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Meta-analysis

Mortality in psoriasis and psoriatic arthritis: systematic review and meta-analysis

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ABSTRACT

We had found contradictory results that have been reported in recent publications regarding the mortality risk of patients with psoriasis (Pso) and psoriatic arthritis (PsA). These patients have aggregated risk behaviors, which directly impacted their morbidity/mortality. We included 15 studies, with a total population of that reported mortality risk in Pso and PsA patients. We calculated crude mortality rate (CMR) of each one and pooled CMR by group and 95% confidence intervals (CI). The pooled CMR for Pso was 14/1000 (95% CI: 6-21%), 12/1000 (95% CI: 10-15%) in mild, 19/1000 (95% CI: 15-23%) in severe and 12/1000 was observed (95% CI: 10-14%) in PsA. Mortality was relatively higher in PsA patients when compared with Pso, with a RR of 1.03 (95% CI: 1.01-1.06, p<0.01). Pso was associated with increased mortality when compared to the general population. Mild Pso and PsA have the same increased mortality, then again as the severity of Pso increased, so does its mortality. The final comparative mortality between patients with PsA and those with Pso was around 3%.

Keywords: Psoriasis, Arthritis psoriatic, Mortality, Crude mortality rate

INTRODUCTION

Pso is a common, chronic, recurrent, inflammatory disease of the skin mediated by TH17 lymphocytes response, it affects 2-4% of the general adult population, its prevalence varies according to geography from 0.9% in USA to 8.5% in Norway and 2% of the dermatological consultation in Mexico.[1-4] Pso patients developed erythematous scaly plaques and can affect nails and joints (PsA) in more than 25% of Pso patients.[5] PsA is a chronic inflammatory arthritis with an estimated incidence rate of up to 6.6 per 100,000 per year.[6] Both Pso and PsA have a negative physical, emotional and psychosocial impact.[7-15] Proliferation and differentiation of keratinocytes are dysregulated in Pso, with an important involvement of interleukin 17 (IL17), IL23 and tumor necrosis factor (TNF). These ILs induce a proinflammatory state, insulin resistance, endothelial dysfunction and cardiovascular disease, thus explaining the increased incidence of comorbidities in Pso and PsA. However, there are other risk factors such as family history, pharmacological adverse effects as well as alcohol and tobacco consumption.[16-20] Treatment depends on the severity of

the disease, which includes a combination of topical and/or systemic agents (e.g. phototherapy, drug modifying antirheumatic drugs and biological agents). Moderate cases, topical resistant patients and cases with nail and/or articulation involvement require a more aggressive approach.[2,21] Some authors have identified an increase in psoriasis mortality rate, which could be associated with the presence of comorbidities such as cardiovascular disease, neoplasms and pulmonary disease, among others. Another group has described an increased mortality risk in patients with severe psoriasis that could be associated with both co-morbidities and short and long term effects of the systemic treatment.[2,10,21-26] Although it is well known that the therapy of PsA and severe psoriasis is similar, in PsA patients, the premature mortality risk is different from Pso patients.[27] Recently, Dhana et al published a meta-analysis that reported an increased mortality risk in psoriasis patients, likewise Wong et al and Ali et al reported a similar increase in PsA, conversely Shbeeb et al and Wilson et al obtained different results.[27-34] Unfortunately, Dhana et al systematic review did not include PsA patients, consequently we considered that it was necessary to do an update to compare the mortality between psoriatic arthropathy and Pso. Until now, mortality in Pso and PsA continued to be an enigma and it was still controversial the association between severity, co-morbidities and therapeutics. The aim of this study was to determine the risk of mortality in patients with Pso and PsA in relation to general population. We also analyzed and described the main characteristics of the cohorts that were included in this systematic review.

METHODS

We performed a systematic review according to the preferred reporting items for systematic reviews and meta-analyses statement (PRISMA) and meta-analyses of observational studies in epidemiology (MOOSE) for systematic reviews and meta-analysis.[35,36]

