STANDARDIZED UPTAKE VALUE (SUV) MEASUREMENT OF NORMAL VERTEBRAE AND PELVIS USING SPECT/CT WITH ^{99m}Tc METHYLENE DIPHOSPHONATE (^{99m}Tc-MDP)

TEE LI WEI

SCHOOL OF HEALTH SCIENCES

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by

TEE LI WEI

Dissertation submitted in partial fulfilment of the requirements for the degree of

Bachelor of Health Science (Honours) (Medical Radiation)

July 2025

CERTIFICATE

This is to certify that the dissertation entitled "STANDARDIZED UPTAKE VALUE (SUV) MEASUREMENT OF NORMAL VERTEBRAE AND PELVIS USING SPECT/CT WITH ^{99m}Tc METHYLENE DIPHOSPHONATE (^{99m}Tc-MDP)" is the bona fide record of research work done by Mr "TEE LI WEI" during the period from October 2024 to July 2025 under our supervision. We have read this dissertation and that in our opinion it conforms to acceptable standards of scholarly presentation and is fully adequate, in scope and quality, as a dissertation to be submitted in partial fulfilment for the degree of Bachelor of Health Science (Honours) (Medical Radiation).

Main supervisor,

\- ---

Dr. Marianie Binti Musarudin

University Lecturer

School of Health Sciences

Universiti Sains Malaysia

Health Campus

16150 Kubang Kerian

Kelantan, Malaysia.

Date: 31st July 2025

Co-supervisor,

Dr. Norazlina Binti Mat Nawi

University Lecturer

School of Medical Sciences

Universiti Sains Malaysia

Health Campus

16150 Kubang Kerian

Kelantan, Malaysia.

Date: 31st July 2025

DECLARATION

I hereby declare that this dissertation is the result of my own investigations, except where otherwise stated and duly acknowledged. I also declare that it has not been previously or concurrently submitted as a whole for any other degrees at Universiti Sains Malaysia or other institutions. I grant Universiti Sains Malaysia the right to use the dissertation for teaching, research and promotional purposes.

TEE LI WEI

Date: 31st July 2025

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LISTS OF SYMBOLS

^{64}Cu	Copper-64
C	Correlation
r	Correlation coefficient (*r*-value)
^{18}F	Fluorine-18
^{124}I	Iodine-124
keV	Kiloelectronvolt
Z_α	Level of statistical significance
Z_β	Power of study
p	p-value
n	Sample size
^{99m}Tc	Technetium-99m

LISTS OF ABBREVIATIONS

^{99m}Tc-MDP	^{99m}Tc Methylene diphosphonate
ACC	Activity concentration
AI	Artificial Intelligence
BMC	Bone mineral content
BMD	Bone mineral density
BMI	Body Mass Index
BSA	Body surface area
BW	Body weight
CGZAS	Conjugate Gradient Reconstruction with Tissue Zoning, Attenuation, and Scatter Corrections
CoV	Coefficients of variation
CT	Computed tomography
DJD	Degenerative joint disease
DL	Deep learning
DPD	Diphosphono-propanedicarboxylic acid
DXA	Dual-Energy X-ray Absorptiometry
EDSR	Enhanced Deep Super-Resolution
ESRGAN	Enhanced Super-Resolution Generative Adversarial Network
FDG	Fluorodeoxyglucose
HDP	Hydroxydiphosphonate
HPUSM	Hospital Pakar Universiti Sains Malaysia
HU	Hounsfield Unit
JBMC	Japanese Bone Mineral Content

JEPeM-USM	Jawatankuasa Etika Penyelidikan Manusia USM
JLBW	Japanese Lean Body Weight
LBM	Lean Body Mass
LBW	Lean Body Weight
LEHR	Low-Energy High-Resolution
MDP	Methylene diphosphonate
OSEM	Ordered Subset Expectation Maximization
PACS	Picture Archiving and Communication System
PET	Positron Emission Tomography
PET/CT	Positron Emission Tomography/Computed Tomography
PSNR	Peak Signal-to-Noise Ratio
RCAN	Residual Channel Attention Network
ROI	Region of interest
SD	Standard deviation
SPECT/CT	Single Photon Emission Computed Tomography/Computed Tomography
SPSS	Statistical Package for Social Sciences
SSIM	Structural Similarity Index
SUV	Standardized uptake values
SUV_{ave}	Average Standardized uptake values
U^2-Net	Going Deeper with Nested U-Structure for Salient Object Detection
VCF	Vertebral compression fractures
VOI	Volume of interest
WBS	Whole body scintigraphy

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PENGUKURAN NILAI PENGAMBILAN STANDARD (SUV) BAGI VERTEBRA DAN PELVIS NORMAL MENGGUNAKAN SPECT/CT DENGAN ^{99m}Tc METHILENE DIFOSPONAT (^{99m}Tc-MDP)

ABSTRAK

Dalam pengimejan Tomografi Berkomputer Pancaran Foton Tunggal / Tomografi Berkomputer (SPECT/CT), kuantifikasi nilai pengambilan standard (SUV) semakin banyak digunakan untuk menilai metabolisme tulang. Walau bagaimanapun, perbezaan nilai SUV antara lokasi anatomi dan kaedah penormalan mengehadkan konsistensi dalam interpretasi klinikal. Bagi meningkatkan kebolehulangan, kajian ini bertujuan untuk mengkuantifikasi SUV pada vertebra dan pelvis normal menggunakan SPECT/CT, mengenal pasti faktor yang mempengaruhi variasi, dan mencadangkan lokasi pengukuran yang standard. **Kaedah**: Satu analisis retrospektif telah dijalankan menggunakan imej SPECT/CT daripada 36 pesakit dewasa yang menjalani pengimejan ^{99m}Tc-MDP di Hospital Pakar Universiti Sains Malaysia (HPUSM) dan mempunyai pelvis serta vertebra yang normal. Tetapan imbasan yang berkaitan dan data pesakit diperoleh daripada buku log dan sistem PACS. SUV_{max} dan SUV_{mean} dikira menggunakan perisian Q.Metrix dan dinormalisasi mengikut berat badan (BW), jisim badan tanpa lemak (LBM), dan luas permukaan badan (BSA) daripada 963 lokasi tulang yang normal. Variasi SUV antara kawasan rangka dinilai menggunakan pekali variasi (CoV). Analisis statistik dijalankan menggunakan SPSS untuk menilai variasi SUV dan hubungannya dengan faktor pesakit. **Keputusan:** Min ± sisihan piawai bagi SUV_{max} dan SUV_{mean} adalah masing-masing

