Aus dem Centrum für Muskuloskeletale Chirurgie

der Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Retrospektive Studie zum Einfluss des Zeitpunktes der Kyphoplastie auf das klinische und radiologische Outcome bei Wirbelkörperfrakturen

Influence of operative timing on the early postoperative radiological and clinical outcome after kyphoplasty

zur Erlangung des akademischen Grades

Doctor medicinae (Dr. med.)

vorgelegt der Medizinischen Fakultät

Charité – Universitätsmedizin Berlin

von

Sophie Balmer

aus Berlin

Datum der Promotion: 26.06.2022

Vorwort

Teilergebnisse dieser Arbeit wurden bereits im European Spine Journal und im Global Spine Journal veröffentlicht.

1. Palmowski Y, Balmer S, Bürger J, Schömig F, Hu Z, Pumberger M

   “Influence of operative timing on the early post-operative radiological and clinical outcome after kyphoplasty”. Eur Spine J. 2020.

2. Palmowski Y, Balmer S, Hu Z, Winkler T, Schnake KJ, Kandziora F, Pumberger M

   Relationship Between the OF Classification and Radiological Outcome of Osteoporotic Vertebral Fractures After Kyphoplasty”. Global Spine J. 2020.

Inhaltsverzeichnis

Abbildungsverzeichnis

Tabellenverzeichnis

Abkürzungsverzeichnis

CA	Cobb angle
CIRSE	Cardiovascular and Interventional Radiological Society of Europe
COPD	Chronic obstructive pulmonary disease
C1-7	Cervical vertebral bodies 1-7
CT scan	Computed tomography scan
DGOU	German Society for Orthopaedics and Trauma (DGOU)
DXA	Dual Energy X-ray Absorptiometry
FSU	Functional spinal unit
GA	Gardner angle
L1-5	Lumbar vertebral bodies 1-5
LKA	Local kyphotic angle
LL	Lumbar Lordosis
MRI	Magnetic Resonance Imaging
OF/AG OF	Arbeitsgruppe Osteoporotische Frakturen der Sektion Wirbelsäule der Deutschen Gesellschaft für Orthopädie und Unfallchirurgie
PI	Pelvic Incidence
PT	Pelvic Tilt
TK	Thoracic Kyphosis
SD	Standard deviation
SERM	Selective Estrogen Receptor Modulator
SS	Sacral Slope
SVA	Sagittal Vertical Axis
T1-12	Thoracic vertebral bodies 1-12

TLA	Thoracolumbar Alignment
TLSL	Thoracolumbar sacral Lordosis
VAS	Visual Analogue Scale
VCF	Vertebral compression fracture
WHO	World Health Organisation

Abstract (deutsch)

Einleitung: Mit der zunehmend alternden Bevölkerung steigt auch die Inzidenz von Wirbelkörperfrakturen. Dies macht deren optimale Behandlung zu einer hochrelevanten medizinischen Aufgabe. Das minimalinvasive Operationsverfahren der Kyphoplastie ist eine effektive Behandlungsoption von stabilen Wirbelkörperfrakturen, welche sowohl eine schnelle Schmerzreduktion als auch eine Rekonstruktion der verlorenen Wirbelkörperhöhe erlaubt. Der optimale Zeitpunkt der Operation wird bisher jedoch kontrovers diskutiert. Ziel dieser Studie war es, zu untersuchen, ob das klinische und radiologische Ergebnis von der Länge der Zeitspanne zwischen Frakturereignis und Kyphoplastie beeinflusst wird.

Methodik: Bei dieser Arbeit handelt es sich um eine retrospektive Kohortenstudie. Eingeschlossen wurden 230 Patienten, bei denen zwischen Januar 2012 und Dezember 2018 eine einzelne Wirbelkörperfraktur mittels Kyphoplastie behandelt wurde. Die Patienten wurden in Abhängigkeit vom Zeitintervall zwischen Frakturereignis und Operation in eine akute (< 2 Wochen; n = 100), eine subakute (2-6 Wochen; n = 91) und in eine chronische (> 6 Wochen; n = 39) Gruppe eingeteilt. Die klinischen Parameter wie der Verlauf des Schmerzes anhand der visuellen Analogskala und der Schmerzmittelbedarf sowie die radiologischen Parameter der Wirbelkörperhöhen, der Kyphosewinkel und des sagittalen Alignments wurden prä- und postoperativ innerhalb und zwischen den Gruppen verglichen.

Ergebnisse: Nach Ballonkyphoplastie kam es zu einer signifikanten Schmerzreduktion in allen drei Gruppen (p < 0,001 in allen Gruppen). Der Schmerzmittelbedarf konnte in der akuten und subakuten Gruppe, nicht aber in der chronischen Gruppe, signifikant (acute: p = 0,001; subacute: p = 0,001; chronic: p = 0,642) gesenkt werden. Dieser Effekt war in der chronischen Gruppe jedoch nicht zu sehen. Gleiches galt für die Reduktion des LKA (acute: p < 0,001; subacute: p < 0,001; chronic: p = 0,053). In allen drei Gruppen konnte eine signifikante postoperative Verbesserung der anterioren und mittleren Wirbelkörperhöhen erreicht werden (p < 0,001 in allen Gruppen). Patienten der subakuten Gruppe zeigten eine signifikant bessere Reduktion des LKA verglichen zur chronischen Gruppe (p = 0,034). Bei den Patienten der akuten Gruppe zeigte sich ebenfalls ein Trend zu einer besseren LKA-Reduktion gegenüber der chronischen Gruppe, welcher allerdings nicht signifikant war (p = 0,137).

Schlussfolgerung: Die Kyphoplastie bietet unabhängig vom Alter der Fraktur eine Möglichkeit zur effektiven Schmerzreduktion sowie zur Rekonstruktion der verlorenen Wirbelkörperhöhe. Die mögliche Korrektur der frakturbedingten lokalen Kyphose nimmt jedoch nach sechs Wochen signifikant ab. Ebenso konnte auch der Schmerzmittelbedarf nur bei Patienten mit akuten und subakuten Frakturen signifikant gesenkt werden. Um ein radiologisch als auch klinisch optimales Ergebnis durch Kyphoplastie erreichen zu können, scheint es daher sinnvoll, innerhalb von sechs Wochen nach dem Frakturereignis eine Entscheidung über operative oder konservative Therapie anzustreben.

Abstract (English)

Objective: With the aging population, the incidence of vertebral body fractures is also increasing, making their optimal treatment strategy a substantial medical challenge. The minimally invasive surgical procedure of kyphoplasty is an effective surgical treatment option for stable vertebral body fractures, which can achieve quick reduction of pain as well as height restoration of the affected vertebral body. However, the optimal timing of kyphoplasty has still been a matter of controversy. The aim of this study was therefore to investigate the relationship between the timing of kyphoplasty and the clinical as well as radiological outcome.

Methods: This work is based on a retrospective cohort study. 230 patients who underwent kyphoplasty of a single vertebral body fracture between January 2012 and December 2018 were included. The patients were divided into an acute (< 2 weeks; n = 100), a subacute (2 - 6 weeks; n = 91) and a chronic (> 6 weeks; n = 39) group, depending on the time interval between fracture occurrence and surgery. Clinical parameters such as pain progression according to the visual analogue scale and the need for pain medication as well as the radiological parameters vertebral body height, local kyphotic angle and sagittal alignment were compared pre- and postoperatively within and between the groups.

Results: After balloon kyphoplasty there was a significant reduction of pain according to the visual analogue scale in all three groups (all groups: $p < 0.001$). The use of analgesics was significantly reduced in the acute and subacute groups until discharge though this effect could not be seen in the chronic group (acute: $p = 0.001$; subacute: $p = 0.001$; chronic: $p = 0.642$). This equally applied to the reduction of LKA (acute: $p < 0.001$; subacute: $p < 0.001$; chronic: $p = 0.053$). In all three groups, a significant postoperative improvement in anterior and middle vertebral body heights was achieved (all groups: $p < 0.001$). Patients of the subacute group showed a significantly better reduction of the LKA compared to the chronic group ($p = 0.034$). Patients of the acute group also showed a trend towards better reduction of LKA compared to the chronic group though it did not reach significance ($p = 0.137$).

Conclusion: Kyphoplasty can effectively reduce pain and restore vertebral height, regardless of the time interval between fracture occurrence and surgery. However, the potential extent of correction of fracture-related local kyphosis is significantly decreased

after six weeks. Similarly, the consumption of analgesics was only significantly reduced in patients with acute and subacute fractures. To ensure optimal results after kyphoplasty, we recommend aiming for a final treatment strategy decision about conservative versus surgical treatment within six weeks after the fracture event.

1. Introduction

1.1. Basic anatomy of the spine

The spinal column is divided into five sections and consists of seven cervical vertebrae, twelve thoracic vertebrae, five lumbar vertebrae, the sacrum and the coccyx. It forms the axial skeleton to which the extremities and ribs are connected. The vertebral bodies transfer the weight of head, neck, upper extremities and most of the trunk via the pelvic girdle to the legs. Vertebral bodies consist mainly of trabeculae, the cancellous bone. The outer frame is formed by the cortical bone and the surfaces of the vertebral bodies are called inferior and superior endplates. Due to the increasing forces acting in the lower sections of the spine, the vertebral bodies enlarge from the cervical through to the lumbar region. Because of its complex construction the spinal column guarantees the mobility of the trunk and the absorption of axial shocks. In addition, it surrounds the spinal cord as a largely bony protective cover. Vertebrae, disci intervertebrales and ligaments guarantee the maximum stability and mobility.

The vertebrae are held together by discs, joints, ligaments and muscles. The discus intervertebralis is located between the vertebral bodies and is a flexible, shock-absorbing functional unit. The discus intervertebralis is composed of an outer annulus fibrosus, which is formed by concentrically attached collagenous connective tissue fibres and fibrous cartilage, and an inner nucleus pulposus, which consists of gelatinous tissue and has a shock-absorbing and force-distributing effect. The intact disci intervertebrales limit the movements of adjacent vertebral bodies and limit a shifting of vertebrae against each other.

The facet joints form small planar, paired joints between the cartilaginous surfaces of the superior articular process and the adjacent inferior articular process of the adjacent vertebrae. They belong to the group of diarthroses and have a relatively wide joint capsule. This results in three degrees freedom in the spinal column. It allows flexion and extension in the sagittal plane, lateral flexion in the frontal plane and rotation. The alignment of the facet joints varies from cranial to caudal, which explains the different mobility of the areas of the spinal column. In the cervical spine, the joint surfaces are almost in the frontal plane, which allows pronounced rotational movement in the cervical region. In the lumbar spine, the joint surfaces are in the sagittal plane, which explains a massive restriction in rotation [1]. The corresponding dominant movements in the lumbar spine are therefore ventral flexion and dorsal extension. This freedom of movement is limited by the ligamentous apparatus, which connects the vertebral bodies to each other at the vertebral arches and the transverse and spinous processes. Viewed from the lateral projection, lordosis is found in the cervical and lumbar spine, while a mild kyphosis predominates in the thoracic spine and in the sacral region as shown in Figure 1 [2]. The other support components are the back muscles. The back muscles are composed of autochthonous and secondary, immigrated muscles and enable stabilisation in the vertical axis.

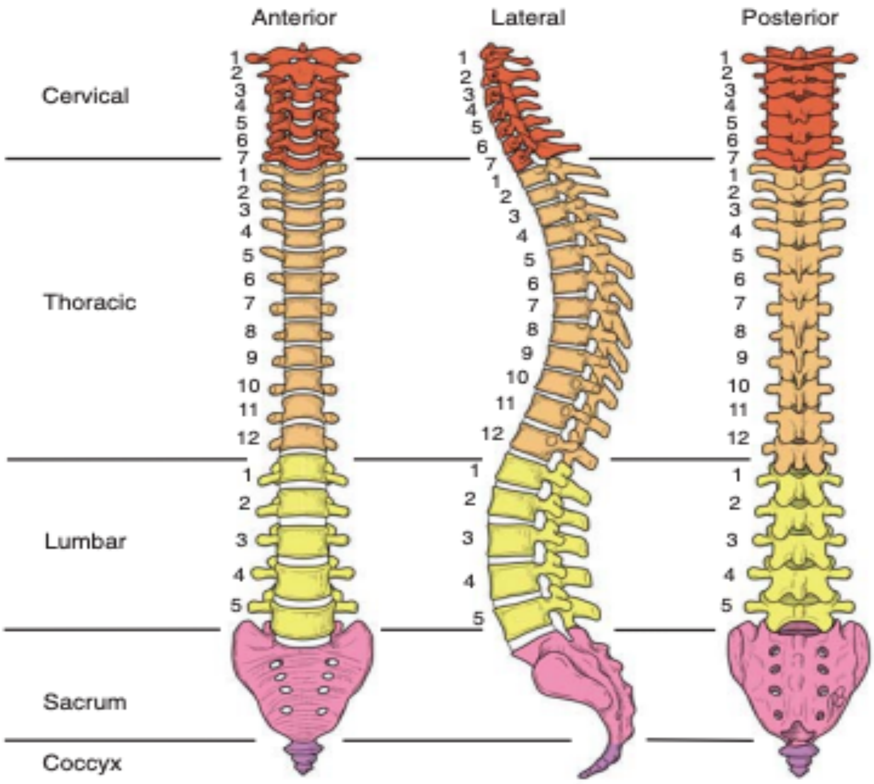

Figure 1: Anterior, posterior and lateral depictions of the entire spine showing the physiological curvature as well as the number of vertebral bodies in each region according to Mathis et al. [2]

1.2. Biomechanics of the thoracic and lumbar spine and sagittal balance

For the assessment of spinal column injuries and their therapy, the biomechanics of the spinal column have to be considered. In order to analyse functional aspects, motion segments are used and were first invented by Junghanns in 1951 [3]. The smallest unit that allows for statements about the motion segment is the functional spinal unit (FSU), which consists of two adjacent vertebral bodies, the intervertebral disc between them, the facet joints, and their ligamentous structures. The ligamentous apparatus that surrounds the spinal column contributes significantly to its stability and guides the segmental and global movements. The longitudinal anterior, longitudinal posterior and supraspinous ligaments form the intersegmental ligament system that spans several FSUs. The intrasegmental ligament system in turn connects two vertebral bodies to form an FSU and consists of the interspinous, intertransverse and capsular ligaments as well as the ligamentum flavum. Furthermore, the musculature contributes significantly to stabilisation. As with the ligaments, the same principle can be applied here. The long muscles (obliquis abdominis, rectus abdominis and erector spinae) generate increased torque and contribute to intersegmental stabilisation as well as to the initiation and control of movements. As with the ligaments, the individual segments are stabilised by shorter and locally acting muscles (transversus abdominis, multifidus, rotatores breves) [4].

There are essentially two opposing forces acting on the spinal column. Firstly, there is a longitudinal force directed caudally, which is compensated by the vertebral bodies and intervertebral discs. This force is compounded by the weights of the individual body parts and reaches its maximum in the lumbar spine. Secondly, muscle and ligament forces counteract the body weight. These forces are directed ventrally and are compensated by the vertebral arch joints, ligaments and intervertebral discs. The actual force acting on the spinal column is therefore the result of longitudinal force and ventral thrust [5]. The extent to which the load is transferred to the spinal column and how much strain is placed on it thus depends on the external load, muscle activity, ligamentary tension, body weight above the section under consideration and the sagittal balance [4]

The importance of the sagittal balance between the individual spinal column sections and the pelvis is now widely acknowledged. The sagittal balance is the result of the interaction of bone morphology, mechanical characteristics of the intervertebral discs and ligaments, muscle strength and the ability to perform compensatory mechanisms. It is indispensable for the functionality and freedom from pain of the spinal column [6-8]. Human bipedalism is characterized by the transmission of force from the spine via the pelvis and thus a narrow base. Economically, an upright gait is only possible if the interaction of muscles and ligaments works, and the sagittal profile of the spine, with the curvatures of the cervical, thoracic and lumbar spine, is preserved [4]. The centre of mass should project as close as possible between the two feet in a stable position and therefore result in low rebalancing efforts. If the centre of mass projects outside this area, rebalancing efforts have to be increased to avoid sagittal disbalance [9]. The global sagittal balance can be evaluated in upright standing radiographs by determining the sagittal vertical axis (SVA). Under ideal static conditions, the SVA falls behind L3, cuts the posterior edge of S1 (first sacral endplate) and runs behind the hip joint axis when drawing a perpendicular line centrally at C7 [6]. In a balanced sagittal profile, kyphosis and lordosis show an interplay - if one is increased, it leads to a decrease in the other, in order to keep the SVA centred over the pelvis [10].

Dubousset had already described by 1975 that apart from the global sagittal alignment parameters, only the physiological spinopelvic alignment enables an energy-efficient posture [11]. The spinopelvic parameters describe the physiological interdependence of individual spinal column sections with each other and with the pelvis. The positioning of the pelvis in relation to the spinal column is of particular importance, since the pelvis acts as a regulator for the sagittal alignment of the spinal column [6]. The spinopelvic parameters can be divided into positional parameters, which can differ because of different body positions, and morphological parameters, which are constitutional and cannot be influenced. By measuring the positional parameters of sacral slope (SS), pelvic tilt (PT), lumbar lordosis (LL) and thoracic kyphosis (TK) as well as the morphological parameter of pelvic incidence (PI), this dependence can be investigated. In contrast to the morphological parameter PI, all other parameters can compensate spinal imbalance, depending on the severity of spinal deformity [12]. The following equation helps to clarify the interdependence of the parameters:

$$PI = PT + SS$$

This formula shows that, because of the invariable PI, any change in SS must lead to a change in PT. This is the basic principle of the most important compensation mechanism for sagittal imbalance.

1.2.1. Change in biomechanics caused by vertebral body fractures

The majority of vertebral body fractures are compression fractures, which are often accompanied by an increase of thoracolumbar kyphosis as shown in Figure 2 [2]. Typically, if the anterior part of the vertebral body collapses, the centre of gravity shifts ventrally, resulting in a large bending moment for which muscles and ligaments must compensate, causing them to be quickly overstrained.

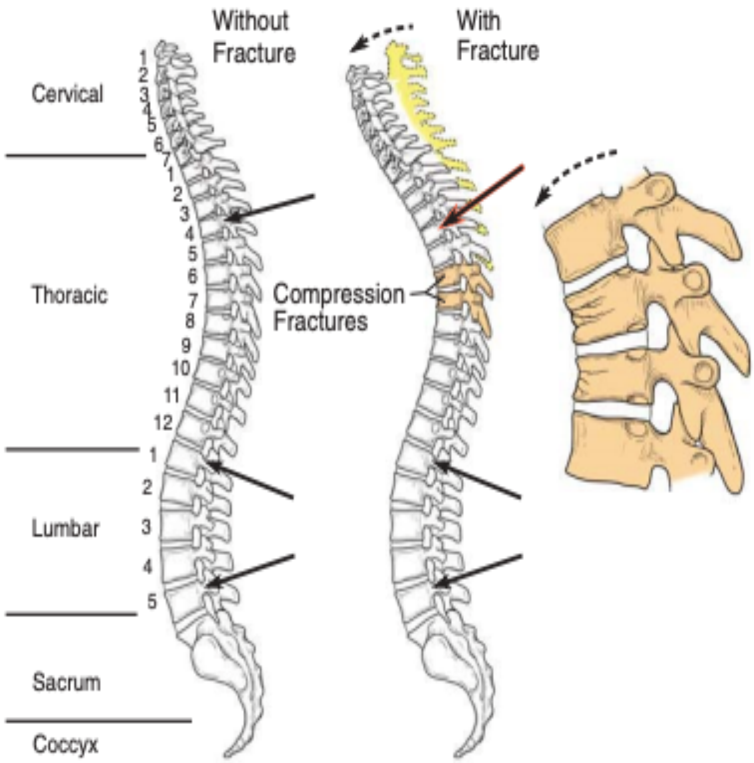

Figure 2: Increased kyphosis due to compression deformity in the thoracic spine and the resulting shift of centre of gravity according to Mathis et al. [2]

To some extent, compensatory mechanisms can compensate the fracture-related spinal malposition by inclining the pelvis and thus increasing the sacral slope, increasing segmental lordosis, and flattening thoracic kyphosis. The key compensatory mechanism is the posterior rotation of the pelvis through hip extension, though this is limited due to anatomical parameters of the pelvis [7]. The extent of compensation also depends on the location of the vertebral body fracture. The more caudal the fracture, the greater the effect on the sagittal balance and the more difficult it is to compensate [6, 13, 14]. The shift of the centre of gravity also leads to a change in the weight force distribution of the remaining vertebral bodies [15] and thus increases the likelihood of future fractures. Therefore, thoracic kyphosis is an independent risk factor for new vertebral fractures. Hence, the effects of vertebral body fractures are not restricted to the area of the fracture but instead affect the whole spine [7, 15, 16].

The resulting deformation often leads to chronic complaints, immobility and loss of function in the musculoskeletal system as a result of altered biomechanics [6, 17].

1.3. Aetiology and epidemiology of vertebral body fractures

Vertebral fractures can result from various underlying pathologies including osteoporosis, trauma, infection or neoplasm. Of these, osteoporosis is the most common underlying aetiology. In 2000 there were an estimated 9 million osteoporotic fractures worldwide, of which 1.4 million were symptomatic vertebral fractures [18]. This number is likely to increase because of the aging population [18]. Assessing the epidemiology of vertebral compression fractures is made difficult by the fact that approximately two thirds of cases do not come to clinical attention [19, 20]. There is no reliable data on the incidence of clinical vertebral body fractures in Europe and Germany. Existing studies differ considerably in terms of methodology and region.

The definition of a fracture is the acute interruption of the continuity of the bone tissue by an adequate trauma. Apart from this, the term fracture also refers to bone fractures to which no adequate trauma can be attributed. These fractures can be of osteoporotic or neoplastic origin and are summarized under the term pathological vertebral body fractures. At an advanced age, the transition between osteoporotic and traumatic fractures is often fluid and classification may be challenging. Therefore, in cases of subsequent surgical intervention, intra-operative biopsies are harvested to analyse the origin of fracture. Spinal column injuries occur significantly more frequently in the thoracic and lumbar spine than in the cervical spine. The thoracolumbar junction is particularly often affected. This can be explained by the changes in biomechanics from the thoracic to the lumbar spine.

1.4. Classification of vertebral body fractures

It is crucial to make the correct diagnosis to enable the right therapeutic procedure. The vertebral body fracture in question must therefore be assessed and classified according to its aetiology and fracture morphology.

One of the first categorisation systems used to classify thoracolumbar fractures was the three-column model invented by Denis in 1983 [21]. This classification was used to describe spinal stability and is still valid today. The three-column system distinguishes between anterior, middle and posterior column. The anterior column includes the anterior part of the vertebral body, the anterior longitudinal ligament and the annulus fibrosus. The middle column includes the posterior part of the vertebral body, the annulus and the posterior longitudinal ligament. The posterior column is made of vertebral arches including the joints, spinous processes and the dorsal ligamentous apparatus (supraspinous ligament, interspinous ligament, capsule, ligamentum flavum) [21]. A fracture is considered unstable if at least two columns are affected including the middle column.

1.5. Vertebral body fractures caused by osteoporosis

Osteoporotic fractures are usually defined as those occurring as a result of osteoporosis, often caused by a fall from standing height or less, without experiencing adequate trauma. These fractures are also known as fragility or low-trauma fractures. The definition of an osteoporotic deformity is characterized by an at least 20% decrease in vertebral body height according to the semiquantitative criteria proposed by Genant et al. [22].

Vertebral compression fractures are the most common osteoporotic fractures and a frequent manifestation of a previously asymptomatic osteoporosis. Higher age, low bone mineral density and pre-existing deformities of the vertebral body are significant risk factors for vertebral body fractures [23]. Osteoporotic fractures are usually stable and occur predominantly in the middle thoracic spine, in the thoracolumbar junction and in the upper lumbar spine. Collapse of the posterior edge as well as vertebral body sintering cranially of T7 should be reminiscent of a neoplastic event.

In osteoporotic fractures, different pathogenetic mechanisms such as loss of bone mass and bony microarchitecture interact. The loss of bone stability is caused by excessive bone resorption with a loss of bone mass and destruction of the trabecular microarchitecture or insufficient bone formation after resorption in the remodelling process [24]. Remodelling is the physiological renewal process of bony tissue in which bone mass is kept constant until menopause by balancing osteoclastic resorption and osteoblastic formation [25]. The balance of permanent bone remodeling is regulated by several systemically acting hormones. The most important of these are cortisone, sex hormones and growth hormones, calcitonin, parathyroid hormone, thyroid hormone, and insulin [26].

The contents of non-collagenous proteins in the bone matrix are altered because of decreased bone mineral density which also leads to structural deterioration and therefore fragile bones. These processes, directly acting on the bony microarchitecture, in combination with an increased tendency to fall, explain the high incidence of fractures after inadequate trauma in patients with osteoporosis [13, 17, 25, 27].