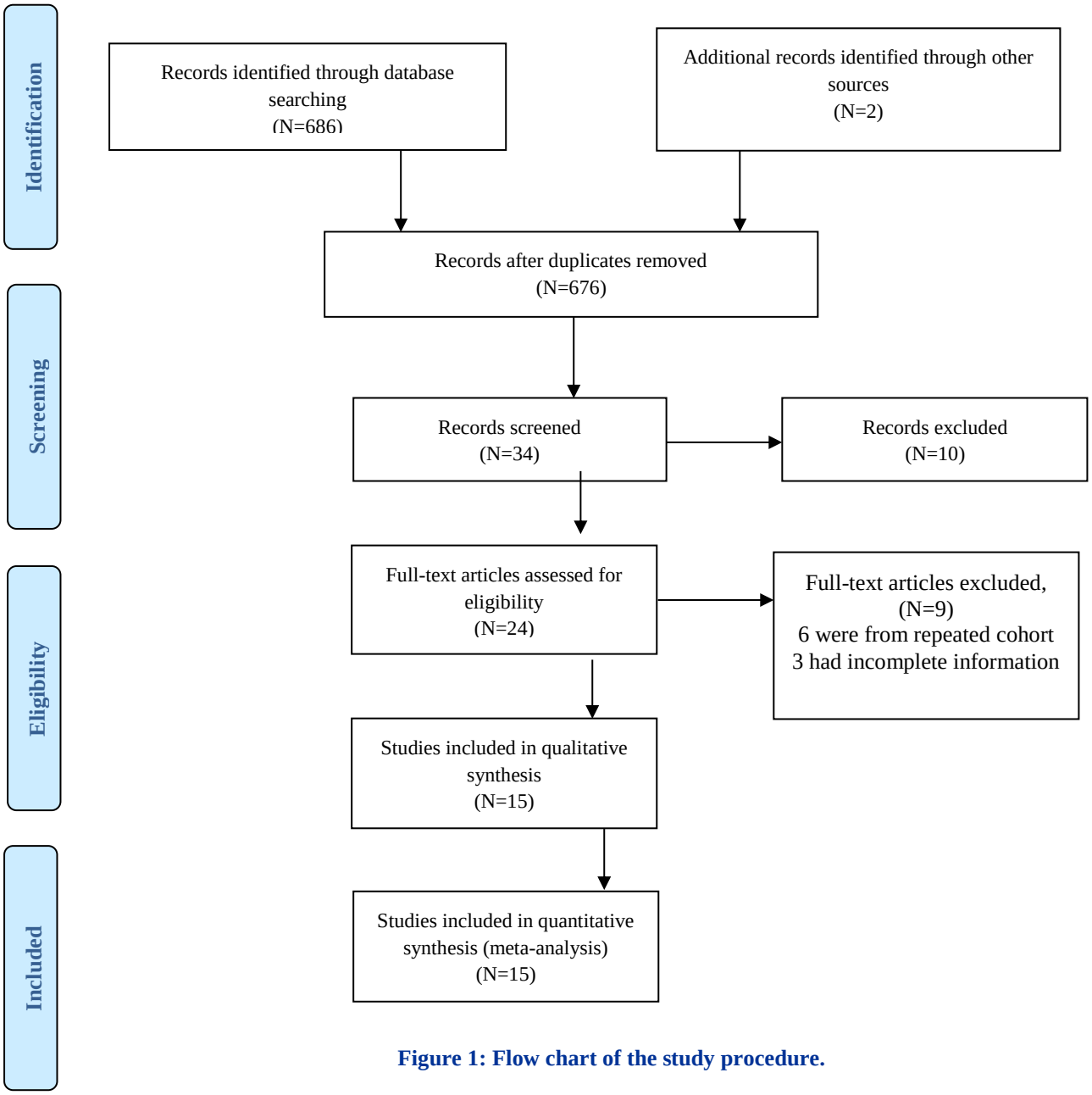

Figure 1: Flow chart of the study procedure.

Data source and search

On 23 May 2019 the electronic search was carried out in PubMed, Ovid, Web of Science, Virtual Health Library (VHL) and Cinni articles databases without date restrictions. We used the following search terms: psoriasis and mortality and cohort or prospective studies or retrospective studies. We also searched the references of the included articles. Two authors independently participated in the literature search, study selection, data extraction and quality assessment (Figure 1). Any disagreements were solved by consensus of two researchers and the intervention of a third researcher in case of doubt. Details of the protocol for this systematic review were registered on PROSPERO and can be accessed at https://www.crd.york.ac.uk/prospero/ (CRD42019123496).

Inclusion criteria

We selected cohort studies that were written in English or Spanish, whose primary outcome was mortality in adults with Pso and PsA that reported cumulative person-years and/or average follow up. If the data was available, we performed subgroups by severity of Pso and PsA.

