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Accuracy of malignant melanoma ICD-9-CM codes in Umbria, Napoli 3 Sud, and Friuli Venezia Giulia administrative healthcare databases

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Abstract

Objectives To assess the sensitivity and specificity of melanoma cancer *International Classification of Diseases 9th Revision – Clinical Modification* (ICD-9-CM) in three Italian administrative databases.

Design A diagnostic accuracy study comparing melanoma ICD-9-CM codes (index test) with medical chart (reference standard). Case ascertainment were based on neoplastic lesion of the skin and a histological diagnosis from a primary or metastatic site positive for melanoma.

Setting Administrative databases from Umbria Region, ASL 3 Napoli Sud (NA), and Friuli Venezia Giulia Region (FVG)

Participants 112, 130 and 130 cases (subjects with melanoma) were randomly selected from Umbria, NA, and FVG, respectively; 94 non-cases (subjects without melanoma) were randomly selected from each unit.

Outcome measures Sensitivity and specificity for ICD-9-CM code 172.x located in primary position.

Results The most common melanoma subtype was malignant melanoma of skin of trunk, except scrotum (ICD-9-CM code: 172.5), followed by malignant melanoma of skin of lower limb, including hip (ICD-9-CM code: 172.7). The mean age of the patients ranged from 60 to 61 years. Most of the diagnoses were performed in surgical departments.

The sensitivities were 100% (95% CI 96% to 100%) for Umbria, 99% (95% CI 94% to 100%) for NA, and 98% (95% CI 93% to 100%) for FVG. The specificities were 88% (95% CI 80% to 93%) for Umbria, 77% (95% CI 69% to 85%) for NA, and 79% (95% CI 71% to 86%) for FVG.

Conclusions The case definition for melanoma based on clinical or instrumental diagnosis, confirmed by histological examination, showed excellent sensitivities and good specificities in the

three operative units. Administrative databases from the three operative units can be used for epidemiological and outcome research of melanoma.

Strengths and limitations of this study

This study is the first that evaluated the accuracy of the International Classification of Diseases-9th Revision – Clinical Modification (ICD-9-CM) codes for melanoma in three large computerized Italian administrative databases using the same melanoma cancer case definition.

The strength of this study includes that of medical chart review as the reference standard and the use of STAR guidelines for reporting.

The results from the present assessment cannot be generalized in other settings.

Introduction

The burden of cancer is increasingly growing across populations and it is associated with major economic expenses and health resource use. Melanoma is probably the most aggressive form of skin cancer and when it spreads beyond the primary site in the skin it has very poor prognosis[1]. Reports indicate that incidence of malignant melanoma has increased globally [2 3] having an impact on the public health and economic burden of disease particularly in Western countries[4-6].

Trends in epidemiology of melanoma, and its survival rates can be assessed using cancer registries or administrative healthcare databases[7]. Compared to cancer registries, administrative databases have the advantage that they can link different sources of information (such as prescription data or comorbidities) providing a comprehensive research. However, these databases need to be adequately validated by comparing their main content, ie, the diagnosis that is represented by the *International Classification of Diseases, 9th Revision* (ICD-9) or *10th Revision* (ICD-10) edition, with another source, which generally is a cancer registry or the medical chart[8].

In Italy, all the Regional Health Authorities maintain large healthcare information systems containing patient data from all hospital and territorial sources. These databases have the potential to address important issues in post-marketing surveillance[9 10], epidemiology[11], quality performance and health services research[12]. However, there is a concern that their considerable potential as a source of reliable healthcare information has not been achieved due to lack of validation including codes related to melanoma[13]. Hence, it is imperative that Regional Health Authorities systematically validate their databases for critical diseases to productively use the information they contain[13-18].

The objective of the present study was to evaluate the accuracy of the ICD-9-CM codes in correctly identifying melanoma using three large Italian administrative healthcare databases. We performed this study applying the same methodological approach as stated in our previous protocol on validation concerning breast, lung and colorectal cancer cases[8].

Methods

Setting and data source

Administrative databases

From the early 90^{s}, local and regional Italian administrative databases have collected healthcare data about residents from public and private hospitals. These data include demographics, vital statistics, hospital admission and discharge dates, the admitting hospital department, principal and secondary discharge diagnoses as well as diagnostic procedures. Additionally, these databases comprise the records of all drug prescriptions listed in the National Drug Formulary and prescriber's information. Since health care is covered almost entirely by the Italian National Health System and each resident has a unique regional identification code, it is possible to reconstruct the disease and prescription history of each resident within the administrative database.

The target administrative databases for the present study were from the Umbria Region (890,000 residents), Local Health Unit 3 of Napoli (NA) (1,170,000 residents), and the Friuli Venezia Giulia (FVG) Region (1,227,000 residents). For the purpose of the present study the corresponding Units (Regional Health Authority of Umbria for Umbria Region, Registro Tumori Regione Campania for Local Health Unit 3 of Napoli, and Centro di Riferimento Oncologico Aviano for Friuli Venezia Giulia Region) conducted the same validation process independently within each own database.

Source population

All residents aged 18 or above of Umbria Region, Local Health Unit 3 of Napoli and the Friuli Venezia Giulia Region represented the target population. Any resident that has been discharged from hospital with a diagnosis of melanoma was considered. Due to difficulty in obtaining the medical charts, subjects that have been hospitalised outside the regional territory of competence were excluded from analysis.

Case selection and sampling method

In each administrative database, patients with the first occurrence of melanoma between 1st January 2012 and 31st December 2014 were identified using the ICD-9-CM codes 172.x located in primary position of hospital discharges. The estimated prevalent cases, that is, melanoma cases (ICD-9-CM codes in any position) in the five years (2007-2011) before the period of interest, were excluded. In the same period, non-cases, i.e. patients having in primary position a diagnosis of cancer (ICD-9 140-239) other than melanoma (ICD-9 172.x) were identified. Subsequently, for each of the above reported groups of ICD-9-CM codes, random samples of cases and non-cases were selected from each administrative database.

Chart abstraction and case ascertainment

The corresponding medical charts of the randomly selected samples of cases and non-cases were obtained from hospitals for validation purposes. Information retrieved from each medical chart included: date of birth and gender of the patient, dates of hospital admission and discharge, and any diagnostic procedure that contributed to the diagnosis of melanoma.

Within each unit, two reviewers received training on data abstraction. Based on a sample of 20 medical charts, within each unit, the inter-rater agreement regarding data abstraction of the several items within the medical charts among the pairs of reviewers was calculated using the κ statistics. The agreement among the pairs of reviewers resulted very high ($\kappa > 0.90$). Following the consensus review, data abstraction has been completed independently.

