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Original Article

Turner syndrome phalangeal screening based on a two-stage linear regression concept

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Abstract ***Background***: Turner syndrome (TS) is a congenital chromosomal abnormality, resulting in short stature, short fourth metacarpal, and retarded skeletal maturation in children. The existing methods of diagnosis, which include carpal angle, metacarpal sign, and body mass index (BMI), cannot accurately diagnose TS. The authors propose a novel procedure for examining the hand skeleton to distinguish between normal individuals and patients with TS.

Methods: This investigation was divided into two parts. In the first part, existing methods (evaluation of the metacarpal sign, measurement of the carpal angle, and determination of BMI) were used. Examination in the second part was based on the two-stage screening method (TSSM). In the first stage in TSSM, the ratio of the lengths of the distal–middle phalanges of the fifth digit was determined in normal subjects with average range of satisfactory body height and TS patients. A suitable cut-off was found on linear regression and used to divide the plot into TS patients and normal subjects. In the second stage, the normal section was transferred to another group based on bone and chronological ages. A greater number of patients were diagnosed with TS using this method. Finally, four cut-off parameters were determined on linear regression analysis. Results with optimal sensitivity and specificity were automatically obtained.

Results: The combination of TSSM with optimal programming (sensitivity = 0.81 and specificity = 0.91) was satisfactory for diagnosing TS patients.

Conclusion: TSSM can suitably evaluate growth of the hand skeleton to distinguish between normal individuals and patients with TS.

Key words carpal angle, metacarpal sign, phalangeal length, Turner syndrome, two-stage screening method.

Gonadal dysgenesis is the diagnostic term applied to patients with a congenital chromosomal abnormality and hypoplasticity with one or more of the following features: primary amenorrhea, minimal secondary sexual development, and short stature.[1–4] Turner syndrome (TS) is a type of gonadal dysgenesis and has been diagnosed in a number of subjects since 1938.

Turner described seven girls, aged between 15 and 23 years, with webbing of the skin of the neck, deformity of the elbow (cubitus valgus), infantilism, and short stature.[5] Besides the features described by Turner, the following additional features are common clinical findings in TS patients: short neck, abnormal upper: low segment body ratio, short metacarpals, Madelung deformity, low posterior hairline, and osteoporosis. Moreover, all diagnosed patients exhibit short stature as a skeletal growth disturbance. Further, the prevalence of skeletal disturbances in TS subjects is 100%.[1] The prevalence of TS had been reported to be between 1/2000 and 1/5000 among newborns who are phenotypically female, and the karyotype is usually 45 XO.[1,6]

Specific differences between normal individuals and patients with TS have been investigated extensively in past years. Archibald *et al.* observed that 2594 outpatients presented with short metacarpals of the fourth digit relative to the third; and the metacarpals of the fourth digit of these patients were particularly short relative to the fifth; this feature is characteristic of patients with gonadal dysgenesis.[7] This metacarpal finding, however, is not a universal criterion for diagnosing TS, and there are reports of variable incidence of this feature, although it is the classic radiological finding in the hand in TS. Baker *et al.* found a much lower incidence of short metacarpals of the fourth digit.[8] In fact, if the metacarpal of the fifth digit is also shortened, the metacarpal sign may be determined to be negative despite a short metacarpal of the fourth digit. Also, the metacarpal sign may be positive in normal individuals. The percentage of positive and borderline metacarpal signs obtained in a study by Bloom[9] are similar to the results of Archibald *et al.*[7]

Kosowicz described a method called carpal angle to distinguish abnormal carpal bone from gonadal dysgenesis in 37 subjects. Furthermore, measuring this angle in 466 normal subjects showed that the mean carpal angle is 131.5° ± 7.2°.[10] Nevertheless,

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the carpal angle may be decreased or increased in various conditions. Harper *et al.* determined the carpal angle in a US population using the hand films of 928 individuals. They found that the carpal angle is altered by many factors such as gender, race, and age.[11] Moreover, most patients with TS do not have an abnormal carpal angle, although an abnormal carpal angle was initially described as a clinical finding in TS.

