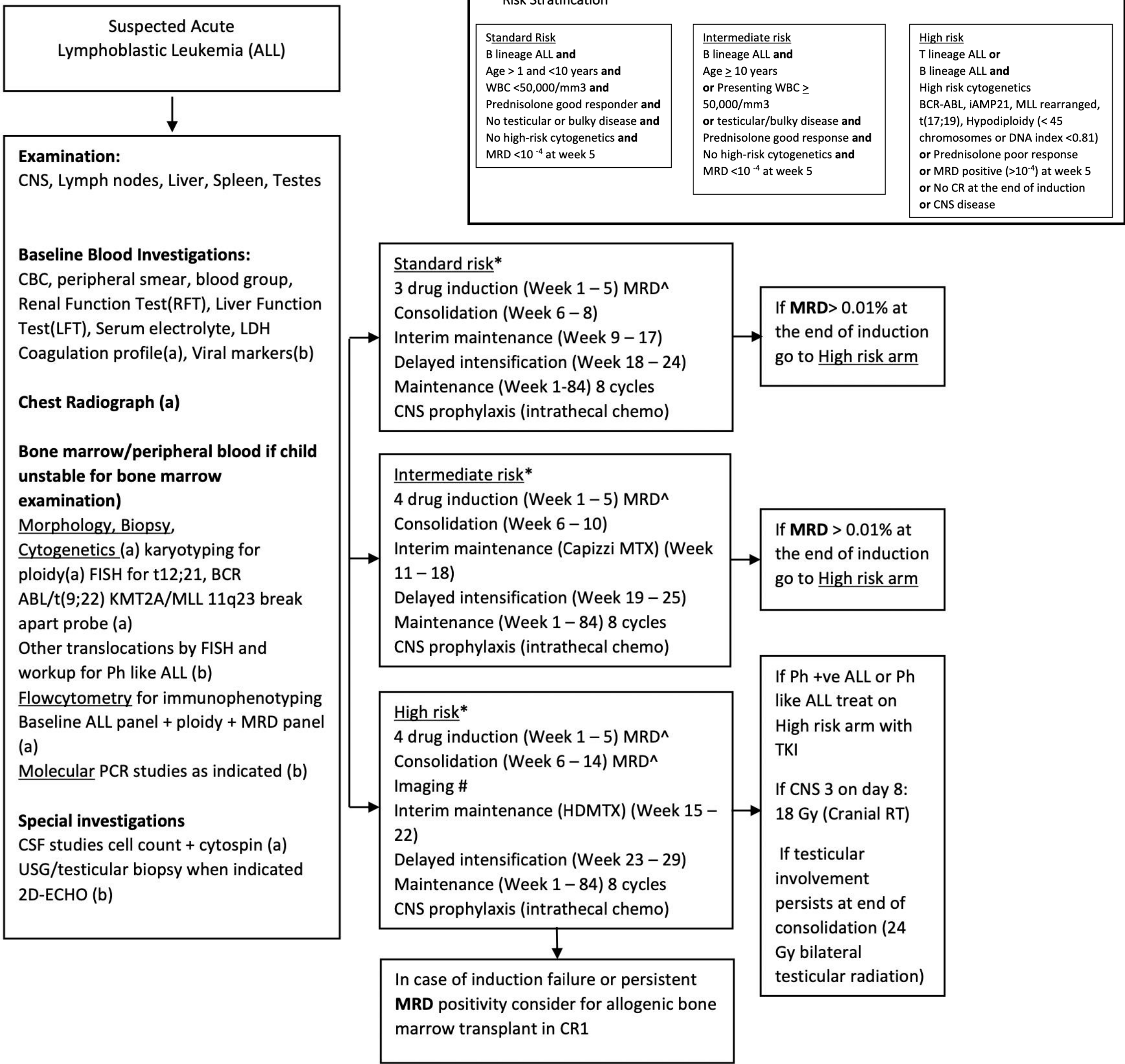


Supplementary Fig 1:- Comprehensive analysis of copy number alterations and their clinical impact in a cohort of paediatric B-cell precursor acute lymphoblastic leukaemia: A collaborative data from two major oncology centres from North India

ICICLE TRIAL

PEDIATRIC ACUTE LYMPHOBLASTIC LEUKEMIA

Treatment Algorithm: Newly diagnosed ALL



[^] MRD = Minimal residual disease by flow cytometry or PCR to assess response to treatment. Risk stratification depends upon MRD assessment. To be done at centers with expertise in flowcytometry and/PCR MRD detection. # Imaging like CXR for patients with T-ALL or LBL with mediastinal mass at the end of consolidation at the end of consolidation to assess response to treatment.

*IR Patients >10 years not eligible for R1

Supplementary Table 1:-Clinico-hematological and treatment outcome parameters in ICICLE risk groups (n=493)

Category	Total (N; %)	ICICLE Risk Group (n=493)			p value
		Standard Risk (N=119; 24.1%)	Intermediate Risk (N=159; 32.3%)	High Risk (N=215; 43.6%)	
Age					<0.001
1-9 years	358 (72.2%)	119 (100%)	86 (54.1%)	153 (71.2%)	
10-18 years	135 (27.8%)	0 (0%)	73 (45.9%)	62 (28.8%)	
Gender					0.8
Male	324 (65.7%)	72 (60.5%)	106 (66.7%)	146 (67.9%)	
Female	169 (34.3%)	47 (39.5%)	53 (33.3%)	69(32.1%)	
WBC					0.41
< 50 x 10 ⁹ /ul	328 (66.3%)	119 (100%)	85 (53.5%)	124 (57.7%)	
>50 x 10 ⁹ /ul	165 (33.7%)	0 (0%)	74 (46.5%)	91 (42.3%)	
NCI Group					<0.001
SR	230 (46%)	119 (100%)	26 (16.4%)	85 (39.5%)	
HR	263 (54%)	0 (0%)	133 (83.6%)	130 (60.5%)	
CR					0.01
Yes	432 (87.6%)	111 (93.3%)	143 (89.9%)	178 (82.8%)	
No	61 (12.4%)	8 (6.7%)	16 (10.1%)	37 (17.2%)	
Primary genetic risk groups					<0.001
GR	83 (16.8%)	30 (33.7%)	26 (30.1%)	27 (36.2%)	
IR	363 (73.6%)	89 (24.5%)	133 (36.9%)	141 (38.6%)	
HR	47 (9.5%)	0 (0%)	0 (0%)	47 (100%)	
Relapse					0.003
No	370 (75%)	92 (77.3%)	132 (83%)	146 (67.9%)	
Yes	123 (25%)	27 (22.7%)	27 (17%)	69 (32.1%)	
Death					0.16
No	362 (73.4%)	95 (79.8%)	111 (69.8%)	156 (72.6%)	
Yes	131 (26.6%)	24 (20.2%)	48 (30.2%)	59 (27.4%)	

Supplementary Table 2:-Clinico-hematological and treatment outcome parameters in primary genetic risk groups (n=493)

Category	Total (N; %)	Primary Genetic Risk Groups (n=493)			p value
		Good Risk (N=83; 16.8%)	Intermediate Risk (N=363; 73.6%)	High Risk (N=47; 9.5%)	
Age					<0.001
1-9 years	358 (72.2%)	75 (90.4%)	255 (70.2%)	28 (59.6%)	
10-18 years	135 (27.8%)	8 (9.6%)	108 (29.8%)	19 (40.4%)	
Gender					0.37
Male	324 (65.7%)	60 (72.3%)	233 (64.2%)	31 (66%)	
Female	169 (34.3%)	23 (27.7%)	130 (35.8%)	16 (34%)	
WBC					0.07
< 50 x 10 ⁹ /ul	328 (66.3%)	60 (72.3%)	246 (67.8%)	25 (53.2%)	
>50 x 10 ⁹ /ul	165 (33.7%)	23 (27.7%)	117 (32.2%)	22 (46.8%)	
NCI Group					<0.001
SR	230 (46%)	52 (62.7%)	167 (46%)	11 (23.4%)	
HR	263 (54%)	31 (37.3%)	196 (54%)	36 (76.6%)	
Remission status Day 35 BM					0.003
CR	432 (87.6%)	80 (96.4%)	316 (87.1%)	36 (76.6%)	
Not in CR	61 (12.4%)	3 (3.6%)	47 (12.9%)	11 (23.4%)	
MRD Status Day 35 (n=444)					0.03
<0.01%	333 (67.5%)	65 (81.3%)	246 (75.2%)	22 (59.5%)	
>0.01%	111 (22.5%)	15 (18.7%)	81 (24.8%)	15 (40.5%)	
Final ICICLE Risk group					<0.001
SR	119 (24.1%)	30 (33.7%)	89 (24.5%)	0 (0%)	
IR	159 (32.3%)	26 (30.1%)	133 (36.9%)	0 (0%)	
HR	215 (43.6%)	27 (36.2%)	141 (38.6%)	47 (100%)	
Relapse					0.013
No	370 (75%)	64 (77.1%)	279 (76.9%)	27 (57.4%)	
Yes	123 (25%)	19 (22.9%)	84 (23.1%)	20 (42.6%)	
Death					0.011
No	362 (73.4%)	71 (85.5%)	261 (71.9%)	30 (63.8%)	
Yes	131 (26.6%)	12 (14.5%)	102 (28.1%)	17 (36.2%)	

SR, standard risk; IR, intermediate risk; HR, high risk; CR, complete remission; MRD, ICICLE, Indian Childhood Collaborative Leukemia protocol.

Supplementary Table3:- Highlights Clinico-hematological and treatment outcome parameters in different CNA deletion sub-groups (except *IKZF1* and *IKZF1^{Plus}* profile) (n=493)

Category	Total	<i>CDKN2A/B</i> del		<i>BTG1</i> del		PAR1 del		<i>PAX5</i> del		<i>ERG</i> del		<i>RB1</i> del		<i>ETV6</i> del		<i>EBF1</i> del	
	(N)		p value		p value		p value		p value		p value		p value		p value		p value
1-9 years	358	114	<0.001	30	0.33	13	0.33	74	<0.001	12	0.25	27	0.86	35	0.89	16	0.955
10-18 years	135	65		8		7		48		2		11		14		6	
Male	324	118	0.94	31	0.03	12	0.58	84	0.4	10	0.64	27	0.47	30	0.48	16	0.478
Female	169	61		7		8		38		4		11		19		6	
< 50 x 10 ⁹ /ul	328	104	0.0035	20	0.062	13	0.89	71	0.028	10	0.68	24	0.66	33	0.87	13	0.46
>50 x 10 ⁹ /ul	165	75		18		7		51		4		14		16		9	
SR	230	59	<.001	15	0.39	7	0.311	38	<0.01	9	0.164	14	0.23	21	0.63	8	0.92
HR	263	120		23		13		84		5		24		28		14	
CR	432	152	0.16	33	0.87	7	<0.001	106	0.774	12	0.03	29	0.02	45	0.34	20	0.63
Not in CR	61	27		5		13		16		2		9		4		2	
<0.01%	333	112	0.32	23	0.186	13	0.49	81	0.84	11	0.41	22	0.827	33	0.57	17	0.8
>0.01%	111	43		12		6		26		2		8		9		5	
ICICLE-SR	119	29	0.009	4	0.051	5	0.69	21	0.101	7	0.03	6	0.38	12	0.95	3	0.46
ICICLE-IR	159	63		6		8		40		5		12		15		9	
ICICLE-HR	215	87		23		7		61		2		20		22		10	
Genetics-GR	83	20	<0.001	10	0.006	5	0.45	12	<0.001	1		8	0.78	13	0.158	6	0.022
Genetics-IR	363	131		20		14		86		14		26		30		11	
Genetics-HR	47	28		8		1		24		0		4		5		5	

Supplementary Table 4:-CNA profile in ICICLE risk groups (n=493)

Category	Total N(%)	ICICLE Risk Group (n=493)			p-value
		Standard Risk (N=119; 24.1%)	Intermediate Risk (N=159; 32.3%)	High Risk (N=215; 43.6%)	
IKZF1 NO DEL	397 (80.52%)	112 (94.1%)	133 (83.6%)	152 (70.7%)	<0.001
IKZF1 DEL	96 (19.5%)	7 (5.9%)	26 (16.4%)	63 (29.3%)	
IKZF1 ^{Plus} NO DEL	427 (86.6%)	116 (97.5%)	140 (88.1%)	171 (79.5%)	<0.001
IKZF1 ^{Plus} DEL	66 (13.4%)	3 (2.5%)	19 (11.9%)	44 (20.5%)	
CNA GR	259 (52.5%)	85 (71.4%)	83 (52.2%)	91 (42.3%)	<0.001
CNA IR-PR	234 (47.5%)	34 (28.6%)	76 (47.8%)	124 (57.7%)	
MRPlus0	259 (53.5%)	85 (71.4%)	83 (52.2%)	91 (42.3%)	<0.001
MRPlus1	168 (34.1%)	31 (26.1%)	57 (35.8%)	80 (37.2%)	
MRPlus2	66 (13.4%)	3 (2.5%)	19 (11.9%)	44 (20.5%)	

Supplementary Table 5:-CNA profile in genetic risk groups (n=493)

Category	Total N(%)	Genetic Risk Group (n=493)			p-value
		Good Risk (N=83; 16.8%)	Intermediate Risk (N=363; 73.6%)	High Risk (N=47; 9.5%)	
IKZF1 NO DEL	397 (80.52%)	77 (92.8%)	302 (83.2%)	18 (38.3%)	<0.001
IKZF1 DEL	96 (19.5%)	6 (7.2%)	61 (16.8%)	29 (61.7%)	
IKZF1 ^{Plus} NO DEL	427 (93.9%)	81 (97.6%)	323 (89%)	23 (48.9%)	<0.001
IKZF1 ^{Plus} DEL	66 (13.4%)	2 (2.4%)	40 (11%)	24 (51.1%)	
CNA GR	259 (52.5%)	53 (63.9%)	195 (53.7%)	11 (23.4%)	<0.001
CNA IR-PR	234 (47.5%)	30 (36.1%)	168 (46.3%)	36 (76.6%)	
MRPlus0	259 (52.5%)	53 (63.9%)	195 (53.7%)	11 (23.4%)	<0.001
MRPlus1	168 (34.1%)	28 (33.7%)	128 (35.3%)	12 (25.5%)	
MRPlus2	66 (13.4%)	2 (2.4%)	40 (11.0%)	24 (51.1%)	

Supplementary Table 6:- Highlights 3-year outcome analysis of *IKZF1* deletion, *IKZF1^{plus}* profile, UKALL-CNA profile, MRplus score interaction with MRD

Category (n)	OS% (range)(n=deaths) at 3 years with 95% CI	Log rank p value	EFS% (range (n=events) at 3 years with 95% CI	Log rank p value	RR% (range) (n=relapse)* at 3 years with 95% CI	Log rank p value
<i>IKZF1</i> no del+ MRD neg (289)	81.9 (79.4-84.4) (44)	0.114	64.7 (61.7- 67.7) (91)	0.001	22.5 (19.7-25.3) (50)	0.002
<i>IKZF1</i> no del+ MRD pos (75)	76.2 (71-81.4) (16)		52.3 (46.2-58.4) (33)		26.1 (20-32.2) (14)	
<i>IKZF1</i> del + MRD neg (44)	71 (62.6-79.4) (9)		49.0 (40.6-57.4) (19)		31.9 (23.3-40.5) (10)	
<i>IKZF1</i> del + MRD pos (36)	60.5 (50.8-70.2) (11)		36.6 (28.1-45.1) (21)		46.7 (37-56.4) (13)	
<i>IKZF1^{plus}</i> no del+ MRD neg (301)	81.7 (79.2-84.2) (46)	0.031	65.2 (62.3-68.1) (93)	< 0.001	21.7 (19-24.4) (50)	< 0.001
<i>IKZF1^{plus}</i> no del+ MRD pos (89)	75.5 (70.5-80.5) (19)		52.4 (46.8-58) (40)		31.3 (25.4-37.2) (20)	
<i>IKZF1^{plus}</i> del + MRD neg (32)	68.2 (57.8-78.6) (7)		39.8 (30.4-49.2) (17)		42.5 (32-53) (10)	
<i>IKZF1^{plus}</i> del + MRD pos (22)	51 (37.8-64.2) (8)		25.2 (15.1-35.3) (15)		55.6 (41.7-69.5) (9)	
CNA GR + MRD neg (195)	85.1 (87.9-82.3) (24)	0.001	69.1 (65.5-72.6) (54)	< 0.001	18.9 (15.7-22.1) (29)	0.001
CNA GR + MRD pos (44)	82.2 (76.1-88.3) (7)		57.5 (49.6-65.4) (17)		29.9 (21.8-38) (10)	
CNA IR+PR + MRD neg (139)	74.2 (69.9-78.5) (29)		53.9 (49.3-58.5) (56)		30.7 (26-35.4) (31)	
CNA IR+PR + MRD pos (66)	63.3 (56.5-70.1) (20)		39.2 (3203-45.5) (37)		41.7 (34.2-49.2) (19)	

*N=456 (cases that died during induction were excluded)

Figure 2a: Overall survival (OS) of whole cohort (n=493)

