Comparison of systemic inflammatory response in patients with trochanteric region fracture fixation with Dynamic Hip Screw versus Proximal Femoral Nail

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UNIVERSITY OF ZAGREB
SCHOOL OF MEDICINE

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This dissertation was completed at the Department of Orthopedic and Traumatology, University Clinical Center of Kosovo in Prishtina, Kosovo, and the Department of Pharmacology and Toxicology University Clinical Center of Kosovo in Prishtina, Kosovo.

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LIST OF ABBREVIATIONS

AO	Working Group for Osteosynthesis Problems (Ger. *Arbeitsgemeinschaft für Osteosynthesefragen*)
ARDS	Acute respiratory distress syndrome
CRP	C-reactive protein
DHS	Dynamic hip screw
ELISA	Enzyme-linked immunosorbent assay
ESR	Erythrocyte sedimentation rate
h	Hours
Hb	Hemoglobin
Hct	Hematocrit
IL	Interleukin
MOF	Multiple organ failure
MRI	Magnetic resonance imaging
OTA	The Orthopaedic Trauma Association
PFN	Proximal femoral nail
SIRS	Systemic inflammatory response syndrome
TNF-α	Tumour necrosis factor-alpha
VTE	Venous thromboembolism

1. INTRODUCTION

1.1. Trochanteric region fractures

1.1.1 Epidemiology

Hip fractures are one of the most common fractures in older adults, with an incidence in the United States of 957.3 per 100,000 for women and 414.4 per 100,000 for men, and are a great public health concern (1). The prevalence of hip fractures is increasing along with an aging population, thereby resulting in considerable societal and financial encumbrances. Advanced age represents a notable risk factor for pertrochanteric fractures, wherein the likelihood of incidence rises proportionally with increasing age. Furthermore, the one-year mortality rate among individuals aged 65 years and above has been reported to be 27.3%, with even higher rates observed in those aged 80 years and older (2,3). Moreover, sex disparities have been identified, with females showing a 2.9-fold greater susceptibility to hip fractures than males, which can attributed to alterations in bone mineral density and strength that occur with aging, especially in females, rendering bones more vulnerable to fracture (4). Osteoporosis is a significant contributing factor in this regard, augmenting the likelihood of fracture occurrence, together with other risk factors that have been identified, with noteworthy contributors including certain medications, smoking, and alcohol abuse (5-7). Conversely, in younger individuals, trochanteric region fractures are relatively infrequent and primarily attributable to high-energy trauma (8). Preventive strategies for hip fractures include lifestyle adjustments, such as routine physical activity and a nutrient-rich diet containing sufficient calcium and vitamin D, as well as pharmacological interventions, such as bisphosphonates for osteoporosis (9). Additionally, fall prevention initiatives incorporating exercise and balance training have demonstrated efficacy in reducing the incidence of falls and consequent hip fractures (10).

1.1.2. Classification

The first classification of extracapsular femoral fractures was pioneered by Boyd and Griffin (11) in 1949. They classified trochanteric fractures into 4 types: 1. A single and stable fracture along the intertrochanteric line; 2. A comminuted fracture, with the main line being alongside the

intertrochanteric line; 3. Fracture at the level of the lesser trochanter with extension into the lateral cortex; and 4. Two-plane fractures extending from the trochanteric region to the proximal femoral shaft (Figure 1). Based on this classification, type 1 fractures are stable fractures, and their reduction can be easily achieved. Type 2 fractures are mainly stable but posteromedial comminution may compromise stability. Type 3 fractures are difficult to reduce due to subtrochanteric involvement, and the complication rate is highest, while the prognosis is the poorest, relative to the other three types. Type 4 fractures are also difficult to reduce, and at the time of publication of this classification, the authors used not only the blade plate but also screws to stabilize the fracture in two planes; however, they reported a low rate of loss of reduction.

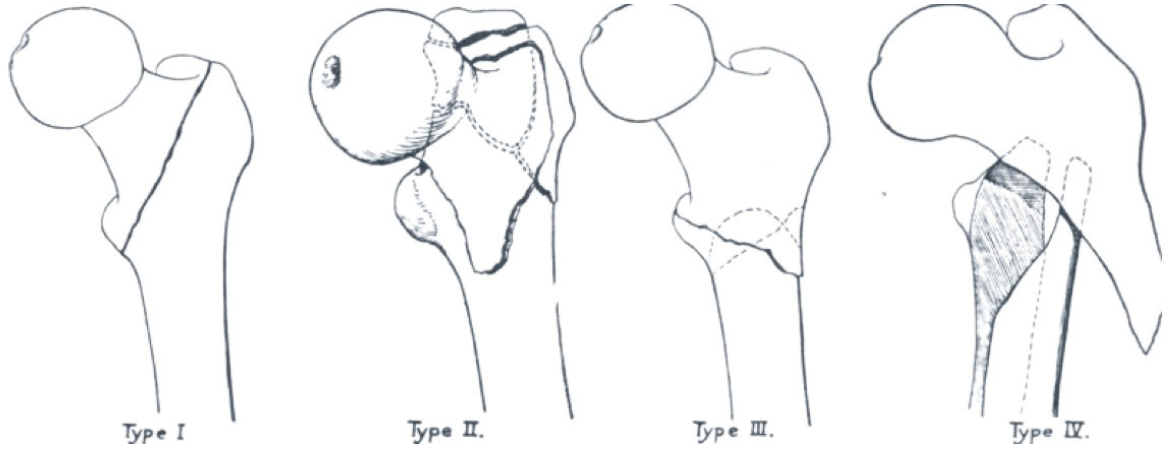

Figure 1. Boyd and Griffin classification of troachnteric fractures. Type I - designates fractures showing a more or less linear break extending along the general direction of the intertrochanteric line from greater to lesser trochanter; Type II - designates fractures with the main line of fracture being along the intertrochanteric line but with multiple breaks occurring in the cortex; Type III - designates fractures which are essentially subtrochanteric, with at least one fracture line passing across the upper end of the shaft just below or in the region of the lesser trochanter; and Type IV - designates comminuted fractures which extend through the trochanteric region and usually on into the shaft, with fracture lines in at least two planes. Modified from Boyd et al. (11).

Another type of classification is the Evans classification, which originally described trochanteric region fractures as two types: stable and unstable (12). The original Evans classification was as follows: type 1, undisplaced 2-fragmentary fracture; type 2, displaced 2-fragmentary fracture; type 3, 3-fragmentary fracture without posterolateral support due to dislocated greater trochanter; type

4, 3-fragmentary fracture without medial support due to dislocated lesser trochanter or femoral; and type 5, 4-fragmentary fracture without medial and posterolateral support, which is essentially a combination of types 3 and 4. Types 1 and 2 are considered fractures that remain stable when reduced, types 3 and 4 are unstable and have a tendency toward varus angulation, and type 5 are reverse oblique, unstable fractures that tend to medialize in relation to the femoral shaft. This classification was later modified by Jensen and Michaelsen (13) and also included two groups: stable and unstable. Unlike the original clasification, in the first group, type 1 stable fractures have high probability of achieving anatomical reduction and were classified as: a. undisplaced 2 – fragmentary fractures, and b. displaced 2 – fragmentary fractures. Type 2 unstable fractures with low probability of achieving anatomical reduction and were classified into three subgroups: a. 3 – fragmentary fractures without posterolateral wall support, b. 3 – fragmentary fractures without medial support, and c. 4 – fragmentary fractures (Figure 2).

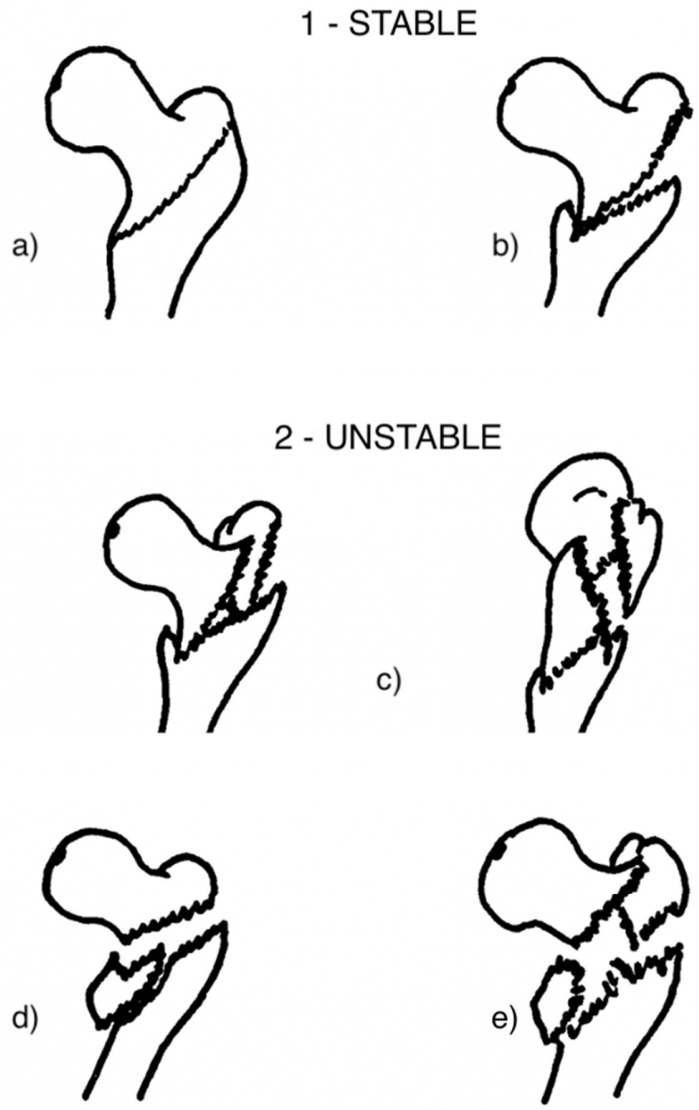

Figure 2. Evans classification of trochanteric fractures. 1 - Stable fracture and are subdivided in a) unidisplaced 2-fragment fracture and b) displaced 2-fragment fracture. 2 – Unstable fractures and are subdivided in c) 3-fragment fracture, without posterolateral support, d) 3-fragment fracture without medial support and e) 4-fragment fracture. Modified from Jensen et al. (13).

Today, the most cited classification is the Working Group for Osteosynthesis Problems (Ger. *Arbeitsgemeinschaft für Osteosynthesefragen* (AO)) /The Orthopaedic Trauma Association (OTA) classification (AO/OTA), which was updated in their 2018 compendium (14). The AO/OTA

system includes, in their classification, a number and a letter, with the number labeling the bone and the letter the type of fracture. Trochanteric region fractures have been labeled as 31A. They are divided into three main groups: simple trochanteric fractures (31A1), multifragmentary pertrochanteric lateral wall fractures (31A2), and intertrochanteric reverse obliquity fractures (31A3) (Figure 3). The three groups are each divided into three subgroups. The 31A1 fractures are stable after reduction and fixation because of the lack of comminution, 31A2 fractures tend to be unstable after reduction and fixation because the medial buttress is fractured, and 31A3 fractures are unstable and can cause significant shortening due to involvement of both femoral cortexes.

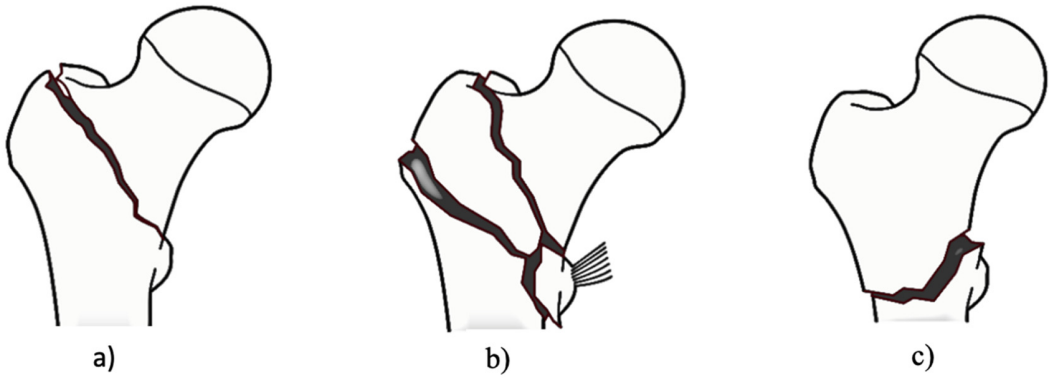

Figure 3. Working Group for Osteosynthesis Problems (Ger. *Arbeitsgemeinschaft für Osteosynthesefragen* (AO))/The Orthopaedic Trauma Association (OTA) classification (AO/OTA) of trochanteric region fractures. a) 31A1 - simple trochanteric fractures, b) 31A2 - multi-fragmentary pertrochanteric lateral wall, c) 31A3 - intertrochanteric reverse obliquity fracture fractures. Modified from Meinberg et al. (14).

Despite numerous attempts, no consensus has been reached regarding the gold standard classification of extracapsular femoral fractures, likely due to variations in the types of fixation employed over time.

1.1.3. Imaging

Imaging is a crucial component in the diagnosis and management of hip conditions. Common imaging techniques employed in hip imaging include X-ray, magnetic resonance imaging (MRI), computed tomography, and ultrasound. Accurate diagnosis of fractures requires standard anteroposterior of the pelvis and cross-table lateral X-ray view of the ipsilateral hip. The view of the contralateral femur is also necessary for measuring the neck-shaft angle on the healthy side, which serves as a template for selecting the appropriate osteosynthetic device. In cases where the surgeon intends to use intramedullary nailing, the femoral shaft must also be included to determine medullary width and assess diaphyseal morphology. Occult fractures, which are prevalent in the elderly population, may not be visible on plain radiographs. In cases where there is a high degree of clinical suspicion of a fracture but radiographs are inconclusive, MRI is the most sensitive modality for identifying the fracture (15). MRI has gradually replaced bone scanning as the preferred diagnostic tool for identifying occult and undisplaced fractures in elderly patients. In the past, bone scanning was considered the standard diagnostic modality for these types of fractures, but MRI has demonstrated superior sensitivity and specificity in detecting these injuries. However, there has been a report that bone scanning might be an option when there is doubt over conventional radiography for a hip fracture (16). Computed tomography has also been reported as a good option for diagnosing hip fractures, mainly due to accessibility in emergency department settings (17); however, MRI is superior to computed tomography for diagnosing occult hip fractures (18).

1.2. Treatment options

The management of hip fractures is multifactorial and predominantly based on the type and location of the fracture and the patient's overall health status and functional status. In elderly patients with hip fractures, surgery must be performed promptly, ideally within the first 48 hours (h) following fracture, as prompt surgery is associated with better postoperative outcomes, such as shorter hospital stay, reduced likelihood of bedsore occurrence, and faster return to independent living (19). However, non-surgical interventions may be considered for patients who are unable to undergo surgery due to significant medical comorbidities or frailty. The two non-surgical treatment

options for hip fractures include traction and bed rest. Traction involves the application of a pulling force to the affected leg to help realign the fractured bones and alleviate discomfort. During bed rest, patients are advised to rest and avoid bearing weight on the affected leg for several weeks to enable fracture healing. However, non-operative treatment is associated with increased mortality; 2.5 times more likely in patients receiving bed rest compared with those receiving surgical treatment (20). Other authors have reported a 15% increase in mortality rate when surgery was delayed for more than 48 h, and mortality rate at 1-year follow-up was doubled when surgery was delayed for more than 3 days (21). Nevertheless, non-operative treatment may be suitable for patients with poor general condition and those medically unfit; two studies reported non-significant differences in the functional outcomes of this patient group compared to those receiving operative treatment (20, 22).

1.2.1. Clinical anatomy

The proximal femur is a complex anatomical region comprising four distinct regions: the femoral head, greater trochanter, lesser trochanter, and proximal femoral diaphysis. The hip is further divided surgically into three regions based on the fracture location, namely the trochanteric region, femoral neck, and femoral head. Understanding the anatomical features of these regions is essential in determining the appropriate management strategy for hip fractures.

The trochanteric region of the hip consists of dense trabecular bone that is responsible for transmitting mechanical stress between the femoral neck and femoral diaphysis. The greater trochanter provides attachment points for muscles like the gluteus medius, gluteus minimus, superior and inferior gemellus, obturator internus, piriformis, and vastus lateralis. These muscles play a crucial role in hip abduction and external rotation. In contrast, the lesser trochanter is the insertion site of the iliopsoas muscle, which flexes and adducts the hip. The posteromedial aspect of the femoral shaft, extending to the posterior portion of the femoral neck, contains a vertical dense bone called the calcar femorale, which has strong stress-transferring properties and is important for stabilizing fractures. In contrast to the femoral head, where blood supply is limited and the risk of osteonecrosis is high, this region is well-supplied with blood, leading to a high rate of union (23).

1.2.2. Fracture reduction

Depending on the fracture stability, fracture reduction may be performed as closed or open reduction. Closed reduction is almost always first tried under fluoroscopy with the patient laid in the supine position on the traction table. The ipsilateral arm is elevated, and the contralateral leg is placed in the leg holder. The ipsilateral hip must be in the adducted position at 10–15º to the contralateral side. Generally, reduction is started by applying traction in the direction of the length extremity. Excessive traction may lead to pelvic rotation of fracture distraction. For this reason, every step of the reduction procedure must be checked using fluoroscopy in anteroposterior and lateral views. Then, internal rotation is applied, and in some types of fracture, other measures must take place. For impacted fractures, in which secondary varus may happen, extra traction force must be applied until the varus is slightly over-reduced, and then slight external rotation and dorsal support may correct the retrocurvature. For reversed fractures, which are very unstable, traction and dorsal support may correct for the displacement, and using manual pressure or a percutaneous hook, the shaft fragment may be mobilized laterally (24). If closed reduction fails, the surgeon can proceed with open reduction and internal fixation. Fixed fracture stability is dependent on five factors: bone quality, fragment geometry, reduction, implant design, and implant placement (25).

