SERVIZIO SANITARIO REGIONALE
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Istituto Ortopedico Rizzoli di Bologna
Istituto di Ricovero e Cura a Carattere Scientifico

***"Calcify2D: assessment of observer variability of a new software for the quantitative evaluation of abdominal aortic calcifications, vertebral morphometry and their relationships in fragile patients, compared to current visual scoring methods"***

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| **Study code** | Calcify 2D |
| **Sponsor's Name and Address:** | Istituto Ortopedico Rizzoli<br>Via di Barbiano 1/10<br>40136 Bologna<br>Italy |
| **Study Number/Version/Date:** | Vers 1.0<br>13/ 09/ 2018 |
| **Coordinating Center:** | IRCCS Istituto Ortopedico Rizzoli<br>Via di Barbiano 1/10<br>40136 Bologna, Italy |
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| **Laboratory:** | Bioengineering and Computing Laboratory (BiC) |
| **Clinical units:** | Spine Surgery prevalently Oncologic and Degenerative (CVOD), Istituto Ortopedico Rizzoli<br>Department of Medicine, University of Padua (DiMed UniPD) |
| **Clinicians responsible for informed consent** | Valerio Pipola (Resident Spine Orthopaedician, IOR)<br>Stefano Bandiera (Spine Oethopaedician, IOR) |
| **Primary Outcome Assessors:** | Giovanni Barbanti Brodano (Spine Orthopedician, IOR)<br>Alberto Bazzocchi (Radiologist, IOR)<br>Maria Fusaro (Nephrologist, DiMed UniPD)<br>Stefania Sella (Internal Medicine Specialist, DiMed UniPD) |
| **Methodology:** | Observational study to define repeatability and reproducibility |
| **Type:** | No profit |
| **Funding:** | None |
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## Protocol Signature

**Sponsor:** Istituto Ortopedico Rizzoli
**Study Title:** Calcify2D: assessment of observer variability of a new software for the quantitative evaluation of abdominal aortic calcifications, vertebral morphometry and their relationships in fragile patients, compared to current visual scoring methods
**Study Acronym/Code:** Calcify 2D
**Protocol Version and Date:** Version 1.0 13Sep2018

I read this protocol and I accept to conduct this trial in accordance with the protocol stipulations, GCP guidelines and the Declaration of Helsinki.

**Coordinating Investigator:**

Dr. Enrico Schileo
Istituto Ortopedico Rizzoli

Local Site Name: Istituto Ortopedico Rizzoli

Local Site Principal Investigator Name: Dr. Enrico Schileo

| Local Site Principal Investigator Signature | Signature Date |
| --- | --- |
| …….. | 13 Sept 2018 |

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**BACKGROUND and STUDY RATIONALE**

In the context of a progressively aging population, monitoring the status of Vascular Calcifications (VC) and Vertebral Fractures (VF) over time would be of primary importance, as VC (Lewis et al., 2018) and VF (Buckens et al., 2014) are recognized to be hallmarks of severe cardiovascular events (hospitalization and/or death) and hip fractures respectively, and VF represent an under-diagnosed cause of progressive disability and pain on its own (Delmas et al., 2005).

Moreover, there is an acknowledged relationships between vascular calcifications (VC) and vertebral fractures, confirmed by a recent meta-analysis (Chen and Yu, 2016).
However, data about the emergence/progression of VC and the emergence/worsening of VF over time are lacking. This is likely due to the absence of monitoring instruments for VC and VF that are both precise and easily accessible/applicable.

As to VC, they can be precisely assessed by coronary multi-slice Computer Tomography (CT), which can be interchangeably applied at the aorta or coronary artery (Takayama et al., 2016) but is unsuitable for routine follow-up controls as it implies high radiation doses and notable costs; cheaper scores based on RX projections that deliver a lower dose exist and are increasingly applied (among them, Kauppila score (Kauppila et al., 1997) is most frequently used) but the precision of their current implementations is questionable as they rely on subjective semi-quantitative grading, thus they do not perform an actual measurement. Notably, a thorough assessment of precision (i.e. observer variability, composed by intra observer variability also known as repeatability, and inter-observer variability also known as reproducibility) is lacking. The few works that addressed observer variability report only the intraclass correlation coefifcient (ICC), which is not free from flaws (Popovic and Thomas, 2017) and do not permit to calculate important parameters such as the Minimum Detectable Difference (MDD). A more structured work to assess interobserver variability for vascular calcifications at the abdominal aorta has been performed on the DXA implementation (Shousboe et al., 2017), but also in that case only ICC is reported, showing values down to 0.6 (moderate agreement) for inter-observer agreement.

