Official Title

Development and Evaluation of an Artificial Intelligence Model for Bone Mineral Density Prediction from X-Ray Images

Date

06th June, 2024

Application for Ethical Clearance

Ibn Sina Medical College
1/1-B, Kallyanpur, Dhaka-1216, Bangladesh

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3. Place of the Study/Institution(s):

i. Ibn Sina Diagnostic and Consultation Center, Uttara
House#52, Garib-E-Newaz Avenue, Sector#13, Uttara,
Dhaka-1230
Other Ibn Sina branches if needed.

4. Title of Study: Development and Evaluation of an Artificial Intelligence Model for Bone Mineral Density Prediction from X-Ray Images

5. Type of Study: Prospective and retrospective study.

6. Duration of Study: 6 months

7. Total Cost: N/A

8. Funding Agency: RISE-BUET

I agree to obtain approval of the Ibn Sina Ethical Review Committee for any changes involving the rights and welfare of subjects or any changes of the methodology before making any such changes.

_____

Dr. Taufiq Hasan
Associate Professor, Biomedical Engineering,
Bangladesh University of Engineering and Technology (BUET), Dhaka – 1205.
Date:

_____

Dr. A.S.M. Shahidul Hossain
Radiology & Imaging Specialist,
Ibn Sina Diagnostic and Consultation Center, Uttara,
House#52, Garib-E-Newaz Avenue, Sector#13, Uttara, Dhaka-1230.
Date:

Circle the appropriate answer to each of the following
(If not Applicable write NA)

1. Source of Population:

(a) ILL Participant — (Yes) No

(b) Non ILL Participant — (Yes) No

(c) Minors or persons under guardianship — (Yes) No

2. Does the study involve?

(a) Physical risks To the subjects — Yes (No)

(b) Social Risks — Yes (No)

(c) Psychological Risks to subjects — Yes (No)

(d) Discomfort to Subjects — Yes (No)

(e) Invasion of the body — Yes (No)

(f) Invasion of Privacy — Yes (No)

(g) Disclosure of Information damaging to Subject or others — (Yes) No

3. Does the study involve?

(a) Use of records, (Hospital, medical, Death, birth or other) — (Yes) No

(b) Use of fetal tissue Or abortus — Yes (No)

(c) Use of organs or Body fluids — Yes (No)

4. Are subjects clearly informed about?

(a) Nature and purposes of study — (Yes) No

(b) Procedures to be followed including alternatives used — N/A

(c) Physical risks — N/A

(d) Private questions — (Yes) No

(e) Invasion of the Body — N/A

(f) Benefits to be Derived — (Yes) No

(g) Right to refuse to participate or to withdraw from study — (Yes) No

(h) Confidential handling of data — (Yes) No

(i) Compensation where there are risks or loss of working time or privacy is involved in any particular procedure — N/A

5. Will signed consent form/verbal consent be required?

(a) From Subjects — (Yes) No

(b) From parent or guardian (if subjects are minors) — (Yes) No

6. Will precautions be taken to protect anonymity of subjects — (Yes) No

RESEARCH PROTOCOL

- **Project Title:** Development and Evaluation of an Artificial Intelligence Model for Bone Mineral Density Prediction from X-Ray Images

Summary: Osteoporosis, a pervasive skeletal disorder characterized by diminished bone strength predisposing individuals to an increased risk of fractures, presents a substantial public health challenge globally [1][2]. It's estimated that osteoporosis and its consequent increase in fracture risk significantly contribute to morbidity, mortality, and economic costs [3][4]. Despite the availability of effective treatments, the condition often remains undiagnosed and untreated until a fracture occurs, underscoring the critical need for early detection and intervention [5][6].

Dual-energy X-ray absorptiometry (DEXA) is the gold standard for assessing bone mineral density (BMD) and fracture risk [7]. However, its utility is hampered by limited availability, especially in rural and low-resource settings, such as Bangladesh, where osteoporosis prevalence is notably high [8]. The scarcity of DEXA units exacerbates the challenge of osteoporosis screening and management, leaving a significant portion of the population at risk [9].

