

Triphasic Bone Scintigraphy Is Not Useful in Diagnosis and May Delay Surgical Treatment of CRPS of the Hand

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Background: Triphasic bone scintigraphy (TPBS) is often used to diagnose complex regional pain syndrome (CRPS). The primary aim of this study is to determine if the diagnosis of CRPS in patients with a positive TPBS (TPBS +ve) is accurate. A secondary aim is to determine if there was delay in treatment of patients who underwent TPBS compared to those who did not have a TPBS.

Methods: Of 225 consecutive patients presenting to the first author's practice with a diagnosis of CRPS, 65 had TPBS performed before referral with 62 having TPBS +ve. The remaining 160 were clinically diagnosed and a TPBS was not done (TPBS-ND). Patients were classified into five categories – wrong diagnosis, dystonic-psychogenic hand, causalgia, flare reaction and irritative carpal tunnel syndrome (ICTS). Patients with flare reaction and ICTS were considered as having true CRPS and the rest were considered as misdiagnosis. The patients' demographics, duration of symptoms, pre- and postoperative pain, functional score and patient satisfaction were compared.

Results: Of the 62 TPBS +ve, there were 38 (61%) misdiagnosis. The proportion of misdiagnoses was fewer in the TPBS-ND group (45%; $p = 0.036$). Thirty-two of the 62 TPBS group (52%) and 92/160 (56%) of the TPBS-ND group had surgical treatment. At a mean follow-up of 19 months, pain dropped 6.5 ± 2.5 points in the TPBS +ve group. Disabilities of the arm, shoulder and hand (DASH) score fell by 56 ± 27 . The mean single assessment numeric evaluation (SANE) score was 8.6 ± 2.3 . These results did not differ substantially from those of the TPBS-ND group.

Conclusions: A significant number of patients in this study who had TPBS +ve were misdiagnosed in this study. Outcomes after treatment of CRPS were consistently good despite the results of the TPBS. Patients with TPBS +ve had a significant delay to diagnosis. We conclude that TPBS is not useful in the management of CRPS.

Level of Evidence: Level III (Therapeutic)

Keywords: Sudeck disease, Reflex sympathetic dystrophy, Complex regional pain syndrome, Chronic pain, Bone scan

INTRODUCTION

Complex regional pain syndrome (CRPS) is a condition characterised by pain disproportionate in time or degree to the usual course of any known trauma or lesion. CRPS is an end-point diagnosis, has an incompletely understood pathophysiology, lacks effective treatment and surgery is rarely recommended.¹⁻³ There is no pathognomonic test or clue to diagnose CRPS, and the diagnosis is based on fulfilling a number of items of the recently refined 'Budapest Criteria'.⁴⁻⁵ A scoring has also

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been devised to assess the severity of the condition that may have a prognostic value.⁶ CRPS frequently affects the upper limb. As hand surgeons, we face these difficult patients, and we have all been taught to have a low threshold in diagnosing CRPS, following the scientifically unsupported lore that early diagnosis leads to better outcomes.^{1,2,7,8} By the same token, we all are aware of the bad prognosis the condition has, and leaders on the topic stress ‘*better to err in too much [diagnosis] than too little*’.^{1,6,8} In this stifling atmosphere of guilt for not properly diagnosing the elusive CRPS in time, a test is desperately needed for the clinician who must refer the patient to the appropriate facility as soon as possible.

While there is some controversy on the sensitivity and specificity of triphasic bone scintigraphy (TPBS),^{9–15} reviews in leading journals^{1,2,6} and major textbooks of hand,⁸ orthopaedic,⁷ neurology¹⁶ and anaesthesia¹⁷ (to name a few examples) recommend the use of TPBS to support and even ‘*confirm*’ the diagnosis of CRPS. This assumption of the CRPS–TPBS link is reinforced with images of positive TPBS in patients ‘suffering from’ CRPS in nearly all textbooks. In all instances, it is stressed that a negative test will not exclude CRPS.

Thus, despite the lack of strong evidence, the prevailing truth is that TPBS is useful as a confirmatory test for diagnosing CRPS. TPBS is also considered a gold-standard test for the diagnosis of CRPS in litigation¹⁸ and in occupational medicine.¹⁹

The first author treats CRPS surgically^{20,21} and does not do a TPBS for patients as part of the diagnostic work-up. Some of the patients referred to him after a period of treatment elsewhere have a TPBS done. This allowed us to determine if TPBS was useful in the diagnosis and management of patients with CRPS. The primary aim of this study is to determine if the clinical diagnosis of CRPS in patients with a positive TPBS (TPBS +ve) is accurate. A secondary aim is to determine if there is delay in surgical treatment of patients who underwent TPBS compared to those in whom a TPBS was not done (TPBS-ND) and if this delay led to a difference in outcomes of surgery. Our null hypothesis is that TPBS +ve correlates with a clinical diagnosis of CRPS.

