Research letter

Mortality in generalized pustular psoriasis: A population-based national register study

To the Editor: Generalized pustular psoriasis (GPP) (prevalence, 1.8-124/million people[1,2]) is a severe form of pustular psoriasis characterized by acute flares with systemic inflammation.[3] GPP is associated with several comorbidities,[1,4] and ~50% of patients with GPP have concomitant psoriasis vulgaris (PV).[1,4] We have assessed mortality and cause of death in GPP compared with the general population (GP) and patients with PV.

From the Swedish National Patient Register, we identified 1093 physician-diagnosed patients with GPP using a criterion of 1 primary or secondary GPP diagnosis (International Classification of Diseases, 10th revision, code L40.1) in 2004-2015. These were matched (1:5) to controls from the GP and (1:3) to controls with PV (and no GPP or palmoplantar pustulosis), on the basis of sex and age (flowcharts; Supplement 1, available via Mendeley at https://data.mendeley.com/datasets/5tt3kgr9kt/1). Individuals deceased between 2004 and 2020 were identified in the Swedish Cause of Death Register. Survival was compared between groups using Kaplan-Meier curves. Age-stratified hazard ratios (HRs) for all-cause mortality were determined by Cox regression models. In subgroup analysis, we limited analyses to patients with ≥2 GPP diagnoses (a stricter GPP criterion) given at different occasions during the study period and matched controls.

In the final GPP cohort ($n = 1022$), 44% had ≥2 GPP diagnoses and 54% had concomitant PV. The GPP cohort had relatively more deaths over the study period and ~50% higher mortality rate compared with both control populations (Table I and Supplement 2, available via Mendeley at https://data.mendeley.com/datasets/5tt3kgr9kt/1). Kaplan-Meier survival curves for the GPP cohort (Fig 1 and Supplement 3, available via Mendeley at https://data.mendeley.com/datasets/5tt3kgr9kt/1) showed a drop in survival immediately after diagnosis, which may be due to GPP life-threatening complication, triggered by factors such as infections, drugs, or hypocalcemia.[3] Thereafter, survival for GPP decreased steadily over the study period and was consistently lower than survival curves for the control groups. The mortality rate was higher in the GPP cohort (33/1000 person-years) compared with both GP and PV control populations (21 and 22/1000 person-years), with higher risks (HRs > 1.5) across all age groups. The highest relative risks (HRs > 2) were observed for the younger age groups. However, the absolute death risk was low in these groups (Table I).

The leading cause of death, grouped by International Classification of Diseases chapters, was diseases of the circulatory system. The GPP cohort had more deaths from circulatory, respiratory, and digestive diseases compared with GP controls ($P < .001$) and from digestive system compared with PV controls ($P = .011$) (Supplement 4, available via Mendeley at https://data.mendeley.com/datasets/5tt3kgr9kt/1).

When limiting the analysis to patients with at least 2 codes for GPP (Supplement 5, available via Mendeley at https://data.mendeley.com/datasets/5tt3kgr9kt/1), we found a higher GPP mortality rate (overall 39.2/1000 person-years) and higher HRs (overall 2.13 compared with both control groups), suggesting that the stricter criterion resulted in selection of patients with more severe disease.

The GPP mortality was in the higher range compared with small clinical studies (mortality rate range, 0-33/1000 person-years)[1] and a large Japanese study ($n = 1516$) on hospitalized patients with GPP (4.2% died over a 10-year period).[5] Limitations include potential GPP misclassification due to lack of standard case definition. Strengths of our study include the large national and representative GPP cohort, the longitudinal design, and the comparison with 2 control populations.

Oskar Ericson, MSc,[a] Sofia Löfvendahl, PhD,[a,b] Jenny M. Norlin, PhD,[a] Harald Gyllensvärd, MSc, Med, Lic,[c] and Marcus Schmitt-Egenolf, MD, PhD[d]

From The Swedish Institute for Health Economics, Lund, Sweden[a]; Division of Occupational and Environmental Medicine, Department of Laboratory Medicine, Faculty of Medicine, Lund University, Lund, Sweden[b]; Boehringer Ingelheim AB, Stockholm, Sweden[c]; and Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden.[d]

Funding sources: This research is the result of a research platform, which has received financial support from AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen Cilag, Leo pharma, and Novartis. This study's design and analysis was funded by

Table I. Baseline characteristics and mortality outcomes (overall and by age at diagnosis) for the GPP cohort and the matched control groups