The clinical consequences of osteoporotic vertebral compression fractures are an increasing kyphosis of the thoracic spine, an increased lordosis of the lumbar spine, loss of body height, typical skin folds from the back to the flanks and a deteriorated gait pattern [13, 28].

1.5.1. Osteoporosis

Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and micro architectonic deterioration of bone tissue, with a consecutive increase in bone fragility and tendency to fracture [29]. Osteoporosis is the most frequent generalised skeletal disease and is one of the most frequent diseases in old age. However, the available studies suggest that at least 30% of people over 75 years of age in Germany are affected by osteoporosis and the actual prevalence is suspected to be much higher if the symptom-free patients were also to be identified [30, 31].

According to the 1994 WHO definition, osteoporosis is present when the bone mineral content in a DXA bone density measurement at the lumbar spine and/or proximal femur deviates by < -2.5 standard deviations from the mean value of a 20-29-year-old woman [32]. The deviation of bone density from that of a healthy 20-29-year-old woman, expressed in standard deviations, is called T-score. This value can also be applied to men over 50, even if the reference value is that of a young woman [33].

Osteoporosis often manifests clinically only through fractures. If these are present, the criterion of manifest osteoporosis is fulfilled.

Osteoporosis can be differentiated into a primary and a secondary form. Primary osteoporosis is caused by continuous loss of bone mass of about 0.5-1 % per year after reaching peak bone mass around the age of 25. In women, one of the predisposing factors is an increase in physiological, age-related bone loss due to the altered hormone balance after the last menstruation. In this postmenopausal accelerated process due to estrogen deficiency, a reduction in bone mass of up to 10% per year is possible [13].

Secondary causes can be of endocrine origin (e.g., hypercortisolism, hypogonadism), but also malassimilation, anorexia nervosa, immobilisation, rheumatic diseases, COPD and various hereditary diseases with collagen synthesis disorders can be triggers. Drugs that can lead to secondary osteoporosis are especially systemic glucocorticoids exceeding the dose of 7.5 mg prednisolone equivalent, which are administered over a long period of time and inhibit osteoblastogenesis and increase the activity of osteoclasts. In addition, when taking, among other things, anti-epileptic drugs, proton pump inhibitors, aromatase inhibitors, anticoagulation with unfractionated heparin, and immunosuppressive therapy, a possible secondary osteoporosis must be considered [33, 34].

The most important risk factors for the occurrence of osteoporosis are age and sex, with the female sex at greater risk due to the postmenopausal decrease of bone-protective estrogen. In addition to the medications and pre-existing conditions, possible nicotine abuse and whether one parent has suffered a proximal femur fracture should also be included in the risk assessment [28, 33].

The guidelines issued by the Dachverband Osteologie e.V. (DVO) [33] recommend the following diagnostic procedures:

- Specific anamnesis (risk factors, previous falls, functional limitations, nutritional habits, level of activity)
- Clinical examination including determining the risk of falling with the help of specific tests (e.g., timed up and go test, chair rising test)
- Measurement of body height and weight and resulting BMI
- DXA bone density measurement
- If necessary, basic osteological laboratory
- Imaging diagnostics for the detection of vertebral body fractures at the appropriate clinic

Basic therapeutic measures for osteoporosis and fracture prophylaxis according to the guidelines [33] are :

- Sufficient physical activity and muscle strength
- Fall prevention/ revaluation of fall-promoting medication
- Balanced diet with sufficient supply or supplementation of calcium and vitamin D

A specific drug therapy is recommended when a vertebral body fracture has already occurred or the estimated 10-year risk for vertebral body and proximal femur fractures is > 30 % [33, 34]. It is also recommended after low-traumatic proximal femur fractures with a DXA T-score < - 2.0 in the lumbar spine or femoral neck or total proximal femur, and also individually with a T-score > 2.0 [33].

According to DVO guidelines, the bisphosphonates alendronate, risedronate, ibandronate and zoledronate, the monoclonal antibody against RANKL Denosumab, the selective estrogen receptor modulators (SERM) raloxifene/ bazedoxifene and the osteoblast stimulating teriparatide are recommended for postmenopausal women with specific indications [33, 35]. For men, however, the drugs approved for osteoporosis therapy are alendronate, risedronate, zoledronate, strontium ranelate and teriparatide [28, 33].

1.5.2. Genant classification

The widely used semiquantitative Genant classification system [22] was published in 1993 and has been established since then for the evaluation of osteoporotic vertebral compression deformities on two-dimensional radiographic images. It is based on the vertebral shape (wedge, concave, crush), with respect to vertebral height loss involving the anterior, middle as well as the posterior vertebral body. A distinction is made between first-, second- and third-degree vertebral body deformities as shown in Table 1. A vertebral body fracture is present if one of the vertebral body heights is at least 20 % less than the comparable height of the adjacent vertebral bodies. The Genant classification score is assessed solely by visual estimation and differentiates vertebral fractures from nonfracture deformities by evaluating vertebral height reduction and morphological change [36].

Table 1: Fracture classification according to Genant [22]

Fracture	Reduction of height relative to adjacent vertebral body	Interpretation
Grade 0	< 20 %	no fracture
Grade 1	20 - 25 %	mild fracture
Grade 2	25 - 40 %	moderate fracture
Grade 3	> 40 %	severe fracture

1.5.3. OF Classification

The German Society for Orthopaedics and Trauma published a new classification for osteoporotic thoracolumbar spine fractures - the OF classification - nationally in 2017 [37] and internationally in 2018 [38, 39]. The OF classification is thought to consider typical morphological patterns and the biomechanical stability of the fracture in order to serve as a foundation for treatment recommendations [38]. It consists of 5 subgroups (Figure 3) and is based on all available radiological examinations. Fractures classified as OF1 and OF2 are considered stable, whereas OF3 fractures can be unstable, and OF4 and OF5 fractures are always unstable.

OF classification according to the German Society for Orthopaedics and Trauma [37, 38]

- OF 1: No vertebral deformation (vertebral body oedema)
- OF 2: Deformation with no or only minor involvement of the posterior wall (< 1/5) affecting only one endplate (impression fracture)
- OF 3: Deformation with distinct involvement of the posterior wall (> 1/5) affecting only one endplate (incomplete burst fracture)
- OF 4: Loss of integrity of the vertebral frame structure (complete burst fracture), vertebral body collapse or pincer-type fracture
- OF 5: Injuries with distraction or rotation affecting the anterior column as well as the posterior bony and ligamentous complex

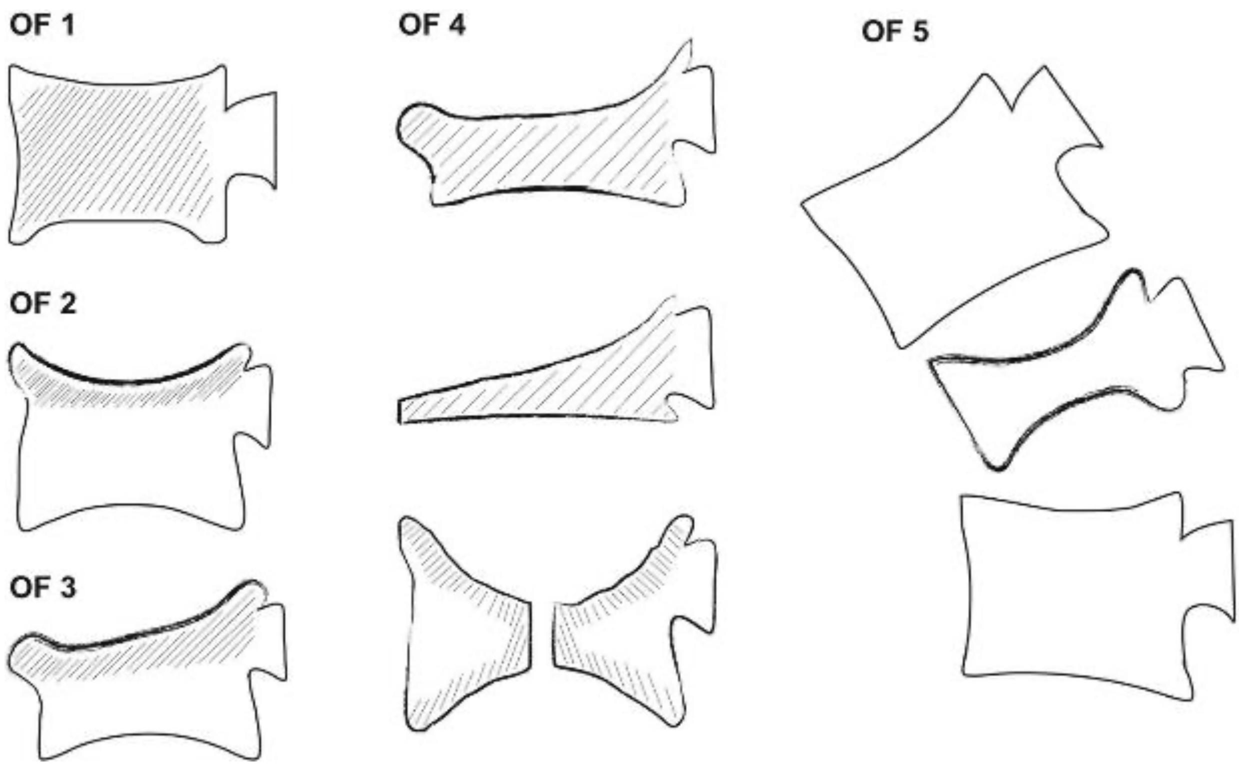

Figure 3: OF classification for osteoporotic thoracolumbar vertebral fractures published by the German Society for Orthopaedics and Trauma according to Schnake et al. [37, 38]

1.6. Vertebral body fractures caused by tumours

Pathological vertebral body fractures are often the result of bone tumours and especially of osseous metastases. The patterns of bone and soft tissue disruption in neoplastic lesions differ significantly from those of traumatic fractures. In neoplastic fractures, ligaments and discs are usually not affected [40]. Due to the rather poor bone quality in cancer patients, the healing process is difficult to assess. Reducing the pain and neurological symptoms caused by instability remains the main focus [41].

However, spinal metastases are twenty times more frequent than primary spinal tumours and have their peak, relative to the average age of cancerous diseases, between 40 and 65 years of age [42]. In the spinal column, 10 % of all primary bone tumours and 30 % of all skeletal metastases are localised. Nearly half of all spinal metastases affect the lumbar spine [41]. Benign bone tumours or tumour-like changes include osteoid osteomas, aneurysmatic bone cysts, haemangiomas and Langerhans cell histiocytosis. Malignant tumours of the bone and bone marrow include multiple myeloma, Ewing's sarcoma, osteosarcoma and chondrosarcoma [13, 43].

The most common primary tumours with osseous metastases are mamma carcinoma, prostate carcinoma, bronchial carcinoma, and renal cell carcinoma [44, 45]. More rarely, the primary tumour is also located in the thyroid, gastrointestinal tract or skin, and in about 10 % of cases the primary tumour remains unknown [46, 47].

Metastasis occurs either through the direct proliferation of tumour cells via the arterial and venous vascular system and lymphatic pathways or through direct growth (per continuitatem). A distribution via the cerebrospinal fluid system in the sense of an intra- or extramedullary metastasis is also possible.

1.7. Vertebral body fractures caused by trauma

Adequate trauma is another common cause of spinal fractures, especially in younger patients due to their lifestyle including sports or occupational risk factors [48]. In contrast to osteoporotic and tumorous vertebral body fractures, traumatic vertebral body fractures are caused by direct forces (e.g., fall on stairs with direct impact of a vertebral body on a stair step) or indirect forces (fall from a great height with compression of the spinal column).

In a large German/Austrian multicentre study with 865 patients included, falls from great heights, traffic accidents and banal falls were identified as the main causes of traumatic spinal column injuries [48]. In the European region, sports injuries and, less frequently, bullet and stab injuries were additionally identified [49].

On one hand, the thoracolumbar transition shows the transition from physiological kyphosis of the thoracic spine to lordosis of the lumbar spine, but on the other, it is more flexible and generally more susceptible to fractures due to the omission of the ribcage in the lumbar spine [4, 13, 50]. Since the line of gravity is located as a plumb line in front of the thoracic spine, vertebral compression fractures are primarily observed in this section of the spine. The injured vertebrae include mostly L1, followed by T12 and L2 [48, 51]. However, in the context of high speed traumas, B injuries (flexion-distraction) and C injuries (rotation) also occur in this section of the spine [50].

Several forces are involved in spinal column injuries: axial compression, flexion/ distraction and torsion. The bony pathomorphology of vertebral body fractures results from axial loading with or without flexion, which leads to different degrees of compression fractures. These can range from mild compression to severe burst fractures. Compression fractures usually involve only the anterior column, while burst fractures affect the anterior and middle columns. In both fracture mechanisms the posterior edge of the vertebral body remains intact. With flexion forces tearing the spinous ligaments, fractures involving the middle and posterior column occur. Rotational or shear forces acting on the spine lead to fracture dislocation if combined with axial or tension loading [52].

1.7.1. AO Spine classification

In 1994 Magerl et al. proposed an extensive classification of thoracic and lumbar spinal injuries based on pathomorphological criteria and main mechanism of injury. To provide a simple classification system, the one used for the AO fracture classification was adopted [53]. AO is an initialism for the German "Arbeitsgemeinschaft für Osteosynthesefragen".

The AO classification is based on the Denis three column model and distinguishes three main groups of typical injury patterns (A: compression injuries, B: distraction injuries, C: translational or rotational injuries). In 2013, a further development based on the Magerl classification was introduced by the AO Spine classification group, which divides thoracolumbar injuries into 3 main groups and 9 subgroups as shown in Table 2 [54]. The classifications are based on radiologically recognisable, pathomorphological characteristics of the fracture.

Table 2: Fracture classification according to AO spine classification group [54]

Type	Subgroup	Description
A: compression injuries	A0	minor, non-structural fractures such as transverse process or spinous process fractures
	A1	fracture of a single endplate without involvement of the posterior wall of the vertebral body
	A2	split fracture of both endplates without involvement of the posterior wall of the vertebral body
	A3	incomplete burst fracture with any involvement of the posterior wall and a single endplate
	A4	complete burst fracture with any involvement of the posterior wall and both endplates
B: distraction injuries	B1	chance fracture/ transosseous tension band disruption with monosegmental pure osseous failure of the posterior tension band
	B2	posterior tension band disruption with bony and/or ligamentary failure of the posterior tension band together with a Type A fracture
	B3	hyperextension injury through the disk or vertebral body leading to a hyperextended position of the spinal column; anterior structures are ruptured but a posterior hinge prevents further displacement
C: translational or rotational injuries		describe displacement or dislocation

1.8. Treatment of vertebral body fractures

Depending on the extent of the fracture, existing comorbidities, age and the patient's level of suffering, various conservative and surgical treatment options have to be considered. Both treatment options aim to ensure spinal stability and preserve neurological function as well as quality of life.

Generally, in Germany a conservative approach is primarily recommended in osteoporotic OF 1 and OF 2 fractures [55] as well as in traumatic A1 and A2 fractures [13, 50]. In the case of surgical intervention, percutaneous augmentation of the vertebral body is the favourable therapy for these subgroups. In all other fracture groups, surgical stabilisation with pedicle screw constructs should be sought, which can be done in a percutaneous or open manner [37].

The ultimate goal of any therapeutic regime should be early mobilisation of the patient to avoid pneumonia, thromboembolism, and loss of strength and coordination due to muscle atrophy. At the same time, satisfactory pain relief needs to be achieved.

1.8.1. Conservative treatment

Conservative fracture treatment requires a stable fracture without neurological deficit. The conservative therapy approach consists of strengthening muscles and improving coordination, changing diet and lifestyle, and the use of appropriate medication. In addition to an early mobilisation, the focus is on analgesia. An adequate analgesic therapy according to the WHO pain ladder should be carried out. In many cases, the age of the patients as well as the increasing multimorbidity and polypharmacy require an individual risk assessment regarding the undesirable side effects of pain medication [56].

Individually adapted physiotherapy is also essential to achieve early mobilisation. Patients should experience a reduction in pain with the help of segment stabilising exercises. Strengthening muscles is supposed to result in an improvement in posture and therefore less falls. Furthermore, local therapeutic measures (heat/cold therapy, interferential current therapy, transcutaneous electrical nerve stimulation) can be applied to reduce muscle tone and pain [57]. The additional use of reclining orthoses is discussed controversially [4, 52, 58]. In younger patients, orthoses are thought to have an adverse effect by deconditioning the trunk musculature and therefore leading to more instability [56]. However, in elderly patients with osteoporotic compression fractures, and in the situation of an uncontrollable pain symptomatology, reclining orthoses can be used as a complementary treatment alternative [59]. Currently, orthoses are indicated on individual factors, rather than for all conservatively treated patients.

Close radiological follow-ups are indispensable during conservative treatment in order to detect further sintering at an early stage and to initiate surgical treatment if necessary [58]. Some patients experience a significant improvement in symptoms within a few weeks. A recent study from Sweden, however, found that 76 % of the patients included still had significant pain affecting their quality of life one year after beginning conservative treatment [60]. In cases of therapy-resistant complaints or relevant further sintering of the vertebral body, a switch to a surgical procedure is indicated. Nevertheless, conservative treatment remains gold-standard first-line therapy for the majority of osteoporotic and traumatic spinal fractures.

1.8.2. Surgical treatment

According to the Spine section of the German Society for Orthopaedics and Trauma (DGOU) there are certain indications for operative therapy. A clear indication for surgical treatment of vertebral body fractures is a neurological deficit that occurred as a result of the fracture. In addition, unstable fractures and fractures with kyphotic malposition of more than 15-20° compared to the physiological alignment should be surgically treated. Scoliotic malalignment of more than 10° as well as immobilisation in the case of therapy-refractory pain are also regarded as indications for surgery. Therapy-refractory pain is defined according to the guidelines as a fresh fracture with severe pain at the localisation of the fracture level that has been unsuccessfully conservatively treated over 6 weeks [61].

The surgical treatment strategies are based on the principles of stabilisation and restoration leading to pain reduction and functional improvement. The main goal of any surgical therapy should be the reconstruction of the individual age-specific sagittal and global spinal alignment. The choice of surgical treatment depends on the extent of the fracture and the individual risk factors of the patient. In stable fractures (OF1/2, A1/2) without or with minor involvement of the posterior wall, percutaneous filling of the fractured vertebra with substances such as polymethylmethacrylate is possible. This procedure can be done with (kyphoplasty) or without (vertebroplasty) prior balloon dilatation. The augmentation of fractured vertebral bodies is the most commonly used procedure for osteoporotic vertebral fractures, reducing pain and stabilising the vertebra. In the case of unstable fractures without neurological deficits, dorsal percutaneous cementless pedicle screw stabilisation can be used with an optional additional kyphoplasty of the index vertebra [37, 57, 58]. In general, the more unstable the fracture, the more segments should be included in dorsal stabilization; however, bisegmental posterior stabilisation is sufficient in most patients. In patients with poor bone quality, for example due to osteoporosis, it is recommended to fix the pedicle screws using PMMA augmentation [55]. Minimally invasive ventral stabilisation is rarely indicated.

In highly unstable fractures with neurological deficits, open treatment concepts can be favourable. Though due to the higher intraoperative morbidity and the often multimorbid patients, minimally invasive procedures should be the preference.

1.9. Balloon kyphoplasty

Even if the vertebroplasty is accompanied by a considerable reduction of pain [62, 63], it might have disadvantages and complications that need to be considered. Since no cavity is created in the vertebral body, very thin cement must be inserted under high manual pressure to fill the intertrabecular cavities and displace the fatty bone marrow [64]. In spite of continuous fluoroscopic monitoring, cement often leaks during vertebroplasty which can lead to severe neurological or pulmonary complications [65]. In 1998, the American orthopaedic surgeon Mark Reiley developed a new augmentation procedure, the so-called kyphoplasty, based on his experience with vertebroplasty [66]. Kyphoplasty is a minimally invasive percutaneous stabilisation method for vertebral body fractures and was developed specifically for the treatment of osteoporotic fractured vertebral bodies. In addition to fracture stabilisation, the balloon kyphoplasty procedure also enables the repositioning of the fracture. The further development of the surgical procedure includes the insertion of a balloon into the vertebral body prior to cement application.

Due to the anatomical situation of the venous plexus that surrounds the vertebra, the patient should be placed in the prone position, with only the thorax and pelvis resting on the table while the abdomen hangs free [2, 67]. This results in a thoroughly desirable lordosis of the spinal column, which can contribute to the repositioning of the fractured vertebral body. It also reduces the intra-abdominal pressure and therefore prevents increased blood flow in the venous collateral circulation involving the vertebral venous system, which could encourage potentially dangerous cement or fat embolism.

Balloon kyphoplasty can be performed under general or local anaesthesia with additional sedatives if general anaesthesia is contraindicated. Which type of anaesthesia is used depends on the medical history of the patient. General anaesthesia is generally preferable, since local anaesthesia increases the level of pain and extends the operation time, and in cases with complications, an intra-operative decision-making process is not affected. Preoperatively, intravenous antibiotics are administered, preferably second generation cephalosporins. Biplanar C-arm imaging guidance is required to ensure the correct position of the surgical area and the correct position of the inserted instruments. After disinfection and sterile covering, skin incision follows. Through the skin incision a needle or guide pin is inserted into the fractured vertebral body. Usually, this can be through a transpedicular approach. After proper needle positioning monitored by C-arm X-ray, a working channel needs to be created. Once the working channel is created, the balloons are inserted as shown in Figure 4 A.

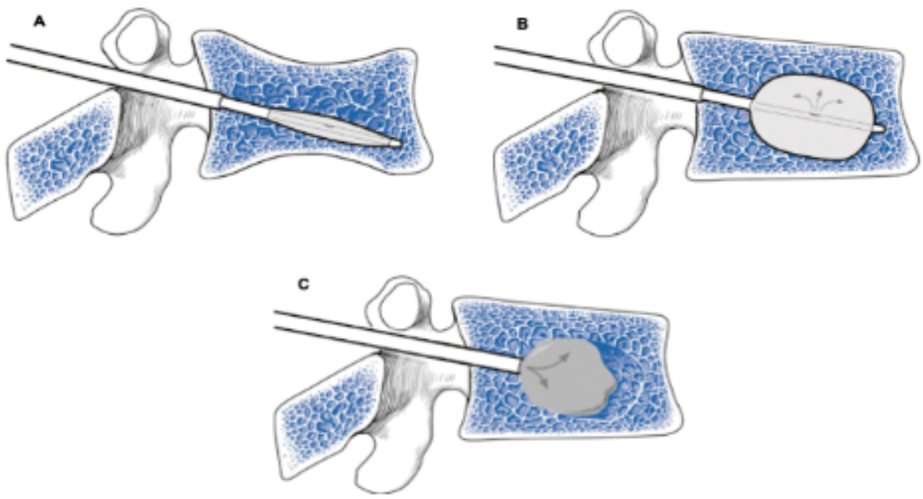

Figure 4: Schematic representation of the balloon kyphoplasty procedure, adapted from the Osteoporosis Manual by Reiner Bartl and Christoph Bartl [26]

After inserting the balloons, they are gradually inflated using visual (radiographic), volume and pressure controls (digital manometer). The created cavity within the vertebra is supposed to reduce the fracture deformity (Figure 4 B). In addition to a circumferential spongiosa compression in the marginal area of the balloon, it also leads to height restoration. Once reduction of fracture deformity has been achieved, the balloons are deflated and removed. Then, semi-solid polymethylmethacrylate cement is injected under low pressure into the newly created cavity (Figure 4 C). Depending on the size of the fractured vertebral body, a total of 2-6 ml per side can be inserted. It takes about 12-15 minutes until the PMMA cement has cured. Afterwards, another X-ray control is carried out. If the X-ray shows a satisfying result, the stab incision is closed and is adequately occluded with an aseptic dressing. Cement options other than polymethylmethacrylate, such as calcium phosphate or calcium sulphate cement are available, and application depends on patient- and surgeon specific factors [68, 69].

The kyphoplasty bone cement is thus no longer filled in directly but set into a preformed intertrabecular cavity. The aims of kyphoplasty are the better repositioning of the fracture and a lower rate of cement leakage than with vertebroplasty. The improved repositioning is supposed to counteract fracture-related kyphosis and consecutive static changes of the corresponding spinal column section. In recent years, this procedure has prevailed against vertebroplasty in everyday clinical practice and is currently the most frequently used method of kyphoplasty in Germany [70].

