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Change in spinal height following correction of adolescent idiopathic scoliosis

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Title: Change in Spinal Height Following Correction of Adolescent Idiopathic Scoliosis

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Abstract: Background Context
Corrective surgery for adolescent idiopathic scoliosis (AIS) leads to vertical growth arrest of the instrumented spine. This might be offset by the immediate gain in spinal height (SH) as a result of correction of the curvature.

Purpose
To identify predictors of gain in spinal height following corrective surgery for AIS. We present a unique model to predict height gain prior to intervention, which could contribute to the preoperative counselling and consenting process.

Study Design
This was a retrospective case series. All surgeries were performed by one of four substantive paediatric spinal surgeons within a single regional centre over a three-and-a-half year period.

Patient Sample
104 patients who had instrumented posterior spinal fusion for AIS were included. There were 93 females and the age range was 11 to 17 years. All patients had posterior instrumented fusion using rods and anchors (pedicle screws +/- hooks).

Outcome Measures
Postoperative spinal height was the primary outcome measure. SH (C7 to L5) and Cobb angles were measured from a pre-and-postoperative standing X-ray of each patient.

Methods
Variables associated with patients (demographic and radiological) and the surgical constructs were analysed for predictability of height gain. A model was derived including only significant predictors of substantive importance using hierarchical regression methods.

Cross-validation procedures verified the adequacy of the model fit. Analysis was performed using SPSS version 20.0.

Results

The major curve was thoracic in 90% of cases. The number of vertebrae fused ranged from 5 to 15. The average preoperative Cobb angle was 66°, with an average correction of 45°. The average change in SH was 4.66cm (SD 2.13 cm). The model presented included preoperative height, preoperative Cobb angle and number of vertebrae within the construct, with coefficients of 1.00 (95% CI: 0.90, 1.09), 0.067 (95% CI: 0.039, 0.095), and 0.26 (95% CI: 0.11, 0.41) respectively. This model had an adjusted-R2value of 0.83 and a R2 for prediction of 0.79; and can be shown to have similar predictive capability as a model comprising a wider range of predictors.

Conclusions

The greatest postoperative height values following posterior spinal fusion for AIS could be expected from a patient with greater preoperative height and Cobb angle, and whose construct spans a large number of vertebrae.

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Many thanks for giving us the further opportunity to revise our manuscript. We have revised the manuscript in the hope of addressing the outstanding concerns. We hope that you find this revision suitable for publication in The Spine Journal. We remain happy to address any further suggestions.

We have copied the review comments and responded (in red text) to each:

1. Please limit all significant digits following the decimal to two in the text and tables. The only exception can be p-values up to 0.001 and then <0.001 as indicated.
We have applied this throughout.

2. The residuals plot is unnecessary and can be removed from a revised work.
The plot itself has been removed.

3. The results and discussion are still overly technical for this clinical journal. Please focus on clinical message for this audience. Limit discussion to five paragraphs and less than 1,000 words in a revised work. first paragraph is qualitative restatement of findings and importance of clinical message, second contrasts current findings with prior work, third presents limitations, fourth discusses next steps and future research, fifth paragraph is the conclusion.
We have followed this advice as far as possible. One paragraph of the results remains technical but only emphasises the complex validation procedures undertaken. The discussion is now just over 500 words. The discussion presents the clinical message and restatement of findings in two paragraphs. The conclusion is separate to the discussion.

4. I am still at a loss to understand the clinical impact of this research and how it can translate into practice. Please describe this in the revised work and be as succinct and clear as possible. This is critical to the acceptance of this work at the time of subsequent review. There must be a clear message of clinical utility with practice implications for our journal's audience.
The introduction and first paragraph of the discussion highlight the clinical importance and practice implications of this work. The discussion and results are more succinct than before.

CHANGE IN SPINAL HEIGHT FOLLOWING CORRECTION OF ADOLESCENT IDIOPATHIC SCOLIOSIS

Abstract

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The greatest postoperative height values following posterior spinal fusion for AIS could be expected from a patient with greater preoperative height and Cobb angle, and whose construct spans a large number of vertebrae.

