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Analysis of patterns of three-phase bone scintigraphy for patients with complex regional pain syndrome diagnosed using the proposed research criteria (the 'Budapest Criteria')

J. Y. Moon[1], S. Y. Park[1]*, Y. C. Kim[1], S. C. Lee[1], F. S. Nahm[2], J. H. Kim[3], H. Kim[1] and S. W. Oh[4]

[1] Department of Anaesthesiology and Pain Medicine, Seoul National University Hospital, 110 Daehang-ro, Jongno-gu, 110-744 Seoul, Republic of Korea
[2] Department of Anaesthesiology and Pain Medicine, Seoul National University Bundang Hospital, Gyonggi-do, Republic of Korea
[3] Department of Anaesthesiology and Pain Medicine, Konkuk University Medical Center, Seoul, Republic of Korea
[4] Department of Nuclear Medicine, Seoul National University Boramae Medical Center, Seoul, Republic of Korea

* Corresponding author. E-mail: soo02@snu.ac.kr

Editor's key points

- Complex regional pain syndrome (CRPS) can be difficult to diagnose.
- This study investigates the role of three-phase bone scintigraphy (TPBS) in the management of CRPS.
- Some clinical signs such as skin colour and oedema were associated with a positive TPBS.
- Particular patterns in the three phases of TPBS may be associated with a diagnosis of CRPS.

Background. Three-phase bone scintigraphy (TPBS) is an established objective diagnostic method for complex regional pain syndrome (CRPS), but its validity remains controversial. The aims of this study were: (i) to re-evaluate the diagnostic performance of TPBS, and (ii) to suggest new TPBS criteria based on the proposed research criteria for CPRS in Budapest (the 2003 Budapest research criteria).

Methods. The medical records of 228 consecutive patients, evaluated using the Budapest research criteria, were retrospectively analysed. Of these, 116 patients were included in the present study, and 69 of 116 were diagnosed to have CRPS based on these criteria. The diagnostic performance of TPBS was assessed by determining its sensitivity, specificity, and positive and negative likelihood ratios, and new criteria for TPBS were identified by pattern analysis using the Budapest research criteria.

Results. The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of TPBS for the diagnosis of CRPS according to the Budapest research criteria were 40.0, 76.5, 1.73, and 0.78, respectively. Furthermore, D–D–D, D–D–S, and D–D–I patterns [i.e. according to decreased (D), symmetrical (S), or increased (I) tracer uptake during Phases I, II, and III] of TPBS were found to be positively predictive for CRPS.

Conclusions. The diagnostic value of a positive TPBS for CRPS is low from the view point of the Budapest research criteria. Our findings suggest that a diagnosis of CRPS using the Budapest research criteria should be considered when decreased patterns of TPBS are observed during Phases I and II.

Keywords: bone; complex regional pain syndromes; diagnosis; radionuclide imaging

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Complex regional pain syndrome (CRPS) has been defined as a neuropathic pain condition since the publication of consensus-based criteria by the International Association for the Study of Pain (IASP).[1] However, the lack of specificity (0.41)[2] and diagnostic consistency (0.43–0.66)[3] of the IASP criteria for CRPS led to a proposal to adopt modified criteria in Budapest in 2003 (the 'Budapest Criteria').[3–6] A unique feature of the Budapest Criteria is the provision of two sets of decision rules—one for clinical diagnoses and the other for research purposes. Clinical diagnosis for CRPS according to the Budapest Criteria is performed when the patient has at least three symptoms in the following four categories: sensory, vasomotor, sudomotor/oedema, and motor/

trophic, and at least two signs from the same four categories. Otherwise, according to the Budapest research criteria, patients should have at least one symptom from all four categories and at least two signs from the same four categories for diagnosing CRPS.[7] Among the existing sets of criteria, the Budapest research criteria have been reported to have highest specificity (0.79).[2]