1.9.1. Indications

The technique of balloon kyphoplasty was initially developed in 1998 for osteoporotic spinal lesions, but shortly after, as the technique spread, the indication was extended to tumours and traumatic compression fractures [71]. Additionally, balloon kyphoplasty can be used as a perioperative, adjuvant method for operational stabilisation. Nevertheless, osteoporotic compression fractures of the thoracic and lumbar spine with persistent pain are still the main indication for kyphoplasty. In the thoracic spine, it is mainly vertebral body fractures of the middle and lower sections that are suitable for treatment with kyphoplasty, whereas kyphoplasty performed on the upper thoracic spine is rather rare. In their indications, a clinical study by McArthur et al. [72] with 1,150 kyphoplasties in 555 patients included fresh traumatic vertebral fractures, painful sintered osteoporotic vertebrae after failure of conservative treatment as well as osteolysis and painful vertebral body collapse caused by multiple myelomas. Additionally, pathological fractures due to metastases of malignant tumours or benign vertebral tumours are indicative for kyphoplasty. Prostate cancer, ovarian cancer, breast cancer and malignant melanoma are examples of malignant tumours that are most common to metastasise into the spine.

In a recent review by Tsoumakidou et al. [73], the Cardiovascular and Interventional Radiological Society of Europe defined the following indications for kyphoplasty in 2017:

- Painful osteoporotic VCFs refractory to conservative treatment, where failure of conservative treatment is defined as insufficient pain relief after 3 weeks or achievement of pain relief with only intolerable narcotic dosages. The 3-week delay depends on the patient status and is open for discussion, as there is no published consensus on whether to wait for 3 or 6 [74] weeks before revaluation

- Painful vertebrae due to benign bone tumours like aggressive haemangioma, giant cell tumour and aneurysmal bone cyst
- Painful vertebrae with extensive osteolysis due to malignant infiltration as palliative treatment aiming at treating pain and achieving bone consolidation
- Painful fractures associated with osteonecrosis
- Symptomatic vertebrae plana
- Acute stable A1 (particularly Magerl A1 with LKA > 15°) and A3 traumatic fractures as defined by the Magerl classification [53]
- Chronic traumatic fractures in non-osteoporotic bone with non-union of fracture fragments
- Adjuvant peri-/intraoperative kyphoplasty as part of surgical stabilisation

1.9.2. Contraindications

Contraindications for kyphoplasty are general limitations such as coagulation disorders and unsuitability for general or local anaesthesia. Severe cardiac or respiratory insufficiencies and in particular the inability of prone positioning are contraindications for surgery. In addition, it must be clarified prior to surgery whether the fracture is primarily osteoporotic or traumatic and whether the pain the patient experiences correlates with the radiological findings. A strict contraindication is given in the case of a severe iodine allergy, as the balloon is filled with contrast medium containing iodine and might burst during inflation. Furthermore, kyphoplasty should not be used in the case of concomitant spinal stenosis or discopathy with radical symptoms. Patients who have an unstable vertebral fracture with involvement of the posterior wall can sometimes be unsuitable for kyphoplasty as there might be an increased risk of cement leakage and posterior displacement of loose fragments. If these patients undergo kyphoplasty, special care must be taken. Kyphoplasty is also more difficult to perform in cases of poor visibility under fluoroscopy, e.g., in a high-thoracic lesion or very obese patients.

The relevant absolute and relative contraindications according to the CIRSE guidelines on kyphoplasty [73] are listed in Table 3.

Table 3: Absolute and relative contraindications for kyphoplasty [73]

Absolute contraindications	Relative contraindications
- asymptomatic, stable vertebral compression fractures	- tumour extension into the vertebral canal or cord compression
- successful conservative treatment	- radicular pain
- unstable spinal fractures	- fracture of the posterior column
- prophylaxis treatment in severe osteoporotic patients	- sclerotic metastasis
- osteomyelitis, discitis or active systemic infection	- diffuse metastases (>5)
- severe uncorrected coagulopathy	- burst fractures (though some Magerl A3.1 fractures can be addressed with kyphoplasty)
- allergy to bone cement or contrast medium	- treatment of more than 3 vertebrae in one operation

1.9.3. Complications

The complication rate for balloon kyphoplasty described in the literature is low and ranges between <1 % [75] and up to 4 % [73] for osteoporotic compression fractures. The complication rate for the treatment of malignant fractures is significantly higher at approximately 11 % [73, 76]. The most frequent complication is cement extravasation, either via the vertebral venous system or directly via loose fracture fragments in the vertebra. An asymptomatic cement extravasation occurred in 20% of cases [77] detected on postoperative X-rays and up to 34% [75] in the large randomised post-interventional computer tomography control studies. Attempts to explain the considerable range in the rate of cement extravasations are seen in subjective evaluation criteria as well as in different diagnostic control and detection methods such as, for example, standardised controls using native X-rays, or computer tomographic and thus more sensitive detection methods with regard to the presence of cement extravasations. However, clinically relevant pulmonary cement embolisms or the affecting of nerve roots or myeloma with intraforaminal or intraspinal cement extravasation are rare [73, 75, 78]. According to Becker et al. [79] the risk of pulmonary embolism is 0.01 % in kyphoplasty. It should be mentioned as a limitation that most of the smaller embolisms are clinically silent and are therefore not documented.

Adjacent level fractures are newly occurring compression fractures of a vertebra above or below the cement augmented vertebral body. In the literature, the occurrence of adjacent level fractures after treatment with kyphoplasty is discussed controversially. It is unclear whether the cause of these fractures is the increased stiffness of the operated vertebral body and the resulting forces acting on the adjacent vertebral bodies or whether the progression of osteoporosis is the cause. While initial biomechanical and clinical studies showed ambiguous results, a recent meta-analysis by Zhang et al. [80] did not find a significantly increased risk of adjacent level or new fractures as well as changes in bone mineral density after kyphoplasty compared to non-surgical treatment. Conversely, Yang et al. analysed the risk factors and correlations, and implicated that patients with lower preoperative bone mineral density values, larger balloon and cement volumes as well as intraoperative bone cement leakage have an increased risk of adjacent vertebral compression fracture after percutaneous kyphoplasty [81].

During operations, in order to keep the risks from patient positioning and anaesthesia as low as possible, the CIRSE guidelines by Tsoumakidou et al. [73] recommend to not exceed an intervention time of 2.5h and to not treat more than 5 vertebral bodies in one session.

1.10. Hypothesis and aims of the study

About 250,000 vertebral body fractures occur in Germany every year [27]. In younger patients those occur as a result of traffic or sports accidents, whereas vertebral body fractures in the elderly are mainly due to loss of bone mineral density. Therefore, even minor trauma often causes one or more vertebral bodies to fracture. Those fractures occur particularly often in postmenopausal women as part of osteoporosis.

Current guidelines mainly recommend an initial conservative approach and to only consider surgical intervention in the case of persistent pain. The latest guidelines by the German Umbrella Organisation of Osteology, published in 2017, suggest anticipating kyphoplasty in patients with VAS scores beyond 5 after an unsuccessful, intensive and documented conservative therapy attempt, after consideration of other causes of the given pain and after documented interdisciplinary discussion of the individual case [33].

However, any conservative treatment inevitably delays the surgical treatment. Meanwhile, the fracture might already start to consolidate. Therefore, it seems conceivable that a prolonged time interval between fracture occurrence and kyphoplasty might limit the achievable height restoration [82]. Hence, it might be favourable to not extend conservative treatment over a specified time. However, the appropriate duration of conservative treatment of a VCF before performing kyphoplasty has not been established yet.

To date, there have been few studies analysing the effect of kyphoplasty on the extent of fracture reduction in terms of the timing. The available studies are rather small, with a total of 28 to 106 patients included, and to the best of my knowledge there are no controlled studies (kyphoplasty versus natural history) on the real value of the procedure according to operative timing. The most recent studies differentiate between acute and chronic fractures, but not subacute fractures [83-85], and only the study by Zhou et al. focused not only on LKA but also on height restoration after kyphoplasty. Previous studies reported a similar clinical outcome after kyphoplasty at different points in time, but also improved local kyphosis and height restoration [83, 84, 86-90] in acute fractures.

Due to the small number of patients and the frequent lack of differentiation between acute, subacute and chronic fractures, those previous studies do not allow reliable recommendations on optimal operative timing.

In the present study, the aim was to investigate the relationship between the time of surgical intervention and clinical as well as radiological outcomes by retrospectively analysing data from single level kyphoplasties of the thoracolumbar spine [82]. We hypothesized that earlier intervention would improve height restoration as well as local kyphosis and overall sagittal alignment. Furthermore, we assumed that pain and the need for analgesic would also be reduced more with earlier intervention.

2. Patients and methods

2.1. Ethics application

Prior to data acquisition an ethics application was handed in to the Ethics Commission of the Charité Universitätsmedizin Berlin, which was approved and is listed as application number EA1/201/18. To ensure the research integrity, the mandatory lecture about good scientific practice was attended at the Charité Berlin. Furthermore, a consultation concerning the statistical analysis took place at the Institute of Biometry and Clinical Epidemiology. The protection of data privacy was strictly adhered to during all times of the study.

2.2. Data acquisition

The data was acquired retrospectively from all patients that underwent kyphoplasty at the department of orthopaedics at the Charité Mitte during the period from the beginning of 2011 to February 2019. 492 patients were identified. Those patients were selected according to the inclusion and exclusion criteria explained below. 230 patients matched the inclusion criteria and were admitted into the database. The data that was relevant for the study (patient demographic information, clinical parameters, radiographic findings) was extracted from the electronic (SAP ERP 6.0, SAP SE, Walldorf, Germany and Centricity Enterprise Web® (GE Healthcare, Buckinghamshire, UK) and the non-electronic patient´s chart. It was then exported to a Microsoft Excel document (Microsoft Office Excel, Version 16.49) where all patients were listed and anonymised.

2.3. Patients

All patients had been treated with kyphoplasty and had a history of focal pain over the fracture site that correlated with findings on imaging studies. Conservatively manageable fractures and asymptomatic patients with incidentally detected fractures did not undergo kyphoplasty. The fractures were diagnosed by X-ray including lateral and anterior/ posterior images. Several patients had additional MRI and CT scans to secure the diagnosis. The age of every fracture was calculated from the time elapsed between the date of onset of symptoms and the date of kyphoplasty. Accordingly, the fractures were assigned to three different groups: acute fractures were defined as up to two weeks old, subacute fractures were older than two weeks but less than 6 weeks old, and chronic fractures were defined as older than 6 weeks (Table 4). The classification was determined empirically as there is no published consensus.

Table 4: Classification according to fracture age

	Group 1	**Group 2**	**Group 3**
Type of fracture	Acute	subacute	chronic
Interval between onset of symptoms and KP	≤ 2 weeks	≥ 2 weeks ≤ 6 weeks	≥ 6 weeks

2.3.1. Inclusion criteria

Patients were included, regardless of age and gender, who had undergone single level kyphoplasty in the thoracic or lumbar spine for a vertebral compression fracture at the Charité Campus Mitte since 2011. In addition, evaluable pre- and postoperative radiographs of sufficient quality had to be available for these patients. In order to answer the hypothesis of this study, it was necessary to know when the pain event had occurred and, accordingly, how much time had elapsed between the onset of symptoms and surgery. A total of 230 patients meeting the above-mentioned criteria were included.

2.3.2. Exclusion criteria

Patients were excluded from the study if other spinal procedure procedures, such as dorsal stabilisation, were performed simultaneously. Furthermore, patients were excluded in whom several vertebral bodies were treated simultaneously during surgery, as the fracture age of the individual fractures would be difficult to determine in these patients. Histologically secured infiltration of tumours in fractured and treated vertebral bodies was another exclusion criterion. As shown in Figure 5, a total of 262 patients were excluded because they either had tumour evidence in the biopsy (n = 10), no histological examination was performed despite known multiple myeloma (n = 1), no sufficient pre- and/ or postoperative X-rays (maximum one month prior to kyphoplasty and 2 weeks after kyphoplasty) were available (n = 73), no date of onset of pain could be determined (n =

8), kyphoplasty was performed on the cervical spine (n = 2), or multi-level kyphoplasty was performed (n = 168).

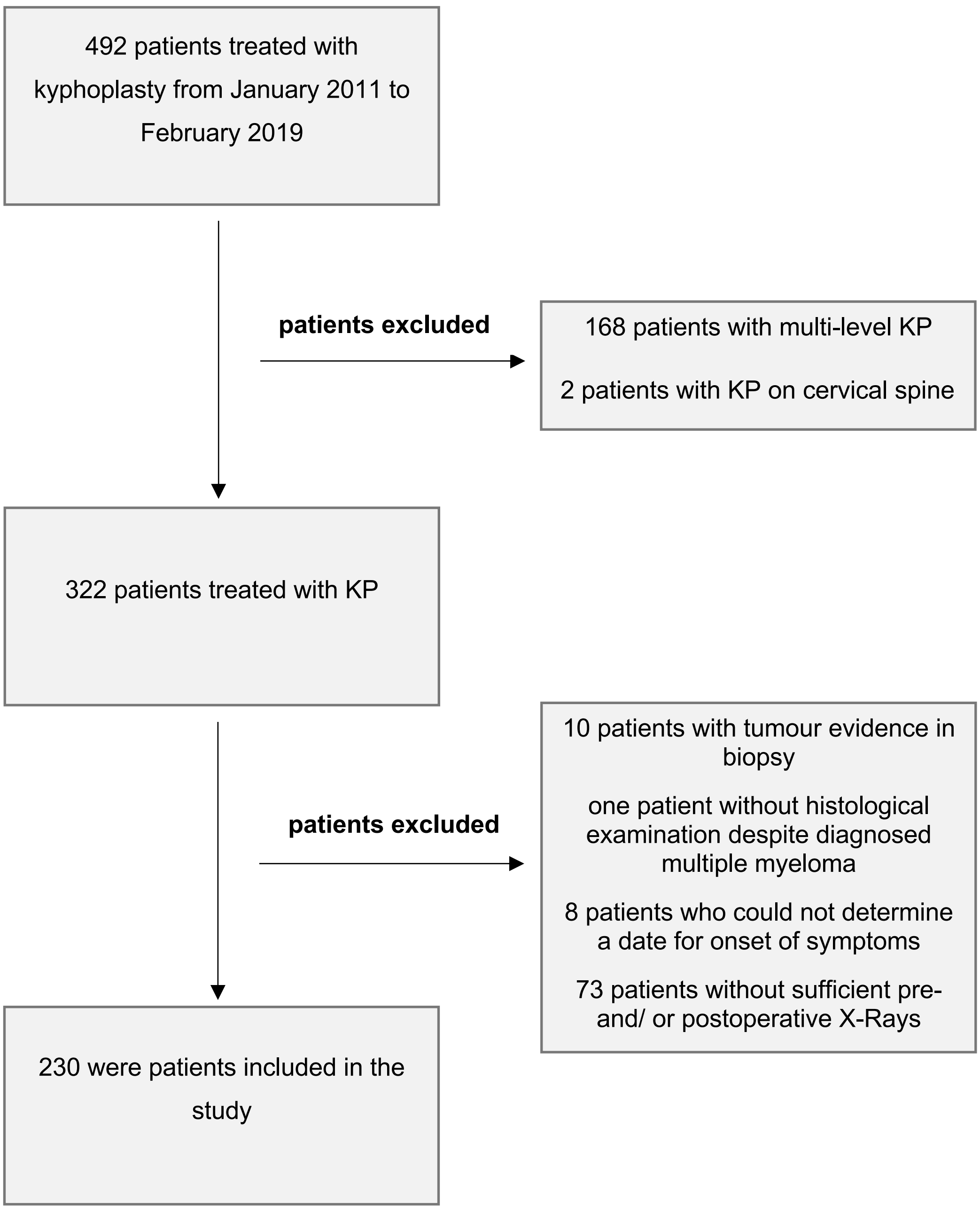

Figure 5: Flowchart visualising the process of patient inclusion in the study

2.3.3. Surgical procedure

All balloon kyphoplasty procedures were performed in the operating room and by orthopaedic surgeons. All patients were treated in a prone position with an extended spine and under general anaesthesia using a bipedicular approach and biplanar C-arm imaging guidance. After the balloons had been inserted, the inflation was controlled visually and manometrically. In all cases, the inflation stopped at a pressure of 300 PSI, when the balloon made contact with either of the endplates or the maximal balloon volume was reached [82]. If a total restoration of the vertebral body height had been achieved earlier, the inflation was also stopped. The inflatable balloon was then withdrawn. After allowing the bone cement to reach a toothpaste-like viscosity, the cavity of the fractured vertebral body was then filled with polymethylmethacrylate or calcium sulphate cement. The patients stayed in a prone position for at least 15 minutes after cement administration so that the curing process would not be compromised and also to reduce the risk of cement leakage [82]. All patients included in the study received perioperative intravenous antibiotics [82].

2.3.4. Assessed parameters

The assessed parameters were either patient, disease or treatment related. The patient and disease related data was the following:

- Patient related data:
    - Case number, name, sex, date of birth, age at the time of the operation, height, weight, BMI
- Preoperative usage of osteoporosis medication
    - Substitution of Vitamin D or calcium
    - Bisphosphonates such as alendronate or risedronate
    - Parathyroid hormones such as teriparatide
    - Human monoclonal antibodies such as denosumab
- Pre-operations on the spine
- Time elapsed between onset of symptoms and surgery
- Cause of fracture

    - Caused by trauma or osteoporosis depending on whether an appropriate trauma or only a low or no trauma had occurred
- Localisation of the fracture
- VAS for pain assessment
- Pain medication usage

The assessed data regarding the treatment was the following:

- Date of operation
- Duration of the operation
- Volume of cement filled into the vertebral body
- Intraoperative and postoperative complications
- First day of mobilisation after surgery
    - The day when the patients were mobilised or mobilised themselves in a standing position
- Duration of hospitalisation
- Number of postoperative days before discharge
- Radiological measurements and classifications

2.3.5. Clinical variables

Clinical outcomes were determined by comparison of data obtained pre- and postoperatively from patient reported outcomes such as the visual analogue scale and the need for pain medication. Both scores were determined one day prior to surgery and the second day postoperatively. In 17 patients who were discharged on the first or second postoperative day, the last VAS score documented in the patient´s chart was used. In addition, not only was the postoperative need of pain medication analysed, but also the discharge medication.

2.3.5.1. Visual Analogue Scale

The visual analogue scale (VAS) is a popular standardised scale for pain evaluation. It is a method for recording pain subjectively, which is used particularly in pain research and pain therapy. The VAS is usually shown as a line drawn with a defined scale from 1 to

10, in which 1 indicates no pain and 10 indicates severe pain. This score is simple, reproducible and easy for patients to understand. It can be used to monitor the success and effectiveness of the treatment with pain medication. The VAS enables medical and nursing staff to assess the current subjective pain situation of the patient and to react appropriately in terms of pain medication.

2.3.5.2. Pain medication usage

As a second clinical outcome, the pain medication usage was analysed. The pain medication documented preoperatively, postoperatively and on the day of discharge was divided into four categories according to the analgesic ladder created by the WHO. The WHO guideline was first published in 1986 for the management of cancer pain but is now widely used for management of all types of pain, although it was slightly modified for some indications.

The pain medication usage of patients treated with kyphoplasty was transformed to an ordinal scale (0 = no pain medication usage; 1 = non-opioid + optional adjuvant; 2 = weak opioid + non-opioid + adjuvant; 3 = strong opioid + non-opioid + optional adjuvant). For the group of patients analysed here, there is a fixed scheme from the orthopaedic department of the Charité Campus Mitte according to which pain medication is administered. Postoperatively, each patient received Metamizol in the form of drops or as an intravenous therapy with a maximum dose of 4 g/d. In case of pain peaks, morphines were administered on demand. If these were frequently required, the fixed medication had to be revised. In the case of patients who had already been taking opioids regularly before admission to the clinic, this scheme was adapted in consideration of their current situation.

2.4. Radiological variables

Radiographic outcomes were determined by comparing standing anterior-posterior and lateral radiographs obtained before and after the procedure. These were evaluated by the author, who did not perform any of the surgeries. The radiographs had to be taken one month or less prior to the operation. Figures 6 and 7 show examples of pre- and post-operative X-ray images used for analysis.

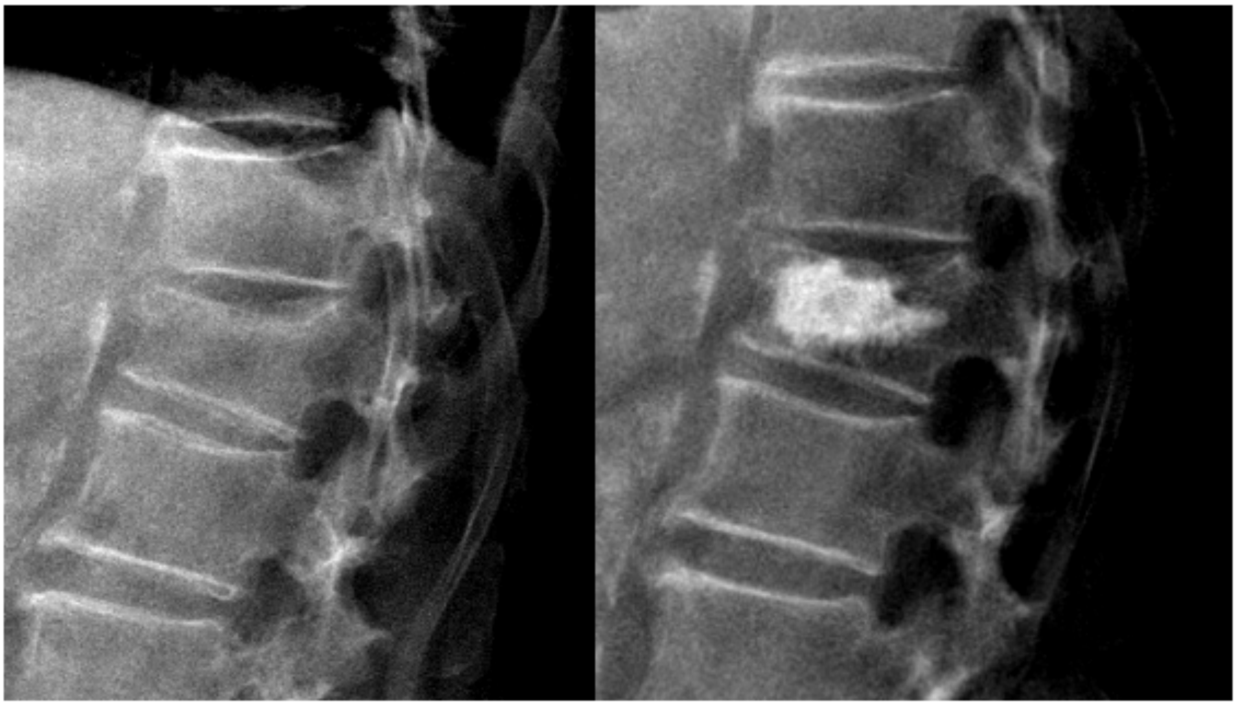

Figure 6: 78-year-old male patient with L1 vertebral compression fracture treated with kyphoplasty three days after the fracture had occurred. Pre- and postoperative X-rays were used for measuring the vertebral body heights and local kyphosis angles

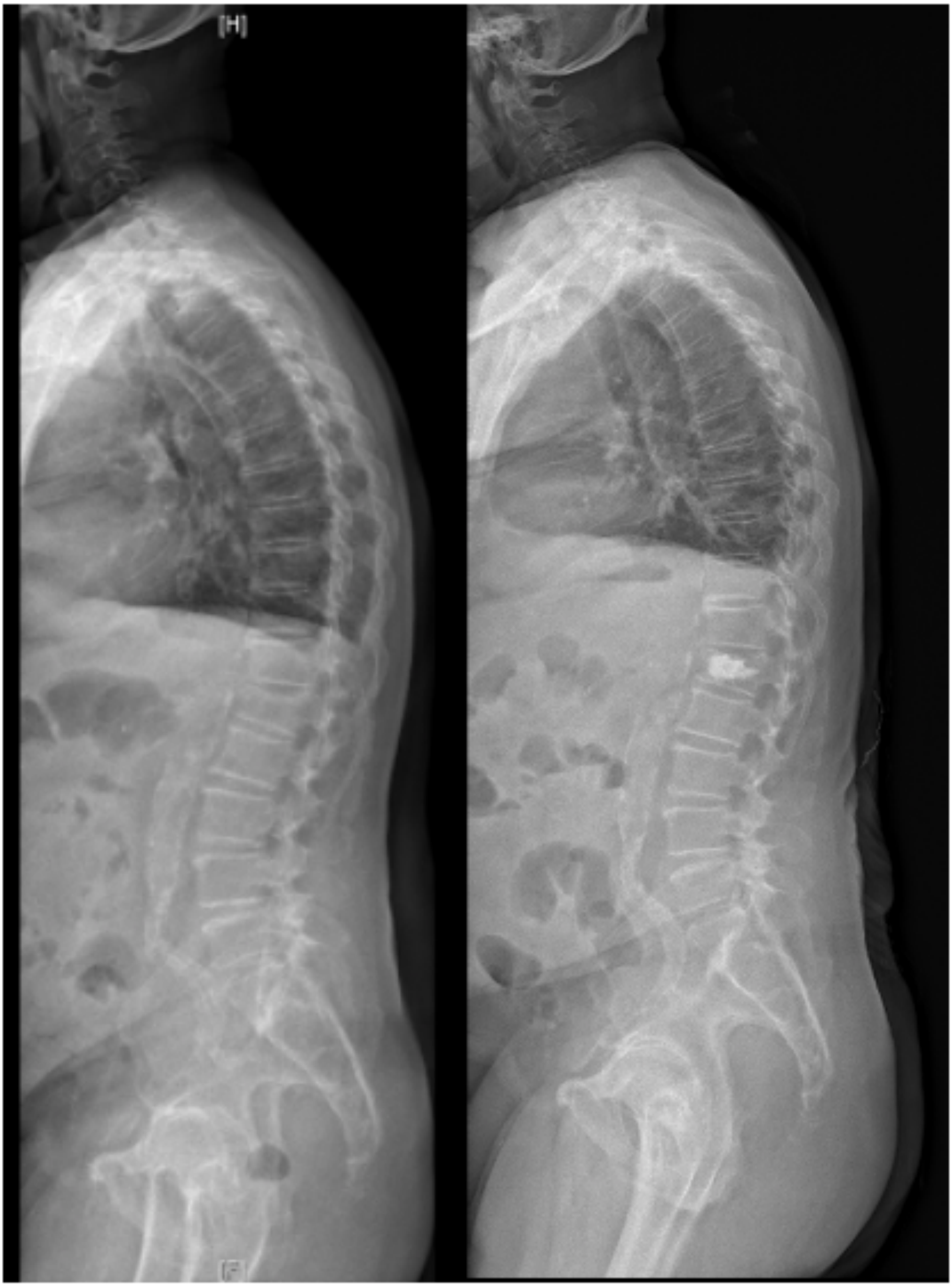

Figure 7: 78-year-old male patient with L1 vertebral compression fracture treated with kyphoplasty three days after the fracture had occurred. Pre- and postoperative whole spine X-rays were used for measuring sagittal balance and spinopelvic alignment

Additionally, the MRI scan results were taken into account. Not all patients had a current MRI scan, but when given, these were examined for any oedema. Since there is no scientific consensus on the classification of oedema in vertebral body fractures, it was transformed into an ordinal scale (0 = no oedema, 1 = slight oedema, 2 = severe oedema).

