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Predictors of treatment success after collagenase *Clostridium histolyticum* injection for Peyronie's disease: development of a nomogram from a multicentre single-arm, non-placebo controlled clinical study

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Objective

To build a nomogram able to predict treatment success after collagenase *Clostridium histolyticum* (CCH) for Peyronie's disease (PD).

Materials and Methods

Between November 2016 and November 2017, we enrolled 135 patients with PD into a multicentre single-arm prospective study. All patients enrolled received CCH treatment. Success of therapy was defined as a decrease in penile curvature (PC) of ≥20° from baseline. Treatment satisfaction was assessed using a scale from 1 to 10, and high satisfaction was arbitrarily defined as a score of ≥8. Calcification level was classified as: absence of calcification; low perilesional calcification; and high calcification.

Results

The median (interquartile range [IQR]) patient age was 56.0 (45.0–65.0) years and the median (IQR) was PC was 30 (30.0–60.0)°. After the treatment protocol, we observed a significant median change in PC of −20.0° ($P < 0.01$). The median (IQR) PC improvement was 44 (28.0–67.0)%. Overall median (IQR) satisfaction score was 8.0 (7.0–9.0). Treatment efficacy was reported in a total of 77 patients (57.04%). When analysing factors associated with PC improvement after treatment, we found that baseline PC (odds ratio [OR] 1.14; $P < 0.01$), basal plaque (OR 64.27; $P < 0.01$), low calcification (OR 0.06; $P < 0.01$) and high calcification (OR 0.03; $P < 0.01$) were significant predictors of PC improvement. The c-index for the model was 0.93.

Conclusions

Patients with longer PD duration, greater baseline PC and basal plaque location had a greater chance of treatment success. These results could be applied to clinical practice before external validation of our nomogram.

Keywords

induratio penis plastica, penile curvature, nomogram, predictive factors, intralesional injections, Peyronie's disease, #andrology, #Peyronies

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Introduction

Peyronie's disease (PD) is a common disorder that results in penile deformity, making sexual intercourse difficult or impossible. PD typically affects men in their 50s and has an incidence of 3–9% [1]. The condition results from a fibrotic process of the tunica albuginea, developed into two phases, acute and chronic. During the initial acute inflammatory phase, plaque starts to form and curvature becomes evident, often accompanied by pain, particularly during erection [2]. These deformities include penile curvature (PC), penile length loss, narrowing and sometimes a variable degree of erectile dysfunction [3,4]. PD can be associated with significant psychological distress and bother, including emotional strain and negative effects on relationship with the partner [5,6]. The aetiology of PD is still not clear, but it is believed that the primary predisposing factor can be trauma or microtrauma during sexual intercourse in genetically susceptible patients [3,7]. There are various therapeutic options for stable PD, including pharmacological and surgical approaches, based on the severity of PC and associated symptoms [4].

Intralesional injection therapy with collagenase *Clostridium histolyticum* (CCH; Xiaflex, Endo Pharmaceuticals, Inc, Malvern, PA, USA) is the first therapy approved by the US Food and Drug Administration for the non-surgical management of men with PD, who have stable palpable plaque and PC of at least 30°, but no more than 90°, at the start of treatment [8].

CCH is a mixture of purified collagenases (Class I, II), which are naturally produced by the bacterium *C. histolyticum*. The two collagenases cause the hydrolysis of the triple helical conformation of types I and III collagen, leading to enzymatic disruption of the PD plaque [2]. CCH also downregulates many of the genes, cytokines and growth factors that are involved in the pathogenic mechanism of PD [9]. CCH has proved to be efficient and safe, as reported in two double-blind, randomized, placebo-controlled, phase III studies (IMPRESS I and II), showing a mean percentage change of −34% of PC vs. −18.2% in men treated wtih CCH or placebo respectively. [10]; however, previous studies have failed to identify useful predictors of success after intralesional therapy.

In the present study, we aimed to build a nomogram able to predict treatment success in terms of PC improvement after CCH treatment for PD.

Materials and Methods

Between November 2016 and November 2017, we enrolled 135 consecutive patients with PD into a multicentre single-arm prospective study. Each patient provided written fully informed consent before enrolling in the study. Inclusion criteria at baseline were: age ≥18 years; presence of symptomatic dorsal or lateral PC ≥30°, but not >90°; currently stable disease; and no previous surgery for PD. Stable disease has been defined as no pain and no deformity deterioration in the last 12 months [11].

