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# Impact of comorbidities on survival in melanoma patients

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## Abstract

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

**Methods** This retrospective population-based cohort study included all CM patients recorded in the regional Veneto Cancer Registry in 2019 and 2021. Comorbidity data (ICD-9-CM coding) were obtained from hospital discharge records and included 17 primary disease categories. Patients with at least two documented conditions were clustered via latent class analysis (LCA), with the optimal number of clusters determined via the Akaike information criterion (AIC).

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

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

**Keywords** Melanoma, Health care services: comorbidity, Health care resources, Survival, Cancer registry, Cohort study

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## Introduction

The incidence of cutaneous melanoma (CM) is steadily increasing in Western populations with lighter skin, and this epidemiological trend has a significant impact on public health [1, 2]. This increase in CM cases has been observed over the past several decades and is particularly pronounced in countries with predominantly fair-skinned populations, such as Australia, New Zealand, North America, and Northern Europe [3]. For this reason, melanoma is rapidly emerging as one of the leading causes of cancer worldwide, making it an increasingly significant public health concern that demands urgent attention and comprehensive management strategies.

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

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

As the global population continues to age, a notable demographic shift is ongoing. Projections indicate a significant increase in the number of individuals aged 65 and older by the year 2050 [10]. This increase has led to numerous challenges and complexities regarding health and longevity. Therefore, understanding the impact not only of the number of comorbidities, such as chronic diseases that often accompany aging but also of their specific patterns is becoming increasingly crucial. In fact, this demographic shift underscores the urgent need for comprehensive research focusing on the impact of comorbidities on CM outcomes to inform evidence-based guidelines for personalized care and ultimately improve overall patient outcomes [11].

This population-based retrospective cohort study aims to evaluate the impact of clusters of comorbidities on the survival of patients with cutaneous melanoma.

## Methods

### Study population

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

### Comorbidities

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

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

### Statistics

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

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

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

**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	58.01%	65.7 (14.4)	9–99	
Female	886	41.91%	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 (14.5)	47–99	
Number of comorbidities					< 0.001
None	1066	50.43%	61.5 (14.9)	14–99	
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

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

## Ethics

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

and used for monitoring and quality assurance purposes. The data analyses were performed on anonymous, aggregated data, ensuring that no individual could be identified. Ethical approval for the study was obtained from the

**Table 2** Probability (%) that a patient belongs to latent classes 1, 2, and 3 for 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%

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

ethics committee of the Veneto Oncological Institute (no. 52/2016).

## Results

The study considered 2,114 CM patients who received a diagnosis of cutaneous melanoma in 2019 and 2021 (M:F = 1.39; overall mean age = 63.4 years (SD 15.3); male mean age = 65.7; female mean age = 60.4) (Table 1).

At least one comorbidity was recorded in 1,048 (49.6%) CM patients (Table 1).

Among the 420 patients with two or more chronic conditions, latent class analysis identified three distinct clusters of comorbidities (Tables 2 and 3): Class 1 (20.96%) was predominantly associated with cardiovascular,

endocrine and respiratory conditions; Class 2 (29.97%) included patients with pregnancy-related and psychosocial conditions and dermatological conditions; and Class 3 (49.08%) included patients with injuries, multiorgan (e.g., genitourinary, digestive, and hematologic disorders) and multifactorial disorders. Class clustering was applied to correlate the comorbidity patterns with the patients' clinical outcomes.

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

Figures 1 and 2 show the Kaplan–Meier survival curves for overall and melanoma-specific mortality, respectively. These methods are based on CM clinical/pathological stage and latent class analysis (LCA).

Cox regression analyses, adjusted for age, sex, stage, and tumor site revealed hazard ratios (HRs) of 2.78, 2.67, and 3.08, respectively, for Classes 1, 2, and 3 rather than 2.30, 2.79, and 1.64, respectively, for overall and melanoma-specific mortality when patients with no comorbidities (1,066/2,114; 50.43%) were used as the reference group (Table 5).

## Discussion

In summary, the findings of this study highlight the significant influence of comorbidity class on both overall mortality rates and melanoma-specific mortality rates. This suggests that additional health conditions alongside melanoma can profoundly impact patient outcomes, emphasizing the need for a comprehensive approach to managing melanoma patients.

