

Impact of comorbidities on survival in melanoma patients

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ARTICLE IN PRESS

1 **Impact of Comorbidities on Survival in**

2 **Melanoma Patients**

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41

42 **ABSTRACT**

43 **Background:** The increasing incidence of cutaneous melanoma (CM) is a
44 significant public health issue. However, few studies have focused on how
45 comorbidity patterns may influence the outcomes of CM patients. This study
46 aimed to identify comorbidity patterns among CM patients and assess their
47 impact on survival rates.

48 **Methods:** This retrospective population-based cohort study included all CM
49 patients recorded in the regional Veneto Cancer Registry in 2019 and 2021.

50 Comorbidity data (ICD-9-CM coding) were obtained from hospital discharge
51 records and included 17 primary disease categories. Patients with at least two
52 documented conditions were clustered via latent class analysis (LCA), with the
53 optimal number of clusters determined via the Akaike information criterion
54 (AIC).

55 **Results:** This population-based retrospective cohort study included 2,114 CM
56 patients. Coexisting medical conditions were documented in 1,048 (49.6%)
57 patients; multiple conditions were documented in 19.9% of the study cohort.
58 Among these patients, the LCA identified three patterns: 1) cardio-endocrine-
59 respiratory (20.96%); 2) pregnancy-psychosocial (29.97%); and 3) injury-
60 multiorgan-multifactorial disorders (49.08%). Patients in the injury-
61 multiorgan-multifactorial class had the highest mortality risk (HR = 3.08, 95%
62 CI: 2.25–4.22).

63 **Conclusions:** Comorbidity class has a significant effect on the survival of CM
64 patients. The incorporation of the comorbidity profile into clinical care
65 strategies can improve prognostic accuracy and enhance patient
66 management.

67
68 **Keywords:** melanoma; health care services; comorbidity; health care
69 resources; survival; cancer registry; cohort study.

70

71

72 INTRODUCTION

73 The incidence of cutaneous melanoma (CM) is steadily increasing in Western
74 populations with lighter skin, and this epidemiological trend has a significant

75 impact on public health (1,2). This increase in CM cases has been observed
76 over the past several decades and is particularly pronounced in countries with
77 predominantly fair-skinned populations, such as Australia, New Zealand,
78 North America, and Northern Europe (3). For this reason, melanoma is rapidly
79 emerging as one of the leading causes of cancer worldwide, making it an
80 increasingly significant public health concern that demands urgent attention
81 and comprehensive management strategies.

82 However, there is still limited information available on how CM comorbidity
83 affects patient outcomes (4). For example, preexisting conditions such as
84 cardiovascular diseases, diabetes, or other cancers may influence treatment
85 decisions, potentially limiting the use of specific therapies or increasing the
86 risk of treatment-related complications (5,6). Testori et al. reported that
87 patients with significant comorbidities were less likely to receive surgical
88 interventions or systemic therapies, potentially leading to suboptimal
89 management of their melanoma (7).

90 The impact of comorbidities on CM outcomes is multifaceted. This may lead to
91 delayed diagnosis due to competing health priorities or misattribution of
92 symptoms to existing conditions (8,9). Overall, the presence of multiple health
93 conditions can impact overall survival and healthcare utilization in ways that
94 are not yet fully understood in the context of CM. A study by Grann et al.
95 revealed that patients with multiple comorbidities had significantly worse
96 survival outcomes than did those without comorbidities, even after adjusting
97 for other prognostic factors (8).

98 As the global population continues to age, a notable demographic shift is
99 ongoing. Projections indicate a significant increase in the number of
100 individuals aged 65 and older by the year 2050 (10). This increase has led to

101 numerous challenges and complexities regarding health and longevity.
102 Therefore, understanding the impact not only of the number of comorbidities,
103 such as chronic diseases that often accompany aging but also of their specific
104 patterns is becoming increasingly crucial. In fact, this demographic shift
105 underscores the urgent need for comprehensive research focusing on the
106 impact of comorbidities on CM outcomes to inform evidence-based guidelines
107 for personalized care and ultimately improve overall patient outcomes (11).
108 This population-based retrospective cohort study aims to evaluate the impact
109 of clusters of comorbidities on the survival of patients with cutaneous
110 melanoma.