As to VF, Quantitative Vertebral Morphometry (QVM) is a plausible, although semi-quantitative RX-based mean to assess them according to Genant's classification (Genant et al., 2000), but it is seldom used; the same issues related to VC estimates apply, i.e. currently the scoring of VF too

often relies on visual-based semi-quantitative grading. There is in fact recent literature confirming the interest in increasing the precision of VF assessment through the development of more automated and quantitative grading systems (Kim et al,. 2012; Oei et al., 2013).

In summary, there is a clear need, both for the monitoring of VC and VF, to:
- assess the precision of current methods, composed by intra-observer variability (i.e. repeatability) and inter-observer variability (i.e. reproducibility);
- develop more quantitative and automated, thus presumably more precise, monitoring methods.

**OBJECTIVE OF THE STUDY**

To evaluate the precision in terms of repeatability and reproducibility of an in-house developed software, called Calcify2D, that offers physicians a computer-assisted procedure to simulteneously score (and reduce scoring variability of) vascular calcifications (at the abdominal aorta and iliac arteries) and lumbar vertebral fractures (according to Quantitative Vertebral Morphometry principles) based on a latero-lateral thoracolumbar spine radiography. The software will be tested on clinical data from the VTP vs KYPHO study conducted recently at Istituto Ortopedico Rizzoli (IOR).

- Primary objective: to verify if the developed computer-assisted procedure reduces intra- and inter-observer variability in the computation of vascular calcifications at the abdominal aorta according to the Kauppila score
- Secondary objectives:
    - to verify if the developed computer-assisted procedure reduces intra- and inter-observer variability in the computation of lumbar vertebral fractures according to the principles of Quantitative Vertebral Morphometry
    - to produce preliminary data about the accuracy (i.e. accordance with measurements from accepted gold standard, taken as true) of the proposed computer-assisted scoring method for vascular calcifications, testing them against three-dimensional assessment from CT data (pending availability of matched CT data)
    - to produce preliminary data about the accuracy of the proposed computer-assisted scoring method for the existence of mild vertebral fractures, testing them against three-dimensional assessment of bone oedema from MRI data (pending availability of matched MRI data)

**STUDY DESIGN**

No-profit monocentric observational study to be conducted on the diagnostic images already collected at IOR within the VTP vs KYPHO study. From that study, diagnostic images of the thoracolumbar spine in different modalities (standard X-ray radiographies (Rx), CT, MRI) are available at several time points of follow-up and will be analysed in the present study.

**Study workflow**

1) Patient informed consent will be acquired

2) RX images showing VC will be used to assess whether the computer assisted VC scoring (primary objective) and Quantitative Vertebral Morphometry (QVM, limited to lumbar spine, secondary objective n.1) are less variable with respect to the traditional visual scoring of VC and QVM.

3) The database will be searched for the existence of CT and MRI taken simultaneously (within one week) to the RX images. In case of positive findings, the study will proceed to the following steps.

4) Computer assisted Rx-based VC scoring will be compared to three dimensional CT quantitative VC computation (acting as gold standard) to produce preliminary data on its accuracy.

5) Computer assisted Rx-based QVM will be compared to three dimensional MRI data (acting as gold standard) to produce preliminary data on its accuracy in detecting mild vertebral fractures.

**POPULATION**

The present study relies on the data of the VTP vs KYPHO study. Data from the population of the VTP vs KYPHO study are particularly relevant and suitable for the scope of the present study since all subjects show vertebral fractures (sometimes multiple fractures), and there is a known association between vertebral fractures and VC. The VTP vs KYPHO study ran at IOR from 2009 to 2014 (Prot. gen. n. 30364 approved on 20.11.2009). Diagnostic images of the thoracolumbar spine in different modalities (RX, CT, MRI) were collected at several time points of follow-up for 109 patients.

