

Supplementary Information

Predisposing conditions in patients with small intestinal adenocarcinomas in the Netherlands: a 20-year nationwide cohort study.

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Table S1. Univariable and multivariable Cox proportional hazard models for overall survival for patients diagnosed with SIA from January 1999 through December 2019 in the Netherlands.

	Univariable			Multivariable		
	n	HR (95% CI)	p-value	n	HR (95% CI)	p-value
Age, years ^a	2693	1.03 (1.03 – 1.03)	<0.001	2506	1.03 (1.02 – 1.03)	<0.001
Sex						
Male	1408	1.00 (reference)	0.904			
Female	1285	1.01 (0.92 – 1.10)				
Period of diagnosis						
1999-2005	575	1.00 (reference)	0.691			
2006-2012	921	0.95 (0.85 – 1.07)				
2013-2019	1997	0.961 (0.86 – 1.08)				
Tumor location						
Duodenum	1631	1.00 (reference)	<0.001	1465	1.00 (reference)	<0.001
Jejunum	501	0.55 (0.48 – 0.62)		497	0.75 (0.66 – 0.85)	
Ileum	367	0.62 (0.55 – 0.71)		363	0.91 (0.78 – 1.05)	
NOS	194	1.03 (0.88 – 1.21)		181	1.08 (0.91 – 1.28)	
TNM Stage at diagnosis						
Stage I	164	0.19 (0.156 – 0.24)	<0.001	164	0.25 (0.20 – 0.31)	<0.001
Stage II	732	0.23 (0.20 – 0.26)		732	0.33 (0.29 – 0.37)	
Stage III	685	0.35 (0.32 – 0.40)		685	0.54 (0.47 – 0.61)	
Stage IV	925	1.00 (reference)		925	1.00 (reference)	
Missing cases	187					
Predisposing condition						
No	2367	1.00 (reference)	<0.001	2189	1.00 (reference)	<0.001
Lynch syndrome	104	0.27 (0.19 – 0.37)		104	0.46 (0.33 – 0.63)	
Polyposis syndrome	41	0.54 (0.36 – 0.81)		37	0.78 (0.50 – 1.20)	
IBD	103	0.62 (0.48 – 0.79)		100	1.06 (0.81 – 1.38)	
Celiac disease	78	0.55 (0.41 – 0.73)		76	0.77 (0.58 – 1.03)	

Surgery of the primary tumor						
No	1194	1.00 (reference)	<0.001	1022	1.00 (reference)	<0.001
Yes	1499	0.26 (0.24 – 0.29)		1484	0.40 (0.36 – 0.45)	
Systemic therapy						
No	2086	1.00 (reference)	0.357			
Yes	607	0.95 (0.86 – 1.06)				
Radiotherapy						
No	2626	1.00 (reference)	0.003	2453	1.00 (reference)	0.235
Yes	67	1.45 (1.13 – 1.86)		53	0.84 (0.63 – 1.12)	
MMR status						
pMMR	440	1.00 (reference)	<0.001			
dMMR	192	0.38 (0.29 – 0.49)				
Missing cases	2061					
Grade of differentiation						
Well differentiated	144	1.00 (reference)	<0.001			
Moderately differentiated	1034	1.23 (0.99 – 1.53)				
Poorly differentiated	657	1.70 (1.36 – 2.13)				
Missing cases	858					
Mucinous differentiation						
No	117	1.00 (reference)	0.397			
Yes, < 50%	242	1.17 (0.90 – 1.52)				
Yes, > 50%	216	1.03 (0.79 – 1.35)				
Missing cases	2118					
Lymphangioinvasion						
No	473	1.00 (reference)	<0.001			
Yes	512	2.01 (1.71 – 2.37)				
Missing cases	1708					
Perineural invasion						
No	262	1.00 (reference)	<0.001			
Yes	208	1.84 (1.44 – 2.34)				

Missing cases

2223

Univariable Cox regression analysis included 2693 patients. Multivariable Cox regression analysis included 2506 patients, 187 patients excluded due to missings.

^a Analyzed as a continuous variable.

n, number of patients; HR, hazard ratio; 95% CI, 95% confidence interval; NOS, not otherwise specified; IBD, inflammatory bowel disease; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient.

