



Elevated Monocytic Myeloid-Derived Suppressor Cells Are Associated with Muscle Mass Loss and Reduced Efficacy of Immune Checkpoint Inhibitors in Patients with Non-Small Cell Lung Cancer: A Prospective Study

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Background

Sarcopenia, characterized by muscle loss, weakness, and diminished physical function, has been reported as a prognostic factor for immunotherapy in cancers^{1,2}. Our previous prospective study demonstrated that non-small cell lung cancer (NSCLC) patients with sarcopenia or pre-sarcopenia exhibited poor responses to immune checkpoint inhibitors (ICIs)³. In this study, we evaluated the relationship between immune status and the efficacy of ICIs in NSCLC patients with muscle mass loss (sarcopenia + pre-sarcopenia).

Materials and Methods

Patients with stage III/IV or recurrent NSCLC receiving ICI as first-line treatment at Niigata University Medical and Dental Hospital were eligible. Eligible patients underwent muscle mass measurement using bioelectrical impedance analysis, grip strength measurement, walking speed measurement, and lifestyle questionnaire related to physical activity before treatment. Before ICI treatments, peripheral mononuclear blood cells (PBMCs) were collected, and immune phenotypic data was obtained by flow cytometry (BD FACS Celesta Multicolor Flow Cytometer). PBMCs were obtained from 44 patients from October 2019 through September 2024. Eight patients and 9 patients were diagnosed with sarcopenia and pre-sarcopenia, respectively.

		Normal N = 27 (%)	Muscle mass loss N = 17 (%)	p-value
Age	Median (range)	68 (36-81)	73 (61-87)	0.0114 ^{*1}
Sex	Male	22 (81)	17 (100)	0.1392 ^{*2}
	Female	5 (19)	0 (0)	
ECOG PS	0	6 (22)	1 (6)	0.0052 ^{*2}
	1	20 (74)	9 (53)	
	2	1 (4)	7 (41)	
Smoking status	Never	3 (11)	0 (0)	0.2722 ^{*2}
	Current/former	24 (89)	17 (100)	
Histology	Squamous	5 (18)	3 (18)	0.5583 ^{*2}
	Adenocarcinoma	21 (78)	11 (64)	
PD-L1 TPS	Others	1 (4)	3 (18)	0.8948 ^{*2}
	< 1%	8 (30)	6 (35)	
	1-49%	8 (30)	6 (35)	
	≥ 50%	9 (33)	5 (30)	
Type of therapy	Unknow	2 (7)	0 (0)	0.2065 ^{*2}
	PD-1 inhibitor	3 (11)	4 (24)	
	PD-1 + CTLA-4 inhibitor	3 (11)	4 (24)	
	ICI + Chemo	21 (78)	9 (52)	

Table 1. Patient characteristics stratified by muscle mass loss classification.

Muscle mass loss group was significantly older than normal group and had a higher proportion of pts with poor PS.