112 **METHODS**

113 **Study population.**

114 This population-based retrospective cohort study included 2,114 CM patients.
115 The CM cases were sourced from the 2019 and 2021 records of the Veneto
116 Region's Regional Cancer Registry (RTV). These years were selected because
117 of the availability of high-resolution CM data recorded in the cancer registry
118 (12). RTV is a certified, population-based cancer registry that records all
119 malignancies diagnosed in the region's residents, who number approximately
120 4.9 million (13). The recording procedures rely on an integrated information
121 network that includes pathology reports (including pT, pN, and M values and
122 the resulting pTNM-AJCC stage; 8th edition (14)), clinical charts, death
123 certificates, and public health administrative records. The mortality data of
124 the patients were tracked by linking RTV digital records with those from the
125 regional mortality registration, which captures events occurring outside the
126 regional territory (15).

127 **Comorbidities**

128 Comorbidity information was based on the ICD-9-CM classification and
129 obtained from hospital records within the six months preceding or following
130 admission (864 patients without any hospitalization were not included in the
131 analysis). Seventeen primary disease categories were considered, with a focus
132 on the presence or absence of major ICD-9-CM disease categories and V
133 codes. Latent class analysis (LCA) was used to identify comorbidity patterns
134 (16). Patients with more than two comorbid conditions were grouped into
135 three latent classes, and the Akaike information criterion (AIC) was used to
136 determine the optimal number of classes.

137 The comorbidity groups were classified as follows: "0": no comorbidities other
138 than CM; "1!": a single comorbidity; and the comorbidity classes resulting
139 from latent class analysis (Class 1, Class 2, and Class 3).

140 **Statistics**

141 Descriptive analyses were conducted to examine the characteristics of the
142 sample. Kaplan–Meier curves were generated to compare survival patterns at
143 different stages over the years. The log-rank test was used to compare
144 survival functions. Cox regression models were also employed to assess
145 overall and CM-specific mortality while adjusting for comorbidity groups, sex,
146 age, melanoma stage at diagnosis, and tumor primary site.

147 The results were deemed statistically significant when $p < 0.05$.

148 The statistical packages R 3.6.2 and SAS 9.4 were used for record linkage and
149 all the statistical analyses.

150 **Ethics**

151 The study was conducted in accordance with the principles outlined in the
152 Declaration of Helsinki. All the data were anonymized in accordance with

153 Italian regulations and used for monitoring and quality assurance purposes.
 154 The data analyses were performed on anonymous, aggregated data, ensuring
 155 that no individual could be identified. Ethical approval for the study was
 156 obtained from the ethics committee of the Veneto Oncological Institute (no.
 157 52/2016).

158

159 RESULTS

160 The study considered 2,114 CM patients who received a diagnosis of
 161 cutaneous melanoma in 2019 and 2021 (M:F= 1.39; overall mean age = 63.4
 162 years (SD 15.3); male mean age = 65.7; female mean age = 60.4) (**Table 1**).
 163 At least one comorbidity was recorded in 1,048 (49.6%) CM patients (**Table**
 164 **1**).

165

166 **Table 1:** Study population: number and distribution of comorbidities

VARIABLE	N	Percentage (%)	Age Mean (SD)	Age min - max	p-value*
Total Sample Size	2114	100%	63.4 (15.3)	9 - 99	
Sex					<0.001
Male	1228	58.1%	65.7 (14.4)	9 - 99	
Female	886	41.9%	60.4 (16.0)	20 - 99	
Age (years)					
<45	258	12.20 %			
45-54	370	17.50 %			
55-64	420	19.87 %			
65-74	489	23.13 %			
75-84	434	20.53 %			
85+	143	6.76 %			
Stage TNM v.8					<0.001
I	1332	63.01 %	61.3 (14.7)	20 - 94	
II	367	17.36 %	68.2 (15.1)	9 - 99	
III	252	11.92 %	61.5 (15.4)	14 - 92	
IV	109	5.16 %	71.4 (13.2)	30 - 92	
Missing	54	2.55 %	79.3	47 - 99	

