Universidade Federal do Rio de Janeiro – UFRJ

Centro de Ciências da Saúde

Faculdade de Odontologia

APLICABILIDADE DAS VÉRTEBRAS CERVICAIS COMO INDICADOR DA MATURIDADE ESQUELÉTICA

Rodrigo César Santiago

CD, MO

Tese submetida ao corpo docente da Faculdade de Odontologia da Universidade do Brasil -UFRJ, como parte dos requisitos, para a obtenção do Título de Doutor em Odontologia (Ortodontia).

Rio de Janeiro

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À Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (**CAPES)**, pela bolsa de estudos concedida.

RESUMO

SANTIAGO, Rodrigo César. **Aplicabilidade das vértebras cervicais como indicador da maturidade esquelética.** Orientador: Dra. Ana Maria Bolognese. Rio de Janeiro: UFRJ/Faculdade de Odontologia, 2013. Tese (Doutorado em Odontologia – Ortodontia). 109f

O objetivo desta pesquisa foi avaliar a aplicabilidade das vértebras cervicais como indicadores da maturidade esquelética. As evidências obtidas na revisão sistemática demonstraram fragilidade dos estudos publicados até 2010. Dentre os poucos artigos incluídos na revisão final, houve um estudo que questionou a utilização dos métodos MVC como única ferramenta de determinação da maturidade esquelética em decorrência de sua fraca reprodutibilidade entre os examinadores. A questão da reprodutibilidade foi, então, reavaliada. O resultado da reprodutibilidade intra e interexaminador, durante a avaliação de 90 radiografias, por cinco ortodontistas, revelou percentuais de concordância diferentes em decorrência do método empregado e da forma de avaliação. O percentual médio de reprodutibilidade intra e interexaminadores foi de 60%, sugerindo variabilidade e fragilidade dos métodos analisados como única ferramenta para determinação da maturidade esquelética. Por fim, foi desenvolvido *software* específico para análise digitalizada das vértebras cervicais (DVA-*Digital Vertebrae Analysis*). Foram verificadas alterações significativas na morfologia dos corpos vertebrais da 2ª e 3ª vértebras cervicais compatíveis com diferentes estágios de maturação esquelética em 236 radiografias. O modelo multinomial final apresentou previsibilidade de acerto de 81,4%, sendo esses valores considerados satisfatórios em se tratando de indicador biológico.

SUMMARY

SANTIAGO, Rodrigo César. **Aplicabilidade das vértebras cervicais como indicador da maturidade esquelética.** Orientador: Dra. Ana Maria Bolognese. Rio de Janeiro: UFRJ/Faculdade de Odontologia, 2013. Tese (Doutorado em Odontologia – Ortodontia). 109f

The aim of this study was to evaluate the applicability of cervical vertebrae to determine skeletal maturity. A systematic review was performed. The evidence observed points to a fragility of the studies regarding the use of different CVM methods for skeletal maturity assessment published until 2010. Among the few articles included on the final review, there was a study that questioned the use of CVM method as the only tool to determine skeletal maturity because of its low reproducibility among clinicians. The reliability was, then, evaluated eliminating some methodological flaws identified in previous studies. The results of intra and interrater reliability showed different levels of agreement regarding to both the methods applied and the use or not of a manual tracing. However, the mean intra/interrater reliability percentage was 60%, which suggest variability and fragility of the methods studied as the only tool to determine skeletal maturity. Finally, with the aim to reduce the subjectivity and variability among examiners of the qualitative methods, new software for digitized vertebrae analysis (DVA) was

developed. Statistically significant differences ($p<.001$) were observed on the morphology of the body of the 2nd, 3rd and 4th cervical vertebrae during different stages of skeletal maturation on 236 radiographs. The final MLRM presented a predictability of 81.4%, a value that was considered satisfactory for a biologic system.

LISTA DE SÍMBOLOS, SIGLAS E ABREVIATURAS

MVC	Maturação das Vértebras Cervicais
AQMC	Alterações Quantitativas durante Maturação Cervical
MRLR	Modelo de Regressão Logística Multinomial
≠	diferença
UFJF/MG	Universidade Federal de Juiz de Fora/Minas Gerais
C2	Segunda vértebra cervical
C3	Terceira vértebra cervical
C4	Quarta vertebra cervical
mm	milímetro
"	polegada
T1	tempo inicial
T2	tempo final
IME	Índice de Maturação Esquelética
ppp	pontos por polegada
ADV	Análise Digitalizada das Vértebras Cervicais
DVA	Digital Vertebrae Analysis
a	vértice superior posterior do corpo vertebral
b	vértice superior anterior do corpo vertebral

c	vértice inferior posterior do corpo vertebral
d	vértice inferior anterior do corpo vertebral
e	ponto mais superior da concavidade inferior do corpo vertebral
f	ponto médio localizado na borda superior do corpo vertebral
f’	ponto de interseção de f na borda inferior do corpo vertebral
g	ponto médio localizado na parede anterior do corpo vertebral
g’	ponto de interseção de g na parede posterior do corpo vertebral
AB	borda superior do corpo vertebral
CD	borda inferior do corpo vertebral
AC	parede posterior do corpo vertebral
BD	parede anterior do corpo vertebral
Ang_C2	ângulo da concavidade de C2
Ang_C3	ângulo da concavidade de C3
Ang_C4	ângulo da concavidade de C4
SP_C3	square proportion de C3
SP_C4	square proportion de C4
MP_C3	maturity proportion de C3
MP_C4	maturity proportion de C4
Kappa	teste estatístico de Kappa
qui^2	teste estatístico qui-quadrado
ANOVA	teste estatístico ANOVA
CVM	Cervical Vertebral Maturation method
HWM	Hand-Wrist Maturation method
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology

STARD	Standards for the Reporting of Diagnostic Accuracy Studies
SR	Systematic Review
TW3	Tanner-Whitehouse maturation method
ROC	Receiver Operating Characteristics analysis
5-stage	CVM method proposed by Baccetti, Franchi and McNamara (2002)
6-stage	CVM method proposed by Baccetti, Franchi and McNamara (2005)
SMI	Skeletal Maturation Index
2nd	Second cervical vertebral
3rd	Third cervical vertebral
4th	Fourth cervical vertebral
MLRM	Multinomial Logistic Regression Model
SD	Standard-deviation
Var 01	MP_C3
Var 02	Ang_C3
Var 03	MP_C4
Var 04	Age
Var 05	SP_C4
Var 06	Gender
β0	MLRM intercept
β1	β coefficient for Var 01
β2	β coefficient for Var 02
β3	β coefficient for Var 03
β4	β coefficient for Var 04
β5	β coefficient for Var 05
β5	β coefficient for Var 06

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1 INTRODUÇÃO

Em Ortodontia, a identificação do estágio de crescimento e desenvolvimento facial é essencial não somente para o correto diagnóstico, planejamento e execução do tratamento, como também para a obtenção da estabilidade, em longo prazo, principalmente nos casos de discrepâncias esqueléticas em que o tratamento se encerra antes que o crescimento puberal esteja completado.

É cada vez mais evidente que a época para o início do tratamento é tão importante quanto à escolha do planejamento em Ortodontia e Ortopedia Facial. A questão sobre o momento ideal está ligada diretamente à identificação dos períodos de aceleração do crescimento que podem contribuir significativamente para correção das discrepâncias esqueléticas da face (Baccetti, Franchi e McNamara, 2005).

O entendimento completo do padrão de desenvolvimento do paciente influencia na escolha clínica da terapia biomecânica a ser empregada, bem como na probabilidade de resultados de tratamento bem sucedidos. Essencialmente, a condição de crescimento individual irá determinar quando a ortopedia dentofacial realmente tem o potencial de corrigir as más oclusões esqueléticas, ou, se outras modalidades de tratamento, como a cirurgia maxilofacial e a compensação dentária, são indicadas (Knoefel, 1999).

Características da maturação sexual (alteração da voz, em meninos e menarca, em meninas), idade cronológica, desenvolvimento dentário, crescimento em altura e desenvolvimento esquelético são parâmetros empregados para determinar a maturidade e são utilizados na identificação dos estágios de crescimento (Moore, 1997). A determinação da idade esquelética é amplamente utilizada e é componente essencial no plano de tratamento ortodôntico.

O estadiamento da maturidade esquelética a partir de análises radiográficas é ferramenta empregada na predição do surto de crescimento, da velocidade e da quantidade de crescimento remanescente. O método padrão utilizado neste contexto é a radiografia da mão e do punho, baseado tanto no momento como na sequência de surgimento dos ossos carpais e determinados eventos de ossificação. Os métodos carpais são válidos pela existência de relação direta entre a velocidade de crescimento facial vertical e horizontal e a maturidade esquelética determinada pelos métodos de mão e punho (Flores-Mir, Nebbe e Major, 2004), pelos estágios de ossificação do número considerável de ossos disponíveis na região e pela análise do início da ossificação do sesamóide. (Tanner *et al.*, 1983; Fishman, 1982; Bowden, 1976; Greulich e Pyle, 1959)

As formas usuais de análise das radiografias carpais são os atlas de comparação desenvolvidos por Greulich and Pyle (1959) e Tanner *et al.,* (1983) e os sistemas que utilizam indicadores específicos que relacionam a maturação esquelética com a curva de crescimento puberal, como os métodos descritos por Bowden (1971) e Fishman (1982). Entretanto, além da preocupação com a exposição adicional à radiação (Chatzigianni e Halazonetis, 2009; Kamal, Rangini e Goyal, 2006; Gandini, Mancini e Andreani, 2006), alguns estudos questionam seu emprego.

Primeiramente, a complexidade de identificação dos pontos de referência pode levar à imprecisão das análises. (Moore, 1990; Houston, 1979). A sequência e a época em que ocorrem os eventos de ossificação dentro da região carpal apresentam polimorfismo e dimorfismo sexual, o que pode limitar o uso clínico preditivo desse método (Houston, 1980; Smith, 1980). Além disso, os eventos da mão e punho são indicadores do pico e do final do surto de crescimento, mas não sinalizam o início do surto de crescimento puberal (Mellion, 2007).

A aplicabilidade e eficiência do indicador biológico da maturidade esquelética estão diretamente relacionadas com alguns fatores como capacidade em detectar o pico de crescimento sem a necessidade de exposição adicional aos raios-x, facilidade de registro, consistência na interpretação dos dados e habilidade de predizer a ocorrência do pico de crescimento. (Franchi e Baccetti, 2002). Nesse contexto, o emprego das vértebras cervicais foi sugerido como alternativa às radiografias de mão e punho na determinação da maturação esquelética.

Existe variedade de métodos MVC na literatura, que incluem desde simples análises do tamanho e forma das vértebras (Lamparski, 1972; Hassel e Farman, 1995), medições quantitativas do formato das vértebras (algumas limitadas às medições da altura e largura e suas proporções) e da profundidade da concavidade do bordo inferior (Baccetti, Franchi e McNamara, 2002; Baccetti, Franchi e McNamara, 2005), além de avaliações mais específicas através de fórmulas de regressão linear (Mito, Sato e Mitani, 2002; Caldas, Ambrosano e Haiter-Neto, 2007; Chen *et al*., 2008) e análises morfométricas (Chatzigianni e Halazonetis, 2009).

A literatura é extensa em pesquisas conduzidas para validar os métodos de maturação das vértebras cervicais (MVC), em razão da necessidade de substituição da radiografia da mão e do punho por método que dispense exame radiográfico adicional, reduzindo a dose total de radiação à que o paciente é exposto (Chatzigianni e Halazonetis, 2009; Kamal, Ragini e Goyal, 2006). Vários trabalhos identificaram correlação substancial entre a idade esquelética determinada pelos métodos de MVC com o método padrão obtido através das radiografias carpais. (Lai *et al*., 2008; Gandini, Manicni e Andreani, 2006; Kamal, Ragini e Goyal, 2006; Uysal *et al.,* 2006; Grave e Townsend, 2003; Chang *et al*., 2001; Hassel e Farman, 1995). Em outros estudos, a validade do método MVC como indicador de maturidade esquelética foi verificada através da correlação entre o crescimento mandibular e as alterações observadas na morfologia dos corpos das vértebras cervicais (Franchi, Baccetti e McNamara, 2000), bem como através da capacidade em discriminar indivíduos prestes a atingir o pico de crescimento puberal daqueles que já alcançaram ou até dos que passaram do mesmo (Soegiharto, Moles Cunningham, 2008).

Entretanto, os trabalhos de Gabriel *et al.,* (2009) e Nestman *et al.,* (2011) questionam a aplicabilidade do método MVC em decorrência da baixa reprodutibilidade, contraindicando o mesmo como único guia na determinação da época ideal para o tratamento ortodôntico.

Em razão dos questionamentos recentes sobre a validade dos métodos MVC e da busca por indicador da maturidade esquelética sensível às alterações do crescimento e reproduzível perante aqueles que o utilizam, o objetivo da pesquisa foi (1) conduzir estudo de revisão sistemática sobre a avaliação da maturação esquelética através das vértebras cervicais, visando análise crítica da aplicabilidade do índice MVC, (2) analisar a reprodutibilidade de dois métodos qualitativos de MVC, buscando eliminar falhas metodológicas observadas em estudos prévios e (3) avaliar, de forma objetiva (quantitativa), possíveis alterações na morfologia das vértebras cervicais durante o crescimento, através de análise computadorizada em *softwarte* específico, bem como avaliar a aplicabilidade deste novo método através de modelo de regressão logística multinomial.

2 PROPOSIÇÃO

Avaliar a aplicabilidade das vértebras cervicais como indicador da maturidade esquelética através de:

2.1 identificação e revisão sistemática da literatura com relação à validade dos métodos de maturação das vértebras cervicais (MVC) na predição do surto puberal;

2.2 análise da reprodutibilidade de dois métodos de maturação das vértebras cervicais (Baccetti, Franchi e McNamara, 2002 e Baccetti, Franchi e McNamara, 2005), bem como da influência da utilização ou não de traçado manual individual na reprodutibilidade dos métodos estudados, e

2.3 desenvolvimento de novo método para análise quantitativa das alterações durante a maturação das vértebras cervicais (AQMC) e avaliação da sua aplicabilidade através do modelo de regressão logística multinomial (MRLM).

3 DELINEAMENTO DA PESQUISA

Na presente pesquisa foi avaliada a validade das vértebras cervicais como indicador da maturidade esquelética através de: revisão sistemática, análise da reprodutibilidade de dois diferentes métodos qualitativos e desenvolvimento e análise da aplicabilidade de novo método quantitativo.

Para análise da reprodutibilidade e desenvolvimento de novo método quantitativo foi submetido projeto ao Comitê de Ética em Pesquisa da Universidade Federal de Juiz de Fora, tendo recebido parecer favorável sob registro 334/2011 (ANEXO 1).

3.2 REVISÃO SISTEMÁTICA

3.2.1 Critério para consideração dos estudos a serem revisados

3.2.1.1 Tipo de estudo

Foram incluídos os estudos observacionais de diagnóstico em humanos envolvendo a utilização das vértebras cervicais na determinação da maturação esquelética.

3.2.1.2 Tipo de participantes

Foram selecionadas pesquisas realizadas com indivíduos em fase de crescimento e que tiveram as imagens radiográficas da mão e punho realizadas na mesma data das telerradiografias laterais.

Estudos com pacientes portadores de doenças sistêmicas e síndromes craniofaciais foram excluídos.

3.2.1.3 Tipo de intervenção

Diagnóstico da maturação esquelética envolvendo telerradiografia lateral para visualização das vértebras cervicais e radiografia da mão e do punho.

3.2.1.4 Tipo de avaliação dos resultados

Avaliação da maturação esquelética pela radiografia da mão e do punho (método padrão).

Avaliação das alterações anatômicas das vértebras cervicais.

Correlação com o método padrão, reprodutibilidade e acurácia dos métodos de identificação da MVC na determinação da idade esquelética.

3.2.2 Estratégia de busca para identificação dos estudos

A busca foi conduzida por dois pesquisadores nas seguintes bases de dados: *MedLine, Ovid MedLine, Virtual Health Library, Cochrane Database,* SCIRUS e eTBlast, até julho de 2010.

3.2.2.1 Palavras-chave para a busca na literatura

Foram empregados os seguintes termos para busca:

“*cervical”* ou *“cervical vertebrae”* ou “*cervical vertebral”* ou “vértebras” e “*maturation”* ou *“maturation method”* ou *“skeletal maturation”* ou *“growth and development”* ou “idade” e “*in human*”.

3.2.2.2 Método de busca para identificação dos estudos

A busca eletrônica por artigos de interesse foi realizada através de bases de dados e a busca manual foi conduzida através da avaliação de dois jornais: *American Journal of Orthodontics and Dentofacial Orthopedics* e *Angle Orthodontist*.

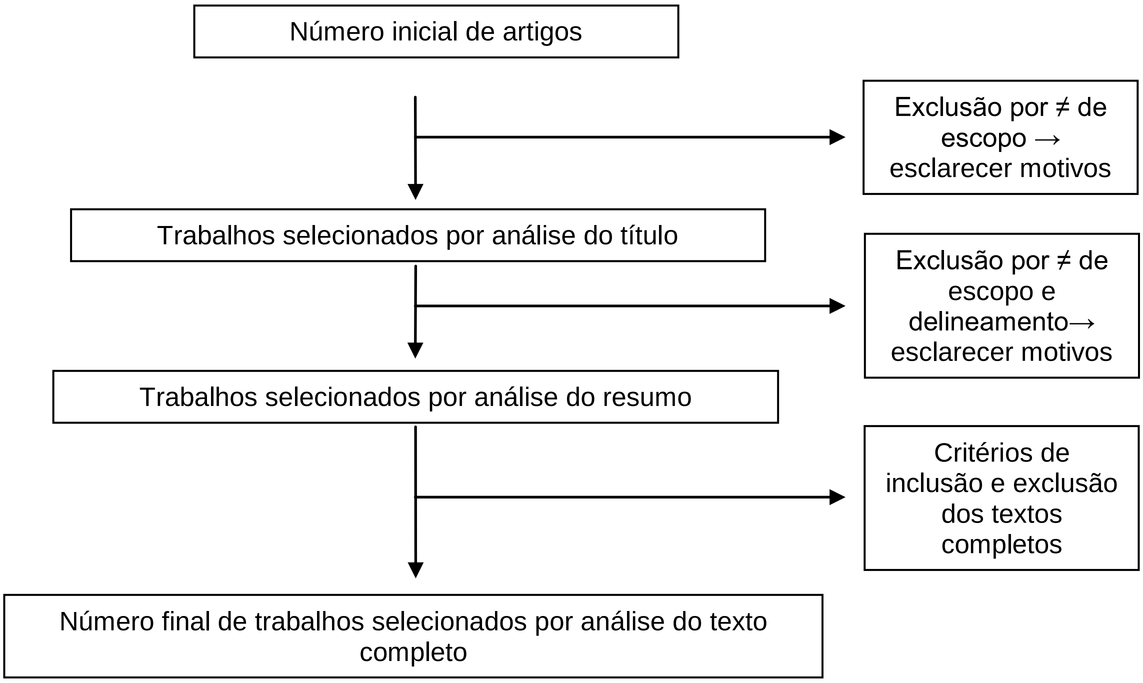
3.2.3 Idioma

Não houve restrição a nenhum trabalho em razão do idioma.