Exclusion criteria

We excluded review articles, commentaries and editorials. Original articles that only reported a specific cause of death, had incomplete data about death or only evaluated co-morbidity and not mortality were also excluded.

Data extraction and assessment of study quality

We extracted information using tables that contained complete information from each study. We assessed study quality using a modified Newcastle-Ottawa scale 37 and classified them by their risk of bias: low (7 points), medium (5 to 6 points), or high (≤4 points) as well as with Joanna Bridges institute (JBI) critical appraisal checklist for cohort studies.[38] Study quality was determined with GRADEpro.[39]

Statistical analysis

For each study, CMR was calculated such as meta-analysis of Manouchehrinia and cols, pooled CMR (pCMR) in Pso and sub groups pCMR including mild, severe Pso and PsA.[40] We used random effects models for analysis and calculated RR with 95% CI to be the measure of association when comparing mortality in Pso versud PsA. We chose a random effects model because of potential between-study heterogeneity, which was measured with I2. In case of a high heterogeneity, subset analysis was repeated multiple times, with removal of one or more studies each time to investigate its source. A funnel plot was used as a visual tool for assessment of publication bias. Beggs and Egger's regression test was used for the investigation of small study bias. All statistical analyses were performed with Stata V.11 (StataCorp, Stata statistical software). Statistical tests with a $p<0.05$ were considered statistically significant.

RESULTS

We found 686 articles, after reading the title and abstract, we evaluated 34 full texts including 12 Pso and 6 PsA articles. Because some articles reported cohorts from the same database, we reviewed the studies and chose the one with the most complete information or with the longest study period, in order to avoid overlapping the sample. Table 1 summarizes the main characteristics of the included articles. Studies were conducted in 7 countries: Taiwan, Argentina, Finland, Canada, United States of America, Denmark and United Kingdom. Study duration varied from 10 to 35 years.

CMR in Pso

The global CMR included data from 6 papers. These studies comprised data from 434,579 patients. A total of 32,934 deaths occurred during follow up time. The pooled CMR was 14/1000 (95% CI: 6-21) with an I^2=99.9%, $p<0.01$, this global pooled result did not show publication bias by Begg's and Egger's test (Figure 2).

Mild, severe Pso and arthritis psoriatic pooled CMR

These included data from 13 papers. Among six studies with mild psoriasis, the pCMR was 12/1000 (95% CI: 10-15%, I^2 99.84%, $p<0.01$). Eight studies for severe Pso, the pCMR was 19/1000 (95% CI: 15-23%, I^2 99.42%, $p<0.01$). Six studies were included in PsA group, pCMR was 12/1000 (95% CI: 10-14%, I^2 96.64%, $p\leq0.01$). Pooled CMR was 15/1000 (95% CI: 13-17%, I^2 99.7%, $p\leq0.01$), this result did not show publication bias by Begg and Eger test (Figure 3).

Pso versus PsA

We made a comparison of patients with Pso vwesus PsA. Among 4 studies of 319,085 patients with Pso and 36,890 with PsA, the results were 25,572 and 2,489 demises respectively. The pooled RR in Psa group was 1.03 (95% CI: 1.01-1.06%, I^2 98.4%, $p<0.01$) and it did not have publication bias (Figure 4).

Sensitivity analyses, publication bias and study quality

We performed sensitivity analyses, influence analyses and risk bias assessment. Studies that did not modify the results were excluded. Funnel plot, Begg and Egger's test showed no evidence of publication bias ($p<0.05$). The evidence review team conducted a series of systematic literature analysis following the methods of the Cochrane Collaboration and GRADE evidence profiles for each outcome. This particular study included observational

studies so it was classified as low quality evidence. For the first 2 outcomes (CMR) we used a narrative description form, as it was calculated using only one group, there was no factor that increased the quality due to the design of the study (Table 2). The last outcome was also classified as low quality and degraded after we made an indirect comparison and observed some of the included articles compared the studied group versus healthy patients (Table 2). The risk of bias was evaluated with Newcastle-Ottawa scale and JBI critical appraisal checklist for cohort studies. The inconsistency found in a small number of studies was not considered serious due to the large sample size. All calculated sample sizes (TOI) were smaller than the total number of patients included.

Table 1: Main characteristics of studies.