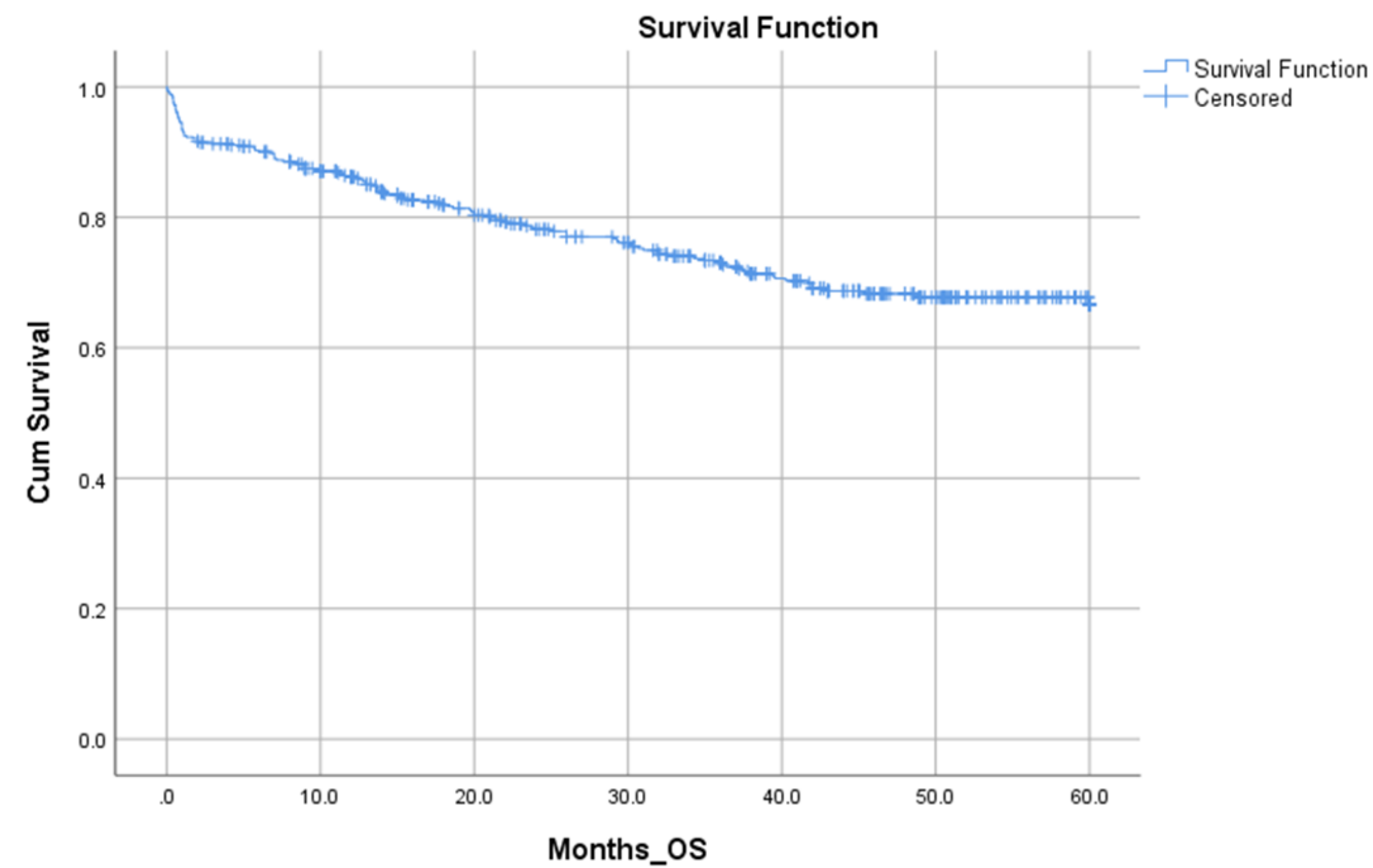


Figure 2b: Event Free survival (EFS) of whole cohort (n=493)

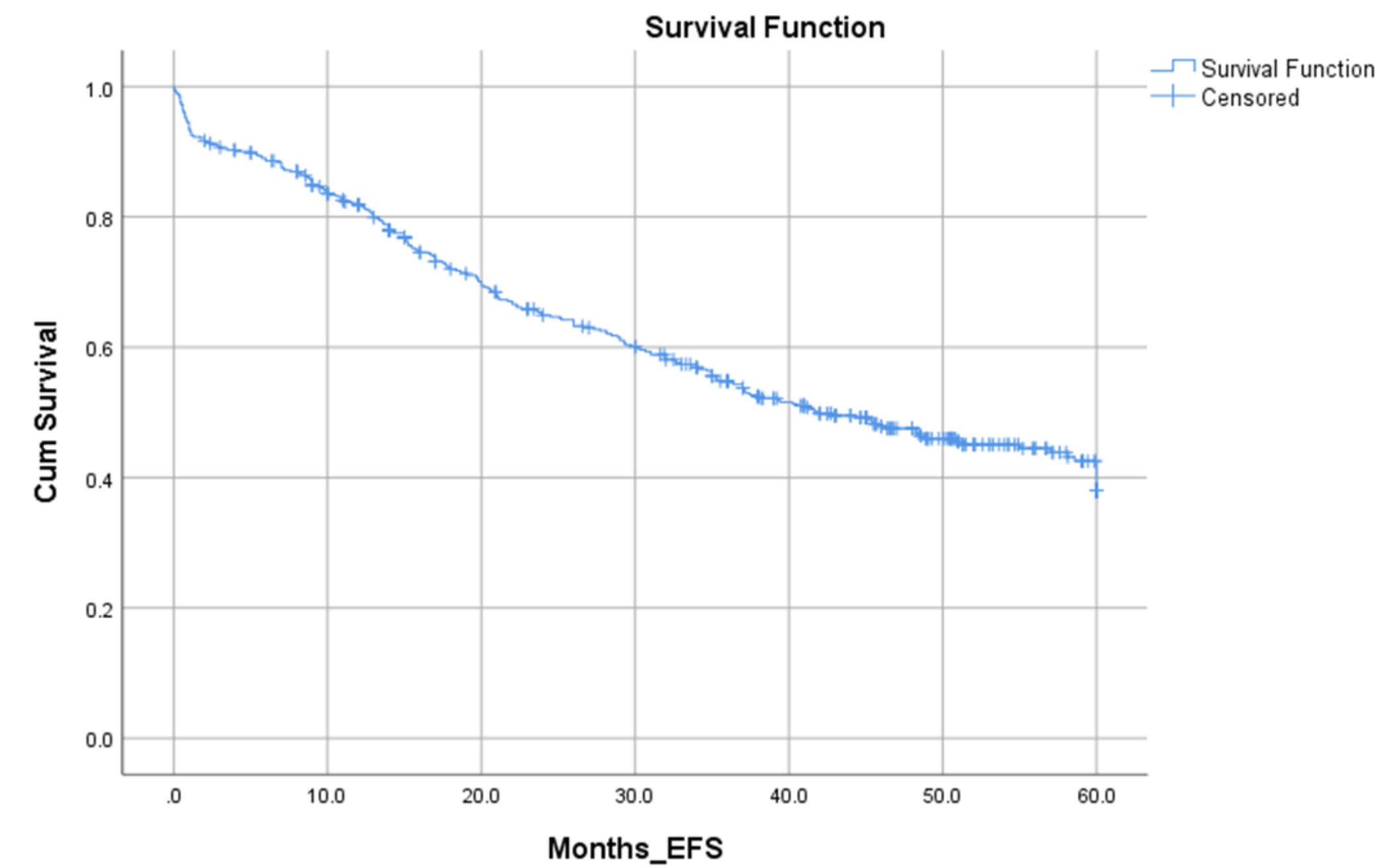
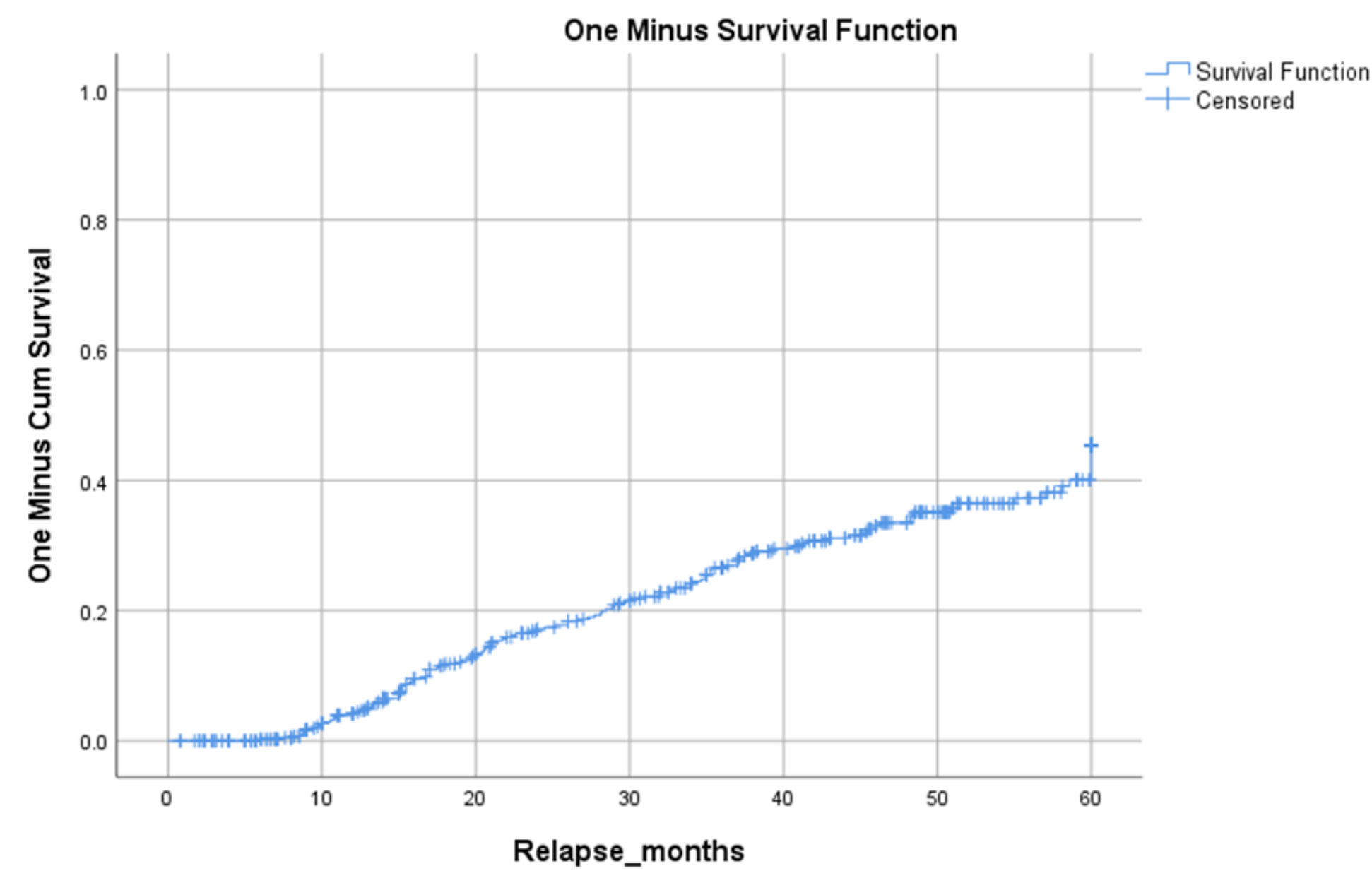
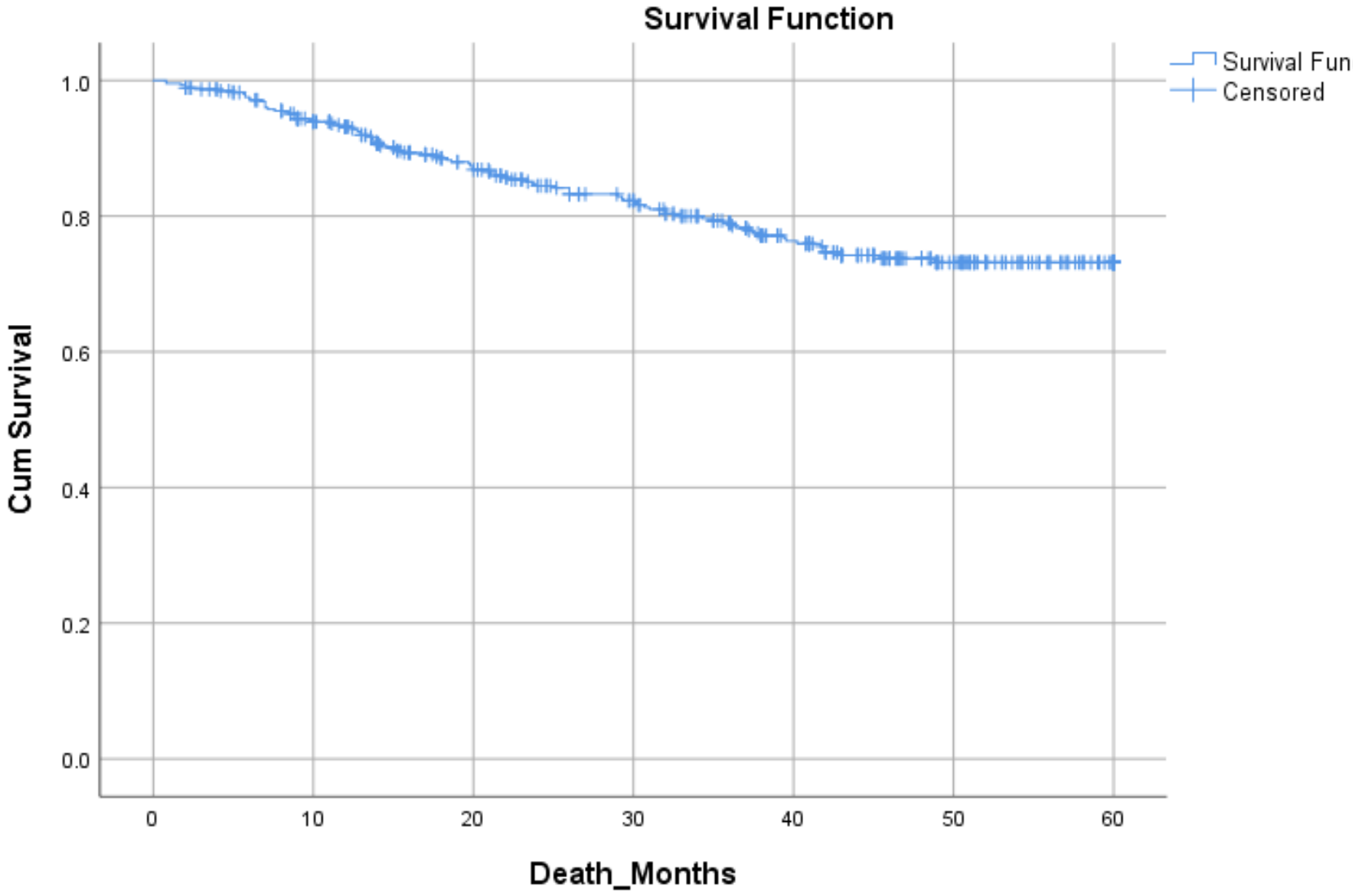


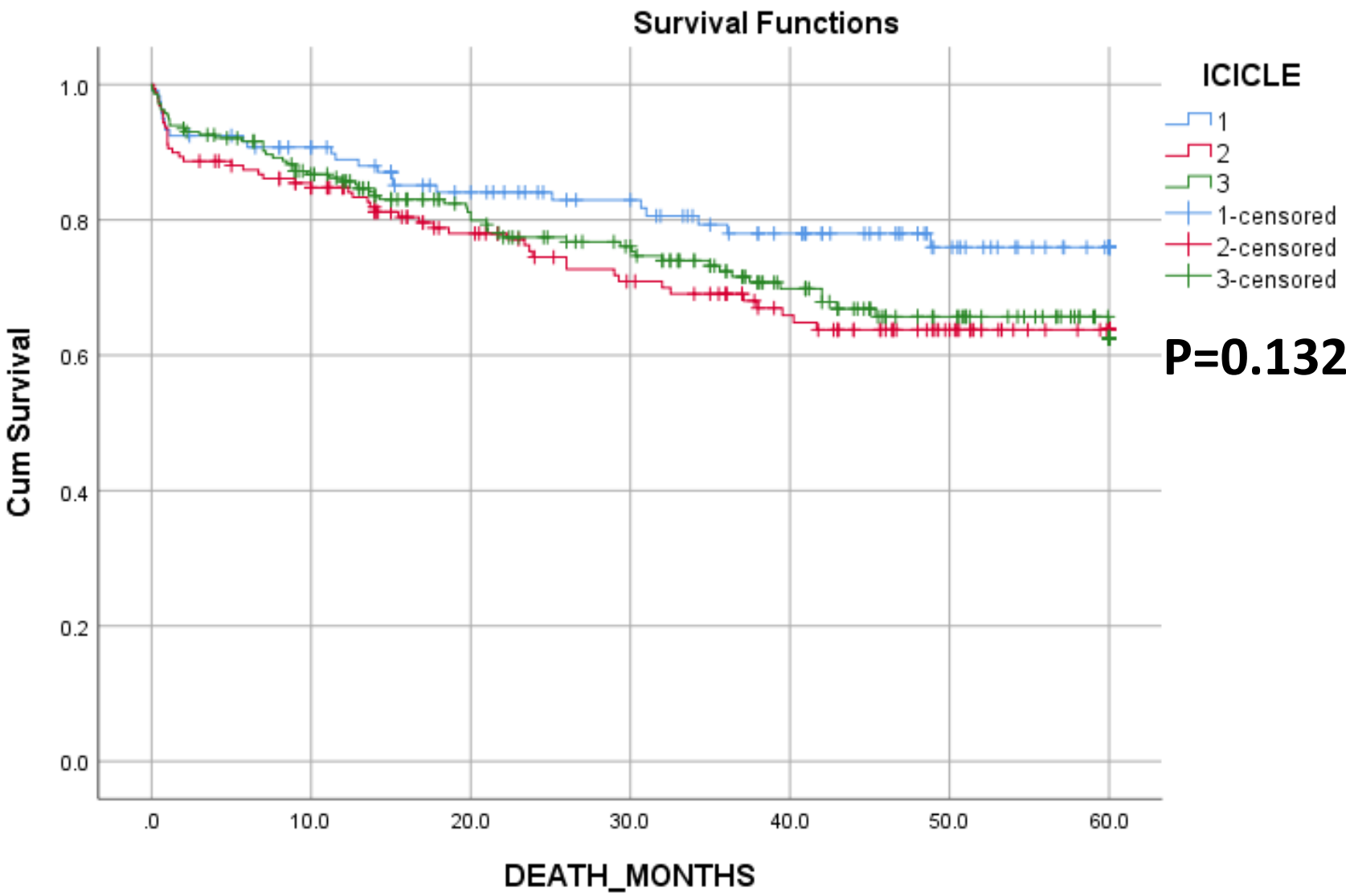
Figure 2c: Relapse Rate (RR) of whole cohort (n=493)