7.082 ± 2.922 dan 3.891 ± 1.352 (BW), 5.152 ± 2.135 dan 2.843 ± 1.039 (LBM), serta 1.803 ± 0.725 dan 0.994 ± 0.354 (BSA). Secara amnya, SUV_{mean} menunjukkan pekali variasi yang lebih rendah berbanding SUV_{max}, dengan SUV_{mean} BW dan BSA mencatatkan nilai paling rendah (0.29). Tiada hubungan signifikan antara SUV dan faktor pesakit (umur, ketinggian dan berat badan). Tahap vertebra T3 (SUV_{max} BSA) dan T5 (SUV_{mean} BW) menunjukkan CoV paling rendah, lalu dicadangkan sebagai lokasi rujukan piawai. Penormalan berdasarkan BSA menunjukkan konsistensi yang lebih baik berbanding BW dan LBM. **Kesimpulan**: SUV_{mean} yang dinormalisasi kepada BSA menawarkan ukuran paling stabil bagi tulang normal dan sesuai digunakan sebagai rujukan dalam kajian SPECT/CT. Vertebra T3 dan T5 masing-masing dicadangkan sebagai tahap rujukan piawai bagi SUV_{max} dan SUV_{mean} dalam kajian ini. Untuk meningkatkan kebolehgunaan dan nilai klinikal, kajian pada masa hadapan perlu melibatkan saiz sampel yang lebih besar dan jenis kanser yang piawai.

STANDARDIZED UPTAKE VALUE (SUV) MEASUREMENT OF NORMAL VERTEBRAE AND PELVIS USING SPECT/CT WITH ^{99m}Tc METHYLENE DIPHOSPHONATE (^{99m}Tc-MDP)

ABSTRACT

In Single Photon Emission Computed Tomography/Computerized Tomography (SPECT/CT) imaging, standardised uptake value (SUV) quantification is being used more and more to evaluate bone metabolism. However, consistency in clinical interpretation is limited by differences in SUV values between anatomical sites and normalisation techniques. In order to improve reproducibility, this study will quantify SUV in normal vertebrae and pelvis using SPECT/CT, identify factors that influence variability, and recommend standardized measurement locations. **Methods:** A retrospective analysis was carried out utilising the SPECT/CT images of 36 adult patients who had ^{99m}Tc-MDP imaging at Hospital Pakar Universiti Sains Malaysia (HPUSM) and had normal pelvis and vertebrae. Relevant scan settings and patient data were gathered from logbooks and PACS. Using Q.Metrix software, SUV_{max} and SUV_{mean} were computed and standardised by body weight (BW), lean body mass (LBM), and body surface area (BSA) from 963 normal sites. The SUV variability between skeletal areas was evaluated using the coefficient of variation (CoV). To evaluate SUV variability and its correlation to patient factors, statistical analysis was carried out using SPSS. **Results:** The mean ± SD for SUV_{max} and SUV_{mean} were 7.082 ± 2.922 and 3.891 ± 1.352 (BW), 5.152 ± 2.135 and 2.843 ± 1.039 (LBM), and 1.803 ± 0.725 and 0.994 ± 0.354 (BSA),

respectively. In general, the SUV_{mean} had a lower coefficient of variation than the SUV_{max}, with the SUV_{mean} BW and BSA having the lowest (0.29). There was no significant correlation between SUVs and patient factors (age, height and weight). The lowest CoV was shown by the T3 vertebral level (BSA SUV_{max}) and T5 level (BW SUV_{mean}), which were suggested as the standard reference locations. BSA normalization showed superior consistency compared to BW and LBM. **Conclusion:** As a reference for SPECT/CT studies, BSA-normalized SUV_{mean} offers the most stable measurement in normal bone. T3 and T5 are proposed as the standard reference levels for SUV_{max} and SUV_{mean}, respectively, in this study. To improve generalisability and clinical value, larger cohorts and standardised cancer types are required for future studies.

CHAPTER 1

INTRODUCTION

1.1. Background of the Study

Since cancer has a propensity to spread to other organs, it is one of the leading causes of death worldwide. Some cancers, like those of the breast and prostate, have a higher propensity to spread to the bone. Thus, between 65 and 75 percent of individuals with stage IV cancer have metastatic bone disease. Hematogenous dispersion is the usual mechanism by which bone metastases occur, as is well documented. This explains why red marrow-rich bones like the vertebrae, ribs, pelvis, and long bone epiphysis are the most frequently found sites for bone metastases. Therefore, it is crucial to identify and monitor patients with bone metastases as soon as possible in order to choose the best course of treatment and assess therapeutic response (Gherghe et al., 2023).

Skeletal scintigraphy, another name for bone scintigraphy, is a practical and versatile nuclear medicine tool. The examination is most commonly carried out using the radiotracer Technetium-99m (^{99m}Tc) complexed to a diphosphonate, either hydroxydiphosphonate (HDP) or methylene diphosphonate (MDP). The most widely used radionuclide in nuclear medicine for labelling is ^{99m}Tc due to its affordability and advantageous imaging properties, including good spatial resolution, a short half-life of 6 hours and an optimal photopeak of 140 keV for gamma cameras, which provide for sufficient time for image capture without exposing patients to excessive radiation doses (Adams and Banks, 2023).

^{99m}Tc-MDP has a biological half-life of two to three minutes and spreads to extracellular fluid areas after intravenous injection. Then, by chemisorption, which is proportional to calcium concentration, the phosphate groups on ^{99m}Tc-MDP attach avidly to the hydroxyapatite crystals in bone. This results in significantly higher fractional bone deposition in bone as opposed to muscle and soft tissues (Bermo et al., 2018).

Traditionally, only a qualitative method has been used to interpret bone scan images, with relative intensity values rather than absolute tracer concentration values being used to assess the images. However, because of the complementary anatomical mapping that the additional Computed Tomography (CT) unit provides, users have been reported to be able to obtain more information on skeletal tracer distribution thanks to the development of advanced imaging modalities, specifically the integrated Single Photon Emission Computed Tomography/Computed Tomography (SPECT/CT) method. This allows for quantitative analysis using standardized uptake values (SUVs) (Mohd Rohani et al., 2020b).