The diagnosis of CRPS using the Budapest Criteria is performed on purely clinical grounds and is based on practical ways of ruling out other conditions.[8 9] Several tests can be used to assist the differential diagnosis, and these include three-phase bone scintigraphy (TPBS).[1 8 10] Unlike a conventional bone scan, TPBS is performed after the injection of a

radioactive substance during Phase I (the blood-flow phase). Approximately 3 min later, during Phase II (the blood-pool phase), another scan is performed and this is followed by an additional scan after 2–4 h during Phase III (the delayed phase).[11] We use the terms 'Increased,' 'Decreased,' and 'Symmetric' to describe the uptake of the affected side with respect to the contralateral unaffected side during each phase. Symmetric uptake during Phase III is usually considered a normal finding in conventional bone scans.

The role of TPBS in the diagnosis of CRPS is to support or even confirm a diagnosis, given its various presentations, and to exclude other diagnoses.[12] Positivity of TPBS for CRPS during Phases I and II must be concordant, and it requires increased uptake in the affected extremity during Phase III.[13 14] Typically, the TPBS pattern in CRPS patients shows increased activity in the affected extremity during all three phases.[11 14] However, the sensitivity (54–100%), specificity (85–98%), positive predictive value (67–95%), and negative predictive value (61–100%) of TPBS for a diagnosis of CRPS vary widely,[13 14] and furthermore, no general consensus has been reached regarding the TPBS criteria that must be met for a diagnosis of CRPS. In a previous study, the positive findings of TPBS were based on reflex sympathetic dystrophy in response to sympathetic blockade,[15] which had been suggested earlier when the concept of the sympathetic independent pain was included in the diagnostic criteria of CRPS.[1] As far as we are aware, no report has been issued on the diagnostic performance of TPBS for CRPS based on the Budapest Criteria, and thus, it is questionable whether current criteria for a positive TPBS finding could be applied to the Budapest Criteria. Furthermore, blood flow differences dependent on clinical stage of CRPS would impact on the likelihood of a positive TPBS.[11 12] If so, a positive TPBS finding should be related to some objective sign of the diagnostic criteria for CRPS related to pain duration.

Accordingly, the aims of this study were: (i) to re-evaluate the diagnostic performance of TPBS, (ii) to investigate the relationship between a positive TPBS finding and the objective signs of CRPS, and finally, (iii) to suggest a new TPBS diagnostic criteria for CRPS based on the Budapest research criteria.[4–6]

Methods

After obtaining approval from the Institute Review Board of Seoul National University Hospital (no. 0908-030-290), we reviewed the medical records of 228 consecutive patients evaluated for CRPS using the Budapest research criteria[4 5] that underwent TPBS at our university-based Pain Management Centre between January 1, 2007 and December 31, 2009.

The exclusion criteria were: (i) bilateral symptoms based on medical history or the physical examination, (ii) an implanted device, such as, a prosthesis[16] or a spinal cord stimulator,[17] and (iii) a history of sympathetic blockade within a month of TPBS.[18]

To evaluate the relationship between objective clinical signs and TPBS results, we selected patients who underwent TPBS within 3 weeks of physical examination.

Procedures used to diagnose CRPS

We used a standardized assessment protocol to evaluate and diagnose CRPS, which included the CRPS database checklist of signs and symptoms (as described by the Budapest research criteria), TPBS, standard radiographs of the affected region and of the contralateral region, electromyography/nerve conduction velocity tests, and psychological assessments. As is required by the Budapest research criteria, patients reported more than one symptom in each of the following four categories: sensory, vasomotor, sudomotor/oedema, and motor/trophic. In addition, the patients were required to have at least two signs from the same four categories. These signs were identified during initial evaluations.

During quantitative sensory testing (QST)[19] using a CASE IV device (CASE IV, WR Medical Electronics Co., Stillwater, MN, USA), vibration and cooling perception thresholds were formally documented. Thresholds for vibration and cooling sensation were calculated for affected and contralateral extremities. Results were given in JND units (empirically derived 'just noticeable difference' values for the vibration and cooling perception thresholds), displacement units (the maximum amplitude of the vibrating stimulator waveform measured in micrometre for the vibration perception threshold), and temperature units (measured in degree-Celsius for the cooling perception threshold). Any discrepancies between an affected and a contralateral extremity were noted.

