

Variable	Total		Enrolled		P
	No. of Patients (n=2657)	%	No. of Patients (n=169)	%	
Age, years					0.335
Mean	57.7		58.5		
SD	12.2		11.7		
Gender					0.747
Male	1580	59.5	98	58.0	
Female	1077	40.5	71	42.0	
Tumor location					0.128
Right hemicolon	652	24.5	47	27.8	
Left hemicolon	1197	45.1	83	49.1	
Rectum	808	30.4	39	23.1	
Tumor grade					0.892
1	24	0.9	2	1.2	
2	1911	71.9	123	72.8	
3	722	27.2	44	26.0	
Histological subtype					0.169
Mucinous	365	13.7	30	17.8	
Other	2292	86.3	139	82.2	
Tumor stage					0.437

T ₁	111	4.2	8	4.7	
T ₂	388	14.6	25	14.8	
T ₃	1789	67.3	120	71.0	
T ₄	369	13.9	16	9.5	
Regional LNs metastasis					0.191
N ₀	1729	65.1	121	71.6	
N ₁	620	23.3	30	17.8	
N ₂	308	11.6	18	10.7	
Perineural invasion					0.259
Negative	2168	81.6	144	85.2	
Positive	489	18.4	25	14.8	
Vascular invasion					0.128
Negative	2153	81.0	145	85.8	
Positive	504	19.0	24	14.2	
Number of retrieved LNs					0.336
<12	1147	43.2	66	39.1	
≥12	1510	56.8	103	60.9	
Chemotherapy					0.577
Yes	1461	55.0	97	57.4	
No	1196	45.0	72	42.6	
Radiotherapy					0.549
Yes	106	4.0	8	4.7	

No

2551

96.0

161

95.3

Abbreviations: SD, Standard Deviation. AJCC, American Joint Committee on Cancer, 7th Edition. LNs, Lymph Nodes.

Table S1. Comparison of clinicopathologic characteristics between enrolled and total pMMR CRC patients.

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i>	HR	95%CI	<i>P</i>
Tumor location (rectum)	2.01	(1.03, 3.93)	0.040	3.32	(0.71, 15.63)	0.129
Regional LNs metastasis						
≥N1	4.70	(1.54, 14.39)	0.007	0.79	(0.16, 3.91)	0.768
Distant metastasis	10.18	(3.32, 31.21)	<0.001	9.82	(2.02, 47.71)	0.005
AJCC stage ≥3	13.55	(3.00, 61.17)	0.001	7.55	(0.85, 67.34)	0.070
Vascular invasion	7.02	(1.83, 26.84)	0.004	5.84	(1.77, 19.33)	0.004
Number of retrieved						
LNs (≥12)	0.23	(0.07, 0.75)	0.014	1.62	(0.51, 5.18)	0.418
Radiotherapy	5.59	(1.72, 18.18)	0.004	10.51	(2.07, 53.35)	0.005
TIL Numbers (>40)	0.46	(0.15, 1.42)	0.177	-	-	-
PD/L1 expression						
(Total)	0.45	(0.15, 1.34)	0.149	0.96	(0.30, 3.11)	0.948
PD/L1 expression (TIL)	0.69	(0.45, 1.07)	0.095	0.42	(0.10, 1.77)	0.238

Abbreviations: HR, Hazard Ratio. dMMR, Mismatch Repair-deficient. pMMR, Mismatch Repair-proficient. AJCC, American Joint Committee on Cancer, 7th Edition. LNs, Lymph Nodes. CA19-9, Carbohydrate Antigen 19-9. PD/L1, Programmed Cell Death 1. TIL, Tumor Infiltrating Lymphocytes.

Table S2. Univariate and Multivariate analyses of prognostic factors for overall survival in dMMR patients.