SUV is calculated by dividing the tracer concentration in the tissue, as determined by a scanner, by the injected activity, which is typically divided by body weight (BW). For investigations in ^{18}F fluorodeoxyglucose (FDG) positron emission tomography (PET), this number has been commonly employed. It has recently been shown that SUV assessments of bone imaging utilizing F-18 NaF PET may be useful as a diagnostic technique (Waterval et al., 2013).

The goal of this study is to use SPECT/CT to quantify SUV in normal vertebrae and pelvis, identify variables that affect variability, and suggest standardized measurement locations to improve reproducibility. By establishing baseline SUV values, this study seeks to increase diagnostic confidence in distinguishing between benign and

malignant bone diseases. Improving patient outcomes and developing bone imaging procedures in nuclear medicine require an understanding of SUV measurement variability and standardization.

1.2. Problem Statement

We took into consideration SUV assessment on normal bone for a number of reasons, such as establishing a baseline for normal bone uptake so that it can be compared to pathological conditions, evaluating the impact of therapies by tracking changes in SUV in normal bone, and distinguishing benign bone conditions from malignant processes. To choose the area of a typical vertebra, there are no particular rules, nonetheless. The criteria for a normal vertebra are described in the Mohd Rohani et al. (2020a)'s study as being met by a vertebra shown on SPECT or CT that does not show metastatic or degenerative lesions. The fluctuation of the SUV values evaluated on normal vertebrae was corroborated by previous studies. In Kaneta et al. (2016)'s study, T4 to L4 region of normal vertebrae was used to measure the SUV_{max} due to insufficient number of samples in T1, T2, T3 L5 and S1. SUV_{max}, SUV_{peak}, and SUV_{mean} had respective mean ± standard deviation (SD) of 7.1 ± 0.4, 6.2 ± 0.4, and 4.4 ± 0.5. SUV_{max}, SUV_{peak}, and SUV_{mean} had respective coefficients of variations (CoVs) of 0.056, 0.059, and 0.106. However, in Qi et al. (2021)' s study that comparing the SUV_{max} of normal cervical, thoracic, lumbar vertebrae in male and female patients, it shows a large variation. The SUV_{max} (mean±SD) of normal cervical, thoracic and lumbar vertebrae in male are 7.66±1.74, 8.01±1.52 and 7.75±1.46 respectively. For female, the SUV_{max} (mean±SD) of normal cervical, thoracic and lumbar vertebrae are 6.85±1.64, 7.01±1.68 and 7.04±1.47 respectively.

The values that are considered "normal" and "abnormal" for a certain evaluation are primarily absent, which makes them useless from a clinical standpoint. The foundation of benchmark values should be the understanding of uptake ranges for certain patient populations. However, there seem to be broad, inter-patient SUV ranges linked to the physiological or metabolic mechanisms underlying osseous absorption, even when scans are carried out on a single gamma camera using the same acquisition methodology and reconstruction algorithm (Ross et al., 2019). The fact that different radiotracers may yield different values for the same lesion should also be taken into account when calculating SUVs. Therefore, it becomes difficult to compare data between patients or over time if SUV readings range dramatically between people or even within various parts of the same vertebra. This influences clinical judgment, particularly in diseases where bone metabolism is crucial, such as cancer or osteoporosis (Arvola et al., 2019). Wang et al., (2018)'s study concluded that it is possible and very reproducible to use ^{99m}Tc-MDP SPECT/CT to determine the SUV value of a normal pelvis. The normal pelvic SUVs displayed a comparatively high degree of variability. The lack of global standards for image capture and reconstruction procedures is a major obstacle to performing a useful meta-analysis of quantitative SPECT/CT studies on metastatic bone lesions. As a result, every gamma camera used for scanning has a different configuration, which can have a big impact on the SUVs (Mutuleanu *et al.,* 2023). To our knowledge, however, there aren't many published data on SUV measurement in bone imaging employing SPECT/CT scans with bone scintigraphic agents labelled with ^{99m}Tc. This study's main objective was to obtain the SUV in normal vertebrae and pelvis using ^{99m}Tc-MDP in SPECT/CT based on BW, lean body mass (LBM) and body surface area (BSA).

1.3. Study Objective

1.3.1. General Objective

The aim of this study is to quantitatively measure the uptake of ^{99m}Tc-MDP by SUV measurement in various normal vertebrae regions and pelvis using SPECT/CT images.

1.3.2. Specific Objectives

1. To calculate the SUV in normal vertebrae and pelvis based on BW, LBM and BSA.
2. To determine the correlation between patient factors such as age, height and weight with calculated SUV values.
3. To propose a standardized reference region in normal vertebrae and pelvis for SUV measurement to minimize variability across similar protocols.

1.4. Study Hypothesis

1.4.1. Null Hypothesis

1. There is no significant variation in SUV values across different vertebral and pelvic locations within each standardization method (BW, LBM, BSA).
2. There is no significant correlation between patient factors (age, height and weight) with calculated SUV values.
3. A standardized reference region in normal vertebrae and pelvis for SUV measurement does not significantly reduce variability in SUV values across similar protocols.

1.4.2. Alternative Hypothesis

1. There is significant variation in SUV values across different vertebral and pelvic locations within each standardization method (BW, LBM, BSA).
2. There is significant correlation between patient factors (age, height and weight) with calculated SUV values.
3. A standardized reference region in normal vertebrae and pelvis for SUV measurement significantly reduce variability in SUV values across similar protocols.

1.5. Significance of the Study

Through the use of SPECT/CT imaging with ^{99m}Tc-MDP, this study has the potential to establish SUV norms for normal vertebrae and pelvic areas, which could enhance the clinical usefulness and diagnostic accuracy of bone scintigraphy. SUVs in healthy bone structures can be quantified to give crucial reference data that helps distinguish between pathological and physiological tracer uptake. In order to correctly detect bone tumours, fractures, or degenerative changes, this separation is essential. Such baseline data are crucial since prior research has shown that utilizing ^{99m}Tc-MDP SPECT/CT to determine SUV values in the normal pelvis is both possible and highly reproducible (Wang et al., 2018).