For the objective evaluation of temperature asymmetry, we applied digital infrared thermography (IRIS® 5000, MEDI-CORE Inc., Seoul, Korea) and determined temperatures in the affected region of interest and in the contralateral region[20] after a minimum period of acclimatization of 30 min in a room temperature environment. A difference in temperature greater than 1°C between the two parts was considered as a positive sign.

Signs of trophic changes, skin colour asymmetry, and asymmetric oedema were recorded by attaching photographs to the patient's electronic chart. Furthermore, an 11-point Numerical Rating Scale (NRS) was used to assess the overall pain intensity during every visit made to our Pain Management Centre.

Three-phase bone scintigraphy

TPBS was performed using large field-of-view gamma cameras equipped with low-energy general purpose collimators (E.CAM, Siemens Medical Solutions, PA, USA or SKYLight, Philips Medical Systems, Best, The Netherlands). I.V. cannulation was secured in an arm antecubital vein. Patients complaining of upper limb pain were cannulated in a pedal vein. With the patient positioned symmetrically, radiopharmacological isotope was injected at least 3–5 min after releasing the tourniquet. The dynamic scan for Phase I was obtained at 1 frame s^{-1} after an i.v. bolus injection of 740 MBq of ^{99m}Tc-methylene diphosphonate, and a static scan for Phase II was acquired over 3 min from injecting the radiotracer. The static Phase III scan was performed 4 h after injecting the radiotracer. The results of TPBS were interpreted by at least three nuclear medical physicians at our institute.

Pattern analysis was conducted by comparing degrees of radiotracer uptake in affected extremities with contralateral extremities. Decreased or increased radiotracer uptakes in affected extremities were compared with those of contralateral extremities for each phase.[13] Focal increased radiotracer uptakes, suggestive of osteoarthritic causes other than CRPS, were excluded from the pattern analysis. The TPBS diagnostic criteria for CRPS were as follows: (i) concordance between Phase I and II findings, in terms of increased or decreased uptake, and (ii) increased uptake in the affected extremity on Phase III. However, during the chronic stage, TPBS changes can show reduced activity during all three phases,[14] and thus, in such patients, TPBS findings and patient history were compared. Patients who show increased uptake during all the three phases, typical TPBS was diagnosed, otherwise atypical TPBS was assumed.[14] Patterns (Phase I–Phase II–Phase III) according to decreased (D), symmetric (S), or increased (I) tracer uptake during each phase were constructed.

Statistical analysis

Data on patient characteristics are presented as mean (SD) or frequencies. The t-test, χ^2 test, and Fisher's exact test were used to analyse parametric data, and the Kruskal–Wallis test was used for non-parametric data, as appropriate. SPSS v. 19.0 (SPSS Inc., Chicago, IL, USA) was used throughout. Statistical analysis was performed in three parts.

First, to assess the diagnostic performance of TPBS for CRPS using the Budapest research criteria, we calculated sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio.[21]

Secondly, to evaluate relationships between TPBS findings and the objective signs of CRPS, we used the following eight signs: sensory (hyperalgesia, allodynia, or both), temperature asymmetry, skin colour (change/asymmetry), oedema, sweating (change/asymmetry), decreased range of motion, motor dysfunction (weakness, tremor, dystonia, or all), and trophic changes (skin, hair, nail). Each sign was scored on a dichotomous scale as '1; presence' or '0; absence'. Binary logistic regression analysis was performed to assess relationships between TPBS results (the dependent variable) and objective signs (the independent variables). Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

To determine new diagnostic TPBS criteria for CRPS based on the Budapest research criteria, risk ratios (RRs)[14 15] of combined patterns (Phase I–Phase II–Phase III) were used.[22] CRPS patients were then assigned to three clinical stages with respect to pain duration: Stage 1 (0–20 weeks from symptom onset), Stage 2 (20–60 weeks), and Stage 3 (>60 weeks).[13] Patterns of TPBS among our CRPS patients by the clinical stage were compared using Fisher's exact test.