In this context, plain X-ray imaging, widely available even in resource-constrained settings, emerges as a promising alternative for osteoporosis screening. Recent advancements in deep learning and computer vision offer the potential to automate the analysis of X-ray images for BMD estimation.

The objective of this thesis is to develop and evaluate an Artificial Intelligence (AI)-based model that predicts BMD from plain X-ray images of the lumbar spine and pelvis. By leveraging Convolutional Neural Networks (CNNs), this model aims to identify individuals at risk of osteoporosis and osteopenic conditions without the need for DEXA. The proposed AI model processes X-ray images to detect subtle changes in bone texture and density, potentially offering a rapid, non-invasive, and cost-effective tool for large-scale osteoporosis screening, particularly beneficial in regions like Bangladesh where DEXA is scarcely available. This research addresses the critical gap in osteoporosis screening and diagnosis, aiming to contribute significantly to public health by enabling earlier detection and management of osteoporosis, thereby reducing the incidence of fractures and associated healthcare costs [10].

- **Introduction:** Globally, osteoporosis poses a significant public health challenge, with an estimated 200 million patients affected worldwide and about it is responsible for nearly 9 million fractures annually, indicating its profound impact on morbidity, mortality, and healthcare costs [11]. In Bangladesh, the prevalence of osteoporosis is concerning, with a study revealing that among a cohort of 526 individuals, 37.3% are at risk of developing the condition [8]. The risk is notably higher in females (43.2%) compared to males (30.3%) and escalates with age, particularly after 50 years, reflecting global trends. Furthermore, the presence of diabetes and cardiovascular diseases significantly increases the risk, with a striking 78% of cardiovascular patients being at risk. Notably, individuals with multimorbidity present an even higher prevalence rate of 90%. This underlines an urgent need for effective screening and early detection strategies to mitigate the burden of osteoporosis, especially in resource-constrained settings.

Recent advancements in deep learning, particularly deep learning, have shown promise in utilizing plain radiographs for BMD prediction, potentially bypassing the need for more expensive and less accessible DEXA scans [12][13]. Studies leveraging CNNs have been successful in extracting clinically relevant features from X-ray images to predict BMD and assess fracture risk, demonstrating AI's potential in osteoporosis screening [14].

Despite these advancements, the application of AI in osteoporosis diagnosis faces challenges, notably the generalizability of models across diverse populations and healthcare settings. Most existing studies utilize datasets from localized patient populations and are often limited by the availability and quality of annotated data. This raises concerns about the models' performance and applicability in different regions, particularly in low- and middle-income countries where the disease burden is highest, and healthcare resources are scarce.

To address these gaps, our research aims to develop and evaluate an AI model for BMD prediction from X-ray images, with a particular focus on enhancing model generalizability and diagnostic accuracy. We intend to collect a comprehensive dataset comprising X-ray images, BMD measurements from local healthcare facilities. This diverse dataset will enable us to train and validate AI models that can robustly predict osteoporosis across different patient populations.

Our goal is to create an AI-assisted diagnostic tool that can be easily integrated into clinical workflows, offering a cost-effective and accessible solution for osteoporosis screening.

- **Objectives:** The primary objective is to curate a comprehensive dataset of X-ray images sourced from publicly available domains and local health facilities, encompassing a diverse representation of patient demographics, geographic locations, and equipment variations. Building upon this dataset, we seek to develop a robust artificial intelligence model capable of prediction of bone mineral density from X-ray images.