Case ascertainment of melanoma within the medical chart was based on (a) the clinically documented presence of a primary lesion of the skin, and (b) the histological documentation of melanoma from a primary or metastatic site[8]. To ensure consistency among reviewers, cases with uncertainty were discussed and resolved through the involvement of an oncologist (Rita Chiari).

Validation criteria

For melanoma, we considered the ICD-9-CM codes 172.x valid, when there is evidence of a neoplastic lesion of the skin and a histological diagnosis from a primary or metastatic site positive for melanoma.

Statistical analysis

As reported elsewhere[8], a random sample of 130 charts of cases was necessary to obtain an expected sensitivity of 80% with a precision of 10% and a power of 80%. For specificity calculation, we randomly selected non-cases from an oncological cohort of subjects within the databases excluding the subjects with the ICD-9-codes of melanoma. A sample of 94 charts of non-cases was deemed necessary to obtain an expected specificity of 90% with a precision of 10% and a power of 80%[8].

Sensitivity and specificity with their corresponding 95% confidence intervals were calculated by constructing 2 x 2 tables.

Results

The incident cases of melanoma were 113 from Umbria, 134 from NA, and 403 from FVG, from which, respectively, 112, 130 and 130 cases were randomly selected and the corresponding medical charts were requested for assessment. Fourteen (11%) and one medical charts (1%) were not available from NA and Umbria, respectively. **Figure 1** shows the study screening process by which incident cases were identified from the three operative units. For the non-cases, each unit randomly selected 94 medical charts. Two medical charts of non-cases from Umbria were missing.

The most common ICD-9-CM subgroup was the code 172.5 (i.e., malignant melanoma of skin of trunk, except scrotum) accounting for 30% in Umbria, 34% in NA, and 38% in FVG, followed by the code 172.7 (i.e., malignant melanoma of skin of lower limb, including hip) accounting for 19% in Umbria, 26% in NA, and 21% in FVG. The mean age of the patients was 61 years in Umbria, and 60 years in the other two operative units. Most of the cases were identified in surgical departments with a percentage ranging from 75% to 86%. The instrumental tools used for diagnosis included ultrasound, full-body CT scan, whole body PET/CT, CT scan of the head or MRI of the brain, and lymphoscintigraphy.

Histological examinations from biopsy were 77 (69%) for Umbria, 33 (28%) for NA, and 55 (42%) for FVG, while histological examinations from resection specimens after surgery were 80 (71%), 94 (81%), and 118 (91%), respectively. **Table 1** displays the basic characteristics of malignant melanoma of skin cases in each unit.

Clinical or instrumental diagnosis together with histological examinations based on melanoma case definition showed high sensitivities in the three operative units. The sensitivities were 100% (95% CI 96% to 100%) for Umbria, 99% (95% CI 94% to 100%) for NA, and 98% (95% CI 93% to 100%) for FVG. The false positive rates were higher than the false negative rates resulting in the following specificities: 88% (95% CI 80% to 93%) for Umbria, 77% (95% CI 69% to 85%) for NA, and 79% (95% CI 71% to 86%) for FVG.

Misclassification of cases and controls is described in **Table 2**. In Umbria, 6 false positive cases were due to histological documentation missing and 7 were due to negative histology of the wide excision of previous melanoma. In NA, 15 false positive cases were due to histological documentation missing and 12 were due to negative histology for melanoma. In FVG, 7 false positive cases were due to histological examination missing, and 15 were due to negative histology for melanoma (11 of which resulted positive for melanoma in situ). Overall, there were only two false negatives, one possible melanoma metastasis (in NA) and another skin cancer of unclear histology (in FVG).

Sensitivity analysis based on the worst case scenario did not show any statistical difference when missing data where considered false negatives (non-cases) or false positives (cases). Due to the 14 medical charts of the cases the specificity for the NA administrative database was reduced from 77% to 69% (95% CI 61% to 77%) albeit with no statistical difference.

Discussion

In administrative databases, the diagnosis of a disease is associated with a specific code from the *International Classification of Diseases, 9th Revision* (ICD-9) or *10th Revision* (ICD-10) edition. Despite its limitation, the ICD code is an innovative tool designed to map health conditions to corresponding generic categories together with specific variations[19]. Within three administrative databases, we have completed the validation of ICD-9 codes related to breast, lung, colorectal and cervix cancer.

In the present study, we evaluated the validity of diagnoses related to melanoma recorded as administrative data, using chart review as the gold standard. Our results suggest that the ICD-9 codes 172.x are accurate to identify incident melanoma cases. The sensitivities were excellent across all the three administrative databases and specificities were good. As far as we know this is the first study that addressed the topic of validation of melanoma in Italy. In the USA, using a linked SEER tumour registry-Medicare database, Barzilai et al determined the accuracy of Medicare claims to identify patients aged 65+ diagnosed with invasive melanoma[20]. The authors found that the overall sensitivity of combined Part A and Part B Medicare to identify incident cases of melanoma was 90%. Specificity and predictive values were not calculated[20].

Recent progresses in the use of immune-mediated or therapies such as targeted immunomodulatory therapies such as vemurafenib and dabrafenib have shown encouraging results in survival for metastatic patients with melanoma[21 22]. Another immunotherapeutic agent, ipilimumab, has shown to have important properties in enhancing the immune response against melanoma[23]. Trends in the epidemiology and evaluation of such innovative immunotherapies in terms of long-term outcomes can be performed using population-based studies in these validated administrative databases.

Strength and limitation

Our main strength is that to ascertain the presence of melanoma we used medical chart in which a clinical diagnosis combined with a histological documentation need to be present. Although we did

not publish a specific protocol for the assessment of the accuracy of melanoma ICD-9 codes, our study was based on the protocol[8] that aimed to assess the validation of codes related to breast, colorectal and lung cancer. With respect to the methodology, we state that no deviation from protocol occurred during study performance. Additionally, we followed recommended guidelines based on the criteria published by the STARD initiative for the accurate reporting of investigations of diagnostic studies. Hence, we used a detailed and explicit eligibility criteria, as well as duplicate and independent processes for medical chart review and data abstraction [24-26].

As declared in our protocol we prioritized the estimation of sensitivity rather than positive predictive value (PPV) because PPVs can be influenced by the prevalence of disease. However, we calculated the PPVs that resulted 88% for Umbria, 77% for NA, and 82% for FVG. To comply with the STARD we provide absolute numbers for the 2 X 2 tables.

Conclusion

Our study showed that administrative healthcare databases from Umbria, Napoli and FVG are accurate in identifying new melanoma cases using the ICD-9 code 172.x. Hence, these databases can confidently be used to monitor melanoma cancer trends, to assess the quality of healthcare delivery for patients with melanoma .