Patients with complete plaque calcification, ventral PC, or those not responding to oral phosphodiesterase-5 inhibitors or to intracavernous injections of prostaglandin E1, were excluded from the study. Patients were also excluded if they had type 1 or 2 diabetes mellitus. Each patient was evaluated according to medical history, physical examination and intracavernous alprostadil injection test plus Doppler ultrasonography. At baseline, we also collected data on plaque calcification level, plaque location, angle of curvature and penile length during erection. Calcification level was classified as: absence of calcification; low perilesional calcification; and high calcification, modifying the previous definition by Levine et al. [12] The plaques were located in the proximal, mid or distal penile side. The stretched penile length was measured in centimetres; the fat pad around the penis was compressed and the measure was taken from the symphysis pubis to the tip of the glans with the penis fully stretched [13].

Outcome Measures

Patients were asked to complete self-administered questionnaires including: the International Index of Erectile Function (IIEF-15) questionnaire [14] and the Peyronie's Disease Questionnaire (PDQ) [10]. The angle of curvature was assessed, using a goniometer protractor, during erection after an intracavernous injection of prostaglandin E1. The IIEF-15 questionnaire considered the severity of erectile dysfunction, classified as follows: severe (score ≤10); moderate (scores 11–16); and mild (scores 17–25). IIEF-15 sub-scores were also assessed, including IIEF-erectile function (IIEF-EF), IIEF-orgasmic function, IIEF-sexual desire, IIEF-intercourse satisfaction and IIEF-overall satisfaction. The PDQ is a 15-question self-reported survey that measures the impact and severity of PD symptoms in three domains: psychological and physical symptoms (psychosexual symptoms symptom severity score; PDQ questions 1–6); penile pain (penile pain score; PDQ questions 7–9); and symptom bother (bother score; PDQ questions 10–15). Patients were asked to complete the PDQ only if they had had vaginal intercourse with a female partner within the previous 3 months.

The Female Sexual Function Index (FSFI), which was used to assess the female sexual partner's sexual function, is a 19-item questionnaire for assessing the key dimensions of sexual function in women, with domains for desire or arousal, lubrication, orgasm, satisfaction and pain [15]. All variables and questionnaires were evaluated before treatment (baseline) and at the end of treatment cycle (4 weeks after the last injection).

All patients received CCH treatment using a new shortened protocol. This consisted of a treatment cycle of three intralesional injections of CCH 0.9 mg, separated by 4-weekly intervals. The injections were administered under local penile anaesthesia with 2% lidocaine 10 mL. The entire vial was used for each administration and CCH was injected in multiple positions at the apex of the curvature of the flaccid penis. After the procedure, patients were advised to keep the penis elevated and to avoid sexual intercourse for 2 weeks. Between injections, the patients were instructed to use a combination of modelling, stretching, and vacuum-pump therapy with a specialized device daily, in order to mechanically stretch the fibrous plaque. Starting 24–48 h after the CCH injection, home modelling was performed, with patients attempting to gently straighten the erect penis. Stretching exercises involved a gradual stretch of the flaccid penis for 60 s. All patients were advised about the importance of adhering to the home stretching exercises. Treatment satisfaction was assessed using a scale from 1 to 10. High satisfaction after treatment has been defined as a score ≥8.

Vacuum-pump therapy was performed using the Rapport Classic Vacuum system (Owen Mumford, Inc., West Oak Commons Court, Marietta, GA, USA, distributed by Medis, Rozzano, Italy). The patients were instructed to use the vacuum device without the constriction ring, only 2–3 days after the CCH injection, twice daily (morning and evening), to mechanically stretch the penis. The cylinder was placed on the penis and slowly inflated until the penis was erect, and maintained in this position for ~1 min. Patients were advised to pump slowly and gently and not to over-pump the penis to avoid complications. The vacuum was then released to allow the erection to subside and the process was repeated again five times during each treatment session. Treatment-emergent adverse events data were collected using self-reported events, defined as any patient-reported event that began or worsened after the first dose of study drug until study completion or early withdrawal. The relationship of adverse events to treatment was evaluated by the investigator based on the temporal relationship to treatment and the likelihood of an alternative aetiology. The study was conducted in accordance with Good Clinical Practice guidelines and the principles of the Declaration of Helsinki.

