Modelling of Patient-Specific Femur with Osteogenesis Imperfecta to Determine the Fracture Risk Under Various Loads

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***Abstract*— Osteogenesis imperfecta (OI) is a fragile bone disease characterized by easy fractures. The femur consists of cortical and cancellous bone, each with different mechanical properties. Bone fractures often occur throughout patients' lifetime. However, doctors still have no quantitative method to predict fractures. Therefore, this project's purpose is to investigate the OI femoral fracture risk to help prevent fractures. The project consists of three sections; cortical and cancellous segmentation, reconstruction of 3D OI femoral model and finite element analysis (FEA) of the OI femur to obtain fracture risk. The fracture risk in daily activities and the fracture load were examined. All the stress values were judged by the fracture criteria, assumed as 115 MPa. The exercises that exerted force more than 6 times of body weight can cause fractures. In addition, the optimal compressive force and tensile force were 919.7 N and 912.1 N, respectively, while medial and lateral impact were 230.8 N. Cancellous bone was not affected even a fracture happen. Based on these findings, we can conclude that when the OI femur is subjected to lateral or medial forces, the femur breaks easily. The bone can be reconstructed into a solid body without having to separate bone into cortical and cancellous.**

***Index Term*— Osteogenesis imperfecta (OI); femur; fracture risk; finite element analysis**

I. INTRODUCTION

Osteogenesis Imperfecta (OI), also known as "brittle bone disease" is a genetic disorder characterized by bones that break easily [1]. It is caused by the mutation in the COL1A1 and COL1A2 genes that encode type I procollagen [2]. The other symptoms included blue eye white, short height, muscle weakness, loose joints, hearing loss, breathing problems, and brittle teeth. There are four types of OI, ranging from mild forms to lethal forms in the perinatal period. Type I is the least serious and Type II is the most severe. There is no cure for this disease.

Femur, also called thigh bone is the longest, strongest and heaviest bone in the entire human body. It serves as an attachment point for all the muscles that exert their force over the hip and knee joints and also supports the body's weight during many activities, such as running, jumping, walking, and standing. Normally, a person with OI whose femur will be deformed and experienced femoral curvature. Bones of OI patients break easily and they break for unknown reasons. They will experience bone fracture frequently throughout their lifetime. Therefore, fracture risk prediction is very important to them. But there is still no established clinical method for indicating the bone fracture. Thus further complicate the medical intervention, since the physicians are unable to predict when and where the fracture will happen in OI patients.

In this project, the fracture risk analysis on the OI femur was investigated. A three-dimensional (3D) femur model from 2D CT images was generated by using VOXELCON software and then performed finite element analysis (FEA) to access the fracture risk. The finite element models constructed from computed tomography (CT) were very helpful in assessing femur fracture risk, as they were based on well-established biomechanical principles and theories [3]. Two main steps involved in generating a 3D model were image segmentation to obtain cortical and cancellous bone images and 3D reconstruction of the segmented bone contours. Bone failure criteria, such as maximum stress was applied to the 3D femur model in order to obtain ultimate stress point for assessing the femoral fracture. The results of FEA on the femur provided important predictive information for determining the risk of fracture in OI patients.

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Otsu thresholding is one of global threshold selection method, which is widely used in medical image segmentation because of its simplicity, effectiveness, efficiency and stability [4]. The optimum global threshold can be calculated automatically to separate the two classes, so that minimize their intra-class variance and maximize the between-class variance. Its assumption is the image has two-pixel classes or has a bi-modal histogram [5]. However, CT images are not bimodal images. Therefore, in order to solve this problem, a region of interest (ROI) is selected and processed, which contains only bone and soft tissue, resulting in a bimodal image. Thus, the cortical bone can be separated while ignoring the remaining images. The cancellous region can be obtained by subtracting the cortical bone from the filled cortical images. This automatic cancellous segmentation is a fast and efficient method.

