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ORIGINAL ARTICLE

Patient-Reported and Clinical Outcomes Among Patients With Calciphylaxis

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Abstract

Objective: To describe the pain intensity among hospitalized patients with calciphylaxis, elucidate the factors associated with pain improvement, and examine the link between pain improvement and clinical outcomes.

Patients and Methods: Patients were identified from the Partners Research Patient Data Registry and the Partners Calciphylaxis Registry and Biorepository (Clinicaltrials.gov ID: NCT03032835). Those with calciphylaxis requiring hospitalization for at least 14 consecutive days during the study period from May 2016 through December 2021 were included. Pain intensity was assessed using patient-reported pain scores on numerical rating scales from 0 to 10. Associations between pain improvement and clinical outcomes, including lesion improvement, amputation, and mortality, were examined using univariate and multivariate regression models.

Results: Our analysis included 111 patients (age, 58±14 years; men, 40%; on maintenance dialysis, 79%). No significant improvement of pain intensity was observed over the 14 days of hospitalization (mean difference, −0.71; P=.08). However, among 49 (44.1%) patients who showed at least 1-point improvement in the pain score, there was an association with surgical debridement during hospitalization (odds ratio, 3.37; 95% CI, 1.17-9.67; P=.02). Hyperbaric oxygen therapy was associated with pain improvement (odds ratio, 5.38; 95% CI, 1.14-25.50; P=.03) in patients on maintenance dialysis. Pain improvement was associated with lower rates of subsequent amputation at 6 months of follow up (6% vs 13%; P<.05) but did not predict lesion improvement or survival.

Conclusion: Pain control remains a challenge among hospitalized patients with calciphylaxis. Surgical debridement and hyperbaric oxygen therapy may improve pain intensity. Pain improvement predicted a lower risk of future amputation.

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Calciphylaxis is a rare, life-limiting disease characterized by ischemic skin lesions caused by microvascular calcification and thrombosis.[1] It mainly affects patients on maintenance dialysis. Several other risk factors (eg, vitamin K antagonists, glucocorticoids, and vitamin D compounds) have also been identified for calciphylaxis; however, there is no approved treatment, and the prognosis remains poor.[2,3] The mortality rate has been reported to be 30%-70% within 1 year.[4] Severe pain despite the use of analgesics, including opioids, is a common feature of calciphylaxis. Patients frequently withdraw from medical care because of uncontrolled severe pain. Ischemia and inflammation around the nerves are likely responsible for calciphylaxis-associated pain.[5]

There is very limited evidence focusing on calciphylaxis-associated pain. In a study analyzing the correlation between the clinical and pathologic features of calciphylaxis, pain severity was found to be associated with the presence of fibrin thrombi during biopsy.[6] According to 1 report, pain improvement within 2 weeks may predict a good clinical response

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in the following months.[7] It has been empirically reported that one of the first indicators of treatment response is decrease in pain intensity, whereas wound healing can take months of therapy.[8] However, there is little evidence supporting the notion that pain improvement could be anticipated within 2 weeks and could indicate a favorable outcome.

We conducted a retrospective analysis focused on pain score improvement during the first 14 days of hospitalization among patients with calciphylaxis and its association with outcomes, including skin lesion improvement, amputation, and survival.

METHODS

Patients Selection

Patients were eligible to be included in this study if they were hospitalized for at least 14 consecutive days for the management of calciphylaxis at Massachusetts General Hospital or Brigham and Women's Hospital during the study period extending from May 2016 to December 2021 and had pain scores reported on days 1 and 14 of hospitalization. Initially, 352 patients were screened. Of them, 176 patients were identified from the institutional electronic research registry (known as the Partners Research Patient Data Registry) using International Classification of Diseases codes, and 176 cases were identified from the Partners Calciphylaxis Biobank and Patient Repository (Clinicaltrials.gov ID: NCT03032835). Eventually, 111 patients met our eligibility criteria. The flowchart of patient selection is shown in Figure 1.

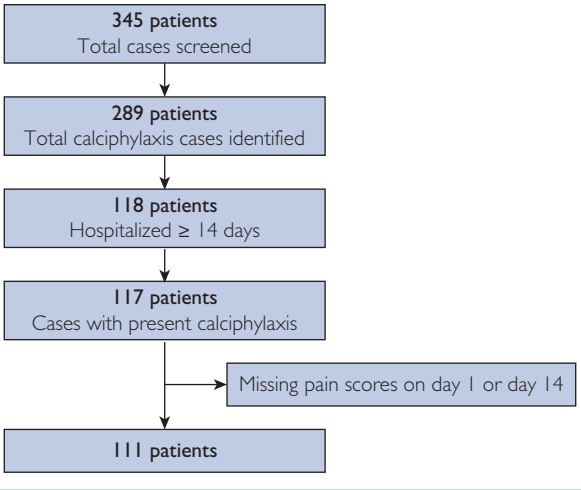

FIGURE 1. Flowchart of patient selection.

