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ORIGINAL PAPER

Psoriasis severity matters when dealing with all-cause mortality in psoriasis patients: a record linkage analysis in Northern Italy

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Abstract
Psoriasis has been linked with several comorbidities and increased all-cause mortality compared with the general population. Data are still limited concerning mortality especially from Southern European countries. Between January 2012 and December 2018, we conducted a retrospective cohort study on psoriasis patients and population controls in Northern Italy. Through record linkage of health-care databases, psoriasis cases were identified, and their morbidity and mortality were compared with the general population. The Charlson index was used as an index of comorbidities. Standardized mortality ratios (SMR) were estimated for overall psoriasis cases and for patients with mild vs moderate-to-severe disease, separately. We identified 12,693 psoriasis patients (mean age: 60.8 ± 16.3 years). They had a significantly higher Charlson index compared with the general population ($p < 0.001$). In spite of the higher rate of comorbidities, age-specific SMR was not increased in the psoriasis population as a whole (1.04 (95% CI 0.89–1.20)) or in people with mild psoriasis. However, a 40% higher than the expected risk of all-cause mortality was documented in individuals with moderate-to-severe psoriasis (SMR: 1.41; 95% CI 1.12–1.75). Notably, an excess mortality in these patients occurred as early as age 40-49 years. The proportion of deaths from malignancies and cardiovascular diseases was remarkably high. Our results support the notion that psoriasis severity influences mortality and indicate that patients with psoriasis, especially those with severe disease, should receive appropriate screening and health education.

Keywords Charlson index · Comorbidity · All-cause mortality · Psoriasis · Record linkage

Introduction

The use of electronic data repositories in health care (HC) for clinical and administrative purposes is well established in many countries. The nature of such data sources may vary significantly across countries. In Italy, HC databases are rooted in the structure of the National Health Service (NHS), which was established in 1978, based on principles of universal coverage, social financing through use of general taxation, and non-discriminatory access. The NHS provides coverage of the whole country population, both in outpatient and inpatient settings.

Record linkage analysis is a way to link together information provided by separate electronic databases and requires that a unique identifier represented by the fiscal code is present for each unit of analysis in the different databases. Specific algorithms can be used to select out of the universe of individuals registered in the databases, those who most likely present a disease of interest. Once such individuals are identified, they may be followed up over time using the information registered in the databases. In this way, HC databases may offer a cost-effective basis to originate real-world evidence on diseases of interest [5, 9, 32].

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So far, the use of HC databases in dermatology in Italy has been scarce compared to their large utilization for other chronic diseases, including rheumatoid arthritis, diabetes and chronic respiratory diseases [6, 8, 24].

Psoriasis is a chronic systemic inflammatory disease, which has been associated with increased risk of disability and significant costs to the society. Several pieces of evidence indicate that psoriasis, particularly the more severe disease, is associated with increased morbidity and all-cause mortality compared with the general population [11, 18, 20, 25]. Limited data are, however, available from Southern European countries, including Italy [21, 22], a country with one of the highest life expectancies in the world [13].

The aim of this study was to identify through record linkage analysis, adult patients with psoriasis in the Northern Italian province of Bergamo, and to estimate their comorbidity and mortality in comparison with the general population.

Methods

Study design

This was a retrospective cohort study, which applied a validated algorithm to select out of linked HC databases people likely suffering from psoriasis. Validation was conducted by comparing the classification of people obtained through the algorithm with data obtained on a sample of well-defined patients with psoriasis and of people not suffering from psoriasis from a population survey in the same geographic area and during the same study interval [29].

Study population

The study population was represented by all adult people (age ≥ 18 years) with a residence in the Bergamo province in Northern Italy (about 1,100,000 total inhabitants).

HC data were linked together through an encrypted unique identifier code. Data were extracted from the databases of the health authority of the province of Bergamo (Agenzia per la Tutela della Salute). HC databases used for the selection of patients with psoriasis included (i) the archive of all residents in the province which contributed demographic data; (ii) the archive of all the certifications of exemption from co-payment of selected chronic diseases, which included a code for severe psoriasis; (iii) the archive of all hospital discharge forms (HDFs) from public or private accredited hospitals, reporting all the diagnoses related to the hospitalization; (iv) the archive of all outpatient drug prescriptions reimbursable by the NHS, either dispensed directly or in hospital (biologics), with Anatomical Classification System (ATC).

