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"MORTALIDAD EN PSORIASIS Y ARTRITIS PSORIASICA: REVISION SISTEMÁTICA Y METANALISIS"

TESIS

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INDICE

ABSTRACT

Background: in recent publications contradictory results have been reported regarding the mortality risk of patients with psoriasis (Pso) and psoriatic arthritis (PsA), these patients have aggregate risk behaviors, which could influence their morbidity and mortality.

Objective: To assess mortality risk in Pso and PsA and perform a systematic review and meta-analysis.

Methods: We included 15 studies, with a total population of that reported mortality risk in psoriasis and psoriatic arthritis patients. We calculated crude mortality rate (CMR) of each one and pooled CMR by group and 95% confidence intervals (CI).

Results: The pooled CMR for Pso is 14/1000 (95%CI 6 – 21), 12/1000 (95%IC 10-15%) in mild, 19/1000 (95%IC 15-23%) in severe and 12/1000 was observed (95%IC 10-14%) in PsA. Mortality was relatively higher in PsA patients when compared with Pso, with a RR of 1.03 (95%IC 1.01-1.06, p <0.01).

Conclusions: Pso is associated with increased mortality with regard to the general population. Mild Pso and PsA have the same increased of mortality, in the other hand as the severity of Pso increases it does so its mortality. The final comparative mortality between patients with PsA and those with Pso was around 3%.

OBJECTIVE

To assess mortality risk in Pso and PsA and perform a systematic review and meta-analysis.

RESEARCH PROBLEM

Psoriasis is a is a common, chronic, recurrent, inflammatory disease of the skin (3), its prevalence varies according to geography, from 0.9% in USA to 8.5% in Norway, and 2% of the dermatological consultation in Mexico(4). An increase in mortality rate has been identified in psoriasis, which could be associated with the presence of comorbidities such as cardiovascular disease, neoplasms, and pulmonary disease, among others (4)(5) (6).

BACKGROUND

Psoriasis is a is a common, chronic, recurrent, inflammatory disease of the skin mediated by TH17 lymphocytes response (1) (2), affects 2–4% of the general adult population (3), its prevalence varies according to geography, from 0.9% in USA to 8.5% in Norway, and 2% of the dermatological consultation in Mexico (4). Psoriasis (Pso) patients developed erythematous scaly plaques, and can affect nails and join (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/year (6). Both Pso and PsA has a negative physical, emotional and psychosocial impact (7) (8) (9) (10) (11) (12) (13) (14) (15)

Proliferation and differentiation of keratinocytes are dysregulated in Pso, with an important involvement of interleukin 17 (IL7), IL23 and tumor necrosis factor (TNF). These interleukines induce 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 and risk habits such as alcohol and tobacco use. (16) (17) (8) (18) (19) (20)

Treatment is based on the severity of the disease, which includes topical to systemic agents (including phototherapy, drug modifying antirheumatic drugs and biological agents) for moderate cases, cases resistant to topical treatment, as well as cases with nail and/or articulation involvement. (21) (2)

An increase in mortality rate has been identified in psoriasis, which could be associated with the presence of comorbidities such as cardiovascular disease, neoplasms, and pulmonary disease, among others. Some authors described an increase in the risk of mortality in patients with severe psoriasis that could be associated with comorbidities or systemic treatment (22) (23) (24) (21) (25) (10) (2) (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 (28) published a meta-analysis that reported an increased mortality risk in psoriasis patients, likewise Wong et al. (29) and Ali et al. (30) reported a similar increase in PsA, nevertheless Shbeeb et al (31) and Wilson´s et al (32) studies are contradictory. (33) (34) (27)

Unfortunately, Dhana's systematic review did not include PsA patients, consequently we consider that it is necessary to do an update to compare the mortality between psoriatic arthropathy and psoriasis. Until now, mortality in Pso and PsA continues to be an enigma, and it is still controversial the association between severity, comorbidities and therapeutics.

The aim of this study is to determine the risk of mortality in patients with Pso and PsA in relation to general population. We also identify and describe the main characteristics of the cohorts that were included in this systematic review.

JUSTIFICATION

Our study suggests that regardless 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 of severity in order to improve the evaluation of each patient.