3.2.4 Estudos não publicados

Com o intuito de diminuir o viés de publicação, foram incluídos na busca trabalhos não publicados como dissertações e teses, pesquisadas na base de dados *Grey Literature* até julho de 2010.

3.2.5 Sequência de seleção de artigos



3.2.6 Coleta dos Dados e Análise

Para a revisão original foi realizada a busca eletrônica e manual por dois pesquisadores, para todos os trabalhos em relação à utilização das vértebras cervicais na determinação da idade esquelética. A lista de artigos gerada foi encaminhada para cada um dos pesquisadores onde foram selecionados os artigos que se enquadraram de acordo com o tipo de estudo, participantes de interesse e intervenção.

A leitura do texto completo dos artigos selecionados foi realizada pelos dois pesquisadores e a avaliação da qualidade de cada artigo levou em consideração critérios estabelecidos pelo *quality assessment*. As variáveis estudadas não foram utilizadas como critérios de inclusão ou exclusão na revisão sistemática. Reunião de consenso foi necessária para dirimir as dúvidas e discordâncias entre os dados coletados pelos pesquisadores. Nova reunião de consenso resolveu a discordância entre os dados coletados.

3.3 CARACTERIZAÇÃO DAS AMOSTRAS

Para facilitar o entendimento, as amostras foram divididas de acordo com o assunto a ser analisado.

3.3.1 Reprodutibilidade

Para análise da reprodutibilidade do método de maturação das vértebras cervicais (MVC), foram selecionadas aleatoriamente, por sorteio, 90 telerradiografias em norma lateral dentre 172 pacientes, brasileiros, pré-selecionados com idade entre 7 e 18 anos de ambos os gêneros, pertencentes ao arquivo do Curso de Especialização em Ortodontia da Faculdade de Odontologia da UFJF/MG.

Para composição da amostra foram respeitados os seguintes critérios de inclusão: (1) sem história prévia de traumas na face e/ou na mão e punho; (2) ausência de mal formações congênitas e/ou adquiridas que afetem as vértebras e/ou a mão e punho; (3) sem alterações de desenvolvimento em decorrência de síndromes ou desordens hormonais e (4) radiografias da mão e do punho e telerradiografias laterais do mesmo paciente realizadas na mesma data.

Com o objetivo de garantir a homogeneidade da amostra, as radiografias de mão e punho dos 172 selecionados foram inicialmente analisadas, para determinação do estágio de maturidade esquelética pelo método desenvolvido por Fishman, 1982 (Figura 1). Segundo um estudo prévio (Hassel e Farman, 1995), existe relação direta entre os estágios de maturação das vértebras cervicais e os 11 estágios estabelecidos por Fishman (1982). Desta forma, foram selecionados, aleatoriamente, 10 indivíduos de cada uma das 06 classificações agrupadas de acordo com Fishman (1982), como demonstrado no Quadro 1.

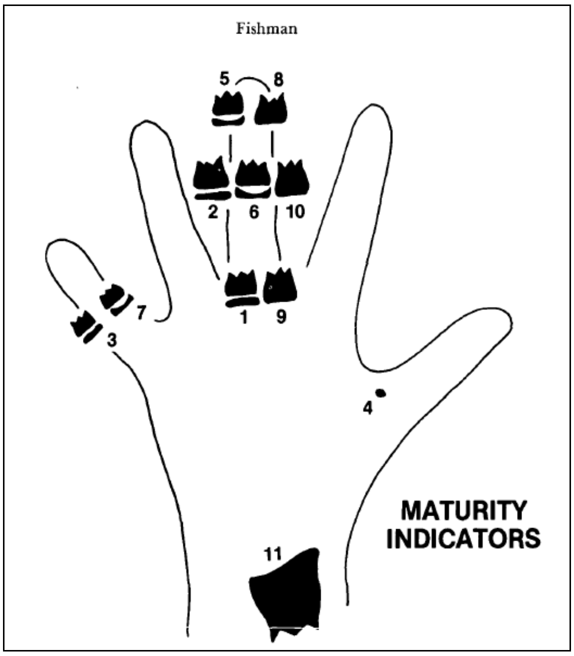


Figura 1 Onze indicadores de maturidade esquelética de Fishman (1982).

Quadro 1Distribuição da amostra de 172 indivíduos de acordo com o método de Fishman (1982) e o método MVC estabelecido por Hassel e Farman (1995).

Estágio de maturação cervical (MVC)	**Classificação agrupada de Fishman**	**Número de pacientes**
1	1,2	48
2	3,4	38
3	5,6	22
4	7,8	31
5	9,10	21
6	11	11

3.3.2 Análise Objetiva das Vértebras Cervicais

Os dados desse estudo transversal foram obtidos a partir de radiografias cefalométricas de perfil e de radiografias de mão e punho, tomadas como parte da documentação ortodôntica de rotina de pacientes pertencentes ao Curso de Especialização em Ortodontia de Faculdade de Odontologia da Universidade Federal de Juiz de Fora, Brasil. O projeto foi submetido e aprovado pelo Comitê de Ética em Pesquisa da Universidade Federal de Juiz de Fora, Brasil.

A amostra incluiu 236 indivíduos, sendo 116 meninos (média de idade de 146,4 meses, ± 25,2) e 120 meninas (média de idade de 146,2 meses, ± 24,1), selecionados consecutivamente entre janeiro e dezembro de 2011. Durante a composição da amostra, os critérios de seleção a seguir foram observados: (1) indivíduos brasileiros brancos, sem história de trauma na face e/ou na mão e punho; (2) ausência de malformações congênitas e/ou adquiridas que afetassem as vértebras ou a mão e punho; (3) boas condições de saúde geral e (4) radiografias cefalométricas e da mão e punho realizadas no mesmo dia e com boa visualização das estruturas de interesse, como as vértebras cervicais C2, C3, and C4.

3.4 AVALIAÇÃO DA REPRODUTIBILIDADE DE DOIS MÉTODOS QUALITATIVOS DE MVC

3.4.1 Análise da maturação das vértebras cervicais (MVC)

Para determinação do estágio de maturidade esquelética através das telerradiografias laterais foram empregados dois métodos qualitativos, Baccetti, Franchi e McNamara (2002) e Baccetti, Franchi e McNamara (2005). O primeiro método faz a análise das vértebras cervicais C2, C3 e C4 através de 5 estágios distintos (Figura 2 e Quadro 2) enquanto o segundo utiliza 6 estágios para a determinação da maturação das mesmas vértebras (Figura 3 e Quadro 3).

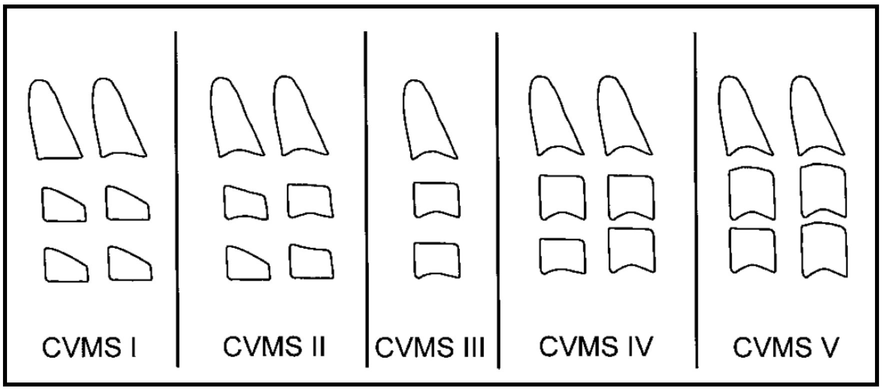


Figura 2 Método desenvolvido por Baccetti, Franchi e McNamara (2002).

Quadro 2 Os cinco estágios de maturação das vértebras cervicais estabelecidos pelo método de Baccetti, Franchi e McNamara (2002).

Estágio	**Descrição**
I	Bordas inferiores da C2, C3 e C4 planas ou achatadas, com possibilidade de existir uma leve concavidade na C2; forma trapezoidal da C3 e C4, afuniladas de posterior para anterior.
II	Presença de concavidades distintas nas bordas inferiores da C2 e C3; C3 e C4 apresentam-se trapezoidais ou retangulares na horizontal.
III	Presença de concavidades distintas nas bordas inferiores da C2, C3 e C4; C3 e C4 apresentam-se retangulares na horizontal.
IV	As concavidades nas fronteiras de C2,C3 e C4 estão presentes. Um dos corpos de C3 e C4 possui o formato quadrático. Se não for quadrado o outro corpo da outra vértebra é retangular na horizontal.
V	Presença de concavidades profundas nas bordas inferiores da C2, C3 e C4; C3 e C4 apresentam-se retangulares na vertical. Se não for vertical o corpo vertebral é quadrado.

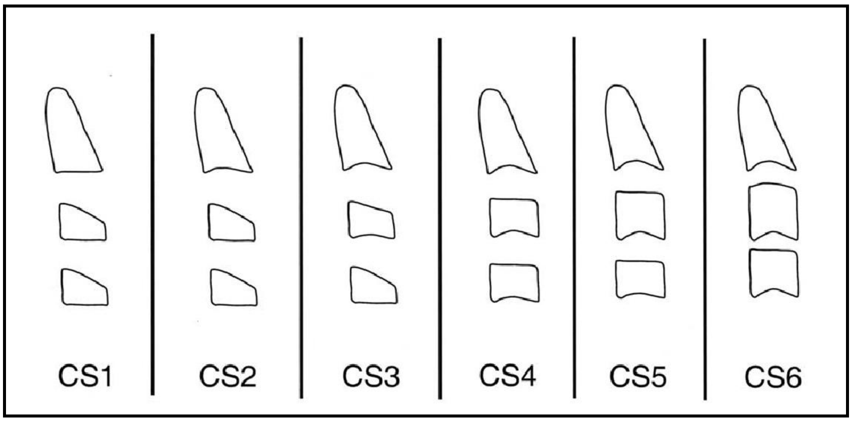


Figura 3 Método desenvolvido por Baccetti, Franchi e McNamara (2005).

Quadro 3 Os seis estágios de maturação das vértebras cervicais estabelecidos pelo método de Baccetti, Franchi e McNamara (2005).

I	As bordas inferiores de todas as três vértebras (C2-C4) são planas. Os corpos de C3 e C4 possui a forma trapezoidal (a borda superior da vértebra apresenta o corpo cônico de posterior para anterior).
II	A concavidade está presente na borda inferior de C2 na grande maioria dos casos (80%). Os corpos de C3 e C4 ainda estão em forma de trapézio.
III	Concavidades nas bordas inferiores de C2 e C3 estão presentes. Os corpos de C3 e C4 podem estar com o formato trapezoidal ou retangular horizontal.
IV	Concavidades nas bordas inferiores de C2, C3, C4 agora estão presentes. Os corpos de C3 e C4 são com formatos retangulares horizontais.
V	As concavidades da borda inferior de C2, C3 e C4 ainda estão presentes. Pelo menos um dos corpos de C3 e C4 possui o formato quadrado. Se não for quadrado, o corpo da vértebra cervical ainda é retangular horizontal.
VI	As concavidades das bordas inferiores de C2, C3, C4 são evidentes. Pelo menos um dos corpos de C3 e C4 é retangular vertical. Se não for vertical, o corpo da outra vértebra é quadrado.

3.4.2 – Análise da reprodutibilidade dos métodos

Foram selecionados, como examinadores, cinco ortodontistas sem experiência prévia com a utilização do método MVC.

Os cinco examinadores receberam o treinamento referente à utilização dos dois métodos MVC, através de apresentações ministradas por cirurgião-dentista, especialista em Imagem e com ampla experiência nos métodos de interesse. As apresentações foram realizadas em formato Power Point (Microsoft®) com duração média de 10 minutos, abordando os métodos exatamente como descritos por Baccetti, Franchi e McNamara (2002) e Baccetti, Franchi e McNamara (2005), com ênfase na definição da morfologia das vértebras C2, C3 e C4, assim como na identificação dos diferentes estágios de maturação esquelética definidos pelos dois métodos.

Imediatamente após o treinamento, as 90 telerradiografias foram analisadas em sala escura com auxílio de negatoscópio para garantir o aprimoramento do contraste das imagens ósseas. As radiografias foram analisadas em 18 rodadas, contendo cinco negatoscópios cada. Não foi permitida nenhuma comunicação entre os avaliadores, que também não tiveram acesso á nenhuma informação adicional a respeito do paciente, como idade, gênero, fase da dentição. Durante a avaliação das vértebras de interesse, foi posicionada em cada negatoscópio, uma folha de cartolina preta com retângulo central vazado que permitia a visualização somente das áreas de interesse (Figura 4). Em cada negatoscópio foram posicionados *templates* contendo os estágios de MVC de acordo com os métodos propostos por Baccetti, Franchi e McNamara (2002) e Baccetti, Franchi e McNamara (2005), como consta nas Figuras 1 e 2.

Figura 4 Método de visualização das vértebras no negatoscópio.

Houve dois tipos de avaliação durante a análise das vértebras cervicais: (Tipo 1) a partir de traçado manual e individual realizado com lapiseira em grafite 0,5 mm (Faber Castel®, Stein, Germany), sobre folha de acetato 8”x10”, lote 253123 (Orthometric, Franklin, IN, USA) abrangendo os corpos vertebrais de C2, C3 e C4 e (Tipo 2) avaliação visual diretamente nas radiografias cefalométricas. Todo o procedimento foi repetido seis semanas (T2) após a primeira avaliação (T1), com distribuição aleatória das radiografias em sequência diferente da primeira avaliação. Todos os examinadores receberam novamente o mesmo treinamento da primeira avaliação.

3.5 APLICABILIDADE DE NOVO MÉTODO QUANTITATIVO

As radiografias de mão e punho foram utilizadas como método padrão para determinar o grau de maturação esquelética de cada indivíduo e analisadas por cirurgião-dentista especialista em imagem com larga experiência no método de interesse. As radiografias foram classificadas de acordo com o índice de maturação esquelética (IME) descrito por Fishman (1982) e foram alocadas em 11 grupos, como mostra a Tabela 1. Toda análise foi realizada em ambiente escuro, no mesmo negatoscópio e o examinador desconhecia informações adicionais, como idade cronológica e gênero. Para análise da confiabilidade em relação ao estadiamento das radiografias de mão e punho, 30 radiografias foram analisadas duas vezes com intervalo de duas semanas entre as avaliações, obtendo o ICC de 0,997.

Os 11 estágios de maturação esquelética (IME) de Fishman (1982) podem ser agrupados, de acordo com Kopecky e Fishman (1993), em períodos de aceleração (IME 1-3), de alta velocidade de crescimento (IME 3-7) e de desaceleração (IME 8-11). No presente estudo, as radiografias foram agrupadas em quatro categorias de maturação das vértebras cervicais levando em consideração os indicadores de maturação esquelética de Fishman (1982), sendo que o período de desaceleração do crescimento foi dividido em dois estágios (8-9 e 10-11), em virtude de alterações significativas na morfologia dos corpos vertebrais (Tabela 1). Desta forma, as alterações quantitativas de maturação das vértebras cervicais (AQMC) compreenderam quatro estágios, a saber: AQMC I (aceleração do crescimento), que inclui os estágios 1-3 de Fishman; AQMC II (alta velocidade de crescimento), que inclui os estágios 4-7 de Fishman; AQMC III (desaceleração do crescimento), que inclui os estágios 8 e 9 de Fishman e AQMC IV (consumação do crescimento), que inclui os estágios 10 e 11 de Fishman (Tabela 1).

Tabela 1 Número de indivíduos de acordo com cada estágio de maturação esquelética de Fishman (IME) e com as alterações quantitativas de maturação das vértebras cervicais (AQMC)

Estágio AQCM	*IME (Fishman)*	*Meninos (n)*	*Meninas (n)*
I	1	35	10
	2	20	5
	3	13	8
Sub-total		68	23
II	4	15	7
	5	3	12
	6	3	12
	7	3	11
Sub-total		24	42
III	8	10	19
	9	1	9
Sub-total		11	28
IV	10	8	15
	11	5	12
Sub-total		13	27
Total		116	120

As radiografias foram escaneadas (Umax Astra 2400 SLT) a 600 ppp (pontos por polegada) e digitalizadas através do *software* Corel Photo-Paint, versão 11.0 (Corel Photo-Paint®, Corel Corporation, Otawa, CAN). A morfologia dos corpos das vértebras cervicais C2, C3 e C4 foi analisada de forma objetiva (quantitativa) através de *software* desenvolvido especificamente para este estudo. O *software* para análise digitalizada das vértebras cervicais ADV (Análise Digitalizada das Vértebras) ou DVA (*Digital Vertebrae Analysis*) foi desenvolvido em Microsoft.NET *Framework*, na linguagem C#, com o intuito de auxiliar o especialista durante análise da imagem, oferecendo medidas e proporções das vértebras C2, C3 e C4 com base em pontos de referência identificados manualmente (Figura 5).

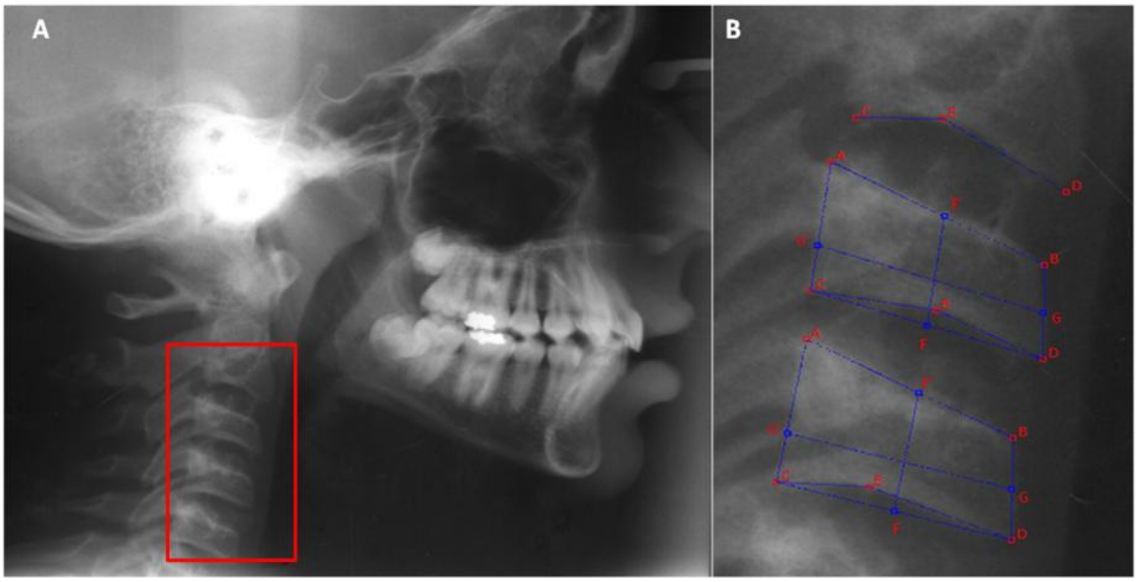


Figura 5 **(A)** Telerradiografia lateral com a delimitação da região de interesse, em vermelho, abrangendo a 2ª, 3ª e 4ª vértebras cervicais. **(B)** Definição dos pontos de interesse na análise computadorizada: A e B, os pontos mais superiores das paredes posterior e anterior, respectivamente; C e D, os pontos mais inferiores das paredes posterior e anterior, respectivamente; E, o ponto mais superior do bordo inferior dos corpos de C2, C3 e C4; F e G, os pontos médios dos bordos inferior(CD) e anterior BD, respectivamente; F', ponto de interseção onde a reta paralela a parede posterior (AC) que parte de F toca o bordo superior (AB); G', ponto de interseção onde a reta paralela ao bordo inferior (CD) que parte de G toca a parede posterior (AC).