All pre-existing fractures which had not undergone surgery were also documented, so as to analyse possible surgery-induced subsequent adjacent level fractures. To evaluate the complications of the procedure, all postoperative X-rays were screened for cement leakage and subsequent adjacent level fractures. As this study is designed as a retrospective analysis, there was no protocol for follow-up checks. X-rays of patients who did have follow-up imaging were screened for further fractures.

2.4.1. Localisation and morphology of the fracture

As mentioned above, only fractures in the thoracic or lumbar spine treated with kyphoplasty were included in the study. In order to determine the frequency of fractures distributed over the various sections of the spine, the first step was to determine which vertebral body was affected.

Four different classification systems were used to classify the fractures. First, the fractures were compared based on morphology. These were differentiated into biconcave, wedge-shaped or crush/compression fractures as shown in Figure 8. A healthy vertebral body with physiologic morphology is shown in the upper row. In the lower row, from left to right, a biconcave, a wedge-shaped and a crushed vertebral body are shown.

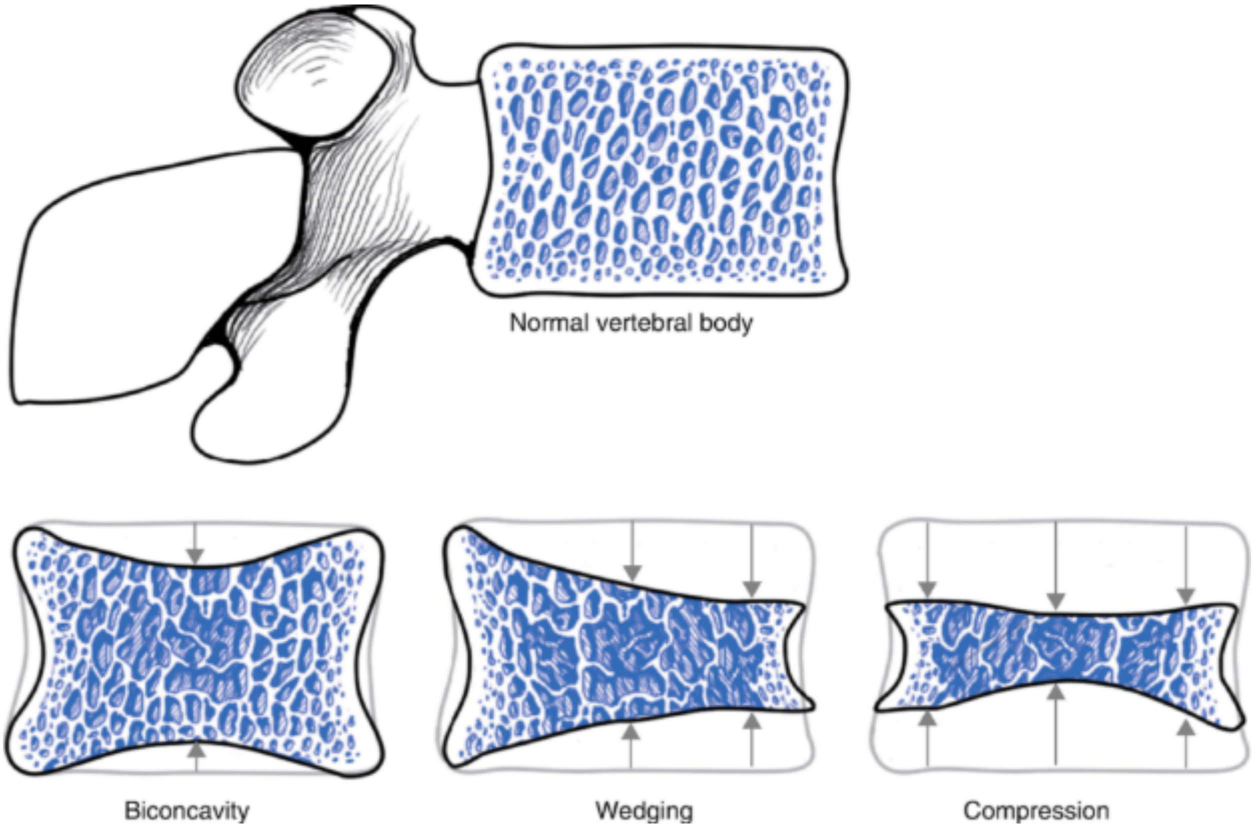

Figure 8: Morphology of a physiological vertebral body and morphology of vertebral compression fractures adapted from the Osteoporosis Manual by Reiner Bartl and Christoph Bartl [26]

Depending on the cause of the fracture, three additional classification systems were used. For traumatic fractures, the AO classification was applied to analyse the severity of the fracture. On osteoporotic fractures, the OF classification was used instead. Additionally, the classification according to Genant was used to determine the severity of osteoporotic fractures.

2.4.2. Radiological measurements

Pre- and postoperative radiographs were analysed to quantify local and overall spinal sagittal alignment correction after kyphoplasty. Pre- and postoperative vertebral heights at the fractured levels were measured and categorised into anterior, posterior or middle vertebral body heights. The program used for evaluation of the radiographs was Centricity Enterprise Web® (GE Healthcare, Buckinghamshire, UK).

2.4.2.1. Anterior, posterior and middle vertebral body height

All lateral X-rays were used to measure the anterior, middle and posterior vertebral body height in order to compare the extent of height reconstruction after kyphoplasty. This corresponds to the distance between the cranial and caudal vertebral endplates (Figure 9). A vertebra immediately caudad or cephalad to the treated level was additionally measured to estimate the pre-fractured height of the treated level. If adjacent vertebrae also showed changes, the next available intact vertebral body was measured.

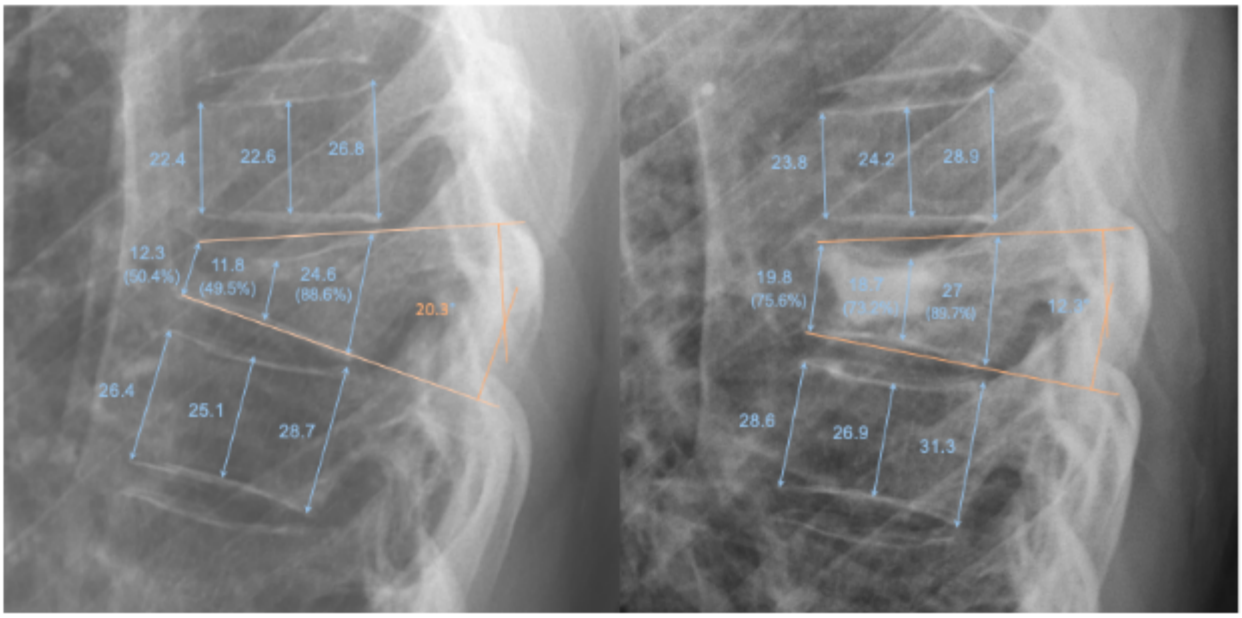

Figure 9: Measurement technique and height restoration of the anterior, middle and posterior portion of the vertebral body in mm (blue lines) as well as measurement of the local kyphosis angle (orange angles)

2.4.2.2. Local kyphosis, Gardner and Cobb angle

To quantify the local spinal sagittal alignment correction after kyphoplasty, LKA, GA (Gardner angle) and CA (Cobb angle) were measured. This added up to three different techniques of measuring the kyphotic deformity. As shown in Figures 9 and 10, LKA was measured between the superior and the inferior endplates of the fractured vertebral body. GA was measured as the angle between the superior endplate of the proximal adjacent vertebra and the inferior endplate of the fractured vertebra. CA was measured as the angle between the superior endplate of the proximal adjacent vertebra and the inferior endplate of the distal adjacent vertebra. The measured values for all three angles were recorded as positive values for kyphotic angles and negative values for lordotic angles.

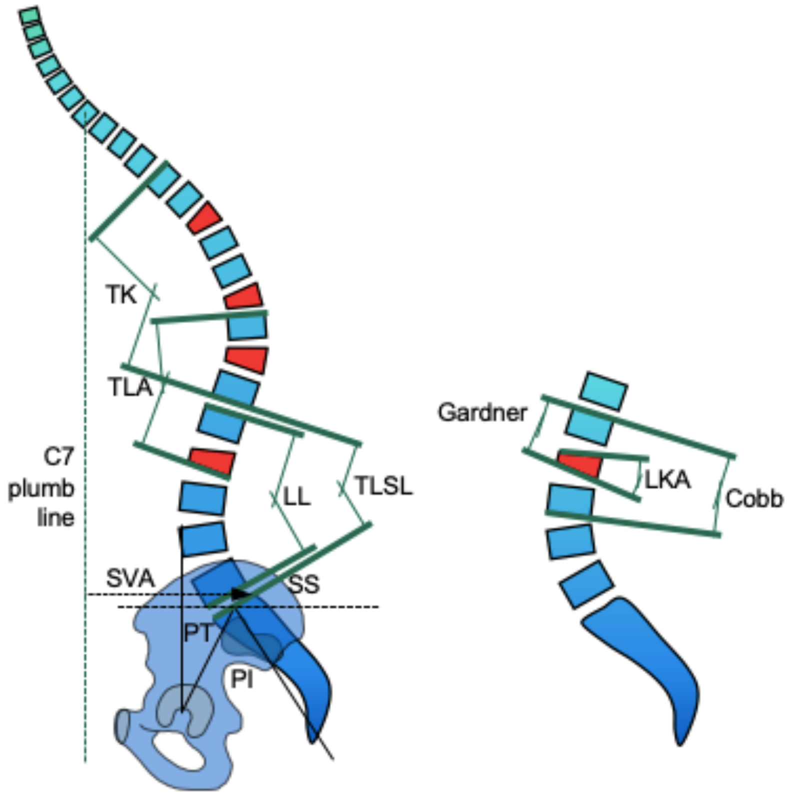

Figure 10: Demonstration of the measurement of local kyphosis, Gardner and Cobb angles on the right side and measurement techniques for sagittal balance and spinopelvic alignment shown on the left according to Pumberger et al. [15]

2.4.2.3. Sagittal and spinopelvic alignment parameters

The evaluation of the sagittal and spinopelvic parameters is an essential part of the examination of any spinal deformity. For that reason, all patients who had undergone whole spine imaging were additionally analysed regarding their whole spine sagittal alignment as shown in Figure 10.

To determine the global balance in the sagittal body plane, the SVA was measured. The SVA is an important index of sagittal balance and measured as the distance from the plumb line of the centre of the seventh cervical vertebra to the posterior edge of the upper sacral endplate surface. If a displacement ventral to the trailing edge of S1 of more than 5 cm occurs due to malposition of individual spinal column sections, this is referred to as a positive sagittal imbalance. Therefore, forward SVA tilt was taken as a positive value whereas backward SVA tilt was taken as a negative value.

To verify the global alignment in terms of kyphosis and lordosis the parameters TK and LL were measured. TK is measured as the angle between the superior endplate surface of T4 and the inferior endplate surface of T12. LL is determined by measuring the angle between the superior endplate of L1 and the inferior endplate of L5.

Since most fractures occur at the thoracolumbar junction, it is important to measure both thoracolumbar alignment (TLA) and thoracolumbar sacral lordosis (TLSL). TLA is the angle measured between the superior endplate surface of T10 and the inferior endplate surface of L2 whereas TLSL is the angle measured between the inferior endplate surface of T12 and the upper sacral endplate surface. For all parameters that measure either a kyphosis or lordosis angle, the measured value was given a negative sign if, contrary to assumptions, it assumed a kyphotic value during lordosis measurement and vice versa.

Also important for sagittal balance is the relationship between pelvis and spine, which is described using spinopelvic parameters. On the one hand, there are positional parameters such as SS and PT which can be influenced, for example, by posture. As the given lateral radiographs were all done in the same standing position, it was possible to assess those parameters as well. Thus, SS was measured as the angle between a horizontal line and the slope of the superior sacral endplate surface. With the help of the PT, it is possible to evaluate the degree of pelvic rotation by measuring the angle between the upper plumb line from the femur head centre and the centre point of the superior sacrum endplate surface.

On the other hand, morphological parameters like PI cannot be influenced by posture or other static influences. The PI describes the position of the spinal column in the pelvis and varies individually, but does not change after becoming fully grown. It corresponds to an angle formed by a line perpendicular to the upper sacral end plate which intersects it at the centre of the end plate and a connecting line between the centre of the bicoxofemoral axis and the centre of the upper sacral endplate. If two femoral heads were seen when measuring PI and PT, the midpoint of the connecting line was selected.

2.5. Documentation of the results

The retrospectively obtained patient data is presented using an Excel table. Each performed kyphoplasty was recorded and represents a single case. To conform with data protection as well as for statistical evaluation, the cases were assigned consecutive numbers for pseudonymisation and then the Excel file was transferred to SPSS. Using

SPSS enabled statistical evaluation to be carried out. The graphs and tables contained in this study were created with a combination of Excel and SPSS.

2.6. Statistical analysis

The statistical evaluation of the collected data was carried out after consultation with the Institute for Biometry and Clinical Epidemiology at the Charité - Universitätsmedizin Berlin. All data was individually evaluated and presented in tabular and graphical form. Descriptive statistics were used to present clinical and demographic data. A descriptive analysis of the study population was performed with regards to age, height, weight, body mass index (BMI), osteoporosis medication, cause of fracture, postoperative day of mobilisation and discharge, volume of cement used, complications and an analysis of radiographic classifications. The metric variables were presented using mean and standard deviation as well as the minimum and maximum and the categorical variables were presented by absolute and relative frequencies. Inductive statistics were used for testing the hypothesis. A paired t-test for parametric variables was used for comparing pre- and postoperative parameters within the groups. The Wilcoxon signed-rank test for non-parametric paired samples was used to analyse the pre- and postoperatively acquired measures of VAS and pain medication usage. Radiological parameters were examined for significant differences between the groups using one-way analysis of variance (ANOVA) with post-hoc analysis according to Games-Howell. When comparing two groups with each other, an unpaired t-test was performed for parametric variables and a Mann-Whitney U test for non-parametric variables. The Spearman's rank correlation coefficient is a non-parametric measure of rank correlation which was used to analyse the statistical dependence of two variables. The significance of correlation tests was always tested bilaterally. Significance was assumed for all tests at a p-value of < 0.05. The statistical analysis was performed using IBM SPSS Statistics® version 25.

3. Results

3.1. Study population

492 patients were identified who were treated with kyphoplasty at the Orthopaedic department at the Charité Berlin Mitte between January 2011 and February 2019. 230 patients were included for further analysis according to the previously explained predefined inclusion and exclusion criteria. Of these 230 patients, 100 presented acute fractures, 91 subacute fractures and 39 chronic fractures. Accordingly, they were assigned to 3 different groups (acute, subacute, chronic). In all patients, the indication for kyphoplasty was persistent focal pain despite intensive conservative treatment.

Table 5 provides an overview of the patient population and the mean values with regard to age and gender distribution, height, weight and the resulting BMI. Furthermore, it shows the average preoperative VAS at rest and in motion, the number of thoracic and lumbar fractures, and the inserted cement volume as well as possible osteoporosis medication such as calcium, vitamin D, bisphosphonates, denosumab and teriparatide. Even though the group sizes differed, there were no significant differences regarding the baseline characteristics between the 3 study groups apart from fracture age.

Table 5: Baseline characteristics of the study population

Parameter	**All Groups**	**Acute**	**Subacute**	**Chronic**	**p**
	(± SD)	**(± SD)**	**(± SD)**	**(± SD)**	
n	230	100	91	39	-
sex	69 m; 161 f	27 m; 73 f	30 m; 61 f	12 m; 27 f	.666
age (years)	71.7 (± 10.7)	72.2 (± 11.5)	71.8 (± 10.3)	70.4 (± 9.6)	.683
weight (kg)	71.3 (± 15.1)	70.2 (± 15.9)	72.2 (± 15.7)	72.2 (± 11)	.633
height (cm)	167.3 (± 8.8)	166.7 (± 8.8)	168 (± 8.8)	167.6 (± 8.4)	.530
BMI (kg/m²)	25.3 (± 4.2)	25.2 (± 4.3)	25.4 (± 4.4)	25.7 (± 3.6)	.786
VAS at rest (n = 221)	3.9 (± 2.4)	4 (± 2.1)	3.9 (± 2.6)	3.4 (± 2.3)	.350
VAS in motion (n = 220)	5.6 (± 2.1)	5.5 (± 1.8)	5.8 (± 2.3)	5.2 (± 2.5)	.322
thoracic fractures	92 (40 %)	39 (39 %)	40 (44 %)	13 (33.3 %)	.511

lumbar fractures	138 (60 %)	61 (61 %)	51 (56 %)	26 (66.7 %)	.551
cement volume in total (ml)	6.8 (± 2)	6.9 (± 1.9)	6.4 (± 2.1)	7.4 (± 2)	.115
calcium	31 (13.5 %)	16 (7 %)	13 (5.7 %)	2 (0.8 %)	.234
vitamin D	78 (33.9 %)	30 (13 %)	33 (14.3 %)	15 (6.5 %)	.534
bisphosphonates	32 (13.9 %)	12 (5.2 %)	12 (5.2 %)	8 (3.5 %)	.417
denosumab	2 (0.9 %)	1 (0.4 %)	0	1 (0.4 %)	.351
teriparatide	0	0	0	0	**-**
time since Injury (days)	33.9 (± 47.1)	8.1 (± 4.3)	28.7 (± 7.7)	112.3 (± 71.1)	-

Of all 230 patients assigned to the study, 161 patients (70 %) were female and 69 patients (30 %) were male. The average age was 71.7 years, with a range from 27 to 94 years and a standard deviation of ± 10.7. It turned out that more than half of the patients (65.7 %) were older than 70 years. With a total of 99 patients (43 %) the 70 to 79-year-old patients represented the biggest group (Figure 11).

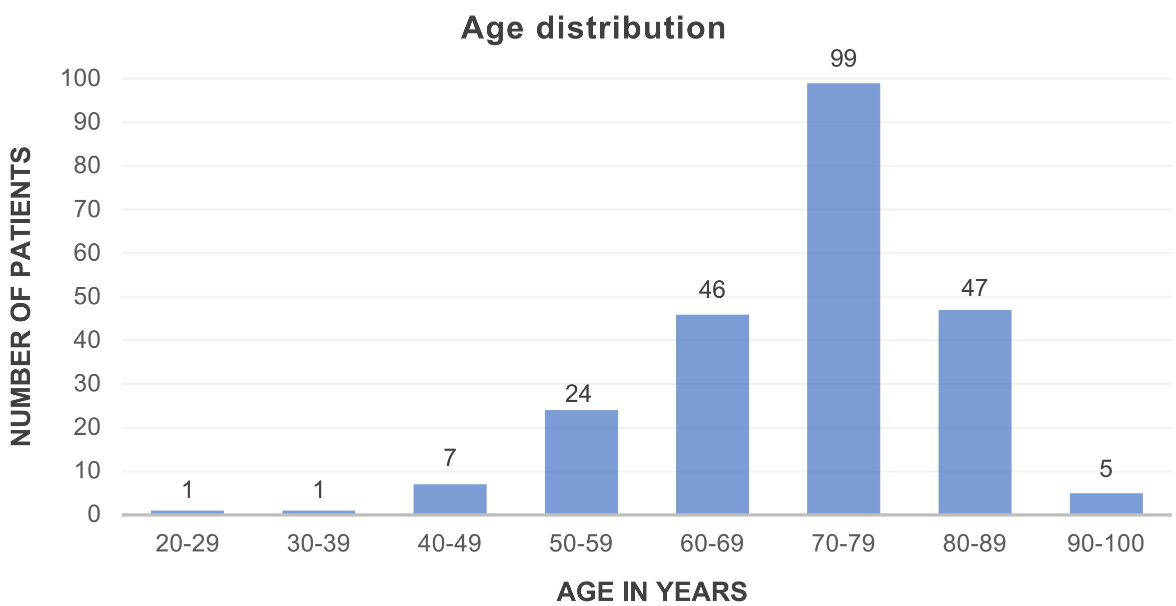

Figure 11: Age distribution of the study population

Height, weight and the resulting Body mass index were taken into account but did not show significant differences between the study groups. The minimum BMI was 14.6, while the maximum BMI was 40.1 with a standard deviation of ± 4.2. 110 patients (47.8 %) presented a normal BMI between 18.5 and 24.9. 85 patients (37 %) were overweight, 27 patients (11.7 %) were obese and 8 patients (3.5 %) were underweight.

In all three groups patients were treated similarly concerning osteoporosis medication. There was no significant difference but a trend towards less preoperative osteoporosis related medication in the chronic group.

3.2. Time interval between onset of pain and balloon kyphoplasty

The mean time between onset of symptoms and surgery for all patients was 33.9 ± 47.1 days. Because of assigning them to different groups depending on fracture age, these time intervals varied. On average, the patients in the acute group were operated on 8.1 ± 4.3 days, in the subacute group 28.7 ± 7.7 days and in the chronic group 112.3 ± 71.1 days after the fracture had occurred. Since all fractures that were older than 6 weeks were considered chronic, there was a wide range varying from older than 6 weeks up to a year in this group.

3.3. Fracture characteristics

3.3.1. Fracture aetiology

All 230 fractures were either caused by trauma (n = 43) or osteoporosis (n = 187) as shown in Figure 12. Fractures caused by tumour (evidence found in biopsy) were excluded from the study according to the previously explained exclusion criteria. Traumatic fractures had to be the result of an appropriate trauma. If fractures had been caused by minor trauma (atraumatic or fall from not more than normal standing height), they were considered osteoporotic.

