



# Long-term outcomes of stage IIB-IV melanoma patients: Nationwide data from Norway

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## Background & Objectives

- The clinical management of cutaneous melanoma often involves surgical intervention. Adjuvant therapy reduces the likelihood of recurrence and has in recent years become available for patients with stage III-IV disease<sup>1,2</sup>
- Ongoing clinical trials are investigating the efficacy of adjuvant therapy for stage IIB/C<sup>3</sup>
- While adjuvant treatment options continue to expand, population level data describing the survival experience and disease burden of melanoma patients are scarce, particularly data with granular detail on TNM stage
- This study aimed to investigate the characteristics and outcomes of Norwegian cutaneous melanoma patients with stage IIB-IV

## Methods

- For this retrospective cohort study, all patients with cutaneous melanoma (ICD-10: C43), diagnosed between Jan-2008 to Dec-2018, were identified in the population based Cancer Registry of Norway
- The population included was intended to represent patients who currently would be eligible for adjuvant therapy (stage III-IV), as well as stage II patients. Stage IV patients with no evidence of surgery were excluded to avoid the inclusion of patients who would be ineligible for adjuvant therapy
- Data from the Incidence Registry was combined with data from the Clinical Melanoma Registry
- The incidence registry provided information on the incidence of all new melanoma cases in Norway during the study period (Jan-2008 to Dec-2018). Data from the Melanoma Registry included more granular information on clinical care and whether a patient's tumour was surgically removed. Information on the receipt of systemic anti-cancer therapy was not available
- Patients contributed data from their initial diagnosis until the end of follow-up (Dec-2018). During this period adjuvant treatments were not commercially available for melanoma patients in Norway
- The primary outcomes of interest were overall survival (OS) and cancer specific survival
- The survival experience overall and stratified by TNM stage were evaluated using Kaplan-Meier estimation and Multivariate Cox proportional hazard regression models

## Results

Table 1. Patient demographic and clinical characteristics at initial diagnosis

Characteristics	Total (n=4339)	Stage IIB (n=1551)	Stage IIC (n=766)	Stage IIIA (n=172)	Stage IIIB (n=357)	Stage IIIC (n=814)	Stage IIID (n=116)	Stage IV (n=563)
<b>Gender, n (%)</b>								
Male	2513 (57.9)	847 (54.6)	413 (53.9)	101 (58.7)	205 (57.4)	518 (63.6)	70 (60.3)	359 (63.8)
Female	1826 (42.1)	704 (45.4)	353 (46.1)	71 (41.3)	152 (42.6)	296 (36.4)	46 (39.7)	204 (36.2)
<b>Age</b>								
Mean	69.9	71.9	78.5	58.4	63.6	67.1	68.3	64.1
Median	72	74	82	59	65	69	69	66
Range (Min - Max)	18 - 102	18 - 102	20 - 99	18 - 85	19 - 95	22 - 96	25 - 93	23 - 92
IQR	60-82	64-84	71-88	49.8-68.3	55-74	58-78	58-81	56-74
<b>Regional Health Authority, n (%)</b>								
South Eastern	2667 (61.5)	946 (61)	490 (64)	85 (49.4)	208 (58.3)	497 (61.1)	85 (73.3)	356 (63.2)
Central	523 (12.1)	198 (12.8)	82 (10.7)	34 (19.8)	39 (10.9)	92 (11.3)	11 (9.5)	67 (11.9)
Northern	224 (5.2)	75 (4.8)	37 (4.8)	11 (6.4)	21 (5.9)	58 (7.1)	2 (1.7)	20 (3.6)
Western	925 (21.3)	332 (21.4)	157 (20.5)	42 (24.4)	89 (24.9)	167 (20.5)	18 (15.5)	120 (21.3)
<b>Anatomic Site, n (%)</b>								
Head & neck	846 (19.5)	355 (22.9)	200 (26.1)	8 (4.7)	43 (12)	101 (12.4)	17 (14.7)	122 (21.7)
Trunk	1673 (38.6)	583 (37.6)	246 (32.1)	75 (43.6)	162 (45.4)	320 (39.3)	38 (32.8)	249 (44.2)
Upper limb & Shoulder	850 (19.6)	324 (20.9)	151 (19.7)	36 (20.9)	70 (19.6)	146 (17.9)	11 (9.5)	112 (19.9)
Lower limb & Hip	946 (21.8)	275 (17.7)	162 (21.1)	53 (30.8)	82 (23)	247 (30.3)	50 (43.1)	77 (13.7)
Unspecified	24 (0.6)	14 (0.9)	7 (0.9)	0 (0)	0 (0)	0 (0)	0 (0)	3 (0.5)
<b>Melanoma Subtype, n (%)</b>								
Superficial spreading	1137 (26.2)	360 (23.2)	101 (13.2)	111 (64.5)	148 (41.5)	221 (27.1)	18 (15.5)	178 (31.6)
Nodular	1965 (45.3)	688 (44.4)	466 (60.8)	26 (15.1)	130 (36.4)	384 (47.2)	56 (48.3)	215 (38.2)
Acral	36 (0.8)	12 (0.8)	7 (0.9)	2 (1.2)	1 (0.3)	8 (1)	4 (3.4)	2 (0.4)
Lentigo Maligna	77 (1.8)	47 (3)	13 (1.7)	0 (0)	5 (1.4)	5 (0.6)	0 (0)	7 (1.2)
Unspecified	1124 (25.9)	444 (28.6)	179 (23.4)	33 (19.2)	73 (20.4)	196 (24.1)	38 (32.8)	161 (28.6)
<b>Breslow thickness (mm)</b>								
Mean	5.1	4.9	8.1	1.2	2.1	5.0	8.2	3.8
Median	4	4	6.5	1.2	2	4	7	2.8
Range (Min - Max)	(0.1 - 85.0)	(0.1 - 85.0)	(2.6 - 80.0)	(0.3 - 2.0)	(0.2 - 4.0)	(0.3 - 60.0)	(0.4 - 31.0)	(0.2 - 33.0)
IQR	2.5-6.0	3.0-5.5	5.0-9.0	1.0-1.5	1.3-2.9	2.5-6.3	5.0-9.5	1.7-5.0