Statistical Analysis

Continuous variables are presented as median and interquartile range (IQR) and were compared using Student's independent *t*-test or the Mann–Whitney *U*-test based on normal or not-normal distribution, respectively (normality of variables' distribution was tested using the Kolmogorov–Smirnov test). Categorical variables were tested with the chi-squared test. Success of therapy was defined as a PC decrease of at least 20° from baseline curvature.

Univariable logistic regression analyses assessed predictors of success of therapy. We then developed a multivariable model predicting success of therapy including significant variables. The discrimination accuracy of multivariable models based on these variables in our cohort was quantified using the receiver-operating characteristic-derived area under the curve. Baseline curvature (°), duration of disease (months), localization of the plaque (distal, base and dorsal or mid), calcification of the plaque (none, low, high) represented the basis for our coefficient-based nomogram.

A decision-curve analysis was used to determine the clinical net benefit associated with the use of the model [16]. Decision-curve analyses were used to determine the clinical net benefit associated with the adoption of these models.

The Hosmer–Lemeshow goodness-of-fit test has been used to test whether observed binary responses were consistent with predictions of the nomogram [17] and 1 000 boot-strap sampling of the nomogram has been performed to internally validate the nomogram.

All statistical analyses were completed using Stata software, version 14 (Stata Corp., College Station, TX, USA). For all statistical comparisons, P values <0.05 were taken to indicate statistical significance with regard to differences between the groups.

Results

In total, 135 patients completed the study protocol. The median (IQR) age was 56.0 (45.0–65.0) years and the median (IQR) PC was 30.0 (30.0–60.0)°.

In all, 51 (37.78%) and 84 patients (62.2%) had a PD duration of <12 months and ≥12 months, respectively. Table 1 lists the baseline characteristics of the study cohort.

After the final follow-up, we observed a significant median change in PC of −20.0° ($P < 0.01$). The median (IQR) PC improvement was 44 (28.0–67.0)%.

The overall median (IQR) treatment satisfaction score was 8.0 (7.0–9.0). Age-adjusted logistic regression analysis showed that penile length ≥15 cm (odds ratio [OR] 4.69, 95% CI 1.83–12.02; $P = 0.001$) and post-treatment IIEF-EF (OR 1.21, 95% CI 1.05–1.39; $P = 0.007$) were associated with high satisfaction after treatment.

Significant changes were reported on all questionnaire and sub-domain scores after treatment (Table 2). We also observed a significant increase in all FSFI subdomain scores (Table 3).

In total, treatment success was achieved in 77 patients (57.04%), defined as a decrease in PC of ≥20°.

Table 1 Baseline characteristics of the study cohort.

Characteristic	
Age, years	56.0 (45.0–65.0)
PD duration, months	12.0 (10.0–16.0)
Calcification, *n* (%)	
None	65 (48.15)
Low	48 (35.56)
High	22 (16.30
Plaque location, *n* (%)	
Base and dorsal	61 (45.19)
Mid	41 (30.37)
Distal	33 (24.44)
Penile length, *n* (%)	
<10 cm	33 (24.44)
10–15 cm	76 (56.30)
>15 cm	26 (19.26)
PC, °	30.0 (30.0–60.0)
IIEF-15 score	59.0 (53.0–66.0)
IIEF-EF score	23.0 (20.0–28.0)
IIEF-OF score	10.0 (8.0–10.0)
IIEF-SD score	9.0 (8.0–10.0)
IIEF-IS score	10.0 (8.0–12.0)
IIEF-OS score	9.0 (8.0–10.0)
PDQ-PS score	8.0 (5.0–10.0)
PDQ-PP score	3.0 (0.0–6.0)
PDQ-SB score	9.0 (4.0–19.0)

IIEF-15, International Index of Erectile Function; IIEF-EF, IIEF-erectile function; IIEF-OF, IIEF-orgasmic function; IIEF-SD, IIEF-sexual desire; IIEF-IS, IIEF-intercourse satisfaction; IIEF-OS, IIEF-overall satisfaction; IQR, interquartile range; PC, penile curvature; PDQ-PS, Peyronie's Disease Questionnaire-psychosexual symptoms; PDQ-PP, PDQ-penile pain; PDQ-SB, PDQ-symptom bother. Data presented as median (IQR), unless otherwise indicated.

Patients with acute-phase PD did not have a higher rate of treatment success (54.9%) than patients with stable disease (58.33%; $P = 0.70$).