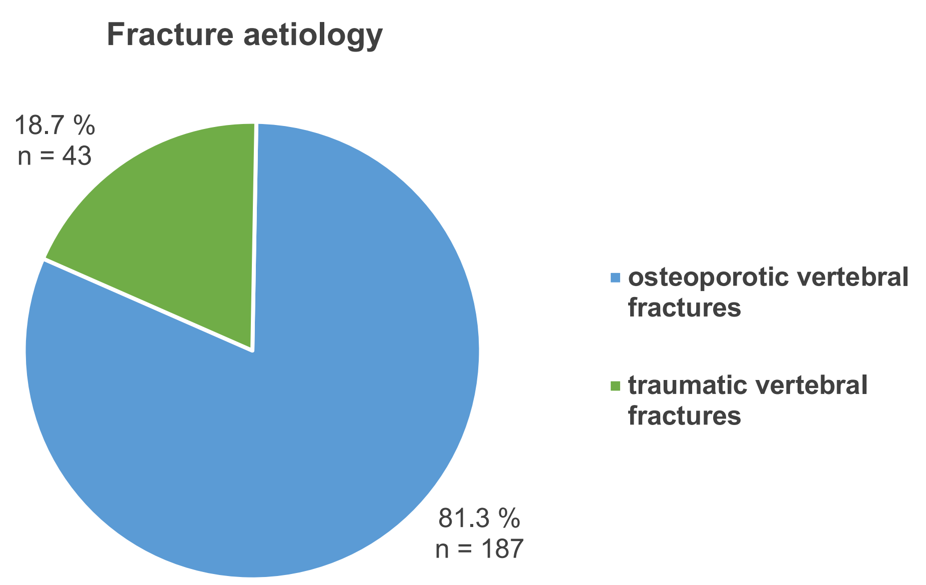

Figure 12: Classification of fractures according to their aetiology

3.3.2. Fracture localisation

Of the 230 patients, 92 (40 %) presented with thoracic fractures (Th4: n = 1, Th5: n = 4, Th6: n = 5, Th7: n = 4, Th8: n = 11, Th9: n = 8, Th10: n = 4, Th11: n = 17, Th12: n = 38), and 138 (60 %) with lumbar fractures (L1: n = 63, L2: n = 25, L3: n = 22, L4: n = 19, L5: n = 9) (Figure 13). The range of levels treated was from Th4 to L5. More than half of all fractures (55 %) occurred in the thoracolumbar junction from Th12 and L2, as shown in Figure 13.

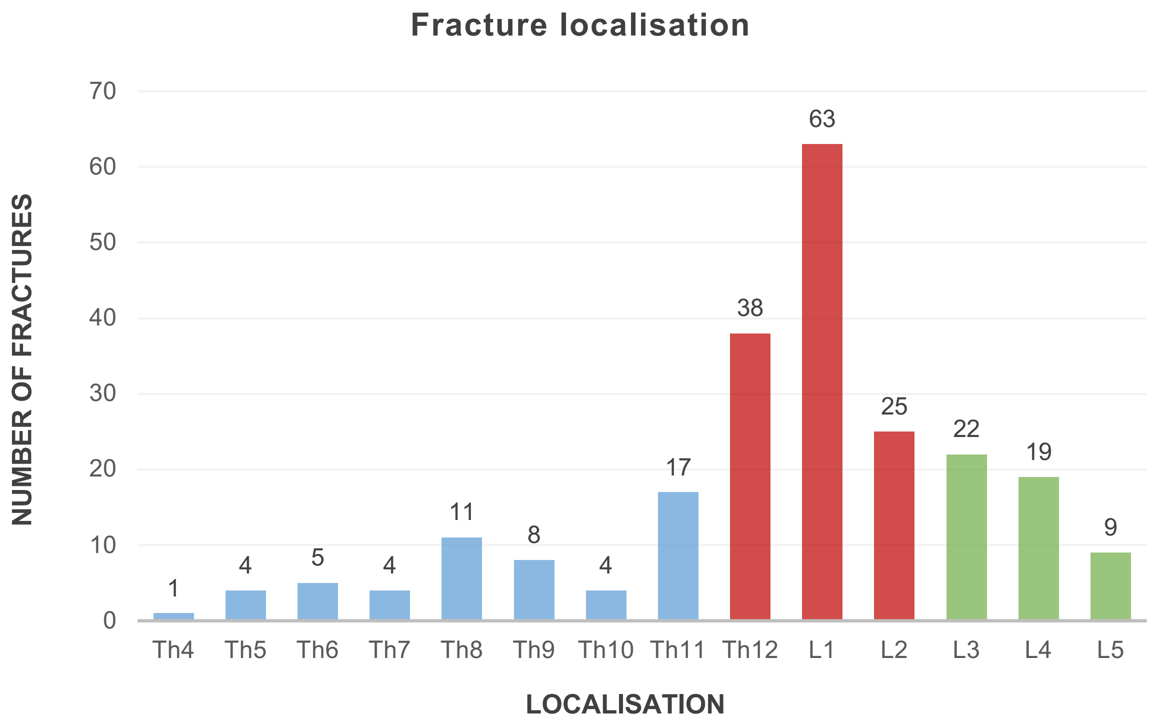

Figure 13: Fracture localisation and distribution (blue bars = thoracic spine, red bars = thoracolumbar junction, green bars = lumbar spine

3.3.3. Fracture morphology and classifications

Vertebral compression fractures were analysed according to their morphology, and additionally according to the fracture classifications, depending on the diagnosis (traumatic, osteoporotic).

When focusing on morphology 94.8 % of the fractures were either wedge-shaped (n = 113; 49.1 %) or biconcave (n = 105; 45.7 %) and only a small number of fractures were crush fractures (n = 12; 5.2 %) (Figure 14).

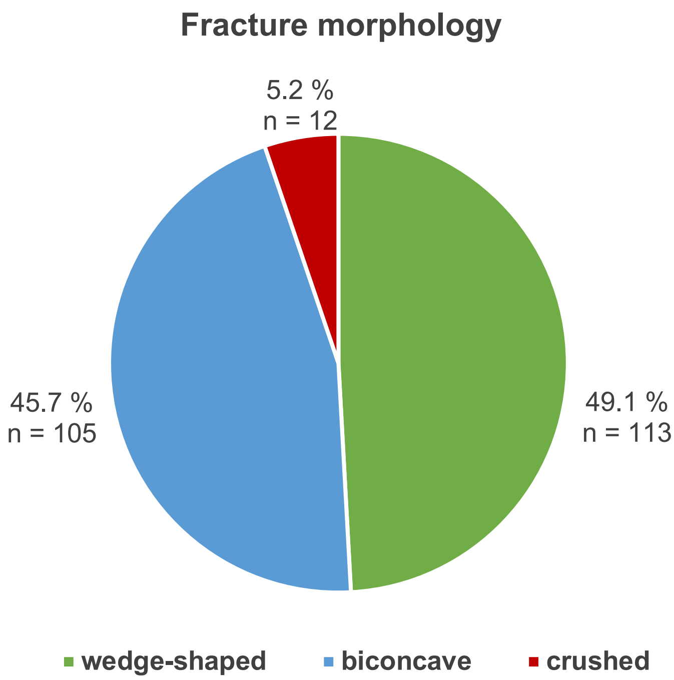

Figure 14: Classification of fractures according to their morphology

The newly published OF classification for thoracolumbar spine fractures by the German Society for Orthopaedics and Trauma [38] was used to examine the severity of osteoporotic fractures. Additionally, the visual semiquantitative fracture assessment method according to Genant [22] was used to analyse the fracture severity. Therefore, all vertebral bodies were evaluated with regard to the difference in height between anterior, middle and posterior portion of the vertebral body.

Of the 189 patients with osteoporotic fractures, 1 was classified OF 1, 76 were classified OF 2, 44 OF 3 and 68 OF 4. No patient with an OF 5 fracture was identified (Figure 15)

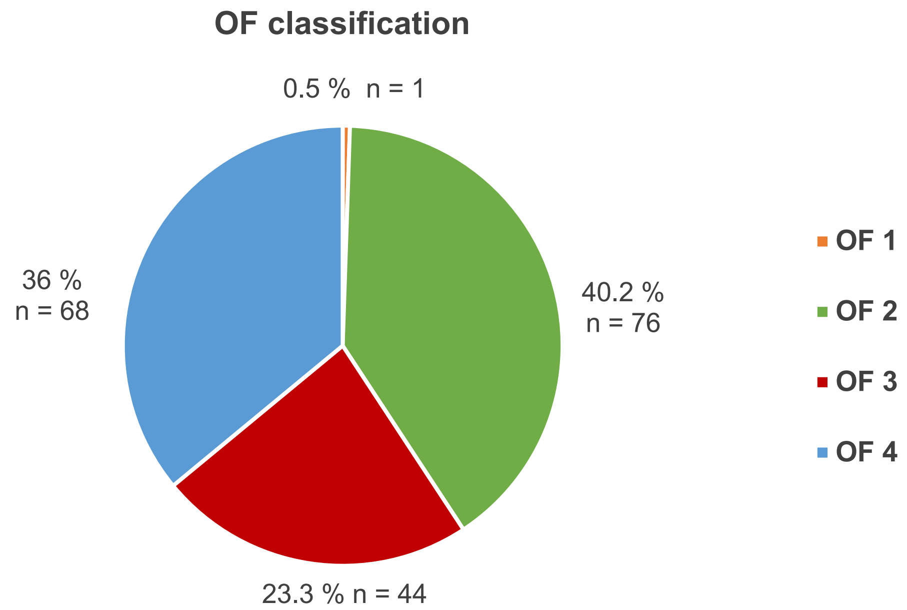

Figure 15: Osteoporotic fractures classified according to the OF classification [37]

Contrary to the OF, the Genant classification only divides into 3 subgroups (Genant 1-3). 47 fractures were categorised Genant 1, 67 Genant 2 and 75 Genant 3 (Figure 16). Unlike the OF classification, the type of deformity (crush, wedge, biconcave) is not linked to the grading of a fracture in the Genant classification. Therefore, the classifications vary when analysing the same fractures.

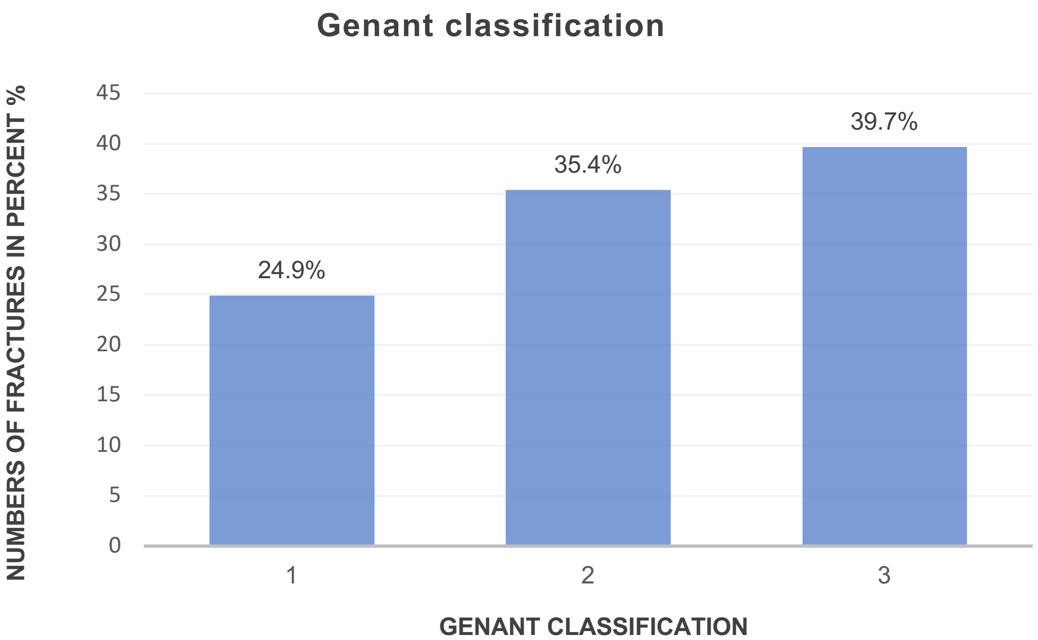

Figure 16: Osteoporotic fractures classified according to Genant [22]

41 traumatic fractures were classified according to the AO classification system [54]. 21 patients (51.2 %) presented A1 compression fractures involving a single endplate without involvement of the posterior wall of the vertebral body. 17 patients (41.5 %) presented A2 fractures that were either coronal split or pincer fractures which involved both endplates but not the posterior wall of the vertebral body. Only 3 A3 burst fractures (7.3 %) that involved a single endplate and the posterior vertebral wall were included in the study (Figure 17). There were no A4 fractures or Type B and C fractures examined.

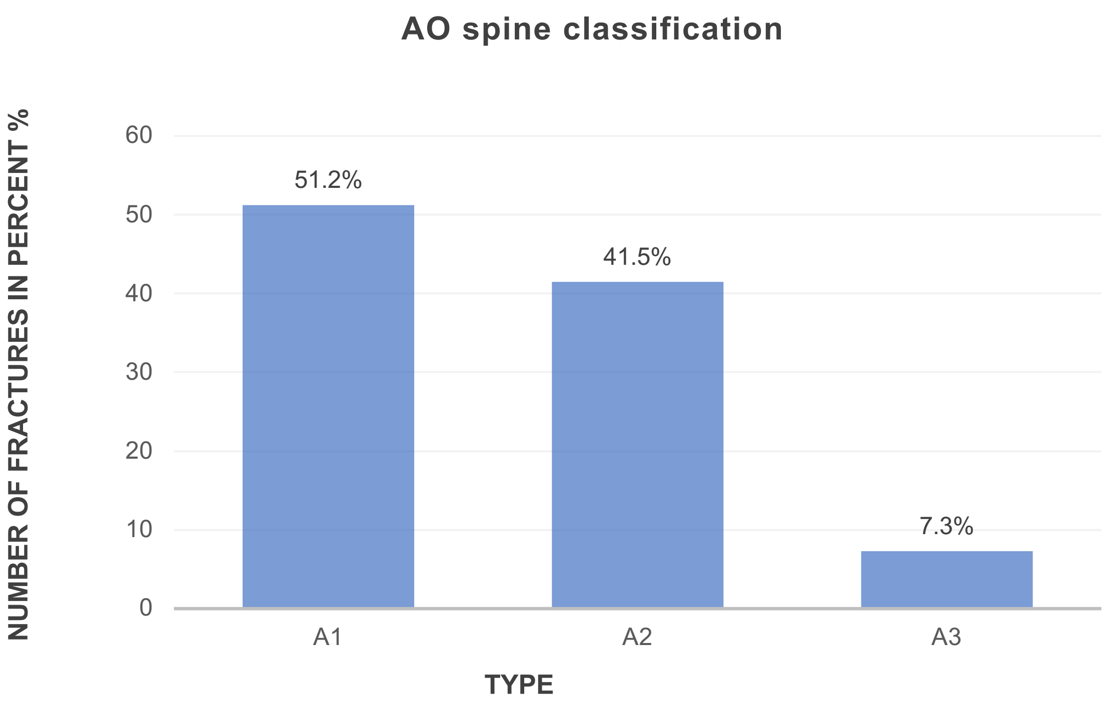

Figure 17: Traumatic fractures classified according to the AO spine classification [52]

3.4. Clinical outcome

On average, the time of in-patient stay was 9 days (8.7) with a range from 2 - 81 days and a standard deviation of ± 7.99. An outlier with a stay of 63 days was a woman with previous internal diseases, who was postoperatively treated in the intensive care unit due to catecholamine requirement. Another outlier was a 73-year-old female patient with a condition after kidney transplantation who was operated without any complications, but needed intensive internal medicine treatment due to her severe pre-existing diseases and therefore remained in hospital for 81 days. Overall, the longer stays of most patients can be explained by an initial conservative therapy approach. On average the patients remained in hospital for another 5 (4.5) days after kyphoplasty (SD: ± 5.2). Because of the above-mentioned reasons, those time intervals varied widely from 1 day to 73 days of postoperative in-patient stay. However, the mostly short postoperative period of hospitalisation is indicative of a good response to the operative therapy. 221 out of 230 patients (96.1 %) were fully mobilized within 1 day after surgery. In case of pre-existent disability, they at least reached their preoperative level of mobility. 100 % of patients were fully mobilized within 5 days. No newly occurred limitations in mobility after surgery were reported.

3.4.1. VAS Score

As mentioned earlier the Wilcoxon signed-rank test for non-parametric paired samples was used to analyse the pre- and postoperatively taken measures of VAS and pain medication usage. Patients from all groups had significant pain reduction at rest (Z-Score -10.1; $p < 0.001$) and in motion (Z-Score -11.3; $p < 0.001$) two days postoperatively. Not only for all patients, but also within the individual groups, there was a significant pain reduction both at rest (acute: Z-score -7; subacute: Z-score -6.3; chronic: Z-score: -3.7; each $p < 0.001$) and in motion (acute: Z-score -7.8; subacute: -6.9; chronic: -4.8; each $p < 0.001$). However, there were no significant differences in pain reduction between the three groups.

The pre- and postoperative VAS scores at rest and in motion are shown in Figure 18 and Figure 19. The mean preoperative VAS scores in the acute group were 4.1 ± 2.1 (range: 0 - 9) in rest and 5.5 ± 1.8 (range: 2 - 10) in motion. Two days postoperatively, the VAS scores had significantly decreased to 1.6 ± 1.7 (range: 0 - 6) in rest and 2.9 ± 2 (range: 0 – 7.5) in motion. Mean preoperative VAS scores in the subacute group were 3.9 ± 2.6 (range: 0 - 10) in rest and 5.8 ± 2.3 (range: 0 - 10) in motion. Two days postoperatively, the VAS scores in the subacute group were also significantly reduced to 1.7 ± 1.7 (range: 0 - 8) in rest and 3.1 ± 2 (range: 0 - 8) in motion. Mean preoperative VAS scores in the chronic group were 3.4 ± 2.3 (range: 0 - 10) in rest and 5.2 ± 2.5 (range: 0 - 10) in motion. Postoperatively, the VAS scores were just like the other groups, being significantly reduced to 1.7 ± 1.3 (range: 0 - 5) in rest and 2.4 ± 1.5 (range: 0 - 5) in motion.

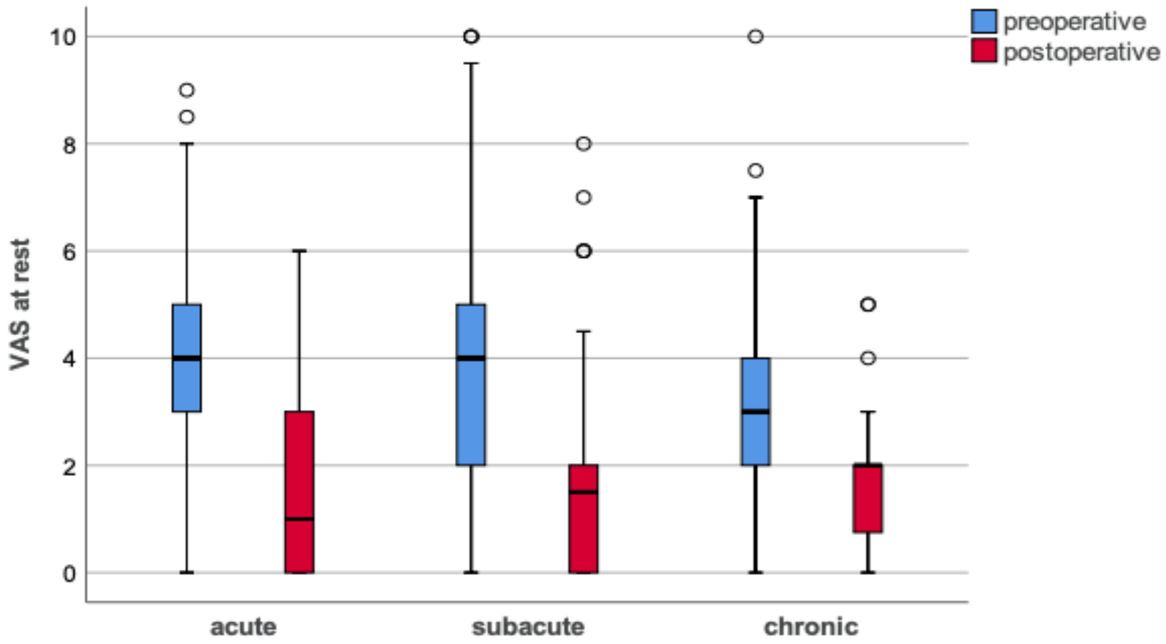

Figure 18: Preoperative (blue) and postoperative (red) pain according to visual analogue scale (VAS) at rest for acute, subacute and chronic group

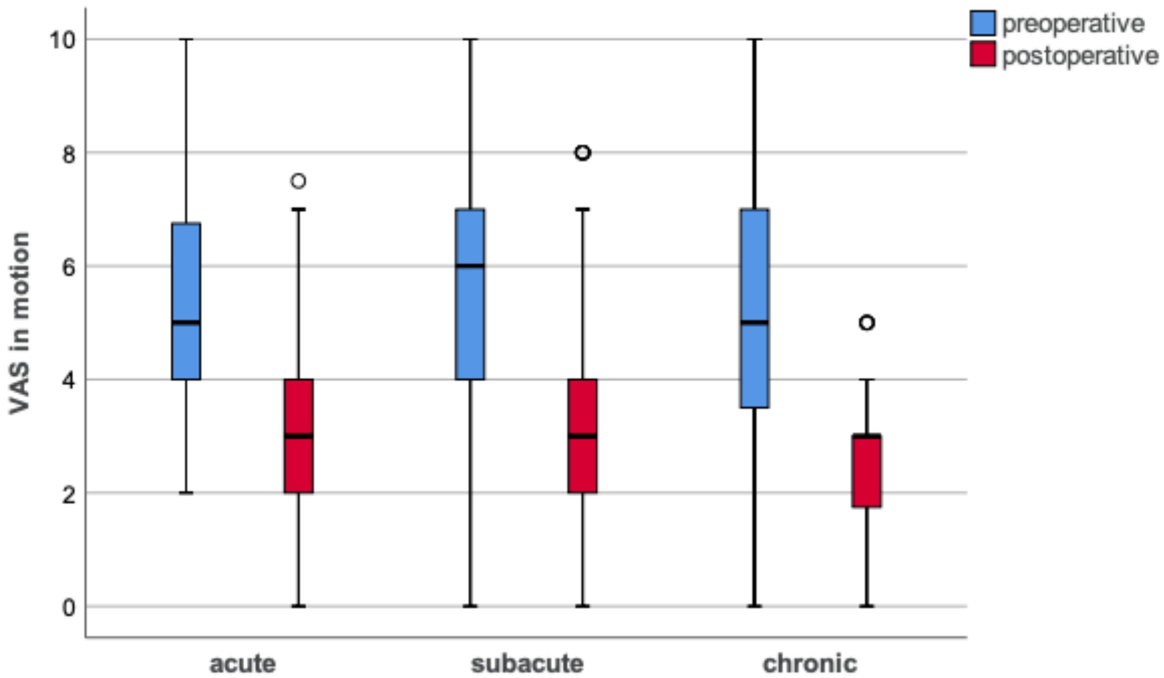

Figure 19: Preoperative (blue) and postoperative (red) pain according to visual analogue scale (VAS) in motion for acute, subacute and chronic group

3.4.2. Pain medication usage

Pain medication usage was estimated by converting the data to an ordinal scale using the WHO pain ladder. In contrast to the VAS scores, there were differences between the groups regarding the need for pain medication.

In patients with acute fractures, the use of analgesics according to the WHO pain ladder was significantly reduced two days postoperatively (Z-score -2.2; p = 0.027) and upon discharge (Z-score: -3.3; p = 0.001). In the subacute group, there was also a trend towards less use of pain medication two days postoperatively, though it did not reach significance (Z-score -1.6; p = 0.118). However, at time of discharge, the need for pain medication in the subacute group was also significantly lower than preoperatively (Z-score: -3.2; p = 0.001). Unlike the patients in the other groups, the patients with chronic fractures did not reach a significant reduction of pain medication usage. There was only a trend towards less use of analgesics two days postoperatively (Z-score: -1.4; p = 0.177) and at discharge (Z-score: -0.5; p = 0.642), which was not significant and was less distinct than in the other two groups.

3.5. Radiological Outcome

3.5.1. Restoration of vertebral body height and local kyphosis correction

The restoration of vertebral body height and local kyphosis correction was evaluated using a t-test for paired samples and two-sided significance.