Incorporating quantitative SUV values into routine clinical practice can improve the sensitivity and specificity of bone scans. Studies have shown that SUV_{max}, which is derived from quantitative SPECT/CT, is a helpful marker for distinguishing benign bone lesions from bone metastases in patients with lung adenocarcinoma, particularly for finding CT-negative bone metastases (Lin et al., 2023). This study also intends to provide

standardized locations and techniques for SUV measurement in order to improve reproducibility across imaging centres and minimize inter-patient variability. Performing practical meta-analyses of quantitative SPECT/CT investigations on metastatic bone lesions has been significantly hampered by the absence of international standards for image acquisition and reconstruction techniques (Mutuleanu et al., 2023).

Additionally, this study advances the creation of trustworthy quantitative imaging biomarkers by establishing a correlation between SUV levels and patient-specific variables such age, weight, and height. Accurate disease assessment and therapy response tracking depend on an understanding of these relationships. Prior studies have demonstrated that standardization with adequate reference data is required to lower measurement variability in SUVs (Kaneta et al., 2016). In conclusion, this study fills important gaps in nuclear medicine by offering uniform SUV measures for normal pelvis and vertebrae, which enhances bone scintigraphy's diagnostic precision and makes improved patient care possible.

1.6. Conceptual Framework

The study's independent variables were the standardized parameters (BW, LBM and BSA) and the patient factors (weight, height, and age). Figure 1.1 illustrated the conceptual framework of this study to determine the significant correlation between patient factors (age, height and weight) with calculated SUV values based on BW, LBM and BSA.

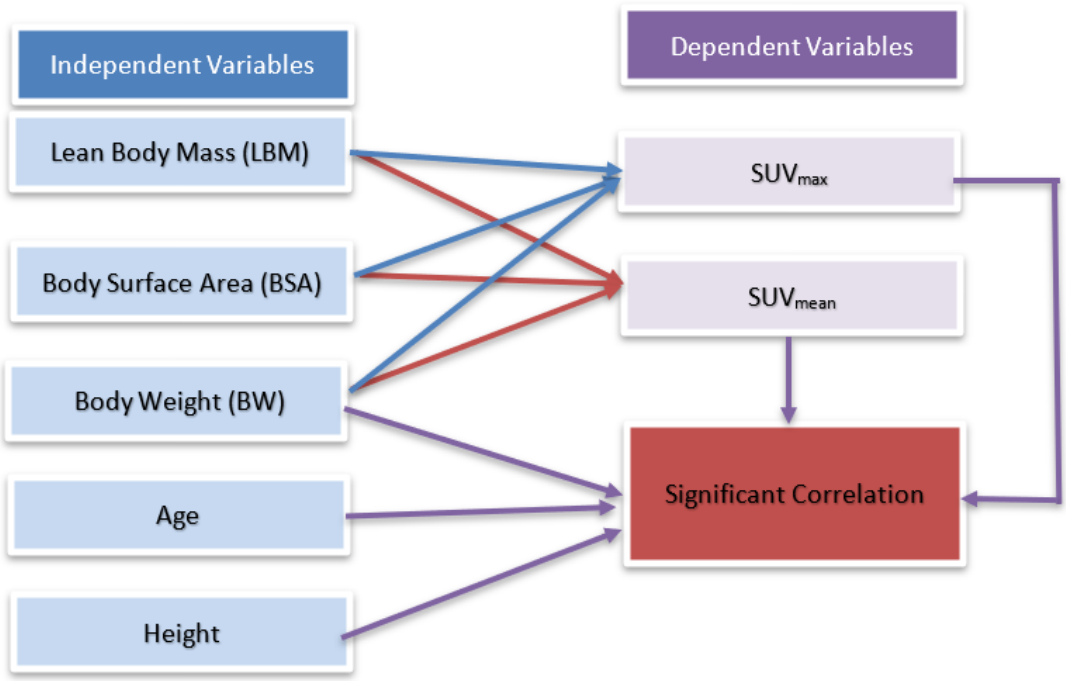

Figure 1.1: Conceptual framework.

CHAPTER 2

LITERATURE REVIEW

2.1. Quantitative SPECT/CT in Bone Imaging

SPECT/CT imaging has long been thought of as PET/CT's inferior cousin for quantitative imaging. However, SPECT/CT quantification has significantly improved thanks to advancements in hardware and software, such as the addition of measured CT-based attenuation correction, scatter correction, and correction for partial volume effects. It is now feasible to quantify SPECT/CT data using contemporary methods in a manner akin to PET/CT. However, compared to PET/CT, quantitative SPECT/CT has numerous advantages that could result in a greater number of applications. Longer physical half-life radiopharmaceuticals that better fit biological processes are used in SPECT. Although PET can use longer half-life radionuclides as ^{64}Cu or ^{124}I, their high effective dosage and poor imaging properties (positron emission probability) reduce some of the benefits of PET imaging. Another benefit of SPECT is that its radiopharmaceuticals can be labelled with many radionuclides, allowing for the simultaneous imaging of several physiological processes (Dickson et al., 2023).

2.1.1. Quantitative SPECT/CT in Bone Imaging in Vertebrae

In order to help with the clinical evaluation of radioactive absorption in normal vertebrae for the treatment of breast cancer, Mohd Rohani et al. (2020b)’s study successfully determined the SUV of ^{99m}Tc-MDP using SPECT/CT. LBM, BSA, and BW of the patients were used to determine the SUV_{mean} and SUV_{max} values for 286 normal vertebrae at the thoracic and lumbar levels.

Wang et al. (2024)'s study assessed the diagnostic efficacy of quantitative bone SPECT/CT imaging utilizing ^{99m}Tc-MDP in identifying new vertebral compression fractures (VCFs) in patients with osteoporosis. In all, 34 VCF patients and 52 control patients were examined. In fresh, nearby normal, and aged VCFs, the SUV_{max} was assessed. Fresh VCFs exhibited a significantly greater SUV_{max} (median 19.80) than all other groups. The cut-off SUV_{max} for diagnosing new VCFs was determined to be 9.925. Furthermore, compared to margin-type fractures, SUVmax was higher in intervertebral fractures. Furthermore, even though there were no discernible variations in CT Hounsfield Units, normal vertebrae in patients had higher SUV_{max} than those in controls. The study comes to the conclusion that SUV measurement in SPECT/CT is useful for diagnosing and evaluating the severity of VCF and may be useful in forecasting future fractures, which calls for more research.