Our study was approved by the Mass General Brigham Institutional Review Board (Protocol ID: 2016P002690). The study was conducted in accordance with the Declaration of Helsinki ethical standards.

Study Data

Pain intensity was assessed using patient-reported numerical rating scales, ranging from 0 to 10. Zero indicates the absence of pain, whereas 10 represents the most intense pain. The highest pain score on each day during the first 14 days of hospitalization was extracted from hospitalization flow sheets. The difference between the pain scores on days 14 and 1 of hospitalization were calculated and categorized by their values.

Pain improvement was defined as any reduction in pain intensity score on day 14 compared with that on day 1. Demographic information at the time of hospital admission (age, sex, race, ethnicity, body mass index, and tobacco smoking) and information regarding comorbidities (hypertension, diabetes mellitus, peripheral vascular disease, malignancy, end-stage kidney disease status, kidney transplantation, and dialysis-related data); relevant medications (warfarin, glucocorticoids, vitamin D therapy, calcium-based phosphate binders, and iron use); number and location of wounds; treatments related to calciphylaxis (intravenous [IV] sodium thiosulphate [STS]), noncalcium-based phosphate binders, cinacalcet, bisphosphonates, vitamin K supplementation, lowering of calcium bath, increased dialysis intensity, initiation of hemodialysis, conversion to hemodialysis among patients previously on peritoneal dialysis, surgical parathyroidectomy, amputation, surgical debridement, hyperbaric oxygen (HBO) therapy, and tissue plasminogen activator (tPA); timing, names, and dosages of opioids; results of laboratory tests (calcium, phosphate, and intact parathyroid hormone); and outcomes during 6 months or the entire follow-up duration (by January 31, 2022), including lesion improvement, amputation, and death, were collected. Morphine milligram equivalents (MMEs) per

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TABLE 1. Baseline Characteristics of 111 Patients With Calciphylaxis With and Without Pain Improvement[a]

Factor	Total population	Pain improvement		*P* value
		No	Yes	
N	111	62	49	
Pain score on d 1, mean (SD)	7.5 (3.1)	6.4 (3.7)	9.0 (1.1)	<.001[b]
Age at admission, mean (SD)	58.3 (13.8)	57.4 (14.2)	59.5 (13.4)	.44
Sex				
Female	67 (60%)	36 (58%)	31 (63%)	.58
Male	44 (40%)	26 (42%)	18 (37%)	
Race				
Black or African American	22 (22%)	13 (24%)	9 (19%)	.86
Caucasian	76 (75%)	40 (73%)	36 (77%)	
Others	4 (4%)	2 (4%)	2 (4%)	
Ethnicity				
Hispanic or Latino	10 (10%)	6 (11%)	4 (9%)	.76
Not Hispanic or Latino	91 (90%)	50 (89%)	41 (91%)	
BMI, mean (SD)	30.5 (8.0)	30.2 (7.2)	30.8 (9.1)	.74
Smoke	35 (32%)	24 (39%)	11 (22%)	.06
Hypertension	92 (83%)	50 (81%)	42 (86%)	.48
Diabetes	68 (61%)	43 (69%)	25 (51%)	<.05[c]
Peripheral vascular disease	34 (31%)	18 (29%)	16 (33%)	.68
ESKD	93 (84%)	53 (85%)	40 (82%)	.58
Dialysis	88 (79%)	50 (81%)	38 (78%)	.85
HD	67 (76%)	37 (74%)	30 (79%)	.58
PD	21 (24%)	13 (26%)	8 (21%)	
Dialysis vintage y, mean (SD)	4.8 (5.8)	4.2 (5.1)	5.5 (6.7)	.28
Kidney transplant	13 (12%)	5 (8%)	8 (16%)	.18
Malignancy	14 (13%)	2 (3%)	12 (24%)	<.001[b]
Warfarin use	66 (59%)	35 (56%)	31 (63%)	.47
Glucocorticoid use	37 (33%)	17 (27%)	20 (41%)	.14
Vitamin D use	84 (76%)	48 (77%)	36 (73%)	.63
Calcium-based phosphate binder	62 (56%)	30 (48%)	32 (65%)	.08
Iron use	54 (49%)	29 (47%)	25 (51%)	.66
Corrected calcium (mg/dL), mean (SD)	9.9 (0.9)	9.8 (0.7)	9.9 (1.0)	.52
Phosphorous (mg/dL), mean (SD)	4.4 (2.0)	4.5 (2.2)	4.4 (1.7)	.73
iPTH (pg/mL), median (interquartile range)	122 (58-213)	99 (56-207)	130 (60.5-223.5)	.24

[a]BMI, body mass index; ESKD, end-stage kidney disease; HD, hemodialysis; iPTH, intact parathyroid hormone; PD, peritoneal dialysis.
[b]*P*<.01.
[c]*P*<.05.

day during the first 14 days of hospitalization were calculated.