Number of comorbidities			(14.5)		
None	1066	50.43%	61.5 (14.9)	14 - 99	<0.001
1 Comorbidity	628	29.71%	63.5 (15.0)	9 - 99	
2 Comorbidities	223	10.55%	62.7 (16.5)	21 - 92	
3 Comorbidities	91	4.30%	71.7 (14.6)	30 - 99	
4 Comorbidities	47	2.22%	75.5 (9.1)	54 - 93	
5 Comorbidities	31	1.47%	76.1 (11.1)	48 - 93	
6 Comorbidities	14	0.66%	82.9 (9.6)	63 - 97	
7 Comorbidities	9	0.43%	80.8 (5.6)	72 - 90	
8 Comorbidities	4	0.19%	83.2 (8.1)	75 - 92	
9 Comorbidities	1	0.05%	88.0 (/)	88 - 88	
ICD-9-CM Diagnoses					
Factors influencing health status (V codes)	583	27.58%	63.3 (16.0)	23-97	0.948
Diseases of the circulatory system	261	12.35%	72.9 (13.3)	9-97	<0.001
Diseases of the genitourinary system	137	6.48%	69.2 (14.4)	30-97	<0.001
Trauma and poisoning	122	5.77%	70.6 (14.7)	29-99	<0.001
Endocrine, nutritional, metabolic diseases	119	5.63%	72.9 (13.0)	22-99	<0.001
Diseases of the respiratory system	99	4.68%	73.8 (13.4)	33-94	<0.001
Diseases of the musculoskeletal system	97	4.59%	72.0 (12.7)	41-97	<0.001
Diseases of the digestive system	92	4.35%	71.0 (13.8)	31-94	<0.001
Symptoms, signs, ill-defined conditions	80	3.78%	70.8 (13.5)	30-93	<0.001
Diseases of the nervous system	73	3.45%	71.9 (13.5)	30-94	<0.001
Diseases of the blood and hematopoietic organs	57	2.70%	77.3 (11.5)	38-99	<0.001
Diseases of the skin and subcutaneous tissue	52	2.46%	67.1 (16.4)	21-92	0.047
Infectious and parasitic diseases	39	1.84%	74.3 (14.0)	35-97	<0.001
Complications of pregnancy, childbirth	32	1.51%	37.9 (4.9)	27-47	<0.001
Mental disorders	27	1.28%	74.6 (15.1)	45-92	<0.001
Congenital malformations	7	0.33%	58.0 (20.2)	21-79	0.537
Certain perinatal conditions	1	0.05%	81.0 (/)	81-81	0.208

167 *Mann-Whitney Test for Age ~ Sex and Age ~ each ICD-9-CM Diagnoses; Kruskal-Wallis Test for Age ~ Number of
 168 comorbidities and Age ~ Stage.

169

170 Among the 420 patients with two or more chronic conditions, latent class

171 analysis identified three distinct clusters of comorbidities (**Tables 2 and 3**):

172 Class 1 (20.96%) was predominantly associated with cardiovascular,
 173 endocrine and respiratory conditions; Class 2 (29.97%) included patients with
 174 pregnancy-related and psychosocial conditions and dermatological conditions;
 175 and Class 3 (49.08%) included patients with injuries, multiorgan (e.g.,
 176 genitourinary, digestive, and hematologic disorders) and multifactorial
 177 disorders. Class clustering was applied to correlate the comorbidity patterns
 178 with the patients' clinical outcomes.

179

180 **Table 2.** Probability (%) that a patient belongs to latent Classes 1, 2, and 3 for
 181 each disease group.

Disease	Class 1	Class 2	Class 3	
Diseases of the circulatory system	96.44%	2.75%	50.29%	
Endocrine, nutritional, metabolic diseases	53.20%	4.93%	28.61%	
Diseases of the respiratory system	32.15%	1.38%	25.21%	
Factors influencing health status (V codes)	60.71%	98.59%	39.53%	
Complications of pregnancy, childbirth	0.00%	23.84%	0.00%	
Diseases of the skin and subcutaneous tissue	0.00%	15.86%	8.75%	
Trauma and poisoning	2.25%	15.65%	31.70%	
Diseases of the genitourinary system	19.31%	13.14%	30.30%	
Diseases of the digestive system	5.51%	7.31%	25.69%	
Diseases of the blood and hematopoietic organs	0.00%	2.43%	23.75%	
Symptoms, signs, ill-defined conditions	9.17%	11.67%	20.98%	
Diseases of the nervous system	3.95%	4.08%	19.59%	
Diseases of the musculoskeletal system	0.00%	14.27%	18.45%	
Infectious and parasitic diseases	0.00%	1.49%	16.56%	
Mental disorders	0.00%	1.89%	8.55%	
Congenital malformations	0.00%	0.00%	3.40%	
	Total*	20.96%	29.97%	49.08%

182 * LCA estimated values. In bold the highest probability that a patient belongs to one of the three LCA classes for the
 183 disease group.