Previous evidence links individual or multiple concurrent comorbidities to cancer prognosis<sup>4</sup>. In fact, since 2010, the traditional use of age as a primary indicator of a patient's comorbidities has been critically re-evaluated. While acknowledging the prognostic significance of age, several authors have emphasized the importance of a more detailed assessment of clinical factors, including

**Table 3** Latent class analysis (LCA)

Comorbidity category	Definition	Typical conditions	Assigned patients N, (%)	Age mean (SD)
No Comorbidities (only Melanoma)	Patients without extra-tumor comorbidities	No additional conditions	1066 (54.43%)	61.0 (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)

COPD Chronic obstructive pulmonary disease

**Table 4** Clinicopathological characteristics of melanoma patients by 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)	

\*Pearson's chi-squared test for Stage, Sex and Tumor primary site; ANOVA Test for Age and Breslow Thickness

multiorgan functional status, cognitive function, psychological well-being, social support, and current medications [17].

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

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

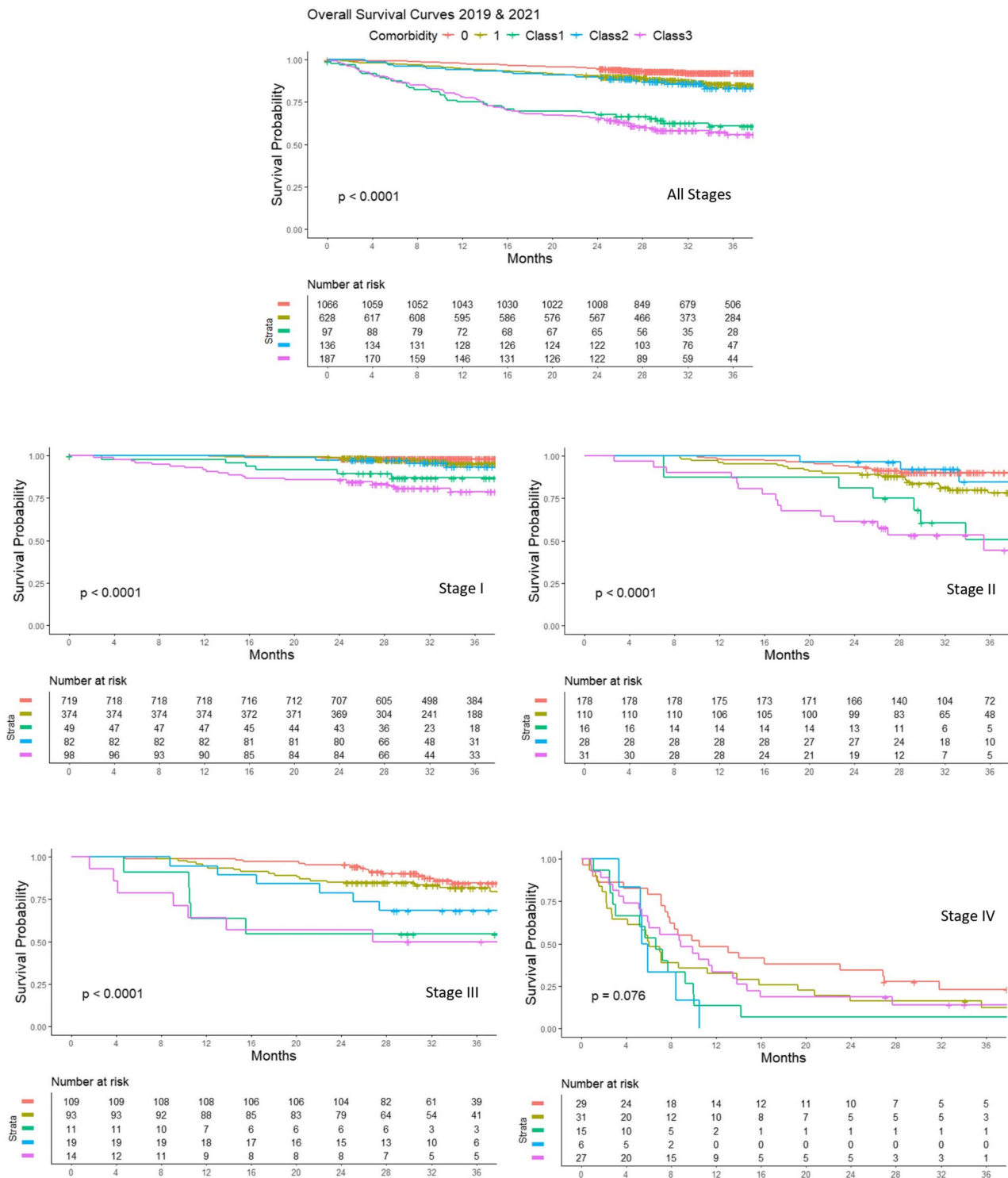
A number of studies support a relevant comorbidity prevalence in CM patients, particularly highlighting the prevalence of hypertension, dyslipidemia, obesity, and diabetes being among the most common [19–22].