Introduction

Patients with adolescent idiopathic scoliosis are known to have abnormal anthropometric measurements (1-8). For instance, AIS females are taller than age-matched healthy controls, and a surgical procedure which is likely to increase their height suddenly and significantly could therefore have an unwanted psychological effect on a patient who is likely to be body conscious already (9-11). It is not surprising that the cosmetic concern caused by this deformity is a reason for patients to seek corrective surgery (12-14). However, correction involves fusion which does halt vertical growth (15). Winter (16) proposed a formula to determine the amount of remaining spinal growth (which would be lost) within the fused segments (0.7mm/segment per year of remaining growth). Growth arrest must therefore be a concern, especially in the young where fusion would have a significant effect on final height (6). It is therefore reassuring that publications have confirmed height gain as a result of curve correction (17-20), but none have predicted this gain ahead of intervention. If AIS patients are concerned with their appearance, then preoperative advice regarding expected change in appearance is important, if not essential. This is emphasized by one of the authors' experience of an AIS patient asking "How much taller will I be after the operation?". We looked at predictors of height gain that would be available to the surgeon ahead of intervention and thereupon present a predictive model.

Method

Patients

Surgery was performed by four substantive paediatric spinal surgeons within a specialist children's hospital. Patients were selected for inclusion if they met the following criteria:

1. Instrumented posterior spinal fusion for AIS
2. A preoperative and postoperative whole spine X-ray performed within 6 months of each other

However, if either of a patient’s preoperative or postoperative X-rays were lacking in reference points for measurement (radiopaque ruler, indistinct vertebral body), he/she was excluded.

Radiological measurement

Our standard whole spine radiographic study comprises a standing posterior-anterior and lateral X-ray of a patient standing alongside a radio-opaque ruler. The authors have measured spinal height between the centre of the C7 and L5 bodies on the lateral X-ray (Figure 1). The centre of the vertebral body is the intersection of the diagonals through the body. T1 body was not reliably visible due to variable shoulder height, and therefore C7 was chosen. Spinal height between C7 and L5 was measured to the millimetre. Change in height was the difference in spinal height between the preoperative and postoperative X-ray. Cobb (21) angles were measured on the posterior-anterior X-ray. Scoliotic curves were classified according to the Lenke (22) method.

Statistical analysis

Development of predictive model

Analysis was conducted on the sample to investigate possible predictors of change in spinal height. The following variables were initially considered: age at operation; gender; screw density (the percentage of the maximum number of screws the construct would allow if all pedicles within the construct contained a screw); system design (related to the design of the rod-screw connectors and classified as side or top loading systems); number of crosslinks between rods; number of vertebrae included in the construct; Lenke classification of curve type (categorised as thoracic or thoraco-lumbar/lumbar); preoperative Cobb angle; and preoperative height (C7 to L5).

Postoperative height (C7 to L5), to be adjusted for preoperative height and other factors, was considered to be the primary outcome for the model.

A sequential (hierarchical) regression procedure was utilised to derive an optimum set of predictors. Following standard procedures, variables considered to be of greater importance were entered on later steps. Four blocks were devised. The first block comprised the demographic variables: age and gender. The second block comprised procedural variables, including: screw density, system design, number of vertebrae included in the construct, and number of crosslinks. The third block comprised variables relating to the patient condition, including: Lenke classification and preoperative Cobb angle. Preoperative height was entered individually in the final block. Within each of the first three blocks, all variables were entered using a backward elimination modelling strategy. Forced entry was used for the final block. The sensitivity of the blocking to the selection of the set of variables remaining in the presented model was tested by varying the composition of the blocks; in particular the order of entry of the key variables of preoperative Cobb angle and preoperative height.

Parameter coefficients and associated 95% confidence intervals, *p*-values and semipartial correlation coefficients (effect sizes representing the proportion of the variance in the outcome associated uniquely with each variable) were reported for all variables remaining in the presented model, plus the R^2 statistic, representing the proportion of variance attributable to the model. Values of semipartial correlation coefficients associated with specific variables were used to develop the most economical model without substantive reductions in predictive capability. Regression assumptions were checked using residual plots.

Model validation

The adjusted-R^2 statistic of the presented model was derived to estimate the proportion of variance which would be accounted for if the prediction equation was derived in the population from which the sample was drawn. The suitability of the regression function as a predictive model was determined by evaluation of an approximate R^2 for prediction, R^2_{PRED}. This statistic is a measure of how well the model is likely to predict responses in a new sample, and is based on the prediction error sum of squares (PRESS) statistic derived from deleted residuals. Good model predictive capability is indicated by a close correspondence between the adjusted-R^2 and R^2_{PRED} values for the model. The existence of outlying values in the sample, which may have implications for the portability of the model, was assessed by determination of standardised residuals, leverage values and Cook's distances for each patient.