In Huang et al. (2020)'s study, 62 individuals who were classified as normal, osteopenic, or osteoporotic based on Dual-Energy X-ray Absorptiometry (DXA) results had their lumbar spine SUV and its relationship to bone mineral density (BMD) measured quantitatively using ^{99m}Tc-MDP SPECT/CT. With an average BMD of 0.85 ± 0.15 g/cm² and a CT value of 145.88 ± 53.99 Hounsfield Unit (HU), the average SUV_{max} and SUV_{mean} for the L1–L4 vertebrae were 7.39 ± 1.84 and 4.90 ± 1.27 correspondingly. SUV values, BMD, and CT numbers gradually decreased from normal to osteoporotic, and there were significant differences between groups ($p < 0.001$). Age had a significant negative correlation with lumbar SUV_{max}, SUV_{mean}, and BMD (r = -0.328 to -0.442, all p <0.05), while body weight and CT value had a positive correlation (r = 0.299–0.737, all p <0.05), but there was no significant correlation with height (r = 0.006–0.175, all p >0.05). Significant increases in lumbar SUV_{max} and SUV_{mean} were observed when BMD increased (r = 0.638, 0.632, $p < 0.001$).

2.1.2. Quantitative SPECT/CT in Bone Imaging in Pelvis

In Wang et al. (2018)'s study, the SUV measurement of a normal pelvis based on BW was examined in 31 cancer patients undergoing ^{99m}Tc-MDP bone SPECT/CT scans. The pelvic region which includes the sacrum, ischial tuberosity, bilateral anterior and posterior superior iliac spines, and facies auricularis ossis ilii are the subject of this investigation. They came to the conclusion that determining the SUV value of a normal pelvis using ^{99m}Tc-MDP SPECT/CT is feasible and highly reproducible.

With the lowest CoV and, thus, the highest consistency, SUV_{bsa} (0.124 ± 0.052) in the pelvic bones revealed significant variability across all normalizing techniques. SUV_{bsa} in the pelvis was the most robust and dependable metric for measuring normal pelvic bone uptake because it was less impacted by individual patient characteristics including age, body mass index (BMI), and CT scan results than other normalizing techniques. This implies that during standard clinical evaluations, SUV_{bsa} might be the favoured reference metric for assessing any bone metastases or metabolic anomalies in the pelvis (Hou et al., 2024).

In Yoshimura et al. (2023)'s study comparing SUVs between two distinct SPECT/CT systems (Symbia T16 and Symbia Intevo), 27 patients with prostate cancer had their ilium evaluated along with four other skeletal areas (humeral head, femoral neck, L1, and L5 vertebrae). By dividing each patient's ilium's SUV_{max} and average SUV (SUV_{ave}) by the humeral head's SUV_{ave}, the SUV measurements at the lower portion of the ilium were normalized. Despite device disparities, comparison was made possible by this standardization. Strong agreement was indicated by the consistent median values of the ilium's SUV_{max} and SUV_{ave} ratios across the two scanners, with correlation coefficients ranging from 0.93 to 1.19. These findings support the use of SUV uptake in the ilium in multi-device clinical or research contexts by showing that it can be

consistently compared across several SPECT/CT systems when adjusted to the humeral head.

2.2. SUV in Nuclear Medicine

SUVs, which are useful for illness staging and follow-up evaluation, can be estimated using quantitative SPECT/CT. SUV is a semi-quantitative metric that is widely used to measure tracer uptake. Its definition is the ratio of activity per entire body volume to activity per volume of interest (VOI) (Nautiyal et al., 2021). The SUV value in PET/CT is calculated by dividing the tracer tissue concentration as determined by a PET scanner by the activity administered, which is typically divided by body weight. The pixel or voxel intensity value in the image's region of interest (ROI) represents the uptake value, which is subsequently translated into the activity concentration. SUVs show tissue activity within a ROI that has been adjusted for body weight and injected activity (Win and Aparici, 2014).

In Hou et al. (2024)'s study, they were employing the SUV_{mean}, which was defined as SUV_{bw}, SUV_{lbm}, SUV_{bmc}, SUV_{bsa}, and SUV_{bmi}, and was standardized based on the patients' BW, LBM, bone mineral content (BMC), BSA, and BMI respectively to determine a reasonably reliable SUV to direct clinical practice by quantitatively measuring and contrasting different normalizing techniques based on the SUV of ^{99m}Tc-MDP in the normal pelvis and spine using an integrated SPECT/CT scanner. All the standardised parameters were calculated based on Equation *1*), Equation *2*) and Equation *3*) (Hou et al., 2024).

$$LBM(kg) = 1.1 \times BW(kg) - 128 \times \left(\frac{BW}{height}\right)^2 \ (for\ men)$$

$$1.07 \times BW(kg) - 148 \times \left(\frac{BW}{height}\right)^2 \ (for\ women) \qquad (1)$$

Equation 1: LBM calculation formula

$$BMC\ (kg) = 1.89 \times height(m) + 0.017 \times BW(kg) - 0.0015 \times age(y) - 1.81\ (for\ men)$$

$$1.57 \times height(m) + 0.017 \times BW(kg) - 0.009 \times age(y) - 1.05\ \ (for\ women) \quad (2)$$

Equation 2: BMC calculation formula

$$BSA\ (m^2) = (BW[kg])^{0.425} \times (height[cm])^{0.725} \times 0.007184 \qquad (3)$$

Equation 3:BSA calculation formula

However, in Kaneta et al. (2016)'s study, they were using various SUV to report the SUV of normal vertebrae together with its intra- and inter-individual variability, deviation, and absolute values. SUV normalization variations were calculated using BW, Lean Body Weight (LBW), Japanese Lean Body Weight (JLBW), and Japanese Bone Mineral Content (JBMC), namely SUV_{bw}, SUV_{lbw}, SUV_{jlbw}, and SUV_{bone} respectively where the SUV_{lbw}, SUV_{jlbw}, and SUV_{bone} were calculated using SUV_{max}.

Using the conjugate gradient reconstruction with tissue zoning, attenuation, and scatter corrections applied (CGZAS) method, Kuji et al. (2017)'s study employed the maximum, peak, and average SUVs (SUV_{max}, SUV_{peak}, and SUV_{ave}, respectively) to elucidate the clinical utility of skeletal SUVs for improving prognostication of active bone metastases, which were obtained by skeletal SPECT/CT scans. The average of the highest value in a 1-cm sphere in the VOI was called SUV_{peak}.