P-values of <0.05 were considered to indicate statistical significance.

Results

Of the original 228 patients considered, 116 were included in the analysis (Fig. 1). Sixty-nine (42 males, 61%) were
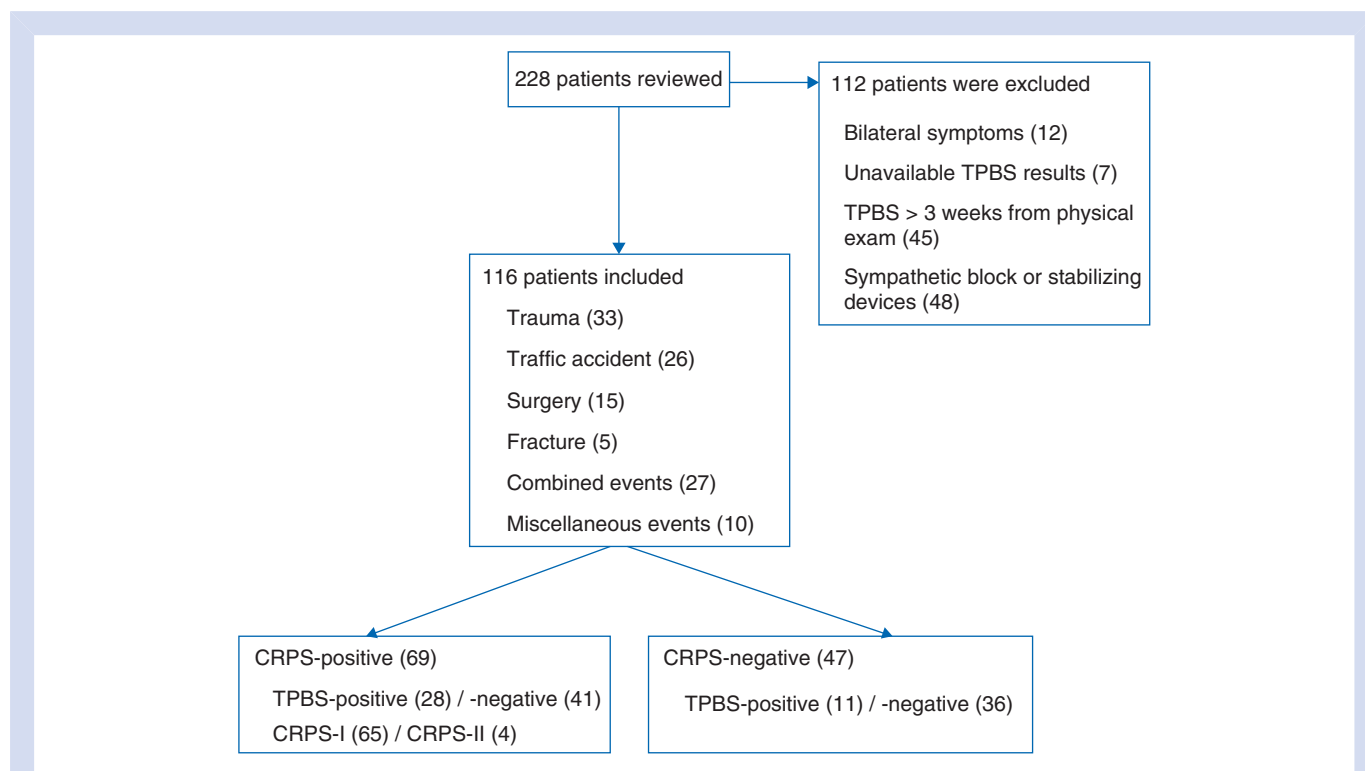

Fig 1 Flow diagram showing the inclusion process of subjects in the study. TPBS, three-phase bone scintigraphy; CRPS, complex regional pain syndrome.

diagnosed as having CRPS (the CRPS group) and 47 not having CRPS (the non-CRPS group). The CRPS patients were assigned to Stage 1 (<5 months, *n*=28), Stage 2 (5–12 months, *n*=24), or Stage 3 (>12 months, *n*=17) based on pain duration.