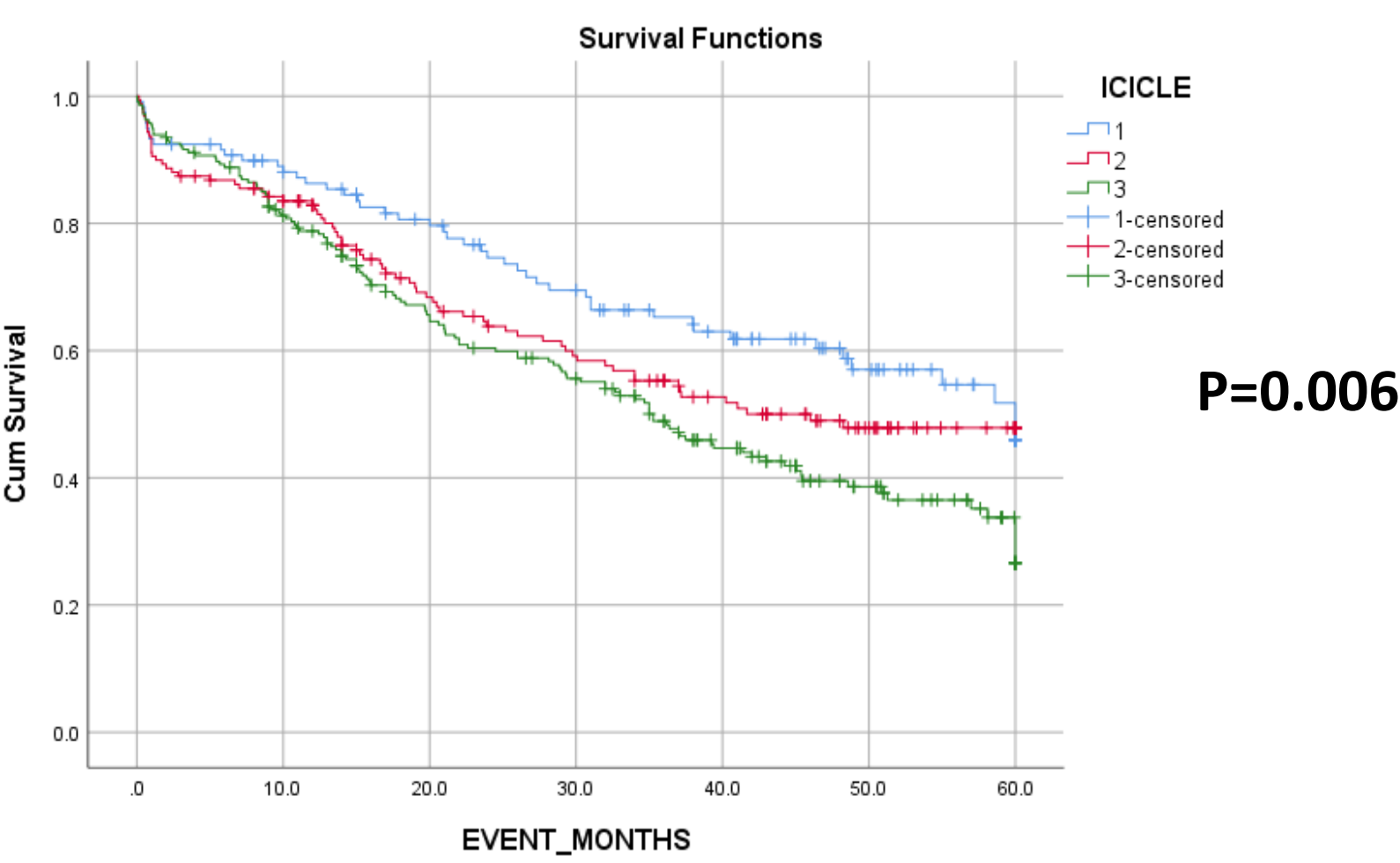
Supplementary Fig 3a:- OS_Remission cases