METHODS

We performed a systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement (PRISMA) (35) and Meta-analyses Of Observational Studies in Epidemiology (MOOSE) (36) for systematic reviews and meta-analysis.

Data source and search

On May 23, 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. Figs. 1 Two authors independently participated in the literature search, study selection, data extraction, and quality assessment. 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 psoriasis and PsA.

Exclusion criteria

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

Data Extraction and Assessment of Study Quality

We extracted information using tables that contain 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). We also assessed study quality with GRADEpro (39).

STATISTICAL ANALYSES

For each study, CMR was calculated such as metanalysis of Manouchehrinia and cols. (40), pooled CMR (pCMR) in Pso and sub groups pCMR including mild, severe Pso and PsA. We used random effects models for analysis, likewise we calculated RR with 95%CI as the measure of association to compare mortality in Pso vs PsA. We chose a random effects model because of potential between-study heterogeneity, which was measured with I^2. 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-value <0.05 were considered statistically significant.

RESULTS

We found 686 articles and by reading the title and abstract, we assessed 34 full-text articles from which 15 articles were included, 12 and 6 of Pso and PsA respectively. 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 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.

Crude mortality rate (CMR) in psoriasis

The global crude mortality rate 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 (Figs. 2).

Mild, severe and arthritis psoriatic pooled CMR

These included data from 13 papers. Among six studies with mild psoriasis, the pCMR was 12/1000 (95%IC 10-15%, I^2 99.84%, p= <0.01). Eight studies for severe Pso, the pCMR was 19/1000 (95%IC 15-23%, I^2 99.42%, p= <0.01). Six studies were included in PsA group, pCMR was 12/1000 (95%IC 10-14%, I^2 96.64%, p= <0.01).

Pooled CMR was 15/1000 (95%IC 13-17%, I^2 99.7%, p= <0.01), this result did not show publication bias by Begg and Eger test. (Figs. 3)

Psoriasis patient vs Arthritis psoriatic

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

Sensitivity analyses, publication bias, and study quality

We performed sensitivity analyses, influence analyses, and risk bias assessment. We randomly exclude studies that do not modified the results. 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 reviews following the methods of the Cochrane Collaboration and GRADE evidence profiles for each outcome. Because this study included observational studies, it was classified as low quality of evidence. For the first 2 outcomes (CMR) we used a narrative description form since it was calculated with 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 of low quality and was degraded because we made an indirect comparison, since some of the included articles compared the studied group against healthy patients. Table 2

The risk of bias was evaluated with Newcastle-Ottawa Scale and JBI Critical appraisal checklist for cohort studies.

The inconsistency was not considered serious due to a small number of studies and a large sample size.

All calculated sample sizes (TOI) were smaller than the total number of patients included

DISCUSSION

According to our meta-analysis, the crude mortality rate for psoriasis was 14 deaths per 1,000 population (95%CI 6 – 21). Our study is the first to summarize the mortality data using CMR in order to compare with data from general population.

Comparing our data with the ten leading causes of death in high-income and upper-middle-income countries in 2016 (41), psoriasis crude mortality rate is ten times higher than the CMR of ischemic heart disease (1.45 deaths per 1000 population), which is the leading cause of death among these countries. When we compared our data with the general crude mortality rate 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), psoriasis mortality is also higher with 14 deaths per 1000 individuals. (42)

We selected these countries to compare because most of the cohorts included in this meta-analysis belong to national registries from those populations, but compared to all countries we observe a CMR similar to the countries with the highest CMR such as Bulgaria, Croatia, Hungary (15.5, 13, 13.5 respectively) (43), etc. In these countries there is 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 psoriasis had a CMR similar to PsA, while in severe psoriasis 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 psoriasis and PsA CMR's observed in our study suggest that mortality increase is not associated with the

systemic therapy administered for PsA (Drug modifying antirheumatic drugs and biologic therapy). Pearce (22), Gelfand (46) and Gulliver (20) have discussed an association (risk or protective) of pharmacological therapy and mortality in psoriasis, but we consider it is a spurious association and must be in mind the burden of other diseases frequently found in this population such as cardiovascular, infectious and neoplastic conditions.