^{*1} Student's t-test, ^{*2} Fisher's exact test

Results

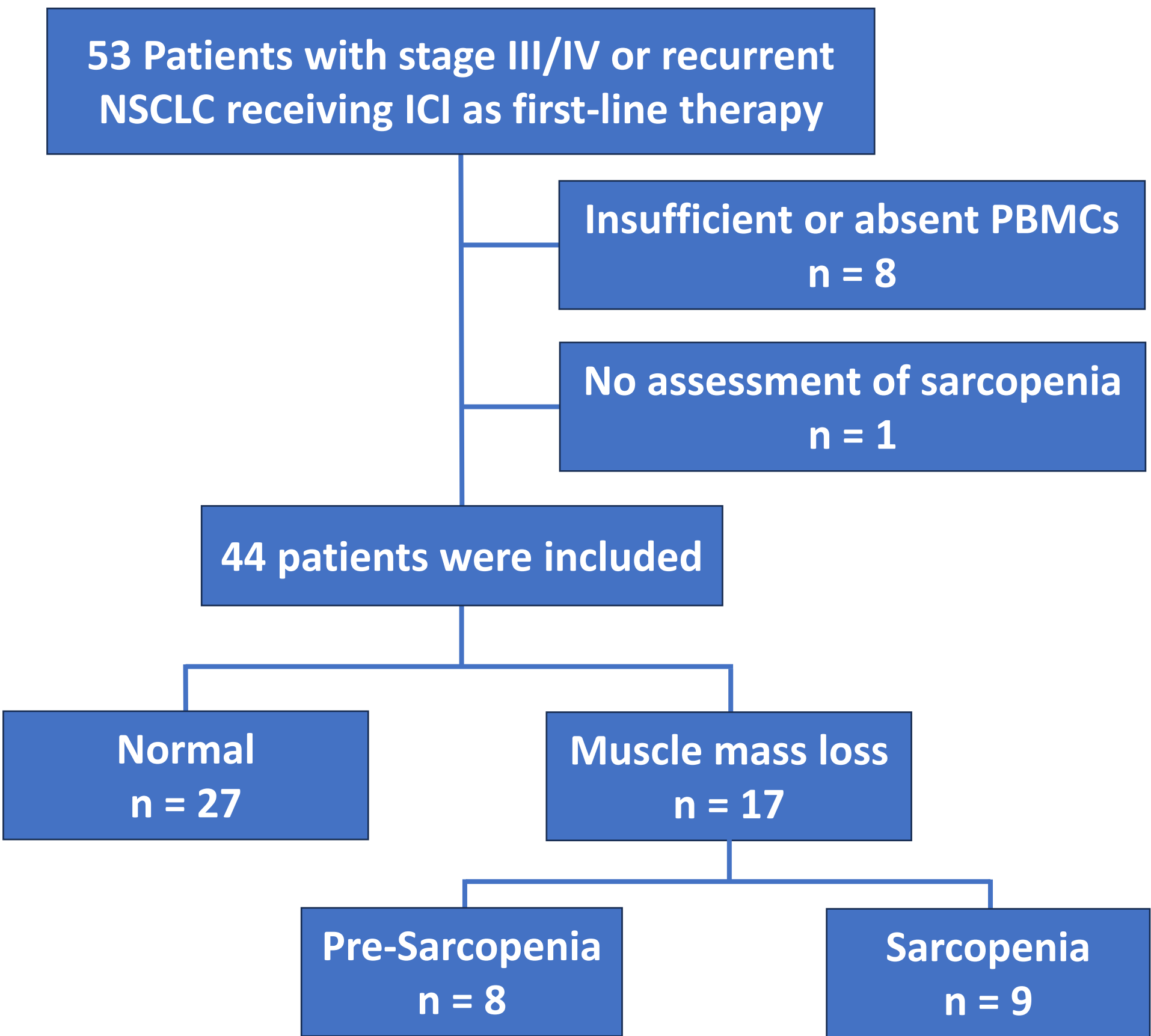


Figure 1. Study flow diagram.

Pre-sarcopenia: Reduction in muscle mass, but no decline in muscle strength or physical function is observed.

Sarcopenia: Decline in muscle strength, muscle mass, and physical function is confirmed.