1.2.3. Proximal femoral nail

The modern day intramedullary nailing for fixation of femoral fractures has been introduced in late 1940s by Gerhard Küntscher and since then has been evolved to treat trochanteric region fractures (26). This method is primarily intended to stabilize the proximal femur, which is the upper segment of the femoral bone that interfaces with the hip joint. The proximal femoral nail (PFN), which consists of specially constructed nails and locking screws, is implanted into the medullary canal of the femur to accomplish this purpose. It has been observed that the utilization of the PFN technique results in superior outcomes in cases involving osteoporotic patients and fractures characterized by weak bone mass and reverse obliquity compared with other fixation modalities (27). Furthermore, the smaller incision required for PFN insertion results in less tissue damage, promoting a quicker recovery time. The technique allows for early mobilization and weight-bearing post-surgery; thus, decreasing the likelihood of complications, such as pneumonia

and blood clots. Additionally, the surgical procedure is relatively uncomplicated. However, there are associated risks with the utilization of the PFN, such as surgical site infection, device loosening or failure, and nerve damage during surgery (28).

1.2.4. Dynamic hip screw

The dynamic hip screw (DHS) is a widely employed treatment method for trochanteric region fractures. Robert Danis was first to design in 1934 for fixation of femoral neck fractures but its clinical use was succesfully practiced by Ernst Pohl in 1951 and, at the end of the 1980s, it became a standard implant for the treatment of trochanteric fractures (28). The DHS is used in internal fixation to secure the stability of the fracture during the healing process. The device comprises a specially designed screw, side plate, and compression screw. The advantages of the DHS over other types of internal fixation devices include early mobilization and weight-bearing post-surgery, which aids in preventing complications, such as pneumonia and blood clots (29). The technique also provides robust fixation and stability of the fractured bone, leading to faster healing time and improved patient outcomes (30). Furthermore, the DHS is a relatively straightforward surgical procedure. However, there are associated risks with the use of DHSs, including surgical site infections, loosening or failure of the internal fixation device, and blood loss during surgery (31).

1.2.5. Blade plates, condylar screws, and external fixators

Blade plates and condylar screws were previously utilized, but they are infrequently employed today. These fixation devices cannot impact the fracture due to their design, and unlike PFN and DHS, they do not penetrate the femoral head in the event of fracture collapse. Nevertheless, their primary advantage lies in their ability to resist lateral translation of the proximal fragment. A study has reported superior outcomes with the use of blade plates compared to DHS (29). Additionally, blade plates and condylar screws may be employed in cases of failed PFN or DHS revision, as they possess a lower point of fixation in the femoral head and do not traverse the previously placed lag screw (30).

In contemporary medical practice, external fixation is utilized as a treatment modality for trochanteric region fractures in elderly patients, notably for AO type 31.A1 and 31.A2 fractures, as it has been shown to significantly reduce operative time, blood loss, and varus collapse in comparison to DHS (31). Nevertheless, it should be noted that in the context of unstable trochanteric region fractures, external fixation is associated with a proclivity towards varus collapse and elevated complication rates (32).

1.2.6. Blood loss during surgery

Blood loss due to surgical treatment of trochanteric region fractures is associated with high mortality risk and is an independent risk factor for the functional mobility of elderly patients (33–35). Moreover, Lin et al. (36) found that contributory factors to blood loss during surgery include the size of the incision and presence of comorbidities, such as hypertension or coagulation disorders. Additionally, the same study revealed the importance of considering the type of hip fracture when assessing blood loss because patients with unstable trochanteric fractures (AO 31 A2.2–A2.3) exhibit a greater drop in hemoglobin (Hb) levels compared to patients with stable fractures (AO 31 A1.1–A2.1). They also found that examining hidden blood loss in patients treated with an unreamed PFN revealed that most hidden blood loss occurred before the surgery and was mainly due to the trauma itself rather than the operation. The amount of blood loss can also vary depending on the type of surgical procedure, with more invasive surgeries typically resulting in higher levels of blood loss (27).

Several studies have attempted to compare the amount of blood loss between PFN and DHS procedures. Jonnes et al. (37) found that PFN outperformed DHS in terms of decreased blood loss, shorter surgery duration, earlier weight-bearing and mobilization, shorter hospital stay, reduced risk of infection, and fewer complications. A meta-analysis of randomized controlled trials conducted by Shen et al. (38) found that PFN was associated with fewer complications and less blood loss than DHS in patients with peritrochanteric fracture. Also, they found that variations in surgical skills and fracture types may explain the significant differences in trial results for blood loss and operative time. An interesting result was found in a study by Ronga et al. (39), in which patients with AO type 31A1 fractures treated with DHS had lower blood loss compared to PFN,

while patients with AO type 31A2 fractures had lower blood loss when treated with PFN compared to DHS.

Despite numerous studies comparing blood loss during orthopedic surgeries, there is still no consensus on the gold standard for measuring blood loss. Various factors, such as the extent and duration of surgery, blood disorders, and the type of fracture, can influence blood loss (40,41). Additionally, quantification of blood loss remains unreliable and inaccurate, especially when gauzes are used in measurement (42,43). However, a recent study by Jaramillo et al. proposed a novel and more accurate method for measuring blood loss using three different formulas (40). These formulas include the Hb mass loss formula, which estimates blood loss in terms of Hb mass loss; the López-Picado's formula; and an empirical volume formula that estimates blood loss in terms of blood volume loss (44). The study found that the estimation of Hb mass loss was the most accurate method for estimating perioperative blood loss.

1.2.7. Postoperative complications

Despite the relatively low complication rate associated with surgery in patients with trochanteric region fracture, functional outcomes can be less favorable. While most of the patients undergoing trochanteric region fracture fixation experience no major complications, only half of the patients can regain their preinjury mobility at one-year follow-up (45). This discrepancy between complication rates and functional outcomes highlights the importance of considering not only the technical success of a surgical procedure but also the impact of that procedure on patients' quality of life and ability to perform daily activities.

The high prevalence of comorbidities in elderly patients makes this population particularly vulnerable to adverse outcomes, with mortality rates as high as 15% during hospitalization and 30% at 1-year follow-up for patients with other comorbidities (46). In comparison to the general population, patients with proximal femoral fractures have a mortality rate that is six times higher when age-matched (47). Another study reported an overall mortality rate of 7.7% at 30 days and 26% at 1-year follow-up (48). These findings underscore the need for diligent assessment and management of comorbidities in elderly patients, with a focus on optimizing clinical outcomes and

minimizing mortality risk. Healthcare providers must be vigilant in their efforts to manage complex medical conditions in elderly patients, utilizing a multidisciplinary approach to ensure the best possible outcomes.

The incidence of postoperative infections in patients with trochanteric region fractures after surgery has been the subject of several studies. A study conducted by Zhao et al. (49) reported a postoperative infection rate of 1.3%, with 1.1% of patients experiencing superficial infections and 0.2% experiencing deep infections. However, another study found a slightly higher infection rate of 1.2% for deep wound infections and 1.1% for superficial wound infections (50). It is worth noting that while the first study included only the patients with trochanteric region fractures, the second study included patients with hip fractures, which may have biased the results. Therefore, the reported infection rates may not accurately reflect the rate of postoperative infections specifically among patients with trochanteric region fractures. Further research is necessary to better understand the risk factors and incidence of postoperative infections in this patient population.

Orthopedic surgeries carry a significant risk of venous thromboembolism (VTE). In patients with hip fractures, the risk of total and proximal deep vein thrombosis rates can be as high as 50% and 27%, respectively, when no VTE prophylaxis is used (51). However, when VTE prophylaxis is used, this risk can be dramatically reduced to 1.34% (52). VTE prophylaxis comprises a comprehensive strategy, not depending only on pharmacological strategies (51,52). Among VTE prophylaxis drugs, such as synthetic anticoagulant agent Factor Xa Inhibitors (Fondaparinux) is considered more efficacious than low molecular-weight heparin, even though many centers continue to use low molecular-weight heparin (53). In addition to pharmacological prophylaxis, mechanical prophylaxis is also utilized in many major hospital centers in the form of stockings worn on both legs, although the cost-effectiveness and efficacy of this approach remain controversial (54). Despite the availability of effective VTE prophylaxis measures, the risk of VTE remains a significant concern for patients undergoing orthopedic surgeries.

Regarding the best fixation method, leading to anatomic bone union, there is still no consensus on the optimal surgical technique between DHS and PFN (55). Malunion and non-union are uncommon in trochanteric region fractures with the incidence of nonunion reported to be 1–2%

(56,57). The treatment of this complication varies, with hip arthroplasty as a salvage method for elderly patients (58,59), while osteosynthesis is preferable for young patients with good bone stock salvage and can be carried with various implants with or without intertrochanteric osteotomy (60,61).

1.3. Systemic inflammatory response syndrome after trauma

Trauma itself is one of the most common causes of death in the general population and the main cause in patients aged under 45 years in the USA (62,63). Death can occur during three time periods after trauma. The majority of patients die immediately or within the first few hours. The second time point occurs within the initial 24 hours, and the proportion of deaths during this period is typically lower. These fatalities are commonly attributed to factors such as hypoxia, massive blood loss, or head injury (65). If the patient survives these two time points, then death can occur in the third period—days or weeks after admission to the intensive care unit—and is mainly due to systemic inflammatory response syndrome (SIRS), which can lead to adult respiratory distress syndrome (ARDS) and multiple organ failure (MOF) (66-69). Patients who develop SIRS are usually more predisposed to a longer hospital stay (70). On the other hand, some patients tolerate this response and go through this period without developing complications.

SIRS is an uncontrolled immune response of the body to stress—for instance, surgery, trauma, infection, and ischemia—in attempt to localize its cause (71). The trauma itself causes an immunological response several h or days after the injury, which may cardiovascular, immunological, or metabolic in nature (72). The main purpose of the immune reaction is to protect the body; nonetheless, the cytokine storm resulting from SIRS triggers a cytokine cascade leading to organ failure or even death (73). Objectively, SIRS is defined by the satisfaction of any two of the criteria below (74)**:**

- Body temperature: >38 or <36 ° C
- Heart rate: >90 beats/min

- Respiratory rate: >20 beats/min or $PaCO_2$ < 32 mmHg
- Leukocyte count: >12,000 or <4,000 mm^3 or >10% immature forms or bands

SIRS has also been linked to infection, and there are reports that most (62%) of the patients with SIRS who present at the emergency department have a confirmed infection (68). Another study found that, among patients who fulfill the SIRS criteria, 26% developed sepsis, 18% severe sepsis, and 4% septic shock within 28 days of hospitalization (75). The death rate of hospitalized patients with SIRS is 6.9 times higher than those without SIRS (68).

Independently of the main factor that leads to SIRS, it usually progresses through complex cytokine, cellular, and humeral cascades in three main stages, outlined below.

Stage 1: Occurs immediately after the injury and comprises a local reaction aimed at containing and limiting the spread of damage from the site of injury, which is a normal defense mechanism for maintaining homeostasis. This inflammatory local response triggers five cardinal signs of inflammation, originally expressed in Latin: rubor (redness), tumor (swelling), dolor (pain), calor (heat), and function laesa (impaired function) (76).

Stage 2: A compensatory anti-inflammatory response to maintain immunological balance. During this stage, cytokines are released to facilitate a local response and lead to the recruitment of macrophages, platelets, and stimulation of growth factors.

Stage 3: Occurs when homeostasis is not restored during the previous two stages and inflammation was not localized. Subsequently, inflammatory cytokines enter the systemic circulation, causing systemic reactions. In this stage, the complex cascades can ultimately manifest multiple organ dysfunction syndrome.

The treatment of SIRS should be done in two parallel directions: 1) finding and treating the primary cause and 2) managing the vital signs to prevent end-organ injury, even though the therapy does not necessarily need to be cause-specific. The most important factor to be managed is hemodynamic stability. It is recommended that isotonic crystalloids be administered with a bolus dose of 30 mL/kg. Vasopressors and inotropes are also administered in case of unresponsive

hypovolemic shock. The type of drugs and their doses are administered based on the standard protocols of treatment of hypovolemic shock. Glucocorticoids have been shown to improve survival in patients with persistent shock, even when fluids and vasopressor drugs were administered. Other treatments may be added depending on the suspectable primary triggering condition that caused SIRS.

1.3.1. Second hit phenomenon

The second hit phenomenon occurs after the first response following trauma and is the physiological response of the body after the subsequent intervention (77). The two-hit phenomenon was initially introduced by Moore and Moore (78) in 1970 who theorized that patients with less injury may be vulnerable to the secondary inflammatory hit due to the inflammatory environment created by the first hit. The concept was later theorized by Bone (79) who proposed that the model of the first and subsequent hit phenomenon is the foundation of SIRS and MOF for most patients. However, he proposed that for SIRS and MOF to develop, patients need to have a preexisting disorder, such as diabetes, immunodeficiency disorders, neoplasms, and metabolic disorders, be old, and have associated abnormal cytokine levels (80).

Surgery has been widely described as one of the factors that induces inflammatory reactions, as well as coagulator and fibrinolytic responses (81,82). In patients with severe traumatic bone fractures, especially of long bones, the risk of developing SIRS is greater and thought to have great importance due to the first and second hit (subsequent surgery) phenomena (83). If the first and second hits are not properly managed, ARDS and multiple organ dysfunction syndrome can develop along with SIRS (84). The strong association between the second hit phenomenon and patient morbidity and mortality has been described by several authors (85,86).

MOF is the leading cause of late post-injury mortality (87). As SIRS is the initial factor leading to MOF, measuring the inflammatory markers of SIRS has been proposed as a method for predicting MOF development risk (88). The factors predicting post-traumatic MOF can be grouped into patient factors (age, sex, genetic polymorphism), injury factors (injury severity, injury pattern, shock severity), and treatment factors (time to hemorrhage control, resuscitation, surgical

interventions) (89). In vascular surgery, it has been reported that the risk of developing MOF was 3.8% for elective operated patients, 38% for patients in the urgent group, and 64% for patients with ruptured abdominal aortic aneurysm (90). In orthopedic surgery, the risk of MOF development is associated not only with the magnitude of the initial trauma but also with the duration of the surgical procedure (91).

ARDS is another dangerous complication that can result from trauma and usually develops with MOF, given both are clinical sequelae of SIRS (92). In some cases, ARDS may be the first manifestation of SIRS; it can be described as an inflammatory form of lung injury ("stiff" lung), and is a life-threatening condition. ARDS was first described in the literature in 1967 by Aschbaugh et al. (93) and has been defined as acute onset respiratory failure, bilateral infiltrates on chest radiograph, hypoxemia – defined by a PaO_2/FiO_2 ratio ≤200 mmHg (ratio of arterial oxygen partial pressure to fractional inspired oxygen) – and no evidence of left atrial hypertension or pulmonary capillary pressure <18 mmHg (if measured) to rule out cardiogenic edema (94). The mortality rate varies between studies, but the overall pooled mortality rate from most of the published studies is reported to be 43% (95). Interestingly, ARDS in trauma patients has a lower mortality rate than that in patients with other etiologies, and the survival rate has increased compared to when it was first described (96). The mortality rate of patients with ARDS is higher when ARDS is associated with MOF, and concurrent development of the two may be one of the strongest predictors of mortality. Clinical presentation depends on whether the patient can communicate; in patients who can, mild dyspnea is a common complaint that worsens within 6 to 72 h of the triggering event and frequently requires mechanical ventilation and intensive care admission. During the clinical examination, dyspnea, tachypnea, cyanosis, and tachycardia are usually identified.

Regarding treatment, no drug has been proven as effective in preventing or managing ARDS. The general strategy is supportive care and focuses on 1) reducing shunt fraction, 2) increasing oxygen delivery, 3) decreasing oxygen consumption, and 4) avoiding further injury.

1.3.2. Role of cytokines in inflammation

The immune response that takes place in the body after trauma is mainly regulated by endogenous mediators typically known as cytokines (97). Cytokine release is a form of communication between cells to maintain homeostasis; they are released in response to local trauma by the systemic immune-inflammatory system. Cytokines have the ability to activate diverse cell types through the activation of intracellular pathways that regulate gene transcription. Numerous cytokines have been established to date, and the list continues to expand over time. Currently, cytokines are divided into pro-inflammatory and anti-inflammatory. Pro-inflammatory cytokines include tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 and initiate the stimulation of the further cytokine release. Anti-inflammatory cytokines include IL-4, IL-10, and IL-13 and control the pro-inflammatory cytokine response. They play an important local role in repairing the local tissues; however, their role during the healing of fractures remains unknown.

One of the most crucial cytokines is IL-6, which has also been recognized in numerous clinical trials as the primary marker indicating the extent of the inflammatory response to trauma, with serum IL-6 consistently aligning with injury severity (98-100). It is released approximately 1 hour after trauma and stays in the blood for a few days until its levels start to decline (101). The main possible reason why IL-6 is used to measure inflammation in clinical trials, as well as in clinical practice, is the long duration of detectability in the blood of patients and the availability of fast measurement systems (99). To date, IL-6 is verified as the most reliable prognostic marker of the pro-inflammatory cascade (100), with high sensitivity but low specificity (102).

The measurement of IL-6 levels has demonstrated utility in predicting patient mortality and identifying those at risk for the development of multiple organ dysfunction syndrome both in adult and pediatric populations (103). It has been suggested that measurement within 24 h of trauma is necessary to achieve predictive accuracy (104). Elevated IL-6 levels have been observed not only after trauma but also after surgery, and advanced age is associated with higher postoperative IL-6 levels (105). Extensive literature has reported on the elevation of IL-6 levels after total hip arthroplasty and total knee arthroplasty (106). Furthermore, an abrupt increase in IL-6 levels within the first few h after hip surgery suggests its involvement in the early stages of the postoperative inflammatory response, particularly in the context of treating hip fractures with various surgical

procedures (107). The invasiveness of selected surgical techniques, such as total hip arthroplasty and DHS implantation, has also been positively correlated with IL-6 levels (108,109).

C-reactive protein (CRP) is an important acute phase protein and inflammatory marker that is commonly measured in surgical facilities to predict postoperative complications and rule out infections (110-112). While CRP is mainly used for the early diagnosis and outcome prediction of sepsis, it can also be induced by non-infectious factors, such as mechanical trauma (113,114). After surgery, CRP levels can rise rapidly, with peak levels occurring approximately 48 to 72 h after surgery (115,116). Studies have shown that the extent of bone injury during surgery, rather than the surgical region, determines the postoperative CRP response after different types of hip arthroplasty (117). Additionally, it has been found that CRP levels following surgical treatment of hip fracture can quantify the degree of tissue damage and invasiveness of a surgical procedure, reflecting the perioperative stress experienced by the patient (118).

