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Research Article

Impact of Underlying Conditions on Zoster-Related Pain and on Quality of Life Following Zoster

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Abstract

Background: Chronic conditions have been investigated as risk factors for developing zoster, but in patients suffering from zoster, the impact of underlying conditions in zoster-related pain and quality of life (QOL) remains unclear.

Methods: We performed a post hoc analysis of a prospective cohort study in immunocompetent zoster patients aged 50 years or older, conducted by general practitioners in Italy between 2009 and 2010. Zoster symptoms, pain intensity and characteristics, and physical and mental health scores were assessed at baseline (zoster diagnosis) and at 1, 3, and 6 months of follow-up.

Results: Among 413 patients enrolled in the study, 73% (303/413) suffered from underlying conditions of which 69% (209/303) were aged 65 or older. Cardiovascular diseases (75%), diabetes (24%), and respiratory diseases (17%) were most frequent. One to three months after onset, zoster patients with underlying conditions experienced more intense zoster-related pain than those without. QOL scores were significantly lower in patients with underlying conditions, and age-adjusted difference in QOL scores between the groups increased over time, demonstrating a slower recovery for patients with underlying conditions.

Conclusions: In addition to age, the main risk factor of zoster occurrence and severity, the presence of underlying conditions results in more painful and impactful zoster episodes, creating a significant burden for these patients.

Keywords: Post-herpetic neuralgia—Chronic diseases—Daily life activities

Varicella zoster virus (VZV) is a herpes virus that causes both varicella (chickenpox) and zoster (shingles). Primary VZV infection (varicella) usually occurs in childhood, after which the virus remains latent in sensory ganglia (1). Reactivation of latent VZV leads to zoster and is thought mainly to occur due to age-related decline in VZV-specific T-cell–mediated immunity (immunosenescence) (2). Data suggest that almost everybody is at risk of zoster (3) and that the incidence of zoster in Europe is comparable across countries (4). Incidence is estimated to be 3.4/1,000, all age groups included, equating to the occurrence of 1.7 million new zoster cases every year in Europe (5). Lifetime risk of zoster has been estimated to be 10%–30%, but the condition affects up to 50% of people who live to 85 years (6). In addition to the burden of zoster, the risk of complications due to zoster increases rapidly after 50 years of age (5), as does zoster-related mortality (7).

Zoster is characterized by a unilateral dermatomal vesicular rash and moderate-to-severe pain, which is reported in up to 90% of patients in the acute phase. The most frequent and debilitating complication of zoster is postherpetic neuralgia (PHN). PHN is a continuation of moderate-to-severe chronic nerve pain in the area of the rash beyond the acute phase (8). Around 10%–20% of immunocompetent patients aged 50 years or older (9) and 40% of patients aged 60 years or older will develop PHN (8). Management of pain is challenging particularly in elderly people with chronic diseases and polypharmacy (10–12). As PHN can persist for months to years (13), it can be extremely detrimental to physical and mental health and can lead to loss of employment, depression, and social isolation (14).

Some chronic diseases may contribute to the occurrence and/or severity of zoster (15,16). In Sweden, as in many other European

countries, Australia, and North America, a 20%–30% prevalence of multiple chronic diseases across the whole population was found, increasing to 55%–98% in older persons (older than 60 years) (17).

The HERpes zoster Outcome Epidemiological Study (HEROES) was a General Practitioners (GP)-based prospective observational study conducted in Italy in 2009–2010 that aimed to investigate zoster-associated chronic pain and its management in a cohort of immunocompetent patients aged 50 years and older. The primary outcomes, the proportion of zoster patients having PHN and its duration, have been reported previously (18): 21% of patients had PHN at 3 months and 9% at 6 months. As more than 70% of the patients in the study presented with underlying conditions, we performed a post hoc analysis aiming to describe the impact of underlying conditions on zoster-related pain and on quality of life (QOL).

Methods

Objective

The objective of the study was to describe zoster-related pain and quality of daily life in zoster patients suffering from underlying conditions and compare this with patients without these conditions.