- A total of 4,339 patients were included in the cohort (Table 1)
- The cohort included 57.9% male and 42.1% female patients, with a median age of 72 (IQR 60-82)
- Stage IIB/C patients made up just over half of the cohort: IIB 35.7% and IIC 17.7%
- The distribution of patients by geographical regions did not vary across TNM stage
- The trunk was consistently the most common anatomical site, with a generally equal distribution of patients between the remaining anatomical sites of head & neck, upper limb and shoulder, and lower limb & hip

Table 2. Overall survival estimates

	Stage IIB (n=1551)	Stage IIC (n=766)	Stage IIIA (n=172)	Stage IIIB (n=357)	Stage IIIC (n=814)	Stage IIID (n=116)	Stage IV (n=563)	Total Patients (n=4339)
<b>Patient status, n(%)</b>								
Died	512 (33)	416 (54.3)	22 (12.8)	113 (31.7)	368 (45.2)	67 (57.8)	365 (64.8)	1863 (42.9)
Censored	1039 (67)	350 (45.7)	150 (87.2)	244 (68.3)	446 (54.8)	49 (42.2)	198 (35.2)	2476 (57.1)
<b>Median OS, months (95% CI)</b>	NA (114.2 - NA)	34 (29.1 - 42.0)	NA (NA - NA)	124.1 (89.1 - NA)	65.1 (56.0 - 77.1)	39.1 (35.0 - 57.0)	46.1 (41.1 - 50.1)	70.06 (66.0 - 76.1)
<b>Absolute Survival Probability, %</b>								
Year 1	91.5%	78.9%	98.7%	96.9%	90.3%	81.8%	94.3%	89.8%
Year 2	81.8%	61.0%	95.0%	86.6%	74.5%	70.9%	79.1%	77.0%
Year 3	74.5%	48.7%	91.5%	76.7%	63.1%	55.4%	63.7%	66.6%
Year 4	69.6%	42.6%	88.1%	71.4%	56.2%	41.3%	48.0%	59.2%
Year 5	64.9%	37.9%	79.3%	66.4%	51.5%	36.7%	39.3%	53.7%
Year 6	61.1%	34.2%	77.2%	59.6%	47.9%	34.7%	32.7%	49.4%
Year 7	58.8%	31.0%	77.2%	56.7%	44.0%	29.5%	28.5%	46.2%
Year 8	57.6%	28.9%	77.2%	54.7%	41.9%	29.5%	25.4%	44.3%
Year 9	55.6%	27.0%	72.0%	53.6%	41.9%	21.1%	21.6%	42.3%
Year 10	53.3%	26.0%	72.0%	51.7%	41.9%	14.1%	17.9%	40.2%