Mortality risk in PsA patients is a controversial issue despite the results of three cohort studies from Taiwan (34), United Kingdom (27) and Denmark (47). The first showed an increase of mortality risk (HR 1.52 95% IC 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 vs. PsO and observed a marginally increase in mortality risk of 3% (RR 1.03 95% IC 1.01-1.06).

With these findings, we can conclude that patients with psoriasis have an increased risk of mortality in comparison with general population, as well as patients with psoriatic arthritis have a slight increase against patients with psoriasis. Further studies are needed to assess the causality of metabolic disease on mortality risk in psoriasis and psoriatic arthritis.

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, to date there are not similar studies. The limitations of our investigation are: the studies were heterogeneous in several aspects such as definition of severe psoriasis (not clinimetrically evaluated); chronic tobacco use, obesity and sedentary lifestyle may contribute to the maintenance of a proinflammatory state and were not controlled in some articles. Table 3 contains the limitation reported in each study.

CONCLUSION

Our study suggests that regardless 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 of severity in order to improve the evaluation of each patient.

The mortality in psoriasis and PsA has not changed over the years, despite the advances in medication.

Competing interests None.

Provenance and peer review not commissioned; externally peer reviewed

REFERENCES

1. Hee Han J, Hyen Lee J, Kyung Do H. Epidemiology and Medication Trends in Patients with Psoriasis: A Nationwide Population-based Cohort Study from Korea. Acta Dermato-Venereologica. 2018; 98: p. 396-400.
2. Meng Sui L, Yi-Chun Y, Yun Ting C. All-Cause and Cause-Specific Mortality in Patients with Psoriasis in Taiwan: A Nationwide Population-Based Study. The Journal of Investigative Dermatology. 2017.
3. Mehta NN, Azfar RS, Shin DB. Patients with severe psoriasis are at increased risk of cardiovascular mortality: cohort study using the General Practice Research Database. European Heart Journal. 2010; 31: p. 1000–1006.
4. Chanussot C, Arenas R. Psoriasis, A Descriptive Study of Comorbidities in 114 patients. Dermatologia CMQ. 2015; 13(1): p. 20-23.
5. Griffiths CEM, Barker JNWN. Pathogenesis and clinical features of psoriasis. Lancet. 2007; 370: p. 263–271.
6. Buckley C, Cavill C, Taylor G. Mortality in Psoriatic Arthritis - A Single-center Study from the UK. The Journal of Rheumatology. 2010; 37(10).
7. Ogdie A, Maliha S, Shin D. Cause-specific mortality in patients with psoriatic arthritis and rheumatoid arthritis. Rheumatology. 2017; 56.
8. Puig L. Cardiometabolic Comorbidities in Psoriasis and Psoriatic Arthritis. International journal of Molecular Sciences. 2018; 19(58).
9. Parisi R, Webb RT, Carr MJ. Global Epidemiology of Psoriasis: A Systematic Review of Incidence and Prevalence. The Society for Investigative Dermatology. 2013; 133: p. 377–385.
10. Griffiths CEM, Van der Walt JM, Ashcroft DM. The global state of psoriasis disease epidemiology: a workshop report. British Journal of Dermatology. 2017; 17: p. 4-7.