Table S2. Univariable and multivariable Cox proportional hazard models for overall survival for patients with Lynch syndrome diagnosed with SIA from January 1999 through December 2019 in the Netherlands.

	Univariable			Multivariable		
	n	HR (95% CI)	p-value	n	HR (95% CI)	p-value
Age, years ^a	104	1.06 (1.02 – 1.09)	<0.001	104	1.06 (1.02 – 1.09)	<0.001
Sex						
Male	68	1.00 (reference)	0.658			
Female	36	0.66 (0.44 – 1.69)				
Period of diagnosis						
1999-2005	15	1.00 (reference)	0.082			
2006-2012	33	2.62 (0.75 – 9.15)				
2013-2019	56	4.10 (1.16 – 14.56)				
Tumor location						
Duodenum	51	1.00 (reference)	0.454			
Jejunum	33	1.01 (0.50 – 2.02)				
Ileum	12	0.54 (0.16 – 1.83)				
NOS	8	0.27 (0.04 – 1.98)				
TNM Stage at diagnosis						
Stage I	10	0.44 (0.14 – 1.43)	0.022	10	0.40 (0.12 – 1.42)	0.170
Stage II	55	0.26 (0.10 – 0.65)		55	0.30 (0.10 – 0.86)	
Stage III	26	0.24 (0.09 – 0.69)		26	0.39 (0.12 – 1.33)	
Stage IV	13	1.00 (reference)		13	1.00 (reference)	
Missing cases	0					
Surgery of the primary tumor						
No	16	1.00 (reference)	0.003	16	1.00 (reference)	0.166
Yes	88	0.33 (0.16 – 0.68)		88	0.54 (0.22 – 1.29)	
Systemic therapy						
No	86	1.00 (reference)	0.307			
Yes	18	1.54 (0.67 – 3.56)				

Radiotherapy				
No	103	1.00 (reference)	0.378	
Yes	1	2.45 (0.33 – 18.03)		
MMR status				
pMMR	1	1.00 (reference)	0.690	
dMMR	103	20.49 (0.0 – 57948814.58)		
Missing cases	0			
Grade of differentiation				
Well differentiated	6	1.00 (reference)	0.627	
Moderately differentiated	57	0.70 (0.20 – 2.43)		
Poorly differentiated	20	0.51 (0.12 – 2.10)		
Missing cases	21			
Mucinous differentiation				
No	13	1.00 (reference)	0.875	
Yes, < 50%	18	1.34 (0.37 – 4.86)		
Yes, > 50%	7	1.47 (0.26 – 8.22)		
Missing cases	66			
Lymphangiogenesis				
No	42	1.00 (reference)	0.938	
Yes	22	1.04 (0.39 – 2.77)		
Missing cases	40			
Perineural invasion				
No	24	1.00 (reference)	0.613	
Yes	7	1.53 (0.29 – 8.04)		
Missing cases	31			

Univariable & multivariable Cox regression analysis included 104 patients.

^a Analyzed as a continuous variable.

n, number of patients; HR, hazard ratio; 95% CI, 95% confidence interval; NOS, not otherwise specified; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient.

Table S3. Univariable and multivariable Cox proportional hazard models for overall survival for patients with a polyposis syndrome diagnosed with SIA from January 1999 through December 2019 in the Netherlands.

	Univariable			Multivariable		
	n	HR (95% CI)	p-value	n	HR (95% CI)	p-value
Age, years ^a	41	1.01 (0.98 – 1.05)	0.455			
Sex						
Male	23	1.00 (reference)				
Female	18	1.33 (0.58 – 3.05)	0.500			
Period of diagnosis						
1999-2005	11	1.00 (reference)				
2006-2012	12	0.93 (0.37 – 2.35)	0.098			
2013-2019	18	0.29 (0.09 – 0.97)				
Tumor location						
Duodenum	22	1.00 (reference)				
Jejunum	11	0.56 (0.20 – 1.53)	0.732			
Ileum	4	0.00 (0.00 – NA)				
NOS	4	0.87 (0.25 – 3.06)				
TNM Stage at diagnosis						
Stage I	5	0.05 (0.02 – 0.34)		5	0.06 (0.01 – 0.35)	
Stage II	9	0.03 (0.01 – 0.23)	<0.001	9	0.05 (0.01 – 0.44)	0.012
Stage III	13	0.17 (0.05 – 0.54)		13	0.30 (0.06 – 1.47)	
Stage IV	10	1.00 (reference)		10	1.00 (reference)	
Missing cases	4					
Surgery of the primary tumor						
No	14	1.00 (reference)		11	1.00 (reference)	
Yes	27	0.22 (0.09 – 0.53)	<0.001	26	0.42 (0.10 – 1.80)	0.243
Systemic therapy						
No	33	1.00 (reference)				
Yes	8	1.49 (0.48 – 4.63)	0.495			