  The specific objectives of the study are:

  a) To develop a deep learning convolutional neural network (CNN) model that can accurately predict Bone Mineral Density (BMD) values from X-ray images, using both prospective and retrospective data collection methods.
  b) To validate the AI model's performance on a diverse dataset encompassing a broad demographic, including variables such as age, gender, height, weight, menopausal status, and the presence of comorbidities like cardiovascular disease and diabetes.
  c) To evaluate the model's performance using a range of metrics, including Area Under the Precision-Recall Curve (AUPRC), accuracy, Mean Absolute Error (MAE), and Pearson Correlation Coefficient (PCC), ensuring its robustness in predicting BMD.
  d) To assess the usability and interpretability of the AI model's output by healthcare professionals, determining its integration into clinical practice and its impact on the diagnostic workflow efficiency.
  e) To measure the generalizability and adaptability of the model across various healthcare settings, ensuring the AI system's reliability on X-ray images from different populations and regions.

f) To investigate the model's potential in enhancing early detection and treatment planning for osteoporosis by providing a non-invasive, cost-effective tool for BMD estimation, potentially leading to better patient management and outcomes.
g) To assess the AI model's role as a decision support tool in determining the necessity for additional diagnostic procedures, such as DEXA scans, thereby optimizing patient care pathways and potentially reducing healthcare costs.

- **Rationale:** The early detection and treatment of osteoporosis are crucial in preventing fractures and ensuring the quality of life for individuals at risk. However, in developing countries like Bangladesh, the standard method for assessing bone health, DEXA, is not widely accessible due to its cost and the scarcity of specialized equipment and trained personnel. Consequently, many cases of osteoporosis remain undiagnosed until a fracture occurs, which significantly impacts patient outcomes and healthcare costs.
  The current pathway for osteoporosis suspicion in Bangladesh typically begins with an X-ray prompted by symptoms of pain or fracture. If osteoporosis is suspected, a subsequent BMD test is recommended. This two-step process not only increases the financial burden on patients but also delays the diagnosis and treatment of osteoporosis, especially in rural areas where BMD testing facilities are scarce.
  Addressing these challenges, our research proposes the use of deep learning algorithms to predict BMD values directly from X-ray images, which are more readily available and cost-effective than DEXA scans. By training a CNN with a dataset that includes demographic and clinical covariates, such as age, gender, menopausal status, cardiovascular disease, and diabetes, our AI model aims to identify correlations that can accurately predict BMD [15]. In this way, the developed AI model is intended to function as an assistive tool, providing a preliminary assessment to guide physicians on whether a more expensive and resource-intensive DEXA scan is warranted. This approach could substantially streamline the diagnostic process, making it more efficient and potentially reducing unnecessary medical expenses for patients.

- **Methodology:** In our data-driven approach to developing a predictive model for Bone Mineral Density (BMD) from X-ray images, we will collect and utilize a comprehensive dataset that includes X-ray images and BMD reports alongside demographic and clinical details of the subjects. The methodology will ensure patient privacy and data security, with all personally identifiable information being excluded from the dataset.

  a) **Study Population:** The study is structured as a prospective and retrospective investigation aimed at developing and evaluating an AI-based diagnostic tool for the prediction of BMD from X-ray image analysis. The population will include subjects with varying bone densities as determined by DEXA scans, which serve as the gold standard for BMD measurement. The study will target a diverse demographic to account for the variability in bone health across different ages, genders, and clinical backgrounds.

- **Inclusion criteria:**
  - Subjects of any gender and age group (18 and above) for whom X-ray imaging of relevant skeletal sites (e.g., spine, hip) is available.
  - Individuals willing to participate and who have provided informed consent for the use of their X-ray images and clinical data for research purposes.
  - Subjects with both X-ray images and DEXA scan results.
  - Accessibility to supplementary medical records that may contribute to the model's predictive accuracy, such as historical data on fractures, calcium levels, and other osteoporosis-related factors.