Author, year, country	Settings	Assessment of mortality	Number of psoriasis patients	Severity or diagnosis	Study period	Years	Conclusions
United Kingdom							
Gelfand et al 2007	GPRD	Registratios codes	Mild 133 568, controls: 560 35, severe: 3951, controls: 15 075	Severe: patient with a history of systemic therapy mild without this	1987-2002	>18	The results of this study demonstrate that patients with severe psoriasis have a 50% increased risk of mortality
Ogdie et al 2017	THIN	Code noting death or transfer due to death	PsA: 8706	Single diagnosis code (positive predictive value 85%)	1994-2010	18-89	Overall mortality and cause-specific mortality risk were not elevated among patients with PsA except for suicide deaths
Ogdie et al 2014	THIN	Code noting death or transfer due to death	PsA: 8,706, AR:41,752, Psoriasis: 138,424 y Controles: 82,258	READ codes	1994-2010	18-89	Patients with RA and psoriasis had a high mortality compared to the general population. However, patients with PsA did not have a significantly elevated risk of mortality.
Megan et al 2018	THIN	NE	8760 adults with psoriasis and 87,600 adults without psoriasis	CDC y National psoriasis foundation severidad: BSA	NE	Adults	Patients with psoriasis affecting >10% BSA have an increased risk of death compared to the general population, patients with psoriasis and a BSA >10% should be subject to preventive health interventions.
Abuabara et al 2010	GPRD	Code noting death	Severe psoriasis 3603 and controls 14,330	ICD 10, definition of severity according to therapeutics	1987-2002	>18	Severe psoriasis is associated with an increased risk of death. Due to cardiovascular , pulmonar and neoplasic causes .

Continued.

Author, year, country	Settings	Assessment of mortality	Number of psoriasis patients	Severity or diagnosis	Study period	Years	Conclusions
Buckley et al 2010	Hospital Base	Registry of deaths (National health service)	PsA 453	Criteria for PsA to Moll and Wright	1985-2007	NE	There is no significant increase in the risk of death in patients with psoriatic arthritis
Springate et al 2017	Clinical practice research datalink (CPRD)	NE	104,441 with psoriasis and 508,457 in the control group.	READ code	1 January 1999 to 31 December 2013.	0 to over 80	Prevalence increased from 2.3% (1999) to 2.8% (2013), not at the expense of incidence, which is explained by the fact that mortality in patients with psoriasis has decreased in UK. However, early mortality in these patients remains high compared to the general population (HR 1.53 in patients aged 0-19 years with psoriasis).
Svedbom et al 2015	VEGA and SHCR	CDR	cohort 1 (136,409 individuals in control group, 34,355 cases with mild psoriasis). cohort 2 (18,366 patients in the control group, 4,719 patients with severe psoriasis).	ICD 10	SHCR: 1 January 2001 to 31 December 2010 VEGA: 1 January 2005 to 31 March 2011	NE	In patients with mild or severe psoriasis, the greatest associations were observed due demise caused by kidney and liver disease, however in general there was an increase in mortality in patients with psoriasis from all causes.
Denmark							
Salahadeen et al 2015	The central population registry, the National patient registry e información de la prescripción	The National causes of death registry	Psoriasis: 5,458,627, mild: 94,069 and severe: 28,253	ICD 10, ICD 8	1997-2011	>18	Higher rates in all the specific causes of death, mainly cardiovascular (for every 1000 patients year 3.6 mild and 5.2 severe), malignant diseases (rate 3.9 mild and 5.4 severe) and gastrointestinal (rate 0.9 mild and 1.8 severe).

Continued.

Author, year, country	Settings	Assessment of mortality	Number of psoriasis patients	Severity or diagnosis	Study period	Years	Conclusions
Skov et al 2019	NPR	Civil registration system	Psoriasis: 12 160 Control: 23 936 PsA: 9817 Control: 19398	ICD 10	1998-2014	NE	Patients with psoriasis have an increased risk of mortality (HR 1.74), but not in patients with PsA (HR 1.06).
Argentina							
Masson et al 2017	Hospital database	In-hospital or out-of hospital death	1,481 patients with psoriasis and 1,500 without it	Medical records	1 January 2010 to 30 June 2015	2010-2015	In the univariate analysis, patients with psoriasis showed 58% more mortality than the non-exposed group. in the multivariate analysis, psoriasis was associated with higher mortality compared to the control group (HR 1.48)
United States of America							
Stern et al 2011	University clinic centers	NDI	1380	ICD 9	1977-2005	NE	Patients with severe and very extensive psoriasis showed an increased risk of mortality from all causes compared to the general population and people with less extensive psoriasis. These increases were not significant due to cardiovascular disease (HR 1.42)
Canada							
Ali et al 2007	Hospital database PsA clinic	Linkage with the provincial cancer registry, telephone interviews, newspaper. Death certificates.	PsA 680	NE	1978-2004	15.5-87.5	The risk of mortality in patients with PsA is decreasing over time
Taiwan							
Dai et al 2018	NHIRD	Withdrawal of insurance patients	Psoriasis 106,701, PsA 8795	Diagnosis: ICD 9 Severity according to the therapeutic	2002-2012	Older and less than 18	Patients with psoriasis have a higher risk of mortality compared to controls, while the severity of psoriasis and PsA