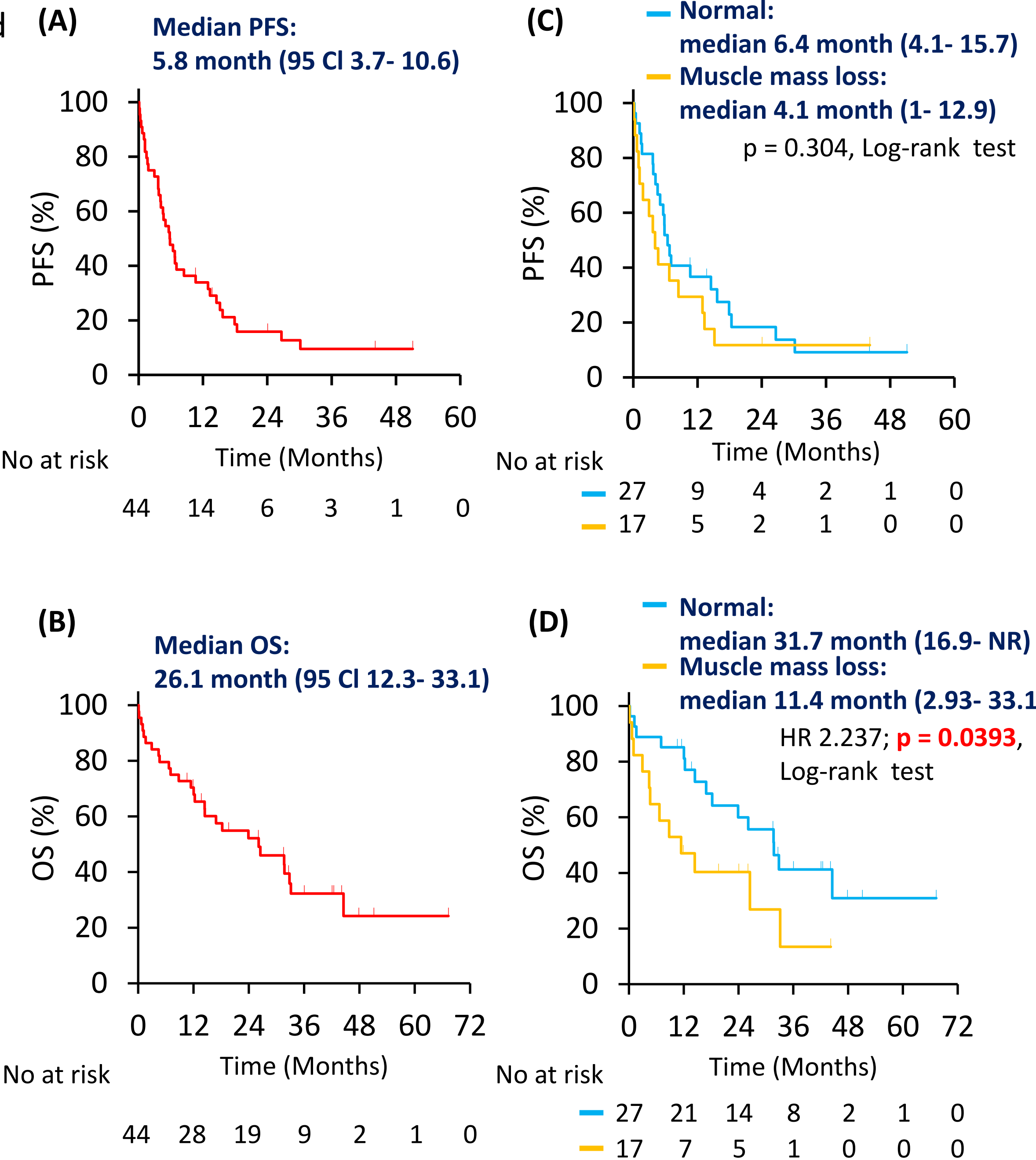


Figure 2. The Kaplan-Meier curve for all pts (A, B). The Kaplan Meier curves stratified by muscle mass loss classification (C, D).

Muscle mass loss group showed a significantly shorter OS compared to normal group.

Conclusions

- M-MDSCs may play a critical role in immune suppression in NSCLC patients with muscle mass loss and could be associated with poor OS following ICI treatment.**
- To improve the survival outcome of patients with muscle mass loss, it is essential to establish strategies to overcome M-MDSCs-mediated immune suppression.**

