See related article on pg 228

Back to the Future: Looking at the Skin to Predict Death—A Lesson from Psoriasis

Luigi Naldi[1,2] and Elena Pezzolo[1,2]

Noe et al. have documented that an objective measure of psoriasis severity, the body surface area as assessed at a single time point, could predict the risk of all-cause mortality in psoriatic patients. The results have important implications for disease management. Socioeconomic variables may, in part, confound the association between severe psoriasis and increased mortality.

Journal of Investigative Dermatology (2018) **138,** 20–22. doi:10.1016/j.jid.2017.08.027

> "Miror quidem Aristotelem non modo credidisse praescita vitae esse aliqua in corporibus ipsis, verum etiam prodidisse…"
>
> "I am surprised not only that Aristoteles believed that signs of the duration of life could be found on the body surface, but also that he wrote about such a topics"
>
> (Pliny the Elder, Historia Naturalis, volume 11, 273–4)

For centuries, the skin has been inspected for signs predicting future events including death. One popular practice is hand reading, that is, palmistry, an art rooted in Greek classical culture as alluded to by the above citation from Pliny the Elder (translated by H.H. Rackham, 1938).

The data presented by Noe et al. (2017) indicate that, at least for psoriatic patients, inspecting the skin could give hints regarding survival chances.

The authors analyzed data from the Health Improvement Network, an electronic medical record database maintained by general practitioners in the UK and enrolling approximately 9 million people. In the context of the Health Improvement Network study, a sample of approximately 9,000 psoriatic patients were identified and followed up with a collection of objective measures of psoriasis involvement, the so-called Incident Heath Outcomes and Psoriasis Events study.

What is really surprising in the data presented by Noe et al. is that a single imprecise measure, such as the extent of psoriasis at a single time point, measured as the body surface area (BSA) involved, could have a powerful effect and predict the chance of death over a long time span. When the BSA was 10% or higher, the probability of death increased by approximately 1.8 times compared with similar matched adults without psoriasis, after adjustment for age, gender, and the Charlson Comorbidity Index (an index of health status considering 19 morbid categories). The risk estimate did not substantially change when body mass index, smoking, diabetes, and history of cardiovascular disease were considered in sensitivity analyses. It should be noted that no increased risk of death could be documented for a BSA less than 10%. Hence, the threshold of 10% had particular value as an indicator of more severe psoriasis involvement. The authors calculated that each year, for every 390 psoriatic patients, there is one excess death that is not explained by traditional risk factors for death and specifically connected with having a psoriasis BSA greater than 10%.

The impact on mortality already suggested by previous studies

The BSA-specific predicting value aside, the findings of Noe et al. are not completely new. An earlier study published in 2007 by Gelfand et al. reported analyses of data from the General Practice Research Database in the UK, spanning from 1987 to 2002 (Gelfand et al., 2007). The analyses documented a 40% increased risk of all-cause mortality in severe psoriatic patients compared with people without psoriasis, after adjustment for known risk factors for mortality. In this study, severe psoriasis was defined as having a diagnostic code of psoriasis and a history of systemic therapy consistent with an extensive involvement of the disease. In 2011, Stern et al. presented analyses of the psoralens and UVA therapy cohort study and showed that death rates among patients enrolled into the cohort were significantly higher than that observed in the general population after adjustment by age, sex, and calendar year (Stern et al., 2011). Moreover, patients with exceptionally severe psoriasis at entry (BSA $>$ 42%) had a significantly increased risk of death compared with less severely affected cohort members (BSA $<$ 15%), with all-cause death hazard ratio, adjusted by all significant confounders in bivariate analysis, including uric acid serum level, but not obesity, alcohol, and blood pressure, equal to 1.42.

More recently, a nation-wide study in Denmark, conducted from 1999 to 2011, and classifying psoriatic patients as mild or severe according to the treatment they received, showed increased death rates in psoriatic patients compared with the general population and further increased rates in severe psoriatic patients compared with milder ones (Salahadeen et al., 2015). Finally, a recent analysis of data from a UK primary care database that is different from the one studied by Noe et al., the Clinical Practice Research Datalink, showed the persistence of excess mortality in psoriatic patients

[1]*Study Center of the Italian Group for Epidemiologic Research in Dermatology (GISED), Bergamo, Italy; and* [2]*Department of Dermatology, Ospedale san Bortolo, Vicenza, Italy*

Correspondence: Luigi Naldi, Unità Complessa di Dermatologia; AULSS 8, Ospedale San Bortolo, viale Rodolfi 37, 36100 Vicenza, Italy. E-mail: luigi.naldi@gised.it

Clinical Implications

- All-cause mortality increases when psoriasis involvement is equal to or higher than 10%.
- Systemic chronic inflammation may influence death rates in psoriasis.
- Unmeasured socioeconomic variables may confound the relation between mortality and psoriasis.

compared with people without psoriasis, especially in younger age groups, during the period 1999–2013, in spite of a general decrease of mortality rates in the overall population during the same period (Springate et al., 2017).

