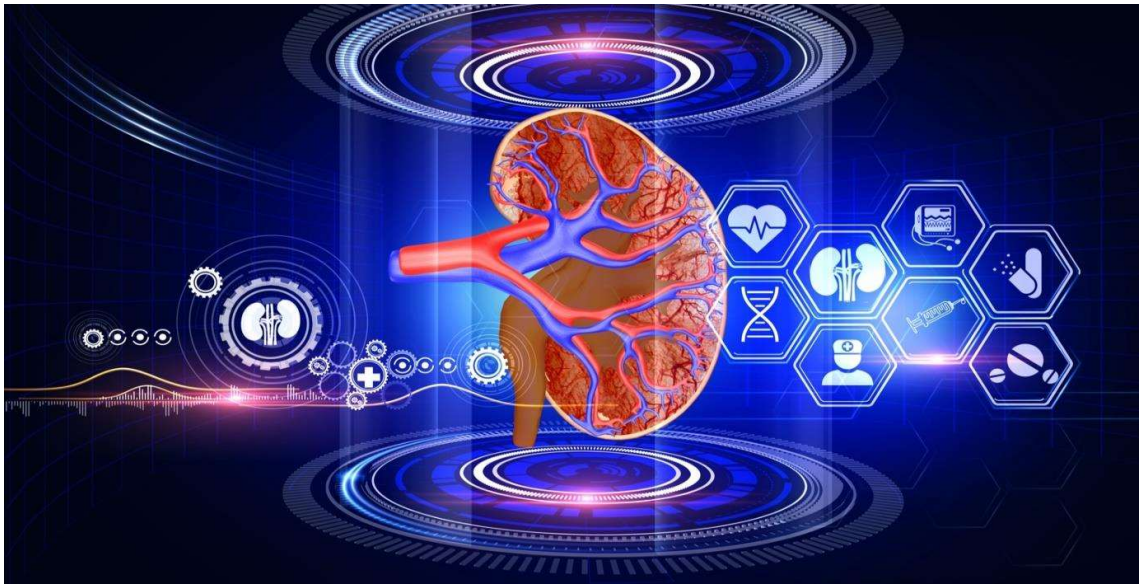


Introduction

AI Chronic Kidney Disease Progression model is a novel artificial intelligence-based disease Progression model that predicts the CKD-diagnosed individual's progression into various stages of CKD in 365 days. Apollo Hospitals developed this model. The methodology helps to stratify the CKD patients' progression into each stage of CKD with an R^2 of 0.44

Why is AICKD different?

1. Machine Learning Model developed with Indian Data having Higher Accuracy than conventional risk score.
   a. Bayesian Regression Model
   b. Model Built and Validated with Over 5,500 CKD patient data since 2010
   c. R^2 – 0.44 and MSE of 0.014 (Development and Validation) Cohort
2. Comprehensive & Holistic Risk Assessment
3. Pioneering Disease progression model for all stages of CKD
4. The tool's objective is to forecast the progression of chronic kidney disease (CKD) in 360-day periods, aiding in strategic treatment planning.
5. The tool uses a diverse set of parameters, such as eGFR value from multiple patient visits, lab parameters, and comorbidities extracted from EMR via NLP techniques. These factors, not utilized in other models, enhance prediction accuracy by providing a holistic understanding of the patient's CKD condition.

What is the Interpretation & Adoption Message

1. AI Algorithm + Clinicians - This Disease progression Assessment tool has been built as an adjunct tool for physicians to identify the progression of CKD patients into different stages and End-stage renal failure.
2. Risk Identification- This Disease progression Assessment Tool is not to be used for diagnosis of chronic kidney disease. Its limitations include paediatric use or for individuals not diagnosed with CKD, those in CKD Stage 5, or patients currently undergoing treatments such as dialysis, transplant, or medications specifically targeting CKD progression
3. Where to use - This Disease progression Assessment tool has been prepared for use at the Outpatient Nephrology Clinics, Inpatient Nephrology units, Standalone Nephrology units, and Dialysis centers.

How to Use (For Clinicians Only) -

1. Provide Appropriate –
    a. Demographic Details
    b. Obtain Patient Consent
2. Risk Factors Included –
    a. Personal – Age | Gender
    b. Time attributes - 365 days
    c. Comorbidities - Hypertension | Diabetes mellitus | CVD | Dyslipidemia | Urological problems | Systemic Illness
    d. Lab parameters - Albumin - Serum | Calcium Serum | Hemoglobin | Potassium | Sodium | Urea | Alkaline Phosphatase | Magnesium | ALT | Total Bilirubin | Platelet Count | Uric Acid | eGFR at first Visit | HBA1C
3. Output
    a. Current CKD Stage
    b. Predicted Rate of Deterioration
    c. Predicted Progression Category - Mild, Moderate, Severe Progression
    d. Based on current stage and progression category, we estimate that your likelihood to Deterioration to Stage 5 is high/moderate/low
    e. CDSS
        i. Lab investigation
        ii. Diagnostics Imaging
        iii. Referral to consultant
        iv. Treatment goals
        v. Educate on

