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REVIEW

Diagnostic value of serum *IGF-1* and *IGFBP-3* in growth hormone deficiency: a systematic review with meta-analysis

Yi Shen · Jian Zhang · Yanhong Zhao · Yu Yan · Yanmei Liu · Jin Cai

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Abstract Serum *insulin-like growth factor-1* (*IGF-1*) and *insulin-like growth factor binding protein-3* (*IGFBP-3*) are conventionally considered available for the diagnosis of growth hormone deficiency (GHD), but the results about their diagnostic values are inconsistent among some recent epidemiological studies. The aim of this study is to assess the diagnostic values of serum *IGF-1* and *IGFBP-3* for GHD by conducting a systematic review and meta-analysis. Studies on serum *IGF-1* and *IGFBP-3* used in GHD diagnosis were systematically searched from databases PubMed, EMBASE, and CNKI (up to December 2013). Characteristics of the studies and data were independently collected according to the inclusion criteria by two authors. The quality of included studies was assessed using quality assessment of diagnostic accuracy studies (QUADAS). Both sensitivity (SEN) and specificity (SPE) of *IGF-1* and *IGFBP-3* in GHD diagnosis were estimated on statistical software Meta-DiSc and Stata. A total of 12 studies were included for the final analysis. *IGF-1* had SEN of 0.66, SPE of 0.69, positive likelihood ratio (PLR) of 2.48, negative likelihood ratio (NLR) of 0.51, area under the summary receiver operating characteristic curve (SROC) of 0.78, and Q^* value of 0.72. Serum *IGFBP-3* had SEN of 0.50, SPE of 0.79, PLR of 2.69, NLR of 0.64, area under SROC of 0.80, and Q^* value of 0.73.

Conclusion: Serum *IGF-1* and *IGFBP-3* are useful for the diagnosis of GHD and can be utilized as auxiliary diagnosis indexes for provocative test.

Keywords Growth hormone deficiency · *Insulin-like growth factor-1* · *Insulin-like growth factor combination protein-3* · Diagnostic value · Meta-analysis

Abbreviations

AUC	Area under the SROC curve
CI	Confidence interval
CNKI	China National Knowledge Infrastructure
CNS	Central nervous system
DOR	Diagnostic odds ratio
EMBASE	Biomedical Database
FN	False-negative
FP	False-positive
GH	Growth hormone
GHD	Growth hormone deficiency
IRMA	Immunoradiometric assay
ISS	Idiopathic short stature

Yi Shen and Jian Zhang contributed equally to this work and should be regarded as joint first authors.

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Y. Shen · J. Zhang
Department of Epidemiology and Medical Statistics, Nantong University, Nantong, Jiangsu, China

Y. Shen
e-mail: stata70@sohu.com

J. Zhang
e-mail: 269109654@qq.com

Y. Zhao
Department of Epidemiology and Medical Statistics, Lanzhou University, Lanzhou, Gansu, China
e-mail: 1592720858@qq.com

Y. Yan
Ruici Hospital, Nantong, Jiangsu, China
e-mail: 908009804@qq.com

Y. Liu
Department of Epidemiology and Medical Statistics, Nantong University, Nantong, Jiangsu, China
e-mail: 137849898@qq.com

J. Cai (✉)
Affiliated Hospital of Nantong University, Nantong 226001, Jiangsu, People's Republic of China
e-mail: jsntcaijin@qq.com

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IGF-1	*Insulin-like growth factor-1*
IGFBP-3	*Insulin-like growth factor binding protein-3*
NLR	Negative likelihood ratio
PLR	Positive likelihood ratio
QUADAS	Quality assessment of diagnostic accuracy studies
RDOR	Relative diagnostic odds ratio
RIA	Radioimmunoassay
r_s	Spearman's rank correlation coefficient
SEN	Sensitivity
SPE	Specificity
SROC	Summary receiver operating characteristic curve
TN	True-negative
TP	True-positive

Introduction

Growth hormone deficiency (GHD) can be conventionally diagnosed using two provocative growth hormone (GH) tests, which are considered as the gold standard [12] [1, 12]. However, these tests are invasive, non-physiological, expensive, and hazardous [4, 9, 19]. Especially, children and their parents could miss the optimal treatment time owing to the difficulty in applying the hazardous provocative tests in repeated blood samples. In addition to the provocative GH tests, the complement for identifying children with GHD is the measurement of serum *insulin-like growth factor-1* (*IGF-1*) and *IGF binding protein-3* (*IGFBP-3*).