All patients eligible for the study according to the following criteria will be contacted to acquire their informed consent to the participation in the study.

**ELIGIBILITY CRITERIA**

**Inclusion criteria**

- Patients included in the previous VTP vs KYPHO study.
- Presence of diagnostic images (Dorso-lumbar radiographies taken in latero-lateral projection).

- Rx images will be screened for the presence of VC, retaining only those showing VC.
- Informed consent obtained prior to any study analysis-evaluation and/or data collection.

**Exclusion criteria**

- Images of the patients included in the study VTP vs KYPHO showing severe artefacts (usually due to presence of metallic devices) that alter the grayscale range and hinder correct identification of VC and vertebral fractures will be excluded.

**MATERIAL AND METHODS**

**Computation of VC score and QVM**

Latero-lateral Rx images will be imported into the software Calcify2D. The software guides the clinician to subsequently:

1) identify the edges of vertebral endplates from T12 to L5 (lines connecting endplates define the regions of interest for the computation of abdominal aortic calcification score according to the current practice (Kauppila et al., 1997);

2) measure the calcified plaques visible in the image, separating the anterior and posterior wall of the abdominal aorta, by tracing lines over them; a review of each traced line is possible; VC are then automatically scored according to the reference scoring system and to the absolute measure of calcification length;

3) refine vertebral contouring by picking a mid-side node on each vertebral endplate; QVM is then automatically computed;

4) review and save the report (with images) of VC and QVM issued automatically by the software application.

**Observer variability tests on VC score and QVM**

The test of observer variability will be performed by four clinicians from four relevant specialties, chosen among those who may often see VC and VF and are already familiar with the traditional scoring systems for both VC and VF (one radiologist and one spine orthopaedics from Istituto Ortopedico Rizzoli, one nefrologist and one internist from University of Padua).

Each clinician will assess all RX images to score VC and QVM, both via computer assisted procedures and via traditional visual inspection. To avoid bias, an interval of at least one week will be left between the computer assisted and visual scoring. To define intra-observer variability (i.e. repeatability), the whole dataset will be re-assessed three times, with an interval of at least one month between each re-assessment to avoid bias.

**Preliminary assessment of the accuracy of computer assisted VC score and QVM against 3D data**

In case time-matched CT data are available, the RX-based computer assisted VC score will be related to the current gold standard scoring system from CT (Takayama et al., 2016).

In case time-matched MRI data are available, they will be used to preliminary assess whether the RX-based computer assisted QVM can accurately detect mild vertebral fractures, which are detected with high sensitivity and specificity from MRI images because of the appearance of bone oedema.

**STUDY END POINT**

**Primary Endpoint**

Observer variability (repeatability and reproducibility) in the assessment of vascular calcifications at the abdominal aorta according to a widely adopted scoring system (Kauppila et al., 1997): comparison between computer assisted and visual scoring.

**Secondary Endpoints**

a) Observer variability (repeatability and reproducibility) in the assessment of vertebral fractures in the lumbar spine according to Quantitative Vertebral Morphometry (Genant et al., 2000): comparison between computer assisted and visual scoring.

b) Accuracy of computer assisted VC score (comparison with gold standard CT-based score)

c) Accuracy of computer assisted QVM in detecting mild vertebral fractures (comparison with gold standard MRI detection)

**STUDY PROCEDURES**

**Screening procedure and Enrollment procedures**

Patients considered eligible will be enrolled in the study, after providing a written informed consent.

**Other study procedures**

Study subjects will not be subjected to any clinical procedures, as the present study intends to perform a re-analysis of the imaging data already collected in a previous study, named VTP vs KYPHO.

**DATA COLLECTION**

Clinical data will be retrieved by patient's source document.

A protocol-specific CRF reporting the results of the VC scores and QVM will be provided.

**DATA MANAGEMENT**

Patient images will be pseudonymised. To avoid bias in the scoring, the four clinicians performing the study will be blind to any personal and clinical information.

CRFs will be handled centrally and filled with the data recorded for each patient (for each trial scoring for each clinician). Computer assisted scores will be automatically saved after each assessment. Visual scores will be annotated by each clinician in a session file.

**DATA HANDLING PROCEDURES**

Secure data transfer will be applied to send imaging data to the all the outcome assessors.