Mortality, a crucial measure of public health

Mortality arguably is the most important measure of the impact of a disease on the population health. Besides age and gender, the main drivers of mortality in westernized populations are those conditions, such as diabetes, cardiovascular disease, or cancer, that directly affect the functioning of vital organs (GBD 2015 Mortality and Causes of Death Collaborators, 2016). But how could psoriasis be linked per se with increased mortality? The systemic inflammatory process of severe psoriasis protracted over time seems to play a role. The best documented influences are those with pathomechanisms promoting atherosclerosis and facilitating cardiovascular disease (Sherer et al., 2006). That severe inflammation could be linked with mortality is well documented for rheumatoid arthritis and lupus erythematosus, among the others (Fernández-Gutiérrez et al., 2017). Interestingly, a previous analysis of the Health Improvement Network database documented an association of psoriasis and rheumatoid arthritis, but not psoriatic arthritis, with increased mortality (Ogdie et al., 2014). No clear explanation was provided for such a discrepancy.

Even a localized chronic inflammatory process such as periodontitis may be associated with increased all-cause and cardiovascular mortality rates (LaMonte et al., 2017). Inflammation at extraoral sites due to translocation of bacteria from the oral cavity has been proposed as a relevant biological feature (Schenkein and Loos, 2013). Interestingly, periodontitis has been consistently associated with psoriasis (Ungprasert et al., 2017). The association remains significant after controlling for recognized risk factors for both psoriasis and periodontitis, including smoking (Skudutyte-Rysstad et al., 2014). Both conditions are characterized by chronic inflammation originating from epithelial tissues (Uluçkan and Wagner, 2017).

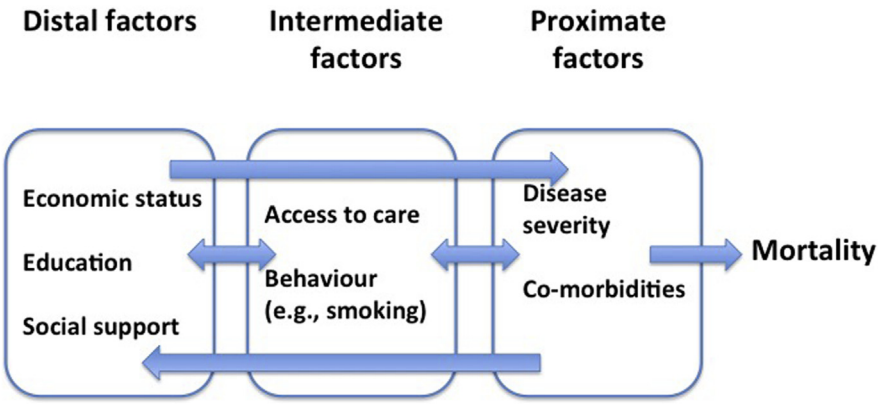

Figure 1. A framework for mortality that merges social and biological influences on health. Distal, socioeconomic, and cultural factors may operate through proximate, or biological, determinants to mortality. Mortality is most commonly derived from the cumulative effect of many interconnected factors.

What about socioeconomic variables?

The analysis of the reported causes of death may provide further insight into determinants of mortality. A study among the Newfoundland and Labrador founder population from 1991 to 2005 showed that patients with psoriasis died at a younger age and with a higher frequency of circulatory disorders and ill-defined conditions compared with the founder population (Collins et al., 2007). Unknown/missing causes of death were also more prevalent in psoriatic patients compared with patients with no history of psoriasis in an analysis of the causes of death based on the General Practice Research Database during the period 1987–2002 (Abuabara et al., 2010).

Deaths are classified as due to ill-defined conditions in cases when the real cause of death cannot be determined. Interestingly, several studies have shown that deaths from ill-defined conditions are more common in the low-income subset of the population and ethnic minorities (Kulhánová et al., 2014). The relationship between income and life expectancy is well established (Chetty et al., 2016), but little is known about income or other socioeconomic variables and psoriasis. Although psoriasis has not been linked per se with household income or education (Helmick et al., 2014), recent data have shown that low socioeconomic status and reduced access to dermatological services are associated with a higher severity of psoriasis at a first consultation (Mahé et al., 2017). Socioeconomic variables may, in part, confound the association between the clinical severity of psoriasis and all-cause mortality documented in several studies (Figure 1).