Psoriasis patients were identified through the study algorithm in the period 1 January 2012 to 31 December 2012. The follow-up started on 1 January 2012 and ended on 31 December 2018.

The study was conducted according to the Declaration of Helsinki principles and received Ethics Committee approval by the local health authority (Agenzia di Tutela della Salute, ATS, of Bergamo). Patient consent was not needed because data were anonymized and encrypted.

Selection of the psoriasis cohort

The algorithm to identify psoriasis included the following items: (i) a psoriasis diagnosis by a dermatologist (the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD9-CM) code 696.0 or 696.1) reported in the HDFs; (ii) a certification of exemption for a psoriasis diagnosis (exemption code 045.696.0 or 045.696.1); (iii) prescription of antipsoriatic drugs including biologics (at least one among adalimumab, certolizumab, efalizumab, etanercept golimumab, infliximab, secukinumab, ustekinumab), conventional systemic treatments (at least 2 prescriptions within 1 year among acitretin, cyclosporine, methotrexate) or phototherapy (at least 2 prescriptions within 1 year) or topical treatments (at least 2 prescriptions within 1 year among betamethasone plus salicylic acid, calcipotriol, calcipotriol plus betamethasone, tacalcitol, tazarotene). All adult patients (aged ≥ 18 years) who met at least one of the criteria were considered for selection as potential patients with psoriasis. Individuals with use of TNF inhibitors, methotrexate or cyclosporine, and a concomitant diagnosis or exemption for ankylosing spondylitis (ICD-9-CM 720.0 or exemption code 054), Crohn's disease or ulcerative colitis (ICD-9-CM 555 or 556 respectively, or exemption code 009), or with use of oral corticosteroids or tacrolimus and a concomitant note AIFA88, i.e. corresponding to individuals with a likely diagnosis of atopic dermatitis, or individuals treated with phototherapy, and a concomitant diagnosis or exemption for atopic dermatitis, lymphoma or history of treatment with systemic steroids, or individuals with an exemption code 045.696.0 or 045.696.1 and a concomitant diagnosis of arthritis by a rheumatologist (ICD-9-CM 716.9) were not considered as psoriasis cases.

Mild psoriasis was considered when only a topical treatment was found in the patient history. Moderate-to-severe psoriasis was considered when a patient was treated systemically at any time for psoriasis during the follow-up or was hospitalized for the condition or when a psoriasis exemption was found. Controls were people without psoriasis at baseline and at any time during the follow-up, matched by age, sex, and area of residence with cases. Each case was matched with four controls.

Comorbidities

The Charlson comorbidity index (CCI) was used as a measure of overall comorbidity. Briefly, comorbidities were based on the ICD diagnostic codes found in HDFs before the index date and then categorized into 17 comorbidity categories [10]. Each comorbidity category had an associated weight, ranging from 1 to 6, based on the adjusted mortality risk. The sum of all weights resulted in a comorbidity score for the individual. The higher the score, the heavier is the burden of comorbidities. The validity of the coded diagnoses has been repeatedly confirmed [1].

Mortality

As a reference, for the calculation of standardized mortality ratios (SMR), we used age-specific mortality rates of the inhabitants of Bergamo referred to the year 2016. Causes of deaths were evaluated based on ICD10 diagnostic codes. For the reference Bergamo population, data on the causes of death were obtained from the National Institute of Statistics (ISTAT).

Statistical analysis

For descriptive purpose, continuous data were presented as mean ± standard deviations (SD), and categorical variables as number with percentages. Age was categorized in decennia.

The measures considered to validate the algorithm were: overall accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) with their 95% confidence intervals (CI). Differences in the distribution of data for continuous and categorical variables were assessed by using two-sample t test and Pearson's χ^2 test, respectively.

Psoriasis mortality was calculated as age-specific mortality rates per 100 person-years, stratified by sex. Standardized mortality ratio (SMR) with 95% CI was estimated by using age-specific mortality rates of the inhabitants of Bergamo. A subgroup analysis was performed for mild and moderate-to-severe psoriasis separately. All of the tests were considered significant at p value < 0.05. This study was reported according to the STROBE [37] and RECORD [5] guidelines. Analyses were performed with STATA (Stata Statistical Software: Release 13. College Station, TX: Stata Corp LP).