- OS varied by stage with an overall trend for higher OS in stage IIIA in comparison to IIB (Table 2)
- This trend in OS persisted in multivariable cox models (IIIA vs IIB, HR 0.63, 95% CI 0.41-0.97, p=0.037) adjusting for potential confounders including age (Table 3)
- However, there was no difference between IIIA and IIB (HR: 0.90, 95% CI 0.55-1.48, p=0.682) in fully adjusted analyses focusing on cancer specific survival
- Overall survival in IIC patients appeared particularly poor (Figure 1), however, this was attenuated when focusing on cancer specific survival both in crude Kaplan Meier analyses (Figure 2) and in adjusted multivariable cox models
- While the survival experience of IIC patients appeared to improve when focusing on cancer specific survival rather than crude overall survival, the confidence intervals for the IIC cancer specific hazard ratio indicated there was no evidence of a difference in their risk when compared to more advanced stage IIIA and IIIB patients

Figure 1. Overall survival stratified by TNM stage

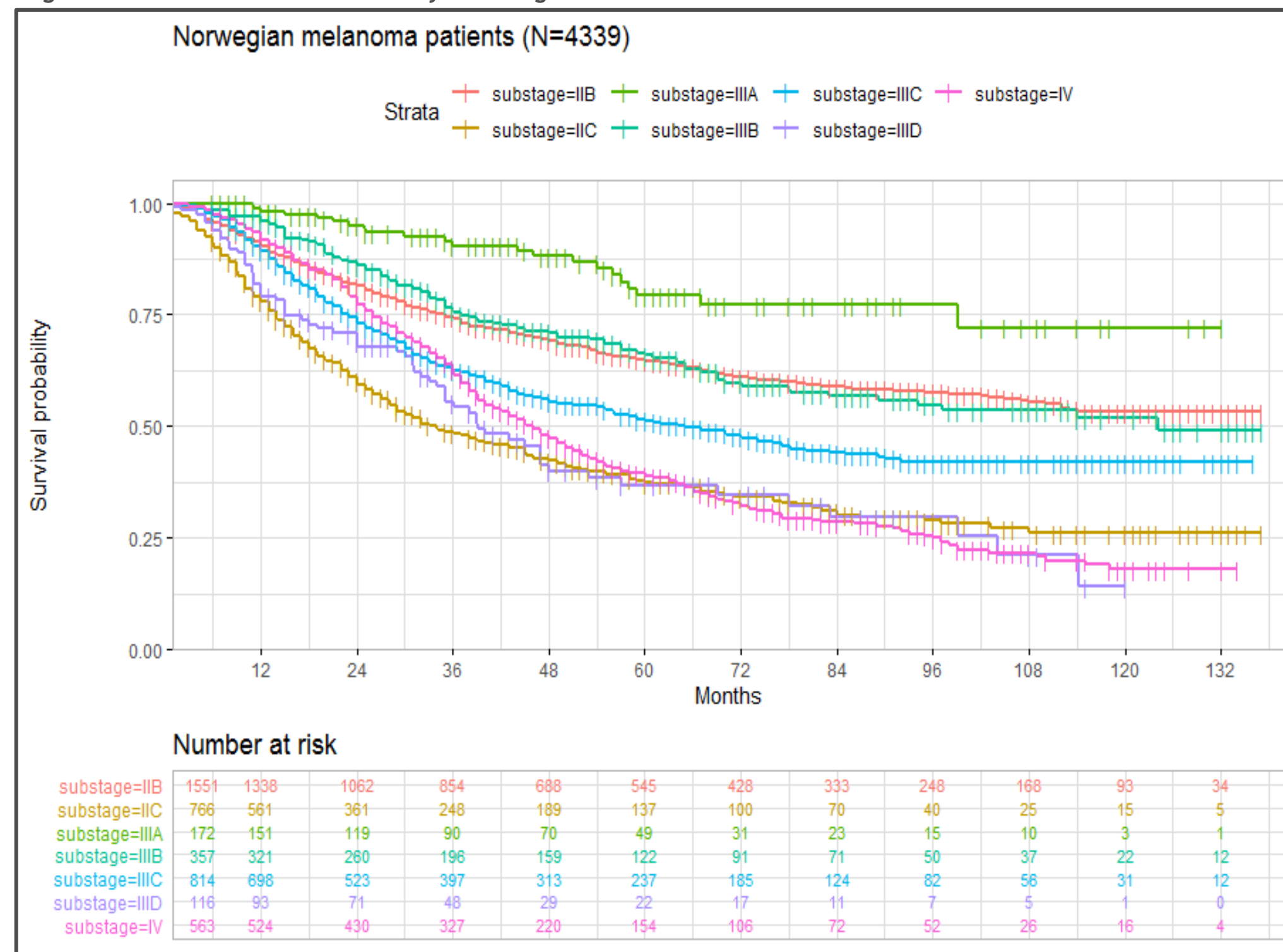


Figure 2. Cancer specific survival stratified by TNM stage

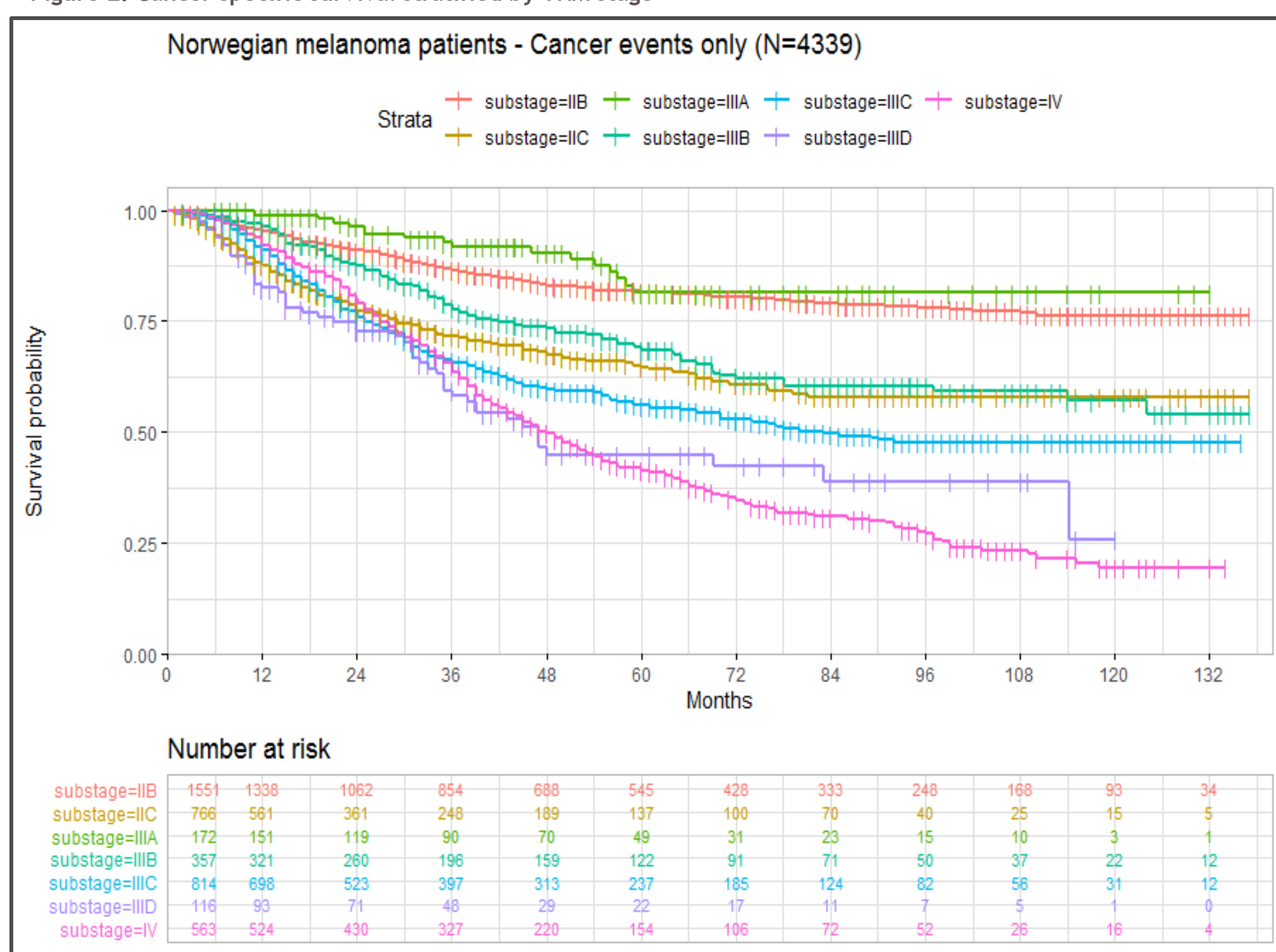


Table 3. Multivariate Cox proportional hazard analysis for factors affecting survival

