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Extracorporeal Shock Wave Therapy for the Treatment of Chronic Pelvic Pain Syndrome in Males: A Randomised, Double-Blind, Placebo-Controlled Study

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Abstract

Background: There is no sufficiently validated therapy for chronic pelvic pain syndrome (CPPS).
Objective: To investigate the effects of extracorporeal shock wave therapy (ESWT) in 60 patients suffering from CPPS.
Design, setting, and participants: Sixty patients suffering from CPPS for at least 3 mo were investigated in two groups. Both groups were treated four times (once per week), each by 3000 impulses; group 2 was performed as a sham procedure. The investigation was designed as a placebo-controlled, prospectively randomised, double-blind phase 2 study. Standardised follow-up was performed 1, 4, and 12 wk after ESWT.
Interventions: Low-energy–density ESWT was performed using a perineal approach without anaesthesia. In the placebo group, the same setting was used without shock wave energy transmission.
Measurements: ESWT effects on pain, quality of life (QoL), erectile function (EF), and micturition were evaluated. The parameters were investigated using validated questionnaires (National Institutes of Health Chronic Prostatitis Symptom Index [NIH-CPSI], International Prostate Symptom Score [IPSS], International Index of Erectile Function [IIEF]) and the Visual Analog Scale (VAS) for pain evaluation.
Results and limitations: All patients completed outpatient treatments and follow-ups without any problems. All 30 patients in the verum group showed statistically (highly) significant improvement of pain, QoL, and voiding conditions following ESWT in comparison to the placebo group, which experienced a continuous deterioration of the same parameters during the follow-up period. Perineal ESWT was easy and safe to perform without anaesthesia or any side-effects.
Conclusions: This is the first prospectively randomised, double-blind study to reveal perineal ESWT as a therapy option for CPPS with statistically significant effects in comparison to placebo. ESWT may in particular be interesting because of its easy and inexpensive application, the lack of any side-effects, and the potential for repetition of the treatment at any time.

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1. Introduction

The incidence of chronic pelvic pain syndrome (CPPS) is increasing [1,2], and the vast majority of male patients suffer from this abacterial form [3,4]. Recently, an incidence of almost 14% was found among >5000 male urologic outpatients, whereas incidence had been estimated to be only 4.5% [5]. The disease reveals substantial morbidity comparable to that of angina pectoris, Crohn's disease, or the status after a heart attack. Disease-typical restrictions are pain sensations most commonly in the prostate, testes, groin, back, pelvic floor, and suprapubic region [6].

The functional CPPS-like symptoms, such as disturbances of micturition and erectile function (EF), can have a crucial diminishing effect on quality of life (QoL) that may be even greater than the pain itself [7–9]. The pathophysiology is almost entirely unknown. Previous infections, pelvic floor hypertension, local chemical alterations, and perfusion disturbances are under discussion [10]. Even the role of the prostate in CPPS is questionable [11,12] because women can also develop CPPS-like symptoms [13]. Neurobiologic and psychiatric factors could play a further role. In a murine model, autoimmune prostatitis induced long-lasting pelvic pain, and the origin could clearly be assigned to the prostate [14]. Prolonged smooth muscle contraction in the bladder and prostate resulting from α_1-adrenergic (α_1-ADR) activation may aggravate the symptoms further [15]. The presence of nanobacteria discovered in CPPS sufferers has opened a completely new field of possible aetiologic factors [16].

According to the actual National Institutes of Health (NIH) classification [17], CPPS (type IIIB, Fig. 1) is characterised by the lack of signs of infection in urine and sperm as well as by the specific symptoms (Fig. 2). Routine diagnostic procedure is still debatable, and the clinical diagnosis of CPPS is made in light of complaints, microbiologic findings, and exclusion of more severe, relevant diseases [18].

No causal or standardised treatment is available at present [19]. Various agents, such as analgesics, antiphlogistics, antibiotics, α-receptor blockers, and 5α-reductase inhibitors (5-ARIs) are used individually and in various combinations [20,21]. A certain group of patients may benefit mostly from α-blockers [22], and there is no rational basis for the widespread use of antibiotics [23]. We need to address the lack of evidence or objective measurement of effectiveness for each of these treatments. Side-effects may predominate over possible treatment effects, thus minimising the benefit to the patient.