Body mass index (BMI), which is the statistical measure of the weight of a person scaled according to height, is also measured for diagnosing TS. Basically, the normal range of BMI is between 18.5 kg/m^2 and 25 kg/m^2.[6,12]

The existing analysis methods, when used for TS patients, lead to many controversial results. Moreover, since 2004 there has been limited research regarding the characteristics of the hand skeleton that may be used to distinguish between normal individuals and patients with TS.[13] Tauber *et al.* found a novel feature, which is termed distal radio-ulnar physeal disparity, in TS.[13] That study reported a significant novel feature in TS that may be used to distinguish between normal individuals and patients with TS. The distal radio-ulnar physeal disparity must be manually measured and is a time-consuming procedure. Hence, we attempted to develop a novel method in the present study. The length of the distal phalanx of the fifth finger in a normal individual is always shorter than that of the middle phalanx. There are other syndromes, however, that involve short middle phalanx of the fifth finger; this includes Russell–Silver syndrome. The shorter middle phalanx of the fifth finger may also be present in normal individuals with comparatively short body height. The metacarpal and phalangeal lengths of the hand for both sexes from infancy through adulthood have been discussed by Garn *et al.*[14] The length of the distal phalanx in patients with TS, however, is usually greater than that of the middle phalanx, which is a feature that has not been previously mentioned. A chronological age–bone age plot is used in combination with this new feature to develop a novel method for distinguishing between normal individuals and patients with TS.

Methods

Database

Roentgenograms of the hand and wrist were randomly obtained by examining 196 films of the female hand, including those of 98 normal individuals and 98 patients with TS. All of the Turner syndrome patients were confirmed on chromosomal analysis. The image of the hand, including the wrist, is examined in the anterior posterior position. The bone age of TS patients' whose roentgenograms were examined was between 2.6 and 13.8 years. The mean bone age $\pm$ SD of normal individuals and patients with TS was 11.81 ± 3.05 and 10.35 ± 2.72 years, respectively. The mean chronological age of normal individuals and patients with TS was 11.6 ± 2.9 years for both. The number of examinations between normal individuals and patients with TS for any one chronological age were equal. MATLAB 7.0 (MATLAB; MathWorks, MA, USA) with SPSS 12.0 (SPSS, Chicago, IL, USA) was used to analyze the data.

Processing procedure

In the present study we developed a novel technique to distinguish between normal individuals and patients with TS. The investigative procedure was divided into two parts. In the first part, in which the existing method was used, three features were examined: BMI, metacarpal sign, and carpal angle; all were direct measurements. The right and the left hand were measured individually. The methods used in the second part were as follows: determination of the ratio of the lengths of distal–middle phalanges of the fifth digit of the left hand and comparison of the bone age of normal individuals with that of patients with TS.

Existing methods

In the first part of this investigation three features were directly measured on roentgenogram. The first feature was the metacarpal sign.[7] Three types of metacarpal sign are shown in Figure 1.

Next, the carpal angle was measured. The carpal angle was first defined by Kosowicz in 1962.[10] The carpal angle is defined as shown in Figure 2. The last feature measured was BMI.

Two-stage screening method

The second category was a novel method defined as the two-stage screening method (TSSM) performed in combination with optimal programming to distinguish between normal individuals and patients with TS. In the first stage the ratio of the maximum length of the distal phalanx of the fifth digit, which included the growth plate, to the maximum length of the middle phalanx of the fifth digit was determined, as shown in Figure 3. Moreover, this measurement obtained for normal individuals and patients with TS were plotted against the chronological age of these persons to obtain a scatter plot. Next, a straight line that approximately divided this scatter plot into two sections was identified; this was termed straight line 1. The section above straight line 1 was called the TS area; it included data for a few normal subjects. The section below straight line 1 included many normal individuals and some patients with TS. The equation of straight line 1 is termed linear Equation 1 and is defined as $y_1 = ax_1 + b$, where a is the coefficient of the first order term of linear Equation 1 and b is the constant of linear Equation 1.

Next, the data of the lower half of scatter plot 1 that included many normal individuals and a few patients with TS were used in the second stage. The method in the second stage was based on the relationship between chronological age and bone age. In the second stage, straight line 2 divided the chronological age–bone age scatter plot into two sections. The section above straight line 2 was termed the normal area and that below straight line 2 was termed the TS area. The equation of straight line 2 was a linear equation and was defined as $y_2 = cx_2 + d$. Coefficients c and d of linear Equation 2 were used to determine the optimal threshold. The best sensitivity was obtained, however, using the data of the area above straight line 1 in combination with that of the area below straight line 2. The optimal programming developed in the present study identified the best parameters a, b, c, and d to automatically obtain the best sensitivity and specificity, as shown in Figure 4.