Design

This is a post hoc analysis of the HEROES study, a study conducted by 108 GPs from 21 local health units located in 12 Italian regions, with a geographic distribution representative for Italy. GPs enrolled 435 patients. For 5 patients, no case report form was filled in, and 17 additional patients were excluded (aged < 50 years; concomitant disease, error of diagnosis), leaving 413 immunocompetent patients aged 50 years and older with a new diagnosis of zoster between March 2009 and July 2010. After the enrollment initial visit (zoster acute phase), each patient was invited to attend three additional visits at 1 (±15 days), 3 (±21 days), and 6 (±30 days) months. The study was approved by the ethical committee of all local health units, and all included patients provided written informed consent.

GP Data Collection

The GPs collected sociodemographic data, the medical history, and zoster symptoms (rash localization and extension and number of vesicles) at initial visit and pain characteristics (allodynia, itching, and paresthesia) at each visit.

In the medical history, underlying conditions were categorized as one of three chronic diseases (diabetes, cardiovascular diseases, and respiratory diseases), or as "other relevant diseases." Where a condition was considered relevant by the GP, but not related to zoster, it was classified as "other relevant diseases," and the GP was invited to provide a description of the condition in free text.

Patient Self-Reported Information

At each visit, the patients were asked to report if they were experiencing zoster-related pain at the time of the visit (yes/no). Furthermore, patients filled in a Visual Analog Scale (VAS) to quantify pain intensity. Patients indicated the worst pain felt during the last 2 weeks on a scale ranging from 0 (no pain) to 10 (worst pain imaginable). A VAS score ≥3 was considered to correlate with pain that interferes with activities of daily living (19). Finally, at each visit patients completed the physical (PCS-12) and mental (MCS-12) components of the Short-Form health Survey (SF-12) questionnaire to assess their QOL (20). This patients' QOL survey includes activities of daily life and scores range from 0 (lowest level of health) to 100 (highest level of health).

Statistical Analysis

Descriptive analyses included frequency tables, number of observations, means, standard deviation, and 95% confidence intervals. A linear mixed model was used to analyze repeated measures data such as the VAS score and the SF-12-derived PCS-12 and MCS-12 (20). Age (continuous variable), group (presence or absence of an underlying condition), and time (visit number) were included in the model, as well as an interaction term between time and group. To account for individual differences in VAS score and PCS-12/MCS-12, patients were included as a random effect. Patients were excluded from the analysis for one visit, if it occurred outside of the time window, but included in the analysis for a subsequent visit, occurring within the time window. All analyses were performed in SAS version 9.3 (SAS Institute, Cary, NC).

Results

Of the 413 patients with a new diagnosis of zoster, 303 (out of 413, 73%) had at least one underlying condition with 128 (out of 303, 42%) having one underlying condition, 128 (42%) having two, 42 (14%) having three, and 5 (2%) having four underlying conditions. Of these patients with underlying conditions, 226 (out of 303, 75%) had a cardiovascular disease, 72 (24%) had diabetes (of which 6 had type 1 and 66 had type 2 diabetes), and 52 (17%) had a respiratory disease. An additional 42 (14%) patients presented with other relevant diseases, including neoplasms (n = 5), depression (n = 4), autoimmune thyroiditis (n = 3), gastroesophageal reflux disease (n = 3), chronic hepatitis C virus infection (n = 3), osteoarthritis (n = 3), benign prostatic hyperplasia (n = 2), and rheumatoid arthritis (n = 2), in addition to a number of other diseases that occurred only once.

A total of 382 patients (92%) attended the final visit, whereas 31 terminated the study prematurely, for various reasons (protocol deviation, informed consent withdrawal, and loss to follow-up). Completeness of follow-up among patients with underlying conditions was comparable with that among patients without underlying conditions (Figure 1).