I Acute bacterial prostatitis	
II Chronic bacterial prostatitis	
III CPPS	
IIIA	Inflammatory CPPS
IIIB	Noninflammatory CPPS
IV Asymptomatic inflammatory prostatitis	

Fig. 1 – Prostatitis classification of the National Institutes of Health (NIH).
CPPS = chronic pelvic pain syndrome.

Physiotherapy, trigger-point massage, electromagnetic treatment, and acupuncture have already been used for CPPS [24]. Orthopaedic pain syndromes, fractures, and wound healing disorders are successfully treated by low-energy extracorporeal shock wave therapy (ESWT). Shock waves could reduce passive muscle tone and improve the range of movement in upper-arm contractures caused by stroke [25]. Ischaemic dysfunctional myocardial areas could be reperfused by local application of shock waves [26]. In an initial feasibility study, we were able to show that shock waves are easily applicable by perineal approach without side-effects, achieving significant improvement of CPPS-related symptoms, particularly with regard to pain [27]. The encouraging results of this first-ever study necessitated a more objective approach for investigating ESWT by a placebo-controlled, double-blind, randomised trial.

I Acute bacterial prostatitis		Acute (urinary tract) infection
II Chronic bacterial prostatitis		Chronic/repeated (urinary tract) infection
III CPPS		Pelvic area paresthesia/pain >3 mo, no evidence of bacteria
IIIA	Inflammatory CPPS	White blood cells in prostate fluid, urine, seminal fluid
IIIB	Noninflammatory CPPS	No white blood cells in prostate fluid, urine, seminal fluid
IV Asymptomatic inflammatory prostatitis		White blood cells in prostate fluid, urine, seminal fluid, prostatic tissue; no symptoms

Fig. 2 – Prostatitis classification of the National Institute of Health (NIH): clinical criteria.
CPPS = chronic pelvic pain syndrome.

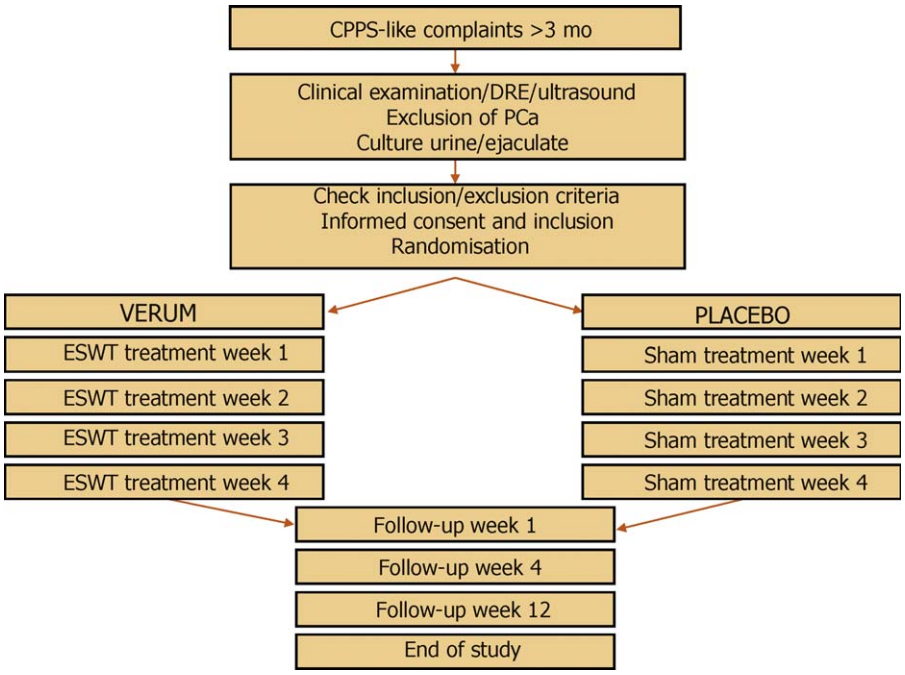

Fig. 3 – Extracorporeal shock wave therapy for chronic pelvic pain syndrome: flow chart.
CPPS = chronic pelvic pain syndrome; DRE = digital rectal examination; ESWT = extracorporeal shock wave therapy; PCa = prostate cancer.