Continued.

Author, year, country	Settings	Assessment of mortality	Number of psoriasis patients	Severity or diagnosis	Study period	Years	Conclusions
							had no impact on mortality risk
Lee et al 2017	National health insurance database	National death registry of Taiwan	Psoriasis 80167 PsA 9572	ICD 9 Severe: if patients received systemic therapeutic agents and mild if they did not receive these	2001-2012	≥18	Patients with severe psoriasis, early-onset psoriasis and PsA had higher mortality risks from various causes.

GPRD (general practitioners participating in the general practice research database), THIN (the health improvement network), NE (not specified),CDC (center for disease control and prevention), BSA (body surface área), NPR (Danish National patient registry), NHIRD (National health insurance research database), CRD (the causes of death register), NDI (National death index), RA (rheumatoid arthritis), ICD (International classification of diseases), SHCR (Skåne health care register), HR (hazzard ratio).

Table 2: Grade quality assessment.

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
CMR in Pso									
6	Observational studies	Not serious	Not serious	Not serious	Not serious	None		⊕⊕◯◯ [a] low	Important
CMR subgroup mild, severe and PsA									
12	Observational studies	Not serious	Not serious	Not serious	Not serious	None		⊕⊕◯◯ low	Important

Table 3: Grade summary of findings.

Certainty assessment							No. of patients		Effect			
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Arthritis psoriatic	Psoriasis	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Pso versus PsA												
4	Observational studies	Not serious	Not serious	Serious [b]	Not serious	None	2489/36890 (6.7%)	25572/319085 (8.0%)	RR 1.03 (1.01 to 1.06)	2 more per 1.000 (from 1 more to 5 more)	⊕◯◯◯ very low	Important

CI: confidence interval; RR: risk ratio; a: certainty is low because these are observational studies that don't include considerations for an increase in risk factors and so it does not adapt to our study; b: we realized comparison of patient with Pso and PsA and some included studies did each comparison versus healthy people.

Table 4: Limitations reported by study.

Authors/cohort	Reported limitations
Gelfand et al 2007	Risk of misclassification
Ogdie et al 2017	Lack of death certificate information and the inferential nature of assigning cause of death and they lack information on disease activity
Ogdie et al 2014	It was not possible to prove mortality according to severity, misclassification of diagnoses and lack of information regarding the use of DMARDs
Megan et al 2017	Future research is needed to better elucidate the specific causes of mortality in patients with extensive psoriasis and to determine the effects of the treatment of psoriasis on the risk of mortality
Abuabara et al 2010	Classification of severity according to the treatment, possibility of attending only patients who request attention (which could include only patients with serious injuries)
Springate et al 2016	Psoriasis cases were identified from general practice electronic health records using relevant diagnostic code lists and so may not necessarily have been verified by dermatologists, this study includes only those patients who present in general practice and thereby receive a physician diagnosis of psoriasis, but this would also be true in other patient populations
Svedbom et al 2015	Retrospective study. Some individuals in the database probably had psoriasis and were not diagnosed
Salahadeen et al 2014	Caucasian population. Reported death causes by a doctor were taken . Patients with psoriasis without treatment or treated only with topical steroids could have been omited , which could lead to an underestimation of the death rate, whereas identifying patients with hospital management could lead to an increase in comorbidities
Skov et al 2018	Retrospective study, probable diagnostic error, hospital-based study which could have biased the result, information regarding the therapist was not included, the cause of death was assigned by a single investigator
Masson et al 2017	The use of a secondary database may cause information bias, no clinimetric tests were performed for an adequate classification, no specific mortality was evaluated, including hospital population could increase comorbidities at the time of diagnosis
Stern et al 2011	Excludes pregnant patients
Poikolainen et al 1999	There is no information regarding the treatment with methotrexate, which could contribute to hepatopathy
Dai et al 2018	Probable misclassification of severity given that the registry does not include clinimetric evaluations (use of treatment patterns as a marker of severity), the causes of death could not be identified, death was taken at the time of insurance withdrawal, however, it could be due to renounce citizenship
Buckley et al 2015	Probably the results may not be extendable to the entire population, given that only white population was included
Ali et al 2007	NE
Lee et al 2017	The absence of clinical assessments limited our ability to classify the severity of psoriasis using the physician global assessment and psoriasis assessment severity index, excess causes of death due to adverse effects of anti-psoriatic therapies, unhealthy lifestyles, comorbidity, and other factors could not be controlled for in the SMR analyses