All analysis was conducted using SPSS (Version 20.0)

Results

104 consecutive patients who were operated on between August 2009 and December 2012 were included in the analysis. Nine patients were excluded as a result of incomplete radiographic information (i.e. missing lateral view, lack of radio-opaque ruler, and 6 months or more between X-rays). A descriptive summary of patient- and instrument-construct characteristics is given in Table 1. Fifteen of the 104 patients had radiographs between 3 months and 6 months apart; the rest being separated by less than 3 months. Instrumentation in all patients was in the form of anchors (pedicles screws +/- hooks) and rods.

Actual postoperative height gain varied from 0.50 to 9.90 cm, with a mean height gain of 4.66 cm (SD 2.13 cm). 85.6% and 37.5% of patients gained up to an inch (2.54cm) or two respectively.

The modelling strategy resulted in a final economical predictive model including number of vertebrae, preoperative Cobb angle and preoperative height as predictors of postoperative height. The following relationship between the outcome and predictors was derived:

Postoperative height (cm) = -2.27 + 0.26 x (number of vertebrae) + 0.067 x (preoperative Cobb angle) + 1.00 x (preoperative height in cm)

95% confidence intervals were calculated for the above parameter estimates; these were 0.11-0.41 for number of vertebrae, 0.039-0.095 for preoperative Cobb angle, and 0.90-1.09 for preoperative height in cm.

In the above model, all the variables were significantly associated with the outcome (p=0.001 for number of vertebrae; p<0.001 for preoperative Cobb angle; p<0.001 for preoperative height).Examination of semipartial correlation coefficients revealed that preoperative height was of the greatest importance in the model (*sr*=0.82), with lesser contributions from the number of vertebrae in the construct (*sr*=0.19) and preoperative Cobb-angle (*sr*=0.18). The model had an adjusted-R^2 statistic of 0.82 and $aR^2_{PRED}$of 0.76 calculated from the PRESS statistic. The close correspondence between these statistics indicates good model reliability, and the high value of the R^2_{PRED}suggests good overall predictive capability of the model. The model was reapplied to the parent population, and the actual and predicted postoperative heights were compared. The average difference per patient was 0.02cm.

Five data points were found to have standardised residuals over 2.0; with the maximum value being 2.91. This is within expectations for a data set of this size. A residual plot indicated no evidence for violation of regression assumptions. The maximum leverage value was found to be 0.098; within the acceptable limit for this data set of 0.12 (calculated as $3(k+1)/n$, where k is the number of variables in a data set of size n). The maximum recorded Cook's distance for all data points was 0.18, again, within acceptable limits. Hence there is no evidence that the data set includes outliers or excessively influential data points.

A larger 5-parameter model (also including the additional predictors of screw density and system design) was derived with only 1.1 – 2.2 percentage point differences in the adjusted-R^2 and R^2_{PRED} statistics. It has therefore not been presented.

Discussion

Although adolescent idiopathic scoliosis patients seek improvement in truncal symmetry, it is not the only change that occurs during correction of adolescent idiopathic scoliosis. Bjure and Nachemson (23) recognised the loss of trunk height due to scoliosis and in 1973 published a simple equation to calculate corrected height. However, scoliosis is never completely corrected during surgery (12). Therefore an equation that could predict postoperative height as a result of modern corrective techniques is more applicable in the clinical setting. This would allow clinicians to more accurately counsel patients on expected outcomes prior to their surgery. This could only be described as informed consent.

We have presented predictors of height gain, and a model that estimates postoperative height which is applicable during the preoperative counselling of an AIS patient. Our analysis shows that controlling for preoperative height, postoperative height is influenced primarily by the number of vertebrae fused and preoperative Cobb angle. Both of these parameters are significantly related to the outcome, with greater height being obtained from cases involving greater numbers of vertebrae and larger Cobb angles. In relative terms, children with lower preoperative heights have the most to be gained from the procedure. In our cohort, the largest possible spinal growth deficit according to Winter (16) is 3.92cm. The average height gain (4.66cm) seen in our study is therefore not insignificant, with most patients gaining an inch or more. The potential height lost by fusion is therefore offset by the immediate surgical gain. With a construct range of 5 to 15 vertebrae over an age range of 11 to 17 years, and a model showing validity across the data set, we are confident that the presented model is applicable to most adolescent idiopathic curves seen in clinical practice.