2. Patients and methods

Patients with type IIIB prostatitis (CPPS) of at least 3 mo duration and no evidence of bacteria in urinary and seminal culture tests (criteria according NIH classification) were eligible for the study. Prostate cancer (PCa) was ruled out clinically and serologically prior to therapy. The study protocol (Fig. 3) was approved by the local ethical committee after approval of the general CPPS study by the committees of two medical universities in Germany and Austria. Patients provided informed consent. No other treatments were permitted during the study and follow-up periods.

Prostate-specific antigen (PSA) testing, digital rectal examination (DRE), and transrectal ultrasound of the prostate (TRUS) had been performed prior to study enrolment to rule out other pathologies. All patients were randomised for placement in the verum group or the placebo group prior to treatment. The verum patients received one perineally applied ESWT treatment weekly (3000 pulses each; maximum total energy flow density: 0.25 mJ/mm^2; frequency: 3 Hz) for 4 wk. Treatment parameters were determined by different urologic and nonurologic case studies and publications. The device used for the study was a standard electromagnetic shock wave unit with a focused shock wave source (Duolith SD1, Storz Medical, Tägerwilen, Switzerland). The focus zone penetration depth was in the range of 35–65 mm (Fig. 4),

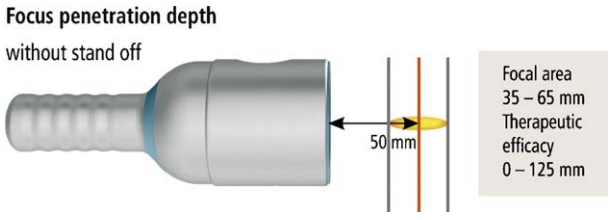

Fig. 4 – Characteristics of the transducer.

which meant that the shock wave focus could be placed in the prostate and pelvic floor from the perineum easily. The position of the shock wave transducer was changed after every 500 pulses to scan virtually the entire prostatic and pelvic floor region. According to the focus geometry of the transducer head, we could not fail to strike the prostatic region when placing the transducer perineally.

The placebo treatment was performed with the same therapy head, which was also fitted with a placebo stand-off. This stand-off contained shock wave–absorbing material, a layer of air, and air-filled microspheres. Performance of the placebo stand-off was validated by measuring the output pressure in a laboratory setup. The setting was identical to the verum treatment. The blinding included the specification that neither the patient nor the investigator/follow-up observer was aware of placebo or verum assignment.

The follow-up schema included clinical examinations and the questionnaire-based reevaluation of QoL and complaints at 1, 4, and 12 wk following ESWT. The degree of pain was evaluated using the Visual Analog Scale (VAS, 0–10). CPPS-related complaints were investigated using the NIH-developed Chronic Prostatitis Symptom Index (NIH-CPSI). Micturition conditions were examined using the International Prostate Symptom Score (IPSS); the International Index of Erectile Function (IIEF) was used for self-assessment of potency function.

The data sets were examined by descriptive analysis methods. The characteristic values, such as mean values plus or minus standard errors (SE) and median values, are listed in Table 2 for all investigated times (0, 1, 4, and 12 wk). SE is defined as the standard deviation (SD) divided by the square root of the patient number (ie, 30 per treatment path). In most instances, the data sets are not normally distributed, so the differences in medians are used to assign the effect of therapy. The significance of differences in before and after states were evaluated using the Wilcoxon signed rank test with $p = 0.05$. The Mann-Whitney test was used in case of the significance for the placebo–verum relationship, also with $p = 0.05$. All statistical analyses were carried out using the statistical software package Sigma Stat 3.1 (Systat Software Inc, San Jose, CA, USA).