Statistical Analyses

Stata IC 16 (StataCorp) was used for statistical analyses. The mean, median, standard deviation, interquartile range, and overall distribution of pain scores were reviewed. Clinical characteristics were compared between patients with pain improvement and those without pain improvement. Continuous variables were compared using the t-test or analysis of variance, whereas categorical variables were compared using the Chi-square

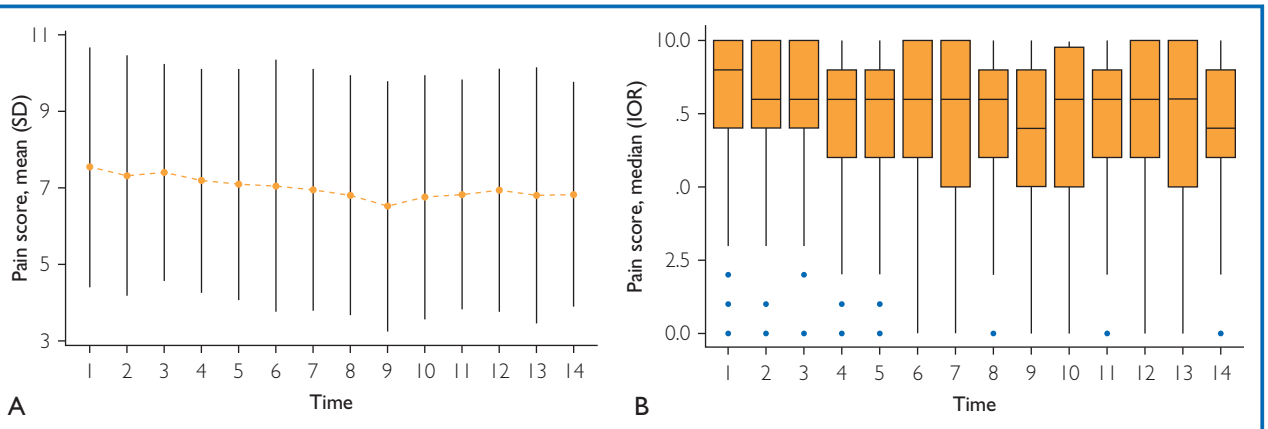

FIGURE 2. Pain score variation among 111 patients with calciphylaxis during 14 days of hospitalization. SD, standard deviation; IQR, interquartile range.

test. The proportions of different pain scores were compared using the z-test.

Logistic regression was used to examine the associations between treatments (IV STS, HBO therapy, and surgical debridement) and pain intensity improvement and between pain improvement and outcomes at 6 months of follow up (lesion improvement,