Baseline Characteristics

Baseline characteristics of zoster patients with and without underlying conditions and by comorbidity are shown in Table 1. The majority (64%) of patients were women. Overall the gender ratio was similar in those with and those without underlying conditions (65% and 63% were women, respectively), although a higher proportion of men (52%) was found in the group with chronic respiratory disease. Although patients with underlying conditions visited their GPs more frequently, the delay in GP visit after rash onset was comparable between patients with and without underlying conditions. Patients with underlying conditions were on average 10 years older than patients without underlying conditions (mean age 70 vs 61), a greater proportion were retired (75% vs 41%), and a higher proportion lived alone (19% vs 11%). Patients with underlying conditions presented with a more severe rash, with significantly more frequent occurrence of ≥ 50 vesicles (22% vs 10%; p = .004) at the acute phase.

Zoster-Related Pain and QOL

At the acute phase, almost all zoster patients (90%) expressed having pain with the same proportion whatever they have underlying conditions or not (Table 2). However, higher frequencies of paresthesia,

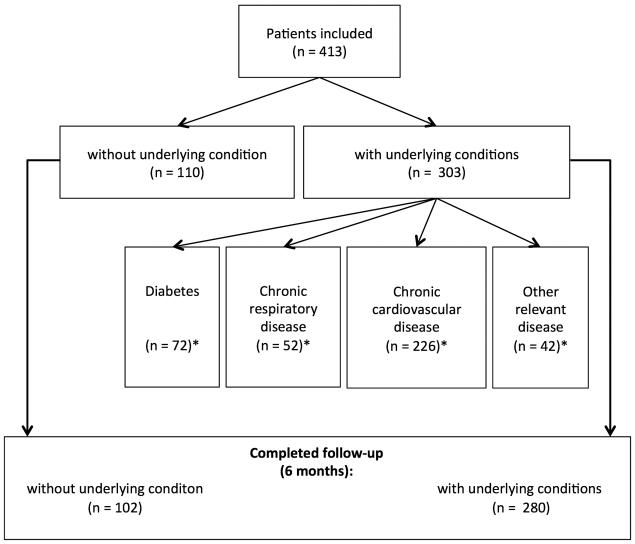

Figure 1. Flow diagram of study participants. *Numbers add up to more than 303, as patients can have multiple diseases.

allodynia, and itch were observed in patients with underlying conditions. Mean pain intensity was above a level (VAS score ≥ 3.0) considered to interfere with activities of daily living and functioning in both groups of patients, although it was significantly higher in patients with underlying conditions (p = .001). The proportion of patients with pain interfering with activities of daily living was higher in the group with underlying conditions (VAS score ≥ 3: 76% vs 70%). Physical and mental health scores were significantly lower in patients with underlying conditions (PCS-12, p < .001; MCS-12, p = .006). We observed a strong effect of age on reporting of pain intensity among patients with underlying conditions (Supplementary Table 1). Proportions of patients experiencing a VAS score ≥ 3 were 63% versus 82% in those younger than 65 years and in those aged 65 and older, respectively. Intensity of pain was not reported differently by patients aged 65 or older versus those younger than 65 years in patients without underlying conditions. The physical and mental health scores were lower in patients aged 65 or older versus those younger than 65 years with a higher difference in the group with underlying conditions.

During the 6-month follow-up period, zoster patients with underlying conditions consistently reported a higher intensity of pain, although the differences in the mean VAS were only significant at Months 1 and 3, see Table 2. The intensity of pain decreased rapidly in the group without underlying conditions (Table 2). After 1 month, the mean VAS score was 3.1, and at 6 months, VAS had decreased by 47% to 2.6. In the group with underlying conditions, the decrease was also 47%, but the mean VAS remained above 3 (Table 2). After having adjusted for age, the significant effect of underlying conditions on the intensity of pain was confirmed; Figure 2 shows that patients with underlying conditions had a higher pain intensity along the 6 months of follow-up.