Table 1 – Changes in parameters for the sham and verum treatment groups

Parameter	Placebo Rel. change % (median values)	Significant changes	Verum Rel. change % (median values)	Significant changes
IPSS (1 wk)–IPSS (pre)	0	No ($p = 0.947$)	−15.6	Yes ($p \leq 0.001$)
IPSS (4wk)–IPSS (pre)	0	No ($p = 0.631$)	−18.8	Yes ($p \leq 0.001$)
IPSS (12wk)–IPSS (pre)	0	No ($p = 0.280$)	−25	Yes ($p \leq 0.001$)
IIEF (1 wk)–IIEF (pre)	0	No ($p = 0.959$)	10.5	Yes ($p = 0.029$)
IIEF (4wk)–IIEF(pre)	0	No ($p = 0.894$)	5.3	Yes ($p = 0.034$)
IIEF (12wk)–IIEF(pre)	0	No ($p = 0.569$)	5.3	Yes ($p = 0.036$)
CPSI (1 wk)–CPSI (pre)	0	No ($p = 0.935$)	−16.7	Yes ($p \leq 0.001$)
CPSI (4wk)–CPSI (pre)	2.1	No ($p = 0.865$)	−16.7	Yes ($p \leq 0.001$)
CPSI (12wk)–CPSI (pre)	4.2	No ($p = 0.935$)	−16.7	Yes ($p \leq 0.001$)
VAS (1 wk)–VAS (pre)	−16.7	No ($p = 0.151$)	−33.3	Yes ($p \leq 0.001$)
VAS (4 wk)–VAS (pre)	0	No ($p = 0.865$)	−50	Yes ($p \leq 0.001$)
VAS (12 wk)–VAS (pre)	0	No ($p = 0.227$)	−50	Yes ($p \leq 0.001$)

CPSI = Chronic Prostatitis Symptom Index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; VAS = Visual Analog Scale.

3. Results

The average age in the verum group was 42 yr (range: 22–52) and in the placebo group was 43 yr (range: 34–61). Because of the wide variety of treatments most patients had received prior to ESWT, it did not seem meaningful to stratify the patients based on these criteria. Prostate volume was not obtained because it had been proven in the preceding feasibility study to be without influence on the treatment outcome.

The placebo group did not show any significant alterations of the median values of IPSS, IIEF, CPSI, and VAS over the follow-up period. In contrast, all these values revealed statistically significant improvement in the verum group. This discrepancy could verify that ESWT is effective in the treatment of CPPS, at least within a limited period of time. Whereas the parameters in the verum group improved continuously after ESWT, the condition of the untreated patients remained stable (CPSI) or even worsened (IPSS, IIEF, VAS), which may reflect the natural course of the disease in the long run.

In the verum group, IPSS improved by 15% after 1 wk and by 25% after 12 wk. IIEF showed an improvement between 5.3% and 10.5% at the same intervals, and the CPSI improved continuously by 16.7%. All patients with a decline in CPSI of ≥ 5 ($n = 13$, 43.3%) were exclusively found in the verum group. The VAS showed the clearest improvement (33%) after 1 wk, even reaching 50% after 4 and 12 wk. All alterations were statistically significant with respect to the pretreatment value as well as with respect to the placebo group parameters. No side-effects were observed in any patients during the treatment and follow-up periods. Detailed parameters are shown in Tables 1 and 2.

Table 2 – Results: mean values for the sham and verum treatment groups

Parameter	Range: placebo	Normal test: placebo	Mean value: placebo	Median value: placebo	Range: verum	Normal test: verum	Mean value: verum	Median value: verum
IPSS pre	13.0–21.0	Failed	16.10 ± 0.38	16.00	10.0–20.0	Passed	15.83 ± 0.39	16.00
IPSS 1 wk	12.0–22.0	Passed	16.10 ± 0.39	16.00	10.0–17.0	Passed	13.53 ± 0.45	13.50
IPSS4wk	10.0–22.0	Passed	16.27 ± 0.43	16.00	9.0–16.0	Passed	12.90 ± 0.30	13.00
IPSS 12 wk	12.0–24.0	Failed	17.03 ± 0.55	16.00	10.0–15.0	Passed	12.53 ± 0.31	12.00
IIEF pre	11.0–23.0	Passed	17.13 ± 0.68	18.00	12.0–23.0	Passed	18.27 ± 0.60	19.00
IIEF1 wk	10.0–22.0	Failed	17.13 ± 0.61	18.00	16.0–23.0	Failed	20.17 ± 0.42	21.00
IIEF4wk	11.0–21.0	Failed	17.33 ± 0.57	18.00	14.0–23.0	Failed	20.07 ± 0.44	20.00
IIEF 12 wk	10.0–22.0	Failed	16.83 ± 0.59	18.00	16.0–23.0	Passed	20.17 ± 0.32	20.00
CPSI pre	21.0–32.0	Failed	25.07 ± 0.48	24.00	7.0–27.0	Failed	23.20 ± 0.66	24.00
CPSI 1 wk	16.0–33.0	Failed	24.77 ± 0.56	24.00	5.0–24.0	Failed	19.93 ± 0.58	20.00
CPSI 4 wk	22.0–34.0	Failed	24.97 ± 0.44	24.50	6.0–25.0	Failed	19.53 ± 0.57	20.00
CPSI 12 wk	21.0–32.0	Failed	25.00 ± 0.50	25.00	6.0–24.0	Failed	19.70 ± 0.67	20.00
VAS pre	4.0–8.0	Failed	5.73 ± 0.20	6.00	1.0–7.0	Failed	5.33 ± 0.26	6.00
VAS 1 wk	3.0–8.0	Failed	5.30 ± 0.22	5.00	1.0–6.0	Failed	3.63 ± 0.22	4.00
VAS 4 wk	3.0–8.0	Failed	5.73 ± 0.20	6.00	1.0–5.0	Failed	3.03 ± 0.20	3.00
VAS12wk	2.0–8.0	Failed	6.13 ± 0.26	6.00	1.0–6.0	Failed	3.13 ± 0.28	3.00