Workflow of AICKD App:

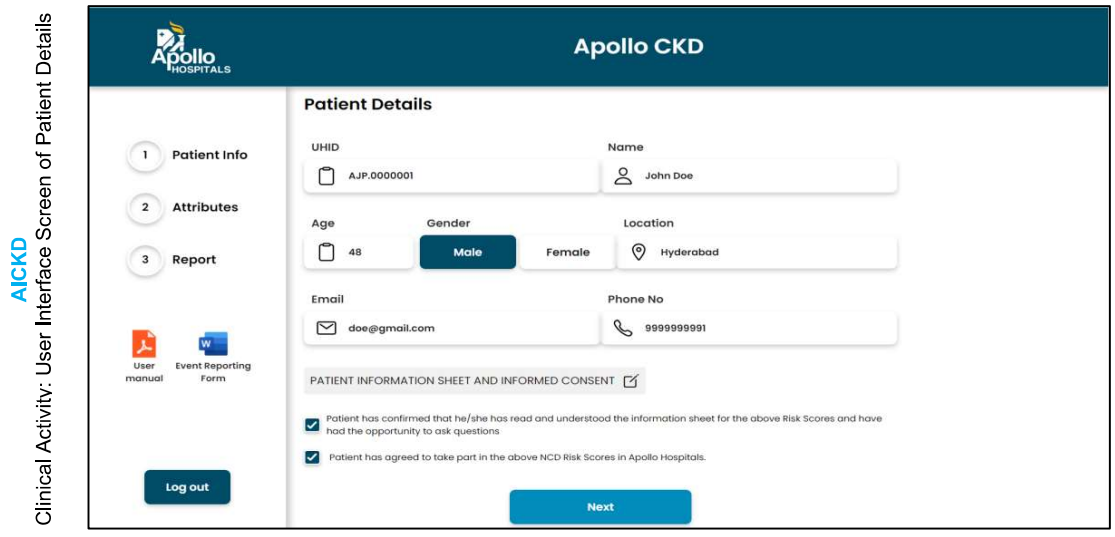


Figure 1– Entry of Patient Personal Details

Patient details Dashboard: The first step to use the AICKD App is to log into the Doctor Dashboard using your unique credentials. After login, Fill in the Patient Details and accept consent.