A cause of concern is that CRP has a low specificity, as high levels of CRP can be found also in patients without complications (112). This issue is important, as this can result in unnecessary treatments that can be harmful to patients. Therefore, clinicians must consider multiple factors when assessing the likelihood of postoperative complications, such as other comorbidities that might affect CRP levels, patients' history, and other laboratory findings in addition to CRP. Despite this limitation, the affordability, rapidity, and almost universal availability of CRP analysis make it one of the preferred markers to date (114). Therefore, CRP remains a reliable marker that allows for safe and early discharge (116).

Another important marker that is used along with CRP and is also an acute-phase reactant is the erythrocyte sedimentation rate (ESR). The ESR can be elevated by infection, tissue injury, trauma, or immunological reactions; however, it can also be raised under various conditions unrelated to inflammation, such as increased age, female sex, obesity, and renal disease (119-121). A rise in the ESR after surgery raises suspicion of infection. Mun et al (122) reported that the ESR can also increase after non-infected spinal surgery, reaching its peak on the first and tenth postoperative days following simple spinal surgery. The increase in the ESR along with CRP level may lead to suspicion of infection (123). Additionally, studies have identified the ESR and CRP as predictive markers for the risk of developing SIRS following surgery (124). Notably, the same study

determined that a cutoff value of 6.5 mm/h for the ESR optimally discriminated between patients who experienced SIRS and those who did not, with a negative predictive value of 80.0%. Similarly, an optimal cutoff value of 0.65 mg/dL for CRP demonstrated an NPV of 71.7%.

1.4. Coagulation disorders in trauma and surgery

Hemorrhage and tissue injury resulting from trauma can cause an imbalance between clotting, anti-coagulation, and fibrinolysis, leading to trauma-induced coagulopathy, which is closely linked to the outcome of trauma patients (125). D-dimer is a protein fragment that results from the destruction of cross-linked fibrin and in critically ill patients, elevated D-dimer levels indicate coagulation activation and correlate with proinflammatory cytokine cascade activation, signaling an imbalance between pro- and anti-inflammatory cytokines and increasing mortality risk (126). Additionally, a correlation between D-dimer levels and the number of fractures in trauma patients has been found (127). D-dimer is also an indicator of the severity of trauma in acute trauma patients, along with the diagnosis of deep vein thrombosis and pulmonary embolus. Liu et al. (128) found that D-dimer and fibrinogen levels increase in preoperative fracture patients, with significantly different D-dimer levels among different fracture locations. Furthermore, they found that D-dimer levels of femur fractures are higher than those of other fracture sites.

D-dimer has also been studied in the postoperative period,; nonetheless, the timing of the increase and decrease of its levels remains controversial. Dindo et al. (129) reported that D-dimer levels increase postoperatively in general surgery, reaching a peak on day 7, indicating an increased risk for the development of venous thromboembolism. Conversely, another study in patients following total joint arthroplasty found that D-dimer levels increase rapidly in the first postoperative day, but by postoperative day 2, they decrease to baseline levels (130). D-dimer values were also found to be correlated with the magnitude of surgery in patients with different types of fractures (83). There are inconsistent reports regarding the role of D-dimer in the second-hit phenomenon, and future investigations may potentially find the correct answer (131).

2. HYPOTHESIS

The systemic inflammatory response, based on our parameters, is higher in patients treated with DHS compared to those treated with PFN.

3. AIMS AND PURPOSE OF THE RESEARCH

3.1. General aims:

To measure the systemic inflammatory response in patients treated with DHS and PFN.

3.2. Specific aims:

The primary objective was to measure the level of IL-6 in patients treated with DHS and PFN.

The secondary objectives were to correlate the levels of CRP and D-dimer, ESR, length of operation, length of incision, blood loss, and complication and mortality rate within 1 month after the surgery.

4. MATERIALS AND METHODS

This study was designed as a prospective comparative study undertaken in the University Clinical Center of Kosovo between January 01, 2019 and June 01, 2020.

The patient's recruitment criteria were as follows.

- Inclusion criteria:
  - Adult patients, older than 50 years with trochanteric region fractures AO/OTA 31.A1–31.A2 diagnosed by examination of plain radiograph in anteroposterior projection
  - Time from fracture till surgery of up to 1 week
  - American Society of Anesthesiologists Classification score I-III
  - Willingness to participate

- Exclusion criteria:
  - Polytrauma patients
  - Open fractures
  - Existing local or systemic infection
  - Pre-existing coagulatory disorder
  - Existing malignancy
  - Corticosteroid use
  - Systemic inflammatory disease
  - Voluntary withdrawal of the patient

4.1. Randomization

The patients were selected randomly on a first-come, first-inclusion basis. The surgery was performed by four orthopedic surgeons with 5+ years of experience and who had completed the AOTRAUMA – Basic and Advanced Principles of Fracture Management courses. Two surgeons performed the DHS procedure, while the other two performed the PFN procedure. Patients who achieved closed reduction under an image intensifier were included in the study.

4.2. Perioperative planning

Antibiotic prophylaxis involved the administration of 2 g cefazolin intravenously at induction, followed by 2 g every 8 h for 48 h. Thromboembolic prophylaxis included the subcutaneous injection of 0.4 mL nadroparin calcium 12 h prior to and 12 h after surgery, with subsequent injections administered once daily in the morning. Intraoperative fluid management was achieved by administering 20 mL/kg of rehydration fluid (sodium 40 mmol/L, potassium 20 mmol/L, glucose 250 mmol/L) upon admission, and infusing isotonic saline (5 mL/kg/h) during the operation, supplemented with 6% hydroxyethyl starch 130/0.4 in the event of hypovolemia. Postoperative intravenous fluids were administered if oral intake was less than 1500 mL per day and in cases where hypovolemia occurred. The criteria for blood transfusion were a Hb level less than 70 g/L or less than 80 g/L when symptoms of anemia were present.

4.3. Surgical technique

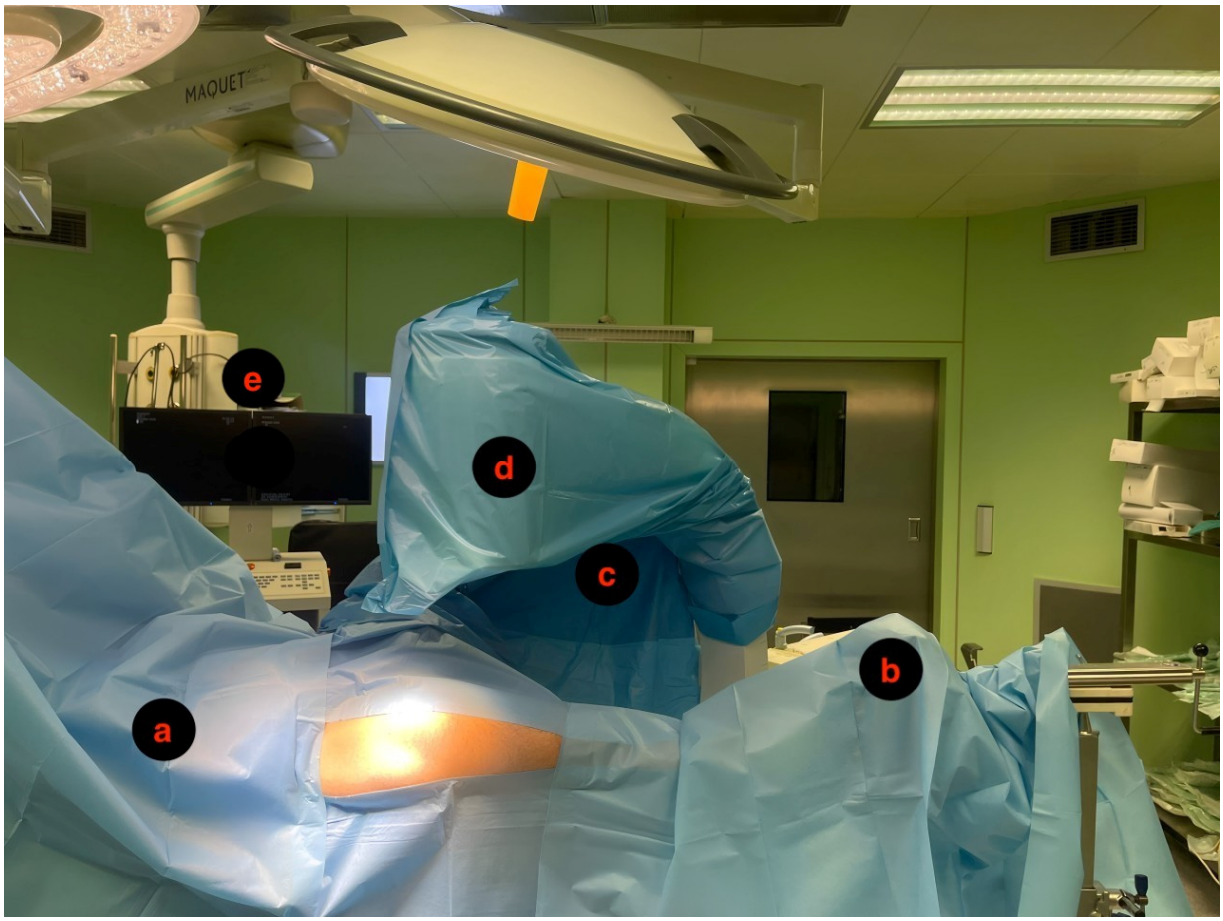

Figure 4. Patient positioning in traction table. Patient in supine position (a); injured leg in traction (b); contralateral leg padded in leg holder, elevated, externally rotated, and abducted (c); flouroscopy (d), display of flouroscopy (e)

DHS

Prior to the start of the procedure, the neck-shaft angle was determined based on the contralateral intact proximal femur, and the selection of the DHS implant with a specific neck-shaft angle was predicated upon this determined configuration.

The patient was positioned supine on a traction table, with the injured leg placed in a traction boot while the contralateral leg in a padded leg holder, and the arms placed over the chest (Figure 4). The fluoroscopy and display unit was positioned at the foot of the table where it was easily brought

in for imaging. Then the fracture was reduced under the guidance of an image intensifier prior to the start of surgery by pulling the traction in the axis of the leg and adjusting the internal rotation of the femoral shaft until the satisfactory length and rotation of the proximal femur were regained. With the aid of flouroscopy, the access references were marked with a pen. The vastus lateralis ridge was regarded as a landmark and adequate point for skin incision was located approximately on this landmark but also fluoroscopic guidance by identification of the site on the hip that corresponds to the position of the fractured neck of femur was used. Based on these landmarks, a lateral skin incision large enough to insert the implant and cortical screws was performed. The fascia lata and the vastus lateralis dissection of the femur were performed until the femoral diaphysis was located at its proximal edge. The aiming device was palced on the lateral cortex of the femur so that the screw trajectory ran through the head-neck axis and the lower half of the femoral neck on an anteroposterior view. Subsequently, a guide wire was inserted through the aiming device until it reached a point approximately 5 mm before reaching the joint. The length of the femoral neck screw was determined with the help of the measuring device. To confirm satisfactory alignment, the flouroscopy was utilized on anteroposterior and lateral views. The canulated drill was inserted through the guide wire and drilling was performed. The cephalic screw was placed. Then the plate was positioned, slid under the vastus lateralis, and, once inside, turned 180° until it locked on the cephalic screw and the plate was applied to the lateral cortex of the femur. Finally, the plate was fixed to the femoral shaft with cortical screws. Typically, a four-hole DHS implant was employed, resulting in the utilization of four cortical screws. Nevertheless, the specific quantity of screws employed was determined according to the discretion of the surgeon. Deep layer closure was performed using 3.0 vicryl sutures. The skin was then closed with 3–0 nylon. The next day after the surgery, an x-ray of the operated hip was done to check the fragments reduction and the position of the implant (Figure 5).

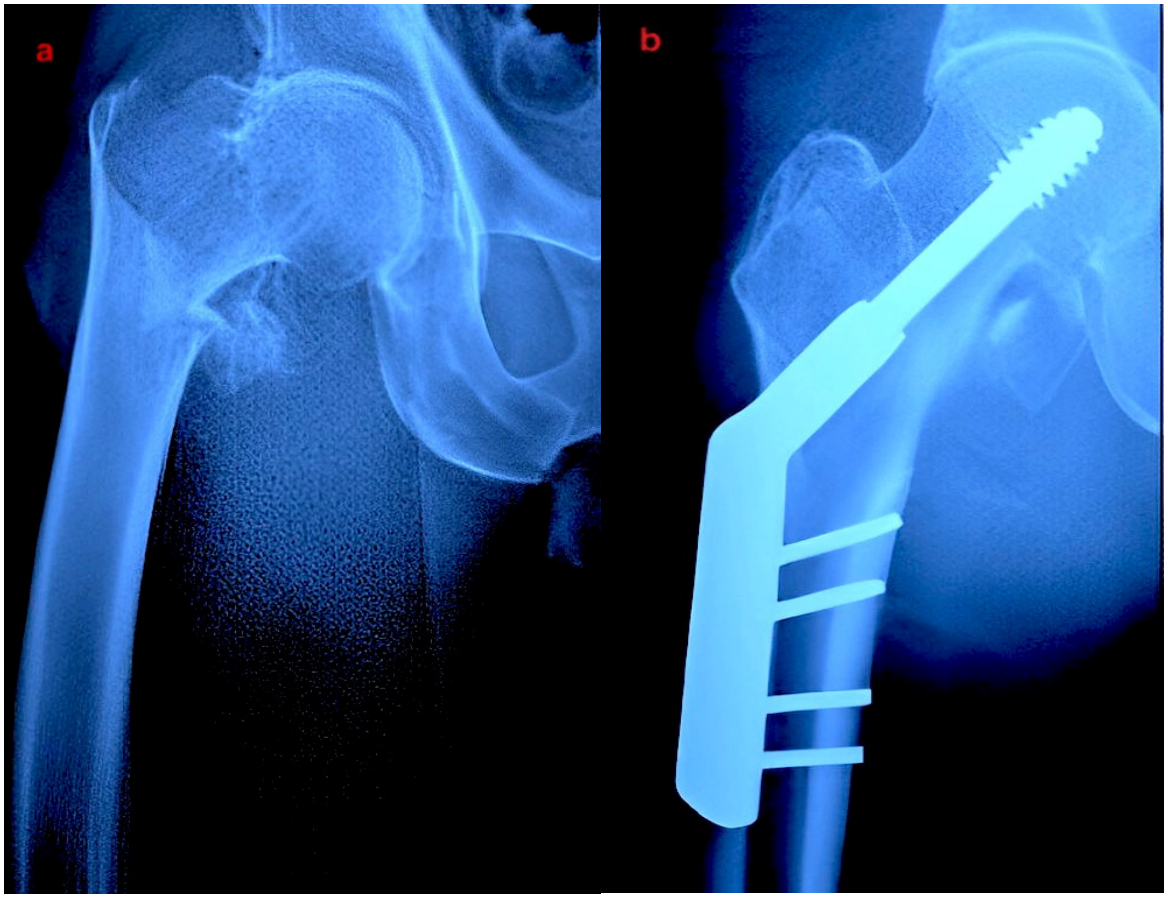

Figure 5. X-rays of a 81 years old male patient with a trochanteric region fracture 31A1.3 (Working Group for Osteosynthesis Problems (Ger. Arbeitsgemeinschaft für Osteosynthesefragen (AO)) /The Orthopaedic Trauma Association (OTA) classification (AO/OTA) treated with Dynamic Hip Screw. Pre-operative x-ray (a); post-operative x-ray (b)

PFN

Before initiating the procedure, the optimal neck-shaft angle was ascertained through the anteroposterior view of the unaffected hip. Subsequently, the nail possessing a specific neck-shaft angle was selected based on this determination.

The patient was positioned supine on a traction table, with the injured leg placed in a traction boot, the contralateral leg in a padded leg holder, and the arms placed over the chest (Figure 4). The image intensifier and display unit were positioned at the foot of the table where it was easily brought in for imaging. Then the fracture reduction was performed under image intensifier guidance by pulling the traction in the axis of the leg and adjusting the internal rotation of the

femoral shaft until the satisfactory length and rotation of the proximal femur were regained. The intramedullary diameter was determined by placing the radiographic ruler over the injured femur at the level of the nail tip and reading the diameter where the indicator filled the canal. The greater trochanter and the femoral axis were identified and marked on the skin with the help of flouroscopy. A skin incision approximately 5-8 cm proximal to the the tip of greater trochanter was made. A parallel incision in the fasciae of the gluteus medius and split the gluteus medius in line with the fibres was made. The tip of the greater trochanter was palpated and the entry point was determined. The insertion guide wire deviating about 5 degree from the axis of the medullary canal was made. The position of the guide wire was checked with flouroscopy. The protection sleeve was slided through the guide wire and soft tissues until it reached the bone. Through the protection sleeve, the drill bit was inserted to open the bone for the insertion of the nail. The femoral canal was reamed up to 1 mm more than the nail diameter, which allowed the nail to be inserted. The nail was mounted in the insertion handle and through the guide wire it was inserted into the medullary canal. The nail was inserted in such a depth that the screw would pas through the lower half of the femoral neck. Then another lateral incision was made and the drill-sleeve assembly through the aiming arm was inserted and it was advanced through the soft tissues to the lateral cortex of the femur. The guide wire was inserted to the femoral neck through the aiming arm until it reached around 5 mm before the joint. Anteroposterior and lateral view with flouroscopy was made to check the proper alignment to the axis of the femoral neck. The depth of the inserted guide wire was measured and the length of the screw was determined. The lateral cortex was then opened with a drill bit. The screw was inserted through the guide wire. The guide wire was then removed and inserted through the drill sleeve for the antirotational screw. After the measurment, the lateral cortex was opened and the antirotational screw was inserted with a length around 20 mm less the the first screw. Another stab incision was made for the distal locking screw and drill sleeve was passsed until it reached the cortex. Both cortices were drilled and the length was measured to determine the length of the screw. A cortical screw was inserted bicocrtically. Based on the surgeon preference, the end cap was inserted. The final position of the nail in anteroposterior and lateral view was checked with flouroscopy. Deep layer closure was performed using 3.0 vicryl sutures. The skin was then closed with 3–0 nylon. A day after the surgery, an x-ray of the operated hip was done to check the fragments reduction and the position of the implant (Figure 6).