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i>	HR	95%CI	<i>P</i>
Distant metastasis	24.99	(5.70, 109.56)	<0.001	10.67	(1.69, 67.23)	0.012
AJCC stage ≥ 3	13.97	(1.70, 114.55)	0.014	-	-	-
Vascular invasion	7.86	(1.76, 35.14)	0.007	19.00	(2.63,137.30)	0.004
No. of retrieved LNs (≥ 12)			0.223	2.57	(0.44,15.06)	0.294
Radiotherapy	16.21	(3.61, 72.78)	<0.001	13.81	(0.92,207.83)	0.058
TIL Numbers (>40)	0.80	(0.50, 1.27)	0.336	-	-	-
PD/L1 expression (Total)	0.39	(0.10, 1.50)	0.171	0.23	(0.02, 2.38)	0.219
PD/L1 expression (TIL)	0.70	(0.41, 1.20)	0.195	0.24	(0.02, 2.79)	0.254

Abbreviations: HR, Hazard Ratio. dMMR, Mismatch Repair-deficient. pMMR, Mismatch Repair-proficient. AJCC, American Joint Committee on Cancer, 7th Edition. LNs, Lymph Nodes. CA19-9, Carbohydrate Antigen 19-9. PD/L1, Programmed Cell Death 1. TIL, Tumor Infiltrating Lymphocytes.

Table S3. Univariate and Multivariate analyses of prognostic factors for overall survival in pMMR patients.

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i>	HR	95%CI	<i>P</i>
Tumor location						
(Rectum)	5.09	(2.19, 11.82)	<0.001	1.41	(0.37, 5.36)	0.615
Regional LNs						
metastasis \geq N1	3.55	(1.73, 7.27)	0.001	1.58	(0.20, 12.46)	0.667
Distant metastasis	5.89	(2.52, 13.78)	<0.001	3.39	(1.40, 8.19)	0.007
AJCC stage \geq 3	4.60	(2.18, 9.69)	<0.001	1.56	(0.15, 16.14)	0.711
Vascular invasion	4.02	(1.51, 10.74)	0.006	4.43	(1.56, 12.63)	0.005
Number of retrieved LNs <12	3.78	(1.80, 7.94)	<0.001	2.52	(0.94, 6.75)	0.066
Chemotherapy	2.85	(1.34, 6.07)	0.006	1.15	(0.41, 3.24)	0.786
Radiotherapy	9.51	(4.40, 20.57)	<0.001	9.64	(4.28, 21.71)	<0.001
CEA (\geq 5 ug/ml)	2.91	(1.40, 6.05)	0.004	1.85	(0.61, 5.59)	0.277
Lymphocyte (\geq 1.12 \times 10 ⁹ /l)	2.92	(1.35, 6.29)	0.006	1.28	(0.38, 4.23)	0.691
TIL Numbers (>40)	1.33	(0.56, 3.19)	0.519	-	-	-
PD/L1 expression (Total)	0.41	(0.20, 0.84)	0.015	0.65	(0.24, 1.75)	0.392
PD/L1 expression (TIL)	3.14	(1.34, 7.33)	0.008	0.61	(0.20, 1.88)	0.384

Abbreviations: HR, Hazard Ratio. dMMR, Mismatch Repair-deficient. pMMR, Mismatch Repair-proficient. AJCC, American Joint Committee on Cancer, 7th Edition. LNs, Lymph Nodes. CA19-9, Carbohydrate Antigen 19-9. PD/L1, Programmed Cell Death 1. TIL, Tumor Infiltrating Lymphocytes.