AICKD
Clinical Activity: User Interface Screen of Data Input

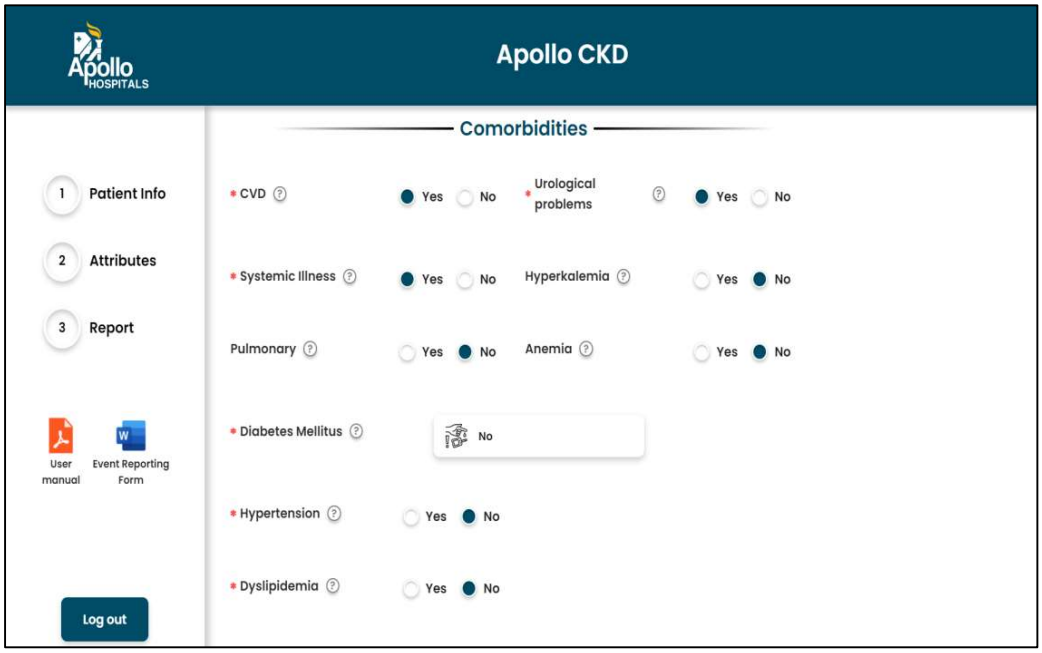


Figure 2 – Entry of Patient Comorbidities

AICKD
Clinical Activity: User Interface Screen of Data Input

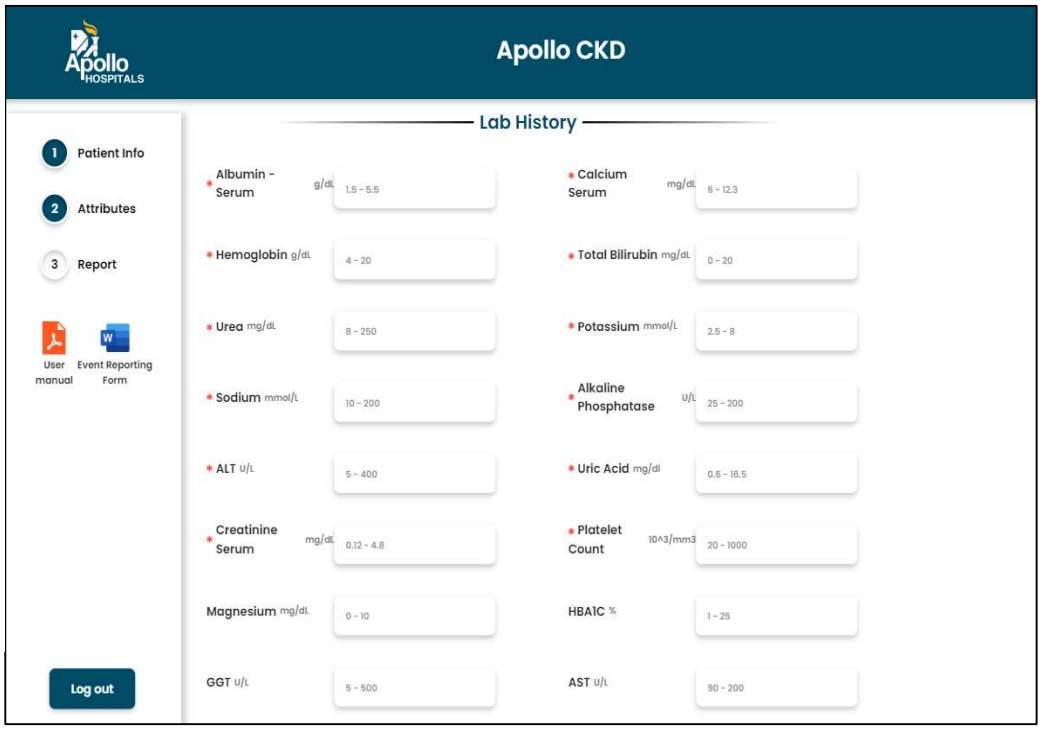


Figure 3– Entry of Patient Laboratory Values

Patient Attributes: The following categories are used to collect the patient attributes data:

- Comorbidities

- Lab Details

These Parameters are considered as data inputs to the model.