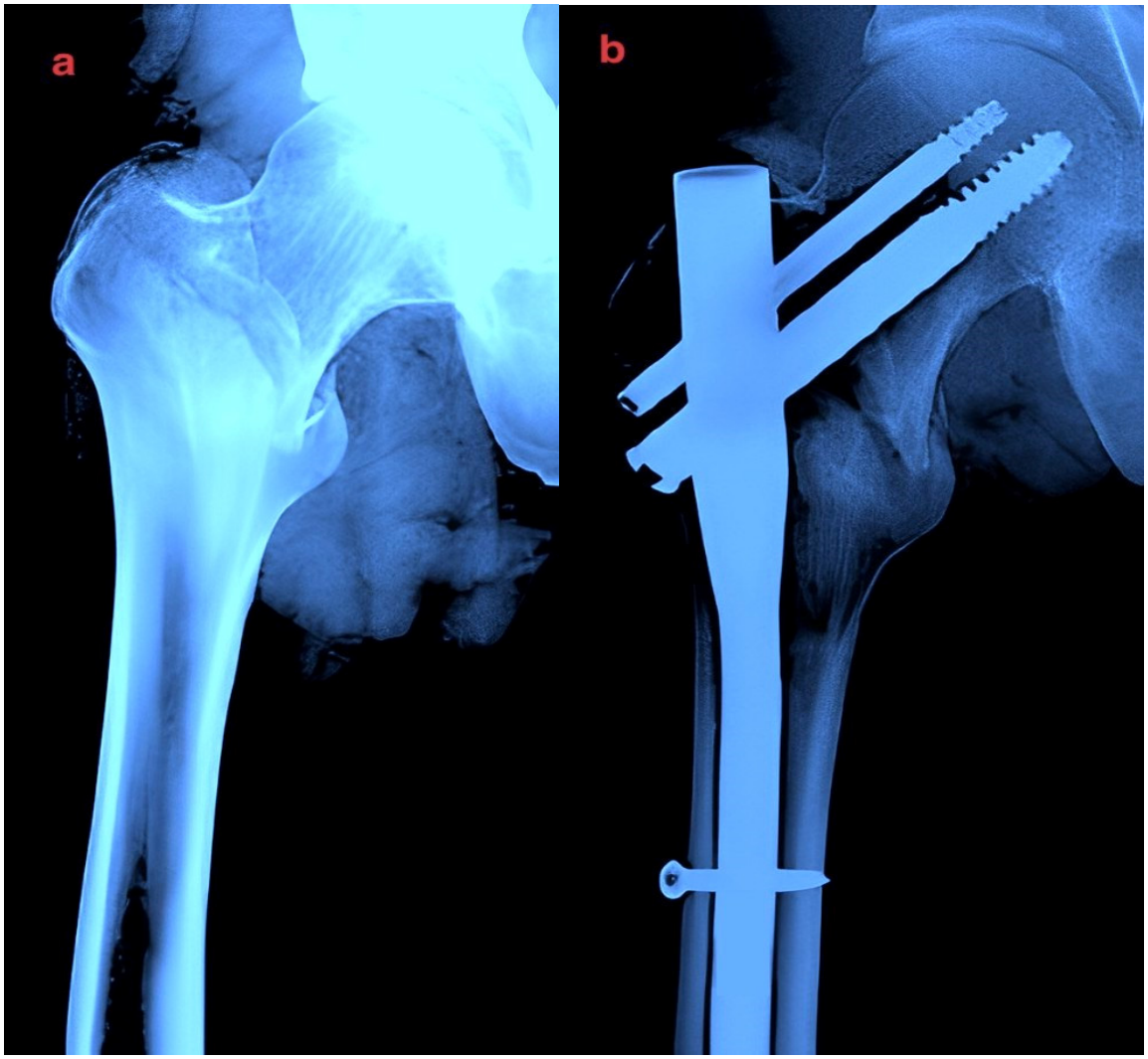

Figure 6. X-rays of a 74 years old female patient with a trochanteric region fracture 31A1.2 (Working Group for Osteosynthesis Problems (Ger. Arbeitsgemeinschaft für Osteosynthesefragen (AO)) /The Orthopaedic Trauma Association (OTA) classification (AO/OTA) treated with Proximal Femoral Nail. Pre-operative x-ray (a); post-operative x-ray (b)

4.4 Laboratory analysis

Venous blood (11 mL) was collected by the researcher from the patients prior to surgery and 24 h after the completion of surgery. Two SST tubes, each containing 2 mL of whole-blood (for IL-6

and CRP analysis), one EDTA tube containing 2 mL of whole-blood (for hemogram analysis), one Wintrobe tube containing 2 mL of whole-blood (for ESR analysis), and one blue-top tube 3.2% sodium citrate containing 2.7 mL of whole-blood (for D-dimer analysis) were used. CRP, ESR, and D-dimer analyses were performed within one hour, while the blood sample for IL-6 analysis was centrifuged and stored at a temperature of -20°C for later testing (within 3 months). The plasma concentration of standard systemic inflammation markers, including complete blood count, CRP, and ESR, was examined using standard methods at the Central Laboratory of the University Clinical Center of Kosovo. The tests were conducted using an Electrochemiluminescence Immunoassay Cobas e411 analyzer (Roche/Hitachi, Roche Diagnostics, Switzerland).

IL-6 was measured using a high sensitivity human IL-6 (hs-IL-6) enzyme-linked immunosorbent assay (ELISA) kit (ab46042; Abcam, Cambridge, MA, USA). This is a commercially available kit designed to quantitatively measure the levels of IL-6 in human serum, plasma, and cell culture supernatant samples. The technique used in this kit is a widely accepted and sensitive method for detecting and quantifying proteins in complex biological samples. The kit includes pre-coated microplate wells, standards, and detection antibodies specific to human IL-6. The assay is based on a sandwich immunoassay principle where the captured antibodies are used to bind the IL-6 protein present in the sample. After washing, a detection antibody labeled with a biotin molecule is added, which in turn binds to the captured IL-6 protein forming a sandwich complex. Streptavidin-horseradish peroxidase is then added, which binds to the biotinylated detection antibody, resulting in a colored product that is directly proportional to the amount of IL-6 present in the sample. The kit has a sensitivity of 0.039 pg/mL and a detection range of 0.078–10 pg/mL. It is intended for research use only and should not be used for diagnostic purposes.

The following protocol for detecting IL-6 in biological samples using ELISA was used:

Materials:

- IL-6 ELISA kit (includes microplate, reagents, standards, and detection antibodies)
- Sample diluent
- Plate reader

Procedure:

1. All reagents and samples were prepared at room temperature.
2. The microplate wells were prepared according to the manufacturer's instructions.
3. 100 µL of sample diluent was added to each well.
4. 100 µL of sample or standard was added to the appropriate wells.
5. The plate was covered and incubated at room temperature for 2 h.
6. The contents of each well were aspirated and washed with 300 µL of wash buffer.
7. The washing process was repeated 4 times.
8. 100 µL of detection antibody was added to each well.
9. The plate was covered and incubated at room temperature for 2 h.
10. The contents of each well were aspirated and washed with 300 µL of wash buffer.
11. The washing process was repeated 4 times.
12. 100 µL of substrate solution was added to each well.
13. The plate was incubated for 30 min at room temperature in the dark.
14. 100 µL of stop solution was added to each well.
15. The absorbance of each well was measured at 450 nm using a plate reader.

Data analysis:

1. The absorbance readings were used to generate a standard curve.
2. Determination of IL-6 concentration of the samples using the standard curve was performed.
3. The IL-6 concentration was normalized to the amount of protein in each sample, if necessary.

D-dimer was measured using Abcam's D-dimer in vitro SimpleStep ELISA® kit that is designed for the quantitative measurement of D-dimer protein in human serum, plasma, urine, and cell culture supernatants (ab196269; Abcam, Cambridge, MA, USA). This kit is designed to measure D-dimer levels in human blood samples using an ELISA technique. The kit includes all the necessary reagents and components to perform the assay.

A blood sample was added to the wells of the 96-well plate, in which the D-dimer present in the sample was bound to the coated antibody. After washing away unbound components, the detection

antibody was added, which bound to the D-dimer captured on the plate. The enzymatic reaction was initiated by added substrate, and the plate was incubated, resulting in the production of a signal that was proportional to the amount of D-dimer in the sample. The signal was then read using a microplate reader, and the D-dimer concentration was determined using the standard curve generated from the standards included in the kit.

The following protocol for detecting D-dimer in biological samples was used:
Materials:

- D-dimer ELISA kit (ab196269)
- Sample diluent
- D-dimer standard
- Wash buffer
- TMB substrate solution
- Stop solution
- Microplate reader capable of measuring absorbance at 450 nm

Procedure:

1. Reagents prepared: The D-dimer standard was diluted and the sample diluent according to the manufacturer's instructions.
2. 100 µL of the D-dimer standard or the sample diluent was added to each well of the microplate.
3. 50 µL of each sample was added to be tested in separate wells.
4. The microplate was covered with a plate sealer and incubated for 1 h at room temperature on a shaker set at 400 rpm.
5. The contents of each well were aspirated and washed in the microplate three times with the wash buffer.
6. 100 µL of TMB substrate solution to each well was added and incubated for 15 min at room temperature in the dark.
7. The reaction was stopped by adding 100 µL of stop solution to each well.
8. The absorbance of each well was measured at 450 nm using a microplate reader.

9. The D-dimer concentrations of the samples were calculated using the standard curve generated from the standards included in the kit.

4.5. Calculation of blood loss

Blood loss was measured using a simple method of calculating the difference in Hb and hematocrit (Hct) before and 24 h after the surgical procedure.

4.6. Statistical analysis

The data in our study are reported as mean ± standard deviation (SD) and 95% confidence interval (CI). Before conducting statistical analyses, descriptive statistics were used to check for normal distribution and homogeneity of variances. Unpaired t-tests were employed to analyze mean differences between groups for continuous outcomes at the patient level, and results are presented as mean ± SD. The protocols in our study were analyzed as an additional difference between the mean ± standard error of the mean. Results were considered significant if $P < 0.05$ GraphPad Prism (6.0 software, San Diego, CA, USA).

4.7. Power analysis

A power analysis was performed before the study, and a sample size of 26 patients per group was determined to be suitable to detect the effect of a given test at the $P < 0.05$ level of significance.

The literature review revealed two comparable studies. Marino et al. (132) investigated the influence of PFN on IL-6 levels in 20 patients 24 hours post-surgery, while Del Prete et al. (108) explored the impact of IL-6 in 36 patients 24 hours after surgery, specifically focusing on DHS. The former reported IL-6 levels at 16.64 ± 9.04 pg/mL, while the latter found levels to be 78.41 ± 67.04 pg/ml. Based on these values, the sample size was determined.

Analysis: A priori: Compute required sample size

Input: Tail(s) = Two

Effect size d = 0.8

α err prob = 0.05

Power (1-β err prob) = 0.8

Allocation ratio N2/N1 = 1

Output: Noncentrality parameter δ = 2.8844410

Critical t = 2.0085591

Df = 50

Sample size group 1 = 26

Sample size group 2 = 26

Total sample size = 52

4.8. Ethical consideration

The study was approved by the Institutional Ethical Committee of Univerity Clinical Center of Kosova (2018.380) and conducted under the Helsinki Declaration of 1975 for biomedical research involving human subjects as revised in 2000. Participation was voluntary, and all patients gave informed consent before inclusion. This study was conducted according to the CONSORT statement for randomized trials (http://www.consort-statement.org/) and registered at ClinicalTrials.gov **(NCT03849014)**.

5. RESULTS

5.1. Patient characteristics

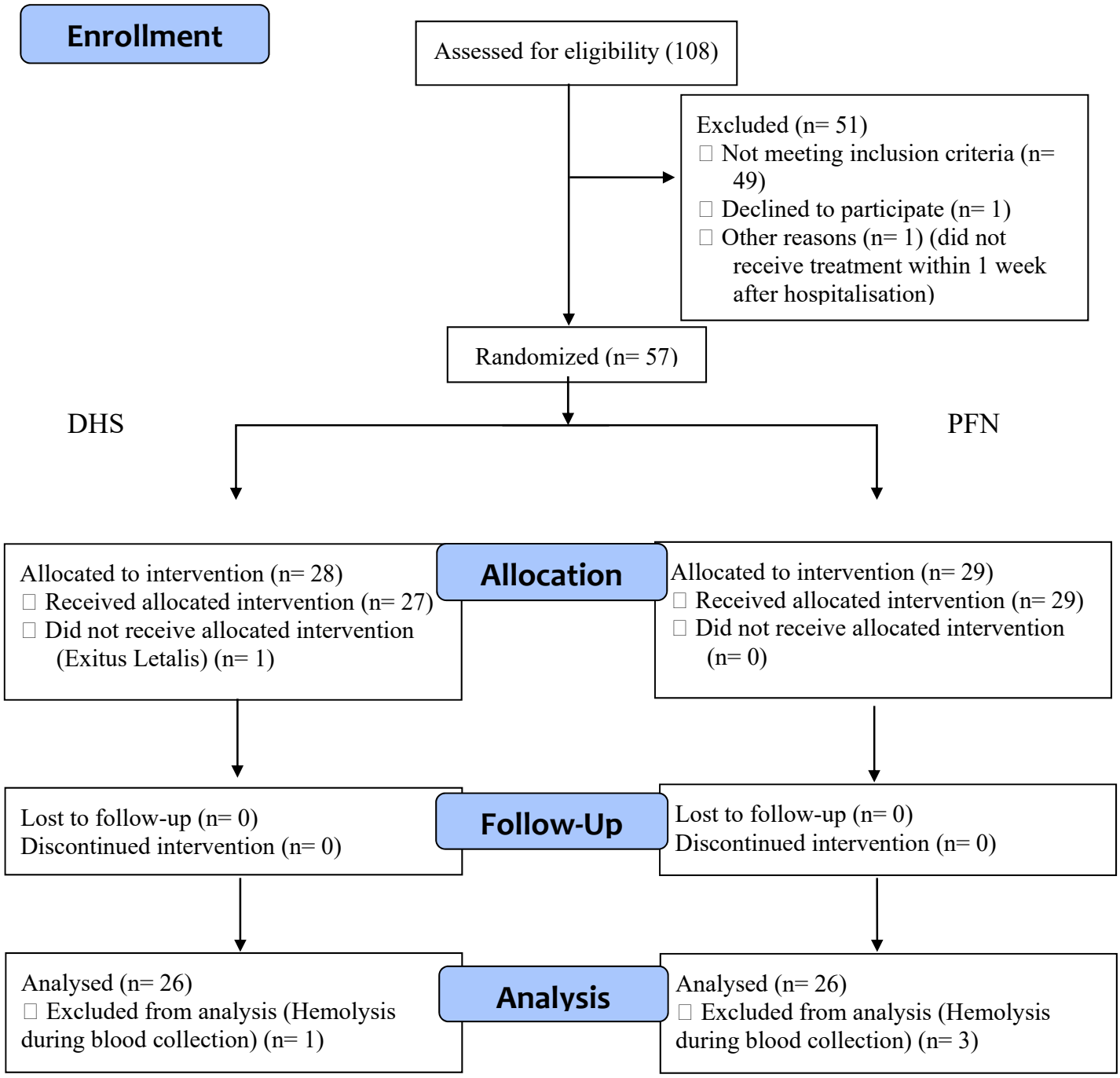

Figure 7. CONSORT flow trial diagram.

Out of 108 patients with trochanteric region fractures, 57 were eligible, randomized into two groups, and treated by two groups of surgeons. In the end, we analyzed 26 patients from each treatment group, DHS and PFN, as shown in the CONSORT flow trial diagram (Figure 7).

The patients were adjusted based on age, sex, BMI, fracture type, and side of the fracture. There was no significant difference between the groups. The sex distribution showed a female predominance, with an overall male-to-female ratio of 8:18 in the DHS group and 7:19 in the PFN group. Demographic parameters are shown in Table 1. Regarding the fracture type, there were no differences between the groups, although there were more patients with A131 fractures (Table 1).

Table 1. Mean value of demographics parameters

Variables	**DHS**	**PFN**	***P***
Number of patients	26	26	
Age (Mean±SD)	78.9±7.1	79.4±7.2	0.73
Sex (M:F), n	8:18	7:19	0.75
BMI (Mean±SD)	26.3±4.3	25.8±3.9	0.41
Fracture type (A1:A2)	14:12	17:9	0.37
Side (left/right)	12:14	13:13	0.92

The Mann–Whitney U test was used to find the inter-group significant differences. DHS = Dynamic hip screw; PFN = Proximal femoral nail anti-rotation; BMI = body mass index; M = male; F = female

Most of the patients sustained fractures due to falls at home, while the rest were injured in traffic accidents. No significant differences were found between the groups (Figure 8).

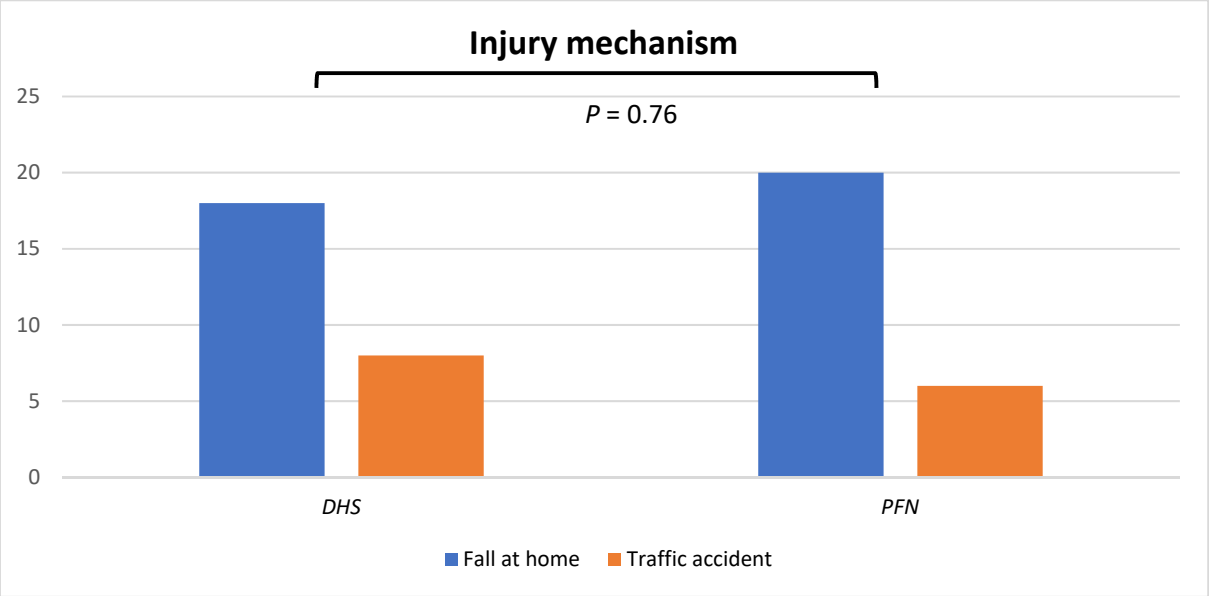

Figure 8. Mechanism of injury of patients in two groups. DHS = Dynamic hip screw; PFN = Proximal femoral nail anti-rotation;

We did not find any statistical differences among patients concerning the American Society of Anesthesiologists Classification score (P = 0.39) (Figure 9).