The current findings confirm that any concurrent medical condition significantly impacts the prognosis of patients with melanoma. Furthermore, the present results indicate that injuries, multiorgan (genitourinary, digestive, hematologic disorders), and multifactorial conditions (i.e., Class 3) are associated with the poorest clinical outcomes among comorbidity classes. This aligns with the increased risk of skin malignancies, particularly CM, in immunocompromised patients, including those with hematological malignancies; moreover, substantial evidence links immunosuppression with unfavorable CM outcomes [23, 24].

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

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

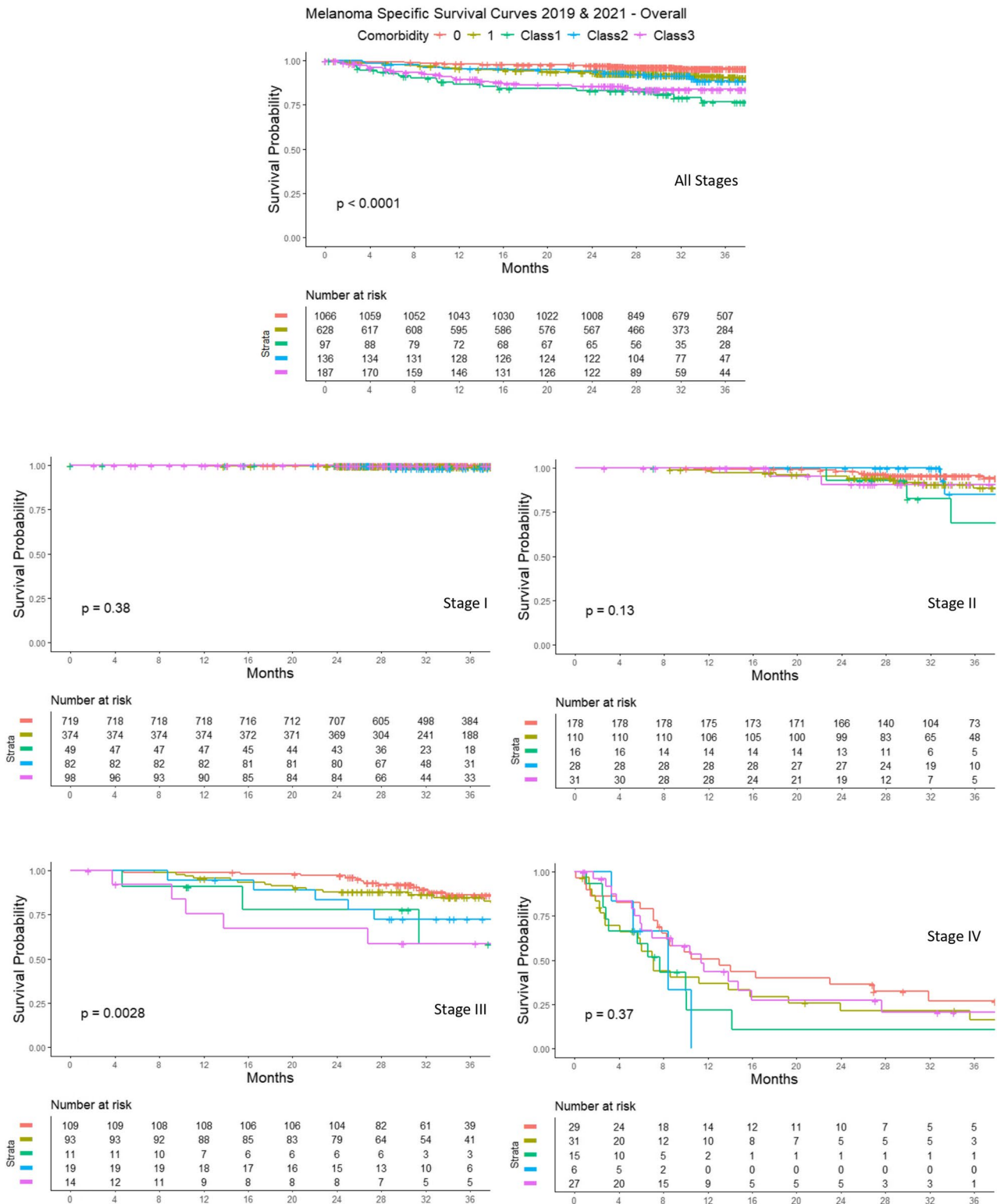
This study has several limitations. While identifying comorbidities via ICD-9-CM coding offers undeniable advantages of a standardized approach, it also reveals significant limitations, such as the lack of granularity for distinguishing between conditions and their severity. Since only hospitalized patients were included, less severe cases were likely excluded, such as patients in lower stages or younger patients. This selection bias may have resulted in an overestimation of the burden of comorbidity and its associated impact on mortality within the study cohort.