Fig. 1 The metacarpal sign. (a) Negative metacarpal sign, (b) borderline metacarpal sign, and (c) positive metacarpal sign.

Results

The relationship between the bone age and chronological age of normal individuals and patients with TS is shown in Figure 5(a). The difference between normal individuals and patients with TS was statistically significant at $P = 0.0005$, which indicates that the data are significant. The metacarpal sign, carpal angle, and BMI were computed for each roentgenogram in the first category.

Fig. 2 Carpal angle. A normal carpal angle ranges between 130°and 137°. L, lunate; T, triquetrum; SC, scaphoid.

The P values of the metacarpal sign of the left hand and right hand were 0.629 and 0.912, respectively; that of the carpal angle of the left and right hand were 0.245and 0.242, respectively; and that of the BMI was 0.636. These data are summarized in Table 1. The aforementioned P values indicate that the features were not significant. Data described as scatter plots are provided in Figure 5(b–d). Consequently, the existing features are not optimal for accurately distinguishing between normal individuals and patients with TS.

In the second category, that is, TSSM, the ratios of the lengths of the distal and middle phalanges of the fifth digit of the left and right hands were determined and found to be significant at $P = 0.003$ and $P = 0.007$, respectively. These values are listed in Table 1. The scatter plot of the lengths of the distal and middle phalanges is shown in Figure 5(e,f). The P value for both hands was significant, and the lower value was used in the present study. In contrast, the bone age and body height were found to be significant, at $P < 0.001$ for both, and chronological age between normal individuals and patients with TS was not ($P = 1$).

The results obtained by combining TSSM with optimal programming are illustrated as scatter plots in Figure 6. Figure 6(a) illustrates the best result for the first stage when coefficient a was set at 0.0421 and b was set at 0.86 to produce a straight line. The area above the straight line in Figure 6(a) is called the TS area and that below the straight line includes many normal individuals and a few patients with TS.

In the second stage, c was set at 0.99 and d was set at –0.36 to produce another straight line. The area above the straight

Fig. 3 Ratio of the lengths of the distal and middle phalanges: the maximum length of the distal phalanx (DL), including the growth plate, is divided by the maximum length of the middle phalanx (ML). DP, length of distal phalanx; MP, length of middle phalanx.

line in Figure 6(b) is called the normal area and that below is called the TS area. The coefficients a, b, c, and d are selected by optimal programming, which is the novel technique used in the study. As a result, TSSM in combination with optimal programming has a sensitivity of 0.81 and specificity of 0.91. These values indicate that our novel method is excellent for distinguishing between normal individuals and patients with TS. In addition, there are 16 data sets with a sensitivity of 0.80612 and specificity of >0.9, which are reproducible, as shown in Table 2.

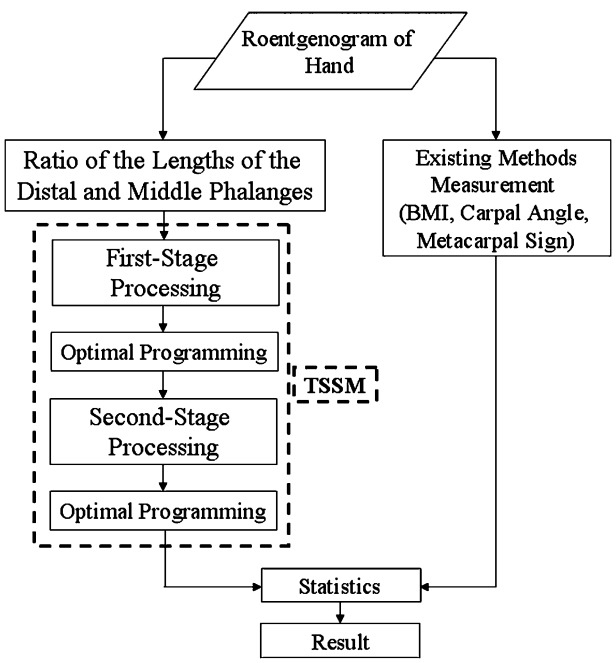

Fig. 4 Two-stage screening method (TSSM) flow chart. BMI, body mass index.