Physical and mental health scores increased during follow-up for both groups of patients, but were significantly lower for patients with underlying conditions at each visit (p < .01; Table 2). The net gain in PCS-12 over 6 months was 10 points for patients without underlying conditions, compared with 7 points in patients with underlying conditions. The net gain in MCS-12 over 6 months was 7 points for patients without underlying conditions, compared with 5 points in patients with underlying conditions. After having adjusted for age, significantly lower physical and mental health scores in

Table 1. Baseline Characteristics of Zoster Patients by Underlying Condition

	Without underlying condition	With underlying condition	Chronic cardiovascular disease[a]	Diabetes[a]	Chronic respiratory disease[a]
	n = 110	*n* = 303	*n* = 226	*n* = 72	*n* = 52
Age (years), mean (*SD*)	60.9 (8.3)	70.5 (10.4)	72.0 (10.2)	69.3 (10.6)	72.3 (10.0)
Sex: % Male	37.3%	35.3%	37.2%	34.7%	51.9%
Demographic condition: *n* (%)					
Alone	12 (10.9%)	58 (19.1%)	42 (18.6%)	13 (18.1%)	12 (23.1%)
Family	96 (87.3%)	240 (79.2%)	180 (79.6%)	58 (80.6%)	39 (75.0%)
Institution		1 (0.3%)		1 (1.4%)	
Other	2 (1.8%)	4 (1.3%)	4 (1.8%)		1 (1.9%)
Employment: *n* (%)					
Employed	57 (51.8%)	47 (15.5%)	27 (11.9%)	11 (15.3%)	6 (11.5%)
Retired	45 (40.9%)	226 (74.6%)	177 (78.3%)	55 (76.4%)	45 (86.5%)
Other	8 (7.3%)	30 (9.9%)	22 (9.7%)	6 (8.3%)	1 (1.9%)
Number of vesicles: *n* (%)					
None	3 (2.7%)	12 (4%)[b]	8 (3.5%)[b]	4 (5.6%)	1 (1.9%)
<50	96 (87.3%)	222 (73.3%)	166 (73.5%)	49 (68.1%)	36 (69.2%)
≥50	11 (10.0%)	68 (22.4%)	51 (22.6%)	19 (26.4%)	15 (28.8%)
GP attendance: *n* (%)					
<1×/year	14 (12.7%)	6 (2.0%)	4 (1.8%)	3 (4.2%)	14 (26.9%)
1–5×/year	60 (54.5%)	88 (29.0%)	56 (24.8%)	16 (22.2%)	15 (28.8%)
6–10×/year	22 (20.0%)	99 (32.7%)	69 (30.5%)	26 (36.1%)	23 (44.2%)
>10×/year	14 (12.7%)	110 (36.3%)	97 (42.9%)	27 (37.5%)	
Visit delay since rash onset (in days): Mean (*SD*)	3.2 (8.0)	2.7 (3.6)	2.5 (3.1)	2.9 (4.7)	2.5 (3.0)

Notes: [a]Sum of chronic conditions is greater than the total number of patients due to multimorbidity.
[b]One missing data.

Table 2. Pain and Quality of Life Characteristics of Zoster Patients by Underlying Condition