However, studies on the evaluative values of serum *IGF-1* and *IGFBP-3* levels in GHD diagnosis are controversial. For instance, Jensen RB et al. found that the sensitivity in GHD diagnosis was 90 % for *IGF-1* and 81 % for *IGFBP-3* [17]. Boquete HR et al. reported that *IGF-1* was better than *IGFBP-3* in GHD diagnosis [3], but in other reports, neither *IGF-1* nor *IGFBP-3* was important in GHD diagnosis for children with short stature [9] and they cannot be used in routine endocrine practice [13, 20].

Therefore, we performed a meta-analysis involving 12 eligible studies to evaluate serum *IGF-1* and *IGFBP-3* levels and their diagnostic values for GHD.

Methods

Study selection criteria for meta-analysis

The published studies on the serum *IGF-1* and *IGFBP-3* levels and their applications in GHD diagnosis were searched from the databases PubMed, Biomedical Database (EMBASE), and China National Knowledge Infrastructure (CNKI) using the combination of terms of "short stature," "dwarfism," "nanism," "growth hormone deficiency," "*Insulin-like growth factor-1*," "*IGF-1*," "*Insulin-like growth factor binding protein-3*," "*IGFBP-3*," and "diagnostic value." The date of the publications we searched was up to December 2013. The search strategies were (short stature or dwarfism or nanism or growth hormone deficiency or GHD) and (*Insulin-like growth factor-1* or *IGF-1* or *Insulin-like growth factor binding protein-3 or IGFBP-3*) and (diagnostic value).

The inclusion criteria were the following: (1) studies on serum *IGF-1* and *IGFBP-3* and their diagnostic values for GHD among children; (2) cases were GHD and controls were non-GHD or idiopathic short stature (ISS); (3) all GHD patients were confirmed by two hormone provocative tests; (4) the true-positive (TP), false-positive (FP), false-negative (FN), and true-negative (TN) values of the diagnostic tests for GHD were described or could be calculated; and (5) studies with the same or overlapped data by the same authors, studies with the most recent publication, or studies with a larger sample size.

Data collection and quality assessment

Detailed information from each included studies was recorded by two authors independently, and the collected data from each study were filled in 2×2 tables. Any inconsistency between the two authors was resolved by discussion or consulting with other authors until a consensus was reached. The methodological quality of the included studies was assessed using quality assessment of diagnostic accuracy studies (QUADAS) [33], which was composed of 14 items and used to assess the quality of studies of diagnostic accuracy included in systematic reviews.

Statistical analyses

The meta-analysis was performed on statistical software Meta-DiSc [34] and Stata 10.0 [6] by calculating the pooled sensitivity (SEN), pooled specificity (SPE), positive likelihood ratio (PLR), negative likelihood ratio (NLR), and their 95 % confidence interval (CI). The study results were summarized using a summary receiver operating characteristic curve (SROC) [27, 30]. The respective area under the SROC curve (AUC) and Q point value (Q*), where SEN=SPE, were estimated. Generally, AUC >0.96 is regarded as excellent, 0.93–0.96 as very good, and 0.75–0.92 as good, but AUC <0.75 can be still reasonable [18].

Publication bias was inspected using Deek's funnel plot [8]. The threshold effect conductive to heterogeneity was checked using Spearman's correlation coefficient (r_s) of log (SEN) and log (1-SPE) [14], while the non-threshold effect was checked using Cochran's Q test for diagnostic odds ratio (DOR). If heterogeneity was significant ($p \leq 0.05$), a random

effects model was selected in the calculation. Otherwise, a fixed effects model was used [11].

The possible sources of heterogeneity among studies were explored using meta-regression analysis. According to standard methods, the change in diagnostic precision in the study per unit increase of covariate was analyzed using calculation of relative DOR (RDOR) [31].

Results

Study characteristics

According to our search strategies, a total of 484 studies were retrieved from the initial search and then 48 studies were selected for further evaluation after the first screening of titles and abstracts. After detailed screening, 12 studies were finally included in our meta-analysis [1, 3, 5, 4, 7, 9, 13, 16, 19, 22, 25, 28]. The process of study selection is shown in Fig. 1.