Previous studies have looked at predictors of gain in spinal height, and have proposed equations/formulae to calculate this (17-20). However, each equation/formula has relied on postoperative indices and would therefore not be applicable during the preoperative consultation. We suggest that measuring the patient’s height before and after surgery would be a simpler and more accurate method to assess the height gain. Our study proposes a model based on three parameters (preoperative radiological measurements and planned surgical strategy) which we feel is easy to use and clinically relevant. The literature suggests greater coronal and sagittal correction with increased anchor density (24, 25), but none have suggested a direct correlation with postoperative height as shown here.

We have no reason to believe that systematic errors have been introduced during the measurement of spinal height from radiographs. Considering the range of height gain (0.5cm to 9.9cm), we feel that measurement in millimetres was subject to less error than measurement rounded to the nearest half or whole centimetre. Whilst extensive cross-validation procedures have confirmed that the model shows good transferability to other samples, as with all inferential procedures, its utility is facilitated by its application to further cohorts. Although we did apply the model to our own patient sample (from which it was derived), therein lies the limitation. A prospective study comparing predicted height to actual height would be the method of validating this work.

Conclusion

For the majority of AIS patients, the greatest postoperative height measurement following posterior spinal fusion could be expected from those with greater preoperative height and a larger preoperative Cobb angle whose construct spans a large number of vertebrae.

References

1. Tarrant RC, Lynch S, et al. (2014) ‘Low body mass index in adolescent idiopathic scoliosis’, Spine, vol. 39, January, pp. 140-48.
2. Oh CH, Yoon SH, Park HC, Park CO, Kim SY. (2014) ‘A comparison of the somatometric measurements of adolescent males with and without idiopathic scoliosis’, Journal of Spinal Disorders & Techniques, vol./is. 27/1, February, pp. E26-31.
3. Ramirez N, Marinez-Llorens J, et al. (2013) ‘Body composition in adolescent idiopathic scoliosis’, European Spine Journal, vol. 22(2), February, pp. 324-9.
4. Wei-jun W, Xu S, et al. (2012) ‘Abnormal anthropometric measurements and growth pattern in male adolescent idiopathic scoliosis’, European Spine Journal, vol. 21, January, pp. 77-83.

5. Barrios C, Cortes S, et al. (2011) ‘Anthropometry and body composition profile of girls with nonsurgically treated adolescent idiopathic scoliosis’, Spine, vol. 36, August, pp. 1470-77.
6. Siu King Cheung K, Tak Keung Lee W, et al. (2003) ‘Abnormal peri-pubertal anthropometric measurements and growth pattern in adolescent idiopathic scoliosis: A study of 598 patients’, Spine, vol. 28, September, pp. 2152-57.
7. Grivas TB, Arvaniti A, Maziotou C, Manesioti MM, Fergadi A. (2002) ‘Comparison of body weight and height between normal and scoliotic children’, Studies in Health Technology & Informatics, vol./is. 91, January, pp. 47-53.
8. Normelli H, Sevastik J, Ljung G, Aaro S, Jonsson-Soderstrom AM. (1985) ‘Anthropometric data relating to normal and scoliotic Scandinavian girls’, Spine, vol./is. 10/2, March, pp. 123-6.
9. Smith FM, Latchford G. (2002) ‘Indications of disordered eating behaviour in adolescent patients with idiopathic scoliosis’, JBJS Br, vol. 84, April, pp. 392-94.
10. Carrasco MI,Ruiz MC (2014) ‘Perceived self-image in adolescent idiopathic scoliosis: an integrative review of the literature’, Revista Da Escola de Enfermagem Da Usp, vol./is. 48/4, August, pp. 748-57
11. NHS Choices. 2013. Scoliosis - NHS Choices. [ONLINE] Available at:http://www.nhs.uk/Conditions/Scoliosis/Pages/Introduction.aspx. [Accessed 06 December 14].
12. Westrick ER, Ward WT. (2011) ‘Adolescent idiopathic scoliosis: 5-year to 20-year evidence-based surgical results’, J Pediatr Orthop, vol. 31(1 Suppl), January-February, pp. S61-S68.
13. Weiss HR. (2007) ‘Adolescent Idiopathic Scoliosis - case report of a patient with clinical deterioration after surgery’, Patient Safety in Surgery [Electronic Resource], vol./is. 1, December, pp. 7.
14. Stuart L. Weinstein, MD; Lori A. Dolan, MA; Kevin F. Spratt, PhD; Kirk K. Peterson, MD; Mark J. Spoonamore, MD; Ignacio V. Ponseti, MD. (2003) ‘Health and Function

of Patients With Untreated Idiopathic Scoliosis A 50-Year Natural History Study', JAMA, vol. 289(5), February, pp. 559-567.