- **Exclusion criteria:**
  - Subjects for whom X-ray images or clinical data are incomplete or of insufficient quality for analysis.
  - Individuals with medical conditions that could significantly alter bone density independently of osteoporosis, such as bone cancers or certain metabolic diseases.
  - Subjects who have undergone treatments or procedures that might significantly impact bone density measurement, such as long-term steroid use or recent orthopedic surgeries.
  - Pregnant women, given the potential impact on screening results and the need for special considerations during pregnancy.

b) **Sample size calculation:** Following the methodology of sample size calculation to evaluate diagnostic performance (for algorithms in this case), we use the following method of calculation for a target sensitivity and specificity incorporating disease prevalence [16]:

$$N_{sen} \geq \frac{Z^2{}_{(1-\alpha)/2} \times sen\,(1-sen)}{c^2 \times p}$$

$$N_{spec} \geq \frac{Z^2{}_{(1-\alpha)/2} \times spec\,(1-spec)}{c^2 \times (1-p)}$$

Where,

N_{sen}	=	Required sample size for sensitivity, sen
N_{spec}	=	Required sample size for specificity, $spec$
α	=	Confidence level
$Z^2{}_{(1-\alpha)/2}$	=	The Z-score for the confidence level α
p	=	Prevalence of osteoporosis
c	=	Precision
sen	=	Estimated sensitivity
$spec$	=	Estimated specificity

The final sample size N is calculated based on the larger of the two values N_{sen} and N_{spec}. In this study, as we are using deep learning techniques, we need the medical image samples to reflect the various osteoporosis, osteopenia and normal cases. For our analysis, we assume an 95% confidence level, precision of 0.05, and prevalence of osteoporosis, p = 0.373 [8]. We estimate the sensitivity and specificity of our algorithms to be at 91.1% and 68.9% respectively ($sen = 0.911$ and $spec = 0.689$) [17]. Using these values, we obtain the sample size values: $N_{sen} = 335$ and $N_{spec} = 526$. Since $N_{spec} > N_{sen}$, the final sample size for the study will be:

$$N = N_{sen} = 526$$

We can set a target of $N = 600$.

c) **Procedures:** In the prospective phase of the study, data collection will be conducted within clinical settings. Eligible patients will be approached during X-ray scans and BMD tests and presented with a consent form for their consideration. Upon agreement, a unique identifier will be assigned to maintain data integrity while preserving patient anonymity. Following the consent process, patients will provide essential clinical information. Healthcare professionals will perform an X-ray or DEXA scan, and the results will be generated and collected. This approach ensures the acquisition of non-identifiable information, unique data identifiers, and informed consent directly within the clinical setting, aligning with the specific requirements of the study.

In the retrospective phase of the study, additional data will be extracted from the clinic's database. We will collect all spine and hip X-ray images and BMD reports from the radiology department. The identification and matching process will rely on patient ID, phone number, date of birth, and other shared clinical information present in both the X-ray and BMD reports. Given the retrospective nature of this approach, tracking down and obtaining consent from individual patients is not feasible. To address privacy concerns, any personally identifiable patient information will be systematically removed from the collected data. This strategy ensures compliance with privacy standards while utilizing valuable information from previous screenings. Although informed consent cannot be obtained for this specific dataset, the study will strictly adhere to ethical guidelines and prioritize patient privacy throughout the data extraction process from the clinic's database.

d) **Methods of Data Collection:** The following fields will be recorded in the data collection for this study:
   - Patient ID (unique identification number)
   - Date & time of the data input
   - Age
   - Gender
   - Phone number
   - X-ray image (hip or spine)

- DEXA scan result
- BMI
- Menopausal status
- Diabetes
- Cardiovascular disease and other clinical covariates

The X-ray images, and DEXA scan result of the subjects along with the relevant clinical covariates will be used to design the algorithms. The standard test status and the corresponding result will be used as the ground truth for our detection algorithm.