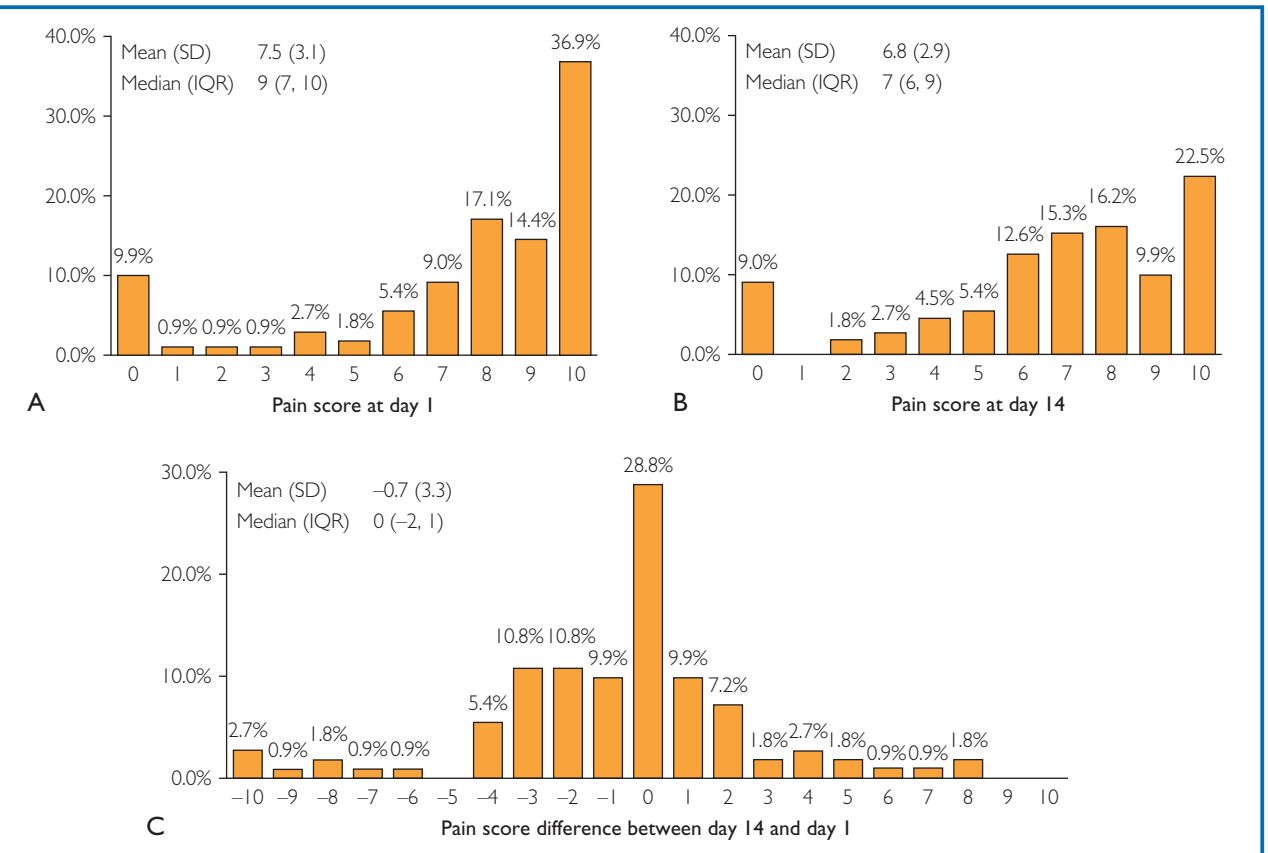

FIGURE 3. Pain score distribution among 111 patients with calciphylaxis. (A) Pain score distribution on day 1. (B) Pain score distribution on day 14. (C) Distribution of pain score differences between days 14 and 1. SD, standard deviation; IQR, interquartile range.

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TABLE 2. Wound Features and Treatment of 111 Patients With Calciphylaxis With and Without Pain Improvement[a]

Factor	Total population	Pain improvement		*P* value
		No	Yes	
N	111	62	49	
Wound number, mean (SD)	3.4 (2.0)	3.5 (1.8)	3.3 (2.3)	.71
Wound location				
Extremity	95 (86%)	57 (92%)	38 (78%)	.03[b]
Trunk	35 (32%)	17 (27%)	18 (37%)	.29
Sodium thiosulphate[c]	42 (38%)	24 (39%)	18 (37%)	.83
Noncalcium-based phosphate binder[d]	91 (82%)	54 (87%)	37 (76%)	.11
Cinacalcet[d]	59 (53%)	32 (52%)	27 (55%)	.71
Bisphosphonates[d]	8 (7%)	4 (6%)	4 (8%)	.73
Vitamin K supplementation[d]	53 (48%)	32 (52%)	21 (43%)	.36
Lowering of calcium bath[d]	47 (42%)	27 (44%)	20 (41%)	.77
Increased dialysis[d]	7 (6%)	2 (3%)	5 (10%)	.13
Initiation or conversion to HD[d]	26 (23%)	14 (23%)	12 (24%)	.81
Parathyroidectomy[d]	7 (6%)	3 (5%)	4 (8%)	.47
Amputation[e]	5 (5%)	2 (3%)	3 (6%)	.46
Surgical debridement[e]	19 (17%)	6 (10%)	13 (27%)	.02[b]
Hyperbaric oxygen[d]	17 (15%)	7 (11%)	10 (20%)	.20
History of tPA use	46 (41%)	28 (45%)	18 (37%)	.37
MME (mg/d), mean (SD)[e]	78.2 (139.2)	78.9 (155.1)	77.3 (117.6)	.95
Opioid use at baseline	97 (88%)	51 (82%)	46 (96%)	.03[b]
Opioid medications				
Hydromorphone	95 (86%)	52 (84%)	43 (90%)	.39
Oxycodone	59 (54%)	33 (53%)	26 (55%)	.83
Morphine	28 (25%)	17 (27%)	11 (23%)	.59
Fentanyl	63 (57%)	35 (56%)	28 (58%)	.84
Meperidine	1 (1%)	1 (2%)	0 (0%)	.38
Remifentanil	7 (6%)	2 (3%)	5 (10%)	.13
Tramadol	15 (14%)	9 (15%)	6 (12%)	.76
Methadone	24 (22%)	13 (21%)	11 (23%)	.81

[a]HD, hemodialysis; MME, morphine milligram equivalent; tPA, tissue plasminogen activator.
[b]$P<.05$.
[c]At least 1 week before admission.
[d]Before the end of 14 days of hospitalization.
[e]During 14 days of hospitalization.

amputation, and death). Cox regression was performed to analyze the association between pain intensity improvement and overall mortality. Four different regression models were fitted in each analysis: (a) model 1: unadjusted; (b) model 2: model 1 adjusted for age, sex, and race; (c) model 3: model 2 adjusted for unbalanced factors in the outcome; and (d) model 4: model 3 adjusted for unbalanced factors in the exposure. A *P* value of less than .05 was considered statistically significant. Sensitivity analyses were performed by setting pain improvement as at least a 30% improvement in pain intensity during the first 14 days of hospitalization and excluding specific groups of patients (patients not on maintenance dialysis, cases with a baseline pain score of 0, or individuals who died

TABLE 3. Pain Improvement in 111 Patients With Calciphylaxis Treated With Different Therapies[a]