Após a definição dos pontos de interesse, a ferramenta utilizou métodos de álgebra linear e de análise espacial para gerar os valores das dimensões, proporções e ângulos. A confiança e reprodutibilidade intra-observador das medidas estabelecidas pelo *software* DVA foi verificada pela análise de 30 radiografias cefalométricas selecionadas aleatoriamente, em dois momentos distintos, com intervalo de duas semanas entre os mesmos.

Medidas de interesse foram determinadas:

AB e CD: bordas superior e inferior, respectivamente;

AC e BD: paredes posterior e anterior, respectivamente;

ANG_C2, ANG_C3 e ANG_C4: ângulo interno (*concavity angle)*, formado pela interseção das retas que conectam os pontos CE e ED nas bordas inferiores de C2, C3 e C4, respectivamente.

SP_C3 e SP_C4: proporção quadrada (*square proportion)* de C3 e C4, respectivamente, dada pela razão entre a reta paralela à borda inferior (CD) que conecta os pontos G e G' e a reta paralela à parede posterior (AC) que conecta os pontos F e F' e

MP_C3 e MP_C4: proporção de maturação (*maturity proportion*) de C3 e C4, respectivamente, dada pela razão entre a parede anterior (BD) e a parede posterior (AC).

A amostra foi avaliada em relação a 10 variáveis: (1) Idade cronológica, (meses); (2) Gênero; (3) Estágio de maturação de Fishman; (4) Ângulo de C2; (5) Ângulo de C3; (6) Ângulo de C4; (7) Proporção quadrada de C3; (8) Proporção quadrada de C4; (9) Proporção de maturação de C3 e (10) Proporção de maturação de C4.

3.6 ANÁLISE ESTATÍSTICA

A análise estatística foi processada com auxílio do programa SPSS 13.0 (SPSS Inc.,Chicago, Illinois) e Medcalc 12.2.1.0 (MedCalc Software, Ostend, Belgium). Para análise da reprodutibilidade foi empregado o teste ponderado de *Kappa*, que avaliou a concordância intra e interobservadores.

Para análise da aplicabilidade do *software* DVA, as médias e desvios-padrão foram calculados. A análise estatística incluiu o teste qui^2, ANOVA, o teste de *kappa* ponderado e a análise de regressão logística multinomial. O nível de significância de $p<$,05 foi estabelecido. O software estatístico Excel (Microsoft Office®, 2007, USA) foi utilizado para análise dos dados e obtenção das probabilidades do modelo de regressão multinomial.

4 DESENVOLVIMENTO DA PESQUISA

4.1 ARTIGO 1

Santiago, R.C.; Costa, L.F.M.C.; Vitral, R.W.F.; Fraga. M.R.; Bolognese, A.M.; Maia, L.C. Cervical vertebral maturation as a biologic indicator of skeletal maturity: A systematic review. **Angle Orthodontist**. v.82, n.6, p.1123-1131, 2012. (Publicado)

4.2 ARTIGO 2

Santiago, R.C.; Duque, P.H.R.; Campos, M.J.S.; Cerrone Jr, G.; Vitral, R.W.F.; Costa, L.F.M.; Bolognese, A.M. Analysis of the reliability of two qualitative cervical vertebrae maturation methods for growth assessment in orthodontic patients. **Orthodontics and Craniofacial Research** (Submetido)

4.3 ARTIGO 3

Santiago, R.C.; Cunha, A.R.; Cerrone Jr, G.; Fernades, N.; Costa, L.F.M.; Vitral, R.W.F.; Bolognese, A.M. New software for cervical vertebral geometry assessment and its relationship to skeletal maturation - a pilot study. **Dentoimaxillofacial Radiology** (Submetido)

4.4 ARTIGO 1

Santiago, R.C.; Costa, L.F.M.C.; Vitral, R.W.F.; Fraga. M.R.; Bolognese, A.M.; Maia, L.C. Cervical vertebral maturation as a biologic indicator of skeletal maturity: A systematic review. **Angle Orthodontist**. v.82, n.6, p.1123-1131, 2012.

Review Article

Cervical vertebral maturation as a biologic indicator of skeletal maturity
A systematic review

Rodrigo César Santiago[a]; Luiz Felipe de Miranda Costa[a]; Robert Willer Farinazzo Vitral[b]; Marcelo Reis Fraga[c]; Ana Maria Bolognese[d]; Lucianne Cople Maia[e]

ABSTRACT

Objective: To identify and review the literature regarding the reliability of cervical vertebrae maturation (CVM) staging to predict the pubertal spurt.

Materials and Methods: The selection criteria included cross-sectional and longitudinal descriptive studies in humans that evaluated qualitatively or quantitatively the accuracy and reproducibility of the CVM method on lateral cephalometric radiographs, as well as the correlation with a standard method established by hand-wrist radiographs.

Results: The searches retrieved 343 unique citations. Twenty-three studies met the inclusion criteria. Six articles had moderate to high scores, while 17 of 23 had low scores. Analysis also showed a moderate to high statistically significant correlation between CVM and hand-wrist maturation methods. There was a moderate to high reproducibility of the CVM method, and only one specific study investigated the accuracy of the CVM index in detecting peak pubertal growth.

Conclusions: This systematic review has shown that the studies on CVM method for radiographic assessment of skeletal maturation stages suffer from serious methodological failures. Better-designed studies with adequate accuracy, reproducibility, and correlation analysis, including studies with appropriate sensitivity-specificity analysis, should be performed. (*Angle Orthod.* 2012;82:1123–1131.)

KEY WORDS: Skeletal maturation; Cervical vertebrae

INTRODUCTION

The issue of optimal timing for orthodontic treatment is linked intimately to the identification of periods of craniofacial growth that can contribute significantly to the treatment of patients with skeletal discrepancies.[1,2]

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The use of radiographic analysis to estimate skeletal maturation stage is a widely used method for predicting the timing of pubertal growth and for estimating growth velocity and the proportion of growth remaining.[3]

The hand-wrist radiograph is considered[4–7] to be the most standardized method of skeletal maturation assessment based upon time and the sequence of appearance of the carpal bones and certain ossification events. Skeletal maturity is generally determined using stages in the ossification of bones of the hand-wrist, because of the relationship between the overall horizontal and vertical facial growth velocity and skeletal maturity determined by hand-wrist methods[3] or because of the quantity of different types of bone available,[8–11] or by evaluating the ossification onset of the sesamoid.[8] The usual means by which to assess the hand-wrist radiograph are the comparison atlas of Greulich and Pyle[8] and Tanner et al.[9] and the processes that use specific indicators that relate skeletal maturation to the pubertal growth curve, such as the methods described by Bowden[10] and Fishman.[11]

There are some limitations in the interpretation of skeletal maturity from hand-wrist radiographs.[3] The ossification sequence and timing of skeletal maturity

Table 1. Electronic Database Searched and Search Strategy

Database	Key Words
MEDLINE, searched via PubMed (1950 to May 2010)	(cervical AND vertebrae OR vertebral AND maturation)
Ovid MEDLINE(R), 1950 to June, week 2, 2010	(cervical vertebrae/gd and growth and development)
ISI Web of Knowledge, searched on July 2010	(cervical vertebral maturation)
VHL (Virtual Health Library) (until May 2010)	(vértebras [vertebras cervicais] AND idade [determinação da idade pelo esqueleto])
Grey Literature (until May 2010), via: http://www.cardiff.ac.uk/insrv/eresources/databases/sigle.html http://www.opengrey.eu/	(cervical vertebrae AND maturation OR Cervical vertebrae/gd AND growth & development)
Cochrane Database of Systematic Reviews, searched via Cochrane Library on 06/14/2010	(cervical AND vertebrae OR vertebral AND maturation)
SCIRUS (until July 2010)	(cervical vertebrae AND [Refined search]/skeletal maturation AND [Refined search]/skeletal age)
eTBlast (1967 to June 2010)	cervical vertebral maturation method to predict peak circumpubertal growth

within the hand-wrist area show polymorphism and sexual dimorphism, which can limit the clinical predictive use of this method.[12,13] Moreover, there are concerns about the extra radiation exposure resulting from use of this method,[14] and its use must be questioned if other comparable methods of assessment are available. Finally, events in the hand and wrist are indicators of the peak and the end of the pubertal growth spurt, but these events do not signal the onset of the pubertal growth spurt.[15]

The cervical vertebrae maturation (CVM) method was introduced by Lamparski[16] for use in growth assessment, allowing skeletal age evaluation and eliminating the need for additional radiographic exposure since the vertebrae are already recorded in the lateral cephalogram taken as a pretreatment record.[1,5,14,17,18] However, the reproducibility of the CVM method has been questioned.[19]

In spite of extensive research about CVM methods applied to skeletal maturity assessment during the past years, statistical and biological details about the relationship between vertebral shape and skeletal maturation are still missing.[20]

Systematic reviews are useful tools with which to obtain evidence-based clinical information.[21] The literature is controversial regarding the CVM method in terms of its utility for determining skeletal maturity. The aim of this systematic review was to identify and qualify the evidence and methodology of those reports and to evaluate the following question: How reliable is CVM staging in terms of predicting the pubertal spurt?

MATERIALS AND METHODS

To identify potentially relevant studies reporting data related to maturational indexes, specifically CVM methods, detailed search strategies were developed and executed. The search also included appropriate changes in the vocabulary and followed each database's syntax rules. Citations to potentially relevant studies in journals, dissertations, and conference proceedings were located by searching the appropriate electronic database in an effort to minimize publication bias.

Table 1 shows the database search and outlines our search strategy. This electronic investigation was conducted through July 2010. We also searched by hand by checking the references of the retrieved articles to identify all possible articles to be included in this review. No language restriction was applied.

The selection criteria for considering studies included in this systematic review (SR) were the following: (1) cross-sectional or longitudinal descriptive studies in humans that evaluated qualitatively or quantitatively an established CVM method on lateral cephalometric radiographs to determine skeletal maturation; (2) studies that used hand-wrist radiographs as the standard method when evaluating correlation or comparison with the CVM method; and (3) studies that evaluated the reproducibility of the CVM method. Studies with inadequate sample sizes (ie, cleft lip/palate patients or repeated samples) that introduced a new or additionally modified version of the CVM method, editor's summaries, reference-only works, patents, meeting abstracts, opinion articles, and reviews were excluded.

Initially, the titles and abstracts identified were reviewed. Duplicate articles appearing in more than one database search were considered only once. Each abstract was checked to determine whether it presented data related to patients' skeletal maturation stage, as assessed by the CVM method. Any investigation not fulfilling this criterion was excluded from further evaluation. If the reviewer could not decide on a study's eligibility by examining the title and abstract, its full text was retrieved.

The full texts of remaining articles were retrieved for further evaluation in duplicate by two reviewers. In addition, to document the methodological soundness of each article, a quality assessment modified from the

Table 2. Criteria for Assessing Quality Components in the Studies Included

	Yes	No
A. Are the objectives clearly formulated?	1	0
B. Are there key elements of study design early in the paper?	1	0
C. Was the sample size calculated?	1	0
D. Does the study report demographic characteristics of the study population?	1	0
E. Were the sample selection criteria clearly described?	1	0
F. Does the study describe specifications of material and methods involved including how and when measurements were taken?	1	0
G. Was there a reliability assessment, with adequate level of agreement intraexaminer or/and interexaminer?	1	0
H. Were there blinding measurements?	1	0
I. Does the study give details of methods of assessment (measurements) for each variable of interest?	1	0
J. Was there a complete and adequate reporting of results, with self-explanatory tables and figures?	1	0
K. Was there a statistical analysis appropriate for data?	1	0
L. Was the *P* value stated or confidence intervals provided?	1	0

Strengthening the Reporting of Observational Studies in Epidemiology (STROBE),[22] Standards for the Reporting of Diagnostic Accuracy Studies (SATRD),[23] and Lagravere et al.[24] was performed (Table 2). When two reviewers disagreed, a third investigator was called in, and consensus was reached.

One point was given to each criterion, if fulfilled. Quality assessment scores ranged from 0 to 12. The studies were classified as "low" (score 0 to 6), "moderate" (score 7 to 10), or "high" (score 11 to 12) according to this assessment. Studies with a low score (<7 points) were considered to be of poor methodological quality and were not considered at all in terms of the SR conclusions. Disagreements between the reviewers were resolved by reexamining the article in question, with discussion until both researchers were satisfied with the decision.

RESULTS

The electronic searches identified 343 records after duplicated references were removed. From these, 109 were selected for abstract evaluation. A total of 39 abstracts were retrieved for complete text detailed evaluation, including two articles added from hand searching. Ultimately, our search yielded 23 articles that met the inclusion criteria (Figure 1). Once the articles were selected, we systematically assigned a methodological score to each study in order to characterize them as useful or not (Table 3). Based on quality assessment, we found that six studies[2,8,19,25–27] were particularly useful, with a moderate to high score. As stated above, 17 studies[4,7,14,28–41] with a low score (<6.5 points) were considered to be of low methodological quality and were not particularly useful. The characteristics of moderate- and high-quality studies are presented in Table 4.

DISCUSSION

One objective of orthodontic treatment in adolescents is to take advantage of potential skeletal growth to treat skeletal discrepancies. Sexual maturation characteristics, chronologic age, dental development, height, weight, and skeletal development are some of the more common methods that have been used to identify stages of growth. Peak growth velocity in standing height is the most valid representation of rate of overall skeletal growth. It forms a useful historic longitudinal measure of an individual's growth pattern but has little predictive value in terms of future growth rate or percentage of total growth remaining. On the other hand, skeletal maturation staging from radiographic analysis is a widely used approach to predict timing of pubertal growth, to estimate growth velocity, and to estimate the proportion of growth remaining.[3]

According to a previous study,[15] skeletal age offers no value over chronological age, either in assessing or predicting the time of pubertal growth. On the other hand, the hand-wrist radiograph is considered to be the most standardized method of skeletal assessment.[4,7,18,27] Although some studies[4,12,13] stated that the use of hand-wrist radiographs to predict growth spurt is not sufficiently accurate to be of value in clinical orthodontics, the validity of skeletal maturity assessment using the hand-wrist radiographs has been observed.[2,3] However, to avoid taking additional radiographs, it is relevant to relate maturational stages to skeletal features other than the bones in the hand and wrist.

The cervical vertebrae are already shown on the lateral cephalogram film taken as a pretreatment record, and it is well known that the lateral view of the cervical vertebrae bodies changes with growth. In recent years, evaluation of the cervical vertebrae has been increasingly used to determine skeletal maturity.[1,5,14,17,18]

None of the studies included in this SR could be used for a meta-analysis because of the different methods of CVM and hand-wrist maturation (HWM) evaluation applied. The study of Imanimoghaddam et al.[25] showed different correlation levels between four different CVM methods and the same HWM (TW3 method) in a unique sample. Thus, accuracy, correlation, and reproducibility may be influenced by the method.

There are a great variety of CVM methods, including simple qualitative analysis of the vertebral shape and

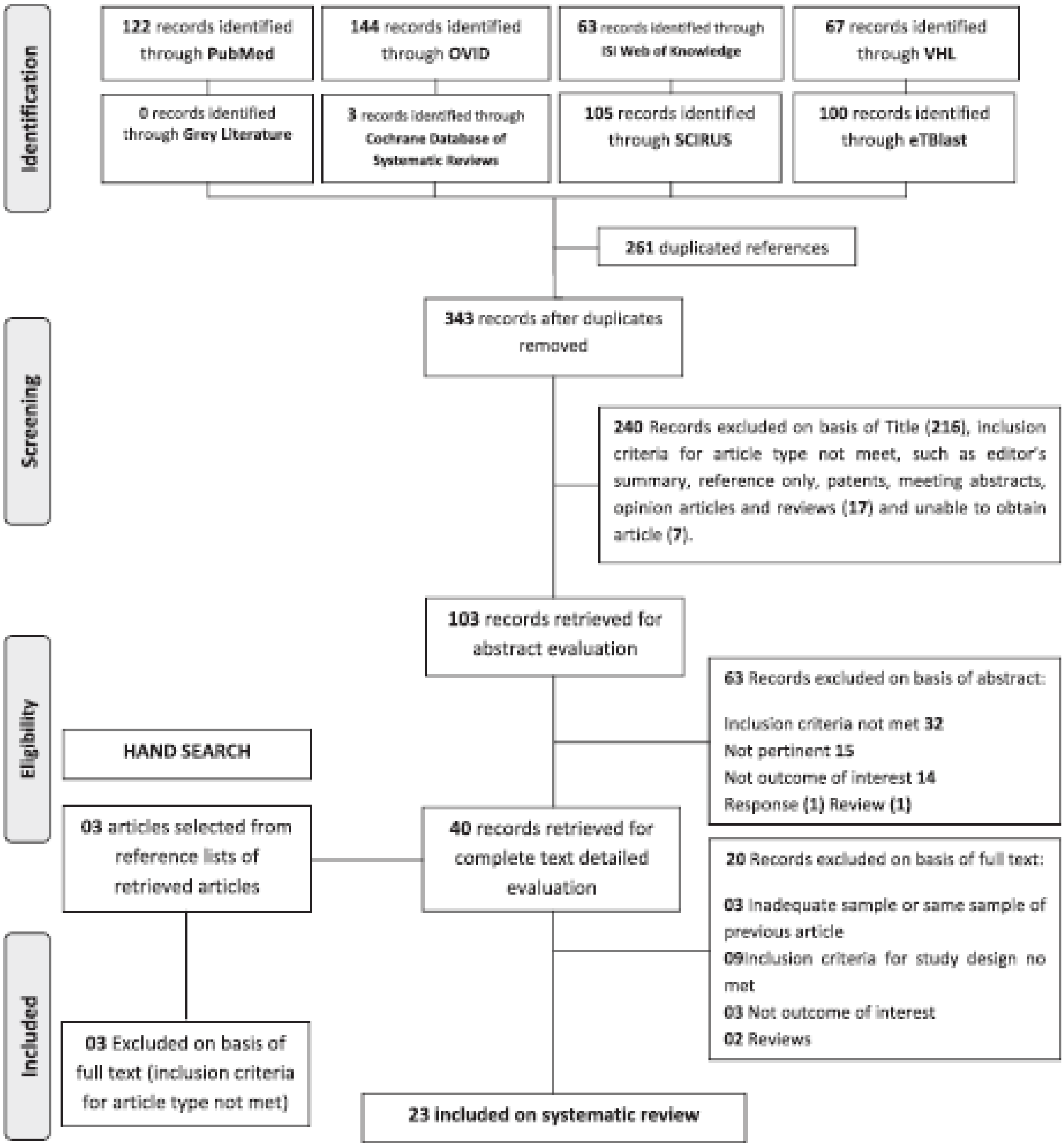

Figure 1. Flow diagram of literature search.

size[5,18] to quantitative measurements of vertebral shape (some of which are limited to height and width distances and ratios) and the depth of the inferior concavity[1,42] and to other, more specific measurements, rendered through geometric morphometric analysis[20] or linear regression formulae.[40,43]

Caution should be taken in the application of the results presented in this SR. Most of the studies investigating the use of cervical vertebral radiographic analysis of skeletal maturation did not report any kind of randomization, blinding, and sample size calculation. Articles that presented methodological deficiencies,