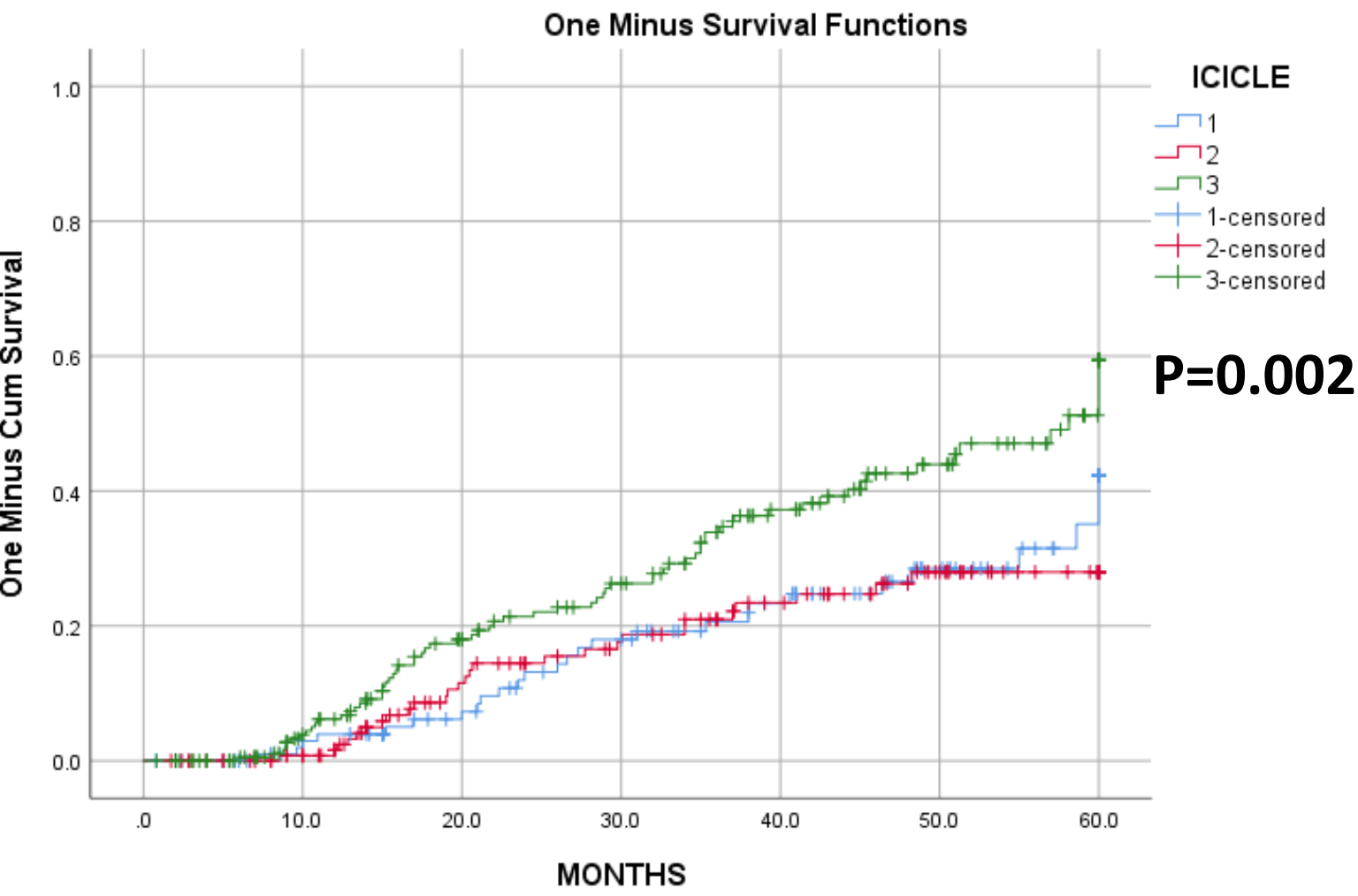
Supplementary Fig 3b:- OS_ICICLE GROUP



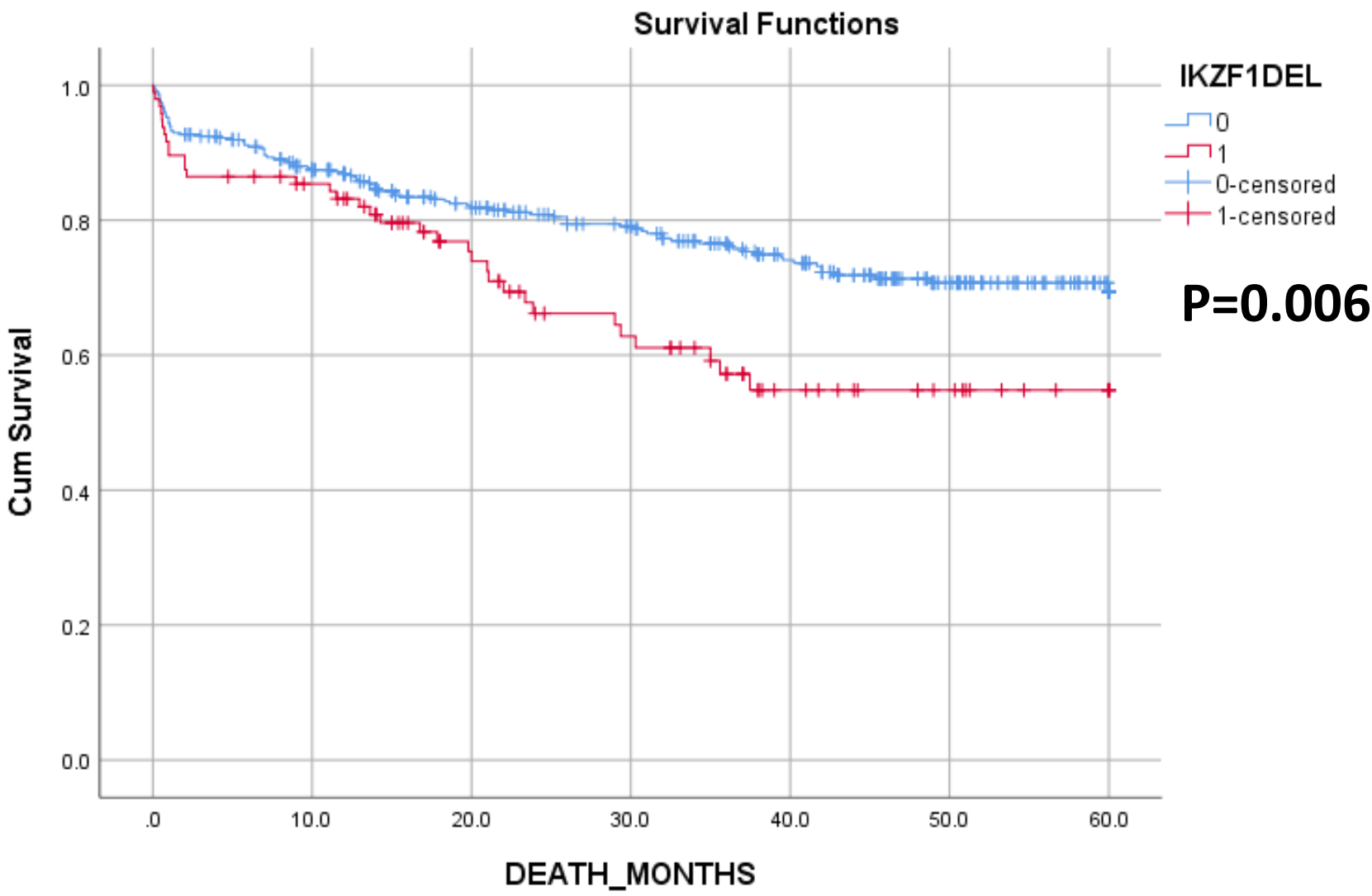
Supplementary Fig 3c:-EFS_ICICLE GROUP



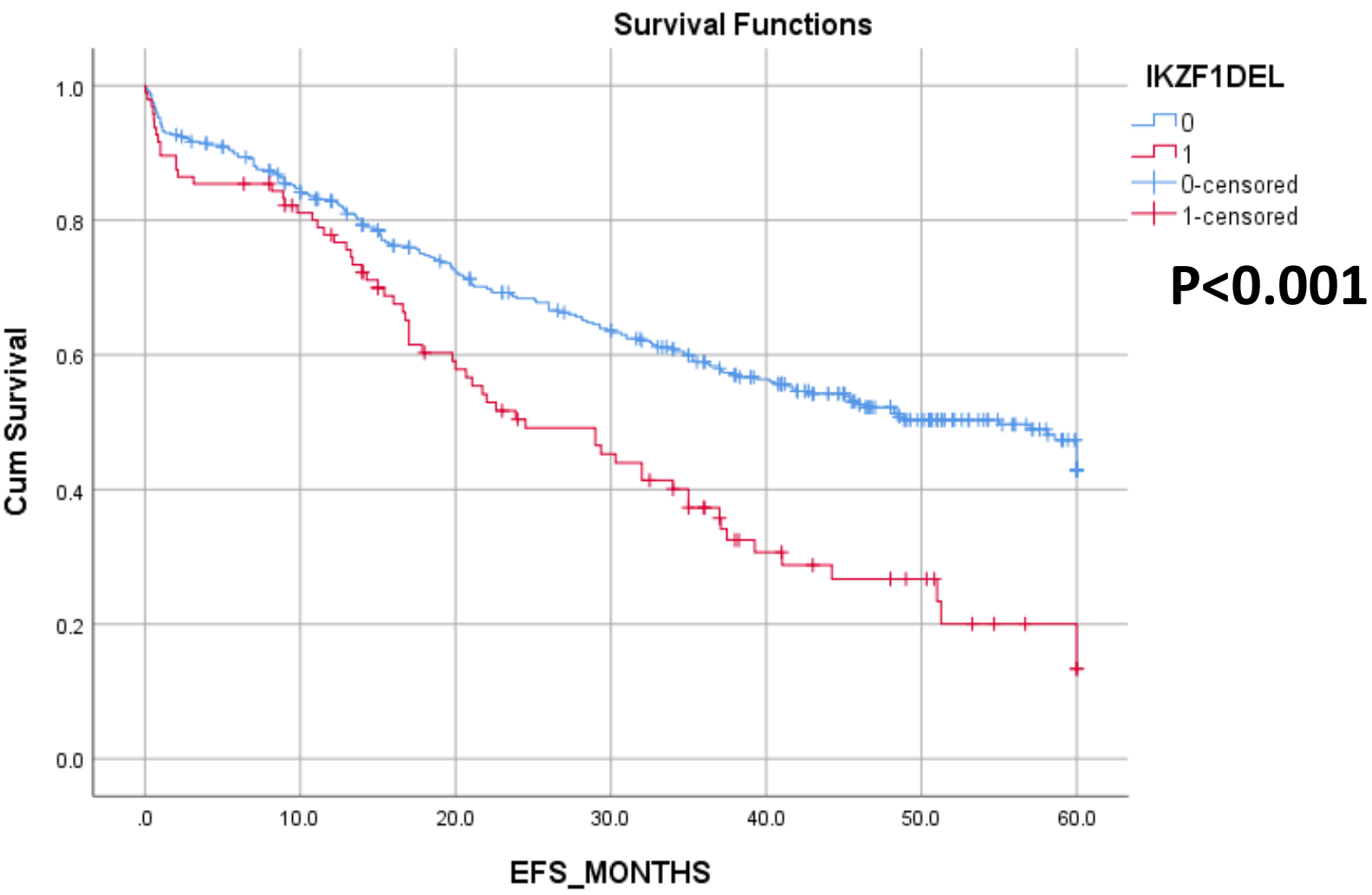
Supplementary Fig 3d:- EFS_ICICLE GROUP



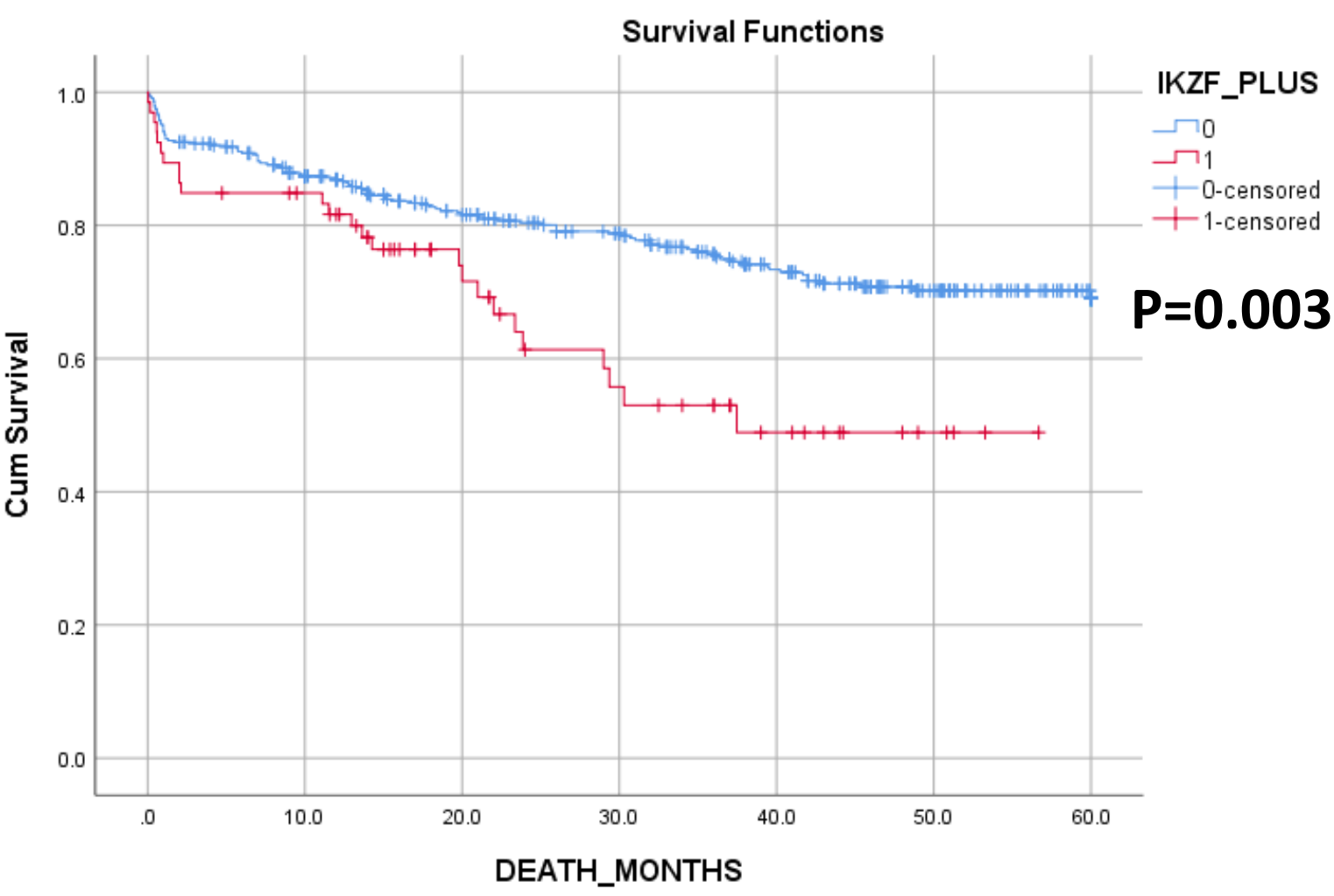
Supplementary Fig 3e:-OS_IKZFDEL



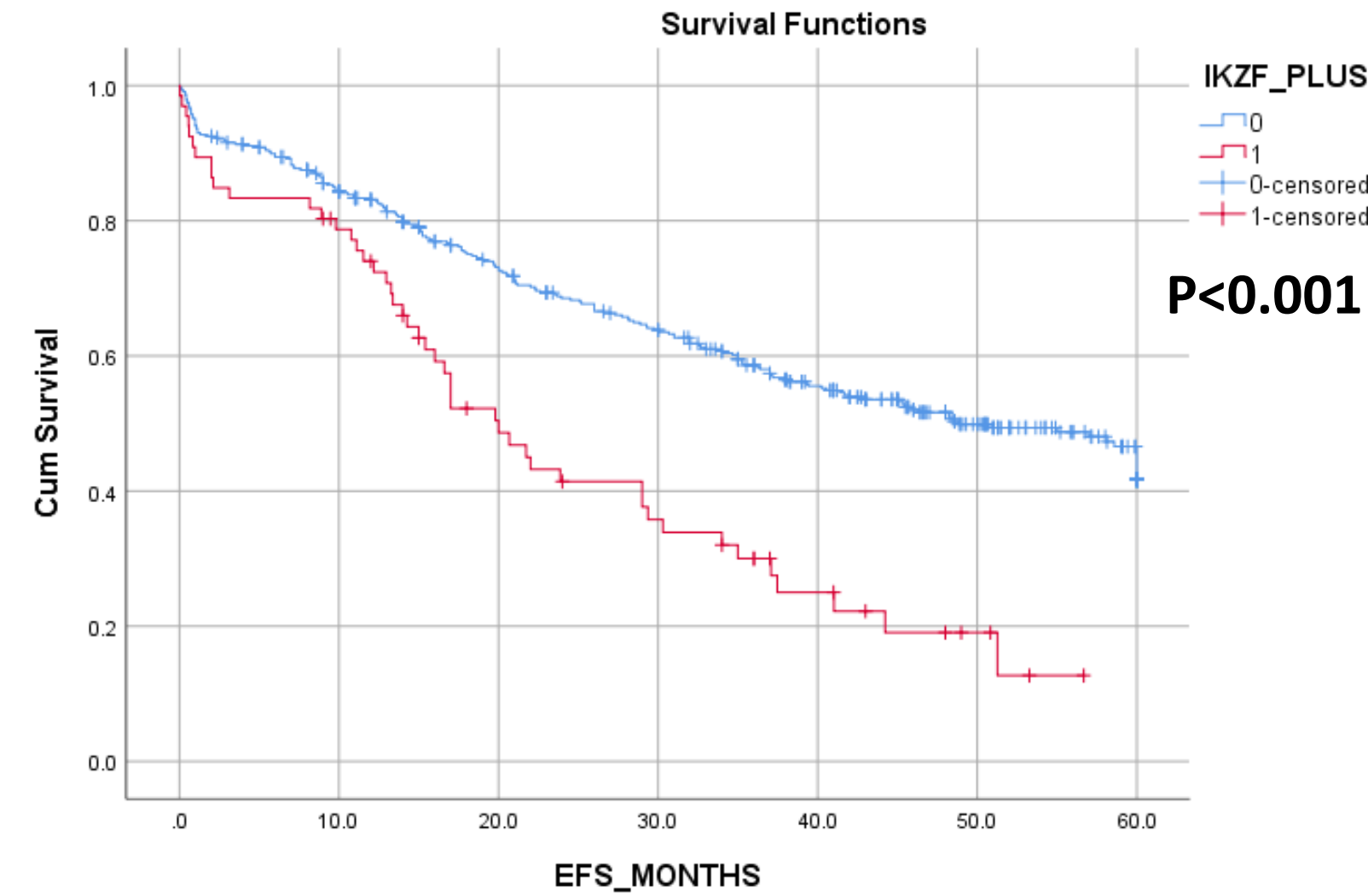
Supplementary Fig 3f:-EFS_IKZFDEL



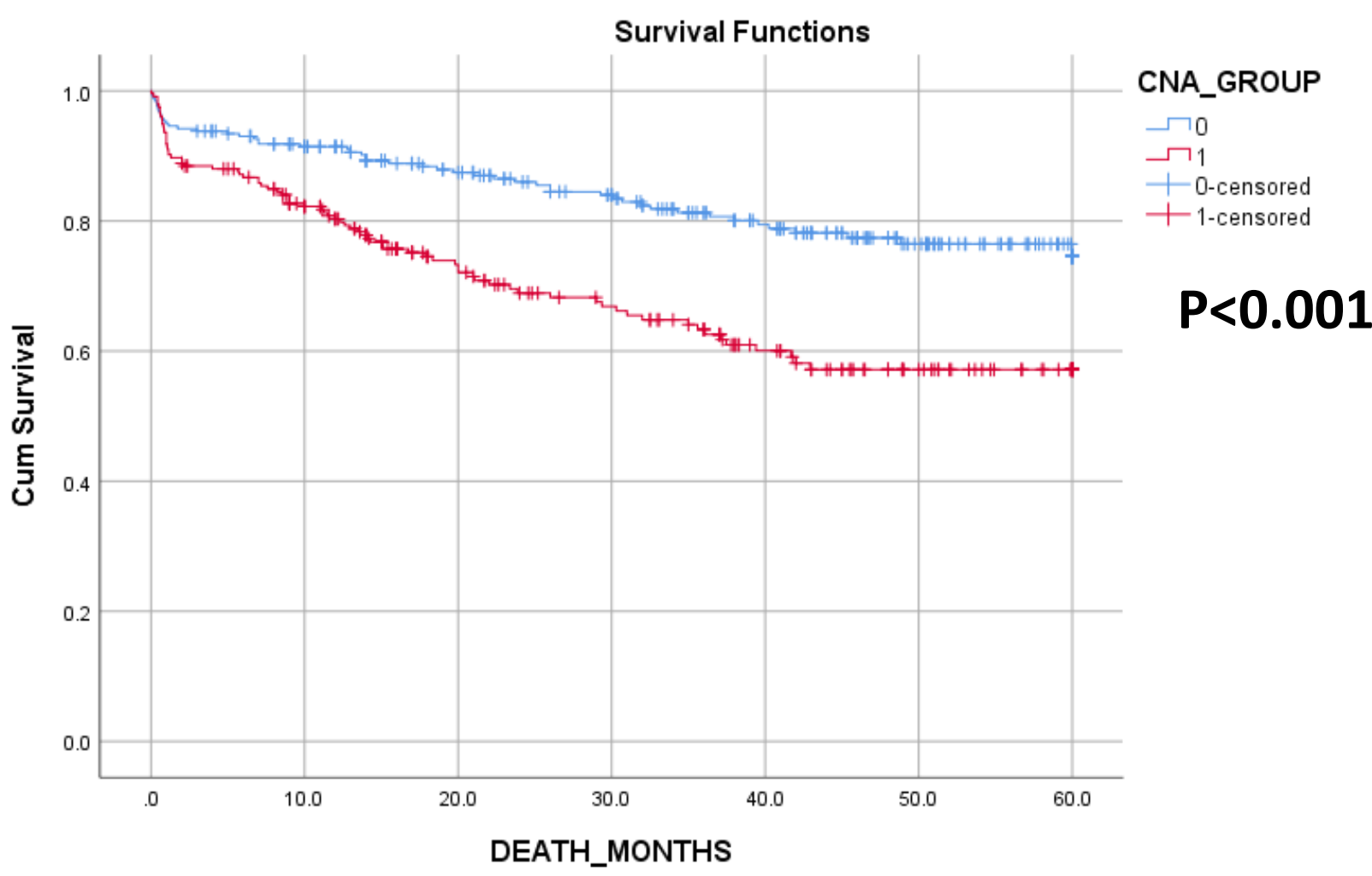
Supplementary Fig 4a:-OS_IKZF PLUSDEL