Factor		Pain improvement			
		No. of pain improvement	Model[b]	OR (95% CI)	*P* value
IV STS (at least 1 wk before hospitalization)	Yes (42)	18 (43%)	1	0.92 (0.42-1.99)	.83
	No (69)	31 (45%)	2	1.05 (0.46-2.38)	.91
			3	0.67 (0.21-2.08)	.48
			4	0.65 (0.19-2.18)	.48
HBO (before the end of 14 d of hospitalization)	Yes (17)	10 (59%)	1	2.01 (0.71-5.75)	.19
	No (94)	39 (41%)	2	2.73 (0.84-8.85)	.09
			3	2.68 (0.60-11.85)	.20
			4	4.09 (0.77-21.76)	.10
Surgical debridement (during 14 d of hospitalization)	Yes (19)	13 (68%)	1	3.37 (1.17-9.67)	.02[c]
	No (92)	36 (39%)	2	2.77 (0.91-8.42)	.07
			3	5.60 (1.08-29.03)	.04[c]
			4	8.45 (1.43-49.66)	.02[c]

[a]HBO, hyperbaric oxygen; IV, intravenous; OR, odds ratio; STS, sodium thiosulphate.
[b]Model 1: no adjustment; model 2: Model 1 + age, sex, and race; model 3: model 2 + baseline pain score, diabetes, malignancy, extremity involvement, surgical debridement, and opioid use at baseline; and model 4: model 3 + amputation, morphine milligram equivalents per day, unincluded therapy (STS or HBO).
[c]$P<.05$.

within 6 months of the first 14 days of hospitalization).

RESULTS

Among the 111 patients identified, 67 (60%) were women. The average age of the patients was 58.3±13.8 years. In addition, 93 (84%) patients had end-stage kidney disease, and 88 (79%) patients were on maintenance dialysis. Detailed baseline characteristics of the patients are presented in Table 1.

Pain Intensity Variation During the First 14 Days of Hospitalization

The overall variations of the mean and median pain scores during the first 14 days of hospitalization are shown in Figure 2. The average pain score on day 1 was 7.5±3.1, whereas it was 6.8±2.9 on day 14. On average, a decrease of 0.71 in the pain scores was observed during the 14-day interval; however, this was not statistically significant (t=1.73; $P=.08$).

The pain score distributions on days 1 and 14 among the 111 patients with calciphylaxis are displayed in Figure 3. Over 50% of the patients had a pain score of 9 or 10 on day 1. Compared with the prevalence on day 1, the prevalence of reporting a pain intensity score of 9 or 10 on day 14 decreased (32.4% on day 14 vs 51.3% on day 1; $z=2.82$; $P=.004$), whereas the proportion of reporting pain intensity scores ranging from 6 to 7 increased (27.9% on day 14 vs 14.4% on day 1; $z=-2.46$; $P=.01$) (Figure 3A and B). The overall distribution of pain score difference between days 14 and 1 is presented in Figure 3C.

Of the 111 patients with calciphylaxis, 49 patients were identified as having pain improvement, whereas 62 were without any improvement. Baseline characteristics were compared between patients with pain improvement and those without pain improvement, which is presented in Tables 1 and 2. Compared with patients without pain improvement, those with pain improvement had a higher baseline pain score (9.0±1.1 vs 6.4±3.7; $P<.001$), lower prevalence of diabetes mellitus (51% vs 69%; $P<.05$), and higher prevalence of malignancy history (24% vs 3%; $P<.001$). In addition, more

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TABLE 4. Associations Between Pain Improvement and Outcomes Among 111 Patients With Calciphylaxis[a]

Factor	Lesion improvement within 6 mo				Amputation within 6 mo				Mortality within 6 mo				Overall mortality			
	N	Model	OR (95% CI)	*P* value	N	Model[b]	OR (95% CI)	*P* value	N	Model[b]	OR (95% CI)	*P* value	N	Model[b]	HR (95% CI)	*P* value
Pain improvement	35/49 (71%)	1	0.94 (0.41-2.17)	.89	3/49 (6%)	1	0.44 (0.11-1.76)	.25	13/47 (28%)	1	0.85 (0.37-1.95)	.69	22/49 (45%)	1	1.03 (0.58-1.81)	.92
		2	0.76 (0.31-1.85)	.55		2	0.50 (0.11-2.24)	.37		2	0.95 (0.38-2.40)	.92		2	1.06 (0.58-1.93)	.86
		3	0.80 (0.32-1.98)	.63		3	0.41 (0.08-2.23)	.30		3	1.04 (0.40-2.72)	.92		3	1.24 (0.65-2.36)	.51
		4	1.19 (0.41-3.48)	.75		4	0.06 (0.003-0.95)	.05[c]		4	1.16 (0.34-3.90)	.81		4	0.96 (0.43-2.15)	.93

[a]OR, odds ratio.
[b]Model 1: no adjustment; model 2: model 1 + age, sex, and race; model 3: model 2 + dialysis for lesion improvement, peripheral vascular disease for amputation, opioids during hospitalization for mortality; and model 4: model 3 + baseline pain score, smoke, diabetes, malignancy, kidney transplantation, sodium thiosulphate, glucocorticoids, calcium-based phosphate binder.
[c]$P<.05$.

patients with pain improvement underwent surgical debridement during the first 14 days of hospitalization (27% vs 10%; $P=.02$), and more were on opioid medication at admission (96% vs 82%; $P=.03$). The MME per day assessed during the first 14 days of hospitalization was comparable between the 2 groups (78.9±155.1 vs 77.3±117.6 mg/d; $P=.95$).