184

185 **Table 3:** Latent Class Analysis (LCA)

Comorbidity category	Definition	Typical conditions	Assigned patients N, (%)	Age mean (SD)
No	Patients without extra-	No additional	1066	61.0

Comorbidities (only Melanoma)	tumor comorbidities	conditions	(54.43%)	(14.9)
One Comorbidity (excluding cancer)	A single additional comorbidity besides melanoma	Hypertension, obesity, mild metabolic disorders	628 (29.71%)	63.0 (15.0)
Class 1	Dominant Cardio, Endocrine, Respiratory conditions.	Heart disease, COPD, stroke, endocrine disorders	97 (4.59%)	72.7 (11.5)
Class 2	Dominant Psychosocial, Pregnancy-related, Dermatological conditions	Pregnancy complications, psychosocial conditions,	136 (6.43%)	57.4 (16.7)
Class 3	Dominant Injury, Multiorgan, Multifactorial diseases	Infections, hematologic malignancies, immune disorders	187 (8.85%)	73.2 (13.6)

186 COPD: chronic obstructive pulmonary disease.

187

188 The clinicopathological characteristics of the patients with melanoma in the
189 comorbidity group are presented in **Table 4**.

190

191 **Table 4:** Clinicopathological characteristics of melanoma patients by
192 comorbidity category

Characteristics	No Comorbidity (n = 1066)	1 Comorbidity (n = 628)	Class 1 (n = 97)	Class 2 (n = 136)	Class 3 (n = 187)	p-value
Stage, n (%)						<0.001
I	722 (67.7%)	376 (59.9%)	50 (51.5%)	82 (60.3%)	102 (54.5%)	
II	180 (16.9%)	112 (17.8%)	16 (16.5%)	28 (20.6%)	31 (16.6%)	
III	113 (10.6%)	95 (15.1%)	11 (11.3%)	19 (14.0%)	14 (7.5%)	
IV	30 (2.8%)	31 (4.9%)	15 (15.5%)	6 (4.4%)	27 (14.4%)	
Missing	21 (2.0%)	14 (2.2%)	5 (5.2%)	1 (0.7%)	13 (7.0%)	
Age at diagnosis, mean (SD)	61.55 (14.89%)	63.47 (14.97%)	73.09 (11.48%)	57.88 (16.60%)	73.63 (13.60%)	<0.001
Sex, n (%)						<0.001
Female	489 (45.9%)	236 (37.6%)	19 (19.6%)	72 (52.9%)	70 (37.4%)	
Male	577 (54.1%)	392 (62.4%)	78 (80.4%)	64 (47.1%)	117 (62.6%)	
Breslow thickness, mm mean (SD)	1.78 (2.74%)	2.10 (3.73%)	3.20 (4.27%)	2.35 (4.26%)	2.33 (3.20%)	0.001
Tumor primary site, n (%)						<0.001
Head and neck	158 (14.8)	70 (11.1)	12 (12.4)	13 (9.6)	34 (18.2)	
Upper limbs	162 (15.2)	106 (16.9)	11 (11.3)	22 (16.2)	30 (16.0)	
Lower limbs	238 (22.3)	131 (20.9)	16 (16.5)	42 (30.9)	25 (13.4)	

Trunk	495 (46.4)	298 (47.5)	56 (57.7)	56 (41.2)	83 (44.4)
Missing	13 (1.2)	23 (3.7)	2 (2.1)	3 (2.2)	15 (8.0)

193

194 **Figure 1** and **Figure 2** show the Kaplan–Meier survival curves for overall
 195 and melanoma-specific mortality, respectively. These methods are based on
 196 CM clinical/pathological stage and latent class analysis (LCA).
 197 Cox regression analyses, adjusted for age, sex, stage, and tumor site revealed
 198 hazard ratios (HRs) of 2.78, 2.67, and 3.08, respectively, for Classes 1, 2, and
 199 3 rather than 2.30, 2.79, and 1.64, respectively, for overall and melanoma-
 200 specific mortality when patients with no comorbidities (1,066/2,114; 50.43%)
 201 were used as the reference group (**Table 5**).

202

203 **Table 5:** Cox regression analyses of overall and melanoma-specific mortality

Overall mortality*			
VARIABLE	Hazard Ratio (HR)	95% CI	p-value
Comorbidities (Reference = No)			
One comorbidity (excluding cancer)	1.48	1.09 - 1.99	0.010
Class 1	2.78	1.89 - 4.10	<0.001
Class 2	2.67	1.67 - 4.29	<0.001
Class 3	3.08	2.25 - 4.22	<0.001
Melanoma-specific mortality*			
Comorbidities (Reference = No)			
One comorbidity (excluding cancer)	1.63	1.10 - 2.42	0.016
Class 1	2.30	1.32 - 4.02	0.003
Class 2	2.79	1.49 - 5.22	0.001
Class 3	1.64	1.00 - 2.69	0.048

204 *Adjusted for sex, age, stage at diagnosis, and tumor primary site.