Footnotes

Contributors: AM, IA, MF, and DS conceived the original idea of the study. IA, DS, AM, MF, EB, GG, FC, MO, FS and WO designed the study. MC, AG, MFV, FC, MO, PE and VC identified the cohort using administrative database with the supervision of PC, GG, WO, EB, DS, MF, AM and FS. IA, FC, MO, AG, MG, VC, MFV, undertook the data abstraction with the supervision of AM, GG, WO, FS, MF, EB, and DS. IA, FS, AM, and DS performed case ascertainment. IA, AM, FC, PE, VC, and MO performed the analysis. DS, MF, GG, PC, AG, MG, FS, MFV, WO, and EB helped in the interpretation of the data.
The initial draft of the manuscript was prepared by IA, AM, EB, FS, MF, and MO. DS, GG, PC, FC, AG, MG, VC, MFV, PE, and WO revised critically the manuscript for important intellectual content. All the authors read and approved the final manuscript. AM, MF and EB are the guarantor of the data for the respective operative units.

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Competing interests None.

Data sharing statement No additional data are available.

Figure Caption

Figure 1. Flow-chart of incident melanoma cancer cases identification in primary position from the three administrative databases and the corresponding charts identified and examined.
Figure 2. Sensitivity and specificity with 95% confidence intervals for malignant melanoma ICD-9-CM codes for the three administrative databases.

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Table 1 Characteristics of subjects with melanoma cancer who were identified in the three administrative healthcare databases

Characteristics	Unit 1 (Umbria)	Unit 2 (Friuli Venezia Giulia)	Unit 3 (Asl Napoli 3 Sud)
Incident cases (N medical chart reviewed)	112	130	116
ICD-9 code			
172.0	-	1 (1)	-
172.1	1 (1)	2 (2)	-
172.2	4 (4)	3 (2)	2 (2)
172.3	9 (8)	13 (10)	8 (7)
172.4	5 (4)	9 (7)	2 (2)
172.5	34 (30)	49 (38)	39 (34)
172.6	19 (17)	15 (12)	11 (10)
172.7	22 (19)	27 (21)	30 (26)
172.8	4 (4)	8 (6)	5 (4)
172.9	14 (13)	3 (2)	19 (16)
Admission to department			
Medical	28 (25)	18 (14)	21 (18)
Surgical	84 (75)	112 (86)	95 (82)
Sex			
Male	64 (57)	69 (53)	52 (45)
Age, N (%)			
< 40	11 (10)	13 (10)	10 (9)
40 - 59	43 (38)	56 (43)	46 (39)
≥ 60	58 (52)	61 (47)	60 (52)
Clinical examination			
Skin lesion	93 (83)	59 (45)	61 (53)
Instrumental diagnosis			
Ultrasound	14	22	30
CT scan	57	14	25
PET/CT	3	3	3
Brain CT scan or RNM	4	-	5

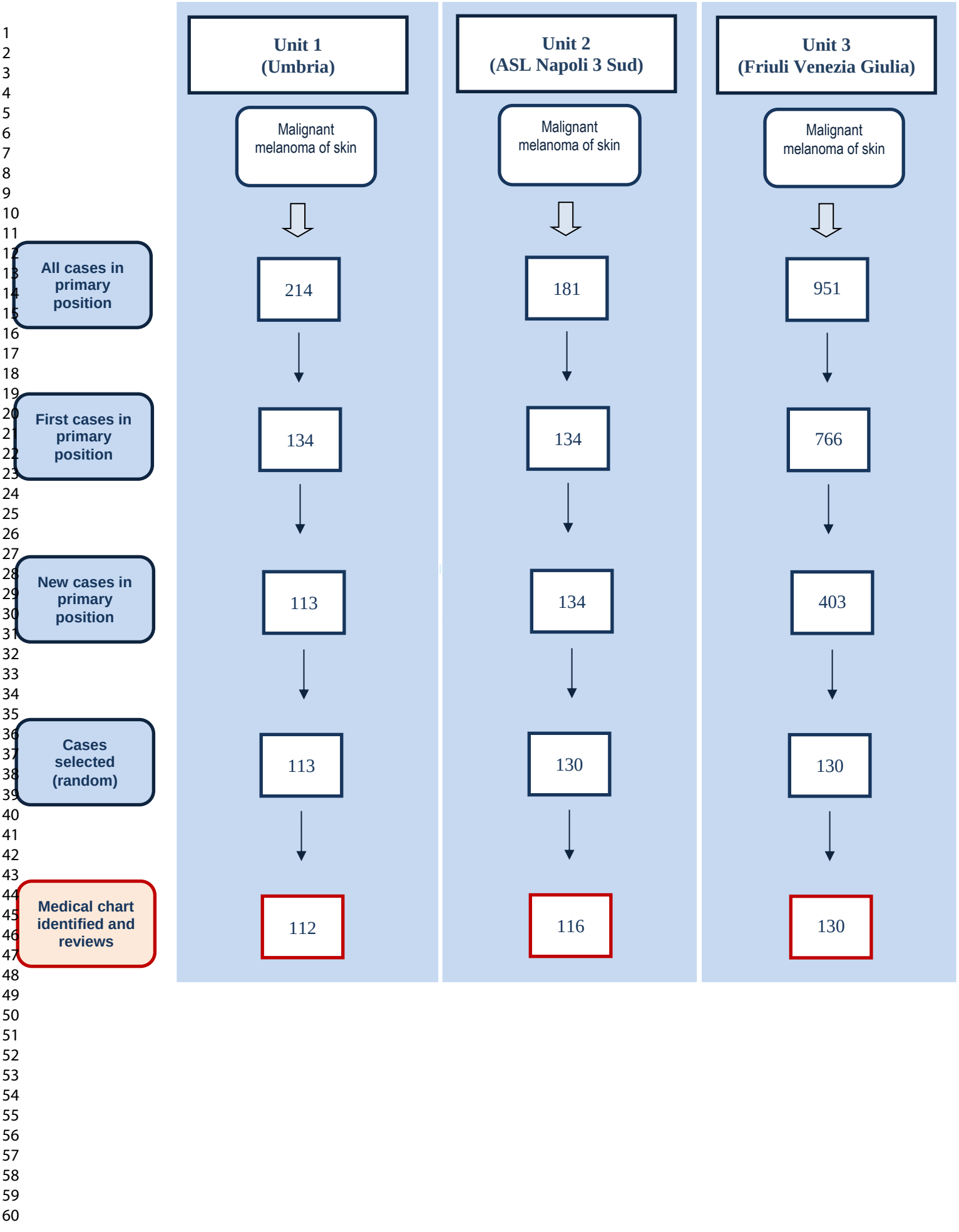
Lymphoscintigrapy	62	64	33
Surgical procedures			
Excisional biopsy, wide excision, sentinel lymph node biopsy and lymphadectomy	94 (84)	119 (92)	92 (79)
Hystological documentation			
Biopsy	77 (69)	55 (42)	33 (28)
Surgical resection specimen	80 (71)	118 (91)	94 (81)