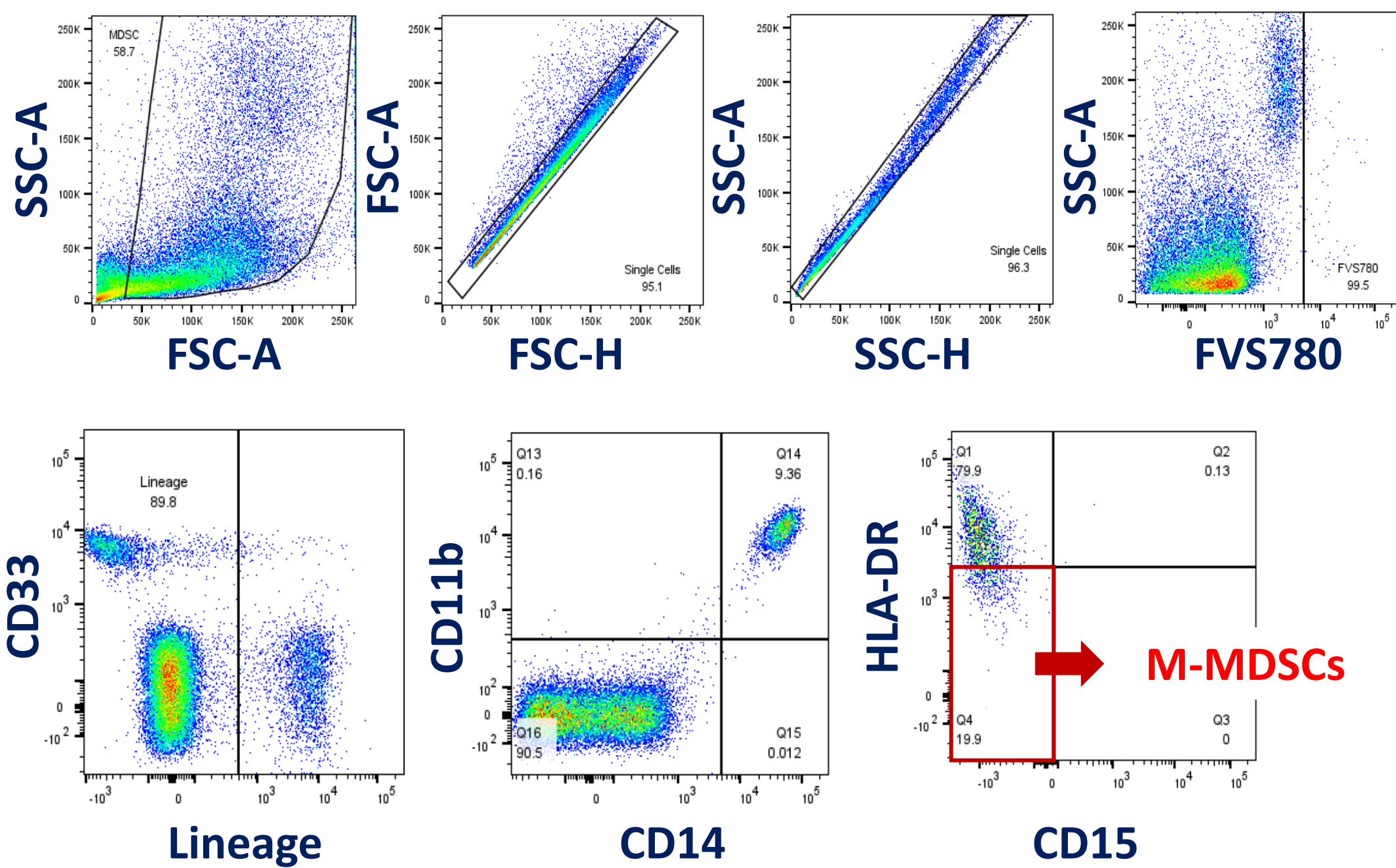


Figure 3. Flow cytometry gating strategy

After exclusion of doublets and dead cells, lineage-negative cells were selected and subsequently gated on CD11b⁺CD14⁺ cells. Monocytic myeloid-derived suppressor cells (M-MDSCs) were defined as Lineage⁻CD11b⁺CD14⁺CD15⁺HLA-DR^{low} cells.