e) **Data Interpretation:** Upon the conclusion of data collection, exploratory data analysis to assess the distribution of patients across different demographics and clinical factors, including age, gender, menopausal status, presence of cardiovascular diseases, diabetes, and their correlation with BMD values. This process will ensure a comprehensive understanding of the dataset's characteristics and the establishment of a balanced dataset that represents a wide spectrum of patient profiles.
The refined dataset will serve as the foundation for training and evaluating our AI model, specifically designed for the regression-based prediction of BMD from X-ray images. Our AI algorithm will leverage CNN to process X-ray images and predict BMD values, aiming to identify potential cases of osteopenia, osteoporosis, and normal.
To ascertain the model's performance and its clinical applicability, we will compare the AI-generated predictions with actual BMD measurements obtained from DEXA scans. This validation process will involve collaboration with orthopedic specialists and radiologists who will review the AI predictions in the context of their clinical experience and available patient information.

f) **Statistical Analysis:** Upon finalizing the dataset, our statistical analysis will concentrate on evaluating the artificial intelligence model's capability to predict BMD from X-ray images accurately. Performance metrics such as Mean Absolute Error (MAE), Pearson Correlation Coefficient (PCC), Area Under the Precision-Recall Curve (AUPRC), and accuracy will be employed to meticulously assess the model's performance. To ensure the reliability of our findings, we will implement k-fold cross-validation techniques, providing a framework for evaluating our model across various subsets of data. This approach will allow us to calculate mean values and standard deviations for each performance metric, offering a comprehensive understanding of the model's predictive accuracy and consistency. The culmination of our analysis will involve a comparative review of different CNN architectures and training methodologies to determine the most effective strategy for BMD prediction from X-ray images.

Utilization of Results: The study results will play a crucial role in the development and evaluation of an automatic BMD prediction algorithm for osteoporosis screening. The algorithm's primary objectives are:

a) BMD Prediction: To accurately predict BMD values from X-ray images, facilitating an automated assessment tool for early detection of osteoporosis and osteopenia. This tool aims to bridge the gap in accessibility to BMD testing, especially in resource-limited settings.

b) Clinical Decision Support: To aid healthcare professionals by providing automated BMD assessments, enhancing their ability to make informed decisions regarding patient care. The model's predictions can help prioritize patients who need further testing or intervention, streamlining the diagnostic process.

c) Correlation Analysis: To explore and identify significant relationships between BMD or osteoporosis and collected clinical covariates such as age, gender, menopausal status, cardiovascular diseases, and diabetes. This analysis aims to enhance understanding of the factors influencing bone health, contributing to personalized and more precise osteoporosis risk assessment and management strategies.

d) Data Management for Bone Health Research: To enable systematic storage and organization of X-ray images along with their corresponding BMD values and clinical data. This will not only support future research in the field of bone health but also ensure the privacy and security of patient data throughout the process.

These outcomes are poised to significantly enhance the efficiency and accuracy of osteoporosis screening, providing valuable support to healthcare professionals in Bangladesh.

- **Facilities:** For the collection of data for our thesis on predicting Bone Mineral Density (BMD) from X-ray images, no extra facilities are necessary beyond those already available in the radiology departments (e.g., X-ray imaging, DEXA scan, and data storage capabilities).

- **Approval / Forwarding of the Head of Department / Institute / IRB:** A forwarding letter from the Department of Biomedical Engineering, Bangladesh University of Engineering and Technology (BUET) is attached.

- **Flow Chart:** The data collection activity and the corresponding timeline is described in the Gantt chart below:

No.	Work/Activities	Months			
		1	2	3	4
1	Initial algorithm with publicly available data				
2	Collection of images, reports and metadata				
3	Homogenization and organization of data				
3	Data processing and analysis				

- **Ethical Implications:** The proposed retrospective/prospective study based on medical records is designed to develop and evaluate the diagnostic performance of AI algorithms that will predict BMD from X-ray images. The study poses minimal to no risk to the subjects according to the HHS (USA) definition.