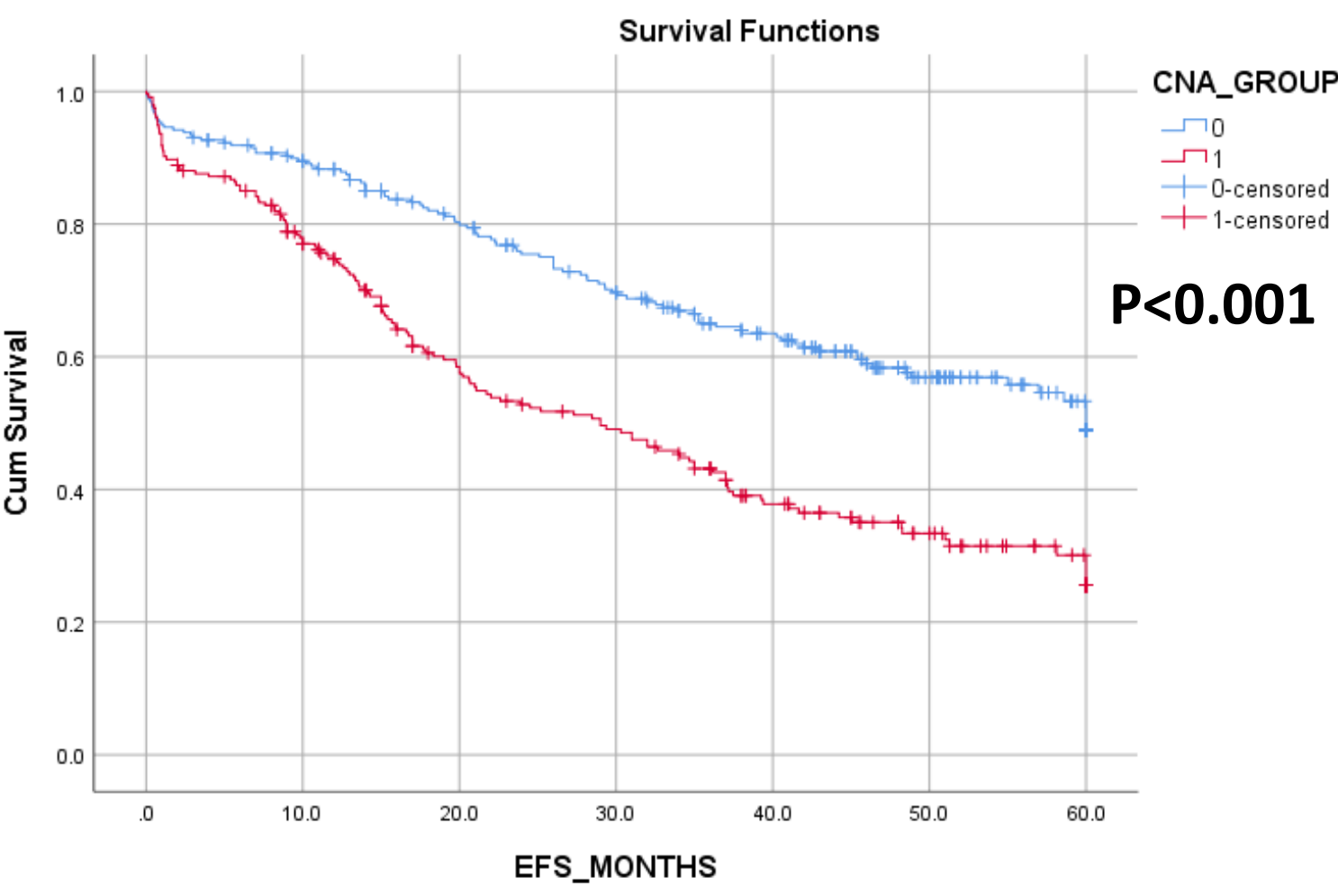
Supplementary Fig 4b:-EFS_IKZF PLUSDEL



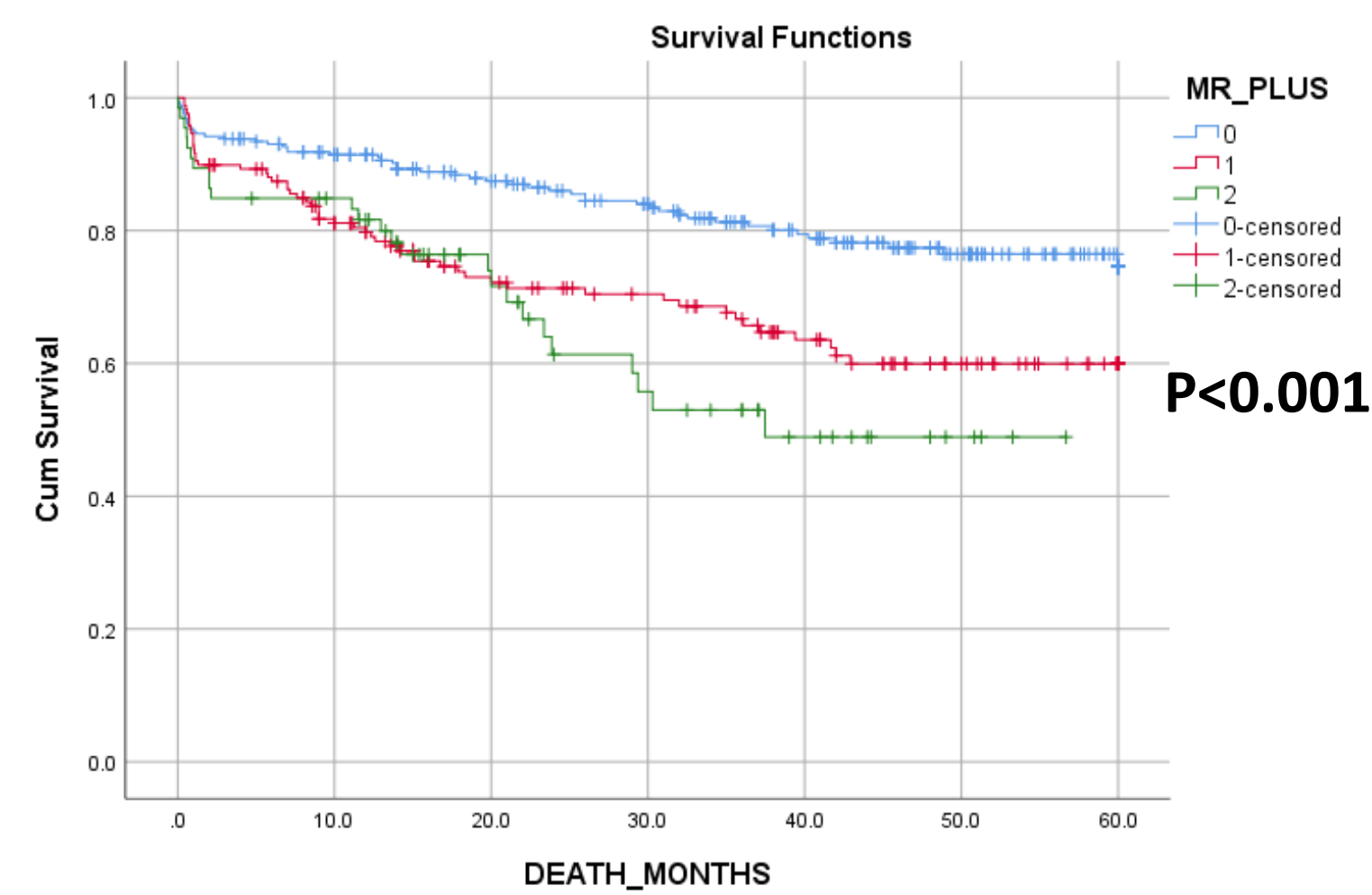
Supplementary Fig 4c:-OS_UKALL-CNA



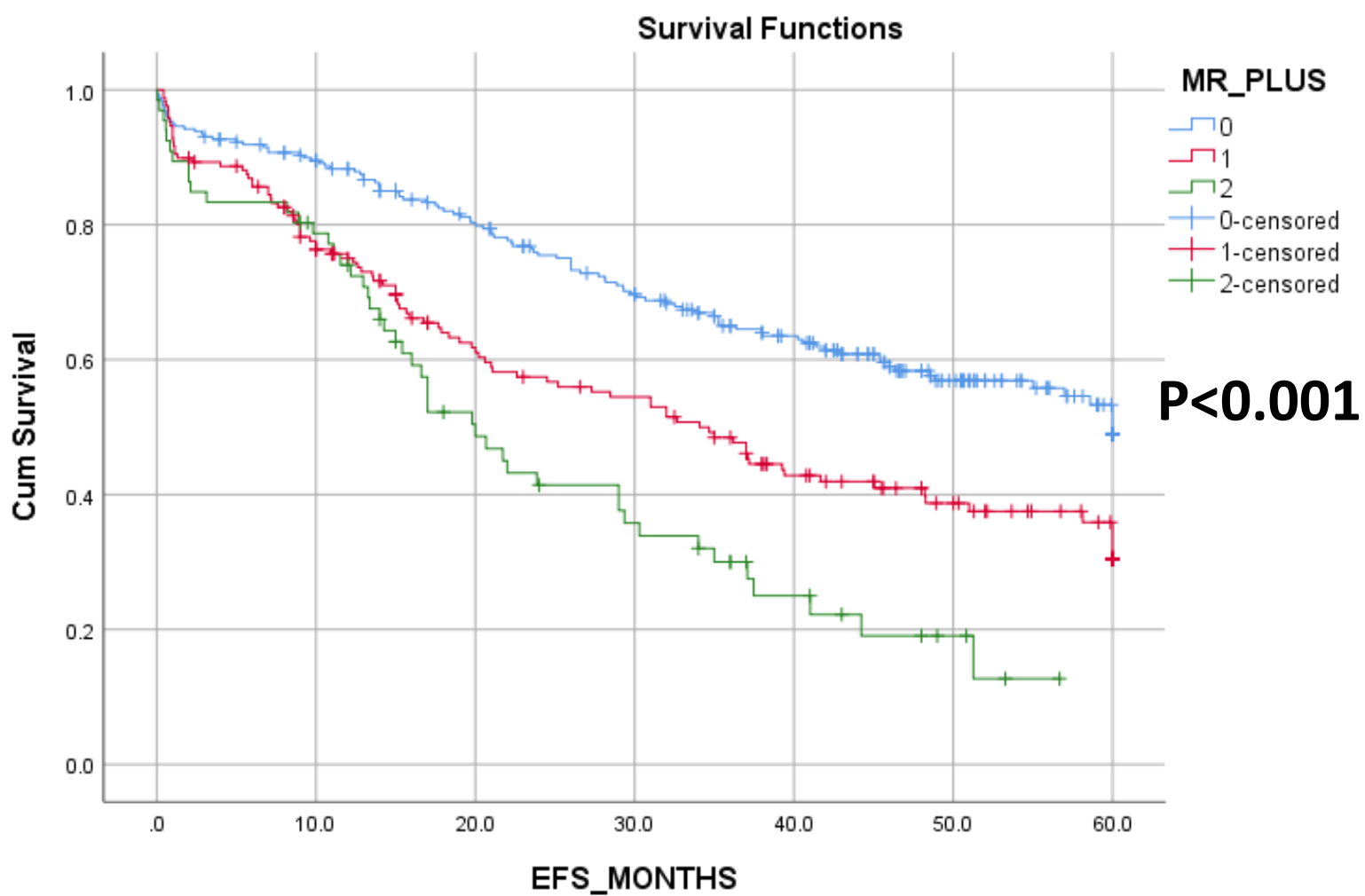
Supplementary Fig 4d:-EFS_UKALL-CNA



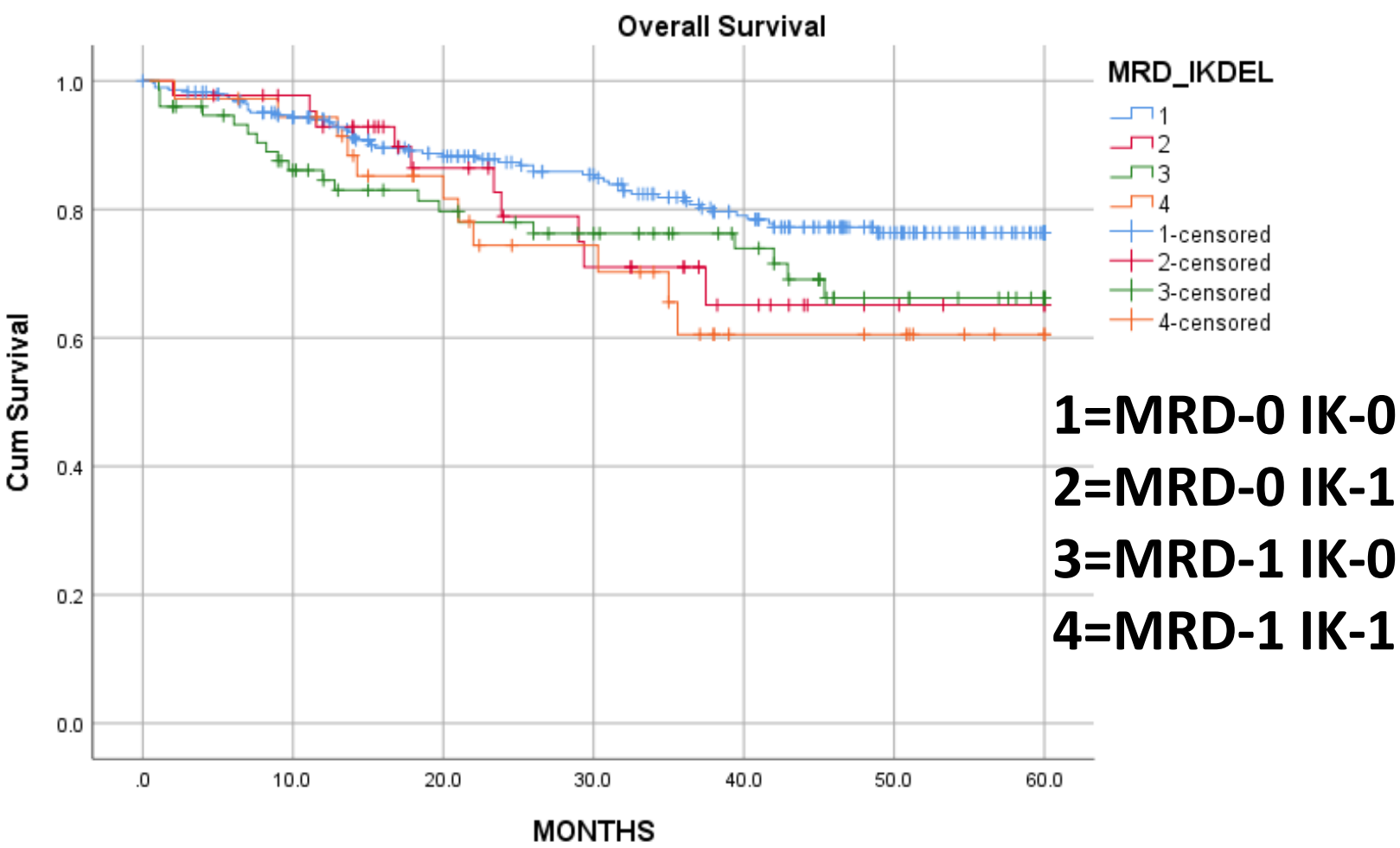
Supplementary Fig 4e:-OS_MRplus



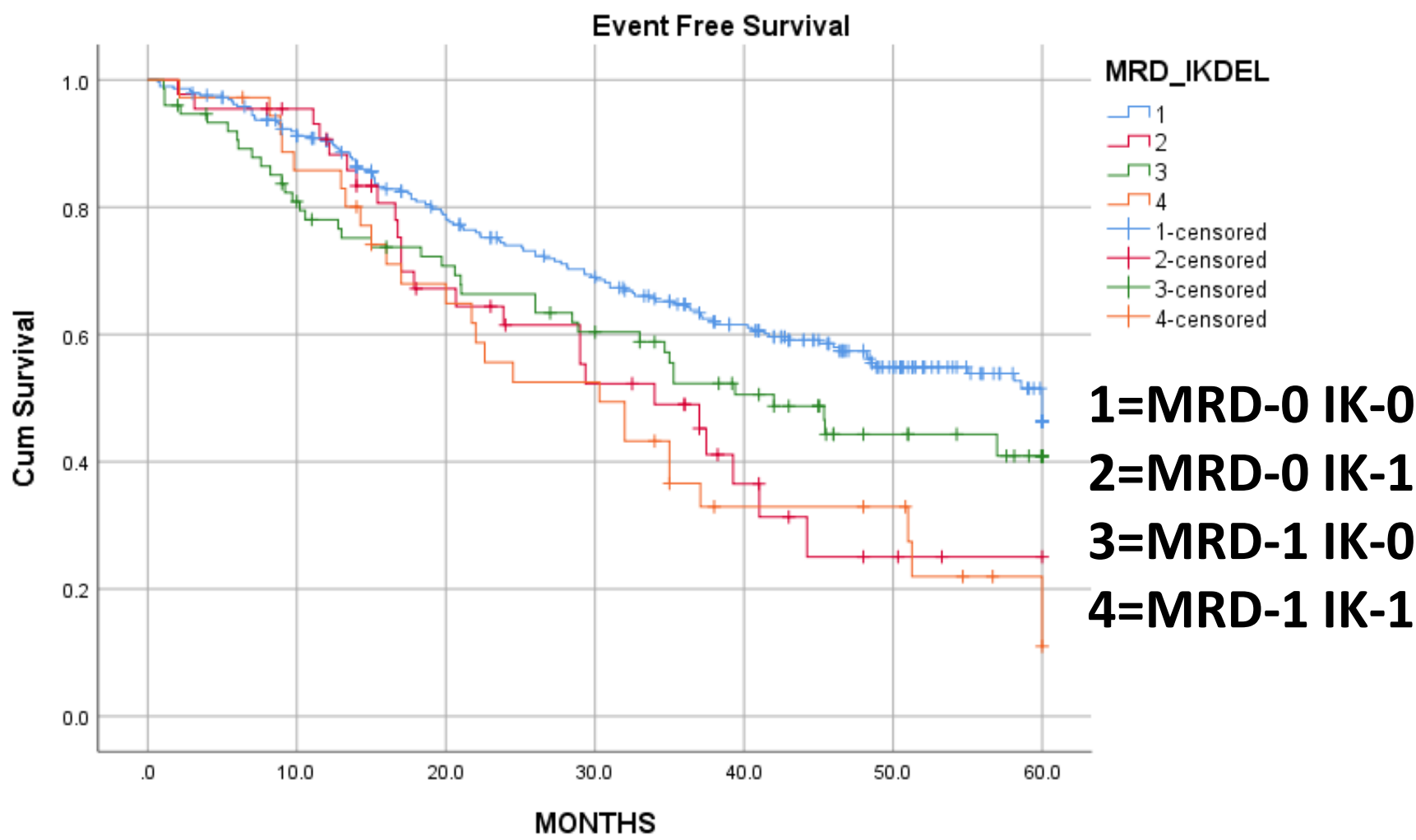
Supplementary Fig 4f:-EFS_MRplus



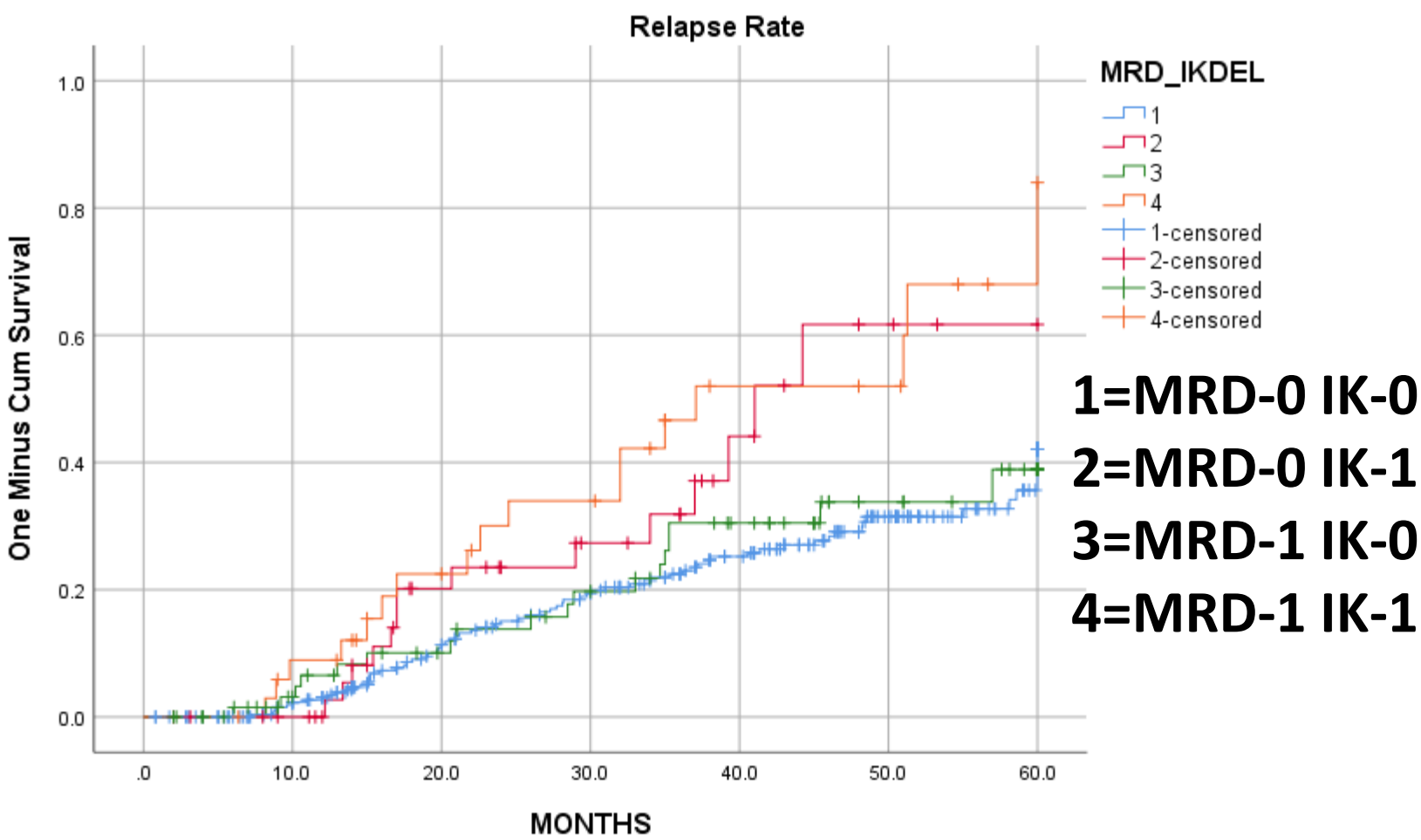
Supplementary Fig 5a:-MRD_IK OS



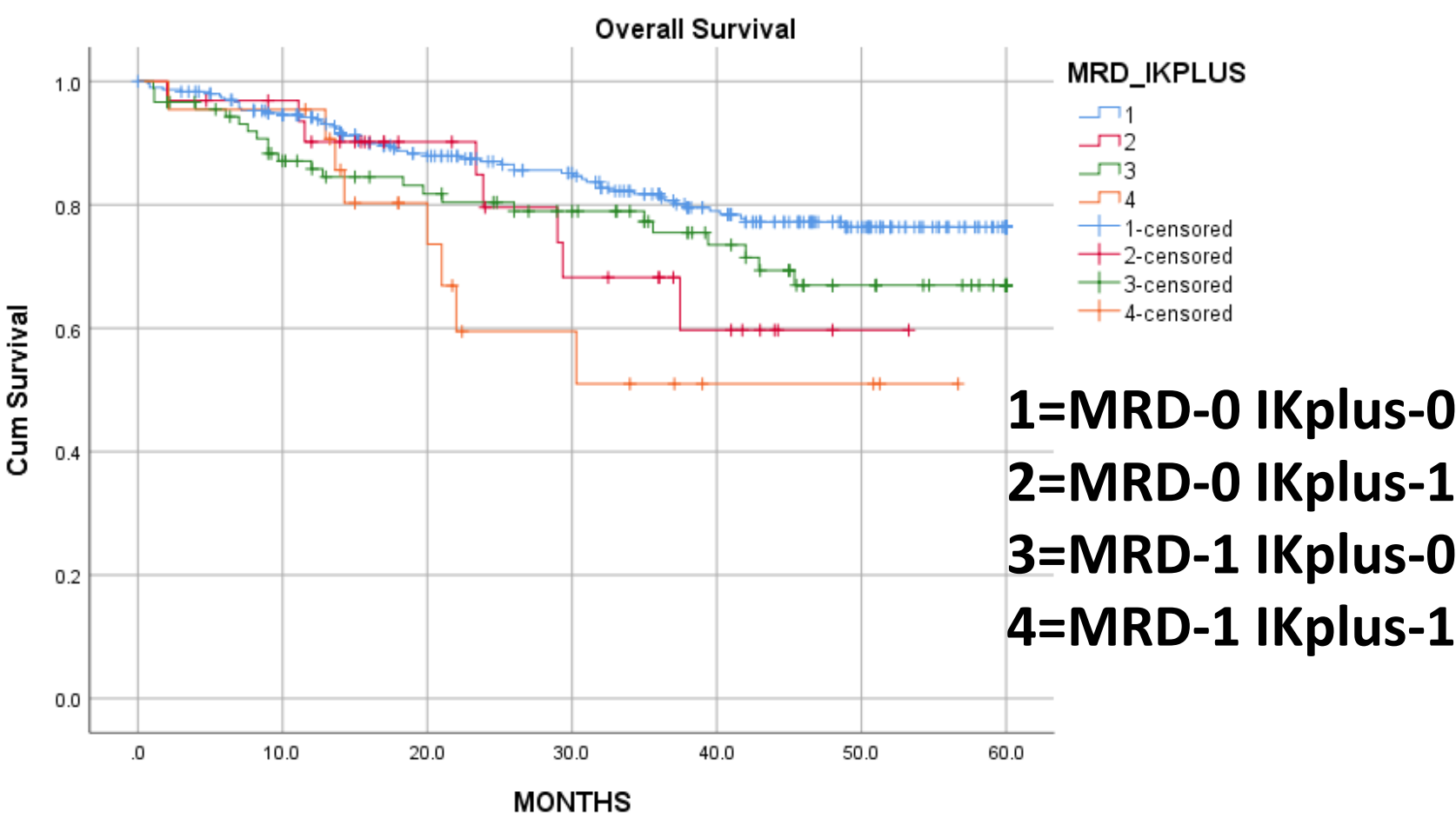