11. Gupta R, Debbaneh MG, Liao W. Genetic Epidemiology of Psoriasis. Current Dermatology Reports. 2014; 3: p. 61–78.
12. Egeberg A, Skov L, Gislason GH. Incidence and Prevalence of Psoriasis in Denmark. Acta Dermato-Venereologica. 2017; 97: p. 808–812.
13. Duarte GV, Porto Silva L, Paim de Oliveira MdF. Epidemiology and treatment of psoriasis: a Brazilian perspective. Psoriasis: Targets and Therapy. 2015; 5: p. 55–64.
14. Langley R, Krueger GG, Griffiths C. Psoriasis: epidemiology, clinical features, and quality of life. Annals of the Rheumatic Diseases. 2005; 64: p. 18-23.
15. Song Hae J, Park Chul J, Kim Tae Y. The Clinical Profile of Patients with Psoriasis in Korea: A Nationwide Cross-Sectional Study (EPI-PSODE). Annals of Dermatology. 2017; 29(4).
16. Noe MH, Shin DB, Wan MT. Objective Measures of Psoriasis Severity Predict Mortality: A Prospective Population- Based Cohort Study. The Journal of Investigative Dermatology. 2018.
17. Salahadeen E, Torp-Pedersen C, Gislason G. Nationwide population-based study of cause-specific death rates in patients with psoriasis. Journal European Academy of Dermatology and Venereology. 2014.
18. Boehncke WH, Boehncke S. Cardiovascular Mortality in Psoriasis and Psoriatic Arthritis: Epidemiology, Pathomechanisms, Therapeutic Implications, and Perspectives. Current Rheumatology Reports. 2012; 14: p. 343–348.
19. Horreau C, Pouplard C, Brenaut E. Cardiovascular morbidity and mortality in psoriasis and psoriatic arthritis: a systematic literature review. Journal of the European Academy of Dermatology and Venereology. 2013; 27: p. 12-29.
20. Gulliver W. Long-term prognosis in patients with psoriasis. British Association of Dermatologists. 2008; 159: p. 2–9.
21. Stern RS, Huibregtse A. Very Severe Psoriasis Is Associated with Increased Noncardiovascular Mortality but Not with Increased Cardiovascular Risk. Journal of Investigative Dermatology. 2011;: p. 1159–1166.
22. Pearce DJ, Higgins KB, Stealey KH. Adverse events from systemic therapies for psoriasis are common in clinical practice. Journal of Dermatological Treatment. 2006; 17: p. 288–293.
23. Masson W, Rossi E, Galimbe ML. Mortalidad en pacientes con psoriasis. Análisis de una cohorte retrospectiva. Medicina Clinica Barcelona. 2017.
24. Abuabara k, Azfar RS, Shin DB. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. British Journal of Dermatology. 2010; 163: p. 586–592.
25. Svedbom A, Dalen J, Mamolo C. Increased Cause-specific Mortality in Patients with Mild and Severe Psoriasis: A Population-based Swedish Register Study. Acta Dermato-Venereologica. 2015; 95: p. 809–815.
26. Armstrong AW, Schupp C, Bebo B. Psoriasis Comorbidities: Results from the National Psoriasis Foundation Surveys 2003 to 2011. Dermatology. 2012; 225: p. 121–126.
27. Ogdie A, Haynes K, Troxel AB. The Risk of Mortality in Patients with Psoriatic Arthritis, Rheumatoid Arthritis, and Psoriasis: A Longitudinal Cohort Study. Annals Rheumatology Diseases. 2014; 1(73).