Fritz et al [6] developed a standard femur model geometry and altered it to match the morphology of the type I OI subject to predict the fracture risk in type I OI patients. In 2017, Wanna et al. [7] also developed ten deformed femur models with different deformed angle using ANSYS software to predict the femoral fracture risk during standing in OI patients. The specimen's mechanical properties of both studies were assumed isotropic and identified by nanoindentation (Young's modulus = 19 GPa and Poisson's ratio = 0.3). The fracture risk was examined via the fracture risk formula created by Keyak et al. [8], [9] and predicted the fracture strength as 115 MPa.

The purpose of this study was to develop OI patient-specific femoral FE models using available CT images. This patient-specific model was used to analyse the distribution of mechanical stress, fracture risk, fracture load under various loads, and the number of affected voxels in the cortical and cancellous bone. It is hypothesized that cortical bone is more affected by stress based on its mechanical properties.

II. Methodology

This project can be divided into two phases; image segmentation using MATLAB software and finite element analysis using VOXELCON software. The process starts with obtaining DICOM images of Osteogenesis Imperfecta (OI) femur from IIUM Medical Centre and ends up with fracture risk analysis of the 3D reconstructed femoral model.

A. Image Segmentation

In this study, the Otsu's thresholding is used to perform cortical segmentation automatically similar to the study conducted by Mansor et al [10]. The optimum threshold is calculated automatically so that minimize the intra-class variance and maximize the inter-class variance. In order to remove unwanted areas and to simplify the subsequent 3D generation process, a region of interest (ROI) is specified by defining the origin of the point and the size of the ROI. Therefore, only pixels in this area will be processed by checking with the Otsu' threshold value, based on the (1). Different part of the femur, which is upper, middle and lower part of the bone, have different size of ROI, in order to segment for the best result.

$$g(x, y) = \begin{cases} 1, & \text{if } f(x, y) > T \\ 0, & \text{if } f(x, y) \leq T \end{cases} \qquad T = \text{Threshold value} \qquad (1)$$

In order to segment cancellous bone, first, filled the region within the segmented cortical bone by holes (white pixel). After that, the pixels between the filled and unfilled cortical image were compared. Unmatched pixels (cancellous bone) were changed to 1 (white) and matching pixels were changed to 0 (black).

B. Image Validation

When a segmentation method was used, it is necessary to compare the results with the ground truth to test and evaluate its performance. The evaluation of segmentation is very essential in medical image processing because the accuracy of segmentation play a crucial role in it. The gold standard, the manual segmentation of a region of interest is required for comparison during segmentation evaluation [11].

In this study, the gold standard is created by using Paint.NET, an image and photo editing software. 8 original CT images were selected, 3 of which were from the upper femur, 2 from the middle femur and 3 from the lower femur, and imported into the Paint.NET to segment manually. Two types of gold standards were created, which are the gold standards for the cortical region and the gold standards for the cancellous area.

Evaluation metrics included Dice Similarity Index (DSI), sensitivity, specificity and accuracy were used to represent the credibility of the proposed segmentation algorithm.

Dice Similarity Index (DSI): It is also known as Dice coefficient or overlap index. It is the measure of the degree of spatial overlap between two binary images [11].

$$\mathrm{DSI} = \frac{2\mathrm{TP}}{\mathrm{FP} + 2\mathrm{TP} + \mathrm{FN}} \tag{2}$$

where, TP = True positive,
FP = False positive,
FN = False negative,
FP = False positive.

Sensitivity: It is also known as True Positive Rate (TPR), or Recall. It is the measure of the portion of positive voxels in the ground truth that are also identified as positive by the proposed segmentation.

$$\mathrm{Sensitivity} = \mathrm{Recall} = \mathrm{TPR} = \frac{\mathrm{TP}}{\mathrm{TP} + \mathrm{FN}} \tag{3}$$

Specificity: Also called true negative rate (TNR), is a measure of the portion of negative voxels in the ground truth that is correctly identified as negative by the proposed segmentation.

$$\mathrm{Specificity} = \mathrm{TNR} = \frac{\mathrm{TN}}{\mathrm{TN} + \mathrm{FP}} \tag{4}$$

Accuracy: Is the fraction of the total samples that are correctly identified. It measures the portion of the voxel that matches the ground truth in segmented images.

$$\mathrm{Accuracy} = \frac{\mathrm{TP} + \mathrm{TN}}{\mathrm{TP} + \mathrm{TN} + \mathrm{FP} + \mathrm{FN}} \tag{5}$$

C. Reconstruction of 3D Femoral Model

After the image segmentation process, the 3D femoral finite element models were reconstructed using VOXELCON (Quint Corporation, Japan) by importing output images from the image segmentation into it. The 3D femoral model was made up of 220 images of cortical bone and 220 images of cancellous bone. By assigning 1 mm to width, 1 mm to height and 1mm to slice pitch of a pixel, a voxel with a volume of 1 mm^3 was created.