Supplementary Fig 5b:-MRD_IK EFS



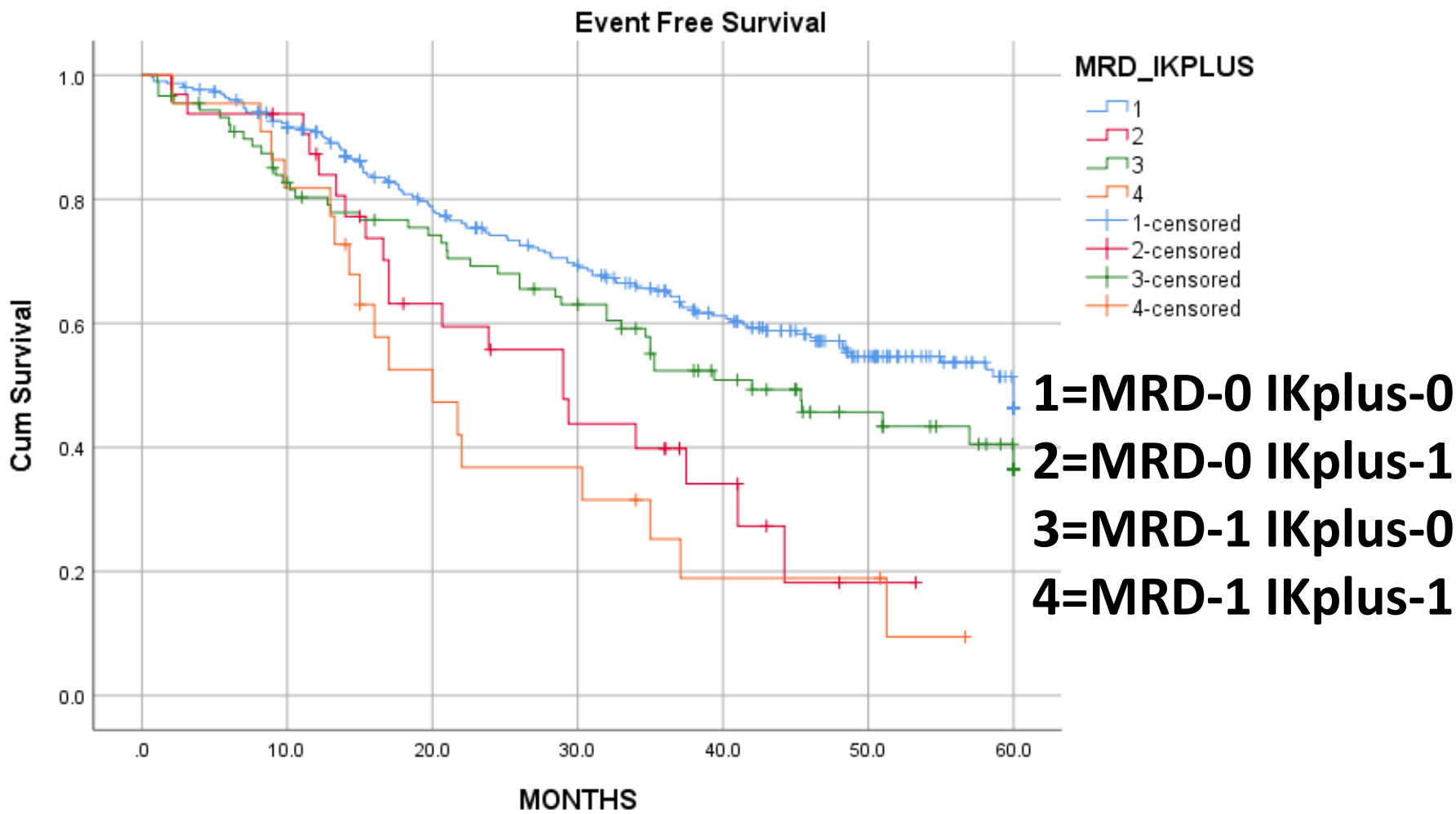
Supplementary Fig 5c:-MRD_IK RR



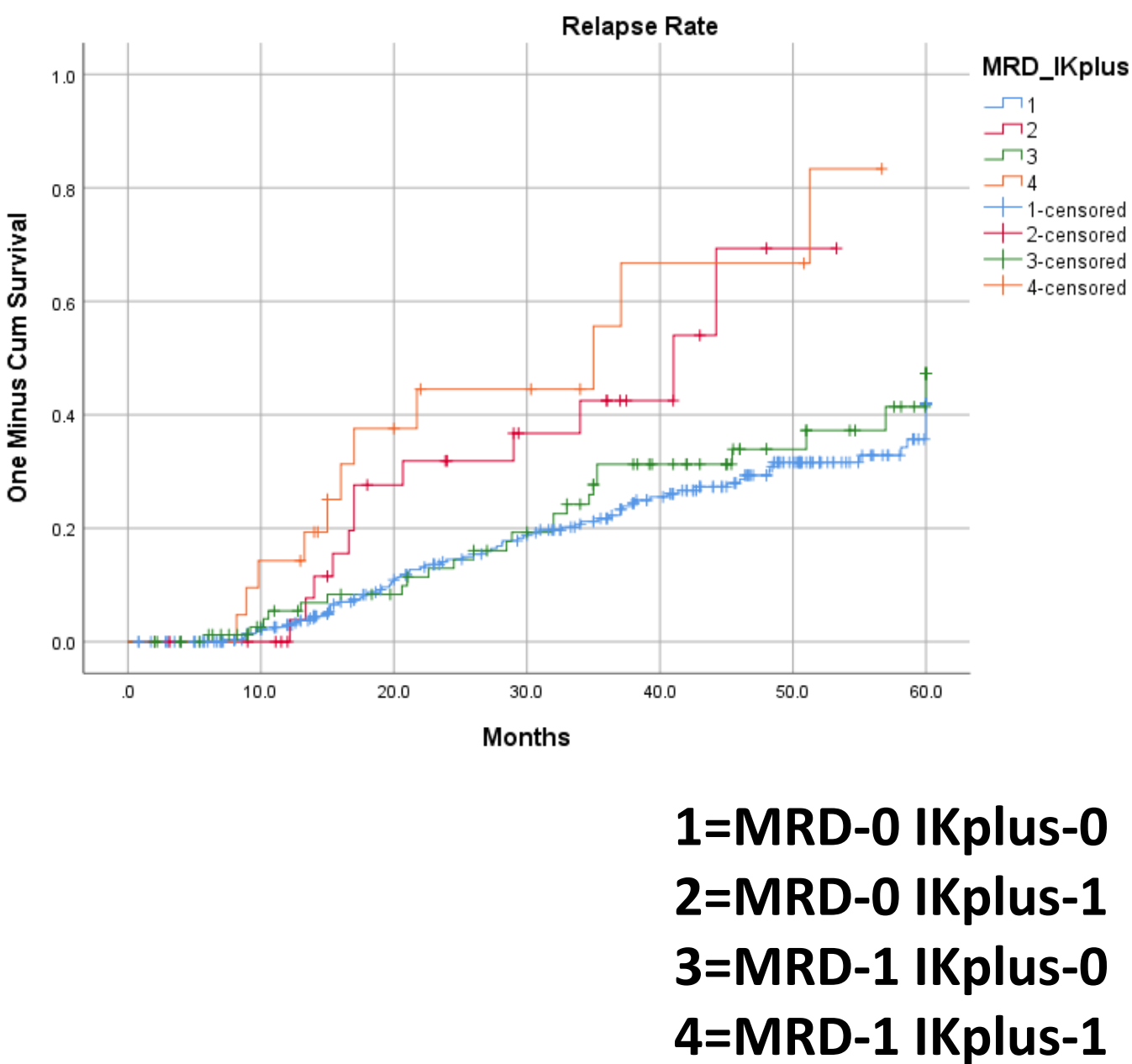
Supplementary Fig 5d:-MRD_IKplus OS



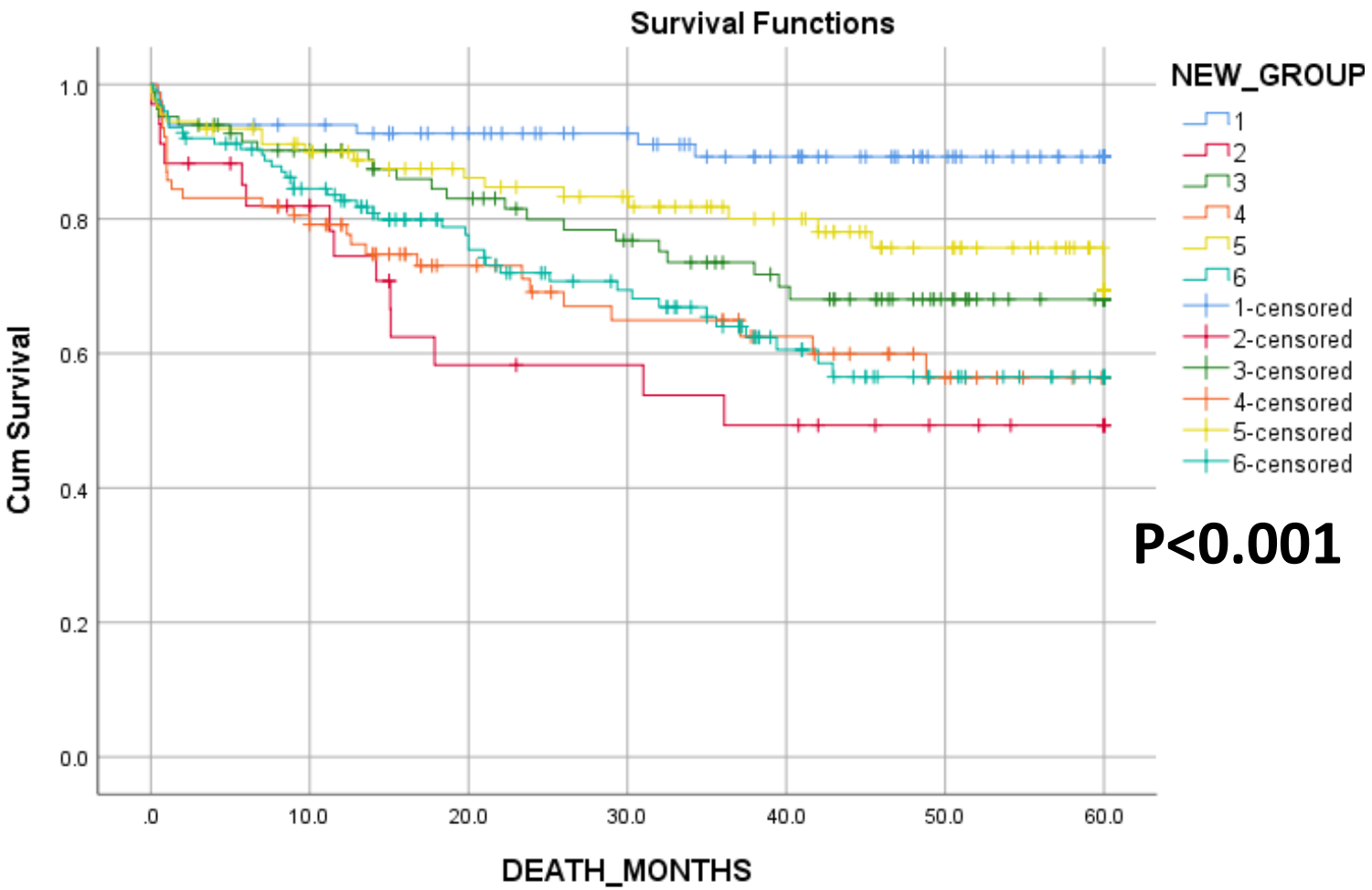
Supplementary Fig 5e:-MRD_IKplus EFS



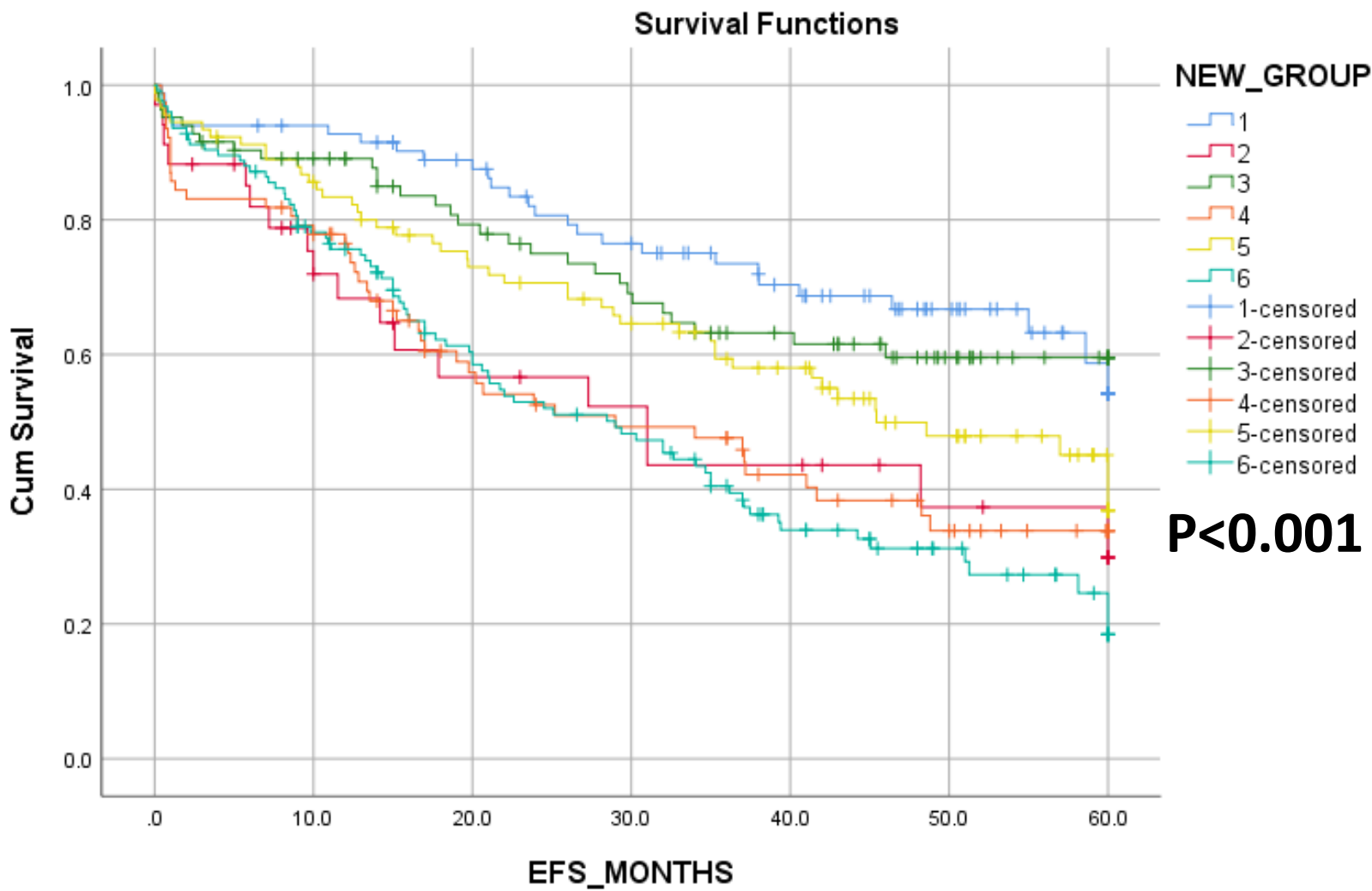
Supplementary Fig 5f:-MRD_IKplus RR



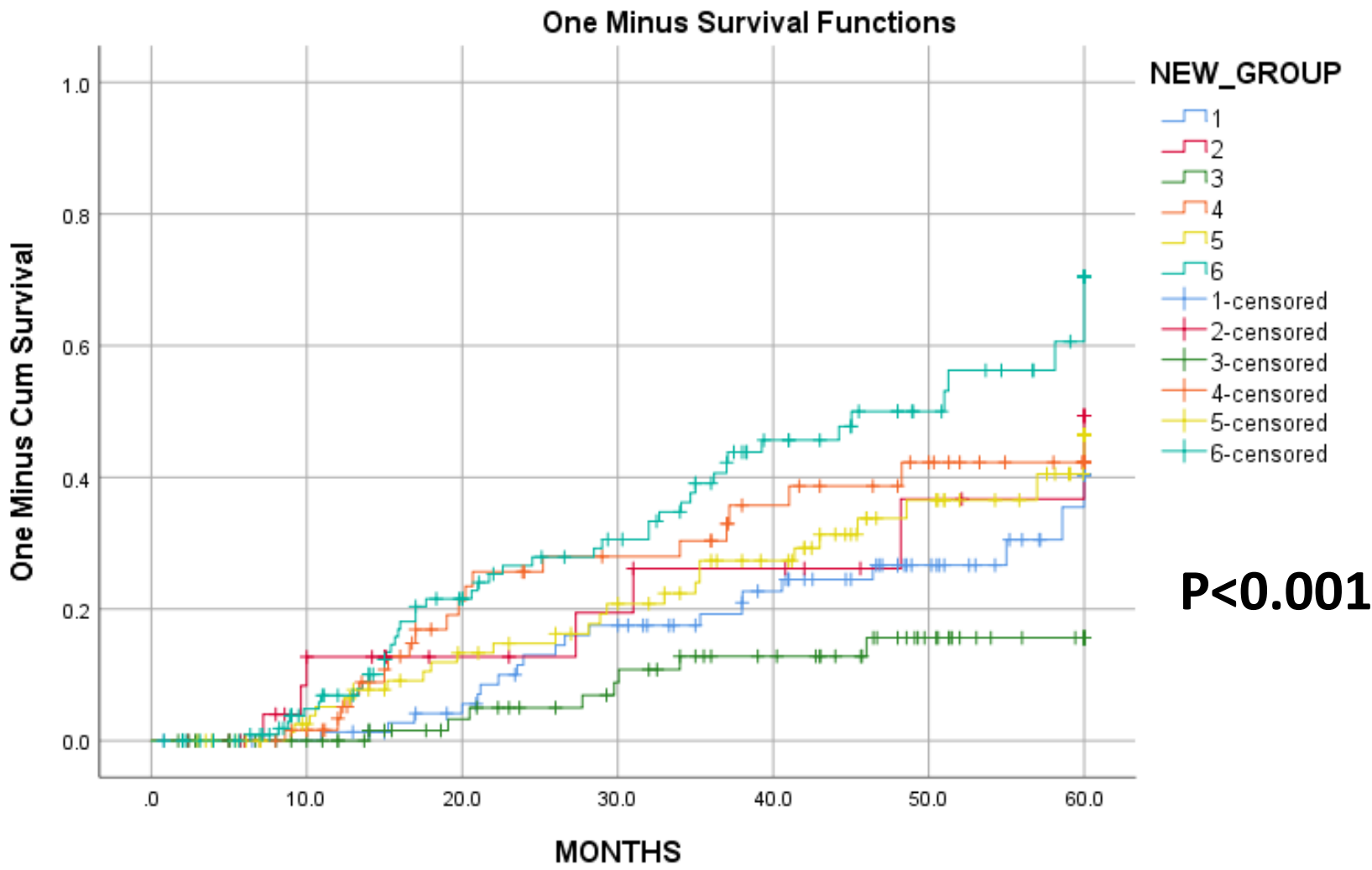
Supplementary Fig 6a:-Overall survival (OS) of proposed new integrated risk stratification groups