METHODS

In the period January 2018–April 2021, the first author received 225 patients diagnosed with and treated for CRPS. All patients were included in this study. The diagnosis was made 1–180 months before consultation

(average 16 ± 26 months) by either a surgeon, rehabilitation doctor or pain specialist. There were 180 females and 45 males, and the average age was 52.4 ± 12.5 years (range: 13–87 years). All of them fulfilled the ‘*Budapest Criteria*’ for the diagnosis of CRPS at some stage along the course of the pain.^{4,5} At the time of the first visit at our centre, the CRPS severity score²² was calculated and this was pathological (more than 4) in 204 (91%) patients. All patients were in different protocols for treatment of their pain and 76 (34%) have received one or more invasive anaesthetic procedures. Out of 225 patients, 65 (29%) had TPBS done. And 62 patients (95%) had TPBS +ve and 3 patients had a negative TPBS (TPBS –ve). Another 160 patients were TPBS-ND.

Grouping Process: All patients were examined by the first author (Level 5 surgical expertise). Tests were ordered as required to reach a diagnosis, including advanced imaging modalities (other than TPBS). Patients were classified into the following five categories (Fig. 1):

1. Wrong diagnosis – If there was an underlying cause that could explain the signs and symptoms (except for nerve injuries).
2. Dystonic-psychogenic hand – Patients with fixed hand posture, unexplained hand positioning and non-anatomical lymphedema.^{13,23}
3. Causalgia – If there was an underlying nerve injury.
4. Flare reaction – A form of minor CRPS that is not well defined in the literature.²⁴ In our study, this included patients who displayed signs and symptoms of CRPS but did not have any sleep disturbances.²¹
5. Irritative carpal tunnel syndrome (ICTS) – ICTS included all patients diagnosed with CRPS who did not fit into any of the four categories (Fig. 1).²¹ The distinction between flare reaction and ICTS is somewhat arbitrary. The patients with milder forms of pain (when pain does not affect sleep) are treated non-surgically first, thus the need to separate this group of patients from ICTS group.

The detailed information and outcomes of the 225 patients were reported in a previous publication.²¹ For studying the effect of having the assistance of TPBS as a diagnostic tool, the first three aforementioned categories (wrong-diagnosis, dystonic-psychogenic hand and causalgia) were grouped under misdiagnosis, while the last two conditions (flare reaction and ICTS) were considered ‘True CRPS’. It is also felt that dystonic-psychogenic