The primary characteristics of the selected studies are listed in Table 1. Serum *IGF-1* was detected in 770 patients and 863 controls and serum *IGFBP-3* in 736 patients and 860 controls. The included studies involved 8 cross-sectional studies [1, 3, 5, 7, 9, 13, 16, 22] and 4 prospective cohort or case–control studies [4, 19, 25, 28]. ISS was selected for control in 7 studies [1, 3, 5, 4, 9, 25, 28] and non-GHD in 5 studies [7, 13, 16, 19, 22]. Radioimmunoassay (RIA) was used in 4 studies [19, 22, 25, 28], while immunoradiometric assay (IRMA) was used in 8 studies [1, 3, 5, 4, 7, 9, 13, 16]. The basic characteristics (TP, FP, TN, and FN values) are also shown in Table 1.

Quality evaluation of the selected studies

The methodological quality assessment for the included studies is shown in Fig. 2. The bars of different colors indicated the proportions of "yes, no, or unclear" for the 14 QUADAS items. Seven items met the level of 50 %.

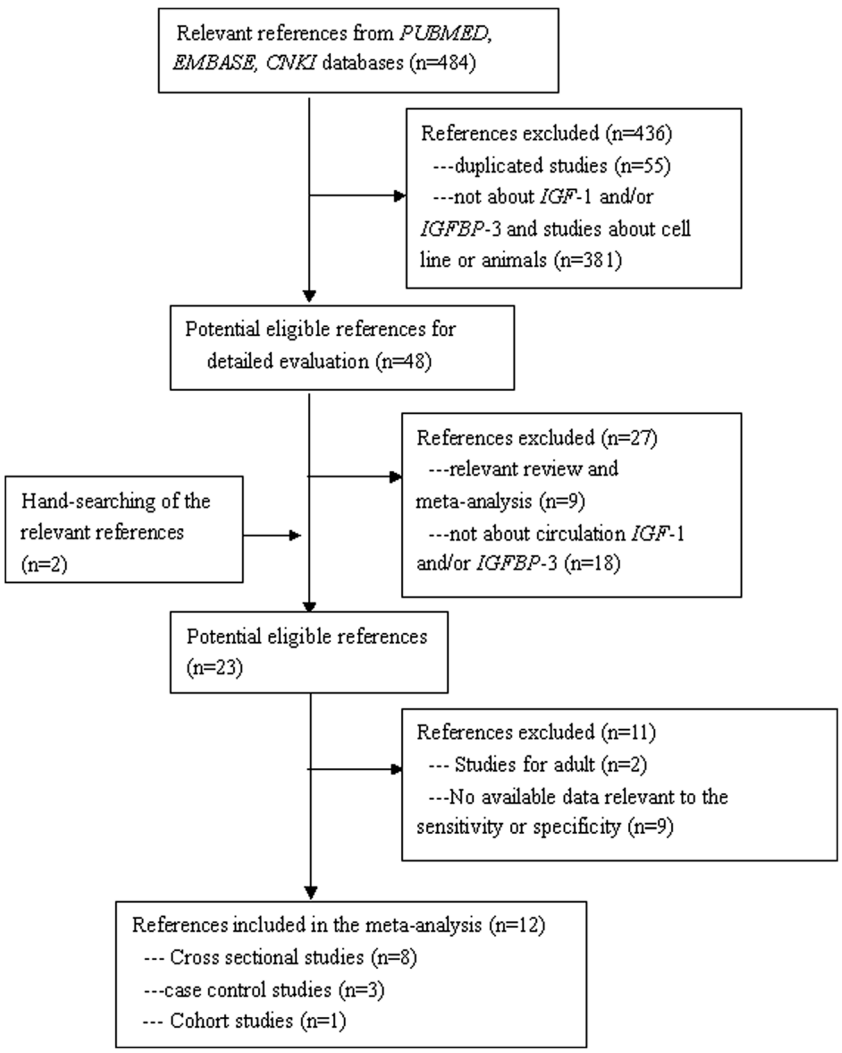

Fig. 1 Flow diagram of the detailed process of study selection in the current study