	Without underlying condition (n = 110)	With underlying condition (n = 303)	p Value[a]
Presence of pain: n (%)			
Visit 1 (acute phase)	99 (90.0%)	271 (89.4%)	.869
Visit 2 (1 month)	46 (41.8%)	147 (48.5%)	.228
Visit 3 (3 months)	7 (6.4%)	66 (21.8%)	<.001
Visit 4 (6 months)	5 (4.5%)	29 (9.6%)	.101
Pain characteristics: n (%)			
Visit 1 (acute phase)			
Allodynia	51 (46.4%)	166 (54.8%)	.130
Itch	77 (70.0%)	222 (73.3%)	.511
Paresthesia	54 (49.1%)	179 (59.1%)	.071
Visit 2 (1 month)			
Allodynia	21 (19.1%)	80 (26.4%)	.127
Itch	13 (11.8%)	62 (20.5%)	.044
Paresthesia	21 (19.1%)	100 (33.0%)	.006
Visit 3 (3 months)			
Allodynia	7 (6.4%)	34 (11.2%)	.145
Itch	5 (4.5%)	21 (6.9%)	.378
Paresthesia	7 (6.4%)	51 (16.8%)	.007
Visit 4 (6 months)			
Allodynia	2 (1.8%)	14 (4.6%)	.192
Itch	2 (1.8%)	8 (2.6%)	.631
Paresthesia	1 (0.9%)	16 (5.3%)	.048
Intensity of pain VAS: Mean (*SD*)			
Visit 1 (acute phase)	4.9 (2.4)	5.9 (2.5)	.001
Visit 2 (1 month)	3.1 (2.0)	4.2 (2.5)	.002
Visit 3 (3 months)	2.4 (1.9)	3.2 (2.2)	.068
Visit 4 (6 months)	2.6 (2.3)	3.1 (2.6)	.400
Patients with VAS ≥ 3: n (%)			
Visit 1 (acute phase)	77 (70.0%)	231 (76.2%)	.198
Visit 2 (1 month)	35 (31.8%)	141 (46.5%)	.008
Visit 3 (3 months)	9 (8.2%)	62 (20.5%)	.004
Visit 4 (6 months)	8 (7.3%)	42 (13.9%)	.070
Physical health score: Mean (*SD*)			
Visit 1 (acute phase)	43.0 (7.4)	39.1 (8.9)	<.001
Visit 2 (1 month)	46.0 (7.5)	40.9 (9.5)	<.001
Visit 3 (3 months)	52.9 (4.4)	45.3 (9.1)	<.001
Visit 4 (6 months)	53.3 (4.2)	46.5 (9.0)	<.001
Mental health score: Mean (*SD*)			
Visit 1 (acute phase)	44.4 (10.2)	40.7 (10.6)	.006
Visit 2 (1 month)	45.7 (10.6)	41.8 (10.9)	.006
Visit 3 (3 months)	50.3 (7.7)	44.0 (10.1)	.008
Visit 4 (6 months)	51.7 (7.0)	45.5 (9.8)	<.001

Notes: VAS = Visual Analog Scale.
[a]p Value for χ^2 test groups comparison.

patients with underlying conditions were confirmed (Figure 3A and B). Furthermore, patients with underlying conditions expressed a significantly higher difficulty to recover their QOL 6 months after the rash onset.

Discussion

In this prospective cohort study on immunocompetent patients aged 50 years and older with a new diagnosis of zoster, nearly three quarters of the patients presented with at least one underlying condition. Although zoster-related pain was similarly reported at the acute phase by both groups of patients, the intensity of pain for patients with underlying conditions remained above the VAS threshold of 3 throughout the 6 months of follow-up—a level of pain that is considered to interfere with activities of daily living and functioning. For chronic pain a change of 20% of VAS score, and for acute pain a change of 12%, is regarded to be clinically significant (21). In both patient groups, the mean VAS pain score showed a clinically significant reduction of 47% between the acute phase and the 6-month visit; furthermore, the mean VAS pain score in patients without underlying condition was 16% lower than the one in patients with underlying conditions at 6 months.

Both physical and mental scores of the SF-12 were lower in patients with underlying conditions whatever the visits. When comparing our study population with the general Italian population of the same age range, both study groups (with and without underlying conditions) fall at the lower end of the expected PCS-12 and MCS-12 range at the acute phase (22), likely due to the newly diagnosed zoster episode. Regrettably, no baseline reference is available for our study participants, predating the zoster episode. Mental and physical health scores increased over time in both patients with and without underlying conditions. For mental health score, the group

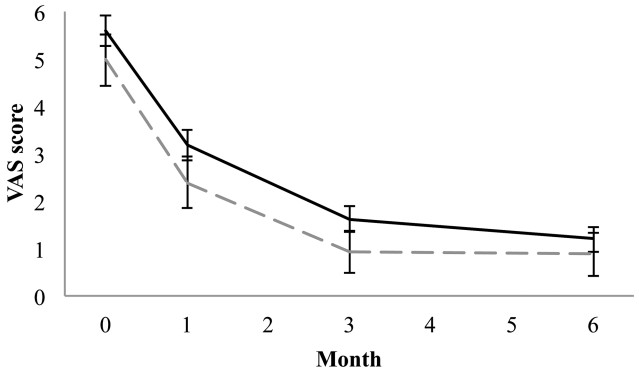

Figure 2. Changes in age-adjusted pain intensity during follow-up: estimated Visual Analog Scale score means by group over time. Solid black line represents patients with underlying conditions. Dashed gray line represents patients without underlying conditions.