Part 1: Diagnostic performance of TPBS for CRPS

Table 1 summarizes differences between the CRPS and non-CRPS groups with regard to patient characteristics and clinical characteristics. Overall, the clinical pain intensity was statistically comparable across groups. Of the 85 patients who underwent QST, the vibration perception threshold JND and displacement of CRPS patients were significantly lower when compared with non-CRPS patients. Additionally, CRPS patients were significantly more sensitive to non-noxious cooling sensation with higher cooling perception threshold during QST evaluation when compared with non-CRPS patients.

The sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of TPBS for the diagnosis of CRPS according to the Budapest research criteria were 40.0, 76.5, 1.73, and 0.78, respectively. The OR of TPBS for diagnosing CRPS according to the Budapest research criteria was 2.24 (95% CI, 0.98–5.12) and not statistically significant (Table 2).

Part 2: Objective signs related to the positive result of TPBS

All included patients (*n*=116) were divided into two groups according to their TPBS results [TPBS-positive (*n*=39) and TPBS-negative (*n*=77)]. After confirming that patient characteristics were similar in these two groups, logistic regression analysis was conducted to evaluate the relationships between the objective signs of CRPS and the positive TPBS finding (Table 3). Of these objective signs, skin colour change and oedema were included as significant predictors of a positive TPBS result. However, sensory and trophic changes were included as significant predictors of a negative TPBS result. The overall accuracy of this model was 74.1%, and the −2 log-likelihood ratio of goodness-of-fit was 118.9.

Part 3: TPBS patterns and the Budapest research criteria for CRPS

According to tracer uptakes during the three phases, 27 patterns were expected mathematically, but we found only 12 in the study subjects. The D–D–D, D–D–S, and D–D–I patterns were found to be reliable positive predictive patterns of CRPS according to their RRs (95% CI; Table 4). Although the S–S–S pattern was the most frequently seen in the study population, it was a negative predictive pattern. The I–I–I pattern was the second most frequent, but it was not significantly associated with predictive TPBS patterns for CRPS.

Disease duration was not found to affect pattern distribution in CRPS patients as shown in Figure 2 (*P*=0.898).

Table 1 Characteristics of study patients by diagnostic subgroups. Data are presented as number of patients or means (SDs). CRPS, complex regional pain syndrome according to the proposed modified research criteria in Budapest, in 2003; TPBS, three-phase bone scintigraphy; UE/LE, upper extremity/lower extremity; onset denotes duration from the initial event. Onset to TPBS denotes duration from the initial event through to the time of TPBS test. Test to TPBS denotes duration between the test for CRPS and TPBS. NRS, 11-points Numeric Rating Scale for pain intensity; JND, just noticeable difference. *P<0.01; **P<0.05

	CRPS (*n*=69)	Non-CRPS (*n*=47)
Male/Female	41/28	25/22
Age (yr)	38.0 (14.2)	43.5 (16.0)
Affected extremity (UE/LE)	19/50	12/35
Onset (months)	11.4 (13.8)	15.4 (15.1)
Onset to TPBS (months)	12.1 (14.3)	16.2 (15.2)
Test to TPBS (day)	7.0 (7.0)	9.3 (7.3)
NRS, 0–10	7.1 (2.0)	6.4 (2.4)
TPBS for a diagnosis of CRPS (positive/negative)	28/41	11/36
Affected side vibration perception threshold		
JND*	12.9 (4.3)	15.9 (4.8)
Displacement (μm)**	38.2 (93.0)	86.4 (149.8)
Affected side cooling perception threshold		
JND**	9.4 (4.8)	12.2 (5.1)
Temperature (°C)*	28.1 (4.5)	25.9 (6.8)