Table 3. Quality Assessment of Selected Full Text Article

Articles	A	B	C	D	E	F	G	H	I	J	K	L	Total	Quality
Alkhal and Wong,[29]	1	1	0	1	0	0	1	0	1	0	0	0	5	Low
Caldas, Ambrosano and Haiter-Neto,[28]	1	1	0	1	0	0	0	0	1	0	1	1	6	Low
Caltabiano, Leonardi and Zaborra,[30]	1	0	0	1	0	0	0	0	1	0	0	1	4	Low
Chang *et al*,[6]	1	1	0	1	1	0	1	0	1	1	1	1	9	Moderate
Flores-Mir *et al*,[31]	1	0	0	0	0	0	1	1	0	1	1	0	5	Low
Gabriel *et al*,[19]	1	1	0	0	0	0	1	1	1	1	1	1	8	Moderate
Gandini, Mancini and Andreani,[7]	1	0	0	0	0	0	1	0	1	0	0	0	3	Low
García-Fernandez *et al*,[32]	1	0	0	1	1	1	1	0	1	0	0	0	6	Low
Grave and Townsend,[33]	1	1	0	1	0	0	0	0	1	1	0	0	5	Low
Grippaudo *et al*,[34]	1	0	0	1	0	0	1	0	1	0	1	1	6	Low
Imanimoghaddam *et al*,[25]	1	1	0	1	1	1	0	0	1	1	1	1	9	Moderate
Kamal, Ragini and Goyal[18]	0	0	0	1	0	0	0	0	1	0	1	1	4	Low
Kucukkeles *et al*,[35]	1	0	0	0	0	0	1	0	1	0	1	1	5	Low
Lai *et al*,[26]	1	1	0	1	0	0	1	1	1	1	1	1	9	Moderate
Learreta and Bono,[36]	1	0	0	0	0	1	0	0	1	0	0	0	3	Low
Lima *et al*,[37]	1	0	0	0	0	0	0	1	1	0	1	1	5	Low
San Román *et al*,[38]	1	0	0	1	0	0	1	0	1	0	1	1	6	Low
Santos *et al*,[40]	0	0	0	1	0	0	1	1	1	1	0	0	5	Low
Santos *et al*,[41]	0	0	0	1	0	0	1	1	1	1	0	0	5	Low
Soegiharto, Moles and Cunningham,[2]	1	1	0	1	0	0	1	0	1	1	1	1	8	Moderate
Stiehl, Muller and Dibbets,[39]	1	0	0	0	0	0	1	0	1	1	1	1	6	Low
Uysal *et al*,[27]	1	1	0	1	1	1	1	1	1	1	1	1	11	High
Wong, Alkhal and Rabie,[14]	1	0	0	1	0	0	1	0	1	0	1	1	6	Low

which would likely compromise the interpretation of reported results, were excluded from this study. We found 23 articles that met the inclusion criteria,[2,6,7,14,18,19,25–42] but only six[2,6,19,25–27] were considered to be of moderate to high methodological quality.

Initially, the research on the direct relationship between cervical vertebral anatomical alterations and facial growth was limited because of the problems of longitudinal radiographic recordings, although there are a few longitudinal databases that can be accessed that have hand-wrist and lateral cephalometric radiographs taken simultaneously.[17] All of the moderate- to high-ranked studies selected in this review were based on cross-sectional data, and these studies' designs have inherent limitations in terms of analyzing growth. Cross-sectional sampling is relatively insensitive to the individual variability seen easily in a longitudinal sample. In the study of growth and development, longitudinal research is an essential method for the detailed study of craniofacial growth, which can determine a patient's unique development type and make possible continuous comparison.

According to Soegiharto et al.,[2] studies of this type should be longitudinal, but the difficulties of obtaining a large sample size and the associated increase in the number of radiographic exposures tend to preclude this methodology. With regard to randomization, only the studies of Chang et al.[6] and Gabriel et al.[19] superficially mentioned that the sample records analyzed were randomly selected. However, the specific criteria for randomization were not described in their articles.

Only the article of Uysal et al.[27] established rigorous sample selection criteria, taking into account confounding factors such as lack of relative medical history, ethnicity, systematic diseases, medical syndromes, and hormonal disorders. Considering the influence of these co-factors on general growth and development, we judge that their rigorous criterion is a pleasant surprise that should be mimicked in future related studies.

The validity of CVM in the evaluation of craniofacial growth has been questioned. According to Gabriel et al.,[19] most of the studies that cited high-reproducibility results for the CVM method (>90%) used tracings of the cervical vertebrae instead of the actual radiographs during the CVM stage process, which may introduce bias in the staging results, and some studies used few rigorous measures of association for measuring agreement between judges. In a sample of 30 untreated subjects randomly selected, Gabriel et al.[19] concluded that CVM was a poorly reproducible method. We do agree that the study of Gabriel et al.[19] was the first specifically designed to eliminate the methodological errors observed in other studies of CVM reproducibility. However, the intraexaminer reproducibility outcome they found was interpreted as "low," while a widely accepted scale of reproducibility[44] would score it from "moderate" to "substantial." Furthermore, during frequency analysis of interobserver agreement and disagreement at the second time point in the study, the percentage of agreement increased 10% (607 to 665), while disagreements decreased (743 to 685). At the second time point,

Table 4. Characteristics of Moderate- and High-Quality Included Studies[a]

Author/ Demography and Study Design	Sample Size, Male/Female	Age Range/Mean Age (Male/Female), y	CVM[a] Evaluation Method	Standard Method (HWM[a] Evaluation Method)	CVM[a] Reproducibility Statistical Analysis
Chang et al.,[8] Taiwan, cross-sectional	244/259	8–18	Lamparski modified by Hassel and Farman (qualitative)	Fishman	Wilcoxon signed rank test
Gabriel et al.,[19] USA, cross-sectional	15/15	Not cited	Baccetti, Franchi, and McNamara (2005) (quantitative)	Not evaluated	Kendall's W Kappa
Imanimoghaddam et al.,[25] Iran, cross-sectional	20/27	10–15	Lamparski and Hassel and Farman (qualitative); San-Román and Mito et al. (quantitative)	TW3[b]	Not evaluated
Lai et al.,[26] Taiwan, cross-sectional	330/379	8.00–18.00	Baccetti, Franchi, and McNamara (2005) (quantitative)	NTUH-SMI[c]	Spearman rank order correlation coefficient
Soegiharto et al.,[2] Indonesia and UK, cross-sectional	Indonesian: 648/774 UK: 303/442	8.00–18.00/10.00–17.00/8.00–15.00	Baccetti, Franchi, and McNamara (2002) (quantitative)	Fishman	Cohen's Kappa
Uysal et al.,[27] (Turkish), cross-sectional	213/290	5.3–24.1/12.00 ± 2.07/ 12.03 ± 3.03	Lamparski modified by Hassel and Farman (qualitative)	Bjork and Grave an Brown	Spearman Brown formula

[a] CVM[a] indicates cervical vertebral maturation; [b]TW3 indicates Tanner & Whitehouse method; [c]NTUH-SMI indicates National Taiwan University Hospital Skeletal Maturation Index; [d]ROC indicates Receiver Operating Characteristics; HWM[a], hand-wrist maturation.

3 weeks after the first observation, the observers were retrained in the CVM method. Finally, the interexaminer reproducibility (Kendall's W) was moderate at the initial and 3-week time periods.

Soegiharto et al.,[2] Chang et al.,[8] Lai et al.,[26] and Uysal et al.[27] cited reproducibility results ranging from 85% to 98% using patients' actual radiographs. To determine values of reproducibility, these studies used the Spearman rank correlation test or Cohen's Kappa statistic. These are adequate measures of association used for ordinal data, recommended for measuring agreement between judges. However, two of these four studies[8,27] used the authors themselves as observers in interobserver and intraobserver agreement. According to Gabriel et al.,[19] authors who serve as observers have a "research-level" understanding of the CVM method, and, because of this, reproducibility results might be overstated. We concluded that in studies in which the authors themselves serve as observers, both the discussion and conclusion sections should report

Table 4. Extended

CVM[a] Correlation Test vs Gold Standard	CVM[a] and HWM[a] Accuracy	Results	Conclusions
Spearman rank order correlation coefficient and Wilcoxon signed rank test	Not evaluated	1: The intrajudge and interjudge reliability test indicated no significant difference for CVM ($P = .500$) and HWM ($P = .500$). 2: The Spearman rank correlation test showed a very strong correlation (r_s = 0.973 for boy and r_s = 0.970 for girl).	The results of this cross-sectional study indicate that skeletal age assessment made from CVM changes is reliable, reproducible, and valid.
Not evaluated	Not evaluated	CVM method showed substantial interobserver agreement with Kendall's W values in the range of 0.72 to 0.76. Weighted Kappa coefficient for intraobserver agreement ranged from 0.6 to 0.65 ($P < .05$).	The reproducibility was significantly below the level that is purported in the literature. The authors do not recommend the CVM method as a strict clinical guideline for the timing of orthodontic treatment.
Pearson correlation and Spearman correlation coefficients	Not evaluated	1: Pearson correlation coefficient between CVM and HWM was r = 0.81 and r = 0.80 for Lamparski's and Mito's CVM methods, respectively. There was no significant correlation between CVM and HWM in 10–13-y boys ($P > .05$). 2: Spearman correlation coefficient between Roman's, Hassel & Farman's CVM methods and HWM was r = 0.997 and r = 0.995, respectively.	The correlation between the TW3 method and Lamparski's and Mito's method was moderately high; therefore, no significant correlation was observed in 10–13-y-old boys. A high correlation coefficient was obtained between TW3 and Roman's and Hassel & Farman's methods, for all groups (considering gender and age).
Spearman rank order correlation coefficient	Not evaluated	1: CVM method showed good or substantial intraexaminer agreement (90%) with Spearman's rank correlation coefficient in the range of 0.963 to 0.981 ($P < .001$). The percentage of interexaminer agreement was 90%–93.3%. 2: Spearman's rank correlation (.910 for males and .937 for females) confirmed a strong and significant correlation between CVMS and NTUH-SMI systems ($P < .001$).	The authors suggest that the CVM system can be used to replace the NTUH-SMI system for the assessment of skeletal maturation of growing subjects in order to avoid additional radiation exposure.
Bland and Altman Method and Lin concordance	ROC[d] analysis	1: CVM method showed good or substantial intraoperator agreement. Kappa results range between 0.85/0.97 for the Indonesian boys and girls, respectively, and 0.94/0.95 for white boys and girls, respectively. 2: The Lin concordance also showed good correlation between the two measurements for both sex and ethnic groups.	This study confirms that both the skeletal maturation index and the CVM index are valid clinical diagnostic methods with which to discriminate patients into those who have not yet attained peak pubertal growth and those who have reached or passed it. The ROC analysis showed that HWM is a more accurate test than the CVM test in terms of predicting skeletal maturation, but the difference is unlikely to be clinically relevant.
Spearman rank order correlation coefficient	Not evaluated	1: CVM showed high reproducibility. Coefficient range between 0.955/0.987 for intra/interexaminer. 2: The correlations between CVM and HWM maturation were 0.86 for sexes combined, 0.78 for male, and 0.88 for female subjects. All were significant at $P < .001$.	The CVM method can be used as a maturity indicator of the pubertal growth spurt with a degree of confidence similar to that of some other indicators, such as hand-wrist radiograph.

clearly that the results were obtained by observers with a high level of expertise in the CVM method.

Three studies[6,26,27] included in this review described significant correlation (variable correlation strength) between hand-wrist skeletal maturation and CVM. Uysal et al.[27] reported moderate to high correlation between CVM and HWM for boys (r = 0.78) and girls (r = 0.88). Chang et al.[6] and Lai et al.[26] found a high degree of correlation between CVM and HWM for boys (r = 0.97/0.91) and girls (r = 0.97/0.94), respectively.

This difference may be attributed to the variety of CVM methods and different sample sizes. The study of Imanimoghaddam et al.[25] reported a different correlation between specific CVM methods and the same HWM (TW3 method) in a unique sample. This finding is consistent with those publications[6,26,27] that identified correlations of varying strengths between CVM and HWM using different CVM methods.

Wong et al.[14] stated that the CVM method is not sensitive for detecting maturity except in the growth-spurt period and that studies with wide age range, such as 5 to 18 years, might affect the correlation coefficient obtained because of the inclusion of subjects with skeletal maturity far from the pubertal growth. They used an age range from 10 to 17 years in a previous study. In four articles[2,6,25,26] from our sample of five selected studies the age ranged from 8 to 18 years, but in two of the studies[6,26] the correlation coefficient seemed not to have been affected by age variety.

According to Soegiharto et al.,[2] correlation values are not able to demonstrate that one method is better than the other. They evaluated the effectiveness of the skeletal maturation index and the CVM index through receiver operating characteristics analysis. We judge that their results provided the unique and best-documented evidence that really introduced a reliable analysis of the effectiveness of the CVM method in detecting peak pubertal growth. They also determined significant differences in the ability of the CVM and HWM methods to predict pubertal growth. Although statistically significant differences were observed between the two methods, their findings indicate that both the skeletal maturation index and the CVM index are valid clinical diagnostic indices for the prediction of peak growth of the maxilla and the mandible.

Finally, the prediction of skeletal maturation methods improves as the time of the growth spurt is approached. As stated by Houston et al.,[4] the use of individual ossification events is of limited use during pubertal growth-spurt prediction, and analysis that includes bone stages as well as ossification events is recommended.[3]

CONCLUSION

- Although some studies indicate that the CVM method shows good correlation with the HWM method, with considerable levels of reproducibility, these parameters are not good enough for determining the validity of the CVM method. Furthermore, these conclusions were based on six articles, which points to a low level of evidence, and the biggest question remains unanswered: How reliable is CVM staging for predicting the pubertal spurt?

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4.5 ARTIGO 2

Santiago, R.C.; Duque, P.H.R.; Campos, M.J.S.; Cerrone Jr, G.; Vitral, R.W.F.; Costa, L.F.M.; Bolognese, A.M. Analysis of the reliability of two qualitative cervical vertebrae maturation methods for growth assessment in orthodontic patients. **Orthodontics and Craniofacial Research** (Submetido)

Analysis of the influence of individual tracing on the reliability of two qualitative CVM methods

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Manuscript ID:	Draft
Manuscript Type:	Original Article
Research Area:	Diagnostic research, Growth & development, Imaging
Keywords (Please write 3 to 5 keywords according to Index Medicus):	skeletal maturity, cervical vertebral maturation, reliability

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Analysis of the influence of individual tracing on the reliability of two qualitative CVM methods

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Reliability of two cervical vertebrae maturation methods

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Abstract

Analysis of the influence of individual tracing on the reliability of two qualitative CVM methods

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Objectives - To assess the interrater and intrarater reliability of two cervical vertebrae maturation (CVM) identification methods (5-stage and 6-stage methods), as well as the influence of manual individual tracing on the reproducibility of the methods studied.

Setting and Sample Population - The Department of Orthodontics at Federal University of Juiz de Fora. Ninety lateral cephalometric radiographs randomly selected by lot.

Material and Methods - Five orthodontists were selected as examiners. Analysis of the radiographs was performed directly on light boxes or by individual tracing of cervical vertebrae at 2 different time points, with 6-week intervals.

Results: The use of the 5-stage method led the examiners to present improved performance, with 61.5% of agreement for intrarater and interrater reliability. Regarding to the use or not of a manual tracing, the direct visual examination of the radiographs led the examiners to present improved performance on interrater reliability, with a 62% of agreement on both time points. The mean values of weighted kappa for intra and interrater agreement ranged from 0.62 to 0.68.

Conclusions: The overall percentage of agreement observed in the present study was similar, regardless of the use or not of a manual tracing. The values of reliability suggest that clinicians need more training in the CVM methods or there is a need to improve existing qualitative methods reducing the variability during interpretations.

Keywords: skeletal maturity; cervical vertebral maturation; reliability.

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Analysis of the influence of individual tracing on the reliability of two qualitative CVM methods

Clinical Relevance

A better understanding regarding to the reliability of the CVM methods, with studies that evaluate its reproducibility using methods that eliminate the methodological shortcomings of previous reports, adding an extra level of sophistication on data analysis, is essential before clinical use of the CVM methods can be advocated

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Analysis of the influence of individual tracing on the reliability of two qualitative CVM methods

Introduction

The applicability and efficiency of a biological indicator of skeletal maturity are directly related to factors such as ability to detect peak growth without the need for additional radiographic exposure, ease of recording data, consistency in interpretation of data, and ability to anticipate occurrence of peak growth.(1) In this context, the use of the cervical vertebrae maturation (CVM) method has been suggested as an alternative to hand–wrist radiographs in determining skeletal maturation.

Extensive research has identified substantial correlation between the CVM method and the standard method using hand–wrist radiographs regarding skeletal age.(2-6) However, according to a previous study,(7) correlation analyses are unable to determine the applicability of a diagnostic method; this requires analysis of the accuracy of the method with identification of discriminatory power in detecting peak pubertal growth.

In musculoskeletal practice and research, there is frequently a need to determine the reliability of measurements made by clinicians—reliability here being the extent to which clinicians agree in their ratings, not merely the extent to which their ratings are associated or correlated. Defined as such, 2 types of reliability exists: (1) agreement between ratings made by 2 or more clinicians (interrater reliability) and (2) agreement between ratings made by the same clinicians on 2 or more occasions (intrarater reliability).(8)

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According to a previous research,(9) the efficiency of the CVM method lies not only in its accuracy but also in its reproducibility at the clinical level. Studies on the reliability of the CVM method report intraobserver and interobserver agreements exceeding 90%.(4,5,10,11) However, this high precision may be due to important methodological shortcomings.(9)

In a previous study,(9) which sought to eliminate methodological flaws that could directly affect the reliability of the method, it was concluded that the CVM method has poor reproducibility and should not be used clinically as the only guide in defining the optimal time for orthodontic treatment. However, the study leaves some questions unanswered, such as how to clearly train examiners, time gap between training and execution of analyses, sample size analyzed, and interpretation of the reproducibility values using a reference scale.

In a recent systematic review(12) it was concluded that the studies on CVM method suffer from serious methodological failures, suggesting that better-designed studies should be performed to validate the CVM method for radiographic assessment of skeletal maturity. Thus, the present study aimed to evaluate the reliability of 2 CVM identification methods, eliminating the methodological flaws observed in previous studies, and analyze the influence of prior individual tracing on the reproducibility of the methods.

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Materials and Methods

Ninety lateral cephalograms were randomly selected from those of 172 male and female patients of 7–18 years of age. To ensure homogeneity of the sample, the hand–wrist radiographs of the 172 subjects were first analyzed to determine the stage of skeletal maturity according to the method developed by Fishman.(13) Fifteen patients were randomly selected by lot from each group, as determined by Fishman's 11 stages (Group 1, SMI 1 and 2; Group 2, SMI 3 and 4; Group 3, SMI 5 and 6; Group 4, SMI 7 and 8; Group 5, SMI 9 and 10; and Group 6, SMI 11), to yield a total of 90 patients in the sample. The groups were established taking into account the direct correspondence between some SMI levels and six different categories of CVM established in a previous study.(11)

In composing the sample the following inclusion criteria were followed: (1) no history of trauma to the face and/or hand and wrist; (2) absence of congenital and/or acquired malformations that would affect vertebrae and/or hand and wrist; (3) no modifications of development due to hormonal syndromes or disorders; and (4) hand–wrist radiographs and lateral radiographs of the same patient performed on the same day.