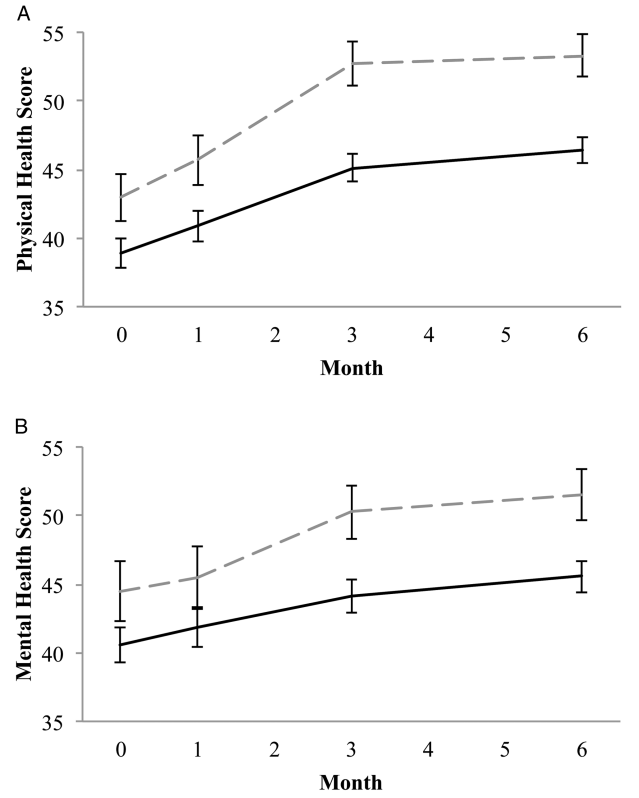

Figure 3. Changes in age-adjusted outcome measures during follow-up. (**A**) Estimated physical health score means by group over time. Solid black line represents patients with underlying conditions. Dashed gray line represents patients without underlying conditions. (**B**) Estimated mental health score means by group over time. Solid black line represents patients with underlying conditions. Dashed gray line represents patients without underlying conditions.

without underlying conditions (mean age = 61 years) increased from 44 at the acute phase to 52 at the 6-month visit, which is above the mean in the general population aged 55–64 years in Italy (mean MCS-12 = 49). For the group with underlying conditions (mean age = 70 years), the mean MCS-12 at the 6-month visit remained below the mean in the population aged 65–74 years (45 vs 48). Our study findings suggest that zoster has a bigger and long-lasting impact on more fragile patients who have underlying conditions, relative to patients without any underlying condition.

The level of multimorbidity in our study is in line with similar studies performed in Europe. In Italy, 40% of patients observed presented with at least one chronic disease, rising with age to 61% in patients aged 60–64 years and to 78.5% in patients aged 65 years or older (23–25). Rates are similarly high in other European countries: in Sweden, 55% of the population (mean age = 84.6 years, range 77–100) had chronic conditions (17), and in the United Kingdom, 58% of the population presented with multimorbidity (26). Previously, it was shown that underlying conditions increased the incidence or the severity of infection and altered the outcome of patients (27). In a prospective cohort study, which looked specifically at multimorbidity alongside zoster in primary care settings in France, 61.6% of the study population (mean age = 67.7, range 50–95) had comorbidities (14.7% diabetes, 63.2% cardiovascular diseases, and 10.2% pulmonary diseases) (28).