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

Moreover, the use of algorithms to identify chronic diseases through administrative records, such as those other than hospital discharge data, could help better identify mild outpatient conditions, thereby refining cluster definitions. Different cancers, other than melanoma, have

not been considered in the LCA or subsequent analyses. Since melanoma often has metachronous and synchronous metastases, new studies that also consider comorbid cancers are needed. Finally, longitudinal follow-up is essential to monitor how evolving immunotherapy



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

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

VARIABLE	Hazard Ratio (HR)	95% CI	p-value
<b>Overall mortality*</b>			
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
<b>Melanoma-specific mortality*</b>			
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

regimens may lead to potential adverse effects and modify the comorbidity patterns present at the time of diagnosis.

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

#### Abbreviations

CM Cutaneous Melanoma  
RTV Veneto Region's Regional Cancer Registry (Registro Tumori del Veneto)  
LCA Latent Class Analysis

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Not applicable.

#### Authors' contributions

AB: Conceptualization, Formal analysis, Methodology, Supervision, Writing – original draft; FC: Investigation, Methodology, Visualization, Writing – original draft; MR: Conceptualization, Writing – original draft; CT: Investigation, Visualization, Writing – original draft; PDF: Investigation; IP: Data curation, Formal analysis, Investigation; CRR: Conceptualization; PC: Conceptualization, Funding acquisition, Methodology, Supervision; ABF: Methodology, Supervision; SM: Funding acquisition, Methodology, Supervision.

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#### Data availability

The data supporting this study's findings are held by the Veneto Tumour Registry (RTV) and were used under license for this work. The anonymized minimal dataset necessary to replicate our findings has been made publicly available in the Figshare repository at the following link: [<https://doi.org/10.6084/m9.figshare.28795190>].

## Declarations

#### Ethics approval and consent to participate

This retrospective study involving human participants was conducted in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The Italian legislation identifies cancer registries as collectors of personal data for surveillance purposes, with no need to obtain individuals' explicit informed consent [REF: <https://www.gazzettaufficiale.it/eli/id/2017/05/12/17A03142/sgj>]. This study project was formally approved by the Ethics Committee of the Veneto Oncological Institute (protocol number 52/2016).

#### Consent for publication

Not applicable.

#### Competing interests

ABF received Consulting fees, Payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events, Support for attending meetings and/or travel, and Participation on a Data Safety Monitoring Board or Advisory Board and from Sanofi, Abbvie, LeoPharma, Pfizer, and Incyte. No other authors report any conflicts. The authors declare that this study was designed and conducted in the absence of any financial or commercial relationships that could be construed as a potential conflict of interest.

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