Table 1 Characteristics of studies included in the meta-analysis

Number	Year	First author	Method	Study design	Control selection	*IGF-1*							*IGFBP-3*						
						Sample size		TP	FP	FN	TN	SEN	SPE	Sample size		TP	FP	FN	TN	SEN	SPE
						Patients	Controls							Patients	Controls						
1 [1]	2001	Audi L	IRMA	Cross-sectional study	ISS	25	54	8	5	17	49	0.32	0.91	25	54	7	3	18	51	0.28	0.94
2 [3]	2003	Boquete HR	IRMA	Cross-sectional study	ISS	34	32	23	1	11	31	0.68	0.97	20	30	18	12	2	18	0.9	0.6
3 [5]	2005	Cianfarani S	IRMA	Cross-sectional study	ISS	72	59	50	11	22	48	0.69	0.81	52	58	14	0	38	58	0.27	1
4 [4]	2002	Cianfarani S	IRMA	Case–control study	ISS	33	56	24	3	9	53	0.73	0.95	33	56	10	1	23	55	0.3	0.98
5 [7]	2004	Darendeliler F	IRMA	Cross-sectional study	NGHD	50	17	35	0	15	17	0.7	1	50	17	34	0	16	17	0.68	1
6 [9]	2010	Galluzzi F	IRMA	Cross-sectional study	ISS	70	137	23	13	47	124	0.33	0.91	70	137	20	59	50	78	0.29	0.57
7 [13]	2009	Haghshenas Z	IRMA	Cross-sectional study	NGHD	17	64	6	12	11	52	0.35	0.81	17	64	2	4	15	60	0.12	0.94
8 [16]	2000	Jaruratanasirikul S	IRMA	Cross-sectional study	NGHD	24	36	24	12	0	24	1	0.67	24	36	24	12	0	28	1	0.7
9 [19]	1997	Juul A	RIA	Case–control study	NGHD	61	142	42	32	19	110	0.69	0.77	61	142	35	21	26	121	0.57	0.85
10 [22]	1999	Mitchell	RIA	Cross-sectional study	NGHD	148	158	92	84	56	74	0.62	0.47	148	158	22	3	126	155	0.15	0.98
11 [25]	2001	Ranke MB	RIA	Case–control study	ISS	187	205	140	139	47	66	0.75	0.32	187	76	125	38	62	38	0.67	0.5
12 [28]	1998	Rikken B	RIA	Cohort study	ISS	49	32	45	17	4	15	0.92	0.47	49	32	47	25	2	7	0.96	0.22

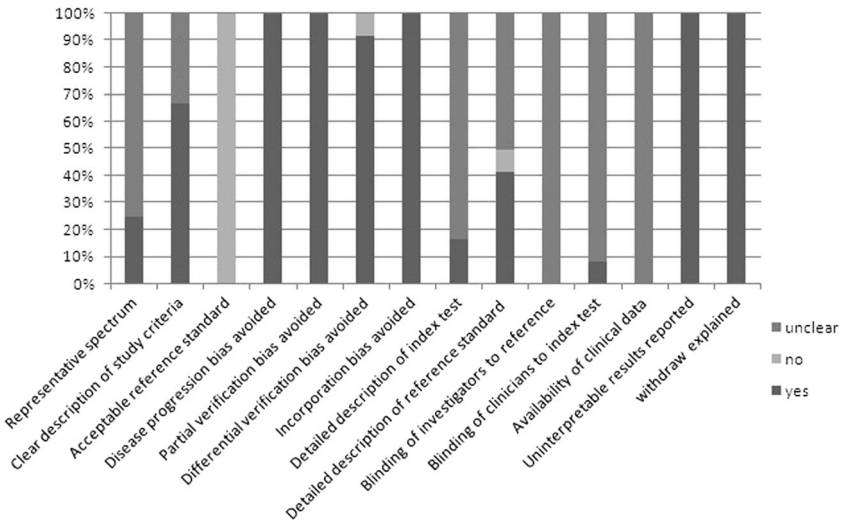

Fig. 2 Quality evaluation results of incorporated documents

Diagnostic values of serum ***IGF-1*** and ***IGFBP-3***

In general, serum *IGF-1* had a pooled SEN of 0.66 (95 % CI, 0.63–0.70), SPE of 0.69 (0.66–0.72), PLR of 2.48 (1.72–3.57), and NLR of 0.51 (0.39–0.66) (Fig. 3). Serum *IGFBP-3* had a pooled SEN, SPE, PLR, and NLR of 0.49 (95 % CI, 0.45–0.52), 0.79 (0.76–0.82), 2.58 (1.63–4.09), and 0.68 (0.55–0.84), respectively (Fig. 4). *IGF-1* had AUC of 0.78 and Q^*=0.71; *IGFBP-3* had AUC of 0.80 and Q^*=0.73 (Fig. 5).