The impact of zoster-related pain on quality of daily life in the general population has been reported previously (9,28–30). A prospective multicenter observational study carried out in French centers specialized in the management of chronic pain found a relatively high rate of patients presenting with PHN, particularly in patients older than 70 years: 11% of those patients consulting for chronic pain presented with PHN. The study confirmed the negative impact of PHN on QOL (31). Similarly, a prospective study performed in the United States, conducted in 160 zoster outpatients aged 60 years and older, reported that zoster-related pain interfered with all activities of daily living (32); however, no data on chronic conditions were presented. The impact of chronic conditions on the evolution of zoster has been described among hospitalized patients, but to our knowledge, our study through this post hoc analysis is the first to investigate the impact of underlying conditions on zoster followed in the ambulatory setting. In Spain, a retrospective study on hospitalization of patients with zoster showed that 61% of patients had chronic conditions (33). These patients had a longer mean length of hospital stay (13.0 vs 11.4 days), a greater mortality rate (4.6% vs 2.1%), and a greater hospital fatality rate (between 1.6 and 2.7, depending on age) compared with zoster patients without these conditions (33). Similar results were found in a retrospective case–control study conducted in France on patients hospitalized for zoster. More than half of hospitalized patients (72%) had comorbidities (mean age = 76 years), and the median length of stay was statistically higher in patients with comorbidities (differed by 3–6 days depending on the diseases) (34). Our findings suggest that underlying conditions also affect the severity and the evolution of zoster cases occurring in the outpatient setting.

This study had some limitations, including, the absence of serious zoster cases (no hospitalizations were reported), the lack of information on quality of daily life before onset of zoster, which might have served as a baseline value, and finally the lack of information on treatment of underlying conditions in patients. Furthermore this post hoc analysis was not powered to detect a difference between the groups of patients with and without underlying conditions. A larger sample size would have benefitted statistical detection of differences between groups. Nevertheless, this study has some important strengths, one of which is its likely high external validity due to its prospective study design, the large network of participating GPs in Italy, the follow-up time of 6 months, with only 7% of patients terminating the study prematurely, and finally, a good representation of chronic diseases in the older population.

It has been argued that even with appropriate treatment, zoster-related pain can have a significant negative impact on the patient's QOL as clinical management tends to produce modest benefit (due to, eg, delay in providing treatment, ineffective drugs chosen, and

poor tolerability) (11). Caution is needed when prescribing medications, particularly in elderly zoster patients with underlying conditions: The oral agents used to manage PHN have systemic and cognitive adverse effects, which may be amplified in older adults (11). Furthermore, poor drug tolerability and the possibility of drug interactions decrease the patient's acceptance of zoster treatment and limit overall clinical benefit, particularly in older, more frail individuals (10). Finally, a zoster episode, or the treatment of PHN in an old person with one or more chronic diseases, can be a cause of decompensation or exacerbation of underlying disease (35). Studies for other infectious diseases, such as influenza, have been shown to cause exacerbations or decompensation of underlying disease (36).

Modeling work of the functional decline of zoster in older people underlined the importance of early treatment and vaccine prevention (12). With the availability of a vaccine to prevent zoster or zoster-related pain (PHN), vaccination has become an important preventive measure for zoster and its associated consequences. Zoster vaccine has been shown to be well tolerated and efficacious in persons with chronic conditions (37,38). Avoiding additional medication for treating zoster or its consequences will be an extra motivation for patients with chronic conditions who may already be on multiple medications. In Europe, Zoster vaccination recommendations are available for Italy, Spain, the UK, and France. As age is the most important risk factor for the occurrence, frequency, and severity of zoster and PHN, it is the main criterion to select populations for vaccination. Alternatively, clinical, epidemiological, and public health criteria can be considered for the selection of priority groups for zoster vaccination: Patients in whom zoster could have a higher impact (severity or risk of decompensation) and patients who frequently visit their GP for an underlying condition and/or are considered a target group for other vaccination programs such as influenza or pneumococcus. For an overview of recommendations, please refer to Supplementary Table 2.

In conclusion, in addition to age, underlying conditions are an additional burden related to zoster severity and loss of quality of daily life, resulting in slower recovery. With more than 20% of the population of the EU aged 60 years or older, and 80% of people aged 65 years or older having at least one chronic disease, prevention of zoster and PHN in elderly people may contribute to maintenance of their functional status and QOL, and thus to healthy aging (39,40).

Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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