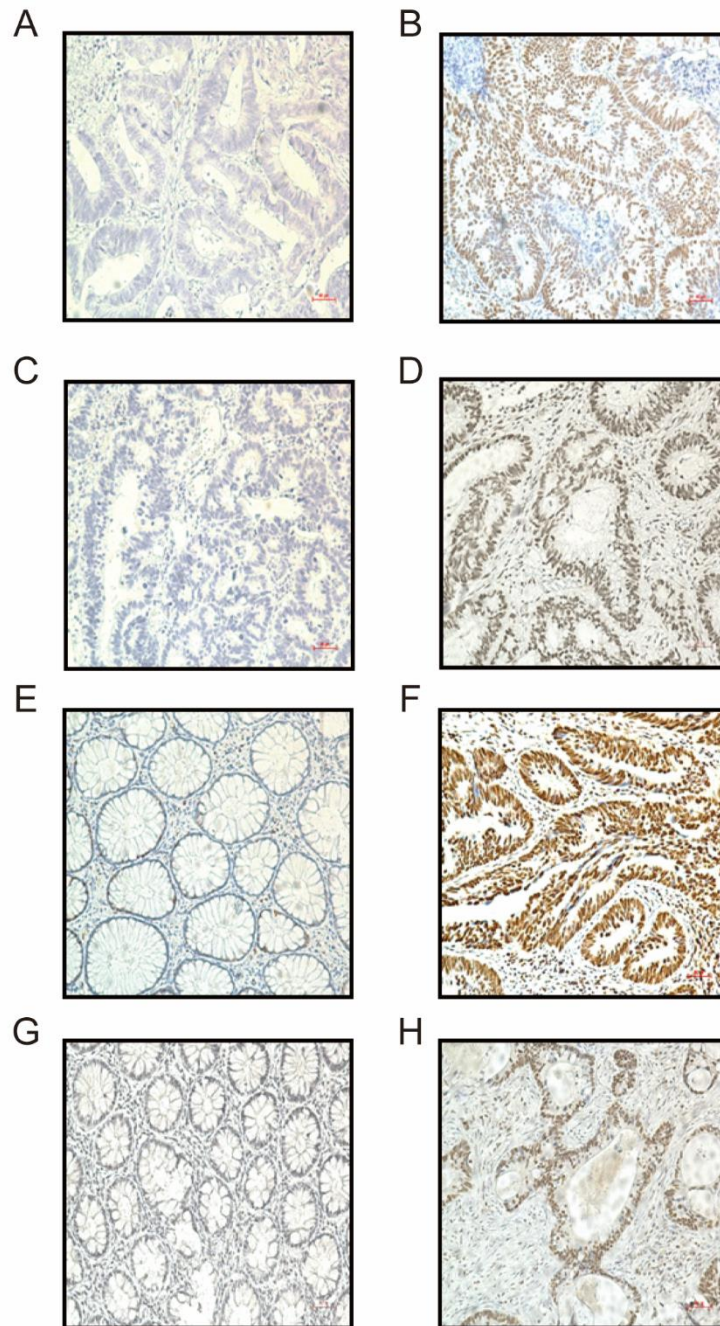
Table S4. Univariate and Multivariate analyses of prognostic factors or disease-free survival in dMMR patients.

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	<i>P</i>	HR	95%CI	<i>P</i>
Distant metastasis	24.99	(5.70, 109.56)	<0.001	7.36	(0.66, 82.50)	0.106
AJCC stage ≥ 3	13.97	(1.70, 114.55)	0.014	2.13	(0.15, 30.76)	0.579
Vascular invasion	7.86	(1.76, 35.14)	0.007	12.91	(1.54, 108.26)	0.018
Radiotherapy	16.21	(3.61, 72.78)	<0.001	22.42	(1.52, 331.10)	0.024
Lymphocyte ($\geq 1.12 \times 10^9/l$)	3.07	(0.78, 12.16)	0.110	0.70	(0.11, 4.58)	0.710
TIL Numbers (>40)	0.33	(0.09, 1.38)	0.132	-	-	-
PD/L1 expression (Total)	0.39	(0.10, 1.50)	0.171	0.23	(0.03, 4.44)	0.244
PD/L1 expression (TIL)	0.35	(0.07, 1.72)	0.195	0.37	(0.02, 2.69)	0.430

Abbreviations: HR, Hazard Ratio. dMMR, Mismatch Repair-deficient. pMMR, Mismatch Repair-proficient. AJCC, American Joint Committee on Cancer, 7th Edition. LNs, Lymph Nodes. CA19-9, Carbohydrate Antigen 19-9. PD/L1, Programmed Cell Death 1. TIL, Tumor Infiltrating Lymphocytes.