The mechanical properties were assigned based on the literature by Fan et al. on pediatric OI bone specimens [12], [13], characterized by nanoindentation tests [6]. Assumed that the femoral model is isotropic, and Young's moduli of the cortical and cancellous bone are 19 GPa and 10 GPa, respectively, and the Poisson's ratio is 0.3.

E. Finite Element Analysis (FEA)

The 3D femoral model meshed for finite element analysis. The voxel element size of the femur model generated was based on the pixel size of original CT image. Therefore, the convergence test is not required. For all analysis cases, the voxel model was constrained at the distal femur as a fixed support to prevent motion. As shown in Figure 1, the force (F) was applied perpendicular to the proximal (upper) region of the sagittal femur, and the distal end of the femoral stem serves as a fixed support.

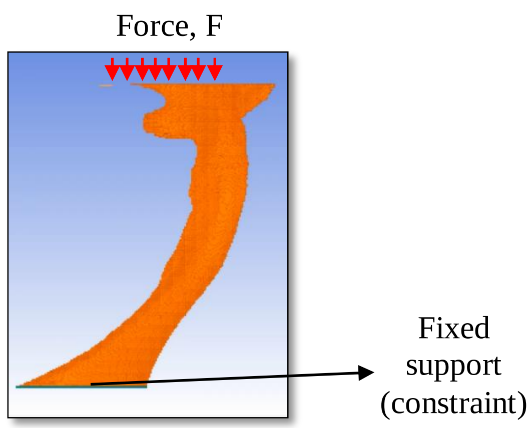


Fig. 1. Surface force applied on the proximal femoral head with fixed support (constraint).

The patient was a 13 years old girl, and her weight of patient was assumed as 37.5 kg based on the literature of Graff et al. [14] in the OI children development chart. Five loading conditions were applied to the distal (upper) region of the femur model to simulate standing, walking and jumping and study their fracture risk. According to Bankoff's work [15], the femur needs to absorb approximately one-third of human body weight during standing (stance phase) and 3-7 times the body weight when walking. Besides, the proximal femur will absorb 15 to 20 times the body weight of the compressive forces while jumping. In addition, the femoral fracture load under compression, tension, lateral and medial impact were investigated. In order to estimate the optimal force that the femur can resist, first apply 1000 N to the femur to obtain the maximum von Mises stress that results. Next, the fracture load can be calculated using (6).

$$\frac{1000\ \mathrm{N}}{F_{frac}} = \frac{VMS_{1000}}{115\ \mathrm{MPa}} \tag{6}$$

where, VMS_{1000} = Resulting maximum von Mises stress when 1000 N applied,
F_{frac} = Fracture load