CPSI = Chronic Prostatitis Symptom Index; IIEF = International Index of Erectile Function; IPSS = International Prostate Symptom Score; VAS = Visual Analog Scale.

4. Discussion

Because of the lack of efficacy of the majority of drug-based therapies, new options for CPPS treatment are of broad interest. Individual therapies are being increasingly scrutinised in relation to their effects. Regrettably, the pathophysiologic backgrounds remain unclear at present, which makes the search for the most effective therapy even more difficult and necessitates a multimodal therapy approach [28,29].

CPPS is assumed either to be a myofascial pain syndrome or to involve neurologic components, thus leading to dysfunctional effects. Many of the complaints may be closely associated with the autonomic nervous system and the interplay between smooth and cross-striated muscles. Previous inflammations occurring via the sympathetic end plate may lead to pain via nociceptive nerve endings and receptors. The prostate seems to have at least a particular role in the pathophysiology of CPPS.

Certain kinds of psychological stress may provoke abnormal electromyographic activity and myofascial pain syndromes. Different coping and environmental factors are of outstanding importance for the successful adjustment of patients with CPPS [30].

Generally, the effects of extracorporeal shock waves on living tissue consist of transformation of mechanical signals into biochemical or molecular-biologic signals that again induce particular alterations within cells (mechanotransduction). Many possible ESWT effects are currently under discussion: Hyperstimulation of nociceptors and interrupting the flow of nerve impulses could lead to pain alleviation. ESWT is able to increase local microvascularisation as well as reduce muscle tone and spasticity.

Shock waves can possibly influence the neuroplasticity of the human pain memory: The prolonged lack of effective pain therapy could lead to a reinforcement of negative impulses (pain) in the brain. Long-term fixation of these impulses could result in the development of a particular *pain memory*. By triggering minimal pain impulses, ESWT could break through this negative-conditioned pain memory by *resetting* the pain [31]—an approach based on the neuron-holographic brain model. It defines the healing effects of ESWT by selective erasing of pathologic reflex patterns and might explain the possibility of influencing areas of pain localised at a distance from the treatment locus.

The results obtained concur with numerous investigations, particularly in the field of orthopaedics. There is a relatively long history of ESWT for painful illnesses of different origins, particularly for chronic plantar fasciitis, which is at present probably the best-evaluated ESWT indication [32–36]. The manner of application, clinical results, and range of side-effects are largely concordant to our present investigation. Besides orthopaedics, there are no similar studies about painful illnesses to which we could refer. In urology and for CPPS, very few comparable studies are to be found regarding shock wave application or study design. Therefore, we cannot really refer to comparable urologic applications.

In contrast with our first study, subjective urination conditions improved significantly for the entire follow-up period of 12 wk. Subjectively perceived urination quality is obviously impaired by CPPS. According to IPSS, the patients showed mainly obstructive symptoms. The interpretation of this effect is of course limited because IPSS reveals only subjective changes. Therefore, we will include in future uroflowmetry and urodynamic evaluation for a subgroup of patients to objectify these results.