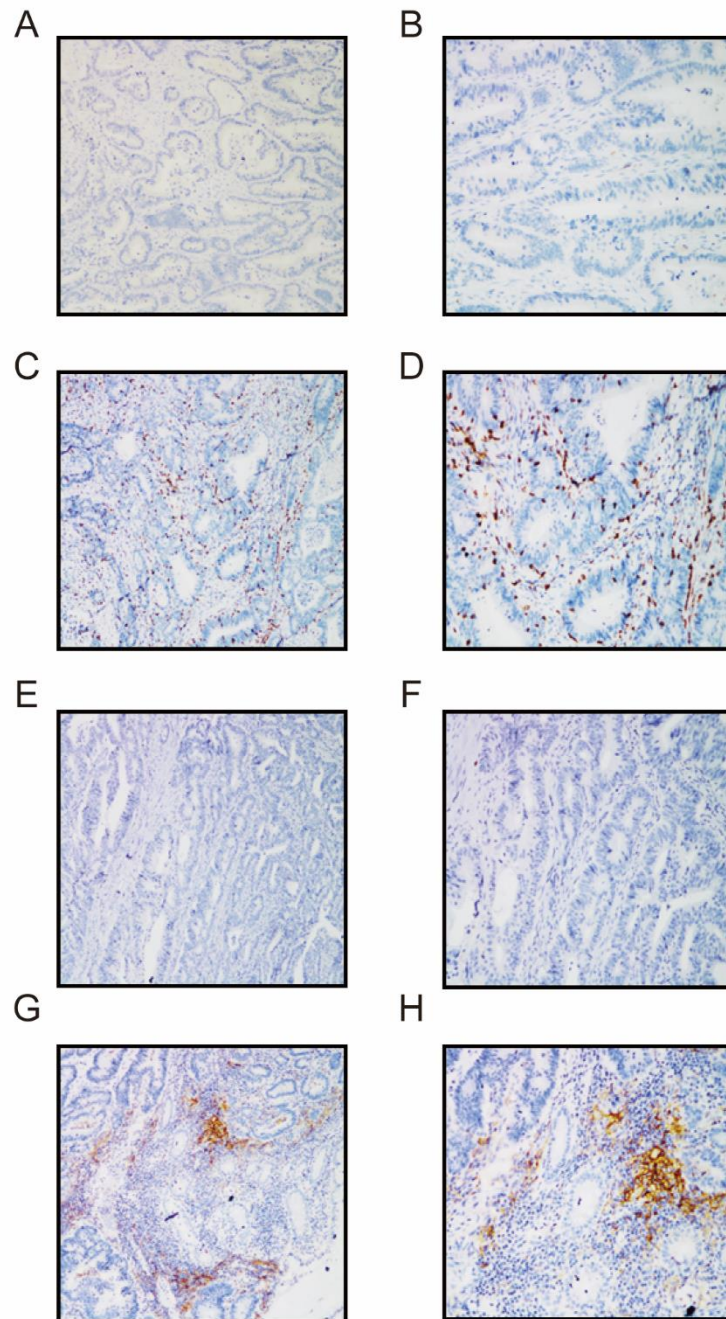
Table S5. Univariate and Multivariate analyses of prognostic factors or disease-free survival in pMMR patients.