F. Fracture Risk

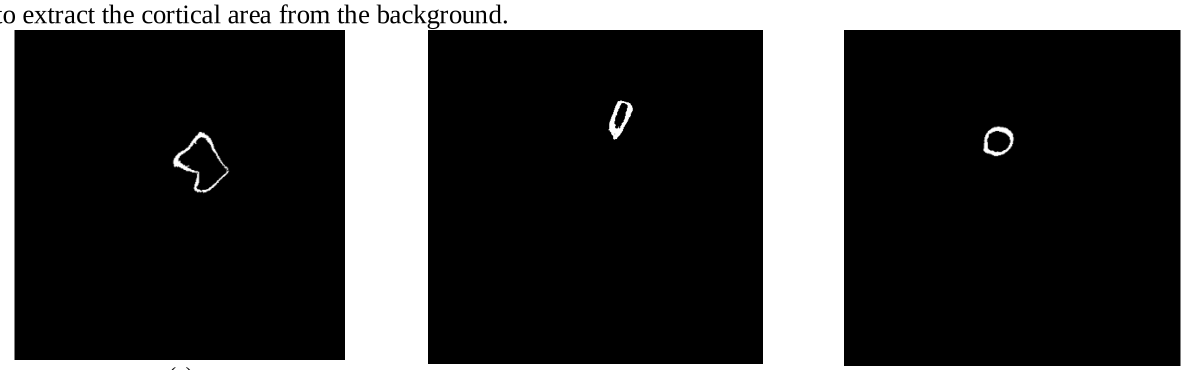
The fracture risk was calculated based on the (7), which was developed by Keyak et al [8]. Based on the nanoindentation test done by the previous study, the fracture strength of 115 MPa was assumed. When the fracture risk value is equal to or less than 1 (FR ≤1), the femur is considered fractured.

$$FR = \frac{\text{Fracture strength}}{\text{von Mises stress}} \tag{7}$$

III. RESULTS AND DISCUSSIONS

A. Image Segmentation

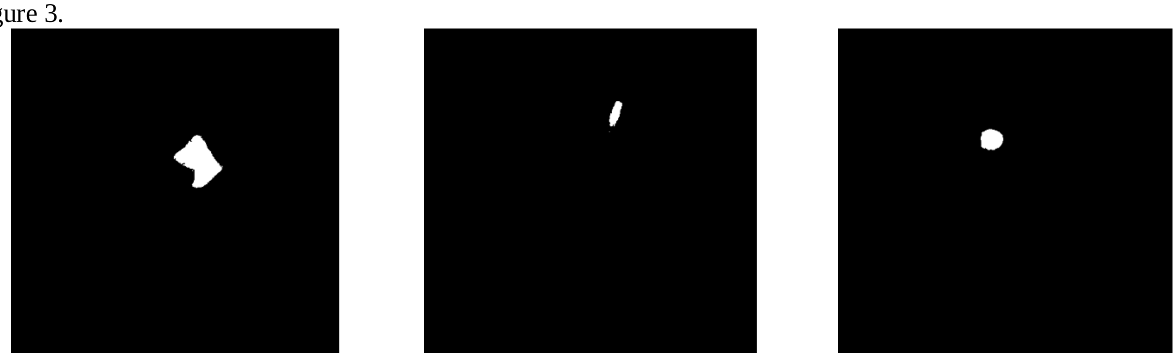
Figure 2 shows the segmented cortical images by Otsu's thresholding method. This method can be applied to the entire femur to extract the cortical area from the background.



(a) (b) (c)

Fig. 2. Segmented image using Otsu's thresholding for (a) proximal femur (b) middle femur (c) distal femur.

By using region filling, a completely white area composed of the cortical and cancellous region is produced. By subtracting the cortical bone from the filled cortical image, the cancellous bone has been extracted successfully, as shown in Figure 3.



(a) (b) (c)

Fig. 3. Output cancellous bone images for (a) proximal femur (b) middle femur and (c) distal femur.

One goal of this study is to segment the cortical and cancellous bone from OI patient's CT images by using simple image segmentation method to distinguish their different behaviour under various load types. As compared to cancellous bone, cortical bone segmentation is much easier due to its high intensity. Otsu's method is very effective for bimodal images, but this CT image is not a bimodal image. In order to solve this problem, a region of interest (ROI) was selected. Only objects within the ROI were processed, and these regions contain only bone and soft tissue, thus producing a bimodal histogram. Therefore, this Otsu method can be applied to this study. Otsu's thresholding is a simple, effective and time-saving method for cortical segmentation.

Cancellous bone has almost the same intensity as the background. Therefore, many methods are not suitable for cancellous segmentation, and this is a challenging process. The proposed technique is simple, time efficient and stable. However, the limitation of this method is only applicable to the image with complete boundary. Due to the ambiguous CT images at the femoral head and distal femur, the extracted cortical bone is incomplete. Therefore, this technique cannot give any results for those images. Due to this limitation, only 220 images were selected from 393 CT images and used in the next steps.