205

206 **DISCUSSION**

207 In summary, the findings of this study highlight the significant influence of
 208 comorbidity class on both overall mortality rates and melanoma-specific
 209 mortality rates. This suggests that additional health conditions alongside
 210 melanoma can profoundly impact patient outcomes, emphasizing the need for

211 a comprehensive approach to managing melanoma patients.

212 Previous evidence links individual or multiple concurrent comorbidities to
213 cancer prognosis⁴. In fact, since 2010, the traditional use of age as a primary
214 indicator of a patient's comorbidities has been critically re-evaluated. While
215 acknowledging the prognostic significance of age, several authors have
216 emphasized the importance of a more detailed assessment of clinical factors,
217 including multiorgan functional status, cognitive function, psychological well-
218 being, social support, and current medications (17).

219 A recent systematic review reported that the weighted average prevalence of
220 comorbidities in patients with neoplastic diseases was 33.4%. In the same
221 study, CM patients ranked fifth among cancer patients with the highest rates
222 of comorbidity, with a prevalence of 28.9% (18).

223 The present study associated CM patients with a heterogeneous spectrum of
224 medical conditions and identified distinct patterns of comorbidities in a large
225 cohort of CM patients. At least one comorbidity was documented in more than
226 one-third of the considered population, and more than 6% of the CM patients
227 presented three to nine coexisting medical conditions.

228 A number of studies support a relevant comorbidity prevalence in CM
229 patients, particularly highlighting the prevalence of hypertension,
230 dyslipidemia, obesity, and diabetes being among the most common (19-22).

231 The current findings confirm that any concurrent medical condition
232 significantly impacts the prognosis of patients with melanoma. Furthermore,
233 the present results indicate that injuries, multiorgan (genitourinary, digestive,
234 hematologic disorders), and multifactorial conditions (i.e., Class 3) are
235 associated with the poorest clinical outcomes among comorbidity classes. This
236 aligns with the increased risk of skin malignancies, particularly CM, in

237 immunocompromised patients, including those with hematological
238 malignancies; moreover, substantial evidence links immunosuppression with
239 unfavorable CM outcomes (23,24).

240 By focusing on physiopathology instead of merely relying on "traditional"
241 chronological age, this comprehensive assessment of an individual's health
242 status can lead to more tailored therapeutic protocols that improve outcome
243 predictions and enhance overall quality of life (25,26). Integrating comorbidity
244 patterns into the treatment plan requires collaboration among primary care
245 providers, specialists, and oncology teams. This collaborative approach may
246 ultimately increase the effectiveness of care and improve resource allocation
247 (27,28).

248 Integrating comorbidity assessments into clinical practice can lead to
249 personalized medicine approaches, where treatment plans are tailored not
250 only to the cancer type but also to the patient's overall health status. This
251 could involve multidisciplinary teams collaborating to address the various
252 health challenges faced by patients, ensuring that all aspects of their health
253 are considered in the treatment process. Furthermore, additional research is
254 needed to investigate the long-term effects of comorbidities on cancer survival
255 rates and quality of life, as well as to identify effective interventions that can
256 mitigate the impact of these comorbidities on patient outcomes.

257 This study has several limitations. While identifying comorbidities via ICD-9-
258 CM coding offers undeniable advantages of a standardized approach, it also
259 reveals significant limitations, such as the lack of granularity for
260 distinguishing between conditions and their severity. Since only hospitalized
261 patients were included, less severe cases were likely excluded, such as
262 patients in lower stages or younger patients. This selection bias may have

263 resulted in an overestimation of the burden of comorbidity and its associated
264 impact on mortality within the study cohort. Moreover, the use of algorithms
265 to identify chronic diseases through administrative records, such as those
266 other than hospital discharge data, could help better identify mild outpatient
267 conditions, thereby refining cluster definitions. Different cancers, other than
268 melanoma, have not been considered in the LCA or subsequent analyses.
269 Since melanoma often has metachronous and synchronous metastases, new
270 studies that also consider comorbid cancers are needed. Finally, longitudinal
271 follow-up is essential to monitor how evolving immunotherapy regimens may
272 lead to potential adverse effects and modify the comorbidity patterns present
273 at the time of diagnosis.

274 In conclusion, this study highlights the clinical importance of comorbidities
275 and their patterns in CM patients. This study also supports the need for a
276 critical reappraisal of comorbidity patterns by introducing new variables and a
277 more granular assessment of their severity. This could lead to more
278 defined/detailed classes of potential risk, potentially resulting in tailoring
279 therapeutic strategies according to the health status of cancer patients.