Results

Study population

We identified 12,693 adult patients with psoriasis. They had an average age of 60.8 ± 16.3 years (mean ± SD), with slight significant difference between sexes (61.5 ± 17.0 in females vs. 59.8 ± 16.0 in males, $p < 0.001$).

Validation of the algorithm

The algorithm to identify psoriasis patients was validated by comparing the classification of 100 people (mean age 53.0 ± 12.9 years) with a definite clinical diagnosis of psoriasis, obtained through the algorithm, with data on 100 individuals (mean age 52.0 ± 9.27 years) without such a diagnosis, obtained from a population survey performed in 2012 in the province of Bergamo [29]. The overall accuracy of the algorithm was 93.5% (95% CI 89.2–96.2), sensitivity was 88% (95% CI 80.2–93.0), specificity was 99% (95% CI 94.5–99.8), the PPV was 98.9% (95% CI 93.9–99.8), and the NPV was 89.2% (95% CI 82.0–93.7).

Charlson index and mortality of psoriasis

The distribution of CCI among 12,693 (20.5%) patients with psoriasis and 49,065 (79.5%) individuals without psoriasis is presented in the Table 1. Most of the patients with psoriasis (86%) and of the individuals without psoriasis (95%) had no comorbidity (CCI = 0). However, patients with psoriasis showed a significantly higher CCI than individuals without psoriasis (for CCI > 0, $p < 0.001$).

Between 2012 and 2018, 1247 (9.8%) deaths occurred among patients with psoriasis. Crude mortality per year was slightly higher in patients with psoriasis than in the general population (1.4% vs. 1%, respectively).

The age-specific SMR of patients with psoriasis was 1.04 (95% CI 0.89–1.20), indicating that mortality in the whole psoriasis cohort was virtually the same as expected in the general population. In subgroup analysis, no meaningful difference between patients with mild psoriasis ($n = 7873$, 62%) and the general population was documented; SMR was 0.73 (95% CI 0.50–1.03) in females and 0.89 (95% CI 0.68–1.13) in males. On the contrary, patients with moderate-to-severe psoriasis ($n = 4820$, 38%) had significantly higher SMR (1.41; 95% CI 1.12–1.75, $p = 0.003$), indicating an increased mortality risk of about 40% in moderate-to-severe psoriasis compared with the general population; in particular, SMR was 1.37 (95% CI 0.99–1.85) in females and 1.46 (95% CI 1.04–1.99) in males. The age-specific mortality rates per 100 person-years in psoriasis patients and in people without psoriasis are shown in the Fig. 1.

Information on the reported causes of death was obtained in 1078 patients with psoriasis who died between 2012 and 2016 and in the general Bergamo population for the year 2016. The distribution of the causes of death is reported in the Table 1. Malignancies and cardiovascular diseases accounted for more than half (63.8%) of the deaths. Higher

Table 1 Distribution of Charlson comorbidity index and mortality in individuals with and without psoriasis