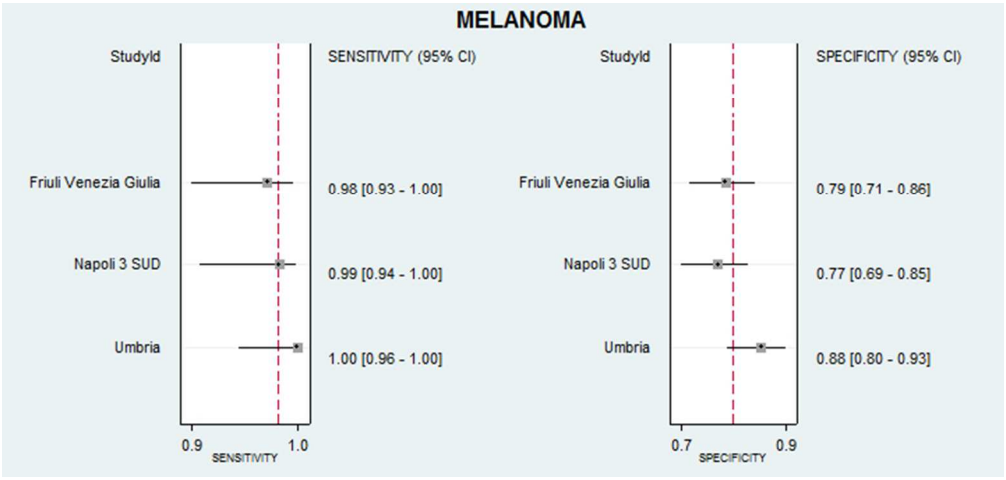
Table 2. Reason for incorrect identification of cases and controls

	Melanoma			
	Type of misclassification	**Umbria**	**ASL 3 Napoli**	**Friuli Venezia Giulia**
	False positives			
1	histological examination missing	6	15	7
2	negative histology	7	12	15
	a) melanoma in situ			11
	b) negative histology of wide excisions of previous melanoma	7	6	-
	c) negative histology (nevus, hyperplasia, dysplasia, verrucoid lesion)	-	4	4
	d) basal-cell carcinoma	-	2	-
Total		13	27	22
	False negatives			
1	possible melanoma relapse	-	-	-
2	possible melanoma metastasis	-	1	-
3	skin cancer of unclear histology	-	-	1
Total		-	1	1

Table 3. Cross tabulation of the index test (ICD-9-CM code 172.x) results by the results of the reference standard (medical chart)

Operative unit	TP	FP	TN	FN
Unit 1 (Umbria)	99	13	92	0
Unit 2 (Friuli Venezia Giulia)	107	23	92	2
Unit 3 (ASL 3 Napoli)	89	27	93	1


Unit 1 (Umbria)
Unit 2 (ASL Napoli 3 Sud)
Unit 3 (Friuli Venezia Giulia)
Malignant melanoma of skin
Malignant melanoma of skin
Malignant melanoma of skin
All cases in primary position
214
181
951
First cases in primary position
134
134
766
New cases in primary position
113
134
403
Cases selected (random)
113
130
130
Medical chart identified and reviews
112
116
130



Sensitivity and specificity with 95% confidence intervals for malignant melanoma ICD-9-CM codes for the three administrative databases.

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
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	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5-6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5-6
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6-7
	11	Rationale for choosing the reference standard (if alternatives exist)	6
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	7
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	7
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	na
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	na
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	na
	16	How missing data on the index test and reference standard were handled	7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	na
	18	Intended sample size and how it was determined	7
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 1
	20	Baseline demographic and clinical characteristics of participants	Page 8 and Table 1
	21a	Distribution of severity of disease in those with the target condition	na
	21b	Distribution of alternative diagnoses in those without the target condition	na
	22	Time interval and any clinical interventions between index test and reference standard	na
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 3
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Page 8-9, Figure 2
	25	Any adverse events from performing the index test or the reference standard	na
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Validating malignant melanoma ICD-9-CM codes in Umbria, ASL Napoli 3 Sud, and Friuli Venezia Giulia administrative healthcare databases: a diagnostic accuracy study

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Validating malignant melanoma ICD-9-CM codes in Umbria, ASL Napoli 3 Sud, and Friuli Venezia Giulia administrative healthcare databases: a diagnostic accuracy study

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Abstract

Objectives To assess the accuracy of *International Classification of Diseases 9th Revision – Clinical Modification* (ICD-9-CM) codes in identifying subjects with melanoma.

Design A diagnostic accuracy study comparing melanoma ICD-9-CM codes (index test) with medical chart (reference standard). Case ascertainment was based on neoplastic lesion of the skin and a histological diagnosis from a primary or metastatic site positive for melanoma.

Setting Administrative databases from Umbria Region, ASL Napoli 3 Sud (NA), and Friuli Venezia Giulia Region (FVG).

Participants 112, 130 and 130 cases (subjects with melanoma) were randomly selected from Umbria, NA, and FVG, respectively; 94 non-cases (subjects without melanoma) were randomly selected from each unit.

Outcome measures Sensitivity and specificity for ICD-9-CM code 172.x located in primary position.

Results The most common melanoma subtype was malignant melanoma of skin of trunk, except scrotum (ICD-9-CM code: 172.5), followed by malignant melanoma of skin of lower limb, including hip (ICD-9-CM code: 172.7). The mean age of the patients ranged from 60 to 61 years. Most of the diagnoses were performed in surgical departments.

The sensitivities were 100% (95% CI 96% to 100%) for Umbria, 99% (95% CI 94% to 100%) for NA, and 98% (95% CI 93% to 100%) for FVG. The specificities were 88% (95% CI 80% to 93%) for Umbria, 77% (95% CI 69% to 85%) for NA, and 79% (95% CI 71% to 86%) for FVG.

Conclusions The case definition for melanoma based on clinical or instrumental diagnosis, confirmed by histological examination, showed excellent sensitivities and good specificities in the three operative units. Administrative databases from the three operative units can be used for epidemiological and outcome research of melanoma.