AICKD

Clinical Activity: User Interface Screen of Report

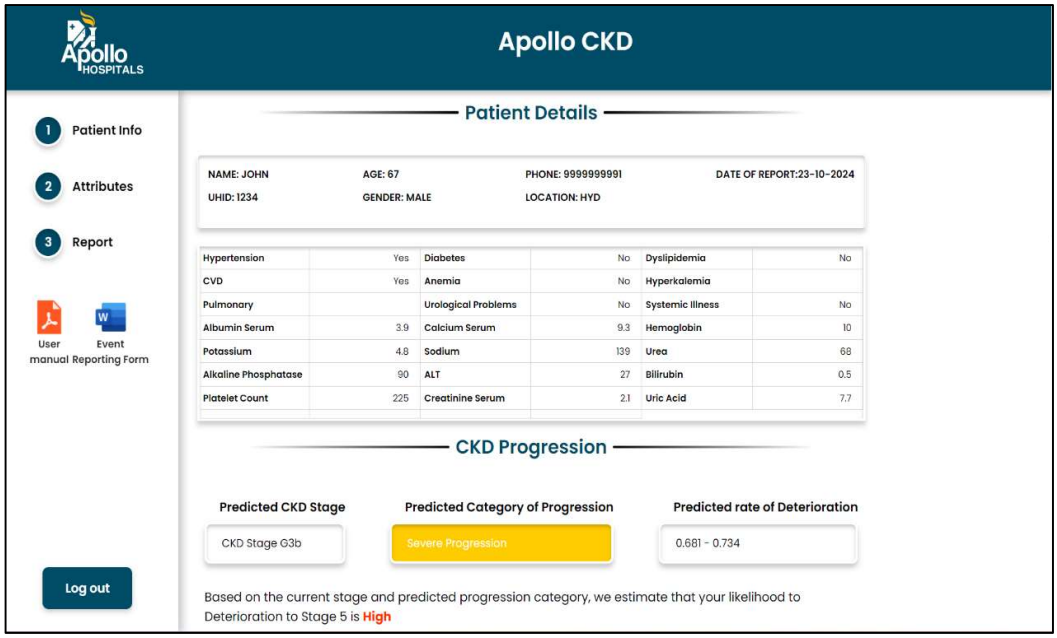
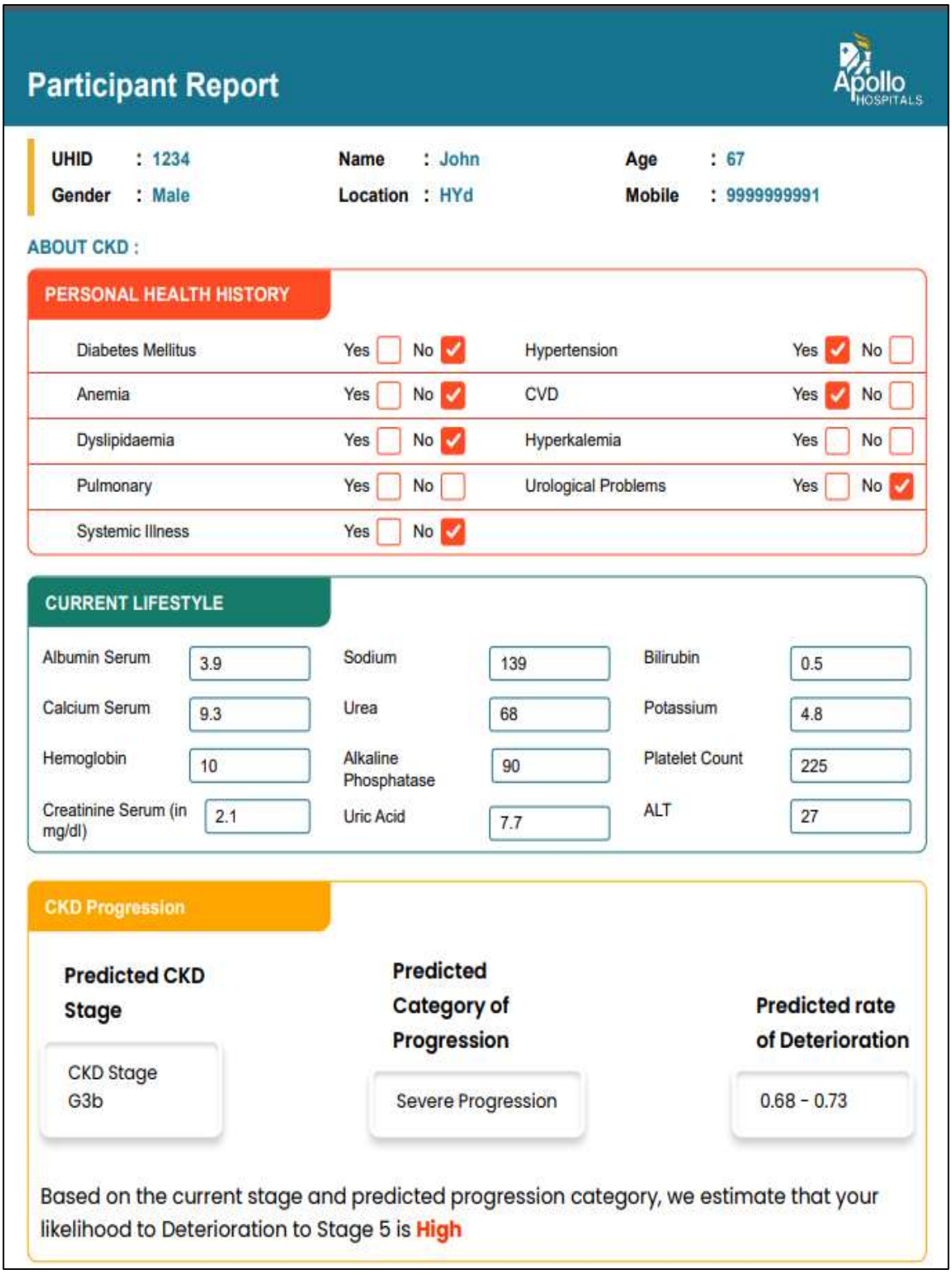


Figure 4– Generation of Report

Output:
Considering all the input parameters given, the model gives an output of

a. Current CKD Stage
b. Predicted Rate of Deterioration
c. Predicted Progression Category - Mild, Moderate, Severe Progression
d. Based on current stage and progression category, we estimate that your likelihood to Deterioration to Stage 5 is high/moderate/low
e. CDSS

Printed Report



Participant Report

UHID	: 1234	**Name**	: John	**Age**	: 67
Gender	: Male	**Location**	: HYd	**Mobile**	: 9999999991

ABOUT CKD :

PERSONAL HEALTH HISTORY

Diabetes Mellitus	Yes ☐	No ☑	Hypertension	Yes ☑	No ☐
Anemia	Yes ☐	No ☑	CVD	Yes ☑	No ☐
Dyslipidaemia	Yes ☐	No ☑	Hyperkalemia	Yes ☐	No ☐
Pulmonary	Yes ☐	No ☐	Urological Problems	Yes ☐	No ☑
Systemic Illness	Yes ☐	No ☑			

CURRENT LIFESTYLE

Albumin Serum	3.9	Sodium	139	Bilirubin	0.5
Calcium Serum	9.3	Urea	68	Potassium	4.8
Hemoglobin	10	Alkaline Phosphatase	90	Platelet Count	225
Creatinine Serum (in mg/dl)	2.1	Uric Acid	7.7	ALT	27

CKD Progression

Predicted CKD Stage	Predicted Category of Progression	Predicted rate of Deterioration
CKD Stage G3b	Severe Progression	0.68 - 0.73