280

281

282 **DECLARATIONS**

283

284 **Abbreviations**

285 CM = Cutaneous Melanoma

286 RTV = Veneto Region's Regional Cancer Registry [Registro Tumori del
287 Veneto]

288 LCA = Latent Class Analysis

289

290 Ethics approval and consent to participate

291 This retrospective study involving human participants was conducted in
292 accordance with the ethical standards of the institutional research committee
293 and with the 1964 Helsinki Declaration and its later amendments or
294 comparable ethical standards. The Italian legislation identifies cancer
295 registries as collectors of personal data for surveillance purposes, with no
296 need to obtain individuals' explicit informed consent [REF:
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298 This study project was formally approved by the Ethics Committee of the
299 Veneto Oncological Institute (protocol number 52/2016).

300

301 Consent for publication

302 Not applicable.

303

304 Availability of data

305 The data supporting this study's findings are held by the Veneto Tumour
306 Registry (RTV) and were used under license for this work. The anonymized
307 minimal dataset necessary to replicate our findings has been made publicly
308 available in the Figshare repository at the following link:

309 <https://doi.org/10.6084/m9.figshare.28795190> [Data under embargo until the
310 study is published].

311

312 Competing interests

313 The authors declare that this study was designed and conducted in the
314 absence of any financial or commercial relationships that could be construed

315 as potential conflicts of interest. ABF received Consulting fees, Payment or
316 honoraria for lectures, presentations, speakers bureaus, manuscript writing or
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329

330 **Authors' Contribution**

331 AB: Conceptualization, Formal analysis, Methodology, Supervision, Writing -
332 original draft;

333 FC: Investigation, Methodology, Visualization, Writing - original draft;

334 MR: Conceptualization, Writing - original draft;

335 CT: Investigation, Visualization, Writing - original draft;

336 MZ: Data curation, Methodology;

337 PDF: Investigation;

338 IP: Data curation, Formal analysis, Investigation;

339 CRR: Conceptualization;

340 PC: Conceptualization, Funding acquisition, Methodology, Supervision;

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347

348 **REFERENCES**

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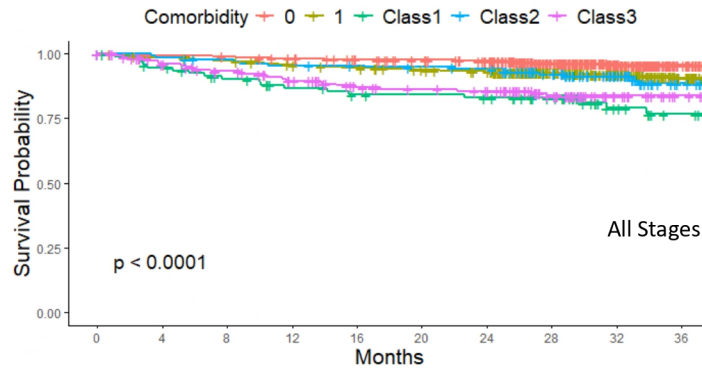
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459 **Figure 1.** Kaplan-Meier overall survival curves by stage and latent class
460 analysis (LCA)

461 **Figure 2.** Kaplan-Meier melanoma-specific survival curves by stage and latent
462 class analysis (LCA)

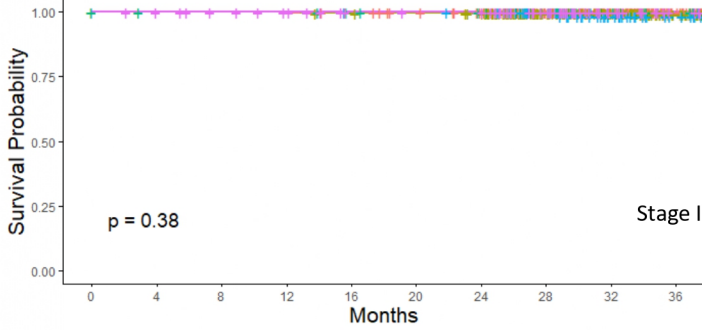
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Melanoma Specific Survival Curves 2019 & 2021 - Overall



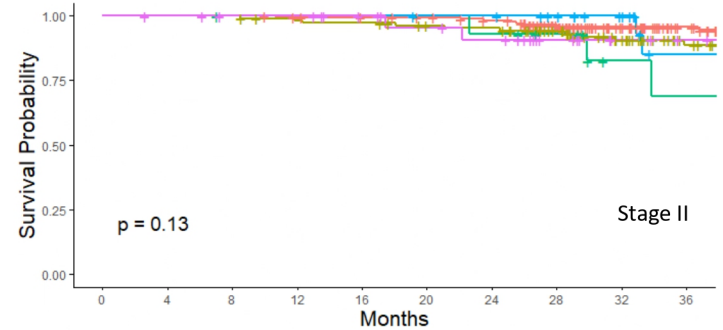
Number at risk

Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	1066	1059	1052	1043	1030	1022	1008	849	679	507
Comorbidity 1	628	617	608	595	586	576	567	466	373	284
Class1	97	88	79	72	68	67	65	56	35	28
Class2	136	134	131	128	126	124	122	104	77	47
Class3	187	170	159	146	131	126	122	89	59	44