The r_s of *IGF-1* and *IGFBP-3* were 0.273 (p=0.391) and 0.559 (p=0.059), respectively, indicating no threshold effect. Cochran's Q values of DOR of *IGF-1* and *IGFBP-3* were 65.70 and 79.66, respectively, indicating that heterogeneity was caused by non-threshold effect. Therefore, the random effects model was selected for the meta-analysis.

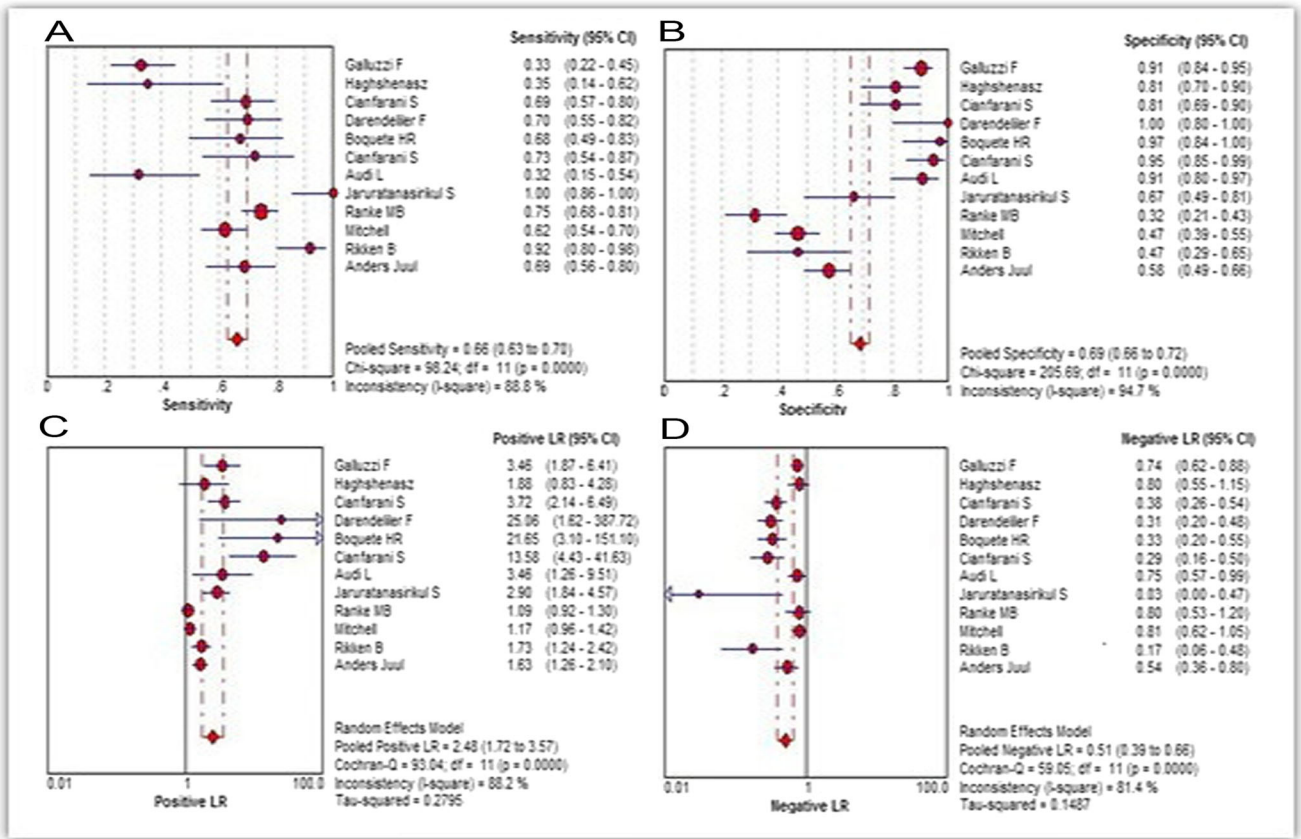

Fig. 3 Forest plot of *IGF-1* for the diagnosis of GHD. **a** Pooled SEN. **b** Pooled SPE. **c** Pooled PLR. **d** Pooled NLR