To determine the stage of skeletal maturity according to the lateral radiographs, 2 qualitative methods were employed, namely, Baccetti, Franchi, and McNamara(14) (5-stage method) and Baccetti, Franchi, and McNamara(15) (6-stage method). The first method analyzes the C2, C3, and C4 cervical vertebrae according to 5 distinct stages (Figure 1), while the second uses 6 stages to determine the maturation of the same

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vertebrae (Figure 2). Complete details about CVM methods can be found elsewhere.(14,15)

Five orthodontists who did not have previous experience using the CVM method were selected as examiners. The 5 examiners received training in the use of the 2 CVM methods by a dental surgeon who specializes in imaging techniques and has extensive experience in the methods of interest. The presentation was held in PowerPoint format (Microsoft®) with an average duration of 10 minutes and communicated the 5-stage(14) and 6-stage(15) methods exactly as described, with emphasis on the definition of the morphology of the C2, C3, and C4 vertebrae, as well as on the identification of the different stages of skeletal maturation defined by the 2 methods.

Immediately after training, the 90 radiographs were analyzed with the aid of light boxes in a darkened room to ensure contrast enhancement of the bone images. The radiographs were analyzed in 18 rounds, each containing 5 light boxes. There was no communication allowed between the examiners and they did not have access to any additional information regarding the patient, such as age, gender, and stage of teething. During evaluation of the vertebrae, a sheet of black cardboard with a central rectangular cutout was placed on each light box (Figure 3), which allowed visualization of only the area of interest. Templates containing the CVM stages according to the methods(13,14) were positioned on each light box, as shown in Figures 1 and 2.

Two types of evaluation were employed for the analysis of cervical vertebrae: Type 1, evaluation using manual individual tracing of the C2, C3, and C4 vertebrae; and Type 2, direct visual assessment of cephalometric radiographs. The whole procedure was repeated 6 weeks (T2) after the first evaluation (T1) with a random distribution of radiographs in different sequence from the first assessment. All examiners received the same training again as for the first evaluation.

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Statistical analysis was performed using the SPSS 13.0 and Medcalc 12.2.1.0 software packages. The overall percentage of agreement intra and interrater was calculated. To analyze reproducibility, the weighted *kappa* test was employed for assessing intraobserver and interobserver agreements.

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Results

Disregarding the method and form of assessment, there were 2074 (57.61%) interrater agreements and 1526 (42.39%) disagreements at T1 and 2119 (58.86%) agreements and 1481 (41.14%) disagreements at T2 (Table 1). Considering the tested method and form of assessment, the highest percentage of interrater agreement at the 2 instances of assessment was evident during the analysis performed without the aid of manual tracing according to the method established by Baccetti, Franchi, and McNamara.(14)

On average, the weighted *kappa* value for interrater agreement ranged between 0.62 and 0.69 (Table 1). The interrater disagreement was evaluated to determine the stage gap involved, for example, 1 stage apart or 2 stages apart during disagreement (Table 2). The 5-stage method(14) without manual tracing showed 87.6% of the disagreements between examiners due to 1 stage apart at T2 (Table 2). Overall, the disagreements by 1 stage apart were seen in 77.8%–82.1% of the observations in the 6-stage method(15) and in 81.4%–87.6% of analyses by the 5-stage method.(14)

There were 1800 intrarater observations performed on the 90 individuals in the sample, 900 through manual individual tracing and 900 by direct visualization of the cervical vertebrae images. Among the methods suggested, the percentage of intrarater agreement was higher when using the 5-stage method(14) (Table 3)

On average, the weighted *kappa* value for intrarater agreement ranged between 0.65 and 0.67 (Table 4). The weighted *kappa* coefficient not only measures the level of agreement, but also factors of level of disagreement. This explains why the observed difference between the percentages of agreement among the methods considered was greater than that observed between the values of the *kappa* coefficient. Thus, the

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frequency of intraobserver disagreement by 2 or more stages apart, employing the methods developed by Baccetti, Franchi, and McNamara(14,15) without tracing, was higher compared with the same methods with tracing (Table 5). The method proposed by Baccetti, Franchi, and McNamara(14) analyzed with manual tracing showed 87.4% of the inconsistencies of an observer in relation to his initial assessment due to 1 stage apart (Table 5).

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Discussion

We attempted to eliminate methodological shortcomings of previous studies in accordance with a recent study(8) and added key points to control possible bias. The first concern of this study was to avoid selection bias in the sample, because certain morphological characteristics of the cervical vertebrae, such as the presence of a concavity in the lower edge, would be more easily identified when compared with the vertebral body shape (trapezoidal, horizontal rectangular, square, or vertical rectangular) and influence the reproducibility of the CVM method.(16)

To reduce the possibility that the sample in this study would contain a number of divergent individuals in a CVM stage that was easier or more difficult to identify, the skeletal maturity was previously determined by the method of Fishman(13). According to a previous study,(11) there is a direct correspondence between a combination of some skeletal maturation levels defined by Fishman's HWM method and different categories of cervical vertebrae skeletal maturation. The final sample was randomly assembled by lot, containing an equivalent number of individuals from each group, as determined by carpal radiography, without the knowledge of the examiners.

With regard to information bias, all 5 examiners were presented with the cephalometric radiographs of the study immediately after training and completed their classifications under the same conditions. Thus, unlike the method adopted in a previous work(9) that does not describe clearly the training of the examiners nor the time and the conditions in which the examiners performed their evaluations after receiving training, the methodology of this work eliminates the possibility of information bias, which can interfere directly in the levels of reproducibility of the method.

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The percentage of interobserver agreement was virtually the same at the two time points of this study, with more agreements (approximately 60%) than disagreements in both evaluations. This result differs from that found in a previous study,(9) in which the percentage of interobserver agreement, regarding the stage of CVM identification, was less than 50% in both evaluations. This difference may be related to the methodology of the present study, which eliminated the possibility of information bias, thus improving the observers agreement.

It was hypothesized that, although the reproducibility of the method could be questionable, it may perform better once the examiners understand the details involved in identifying the different stages of maturation of the cervical vertebrae. In the present research, a slightly higher level of interrater agreement in T2 was observed, may be linked to the fact that the examiners already had a prior understanding of the methods under analysis, but these differences were not statistically significant ($p>.05$).

An intra-examiner agreement of 60% on average was observed in this study. This result is similar to that of a previous study.(9) The percentages of inter- and intraobserver agreements show that, on average, examiners disagree in their own assessments or among themselves in 1 of every 3 evaluations, demonstrating the variability of the methods for CVM identification analyzed in this study.

The percentage agreement between staging is an unequivocal measurement of reproducibility.(9) However, the overall percentage agreement did not takes into account the agreement that would be expected purely by chance. On the other hand, the *Kappa* coefficient is a specific statistical method commonly used to assess reliability, indicating the proportion of agreement beyond that expected by chance.(8)

The coefficients of interobserver agreement (0.62 to 0.69) and intraobserver agreement (0.65 to 0.67) of the present study are well below those found in the

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literature, where agreement coefficients of 0.85–0.98 have been reported.(3,5,7,10) However, according to another research,(9) the majority of these studies did not use rigorous statistical measures of association regarding the evaluation of inter- and intraobserver agreements for ordinal data. The cited authors used the same statistical test applied in this study, the weighted *kappa* coefficient for analysis of intraobserver agreement, which ranged between 0.60 and 0.65. Although these values are comparable with the mean values observed in the present study, the confidence intervals associated with the *Kappa* values calculated in the present study differed from those of Gabriel and colleagues,(9) with a small range of plausible values for the value of *Kappa*, with a 95% level of confidence.

According to a previous research,(9) the validity of the CVM identification method is in its reproducibility between examiners. If clinicians do not agree with respect to maturation stage, the method has no clinical relevance. Furthermore, the number of stages apart in disagreement between 2 observations indicates the degree of randomness in the staging according to the CVM method. In their study, interobserver disagreement by 2 or more stages apart occurred 29% of the time on average. With respect to intraobserver disagreements, these occurred by 2 or more stages apart in 34% of cases between evaluations. In the present work, the disagreements by 2 or more stages apart occurred, on average, in 16.7% of cases among examiners and 17.2% of the time in intraobserver assessments. Probably, the method of training of observers, as well as control of information bias, adopted in this study may have contributed to the better performance of the CVM identification method with respect to the observed discrepancies. Finally, stating that the validity of a diagnostic method is in its reproducibility is misleading. Actually, its validity relates to how well it enables the clinician to predict growth spurt.

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To date, no studies have evaluated the influence of manual individual tracing of cervical vertebrae on the reproducibility of the CVM identification method. In the present research, it was hypothesized that the comparison between the tracing and the template could interfere on the reproducibility of the method. This fact was not considered in a previous study(9), and an improvement in terms of reproducibility could be expect because the examiners made their evaluations comparing their individual manual tracings directly with the templates containing the images of the different CVM stages. However, the results showed that the use of manual tracing was not directly reflected in higher reproducibility of the methods evaluated. Rather, the use of manual tracing reduced the interrater percentage agreement and the kappa concordance coefficient between examiners.

Studies on reproducibility of a method using the authors as examiners may produce overstated results due to greater understanding of the CVM method.(9) However, this hypothesis was not verified in this study, in which the 5 examiners were also authors of the study but did not have any in-depth understanding or experience of the CVM methods of identification. The reproducibility found in the results was well below that observed in previous studies(4,5,6,10) in which the authors were also examiners. When authors act as examiners, clarification of their level of understanding and experience in relation to the method of determining CVM is appropriate.

Finally, the possibility of the CVM method employed influencing the reproducibility was considered. The results of this study indicate that the method advocated by Baccetti, Franchi, and McNamara(14) showed better performance in terms of inter- and intraobserver agreements. This fact may be associated with fewer stages adopted by the Baccetti, Franchi, and McNamara(14) (5 stages), when compared with

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the Baccetti, Franchi, and McNamara(15) method (6 stages), reducing the possibility of disagreement between assessments.

The results showed that the reproducibility of the CVM identification method analyzed could be affected by factors such as sample quality, adequate training, evaluation method, and experience of the examiners appear to directly influence reproducibility. However, the questionable reproducibility of the method of determining CVM does not, by itself, prevent its use. The hand–wrist radiograph, which is considered the most standardized and utilized method in orthodontics to analyze skeletal maturity,(5,17,18) also presents questionable reproducibility, as was shown in a previous work.(19)

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Conclusions

The use of manual tracing is not directly reflected in higher reproducibility of the methods evaluated, and the method advocated by Baccetti, Franchi, and McNamara(11) showed the same performance when compared with the Baccetti, Franchi, and McNamara(12) according to the weighted *Kappa* concordance coefficient.

There was a significant variability of the CVM methods evaluated, with an intra- and interrater disagreement of approximately 40% on average. It might mean that there is a need to improve existing qualitative methods with adequate examiners training, or to develop objective (quantitative) methods, that reduce the variability of inference analysis of the CVM stage due to individual interpretations.

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FIGURES LEGENDS

Figure 1- Method developed by Baccetti, Franchi e McNamara.(14)

Figure 2- Method developed by Baccetti, Franchi e McNamara.(15)

Figure 3- Method of cervical vertebrae visualization on light box.

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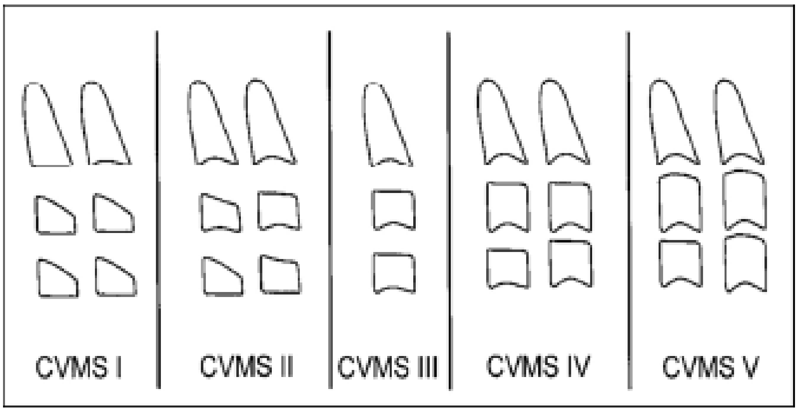

Method developed by Baccetti, Franchi e McNamara.(14)
122x62mm (300 x 300 DPI)

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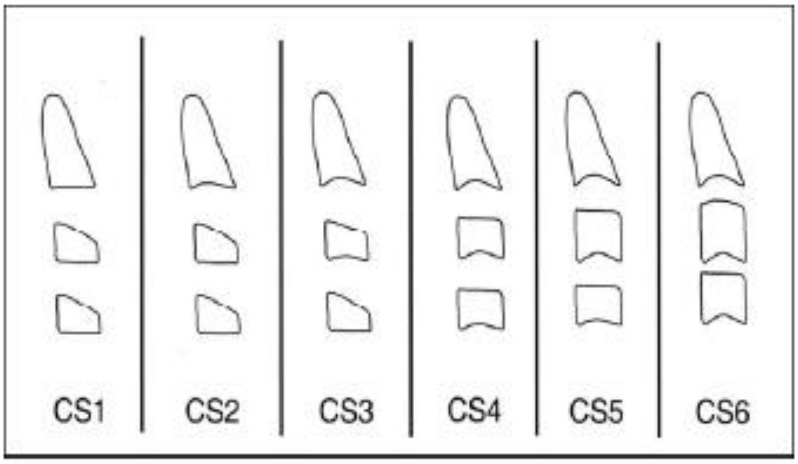

Method developed by Baccetti, Franchi e McNamara.(15)
177x101mm (300 x 300 DPI)

Method of cervical vertebrae visualization on light box.
116x106mm (300 x 300 DPI)

Table 1. Interrater agreement percentage and the Weighted Kappa coefficients for interrater agreement analysis between the initial (T1) and 6-week times (T2)

Time of evaluation	*Method employed*	*Type of evaluation*	*Agreement/ Disagreement*	*% agreement*	*Weighted Kappa Coefficient (95% confidence limits)*
T1	*6-stage method*[15]	1*	459/441	51.00	0.62 (0.52-0.71)
		2**	535/365	59.44	0.67 (0.57-0.77)
	5-stage method[14]	1*	503/397	55.88	0.62 (0.51-0.73)
		2**	577/323	64.11	0.67 (0.57-0.76)
		SUB-TOTAL	2074/1526	57.61	0.65 (0.56-0.75)
T2	*6-stage method*[15]	1*	480/420	54.66	0.63 (0.53-0.73)
		2**	532/368	59.11	0.67 (0.57-0.76)
	5-stage method[14]	1*	522/378	58.00	0.63 (0.53-0.73)
		2**	585/315	65.00	0.69 (0.59-0.80)
		SUB-TOTAL	2119/1481	58.86	0.66 (0.56-0.76)
		TOTAL	4180/3020	58.23	0.66 (0.55-0.76)

*Evaluation using manual individual tracing of the C2, C3, and C4 vertebrae; **Direct visual assessment of cephalometric radiographs.

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Table 2. Cervical stage differences for interrater disagreements according to the method developed by Baccetti, Franchi e McNamara[15] and Baccetti, Franchi and McNamara[14] at the initial (T1) and 6-week times (T2)

T1				*T2*			
With manual tracing		*With direct visual assessment*		*With manual tracing*		*With direct visual assessment*	
Cervical stages apart	*Total disagreement (%)*	*Cervical stages apart*	*Total disagreement (%)*	*Cervical stages apart*	*Total disagreement (%)*	*Cervical stages apart*	*Total disagreement (%)*
6-stage method [15]							
1	82.1	1	77.8	1	81.9	1	81.0
2	16.1	2	17.8	2	14.5	2	16.5
3	1.8	3	4.4	3	3.3	3	1.8
4	0	4	0	4	0.3	4	0.7
5	0	5	0	5	0	5	0
5-stage method [14]							
1	85.0	1	81.4	1	85.0	1	87.6
2	13.8	2	17.3	2	13.7	2	11.1
3	1.2	3	1.3	3	1.3	3	1.3
4	0	4	0	4	0	4	0

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Table 3. Intrarater agreement percentage between the initial (T1) and 6-week times (T2)

	6-stage method [13]				*5-stage method* [14]			
Examiner	*With manual tracing*		*With direct visual assessment*		*With manual tracing*		*With direct visual assessment*	
1	60.0%	(54/90)	66.6%	(60/90)	62.2%	(56/90)	70.0%	(63/90)
2	63.3%	(57/90)	68.8%	(62/90)	67.7%	(61/90)	74.4%	(67/90)
3	63.3%	(57/90)	51.1%	(46/90)	60.0%	(54/90)	55.5%	(50/90)
4	47.8%	(43/90)	53.3%	(48/90)	53.3%	(48/90)	56.7%	(51/90)
5	52.2%	(47/90)	48.9%	(44/90)	63.3%	(57/90)	52.2%	(47/90)
Total	57.3%	(258/450)	57.8%	(260/450)	61.3%	(276/450)	61.8%	(278/450)

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Table 4. Weighted Kappa coefficients for intrarater agreement analysis between the initial (T1) and 6-week times (T2)

	Weighted Kappa coeficient for the 6-stage method[15] (95% confidence limits)				*Weighted Kappa coeficient for the 5-stage method[14] (95% confidence limits)*			
Examiner	*With manual tracing*		*With direct visual assessment*		*With manual tracing*		*With direct visual assessment*	
1	0.67	(0.57-0.77)	0.72	(0.62-0.82)	0.66	(0.55-0.76)	0.73	(0.64-0.83)
2	0.73	(0.64-0.82)	0.76	(0.67-0.85)	0.73	(0.64-0.82)	0.76	(0.67-0.86)
3	0.71	(0.61-0.81)	0.59	(0.48-0.70)	0.64	(0.53-0.75)	0.60	(0.49-0.71)
4	0.62	(0.52-0.72)	0.59	(0.49-0.70)	0.60	(0.50-0.71)	0.59	(0.48-0.70)
5	0.63	(0.54-0.73)	0.64	(0.54-0.73)	0.70	(0.61-0.79)	0.59	(0.48-0.70)
Mean	0.67	(0.58-0.77)	0.66	(0.56-0.76)	0.67	(0.51-0.77)	0.65	(0.55-0.76)

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Table 5. Cervical stage differences for intrarater disagreements according to the method developed by *Baccetti, Franchi and McNamara*[16] and *Baccetti, Franchi and McNamara*[14] between the initial (T1) and 6-week times (T2)

With manual tracing		*With direct visual assessment*	
Cervical stages apart	*Total disagreement (%)*	*Cervical stages apart*	*Total disagreement (%)*
	6-stage method[14]		
1	83.3	1	80.0
2	15.1	2	16.3
3	1,6	3	2.6
4	0	4	1.1
5	0	5	0
	5-stage method[16]		
1	87.4	1	82.5
2	10.9	2	15.8
3	1.7	3	1.1
4	0	4	0.6

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4.6 ARTIGO 3

Santiago, R.C.; Cunha, A.R.; Cerrone Jr, G.; Fernades, N.; Costa, L.F.M.; Vitral, R.W.F.; Bolognese, A.M. Computerized cervical vertebral geometry assessment and its relationship to skeletal maturation - A Multinomial Logistic Regression analysys. **Dentomaxillofacial Radiology** (Submetido)

Dentomaxillofacial Radiology

New software for cervical vertebral geometry assessment and its relationship to skeletal maturation - a pilot study

--Manuscript Draft--

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Abstract:	Objectives: The aim of this study was to develop new software for quantitative analysis of cervical vertebrae maturation (CVM), and to evaluate its applicability through a multinomial logistic regression model (MLRM). Methods: Digitized images of the bodies of the 2nd (C2), 3rd (C3), and 4th (C4) cervical vertebrae were analyzed in cephalometric radiographs of 236 subjects (126 boys and 120 girls) by using software developed for digitized vertebrae analysis (DVA). The sample was initially distributed into 11 categories according to the Fishman's skeletal maturity indicators and were then grouped into 4 stages for quantitative cervical maturational change analysis (QCMC I, II, III, and IV). Seven variables of interest were measured and were analyzed to identify morphologic alterations of the vertebral bodies in each QCMC category. Results: Statistically significant differences ($p < 0.05$) were observed among all QCMC categories for the variables analyzed. The MLRM utilized to calculate the probability that an individual belonged to each of the 4 CVM categories was constructed by taking into account gender, chronological age, and 4 variables determined by DVA (Ang_C3, MP_C3, MP_C4, and SP_C4). The MLRM presented a predictability of 81.4%. Conclusions: Significant alterations in the morphologies of the C2, C3, and C4 vertebral bodies analyzed through the DVA software occur during the different stages of skeletal maturation. The model that combines the four parameters measured on the vertebral bodies, the age and the gender showed an excellent prediction.