Radiotherapy				
No	40	1.00 (reference)	0.158	
Yes	1	4.48 (0.56 – 35.83)		
MMR status				
pMMR	8	1.00 (reference)	0.367	
dMMR	3	2.47 (0.35 – 17.65)		
Missing cases	30			
Grade of differentiation				
Well differentiated	4	1.00 (reference)	0.003	
Moderately differentiated	21	5.31 (0.65 – 43.52)		
Poorly differentiated	6	31.32 (2.99 – 328.64)		
Missing cases	10			
Mucinous differentiation				
No	2	1.00 (reference)	0.720	
Yes, < 50%	5	55.94 (0.00 – 15035079483)		
Yes, > 50%	5	1.12 (0.00 - 4848254890.20)		
Missing cases	29			
Lymphangioinvasion				
No	11	1.00 (reference)	0.597	
Yes	10	1.55 (0.31 – 7.86)		
Missing cases	20			
Perineural invasion				
No	9	1.00 (reference)	0.779	
Yes	4	1.50 (0.09 – 25.39)		
Missing cases	28			

Univariable Cox regression analysis included 41 patients. Multivariable Cox regression analysis included 37 patients, 4 patients excluded due to missings.

^a Analyzed as a continuous variable.

n, number of patients; HR, hazard ratio; 95% CI, 95% confidence interval; NOS, not otherwise specified; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient.

Table S4. Univariable and multivariable Cox proportional hazard models for overall survival for patients with IBD diagnosed with SIA from January 1999 through December 2019 in the Netherlands.

	Univariable			Multivariable		
	n	HR (95% CI)	p-value	n	HR (95% CI)	p-value
Age, years ^a	103	1.03 (1.01 – 1.05)	0.006	100	1.03 (1.01 – 1.06)	0.003
Sex						
Male	54	1.00 (reference)	0.806			
Female	49	1.06 (0.66 – 1.72)				
Period of diagnosis						
1999-2005	16	1.00 (reference)	0.285			
2006-2012	43	0.59 (0.30 - 1.14)				
2013-2019	44	0.74 (0.37 – 1.46)				
Tumor location						
Duodenum	16	1.00 (reference)	0.008	14	1.00 (reference)	0.707
Jejunum	69	1.02 (0.40 – 2.56)		7	0.68 (0.23 – 2.05)	
Ileum	7	0.43 (0.23 – 0.81)		68	0.99 (0.47 – 2.06)	
NOS	11	1.04 (0.45 – 2.39)		11	1.38 (0.56 – 3.40)	
TNM Stage at diagnosis						
Stage I	13	0.10 (0.04 – 0.28)	<0.001	13	0.09 (0.03 – 0.30)	<0.001
Stage II	42	0.12 (0.06 – 0.24)		42	0.08 (0.03 – 0.22)	
Stage III	25	0.33 (0.17 – 0.64)		25	0.33 (0.14 – 0.78)	
Stage IV	20	1.00 (reference)		20	1.00 (reference)	
Missing cases	3					
Surgery of the primary tumor						
No	22	1.00 (reference)	0.002	19	1.00 (reference)	0.659
Yes	81	0.42 (0.25 – 0.73)		81	1.20 (0.54 – 2.67)	
Systemic therapy						
No	80	1.00 (reference)	0.495			
Yes	23	1.21 (0.70 – 2.11)				