B. Image Validation

Table 1 shows the average DSI, sensitivity, specificity, and accuracy of cortical and cancellous bone segmentation. The average DSI, sensitivity, specificity and accuracy for cortical segmentation is 0.878, 99.39%, 99.93% and 99.93%, respectively. While, for cancellous segmentation, its average DSI, sensitivity, specificity and accuracy is 0.972, 98.23%, 99.98% and 99.98%, correspondingly.

Table I
Average DSI, sensitivity, specificity, and accuracy of cortical and cancellous segmentation.

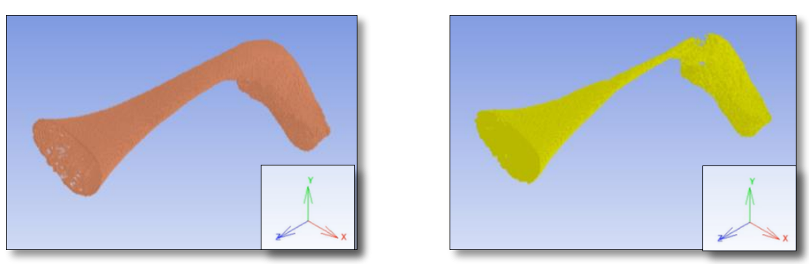
Segmentation	**Average DSI**	**Average Sensitivity (%)**	**Average Specificity (%)**	**Average Accuracy (%)**
Cortical	0.878	99.93	99.93	99.93
Cancellous	0.972	98.23	99.98	99.98

DSI is the measure of the similarity between proposed and manual cortical segmentation. In term of similarity, cancellous bone segmentation is performed better than cortical segmentation. While in term of sensitivity, cortical segmentation is better, which indicates its good ability to correctly identify the portion of positive voxels in the ground truth. Besides, in term of specificity and accuracy, both segmentations have the very good result, which is almost perfect (100%). This indicates that both segmentations can correctly identify the region of not interest from the images and able to correctly distinguish the areas of interest and non-interest.

From the results, we can conclude that the Otsu's thresholding and also the proposed hybrid cancellous segmentation method performed very well in this study. They capable to give a very high-quality result and play a very important role in the 3D reconstruction of OI femur in VOXELCON.

C. 3D Reconstruction of OI Femoral Model

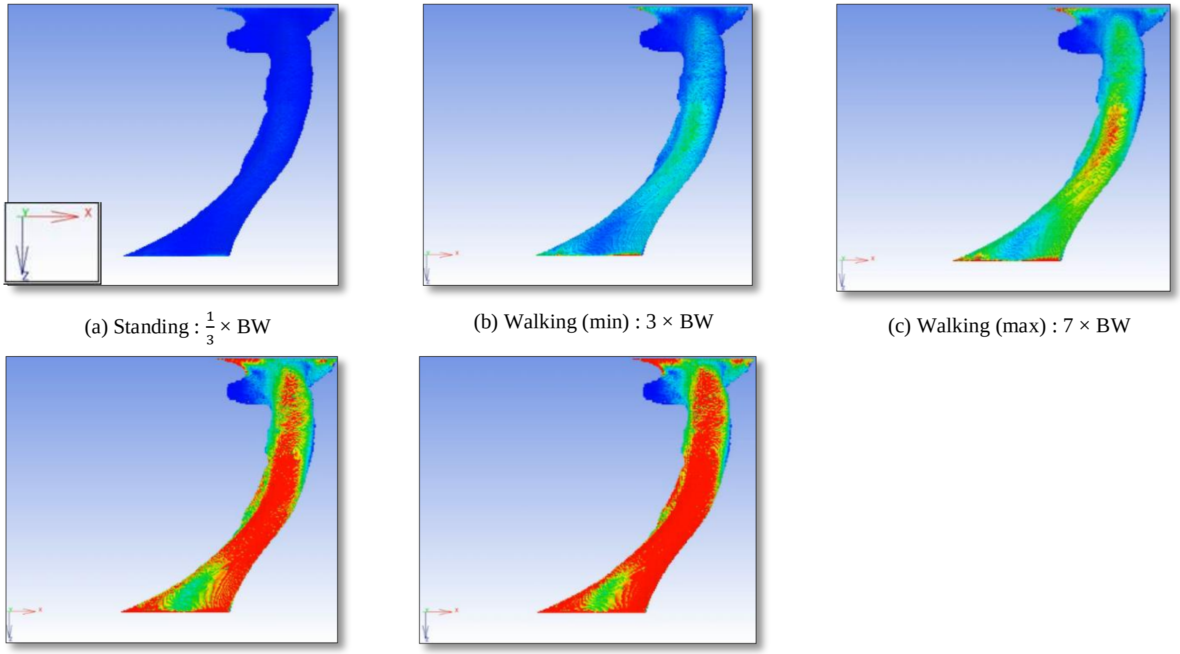
Figure 4 shows the 3D OI femur model that reconstructed using VOXELCON software. This femur bone model consists of 220 cortical bone images and cancellous bone images. The whole femoral model has a total 383066 voxels elements, while the cortical and cancellous bone model has 190955 and 192111 voxels elements, respectively.