Therapies Associated With Pain Improvement

Specific therapies, including IV STS, HBO therapy, and surgical debridement, were examined for their effects on pain improvement. As shown in Table 3, no association was found between pain improvement from days 1 to 14 of hospitalization and treatments, including IV STS (defined as being started at least 1 week before hospitalization) and HBO therapy (initiated before the end of the first 14 days), in all the models. However, surgical debridement (during the 14 days of hospitalization) was associated with pain intensity improvement in unadjusted model 1 (odds ratio [OR], 3.37; 95% CI, 1.17-9.67; $P=.02$), adjusted model 3 (OR, 5.60; 95% CI, 1.08-29.03; $P=.04$), and adjusted model 4 (OR, 8.45; 95% CI, 1.43-49.66; $P=.02$).

Clinical Outcomes and Pain Intensity Improvement During Hospitalization

At 6 months, lesion improvement was seen in 80 (72.1%) patients, amputation was performed in 11 (9.9%) patients, and 48 (43.2%) patients died. As shown in Table 4, the outcomes within 6 months of the first 14 days of hospitalization, including lesion improvement, amputation, and mortality, were compared between patients with pain improvement and those without pain improvement.

In adjusted model 4, pain improvement was associated with lower odds of subsequent amputation (OR, 0.06; 95% CI, 0.003-0.95; $P<.05$). No association was found between the other outcomes (lesion improvement and mortality) within 6 months and pain intensity improvement (Table 4). No difference was observed between the mortality rates of patients with pain improvement and those without pain improvement at different time points ($P>.05$) (Supplemental Table 1, available online at http://www.mcpiqojournal.org).

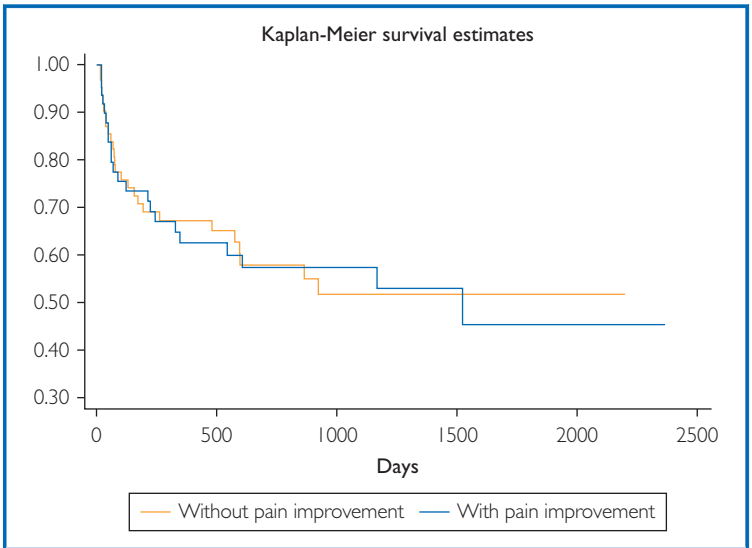

FIGURE 4. Kaplan-Meier survival curve of 111 patients with calciphylaxis with and without pain improvement.

During the entire follow-up duration, the median follow-up time of the 111 patients was 481 days. The Kaplan-Meier survival curves of patients with pain improvement and those without pain improvement are shown in Figure 4. In all the models fitted, the overall mortality was comparable between patients with pain improvement and those without pain improvement during the entire follow-up duration ($P>.05$, Table 4).

Factors Associated With Pain Improvement in Patients With Calciphylaxis on Maintenance Dialysis

Of the 111 patients, 88 were on maintenance dialysis, of whom 67 were on hemodialysis and 21 on peritoneal dialysis (17 converted to hemodialysis after diagnosis). In analyses limited to patients on dialysis (Table 5), patients who underwent surgical debridement during the first 14 days of hospitalization were more likely to show pain improvement in model 3 (OR, 8.43; 95% CI, 1.17-60.68; $P=.03$) and model 4 (OR, 19.08; 95% CI, 1.92-189.75; $P=.01$). Patients who received HBO therapy before the end of the first 14 days of hospitalization had 5.38 (95% CI, 1.14-25.50) times the odds of having pain improvement compared with those who did not receive HBO therapy after adjusting for age, sex, and race ($P=.03$). However, there was no significant association between HBO and pain improvement in models 3 and 4 ($P>.05$). No association was found between IV STS therapy administered at least 1 week before admission and pain improvement.

Furthermore, no association was found between pain intensity improvement and consequences, including lesion improvement, amputation, and mortality, within 6 months (Supplemental Table 2, available online at http://www.mcpiqojournal.org). The median follow-up time of the 88 patients on dialysis was 510.5 days. The Kaplan-Meier survival curves of patients with pain improvement and those without pain improvement are shown in Figure 5. A lower mortality rate was observed in patients with pain improvement than among those without (42% vs 47%, respectively); however, no difference in survival was noted ($P>.05$) (Supplemental Table 2).