Table 2 Diagnostic performance of TPBS in the proposed modified research criteria for complex regional pain syndrome. Data are presented as frequencies, OR or likelihood ratios with (95% CI), and percentages. CRPS denotes complex regional pain syndrome according to the proposed modified research criteria in Budapest in 2003. TPBS, three-phase bone scintigraphy; OR, odds ratio; PLR, positive likelihood ratio; NLR, negative likelihood ratio. Sensitivity=$a/(a+c)$—the percentage of patients with clinical CRPS who have positive scans for CRPS. Specificity=$d/(b+d)$—the percentage of patients without clinical CRPS who have negative scans for CRPS. Positive predictive value=$a/(a+b)$—the likelihood that a patient has clinical CRPS when the scan is positive. Negative predictive value=$d/(c+d)$—the likelihood that a patient will not have clinical CRPS when the scan is negative

	CRPS	Non-CRPS
TPBS (+)	28 (True-positive, a)	11 (False-positive, b)
TPBS (−)	41 (False-negative, c)	36 (True-negative, d)
OR	2.24 (0.98–5.12)	
Sensitivity (%)	40.6	
Specificity (%)	76.6	
PLR	1.73 (1.2–2.4)	
NLR	0.78 (0.4–1.3)	

Discussion

In this study, a positive TPBS result was found to be clearly related to skin colour changes and oedema. However, the diagnostic performance of TPBS for CRPS based on the Budapest research criteria was low in the present study, with a sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of 40.0, 76.6, 1.73 (95% CI 1.3–2.4), and 0.78 (95% CI 0.4–1.3), respectively. Our analysis of TPBS patterns in CRPS patients diagnosed using the Budapest research criteria suggests that we considered a diagnosis of CRPS in patients with the D–D–D, D–D–I, or D–D–S patterns regardless of clinical stage.

Two topics regarding the patient characteristic data included in this study warrant consideration. First, the gender distribution of our subjects was not in agreement with previous studies, which found a higher incidence and prevalence in females.[3][23] However, in the present study, the female to male ratio of CRPS diagnosed using the Budapest research criteria was 1:1.56 (27 females and 42 males).

Table 3 A logistic regression of the objective signs related to the positive three-phase bone scintigraphy. Data are presented as odds ratio (OR) (95% confidence interval, CI). ROM, range of motion. *$P<0.05$

Objective signs	B	SE	OR	95% CI
Sensory*	−1.052	0.533	0.35	0.12–0.99
Skin colour*	1.487	0.616	4.42	1.32–14.79
Temperature	−0.132	0.494	0.88	0.33–2.31
Oedema*	1.519	0.543	4.57	1.58–13.24
Sweating	1.108	0.648	3.03	0.85–10.79
Decreased ROM	−0.221	0.552	0.80	0.27–2.37
Motor dysfunction	0.191	0.618	1.21	0.36–4.07
Trophic change*	−1.731	0.669	0.18	0.05–0.66

Interestingly, this may have been owing to the conscription system in Korea because obligatory military service may have increased the risk of trauma among men ($n=19$, 45%).[24] Secondly, four patients with CRPS-II were included in the present study, and their TPBS patterns were I–I–I (2), D–D–D (1), and S–S–S (1). In a separate analysis, we excluded these four patients and restricted the analysis to the 112 CRPS-I patients. However, this was found to have no differences on the results, with the exception of objective signs related to a positive TPBS result; patients' symptoms such as changes in sweating ($P=0.033$) were included in positive significant predictors of a positive TPBS.