Based on the current stage and predicted progression category, we estimate that your likelihood to Deterioration to Stage 5 is **High**

4. Disclaimer
   a. This is not a diagnostic tool, it does not guarantee the accuracy of the result and cannot be independently acted upon.
   b. This Disease Progression Model and Clinical Algorithm are general guideline for Physicians. Any additional laboratory investigations, Diagnostic Imaging, Treatment, or Patient Education related to lifestyle management are under the Physician's /Nephrologist's discretion.
   c. To ensure the information in the report is up to date, accurate, and correct, the Doctor shall be consulted to interpret the report.
   d. Apollo Hospitals and its Staff do not offer any assurance on the information made available or be liable for any loss or damage as the said report is based on the AICKD without any intervention from their side.
   e. By usage of AICKD, it is deemed that the beneficiary of this service has agreed to get the same done at his own risk and further agrees with this disclaimer without any limitation or any clauses or sub-clauses.

The Research

Bayesian Deep Learning Algorithms to Predict the Rate of Deterioration in Chronic Kidney Disease

Objective: This study aimed to predict the rate of eGFR deterioration over a time period using the Chronic Kidney Disease AI Tool developed at Apollo Hospitals, utilizing Bayesian Deep Learning Algorithms.

Background: Progression to chronic kidney disease (CKD) is often asymptomatic warranting early detection for effective management and improved outcomes. Objective of the study is to predict the rate of progression using the Clinical & Lab Data (OMOP Ver 4.5) and various machine learning (ML) techniques in chronic kidney disease and to use insights for therapeutic interventions.

Methods: The study was conducted at ~~five~~ seven major Apollo Hospitals in India using a retrospective cohort design. Over 60,000 patient records aged between 20 and 80 years were initially considered. After applying specific exclusion criteria, a final cohort of 1,529 patients with Chronic Kidney Disease (CKD) was obtained. These patients showed disease progression over a period of 3 years, characterized by a decrease in estimated glomerular filtration rate (eGFR). The clinical parameters considered in the study included age, gender, type 2 diabetes, hypertension, dyslipidemia, frequent urinary tract infection, systemic disease, significant cardiovascular disease, and lab parameters such as Creatinine, Albumin, Urea, Uric Acid, and serum electrolytes. Bayesian Neural Networks (BNNs) were employed for modelling to predict the rate of eGFR deterioration. The models were developed and validated using a K-fold cross-validation technique (K=5) to prevent overfitting or underfitting.

Results: Multivariate Odds Ratio showed significance for diabetes (OR 3.2 CI-2.85 - 3.55), age (OR 2.6 CI2.14-2.93), hypertension (OR3.3 CI-2.97-3.63) amongst the clinical features. Similarly, feature importance was high for creatinine, eGFR, urea, hemoglobin, albumin and sodium levels with the outcome variable being the Rate of deterioration or Progression of CKD . The results for regression equations are provided in Fig 1 with R being notable in early CKD changes (G1 - >90 ml/min/1.73 m). Overall Bayesian Deep Learning Regression results with K-Fold show an average R2 - 0.4265 with Mean Squared Error - 0.0147. A Bayesian Neural Network (BNN) Classifier is used to extend NN by

incorporating uncertainty estimates related to eGFR deterioration along with K-Fold Validation. It's AUC at threshold 0.05 shows 0.85 (AP at 0.83) and 0.10 is at 0.88 (AP at 0.73) with varying Thresholds of eGFR deterioration at 0.05, 0.10, 0.15 & 0.20 (ml/min/1.73 m) / day multiple classification models were Developed.

Conclusion:
Bayesian Deep Learning algorithms effectively predicted CKD progression. The regression model achieved an R^2 of 0.4265 and an MSE of 0.0147. The best classification performance was a PRC of 0.83 (AUC 0.85) at a 0.05 deterioration rate threshold and an AUC of 0.88 (AP 0.73) at a 0.10 threshold, highlighting their potential for early detection and intervention planning.

Keywords
Chronic Kidney Disease (CKD), CKD Progression, eGFR, Bayesian Neural Network (BNN), Artificial Intelligence (AI), Machine Learning, K-fold Cross Validation, Classification, Regression, Multivariate Odds Ratio

RESULTS
The results of the study are based on the Bayesian Neural Network (BNN) models, both for regression and classification, as they pertain to the rate of deterioration or progression in chronic kidney disease (CKD).