15. Papin P, Labelle H, Delorme S, Aubin CE, de Guise JA, Dansereau J (1999) 'Long-term three-dimensional changes of the spine after posterior spinal instrumentation and fusion in adolescent idiopathic scoliosis', European Spine Journal, vol./is. 8(1), February, pp. 16-21.
16. Winter RB. (1977) 'Scoliosis and spinal growth', Orthop Rev, vol. 6(1), pp. 17-20.
17. Spencer HT, Gold ME, et al. (2014) 'Gain in spinal height from surgical correction of Idiopathic Scoliosis', Journal of Bone and Joint Surgery Am, vol. 96, January, pp. 59-65.
18. Hwang SW, Samdani AF, et al. (2013) 'A multicentre analysis of factors associated with change in height after adolescent idiopathic scoliosis deformity surgery in 447 patients', J Neurosurg Spine, vol. 18, March, pp. 298-302.
19. Watanabe K, Hosogane N, et al. (2012) 'Increase in spinal longitudinal length by correction surgery for adolescent idiopathic scoliosis', European Spine Journal, vol. 21, October, pp. 1920-1925.
20. Sarlak AY, Atmaca H, et al. (2012) 'The height gain in scoliotic deformity correction: Assessed by new predictive formula', Computational Mathematical Methods in Medicine, Epub, May, 7 pages.
21. Cobb JR. (1948) 'Outline for the study of scoliosis', Instructional course lectures, American Academy of Orthopaedic Surgeons, Ann Arbor, MI, pp 261-75.
22. Lenke LG, Betz RR, Harms J, Bridwell KH, Clements DH, Lowe TG, Blanke K. (2001) 'Adolescent idiopathic scoliosis: a new classification to determine extent of spinal arthrodesis', Journal of Bone & Joint Surgery – American Volume, vol. 83-A, Aug, pp. 1169-81.

23. Bjure J, Nachemson A. (1973) ‘Non-treated scoliosis’, Clin Orthop Relat Res, vol. 93, June, pp. 44-52.

24. Larson AN, Polly DW Jr, Diamond B, Ledonio C, Richards BS 3rd, Emans JB, Sucato DJ, Johnston CE, Minimize (2014) ‘Does higher anchor density result in increased curve correction and improved clinical outcomes in adolescent idiopathic scoliosis?’, Spine, vol./is. 39/7, April, pp. 571-8.

25. Clements DH, Betz RR, Newton PO, Rohmiller M, Marks MC, Bastrom T (2009) ‘Correlation of scoliosis curve correction with the number and type of fixation anchors’, Spine, vol./is. 34/20, September, pp. 2147-50.

Legends

Table 1: Descriptive summary of sample

Figure 1: Lateral X-ray showing radiological method (vertebral diagonals, ruler)

Table 1

Variable (n=104)	Frequency	Percentage		
Gender				
Male	11	10.6		
Female	93	89.4		
Lenke classification				
Thoracic	**93**	**89.4**		
MT	42			
DT	33			
DM	6			
TM	12			
Thoraco-lumbar/lumbar	**11**	**10.6**		
TL/L	9			
TL/L - MT	2			
System design				
Side loading	74	71.2		
Top loading	30	21.8		
	Minimum	Maximum	Mean	SD
Age at surgery (years)	11	17	14.4	1.45
Screw density (%)	55	100	77.2	14.4
Number of vertebrae in construct	5	15	10.6	2.46
Number of crosslinks	0	2	0.48	0.76
Preoperative Cobb angle (degrees)	35.0	107	66.0	15.0
Postoperative Cobb angle (degrees)	8	42	21.3	7.3
Preoperative height (cm)	29.4	52.7	41.7	4.08
Postoperative height (cm)	32.8	57.5	46.3	3.71
Height gain (cm)	0.50	9.90	4.66	2.13