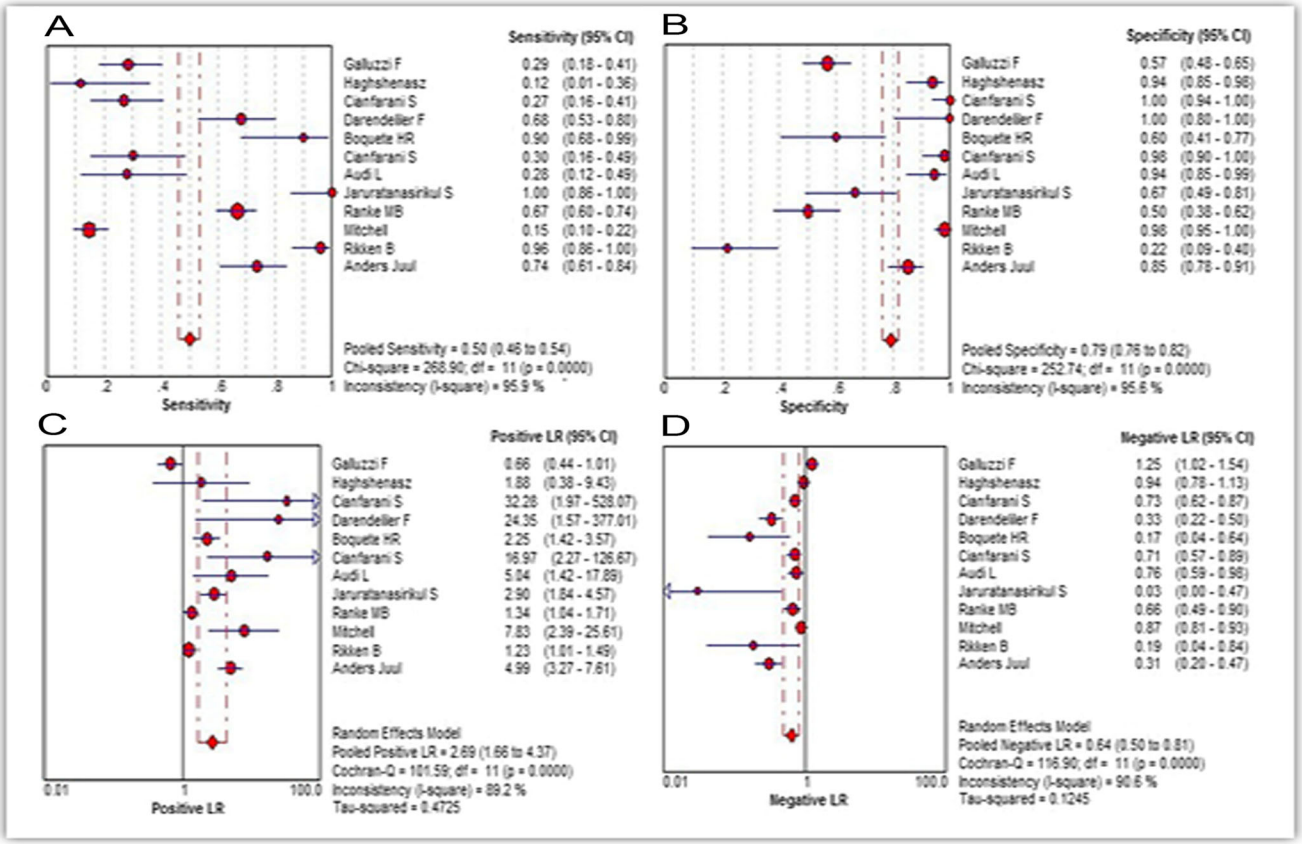

Fig. 4 Forest plot of *IGFBP-3* for the diagnosis of GHD. **a** Pooled SEN. **b** Pooled SPE. **c** Pooled PLR. **d** Pooled NLR