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New software for cervical vertebral geometry assessment and its relationship to skeletal maturation - a pilot study

ABSTRACT

Objectives: In the present study, we developed a new software for quantitative analysis of cervical vertebrae maturation (CVM), and we evaluated its applicability through a multinomial logistic regression model (MLRM). **Methods:** Digitized images of the bodies of the 2nd (C2), 3rd (C3), and 4th (C4) cervical vertebrae were analyzed in cephalometric radiographs of 236 subjects (126 boys and 120 girls) by using software developed for digitized vertebrae analysis (DVA). The sample was initially distributed into 11 categories according to the Fishman's skeletal maturity indicators and were then grouped into 4 stages for quantitative cervical maturational change analysis (QCMC I, II, III, and IV). Seven variables of interest were measured and were analyzed to identify morphologic alterations of the vertebral bodies in each QCMC category. **Results:** Statistically significant differences ($p < 0.05$) were observed among all QCMC categories for the variables analyzed. The MLRM utilized to calculate the probability that an individual belonged to each of the 4 CVM categories was constructed by taking into account gender, chronological age, and 4 variables determined by DVA (Ang_C3, MP_C3, MP_C4, and SP_C4). The MLRM presented a predictability of 81.4%. The weighted *kappa* test showed almost perfect agreement (k = 0.832) between the categories defined initially by the method of Fishman and those allocated by the MLRM. **Conclusions:** Significant alterations in the morphologies of the C2, C3, and C4 vertebral bodies analyzed through the DVA software occur during the different stages of skeletal maturation. The model that combines the four parameters measured on the vertebral bodies, the age and the gender showed an excellent prediction.

Keywords: cervical vertebrae; skeletal maturity; quantitative method.

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New software for cervical vertebral geometry assessment and its relationship to skeletal maturation - a pilot study

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INTRODUCTION

The identification of the pubertal growth spurt has great value in dentistry. The highest response to functional orthopedic stimuli applied to the jaw bones tend to occur during this period and its effectiveness is directly related to bone maturation [1,2,3,4]. Among the various indicators of skeletal maturity, hand and wrist radiographs have been used as a standard method. Nevertheless, in addition to concerns regarding additional exposure to radiation[5], some studies have questioned this method's utility due to the complexity of identifying reference points, which can lead to inaccurate analysis [6,7].

The effectiveness of a biological indicator of skeletal maturity is directly related to factors such as the ability to detect and predict the growth spurt peak without the need for additional radiation exposure, and the high level of agreement between examiners for the definition of the stages [8]. In this context, the use of the cervical vertebrae has been suggested as an alternative to hand and wrist radiographs in the determination of skeletal maturation.

In the last 2 decades, several studies have analyzed the applicability of lateral cephalometric radiographs to determine skeletal maturity based on the analysis of alterations in the morphology of the cervical vertebrae, especially the 2nd (C2), 3rd (C3), and 4th (C4) vertebrae [1,2,9-14]. Although several studies [1,5,12,15,16] have validated the use of the cervical vertebrae as indicators of skeletal maturation through the strong correlation between the methods of cervical vertebrae maturation (CVM) and hand and wrist skeletal maturity, recent studies have questioned its applicability [17,18].

The first concerns regarding the validity of qualitative methods for identifying CVM are related to the consistency during data interpretation. These methods (CVM) [10,15,19-21] take into account a subjective comparison between images of the vertebrae and a reference atlas containing the CVM stages. This type of analysis does not seem to be the most appropriate because, according to previous studies [13], the cervical vertebrae have less skeletal maturity indicators and their signs of morphological alterations during growth are not as specific and recognizable when compared to hand and wrist radiographs, leading to a questionable reproducibility between examiners.

A previous study conducted by Gabriel et al. [22], which sought to eliminate methodological flaws that could directly affect the reproducibility of the evaluated methods, concluded that the reproducibility of the studied CVM model was poor between clinicians and should not be used clinically as the only guide to define the optimal time for orthodontic treatment.

The low reproducibility of a diagnostic method, in particular qualitative methods for identifying CVM [9,15,19], brings into question the accuracy of those models in the way they are proposed. Several studies [23-25] have established the skeletal age of individuals from multiple regression analyses with the aim of developing new quantitative methods for objective analysis of the maturation of cervical vertebrae and reducing the variability of interpretations among examiners. However, questions remain regarding the standard method utilized for the determination of the skeletal age [26] and the lack of accuracy in the prediction of the proposed methods [27].

Thus, the present study aimed to develop a new quantitative method for the identification of cervical vertebrae maturation through computer analysis by using specific software design by the authors and to evaluate the applicability of this new method by using a multinomial logistic regression model (MLRM). Additionally, we also evaluated the predictability of a MLRM using solely chronological age or a combination of age and gender as skeletal maturation predictors.

MATERIALS AND METHODS

The data from this cross-sectional study were obtained from lateral cephalometric radiographs and hand and wrist radiographs taken as part of the routine orthodontic records. The sample included 236 children, 116 boys (mean[SD], 146.4, 25.21months) and 120 girls (mean [SD], 146.2, 24.1 months), consecutively selected between January and December 2011. The following selection criteria were used during the sample composition: (1) white Brazilian subjects with no history of trauma to the face and/or hand and wrist, (2) absence of congenital and/or acquired malformations that could affect the vertebrae or the hand and wrist, (3) general good health, and (4) cephalometric and hand and wrist radiographs taken on the same day and with good visualization of the structures of interest, such as the C2, C3, and C4 cervical vertebrae.

The radiographs of the hands and wrists were used as the standard method for determining the degree of skeletal maturation of each individual and were analyzed by a dental surgeon who specializes in images techniques with extensive experience in the method of interest. The radiographs were classified according to the skeletal maturation index (SMI) described by Fishman [28] and were divided into 11 groups (Table I). All analyses were performed in the dark with the same light box, and the examiner was unaware of any additional information such as chronological age and gender. For reliability analysis in relation to the staging of the hand and wrist radiographs, 30 radiographs were examined twice with an interval of 2 weeks between assessments.

The 11 stages of Fishman's skeletal maturity [28] can be grouped into periods of acceleration (SMI 1–3), high velocity (SMI 3–7), and deceleration (SMI 8–11) [29]. In the present study, the radiographs were grouped into 4 stages of cervical vertebrae maturation, taking into account Fishman's indicators of skeletal maturity, but segregating the period of deceleration (SMI 8-11) into 2 different stages due significant anatomical differences between SMI 8-9 and SMI 10-11in the morphologies of the C2, C3 and C4 cervical vertebrae bodies.

The quantitative cervical maturational changes (QCMC) comprised 4 stages: QCMC I (acceleration of growth), which includes Fishman's stages 1–3; QCMC II (high growth rate), which includes Fishman's stages 4–7; QCMC III (decelerated growth), which includes Fishman's stages 8 and 9; and QCMC IV (consummation of growth), which includes Fishman's stages 10 and 11(Table I).

The radiographs were scanned (Umax Astra 2400 SLT) at 600 dots per inch (dpi) and digitalized through the Corel Photo-Paint software, version 11.0 (Corel Photo-Paint ®, Corel Corporation, Ottawa, CAN). The morphologies of the C2, C3, and C4 cervical vertebrae were analyzed in an objective manner (quantitative) through software developed specifically for this study. The software for digitized vertebrae analysis (DVA) was developed in Microsoft.NET

Framework in the C# language in order to aid the specialist in the analysis of the image; this software provided measurements and proportions of the C2, C3, and C4 vertebrae based on reference points marked manually on the image (Figure 1). After defining the points of interest, the tool used methods of linear algebra and spatial analysis to generate the dimension, proportion, and angle values. The reliability and intra-observer reproducibility of the measures established by the DVA software were verified by analyzing 30 randomly selected cephalometric radiographs. The measures of interest were analyzed at 2 different times separated by an interval of 2 weeks.

The measurements of interest were determined as follows (Figure 2):

AB and CD: superior and lower borders of the body, respectively;

AC and BD: posterior and anterior borders of the body, respectively;

ANG_C2, ANG_C3, and ANG_C4: internal angle formed by the intersection of the lines that connect the points CE and ED at the lower borders of C2, C3, and C4, respectively.

SP_C3 and SP_C4: square proportion of C3 and C4, respectively, given by the ratio between the line parallel to the lower border (CD) connecting the points G and G ' and the line parallel to the posterior border (AC) that connects points F and F '.

MP_C3 and MP_C4: maturity proportion of C3 and C4, respectively, given by the ratio between the anterior border (BD) and the posterior border(AC).

The sample was evaluated regarding 9 variables: (1) chronological age (months); (2) gender; (3) ANG-C2; (4) ANG_C3; (5) ANG_C4; (6) SP_C3; (7) SP_C4; (8) MP_C3; and (9) MP_C4.

Statistical analysis

All statistical analysis was performed with a software package (SPSS for Windows, version 13.0, SPSS, Chicago, Ill). The averages and standard deviations were calculated. Statistical analysis included the χ^2 test, ANOVA test, weighted *kappa* test, Spearman's rank correlation coefficient and multinomial logistic regression analysis. A significance level of $p < 0.05$ was established. The statistical Excel software (Microsoft Office ® 2007, USA) was used to analyze the data and obtain the probabilities of the multinomial regression model.

The logistic model enables the direct estimation of the probability of the occurrence of an event, such as whether an individual belongs to a certain category [30]. The logistic regression model, originally developed for binary response variables, can be extended to multinomial response variables (3 or more categories), as observed in the current study, where the sample was divided into 4 stages of QCMC (QCMC I–IV). Although the multinomial logistic regression model (MLRM) is appropriate for nominal data, ordinal variables can be treated as nominal data, minimizing some issues such as lack of homoscedasticity, linearity, and incorporating outliers.

In this study, each of the variables analyzed (chronological age, gender, hand and wrist maturity, ANG_C2, ANG_C3, ANG_C4, SP_C3, SP_C4, MP_C3, and MP_C4) was inserted individually in a MLRM that adopted the QCMC I as reference, due to the greatest number of subjects on this stage . The variables that contributed significantly to the differentiation of the QCMC stages II, III, and IV from the reference category (QCMC I) remained in the final model. Three linear functions *g(x)* were generated and it was possible to calculate the conditional probabilities that each radiograph analyzed belonged to a QCMC stage. Finally, the model was established by the intercept of the independent variables that contributed significantly to the discrimination between categories and their respective B coefficients (variable coefficient).

In an attempt to compare the predictability of the present model with some simpler methods of skeletal age estimation, such as the use of age and gender, we did evaluate the MLRM model using only chronological age or a combination of age and gender to compare the total and partial percentages of the correctness of the model obtained with the final model established in the present study.

The spreadsheet generated in Excel software by the insertion of data from the 6 independent variables included in the final model allowed the determination of the probability that each radiograph belonged to 1 of 4 QCVM categories (QMVC I, II, III, or IV). The most likely probability for distribution of the sample in each category (QMVC I, II, III, or IV) was adopted.

RESULTS

The intra-class correlation coefficient (ICC = 0.997) revealed intra-observer reproducibility and reliability in the classifications of HWM stages. Regarding the reproducibility of the examiner while using the software, the paired t test did not show a statistically significant difference for any of the measures analyzed (*p*= 0.562; mean standard error= ANG_C2[±0.52], ANG_C3[±0.40], ANG_C4[±0.68], SP_C3[±1.18]. MP_C3[±0.54], SP_C4[±1.19], MP_C4[±0.74]).

The distribution of individuals according to the SMI and QCVM is shown in Table I. The distributions of gender and means and standard deviations for the variables of interest are shown in Table II. A statistically significant difference ($p < 0.05$) was observed in the distribution of all variables for each of the QCVM categories.

The correlation between 7 parameters of cervical vertebrae morphology and the SMI was derived through Spearman rank correlation coefficient (CC) analysis (Table III).

The 6 independent variables of interest (Var1–Var6) that remained in the model after the multinomial logistic regression analysis are presented in Table IV. The model provided 3 logit g(x) functions, 1 for each QCVM category (II, III, and IV), which took into account the observed values for the 6 independent variables (Var1–Var6), the intercept (β0), and the coefficients for each independent variable (B1–B6).

The total and partial percentages of the correctness of the model obtained in this study are shown in Table V. The total and partial percentages of the correctness of the model obtained with the use of chronological age or a combination of age and gender are shown in Table VI. The result of the weighted *kappa* test, which analyzed the correlation between the categorizations established by the logistic regression model and the 4 QCMC stages established according the 11 stages of Fishman's skeletal maturity [28] showed an almost perfect agreement (Table VII).

DISCUSSION

The methodology of the present study was established while taking into consideration criteria for assessing the quality of studies on cervical vertebrae maturation established in a recent systematic review [17] in order to avoid methodological flaws that could impair the validity of the presented results.

The development of specific software (DVA) for analyzing the morphology of the cervical vertebrae and possible alterations during different stages of skeletal maturation allowed the obtainment of automatic measures of interest from the identification of specific points located on the body of C2, C3, and C4. Unlike other studies [13,23,24] in which the measures of interest were obtained manually in individual cephalometric traces, the methodology used with the DVA software aimed to reduce interferences by the examiner. This is particularly relevant with regard to obtaining the angular variables, where the simple identification of points of interest in the vertebral bodies was enough for the software to provide all of the necessary measures.

The quantitative method proposed in this research initially aimed to reduce the variability of interpretation during the determination of the cervical vertebrae maturation stages, which, according to Gabriel et al, [22] compromises the validity of the CVM method as an indicator of skeletal maturity. Regarding the reproducibility of the measurements using the software in the present study, no significant difference between the analyzed measures was observed.

Among the few studies that have developed new methods for quantitative analysis of the CVM [13,23-25], controversy exists about the adequacy of the analysis of hand and wrist radiographs. Most of these studies [23-25] used the TW2 and TW3 methods as the standards in the analysis of carpal skeletal maturity. According to a previous study [26], carpal analyses that determine bone-specific age, such as TW2 [31] and TW3 [32], are less useful because they are more susceptible to the influence of the environment and the gender and racial composition of the sample. Methods that determine the relative growth rate and the percentage of remaining growth, such as those proposed by Fishman [28] and that used in the present study, are more suitable because they use bone developmental stages associated with ossification events and define the percentage of remaining growth [26].

The results obtained with the DVA analysis software revealed some interesting details. Several studies suggest an association between anatomical alterations in the bodies of the cervical vertebrae and growth [2,10,15,21]. One of these alterations is related to the increase of the concavity on the lower edges of C2, C3, and C4 in advanced stages of maturation [10,13]. This fact is consistent with the findings of the present study, where a significant reduction of the angle of the concavity of C2, C3, and C4, consistent with an increase in the concavity, was observed when the degree of skeletal maturity between QCMC stages increased.

Another important alteration in the morphology of the cervical vertebrae concerns the shape of the C3 and C4 vertebral bodies. In the early stages of skeletal maturation, the vertebral bodies are expected to have a trapezoidal shape, which changes to a horizontal rectangular, square, and rectangular vertical shape as growth progresses [10,13,19]. Mathematically, the proportion between the anterior and posterior wall is expected to be smaller in the early stages, which subsequently approaches and equates to 1 as maturity increases and the vertebral bodies become rectangular or square. The objective analysis of the present study verified this relationship through the maturity proportion

(MP) and further revealed that the anterior wall remains smaller than the posterior wall on average as this ratio increases towards 1, even in advanced stages of maturation, although significant differences exist between the QCMC stages. This observation casts uncertainty on the rectangular or square shape suggested for these vertebral bodies, which was used as the standard in the proposed atlas in previous qualitative analyzes [10,15,19,21].

An additional observation regarding the shape of the bodies of C3 and C4 is that the ratio was greater than 1 on average between the width and height (square proportion) in all QCMC stages in this study. This porportion was significantly reduced between the QCMC stages I and IV, which suggests an increase in the height of the vertebral bodies in the later stages of growth and confirms the findings of another study [13]. However, the present results demonstrate that the bodies of the vertebrae fail to provide a vertical rectangular shape on average, as suggested in the qualitative methods previously proposed [10,15,19,21]. With maturation, we observed that the vertebral bodies tended to acquire a shape that was increasingly quadrangular, with an increase in the concavity of the lower border; this change was initially more evident in C2 and subsequently in C3 and C4.

After analyzing the individual behavior of the variables used in the software, the multinomial logistic regression model was applied to identify the parameters that best distinguished the 4 QCMC stages. Unlike the linear regression model adopted in other quantitative studies [13,23-25], our multinomial model does not adopt cutoffs for categorization of a particular stage of maturation and does not provide a specific skeletal age. The multinomial model selected variables that best differentiated the categories and provided the predictability (confidence level) of these categorizations. Although the MLRM is appropriate for nominal data, we adopted this model, instead an ordered logistic regression (OLR), because the predictability of the OLR was lower than that observed with the MLRM, which minimize issues such as lack of homoscedasticity, linearity, and incorporate outliers.

In a previous study, Chen et al,[13] analyzed 42 morphologic characteristic parameters of C2, C3 and C4 during 11 Fishman's developmental stages. Although it was a well conducted paper with a mixed longitudinal study design and a significant sample size, there are some concerns with the statistical analysis and the interpretation of the data. They formed a linear equation that could accurately estimate the cervical vertebral maturation with 3 variables, but the accuracy of prediction was not quantified with a confidence interval. Furthermore, the sexual dimorphism was not evaluated nor considered. According to the results of another research,[27] sexual dimorphism was found in both size and shape of cervical vertebral bodies. Thereby, the multinomial logistic model adopted in the present study seems to be more appropriated, firstly by including 4 variables in the final model, which formed 3 nonlinear equations. Secondly, gender and chronological age were included in the model. Thus, it was not necessary to segregate the sample into boys and girls because of gender differences in the process of skeletal maturation[34,35]. The overall accuracy of prediction was quantified in the present study. Unfortunately, no prediction interval was reported by Chen et al,[13] which make it impossible to compare their model with the system developed in the present research.