Table 6 shows the mean differences of the measured pre- and postoperative values for vertebral body heights and kyphosis angles. Anterior vertebral body height and middle vertebral body height were significantly restored in the entire population as well as in each subgroup. The mean anterior height in acute vertebral body fractures was restored from 20.1 (± 7.4) mm to 23.5 (± 6.1) mm (10.8 %), in subacute fractures from 18.6 (± 7.6) mm to 21.7 (± 6.4) mm (13.3 %), and in chronic fractures from 19.8 (± 7) mm to 22.4 (± 6.3) mm (9.7 %).

The mean middle vertebral body height in the acute group was restored from 19.8 (± 6.5) mm to 22.7 (± 5.2) mm (12 %), in the subacute group from 17.8 (± 6.5) mm to 21.1 (± 5.8) mm (13.5 %), and in the chronic group from 19.3 (± 6) mm to 22.4 (± 5.5) mm (11.8 %).

The posterior vertebral body height restoration was lower than the changes of the other height parameters but still reached significance for the entire study population as well as for the subacute and the chronic group. The mean posterior height in acute vertebral body fractures was restored from 29.3 (± 5.3) mm to 29.5 (± 4.9) mm (1.3 %), in subacute fractures from 27.8 (± 5.3) mm to 28.3 (± 5.1) mm (2.3 %), and in chronic fractures from 28.3 (± 5.5) mm to 29.6 (± 4.2) mm (4.1 %).

The mean local kyphotic angle (LKA) was reduced in all groups, though the improvement in the chronic group did not reach significance (p = 0.053). The mean local kyphotic angle in the acute group was reduced from 12.2 (± 8.6)° to 8.8 (± 6.7)°. The LKA in subacute fractures was corrected best, with a reduction from 14.3 (± 8.4)° to 10.2 (± 6.4)°. The LKA in chronic fractures was only corrected by 1.7°, reducing the mean LKA from 13.2 (± 8.1)° to 11.6 (± 6.4)°.

The Cobb angle (CA) and Gardner angle (GA) were additionally measured to determine the extent of fracture related kyphosis. The GA improved significantly in all groups, whereas the CA was not significantly improved in the acute group.

Table 6: Restoration of vertebral body height and local kyphotic angles

Parameter	**Mean difference**	**Standard deviation**	**95% Confidence interval**		**p**
			Lower	**Upper**	
		All patients			
AVBH [%]	11.6	14.2	9.8	13.4	.000
MVBH [%]	12.6	13.7	10.8	14.3	.000
PVBH [%]	2.2	8.2	1.1	3.3	.000
LKA [°]	3.4	6.1	2.6	4.2	.000
Gardner [°]	2.4	7.6	1.4	3.4	.000
Cobb [°]	1.7	9.4	0.4	2.9	.009
		Acute			
AVBH [%]	10.8	14.8	7.9	13.7	.000
MVBH [%]	12.0	14.5	9.2	14.9	.000

PVBH [%]	1.3	7.1	0.1	2.8	.062
LKA [°]	3.4	5.6	2.3	4.5	.000
Gardner [°]	2.1	8.3	0.4	3.7	.015
Cobb [°]	1.1	12.4	1.4	3.6	.379
			Subacute		
AVBH [%]	13.3	14.6	10.3	16.4	.000
MVBH [%]	13.5	12.3	10.9	16.0	.000
PVBH [%]	2.3	9.0	0.4	4.2	.017
LKA [°]	4.1	6.9	2.7	5.6	.000
Gardner [°]	2.8	7.7	1.2	4.4	.001
Cobb [°]	2.0	6.2	0.7	3.3	.004
			Chronic		
AVBH [%]	9.7	11.1	6.1	13.3	.000
MVBH [%]	11.8	15.2	6.8	16.7	.000
PVBH [%]	4.1	8.9	1.3	7.0	.006
LKA [°]	1.7	5.2	0.02	3.4	.053
Gardner [°]	2.5	5.3	0.8	4.3	.006
Cobb [°]	2.5	6.0	0.4	4.5	.019

AVBH: vertebral body height in the anterior portion; **MVBH:** vertebral body height in the middle portion; **PVBH**: vertebral body height in the posterior portion; **LKA:** local kyphotic angle; **Gardner:** Gardner angle; **Cobb:** Cobb Angle

3.5.2. Influence of operative timing on height restoration

In order to estimate the influence of operative timing on height restoration, radiological outcomes of the different groups were compared (Table 7). One-way analysis of variance (ANOVA) and post-hoc analysis were used to compare differences between the groups and to evaluate their significance.

Table 7: Comparison of vertebral body height restoration and local kyphosis correction between groups

Parameter	Mean difference	95% Confidence interval		p
		Lower	Upper	
		Acute vs. subacute		
AVBHR [mm]	-2.5	-6.6	1.5	.221
MVBHR [mm]	-1.4	-5.4	2.5	.479
PVBHR [mm]	-0.9	-3.3	1.4	.428
LKAR [°]	0.8	-1.0	2.5	.388
		Acute vs. chronic		
AVBHR [mm]	1.1	-4.1	6.4	.671
MVBHR [mm]	0.3	-4.8	5.4	.914
PVBHR [mm]	-2.8	-5.9	0.3	.073
LKAR [°]	-1.7	-4.0	-0.5	.137
		Subacute vs. chronic		
AVBHR [mm]	3.7	-1.7	9.0	.179
MVBHR [mm]	1.7	-3.5	6.9	.520
PVBHR [mm]	-1.9	-4.9	1.2	.240
LKAR [°]	-2.5	-4.8	-0.2	.034

AVBHR: restoration of vertebral body height in the anterior portion; **MVBHR**: restoration of vertebral body height in the middle portion; **PVBHR:** restoration of the vertebral body height in the posterior portion; **LKAR** restoration of the local kyphotic angle

When comparing postoperative height restoration of the vertebral bodies, it is noticeable that although there was a trend towards better restoration of AVBH and MVBH in the acute and subacute groups, it did not differ significantly from height restoration in the chronic group. In contrast, when comparing the kyphosis angles between the different groups, patients from the subacute group showed a significantly higher decrease in LKA postoperatively than patients from the chronic group (p = 0.034). Furthermore, there was a trend towards better LKA correction in the acute group compared to the chronic group, which did not reach significance (p = 0.137). There were no significant differences in height restoration or kyphosis correction between the acute and the subacute groups.

The Spearman's rank correlation test for non-parametric variables was used to analyse possible correlations between the timing of surgery and radiological outcome (two-sided significance). The resulting Spearman's correlation coefficient measures the strength and direction of monotonic association between the given variables and is expressed in numbers from zero (no correlation) to one (linear correlation). Negative or positive signs determine the direction of the correlation. If one variable increases when the second variable also increases, the Spearman's correlation coefficient is positive. However, if one variable tends to decrease when the other variable increases, the correlation coefficient is negative. For interpretation of the coefficient according to Cohen et al. [91], Table 8 can be used as a guide.

Table 8: Interpretation of the correlation coefficient r according to Cohen et al. 1992 [87]

correlation coefficient r	interpretation
0	no correlation
0.1	weak correlation
0.3	moderate correlation
0.5	strong correlation
1	linear correlation

The Spearman´s rank correlation test did not show a significant correlation and therefore no linear correlation between operative timing and restoration of AVBH (r = 0.045, p = 0.498), MVBH (r = 0.061, p = 0.358), PVBH (r = 0.080, p = 0.227) and LKA (r = 0.057, p = 0.389).

The restoration of AVBH correlated significantly with the restoration of MVBH (r = 0.600; p = 0.000; Figure 20). It also had a significant negative correlation with the restoration of LKA (r = -0.679; p = 0.000; Figure 21). This means that the better the AVBH was restored, the more the LKA could be reduced, which then resulted in less local kyphosis and a better radiological outcome. Both correlations showed a correlation coefficient greater than 0.6 and thus a strong correlation.

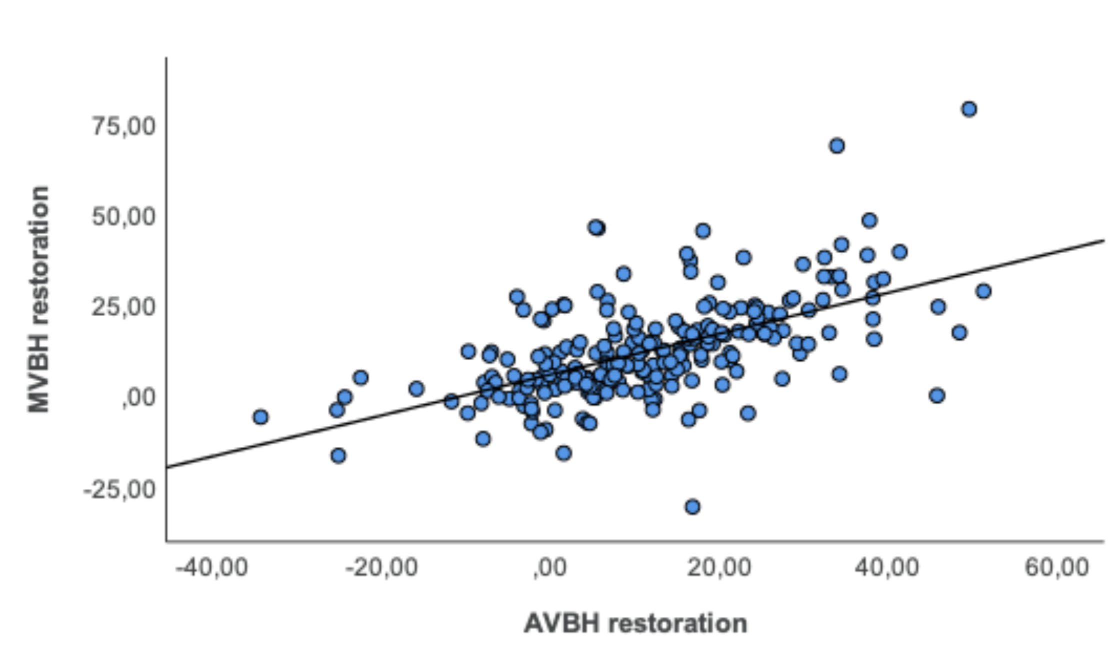

Figure 20: Correlation between mean anterior vertebral body height (AVBH) restoration and middle vertebral body height (MVBH) restoration

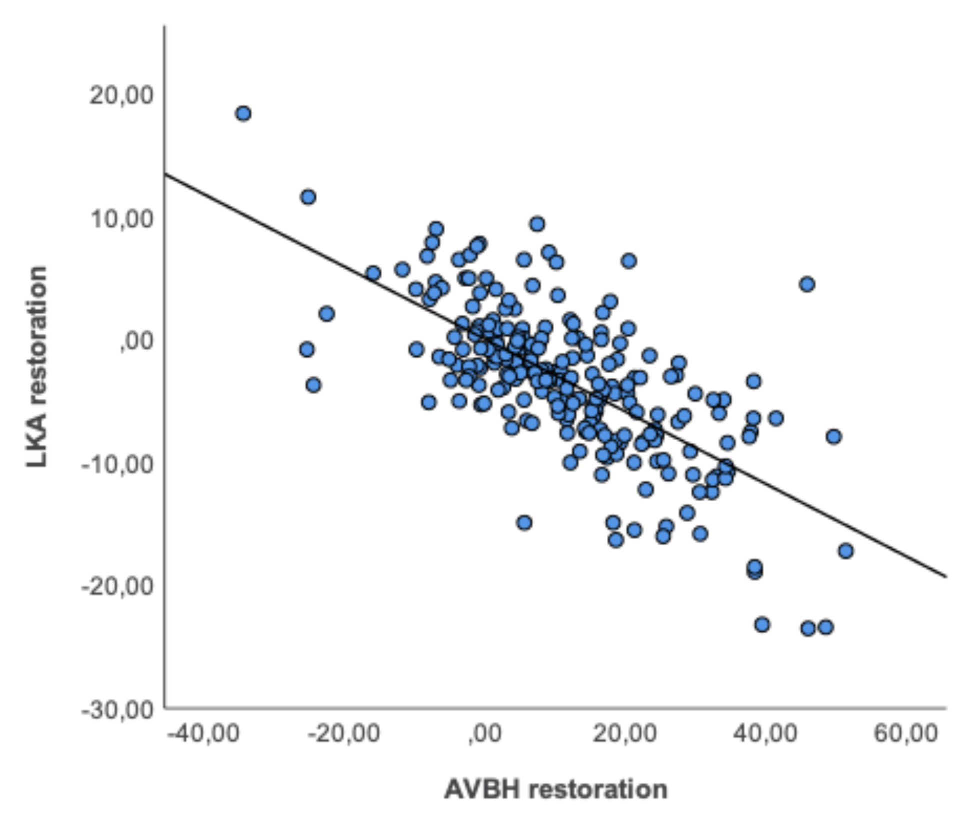

Figure 21: Correlation between mean anterior vertebral body height (AVBH) restoration and local kyphosis angle (LKA) restoration

There was also a significant but weak correlation between the restoration of AVBH and PVBH (r = 0.218; p = 0.001). Analysing the MBHP, a weak correlation between the restoration of PVBH (r = 0.261; p = 0.000) and a moderate negative correlation between LKA restoration (r = -0.468; p = 0.000), both significant, were found. Again, the better the MBPH was restored, the more the LKA could be reduced, and this resulted in a better radiological outcome. Furthermore, there was no linear correlation found between restoration of the vertebral body height and the applied volume of cement.

3.5.3. Influence of fracture morphology on height restoration

Using one-way ANOVA and post-hoc analysis, the radiological outcome of different fracture morphologies was compared. AVBH was significantly better restored in wedge-shaped fractures than in biconcave vertebral bodies (mean difference = 12.0 mm; p = 0.000). There was no significant difference between the AVBH restoration in crush fractures compared to wedge-shaped (mean difference = -4.4 mm; p = 0.269) and biconcave fractures (mean difference = 7.7 mm; p = 0.054).

MVBH was also significantly better restored in wedge-shaped fractures than in biconcave fractures (mean difference = 4.9 mm; p = 0.008). No significant differences in MVBH restoration were found for the other fracture types. The restoration of PVBH did not differ significantly when comparing the different fracture morphologies. With regard to the restoration of LKA, it was noticeable that a significantly better reduction of LKA was achieved with both wedge-shaped (mean difference = -5.4 mm; p = 0.000) and crush fractures (mean difference: -3.9 mm; p = 0.024) compared to biconcave fractures. However, there was no significant difference between crush fractures and wedge-shaped fractures (mean difference: 0.59 mm; p = 0.736). Both Cobb angle (mean difference: -2.8 mm; p = 0.030) and Gardner angle (mean difference: -4.6 mm; p = 0.000) were also significantly better reduced in wedge-shaped fractures than in biconcave fractures. No further significant differences in Cobb angle and Gardner angle restoration were found.

3.5.4. Sagittal and spinopelvic alignment

The detailed mean differences of pre- and postoperative radiographic measurements are presented in Table 9. Analysing the whole study population SVA, PI, LL and TLA changed significantly though this was not applicable to the individual groups. SVA was significantly improved only in the subacute group, i.e., by 10.8 mm (± 35.3 mm; p = 0.037).

Using ANOVA and post-hoc analysis, no significant differences between the groups could be determined.

Table 9: Mean differences between pre- and postoperative global alignment in the whole study population as well as in acute, subacute and chronic groups

Parameter	Mean difference	Standard deviation	95% Confidence interval		p
			Lower	Upper	
			All patients		
SVA [mm]	7.2	31.9	1.0	13.5	.024
SS [°]	0.5	5.9	0.3	1.3	.238
PT [°]	0.5	5.3	0.4	1.3	.258
LL [°]	1.6	7.8	0.5	2.8	.005
TLSL [°]	0.7	10.1	0.7	2.1	.336
TLA [°]	2.3	13.5	0.2	4.3	.030
TK [°]	0.6	7.3	0.7	2.0	.348
			Acute		
SVA [mm]	2.8	29.1	7.7	13.3	.593
SS [°]	0.4	6.6	1.0	1.9	.549
PT [°]	0.6	5.3	0.8	1.9	.412
LL [°]	2.1	7.8	0.5	3.8	.013
TLSL [°]	0.4	9.9	1.7	2.6	.681
TLA [°]	3.4	15.2	0.2	6.9	.063
TK [°]	0.6	4.8	0.9	2.1	.409

			Subacute		
SVA [mm]	10.8	35.2	0.7	20.9	.037
SS [°]	0.8	5.0	0.3	2.0	.153
PT [°]	1.2	4.2	0.2	2.3	.022
LL [°]	0.8	8.5	1.3	2.8	.455
TLSL [°]	1.4	11.1	1.2	3.9	.295
TLA [°]	1.3	12.1	1.7	4.3	.391
TK [°]	1.2	8.8	1.1	3.6	.295
			Chronic		
SVA [mm]	5.7	28.5	6.9	18.4	.355
SS [°]	0.1	5.9	2.0	2.2	.942
PT [°]	1.2	7.1	1.4	3.9	.345
LL [°]	2.2	6.2	1.1	4.5	.051
TLSL [°]	0.1	8.2	1.5	2.8	.937
TLA [°]	1.8	11.9	2.2	6.3	.422
TK [°]	1.5	7.0	1.5	1.7	.346

SVA: sagittal vertical axis; **SS**: sacral slope; **PT:** pelvic tilt; **PI:** pelvic incidence; **LL:** lumbar lordosis; **TLSL:** thoracolumbosacral lordosis; **TLA:** thoracolumbar alignment; **TK:** thoracic kyphosis

3.6. Complications

In Figure 22, all complications are presented that occurred in the study population. 51 (22.2 %) complications were documented in 230 kyphoplasty procedures. Cement leakage detected on postoperative radiographs was the most frequent complication, with 33 affected patients (14.3 %). However, no patient suffered from any symptoms or needed further intervention. Seven patients (3 %) suffered subsequent adjacent level fractures that were detected in the postoperative radiographs. Two patients (0.9 %) had both a cement leakage and an adjacent level fracture. The kyphoplasty balloon burst during inflation during three kyphoplasty procedures (1.3 %). Two patients (0.9 %) had to be monitored in the intensive care unit due to postoperative respiratory insufficiency. Both patients recovered without any sequelae. One patient (0.4 %) developed a radiculopathy after the intervention. Three patients (1.3 %) had to be transferred to internal medicine wards for further treatment due to their pre-existing illnesses. None of the patients suffered from any procedure related fatal complication or spinal infection. Looking at the individual groups, the percentage of complications was lowest in the acute group with 16 %, followed by the subacute group with 25.3 %. In the chronic group, complications were documented in 30.8 % of interventions.

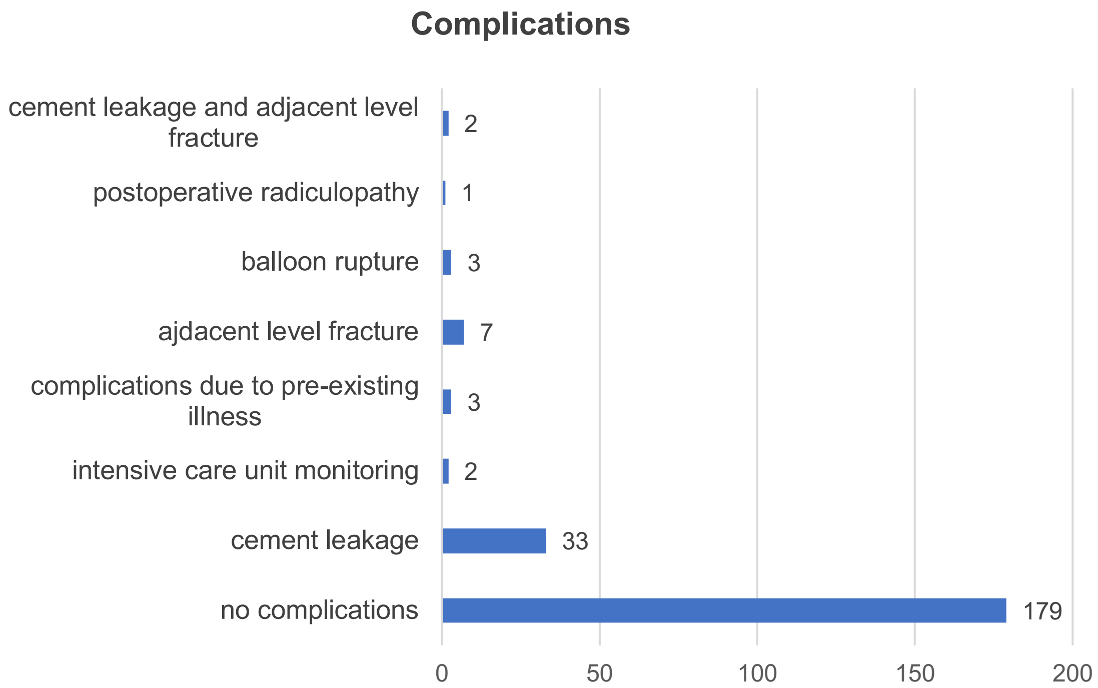

Figure 22: Number of different complications that occurred during and/or after kyphoplasty in 230 patients

The Mann-Whitney U test for non-parametric independent sampling was used to investigate whether cement volumes differed in patients with cement leakage compared to the patients who did not suffer cement leakage. However, no significant difference in cement volume was found (Z-Score: -0.4; p = 0.681).

3.6.1. Subsequent fractures

Of 230 patients, 7 suffered subsequent adjacent level fractures either intraoperatively or while still in hospital. When evaluating post discharge radiographs, in another 26 patients subsequent adjacent level fractures were detected. In total, 33 patients (14.3 %) suffered from adjacent level fractures. Post discharge images also revealed 17 patients (7.3 %) who sustained new fractures in distant spinal segments. Another 17 patients (7.3 %) suffered from both subsequent adjacent level fractures and further sintering fractures in other spinal segments.

4. Discussion

Vertebral compression fractures are increasingly encountered among the elderly and represent a major health problem resulting in long-lasting pain, progressing kyphosis and disability as well as reduction of health-related quality of life [17, 60, 92, 93]. VCFs are most commonly attributed to osteoporosis, especially in the older population, whereas in younger patients, traumatic events or neoplasia represent additional causes of fractures. Several treatment strategies for VCFs, including conservative treatment, vertebroplasty and kyphoplasty can achieve pain reduction and functional improvement. A recent meta-analysis based on evidence from randomized controlled trials by Zhu et al. assessed the treatment effects of kyphoplasty in comparison to vertebroplasty. The conclusion of the study was that kyphoplasty is a safe and effective procedure which has clinically beneficial effects on pain and disability and significantly fewer cement leakages [94]. With the minimally invasive surgical technique of kyphoplasty, an attempt is made to achieve optimal treatment of vertebral body fractures by realising quick and lasting pain relief and correction of deformity. Despite the improvement in outcomes from kyphoplasty demonstrated by various studies [64, 72, 77, 78, 95-101], the optimal surgical timing remains unclear. With this work, we aimed to investigate the clinical and radiological outcome after kyphoplasty in patients with VCFs and the dependence on operative timing.

In the present work, we have accomplished the largest study so far regarding the influence of operative timing on the patient´s outcome. To the best of our knowledge, we were able to demonstrate for the first time that kyphoplasty results in better height restoration and kyphosis correction, as well as a better reduction of use of analgesics if performed within six weeks after the fracture has occurred.

4.1. Patient and fracture specific aspects

Of the 492 patients treated with kyphoplasty, only 230 patients were enrolled in the study due to our strict inclusion and exclusion criteria. In contrast to comparable studies [86, 89], only single level kyphoplasties were included in order to determine the age of the fracture as accurately as possible. Other previous studies with similar designs have been rather small so far, with less than 100 patients.

To evaluate the influence of operative timing, patients were categorised into different groups according to the time interval between the onset of symptoms and kyphoplasty (acute (n = 100), subacute (n = 91), chronic (n = 39)). Apart from the number of patients included in the different groups and the time interval between symptom onset and surgery, the baseline characteristics were very similar and did not show any significant differences. This ensures good comparability, though same sized groups would have been optimal. Due to the retrospective nature of the study, the group size could not be influenced and resulted in less patients in the chronic group. However, this was not surprising since patients get referred to our institution for the evaluation of surgical indication following an external conservative therapy.

Of the 230 patients examined in this study 70 % were women and 30 % were men. The predominance of the female sex can be explained by the generally higher postmenopausal osteoporosis predisposition and the correspondingly higher osteoporosis prevalence. In addition, osteoporotic fractures were more strongly represented in our study population (81.3 %) than traumatic fractures (18.7 %). The mean age was 71.7 years, with a range from 27 to 94 years. The wide range can again be explained by the origin of the fracture. Younger patients presented more often with traumatic fractures. Hillmeier et al. were able to show in 2010 that the duration of hospitalisation for younger patients after acute spinal fractures was significantly reduced with kyphoplasty and that patients were able to return to their working life more quickly [64]. Additionally, the variance of age shows that kyphoplasty can be a surgical procedure suitable for all age groups.