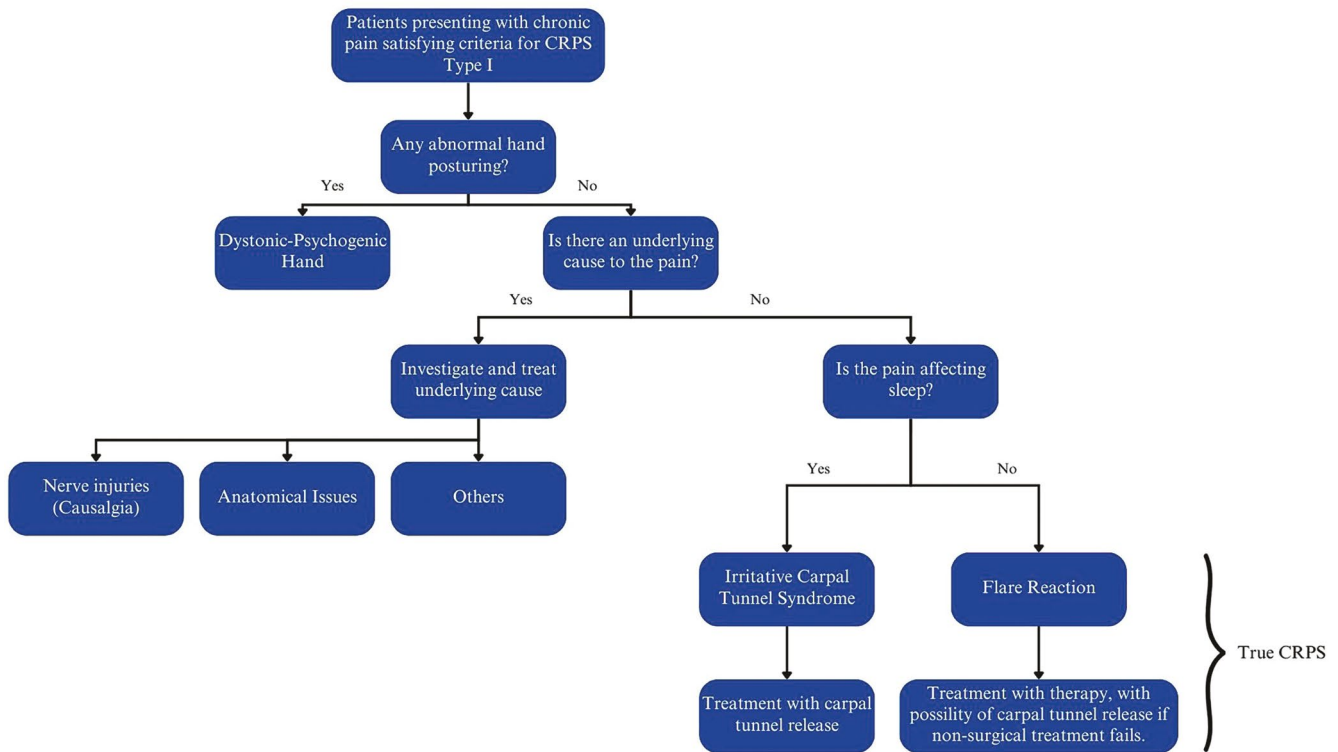


Fig. 1. Diagnostic process for patients presenting with CRPS.

hands are better grouped as a functional disorder.^{25,26} On the other hand, flare reaction is a minor form of ICTS that is self-resolving for most cases but is similar in all respects to ICTS.^{20,21,24}

Treatment: The treatment approach for patients is tailored to their specific diagnosis. Patients under the wrong diagnosis group will receive appropriate treatment tailored to their actual condition, e.g. malunions with corrective osteotomies, and herpetic whitlow with medical treatment. Managing patients diagnosed with dystonic-psychogenic hands can be particularly challenging. While some patients show significant improvement following carpal tunnel release, this outcome is not consistent for all. We are currently conducting an in-depth study to better understand the variations in treatment response amongst these patients. Patients diagnosed with causalgia will usually have diagnostic nerve blocks done, followed by appropriate surgical treatment of the injured nerve. Those diagnosed with ICTS undergo a carpal tunnel release. Patients with flare reaction are treated with therapy initially, failing which, carpal tunnel release is done.

Outcome Assessment: The patient's demographics and duration of symptoms in each group (misdiagnosis and true CRPS) were recorded. Pre- and postoperative pain on a numerical rating scale (NRS) – where

0 was no/minimum and 10 was unbearable/maximum was recorded. All patients completed a disabilities of the arm, shoulder and hand (DASH)²⁷ questionnaire preoperatively, and, as a minimum, 6 months after their operation. Finally, patients were asked to rate their satisfaction with the operation following the mean single-assessment numeric evaluation (SANE) score in an NRS (0 not satisfied, 10 very satisfied). All the data concerning patients of this study are presented in full detail in the appendix.

Statistical Analysis: Results involving categorical variables were expressed as proportions, whereas results involving continuous variables were expressed as means, standard deviations and ranges. The Fisher's exact test was used to analyse differences between categorical variables. Because continuous variables did not follow a normal distribution, the non-parametric Mann–Whitney *U* test was used to analyse the differences between TPBS +ve and TPBS-ND (Age, CRPSSS, average time to diagnosis, postoperative follow-up, Pain and DASH pre- and postoperative, SANE). Non-parametric tests have been shown to have greater power than parametric tests when analysing data that do not follow a normal distribution. *P*-values less than 0.05 were considered statistically significant. With the variable 'difference from preoperative to postoperative scoring',²⁸ we calculated that the sample

size necessary to find differences between TPBS +ve and TPBS-ND (two-sided test without dropouts and alpha risk = 0.05, Beta risk = 0.2, standard deviation = 2, minimum expected difference = 3 and TPBS +ve/TPBS-ND size ratio = 3) is 5 subjects in the first group and 15 in the second one. Statistical analysis was performed using IBM SPSS version 24 (IBM Corp., Armonk, NY).