Sensitivity Analysis

In the sensitivity analysis, patients who died within 6 months were excluded to account for competing risks in the analysis of lesion improvement and amputation within 6 months. However, no association was observed between pain improvement and the other 2 outcomes (lesion improvement and amputation) (Supplemental Tables 3 and 4, available online at http://www.mcpiqojournal.org). While setting a stricter pain improvement criterion of at least a 30% decrease in pain scores, we did not find any association between pain improvement and outcomes or treatments (Supplemental Tables 5 and 6, available online at http://www.mcpiqojournal.org). Lower risk of amputation and higher rates of surgical debridement were associated with pain intensity improvement after excluding patients with a baseline pain score of 0 (Supplementary Tables 7 and 8, available online at http://www.mcpiqojournal.org).

DISCUSSION

To the best of our knowledge, this is the first and largest study to comprehensively explore the clinical importance of patient-reported pain in patients with calciphylaxis. We reported that the pain associated with

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TABLE 5. Pain Improvement in 88 Patients With Calciphylaxis on Maintenance Dialysis Treated With Different Therapies[a]

Factor		Pain improvement			
		No. of pain improvement	Model[b]	OR (95% CI)	*P* value
IV STS (at least 1 wk before hospitalization)	Yes (36)	15 (42%)	1	0.91 (0.38-2.13)	.81
	No (52)	23 (44%)	2	0.92 (0.37-2.29)	.86
			3	0.38 (0.09-1.58)	.18
			4	0.36 (0.08-1.66)	.19
HBO (before the end of 14 d of hospitalization)	Yes (12)	8 (67%)	1	3.07 (1.85-11.09)	.09
	No (76)	30 (39%)	2	5.38 (1.14-25.50)	.03[c]
			3	4.51 (0.55-37.02)	.16
			4	7.69 (0.72-82.18)	.09
Surgical debridement (during 14 d of hospitalization)	Yes (15)	10 (67%)	1	3.21 (1.00-10.38)	.05
	No (73)	28 (38%)	2	3.05 (0.90-10.26)	.07
			3	8.43 (1.17-60.68)	.03[c]
			4	19.08 (1.92-189.75)	.01[c]

[a]HBO, hyperbaric oxygen; IV, intravenous; STS, sodium thiosulphate.
[b]Model 1: no adjustment; model 2: model 1 + age, sex, and race; model 3: model 2 + baseline pain score, diabetes, malignancy, extremity involvement, surgical debridement, and opioid use at baseline; and model 4: model 3 + amputation, morphine milligram equivalents per day, unincluded therapy (STS or HBO).
[c]$P<.05$.

calciphylaxis does not significantly improve during the first 2 weeks of hospitalization. Pain improvement may indicate a lower risk of undergoing amputation within 6 months. Hyperbaric oxygen therapy and surgical debridement may be beneficial for pain improvement among patients with calciphylaxis treated with maintenance dialysis.

In a systematic review, Riemer et al[9] pointed out that patient-reported outcomes, including pain, have been underreported in calciphylaxis. In a previous study, the initial pain score among patients with calciphylaxis was uniformly high, and the severity of pain was associated with decreased quality of life (QoL). In our study, severe pain (a pain score of from 7 to 10) was reported in 77.4% of the 111 hospitalized patients with calciphylaxis. Chinnadurai et al[5] conducted a survey on the management of pain in patients with calciphylaxis and highlighted the importance of referral to palliative care specialists. Our study reported that opioid use at baseline may be associated with pain improvement over the course of hospitalization, indicating the benefits of early intervention. Of note, a high dose of opioids was used in the patients in our study. However, MMEs were not associated with pain improvement, whereas therapies targeting lesions (HBO therapy and surgical debridement) showed some benefits in pain improvement over the 14-day interval. To achieve pain improvement more quickly, early and precise multidisciplinary interventions are recommended.[10] Furthermore, emerging interventions that include both patient and family caregivers for pain management in other contexts have exhibited promising results that have implications for the care of patients with calciphylaxis.[11]

As treatment strategies evolve, the lesion improvement rate could reach 60%-80%, whereas pain improvement rates of 50%-100% have been observed in several studies.[12-16] However, mortality remains high and has not been found to be improved by any of the current therapies. In our study, pain improvement in 14 days was not associated with survival within 6 months or during the entire follow-up duration. Amputation in