When analysing factors associated with PC improvement after treatment, we found that baseline PC (OR 1.14; $P < 0.01$), basal and dorsal plaque location (OR 64.27; $P < 0.01$), low calcification (OR 0.06; $P < 0.01$) and high calcification (OR 0.03; $P < 0.01$) were significant predictors of PC improvement (Table 4). Figure 1 shows the multivariable effect of each variable on the probability of PC improvement after treatment in the form of a nomogram. The c-index for the model was 0.93 (95% CI 0.90–0.98).

The decision-curve analysis showed that the novel nomogram improved clinical prediction compared with threshold probabilities of PC (Fig. 2). A calibration plot of predicted probabilities against observed PC is shown in Fig. 3 ($P = 0.25$).

Table 5 shows errors associated with the use of the novel nomogram when predicting PC improvement. Using a 40% cut-off threshold, 56 (41.48%) CCH injections would be spared and PC improvement would be avoided in eight patients (14.29).

Finally, we reported an overall rate of complications in 125 patients (92.59%), including ecchymosis in 108 (80.0%) and haematoma in 17 patients (12.6%).

Table 2 Mean changes from baseline to post-treatment in penile curvature, International Index of Erectile Function and sub-domain scores and Peyronie's Disease Questionnaire scores.

Variable	Mean	IQR	*P**
PC (°)	19.07	15.0 to 20.0	<0.01
IIEF-15	5.32	3.0 to 7.0	<0.01
IIEF-EF	1.6	0.0 to 2.0	<0.01
IIEF-OF	0.73	0.0 to 1.0	<0.01
IIEF-SD	1.01	0.0 to 2.0	<0.01
IIEF-IS	1.50	0.0 to 2.0	<0.01
IIEF-OS	1.21	0.0 to 2.0	<0.01
PDQ-PS	−2.62	−3.0 to −2.0	<0.01
PDQ-PP	−1.55	−2.0 to 0.0	<0.01
PDQ-SB	−4.43	−7.0 to −2.0	<0.01

*IIEF-15, International Index of Erectile Function; IIEF-EF, IIEF-erectile function; IIEF-OF, IIEF-orgasmic function; IIEF-SD, IIEF-sexual desire; IIEF-IS, IIEF-intercourse satisfaction; IIEF-OS, IIEF-overall satisfaction; IQR, interquartile range; PC, penile curvature; PDQ-PS, Peyronie's Disease Questionnaire-psychosexual symptoms; PDQ-PP, PDQ-penile pain; PDQ-SB, PDQ-symptom bother. *Wilcoxon signed rank test for paired observations.*

Table 3 Mean changes from baseline to post-treatment in Female Sexual Function Index and sub-domain scores.

Variable	Mean	IQR	*P**
FSFI total score	3.94	2.0–5.0	<0.01
FSFI-desire	0.5	0.2–0.8	<0.01
FSFI-arousal	0.8	0.5–1.0	<0.01
FSFI-lubrication	1.0	0.5–1.2	<0.01
FSFI-satisfaction	1.2	0.6–1.8	<0.01
FSFI-orgasm	0.8	0.4–1.2	<0.01
FSFI-pain	0.7	0.2–1.1	<0.01

*FSFI, Female Sexual Function Index; IQR, interquartile range. *Wilcoxon signed rank test for paired observations.*

Table 4 Age-adjusted multivariate logistic regression for factors associated with penile curvature improvement (≥20°).

Variables	OR	95% CI	*P*
Baseline curvature (°)	1.14	1.08–1.19	<0.01
Duration of disease (months)	1.14	0.99–1.30	0.055
Location of plaque			
Distal	Reference		
Base and dorsal	64.27	11.94–346.00	<0.01
Mid	5.17	0.75–35.76	0.09
Plaque calcification			
None	Reference		
Low	0.06	0.02–0.22	<0.01
High	0.03	0.01–0.27	<0.01

OR, odds ratio.

Discussion

In the present study, we report a derived model predicting the benefit of CCH injection for PD. We found that high baseline PC, long duration of disease and basal and dorsal location of plaque were positive predictors of success, while the presence of calcification was found to be a worse

Fig. 1 Novel nomogram predicting the probability of penile curvature (PC) improvement (−20°) in patients treated with CCH injections. Instructions: Locate the patient's baseline PC on the corresponding axis. Draw a line straight upward to the point axis to determine how many points toward the probability of PC improvement the patient receives for his baseline PC value. Repeat the process for each additional variable. Sum the points for each of the predictors. Locate the final sum on the total point axis. Draw a line straight down to find the patient's PC improvement.