- **References:**

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PART - C

INFORMED CONSENT FORM (PROSPECTIVE STUDY)

Title: Development and Evaluation of an Artificial Intelligence Model for Bone Mineral Density Prediction from X-Ray Images

Coordinator: Dr. Taufiq Hasan, Associate Professor,
Department of Biomedical Engineering,
Bangladesh University of Engineering and Technology,
Dhaka – 1205

PURPOSE OF PROJECT

You are invited to participate in a project entitled **Development and Evaluation of an Artificial Intelligence Model for Bone Mineral Density Prediction from X-Ray Images.** This project focuses on developing an algorithm that will automatically predict BMD value from X-ray images.

You are selected as a possible participant in the study.

*If you decide to terminate your participation in this study, you should notify Dr. Taufiq Hasan at +8801817579844.

PROCEDURES

If you choose to participate, you will provide essential clinical information during BMD test. The recorded data includes:

- Age
- Gender
- Phone number
- BMD test results
- BMI
- Menopausal status
- Diabetes
- Cardiovascular disease

Furthermore, your X-ray images will be collected. Some personally identifiable data will be used for correlating X-ray images with BMD reports. However, no personally identifiable data is stored in the final dataset, ensuring privacy. The collected dataset will train the AI algorithm for automatic prediction, emphasizing patient privacy throughout the process.

THE PROCEDURE IS NON-INVASIVE

The data collected during these sessions will be put into one of the databases of the Department of BME, BUET, and will be used for future research.

No traditionally used identifying information about you, such as your name, address, telephone number, or national ID number, will be put into the public database. Your privacy is very important to us, and we will use safety measures to protect it. Despite all the safety measures that we will use, we cannot guarantee that your identity will never become known.

PARTICIPANT RESPONSIBILITIES

As a participant, your responsibilities include:

- Follow the instructions of the data collection coordinators and study staff.
- Tell the data collection coordinator or research study staff if you feel any discomforts.
- Ask questions as you think of them.
- Inform the coordinator or research staff if you change your mind about staying in the study.

WITHDRAWAL FROM STUDY

If you first agree to participate and then you change your mind, you are free to withdraw your consent and discontinue your participation at any time.

If you decide to withdraw your consent to participate in this study, you can directly inform Dr. Taufiq Hasan at +8801817579844 or notify the study staff.

If you withdraw from the study for any reason all the data acquired from you will be removed from the databases.

YOU MUST NOTIFY YOUR DISSENT WITHIN THE PERIOD OF THE STUDY BEING CONDUCTED.

The Protocol Director may also withdraw you from the study without your consent for one or more of the following reasons:

- Failure to follow the instructions during data collection.
- The Protocol Director decides that continuing your participation could be harmful to you.
- You need other treatments that are not allowed in the study.
- The study is canceled.
- Unanticipated circumstances.
- Other administrative reasons.

POSSIBLE RISKS, DISCOMFORTS, AND INCONVENIENCES

There is no risk associated with the study other than the risk due to radiation which is present in any radiographic test. You should contact the Protocol Director or the study staff if you have any questions.

POTENTIAL BENEFITS

We cannot and do not guarantee or promise that you will receive any benefits from this study. The study is being conducted for humanitarian purposes, which envision a long-term goal that will benefit patients suffering from or at the risk of having osteoporosis.

PARTICIPANT'S RIGHTS

You should not feel obligated to agree to participate. Your questions should be answered clearly and to your satisfaction. If you decide not to participate, notify the project coordinator or the study staff.

CONFIDENTIALITY

The results of this research study may be presented at scientific or medical meetings or published in scientific journals. Your identity and/or your personal health information will not be disclosed except as authorized by you or as required by law.

CONTACT INFORMATION

Questions, Concerns, or Complaints: If you have any questions, concerns or complaints about this research study, its procedures, risks and benefits, or alternative courses of treatment, you should ask the data collection coordinator, **Dr. Taufiq Hasan**. You should also contact him at any time if you feel you have been harmed by being a part of this study at **+8801817579844.**

May we contact you about future studies that may be of interest to you?