RESULTS

The 225 patients seen included 112 misdiagnosis (74 wrong diagnosis, 16 dystonic-psychogenic hands and 22 causalgia) and 113 true CRPS (20 flare reactions and 93 ICTS). Out of the 225 patients, 65 had TPBS (40 misdiagnosis [22 wrong diagnosis, 10 dystonic-psychogenic hands and 8 causalgia] and 15 true CRPS [5 flare reaction and 10 ICTS]) and 160 was in the TPBS-ND group (total of 72 misdiagnosis, including 52 wrong diagnosis, 6 dystonic-psychogenic hand, 14 causalgia and total of 88 True CRPS including 15 flare reaction and 73 ICTS; Table 1). There is a significant difference ($p < 0.029$) between the percentage of True CRPS in TPBS +ve and TPBS-ND group. And 39% of TPBS +ve had True CRPS, while 55% of TPBS-ND group had True CRPS. Surgical treatment was offered to 175 patients with a surgically correctable cause and 125 agreed. They include 33 out of 65 TPBS patients and 92 out of 160 TPBS-ND patients.

Sensitivity and Specificity of the TPBS: A total of 65 patients had TPBS done. And 62 had a TPBS +ve for CRPS and 3 had a TPBS -ve. The breakdown of the diagnosis of the +ve and -ve TPBS groups are summarised in Table 1. Briefly, 38 (61%) of the TPBS +ve had other causes explaining their pain that was not CRPS and thus were misdiagnosis. For the three patients who had a TPBS -ve, one was a false negative, while the other two were true negatives for CRPS. Considering the above information, the performance of the TPBS regarding specificity, sensitivity, positive and negative predictive values are presented in Table 2.

Table 1. Diagnosis of Patients Who Had TPBS

Category	Group	TPBS +ve	TPBS -ve	TPBS-ND	Total
Wrong diagnosis		21	1	52	74
Dystonic-psychogenic hand	Misdiagnosis	9	1	6	16
Causalgia		8	0	14	22
Flare reaction	True CRPS	5	0	15	20
Irritative carpal tunnel syndrome		19	1	73	93
Total		62	3	160	225

Outcomes (TPBS Group [n = 65; TPBS +ve = 62; TPBS -ve = 3]): The average time from onset of pain to presentation at our centre was 27.4 ± 36.1 months (range: 3–160) in the TPBS +ve group. In the TPBS +ve group ($n = 62$), 30 patients (48.4%) were not operated on either because they were not surgical candidates (13 patients with dystonic-psychogenic hand, flare reactions, etc.) or because they declined to have surgery done (17 patients). The data from this group is summarised in Table 3. Surgery was carried out in 32 patients (51.6%). At a mean follow-up of 19 months, the pain in the operated patients diminished from 7.9 ± 2.01 to 1.3 ± 2.5 ($p < 0.001$). The DASH score decreased from 75.6 ± 15.9 to 19.5 ± 22.5 ($p < 0.001$). Despite a high satisfaction (8.6 ± 2.3) in the group, there were four patients (12.5%) who could not be

Table 2. Sensitivity, Specificity, Positive and Negative Predictive Value of TPBS in CRPS

	TPBS +ve	TPBS -ve
CRPS	24	1
No CRPS	38	2

Positive predictive value = $24/(24 + 38) = 0.39$

Negative predictive value = $2/(2 + 1) = 0.67$

Sensitivity = $24/25 = 0.96$

Specificity = $2/40 = 0.05$

Table 3. Patients with TPBS +ve Who Did Not Require or Refused Surgery

Author's diagnosis	Number of patients
Dystonic-psychogenic hand	8
ICTS	7
Radius malunion/carpal issues	6
Flare reaction	2
Neuroma/operated nerve conditions	2
PIP malunions/issues with prosthesis	2
Metastatic tumour	1
Overdiagnosis	1
Herpetic neuritis	1
Total	30

Table 4. Outcomes of Patients Surgically Treated for CRPS between TPBS +ve and TPBS-ND Groups