The PI will be responsible for the data pseudonymisation.

**STATISTICS**

Sample size considerations were made on the primary endpoint, i.e. observer variability of the VC score.

The most appropriate measure to assess observer variability has been identified in the Standard Error of the Measurement (SEM), less ambiguous than the often used Intra-class Correlation Coefficient according to a recent review (Popovic and Thomas, 2017).

It must be noted that there is currently no estimate of the Minimum Detectable Difference (MDD) of current methods for monitoring VC. Indeed, an estimate of the MDD for the current visual and the computer assisted scoring methods will be obtained from the SEM computed in the present study.

There is also neither agreement in the literature about threshold VC values (according to Kauppila score) for adverse event prediction (they range from 4 (Vannini et al., 2016) or 5 (Szulc et al., 2014), to 8 (Kwon et al., 2014), to even 12 (Elmasri et al., 2016) in a 0-24 scale), nor consensus on a Minimal Clinically Important Difference (MCID) i.e. the minimum increase in VC score that is associated to a significantly increased risk of adverse events and/or warrants a change in treatment. It is worth noting that also in this case the present study is likely to bring an advancement to the field, by defining a reliable MDD, under which any MCID could not be set.

In absence of consistent MDD and MCID values, sample size computation may happen only by deciding how accurate the SEM estimate should be. We here take a reverse line of reasoning, i.e. we verify whether the analysis of the full data sample (we have the commitment of four clinicians

from four different relevant specialties to analyse three times the data) results in an acceptable accuracy of the SEM estimate. For these calculations, we refer to the technical note Bland dedicated to the sample size for a repeatability study (Bland MJ, 2010).

Considering that 109 patients were enrolled in the VTP vs KYPHO study, that their mean age was 73 (SD 8, range 54-97), and that all of them had vertebral fractures, we can estimate in 55% the prevalence of aortic calcifications, based on the results of a larger vascular calcification study that involved a similar population (mediterranean men and women over 50) (Naves et al., 2008). Therefore we expect data from 60 subjects will judged available for the study after initial data screening. Being this a retrospective study not involving additional exams/clinical procedures/treatments we expect a relatively high success rate of the enrolment. We here prudentially state it at 75%, resulting in a final estimate of sample size of 45.

The 95% Confidence Interval (95% CI) of the SEM estimate for 45 subjects analysed three times by four observers, according to (Bland JM, 2010), is 6%. We deem this a very good value since it is seldom observed in observer variability studies, and may be robust to the occurrence of unexpected events (e.g. failure to complete a round of assessment plus reduction of subjects by 10 would still lead to a 95% CI below 10%).

Other statistical analyses for the primary endpoint will include further evaluation of intra- and inter-observer variability by the two-way ANOVA used to compute SEM (Eliasziw et al., 1994), Bland-Altman plots to assess agreement between methods, and Kappa statistics to assess inter-rater and inter-method agreement according to published thresholds (taking note of the above defined caveat about lack of consensus in threshold definition).

**Additional analyses (per objective)**

Objective 2 (observer variability in QVM): same analyses than in primary endpoint apply.

Objectives 3 and 4 (preliminary evaluation of the accuracy of computer-based assessment of VC and mild VF respectively against CT and MRI data): as we expect only few data points will be available, we plan to perform a simple correlation and residual analysis.

**ETHICS AND QUALITY ASSURANCE**

The clinical trial protocol and its documents will be sent before initiating the study to the competent Authorities and Ethics Committees for its approval.

The responsible investigator will ensure that this study is conducted in agreement with either the most updated Declaration of Helsinki and all the international and local laws that apply to clinical trials and to patient protection.

The protocol has been written, and the study will be conducted according to the principles of the ICH Harmonized Tripartite Guideline for Good Clinical Practice

(ref: http://www.emea.eu.int/pdfs/human/ich/013595en.pdf).

**INFORMED CONSENT**

All patients will be informed, by the investigator, of the aims of the study, the possible risks and benefits that will derive from the study participation.

The Investigator must clearly inform that the patient is free to refuse participation in the study and that can withdraw consent at any time and for any reason.

They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

The informed consent procedure must conform to the ICH guidelines on Good Clinical Practice. This implies that "the written informed consent form should be signed and personally dated by the patient or by the patient's legally acceptable representative".