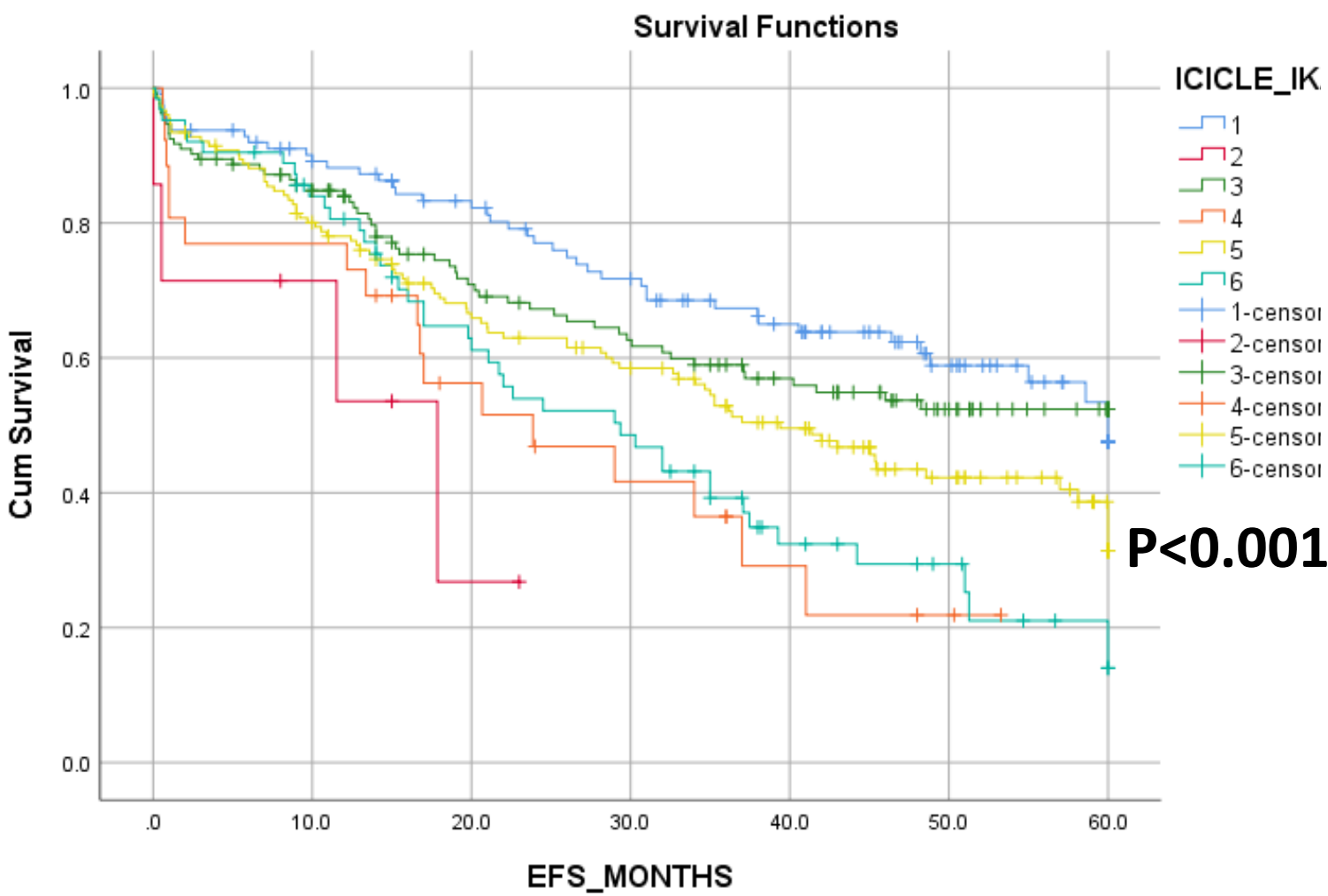
Supplementary Fig 6b:-EFS_NEW GROUP



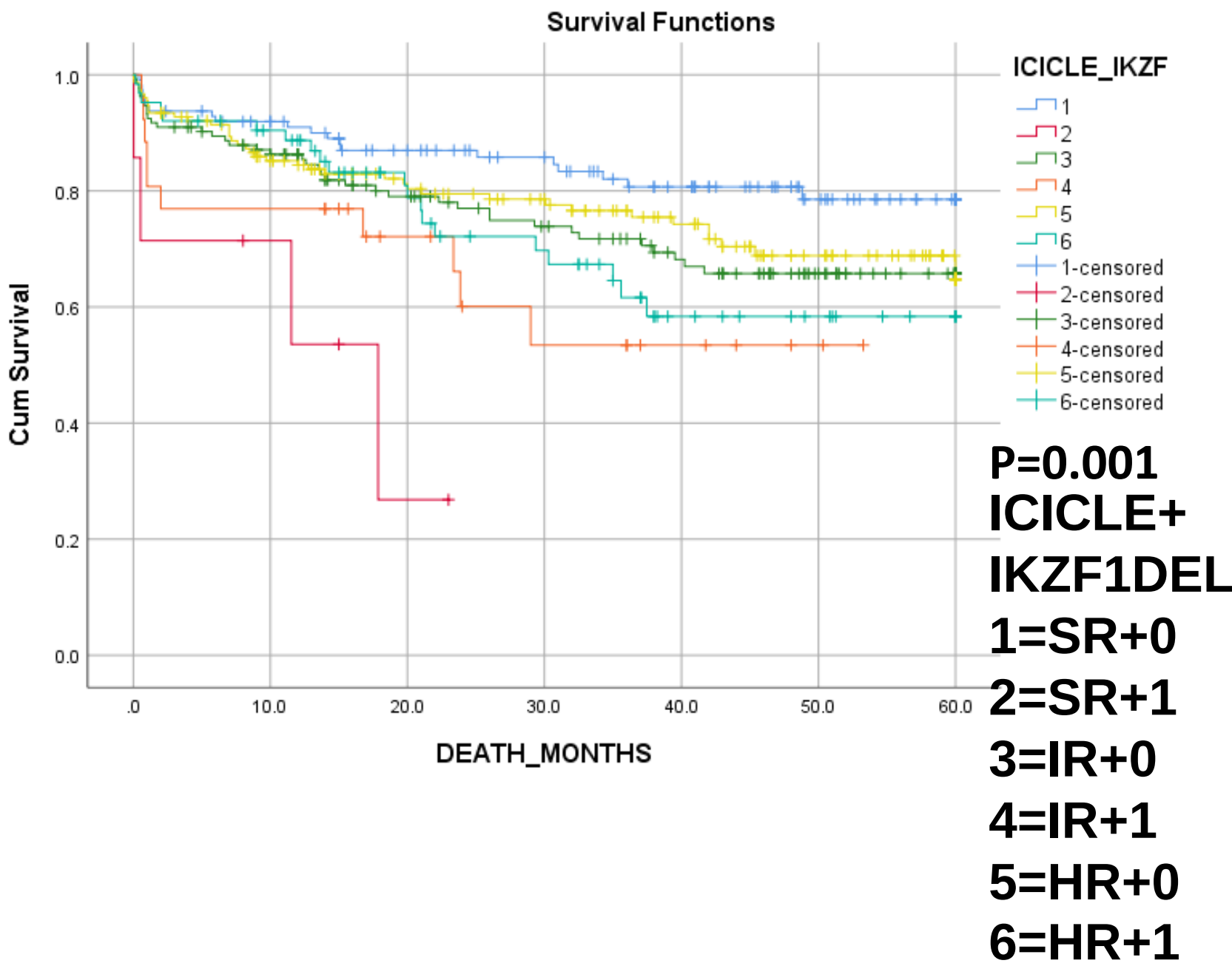
Supplementary Fig 6c:-RR_NEW GROUP



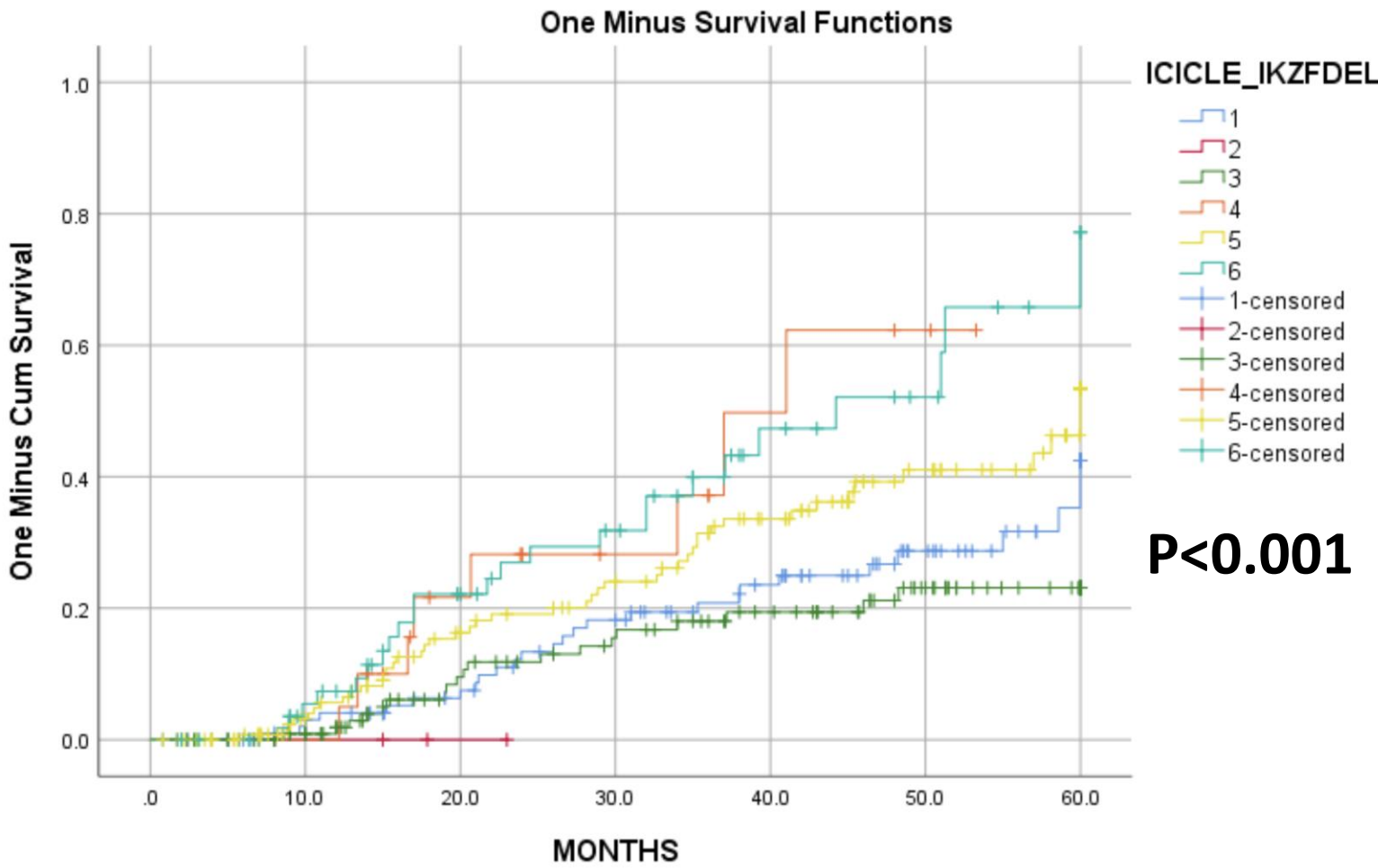
Supplementary Fig 6d:-EFS_ICICLE+IKZF DEL



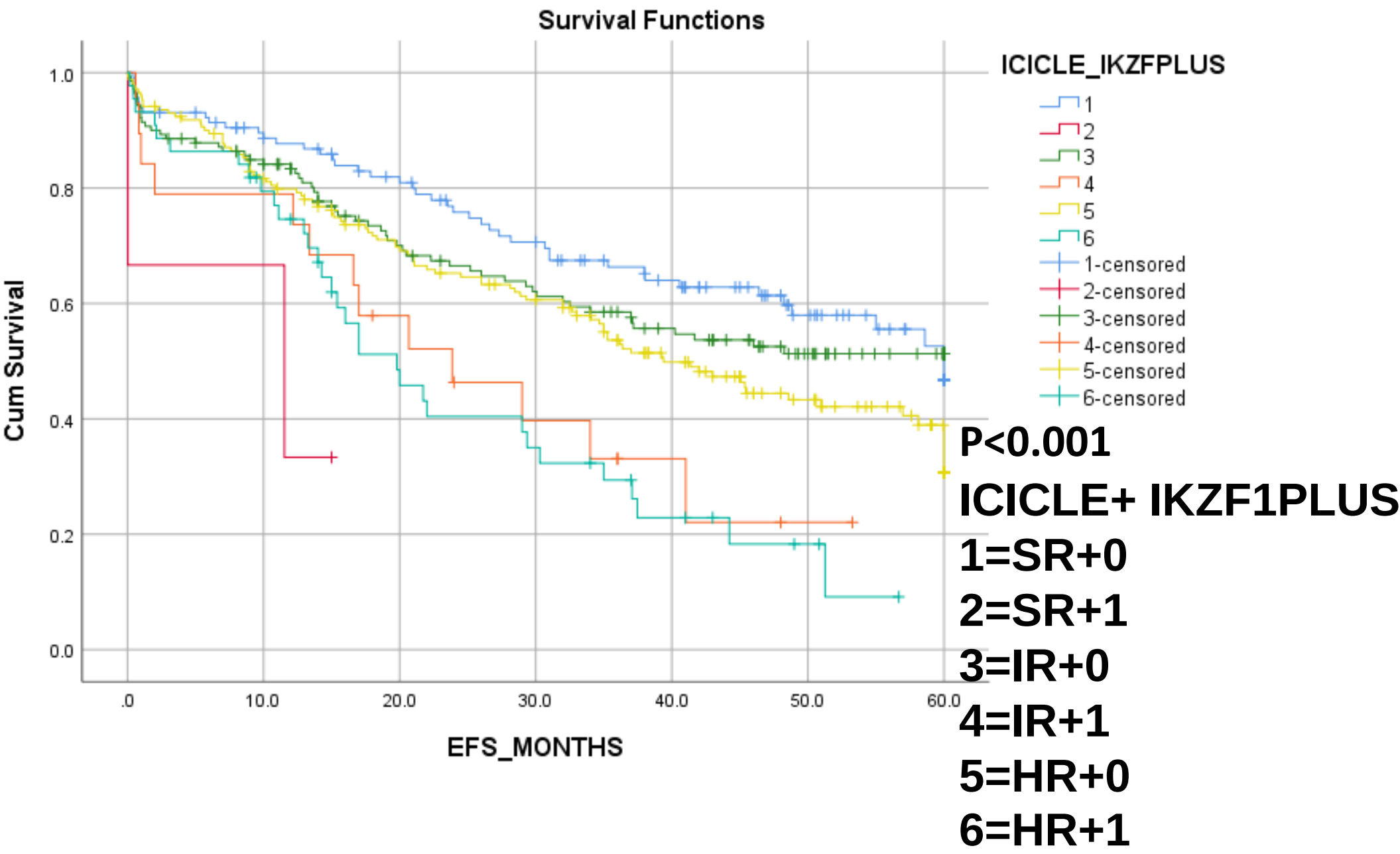
Supplementary Fig 6e:-OS_ICICLE+IKZF DEL