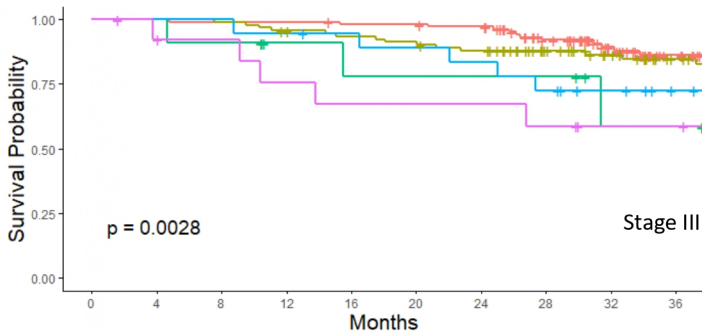
Number at risk

Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	719	718	718	718	716	712	707	605	498	384
Comorbidity 1	374	374	374	374	372	371	369	304	241	188
Class1	49	47	47	47	45	44	43	36	23	18
Class2	82	82	82	82	81	81	80	67	48	31
Class3	98	96	93	90	85	84	84	66	44	33



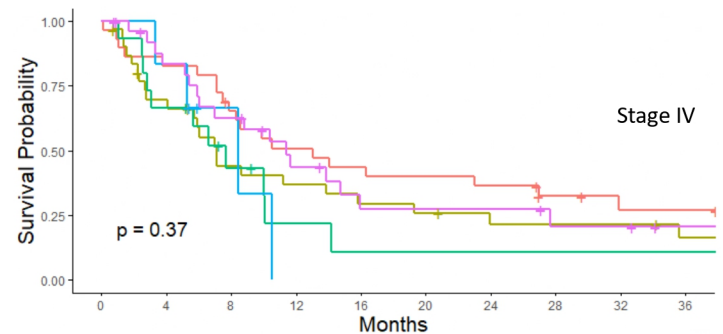
Number at risk

Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	178	178	178	175	173	171	166	140	104	73
Comorbidity 1	110	110	110	106	105	100	99	83	65	48
Class1	16	16	14	14	14	14	13	11	6	5
Class2	28	28	28	28	28	27	27	24	19	10
Class3	31	30	28	28	24	21	19	12	7	5



Number at risk

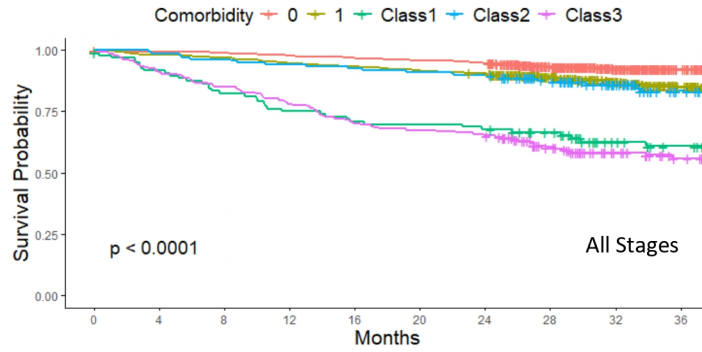
Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	109	109	108	108	106	106	104	82	61	39
Comorbidity 1	93	93	92	88	85	83	79	64	54	41
Class1	11	11	10	7	6	6	6	6	3	3
Class2	19	19	19	18	17	16	15	13	10	6
Class3	14	12	11	9	8	8	8	7	5	5



Number at risk

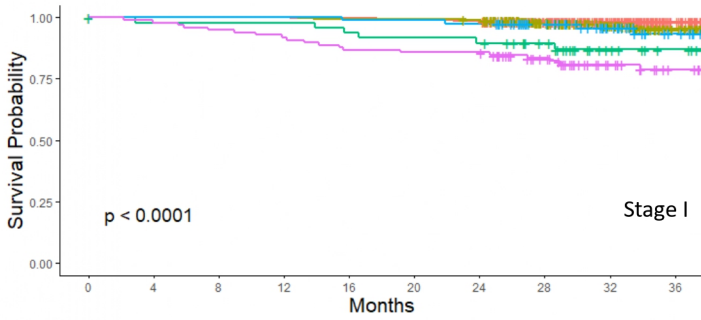
Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	29	24	18	14	12	11	10	7	5	5
Comorbidity 1	31	20	12	10	8	7	5	5	5	3
Class1	15	10	5	2	1	1	1	1	1	1
Class2	6	5	2	0	0	0	0	0	0	0
Class3	27	20	15	9	5	5	5	3	3	1