Variables	Overall			Cancer specific		
	n	Adjusted HR (95% CI)	p-value	n	Adjusted HR (95% CI)	p-value
<b>Gender</b>						
Male (ref)	2513	1.00	-	2513	1.00	-
Female	1826	0.89 (0.81 - 0.98)	<b>0.015</b>	1826	0.82 (0.73 - 0.92)	<b>0.001</b>
<b>Age Category</b>						
<50 years (ref)	482	1.00	-	482	1.00	-
50-69 years	1448	1.45 (1.18 - 1.79)	<b>&lt;0.001</b>	1448	1.38 (1.11 - 1.71)	<b>0.003</b>
>=70 years	2409	3.67 (3.01 - 4.48)	<b>&lt;0.001</b>	2409	2.55 (2.07 - 3.14)	<b>&lt;0.001</b>
<b>Regional Health Authority</b>						
South Eastern (ref)	2667	1.00	-	2667	1.00	-
Central	523	1.01 (0.87 - 1.16)	0.908	523	1.09 (0.92 - 1.29)	0.340
Northern	224	1.06 (0.86 - 1.3)	0.611	224	1.12 (0.87 - 1.43)	0.390
Western	925	0.95 (0.84 - 1.07)	0.383	925	0.98 (0.85 - 1.13)	0.815
<b>Anatomic Site</b>						
Trunk (ref)	1673	1.00	-	1673	1.00	-
Head & neck	846	1.03 (0.91 - 1.17)	0.638	846	0.88 (0.75 - 1.03)	0.112
Upper limb/shoulder	850	0.92 (0.81 - 1.05)	0.218	850	0.80 (0.69 - 0.94)	<b>0.005</b>
Lower limb/hip	946	0.80 (0.7 - 0.91)	<b>0.001</b>	946	0.70 (0.6 - 0.83)	<b>&lt;0.001</b>
Unspecified	24	1.59 (0.95 - 2.66)	0.077	24	1.07 (0.48 - 2.41)	0.863
<b>Melanoma Subtype</b>						
Superficial Spreading (ref)	1137	1.00	-	1137	1.00	-
Nodular	1965	1.10 (0.98 - 1.25)	0.114	1965	1.10 (0.95 - 1.26)	0.210
Acral	36	1.04 (0.58 - 1.85)	0.899	36	1.25 (0.64 - 2.45)	0.514
Lentigo Maligna	77	0.79 (0.54 - 1.17)	0.238	77	0.62 (0.34 - 1.11)	0.106
Unspecified	1124	1.10 (0.96 - 1.25)	0.162	1124	1.12 (0.96 - 1.31)	0.143
<b>Substage</b>						
IIB (ref)	1551	1.00	-	1551	1.00	-
IIC	766	2.09 (1.83 - 2.39)	<b>&lt;0.001</b>	766	2.23 (1.84 - 2.7)	<b>&lt;0.001</b>
IIIA	172	0.63 (0.41 - 0.97)	<b>0.037</b>	172	0.90 (0.55 - 1.48)	0.682
IIIB	357	1.17 (0.95 - 1.44)	0.131	357	2.11 (1.67 - 2.68)	<b>&lt;0.001</b>
IIIC	814	1.72 (1.5 - 1.98)	<b>&lt;0.001</b>	814	3.10 (2.61 - 3.68)	<b>&lt;0.001</b>
IIID	116	2.43 (1.88 - 3.15)	<b>&lt;0.001</b>	116	4.25 (3.14 - 5.74)	<b>&lt;0.001</b>
IV	563	2.44 (2.12 - 2.79)	<b>&lt;0.001</b>	563	4.58 (3.87 - 5.43)	<b>&lt;0.001</b>

\*p-values <0.05 are indicated in bold

## Conclusion

- Our cohort included 4339 patients and these large scale population level data provide insight into the long term survival experience of melanoma patients in Norway and highlight some variation in overall and cancer specific mortality.
- The OS for stage II melanoma patients, and particularly IIC, is poor and in some cases worse than patients with more advanced stage melanoma. Our data highlight a high and unmet need amongst the stage II population for effective adjuvant treatment options.
- These findings are driven in part by age, which is likely a result of elderly stage II patients presenting with larger tumours that have remained localised.
- Nevertheless, even when focusing on cancer specific mortality, the outcomes of stage IIC patients remained poor and equivalent to patients with more advanced disease, reinforcing the high burden of disease in this patient group.

## References

- Eggermont AMM, et al. Nat Rev Clin Oncol. 2018 Sep;15(9):535-536