In this study, a positive TPBS result could reflect the two objective signs of skin colour asymmetry and oedema, but the pathophysiological mechanisms responsible are still unclear.[1][8][13] Trophic change was found to be a negative predictive sign for a positive TPBS result. A relatively lower incidence of trophic change might be seen in patients with CRPS, which is a reflection of the emphasis placed on warm CRPS rather than on cold CRPS by current TPBS criteria, and trophic change would occur earlier in the latter case.[25] Sensory changes such as hyperalgesia, allodynia, or both were also found to be negative predictors, but this might have been owing to the fact that patients in the CRPS and non-CRPS groups had similar symptoms.

The D–D–D, D–D–S, and D–D–I patterns were found to be reliable positive predictive patterns of CRPS in the present study. The S–S–S pattern was the most frequent in the CRPS group, but it was a negative predictive pattern. This might reflect the fact that this pattern was also frequently seen in the non-CRPS group. On the other hand, the I–I–I pattern was the second most frequent feature, but it was not statistically significant because vasodilatation can occur in acute limb trauma, which was similar to CRPS in terms of local oedema, skin colour change, and temperature asymmetry.[18] Therefore, we suggest that 'CRPS' is diagnosed

Table 4 The combined patterns found on three-phase bone scintigraphy by diagnostic subgroups based on the Budapest research criteria for CRPS. Data are presented as number of patients (%) and risk ratio (95% CI). I (Increased)/S (Symmetric)/D (Decreased)=increased uptake in an affected extremity/symmetric uptake in an affected extremity/decreased uptake in an affected extremity in relation to the contralateral one. TPBS, three-phase bone scintigraphy; CRPS, complex regional pain syndrome according to the proposed research criteria in Budapest in 2003. RR, risk ratio which is derived from the following formula:[22] $RR=OR_{crude}/[(1-P_0)+P_0 \times OR_{crude}]=OR_{crude} \times (1-P_1)/(1-P_0)$, where P_1 is the positive predictive value and $P_0=1$ − negative predictive value. *$P<0.05$. [†]A positive TPBS for CRPS of Phases I and II must be concordant, and it requires an increased uptake in the affected extremity in Phase III. The D–D–D pattern is accepted as a positive TPBS finding for diagnosing a chronic stage of CRPS. [‡]Typical TPBS is diagnosed in patients showing increased uptake during all the three phases, otherwise atypical TPBS is assumed. [§]Others are combined patterns such as D–S–I (1/0), S–S–D (0/1), S–I–S (1/1), and S–I–I (1/1)

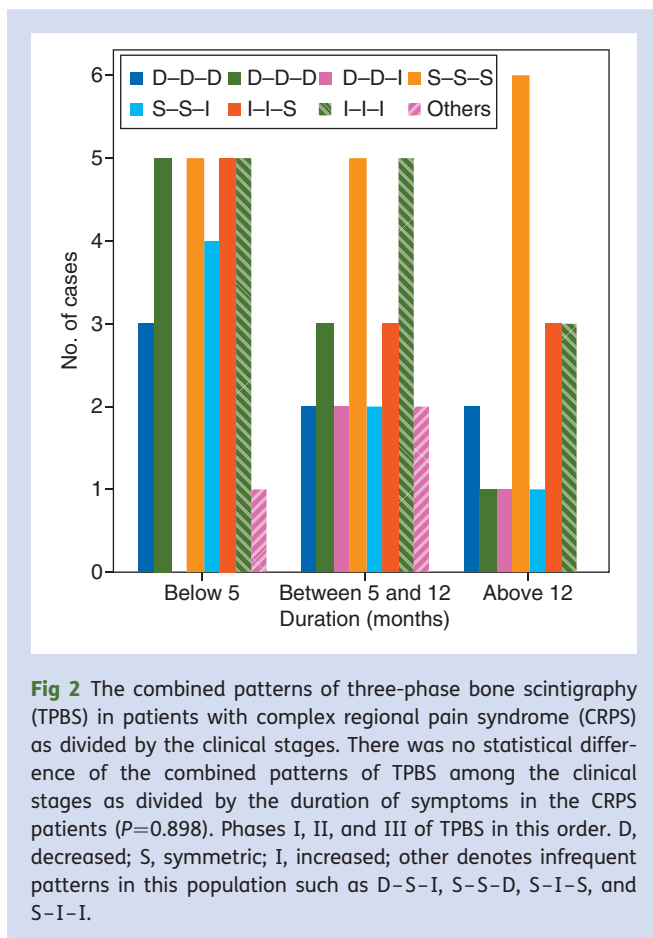| TPBS		TPBS pattern Phase I–II–III	CRPS (n = 69)	Non-CRPS (n = 7)	RR	95% CI
Positive[†]	Typical[‡]	I–I–I	13 (18.8%)	7 (14.9%)	1.11	0.90–1.38
	Atypical	S–S–I	7 (10.1%)	3 (6.4%)	1.20	0.98–1.46
		D–D–I*	3 (4.3%)	0 (0%)	1.71	1.47–2.00
		D–D–D*	7 (10.1%)	2 (4.3%)	1.34	1.11–1.62
Negative		**D–D–S***	9 (13.0%)	1 (2.1%)	1.59	1.33–1.90
		S–S–S*	16 (23.2%)	24 (51.1%)	0.57	0.44–0.75
		I–I–S	11 (15.9%)	7 (14.9%)	1.03	0.83–1.29
		Others (four patterns)[§]	3 (4.3%)	3 (6.4%)	0.83	0.66–1.06