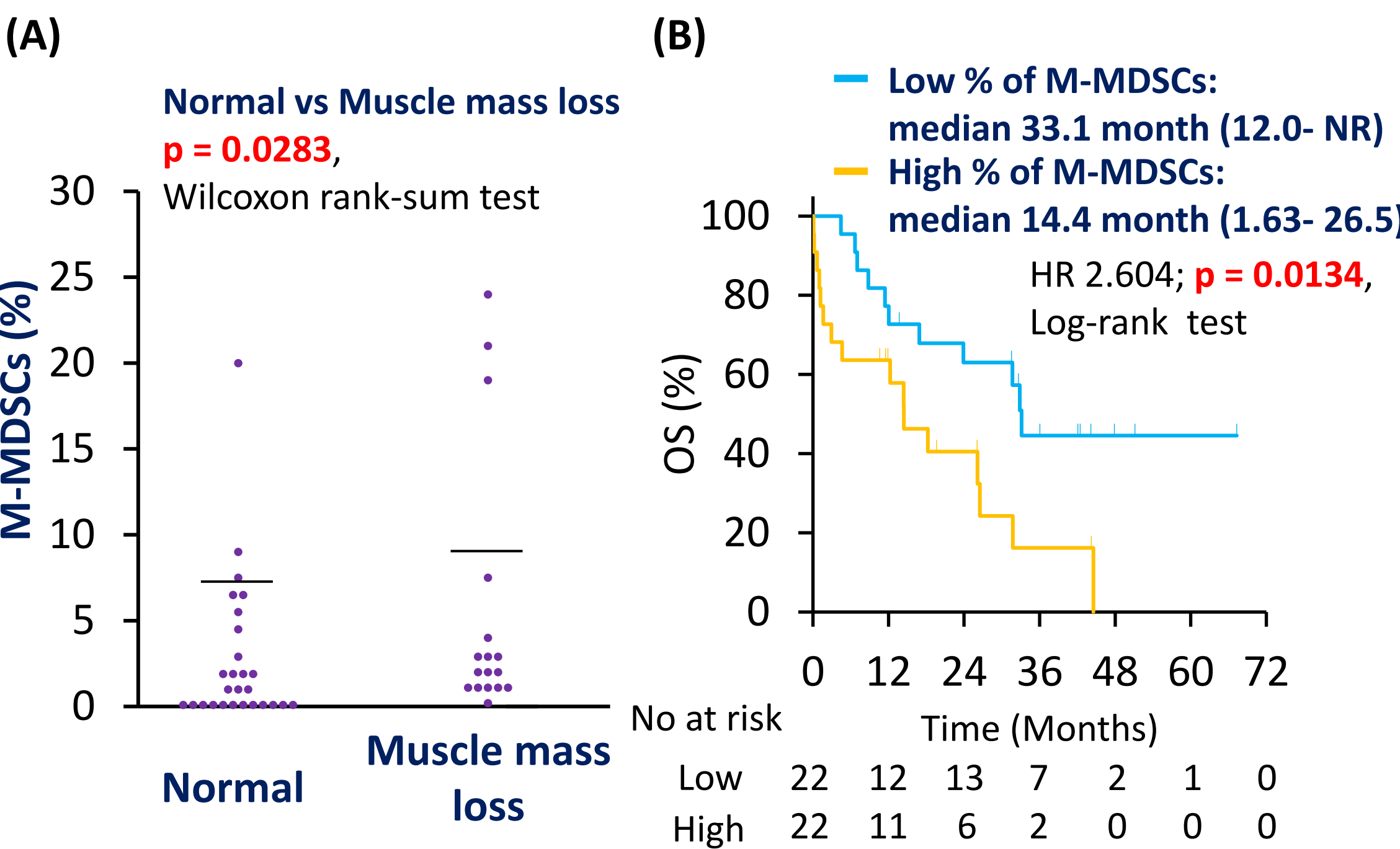


Figure 4. The relationship between M-MDSCs and Muscle mass loss (A). The Kaplan Meier curves stratified by the percentage of M-MDSCs (B).

The percentage of M-MDSCs was significantly higher with muscle mass loss group. Pts with a high percentage of M-MDSCs showed a significantly shorter OS compared to pts with a low percentage.

		M-MDSCs low n = 22 (%)	M-MDSCs high n = 22 (%)	p-value
Age	Median (range)	71 (36-87)	70 (54-81)	0.1919 ^{*1}
Sex	Male	17 (77)	22 (100)	0.0485 ^{*2}
	Female	5 (23)	0 (0)	
ECOG PS	0	6 (27)	1 (5)	0.024 ^{*2}
	1	15 (68)	14 (63)	
	2	1 (5)	7 (32)	
Smoking status	Never	3(14)	0 (0)	0.2326 ^{*2}
	Current/former	19(86)	22 (100)	
Histology	Squamous	6 (27)	2 (9)	0.2451 ^{*2}
	Adenocarcinoma	15 (68)	17 (77)	
PD-L1 TPS	Others	1 (5)	3 (14)	0.0491 ^{*2}
	< 1%	11 (50)	3 (14)	
	1-49%	6 (27)	8 (36)	
	≥ 50%	4 (18)	10 (45)	
Type of therapy	Unknow	1 (5)	1 (5)	0.0263 ^{*2}
	PD-1 inhibitor	1 (5)	6(27)	
	PD-1 + CTLA-4 inhibitor	6 (27)	1 (5)	
	ICI + chemo	15 (68)	15 (68)	

Table 2. Patient characteristics stratified by the percentage of M-MDSCs.

Compared with M-MDSCs low group, the high group was entirely male, with more pts having poor PS and high PD-L1 TPS, and ICI monotherapy was more frequently selected.

^{*1} Student's t-test, ^{*2} Fisher's exact test

	Univariate		
	HR	95%CI	P-value
Age (≥75/<75)	1.257	0.526-3.006	0.607
Sex (female/male)	0.383	0.09-1.63	0.194
Smoking status (+/-)	2.672	0.361-19.776	0.336
PS (2/0-1)	3.499	1.458-8.398	0.0051
Histology (nonsq/sq)	2.45	0.732-8.205	0.146
PD-L1 TPS (<1%/≥1%)	0.667	0.286-1.556	0.349
Brain metastasis (+/-)	0.645	0.222-1.874	0.42
Liver metastasis (+/-)	2.019	0.467-8.72	0.347
NLR (≥5/<5)	1.127	0.521-2.436	0.762
Alb (<3.5/≥3.5)	1.712	0.8-3.663	0.166
LDH (≥225/<225)	0.996	0.4667-2.125	0.992
CRP (≥0.2/<0.2)	1.161	0.438-3.078	0.764
PMN-MDSCs (high/low)	1.536	0.705-3.35	0.28
M-MDSCs (high/low)	2.604	1.188-5.709	0.0168
Muscle mass loss/Normal	2.237	1.02-4.903	0.0444

Table 3. Univariate Cox proportional hazards analysis for OS.

Polymorphonuclear MDSCs (PMN-MDSCs) were defined as Lineage⁻CD11b⁺CD14⁺CD15⁺ cells.

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