	TPBS +ve	TPBS-ND	TPBS +ve vs. TPBS-ND
True CRPS (%)	24 (39%)	88 (55%)	0.029
Operated patients	32 (51.6%)	92 (57.5%)	0.454
Average time to diagnosis (in months)	27.4 ± 36.1 (3–160)	10.9 ± 18.2 (1–156)	0.001
CRPS Severity Score	6.8 ± 2.1 (4–10)	7.5 ± 2 (1.5–10)	0.097
Age (in years)	51.1 ± 14.5 (13–78)	53 ± 12.5 (23–87)	0.497
Postop F/U (in months)	19.4 ± 9.2 (6–35)	21.0 ± 8.7 (7–45)	0.371
Δ Pain pre/postop	6.5 ± 2.5 (1–10)	7.9 ± 2.0 (2–10)	0.007
Δ DASH pre/postop	56.2 ± 25.9 (5–92)	65.7 ± 19.2 (16–98)	0.1
Satisfaction (SANE)	8.6 ± 2.32 (0–10)	8.9 ± 1.7 (3–10)	0.995
Failures	4 (12.5%)	4 (4.3%)	0.203

weaned off neuropathic drugs and are considered failures. In the TPBS –ve group, two were not surgical candidates and the operated patient, with an ICTS, recovered well after a carpal tunnel release. No further analysis of the TPBS –ve group was made due to the small sample size.

Outcomes (TPBS-ND Group [n = 160]): The average time from onset of pain to presentation at our centre was 10.9 ± 18.2 months (range: 1–156) in the TPBS-ND group. This group included 72 misdiagnosis (45%) and 88 True CRPS (55%; Table 1). Ninety-two (57.5%) patients out of the 160 had surgical treatment and the rest of the 160 were either not surgical candidates or declined surgical treatment. The pain in the operated group diminished from 8.7 ± 1.3 to 0.9 ± 1.7 ($p < 0.001$). The DASH score also decreased from 81.2 ± 12.9 to 15.5 ± 15.4 ($p < 0.001$). Despite a high satisfaction (8.9 ± 1.7) score, there were four failures (4.3%) because these patients could not be weaned off neuropathic drugs (Table 4).

Comparison of Outcomes (TPBS +ve [n = 62] vs. TPBS-ND [n = 160]): There were more misdiagnosis in the TPBS +ve group ($p = 0.036$). The average time from onset of pain to definitive diagnosis was also greater in the TPBS +ve group ($p = 0.001$). The data and comparison amongst operated patients are summarised in Table 4. The difference in pain score pre- and postoperatively was greater in the TPBS-ND group ($p = 0.007$). There were no differences in other outcomes (DASH and SANE) between the two groups (TPBS +ve and TPBS-ND) in patients who underwent surgery.

DISCUSSION

Our study highlights significant misdiagnosis of CRPS in both TPBS +ve and TPBS-ND groups due to a failure to exclude underlying pathologies, including symptomatic fracture malunion, arthritis, causalgia and

dystonic-psychogenic hand. Not surprisingly, the positive and negative predictive value of TPBS is poor (Table 2) in the context of diagnosing CRPS. We also showed that there is a significantly higher percentage of patients with True CRPS in the TPBS-ND group (Tables 1 and 4). This shows that TPBS is not useful in the diagnosis of CRPS. Considering our data, it is possible that a positive TPBS falsely validates the diagnosis of CRPS, contributing to the higher rate of misdiagnosis in the TPBS +ve group. In addition, our results also show that there is a significant delay to seeking another opinion and accurate diagnosis in the TPBS +ve group. The TPBS +ve group had 2.7 times longer duration of pain compared to the TPBS-ND group prior to presentation at our centre (Table 4). This delay in seeking further evaluation may be attributed to the false sense of assurance provided by a positive TPBS, hindering physicians from pursuing additional investigations into the root cause of chronic pain. Results after surgery were essentially similar in both TPBS +ve and TPBS-ND groups, with complete remission in 117/125 (94%) surgically treated patients at an average follow-up of 21 ± 9 months. However, we note that there is significantly better pain relief in the TPBS-ND group (Table 4), which may be attributed to the earlier treatment received. It should be emphasised that ICTS is not the exact same condition as Carpal Tunnel Syndrome but responds to the same operative procedure as previously described.²⁹

Despite a high sensitivity, our study demonstrates an embarrassingly low specificity (0.05) for TPBS in the CRPS scenario. We should consider that TPBS is positive in fractures, immobilisation, many post-traumatic conditions and infections, thus yielding a high sensitivity, even if the patient did not have CRPS.¹³ Holder and Mackinnon presented one of the earliest reports advocating the use of TPBS for diagnosis of CRPS.¹¹ They reported 96% sensitivity and 97% specificity. However, it is important

to note that there were several false positives, including patients with flexor tenosynovitis, inflammatory arthritis and osteomyelitis. One meta-analysis¹³ found several issues with regard to the prior studies looking at TPBS and CRPS. A large proportion of studies did not include a control group. There were also multiple studies that either did not specify their diagnostic criteria for CRPS or used a set of their own criteria. Out of all the studies that gave enough information, only half of them used a reasonable reference standard to diagnose CRPS. A glaring problem was the fact that many of the studies did not mention whether the examiners were blinded.