Strengths and limitations of this study

- This study is the first that evaluated the accuracy of the International Classification of Diseases-9th Revision – Clinical Modification (ICD-9-CM) codes for melanoma in three large computerized Italian administrative databases using the same case definition for melanoma.
- The strength of this study includes the use of medical chart review as the reference standard and the use of STARD guidelines for reporting.
- The results from the present assessment cannot be generalized in other settings.
- We are unsure whether the results presented for the ICD-9 code 172.x related to malignant melanoma of the skin could be also valid for the corresponding ICD-10 code C43.x.

Introduction

The burden of cancer is increasingly growing across populations and it is associated with major economic expenses and health resource use. Melanoma is probably the most aggressive form of skin cancer and when it spreads beyond the primary site in the skin it has very poor prognosis[1]. Reports indicate that incidence of malignant melanoma has increased globally [2 3] having an impact on the public health and economic burden of disease particularly in Western countries[4-6].

Trends in epidemiology of melanoma, and its survival rates can be assessed using cancer registries or administrative healthcare databases[7]. Compared to cancer registries, administrative databases have the advantage that they can link different sources of information (such as prescription data or comorbidities) providing a comprehensive research. However, these databases need to be adequately validated by comparing their main content, ie, the diagnosis that is represented by the *International Classification of Diseases, 9th Revision* (ICD-9) or *10th Revision* (ICD-10) edition, with another source, which generally is a cancer registry or the medical chart[8].

In Italy, all the Regional Health Authorities maintain large healthcare information systems containing patient data from all hospital and territorial sources. These databases have the potential to address important issues in post-marketing surveillance[9 10], epidemiology[11], quality performance and health services research[12]. However, there is a concern that their considerable potential as a source of reliable healthcare information has not been achieved due to lack of validation including codes related to melanoma[13]. Hence, it is imperative that Regional Health Authorities systematically validate their databases for critical diseases to productively use the information they contain[13-18].

The objective of the present study was to evaluate the accuracy of the ICD-9-CM codes in correctly identifying melanoma using three large Italian administrative healthcare databases. We performed this study applying the same methodological approach as stated in our previous protocol on validation concerning breast, lung and colorectal cancer cases[8].

Methods

Setting and data source

Administrative databases

From the early 90s, local and regional Italian administrative databases have collected healthcare data about residents from public and private hospitals. These data include demographics, vital statistics, hospital admission and discharge dates, the admitting hospital department, principal and secondary discharge diagnoses as well as diagnostic procedures. Additionally, these databases comprise the records of all drug prescriptions listed in the National Drug Formulary and prescriber's information. Since health care is covered almost entirely by the Italian National Health System and each resident has a unique regional identification code, it is possible to reconstruct the disease and prescription history of each resident within the administrative database. However, within the environment of the databases and new code is generated to secure the identity of the residents.

The administrative databases contains also the number of the Hospital Discharge Register with which it is possible to identify the medical charts that are stored physically in their respective hospital or local health unit. The registration number contains the codes of the hospital and department of admission and is generated in way that it becomes a single code at national level to avoid any duplicate.

The target administrative databases for the present study were from the Umbria Region (890,000 residents), ASL Napoli 3 Sud (NA) (1,170,000 residents), and the Friuli Venezia Giulia (FVG) Region (1,227,000 residents). For the purpose of the present study the corresponding Units (Regional Health Authority of Umbria for Umbria Region, Registro Tumori Regione Campania for ASL Napoli 3 Sud, and Centro di Riferimento Oncologico Aviano for Friuli Venezia Giulia Region) conducted the same validation process independently within each own database.

Source population

All residents aged 18 or above of Umbria Region, ASL Napoli 3 Sud and the Friuli Venezia Giulia Region represented the target population. Any resident that has been discharged from hospital with a diagnosis of melanoma was considered. Due to difficulty in obtaining the medical charts, subjects that have been hospitalised outside the regional territory of competence were excluded from analysis.

Patient and Public Involvement

Patients were not directly involved. This was a retrospective study based on the consultation of medical charts. Ethical approval for the present study including the access to medical charts was obtained from the Ethics Committee of the Umbria Region Health Authority (CEAS).

Case selection and sampling method

In each administrative database, patients with the first occurrence of melanoma between 1st January 2012 and 31st December 2014 were identified using the ICD-9-CM codes 172.x located in primary position of hospital discharges. From this cohort, prevalent cases, that is, melanoma cases (ICD-9-CM codes in any position) in the five years (2007-2011) before the period of interest, were excluded. This cohort represented our target population from which a sample of cases was obtained using a simple random method.

In the same time frame, non-cases, i.e. patients having in primary position a diagnosis of cancer (ICD-9 140-239) other than melanoma (ICD-9 172.x) were identified. From this cohort prevalent cases, that is, those with the same diagnosis (ICD-9 140-239 codes in any position) in the five years (2007-2011) before the period of interest, were excluded. This cohort represented our target population from which a sample of non-cases (controls) was obtained using a simple random method.

Chart abstraction and case ascertainment

The corresponding medical charts of the randomly selected samples of cases and non-cases were obtained from hospitals for validation purposes. Information retrieved from each medical chart included: date of birth and gender of the patient, dates of hospital admission and discharge, and any diagnostic procedure that contributed to the diagnosis of melanoma.

Within each unit, two reviewers received training on data abstraction. Based on a sample of 20 medical charts, within each unit, the inter-rater agreement regarding data abstraction of the several items within the medical charts among the pairs of reviewers was calculated using the κ statistics. The agreement among the pairs of reviewers resulted very high ($\kappa > 0.90$). Following the consensus review, data abstraction has been completed independently.

Case ascertainment of melanoma within the medical chart was based on (a) the clinically documented presence of a primary lesion of the skin, and (b) the histological documentation of melanoma from a primary or metastatic site[8]. To ensure consistency among reviewers, cases with uncertainty were discussed and resolved through the involvement of an oncologist (Rita Chiari).

Validation criteria

For melanoma, we considered the ICD-9-CM codes 172.x valid, when there is evidence of a neoplastic lesion of the skin and a histological diagnosis from a primary or metastatic site positive for melanoma.

Statistical analysis

As reported elsewhere[8], a random sample of 130 charts of cases was necessary to obtain an expected sensitivity of 80% with a precision of 10% and a power of 80% according to binomial exact calculation[19]. For specificity calculation, we randomly selected non-cases from an oncological cohort of subjects within the databases excluding the subjects with the ICD-9 codes of melanoma. A

sample of 94 charts of non-cases was deemed necessary to obtain an expected specificity of 90% with a precision of 10% and a power of 80%[8].

Sensitivity and specificity with their corresponding 95% confidence intervals were calculated by constructing 2 x 2 tables.