28. Dhana A, Yen H, Yen H. All-cause and cause-specific mortality in psoriasis: a systematic review and meta-analysis. Journal of the American Academy of Dermatology. 2019.
29. Wong K, Gladman DD, Husted J. Mortality Studies in psoriatic Arthritis. Arthritis & Rheumatism. 1997; 40(10): p. 1868-1872.
30. Yaser A, Brian D. M. T, Schentag CT. Improved Survival in Psoriatic Arthritis With Calendar Time. Arthritis & Rheumatism. 2007; 56(8): p. 2708–2714.
31. Shbeeb M, Uramoto K, Gibson L. The epidemiology of psoriatic arthritis in Olmsted County, Minnesota, USA, 1982-1991. The Journal of Rheumatology. 2000; 27(5): p. 1247-1250.
32. Wilson FC, Icen M, Crowson CS. Time Trends in Epidemiology and Characteristics of Psoriatic Arthritis Over 3 Decades: A Population-based Study. The Journal of Rheumatology. 2009; 36: p. 361-367.
33. Springate D, Parisi R, Kontopantelis E. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. British Journal of Dermatology. 2016; 176: p. 650–658.
34. Ying-Xiu D, Ming-Chun H, Hsiao-Yun H. The Risk of Mortality among Psoriatic Patients with Varying Severity: A Nationwide Population-Based Cohort Study in Taiwan. International Journal Environmental Research and Public Health. 2018; 15(2622): p. 2-8.
35. Moher D, Shamseer L, Clarke M. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Systematic Reviews. 2015; 4(1).
36. Stroup DF, Berlin JA, Morton SC. Meta-analysis of Observational Studies in Epidemiology. Journal American Medical Association. 2000; 283(15).
37. Wells G, Shea B, Connel D. The Newcastle-Ottawa scale (NOS) for assessing the quailty of nonrandomised studies in meta-analyses. 2009.
38. Moola S, Munn Z, Tufanaru C. Chapter 7: Systematic reviews of etiology and risk. Joanna Briggs Institute Reviewer's Manua. 2017.
39. GRADEpro Guideline Development Tool. McMaster University. [Online].; 2015 [cited 2019 June 20. Available from: https://gradepro.org/cite/.
40. Manouchehrinia A, Tanasescu R, Tench CR. Mortality in multiple sclerosis: meta-analysis of standardised mortality ratios. Journal of neurology, neurosurgery, and psychiatry. 2015;: p. 1-8.
41. World Health Organization. The top 10 causes of death. [Online].; 2016 [cited 2019 July 10. Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
42. Knoema Corporation. Population Estimates and Projections. [Online].; 2017 [cited 2019 July 10. Available from: https://knoema.com/WBPEP2018Oct/population-estimates-and-projections?country=1000530&series=1000140.
43. The world bank. Death rate, crude (per 1,000 people). [Online].; 2017 [cited 2019 July 15. Available from: https://data.worldbank.org/indicator/SP.DYN.CDRT.IN?contextual=aggregate.
44. Alcañiz M. Cambios demográficos en la sociedad global. Papeles de POBLACIÓN. 2008.
45. Bloom DE, Luca DL. The Global Demography of Aging: Facts, Explanations, Future. IZA

Discussion Paper No. 10163. 2016.
46. Gelfand JM, Troxel AB, Lewis JD. The Risk of Mortality in Patients With Psoriasis. Archives of Dermatology. 2007; 143(12): p. 1493-1499.
47. Skov L, Thomsen SF, Kristensen LE. Cause-specific mortality in patients with psoriasis and psoriatic arthritis. British Journal of Dermatology. 2019; 180: p. 100-107.

FIGURES AND TABLES

Table I. Main characteristics of studies

uthor, ear, ountry	Setting	Assessment of mortality	Number of psoriasis patients	Severity or diagnosis	Study period	Years	Conclusion
NITED KINGDOM							
elfand, 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 years	The results of this study demonstrate that patients with severe psoriasis have a 50% increased risk of mortality
gdie, 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 years	Overall mortality and cause-specific mortality risk were not elevated among patients with PsA except for suicide deaths
gdie A, 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 years	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.
legan H, 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.
buabara, et al 010	GPRD	Code noting death	Severe psoriasis 3603 and controls 14 330	ICD 10, definition of severity according to therapeutics	1987-2002	>18 years	Severe psoriasis is associated with an increased risk of death. Due to cardiovascular , pulmonar and neoplasic causes .
uckley, 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
pringate D, et al 017	Clinical Practice Research Datalink (CPRD)	NE	104, 441 with psoriasis and 508, 457 in the control group.	READ code	January 1, 1999 to December 31, 2013.	From 0 to over 80 years	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 U.K. However, early mortality in these patients remains high compared to the general population (HR 1.53 in patients aged 0-19 years with psoriasis).
vedbom A, et al 015	VEGA and SHCR	CDR	**Cohort 1** (136, 409 individuals in control group, 34, 355 cases with mild psoriasis). **Cohort 2 (**18,366	ICD 10	**SHCR:** January 1, 2001 to December 31, 2010 **VEGA:** January 1, 2005 to	NE	In patients with mild or severe psoriasis, the greatest associations were observed due to death due to kidney and liver disease, however in general there was an increase in mortality in patients with psoriasis