The correlation coefficients between the independent variables and SMI was above 0.800 (p<.01). These values were lower than that observed in another research,[13] despite this study adopted different variables. Nevertheless, the multinomial model established in the present study took into account the correlation between one variable and another, controlled by all the other variables included in the final model, named partial correlation. The partial correlation observed during statistical analysis with the MLRM showed low values of correlation, demonstrating that the present model did not suffers from high collinearity.

According to a previous study,[27] the accuracy of the methods of cervical vertebrae maturation assessment should be compared with other evaluation systems, such as age. In the present study, we analyzed the predictability of the MLRM model using only chronological age or a combination of age and gender as independent variables. The best prediction (81.4%) was achieved with the combination of four parameters measured on the vertebral bodies, plus age and gender. The total percentage of the correctness of the model obtained with the use of chronological age solely as independent variable was 49.5%, and 64.5% with a combination of age and gender. Different from the results reported in a another study,[27] when the analyses of cervical vertebrae shape could not predict skeletal maturation better than chronological age, the value added by the present model that used the four parameters, age and gender was 17% (the difference between 81% and 64.5% when only age and gender were used). In other words, the addition of the parameters of the cervical vertebrae bodies in the final model did explain almost 50% of the 35.5% of the predictability that could not be achieved with the age and gender solely.

Fishman[33] tested the accuracy of the SMIs for maturational prediction and reported a prediction success rate of greater than 80%, a value that he considered exceptionally high for a biologic system. The results of the present study are similar with those stated above, with an overall predictability of the final model of 81.4%, with a better prediction of an individual's maturational status on QCMC stages I and IV. Corroborating with Fishman,[33] it seems to be satisfactory in terms of diagnosis, especially considering that most orthodontists do not use the analysis of cervical vertebrae when determining the degree of skeletal maturity.

Figure 2 illustrates the applicability of the MLRM. The patient's skeletal maturational level was 10, according to Fishman's method. The MLRM showed the most likely probability for this subject belonging to QCVM IV and agreeing with the hand-wrist skeletal age. However, the qualitative analysis of CVM showed that the patient belonged to CS4, which disagreed with the complete level of growth as shown by SMI.

Regarding the validity of the CVM method to determine skeletal maturity, which involves the reproducibility of the analysis, the method proposed in this study is consistent with respect to intra-observer reproducibility. Improving the DVA software with the automatic identification of the points of interest located in the bodies of C2, C3, and C4 and the inclusion of other measures of interest aimed at reducing the interference examiner analyses and increasing the predictability of the model could be the objectives of further research.

The results of this study revealed that significant alterations exist in the morphology of the C2, C3, and C4 vertebral bodies that are compatible with the maturation of the skeleton, enabling a categorization consistent with that defined by the standard method, which was evidenced by the almost perfect concordance coefficient. However, the major question regarding the reliability of the CVM method to predict the pubertal growth spurt remains unanswered. Longitudinal studies on a larger sample that analyze the sensitivity and specificity of the method proposed in this study compared to other methods such as hand-wrist radiographs, analysis of the growth in stature, and growth hormone indicators can help to answer that question.

In conclusion, the quantitative method implemented through specific software described herein was demonstrated to be reproducible in terms of intra-examiner concordance. There were significant anatomical alterations observed in the bodies of C2, C3, and C4 through the DVA software analysis between the four QCMC stages. Regarding the concavity of the lower edges of C2, C3, and C4, the behavior was compatible with that described by qualitative analyses [10,15,19,21]. However, the anatomical alterations observed in the vertebral bodies of C3 and C4 differed from those described in the existing atlas [10,15,19,21] since the vertical rectangular format is not the pattern seen in the late stages of growth in the bodies of the 3rd and 4th cervical vertebrae. The model that combines the four parameters measured on the vertebral bodies, the age and the gender showed a prediction of 81.4%. An almost perfect significance level was observed when comparing the correlation between the quantitative stages previously defined by hand and wrist radiographs and the stages of highest probability determined by the MLRM.

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TABLE AND FIGURE LEGENDS

Table 1 – Distribution of individuals according to the SMI (Fishman, 1982[28]) and Quantitative Cervical Maturational Changes (QCMC).

Table 2 - Distributions of age, gender and means and standard deviations for the seven variables of interest for each of the QCMC stages (I,II,III e IV)

Table 3 - Correlation coefficient (CC) between the 7 parameters of cervical vertebrae morphology and SMI.

Table 4 – Coefficients values ($\beta_0, \beta_{1...}\beta_6$) and the 6 independent variables of interest (Var1–Var6) that remained in the model after the multinomial logistic regression analysis used to provide 3 logit g(x) functions = $\beta_0 + \beta_1 Var_1 - \beta_2 Var_2 + \beta_3 Var_3 + \beta_4 Var_4 - \beta_5 Var_5 - \beta_6 Var_6$, for each of QCMC stages, with QCMC stage I as reference category

Table 5 – Total and partial percentages of the correctness of the MLRM during skeletal stage estimation.

Table 6 – Total and partial percentages of the correctness of the Age and a combination of Age and Gender during skeletal stage estimation.

Table 7 – Weighted Kappa for correlation analysis between the categorizations established by the QCMC stage and the MLRM

Figure 1 – **(A)** Lateral cephalometric radiograph with the region of interest and the definition of the reference points **(B)**, marked manually on the image by the DVA software: A and B, the most superior points of the posterior and anterior borders, respectively, of the bodies of C3 and C4; C and D, the most inferior points of the posterior and anterior borders, respectively, of the bodies of C3 and C4; E, the most superior point of the lower border of the bodies of C2, C3 and C4; F e G, midpoints of the lower (CD) and anterior (BD) borders, respectively; F', intersection point where the line from F point, parallel to the posterior border, touch the superior border; G', intersection point where the line from G point, parallel to the inferior border, touch the posterior border;

Figure 2 – **(A)** Subject in the CVM stage 4, according to Baccetti, Franchi and McNamara, 2005[10] **(B)**. **(C)** Quantitative analysis of C2, C3 and C4 maturation by the DVA software. The MLRM indicated a 86.6% of the probability for this patient belonged to QCMC IV, which is more consistent with the skeletal maturational level 10 of Fishman[28], observed for this patient.

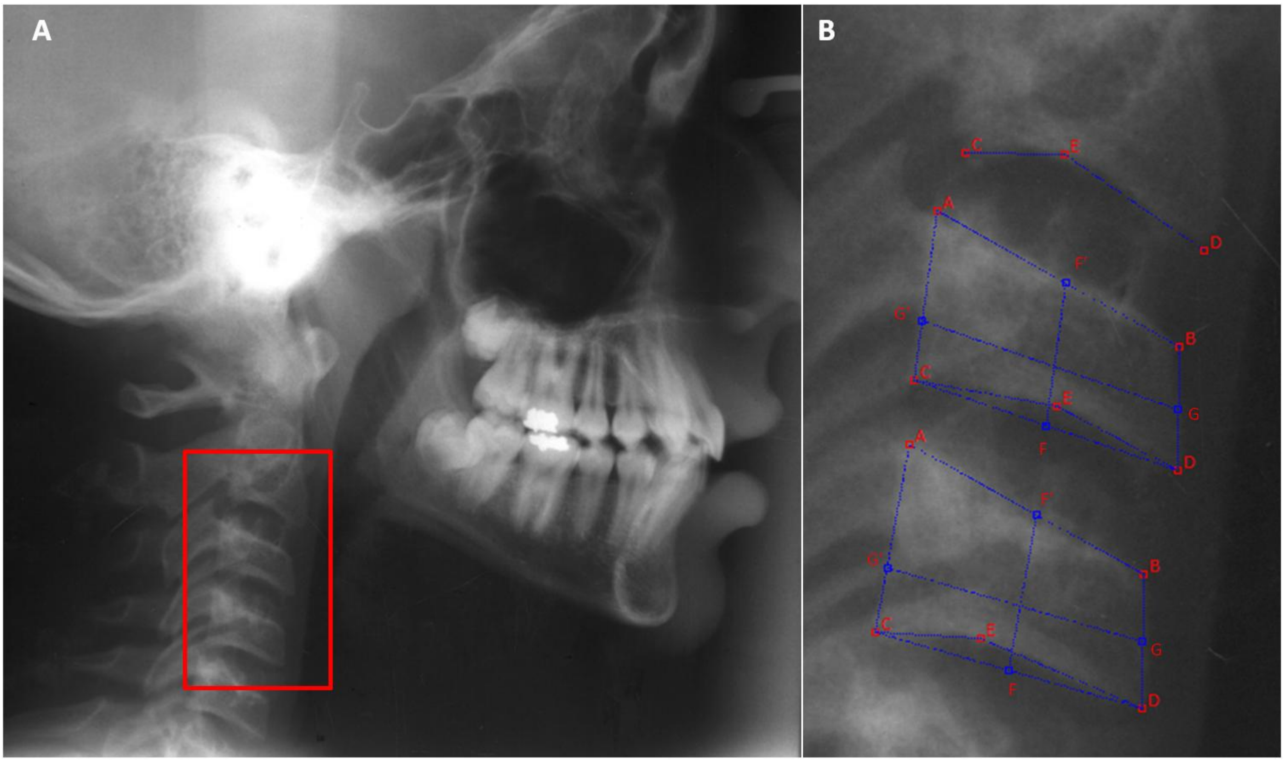
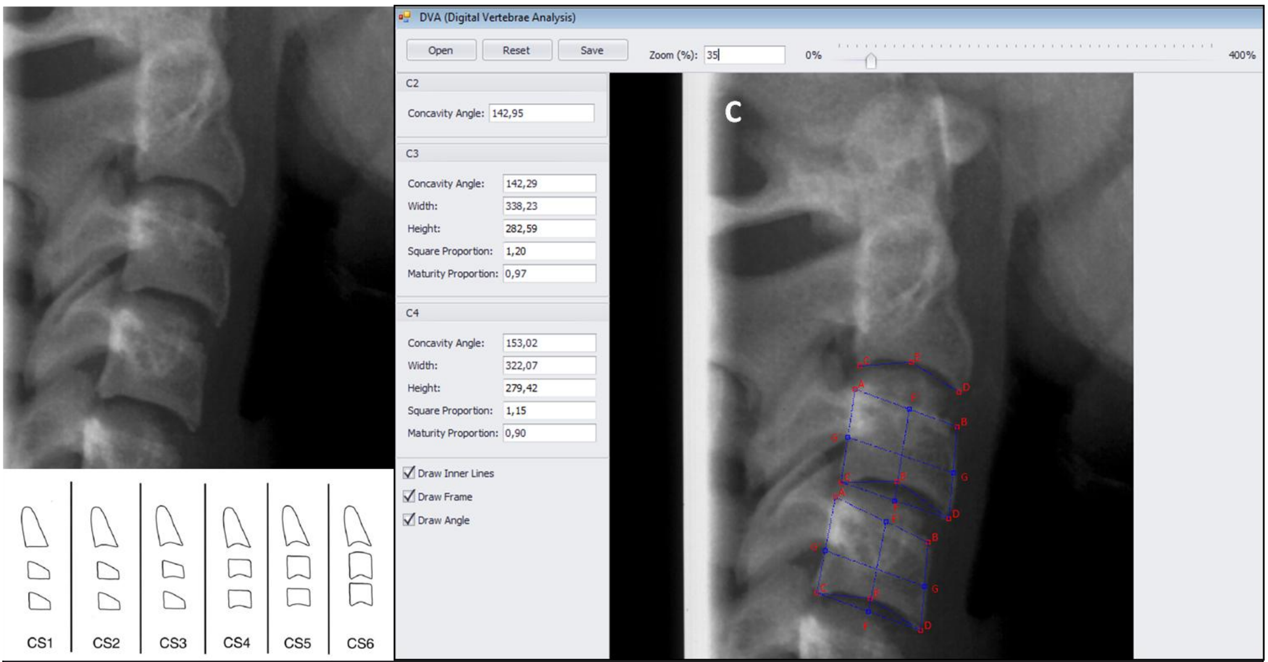


Figure 1



QCMC I Probability	2,07842E-07	0%
QCMC II Probability	0,001798786	0,10%
QCMC IIII Probability	0,102466851	10,30%
QCMC IV Probability	0,895734155	89,60%
	1	

Figure 2

Table 1

Table 1 - Distribution of individuals according to the SMI (Fishman, 1982[28]) and Quantitative Cervical Maturational Chande (QCMC).

QCMC Stage	*SMI Stage*	*Boys (n)*	*Girls (n)*
	1	35	10
I	2	20	5
	3	14	8
	Sub-total	69	23
	4	14	7
II	5	3	12
	6	3	11
	7	3	11
	Sub-total	23	41
III	8	10	19
	9	1	10
	Sub-total	11	28
IV	10	8	15
	11	5	12
	Sub-total	13	27
	Total	116	120

Table 2

Table 2. Distributions of age, gender and means and standard deviations for the seven variables of interest for each of the QCMC stages (I,II,III e IV)

	Stages				
Variables	*QCMC I*	*QCMC II*	*QCMC III*	*QCMC IV*	*p-value*
Age (months)	128±18	144±16	158±10	177±18	.000*
Gender	69m/23f	23m/41f	11m/29f	13m/27f	.000**
ANG_C2(°)	171.71±7.48	161.97±6.31	153.58±8.53	147.77±7.97	.000*
ANG_C3(°)	176.30±6.33	165.46±6.79	157.73±7.89	151.48±6.82	.000*
ANG_C4(°)	177.70±6.16	169.41±6.89	161.93±7.47	152.43±8.83	.000*
SP_C3	1.61±0.18	1.41±0.19	1.22±0.13	1.08±0.12	.000*
SP_C4	1.61±0.16	1.42±0.18	1.24±0.12	1.07±0.11	.000*
MP_C3	0.68±0.07	0.80±0.06	0.87±0.07	0.92±0.06	.000*
MP_C4	0.69±0.07	0.77±0.06	0.83±0.04	0.89±0.05	.000*

* ANOVA analysis of variance for mean comparison between each of the QCMC stages (*p*<.05)

**χ^2 test for gender distribution analysis between each of the QCMC stages (*p*<.05).

Table 3

Table 3 - Correlation coefficient (CC) between the 7 parameters of cervical vertebrae morphology and SMI.

Parameter	*CC*	*Parameter*	*CC*
ANG_C2	-0.826*	MP-C3*	0.817
ANG_C3	-0.836*	MP-C4*	0.804
ANG_C4	-0.818*	SP-C3*	-0.812
		SP-C4*	-0.817

*Correlation significant at .01 level.

Table 4

Table 4 – Coefficients values ($\beta_0, \beta_1 ... \beta_6$) and the 6 independent variables of interest (Var1–Var6) that remained in the model after the multinomial logistic regression analysis used to provide 3 logit g(x) functions = $B_0 + (B_1 Var_1) - (B_2 Var_2) + (B_3 Var_3) + (B_4 Var_4) - (B_5 Var_5) - (B_6 Var_6)$, for each of QCMC stages, with QCMC stage I as reference category

Stages	Coefficients (β) and variables of interest												
	B_0	B_1	Var_1	B_2	Var_2	B_3	Var_3	B_4	Var_4	B_5	Var_5	B_6	Var_6
QCMC II*	7.877	.128	MP_C3	.142	ANG_C3	.035	MP_C4	.053	Age	.013	SP_C4	2.374	$Gender^{0,1}$
QCMC III**	5.565	.162	MP_C3	.199	ANG_C3	.067	MP_C4	.125	Age	.052	SP_C4	2.784	$Gender^{0,1}$
QCMC IV***	16.521	.001	MP_C3	.289	ANG_C3	.354	MP_C4	.179	Age	.189	SP_C4	3.301	$Gender^{0,1}$

*Logit g(x1) function = 7.877 + 0.128(MP_C3) - 0.142(ANG_C3) + 0.035(MP_C4) + 0.053(Age) - 0.013(SP_C4) - 2.374(Gender)

**Logit g(x2) function = 5.565 + 0.162(MP_C3) - 0.199(ANG_C3) + 0.067(MP_C4) + 0.125(Age) - 0.052(SP_C4) - 2.784(Gender)

***Logit g(x3) function = 16.521 + 0.001(MP_C3) - 0.289(ANG_C3) + 0.354(MP_C4) + 0.179(Age) - 0.189(SP_C4) - 3.301(Gender)

^{0}=male; ^{1}=female

Table 5

Table 5 – Total and partial percentages of the correctness of the MLRM during skeletal stage estimation.

QCMC stage[1] Observed	*MRLM[2] Predicted*				
	I	*II*	*III*	*IV*	*Correctness Percentage*
I	86	6	0	0	*93.5%*
II	9	45	8	2	*70.3%*
III	0	11	29	0	*72.5%*
IV	0	1	7	32	*80.0%*
Overal percentage	40.3%	26.7%	18.6%	14.4%	***81.4%***

[1] Quantitative Cervical Maturational Change stage; [2] Most likely probability according to the multinomial linear regression model (MLRM);

Table 6

Table 6 – Total and partial percentages of the correctness of the Age and a combination of Age and Gender during skeletal stage estimation.

QCMC stage[1] Observed	*AGE[2] Predicted*				
	I	*II*	*III*	*IV*	*Correctness Percentage*
I	67	21	3	1	*73.6%*
II	28	24	5	7	*36.4%*
III	1	26	9	4	*23.1%*
IV	1	7	6	26	*65.0%*
Overal percentage	40.3%	26.7%	18.6%	14.4%	***49.5%***
	AGE and GENDER[3] Predicted				
I	79	11	2	0	*86.8%*
II	16	40	7	1	*60.6%*
III	2	16	16	6	*41.0%*
IV	2	3	7	28	*70.0%*
Overal percentage	40.3%	26.7%	18.6%	14.4%	***64.5%***

[1] Quantitative Cervical Maturational Change stage; [2] Most likely probability according to the chronological age; [3] Most likely probability according to the chronological age and gender.

Table 7

Table 7 – Weighted Kappa for correlation analysis between the categorizations established by the QCMC stage and the MLRM

	Weighted Kappa	*95% confidence interval*	*Statistical Level of Agreement*
QCMCstage X MRLM	0.832	0.784-0.881	Almost perfect*

*Landis and Koch (1977)[35]

5 DISCUSSÃO

O entendimento completo tanto do padrão de crescimento normal como do mecanismo que o fundamenta são necessários em Ortodontia. (Proffit, Fields e Sarver, 2007). Embora o padrão de crescimento seja similar entre os pacientes, o momento em que cada fase ocorre apresenta grande variabilidade, o que dificulta o diagnóstico preciso de suas diferentes etapas. (Mellion, 2007).

Estudos clínicos demonstraram que a resposta mais eficaz às forças ortopédicas aplicadas aos ossos maxilares tende a ocorrer durante o surto de crescimento puberal (Baccetti *et al.,* 2000; Hagg e Pancherz, 1988; Malmgren *et al.,* 1987; McNamara, Bookstein e Shaughnessy, 1985). Nesse contexto, análises radiográficas de eventos de maturação em áreas específicas, como a mão e punho e as vértebras cervicais, são algumas das maneiras utilizadas para determinar os estágios de crescimento.

Os autores avaliaram, inicialmente, através de revisão sistemática, o emprego das vértebras cervicais como indicador da maturidade esquelética, verificando sua aplicabilidade como método de diagnóstico. Revisões sistemáticas e meta-análises podem resumir os resultados de vários estudos e oferecer aos leitores análise crítica sobre onde se encontra o peso da evidência. Esses modelos de estudos podem, portanto, produzir e defender conclusões baseadas nas melhores evidências existentes ou, em alguns casos, concluir que a evidência atualmente disponível não permite chegar à conclusão alguma (Papadopoulos, 2003).