When looking at the distribution of fractures, it is noticeable that the thoracolumbar region from T12 to L2 was most affected, with 55 % of the fractures. This is supported by similar results in previous studies [17, 86, 87]. An explanation can be given by the biomechanics in the spinal column. The thoracolumbar region is considered a transition zone between the more rigid thoracic vertebral column and the more flexible lumbar vertebral column. Due to this transition zone with different forces acting on it, the thoracolumbar region is more prone to fractures than the rest of the spine.

Interestingly, in 42.6 % of the patients, older vertebral compression fractures were also diagnosed which did not require intervention. This number seems very high given that only 33.9 % of the study population supplemented vitamin D and 13.5 % additionally calcium as a basic anti osteoporotic treatment, and only 14.8 % of patients received osteoporosis-specific therapy with bisphosphonates (13.9 %) or denosumab (0.9 %). However, a total of 145 patients had not been previously treated with any anti-osteoporotic therapy, which seems questionable in the context of the average age in our study population and the number of diagnosed additional, asymptomatic vertebral compression fractures. This supports the results of the BoneEVA study by Haeussler et al. which drew attention to the undertreatment of osteoporosis in Germany [31].

4.1.1. Clinical Outcome

According to the most recent guidelines, the main indication for kyphoplasty is, in addition to kyphosis correction and increased stability of the fractured spinal segment, the reduction of intolerable pain when conservative treatment options are exhausted [33]. Pain levels were assessed by analysing pre- and postoperative VAS scores and use of analgesics according to the WHO pain ladder. The VAS is very popular in clinical practice due to its simplicity and quick implementation. It is particularly popular for quantifying pain before and after an intervention.

Analysing the VAS score, irrespective of the operative timing, the majority of patients in all fracture groups experienced significant fracture-related pain relief two days after surgery. Comparing the groups, there was no significant difference in VAS score reduction. Previous studies comparing the effect of surgical timing report a similar significant pain relief in patients with both acute and chronic fractures [83, 86-89]. By contrast, the studies by Minamide et al., Takahashi et al. and Trieb et al. concluded that pain reduction was significantly better in the group of acute fractures [84, 85, 90]. In the study by Trieb et al. the time between onset of symptoms and surgery was up to 23 days for acute fractures, in the study by Minamide et al. up to four weeks and in the study by Takahashi et al. up to two months. [84, 85, 90]. Due to the slightly different classification of fractures, those results are not exactly comparable to our study. Overall, our analysis of VAS scores showed that significant pain relief was achieved in all groups. As a result, kyphoplasty should not only be considered for acute but also for chronic fractures. These patients still benefit from surgical intervention if a satisfactory pain relief could not be achieved by conservative therapy before.

The second parameter analysed to determine differences in the clinical outcome was the use of analgesics preoperatively, two days postoperatively and at the time of discharge. There was a general trend towards lower use of analgesics in all groups, though differences between the groups were observed. Patients from the acute group took significantly less pain medication two days postoperatively as well as at the time of discharge. Patients with subacute fractures also took less painkillers even though this was only significant at discharge, not two days after surgery. However, the only group in which the differences were not significant was the chronic group. There was still a trend towards lower use of analgesics postoperatively, but no significant reduction was observed during the time of hospitalisation. This seems surprising, considering that the VAS scores, and thus pain, were also significantly reduced in patients with chronic fractures as mentioned earlier. This observation indicates that although pain levels were reduced, patients might struggle to diminish their consumption after taking painkillers for prolonged periods. This might be because of the habituation effect of painkillers and patients' fear that they may suffer from pain again when taking less analgesics. Due to the chronicity of the fractures and the kyphoplasty that was performed after a prolonged period, it can be assumed that these patients did not experience sufficient pain relief with conservative treatment, and that the establishment of pain memory had a further influence on the perception of pain and thus the need for painkillers. The finding that kyphoplasty reduces the consumption of analgesics is of particular importance considering the average age of 71.7 years in our study population. Polypharmacy is widespread among the elderly and has been shown to be an independent risk factor for morbidity and mortality [102]. Especially with those patients, an early reduction of the use of analgesics might be favourable considering the side effects such as renal damage and gastrointestinal ulcers from NSAIDs, addiction and obstipation from opioids or adverse effects due to drug interactions.

Previous studies showed that kyphoplasty significantly reduced the use of analgesics. However, they either did not reveal whether there was a difference between acute or chronic fractures [85] or only analysed the frequency of taking painkillers, but not the kind of analgesics used [86]. Only the study by Crandall et al. evaluated the use of pain medication according to the WHO pain ladder and compared the results of the different groups, concluding that there was significantly less use of analgesics postoperatively but no significant difference between the groups [89].

To the best of our knowledge, we were able to show for the first time that with later surgery painkiller consumption is not only prolonged until the time of surgery, but even further after surgery, whereas in patients who have early intervention, significant reduction of analgesic consumption can be achieved postoperatively or at discharge.

4.1.2. Radiological Outcome

Pre- and postoperative lateral radiographs were analysed to quantify local kyphosis angle and vertebral height restoration as well as overall spinal sagittal alignment correction after kyphoplasty. All 230 VCFs were stable VCFs of the thoracic and lumbar spine and of traumatic or osteoporotic origin. These showed little or no involvement of the posterior wall.

The main question in our study was whether the operative timing influences the achievable restoration of fracture-related loss in vertebral body height. In general, our results confirmed those of previous studies reporting good efficacy of kyphoplasty in restoring the local kyphosis angle and also the vertebral body height in VCFs. [64, 96, 103].

4.1.2.1. Restoration of vertebral body height

Regarding the effects of kyphoplasty on the vertebral body height, our study showed good repositioning for the anterior and middle portions. The height of those portions was significantly restored in all groups by around 10-14 % of the estimated pre-fracture height of the respective vertebra. Though there was a trend towards less restoration in the chronic group, the difference between pre- and postoperative anterior and middle vertebral body height still reached significance. Thus, even in chronic fractures, which had on average occurred 110 days previously, significant restoration could be achieved.

There was only a small restoration of the posterior vertebral body height of around 1-4 %. This is not surprising and can be explained by the fact that vertebral compression fractures usually affect the posterior wall far less than the anterior wall and the middle portion. Severe affecting of the posterior wall is a criterion for unstable fractures, which require instrumented stabilisation and should not be treated with kyphoplasty. Therefore, the absence of fractures with a great restoration of the posterior portion implicates adequate indications for surgical intervention with kyphoplasty.

When comparing the outcome of the different groups with each other, it is noticeable that, similarly to the study by Takahashi et al., a trend towards better height restoration in the acute and subacute groups was discernible but did not reach significance [90]. Other previous studies also reported significant vertebral height restoration in both acute and chronic fractures but additionally found significant differences between the groups in favour of height restoration in acute fractures [83, 86, 88, 89]. The reasons for less vertebral height restoration in chronic fractures could be the advanced bone healing process, and therefore fibrous tissue, which makes it more difficult to inflate the balloon and to create an appropriate cavity.

4.1.2.2. Local kyphosis

The importance of local kyphotic deformity resulting from compromise of the anterior column has been increasingly recognised. As explained earlier, changes of biomechanics due to kyphotic deformity result in a shift of the patient´s centre of gravity. This shift leads to higher flexion bending moments around the apex of the kyphosis [82]. Various studies have already shown that these biomechanical changes significantly affect the quality of life and mental health. Severe pain, loss of physical function and mobility as well as adjacent fractures can be the consequences of these changes [83, 88, 93]. Accordingly, the reduction of kyphosis angle is as important as height restoration. By measuring the local kyphosis angle, Gardner angle and Cobb angle, the severity of the deformity could be assessed. LKA was significantly reduced in the acute and subacute group. This was not achieved in the chronic fractures. However, significant differences were only be shown between the subacute and the chronic groups. This is of high clinical relevance as a prolonged conservative treatment attempt might reduce the benefits of kyphoplasty because of natural fracture consolidation. Therefore, patients with chronic fractures and less reduction of LKA have a higher risk of experiencing disability and long-term effects on their quality of life.

These findings are consistent with previous studies though these studies only differentiated between acute (fractures up to two/four weeks old) and chronic fractures (fractures older than two/ four weeks) [83, 88]. Other studies reported either significant improvement of LKA in all patients and no differences between the groups [86, 89] or LKA reduction only in the acute group, which did not reach significance [90]. In addition, the correlation between local kyphosis reduction and anterior height restoration was investigated. We were able to prove that there is a strong correlation between the restoration of the vertebral body height in the anterior portion and the reduction of LKA. Thus, it was shown that the better the AVBH was restored, the more the LKA was reduced. As there was no correlation found between repositioning and cement volume, the use of high cement volumes must be evaluated critically.

4.1.2.3. Global sagittal alignment

Significant changes of the SVA, LL and TLA were found when analysing the whole study population. However, significant changes in LL were only observed in the acute group while SVA and PT changed significantly in the subacute group. In chronic fractures, no significant changes were found. Significant changes in SVA were only found in the subacute group. It seems reasonable that pain relief itself can lead to a more upright posture and therefore to postoperative improvement of the SVA. With significant pain relief observed in patients from all groups, SVA improvement would have also been expected in all groups. However, an earlier study by Pumberger et al. was able to show that the change of SVA correlated significantly with the reduction of LKA but not with postoperative pain reduction [15].

Only a subpopulation of the 230 originally included patients had whole spine radiographs which allowed us to analyse the global sagittal alignment. Given that patients of this subpopulation were also categorised into patients with acute, subacute and chronic fractures, the groups tended to be small. Therefore, these results must be evaluated critically regarding their significance for the overall population.

Few other studies, with small study populations, have been conducted on the effects of kyphoplasty on the global sagittal alignment of the spine, and they came to conflicting conclusions. A previous study with 21 patients by Yokoyama et al. reported significantly improved sagittal balance after kyphoplasty [104], whereas other previous studies did not find significant changes in the SVA [105-107]. However, these studies only investigated whether kyphoplasty results in an improvement of the sagittal balance, but did not differentiate groups according to the age of the fracture. Only two previous studies have considered the dependence of SVA reduction on fracture age. These studies, by Erkan et al. and Park et al. describe an improvement of SVA and concluded that according to their results earlier intervention might be justified if correction of deformity is a goal of kyphoplasty [86, 88].

4.2. Complications

On the whole, previous studies have shown a low risk of complications [72, 75, 77, 101], which was supported by the findings in our study. Although cement leakage was radiologically observed in 14.3% of patients, none of the patients needed further intervention or showed respiratory complications resulting from pulmonary embolism [82]. No procedure related spinal infections or fatal complications were observed.

Even though the number of cement leakages was relatively high, no pulmonary embolisms occurred in our study population, partly because every extravasation detected during or after surgery was critically assessed. Some authors call for a routine CT scan to detect potentially dangerous extravasations [108]. In the 230 patients included in this study, we did not find any severe cement leakages and therefore, in consideration of the radiation exposure, we do not see the need for a routine postoperative CT scan. Based on the data obtained in this study, the indication can only be made in case of clinical symptoms, recent embolisms or for the control of a perioperatively observed extravasation. When examining the cement volume, no significant difference was found between patients with or without cement leakages. Therefore, from our data it cannot be concluded that greater volumes of cement lead to more frequent cement leakages.

Another controversially discussed complication is the adjacent level vertebral fracture after kyphoplasty. In our study population, 14.3 % of patients suffered from adjacent level fractures. Only 0.03 % of these were detected intraoperatively or directly postoperatively. However, these numbers should be interpreted critically, as no standardised follow-up was carried out. Therefore, missing data might distort the results and a selection bias can be suspected, since patients in a better general condition and with fewer hospital stays usually receive their follow-up treatment in an orthopaedic practice and not in a hospital setting. There is still a lack of clarity in the literature regarding the risk of adjacent level fractures. While some studies demonstrated a reduction of the risk of subsequent fractures with kyphoplasty compared to vertebroplasty and non-surgical treatment [75], this has not been clearly proven in clinical trials in recent years. Recent studies have shown that the risk of adjacent level fractures after kyphoplasty is equal to that of after non-surgical treatment [99, 101] or even increased [109]. Another meta-analysis showed that not only the treatment method but also risk factors such as reduced bone density, larger balloon volume, cement volume, recovery rate of vertebral height and intraoperative bone cement leakage have an effect on the risk of adjacent VCFs [81]. In addition, consideration needs to be given to the natural progression of osteoporosis which can also be the reason for new fractures.

Despite the predominantly geriatric patients, with sometimes considerable pre-existing conditions, there were no fatal complications, which suggests that kyphoplasty is a safe and well-tolerated intervention. This is supported by the finding that 96 % of the patients in our study population were fully mobilized within one day after surgery or, in the case of pre-existing disability, reached their preoperative level of mobility [82].

4.3. Interpretation

Considering the excellent clinical results, the low rate of complications and the immediate pain reduction, an early therapy with kyphoplasty might be beneficial to avoid long-term pain with the resulting long-term use of analgesics and permanent kyphosis with its consequences. We were able to demonstrate that the best results can be achieved within the first 6 weeks after fracture occurrence in cases where an initial conservative treatment attempt remains possible. It has also been shown that even patients with chronic fractures benefit from kyphoplasty. A significant reduction in pain was achieved in these patients. Nevertheless, a significant reduction of pain medication was only achieved in patients with acute and subacute fractures. Especially in older, often multimorbid patients, this should be considered when choosing between treatment options. Polypharmacy is common in these patients and is an individual risk factor for falls, which in turn can lead to further fractures.

Radiologically, it was shown that restoration of the vertebral body height as well as an improvement of the LKA, Gardner angle and Cobb angle was achieved. Kyphoplasty is therefore a suitable treatment to reduce kyphotic deformity of the spinal column. A direct comparison of the groups showed, however, that a significantly better reduction of the LKA could be achieved in patients who had undergone surgery within six weeks after the fractures had occurred. A possible explanation for these results can be the assumption that, as described by Crandall et al., reparative processes with progressive callus and bone formation are present in the vertebral bodies beyond the 6 - week limit, which influence both the extent of the repositioning and the kyphosis correction [89].

When analysing all the patients with whole spine radiographs, an improvement of the sagittal vertical axis was detected. It can be assumed that the effect of kyphoplasty on pain relief might also be attributed to an improved sagittal profile of the spine. An improved curvature leads to a reduction of compensatory activities of muscles and might additionally promote natural fracture healing [87].

4.4. Limitations

Despite all efforts for a rigorous methodology to ensure dependable results, there are unavoidable limitations to the study. All data was obtained retrospectively and therefore there are inherent limitations due to the study design. Not all data could be acquired from all patients. For example, some patients did not have whole spine imaging and therefore had to be excluded from the analysis of the parameters of the global sagittal balance. Measurements were done by a single investigator, which means that the possibility of an observer bias cannot be excluded.

Missing prospective randomisation might have introduced selection bias. Additionally, another selection bias might be existent in the inclusion and exclusion criteria, in that patients with multilevel kyphoplasties were excluded. This was necessary to estimate the age of the symptomatic fracture as well as the clinical and radiological outcome as accurately as possible. Furthermore, the actual time the fracture had occurred remained an estimation which is an additional limitation of the study. However, excluding patients that were treated with multilevel kyphoplasty might have excluded patients with more severe osteoporosis which makes the results of the study not universally applicable.

To the best of our knowledge, we have conducted the largest study in terms of population to date. The baseline characteristics showed good comparability of the three study groups. However, it is necessary to point out that the chronic group was rather small with 39 patients compared to 100 patients in the acute and 91 patients in the subacute groups. This might have introduced additional bias and also lowered the statistical power in the chronic group. Although our classification by fracture age is similar to that of comparable studies, there is no published consent in the literature regarding the definition of acute, subacute and chronic fractures.

Furthermore, our study contains a short-term follow-up until the day of discharge for all patients and only limited long-term follow-up, which was not obtained in a standardised manner. Therefore, the long-term outcomes need to be further investigated. As the study relies on data gathered retrospectively, a control group is missing and it is not possible to precisely identify the actual advantage over conservative treatment.

Finally, the statistical analysis has to be interpreted as exploratory, which is also a considerable limitation.

4.5. Conclusion

In conclusion, our results demonstrate that patients can still benefit from the full restoration potential even if the surgery is delayed for up to six weeks [82]. Kyphoplasty can additionally achieve significant pain reduction, height restoration as well as partial kyphosis reduction, and improve the quality of life even in patients with chronic fractures and previous insufficient pain relief.

Due to the aging population, the incidence of osteoporosis is increasing and, accordingly, the incidence of vertebral body fractures [18]. After analysing and evaluating the data and comparing it with other studies on kyphoplasty, it can be assumed that the method is generally effective and safe. However, similarly to the results of other studies, we were able to show that surgery should be considered earlier rather than later in order to achieve the optimal outcome. While widely acknowledged guidelines mainly recommend to only consider kyphoplasty after an unsuccessful conservative treatment attempt, the attending physicians should bear in mind that restoration of the natural curvature might only be possible for a certain time. For this reason, a final decision upon conservative or surgical treatment should be made during the first six weeks after fracture occurrence. Our study analysed the short-term outcome. It remains unclear whether the differences between the acute, subacute and chronic group would extend over the long-term. Prospective controlled studies (kyphoplasty versus natural evolution) are needed to further evaluate the long-term effects.

5. Literaturverzeichnis

1. Masharawi Y, Rothschild B, Dar G, Peleg S, Robinson D, Been E, Hershkovitz I. Facet orientation in the thoracolumbar spine: three-dimensional anatomic and biomechanical analysis. Spine (Phila Pa 1976). 2004;29(16):1755-63.

2. Mathis JM, Deramond H, Belkoff SM. Percutaneous Vertebroplasty and Kyphoplasty edited by John M. Mathis, Herve Deramond, Stephen M. Belkoff. 2nd ed. ed. New York, NY: New York, NY : Springer New York : Imprint: Springer; 2006. 1 online resource (316 p.) p.

3. Junghanns H. Die funktionelle Pathologie der Zwischenwirbelscheiben als Grundlage für klinische Betrachtungen. Langenbecks Archiv für klinische Chirurgie. 1951;267(1):393-417.

4. Börm W, Meyer F, Bullmann V, Knop C, Weidner A, Deutsche Wu. Wirbelsäule interdisziplinär : operative und konservative Therapie. Stuttgart, Germany: Stuttgart, Germany : Schattauer; 2017. XXIV, 716 Seiten : p.

5. Stofft E. Funktionelle Anatomie und Physiologie der Lendenwirbelsäule und physiologische Alterungsprozesse. In: Eckardt A, editor. Praxis LWS-Erkrankungen: Diagnose und Therapie. Berlin, Heidelberg: Springer Berlin Heidelberg; 2011. p. 9-26.

6. Ferraris L, Koller H, Meier O, Hempfing A. Die Bedeutung der sagittalen Balance in der Wirbelsäulenchirurgie2012; p. 502-508(2012; 1 (12)):[7 p.].

7. Fechtenbaum J, Etcheto A, Kolta S, Feydy A, Roux C, Briot K. Sagittal balance of the spine in patients with osteoporotic vertebral fractures. Osteoporos Int. 2016;27(2):559-67.

8. Shah AA, Lemans JV, Zavatsky J, Agarwal A, Kruyt MC, Matsumoto K, Serhan H, Agarwal AK, Goel V. Spinal Balance/Alignment - Clinical Relevance and Biomechanics. J Biomech Eng. 2019.

9. Le Huec JC, Thompson W, Mohsinaly Y, Barrey C, Faundez A. Sagittal balance of the spine. Eur Spine J. 2019;28(9):1889-905.

10. Roussouly P, Pinheiro-Franco JL. Sagittal parameters of the spine: biomechanical approach. Eur Spine J. 2011;20 Suppl 5(Suppl 5):578-85.

11. Dubousset J. Three-dimensional analysis of the scoliotic deformity. In Weinstein SL (ed) The pediatric spine: Principles and Practice. New York: Raven Press Ltd.; 1994. p. 479-96.

12. Pumberger M, Schmidt H, Putzier M. Spinal Deformity Surgery: A Critical Review of Alignment and Balance. Asian Spine J. 2018;12(4):775-83.

13. Stein G, Eysel P, Scheyerer MJ. Wirbelsäule / herausgegeben von Gregor Stein, Peer Eysel, Max Joseph Scheyerer ; mit Beiträgen von Alexander Aichmair, Christof Birkenmaier, Chstiane Birkmann, Simon Bischofberger [und 45 weiteren]. Stuttgart ; New York: Georg Thieme Verlag; 2019.

14. Pingel A, Franke J, Kandziora F. Sagittale Balance und posttraumatische Kyphose. Orthopädie und Unfallchirurgie up2date. 2018;13(02).

15. Pumberger M, Schitz F, Bürger J, Schömig F, Putzier M, Palmowski Y. Kyphoplasty Restores the Global Sagittal Balance of the Spine Independently from Pain Reduction. Sci Rep. 2020;10(1):8894.

16. Huang MH, Barrett-Connor E, Greendale GA, Kado DM. Hyperkyphotic posture and risk of future osteoporotic fractures: the Rancho Bernardo study. J Bone Miner Res. 2006;21(3):419-23.

17. Alexandru D, So W. Evaluation and management of vertebral compression fractures. Perm J. 2012;16(4):46-51.

18. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17(12):1726-33.

19. Cooper C, O'Neill T, Silman A. The epidemiology of vertebral fractures. European Vertebral Osteoporosis Study Group. Bone. 1993;14 Suppl 1:S89-97.

20. Fink HA, Milavetz DL, Palermo L, Nevitt MC, Cauley JA, Genant HK, Black DM, Ensrud KE. What proportion of incident radiographic vertebral deformities is clinically diagnosed and vice versa? J Bone Miner Res. 2005;20(7):1216-22.

21. Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. Spine (Phila Pa 1976). 1983;8(8):817-31.

22. Genant HK, Wu CY, van Kuijk C, Nevitt MC. Vertebral fracture assessment using a semiquantitative technique. J Bone Miner Res. 1993;8(9):1137-48.

23. The European Prospective Osteoporosis Study G, O'Neill TW. The Relationship Between Bone Density and Incident Vertebral Fracture in Men and Women. Journal of Bone and Mineral Research. 2002;17(12):2214-21.

24. Bono CM, Einhorn TA. Overview of osteoporosis: pathophysiology and determinants of bone strength. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2003;12 Suppl 2(Suppl 2):S90-S6.

25. Priemel M, Münch C, Beil FT, Ritzel H, Amling M. Pathophysiologie und Pathomorphologie der Osteoporose. Der Radiologe. 2006;46(10):831-8.

26. Bartl R, Bartl C. The Osteoporosis Manual [electronic resource] : Prevention, Diagnosis and Management / by Reiner Bartl, Christoph Bartl. 1st ed. 2019. ed. Cham: Springer International Publishing; 2019.

27. Gonschorek O, Lorenz M, Bühren V. Wirbelsäulenverletzungen. Trauma und Berufskrankheit. 2015;17(1):157-63.

28. Peters KM. Osteoporose. Orthopädie und Unfallchirurgie up2date. 2013;8(5):403-15.

29. Consensus development conference: prophylaxis and treatment of osteoporosis. Am J Med. 1991;90(1):107-10.

30. Schürer C, Wallaschofski H, Nauck M, Völzke H, Schober H-C, Hannemann A. Fracture Risk and Risk Factors for Osteoporosis. Dtsch Arztebl Int. 2015;112(21-22):365-71.

31. Häussler B, Gothe H, Göl D, Glaeske G, Pientka L, Felsenberg D. Epidemiology, treatment and costs of osteoporosis in Germany--the BoneEVA Study. Osteoporos Int. 2007;18(1):77-84.

32. Kanis JA. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: synopsis of a WHO report. WHO Study Group. Osteoporos Int. 1994;4(6):368-81.

33. e.V. DdDWOG. Prophylaxe, Diagnostik und Therapie der Osteoporose bei postmenopausalen Frauen und bei Männern, 2017: Dachverband Osteologie e.V. ; 2017 [Available from: https://www.dv-osteologie.org/uploads/Leitlinie%202017/Finale%20Version%20Leitlinie%20 Osteoporose%202017_end.pdf.

34. Michels G, Faust M. Osteoporose. Berlin, Heidelberg: Berlin, Heidelberg: Springer Berlin Heidelberg; 2010. p. 654-9.

35. Knauerhase A, Willenberg HS. Neue Antiosteoporotika am Horizont. Zeitschrift für Rheumatologie. 2016;75(5):466-70.

36. Grigoryan M, Guermazi A, Roemer FW, Delmas PD, Genant HK. Recognizing and reporting osteoporotic vertebral fractures. Eur Spine J. 2003;12 Suppl 2(Suppl 2):S104-12.

37. Schnake KJ, Bula P, Spiegl UJ, Müller M, Hartmann F, Ullrich BW, Blattert TR. Thorakolumbale Wirbelsäulenfrakturen beim alten Menschen. Der Unfallchirurg. 2017;120(12):1071-85.