Discussion

Results obtained using the existing method

The incidence of a positive metacarpal sign in the left hand in both normal individuals and patients with TS is 8.16%, (P = 0.629). For the right hand, the incidence of a positive metacarpal sign in normal individuals and patients with TS is 7.14% and 6.12% (P = 0.912). Thus, the incidence of a positive metacarpal sign in the left hand is appreciably higher than that in the right hand. This result is in complete agreement with the study of Archibald *et al.*[7] They noted that a positive metacarpal sign was more frequent and present to a greater extent in the left hand than in the right. Furthermore, the borderline metacarpal sign is found with approximately equal frequency in the left and right hands. Although Archibald *et al.* considered that a borderline or positive metacarpal finding would be useful for diagnosing gonadal dysgenesis, subsequent researchers found that this may lead to confusion and inaccurate results.[1,9]

The carpal angle for normal individuals and patients with TS in the left hand is 133.1° ± 11.85° and 132.7° ± 8.86°, respectively. That for the right hand is 133.8° ± 12.85° and 132.8° ± 11.53°, respectively. The carpal angle in the present study had P = 0.245 and P = 0.242 in the left and right hands,

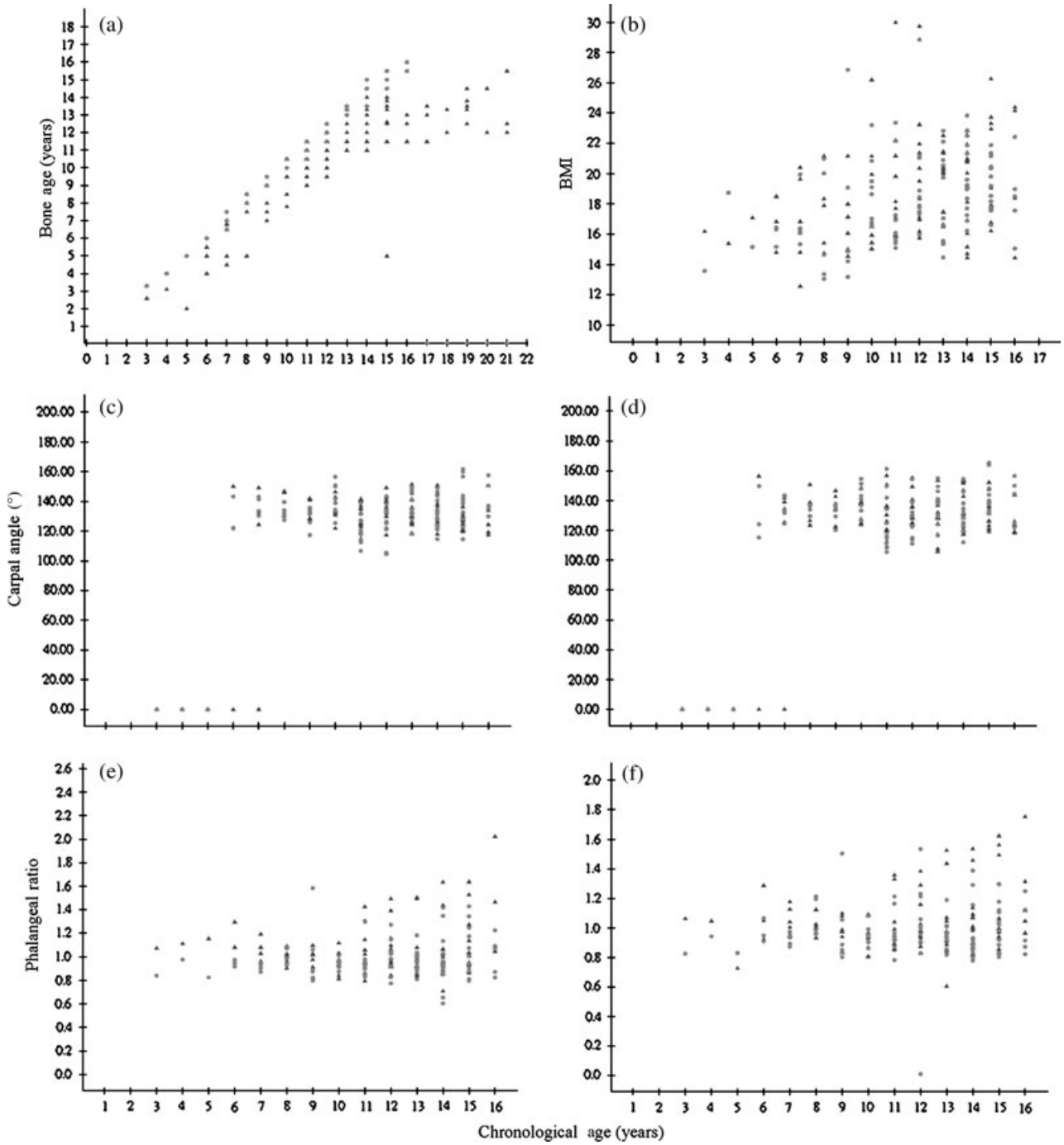

Fig. 5 Existing method in which direct measurements are obtained from roentgenograms; these are the results of the first section: normal individuals and patients with Turner syndrome (TS). (a) Bone age (BA) versus chronological age (▲, TS_BMI chronological age; •, normal_BMI chronological age); (b) body mass index (BMI) versus chronological age (▲, TS_BA chronological age; •, normal_BA chronological age); (c,d) carpal angle of (c) left hand (▲, TS_CarpalAngle_L chronological age; •, normal_CarpalAngle_L chronological age)and (d) right hand (▲, TS_CarpalAngle_R chronological age; •, normal_CarpalAngle_R chronological age) versus chronological age; (e,f) ratio of the length of the distal and middle phalanges of the fifth digit of the (e) left hand (▲, TS_DM_ratio_L chronological age; •, normal_DM_ratio_L chronological age) and (f) right hand (▲, TS_DM_ratio_R chronological age; •, normal_DM_ratio_R chronological age) versus chronological age. DM, distal-middle.