Results

The incident cases of melanoma were 113 from Umbria, 134 from NA, and 403 from FVG, from which, respectively, 113, 130 and 130 cases were randomly selected and the corresponding medical charts were requested for assessment. Fourteen (11%) and one medical charts (1%) were not available from NA and Umbria, respectively. **Figure 1** shows the study screening process by which incident cases were identified from the three operative units. For the non-cases, each unit randomly selected 94 medical charts. Two medical charts of non-cases from Umbria were missing.

The most common ICD-9-CM subgroup was the code 172.5 (i.e., malignant melanoma of skin of trunk, except scrotum) accounting for 30% in Umbria, 34% in NA, and 38% in FVG, followed by the code 172.7 (i.e., malignant melanoma of skin of lower limb, including hip) accounting for 19% in Umbria, 26% in NA, and 21% in FVG. The mean age of the patients was 61 years in Umbria, and 60 years in the other two operative units. Most of the cases were identified in surgical departments with a percentage ranging from 75% to 86%. The instrumental tools used for diagnosis included ultrasound, full-body CT scan, whole body PET/CT, CT scan of the head or MRI of the brain, and lymphoscintigraphy.

Histological examinations from biopsy were 77 (69%) for Umbria, 33 (28%) for NA, and 55 (42%) for FVG, while histological examinations from resection specimens after surgery were 80 (71%), 94 (81%), and 118 (91%), respectively. **Table 1** displays the basic characteristics of malignant melanoma of skin cases in each unit.

Clinical or instrumental diagnosis together with histological examinations based on melanoma case definition showed high sensitivities in the three operative units. The sensitivities were 100% (95% CI 96% to 100%) for Umbria, 99% (95% CI 94% to 100%) for NA, and 98% (95% CI 93% to 100%) for FVG. The false positive rates were higher than the false negative rates resulting in the following specificities: 88% (95% CI 80% to 93%) for Umbria, 77% (95% CI 69% to 85%) for NA, and 79% (95% CI 71% to 86%) for FVG. **Figure 2** displays accuracy results with their confidence intervals.

Misclassification of cases and controls is described in **Table 2**. In Umbria, 6 false positive cases were due to histological documentation missing and 7 were due to negative histology of the wide excision of previous melanoma. In NA, 15 false positive cases were due to histological documentation missing and 12 were due to negative histology for melanoma. In FVG, 7 false positive cases were due to histological examination missing, and 15 were due to negative histology for melanoma (11 of which resulted positive for melanoma in situ). Overall, there were only two false negatives, one possible melanoma metastasis (in NA) and another skin cancer of unclear histology (in FVG).

Sensitivity analysis based on the worst case scenario did not show any statistical difference when missing data were considered false negatives (non-cases) or false positives (cases). Due to the 14 medical charts of the cases, the specificity for the NA administrative database was reduced from 77% to 69% (95% CI 61% to 77%) albeit with no statistical difference.

Discussion

In administrative databases, the diagnosis of a disease is associated with a specific code from the *International Classification of Diseases, 9th Revision* (ICD-9) or *10th Revision* (ICD-10) edition. Despite its limitation, the ICD code is an innovative tool designed to map health conditions to corresponding generic categories together with specific variations[20]. Within three administrative databases, we have completed the validation of ICD-9 codes related to breast, lung, colorectal and cervix cancer. We limited our analysis to ICD-9 codes because in Italy they are still used in the hospital discharge data.

In the present study, we evaluated the validity of diagnoses related to melanoma recorded as administrative data, using chart review as the gold standard. Our results suggest that the ICD-9 codes 172.x are accurate to identify incident melanoma cases. The sensitivities were excellent across all the three administrative databases and specificities were good. As far as we know this is the first study that addressed the topic of validation of melanoma in Italy. In the USA, using a linked SEER tumour registry-Medicare database, Barzilai et al determined the accuracy of Medicare claims to identify patients aged 65+ diagnosed with invasive melanoma[21]. The authors found that the overall sensitivity of combined Part A and Part B Medicare to identify incident cases of melanoma was 90%. Specificity and predictive values were not calculated[21].

Recent progresses in the use of immune-mediated or therapies such as targeted immunomodulatory therapies such as vemurafenib and dabrafenib have shown encouraging results in survival for metastatic patients with melanoma[22 23]. Another immunotherapeutic agent, ipilimumab, has shown to have important properties in enhancing the immune response against melanoma[24]. Trends in the epidemiology and evaluation of such innovative immunotherapies in terms of long-term outcomes can be performed using population-based studies in these validated administrative databases.

Strength and limitation

Our main strength is that to ascertain the presence of melanoma we used medical chart in which a clinical diagnosis combined with a histological documentation need to be present. Although we did not publish a specific protocol for the assessment of the accuracy of melanoma ICD-9 codes, our study was based on the protocol[8] that aimed to assess the validation of codes related to breast, colorectal and lung cancer. With respect to the methodology, we state that no deviation from protocol occurred during study performance. Additionally, we followed recommended guidelines based on the criteria published by the STARD initiative for the accurate reporting of investigations of diagnostic studies. Hence, we used a detailed and explicit eligibility criteria, as well as duplicate and independent processes for medical chart review and data abstraction [25-27].

As declared in our protocol we prioritized the estimation of sensitivity rather than positive predictive value (PPV) because PPVs can be influenced by the prevalence of disease. However, we calculated the PPVs that resulted 88% for Umbria, 77% for NA, and 82% for FVG. To comply with the STARD we provide absolute numbers for the 2 X 2 tables (**Table 3**).

The mean age of our sample population ranged between ranged between 60 to 61 years that is higher than the mean age (55 years) reported in the medical literature[28]. Age variability can be due to thickness and histological subtype of the melanoma but we were able to plan the acquirement of these data[28].

A possible limitation of our results for future research is that validation studies of administrative databases are related to the context where they are generated, and may not be generalizable to other settings. Another limitation is that we are unsure whether the results presented for the ICD-9 code 172.x related to malignant melanoma of the skin could be also valid for the corresponding ICD-10 code C43.x.

Conclusion

Our study showed that administrative healthcare databases from Umbria, Napoli and FVG are accurate in identifying new melanoma cases using the ICD-9 code 172.x. Hence, these databases can confidently be used to monitor melanoma trends, and to assess the quality of health care for patients with melanoma.