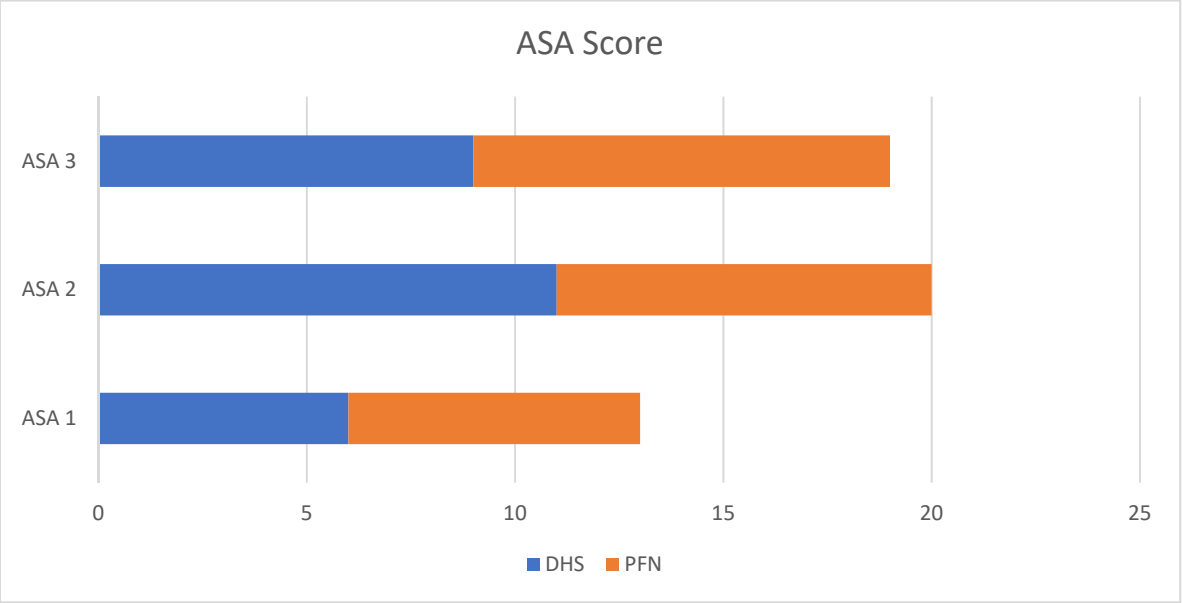

Figure 9. Patient distribution with different ASA scores. ASA Score = American Society of Anesthesiologists; DHS = Dynamic hip screw; PFN = Proximal femoral nail anti-rotation;

There were no differences between the groups in terms of time from hospitalization to surgery and postoperative drainage. However, the mean operative time in the PFN group was 38.3±15.9 min, which was significantly shorter than that in the DHS group (51.2±22.1 min) ($P < 0.03$). Additionally, the length of incision in the PFN group was 9.1±1.6 cm, significantly less than that in the DHS group (16.7±2.1 cm) ($P < 0.0001$). There was one case of superficial infection in the DHS group, one death in the PFN group due to pulmonary embolism, and one patient in each group had prolonged drainage (Table 2).

Table 2. Mean value of perioperative parameters and early complications

Variables	**DHS**	**PFN**	***P***
Time from hospitalization to surgery, h (Mean±SD)	28.3±21.2	27.1±23.2	0.63
Operative time, min (Mean±SD)	51.2±22.1	38.3±15.9	**0.03**
Length of incision, cm (Mean±SD)	16.7±2.1	9.1±1.6	**0.0001**
Postoperative drainage, mL	78.8±27.2	64.3±24.6	0.735
Deaths	0	1	
Superficial infections	1	0	
Prolonged drainage	1	1	
DVT	0	0	

The Mann–Whitney U test was used to find the inter-group significant differences. Significant p-values are indicated by bold characters. DHS = Dynamic hip screw; PFN = Proximal femoral nail anti-rotation; DVT = Deep vein thrombosis

Effects of PFN and DHS in the early post-inflammation response

IL-6

To study the impact and comparison of PFN and DHS in hs-IL-6, we measured plasma levels of hs-IL-6 in the 1 h pre-surgical and 24 h post-surgical period. Relative to before surgery, hs-IL-6 levels increased after surgery both for DHS (from 32.47± 27.12 to 141.45± 90.21 pg/mL, respectively; $P < 0.0001$) and PFN (from 36.65±25.93 to 93.12±68.23 pg/mL, respectively; $P < 0.001$) (Table 3).

Based on this understanding, our research revealed a pivotal insight: DHS surgery leads to a more pronounced increase in IL-6 levels than does PFN (108.98±76.32 vs. 56.47±57.68; $P = 0.011$) (Figure 10).

Table 3. Levels of hs-IL-6 pre- and post-operatively.

Variables	1 h pre-op	24 h post-op	*P*
DHS (hs-IL-6)	32.47±27.12 (20.13 to 45.48)	141.45±90.21 (101.09 to 185.5)	**0.0001**
PFN (hs-IL-6)	36.65±25.93 (24.66 to 48.97)	93.12±68.23 (60.74 to 125.6)	**0.0006**

DHS = Dynamic hip screw; PFN = Proximal femoral nail; IL-6 = Interleukin-6

In the table, we have shown the levels of IL-6 before and after the operation. The values are expressed as pg/mL and were analyzed using an unpaired t-test.

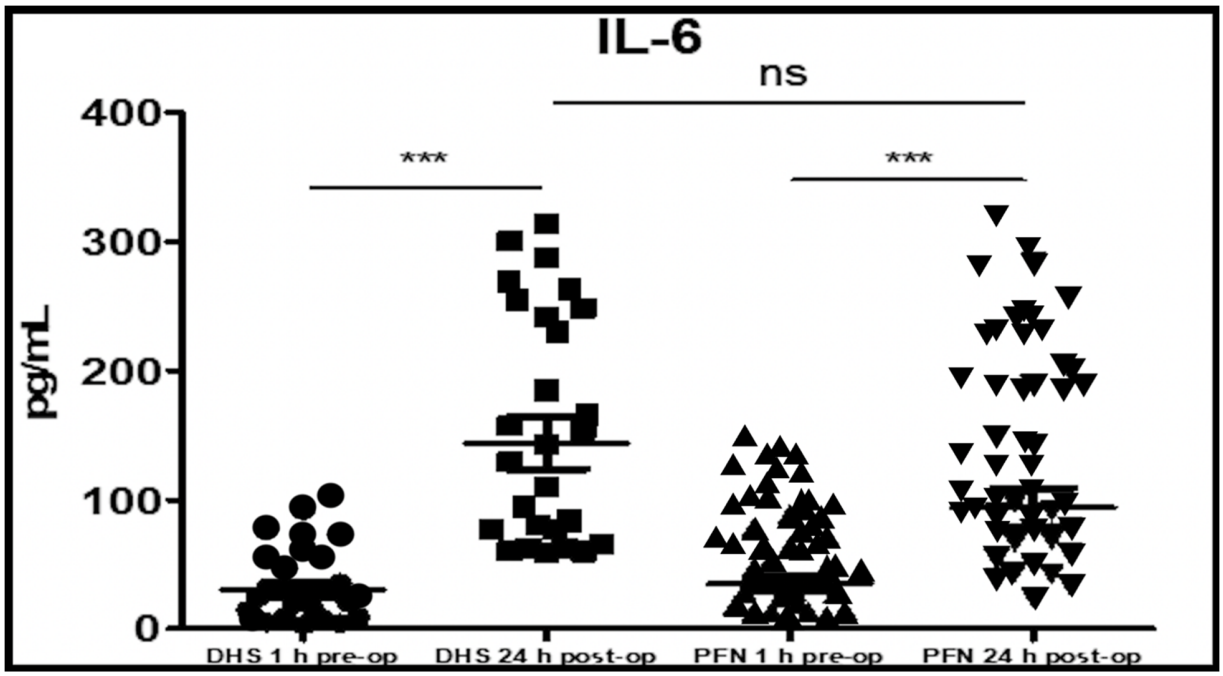

Figure 10. Effects of PFN and DHS on plasma levels of IL-6 (pg/ml) in patients treated for trochanteric region fracture a 1 h pre- and 24 h post-operatively. Values are expressed as mean±standard deviation (n=26).

CRP

We also measured CRP levels, which increased from before to after surgery both for DHS (1 h, 53.27±29.42 to 97.56±31.97 mg/L, respectively; $P < 0.0001$) and PFN (55.13±28.98 to 103.25±32.01 mg/L, respectively; $P < 0.0001$) (Table 4). However, non-significant changes were observed from baseline to 24 h post-surgery for CRP (43.78 ± 23.09 vs 43.89 ± 21.62, $P = 0.734$) after comparing both groups, PFN and DHS ($P > 0.05$) (Figure 11).

Table 4. CRP levels pre- and post-operatively

Variables	1 h pre-op	24 h post-op	*P*
DHS	53.27±29.42 (39.42 to 69.32)	97.56±31.97 (81.08 to 119.24)	**0.0001**
PFN	55.13±28.98 (41.27 to 70.38)	103.25±32.01 (84.27 to 119.3)	**0.0001**

DHS = Dynamic hip screw; PFN = Proximal femoral nail; CRP = C-reactive protein

The table displays CRP levels before and after the operation. The values are expressed as mg/L and were analyzed using an unpaired t-test.

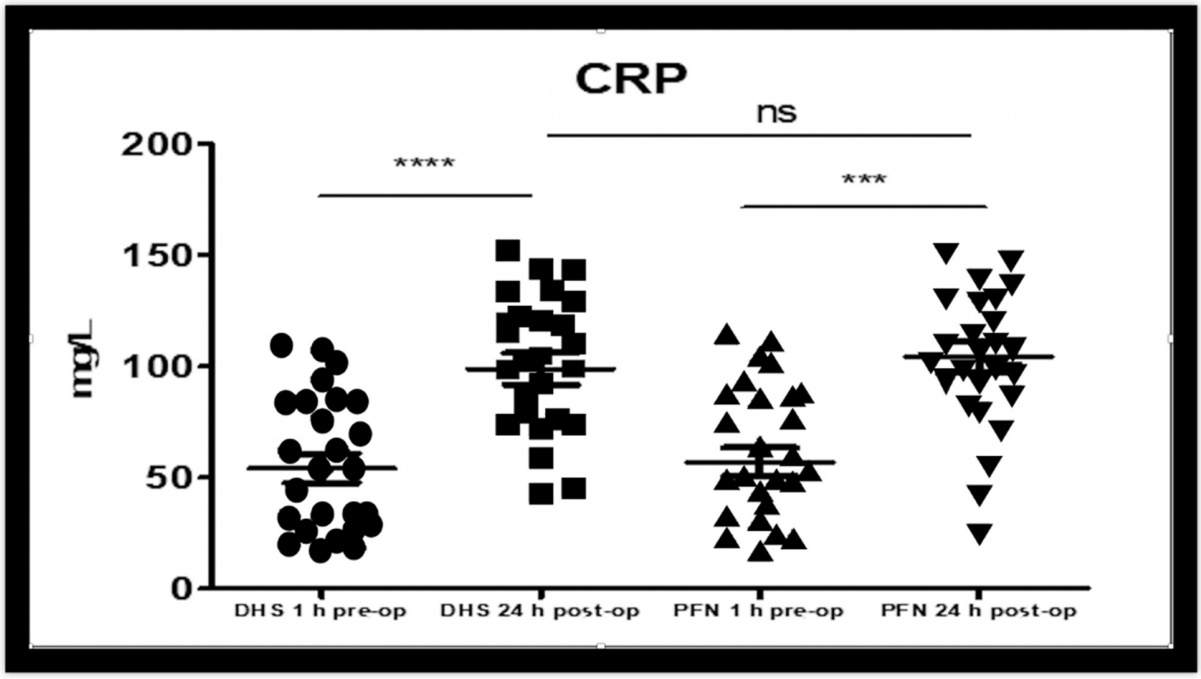

Figure 11. Effects of PFN and DHS on plasma levels of CRP (mg/L) in patients treated for trochanteric region fracture at 1 h pre- and 24 h post-operatively. Values are expressed as mean±SD (n=26).

ESR

Regarding the ESR, we found no significant increase from before to after surgery for DHS (30.26±16.12 to 35.34±20.12 mm/h, respectively; P = 0.3838) and PFN (31.79±19.01 and 36.14±20.94 mm/h, respectively; P = 0.3542) (Table 5). Also, there were non-significant changes between baseline and 24 h post-surgical measurements (4.87±9.74 vs. 6.25±8.37, P = 0.7462) after comparing PFN with DHS (P > 0.05) (Figure 12).

Table 5. ESR values pre- and post-operatively

Variables	**1 h pre-op**	**24 h post-op**	***P***
DHS	30.26±16.12 (22.72 to 37.97)	35.34±20.12 (26.21 to 46.65)	0.3838
PFN	31.79±19.01 (22.97 to 40.95)	36.14±20.94 (27.19 to 48.32)	0.3542

DHS = Dynamic hip screw; PFN = Proximal femoral nail; ESR = erythrocyte sedimentation rate. The table shows the ESRs before and after the operation. The values are expressed as mm/h and were analyzed using an unpaired t-test.

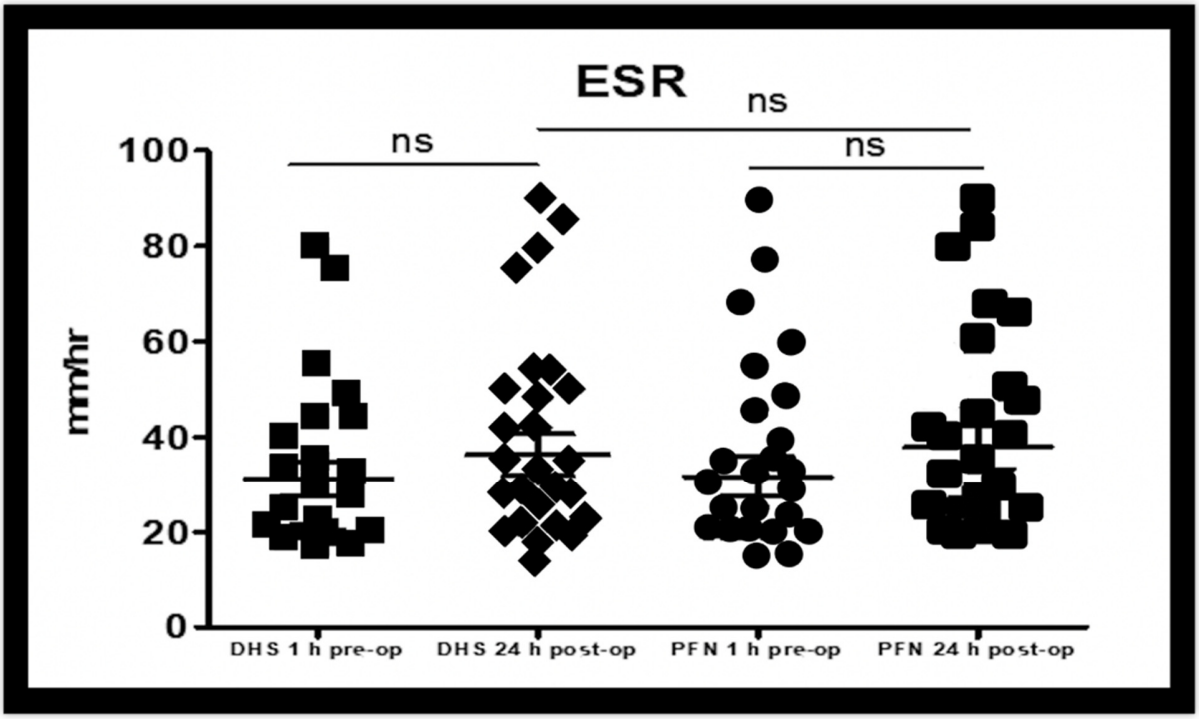

Figure 12. Effects of PFN and DHS on the ESR (mm/h) of patients treated for trochanteric region fracture at 1 h pre- and 24 h post-operatively. Values are expressed as mean±SD (n=26).

D-dimer

D-dimer values did not significantly increase from before to after surgery for DHS (2036.34±893.43 to 2146.32±967.21 ng/mL, respectively; P = 0.834) and PFN (1912.43±799.02 to 2231.55±1044.89 ng/mL, respectively; P = 0.755) (Table 6). Also, there were non-significant changes between baseline to 24 h post-surgery measurements (109.98±51.46 vs. 190.12±97.04, P = 0.394) after comparing PFN with DHS (P > 0.05).

Table 6. D-dimer levels pre- and post-operatively.

Variables	1 h pre-op	24 h post-op	*P*
DHS	2036.34±893.43 (367.43 to 9156.23)	2146.32±967.21 (274.22 to1164.45)	0.834
PFN	1912.43±799.02 (425.44 to 1024.56)	2102.55±1044.89 (103.22 to 1378.92)	0.755

DHS = Dynamic hip screw; PFN = Proximal femoral nail; ESR = erythrocyte sedimentation rate
The table shows the levels of D-dimer before and after the operation. The values are expressed as ng/mL and were analyzed using an unpaired t-test.