Fig. S1



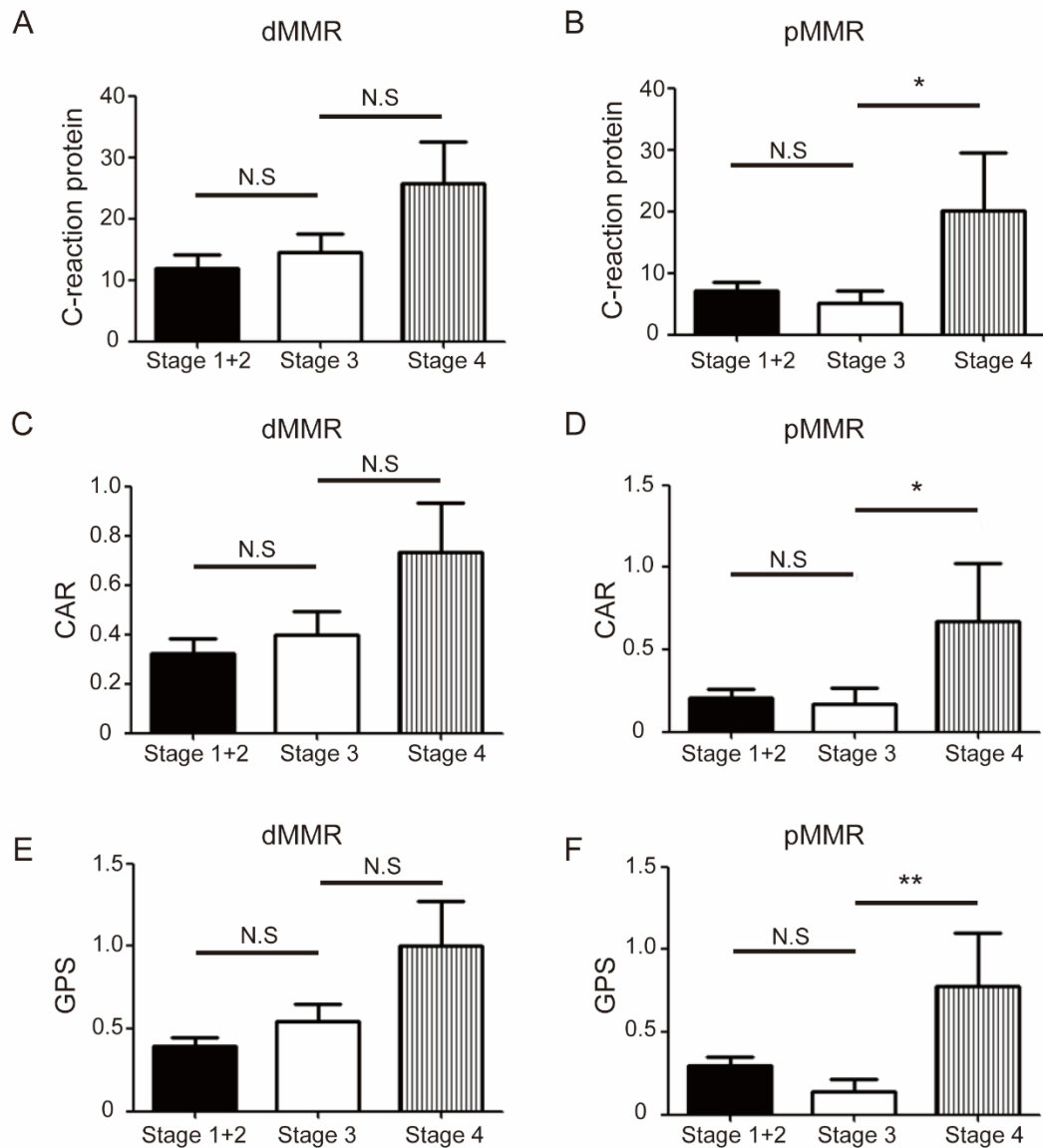
The representative results of IHC staining of MMR proteins. (A) MLH1 negative (200×); (B) MLH1 positive (200×); (C) MSH2 negative (200×); (D) MSH2 positive (200×); (E) MSH6 negative (200×); (F) MSH6 positive (200×); (G) PMS2 negative (200×); (H) PMS2 positive (200×).