38. Schnake KJ, Blattert TR, Hahn P, Franck A, Hartmann F, Ullrich B, Verheyden A, Mörk S, Zimmermann V, Gonschorek O, Müller M, Katscher S, Saman AE, Pajenda G, Morrison R, Schinkel C, Piltz S, Partenheimer A, Müller CW, Gercek E, Scherer M, Bouzraki N, Kandziora F. Classification of Osteoporotic Thoracolumbar Spine Fractures: Recommendations of the Spine Section of

the German Society for Orthopaedics and Trauma (DGOU). Global Spine J. 2018;8(2 Suppl):46s-9s.

39. Palmowski Y, Balmer S, Hu Z, Winkler T, Schnake KJ, Kandziora F, Pumberger M. Relationship Between the OF Classification and Radiological Outcome of Osteoporotic Vertebral Fractures After Kyphoplasty. Global Spine J. 2020:2192568220964051.

40. Fourney DR, Gokaslan ZL. Spinal instability and deformity due to neoplastic conditions. Neurosurg Focus. 2003;14(1):e8.

41. Pilge H, Holzapfel BM, Prodinger PM, Hadjamu M, Gollwitzer H, Rechl H. Diagnostik und Therapie von Wirbelsäulenmetastasen. Der Orthopäde. 2011;40(2):185-96.

42. Meyer SA, Singh H, Jenkins AL. Surgical treatment of metastatic spinal tumors. Mt Sinai J Med. 2010;77(1):124-9.

43. Reith W, Yilmaz U. Extradurale Tumoren. Der Radiologe. 2011;51(12):1018-24.

44. Schaser KD, Melcher I, Mittlmeier T, Schulz A, Seemann JH, Haas NP, Disch AC. Chirurgisches Management von Wirbelsäulenmetastasen. Der Unfallchirurg. 2007;110(2):137-62.

45. Saad F, Lipton A, Cook R, Chen YM, Smith M, Coleman R. Pathologic fractures correlate with reduced survival in patients with malignant bone disease. Cancer. 2007;110(8):1860-7.

46. Rades D, Fehlauer F, Veninga T, Stalpers LJ, Basic H, Hoskin PJ, Rudat V, Karstens JH, Schild SE, Dunst J. Functional outcome and survival after radiotherapy of metastatic spinal cord compression in patients with cancer of unknown primary. Int J Radiat Oncol Biol Phys. 2007;67(2):532-7.

47. Ulmar B, Huch K, Kocak T, Catalkaya S, Naumann U, Gerstner S, Reichel H. [The prognostic influence of primary tumour and region of the affected spinal

segment in 217 surgical patients with spinal metastases of different entities]. Z Orthop Ihre Grenzgeb. 2007;145(1):31-8.

48. Reinhold M, Knop C, Beisse R, Audigé L, Kandziora F, Pizanis A, Pranzl R, Gercek E, Schultheiss M, Weckbach A, Bühren V, Blauth M. [Operative treatment of traumatic fractures of the thorax and lumbar spine. Part II: surgical treatment and radiological findings]. Unfallchirurg. 2009;112(2):149-67.

49. Bühren V. Verletzungen der Brust- und Lendenwirbelsäule. Der Unfallchirurg. 2003;106(1):55-69.

50. Maier B, Ploss C, Marzi I. Verletzungen der thorakolumbalen Wirbelsäule. Der Orthopäde. 2010;39(3):247-55.

51. Wang XR, Xu FR, Huang QL, Wáng YXJ. Radiological features of traumatic vertebral endplate fracture: an analysis of 194 cases with 263 vertebral fractures. Chin Med J (Engl). 2020.

52. Whitney E, Alastra AJ. Vertebral Fracture. StatPearls. Treasure Island (FL): StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC.; 2020.

53. Magerl F, Aebi M, Gertzbein SD, Harms J, Nazarian S. A comprehensive classification of thoracic and lumbar injuries. Eur Spine J. 1994;3(4):184-201.

54. Vaccaro AR, Oner C, Kepler CK, Dvorak M, Schnake K, Bellabarba C, Reinhold M, Aarabi B, Kandziora F, Chapman J, Shanmuganathan R, Fehlings M, Vialle L. AOSpine thoracolumbar spine injury classification system: fracture description, neurological status, and key modifiers. Spine (Phila Pa 1976). 2013;38(23):2028-37.

55. Schnake KJ, Scheyerer MJ, Spiegl UJA, Perl M, Ullrich BW, Grüninger S, Osterhoff G, Katscher S, Sprengel K, Arbeitsgruppe Osteoporotische Frakturen der Sektion W. Minimal-invasive Stabilisierung bei thorakolumbalen osteoporotischen Frakturen. Der Unfallchirurg. 2020.

56. Yildiz U, Schleicher P, Castein J, Kandziora F. Konservative Behandlung von Wirbelfrakturen in BWS und LWS – was geht wie? Zeitschrift für Orthopädie und Unfallchirurgie. 2019;157(5):574-96.

57. Blattert TR, Schnake KJ, Gonschorek O, Katscher S, Ullrich BW, Gercek E, Hartmann F, Mörk S, Morrison R, Müller ML, Partenheimer A, Piltz S, Scherer MA, Verheyden A, Zimmermann V, die Sektion Wirbelsäule der Deutschen Gesellschaft für Orthopädie und U. Nichtoperative und operative Behandlung der osteoporotischen Wirbelkörperfraktur. Der Orthopäde. 2019;48(1):84-91.

58. Chmielnicki M, Prokop A, Kandziora F, Pingel A. Surgical and Non-surgical Treatment of Vertebral Fractures in Elderly. Z Orthop Unfall. 2019;157(6):654-67.

59. Pfeifer M, Kohlwey L, Begerow B, Minne HW. Effects of two newly developed spinal orthoses on trunk muscle strength, posture, and quality-of-life in women with postmenopausal osteoporosis: a randomized trial. Am J Phys Med Rehabil. 2011;90(10):805-15.

60. Suzuki N, Ogikubo O, Hansson T. The course of the acute vertebral body fragility fracture: its effect on pain, disability and quality of life during 12 months. European spine journal : official publication of the European Spine Society, the European Spinal Deformity Society, and the European Section of the Cervical Spine Research Society. 2008;17(10):1380-90.

61. Verheyden AP, Spiegl UJ, Ekkerlein H, Gercek E, Hauck S, Josten C, Kandziora F, Katscher S, Kobbe P, Knop C, Lehmann W, Meffert RH, Müller CW, Partenheimer A, Schinkel C, Schleicher P, Scholz M, Ulrich C, Hoelzl A. Treatment of Fractures of the Thoracolumbar Spine: Recommendations of the Spine Section of the German Society for Orthopaedics and Trauma (DGOU). Global spine journal. 2018;8(2 Suppl):34S-45S.

62. Clark W, Bird P, Gonski P, Diamond TH, Smerdely P, McNeil HP, Schlaphoff G, Bryant C, Barnes E, Gebski V. Safety and efficacy of vertebroplasty for acute painful osteoporotic fractures (VAPOUR): a multicentre, randomised, double-blind, placebo-controlled trial. Lancet. 2016;388(10052):1408-16.

63. Pérez-Higueras A, Alvarez L, Rossi RE, Quiñones D, Al-Assir I. Percutaneous vertebroplasty: long-term clinical and radiological outcome. Neuroradiology. 2002;44(11):950-4.

64. Hillmeier J. Balloon kyphoplasty. Der Orthopäde. 2010;39(7):665-72.

65. Schmidt R, Cakir B, Mattes T, Wegener M, Puhl W, Richter M. Cement leakage during vertebroplasty: an underestimated problem? Eur Spine J. 2005;14(5):466-73.

66. Garfin SR, Yuan HA, Reiley MA. New technologies in spine: kyphoplasty and vertebroplasty for the treatment of painful osteoporotic compression fractures. Spine (Phila Pa 1976). 2001;26(14):1511-5.

67. Becker S, Boszczyk B, Bierschneider M. Technik der Kyphoplastie. Becker S, Ogon M, editors. Vienna: Vienna: Springer Vienna; 2006. 51-71 p.

68. Blattert TR, Weckbach A. Kalziumphosphat vs. Polymethylmethacrylat. Trauma und Berufskrankheit. 2004;6(2):S273-S8.

69. Perry A, Mahar A, Massie J, Arrieta N, Garfin S, Kim C. Biomechanical evaluation of kyphoplasty with calcium sulfate cement in a cadaveric osteoporotic vertebral compression fracture model. Spine J. 2005;5(5):489-93.

70. Krüger A, Hierholzer J, Bergmann M, Oberkircher L, Ruchholtz S. [Current status of vertebroplasty and kyphoplasty in Germany: an analysis of surgical disciplines]. Unfallchirurg. 2013;116(9):813-24.

71. Teyssédou S, Saget M, Pries P. Kyphopasty and vertebroplasty. Orthopaedics & Traumatology: Surgery & Research. 2014;100(1, Supplement):S169-S79.

72. McArthur N, Kasperk C, Baier M, Tanner M, Gritzbach B, Schoierer O, Rothfischer W, Krohmer G, Hillmeier J, Kock HJ, Meeder PJ, Huber FX. 1150 kyphoplasties over 7 years: indications, techniques, and intraoperative complications. Orthopedics. 2009;32(2):90.

73. Tsoumakidou G, Too CW, Koch G, Caudrelier J, Cazzato RL, Garnon J, Gangi A. CIRSE Guidelines on Percutaneous Vertebral Augmentation. Cardiovasc Intervent Radiol. 2017;40(3):331-42.

74. Luthman S, Widén J, Borgström F. Appropriateness criteria for treatment of osteoporotic vertebral compression fractures. Osteoporos Int. 2018;29(4):793-804.

75. Marcia S, Muto M, Hirsch JA, Chandra RV, Carter N, Crivelli P, Piras E, Saba L. What is the role of vertebral augmentation for osteoporotic fractures? A review of the recent literature. Neuroradiology. 2018;60(8):777-83.

76. Astur N, Avanzi O. Balloon Kyphoplasty in the Treatment of Neoplastic Spine Lesions: A Systematic Review. Global Spine J. 2019;9(3):348-56.

77. Prokop A, Dolezych R, Chmielnicki M. [Kyphoplasty in the treatment of osteoporotic spine fractures - experience with 1069 cases]. Z Orthop Unfall. 2014;152(4):315-8.

78. Filippiadis DK, Marcia S, Masala S, Deschamps F, Kelekis A. Percutaneous Vertebroplasty and Kyphoplasty: Current Status, New Developments and Old Controversies. Cardiovasc Intervent Radiol. 2017;40(12):1815-23.

79. Becker S, Ogon M. Balloon Kyphoplasty. 1st ed. 2008. ed. Vienna: Vienna : Springer Vienna : Imprint: Springer; 2008. 1 online resource (176 p.) p.

80. Zhang H, Xu C, Zhang T, Gao Z, Zhang T. Does Percutaneous Vertebroplasty or Balloon Kyphoplasty for Osteoporotic Vertebral Compression Fractures Increase the Incidence of New Vertebral Fractures? A Meta-Analysis. Pain Physician. 2017;20(1):E13-e28.

81. Yang S, Liu Y, Yang H, Zou J. Risk factors and correlation of secondary adjacent vertebral compression fracture in percutaneous kyphoplasty. Int J Surg. 2016;36(Pt A):138-42.

82. Palmowski Y, Balmer S, Bürger J, Schömig F, Hu Z, Pumberger M. Influence of operative timing on the early post-operative radiological and clinical outcome after kyphoplasty. Eur Spine J. 2020.

83. Zhou X, Meng X, Zhu H, Zhu Y, Yuan W. Early versus late percutaneous kyphoplasty for treating osteoporotic vertebral compression fracture: A retrospective study. Clin Neurol Neurosurg. 2019;180:101-5.

84. Minamide A, Maeda T, Yamada H, Murakami K, Okada M, Enyo Y, Nakagawa Y, Iwasaki H, Tsutsui S, Takami M, Nagata K, Hashizume H, Yukawa Y, Schoenfeld AJ, Simpson AK. Early versus delayed kyphoplasty for thoracolumbar osteoporotic vertebral fractures: The effect of timing on clinical and radiographic outcomes and subsequent compression fractures. Clin Neurol Neurosurg. 2018;173:176-81.

85. Trieb K, Nittinger M. [Timing of kyphoplasty influences the outcome: a prospective study]. Sportverletz Sportschaden. 2020;34(1):42-7.

86. Erkan S, Ozalp TR, Yercan HS, Okcu G. Does timing matter in performing kyphoplasty? Acute versus chronic compression fractures. Acta Orthop Belg. 2009;75(3):396-404.

87. Oh GS, Kim HS, Ju CI, Kim SW, Lee SM, Shin H. Comparison of the results of balloon kyphoplasty performed at different times after injury. J Korean Neurosurg Soc. 2010;47(3):199-202.

88. Park H, Lee C, Ha J, Choi S, Kim M, Ha J. Results of kyphoplasty according to the operative timing. Current Orthopaedic Practice. 2010;21:489-93.

89. Crandall D, Slaughter D, Hankins PJ, Moore C, Jerman J. Acute versus chronic vertebral compression fractures treated with kyphoplasty: early results. Spine J. 2004;4(4):418-24.

90. Takahashi S, Hoshino M, Terai H, Toyoda H, Suzuki A, Tamai K, Watanabe K, Tsujio T, Yasuda H, Kono H, Sasaoka R, Dohzono S, Hayashi K, Ohyama S, Hori Y, Nakamura H. Differences in short-term clinical and radiological

outcomes depending on timing of balloon kyphoplasty for painful osteoporotic vertebral fracture. J Orthop Sci. 2018;23(1):51-6.

91. Cohen J. A power primer. Psychol Bull. 1992;112(1):155-9.

92. Lips P, Cooper C, Agnusdei D, Caulin F, Egger P, Johnell O, Kanis JA, Kellingray S, Leplege A, Liberman UA, McCloskey E, Minne H, Reeve J, Reginster JY, Scholz M, Todd C, de Vernejoul MC, Wiklund I. Quality of life in patients with vertebral fractures: validation of the Quality of Life Questionnaire of the European Foundation for Osteoporosis (QUALEFFO). Working Party for Quality of Life of the European Foundation for Osteoporosis. Osteoporos Int. 1999;10(2):150-60.

93. Jung HJ, Park Y-S, Seo H-Y, Lee J-C, An K-C, Kim J-H, Shin B-J, Kang TW, Park SY. Quality of Life in Patients with Osteoporotic Vertebral Compression Fractures. J Bone Metab. 2017;24(3):187-96.

94. Zhu Y, Cheng J, Yin J, Zhang Z, Liu C, Hao D. Therapeutic effect of kyphoplasty and balloon vertebroplasty on osteoporotic vertebral compression fracture: A systematic review and meta-analysis of randomized controlled trials. Medicine (Baltimore). 2019;98(45):e17810.

95. Wang H, Sribastav SS, Ye F, Yang C, Wang J, Liu H, Zheng Z. Comparison of Percutaneous Vertebroplasty and Balloon Kyphoplasty for the Treatment of Single Level Vertebral Compression Fractures: A Meta-analysis of the Literature. Pain Physician. 2015;18(3):209-22.

96. Taylor RS, Fritzell P, Taylor RJ. Balloon kyphoplasty in the management of vertebral compression fractures: an updated systematic review and meta-analysis. Eur Spine J. 2007;16(8):1085-100.

97. Wardlaw D, Cummings SR, Van Meirhaeghe J, Bastian L, Tillman JB, Ranstam J, Eastell R, Shabe P, Talmadge K, Boonen S. Efficacy and safety of balloon kyphoplasty compared with non-surgical care for vertebral compression fracture (FREE): a randomised controlled trial. Lancet. 2009;373(9668):1016-24.

98. Müller CW, Gösling T, Mameghani A, Stier R, Klein M, Hüfner T, Krettek C. Osteoporosebedingte Wirbelkörperfrakturen: Kyphoplastie und Vertebroplastie vs. konservative Therapie. Der Orthopäde. 2010;39(4):417-24.

99. Epstein NE. A Comparison of Kyphoplasty, Vertebroplasty, or Non-Surgical Treatment of Traumatic/Atraumatic Osteoporotic Vertebral Compression Fractures: A Short Review. Surg Neurol Int. 2019;10:54.

100. Ee GW, Lei J, Guo CM, Yeo W, Tan SB, Tow PB, Chen LT, Yue WM. Comparison of Clinical Outcomes and Radiographic Measurements in 4 Different Treatment Modalities for Osteoporotic Compression Fractures: Retrospective Analysis. J Spinal Disord Tech. 2015;28(6):E328-35.

101. Beall D, Lorio MP, Yun BM, Runa MJ, Ong KL, Warner CB. Review of Vertebral Augmentation: An Updated Meta-analysis of the Effectiveness. Int J Spine Surg. 2018;12(3):295-321.

102. Davies LE, Spiers G, Kingston A, Todd A, Adamson J, Hanratty B. Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews. J Am Med Dir Assoc. 2020;21(2):181-7.

103. Tolba R, Bolash RB, Shroll J, Costandi S, Dalton JE, Sanghvi C, Mekhail N. Kyphoplasty increases vertebral height, decreases both pain score and opiate requirements while improving functional status. Pain Pract. 2014;14(3):E91-7.

104. Yokoyama K, Kawanishi M, Yamada M, Tanaka H, Ito Y, Kawabata S, Kuroiwa T. Postoperative change in sagittal balance after Kyphoplasty for the treatment of osteoporotic vertebral compression fracture. Eur Spine J. 2015;24(4):744-9.

105. Kanayama M, Oha F, Iwata A, Hashimoto T. Does balloon kyphoplasty improve the global spinal alignment in osteoporotic vertebral fracture? Int Orthop. 2015;39(6):1137-43.

106. Korovessis P, Zacharatos S, Repantis T, Michael A, Karachalios D. Evolution of bone mineral density after percutaneous kyphoplasty in fresh osteoporotic vertebral body fractures and adjacent vertebrae along with sagittal spine alignment. J Spinal Disord Tech. 2008;21(4):293-8.

107. Pradhan BB, Bae HW, Kropf MA, Patel VV, Delamarter RB. Kyphoplasty reduction of osteoporotic vertebral compression fractures: correction of local kyphosis versus overall sagittal alignment. Spine (Phila Pa 1976). 2006;31(4):435-41.

108. Schulz C, Efinger K, Schwarz W, Mauer UM. [Experiences with cement leakage after balloon kyphoplasty]. Orthopade. 2012;41(11):881-8.

109. Zhu RS, Kan SL, Ning GZ, Chen LX, Cao ZG, Jiang ZH, Zhang XL, Hu W. Which is the best treatment of osteoporotic vertebral compression fractures: balloon kyphoplasty, percutaneous vertebroplasty, or non-surgical treatment? A Bayesian network meta-analysis. Osteoporos Int. 2019;30(2):287-98.

6. Eidesstattliche Versicherung

„Ich, Sophie Balmer, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: „Retrospektive Studie zum Einfluss des Zeitpunktes der Kyphoplastie auf das klinische und radiologische Outcome bei Wirbelkörperfrakturen, Influence of operative timing on the early postoperative radiological and clinical outcome after kyphoplasty“ selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.

Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem Erstbetreuer, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum

Unterschrift

7. Anteilserklärung an etwaigen erfolgten Publikationen:

Sophie Balmer hatte folgenden Anteil an den folgenden Publikationen:

1. Palmowski Y, Balmer S, Bürger J, Schömig F, Hu Z, Pumberger M
   "Influence of operative timing on the early post-operative radiological and clinical outcome after kyphoplasty". Eur Spine J. 2020.

   Beitrag im Einzelnen: Konzeptionierung der Studie und des Studiendesigns, komplette Datenerhebung inklusive der radiologischen Messungen, aus der alle in der Publikation berichteten Ergebnisse hervorgegangen sind (Tabelle 1,2,3 sowie Abbildung 1,2,3), Auswertung und Datenanalyse der Ergebnisse

2. Palmowski Y, Balmer S, Hu Z, Winkler T, Schnake KJ, Kandziora F, Pumberger M
   "Relationship Between the OF Classification and Radiological Outcome of Osteoporotic Vertebral Fractures After Kyphoplasty". Global Spine J. 2020.

   Beitrag im Einzelnen: komplette Datenerhebung inklusive radiologischer Messungen (hieraus entstanden sind die Tabellen 1,2,3,4 sowie die Abbildungen 2,3,4,5), Auswertung und Datenanalyse der Ergebnisse

PD Dr. med. Matthias Pumberger	Sophie Balmer
Betreuender Hochschullehrer	Promovendin

8. Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtlichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

9. Publikationsliste

1. Holle J, Gratopp A, Balmer S, Varnholt V, Henning S, Bufler P, Müller D, Rosenfeld L

   “Single-Pass Albumin Dialysis in the Treatment of Children with Liver Failure”. Blood Purif. 2019:1-8.

2. Palmowski Y, Balmer S, Bürger J, Schömig F, Hu Z, Pumberger M

   “Influence of operative timing on the early post-operative radiological and clinical outcome after kyphoplasty”. Eur Spine J. 2020.

3. Palmowski Y, Balmer S, Hu Z, Winkler T, Schnake KJ, Kandziora F, Pumberger M

   “Relationship Between the OF Classification and Radiological Outcome of Osteoporotic Vertebral Fractures After Kyphoplasty”. Global Spine J. 2020.

10. Danksagung

Im Rahmen der Fertigstellung dieser Arbeit möchte ich mich bei den Menschen bedanken, ohne die diese Arbeit nicht möglich gewesen wäre.

Allen voran möchte ich mich bei PD Dr. med Matthias Pumberger und Dr. med. Yannick Palmowski für das entgegengebrachte Vertrauen, die außerordentlich gute Zusammenarbeit und die verlässliche Unterstützung bedanken. Sowohl bei inhaltlichen als auch organisatorischen Problemen fand ich stets ein offenes Ohr und konnte außerdem sehr von ihrer Expertise beim Erstellen wissenschaftlicher Arbeiten profitieren. Vielen Dank für die immer sachliche Kritik sowie die anhaltende Motivation und auch dafür, dass mein Weg mit dieser Arbeit ein Stück weiter in die Orthopädie gelenkt wurde.

Außerdem danke ich Wiebke Ashby von Herzen für ihre Akribie und Geduld bei der sprachlichen Kontrolle meiner Dissertation.

Mein größter Dank gilt jedoch meiner Familie und meinen Freunden, die mir stets der wertvollste Rückhalt sind. Ganz besonders möchte ich meinen lieben Eltern, Ines und Uwe Balmer, für Ihre Unterstützung auf all meinen Wegen sowie ihre Geduld, ihr Verständnis und ihr Vertrauen danken. Marius Sauerbrey danke ich von ganzem Herzen für die ausdauernde Unterstützung und Motivation bei Erstellung dieser Arbeit.

11. Bescheinigung Statistik

CHARITÉ

CharitéCentrum für Human- und Gesundheitswissenschaften

Charité | Campus Charité Mitte | 10117 Berlin

Institut für Biometrie und klinische Epidemiologie (iBikE)

Direktor: Prof. Dr. Geraldine Rauch

Postanschrift:
Chariteplatz 1 | 10117 Berlin
Besucheranschrift:
Reinhardtstr. 58 | 10117 Berlin

Tel. +49 (0)30 450 562171
geraldine.rauch@charite.de
https://biometrie.charite.de/

Name: Balmer, Sophie

Emailadresse: sophie.balmer@charite.de

Matrikelnummer: 221296

PromotionsbetreuerIn: PD Dr. med. Matthias Pumberger

Promotionsinstitution / Klinik: CCM Klinik für Orthopädie

Bescheinigung

Hiermit bescheinige ich, dass Frau *Sophie Balmer* innerhalb der Service Unit Biometrie des Instituts für Biometrie und klinische Epidemiologie (iBikE) bei mir eine statistische Beratung zu einem Promotionsvorhaben wahrgenommen hat. Folgende Beratungstermine wurden wahrgenommen:

- Termin 1: *27.06.2019*
- Termin 2: *28.04.2020*

Folgende wesentliche Ratschläge hinsichtlich einer sinnvollen Auswertung und Interpretation der Daten wurden während der Beratung erteilt:

- Studiendesign inkl. Gruppenbildung zum Vergleich von drei Studiengruppen
- Datenmanagement, Umgang mit fehlenden Werten.
- Verschiedene Testverfahren in Abhängigkeit vom Datenniveau
- Interpretation und Präsentation der Ergebnisse sowie Limitationen der Studie

Diese Bescheinigung garantiert nicht die richtige Umsetzung der in der Beratung gemachten Vorschläge, die korrekte Durchführung der empfohlenen statistischen Verfahren und die richtige Darstellung und Interpretation der Ergebnisse. Die Verantwortung hierfür obliegt allein dem Promovierenden. Das Institut für Biometrie und klinische Epidemiologie übernimmt hierfür keine Haftung.

Datum: 28.04.2020

Name des Beraters/ der Beraterin: Ralph Schilling

Unterschrift BeraterIn, Institutsstempel