Although an association of severe psoriasis with increased mortality seems to be well established, further analyses should be conducted on the determinants of mortality in psoriatic patients including socioeconomic variables, that is, education, household income, and marital status, which have a major impact on all-cause mortality worldwide.

CONFLICT OF INTEREST

The authors state no conflict of interest.

REFERENCES

Abuabara K, Azfar RS, Shin DB, Neimann AL, Troxel AB, Gelfand JM. Cause-specific mortality in patients with severe psoriasis: a population-based cohort study in the U.K. Br J Dermatol 2010;163:586–92.

Chetty R, Stepner M, Abraham S, Lin S, Scuderi B, Turner N, et al. The association between income and life expectancy in the United States, 2001–2014. JAMA 2016;315:1750–66.

Collins KD, MacDonald D, Gulliver WP, Alaghehbandan R, Gladney N, Tomi Z. Mortality profiles of patients with psoriasis in the Newfoundland and Labrador founder population. Ann Epidemiol 2007;17:725–6.

Fernández-Gutiérrez B, Perrotti PP, Gisbert JP, Domènech E, Fernández-Nebro A, Cañete JD, et al. Cardiovascular disease in immune-mediated inflammatory diseases: a cross-sectional analysis of 6 cohorts. Medicine (Baltimore) 2017;96:e7308.

GBD 2015 Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459–544.

Gelfand JM, Troxel AB, Lewis JD, Kurd SK, Shin DB, Wang X, et al. The risk of mortality in patients with psoriasis: results from a population-based study. Arch Dermatol 2007;143:1493–9.

Helmick CG, Lee-Han H, Hirsch SC, Baird TL, Bartlett CL. Prevalence of psoriasis among adults in the U.S.: 2003-2006 and 2009-2010 National Health and Nutrition Examination Surveys. Am J Prev Med 2014;47:37–45.

Kulhánová I, Menvielle G, Bopp M, Borrell C, Deboosere P, Eikemo TA, et al. Socioeconomic differences in the use of ill-defined causes of death in 16 European countries. BMC Public Health 2014;14:1295.

LaMonte MJ, Genco RJ, Hovey KM, Wallace RB, Freudenheim JL, Michaud DS, et al. History of periodontitis diagnosis and edentulism as predictors of cardiovascular disease, stroke, and mortality in postmenopausal women. J Am Heart Assoc 2017;6:e004518.

Mahé E, Beauchet A, Reguiai Z, Maccari F, Ruer-Mulard M, Chaby G, et al. Socioeconomic inequalities and severity of plaque psoriasis at a first consultation in dermatology centers. Acta Derm Venereol 2017;97:632–8.

Noe MH, Shin DB, Wan MT, Gelfand JM. Objective measures of psoriasis severity predict mortality: a prospective population-based cohort study. J Invest Dermatol 2018;138:228–30.

Ogdie A, Haynes K, Troxel AB, Love TJ, Hennessy S, Choi H, et al. Risk of mortality in patients with psoriatic arthritis, rheumatoid arthritis and psoriasis: a longitudinal cohort study. Ann Rheum Dis 2014;73:149–53.

Pliny the Elder. Natural history [Horance H. Rackham, Trans.]. Boston: Loeb Classical Library, Harvard University Press; 1938.

Salahadeen E, Torp-Pedersen C, Gislason G, Hansen PR, Ahlehoff O. Nationwide population-based study of cause-specific death rates in patients with psoriasis. J Eur Acad Dermatol Venereol 2015;29:1002–5.

Schenkein HA, Loos BG. Inflammatory mechanisms linking periodontal diseases to cardiovascular diseases. J Periodontol 2013;84:S51–69.

Sherer Y, Shoenfeld Y. Mechanisms of disease: atherosclerosis in autoimmune diseases. Nat Clin Pract Rheumatol 2006;2:99–106.

Skudutyte-Rysstad R, Slevolden EM, Hansen BF, Sandvik L, Preus HR. Association between moderate to severe psoriasis and periodontitis in a Scandinavian population. BMC Oral Health 2014;14:139.

Springate DA, Parisi R, Kontopantelis E, Reeves D, Griffiths CE, Ashcroft DM. Incidence, prevalence and mortality of patients with psoriasis: a U.K. population-based cohort study. Br J Dermatol 2017;176:650–8.

Stern RS, Huibregtse A. Very severe psoriasis is associated with increased noncardiovascular mortality but not with increased cardiovascular risk. J Invest Dermatol 2011;131:1159–66.

Uluçkan Ö, Wagner EF. Chronic systemic inflammation originating from epithelial tissues. FEBS J 2017;284:505–16.

Ungprasert P, Wijarnpreecha K, Wetter DA. Periodontitis and risk of psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2017;31:857–62.