(a) (b)
Fig. 4. xyz- plane: (a) Cortical bone model and (b) Cancellous bone model.

D. Finite Element Analysis (FEA)

Figure 5 shows that the higher the load force is, the greater the area with the highest stress (red). During standing, all areas are blue, experiencing von Mises stress ranging from 0 Pa to 3 MPa. However, when walking with 3 times the body weight, the large area on the femur becomes light blue, while the small area on the femoral shaft becomes green. This shows that the femur is more stressed when walking than standing. In addition, when the proximal femur absorbs 7 times of body weight while walking, the small area on the femoral stem appears orange/red, which is a medium and high-stress area. Most areas on the femur turn red during the jump. The red coloured areas are key areas, which are prone to fracture.



(a) Standing : $\frac{1}{3}$ × BW

(b) Walking (min) : 3 × BW

(c) Walking (max) : 7 × BW

(d) Jumping (min) : 15 × BW

(e) Jumping (max) : 20 × BW

Fig. 5. Von Mises stress distribution of femoral model under different loading conditions.

Table II shows that the maximum von Mises stress increases with the surface forces. The standing has the lowest von Mises stress, 7.7 MPa, while the jumping with maximum force shows the highest von Mises stress, which is 419.3 MPa. The von Mises stress of maximum walking loading and both of maximum and minimum jumping condition are exceeded the fracture strength, 115 MPa.

Table II
Maximum von Mises stress of different daily activity.

Activities of daily living, ADL	**Standing**	**Walking**		**Jumping**	
	1/3 × BW	**3 × BW (min)**	**7 × BW (max)**	**15 × BW (min)**	**20 × BW (max)**
Max von Mises stress (MPa)	7.7	62.9	146.8	314.5	419.3

The bar chart, Figure 6 shows that the more intense the activity, the lower the value, the higher the risk of fracture. The standing and walking with 3 times the body weight force will not cause any fracture to OI patients due to their high value of fracture risk. When the proximal femur absorbs 7 times or more of body weight, the value of fracture risk drops below 1. This shows that these activities are dangerous to patients.

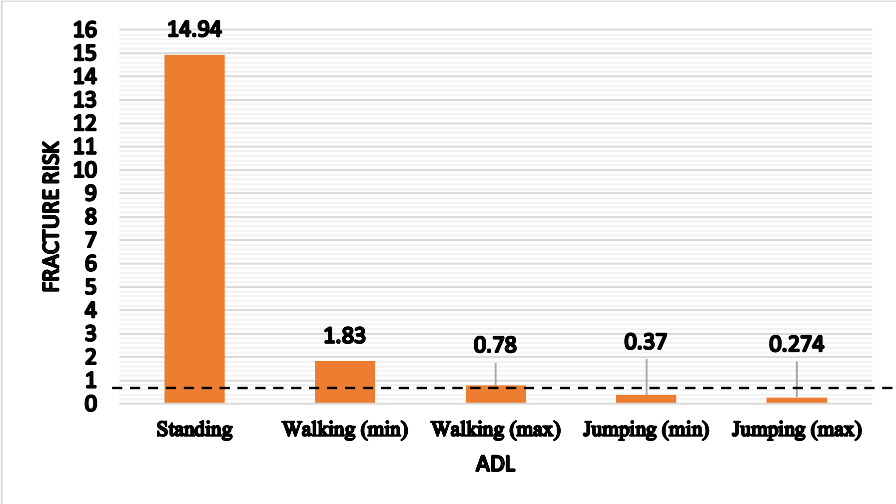


Fig. 6. Fracture risk of the different daily activity. The lower the value, the higher the fracture risk.