Figure 1


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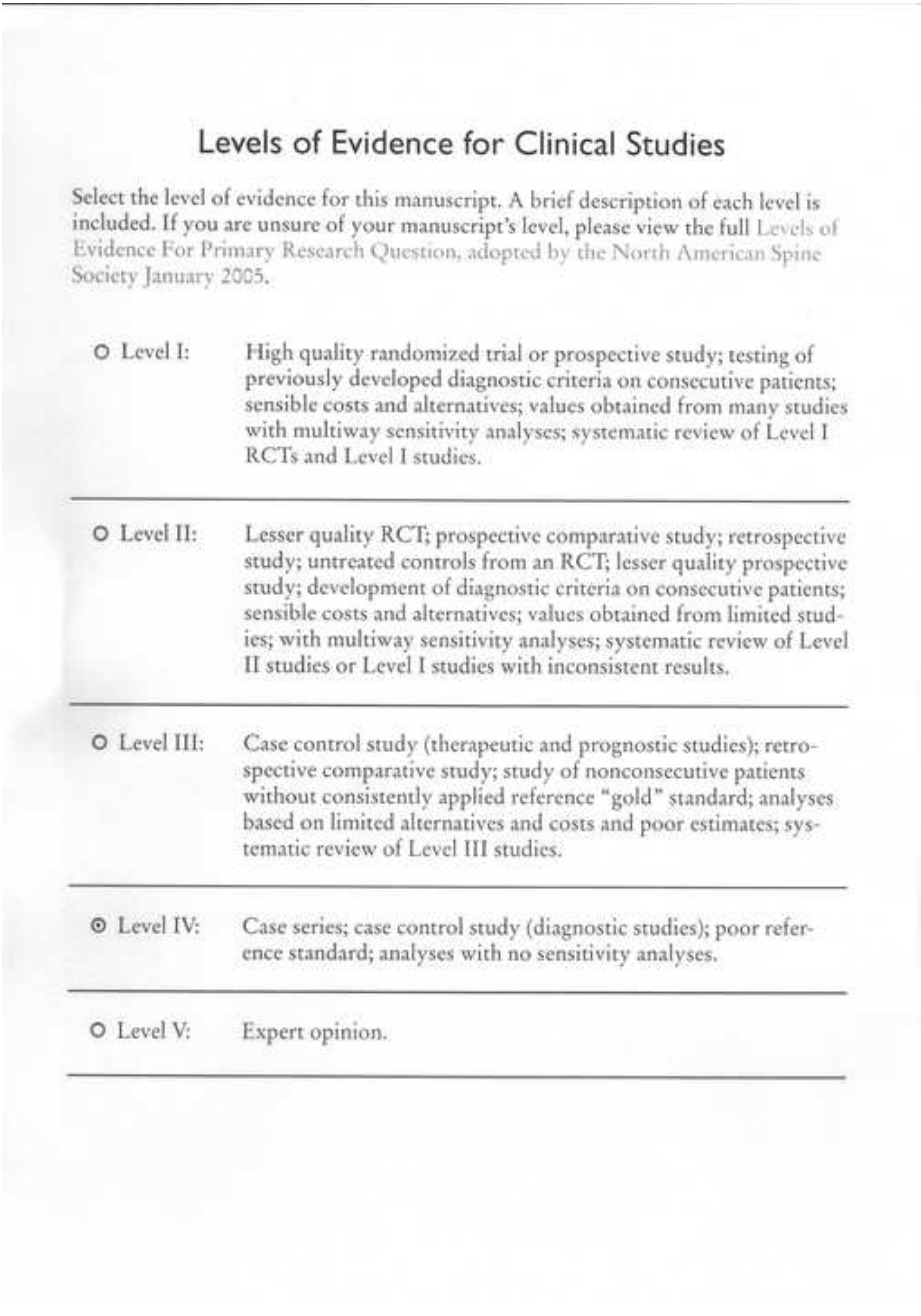
*Levels of Evidence for Clinical Studies



Levels of Evidence for Clinical Studies

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○ Level I:	High quality randomized trial or prospective study; testing of previously developed diagnostic criteria on consecutive patients; sensible costs and alternatives; values obtained from many studies with multiway sensitivity analyses; systematic review of Level I RCTs and Level I studies.
○ Level II:	Lesser quality RCT; prospective comparative study; retrospective study; untreated controls from an RCT; lesser quality prospective study; development of diagnostic criteria on consecutive patients; sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses; systematic review of Level II studies or Level I studies with inconsistent results.
○ Level III:	Case control study (therapeutic and prognostic studies); retrospective comparative study; study of nonconsecutive patients without consistently applied reference "gold" standard; analyses based on limited alternatives and costs and poor estimates; systematic review of Level III studies.
● Level IV:	Case series; case control study (diagnostic studies); poor reference standard; analyses with no sensitivity analyses.
○ Level V:	Expert opinion.

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