Fig. S2



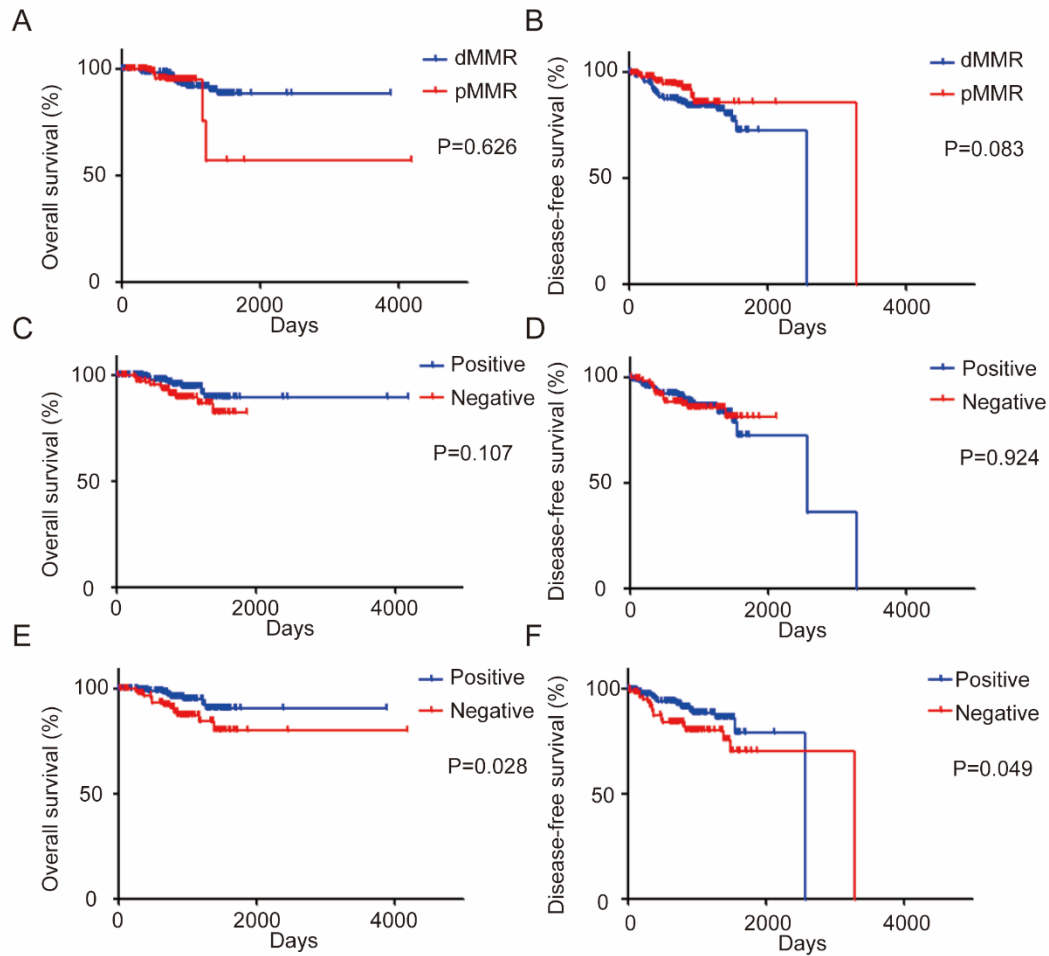
The representative results of IHC staining of PD-1 and PD-L1. (A) PD-1 negative (100 \times); (B) PD-1 negative (200 \times); (C) PD-1 positive (100 \times); (D) PD-1 positive (200 \times); (E) PD-L1 negative (100 \times); (F) PD-L1 negative (200 \times); (G) PD-L1 positive (100 \times); (H) PD-L1 positive (200 \times).