respectively, and is not a significant feature. The mean value of the carpal angle in patients with TS is only slightly below the normal mean value. The result in the present study is an approximation of the result obtained by Kosowicz, who measured the carpal angle in 466 normal individuals and obtained a mean carpal angle of 131.5° ± 7.2°.[10] Tauber *et al.* noted, however,

Table 1 Subject details (mean ± SD)

	Normal (n = 98)	Turner syndrome (n = 98)	P
Metacarpal sign (L) (%)	8.16	8.16	0.629
Metacarpal sign (R) (%)	7.14	6.12	0.912
Carpal angle (L) (°)	133.1 ± 11.85	132.7 ± 8.86	0.245
Carpal angle (R) (°)	133.8 ± 12.85	132.8 ± 11.53	0.242
Ratio of the lengths of the distal and middle phalanges (L)	0.98 ± 0.16	1.04 ± 0.21	0.003
Ratio of the lengths of the distal and phalanges (R)	0.98 ± 0.15	1.03 ± 0.2	0.007
Bone age (years)	11.81 ± 3.1	10.35 ± 2.72	<0.001
BMI (kg/m^2)	18.35 ± 2.98	18.82 ± 3.31	0.636
Body height (cm)	139.1 ± 13.8	128.7 ± 15.4	<0.001
Chronological age (years)	11.6 ± 2.9		1
Sex	Female		

BMI, body mass index.

that the carpal angle is not a significant feature for distinguishing between normal individuals and patients with TS.[13] The present result is in agreement with this. The Kosowicz study, however, demonstrated that the carpal angle is significantly different between normal people and patients with gonadal dysgenesis,[10] but the carpal angle is not related with TS in patients in Taiwan.

The BMI of normal individuals and patients with TS in the present study was 18.35 ± 2.98 kg/m^2 and 18.82 ± 3.31 kg/m^2, respectively. The normal range of BMI is between 18.5 and 25 kg/m^2. P = 0.636 for BMI, implying that BMI is not a significant feature in TS. In addition, Vakili *et al.* found that the BMI of patients with TS was 18.44 ± 3.32 kg/m^2, and the mean age at diagnosis was 11.2 years.[6] The present result is in agreement with this. Nevertheless, these ranges of BMI are valid only as statistical categories when applied to adults and cannot predict health.