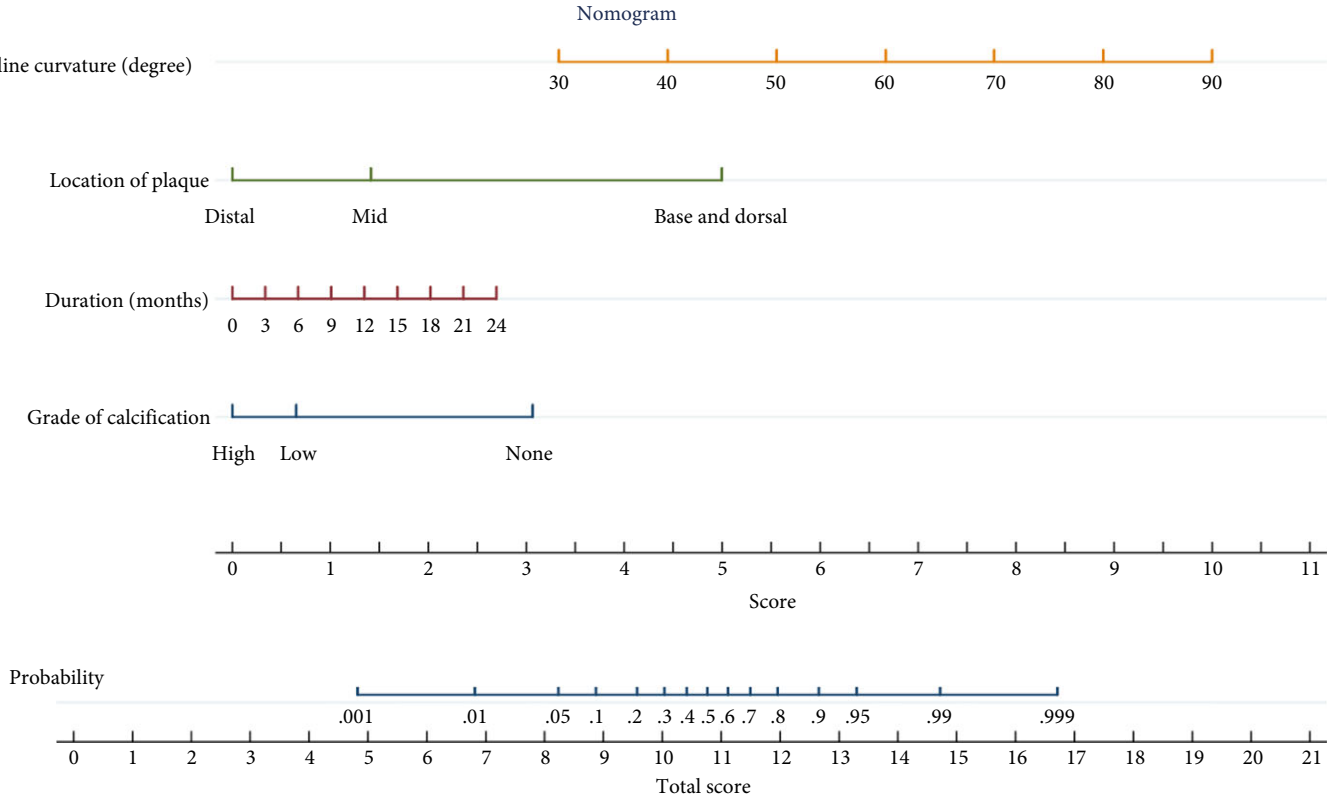


Fig. 2 Decision-curve analyses demonstrating the net benefit associated with the use of the novel nomogram on penile curvature improvement.