In case of BNN regression, the following results (refer table 3) are the best performing results obtained through K-Fold Cross validation and then testing on the same model are as follows:

BNN Regression Model Parameters							
Hidden Sizes	**Activation**	**Loss Function**		**Optimizer**	**Learning rate**	**Epochs**	**Batch Size**
(64, 16)	ELU (alpha = 1.0)	Negative-Log Likelihood		adam	0.0001	750	16
K-Fold - Validation Scores				**K-Fold - Test scores**			
avg_r2	**avg_mse**	**avg_mae**	**avg_adj_r2**	**r2**	**mse**	**mae**	**adj_r2**
0.3843	0.0249	0.08	0.3603	**0.4265**	0.0147	0.0636	0.4163

Ethics Perspective

Title	AICKD – Chronic Kidney Disease Progression Model	Centers	India – Apollo Hospitals - Hyderabad, Chennai, Kolkata, Bhubaneshwar, Mumbai, Bangalore, Nashik
Principal Investigators	Nephrology Consortium Doctors	Institutional Ethics Committee Approval	Applied For
Data	Retrospective – 2010 to 2022	Safety	Model advocates risk scores that are interpreted by clinicians through safe Machine (API) – Human (Clinician) Interaction
Sample Size + Missing Data	5.5 k Inpatients data - No imputations	Inclusiveness & Fairness	At admission data includes clinical comorbidities & conditions | No socioeconomic discrimination
Personal Health information	De-identified all PHI during analysis, model building, API hosting and Prospective Use	Privacy & Confidentiality	Data secured at Apollo Azure Tenant with all relevant compliance + conforming to laws
Addressing Bias (Geographical / Ethnic / Temporal / Gender etc.)	Multiethnic – All Adult Population Group – Male to Female –69:31 – Time Period – 2010 to 2022 Automation Bias addressed at API Clinical Use	Accuracy + Efficacy	Regression Metrics - R^2 - 0.4265
Risk Groups /Output	Predicted CKD stage & e GFR range of CKD Diagnosed Patients	Informed Consent	Yes – Template & Protocol (Prototype Attached)
Model Specification	Bayesian Regression Model Hazard Ratio + KM Plots	API – Ease of Use + Interpretation	Flows to Clinical Algorithm Standard Clinical Definitions + Lab Units Used
Clinical Algorithm Update (Version)	Version 2 – October 2024	Validation + Peer Review	Abstract Accepted by ISN World Congress of Nephrology 2025 (WCN'25)
Intellectual Property Rights (IPR)	Patent Application| In Process	Certifications & Compliance	ISO 13485:2016 Certification | MD 763515 CDSCO Application No for Medical Device| Apollo-Hyder-TE/M/MD/007509

Frequently Asked Questions

Introduction

AI Chronic Kidney Disease Progression model is a novel artificial intelligence-based disease Progression model that predicts the CKD-diagnosed individual's progression into various stages of CKD in 365 days. Apollo Hospitals developed this model. The methodology helps to stratify the CKD patients' progression into each stage of CKD with an R^2 of 0.44

Why is AICKD different or What is the advantage of this score?

1. The machine learning model was developed with Indian data and has higher accuracy than the conventional risk score.
    a) Classification models + Extreme Gradient Boost model + Regression Models
    b) Model built and validated with Over 5,500 CKD Patient data since 2010
    c) R^2 – 0.44 (Development and Validation) Cohort
2. Comprehensive & Holistic Risk Assessment
3. Pioneering Disease progression model for all stages of CKD
4. The tool's objective is to forecast the progression of chronic kidney disease (CKD) within either 180-day or 360-day periods, aiding in strategic treatment planning.
5. The tool uses a diverse set of parameters, such as eGFR value from multiple patient visits, lab parameters, and comorbidities extracted from EMR via NLP techniques. These factors, not utilized in other models, enhance prediction accuracy by providing a holistic understanding of the patient's CKD condition.

What is the Interpretation & Adoption Message

1. AI Algorithm + Clinicians - This Disease progression Assessment tool has been built as an adjunct tool for physicians to identify the progression of CKD patients into different stages and End-stage renal failure.
2. CKD Progression - This Disease progression Risk Assessment Tool is not Intended to be used for diagnosis of chronic kidney disease. Its limitations include Undiagnosed Chronic Kidney Disease.

Where can the physicians use the AICKD tool –

This Disease progression Assessment tool is Intended for use at Outpatient Nephrology Clinics, Inpatient Nephrology units, Standalone Nephrology units, and Dialysis centers.

What are the Risk Factors Included –

a. Personal – Age | Gender
b. Time attributes - 365 days
c. Comorbidities - Hypertension | Diabetes mellitus | CVD | Dyslipidemia | Urological problems | Systemic Illness
d. Lab parameters - Albumin - Serum | Calcium Serum | Hemoglobin | Potassium | Sodium | Urea | Alkaline Phosphatase | Magnesium | ALT | Total Bilirubin | Platelet Count | Uric Acid | eGFR at first Visit | HBA1C

What is the Output and Follow-Up for the CKD Progression Model

a. Current CKD Stage
b. Predicted Rate of Deterioration
c. Predicted Progression Category - Mild, Moderate, Severe Progression

d. Based on the current stage and progression category, we estimate that your likelihood to Deterioration to Stage 5 is high/moderate/low
e. CDSS

Is this a diagnostic tool?

This is not a diagnostic tool, it does not guarantee the accuracy of the result and cannot be independently acted upon. It is designed to predict the progression of chronic kidney disease (CKD) in patients who have already been diagnosed with the condition.

Does this contradict the Physician's view?

This Disease Progression Model is a general guideline for physicians or Nephrologists. It complements a physician's expertise, providing an AI-backed prediction of CKD progression to assist in strategic treatment planning.