In Mohd Rohani et al. (2020a)'s study, SUV_{max} was used to assess the effectiveness of semi-quantitative evaluation using SPECT SUV in distinguishing between bone metastases of the spine and degenerative joint disease (DJD) in patients with prostate cancer who had bone scans at HUSM as compared to BSA and LBW. It is because of the SPECT SUV based on BW shown the lowest coefficient of variation. Furthermore, SUV_{max} is a commonly used metric that is reproducible and unaffected by the size of the VOI. Table 2.*1* illustrated the summary of SUV used in previous articles.

Table 2.1: Summary of SUV used in previous articles

Study	SUV used
Hou et al. (2024)	SUV_{mean} values normalized by BW, LBM, BMC, BSA, and BMI.
Mohd Rohani et al. (2020a)	SUV_{max} based on BW
Kuji et al. (2017)	SUV_{max}, SUV_{peak}, and SUV_{ave}
Kaneta et al. (2016)	SUV_{max} values normalized by LBW, JLBW and JBMC.

2.3. Factors Influencing SUV Variability in Normal Bone

Several studies investigated about the factors that influence the SUV variability in normal bone. In Qi et al. (2021)'s study, a large sample size of 221 patients (116 men and 105 women) who had SPECT/CT scans with ^{99m}Tc-MDP were included in the retrospective analysis. Age, height, weight, BMI, SUV_{max} of normal vertebrae, and CT values of normal vertebrae were all correlated in this study. They discovered in males, SUV_{max} of normal vertebrae was significantly correlated with weight, height, and BMI, while in females, it was significantly correlated with weight and BMI.

However, in Ross et al. (2019)'s study, they found out that there seem to be broad, inter-patient SUV ranges related to the physiological or biochemical mechanisms underlying osseous uptake when scans are carried out on a single gamma camera using the same acquisition protocol and reconstruction algorithm. This situation is supported by

Kuji et al. (2017)'s study that concluded about as people age, calcification and ossification are caused by inflammation and tissue remodelling in the chondral tissue surrounding bones. Because prostate cancer activity is pathologically osteoblastic, a distinct osteoblastic mechanism may impact SUV in cases of bone metastases and degenerative alterations.

In Yoon et al. (2024)'s study, their study's objective was to examine the connection between bone radionuclide uptake and chondroid matrix mineralization in central cartilaginous bone tumours. Additionally, subgroup analysis was conducted to compare the SUV_{max} and radiodensity in HU measures between the benign and malignant groups. They found that HU measures, such as HU_{max}, HU_{mean}, and HU_{SD}, showed a significant negative correlation with SUV_{max}, while for HU_{min} was significant positive correlation with SUV_{max}.

In Tiberiu et al. (2024)'s study, they were using the ^{99m}Tc-HDP to provide a more dependable substitute for BW-based SUV calculations for normalization, finding correlations between patient attributes (gender, age, height, bone density on CT (HU), and BW) and routine tracer uptake on quantitative SPECT/CT. They found that in comparison to the commonly used BW adjusted SUV_{BW}, the interindividual variability of normal uptake on quantitative SPECT/CT was dramatically reduced by using an age, bone density, and weight-based normalization.

In Cachovan et al. (2013)'s study, the activity concentration (ACC) of ^{99m}Tc-diphosphono-propanedicarboxylic acid (DPD) in spongious bone tissue was investigated in women who were sent for bone scintigraphy and did not exhibit focal SPECT or CT abnormalities, finding correlation between tracer concentration with bone density and age as well. They found out that the normal spongious bone tissue had an average ACC of

48.15 ± 13.66 kBq/ml. Additionally, there were significant negative correlations found between age and SUV (r = -0.385, $p < 0.0001$) and HU (r = -0.650, $p < 0.0001$). Table 2.2 illustrated the summary of studies investigating factors influencing SUV variability in normal bone.

Table 2.2:Summary of Studies Investigating Factors Influencing SUV Variability in Normal Bone

Study	Sample Size & Population	Key Findings	Comments
Yoon et al. (2024)	65 patients from 2017 to 2022 with central cartilaginous bone tumours	SUV_{max} showed a moderately negative correlation with HU_{SD} (r = -0.52, $p <$ 0.001), a fair negative correlation with HU_{max} (r = -0.45, $p < 0.001$), a fair positive correlation with HU_{min} (r = 0.32, p = 0.010), and a fair negative correlation with HU_{mean} (r = -0.31, p = 0.012).	Correlated the SUV_{max} with HU and CT features using Pearson's Correlation analysis.
Tiberiu et al. (2024)	119 patients from four BW classes (< 60 kg, 60–80 kg, 80–100 kg, > 100 kg), (66 females and 53 males)	L1 SUV_{BW} had a very weak positive correlation with height (r = 0.18, p = 0.047) and weight (r = 0.15, p = 0.09). L1 bone density (measured in HU) showed a moderate positive correlation with SUV_{BW} (r = 0.53, $p < 0.001$), while age showed a moderate negative correlation (r = -0.5, $p < 0.001$).	SUV_{mean} normalised by BW is used at L1 only.
Qi et al. (2021)	221 patients (116 men, 105 women)	In males, SUV_{max} of normal vertebrae showed significant correlations with weight (r = 0.4, $p < 0.0009$), height (r = 0.28, p= 0.005), and BMI (r = 0.22, p= 0.026). In females, SUV_{max} was significantly correlated with weight ($_r$ = 0.32, p= 0.009) and BMI ($_r$ = 0.23, p = 0.031).	Analysed correlations separately for males and females.
Ross et al. (2019)	Not specified	Broad inter-patient SUV variability even with the same imaging protocol and equipment.	Attributed variability to physiological and biochemical mechanisms.