			patients in the control group, 4,719 patients with severe psoriasis).		March 31, 2011		from all causes.
enmark							
Salahadeen E, et l 2015	The Central Population Registry, The National Patient Registry e informaci ón de la prescripci ón	The National Causes of Death Registry	Psoriasis: 5,458,627, mild: 94,069 and severe: 28,253	ICD 10, ICD 8	1997 to 2011	>18 years	Higher rates of 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).
kov L, 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).
rgentina							
lasson W, et al 017	Hospital database	In-hospital or out-ofhospital death	1,481 patients with psoriasis and 1,500 without it	Medical records	1-Jan-2010 to 30-Jun-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)
nited States of America							
tern, et al 2011	Universit y Clinic Centers	NDI	1380	ICD 9	1977-2005	NE	Patients with severe and very extensive psoriasis were those who had 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)
anada							
li , 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 years	The risk of mortality in patients with PsA is decreasing over time
aiwan							
ai, et al 2018	NHIRD	Withdrawal of insurance patients	Psoriasis 106,701, PsA 8795	Diagnosis: ICD 9 Severity according to the	2002-2012	Older and less than 18 years old	Patients with psoriasis have a higher risk of mortality compared to controls, while the severity of psoriasis and

				therapeutic			PsA had no impact on mortality risk
ee, et al 2017	National Health Insuranc e 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 years	Patients with severe psoriasis, early-onset psoriasis, and PsA had higher all-cause mortality risks.

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 (Reumatoid arthritis), ICD (International Classification of Diseases), SHCR (Skåne Health Care Register), HR (Hazzard ratio)

Table 2. Crude mortality rate in psoriasis (global, mild,severe and psoriatic arthritis) and psoriatic arthritis

Certainty assessment							Impact	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
CMR in psoriasis									
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

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Arthritis psoriatic	Psoriasis	Relative (95% CI)	Absolute (95% CI)		
soriasis vs Psoriatic arthritis												
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. The certainly is low because are observational studies and do not exist considerations for increase since some factors does not adapt to our study

b. We realized comparison of patient with psoriasis and psoriatic arthritis and some included studies did each comparison vs healthy people

Table 3. Limitations reported by study

Author / 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 A, 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 H, 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 D, 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 A, et al 2015	Retrospective study. Some individuals in the database probably had psoriasis and were not diagnosed.
Salahadeen E, 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 W, 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 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 1. Flow chart of the study procedure