The meta-regression analysis indicates that the heterogeneity of *IGF-1* resulted from study design, selection of control group, sample size, and use of different assays. However, the accuracy of IRMA was 13.99 times higher compared with RIA (RDOR=13.99; 95 % CI, 1.41–133.31), indicating that use of different assays could be one potential source of heterogeneity. After removal of four RIA studies, the pooled SEN, SPE, PLR, and NLR (95 % CI) increased to 0.59 (0.54–0.65), 0.87 (0.84–0.90), 4.13 (2.56–6.64), and 0.46 (0.32–0.67), respectively, with AUC=0.90 and Q *=0.83. Other factors such as study design, control selection, and sample size had no significant effect on SEN or SPE (data not

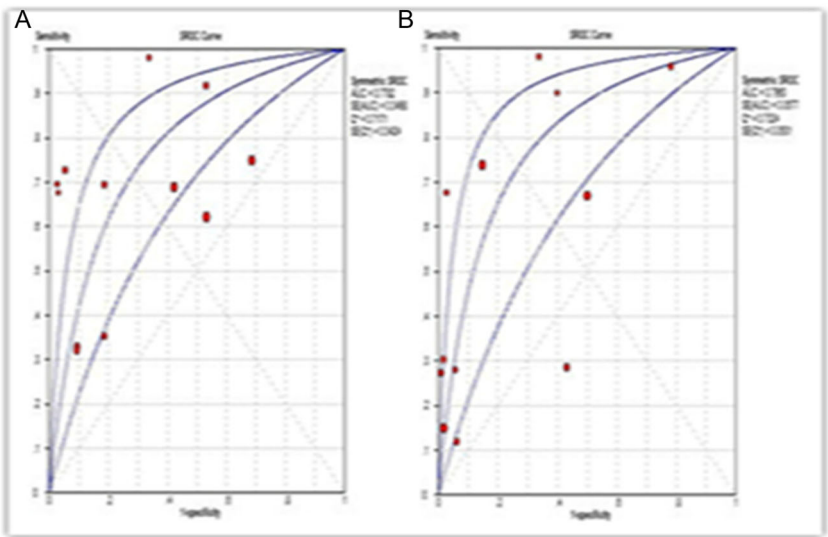

Fig. 5 SROC curves of *IGF-1* (**a**) and *IGFBP-3* (**b**) for the diagnosis of GHD. Heterogeneity assessment and meta-regression analysis

presented). The heterogeneity of *IGFBP-3* resulted from study design, control selection, sample size, and assay, but these factors did not affect SEN or SPE.

Publication bias

The asymmetry test for Deek's funnel plot (Fig. 6) showed that there was publication bias for *IGF-1* (p=0.008), but there was no evident publication bias for *IGFBP-3* (p=0.194)

Discussion

The diagnosis of GHD in short-statured children is very important because GHD may be accompanied with other pituitary hormone deficiency and/or central nervous system (CNS) tumors and responds better to GH treatment, compared to other causes of short stature [13]. Furthermore, appropriate replacement therapy enables the GHD child to achieve a normal adult height.

However, the diagnosis of GHD is a multifaceted process requiring comprehensive clinical anthropometric, endocrine, and neuroradiological assessment. Several pitfalls may be encountered in the diagnosis of GHD. If the patient is deficient in thyroxin, tests of GH secretion should be postponed until the deficiency is resolved; otherwise, GH secretion may be subnormal merely because of the hypothyroidism. If GHD is suspected in a prepubertal patient with a growth pattern resembling constitutional delay of growth and development, sex steroid priming before testing of GH secretion has been recommended by some investigators [10].

Serum levels of *IGF-1* and *IGFBP-3* reflect the endogenous GH secretion in healthy children and exhibit little diurnal variation, which makes them potential candidates for screening of GHD [19]. However, both SEN and SPE of serum *IGF-1* and *IGFBP-3* varied greatly in previous studies [1, 3, 5, 4, 7, 9, 13, 16, 19, 22, 25, 28].

Measurement of *IGF-1* has been introduced into GHD diagnosis since 1982, but it has several limitations, such as its dependency on age, nutritional status, and pubertal status [23]. Our results showed that the pooled SEN and SPE of *IGF-1* are 66 and 69 %, respectively, which are different from previous studies: SEN of 82 % and SPE of 80 % [26, 29] or SEN of 34 % and SPE of 72 % [32]. The difference of sensitivity and specificity of *IGF-1* levels in the diagnosis of GHD between our study and previous studies may be attributed to such factors as the ages of the children in the studies, differences in the severity of GHD, and different sample sizes.