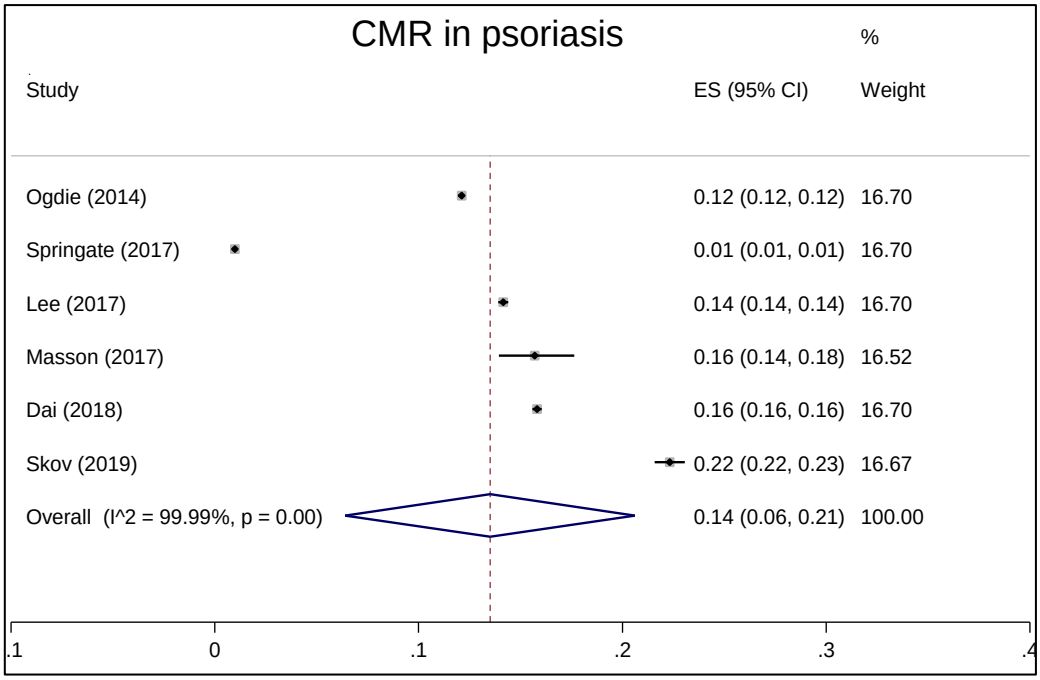

Figure 2: Forest plot of CMR in psoriasis patients.