In addition, the line graph, Figure 7 shows that when the applied force increases, not only the stress experienced by the 3D model increases, but also the percentage of voxels that exceeded the fracture strength, 115MPa increases. It shows a growing trend. In the condition of standing and walking with the lowest force, no cortical voxel is affected. But the percentage of volume affected increases drastically when the compression force exceeds seven times or more of the body weight. There are 181 voxels exceeding 115 MPa, corresponding to 0.0905% of the cortical model fracturing during maximum jumping force. No cancellous voxel was found to exceed the fracture strength.

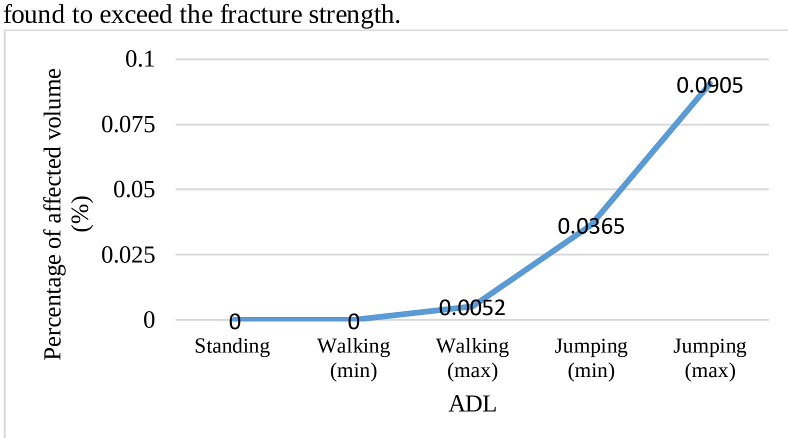
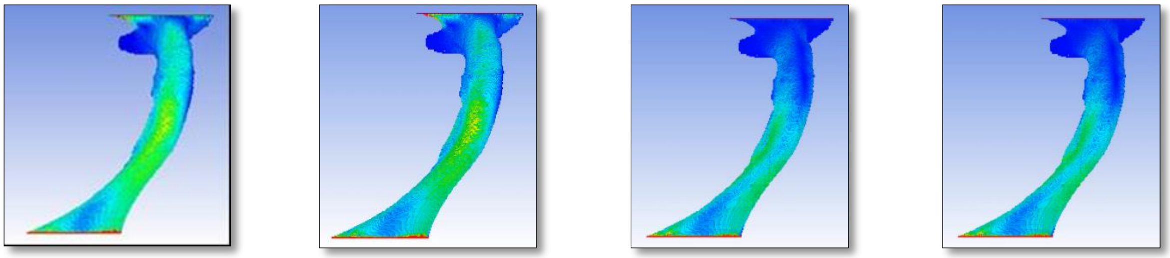


Fig. 7. Graph of percentage of affected volume against ADL.

Besides, the femur fracture load is a force capable of producing a maximum von Mises stress of about 115 MPa and a fracture risk value of about 1. Table 3 shows the femoral fracture load under various type of loading. This result shows that the fracture load of the femur under compression and tension is almost the same, which equivalent to 5 times the patient’s body weight while the effects on the lateral and medial sides are completely similar. From Figure 8, it can be seen that when the compressive and tensile fracture load is applied, the stress is mainly concentrated in the central region of the femoral shaft, however, at the maximum lateral and medial impact, it will be located in the outer region of the femoral shaft.

Table III
Femoral fracture load under various type of loading.