	Psoriasis *N* = 12,693	Moderate to severe *N* = 4820	Mild *N* = 7873	No psoriasis *N* = 49,065	*P* value[a]
Age (yrs), mean ± SD	60.8 ± 16.3	60.9 ± 17.1	60.7 ± 18.3	60.8 ± 10.1	
Sex (females)	6929 (54.6%)	2274 (47.2%)	4655 (59.1%)	26,595 (54.0)	
Follow-up (years), mean ± SD	6.7 ± 1.0	6.6 ± 1.1	6.7 ± 1.0	6.8 ± 1.0	
Charlson comorbidity index, *n* (%)					< 0.001
0	10,891 (85.8)	3900 (80.9)	6991 (88.8)	46,437 (94.6)	
1	608 (4.8)	293 (6.1)	315 (4.1)	964 (2.0)	
≥ 2	1194 (9.4)	627 (13.0)	567 (7.2)	1664 (3.4)	
	Psoriasis *N* = 12,693	Moderate to severe *N* = 4820	Mild *N* = 7873	Bergamo adult population, 2016 *N* = 928,403	*P* value[a]
Deaths	1247	578	669	9464	
SMR (95% CI)	1.04 (0.89–1.20)	1.41 (1.12–1.75)	0.83 (0.67–1.01)	1	
Causes of death, *n* (%)[b]					< 0.001
Malignancies	485 (38.9)	238 (41.2)	247 (36.9)	3,164 (33.4)	
Cardiovascular disease	311 (24.9)	127 (22.0)	184 (27.5)	1,822 (19.3)	
Respiratory disease	94 (7.5)	29 (5.0)	65 (9.7)	657 (6.9)	
Metabolic disease	50 (4.0)	30 (5.2)	20 (3.0)	331 (3.5)	
Neurologic disease	46 (3.7)	21 (3.6)	25 (3.7)	631 (6.7)	
Liver disease	23 (1.8)	11 (1.9)	12 (1.8)	185 (2.0)	
Renal disease	24 (1.9)	17 (2.9)	7 (1.0)	146 (1.5)	
Infectious disease	45 (3.6)	26 (4.5)	19 (2.8)	347 (3.7)	

SMR standardized mortality rate, *CI* confidence interval

[a]Pearson's χ^2 test for psoriasis vs no psoriasis considering the overall distribution

[b]The analyses are restricted to 1078 individuals with psoriasis with available information up to 2016. Causes of death ($n = 7283$) in the general adult population of Bergamo were taken from ISTAT data for the same year (data available at: http://demo.istat.it/pop2018/index.html Accessed February 22, 2020). The causes of death are classified and coded in accordance with the International Statistical Classification of Diseases and Related Health Problems. Tenth Edition

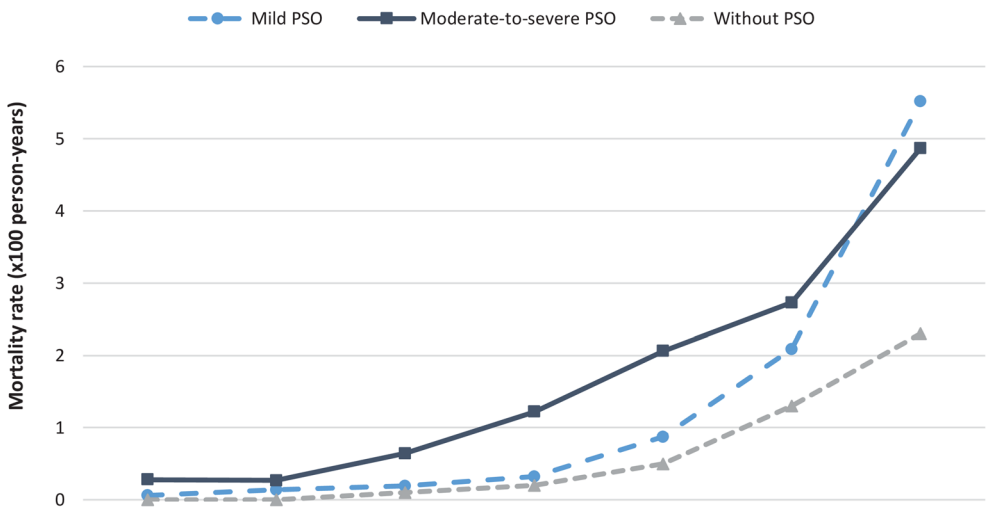
rates of death from respiratory, metabolic, and infectious diseases were also documented.

Discussion

Our study confirmed that psoriasis is associated with increased comorbidities as compared with the general population [3, 4, 21, 23, 38]. In spite of the higher CCI in psoriatic patients, we did not find an increased risk of mortality in such a population as a whole or in people with mild psoriasis. On the other hand, a 40% higher than expected risk of all-cause mortality was documented in individuals with moderate-to-severe psoriasis. Notably, an excess mortality in these patients occurred as early as age 40-49 years. The proportion of deaths from cancer and cardiovascular disease was remarkable high; however, these proportions cannot be taken as true risk estimates.