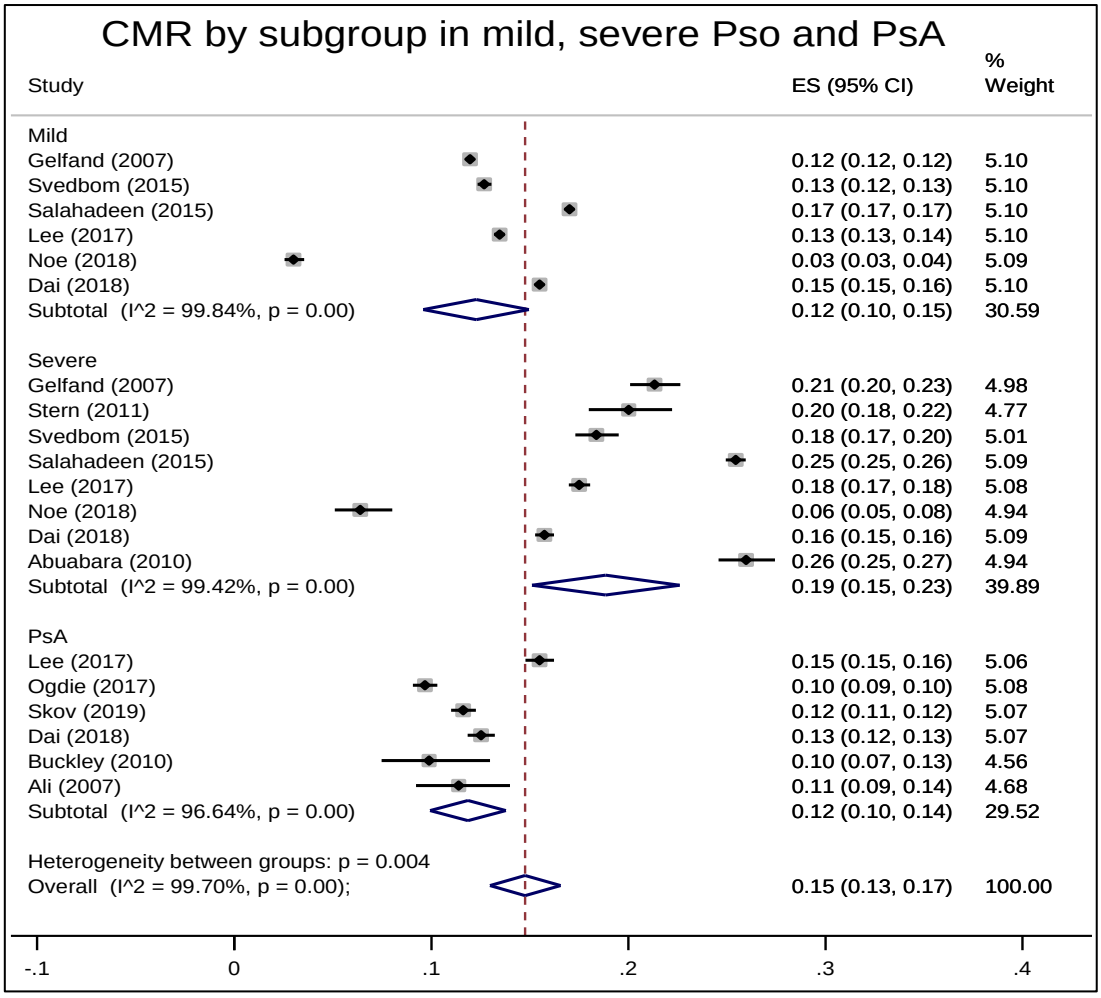

Figure 3: Forest plot of CMR in mild, severe Pso and PsA patients.