Radiotherapy			
No	102	1.00 (reference)	0.451
Yes	1	2.15 (0.30 – 15.64)	
MMR status			
pMMR	28	1.00 (reference)	0.528
dMMR	5	0.61 (0.14 – 2.79)	
Missing cases	70		
Grade of differentiation			
Well differentiated	12	1.00 (reference)	0.001
Moderately differentiated	35	2.89 (0.86 – 9.72)	
Poorly differentiated	29	6.55 (1.98 – 22.34)	
Missing cases	27		
Mucinous differentiation			
No	6	1.00 (reference)	0.329
Yes, < 50%	14	2.22 (0.61 – 8.11)	
Yes, > 50%	13	1.22 (0.32 – 4.74)	
Missing cases	70		
Lymphangiogenesis			
No	24	1.00 (reference)	0.027
Yes	29	2.37 (1.10 – 5.09)	
Missing cases	50		
Perineural invasion			
No	10	1.00 (reference)	0.152
Yes	5	3.72 (0.62 – 22.41)	
Missing cases	88		

Univariable Cox regression analysis included 103 patients. Multivariable Cox regression analysis included 100 patients, 3 patients excluded due to missings.

^a Analyzed as a continuous variable.

n, number of patients; HR, hazard ratio; 95% CI, 95% confidence interval; NOS, not otherwise specified; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient.

Table S5. Univariable and multivariable Cox proportional hazard models for overall survival for patients with celiac disease diagnosed with SIA from January 1999 through December 2019 in the Netherlands.

	Univariable			Multivariable		
	n	HR (95% CI)	p-value	n	HR (95% CI)	p-value
Age, years ^a	78	1.04 (1.01 – 1.07)	0.017	76	1.04 (1.01 – 1.08)	0.015
Sex						
Male	44	1.00 (reference)	0.554			
Female	34	0.84 (0.47 – 1.50)				
Period of diagnosis						
1999-2005	18	1.00 (reference)	0.914			
2006-2012	26	1.05 (0.52 – 2.12)				
2013-2019	34	0.90 (0.41 – 1.97)				
Tumor location						
Duodenum	30	1.00 (reference)	0.025	28	1.00 (reference)	0.005
Jejunum	34	0.41 (0.22 – 0.79)		34	0.30 (0.14 – 0.63)	
Ileum	7	0.82 (0.28 – 2.38)		7	1.14 (0.36 – 3.59)	
NOS	7	1.29 (0.51 – 3.24)		7	1.51 (0.56 – 4.10)	
TNM Stage at diagnosis						
Stage I	9	0.34 (0.11 – 1.08)	0.041	9	0.72 (0.21 – 2.45)	0.477
Stage II	28	0.33 (0.15 – 0.72)		28	0.81 (0.32 – 2.06)	
Stage III	26	0.48 (0.22 – 1.02)		26	1.35 (0.55 – 3.27)	
Stage IV	13	1.00 (reference)		13	1.00 (reference)	
Missing cases	2					
Surgery of the primary tumor						
No	19	1.00 (reference)	<0.001	18	1.00 (reference)	<0.001
Yes	59	0.25 (0.14 – 0.46)		58	0.26 (0.13 – 0.51)	
Systemic therapy						
No	66	1.00 (reference)	0.152			
Yes	12	0.53 (0.22 – 1.26)				

Radiotherapy			
No	78	NA	NA
Yes	0	NA	
MMR status			
pMMR	8	1.00 (reference)	0.274
dMMR	9	0.45 (0.11- 1.89)	
Missing cases	61		
Grade of differentiation			
Well differentiated	3	1.00 (reference)	0.854
Moderately differentiated	27	1.71 (0.22 – 12.99)	
Poorly differentiated	34	1.78 (0.24 – 13.42)	
Missing cases	14		
Mucinous differentiation			
No	3	1.00 (reference)	0.190
Yes, < 50%	6	1.85 (0.29 – 11.89)	
Yes, > 50%	5	0.29 (0.05 – 1.87)	
Missing cases	64		
Lymphangioinvasion			
No	23	1.00 (reference)	0.396
Yes	15	1.54 (0.57 – 4.15)	
Missing cases	40		
Perineural invasion			
No	8	1.00 (reference)	0.405
Yes	4	2.15 (0.35 – 13.13)	
Missing cases	66		

Univariable Cox regression analysis included 78 patients. Multivariable Cox regression analysis included 76 patients, 2 patients excluded due to missings.