Measurement of *IGFBP-3* was confirmed useful in the diagnosis of GHD children later and suggested to be an excellent method to discriminate between GHD children and short-statured children with normal GH level [2]. *IGFBP-3* is particularly useful in young children, in whom serum *IGF-1* levels are in the same range in GHD and non-GHD [19]. But it has been disputed by others for the low SEN in spite of high SPE [15, 24]. In our study, the pooled SEN and SPE of *IGFBP-3* are 50 and 79 %, respectively.

The diagnostic characteristics are summarized in the SROC curves. The AUCs were determined to assess the discriminating ability [30]. In our study, AUCs were larger than 0.75 (0.78, 0.80), indicating that *IGF-1* and *IGFBP-3* had acceptable accuracy in GHD diagnosis.

IGF-1 had higher SEN and AUC, compared with *IGFBP-3* [13, 17, 21], suggesting the usefulness of *IGF-1*. Our study showed that *IGF-1* had higher *SEN* as well as that *IGFBP-3* had larger AUC and Q^* value suggesting that serum *IGFBP-3* can also be used as a reliable and simple screening indicator in the work-up of short-statured children.

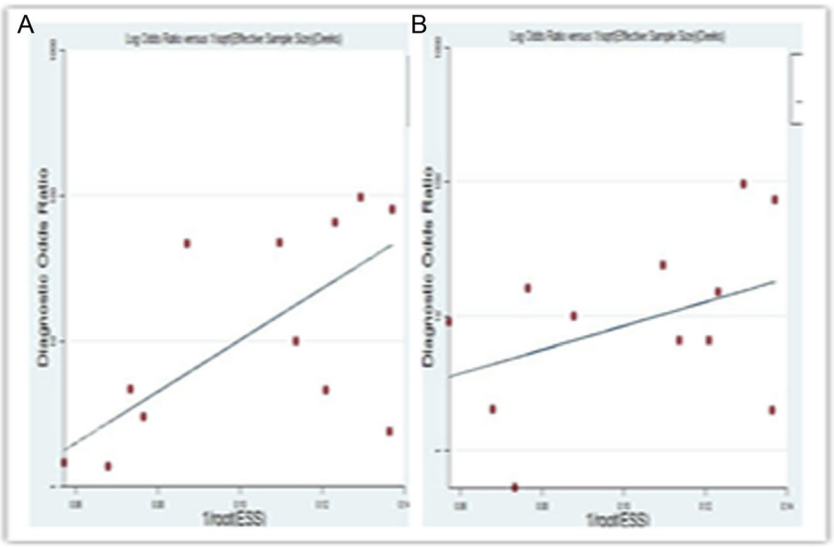

Fig. 6 Diagram of publication bias. Deek's funnel plots for studies on serum *IGF-1* (**a**) and serum *IGFBP-3* (**b**)

Since GH testing is time-consuming, invasive, costly, and even hazardous, simple methods are necessary to identify those short children in whom GH testing is most appropriate. Our meta-analysis indicated that both *IGF-1* and *IGFBP-3* had high SPE (0.69 vs. 0.79) but low SEN (0.66 vs. 0.50). The high SPE but low SEN suggested that in deciding whether or not a short child should be subjected to GH testing, the positive result should undergo provocative tests. Although *IGF-1* and *IGFBP-3* could not replace the provocative tests in the diagnosis of GHD, they could be combined as an auxiliary method and a complementary tool to avoid repeated provocative tests.

To our knowledge, this is the first systematic review and meta-analysis in evaluating the values of serum *IGF-1* and *IGFBP-3* in GHD diagnosis. The strength of our study is that it explores the reasons for heterogeneity rather than the computation of a single summary measure of serum *IGF-1* or *IGFBP-3*. However, this meta-analysis has some limitations. First, Deek's funnel plot asymmetry test showed publication bias in serum *IGF-1*. Unpublished studies from conferences were not included and the quality control standards were not completely uniform. These might cause publication bias. Second, subgroup analysis was restricted by limited original data.

In conclusion, serum *IGF-1* and *IGFBP-3* had clinically acceptable SEN and SPE in the diagnosis of GHD and thus may be helpful in this field.

Conflict of interest None.

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