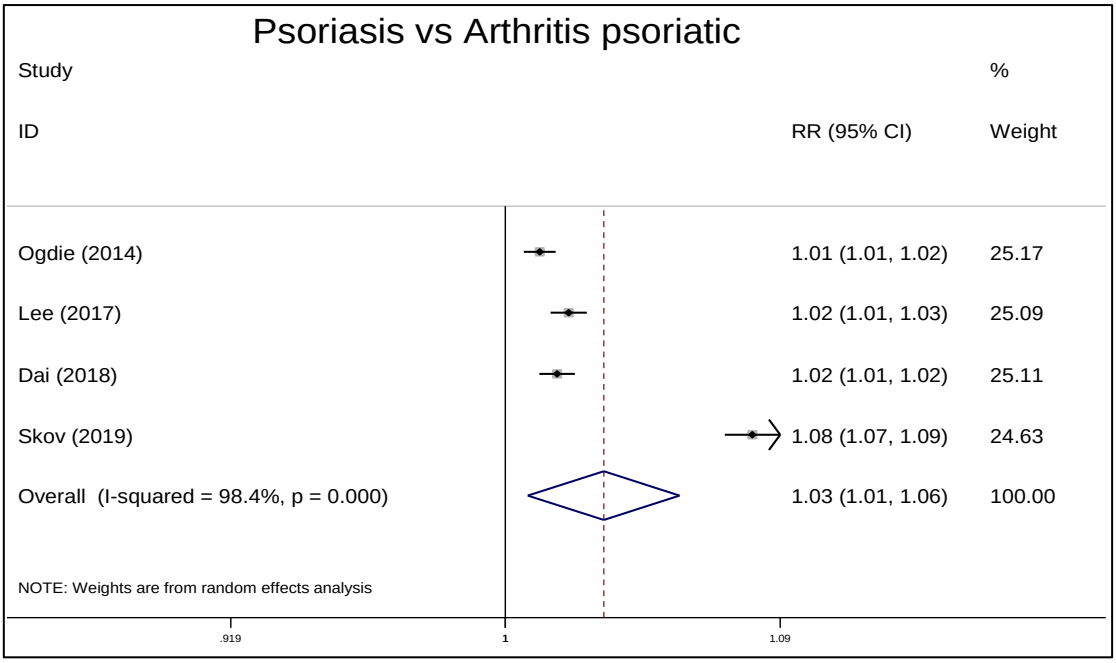

Figure 4: Forest plot of mortality in Pso versus PsA patients.

DISCUSSION

According to our meta-analysis, the CMR for Pso was 14 deaths per 1,000 population (95% CI: 6-21). Our study was the first to summarize the mortality data using CMR and compare it to data from general population. Comparing our data with the ten leading causes of death in high-income and upper-middle-income countries in 2016, Pso CMR was ten times higher than the CMR of ischemic heart disease (1.45 deaths per 1000 population), which was the leading cause of death among these countries.[41] When we compared our data with the general CMR in 2017 of Denmark (8.2 deaths per 1000 people), United Kingdom (9.2 deaths per 1000 people), Argentina (7.56 deaths per 1000 people), Canada (7.5 deaths per 1000 people), United States of America (8.5 deaths per 1000 people) and China (7.11 deaths per 1000 people), Pso mortality was also higher with 14 deaths per 1000 individuals.[42] These countries were selected to make the comparison because most of the cohorts included in this meta-analysis contain data from national registries of those populations, but compared to all countries we observed a CMR similar to the countries with the highest CMR such as Bulgaria, Croatia, Hungary (15.5, 13, 13.5 respectively).[43] In these countries there was a demographic aging, one of the central characteristics in the population of the most developed countries.[44,45] When we analyzed data by severity of the disease, mild Pso had a CMR similar to PsA, while in severe Pso the CMR was higher than the global, 19 deaths per 1000 people. Compared with the CMR per country, mortality in psoriasis patients was also higher than mortality in general population. The similarity of mild Pso and PsA CMR's observed in our study suggested that mortality increase was not associated with the systemic therapy administered for PsA (drug modifying antirheumatic drugs DMARDs and biologic therapy). Pearce et al, Gelfand et al and Gulliver 20 have discussed an association (risk or protective) of pharmacological therapy and mortality in psoriasis, but we considered it was a spurious association as we have added factors to the equation including the burden of other diseases frequently found in this population such as cardiovascular, infectious and neoplastic conditions.[20,22,46] Mortality risk in PsA patients is a controversial issue despite the results of three cohort studies from Taiwan, United Kingdom and Denmark.[27,34,47] The first showed an increase of mortality risk (HR: 1.52 95% CI: 1.39-1.66) while the others reported no association with mortality (HR: 0.94 95% CI: 0.80-1.10, HR: 1.06, p=0.19 respectively). In our meta-analysis, we compared PsA patients versus PsO and observed a marginally increase in mortality risk of 3% (RR: 1.03 95% CI: 1.01-1.06).

The limitations of our investigation were the studies were heterogeneous in several aspects such as definition of severe Pso (not clinimetrically evaluated); chronic tobacco use, obesity and sedentary lifestyle may contribute to the maintenance of a proinflammatory state and were not taken into account in some articles. Table 4 contained the limitation reported in each study.

CONCLUSION

With these findings, we can conclude that patients with psoriasis have an increased risk of mortality in comparison to general population as well as patients with

psoriatic arthritis have a slight increased risk when compared to patients with Pso. Further studies are needed to assess the causality of metabolic disease on mortality risk in Pso and PsA. Our study has several strengths. We perform a calculation of the CMR with the intention to unify values and to be able to compare the general mortality rate with the one associated with Pso and PsA. We included patients with PsA, no similar studies have been found to this date

Our study suggested that regardless of the severity; the patients with Pso and PsA should receive appropriate screening and preventive intervention. We consider that it is important to perform a clinimetric evaluation to accurately determine the severity of the disease in order to improve the evaluation of each patient. The mortality in psoriasis and PsA has not been modified over the years, despite the pharmacological improvements.

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