Loading Type	Fracture Load (N)
Compression	919.7
Tension	912.1
Lateral Impact	230.8
Medial Impact	230.8



(a)Compression (b)Tension (c)Lateral impact (d) Medial impact

Fig. 8. Von Mises stress distribution of the femur model when various loading types of fracture loads are applied.

This study reveals the feasibility of using the segmented cortical and cancellous images to create the geometric shape of the OI femur. The key parameters involved are the femur geometry, material properties and boundary conditions. Unlike normal bone tissue, the OI femur shows more isotropic material properties. This is considered to be the result of an abnormal collagen network [13]. The Young's modulus of cortical and cancellous bones is lower compared to normal bone. However, the cortical bone Young's modulus decreased more than cancellous bone. This is due to its higher collagen density, which leads to more sensitivity to collagen network deformation [13].

One of the goals of this study is to investigate the mechanical behaviour of OI femur from the finite element analysis. The stress distribution of von Mises stress indicates the starting point of fracture. Regardless of compression, tension, or even lateral and medial impacts, the stress is concentrated in the deformed area, the diaphysis (femoral shaft). If the force applied to exceed the femur stress limits, this critical site will become a fracture site. This is believed to be caused by the lateral curvature of OI femur. This is due to the lateral bending that causes more bone is away from the mechanical axis. Therefore, when standing, walking or jumping, the compression load of the femur on the hip causes the bending moment to increase. This leads to an increase in the maximum stress on the lateral side of the bone. As compared to normal bone, OI femur diaphysis also narrower.

From the result, it reflects the fact that exercises that exert force more than 6 times of body weight can cause fractures. This shows the OI patient able to withstand their own weight during standing and normal walking. The finding of standing is similar to Wanna et al. [7]. Besides, we do not recommend that OI patients walk too fast and jump. The optimal compressive force and tensile force is 919.7 N and 912.1 N, respectively, which are very close. Both optimal medial and lateral impact is 230.8 N, which is totally similar. This is because of the same area of the femoral model, and only the force is in opposite direction. Therefore, similar results are produced. The result also shows that the lateral and medial loads will more easily cause femoral fractures rather than compression and extension forces. Therefore, we recommend that OI patients should avoid collisions and falls. However, they can participate in bouncing, shooting and throwing ball practices, but it is better to use a softer, lighter, spongier ball [16].

This study also indicates the affected voxel number of the cortical and cancellous bone based on the fracture criteria, where the fracture strength assumed as 115 MPa. The affected voxels exceeding 115 MPa are easily broken. The number of voxels affected increases with the exerted force. The purpose of calculating the number of affected voxels of cortical and cancellous bone is to investigate the effects of different type of load has on them. From the results, it is clear that only the cortical bone was affected by the loading force. This is because, when the force is applied in transverse plane, most of force is absorbed by the cortical bone, and the effect of stress on the cancellous bone is negligible. The stress will be concentrated at the bowed area, as shown in the von Mises stress distribution of femur model and the fracture will initiated at this site.

IV. CONCLUSION

The objectives of this study have been fulfilled. The cortical bone and cancellous bone were separated successfully by using Otsu's thresholding and proposed cancellous segmentation. They have proved successful in obtaining the accurate and good quality results. However, the limitation of the proposed cancellous bone segmentation algorithm is that it only applies to the complete and gapless images of the boundary. Accurate image processing is very important for rebuilding bone geometry. It allows the 3D reconstruction of OI femur by VOXELCON software. Then, we can conclude that OI patient can bear her weight during standing and normal walking. However, walk too fast and jumping are very risky to them. The femoral fracture load under different loading type also investigated in order to provide important information in fracture prediction. The optimal compressive force is very close to optimal tensile strength, while the optimal lateral and medial impact are the same. In addition, we can conclude that lateral and medial impacts are more likely to cause fractures than compressive and tensile forces. From the results, we found that only cortical bone was affected when force was applied. Only when very high forces are applied can the cancellous bone be affected, which far exceeds the fracture load. Therefore, we can conclude that the effects of force and stress on cancellous bone are negligible, and its impact on fracture risk is negligible. Therefore, we can conclude that the femur can actually be reconstructed into a solid body without the need to separate the bone into cortical and cancellous, which also yields reliable results.

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