TSSM results

Garn *et al.* used data for normal individuals, including metacarpal and phalangeal lengths and variability. Conventionally, the length of the middle phalanx is always greater than the length of the distal phalanx of the fifth digit.[14] In the present study, unconventional results were obtained. The length of the middle phalanx was usually shorter than the length of the distal phalanx of the fifth finger in patients with TS. Russell–Silver syndrome involves a short and/or incurved fifth finger, but this syndrome occurs in approximately one out of every 75 000 births. Turner syndrome, however, occurs in one out of every 2500 girls. Therefore, Russell–Silver syndrome is very rare and would not influence the accuracy in the present system although there is some confusion between Russell–Silver syndrome and Turner syndrome. The ratio of the distal and middle phalanges was significant, with P = 0.003 for the left hand and P = 0.007 for the right hand (Table 1). The best sensitivity of 0.806 and specificity of 0.908 were obtained using the coefficient of the linear regression equations a, b, c, and d indicated in Table 2. Furthermore, 16 of the best results were obtained by optimal programming and these results are reproducible. This novel method can accurately distinguish between normal individuals and patients with TS.

Conclusion

Roentgenograms of the hand were examined using the existing method, which includes examination of the metacarpal sign, carpal angle, and BMI. Unfortunately, these three features were found to be non-significant in the present study and hence could not be used to identify patients with TS. Therefore, TSSM was developed. In the first stage of TSSM, the ratio of the lengths of the distal and middle phalanges of the fifth digit was calculated. Although the P-value of both hands is significant, traditionally, the left hand image is often used as the reference. In our case, the difference of the P-value of the two hands is so small; the smaller one is chosen. In fact, the left hand image was selected.

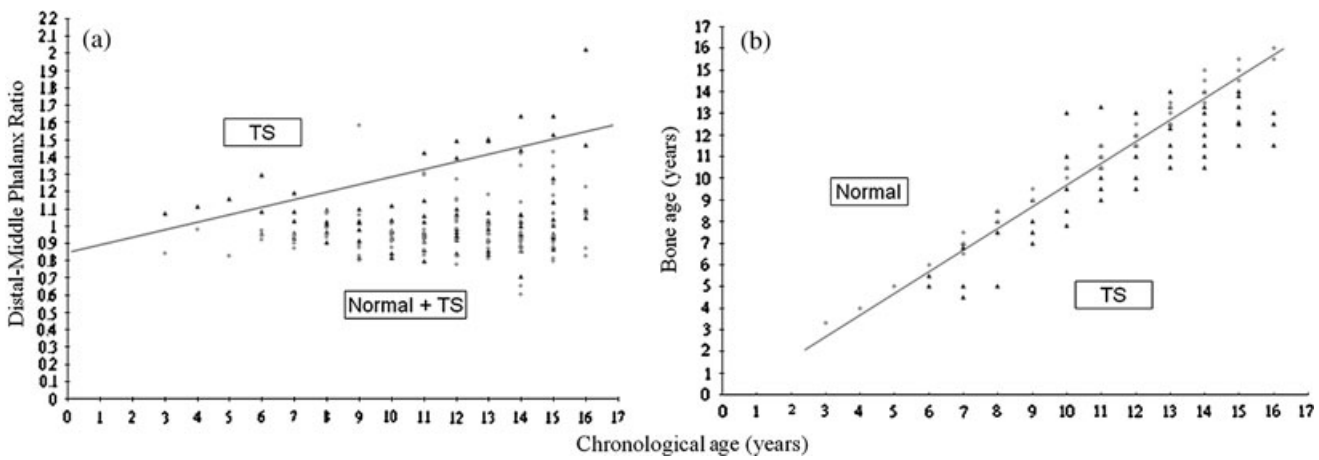

Fig. 6 Two-stage screening method (TSSM) used in combination with optimal programming: best classification. (a) First stage (▲, TS D-M ratio [L]; •, normal D-M [L]); (b) second stage (▲, TS BA; •, normal BA). (a) $y = 0.0421x + 0.88$; (b) $y = 0.99x - 0.36$. BA, bone age; DM, distal-middle; TS, Turner syndrome.