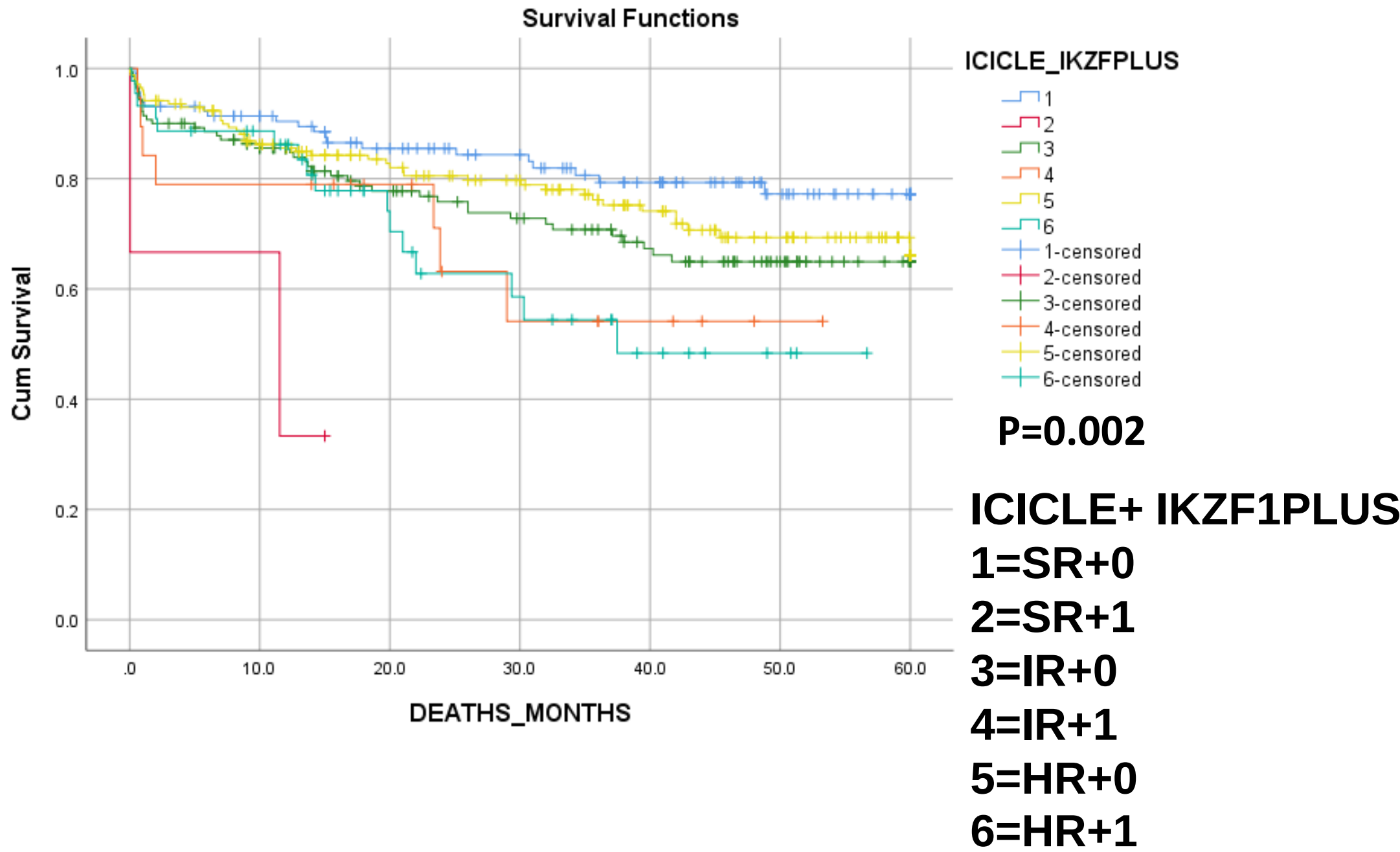
Supplementary Fig 6f:-Relapse rate (RR) of ICICLE risk groups with *IKZF1* deletion status (n=493)



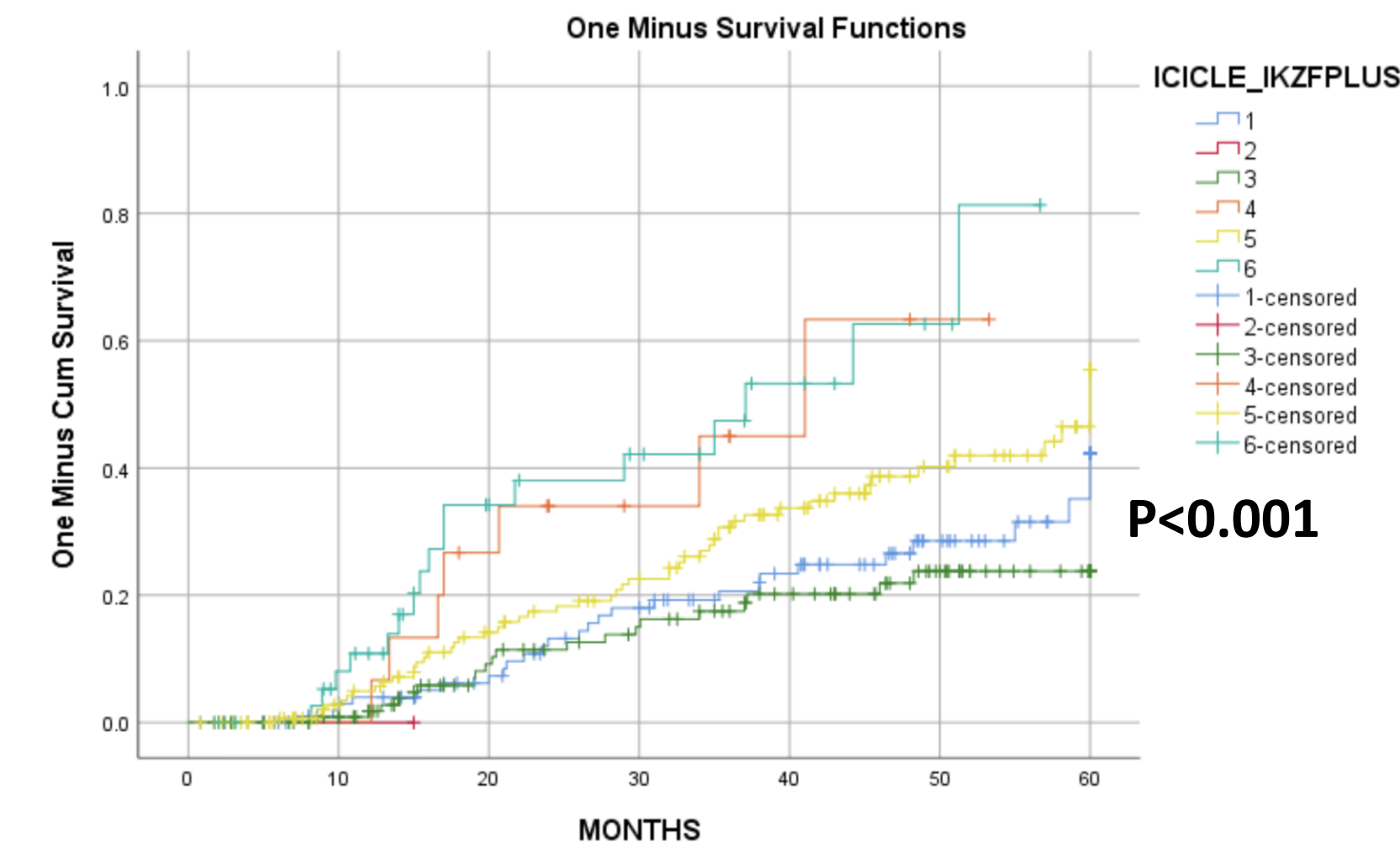
Supplementary Fig 7a:-EFS_ICICLE+IKZF PLUS



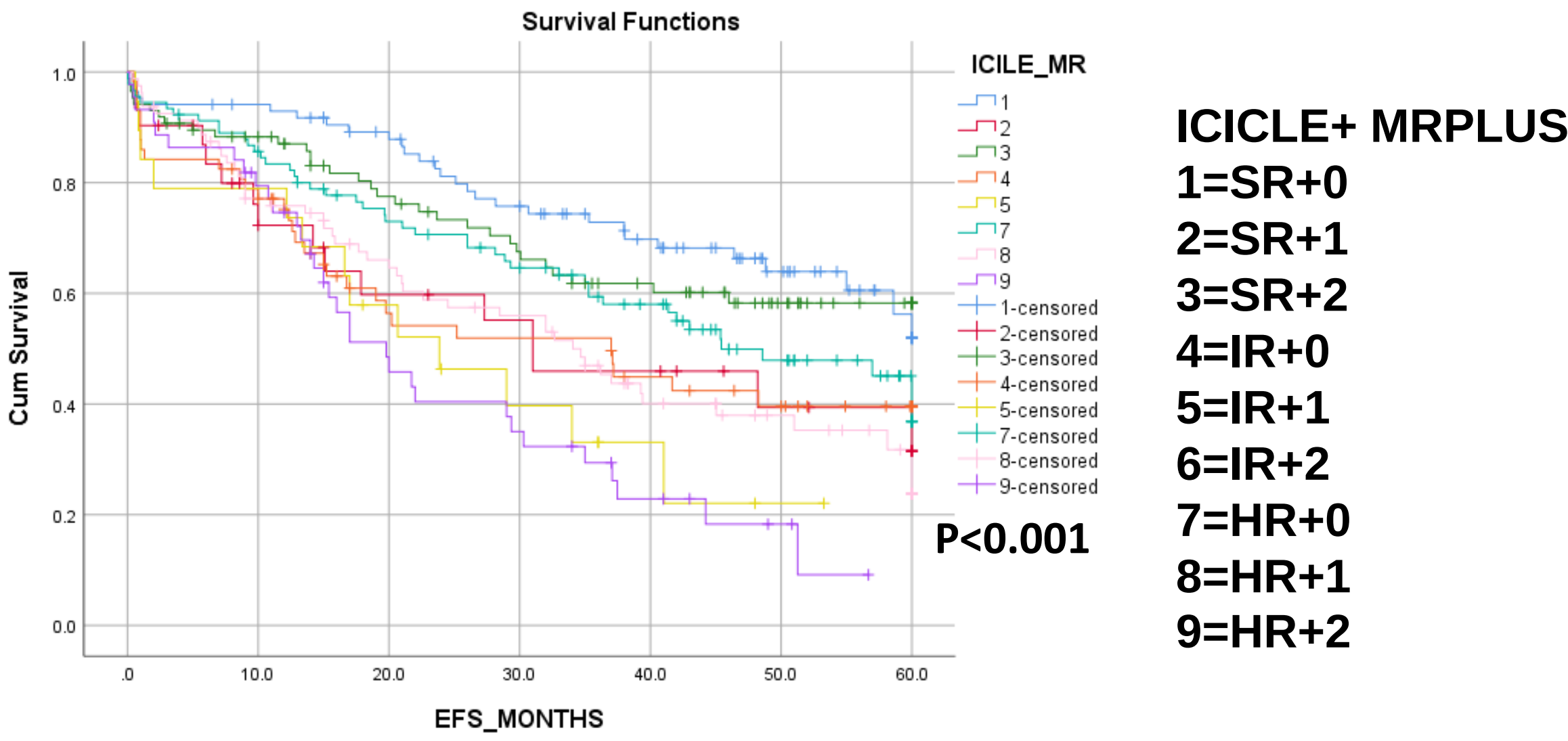
Supplementary Fig 7b:-OS_ICICLE+IKZF PLUS



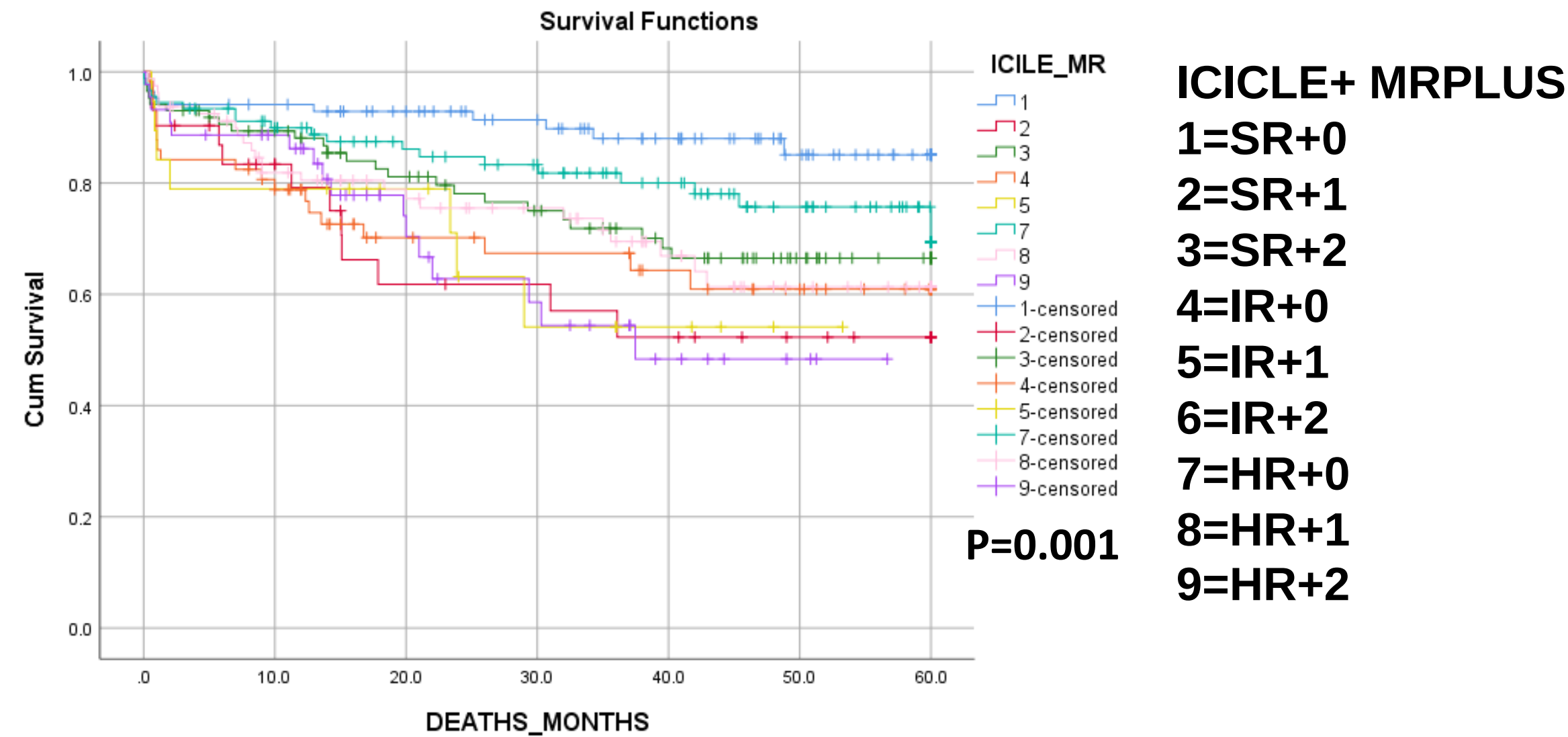
Supplementary Fig 7c:-Relapse rate (RR) of ICICLE risk groups with *IKZF1^{plus}* profile (n=493)



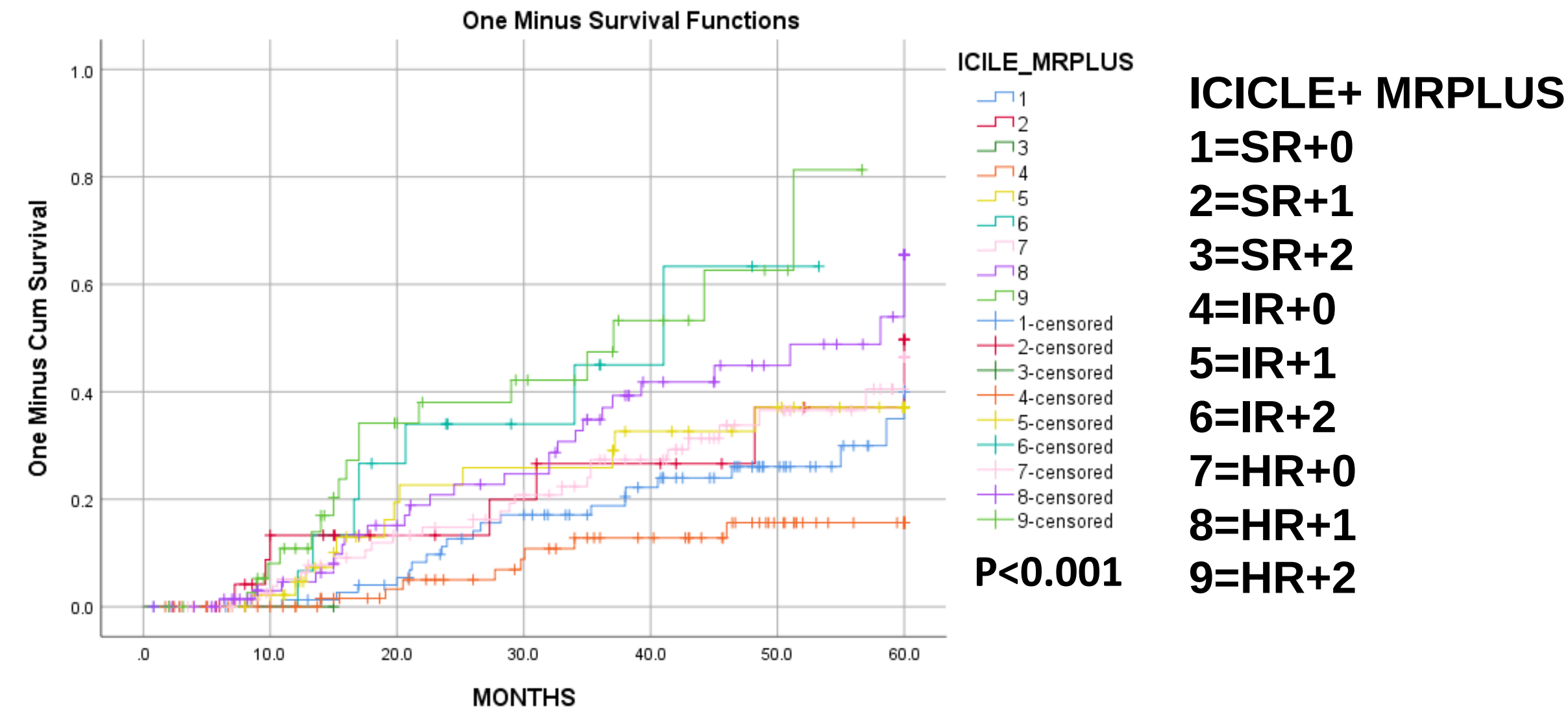
Supplementary Fig 7d:-EFS_ICICLE+MR PLUS



Supplementary Fig 8a:-OS_ICICLE+MR PLUS



Supplementary Fig 8b:-RR_ICICLE+MR PLUS



Supplementary Fig 8c:-EFS_Combined ICICLE+UKALL-CNA (Groups 1,3,5 vs 2,4,6