In another review,¹³ it was found that a bone scan correlated best with a diagnosis of CRPS within the first 20–26 weeks of onset with a sensitivity of only 50%. There was poor correlation if symptoms were longer than 26 weeks. Wertli et al.¹⁴ found that sensitivity and specificity changes with the reference standards and recommended against the use of bone scans in the diagnosis of CRPS. Due to these limitations in the previous studies, we cannot conclude that TPBS is a useful adjunct in the diagnosis of CRPS. As such, a potential area of research will be to run studies with better methodology and importantly, blinding of the examiners during interpretation of the TPBS.

We acknowledge that there are limitations to our study. The study is based on data compiled by the first author who, at the same time, diagnosed all patients and operated on all patients. Nevertheless, the occurrence of systematic error was prevented because the data presented is subjective, and validated questionnaires using patient-reported outcomes were administered. Furthermore, self-reported pain, though subjective, provides the ‘gold standard’ in assessing pain and allows comparison with any other study.³⁰ Operating on CRPS patients can be considered nonsensical, as the literature advises against treating CRPS patients surgically, except under exceptional conditions.^{1,2,6–8} Nevertheless, our result with 94% cure rate in CRPS patients stand up for itself and are much better than any other known protocol for CRPS. These results had already been previously published in other peer-reviewed journals.^{20,21} Even though the number of patients lost to follow-up with TPBS +ve is small (7 out of 62 patients, 11%), it can be considered a potential weakness of the study. However, this does not discredit the study, as this decision did not depend on selection but was made by the patients themselves. The reasons given to refuse surgery were the cost of private care and the lack of confidence in the possibility of resolving their symptoms, supported by the original physician and, in turn, by the current

literature. The remaining non-operated patients (23 in total) did not require surgical treatment and were referred to the relevant specialties for management (Table 3). Bias may also manifest because of our private practice setting. Our patient pool consists of individuals who have sought treatment elsewhere and turned to us after experiencing treatment failures. Consequently, there’s a likelihood that this situation may inflate the proportion of patients in the wrong diagnosis group.

A significant critique of the study is the possibility that its categorisations and conclusions stem from inaccurate assertions and subjective interpretations by the authors. The current categorisation was based on the 30 years of experience and treatment of nearly 400 patients with CRPS by a single treating physician, and details of our findings and success of our treatment strategies had been previously published.^{20,21,29} There are patients who presents with more esoteric signs and symptoms and the definitions for patient categorisation under ‘dystonic-psychogenic hand’²³ and ‘flare reactions’,²⁴ though rare in itself, were previously reported in the literature. It is important to note that conditions such as fracture malunion and proximal interphalangeal joint issues can coexist with CRPS. While this coexistence might lead to misinterpretation of our data, we want to highlight that treating the malunion promptly and effectively resolves pain, often resulting in a rapid decrease in pain medication usage without the need for any nerve procedures. Hence, it is probable that the underlying pathology, rather than CRPS, is the primary cause of the chronic pain. While acknowledging that our categorisations and treatment of this condition deviates from current lore, we want to emphasise that CRPS is still poorly understood, and we believe that its definitions and diagnostic criteria will undergo ongoing refinement as our understanding deepens.

In conclusion, our study supports our hypothesis by demonstrating that a TPBS +ve does not affect the management or outcome of treatment of CRPS. Our data shows that there is a high number of false positives, in addition to causing a significant delay to diagnosis and definitive treatment for the patients with a TPBS +ve. We suggest that the diagnosis of CRPS should remain clinical, with a high index of suspicion for other causes of chronic pain, including fracture malunion, symptomatic arthritis and rare causes like malignancy. We caution against the use of a TPBS to confirm or even support the diagnosis of CRPS, due to the high number of false positives and resultant delay to diagnosis. Instead, advanced imaging modalities like computed tomography and

magnetic resonance imaging will help to identify specific anatomical causes to the chronic pain, which in turn will have more effective treatment strategies.

DECLARATIONS

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Informed Consent: There is NO information (names, initials, hospital identification numbers or photographs) in the submitted manuscript that can be used to identify patients.

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