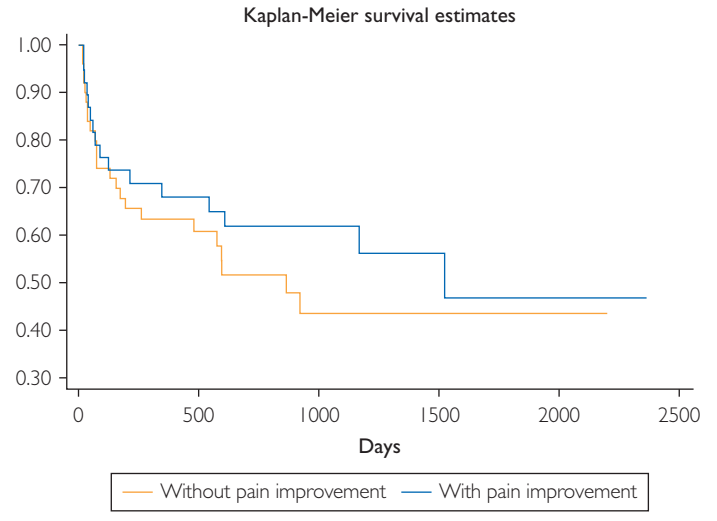

FIGURE 5. Kaplan-Meier survival curve of 88 patients with calciphylaxis on maintenance dialysis with and without pain improvement.

patients with calciphylaxis is always secondary to uncontrolled lesions or complicated peripheral vascular disease and greatly impacts QoL.[17,18] In our study, pain improvement may indicate a lower risk of amputation in the future. Its impact on QoL needs more investigation.

On the basis of our analysis, a history of the use of HBO therapy was suggested to improve pain in patients undergoing dialysis. In a narrative review summarizing calciphylaxis cases reported in the literature, 45% had a full response to HBO therapy, whereas 13% experienced partial improvement in lesions.[19] During HBO therapy, chronic hypoxia can be reversed, and growth factor production, neoangiogenesis, fibroblast proliferation, and collagen synthesis are facilitated.[20] However, we failed to report that the effect of HBO therapy on patients with calciphylaxis on dialysis was independent of other treatments such as surgical debridement, opioids, and STS. Whether HBO therapy can resolve the pain associated with calciphylaxis needs further exploration. Surgical debridement is performed to completely ablate necrotic tissue and prevent the worsening of wound infection.[21] Weenig et al[22] observed that better survival in patients with calciphylaxis was associated with surgical debridement. Here, we discovered that pain improvement within 14 days is likely to be achieved with surgical debridement. The role of STS has been reported in both lesion improvement and pain improvement in the literature.[4] However, we did not find an association between the use of IV STS and pain improvement. Beyond current therapies, SNF472 (the hexasodium salt of phytate), a new medication that can inhibit the formation of vascular hydroxyapatite crystals, has been reported to be effective in improving pain in patients with calciphylaxis.[23] SNF472 is currently being assessed in a phase 3 clinical trial (NCT04195906; CALCIPHYX).[24]

Ischemia and thrombosis are both predominant pathologic features of calciphylaxis that could be associated with pain.[6,25] Disturbance between the coagulation and anticoagulation systems caused by warfarin use, vitamin K deficiency, or systematic disease (eg, antiphospholipid syndrome) could be an essential underlying cause.[25] Therapies such as low-dose tPA have been experimentally used in patients with calciphylaxis.[26,27] Here, we reported warfarin use, vitamin K supplementation, and tPA treatment history among 111 patients with calciphylaxis. However, no difference was observed between patients with pain improvement and those without pain improvement. Randomized controlled trials are needed to clarify the relationship between certain anticoagulant regimens and pain improvement.

Several limitations could be noted in our study. First, only a hospitalized population was enrolled to achieve completed pain scores; however, this population was selected because it had data on pain intensity and other study variables of interest. Second, selection biases may have been generated because patients with pain improvement may have had differences that may not have been obvious in an observational study. Another limitation is that pain improvement was only examined on day 14 compared with that on day 1, whereas variations during the first 14 days were not considered. In addition, the clinical importance of a 1-point decrease in the pain score needs further justification. We used stricter criteria for pain improvement and repeated the analyses in our sensitivity analyses. However, no association was found between pain improvement and the outcomes

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studied. We only reported the highest pain scores. Analyses on the basis of average pain scores are warranted in the future. Furthermore, data regarding wound care other than surgical debridement were not analyzed in our study. Larger prospective cohort studies including both outpatient and inpatient cases of calciphylaxis are warranted to further investigate the clinical importance of pain improvement and related treatments.

CONCLUSION

Pain control remains a challenge among hospitalized patients with calciphylaxis. Surgical debridement and HBO may contribute to improvement of pain. Pain improvement indicates a lower risk of amputation. Large, pragmatic studies are warranted to further establish the clinical significance of pain improvement in calciphylaxis.

POTENTIAL COMPETING INTERESTS

Dr Nigwekar received grant support from Hope Pharmaceuticals, Laboratoris Sanifit, and Inozyme Pharma. Dr Malhotra receives research funding from Amgen and serves as a consultant for Myokardia/BMS, Renovacor, and Third Pole. The results presented in this paper have not been published previously in whole or part.

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SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **HBO,** hyperbaric oxygen; **IV,** intravenous; **MME,** morphine milligram equivalent; **OR,** odds ratio; **QoL,** quality of life; **STS,** sodium thiosulphate; **tPA,** tissue plasminogen activator

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