Blood loss measurement

We analyzed the data of Hb and Hct levels of the patients in both groups, PFN and DHS. We analyzed the levels in the pre- and post-operative period, and there were no significant changes between the groups in the preoperative period (P > 0.05). However, we found that patients treated with DHS had significantly lower postoperative Hb levels then PFN (-26.5±16.21 vs -9.76; P = 0.006). Moreover, the levels of Hct were also lower in DHS compared to PFN group (-13.71±9.76 vs -5.41± 5.47; P = 0.003 (Table 7).

Table 7. Pre- and post-operative changes in Hb levels

	DHS	**PFN**	***P***
Preoperative Hb level (g/L)	118.92 ± 1.63	119.13 ± 1.54	0.832
Preoperative Hct (%)	35.72 ± 4.77	34.21 ± 3.98	0.779
Postoperative Hb level (g/L)	92.36 ± 2.32	109.37 ± 1.76	**0.006**
Postoperative Hct (%)	22.01 ± 3.48	28.81 ± 3.32	**0.003**

DHS = Dynamic hip screw; PFN = Proximal femoral nail; Hb = hemoglobin; Htc = Hematocrit
The table shows the levels of Hb and Hct before and after the operation. Data were analyzed using the student's *t*-test.

6. DISCUSSION

This study investigated two widely employed surgical procedures, PFN and DHS, on postoperative changes in inflammation in patients with fractures in the trochanteric region AO/OTA 31.A1–31.A2. The study sought to compare the levels of specific inflammatory markers, namely IL-6, CRP, and the ESR, before and after the surgical interventions. Additionally, the research aimed to assess fibrinolytic changes and blood loss by monitoring changes in D-dimer, Hct, and Hb levels pre and post-surgery. To our best knowledge, this is the first study to compare both devices concerning IL-6 along with other inflammatory and soft tissue markers.

The key finding in this study was the significant difference between levels of IL-6 after treatment with DHS and PFN. This reflected the superiority of PFN against DHS in terms of systemic inflammatory response. Along with IL-6, we also found a significant differences on blood loss, which favours the PFN over DHS technique. By comparing the systemic inflammatory response after treatment with PFN and DHS, the study aimed to provide a better understanding of this topic and ultimately guide surgical decision-making and postoperative care. Our results suggest that the IL-6 levels can be an indication of the extent of postoperative inflammatory reaction. Therefore, interpretation of the preoperative and postoperative IL-6 levels should take into account the influence of trauma caused by surgery.

IL-6

IL-6 serves as a primary indicator of inflammatory alterations after trauma (100). Notably, surgical procedures have been observed to influence IL-6 concentrations, especially in patients who have undergone hip fracture treatments, as evidenced by prior studies (108,131). Based on this understanding, our research revealed a pivotal insight: DHS surgery leads to a more pronounced increase in IL-6 levels than does PFN. We also found that both the DHS and PFN surgical techniques resulted in significant increases in IL-6 levels from the preoperative to the postoperative period. This finding is consistent with previous studies that have demonstrated increased levels of IL-6 following surgery (107,108,133). Additionally, a previously published study, employing analogous parameters, albeit with fewer number of patients, observed consistent findings (134).

Sedlar et al. (107) conducted a study to investigate the relationship between hip fractures, surgery, and postoperative inflammatory responses. Among other markers, they evaluated the level of IL-6 and its dynamics in 125 elderly patients with extracapsular hip fractures undergoing OS, hemiarthroplasty, or total hip arthroplasty. They found that IL-6 levels peaked immediately after surgery with values of 151.1±101.2 pg/L. Patients with intracapsular fractures treated with hemiarthroplasty had higher IL-6 levels compared to patients extracapsular fractures treated with OS. They also found an association between age and IL-6 levels, suggesting that adjustments should be made when analyzing the prognostic implications of IL-6 concerning morbid events, progression to severe systemic inflammation, and multiorgan dysfunction. In accordance with the present investigation, we document a sustained pattern of IL-6 levels, accompanied by a notable elevation. However, numerical variations exist when comparing this study findings with the study conducted by Sedlar et al. The observed disparities in values could potentially be attributed to the utilization of different assay kits during the research process and different number of patients. Notably, our study employed high-sensitivity ELISA kits, in contrast to Sedlar et al.'s utilization of standard ELISA kits. Furthermore, previous studies have aimed to evaluate IL-6 levels specifically in patients treated with DHS and PFN. Del Prete et al. (108) conducted a study to quantify the invasiveness of surgical procedures in patients with pertrochanteric fractures by measuring different inflammatory markers, including IL-6, IL-10, IL-8, and TNF-α. Blood samples were collected from patients with trochanteric region fractures treated with either a conventional or minimally invasive technique using DHS. They found that only IL-6 levels showed a significant difference between the two techniques, with patients treated with the minimally invasive method having lower levels of IL-6 than those treated with the conventional method. However, their study measured IL-6 levels one hour before and one hour after surgery, which might not represent the peak of pro-inflammatory reponse (135). Therefore, the results of this study, which evaluated the levels of IL-6 before and 24 h after surgery, may provide a more accurate representation of the peak inflammatory response to the surgical intervention.

Marino et al. (132) conducted a prospective randomized study to evaluate the effects of PFN on IL-6 levels in patients with pertrochanteric fractures. The study included 20 patients who were treated with PFN, and the levels of TNF-α, IL-6, CRP, and creatine kinaze were analyzed 1 hour preoperatively and 24 h postoperatively. The results showed that IL-6 levels in the postoperative period were low and not statistically different from the preoperative period. The authors concluded

that PFN has a low biomechanical-inflammatory profile, representing an advantage over other techniques. In comparison to our study, the IL-6 values were lower both in the preoperative period (16.14 ± 14.96 pg/mL) and postoperative period (16.64 ± 9.04 pg/mL). This difference from our to the previous study might be explained by the use of a different ELISA kit and a different methodology of measurement. Nonetheless, their findings are consistent with ours in demonstrating the low inflammatory response associated with PFN.

Ebrahimpour et al. (133) conducted a study on the effect of percutaneous plating, open reduction and internal fixation, and intramedullary nailing on IL-6 levels in patients with tibia shaft fracture. In their study, which included 30 patients, they found that percutaneous plating had a significantly lesser effect on IL-6 release compared to two other employed techniques, which they attributed to the low invasiveness of percutaneous plating. Similarly, Pape et al. (83) conducted a study on the biochemical changes occurring after trauma and skeletal surgery of the lower extremity. They found that major surgery of the lower extremity, such as joint replacement or fracture fixation, can trigger a systemic inflammatory response and result in changes to the inflammatory cascades in patients.

CRP

Besides evaluating IL-6 levels, we analyzed another inflammatory biomarker, CRP, which is a well-known inflammatory biomarker that has been used widely in the field of orthopedics as an indicator for postoperative complications (136). CRP levels increase in response to various stimuli, such as inflammation, and the magnitude of the increase in CRP levels has been demonstrated to be proportional to the severity of surgical trauma (137,138). Previous studies have shown that CRP levels are associated with the region of the trauma and the type of surgery (118,139). Therefore, we included CRP in our study to gain a better understanding of the inflammatory response after PFN and DHS surgeries for pertrochanteric fractures. Measuring CRP levels can provide valuable information about the extent of tissue damage, the severity of the inflammatory response, and the potential for postoperative complications (110,112-114,118).

In our study, we observed a statistically significant increase in CRP levels after surgery both for DHS and PFN, which indicates that the surgical trauma caused an inflammatory response. This finding is consistent with previous studies that have reported higher CRP levels after more invasive

surgical procedures (140,141). However, after comparing both PFN and DHS techniques, the increase in CRP levels from baseline to 24 h post-surgery was not significant.

Beloosesky et al. (140) undertook a comprehensive prospective analysis involving 41 geriatric patients who had sustained hip fractures and subsequently underwent treatment with hemiarthroplasty and nailing. A primary focus of their investigation was the comparison of CRP levels, among other cytokines and clinical parameters, before and 48 h, 7 days, and 30 days after the surgical intervention. Their findings echoed the results of our study, highlighting a marked elevation in postoperative CRP levels. Moreover, despite the utilization of diverse surgical techniques in their cohort, no statistically significant disparities were observed in postoperative CRP concentrations across the different patient groups.

In another study conducted by Hong et al. (141), the CRP levels of 20 elderly patients were analyzed before and 1, 8, 16, 24, 36, 48, and 72 h after surgery. These individuals experienced a stable intertrochanteric fracture and were treated by a single surgeon using either PFN or DHS. Mirroring the findings of our investigation, Hong and his colleagues observed a marked rise in CRP levels post-surgery. Furthermore, akin to our results, their study also concluded that there was no statistically significant disparity in CRP levels between the two treatment groups.

Neumaier et al. (118) investigated the CRP response in patients with proximal femoral fractures who were treated with various surgical techniques. The study included 349 patients who underwent surgery with 1 of 5 techniques: 3–4 percutaneous cancellous screws, DHS, PFN, hemiarthroplasty, or total hip arthroplasty. The authors found that patients treated with percutaneous cancellous screws had significantly lower CRP levels compared to those treated with other techniques, indicating a lower degree of surgical invasiveness. In line with the findings of our study, Neumaier et al. did not observe a significant difference in CRP values between patients treated with DHS and PFN, although the CRP values in the PFN group were slightly higher.

ESR

In addition to IL-6 and CRP, we also included the ESR as a marker of inflammation (122,123, 142). The ESR measures the rate at which red blood cells settle to the bottom of a test tube over a certain period (119). The ESR level is reported to increase in response to various inflammatory conditions, including surgical procedures and major trauma (143). By measuring the the ESR before and after surgery, we aimed to assess the extent of inflammation in the body as a response

to surgical trauma. Nonetheless, measuring the ESR along with other inflammatory markers, such as IL-6 and CRP, can provide a more comprehensive understanding of the inflammatory response in the body after surgery (144).

In our study, we found no significant difference in the ESR before and after surgery in neither the DHS nor PFN group. Additionally, there was no significant difference in the baseline to 24-hour post-surgical ESR levels between PFN and DHS.

In a study conducted by Aalto et al. (145) involving 35 patients with hip osteoarthritis treated with total hip arthroplasty, the ESR increased after surgery, along with CRP; however, there were no significant changes in the ESR a day after surgery. In another study by Ellitsgaard et al. (142), 140 patients with hip fractures were treated with screws, hemiarthroplasty, or DHS. The researchers observed that changes in the ESR within the first 24 h post-surgery were not significant. However, there were significant changes in the ESR several days after the procedure, with rates peaking one-week post-surgery. Both studies observed that changes in CRP levels occurred more rapidly than those in the ESR (142,144).

D-Dimer

Another blood marker that can be used as a predictive factor for postoperative clinical complications is D-dimer. Postoperative D-dimer levels have been reported to be independently influenced by surgery, including the type and duration of surgery, and elevated D-dimer levels pre-operatively (129). Moreover, alterations in coagulation have been reported to be affected by surgical trauma after hip replacement (130). We studied D-dimer levels both in the preoperative and postoperative periods around two surgical procedures, DHS and PFN. Contrary to other studies, we were unable to demonstrate any increase in D-dimer levels after hip fractures or subsequent surgeries. D-dimers were not significantly increased before and after surgery for DHS and PFN. Also, there were no significant changes between baseline and 24 h post-surgery.

Blood loss

The assessment of blood loss during surgical procedures is an important component for evaluating surgical outcomes, as excessive blood loss can increase the risk of postoperative complications (145). Therefore, measuring and comparing the amount of blood loss before and after surgery is an essential aspect of surgical research. In the present study, blood loss was measured by

comparing the values of Hb and Hct before and 24 h after surgery. We observed that patients who received treatment with DHS experienced significantly higher blood loss compared to those treated with PFN. The conclusion was drawn based on significantly lower Hb levels in the DHS group, as well as lower Hct levels, compared to the PFN group.

Although the primary aim of this investigation was to quantify intraoperative blood loss through the assessment of suction volume combined with the weight of blood-soaked swabs, including total blood loss, practical challenges impeded accurate results. Consequently, the measurement of blood loss was executed by assessing Hb and Hct, a methodology consistently employed by other authors in similar studies (33, 34,141).

Several studies have been published on blood loss after DHS and PFN, employing different measurement methods, but not all have yielded the same results. For example, Giraud et al. (146) compared PFN and DHS in 60 patients with pertrochanteric fractures who were hospitalized in the emergency setting and reported lower blood loss in the DHS group. In contrast, Kumar et al. (27) compared intraoperative blood loss and operative time in 50 patients who underwent surgery for A1–A3 intertrochanteric femoral fractures treated with DHS or PFN and found lower intraoperative blood loss and shorter operative times in patients treated with PFN compared to DHS. In line with this study, we also found that the mean surgical time in the PFN group was significantly shorter than the time in the DHS group. Another prospective comparative study by Jonnes et al. (147) involved 30 patients with type II intertrochanteric fractures and concluded that PFN is superior over DHS in terms of lower blood loss, along with other clinical outcomes, such as reduced duration of surgery, early weight bearing and mobilization, reduced hospital stay, decreased risk of infection, and decreased complications. These results are comparable to ours in terms of blood loss.

Limitations of the study

Our study has several limitations. The principal constraint of the present study is the relatively small sample size employed. Our limited cohort restricts the generalizability of the study findings, potentially yielding results that may not be reflective of the broader population. Furthermore, the investigation was restricted to the measurement of a select few common pro-inflammatory mediators, thereby providing a somewhat constrained evaluation of the early post-inflammatory response. This selective approach to measuring inflammatory mediators omits a spectrum of other

potential inflammatory markers, such as IL-10, IL-8, TNF-α, and calprotectin; these have been shown to constitute a reliable panel for monitoring post-surgical inflammation (108,148). Consequently, we might have missed additional insights into the complex inflammatory processes unfolding in the immediate postoperative period (149). Moreover, our measurements might have failed to detect peak CRP levels, since previous studies have reported that CRP increases rapidly after surgery and peaks on the second or third day after surgery; thus, our specific methodology of measuring CRP levels 24 h postoperatively may not reflect the peak levels (118,144,150). Furthermore, the same limitation might be true for the ESR. The ESR was found to be elevated during the first week following surgery and remained elevated for a year post-surgery compared to the preoperative values (142,144). Therefore, it is important to consider the timing of ESR measurements in postoperative monitoring.

Some considerations have to be taken into account while interpreting our results regarding D-dimer. Firstly, we measured D-dimer levels with high-sensitivity kits that other studies reporting higher levels of D-dimer after trauma or surgery did not use (129,130,151). Secondly, it has been reported that the rising peak of D-dimer after surgery occurs on the 7th postoperative day, and we only measured its levels 24 h after surgery (129).

Another limitation is the accuracy of method we used to estimate blood loss, as we measured only postoperative Hb and Hct concentrations. The measurements can vary depending on the method used, with some studies relying on visual estimation and others using more precise measurements (148,152). Also, blood loss was not compared between AO 31.A1 and 31.A2 fracture type groups, which potentially would show different results when treated with DHS versus PFN, as Ronga et al. found (37).

Future research and potential applications of the study

For the study to proceed, additional research is important. The initial phase of the ensuing research involves the ongoing recruitment and processing of wider patient groups. This sustained effort in research will facilitate the validation of trends identified in our study, using a comprehensive cohort of more patients per group.

In the course of the initial study, sample collections were systematically carried out at specified time intervals post-injury of 24 h. Future research endeavors may require the inclusion of additional time points for measurement. Specifically, CRP should be measured for at least a week,

and the ESR should be monitored for two weeks. This extended monitoring period is crucial for capturing the peak levels both of CRP and the ESR, allowing for a better understanding of their changing trajectories post-surgery (118,142,144,150). Moreover, incorporating additional samples during the initial post-trauma period, such as IL-10, IL-8, and TNF-α, would give a more comprehensive evaluation of the inflammation triggered by surgery (137).

Future research on measuring intraoperative blood should focus on developing and validating innovative technologies and methodologies that can offer real-time, accurate quantification of blood loss. Incorporating artificial intelligence in the measurement of hidden blood loss, perioperative blood management strategies, and machine learning algorithms may facilitate the automatic detection and measurement of lost blood volume, thereby reducing reliance on visual estimates, which are often inaccurate (37,152,153). Additionally, research should explore the integration of these novel tools into existing surgical workflows without disrupting the efficiency and effectiveness of the surgical team.

7. CONCLUSIONS

Based on the results of our study, we were able to draw the following conclusions:

- Both DHS and PFN increased the early postoperative inflammatory response
- PFN induced a lower early postoperative inflammatory response than did DHS
- Blood loss is lower in patients treated with PFN compared to those treated with DHS
- ESR and D-dimmer were not elevated within 24 h after surgery with DHS or PFN

8. ABSTRACT

Comparison of the systemic inflammatory response in patients with trochanteric region fracture fixation with Dynamic Hip Screw versus Proximal Femoral Nail

Objective: This study aimed to investigate the differences in the early postoperative inflammatory response after treatment of trochanteric region fractures using a dynamic hip screw (DHS) compared with proximal femoral nail (PFN).

Methods: In this prospective comparative study, 52 patients with Working Group for Osteosynthesis Problems (Ger. Arbeitsgemeinschaft für Osteosynthesefragen (AO))/The Orthopaedic Trauma Association (OTA) classification (AO/OTA) 31. A1–31.A2 pertrochanteric fractures were enrolled and allocated to one of two groups based on the treatment type: DHS group (n = 26, mean age = 78.9±7.1 years) and PFN group (n = 26, mean age = 79.4±7.2 years). Operation time was recorded in both groups. In each patient, circulating levels of interleukin-6 (IL-6), C-reactive protein (CRP), and the erythrocyte sedimentation rate (ESR) were measured from blood samples collected 1 hour preoperatively and 24 hours postoperatively.

Results: The operation time was slightly shorter in the PFN group than in the DHS group (38.3±15.9 and 51.2±22.1 min, respectively; P = 0.03). DHS and PFN both increased IL-6 (141.45±90.21 and 93.12±68.23 pg/mL, respectively), CRP (97.56±31.97 and 103.25±32.01 mg/L, respectively) levels, and the ESR (35.34±20.12 and 36.14±20.94 mm/h, respectively) 24 hours postoperatively. However, PFN compared to DHS resulted in a lesser increase from baseline to 24 hours postoperatively only in IL-6 (57.43±60.13 vs. 122.41±77.54 pg/mL, respectively; P = 0.011).