The high specificity (99%) of our HC data enabled an accurate evaluation of comorbidities, which were significantly more frequent in psoriasis patients compared with the general population. Other studies have associated psoriasis with an increased risk of several systemic disorders, including metabolic syndrome, cardiovascular disease, chronic obstructive pulmonary disease, liver and renal disease, infections, and malignancies [3, 4, 7, 14, 23, 26, 30, 33, 35, 38]. The factors underlying the link between psoriasis and increased comorbidities are unclear. The association may result from common genetic background, systemic inflammation, adverse effects of antipsoriatic treatments, or traditional risk factors for psoriasis such as smoking and obesity [30].

In spite of the higher CCI in psoriatic patients, we did not find an increased risk of mortality in such a population as a whole, but an increased risk of all-cause mortality limited to moderate-to-severe psoriasis, with malignancies and cardiovascular diseases accounting for more than half of the deaths. Our data are in line with those of a few large population studies and a recent systematic review showing a higher mortality risk in patients with psoriasis,



	18-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-69 yrs	70-79 yrs	80+ yrs
Mild PSO	0.1 (0.0-0.7)	0.1 (0.0-0.7)	0.2 (0.0-0.6)	0.3 (0.1-0.7)	0.9 (0.5-1.5)	2.1 (1.4-3.0)	5.5 (4.0-7.4)
Moderate-to-severe PSO	0.3 (0.0-1.9)	0.3 (0.0-1.3)	0.6 (0.0-1.4)	1.2 (0.6-2.1)	2.0 (1.3-3.2)	2.7 (1.8-4.0)	4.9 (2.9-7.8)
Without PSO	0.0 (0.0-0.1)	0.0 (0.0-0.1)	0.1 (0.0-0.2)	0.2 (0.1-0.3)	0.5 (0.3-0.7)	1.3 (1.0-1.6)	2.3 (1.8-2.8)

Fig. 1 Age-specific mortality rates in psoriasis patients according to severity (mild vs moderate to severe) and in people without psoriasis. At the bottom are indicated age-specific rates and, in parentheses, their 95% confidence intervals

especially high or restricted to severe psoriasis [2, 11, 19, 27, 28, 36].

Interestingly, a recent systematic review showed that the overall risk of developing cancer was significantly elevated in people with psoriasis, but the risk of cancer mortality was found to be elevated only in patients with severe psoriasis [31]. Similar discrepancy between morbidity and mortality has been documented for cardiovascular disease [12, 15]. In a study, a single measure of the body surface area (BSA) was able to predict long-term mortality in psoriasis patients [19]. We confirm that disease severity influences mortality by using a different indicator for severity, namely a combination of management variables.

Overall, there is an increasing body of evidence in favor of higher all-cause and cause-specific mortality in patients with moderate-to-severe disease compared to the general population. The systemic inflammation protracted over time seems, at least partly, to play a role in the apparently direct link between psoriasis severity and increased mortality [34].

A strength of our study is the whole population coverage by record linkage of HC data. All data sources underwent accurate monitoring and quality checks by the local health authority, since the data are used for resource allocation and planning of services. In addition to the internal validation, we measured the algorithm diagnostic accuracy using samples obtained from the general population. The diagnostic accuracy was high (93.5%), although the cross-sectional study design may have overestimated it.

The limitations of our analysis are the lack of detailed clinical information on psoriasis patients, such as severity indexes, e.g., psoriasis area and severity index (PASI), and the inability to control for covariates such as personal lifestyle data, including smoking or dietary habits, when analysing morbidity or mortality data.

Conclusion

By using record linkage analysis, our study provided real life evidence of an increased rate of comorbidities in psoriasis patients and a higher all-cause mortality restricted to moderate-to-severe psoriasis patients, compared with the general population in Northern Italy.

Our results support the notion that inspecting the skin of patients with psoriasis may give a hint on their survival chances [17] and indicate that patients with psoriasis, especially those with severe disease, should receive adequate screening and health education [18].

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Availability of data and material Data used for the analyses are available upon request from the corresponding author.

Compliance with ethical standards

Conflict of interest The authors report no conflict of interest in this work.

Ethical approval The study was conducted according to the Declaration of Helsinki principles and received Ethics Committee approval by the local health authority.

Informed consent Patient consent was not needed because data were anonymised and encrypted.

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