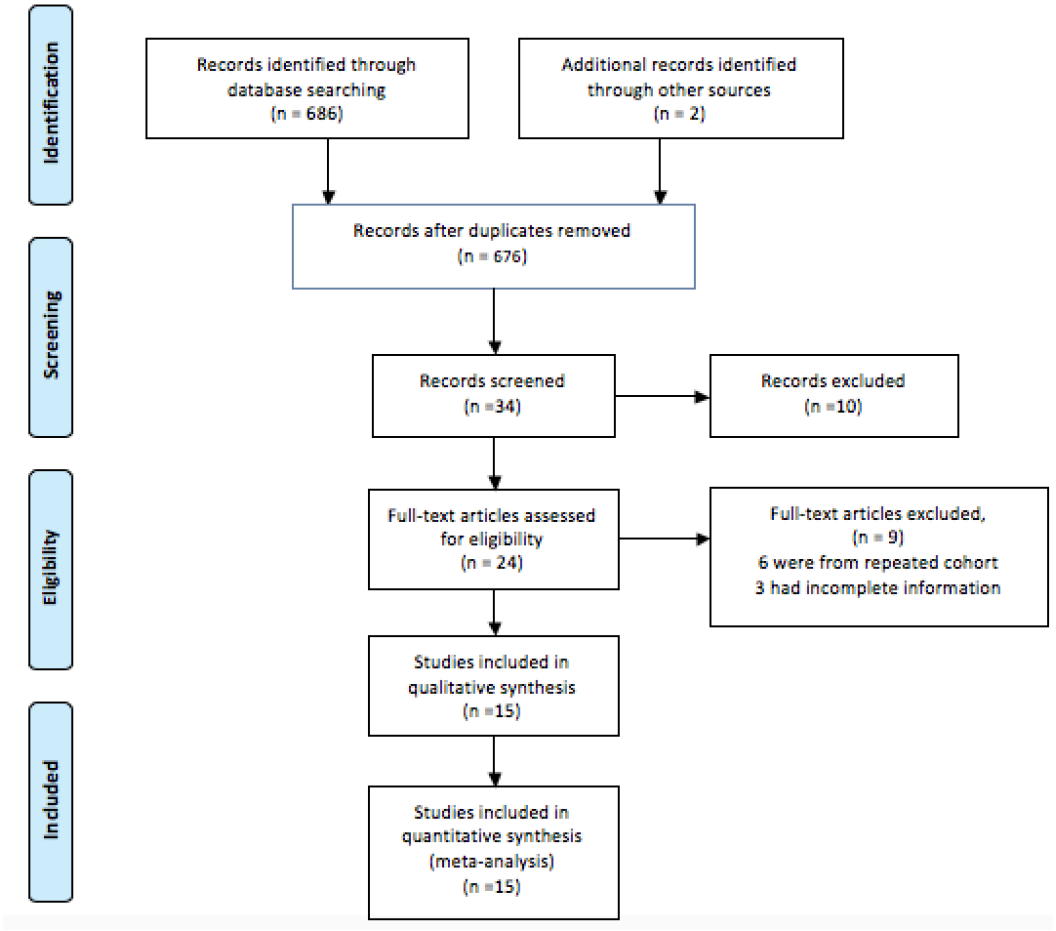

Figure 2. Forest plot of CMR in psoriasis patients

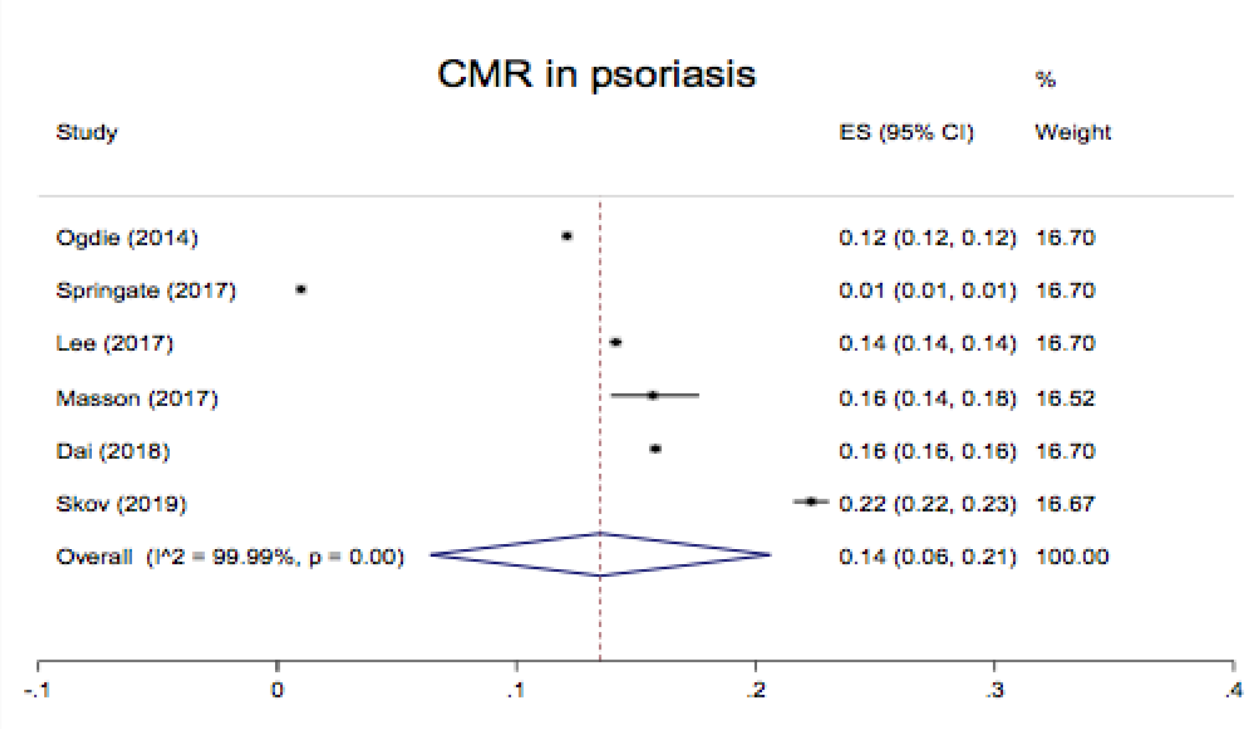