Table 2 Parameters a, b, c, and d vs sensitivity and specificity

a	b	c	d	Sensitivity	Specificity
0.0381	0.89	0.99	–0.36	0.80612	0.90816
0.0381	0.9	0.99	–0.36	0.80612	0.90816
0.0401	0.87	0.99	–0.36	0.80612	0.90816
0.0401	0.88	0.99	–0.36	0.80612	0.90816
0.0401	0.89	0.99	–0.36	0.80612	0.90816
0.0411	0.86	0.99	–0.36	0.80612	0.90816
0.0411	0.87	0.99	–0.36	0.80612	0.90816
0.0411	0.88	0.99	–0.36	0.80612	0.90816
0.0411	0.89	0.99	–0.36	0.80612	0.90816
0.0411	0.9	0.99	–0.36	0.80612	0.90816
0.0421	0.85	0.99	–0.36	0.80612	0.90816
0.0421	0.86	0.99	–0.36	0.80612	0.90816
0.0421	0.87	0.99	–0.36	0.80612	0.90816
0.0421	0.88	0.99	–0.36	0.80612	0.90816
0.0421	0.89	0.99	–0.36	0.80612	0.90816
0.0421	0.9	0.99	–0.36	0.80612	0.90816

Next, scatter plots 1 and 2 were divided depending on the combination of the coefficients a, b, c, and d determined by optimal programming. Finally, satisfactory results were obtained: sensitivity was 0.806 and specificity was 0.908. In the future, using TSSM with fuzzy logic, patients with TS may be identified using data obtained from examination of roentgenograms of the hand and wrist.

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References

1 Lippe BM. Turner syndrome. In: Sperling MA (ed.). Pediatric Endocrinology, 1st edn. WB Saunders, PA, USA, 1996; 387–416.
2 Finby N, Archibald RM. Skeletal abnormalities associated with gonadal dysgenesis. *Am. J. Roentgenol. Radium Ther. Nucl. Med*. 1963; **89**: 1222–35.
3 Kosowicz J. The roentgen appearance of the hand and wrist in gonadal dysgenesis. *Am. J. Roentgenol. Radium Ther. Nucl. Med*. 1965; **93**: 354–61.
4 Poznanski AK. *The Hand in Radiologic Diagnosis*, 2nd edn. WB Saunders, PA, USA, 1984.
5 Turner HH. A syndrome of infantilism, congenital webbed neck, and cubitus valgus. *Endocrinology* 1938; **23**: 566–74.
6 Vakili R, Horri M, Mothaghi H. Body mass index in Turner syndrome before and after growth hormone therapy. *Int. J. Endocrinol. Metab*. 2004; **2**: 78–81.
7 Archibald RM, Finby N, Vito FD. Endocrine significance of short metacarpals. *J. Clin. Endocrinol. Metab*. 1959; **19**: 1312–22.
8 Baker DH, Berdon WE, Morishima A, Conte F. Turner's syndrome and pseudo-Turner's syndrome. *Am. J. Roentgenol. Radium Ther. Nucl. Med*. 1967; **100**: 40–7.
9 Bloom RA. The metacarpal sign. *Br. J. Radiol*. 1970; **43**: 133–35.
10 Kosowicz J. The carpal sign in gonadal dysgenesis. *J. Clin. Endocrinol. Metab*. 1962; **22**: 949–52.
11 Harper HAS, Poznanski AK, Garn SM. The carpal angle in American populations. *Invest. Radiol*. 1974; **9**: 217–21.
12 Bechtold S, Rauch F, Noelle V, Donhauser S, Neu CM, Schwarz HP. Musculoskeletal analyses of the forearm in young women with Turner syndrome: A study using peripheral quantitative computed tomography. *J. Clin. Endocrinol. Metab*. 2001; **86**: 5819–23.
13 Tauber M, Lounis N, Coulet J, Baunin C, Cahuzac JP, Rochiccioli P. Wrist anomalies in Turner syndrome compared with Leri-Weill dyschondrosteosis: A new feature in Turner syndrome. *Eur. J. Pediatr*. 2004; **163**: 475–81.
14 Garn SM, Hertzog KP, Poznanski AK, Nagy JM. Metacarpophalangeal length in the evaluation of skeletal malformation. *Radiology* 1972; **105**: 375–81.