O ponto de partida para o processo de revisão ocorre com a elaboração de pergunta que conduzirá toda a análise sistematizada. Na presente pesquisa, houve dificuldade na definição do que seria necessário para o método de diagnóstico da maturação das vértebras cervicais (MVC) ser aplicável. Após análise criteriosa de vários estudos relacionados ao emprego das vértebras cervicais na identificação da maturidade esquelética, foi definido que, para ser válido, o método de diagnóstico deve ser reproduzível entre aqueles que o utilizam, estar não somente correlacionado, mas também ser acurado, quando comparado ao padrão-ouro. Entretanto, em razão de alguns estudos (Turpin, 2008; Flores-Mir, Mebe e Major, 2004) que questionam a validade das radiografias carpais como indicadores de maturidade esquelética, o termo "padrão-ouro" não foi empregado, sendo a radiografia da mão e punho definida como método-padrão.

Uma das etapas fundamentais durante o processo de revisão sistemática foi a identificação da solidez metodológica dos artigos selecionados de acordo com os critérios de inclusão. Na presente pesquisa, a análise da qualidade (*quality assessment*) dos estudos incluídos na revisão foi feita não somente por meio de único modelo, mas através de *quality assessment* modificado, que considerou alguns componentes do STROBE (*Strengthening the Reporting of Observational Studies in Epidemiology*), do STARD (*Standards for the Reporting of Diagnostic Accuracy Studies*) e do estudo de Lagravere *et al.* (2005), utilizados na identificação da qualidade metodológica de estudos observacionais e de diagnóstico. Vinte e três artigos foram avaliados em relação à qualidade metodológica e somente cinco estudos (Gabriel *et al.,* 2009; Imanimoghaddam *et al.,* 2008; Lai *et al.,* 2008; Soegiharto, Moles e Cunningham, 2008; Chang *et al.,* 2001) apresentaram qualidade moderada e um estudo (Uysal *et al.,* 2006) qualidade alta, sendo utilizados para a busca da melhor evidência em relação à validade dos métodos MVC.

A presente revisão sistemática identificou forte correlação entre o método-padrão, que utiliza as radiografias da mão e punho, e os métodos de identificação da maturidade esquelética, que utilizam as vértebras cervicais. Embora alta reprodutibilidade intra e inter-examinadores tenha sido reportada em vários estudos (Lai *et al.,* 2008; Soegiharto, Moles e Cunningham, 2008; Uysal *et al.,* 2006; Chang *et al.,* 2001), o trabalho conduzido por Gabriel *et al.* (2009) encontrou falhas metodológicas que poderiam interferir diretamente nos resultados dessas pesquisas. Em seu trabalho, eliminando os erros metodológicos de estudos prévios, Gabriel *et al.* (2008) observaram reprodutibilidade pobre intra e inter-examinadores, contraindicando o método MVC como única ferramenta de diagnóstico do estágio de maturação esquelética. Acrescentando, único estudo concluiu ser o método MVC tão acurado quanto o método-padrão, em termos de identificação da maturidade esquelética (Soegiharto *et al*., 2008). Entretanto, em razão do número reduzido de artigos selecionados durante o processo de revisão, que em sua maioria apresentaram qualidade metodológica moderada, as conclusões apontaram para baixo nível de evidência, sugerindo que estudos mais bem delineados e com qualidade metodológica elevada fossem conduzidos para que a questão sobre a aplicabilidade das vértebras cervicais como identificador de maturidade esquelética fosse respondida.

Mediante a necessidade de evidências mais fortes no que diz respeito a aplicabilidade das vértebras cervicais e levando em consideração as fortes críticas ao método MVC no trabalho conduzido por Gabriel *et al.* (2009, os autores avaliaram, num segundo estudo, a reprodutibilidade de dois métodos qualitativos de identificação da MVC. Apesar de ser um trabalho que se enaltece pela qualidade metodológica, o estudo conduzido por Gabriel *et al.* (2009) deixa algumas questões em aberto, como a forma clara de treinamento dos examinadores, o intervalo de tempo entre o treinamento e a execução das análises, o tamanho da amostra analisada, o tipo de método e avaliação adotados bem como a interpretação dos valores de reprodutibilidade.

Primeiramente, o estudo de Gabriel *et al.* (2009) analisou a reprodutibilidade do método proposto por Baccetti, Franchi e McNamara (2005) em 30 radiografias. O número de 30 radiografias é reduzido para análise desta natureza, podendo conter quantidade discrepante de radiografias em estágios mais fáceis ou difíceis de serem identificados, pois, segundo pesquisa anterior (Nestman *et al,* 2009), determinadas características morfológicas das vértebras cervicais, como a presença de concavidade no bordo inferior, seriam mais fáceis de serem identificadas quando comparadas ao formato do corpo vertebral (trapezoidal, retangular horizontal, quadrado ou retangular vertical) e influenciariam na reprodutibilidade do método MVC.

Desta forma, além de analisar 90 radiografias, a metodologia adotada na presente pesquisa visou obter amostra mais homogênea, em termos de estágios de crescimento, avaliando as radiografias da mão e punho previamente, de acordo com o método proposto por Fishman (1982). Embora a reprodutibilidade intra e inter-examinadores tenha sido bem próxima àquela observada no trabalho de Gabriel *et al.* (2009), o risco do viés de seleção foi controlado com a metodologia adotada no presente estudo.

Para evidenciar a reprodutibilidade foram avaliados dois métodos qualitativos de identificação da MVC, propostos por Baccetti, Franchi e McNamara (2002) e

Baccetti, Franchi e McNamara (2005). A intenção em avaliar dois métodos foi observar se haveria, ou não, influência direta do estágio adicional de maturação das vértebras cervicais no método proposto por Baccetti, Franchi e McNamara (2005) na reprodutibilidade entre os examinadores, o que não foi considerado no estudo de Gabriel *et al.* (2009). Embora o percentual de concordância intra e inter-examinadores tenha sido maior com o método proposto por Baccetti, Franchi e McNamara (2002), o coeficiente de concordância de *Kappa* ponderado foi praticamente o mesmo para os dois métodos avaliados, e, apesar da concordância *Kappa* ser considerada moderada (0,4-0,8), o percentual total de 60% de concordância, em média, revelou variabilidade significativa dos modelos avaliados, sugerindo que os métodos qualitativos, da forma como são propostos, sejam aprimorados ou que os examinadores recebam treinamento mais específico e detalhado sobre características envolvidas em cada estágio de identificação de MVC (Sim e Wright, 2005).

Por fim, foi levantada a hipótese, na atual pesquisa, de que a análise dos diferentes estágios de crescimento com o auxílio de traçado manual dos corpos vertebrais de C2, C3 e C4, realizado por cada examinador separadamente, poderia interferir no nível de concordância. Tal fato não foi considerado no trabalho de Gabriel *et al.* (2009), porém, melhora em termos de reprodutibilidade poderia ser esperada com a utilização de traçados manuais das regiões de interesse, tendo em vista que a classificação leva em consideração a comparação direta entre a imagem observada nas radiografias cefalométricas e um atlas, contendo o desenho dos corpos vertebrais nos diferentes estágios de maturação. No presente trabalho, o uso de traçado não refletiu diretamente na reprodutibilidade intra-examinadores. Porém, a utilização de traçado manual reduziu tanto a frequência quanto o índice de concordância de *Kappa* entre os examinadores, o que pode ser reflexo da variabilidade com que cada examinador interpretou o formato dos corpos vertebrais, além da dificuldade de associação direta entre formato observado nos traçados manuais com as imagens demonstradas nos atlas.

É importante ressaltar que tanto as conclusões do presente estudo de revisão sistemática e de reprodutibilidade, quanto as críticas feitas pelo trabalho de Gabriel *et al.* (2009), referem-se aos métodos qualitativos de maturação das vértebras cervicais, que utilizam atlas como referência, contendo os diferentes estágios de maturidade, caracterizando-se por análises totalmente subjetivas. Por outro lado, existem os métodos quantitativos (objetivos), como os propostos por Chatzigianni e Halazonetis (2009), Chen *et al.* (2008), Caldas, Ambrosano e Haiter-Neto (2007), Mito, Sato e Mitani (2002), que visam reduzir a variabilidade das interpretações entre os examinadores, determinando a maturidade esquelética através de análises morfométricas ou de regressão linear . Segundo Chen *et al.* (2008), métodos quantitativos de identificação da MVC são mais adequados pois, os sinais das mudanças morfológicas nas vértebras cervicais durante o crescimento são menos específicos e identificáveis como os observados na mão e no punho, e um atlas não deve ser utilizado para avaliar o crescimento de maneira detalhada e objetiva como nas radiografias carpais, podendo haver divergências entre os examinadores durante o diagnóstico do estágio de maturação.

O presente estudo teve como último objetivo o desenvolvimento de novo método quantitativo para análise das alterações morfológicas observadas nos corpos vertebrais de C2, C3 e C4 e apresentou algumas vantagens, quando comparado aos demais modelos quantitativos reportados na literatura. Primeiramente, o método permitiu o cálculo das medidas de interesse nos corpos vertebrais a partir de software DVA (*Digital Vertebrae Analysis*), desenvolvido especificamente para esse estudo. Desta forma, não foi necessária a realização de traçados manuais sobre os corpos vertebrais nem mesmo a interferência do examinador na obtenção das medidas angulares, lineares e de proporção, como observado nos trabalhos de Chen *et al.,* 2008, Caldas, Ambrosano e Haiter-Neto 2007 e Mito, Sato e Mitani, 2002.

O modelo de regressão logística multinomial adotado no presente trabalho forneceu a probabilidade de cada radiografia pertencer ou não a uma determinada categoria da maturação esquelética. Diferente do modelo de regressão linear proposto nos estudos de Chen *et al.* (2008), Caldas, Ambrosano e Haiter-Neto (2007), Mito, Sato e Mitani (2002), que utiliza única fórmula na definição do estágio de maturação e não fornece a acurácia da previsão, no modelo do atual estudo foi calculada a possibilidade de uma radiografia pertencer um dos estágios de maturação das vértebras cervicais através de três equações, obtendo previsibilidade de acerto total final de 81,4%, que, segundo Fishman (1987), é bastante satisfatória para um indicador biológico.

O método quantitativo proposto por Chatzigianni e Halazonetis (2009), leva em consideração análise morfométrica dos corpos vertebrais de C1, C2, C3 e C4, além de seus processos articular, vertebral e espinhoso, através de software que utiliza 187 pontos de referência para cada radiografia analisada. Além da complexidade do software, a visualização precisa da 1ª vértebra (atlas) e dos processos vertebrais durante a análise das vértebras cervicais pode não ocorrer em muitas radiografias cefalométricas, sendo que o mesmo não acontece com os corpos vertebrais de C2 a C4. No presente estudo, a análise da morfologia das vértebras cervicais utilizou 19 pontos de referência localizados somente nos corpos da 2ª, 3ª e 4ª vértebras, com o objetivo de tornar a análise mais prática e viável, quando comparado ao modelo proposto por Chatzigianni e Halazonetis (2009).

A previsibilidade total do modelo estabelecido na presente pesquisa foi inferior à observada no estudo conduzido por Chatzigianni e Halazonetis (2009) que apresentou acurácia de 90%. A capacidade preditiva do modelo de regressão linear múltipla estabelecido por Chatzigianni e Halazonetis (2009), que levou em consideração o formato das vértebras cervicais, não foi melhor do que a idade cronológica isoladamente. Tal fato não foi constatado na atual pesquisa, onde o modelo multinomial composto unicamente pela idade cronológica apresentou valores de previsibilidade bem inferiores ao modelo final, que foi constituído por 4 variáveis relacionadas ao formato dos corpos vertebrais, o gênero e a idade cronológica.

Finalmente, a inclusão do gênero como variável independente no modelo final do presente estudo tornou desnecessária a segregação da amostra, o que é grande vantagem levando-se em consideração o dimorfismo sexual envolvido no processo de maturação esquelética (Hassel e Farman, 1995; Lamparsky, 1972), e as diferenças observadas, entre meninos e meninas, no tamanho e formato das vértebras cervicais C1, C2, C3 e C4 no estudo conduzido por Chatzigianni e Halazonetis (2009).

A aplicabilidade das vértebras cervicais como indicador da maturidade esquelética vai muito além da constatação de que os modelos qualitativos propostos, até o momento, apresentam reprodutibilidade insuficiente entre aqueles que o utilizam, bem como da necessidade de desenvolvimento de métodos mais objetivos como proposto no presente trabalho. A verificação de que alterações geométricas significativas ocorrem nos corpos vertebrais de C2, C3 e C4 à medida que o grau de maturidade esquelética aumenta, parece ser evidência forte o suficiente para que pesquisas futuras sejam realizadas, com o objetivo de estabelecer a validade das vértebras cervicais como indicador biológico confiável, que permita não somente identificar os estágios de maturação, como também prever, com segurança, as épocas em que ocorrem o início, o pico e o final de surto de crescimento puberal.

6 CONCLUSÃO

No presente estudo foi avaliada a aplicabilidade das vértebras cervicais como indicador da maturidade esquelética e concluiu que:

6.1 *em relação ao estudo de revisão sistemática:*

6.1.1 não foi possível verificar a aplicabilidade dos métodos de identificação MVC, em virtude das falhas metodológicas observadas na maioria dos estudos analisados e pelo baixo nível de evidência verificado no número reduzido de artigos de qualidade metodológica satisfatória.

6.2 *em relação ao estudo de reprodutibilidade:*

6.2.1 reprodutibilidade próxima a 60% intra e interexaminadores sugere variabilidade dos métodos qualitativos analisados. Não houve diferença significativa na reprodutibilidade entre os dois tipos de métodos MVC analisados e as duas formas de avaliação, com e sem traçado manual.

6.3 *em relação ao novo método quantitativo proposto:*

6.3.1 o modelo quantitativo identificou alterações significativas nos corpos vertebrais de C2, C3 e C4 em diferentes estágios de maturidade esquelética e o modelo multinomial final apresentou previsibilidade satisfatória.

7 RECOMENDAÇÕES

Diante dos dados obtidos no presente trabalho, sugere-se:

- A incorporação de novas medidas na análise quantitativa das alterações morfológicas dos corpos vertebrais de C2, C3 e C4, com o objetivo de aumentar a previsibilidade final do modelo multinomial.

- Aprimoramento do software DVA, com a identificação automática dos pontos de interesse, reduzindo a interferência do examinador.

- Aplicação do modelo multinomial em outra amostra mais representativa.

- Elaboração de estudo longitudinal, com a análise das alterações anatômicas observadas nos corpos vertebrais da 2ª, 3ª e 4ª vértebras cervicais registradas periodicamente, tendo as análises da radiografia da mão e punho, do crescimento em altura e, possivelmente, de hormônios do crescimento como métodos-padrão para comparação.

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9 ANEXOS

ANEXO 1 – Aprovação do Comitê de Ética da UFJF-MG.

UNIVERSIDADE FEDERAL DE JUIZ DE FORA
PRÓ-REITORIA DE PESQUISA
COMITÊ DE ÉTICA EM PESQUISA - CEP/UFJF
36036900- JUIZ DE FORA - MG – BRASIL

Parecer nº «334/2011»

Protocolo CEP-UFJF: «2575.515.2011» **FR**: «481994» **CAAE**: «0308.1.180.000-11»
Projeto de Pesquisa: "«Comparação da reprodutibilidade de 3 métodos de avaliação da maturação das vértebras ce4rvicais»"
Area Temática: *«Grupo III»*
Pesquisador Responsável: «Robert Willer Farinazzo Vitral»
Data prevista para o término da pesquisa: julho 2012
Pesquisadores Participantes: "Rodrigo César Santiago, Márcio José da Silva Campos e Paulo Henrique da Rocha Duque"
Instituição Proponente: Faculdade de Odontologia / UFJF

Análise do protocolo:

Itens Avaliados			Sim	Não	P	NA
Justificativa	O estudo proposto apresenta pertinência e valor científico		x			
	Objeto de estudo está bem delineado		x			
Objetivo(s)	Apresentam clareza e compatibilidade com a proposta		x			
Material e Métodos	Atende ao(s) objetivo(s) proposto(s)		x			
	Informa	Tipo de estudo	x			
		Procedimentos que serão utilizados	x			
		Número de participantes	x			
		Justificativa de participação em grupos vulneráveis				
		Critérios de inclusão e exclusão	x			x
		Recrutamento				x
		Coleta de dados	x			
		Tipo de análise	x			
		Cuidados Éticos	x			
Revisão da literatura	Atuais e sustentam o(s) objetivo(S) do estudo		x			
Resultados	Informa os possíveis impactos e benefícios		x			
Cronograma	Agenda as diversas etapas de pesquisa		x			
	Informa que a coleta de dados ocorrerá após aprovação do projeto pelo comitê		x			
Orçamento	Lista a relação detalhada dos custos da pesquisa		x			
	Apresenta o responsável pelo financiamento		x			
Referências	Segue uma normatização		x			
Instrumento de coleta de dados	Preserva o sujeito de constrangimento					x
	Apresenta pertinência com o(s) objetivo(s) proposto(s).		x			
Termo de dispensa de TCLE	Solicita dispensa		x			
Termo de	Apresenta o termo em caso de participação de					x

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assentimento	menores					
TCLE	Está em linguagem adequada, clara para compreensão do sujeito					x
	Apresenta justificativa e objetivos					x
	Descreve suficientemente os procedimentos					x
	Apresenta campo para a identificação dos sujeitos					x
	Informa que uma das vias do TCLE deverá ser entregue ao sujeito					x
	Assegura liberdade do sujeito recusar ou retirar o consentimento sem penalidades					x
	Garante sigilo e anonimato					x
	Explicita	Riscos e desconfortos esperados				x
		Ressarcimento de despesas				x
		Indenização diante de eventuais danos decorrentes da pesquisa				x
		Forma de contato com o pesquisador				x
		Forma de contato com o CEP				x
		Como será o descarte de material coletado (no caso de material biológico)				x
		O arquivamento do material coletado pelo período mínimo de 5 anos				x
Pesquisador (es)	Apresentam titulação e experiência compatível com o projeto de pesquisa		x			
	Apresenta comprovante do Currículo Lattes do pesquisador principal e dos demais participantes.		x			
Documentos	Carta de Encaminhamento à Coordenação do CEP		x			
	Folha de Rosto preenchida		x			
	Projeto de pesquisa, redigido conforme Modelo de Apresentação de Projeto de Pesquisa padronizado pela Pró-Reitoria de Pesquisa (PROPESQ)		x			
	Declaração de infraestrutura e de concordância com a realização da pesquisa, assinada pelo responsável pelo setor/serviço onde será realizada a pesquisa		x			

P= parcialmente **NA=Não se aplica**

Diante do exposto, o Comitê de Ética em Pesquisa – CEP/UFJF, de acordo com as atribuições definidas na Res. CNS 196/96, manifesta-se pela aprovação do protocolo de pesquisa proposto, devendo o pesquisador entregar o relatório no final da pesquisa.

Situação: Projeto Aprovado
Juiz de Fora, 15 de Dezembro de 2011

Prof. Dra. Iêda Maria A. Vargas Dias
Coordenadora – CEP/UFJF