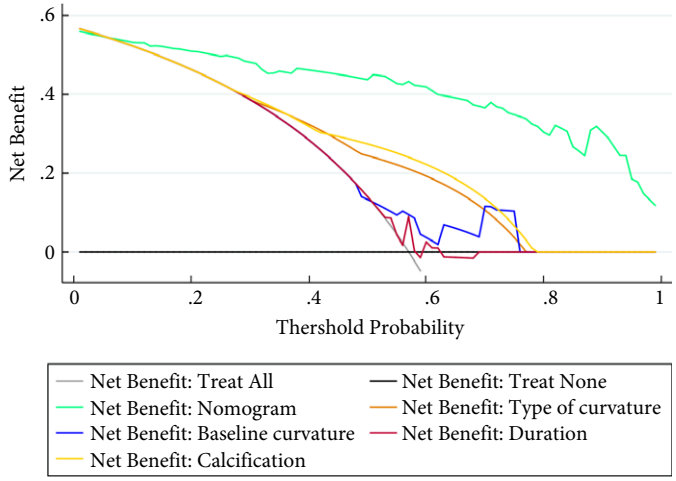
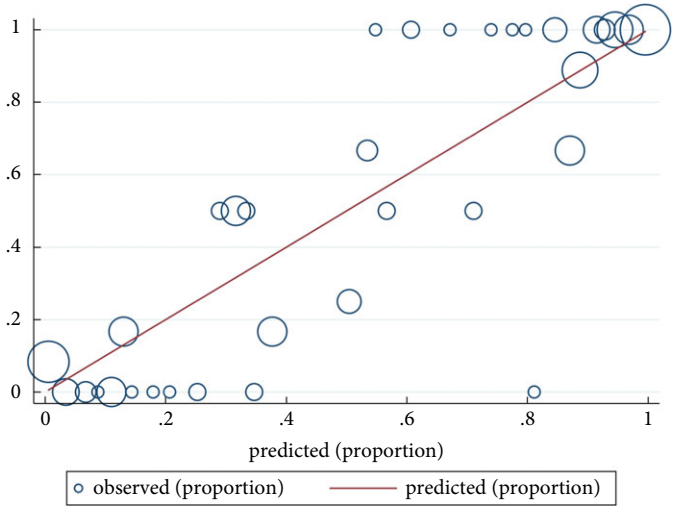


Fig. 3 Hosmer–Lemeshow goodness-of-fit test of observed proportion vs predicted probability of penile curvature improvement using the novel nomogram.



predictor. These results are important for two main reasons. Firstly, this is the first nomogram able to predict clinical response after CCH injections, offering a new tool for identifying patients who may benefit from this protocol.

Secondly, sparing unnecessary CCH injections could be of interest for both patients and clinicians from the point of view of cost-effectiveness.

Table 5 Systematic analyses of the novel nomogram-derived thresholds used to discriminate between patients with or without PC after CCH injections.

Nomogram calculated probability of PC improvement, threshold (%)	Patients in whom intralesional injection of CCH is not recommended according to the threshold (below threshold), *n* (%)	Patients below threshold without PC improvement, *n* (%)	Patients below threshold with PC improvement, *n* (%)	Patients in whom intralesional injection of CCH is recommended according to the threshold (below threshold), *n* (%)	Patients above threshold without PC improvement, *n* (%)	Patients above threshold with PC improvement, *n* (%)
10	21 (15.56)	20 (95.24)	1 (4.76)	114 (84.44)	38 (33.33)	76 (66.67)
20	35 (25.93)	100 (74.07)	2 (5.71)	33 (94.29)	25 (25.00)	75 (75.00)
30	40 (29.63)	95 (70.37)	3 (7.50)	37 (92.50)	21 (22.11)	74 (77.89)
40	56 (41.48)	79 (58.52)	8 (14.29)	48 (85.71)	10 (12.66)	69 (87.34)
50	56 (41.48)	79 (58.52)	8 (14.29)	48 (85.71)	10 (12.66)	69 (87.34)
60	66 (48.89)	69 (51.11)	13 (19.70)	53 (80.39)	5 (7.25)	64 (92.75)
70	69 (51.11)	66 (48.89)	16 (23.19)	53 (76.81)	5 (7.58)	61 (92.42)
80	74 (54.81)	61 (45.19)	20 (27.03)	54 (72.97)	4 (6.56)	57 (93.44)
90	94 (69.93)	41 (30.37)	36 (38.30)	58 (61.70)	0 (0.0)	41 (100)

CCH, collagenase Clostridium histolyticum; PC, penile curvature.

In addition, the study provides a useful analysis of clinical factors associated with clinical improvement after CCH injections, which was defined as a decrease in PC of at least 20°.