The Investigator must also sign the Informed Consent form, and will keep the original at the site and a copy of the original must be handed to the patient.

The competent ethics committee for each Institution participating to the study must validate local informed consent documents before the study can be opened. It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the study whenever he/she wants. This will not prejudice the patient's subsequent care.

Since the Study VTP vs KYPHO included also oncological patient, due to the high incidence of mortality the disease, it would be possible that some potential eligible subjects will be deceased, according to the Italian "*Autorizzazione generale n. 9/2016 al trattamento dei dati personali effettuato per scopi di ricerca scientifica"* of the Privacy Tutor, the informed consent is not required to be obtained by the deceased subjects according the aforementioned disposition.

**CONFIDENTIALITY (CONFIDENTIALITA')**

In order to ensure confidentiality of clinical trial data as disposed the national and European applicable regulation, data will be only accessible for the trial Sponsor and its designees, for monitoring/auditing procedures, the Investigator and collaborators, the Ethics Committee of each corresponding site and the Health Authority.

Investigator and the Institution will allow access to data and source documentation for monitoring, auditing, Ethic Committee revision and inspections of Health Authority, but maintaining at all times subject personal data confidentiality as per applicable regulation.

The Investigator must guarantee that patient anonymity is kept at all times and their identity must be protected from unauthorized persons and institutions.

All patients included in the study will be identified with a numeric code, so that no identifiable personal data will be collected.

The Investigator must have and conserve a patients' inclusion registry where it figures the personal data of the patient: name, surname, address and corresponding identification code into the study, this register will be kept on the Investigator File.

**CONFLICT OF INTEREST**

**Istituto Ortopedico Rizzoli (IOR)**

Enrico Schileo (PI): none (see form)

Giovanni Barbanti Brodano (Spine Orthopaedician), Stefano Bandiera (Spine Orthopaedician), Valerio Pipola (Resident Spine Orthopaedician), Alberto Bazzocchi (Radiologist), (Bioengineer), Fulvia Taddei (Bioengineer), Gianluigi Crimi (Computer Scientist): none relevant for the purpose of this study

**University of Padua**

Maria Fusaro (Nephrologist), Stefania Sella (Internal Medicine Specialist), Andrea Aghi (Biotechnologist): none relevant for the purpose of this study.

**PUBLICATION POLICY AND DATA OWNERSHIP**

The sponsor institution, Istituto Ortopedico Rizzoli (IOR) is the owner of the data.

Two researchers in Bioengineering (the PI and Fulvia Taddei, from Bioengineering and Computing Laboratory at IOR) will be responsible of the data collection.

Four clinicians (Giovanni Barbanti Brodano Spine Orthopaedician at IOR, Alberto Bazzocchi Radiologist at IOR, Maria Fusaro Nephrologist at University of Padua, Stefania Sella Internal Medicine Specialist at University of Padua) will perform the scoring of VC and QVM on the patient images. Letter of committment to the partecipation of clinicians from the University of Padua are given as separate attachment. The four clinicians will access only pseudo-anonymised data. Clinicians will be assisted for training in the use of the computer assisted procedures and for any technical problems that may arise by Gianluigi Crimi (researcher in Computer Science from Bioengineering and Computing Laboratory at IOR) in Bologna, and Andrea Aghi (Biotechnologist at University of Padua). The two aforementioned researchers in Bioengineering (PI and Fulvia Taddei) will be responsible for the results analysis.

The results from this study can be published or shown at scientific conferences. The publication/s regarding the results of the present study will be written by the investigators; the authors' role and position in the manuscript/s will be subjected to an agreement between the investigators prior to writing the manuscript/s.

**SPONSOR ROLE AND RESPONSIBILITY**

The sponsor institution, Istituto Ortopedico Rizzoli (IOR) is the owner of the data and is responsible of all the clinical trial activities from study design, development, data collection, management, analysis, interpretation of data, writing and the decision to submit the report for publication written by the Principal Investigator.

**ADMINISTRATIVE ASPECTS**

**Funding**

This study receives no funding.

**Insurance**

Being an observational study involving only the re-analysis of diagnostic images already collected, insurance issues do not apply.

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