Footnotes

Contributors: AM, IA, MF, and DS conceived the original idea of the study. IA, DS, AM, MF, EB, GG, FC, MO, FS and WO designed the study. MG, AG, MFV, FC, MO, PE and VC identified the cohort using administrative database with the supervision of PC, GG, WO, EB, DS, MF, AM and FS. IA, FC, MO, AG, MG, VC, MFV, undertook the data abstraction with the supervision of AM, GG, WO, FS, MF, EB, and DS. IA, FS, AM, and DS performed case ascertainment. IA, AM, FC, PE, VC, and MO performed the analysis. DS, MF, GG, PC, AG, MG, FS, MFV, WO, and EB helped in the interpretation of the data.
The initial draft of the manuscript was prepared by IA, AM, EB, FS, MF, and MO. DS, GG, PC, FC, AG, MG, VC, MFV, PE, and WO revised critically the manuscript for important intellectual content. All the authors read and approved the final manuscript. AM, MF and EB are the guarantor of the data for the respective operative units.

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Competing interests None.

Ethics approval Regional Committee Ethics of Umbria (CEAS), authorization number 2656/15 (04/11/2015).

Data sharing statement No additional data are available.

Figure Caption

Figure 1. Flow-chart of incident melanoma cases identification in primary position from the three administrative databases and the corresponding charts identified and examined.
Figure 2. Sensitivity and specificity with 95% confidence intervals for malignant melanoma ICD-9-CM codes for the three administrative databases.

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Table 1 Characteristics of subjects with melanoma who were identified in the three administrative healthcare databases

Characteristics	Unit 1 (Umbria)	Unit 2 (Asl Napoli 3 Sud)	Unit 3 (Friuli Venezia Giulia)
Incident cases (N medical chart reviewed)	112	116	130
ICD-9 code, N (%)			
172.0 Malignant melanoma of skin of lip	-	-	1 (1)
172.1 Malignant melanoma of skin of eyelid, including canthus	1 (1)	-	2 (2)
172.2 Malignant melanoma of skin of ear and external auditory canal	4 (4)	2 (2)	3 (2)
172.3 Malignant melanoma of skin of other and unspecified parts of face	9 (8)	8 (7)	13 (10)
172.4 Malignant melanoma of skin of scalp and neck	5 (4)	2 (2)	9 (7)
172.5 Malignant melanoma of skin of trunk, except scrotum	34 (30)	39 (34)	49 (38)
172.6 Malignant melanoma of skin of upper limb, including shoulder	19 (17)	11 (10)	15 (12)
172.7 Malignant melanoma of skin of lower limb, including hip	22 (19)	30 (26)	27 (21)
172.8 Malignant melanoma of other specified sites of skin	4 (4)	5 (4)	8 (6)
172.9 Melanoma of skin, site unspecified	14 (13)	19 (16)	3 (2)
Admission to department, N (%)			
Medical	28 (25)	21 (18)	18 (14)
Surgical	84 (75)	95 (82)	112 (86)
Sex, N (%)			
Male	64 (57)	52 (45)	69 (53)
Age, N (%)			
< 40	11 (10)	10 (9)	13 (10)
40 - 59	43 (38)	46 (39)	56 (43)
≥ 60	58 (52)	60 (52)	61 (47)
Clinical examination, N (%)			
Detailed clinical description of the skin lesion	93 (83)	61 (53)	59 (45)
Instrumental diagnosis, N (%)			
Ultrasound	14 (13)	30 (26)	22 (17)

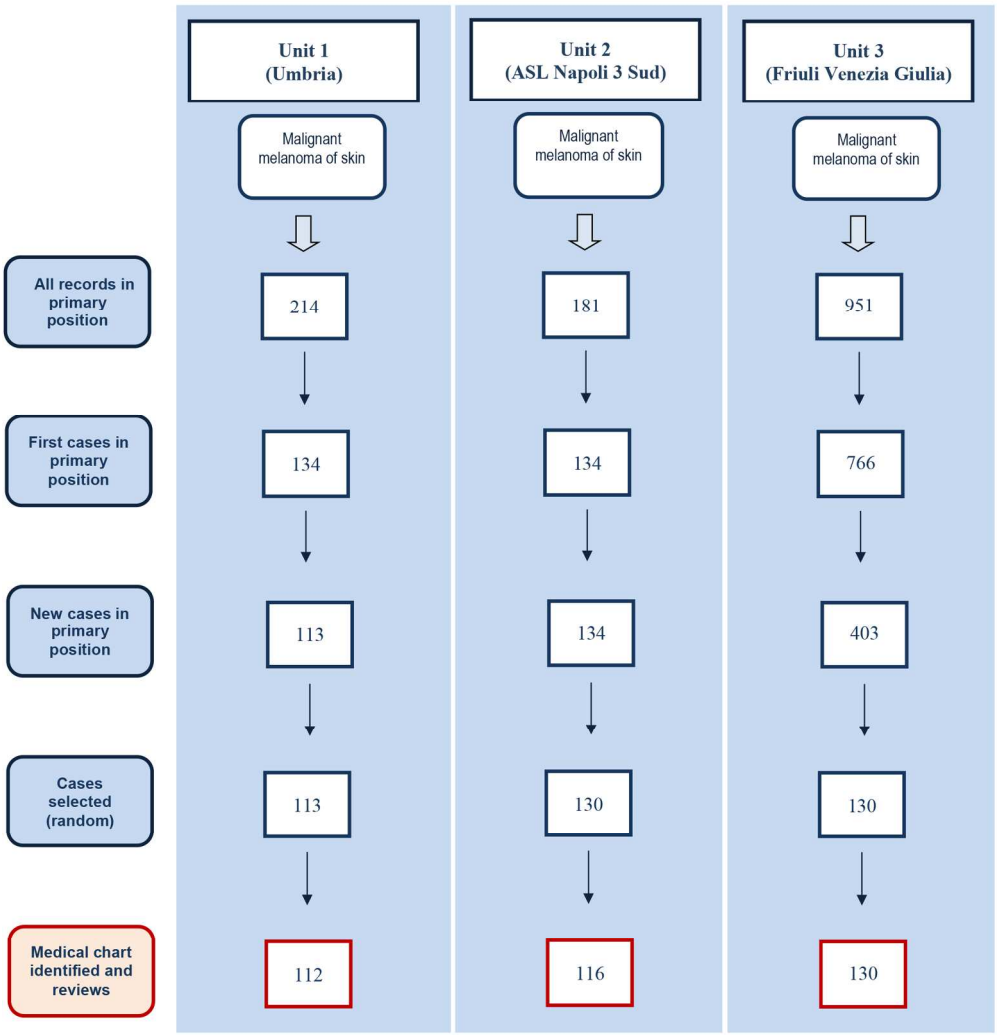
CT scan	57 (51)	25 (22)	14 (11)
PET/CT	3 (3)	3 (3)	3 (2)
Brain CT scan or MRI	4 (4)	5 (4)	-
Lymphoscintigraphy	62 (55)	33 (28)	64 (49)
None instrumental examinations	48 (43)	43 (37)	58 (45)
Surgical procedures, N (%)			
Excisional biopsy, wide excision, sentinel lymph node biopsy and lymphadenectomy	94 (84)	92 (79)	119 (92)
Hystological documentation, N (%)			
Diagnostic biopsy	77 (69)	33 (28)	55 (42)
Excision biopsy	80 (71)	94 (81)	118 (91)
Both diagnostic and excision biopsies	56 (50)	28 (24)	52 (40)