Table 2.2, continued

Study	Sample Size & Population	Key Findings	Comments
Kuji et al. (2017)	170 male patients with prostate cancer	The skeletal SUV_{max} values were 7.58 ± 2.42 for normal thoracic vertebrae, 8.12 ± 12.24 for normal lumbar vertebrae, 16.73 ± 6.74 for vertebrae with degenerative changes, and 40.90 ± 33.46 for those with bone metastases. Age-related bone changes (calcification, ossification) may influence SUV values.	Emphasized the effects of inflammation, aging, and osteoblastic cancer activity.
Cachovan et al. (2013)	50 female patients	On average, the normal spongy bone had an ACC of 48.15 ± 13.66 kBq/ml. They also found that significant negative correlations found between age and SUV (r = -0.385, $p < 0.0001$) and HU (r = -0.650, $p < 0.0001$).	Correlated the SUVs with age and HU by using ^{99m}Tc-DPD

2.4. Variability and Standardization in SUV Measurements

Several studies have mentioned that the variability of using SUV measurement is high and there is lack of standardization in it. The normal pelvic SUVs displayed a comparatively high degree of variability. SUVs may need to be standardized with sufficient reference data for the person in order to reduce variability as a quantitative imaging biomarker (Wang et al., 2018). In Mohd Rohani et al. (2020a)'s study that calculates SUV_{max} in 238 normal vertebrae from 34 patients with prostate cancer depending on BW, they found that compared to DJD, bone metastases had a substantially higher SPECT SUV_{max}. Qualitative analysis can be enhanced by semi-quantitative evaluation using SUV_{max}. A threshold SUV_{max} of > 20 can be used to differentiate bone metastases from DJD. However, Kaneta et al. (2016) demonstrated that normal vertebral SUVs showed a small intra-individual variability and a rather large inter-individual variability in their study that computes various SUVs based on LBW, BW, JLBW, and

JBMC from 29 individuals with joint problems or cancer (8 women and 21 men; mean age, 68.2 ± 6.7 years; age range, 44-87 years). As a quantitative imaging biomarker, SUVs might require standardization utilizing adequate reference data for the same patient to minimize variability.

In Wang et al. (2021)'s study, their goal was to obtain SUVs for every vertebral body segment in order to investigate the cause of the high degree of variability found in normal vertebrae. Images and data from 39 cancer patients who had bone SPECT/CT scans using ^{99m}Tc-MDP were retrieved for this investigation and the SUV_{max} and SUV_{mean} of the lumbar vertebrae 1–5 were computed for the anterior, middle, posterior, left, middle, right, top, middle, and lower regions. As a quantitative imaging metric, they came to the conclusion that, like Kaneta et al. (2016)'s study, the SUVs could need to be standardized with sufficient reference data to reduce participant variability.

In Hou et al. (2024)'s study, the robustness of several SUV normalization procedures was investigated using ^{99m}Tc-MDP bone SPECT/CT to support clinical interpretation of normal bone uptake in the spine and pelvis in 500 cancer patients (mean age: 60.9 years; 66% male). Based on the patients' BW, LBM, BMC, BSA, and BMI, the SUV_{mean} of 4962 spinal and pelvic bones was determined. These values are denoted as SUV_{bw}, SUV_{lbm}, SUV_{bmc}, SUV_{bsa}, and SUV_{bmi}, respectively. The average SUVs in the normal spine and pelvis showed a comparatively wide range of variability: SUV_{bw} was 4.573 ± 1.972, SUV_{lbm} was 3.555 ± 1.517, SUV_{bmc} was 0.163 ± 0.071, SUV_{bsa} was 0.124 ± 0.052, and SUV_{bmi} was 1.668 ± 0.732. The one that demonstrated the most stability among patients was SUV_{bsa}, which had the lowest CoV of 0.421.

In Nautiyal et al. (2021)'s study, they used quantitative SPECT/CT to estimate the SUVs of ^{99m}Tc-MDP from normal skeletal sites in 60 patients with breast cancer. They divided the patients into four study groups (n = 15 each) based on postinjection acquisition time: Ist (2 h), IInd (3 h), IIIrd (4 h), and IVth (5 h). They discovered that Group I's lumber and thoracic vertebra had the highest normal SUV_{max} and SUV_{mean} values (8.89 ± 2.26 and 2.89 ± 0.58), while Group II, III, and IV had the highest normal SUV_{max} and SUV_{mean} values in the pelvis and thoracic (9.6 ± 1.32 and 3.04 ± 0.64), 10.93 ± 3.91 and 3.65 ± 0.97), and 11.33 ± 2.67 and 3.65 ± 0.22, respectively. While Group II had relatively lower overall CoV values for SUV_{max} compared to rest imaging groups, Group IV had relatively lower overall CoV values for SUV_{mean} compared to rest groups. The sternum and femur (0.39 and 0.32) for Group I had the greatest SUV_{max} and SUV_{mean} CoV values of any bone location, while the skull (0.34 and 0.35), (0.45 and 0.45), and (0.40 and 0.40) for Groups II, III, and IV had the highest CoV values, respectively. However, of all the skeletal sites, the cervical and pelvic (0.08 and 0.16) for Group I, the scapula and pelvis (0.08 and 0.13) for Group II, the scapula (0.13 and 0.12) for Group III, and the ribs and thoracic (0.05 and 0.06) for Group IV had the lowest CoV values of the SUV_{max} and SUV_{mean}, respectively.

However, in Mohd Rohani et al. (2020b)'s study, they had the different result. In their study, the T5 thoracic level had the greatest SUV_{max} and SUV_{mean} CoV values among all the vertebral level, with 0.599 and 0.595 for BW, 0.583 and 0.571 for BSA, and 0.591 and 0.571 for LBM, respectively. Meanwhile, the L4 lumbar level for BW (0.339, 0.247), L5 for BSA (0.203, 0.221), and L5 for LBM (0.205, 0.221) had the lowest CoV values of the SUV_{max} and SUV_{mean} of all the vertebral levels, respectively. Table 2.*3* represented the summary of methods and key findings on variability and standardization of SUV measurements in SPECT/CT studies.