Conclusion: The results of this study have shown that PFN induced a lower early postoperative inflammatory response, based on the assessment of IL-6, compared to DHS after surgical treatment of patients with pertrochanteric fractures.

Keywords: Dynamic hip screw, Inflammation, Pertrochanteric fractures, Proximal femoral nail

9. SAŽETAK

Usporedba sustavnoga upalnoga odgovora u bolesnika u kojih je prijelom u području trohantera saniran Dynamic Hip Screw ostecsintezom i onih liječenih Proximal Femoral Nail metodom

Uvod: Cilj ovog istraživanja bio je istražiti razlike u indukciji ranog postoperativnog upalnog odgovora nakon liječenja pertrohanternih prijeloma dinamičkim vijkom kuka (DHS) ili proksimalnim femoralnim čavlom (PFN).

Metode: 52 pacijenta s pertrohanternim prijelomima klasificiranim prema klasifikaciji radne skupine za osteosintezu (njem. Arbeitsgemeinschaft für Osteosynthesefragen (AO))/The Orthopaedic Trauma Association (OTA) classification (AO/OTA) 31.A1–31.A2) uključeno je u jednu od dvije skupine na temelju vrste liječenja: skupina DHS, i skupina PFN. Vrijeme operacije bilježeno je u obje skupine. Kod svakog pacijenta, cirkulirajuće razine interleukina-6 (hs-IL-6), C-reaktivnog proteina (CRP), brzine sedimentacije eritrocita (ESR) mjerene su iz uzoraka krvi prikupljenih 1 sat prije operacije i 24 sata poslije operacije.

Rezultati: Vrijeme operacije bilo je nešto kraće u skupini PFN nego u skupini DHS (38,3±15,9 odnosno 51,2±22,1 min; P = 0,03). DHS i PFN povećali su hs-IL-6 (141,45±90,21 odnosno 93,12±68,23 pg/mL), CRP (97,56±31,97 odnosno 103,25±32,01 mg/L) i ESR (35,34±20,12 odnosno 36,14±20,94 mm/h) 24 sata postoperativno.

Zaključak: PFN inducira niži rani postoperativni upalni odgovor na temelju procjene hs-IL-6, u usporedbi s DHS u bolesnika s pertrohanternim prijelomima nakon liječenja.

REFERENCES

1. Brauer CA, Coca-Perraillon M, Cutler DM, Rosen AB. Incidence and mortality of hip fractures in the United States. JAMA. 2009;302(14):1573–9.
2. Panula J, Pihlajamäki H, Mattila VM, Jaatinen P, Vahlberg T, Aarnio P, et al. Mortality and cause of death in hip fracture patients aged 65 or older - A population-based study. BMC Musculoskelet Disord. 2011;12:105.
3. Daraphongsataporn N, Saloa S, Sriruanthong K, Philawuth N, Waiwattana K, Chonyuen P, et al. One-year mortality rate after fragility hip fractures and associated risk in Nan, Thailand. Osteoporos Sarcopenia. Osteoporos Sarcopenia. 2020;6(2):65–70.
4. Alpantaki K, Papadaki C, Raptis K, Dretakis K, Samonis G, Koutserimpas C. Gender and age differences in hip fracture types among elderly: a retrospective cohort study. Maedica (Buchar). 2020;15(2):185–90.
5. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. Osteoporos Int. 2006;17(12):1726–33.
6. Boonen S, Dequeker J, Pelemans W. Risk factors for falls as a cause of hip fracture in the elderly. Acta Clin Belg. 1993;48(3):190–4.
7. Grisso JA, Kelsey JL, Strom BL, O'Brien LA, Maislin G, Lapann K, et al. Risk factors for hip fracture in black women. Obstet Gynecol Surv. 1994;49(11):776–9.
8. Verettas DAJ, Galanis B, Kazakos K, Hatziyiannakis A, Kotsios E. Fractures of the proximal part of the femur in patients under 50 years of age. Injury. 2002;33(1):41–5.
9. Reid IR, Bolland MJ. Calcium and/or vitamin D supplementation for the prevention of fragility fractures: Who needs it? Nutrients. 2020;12(4):1–9.
10. Papalia GF, Papalia R, Diaz Balzani LA, Torre G, Zampogna B, Vasta S, et al. The Effects of Physical Exercise on Balance and Prevention of Falls in Older People: A Systematic Review and Meta-Analysis. J Clin Med. 2020;9(8):2595.
11. Boyd HB, Griffin LL. Classification and treatment of trochanteric fractures. Arch Surg. 1949;58(6):853–66.
12. EVANS EM. The treatment of trochanteric fractures of the femur. J Bone Joint Surg Br. 1949;31(2):190–203.
13. Jensen JS, Michaelsen M. Trochanteric femoral fractures treated with McLaughlin

osteosynthesis. Acta Orthop. 1975;46(5):795–803.
14. Meinberg E, Agel J, Roberts C, Karam M, Kellam J. Fracture and Dislocation Classification Compendium-2018. J Orthop Trauma. 2018;32 (Suppl 1):S1–S170.
15. Feldman F, Staron R, Zwass A, Rubin S, Haramati N. MR imaging: its role in detecting occult fractures. Skeletal Radiol. 1994;23(6):439–44.
16. Fairclough J, Colhoun E, Johnston D, Williams LA. Bone scanning for suspected hip fractures. J Bone Joint Surg Br. 1987;69(2):251–3.
17. Heikal S, Riou P, Jones L. The use of computed tomography in identifying radiologically occult hip fractures in the elderly. Ann R Coll Surg Engl. 2014;96(3):234–7.
18. Foex BA, Russell A. BET 2: CT versus MRI for occult hip fractures. Emerg Med J. 2018;35(10):645–7.
19. Seong YJ, Shin WC, Moon NH, Suh KT. Timing of Hip-fracture Surgery in Elderly Patients: Literature Review and Recommendations. Hip Pelvis. 2020;32(1):11–6.
20. Jain R, Basinski A, Kreder HJ. Nonoperative treatment of hip fractures. Int Orthop. 2003;27(1):11–7.
21. McGuire KJ, Bernstein J, Polsky D, Silber JH. The 2004 Marshall Urist Award: Delays until surgery after hip fracture increases mortality. Clin Orthop Relat Res. 2004;(428):294–301.
22. Kawaji H, Uematsu T, Oba R, Takai S. Conservative treatment for fracture of the proximal femur with complications. J Nippon Med Sch. 2016;83(1):2–5.
23. Grose AW, Gardner MJ, Sussmann PS, Helfet DL, Lorich DG. The surgical anatomy of the blood supply to the femoral head: Description of the anastomosis between the medial femoral circumflex and inferior gluteal arteries at the hip. J Bone Joint Surg Br. 2008;90(10):1298–303.
24. Biber R, Berger J, Bail HJ. The art of trochanteric fracture reduction. Injury. 2016;47 (Suppl 7):S3–S6.
25. Kaufer H. Mechanics of the Treatment of Hip Injuries. Clin Orthop Relat Res. 1980;(146):53–61.
26. Bekos A, Sioutis S, Kostroglou A, Saranteas T, Mavrogenis AF. The history of intramedullary nailing. Int Orthop. 2021;45(5):1355-61.
27. Kumar R, Singh RN, Singh BN. Comparative prospective study of proximal femoral nail

and dynamic hip screw in treatment of intertrochanteric fracture femur. J Clin Orthop Trauma. 2012;3(1):28–36.

28. Bartoníček J, Rammelt S. The history of internal fixation of proximal femur fractures Ernst Pohl-the genius behind. Int Orthop. 2014;38(11):2421-6.
29. Haidukewych GJ, Israel TA, Berry DJ. Reverse obliquity fractures of the intertrochanteric region of the femur. J Bone Joint Surg Am. 2001;83(5):643–50.
30. Haidukewych GJ, Berry DJ. Salvage of Failed Internal Fixation of Intertrochanteric Hip Fractures. Clin Orthop Relat Res. 2003;(412):184–8.
31. Moroni A, Faldini C, Pegreffi F, Hoang-Kim A, Vannini F, Giannini S. Dynamic hip screw compared with external fixation for treatment of osteoporotic pertrochanteric fractures. A prospective, randomized study. J Bone Joint Surg Am. 2005;87(4):753–9.
32. Petsatodis G, Maliogas G, Karikis J, Christodoulou AG, Venetsanakis G, Sachinis N, et al. External Fixation for Stable and Unstable Intertrochanteric Fractures in Patients Older Than 75 Years of Age: A Prospective Comparative Study. J Orthop Trauma. 2011;25(4):218–3.
33. Wang J, Wei J, Wang M. The risk factors of perioperative hemoglobin and hematocrit drop after intramedullary nailing treatment for intertrochanteric fracture patients. J Orthop Sci. 2015;20(1):163–7.
34. Kumar D, Mbako AN, Riddick A, Patil S, Williams P. On admission haemoglobin in patients with hip fracture. Injury. 2011;42(2):167–70.
35. Hu F, Jiang C, Shen J, Tang P, Wang Y. Preoperative predictors for mortality following hip fracture surgery: A systematic review and meta-analysis. Injury. 2012;43(6):676–85.
36. Lin PH, Chien JT, Hung JP, Hong CK, Tsai TY, Yang CC. Unstable intertrochanteric fractures are associated with a greater hemoglobin drop during the perioperative period: a retrospective case control study. BMC Musculoskelet Disord. 2020;21(1):244.
37. Jonnes C, Sm S, Najimudeen S. Type II Intertrochanteric Fractures: Proximal Femoral. Arch Bone Jt Surg. 2016;23:23–8.
38. Shen L, Zhang Y, Shen Y, Cui Z. Antirotation proximal femoral nail versus dynamic hip screw for intertrochanteric fractures: A meta-analysis of randomized controlled studies. Orthop Traumatol Surg Res. 2013;99(4):377–83.
39. Ronga M, Bonzini D, Valoroso M, La G, Tamini J, Cherubino M, et al. Blood loss in trochanteric fractures: multivariate analysis comparing dynamic hip screw and Gamma nail.

Inj Int J Care Inj. 2020;48(2017):S44–7.

40. Jaramillo S, Montane-muntane M, Capitan D, Aguilar F, Vilaseca A, Blasi A, et al. Agreement of surgical blood loss estimation methods. Transfusion. 2018;59(2):508–15.
41. Lawrence T. Goodnough AKP. Estimating Blood Loss. Anesth Analg. 2017;125(1):13–4.
42. Flordal PA. Measurement of blood loss in clinical studies. Eur J Anaesthesiol. 1997;14(Suppl 14):S35–7.
43. Albinarrate A, Barrachina B. Determination of Perioperative Blood Loss: Anesth Analg. 2017;125(1):280–6.
44. Jaramillo S, Montane-muntane M, Gambus PL, Capitan D. Perioperative blood loss: estimation of blood volume loss or haemoglobin mass loss? Blood Transfus. 2020;18(1):20–9.
45. Chirodian N, Arch B, Parker MJ. Sliding hip screw fixation of trochanteric hip fractures: outcome of 1024 procedures. Injury. 2005;36(6):793–800.
46. Parker MJ, Khan RJ, Crawford J, Pryor GA. Hemiarthroplasty versus internal fixation for displaced intracapsular hip fractures in the elderly. A randomised trial of 455 patients. J Bone Joint Surg Br. 2002;84(8):1150–5.
47. White BL, Fisher WD, Laurin CA. Rate of mortality for elderly patients after fracture of the hip in the 1980's. J Bone Joint Surg Am. 1987;69(9):1335–40.
48. Mattisson L, Bojan A, Enocson A. Epidemiology, treatment and mortality of trochanteric and subtrochanteric hip fractures: data from the Swedish fracture register. BMC Musculoskelet Disord. 2018;19(1):369.
49. Zhao K, Zhang J, Li J, Meng H, Wang Zh, Zhu Y, et al. Incidence and risk factors of surgical site infection after intertrochanteric fracture surgery: A prospective cohort study. Int Wound J. 2020;17(6):1871–80.
50. Edwards C, Counsell A, Boulton C, Moran CG. Early infection after hip fracture surgery: risk factors, costs and outcome. J Bone Joint Surg Br. 2008;90(6):770–7.
51. Powers PJ, Gent M, Jay RM, Julian DH, Turpie AG, Levine M, et al. A randomized trial of less intense postoperative warfarin or aspirin therapy in the prevention of venous thromboembolism after surgery for fractured hip. Arch Intern Med. 1989;149(4):771–4.
52. Rosencher N, Vielpeau C, Emmerich J, Fagnani F, Samama CM; ESCORTE group. Venous thromboembolism and mortality after hip fracture surgery: the ESCORTE study. J Thromb

Haemost. 2005;3(9):2006–14.

53. Marsland D, Mears SC, Kates SL. Venous thromboembolic prophylaxis for hip fractures. Osteoporos Int. 2010;21(Suppl 4):S593–604.

54. Protty MB, Aithal S, Hickey B, Pettit R, Johansen A. Mechanical prophylaxis after hip fracture: what is the risk of deep vein thrombosis? A retrospective observational study. BMJ Open. 2015;5(2):e006956.

55. Avakian Z, Shiraev T, Lam L, Hope N. Dynamic hip screws versus proximal femoral nails for intertrochanteric fractures. ANZ J Surg. 2012;82(1–2):56–9.

56. Hunter GA. The results of operative treatment of trochanteric fractures of the femur. Injury. 1975;6(3):202–5.

57. Davis TR, Sher JL, Horsman A, Simpson M, Porter BB, Checketts RG. Intertrochanteric femoral fractures. Mechanical failure after internal fixation. J Bone Joint Surg Br. 1990;72(1):26–31.

58. Luthringer TA, Elbuluk AM, Behery OA, Cizmic Z, Deshmukh AJ. Salvage of failed internal fi xation of intertrochanteric hip fractures: clinical and functional outcomes of total hip arthroplasty versus hemiarthroplasty. Arthroplast Today. 2018;4(3):383–91.

59. Petrie J, Sassoon A, Haidukewych GJ. When femoral fracture fixation fails: salvage options. Bone Joint J. 2013;95-B(11 Suppl A):7-10.

60. Liu P, Jin D, Zhang C, Gao Y. Revision surgery due to failed internal fixation of intertrochanteric femoral fracture: current state-of-the-art. BMC Musculoskelet Disord. 2020;21(1):573.

61. Said GZ, Farouk O, El-Sayed A, Said HG. Salvage of failed dynamic hip screw fixation of intertrochanteric fractures. Injury. 2006;37(2):194–202.

62. MacKenzie EJ. Epidemiology of injuries: current trends and future challenges. Epidemiol Rev. 2000;22(1):112–9.

63. Acosta JA, Yang JC, Winchell RJ, Simons RK, Fortlage DA, P Hollingsworth-Fridlund, et al. Lethal injuries and time to death in a level I trauma center. J Am Coll Surg. 1998;186(5):528–33.

64. Trunkey DD. Trauma. Accidental and intentional injuries account for more years of life lost in the U.S. than cancer and heart disease. Among the prescribed remedies are improved preventive efforts, speedier surgery and further research. Sci Am. 1983;249(2):28–35.

65. Rogers FB, Shackford SR, Hoyt DB, Osler TM, Mackersie RC, Davis JW. Trauma deaths in a mature urban vs rural trauma system. A comparison. Arch Surg. 1997;132(4):376–81.
66. Nast-kolb D, Aufmkolk M, Rucholtz S, Obertacke U, Waydhas C. Multiple Organ Failure Still a Major Cause of Morbidity but Not Mortality in Blunt Multiple Trauma. J Trauma. 1990;51(5):841–2.
67. C Brun-Buisson. The epidemiology of the systemic inflammatory response. Intensive Care Med. 2000;26 (Suppl 1):S64–74.
68. Comstedt P, Storgaard M, Lassen AT. The Systemic Inflammatory Response Syndrome (SIRS) in acutely hospitalised medical patients: a cohort study. Scand J Trauma Resusc Emerg Med. 2009;6:1–6.
69. Fowler AA, Hamman RF, Good JT, Kim N, Baird M, Eberle DJ, et al. Adult Respiratory Distress Syndrome: Risk with Common Predispositions. Ann Intern Med. 1983;98(5 Pt 1):593–7.
70. Tarara D, Costigan M, Rempe L, Tarara DPSRD, Wenzel MCRP, Li N. Systemic inflammatory response syndrome, sepsis, severe sepsis and septic shock: incidence, morbidities and outcomes in surgical ICU patients. Intensive Care Med. 1995;21(4):302–9.
71. Nuytinck JK, Goris JA, Redl H, Schlag G, van Munster PJ. Posttraumatic complications and inflammatory mediators. Arch Surg. 1986;121(8):886–90.
72. Foex BA. Systemic responses to trauma. Br Med Bull. 1999;55(4):726–43.
73. Cavaillon JM, Adib-Conquy M, Fitting C, Adrie C, Payen D. Cytokine cascade in sepsis. Scand J Infect Dis. 2003;35(9):535–44.
74. Lenz A, Franklin GA, Cheadle WG. Systemic inflammation after trauma. Injury. 2007;38(12):1336–45.
75. Dremsizov T, Clermont G, Kellum JA, Kalassian KG, Fine MJ, Angus DC. Severe sepsis in community-acquired pneumonia: when does it happen, and do systemic inflammatory response syndrome criteria help predict course? Chest. 2006;129(4):968-–78.
76. Scott A, Khan KM, Cook JL, Duronio V. What is “inflammation”? Are we ready to move beyond Celsus ? Br J Sports Med. 2004;38(3):19–21.
77. Giannoudis PV. Surgical priorities in damage control in polytrauma. J Bone Joint Surg Br. 2003;85(4):478–83.
78. Moore FA, Moore EE. Evolving concepts in the pathogenesis of postinjury multiple organ

failure. Surg Clin North Am. 1995;75(2):257–77.