Fig 2 The combined patterns of three-phase bone scintigraphy (TPBS) in patients with complex regional pain syndrome (CRPS) as divided by the clinical stages. There was no statistical difference of the combined patterns of TPBS among the clinical stages as divided by the duration of symptoms in the CRPS patients (*P*=0.898). Phases I, II, and III of TPBS in this order. D, decreased; S, symmetric; I, increased; other denotes infrequent patterns in this population such as D–S–I, S–S–D, S–I–S, and S–I–I.

in patients showing positive predictive TPBS patterns, such as, D–D–D, D–D–S, or D–D–I, otherwise 'non-CRPS' should be assumed or a clinical correlation is required. In this study population, the specificity of TPBS for CRPS increased to 93.6% (range: 88.9–93.6%) when we applied these rules.

In a previous report, three separate scintigraphic patterns were observed and found to be related to the three clinical stages of CRPS, for example I–I–I to Stage 1, S–S–I to Stage 2, and D–D–D to Stage 3.[13] In addition, previous studies have emphasized the optimum time to use TPBS in the diagnosis of CRPS is within 5 months (Stage 1) after symptom onset.[26 27] However, there are some reports that argue against existences of three clinical stages of CRPS.[4 28] In the present study, times between initial onset and TPBS were assessed, but were not found to affect patterns or tracer uptake during each phase. This finding supports the absence of pure clinical stages of CRPS[28] and the possible coexistence of cold CRPS and warm CRPS regardless of pain duration.[25]

Three study limitations should be considered, namely selection bias, information bias, and confounding. First, this was a university hospital-based study, and therefore, findings may reflect those of a university hospital patient population rather than the general population. Secondly, it is possible that medications, such as analgesics, acted as confounding factors, because times between physical examinations and TPBS varied, even though no differences in medical

prescriptions were found between positive and negative TPBS groups. Thirdly, we used the Budapest research criteria to discriminate between CRPS and non-CRPS, and these criteria have not been officially endorsed, although a previous study that evaluated the diagnostic performance of the Budapest research criteria for CRPS revealed that it had a higher specificity than the current IASP criteria.[2]

In conclusion, the diagnostic value of TPBS as a screening or a confirmatory test for CRPS according to the Budapest research criteria is low. The current study supports that no specific test is available for CRPS, which is diagnosed primarily through observation of the symptoms and signs. If TPBS is used to build up a picture of the disorder, a diagnosis of CRPS can be considered in case of D–D–D, D–D–I, and D–D–S TPBS patterns regardless of the clinical stage of CRPS.

Declaration of interest

None declared.

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