Table 2.3: Summary of Methods and Key Findings on Variability and Standardization of SUV Measurements in SPECT/CT Studies

Study	Method	Key Findings
Hou et al. (2024)	Measured 5 SUV types (BW, LBM, BMC, BSA, BMI) in 500 cancer patients	SUV_{bsa} was the most stable (lowest CoV of 0.421) within the vast range of SUV values.
Nautiyal et al. (2021)	Compared SUV values at 2, 3, 4, and 5 hours post-injection	Time and site affected SUV variability; Group IV (5h) had lowest CoV for SUV_{mean}
Wang et al. (2021)	Analysed SUV_{mean} and SUV_{max} from L1–L5 vertebrae	SUV values varied across regions and individuals; supports need for standardization
Mohd Rohani et al. (2020a)	Calculated SUV_{max} in 238 vertebrae using BW	Bone metastases had significantly higher SUV_{max} than DJD; SUV_{max} > 20 useful threshold
Mohd Rohani et al. (2020b)	Semiquantitatively evaluate the SUVs across vertebral levels in 30 randomly selected female breast cancer patients	T5 had highest variability; L4/L5 had lowest depending on normalization method
Wang et al. (2018)	Assessed pelvic SUV values from SPECT/CT scans	High variability in pelvic SUVs; standardization needed for SUV to be reliable
Kaneta et al. (2016)	Computed SUVs using LBW, BW, JLBW, JBMC from 29 patients	High inter-individual SUV variability but low intra-individual SUV variability; individual-based reference data are required

2.5. Deep Learning Approaches for Enhancing SPECT/CT Image Quality and Quantification

Recent developments in deep learning, including the application of networks like Enhanced Deep Super-Resolution (EDSR), Residual Channel Attention Network (RCAN), Enhanced Super-Resolution Generative Adversarial Network (ESRGAN), and Going Deeper with Nested U-Structure for Salient Object Detection (U^2-Net), have demonstrated encouraging outcomes in enhancing the quality of SPECT images. In Pan et al. (2022)'s study, half of the phantom images including the centre positions were utilized for testing, and the other half were used for training models. To assess the correctness of the models, SUV_{max} and SUV_{mean} values were measured and compared for several spheres. To evaluate advances in image quality, metrics such as Structural Similarity Index (SSIM) and Peak Signal-to-Noise Ratio (PSNR) were computed. They showed that the suggested approach might reduce acquisition time by seven times. The thorough findings demonstrated that the suggested approach can produce a notable improvement in image quality in terms of noise level, anatomical structure clarity, and SUV accuracy, allowing for use in actual clinical situations (Pan et al., 2022).

SPECT bone scintigraphy's capacity to deliver sensitive whole-body imaging has kept it at the forefront of nuclear medicine. But its lack of specificity and the lengthier acquisition durations of SPECT/CT imaging can make radiation exposure and patient comfort difficult. Pan et al. (2022)'s study have shown that recent developments, especially the application of deep learning (DL) algorithms, have showed encouraging results in enhancing image quality while drastically cutting scan durations. In Qi et al. (2023)'s study, they assessed the diagnostic performance and image quality of deep learning-enhanced ultrafast SPECT/CT bone imaging in a large patient group. The deep learning-enhanced scans were seven times faster than typical protocols and were

compared to traditional SPECT/CT scans in both qualitative and quantitative clinical evaluations. The findings imply that ultra-fast and maybe ultra-low-dose SPECT imaging may become a viable alternative in ordinary clinical practice in the future thanks to deep learning techniques.

Fast scans were made possible without sacrificing crucial information thanks to these improved images, which preserved SUV accuracy and diagnostic quality. Ultrafast and low-dose SPECT/CT imaging could be incorporated into standard clinical practice using deep learning, particularly for patients who have trouble remaining still for extended periods of time (Qi et al., 2023). Future research should concentrate on increasing sample sizes, standardizing image acquisition and reconstruction settings, and incorporating more SPECT/CT study types beyond bone scans. Investigating how various CT scan parameters affect SPECT enhancement is also crucial. Deep learning can assist establish more consistent SUV values for normal vertebrae and pelvis by supporting faster scanning times while preserving diagnostic confidence. Patient care and clinical decision-making will both benefit from this.

CHAPTER 3

METHODOLOGY

3.1. Study Design

To understand SUV variability and the factors influencing it, a retrospective analysis was used as a technique to look at patient imaging data that was already available after getting the ethical approval from Jawatankuasa Etika Penyelidikan Manusia USM (JEPeM-USM) (refer to APPENDIX A for the ethical approval letter).. This approach made use of SPECT/CT images as shown in Figure 3.*1* from adult patients with normal vertebrae and no obvious diseases who received bone imaging for other clinical purposes. By evaluating this current data, a larger sample can be included without the ethical and technological difficulties of a prospective study.

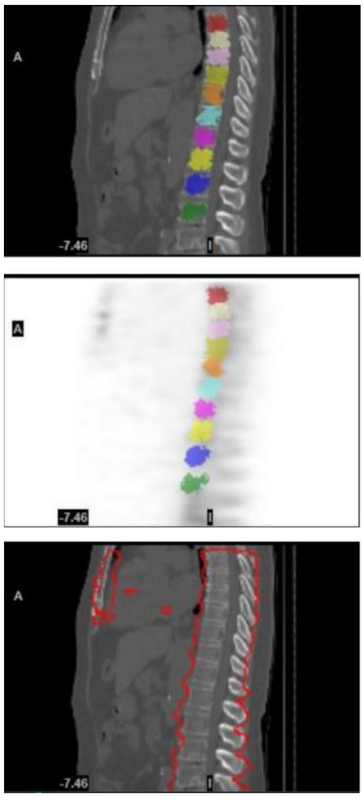

Figure 3.1: SPECT/CT images

3.2. Target Population

Target population for this study was the adult patients that had undergone ^{99m}Tc-MDP SPECT/CT imaging in HPUSM that have availability of information on measured injection activity, measurement time, injection time, age, height and weight.

3.3. Selection Criteria

3.3.1. Inclusion Criteria

Adult patients with ^{99m}Tc-MDP SPECT/CT imaging show normal vertebrae and pelvis were included in this study.

3.3.2. Exclusion Criteria

Patients who have a history of bone cancer and metabolic bone illnesses, such as osteoporosis, osteopenia, and Paget's disease, with evidence of degenerative bone disease, including osteoarthritis, spondylosis or other degenerative joint conditions and with aberrant real function were excluded from this study.

3.4. Sample Size Calculation

To determine the sample size, the Equation 4 was used for the sample size calculation using Fisher z-transformation, where r is the correlation coefficient of SUV_{max} and weight that had significant correlation found from previous study done by Mohd Rohani et al. (2020b) which is 0.457, Z_α is the Z score that corresponds to a level of statistical significance set at 95% which is 1.96 and Z_β is the Z score that corresponds to a power of study set at 80% that corresponds to 0.84.