Table 2. Reason for incorrect identification of cases and controls

Melanoma				
	Type of misclassification	**Umbria**	**ASL Napoli 3**	**Friuli Venezia Giulia**
	False positives			
1	histological examination missing	6	15	7
2	negative histology	7	12	15
	a) melanoma in situ	-	-	11
	b) negative histology of wide excisions of previous melanoma	7	6	-
	c) negative histology (nevus, hyperplasia, dysplasia, verrucoid lesion)	-	4	4
	d) basal-cell carcinoma	-	2	-
Total		13	27	22
	False negatives			
1	possible melanoma relapse	-	-	-
2	possible melanoma metastasis	-	1	-
3	skin cancer of unclear histology	-	-	1
Total		-	1	1

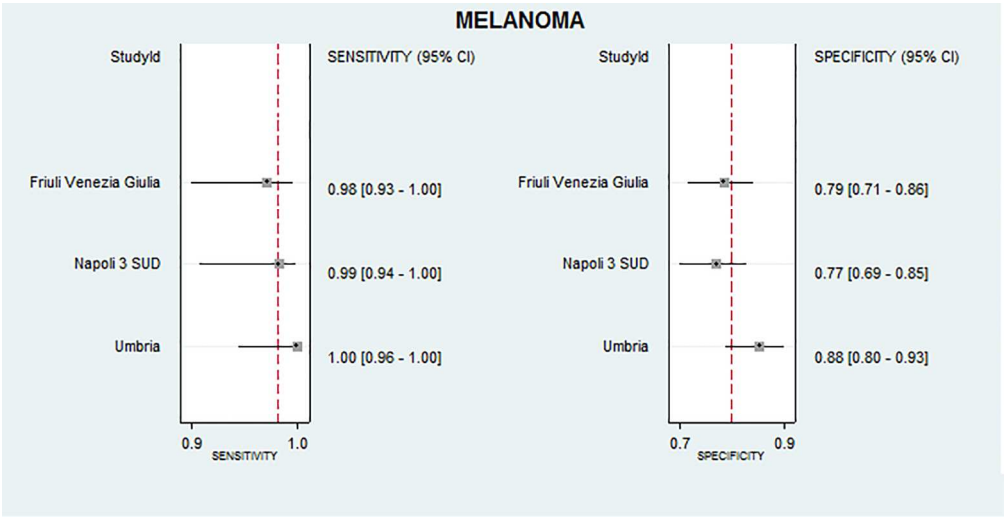
Table 3. Cross tabulation of the index test (ICD-9-CM code 172.x) results by the results of the reference standard (medical chart)

Operative unit	TP	FP	TN	FN
Unit 1 (Umbria)	99	13	92	0
Unit 2 (ASL Napoli 3 Sud)	89	27	93	1
Unit 3 (Friuli Venezia Giulia)	107	23	92	2



Flow-chart of incident melanoma cases identification in primary position from the three administrative databases and the corresponding charts identified and examined.

173x181mm (300 x 300 DPI)



Sensitivity and specificity with 95% confidence intervals for malignant melanoma ICD-9-CM codes for the three administrative databases

173x88mm (300 x 300 DPI)

Section & Topic	No	Item	Reported on page #
TITLE OR ABSTRACT			
	1	Identification as a study of diagnostic accuracy using at least one measure of accuracy (such as sensitivity, specificity, predictive values, or AUC)	1
ABSTRACT			
	2	Structured summary of study design, methods, results, and conclusions (for specific guidance, see STARD for Abstracts)	2
INTRODUCTION			
	3	Scientific and clinical background, including the intended use and clinical role of the index test	4
	4	Study objectives and hypotheses	4
METHODS			
Study design	**5**	Whether data collection was planned before the index test and reference standard were performed (prospective study) or after (retrospective study)	5
Participants	**6**	Eligibility criteria	5-7
	7	On what basis potentially eligible participants were identified (such as symptoms, results from previous tests, inclusion in registry)	5-6
	8	Where and when potentially eligible participants were identified (setting, location and dates)	5-6
	9	Whether participants formed a consecutive, random or convenience series	6
Test methods	**10a**	Index test, in sufficient detail to allow replication	6
	10b	Reference standard, in sufficient detail to allow replication	6-7
	11	Rationale for choosing the reference standard (if alternatives exist)	6
	12a	Definition of and rationale for test positivity cut-offs or result categories of the index test, distinguishing pre-specified from exploratory	7
	12b	Definition of and rationale for test positivity cut-offs or result categories of the reference standard, distinguishing pre-specified from exploratory	7
	13a	Whether clinical information and reference standard results were available to the performers/readers of the index test	na
	13b	Whether clinical information and index test results were available to the assessors of the reference standard	na
Analysis	**14**	Methods for estimating or comparing measures of diagnostic accuracy	7
	15	How indeterminate index test or reference standard results were handled	na
	16	How missing data on the index test and reference standard were handled	7
	17	Any analyses of variability in diagnostic accuracy, distinguishing pre-specified from exploratory	na
	18	Intended sample size and how it was determined	7
RESULTS			
Participants	**19**	Flow of participants, using a diagram	Figure 1
	20	Baseline demographic and clinical characteristics of participants	Page 8 and Table 1
	21a	Distribution of severity of disease in those with the target condition	na
	21b	Distribution of alternative diagnoses in those without the target condition	na
	22	Time interval and any clinical interventions between index test and reference standard	na
Test results	**23**	Cross tabulation of the index test results (or their distribution) by the results of the reference standard	Table 3
	24	Estimates of diagnostic accuracy and their precision (such as 95% confidence intervals)	Page 8-9, Figure 2
	25	Any adverse events from performing the index test or the reference standard	na
DISCUSSION			
	26	Study limitations, including sources of potential bias, statistical uncertainty, and generalisability	10-11
	27	Implications for practice, including the intended use and clinical role of the index test	11
OTHER INFORMATION			
	28	Registration number and name of registry	na
	29	Where the full study protocol can be accessed	4
	30	Sources of funding and other support; role of funders	12