(Yes/No) _____

Are you participating in any other research studies?

(Yes/No) _____

Signing your name means you agree to be in this study.

_____ _____

Signature of Adult Participant Date

_____

Name of Adult Participant

Questionnaire Form

Project Title: Development and Evaluation of an Artificial Intelligence Model for Bone Mineral Density Prediction from X-Ray Images

General Information		
Have you had your X-ray done at Ibn Sina, Uttara within the last 3 months?	□ (1) Yes □ (2) No	
	If yes, what type of X-ray did you do? □ (1) Lumbar spine □ (2) Hip □ (3) Others	
	X-ray ID	Date

Participant Information			
Patient ID		Date of birth	
Patient's name		Occupation	
Contact no.		Gender	□ (1) Male □ (2) Female
Is written informed consent obtained?		□ (1) Yes □ (2) No	
Date of interview			
Name of interviewer			

Anthropometric information	
Height (Feet/Inches)	
Weight (Kg/Kilogram)	
Have you had any fractures?	□ (1) Yes □ (2) No
	If yes, specify the affected area

Clinical Information	
Menopause age	
No. of Pregnancies	
Diabetes	□ (1) Yes □ (2) No
Cardiovascular disease	□ (1) Yes □ (2) No
Parent fractured hip	□ (1) Yes □ (2) No
Currently smoking	□ (1) Yes □ (2) No
Glucocorticoids	□ (1) Yes □ (2) No
Rheumatoid arthritis	□ (1) Yes □ (2) No
Secondary osteoporosis	□ (1) Yes □ (2) No
Alcohol 3 or more units/day	□ (1) Yes □ (2) No

JUSTIFICATIONS FOR INFORMED CONSENT WAIVER (RETROSPECTIVE STUDY)

The proposed research is a study that only uses medical records of X-ray examinations and DEXA scans. As the number of samples required is large (600 according to our sample size calculation) compared to the monthly recorded cases, it is not possible to return to the patients for acquiring their consent in case of previously recorded data. Considering the high potential impact of the study, we earnestly request waiver of informed consent. The justification for this request is provided below:

1. On the topic of informed consent waiver, the regulatory authority of the United States, Department of Health and Human Services (HHS) mentions in 45 C.F.R. § 46.116(d):

   > "*An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:*
   >
   > *(1) The research involves no more than minimal risk to the subjects;*
   >
   > *(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;*
   >
   > *(3) The research could not practicably be carried out without the waiver or alteration; …*"

2. On the topic of case control studies, the Bangladesh Medical Research Council (BMRC) "Ethical Guidelines for Conducting Research Studies Involving Human Subjects" mentions on Page 45:

   > "*However, if it entails only a review of medical records, informed consent may not be required and indeed may very often not be feasible*".

In light of the abovementioned regulatory guidelines described by HHS (USA) and BMRC, we want to highlight that our study fulfills all of the above conditions as explained below:

1. The proposed research involves no more than minimal risk to subjects. According to HHS document 45 C.F.R. § 46.102(i):

   > "*Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.*"

   We will use de-identified medical records for the study. This falls into the category of minimal risk as described above.

2. The research could not be carried out practicably without the waiver or alteration. Training artificial intelligence algorithms requires a huge amount of data from a large number of patients due to the overfitting problem (further detailed in the sample size calculation section below). It is practically not possible to collect signed or verbal informed consent from each patient from each hospital.
3. The waiver or alteration will not adversely affect the rights and welfare of the subjects. Only their digital medical images and clinical history data will be used for the research. Personal identifying information (name, etc.) will be removed after linking data.

With the explanations provided above, we hope that the ethical review committee will be kind enough to approve our request to waive the informed consent requirement for this study using medical records. As we have mentioned above, the study is of potentially high impact and unfortunately not feasible without the waiver.