How does one ensure the accuracy of the AICKD tool

To ensure the information in the report is up to date, accurate, and correct, the Doctor shall be consulted to interpret the report. Additionally, the input data should be accurate and as per the conventional metrics used.

Is this a substitute for any diagnostic test or clinician's advice

Absolutely Not. This is an adjunct tool made with the Clinical Features of the Patient. It doesn't substitute for any tests or advice.

What are the disclaimers for the use of this tool?

Apollo Hospitals and its Staff do not offer any assurance on the information made available or be liable for any loss or damage as the said report is based on the AICKD Disease Progression Model, without any intervention from their side.

By usage of the AICKD Disease Progression Model, it is deemed that the beneficiary of this service has agreed to get the same done at his own risk and further agrees with this disclaimer without any limitation or any clauses or sub-clauses.

Can the report be shared with other clinicians?

Yes, each patient shall get a printed report or PDF copy which can be kept by the patient maintaining privacy and confidentiality.

How is Safety addressed?

The model advocates disease progression that is interpreted by clinicians through safe Machine (API) – Human (Clinician) Interaction. Informed consent from each individual is obtained before the Disease Progression.

Definitions

Chronic Kidney Disease

CKD is defined as kidney damage or glomerular filtration rate (GFR) <60 mL/min/1.73 m2 for 3 months or more, irrespective of cause. Kidney damage can be detected by the presence of albuminuria, which is an excess amount of protein in the urine.

Classification: CKD is classified into five stages based on the level of GFR, from stage 1 (GFR >90 mL/min/1.73 m2) to stage 5 (GFR <15 mL/min/1.73 m2 or dialysis or transplantation). The cause, GFR,

and albuminuria criteria (CGA classification) are used to further stratify CKD patients and assess their risk of progression and complications.

Source:
https://kdigo.org/wp-content/uploads/2017/01/Position-Paper-Definition-and-Classification-of-Chronic-Kidney-Disease-in-Adults-Worldwide-2004.pdf.
https://www.kidney-international.org/article/S0085-2538%2815%2954924-7/pdf.

eGFR

eGFR is a measure of kidney function that is estimated from the level of creatinine in the blood. It is expressed in milliliters per minute per 1.73 square meters of body surface area (mL/min/1.73 m^2). An eGFR of 60 mL/min/1.73 m^2 or higher is considered normal. An eGFR of less than 60 mL/min/1.73 m^2 indicates kidney disease.

Stage	eGFR(mL/min/1.73 m^2)	Description
G1	≥90	Normal or high kidney function
G2	60-89	Mildly decreased kidney function
G3	30-59	Moderately decreased kidney function
G4	15-29	Severely decreased kidney function
G5	<15	Kidney failure

Source: National Kidney Foundation

Risk factors for chronic kidney disease (CKD)

Domains	Example Conditions
Common risk factors	Hypertension Diabetes Cardiovascular Diseases (including heart failure) Prior AKI
People who live in geographical areas with a high prevalence of CKD	Areas with endemic CKD Environmental exposures
Genitourinary disorders	Structural urinary tract disease Recurrent kidney calculi Gestational conditions
Multisystem diseases	Systemic lupus erythematosus Gout HIV Preeclampsia/eclampsia
Occupational exposures that promote CKD risk	Cadmium, lead, and mercury exposure Polycyclic hydrocarbons Pesticides
Family history	Kidney failure, regardless of identified genetic abnormality Hereditary kidney disease recognized to be associated with genetic abnormality (e.g., PKD, APOLI Disease, Alport syndrome)

Gestational conditions	Preterm birth Small gestational size Preeclampsia

Source: Kdigo 2023 clinical practice guideline for the evaluation and management of chronic kidney disease

Taking into account the suggested risk factors mentioned above, we have identified specific risk factors aligned with the available electronic medical records (EMR) data.
We have considered the following risk factors as a subset of the above parameters.

Cardiovascular disease
Cardiovascular disease (CVD), also called heart and circulatory disease, is an umbrella name for conditions that affect your heart or circulation. These include high blood pressure, stroke, and vascular dementia.
Source: British Heart Foundation

Coronary Artery Disease
Coronary artery disease (CAD) is a common type of heart disease that affects the blood flow to the heart muscle. It is caused by the buildup of plaque, a fatty substance, in the walls of the coronary arteries, which supply oxygen and nutrients to the heart. This plaque can narrow or block the arteries, reducing the blood supply to the heart and causing chest pain, shortness of breath, fatigue, or heart attack.