^a Analyzed as a continuous variable.

n, number of patients; HR, hazard ratio; 95% CI, 95% confidence interval; NOS, not otherwise specified; pMMR, mismatch repair proficient; dMMR, mismatch repair deficient.

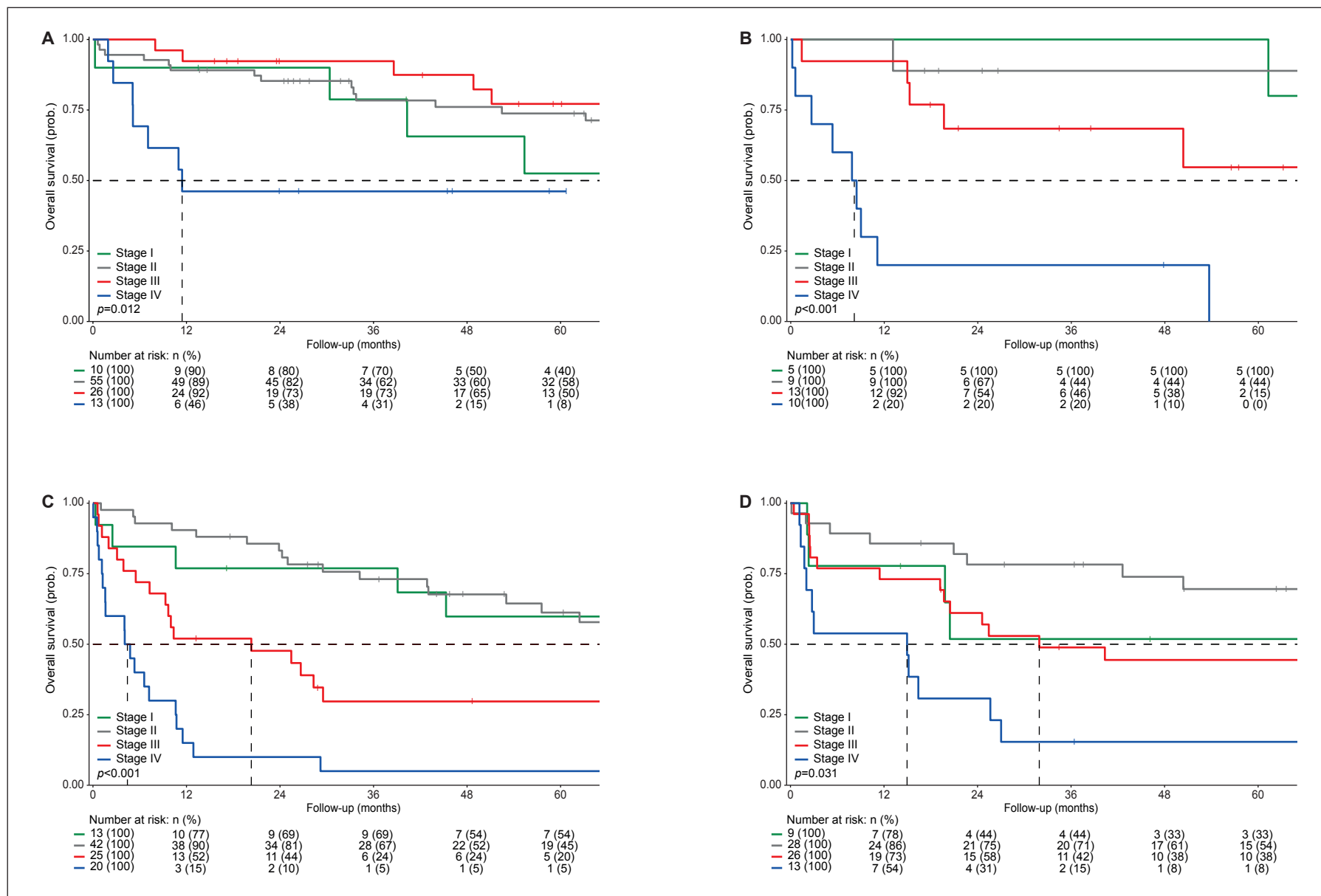


Figure S1. Five-year overall survival per stage of disease of patients diagnosed with SIA and a diagnosis of (A) Lynch syndrome, (B) polyposis syndrome, (C) inflammatory bowel disease and (D) celiac disease. n, number of patients; Prob., probability.