Overall Survival Curves 2019 & 2021



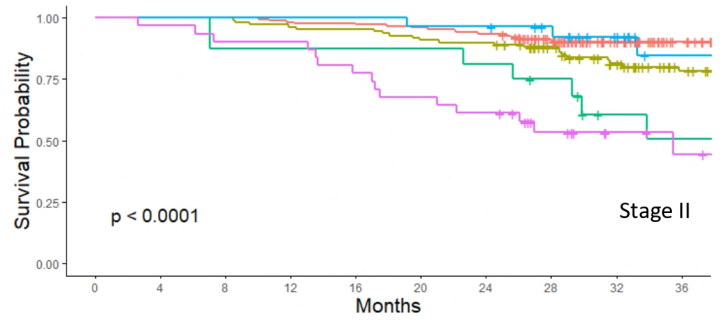
Number at risk

Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	1066	1059	1052	1043	1030	1022	1008	849	679	506
Comorbidity 1	628	617	608	595	586	576	567	466	373	284
Class1	97	88	79	72	68	67	65	56	35	28
Class2	136	134	131	128	126	124	122	103	76	47
Class3	187	170	159	146	131	126	122	89	59	44



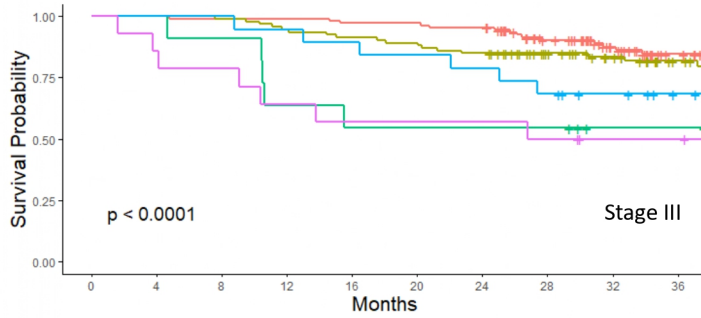
Number at risk

Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	719	718	718	718	716	712	707	605	498	384
Comorbidity 1	374	374	374	374	372	371	369	304	241	188
Class1	49	47	47	47	45	44	43	36	23	18
Class2	82	82	82	82	81	81	80	66	48	31
Class3	98	96	93	90	85	84	84	66	44	33



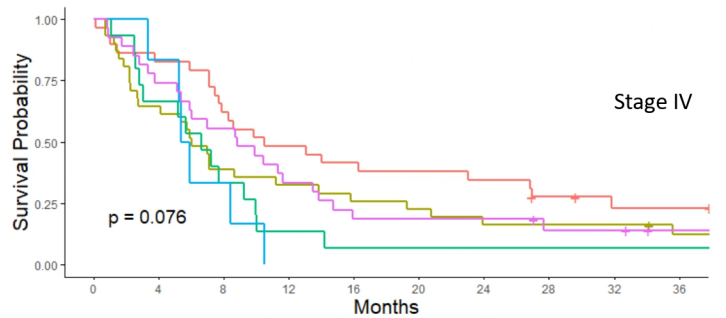
Number at risk

Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	178	178	178	175	173	171	166	140	104	72
Comorbidity 1	110	110	110	106	105	100	99	83	65	48
Class1	16	16	14	14	14	14	13	11	6	5
Class2	28	28	28	28	28	27	27	24	18	10
Class3	31	30	28	28	24	21	19	12	7	5



Number at risk

Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	109	109	108	108	106	106	104	82	61	39
Comorbidity 1	93	93	92	88	85	83	79	64	54	41
Class1	11	11	10	7	6	6	6	6	3	3
Class2	19	19	19	18	17	16	15	13	10	6
Class3	14	12	11	9	8	8	8	7	5	5



Number at risk

Strata	0	4	8	12	16	20	24	28	32	36
Comorbidity 0	29	24	18	14	12	11	10	7	5	5
Comorbidity 1	31	20	12	10	8	7	5	5	5	3
Class1	15	10	5	2	1	1	1	1	1	1
Class2	6	5	2	0	0	0	0	0	0	0
Class3	27	20	15	9	5	5	5	3	3	1