Currently, although the European Association of Urology guidelines on male infertility recommend intralesional CCH, verapamil or interferon with a level of evidence 1b [11], only a small percentage of patients treated will experience significant straightening of the penis and satisfactory intercourse. Analyses of predictors of efficacy of intralesional injections for PD have yielded discordant results. Wolff et al. [18] found that only younger age was associated with better outcomes after intralesional injections of verapamil for PD. Moskovic et al. [18] also reported that age, as well as the degree of curvature, were predictive of the response to intralesional injections of verapamil [19], while Trost et al. [20] found, in their univariate analysis, that pre-treatment curvature was a predictor of response to therapy [20]. Apart from degree of curvature, however, which should be considered an obvious clinical predictor of response to intralesional injections, previous data have failed to identify significant predictors, as age may be considered as a confounding factor.

The presence of plaque calcification in PD has been previously reported in the literature [12]. Smith et al. [21] reported plaque calcification in 20–25% of patients with PD, but this rate has ranged as high as 53% [22].

Interestingly, plaque calcification has been found to be associated with worse PC [12]. In fact, Levine et al. [12] showed that the presence of a grade 3 calcification was associated with a greater probability of undergoing a grafting procedure, as these patients were found to have severe deformity (PC >60°) [12]. Although, it has generally been agreed that the finding of calcification within the plaque on power Doppler ultrasonography is suggestive of longer disease duration [23,24], >17% of men can manifest calcified plaques at an early stage. There is no consensus, however, on the definition of acute-phase PD. On this basis, we considered all patients in the present cohort to have stable PC, without symptoms.

Results from the two large, randomized, double-blind, placebo-controlled phase III IMPRESS trials showed clinical efficacy of CCH in decreasing PC by an average of 34% after four cycles of treatment [10]; however, these trials excluded from the analysis those patients with calcified plaque and acute-phase PD, leaving doubts about the efficacy of CCH in these categories of patients.

In the present cohort, 39% of patients received CCH at an early phase of PD (<12 months) and we showed that duration of the disease may influence treatment success.

In contrast to the findings of the present study, Nguyen et al. [25] demonstrated no statistical difference in CCH treatment efficacy between those in the acute phase of the disease and those in the stable phase. These discrepancies may be explained by the rigid definition of stable disease, which was based on the PD duration in that study, while we considered PD duration as a continuous variable, expressed in months, to be more accurate.

Baseline PC also represents a significant predictor of success. In a prospective, randomized, double-blind, placebo-controlled study of CCH in 49 men with PD, significant improvements in penile deformity were observed in those with PC of 30–60° and in those with PC of >60° [26]. In addition, in a *post hoc* analysis in the IMPRESS clinical trial, the authors showed that PC deformity reductions were significantly greater in the following subgroups: baseline penile 30–60 and 61–90°; disease duration >2 to ≤4 years and >4 years; no calcification; and IIEF score ≥17 [27].

In a prospective, randomized, double-blind, placebo-controlled study of CCH in 49 men with PD, significant improvements in plaque size and penile deformity were observed overall with CCH treatment compared with placebo [18]. Men were divided into three groups for analysis: (i) those with PC of ≤30° and/or palpable plaque <2 cm ($n = 7$); (ii) those with PC of 30–60° and/or 2–4 cm of palpable plaque ($n = 24$); and (iii) those with PC of >60° and/or >4 cm of palpable plaque ($n = 18$) [18]. Significant differences between CCH and placebo were observed in the latter two groups but not the first group, although this may have been attributable to the small number of men in that group.

Despite several strengths, the present study has some limitations. First, the number of patients may be considered small. Second, the study was not designed as placebo-controlled, but this would not have added clinical significance to the derived nomogram.

Nevertheless, the present analysis highlights the clinical benefit of CCH for the treatment of PD. Our nomogram could be of clinical benefit in selecting the optimum candidates for CCH therapy.

In conclusion, in this large single-arm multicentre clinical study, we identified clinically significant predictors of treatment success after treatment with CCH for PD. Patients with longer PD duration, greater baseline PC and basal and dorsal plaque location had a greater chance of treatment success. The definition of stable disease (<12 months vs ≥12 months) did not have impact on success of treatment. These results could be applied in clinical practice before external validation of our nomogram has been carried out.

Conflict of Interest

Dr. Russo received travel grant by SoBI drug company.

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Abbreviations: CCH, collagenase *Clostridium histolyticum*; FSFI, female sexual function index; IIEF-15, 15-item International Index of Erectile Function; IIEF-EF, IIEF-erectile function domain; IQR, interquartile range; OR, odds ratio; PC, penile curvature; PD, Peyronie's disease; PDQ, Peyronie's Disease Questionnaire.