Source: https://www.cdc.gov/heartdisease/coronary_ad.htm

Hyperkalemia
Hyperkalemia is the medical term that describes a potassium level in your blood that's higher than normal.
Source: Mayo clinic.org

Pulmonary Disease/ Lung Disease:
Definition and classification of COPD and asthma:

i. Chronic Obstructive Pulmonary Disease (COPD) is a group of diseases that cause airflow limitation and inflammation of the airways. It is usually caused by exposure to noxious particles or gases, such as cigarette smoke. COPD is diagnosed by a post-bronchodilator FEV1/FVC ratio of less than 70%. The severity of COPD is classified by the degree of airflow obstruction, measured by the percentage of predicted FEV1[1].
ii. Asthma is a chronic inflammatory disorder of the airways that causes variable and recurrent symptoms, such as wheezing, coughing, and shortness of breath. It is often triggered by allergens, irritants, or infections. Asthma is diagnosed by the presence of bronchial hyperresponsiveness, which can be assessed by a bronchodilator or a methacholine challenge test. The severity and control of asthma are determined by the frequency and intensity of symptoms, the use of rescue medication, and the level of lung function[2].
iii. Asthma-COPD overlap syndrome (ACOS) is a condition that has features of both asthma and COPD. It is characterized by persistent airflow limitation, eosinophilic inflammation, and increased reversibility of airway obstruction. ACOS is more common in older patients, smokers, and those with a history of asthma. The diagnosis of ACOS is based on clinical criteria, such as a history of asthma before the age of 40, a history of allergies, and a positive bronchodilator response of more than 12% and 200 mL[34].

Source: COPD and Asthma | World Allergy Organization. https://www.worldallergy.org/education-and-programs/education/allergic-disease-resource-center/professionals/copd-and-asthma.
Asthma & COPD Overlap: Definitions, Measures | Journal of COPD Foundation. https://journal.copdfoundation.org/jcopdf/id/1142/Asthma-and-Chronic-Obstructive-Pulmonary-Disease-Overlap-The-Effect-of-Definitions-on-Measures-of-Burden.

Diabetes mellitus
The American Diabetes Association (ADA) defines Diabetes Mellitus as follows:

a. A fasting plasma glucose (FPG) ≥126 mg/dl. Fasting is defined as no caloric intake for at least 8 hr.
b. Symptoms of hyperglycemia and a casual (random) plasma glucose ≥200 mg/dl. Classic symptoms of hyperglycemia include polyuria, polydipsia, and unexplained weight loss. (At the time of diagnosis as a diabetic, B cell function is at 25% to 30%.)
c. An oral glucose tolerance test (OGTT) with a plasma glucose ≥200 mg/dl 2 hr after a 75 g (100 g for pregnant women) glucose load.
d. A haemoglobin A1c (HbA1c) value ≥6.5%.

In the context of the study, data collection method, and overall clarity, please follow the –

a. Patient with no history of diabetes and previous record of normal FPG / OGTT / HbA1c – Select NO
b. Patient with a history of diabetes and a current record of HbA1c <7.5% - Select Controlled (this is irrespective of a patient under / not under medication/treatment)
c. Patient with a history of diabetes and a current record of HbA1c ≥7.5% - Select Uncontrolled (this is irrespective of a patient under / not under medication/treatment)

Source – ACP Guideline 2018 - American Diabetes Association. Standards of Medical Care in Diabetes-2018 Abridged for Primary Care Providers. Clin Diabetes. 2018 Jan;36(1):14-37. Doi: 10.2337/cd17-0119. PMID: 29382975; PMCID: PMC5775000.

Hypertension
Normal blood pressure (BP) in adults can be defined as systolic BP <120 mm Hg and diastolic BP <80 mm Hg.
Prehypertension is defined as systolic BP between 120 and 139 mm Hg or diastolic between 80 and 89 mm Hg.
Hypertension can be divided into
Stage 1: systolic BP from 140 to 159 mm Hg or diastolic BP from 90 to 99 mm Hg and
Stage 2: systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg.

Source - Giles TD, Materson BJ, Cohn JN, Kostis JB. Definition and classification of hypertension: an update. J Clin Hypertens (Greenwich). 2009 Nov;11(11):611-4. doi: 10.1111/j.1751-7176.2009.00179.x. Erratum in: J Clin Hypertens (Greenwich). 2010 Jan;12(1):13. PMID: 19878368; PMCID: PMC8673286.

Dyslipidemia or Elevated Lipids

1. An elevated lipids diagnosis
2. A prescription for elevated lipids medication
    a. statins or statin combinations
    b. fibrates
    c. niacin
    d. bile acid sequestrates, and/or

e. other lipid-modifying agents

3. Lab results
    a. triglyceride level ≥250 mg/dL
    b. HDL <40 mg/dL for males and <50 mg/dL for females.
    c. non-HDL value ≥ 160 mg/dL

Source: National Cholesterol Education Program (NCEP) Expert Panel on Cholesterol Levels
Preventive Cardiology: Companion to Braunwald's Heart Disease

Anemia
Anemia is a condition in which the number of red blood cells or the hemoglobin concentration within them is lower than normal.
Source: World Health Organization

Systemic Illness /Diseases
A systemic disease affects a number of organs and tissues, or affects the body as a whole
Source: Dorland's Illustrated Medical Dictionary,28th edition (Harcourt Brace & Company). Page 489,1653

Urological Problems - Renal and Urological Disorders
A renal disorder refers to any disease of the kidneys. Urological disorders are diseases of the kidneys and urinary tract.
Source: MedlinePlus.gov: National Library of Medicine