			Matched control groups	
		GPP cohort *n* = 1022	General population* *n* = 4842	Psoriasis vulgaris† *n* = 3048
Women, *n* (%)		631 (61.7)	3015 (62.3)	1886 (61.9)
Patients with at least 2 GPP diagnoses (given at different occasions) 2004-2015, *n* (%)		452 (44.2)	N/A	N/A
Patients with a psoriasis vulgaris diagnosis‡ 2004-2015, *n* (%)		555 (54.3)	N/A	N/A
Age at diagnosis, mean (SD)	All	58.4 (16.6)	58.1 (16.5)	58.3 (16.5)
	Men	58.0 (16.0)	57.6 (16.0)	57.8 (16.0)
	Women	58.6 (16.9)	58.3 (16.8)	58.6 (16.9)
Age (intervals) at diagnosis, *n* (%)	18-44	211 (20.7)	1015 (21.0)	633 (20.8)
	45-64	424 (41.5)	2038 (42.1)	1267 (41.6)
	65-79	284 (27.8)	1331 (27.5)	845 (27.7)
	≥80	103 (10.1)	458 (9.5)	303 (9.9)
Follow-up time in years (overall and across age at diagnosis intervals), mean (SD)	Overall	9.3 (4.6)	10.0 (4.3)	10.1 (4.1)
	18-44	11.3 (3.9)	11.2 (3.9)	11.5 (3.6)
	45-64	10.4 (4.3)	11.0 (4.1)	11.1 (3.8)
	65-79	8.1 (4.2)	8.9 (4.1)	9.0 (3.8)
	≥80	4.2 (3.5)	5.8 (3.7)	6.4 (3.6)
No. of deaths during follow-up, *n* (%)	Overall	315 (30.8)	1027 (21.2)	679 (22.2)
	18-44	7 (0.7)	9 (0.2)	6 (0.2)
	45-64	81 (7.9)	198 (4.1)	145 (4.8)
	65-79	135 (13.2)	463 (9.6)	291 (9.5)
	≥80	92 (9.0)	357 (7.4)	237 (7.8)
Person-years at risk§	Overall	9550	48,236	30,926
	18-44	2386	11,362	7302
	45-64	4415	22,338	14,059
	65-79	2314	11,861	7622
	≥80	435	2675	1943
Mortality rate (per 1000 person-years)	Overall	33.0	21.3	22.0
	18-44	2.9	0.8	0.8
	45-64	18.3	8.9	10.3
	65-79	58.3	39.0	38.2
	≥80	211.3	133.5	122.0
Hazard ratios for all-cause mortality in GPP vs general population controls, (CI); (*P* value)	Overall		1.81 (1.58-2.08); ($p < .001$)	
	18-44		3.49 (1.30-9.42); ($P = .013$)	
	45-64		2.07 (1.58-2.70); ($P < .001$)	
	65-79		1.61 (1.31-1.97); ($P < .001$)	
	≥80		1.88 (1.43-2.46; ($P < .001$)	
Hazard ratios for all-cause mortality in GPP vs psoriasis vulgaris controls, (CI); (*P* value)	Overall		1.90 (1.63-2.21); ($P < .001$)	
	18-44		3.50 (1.18-10.41); ($P = .024$)	
	45-64		2.03 (1.52-2.71); ($P < .001$)	
	65-79		1.66 (1.32-2.09); ($P < .001$)	
	≥80		2.14 (1.58-2.90); ($P < .001$)	

GPP, Generalized pustular psoriasis (L40.1 as primary or secondary diagnosis); *N/A*, not applicable; *PPP*, palmoplantar pustulosis; *PV*, psoriasis vulgaris.

*Matched on year of birth, sex, and residential area.

†Matched on year of birth, sex, and index year (ie, year of first PPP or PV diagnosis).

‡L40.0 or L40.9 as primary diagnosis.

§The total sum of the number of years that each member of a study population has been under observation.

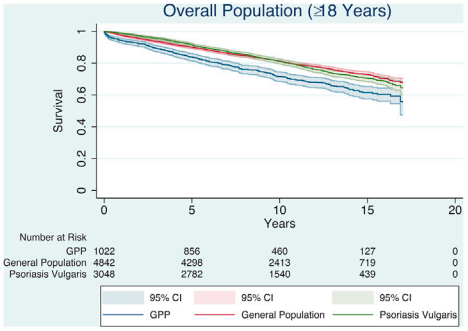

Fig 1. Kaplan-Meier survival estimates for the overall GPP cohort and the 2 matched control populations representing the general population and patients with psoriasis. As both the general population and PV controls were matched against the GPP cohort (but not against each other), direct comparisons between the control groups cannot be made. *GPP,* Generalized pustular psoriasis; *PV,* psoriasis vulgaris.

Boehringer Ingelheim. The authors had full independence regarding study design, data collection, analysis, result interpretation, and decision to publish.

IRB approval status: This study was approved by the Regional Ethical Review Board at Umeå University, Sweden.

Key words: epidemiology; generalized pustular psoriasis; health care register; Kaplan-Meier survival; mortality; population-based.

Correspondence to: Marcus Schmitt-Egenolf, MD, PhD, Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden

E-mail: marcus.schmitt-egenolf@umu.se

Conflicts of interest

Dr Schmitt-Egenolf is responsible for dermatology in the project management for the national guidelines for psoriasis at the Swedish Board of Health and Welfare. Drs Norlin and Löfvendahl have been involved in the health economic analyses of the national guidelines for psoriasis at the Swedish Board of Health and Welfare. Mr Gyllensvärd is an employee of Boehringer Ingelheim AB, Sweden. Drs Schmitt-Egenolf, Norlin, and Löfvendahl and Mr Gyllensvärd have no conflicts of interest to declare.

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https://doi.org/10.1016/j.jaad.2023.04.066