79. Bone RC. Toward a theory regarding the pathogenesis of the systemic inflammatory response syndrome: what we do and do not know about cytokine regulation. Crit Care Med. 1996;24(1):163–172.
80. Bone RC. Immunologic dissonance: a continuing evolution in our understanding of the systemic inflammatory response syndrome (SIRS) and the multiple organ dysfunction syndrome (MODS). Ann Intern Med. 1996;125(8):680–7.
81. Roumen RM, Hendriks T, van der Ven-Jongekrijg J, Nieuwenhuijzen A, Sauerwein W, van der Meer J, et al. Cytokine patterns in patients after major vascular surgery, hemorrhagic shock, and severe blunt trauma. Relation with subsequent adult respiratory distress syndrome and multiple organ failure. Ann Surg. 1993;218(6):769–76.
82. Murphy WG, Davies MJ, Eduardo A. The haemostatic response to surgery and trauma. Br J Anaesth. 1993;70(2):205–13.
83. Pape HC, Schmidt RE, Rice J, Van Griensven M, Das Gupta R, Krettek C, et al. Biochemical changes after trauma and skeletal surgery of the lower extremity: Quantification of the operative burden. Crit Care Med. 2000;28(10):3441–8.
84. Waydhas C, Nast-Kolb D, Trupka A, Zettl R, Kick M, Wiesholler J, et al. Posttraumatic Inflammatory Response, Secondary Operations, and Late Multiple Organ Failure. J Trauma - Inj Infect Crit Care. 1996;40(4):624–30.
85. Klava A, Windsor ACJ, Farmery SM, Woodhouse LF, Reynolds JV., Ramsden CW, et al. Interleukin-10: A role in the development of postoperative immunosuppression. Arch Surg. 1997;132(4):425–9.
86. Li H, Liu J, Yao J, Zhong J, Guo L, Sun T. Fracture initiates systemic inflammatory response syndrome through recruiting polymorphonuclear leucocytes. Immunol Res. 2016;64(4):1053–9.
87. Fröhlich M, Lefering R, Probst C, Paffrath T, Schneider MM, Maegele M, et al. Epidemiology and risk factors of multiple-organ failure after multiple trauma: An analysis of 31,154 patients from the TraumaRegister DGU. J Trauma Acute Care Surg. 2014;76(4):921–7.
88. Qureshi SS, Lewis SM, Gant VA, Treacher D, Davis BH, Brown KA. Increased distribution and expression of CD64 on blood polymorphonuclear cells from patients with the systemic

inflammatory response syndrome (SIRS). Clin Exp Immunol. 2001;125(2):258–65.

89. Briggs GD, Lemmert K, Lott NJ, de Malmanche T, Balogh ZJ. Biomarkers to guide the timing of surgery: Neutrophil and monocyte l-selectin predict postoperative sepsis in orthopaedic trauma patients. J Clin Med. 2021;10(10):1–2.
90. Bown MJ, Nicholson ML, Bell PR, Sayers RD. The systemic inflammatory response syndrome, organ failure, and mortality after abdominal aortic aneurysm repair. J Vasc Surg. 2003;37(3):600–6.
91. Hildebrand F, Giannoudis P, Van Griensven M, Chawda M, Probst C, Harms O, et al. Secondary effects of femoral instrumentation on pulmonary physiology in a standardised sheep model: What is the effect of lung contusion and reaming? Injury. 2005;36(4):544–55.
92. Hukkanen RR, Liggitt HD, Murnane RD, Frevert CW. Systemic inflammatory response syndrome in nonhuman primates culminating in multiple organ failure, acute lung injury, and disseminated intravascular coagulation. Toxicol Pathol. 2009;37(6):799–804.
93. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. Lancet. 1967;2(7511):319–23.
94. Fanelli V, Vlachou A, Ghannadian S, Simonetti U, Slutsky AS, Zhang H. Acute respiratory distress syndrome: New definition, current and future therapeutic options. J Thorac Dis. 2013;5(3):326–34.
95. Sedhai YR, Yuan M, Ketcham SW, Co I, Claar DD, McSparron JI, et al. Validating Measures of Disease Severity in Acute Respiratory Distress Syndrome. Ann Am Thorac Soc. 2021;18(7):1–2.
96. DiRusso SM, Nelson LD, Safcsak K, Miller RS. Survival in patients with severe adult respiratory distress syndrome treated with high-level positive end-expiratory pressure. Crit Care Med. 1995;23(9):1485–96.
97. Giannoudis PV. Current concepts of the inflammatory response after major trauma: An update. Injury. 2003;34(6):397–404.
98. Okeny PK, Ongom P, Kituuka O. Serum interleukin-6 level as an early marker of injury severity in trauma patients in an urban low-income setting: a cross-sectional study. BMC Emerg Med. 2015;15:22.
99. Watanabe E, Hirasawa H, Oda S, Matsuda K, Hatano M, Tokuhisa T. Extremely high interleukin-6 blood levels and outcome in the critically ill are associated with tumor necrosis

factor- and interleukin-1-related gene polymorphisms. Crit Care Med. 2005;33(1):89–97.

100. Cuschieri J, Bulger E, Schaeffer V, Sakr S, Nathens AB, Hennessy L, et al. Early elevation in random plasma IL-6 after severe injury is associated with development of organ failure. Shock. 2010;34(4):346–51.
101. Giannoudis PV, Hildebrand F, Pape HC. Inflammatory serum markers in patients with multiple trauma. Can they predict outcome?. J Bone Joint Surg Br. 2004;86(3):313-23.
102. Ettinger M, Savov P, Calliess T, Windhagen H, Lichtinghagen R, Lukasz A, et al. Improved diagnostic accuracy with the classification tree method for diagnosing low-grade periprosthetic joint infections by quantitative measurement of synovial fluid alpha-defensin and C-reactive protein. Int Orthop. 2020;44(1):31–8.
103. Frink M, Van Griensven M, Kobbe P, Brin T, Zeckey C, Vaske B, et al. IL-6 predicts organ dysfunction and mortality in patients with multiple injuries. Scand J Trauma Resusc Emerg Med. 2009;17(1):1–2.
104. Qiao Z, Wang W, Yin L, Luo P, Greven J, Horst K, et al. Using IL-6 concentrations in the first 24 h following trauma to predict immunological complications and mortality in trauma patients: a meta-analysis. Eur J Trauma Emerg Surg. 2018;44(5):679–87.
105. Hsu TC, Lin CH, Sun FJ, Chen MJ. Postoperative Serum Levels of Interleukin-6 are Affected by Age in Patients with Colorectal Cancer. Int J Gerontol. 2017;11(2):75–9.
106. Honsawek S, Deepaisarnsakul B, Tanavalee A, Sakdinakiattikoon M, Ngarmukos S, Preativatanyou K, et al. Relationship of serum IL-6, C-reactive protein, erythrocyte sedimentation rate, and knee skin temperature after total knee arthroplasty: A prospective study. Int Orthop. 201;35(1):31–5.
107. Sedlář M, Kudrnová Z, Erhart D, Trča S, Kvasnička J, Krška Z, et al. Older age and type of surgery predict the early inflammatory response to hip trauma mediated by interleukin-6 (IL-6). Arch Gerontol Geriatr. 2010;51(1):1–6.
108. Del Prete F, Nizegorodcew T, Regazzoni P. Quantification of surgical trauma: Comparison of conventional and minimally invasive surgical techniques for pertrochanteric fracture surgery based on markers of inflammation (interleukins). J Orthop Traumatol. 2012;13(3):125–30.
109. Bergin PF, Doppelt JD, Kephart CJ, Benke MT, Graeter JH, Holmes AS, et al. Comparison of minimally invasive direct anterior versus posterior total hip arthroplasty based on

inflammation and muscle damage markers. J Bone Joint Surg Am. 2011;93(15):1392–8.
110. Santonocito C, De Loecker I, Donadello K, Moussa MD, Markowicz S, Gullo A, et al. C-reactive protein kinetics after major surgery. Anesth Analg. 2014;119(3):624–9.
111. Warschkow R, Tarantino I, Torzewski M, Näf F, Lange J, Steffen T. Diagnostic accuracy of C-reactive protein and white blood cell counts in the early detection of inflammatory complications after open resection of colorectal cancer: A retrospective study of 1,187 patients. Int J Colorectal Dis. 2011;26(11):1405–13.
112. Straatman J, Harmsen AMK, Cuesta MA, Berkhof J, Jansma EP, Van Der Peet DL. Predictive value of C-reactive protein for major complications after major abdominal surgery: A systematic review and pooled-analysis. PLoS One. 2015;10(7):1–2.
113. Meisner M, Adina H, Schmidt J. Correlation of procalcitonin and C-reactive protein to inflammation, complications, and outcome during the intensive care unit course of multiple-trauma patients. Crit Care. 2005;10(1):1–2.
114. Anush MM, Ashok VK, Sarma RIN, Pillai SK. Role of c-reactive protein as an indicator for determining the outcome of sepsis. Indian J Crit Care Med. 2019;23(1):11–4.
115. Kunakornsawat S, Tungsiripat R, Putthiwara D, Piyakulkaew C, Pluemvitayaporn T, Pruttikul P, et al. Postoperative Kinetics of C-Reactive Protein and Erythrocyte Sediment Rate in One-, Two-, and Multilevel Posterior Spinal Decompressions and Instrumentations. Glob Spine J. 2017;7(5):448–51.
116. Plat VD, Voeten DM, Daams F, van der Peet DL, Straatman J. C-reactive protein after major abdominal surgery in daily practice. Surg. 2021;170(4):1131–9.
117. Shen H, Zhang N, Zhang X, Ji W. C-reactive protein levels after 4 types of arthroplasty. Acta Orthop. 2009;80(3):330–3.
118. Neumaier M, Metak G, Scherer MA. C-reactive protein as a parameter of surgical trauma: CRP response after different types of surgery in 349 hip fractures. Acta Orthop. 2006;77(5):788–90.
119. Hayes GS, Stinson IN. Erythrocyte Sedimentation Rate and Age. Arch Ophthalmol. 1976;94(6):939–40.
120. Lef R AS. Obesity and the Erythrocyte Sedimentation Rate. Ann Intern Med. 2015;105(1):143.
121. Bathon J, Graves J, Jens P, Hamrick R, Mayes M. The Erythrocyte Sedimentation Rate in

End-Stage Renal Failure. Am J Kidney Dis. 1987;10(1):34–40.

122. Mun JH, Kim DH, Ryu KS, Park CK, Kim MC. Diagnostic Value of Early Inflammatory Reaction in Postoperative Infection of the Lumbar Spine. J Korean Neurosurg Soc. 2019;38(3):206–10.
123. Piper KE, Fernandez-Sampedro M, Steckelberg KE, Mandrekar JN, Karau MJ, Steckelberg JM, et al. C-reactive protein, erythrocyte sedimentation rate and orthopedic implant infection. PLoS One. 2010;5(2):1–2.
124. Ganesan V, Brown RD, Jiménez JA, De S, Monga M. C-Reactive Protein and Erythrocyte Sedimentation Rate Predict Systemic Inflammatory Response Syndrome after Percutaneous Nephrolithotomy. J Endourol. 2017;31(7):638–44.
125. Peng N, Su L. Progresses in understanding trauma-induced coagulopathy and the underlying mechanism. Chin J Traumatol. 2017;20(3):133-6.
126. Shorr AF, Thomas SJ, Alkins SA, Fitzpatrick TM, Ling GS. D-dimer correlates with proinflammatory cytokine levels and outcomes in critically ILL patients. Chest. 2002;121(4):1262–8.
127. Zhang LD, Liu HB, Li YN, Ma HM, Liu YB, Wang MY. Correlation analysis between plasma D-dimer levels and orthopedic trauma severity. Chin Med J (Engl). 2012;125(17):3133-6.
128. Liu C, Song Y, Zhao J, Xu Q, Liu N, Zhao L, et al. Elevated D-dimer and fibrinogen levels in serum of preoperative bone fracture patients. SpringerPlus. 2016;5(1):1–5.
129. Dindo D, Breitenstein S, Hahnloser D, Seifert B, Yakarisik S, Asmis LM, et al. Kinetics of D-dimer after general surgery. Blood Coagul Fibrinolysis. 2009;20(5):347–52.
130. Lee YS, Lee YK, Han SB, Nam CH, Parvizi J, Koo KH. Natural progress of D-dimer following total joint arthroplasty: A baseline for the diagnosis of the early postoperative infection. J Orthop Surg Res. 2018;13(1):1–2.
131. Lasanianos NG, Kanakaris NK, Giannoudis P V. Intramedullary nailing as a “second hit” phenomenon in experimental research: Lessons learned and future directions. Clin Orthop Relat Res. 2010;468(9):2514–29.
132. Marino M, Palmieri G, Peruzzi M, Scuderi F, Bartoccioni E. A study of inflammatory/necrosis biomarkers in the fracture of the femur treated with proximal femoral nail antirotation. Mediators Inflamm. 2015;2015:189864.

133. Ebrahimpour A, Okhovatpour MA, Sadighi M, Sarejloo AH, Sajjadi MRM. Comparative investigation of percutaneous plating and intramedullary nailing effects on IL-6 production in patients with tibia shaft fracture. Acta Orthop Traumatol Turc. 2017;51(6):478–81.
134. Grezda K, Jelic M, Daci A, Bytyqi C, Kida Q. Comparison of systemic inflammatory responses of proximal femoral nail versus dynamic hip screw after treatment of patients with pertrochanteric fractures: A prospective comparative study. Acta Orthop Traumatol Turc. 2021;55(4):293–8.
135. Gallucci S, Provenzano C, Mazzarelli P, Scuderi F, Bartoccioni E. Myoblasts produce IL-6 in response to inflammatory stimuli. Int Immunol. 1998;10(3):267–73.
136. Kruidenier J, Dingemans SA, Van Dieren S, De Jong VM, Goslings JC, Schepers T. C-reactive protein kinetics and its predictive value in orthopedic (trauma) surgery: A systematic review. Acta Orthop Belg. 2018;84(4):397–406.
137. Christensen MB, Eriksen T, Kjelgaard-Hansen M. C-reactive protein: Quantitative marker of surgical trauma and post-surgical complications in dogs: A systematic review. Acta Vet Scand. 2015;57(1):1–2.
138. Malin K, Witkowska-Piłaszewicz O. C-Reactive Protein as a Diagnostic Marker in Dogs: A Review. Animals. 2022;12(20).
139. Kragsbjerg P, Holmberg H, Vikerfors T. Serum concentrations of interleukin-6, tumour necrosis factor-alpha, and C-reactive protein in patients undergoing major operations. Eur J Surg. 1995;161(1):17-22.
140. Beloosesky Y, Hendel D, Weiss A, Hershkovitz A, Grinblat J, Pirotsky A, et al. Cytokines and C-reactive protein production in hip-fracture-operated elderly patients. J Gerontol A Biol Sci Med Sci. 2007;62(4):420–6.
141. Hong JY, Suh SW, Park JH, Shin YS, Yoon JR, Yang JH. Comparison of soft-tissue serum markers in stable intertrochanteric fracture: Dynamic hip screw versus proximal femoral nail - A preliminary study. Injury. 2011;42(2):204–8.
142. Ellitsgaard N, Andersson AP, Jensen K V., Jorgensen M. Changes in C-reactive protein and erythrocyte sedimentation rate after hip fractures. Int Orthop. 1991;15(4):311-4.
143. Schulak DJ, Rayhack JM, Lippert FG 3rd, Convery FR. The erythrocyte sedimentation rate in orthopaedic patients. Clin Orthop Relat Res. 1982;(167):197–202.
144. Aalto K, Osterman K, Peltola H, Räsänen J. Changes in erythrocyte sedimentation rate and

C-reactive protein after total hip arthroplasty. Clin Orthop Relat Res. 1984;(184):118–20.

145. Akkose S, Ozgurer A, Bulut M, Koksal O, Ozdemír F, Ozguç H. Relationships between markers of inflammation, severity of injury, and clinical outcomes in hemorrhagic shock. Adv Ther. 2007;24(5):955–62.
146. Giraud B, Dehoux E, Jovenin N, Madi K, Harisboure A, Usandizaga G, et al. Comparaison vis-plaque dynamique et ostéosynthèse intra-médullaire antérograde dans les fractures pertrochantériennes: une étude prospective randomisée [Pertrochanteric fractures: a randomized prospective study comparing dynamic screw plate and intramedullary fixation]. Rev Chir Orthop Reparatrice Appar Mot. 2005;91(8):732–6.
147. Jonnes C, Shishir SM, Najimudeen S. Type II intertrochanteric fractures: Proximal femoral nailing (PFN) versus Dynamic Hip Screw (DHS). Arch Bone Jt Surg. 2016;4(1):23–8.
148. Paruk F, Chausse JM. Monitoring the post surgery inflammatory host response. J Emerg Crit Care Med. 2019;3:47.
149. Arias JI, Aller MA, Arias J. Surgical inflammation: a pathophysiological rainbow. J Transl Med. 2009;7:19.
150. Larsson S, Thelander U, Friberg S. C-reactive protein (CRP) levels after elective orthopedic surgery. Clin Orthop Relat Res. 1992;(275):237–42.
151. Verni CC, Davila A, Sims CA, Diamond SL. D-Dimer and Fibrin Degradation Products Impair Platelet Signaling: Plasma D-Dimer Is a Predictor and Mediator of Platelet Dysfunction During Trauma. J Appl Lab Med. 2020;5(6):1253–64.
152. Schorn MN. Measurement of blood loss: review of the literature. J Midwifery Womens Health. 2010;55(1):20–7.
153. Fang Q, Wang G. Comment on "Comparison of systemic inflammatory responses of proximal femoral nail versus dynamic hip screw after treatment of patients with pertrochanteric fractures: A prospective comparative study". Acta Orthop Traumatol Turc. 2022;56(3):236–7.

11. BIOGRAPHY

Kushtrim Grezda, a native of Gjakova, Kosovo, was born on March 30th, 1989. He obtained his Bachelor's degree from the University of Prishtina "Hasan Prishtina" in 2013. Subsequently, he completed his residency in Orthopedics and Trauma at the University Clinical Center of Kosovo in 2021. During his residency, he pursued two fellowships, the first of which was a one-month program in the department of hip and knee arthroplasty at the University of Szeged. The second fellowship, lasting four months, was undertaken at the University of Iowa Hospital and Clinics in the Department of Hip Preserving Surgery. After completing his residency, he pursued a year-long fellowship at the University Hospital of Basel.

Currently, Dr. Grezda is employed at the Royal Medical private hospital in Prishtina, Kosovo. Additionally, he serves as a consultant in University Clinical Center of Kosovo and as a teaching assistant at University of Prishtina "Hasan Prishtina".