Fig. S3



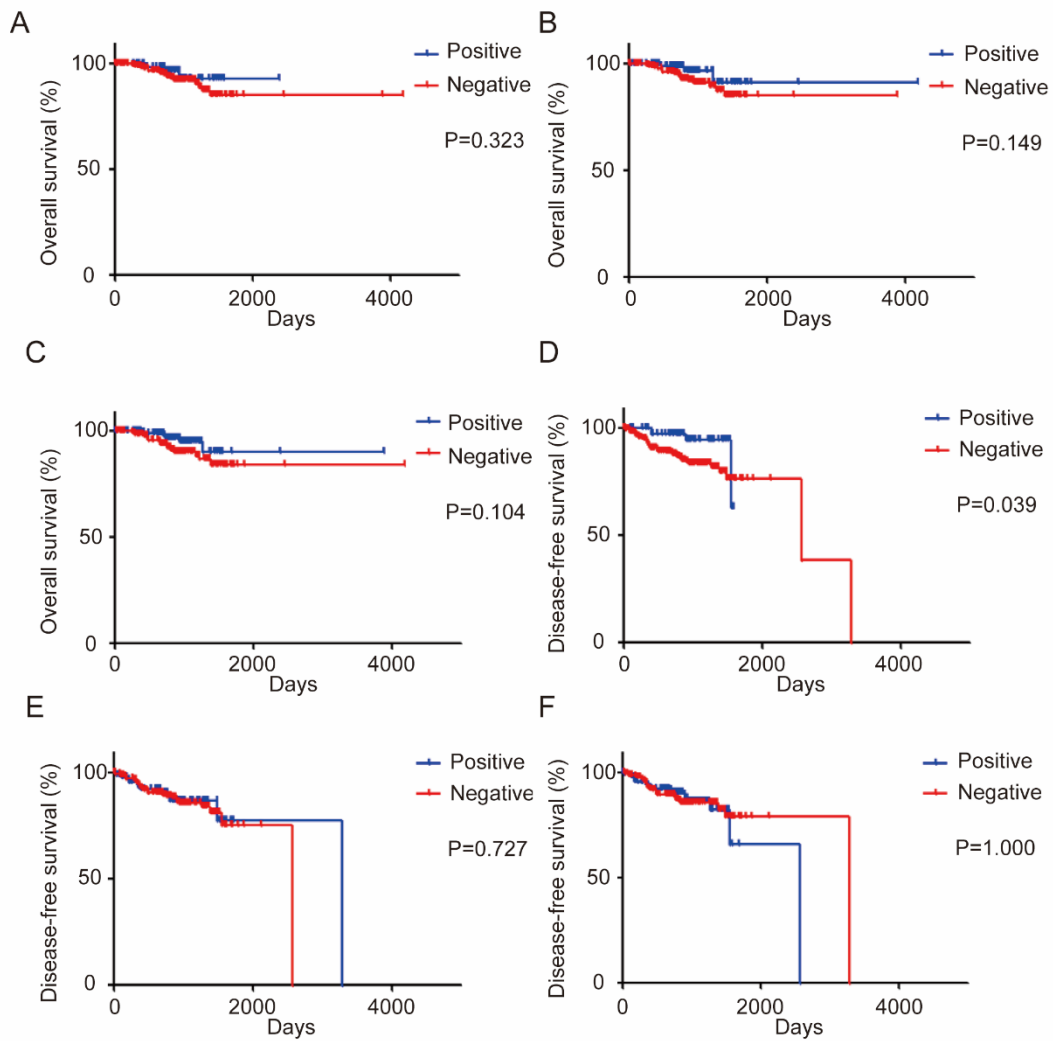
Inflammatory status difference between dMMR and pMMR CRC patients. (A-B). Group comparison combined the level of circulating serum C-reaction protein and AJCC stages in dMMR (A) or pMMR patients (B). (C-D) Group comparison combined the level of CAR and AJCC stages in dMMR (C) or pMMR patients (D). (E-F). Group comparison combined the level of GPS status and AJCC stages in dMMR (E) or pMMR patients (F). * P<0.05, ** P<0.01, N.S, not significant.

Fig. S4



Different association of PD-1 and PD-L1 expression with survival between dMMR and pMMR CRC patients. (A-B). Kaplan-Meier survival curves comparing the overall survival (A), and the disease-free survival (B) of the CRC patients with different MMR status. (C-D) Kaplan-Meier survival curves comparing the overall survival (C) and the disease-free survival (D) of the level of total PD-1 expression in CRC patients. (E-F). Kaplan-Meier survival curves comparing the overall survival (E) and the disease-free survival (F) of the level of total PD-L1 in CRC patients. * $P < 0.05$, ** $P < 0.01$, N.S, not significant.

Fig. S5



PD-1 expression at different locations are differently associated with CRC patient survival. (A-C). Kaplan-Meier survival curves comparing the overall survival of the level of tumor PD-1 (A), stroma PD-1 (B), or TIL PD-1 (C) expression in CRC patients. (d-f). Kaplan-Meier survival curves comparing the disease-free survival of the level of tumor PD-1 (D), stroma PD-1 (E), or TIL PD-1 expression (F) in CRC patients.