Figure 3. Forest plot of CMR in mild, severe Pso and PsA patients

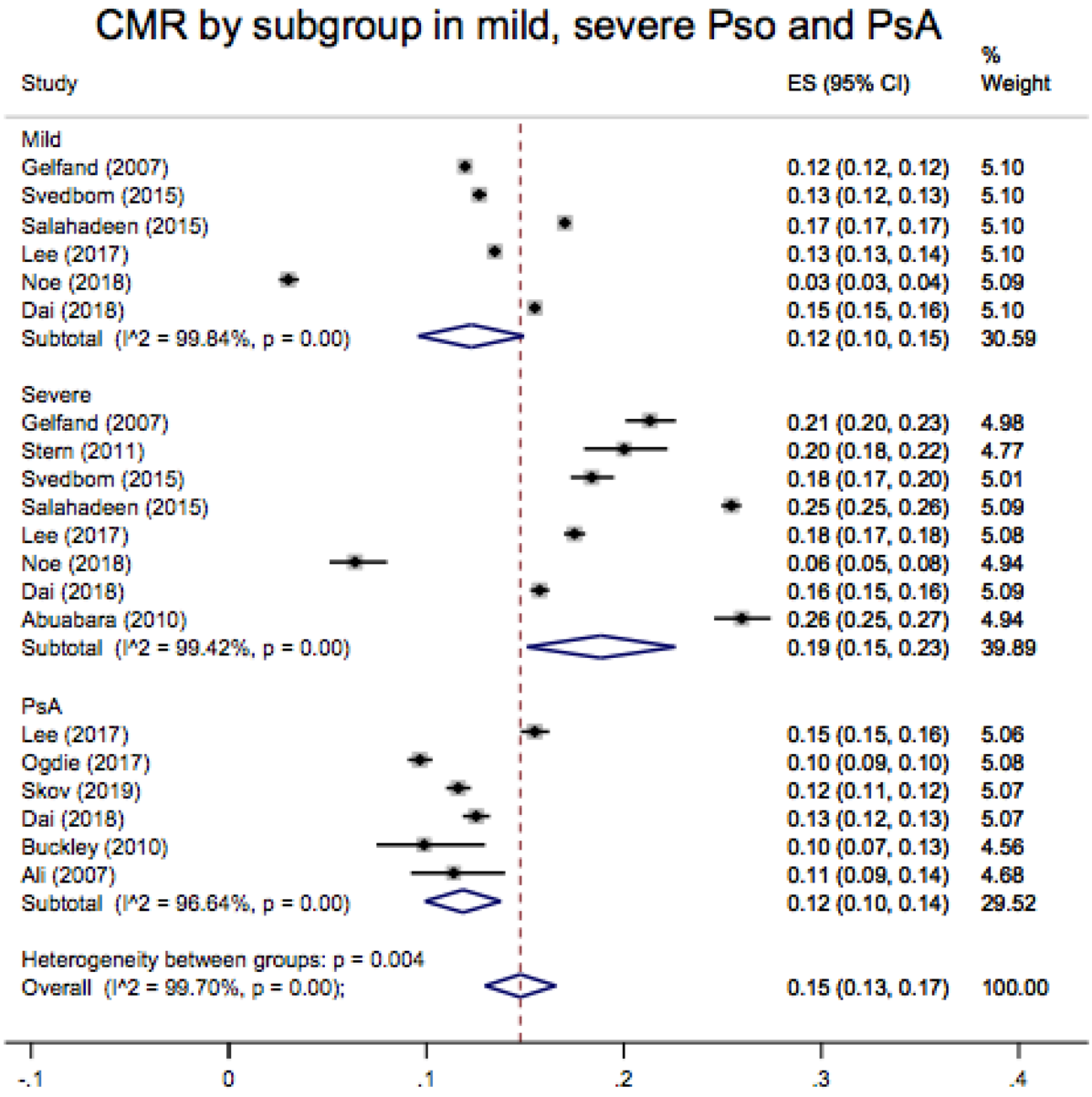

Figure 4. Forest plot of mortality in Pso vs PsA patients