The improvement of the IIEF was another unexpected result. It may be explained by the comprehensible fact that the general improvement in QoL also has a positive impact on sexual function, which is well known to be markedly reduced among CPPS patients [37]. Pain reduction can naturally support the functionality of erection and the individual capacity for enjoying sexuality in general. Furthermore, some facts do indeed suggest that local (penile) application of shock waves could possibly have positive effects on erectile tissue.

The most important parameter both clinically and with respect to daily life was pain, which we were able to reduce significantly in this study. Satisfyingly, the effect of the pain reduction continued over the entire follow-up period and was even intensified after 4 and 12 wk.

As expected, pain alleviation led to an improvement in CPPS-specific QoL. The CPSI could be improved for the whole follow-up time, whereas the symptoms of the patients in the placebo group became even worse. According to recent literature, an improvement of approximately 30% of the pain scale represents a clinically important difference [38] that makes the improvement achieved in this study relevant for daily life. A six-point decline in the CPSI total score represents the optimal threshold for predicting treatment response [39]. By using ESWT as a monotherapy, we were able to reach a mean five-point decline—not optimal according to the mentioned definition but nevertheless having clinical importance for the patients [40]. It is of particular importance that all patients showing a CPSI score decline of $\geq$5 (43.3%) were exclusively in the verum group, a fact that we think underscores the effectiveness of shock wave treatment.

The anticipated placebo effect could not be observed in this investigation. The reasons for this lack remains speculative, particularly because the study was conducted in a strict double-blind setting. The efficacy of blinding, however, has not been assessed.

Many studies have shown that directing the shock waves to the most tender point in comparison to exclusive ultrasound targeting leads to the best results [32]. This fact and the verification of intra-/periprostatic shock wave focus, when the transducer is placed perineally (as obtained in our previous feasibility study), allowed us to omit ultrasound guidance, which simplified the ESWT sequence considerably.

For the present study, the follow-up duration has so far been restricted to 12 wk. We are continuing to evaluate the patients at 6 and 12 mo after the end of ESWT treatment to obtain long-term results, particularly because of the good

results and because most shock wave therapies usually require a longer period of time to show clinically significant effects on pain relief.

As proven in many investigations, the total applied ESWT energy significantly influences the final outcome. Therefore, ESWT effect can be considered dose dependent [33]. Our treatment schedule is partly empirical but similar to various nonurologic schematas, with proven efficiency and a very low or absent side-effect rate [32,34–36]. In urology, we do not have comparable investigations to refer to besides our own study [27]. In future, the treatment regime will be adapted in the light of the results observed at any stage of follow-up to obtain more objective treatment procedures. It might be possible, for example, to extend the intervals between the treatments by a significant extent to intensify the time-dependent tissue influence of ESWT and prolong the treatment effects. Because of the lack of any therapy-specific side-effects and the ease of application, it would be possible in theory to repeat the ESWT cycle at any time. Therefore, patients whose complaints become worse again after ESWT will be treated by a second cycle in the context of a separate study.

The major strength of this study is certainly the randomised, double-blind design, including the placebo-controlled group. Additionally, this investigation has not been performed by the original workgroup that introduced ESWT for CPPS into clinical practice but by an independent centre with members who had no personal interest in the establishment of this new therapy.

5. Conclusions

ESWT could be of significant importance in the treatment of CPPS (type IIIB prostatitis) because of the straightforwardness of its application and the lack of any appreciable side-effects. With ESWT, it has been possible for the first time to establish a rapid and therefore financially appealing outpatient CPPS therapy option (1) that uses a standard unit, (2) that can be repeated as often as required, and (3) that requires little expenditure in terms of either time or personnel. An additional advantage lies with the local application to the affected region compared with the systemic load caused by drugs (eg, analgesics), which typically leads to not-inconsiderable side-effects, especially when administered over longer periods of time.

Author contributions: Reinhold Zimmermann had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Zimmermann.
Acquisition of data: Cumpanas, Miclea.
Analysis and interpretation of data: Cumpanas, Zimmermann.
Drafting of the manuscript: Zimmermann.
Critical revision of the manuscript for important intellectual content: Janetschek.
Statistical analysis: Zimmermann.
Obtaining funding: None.
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Supervision: Janetschek, Miclea.
Other (specify): None.

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