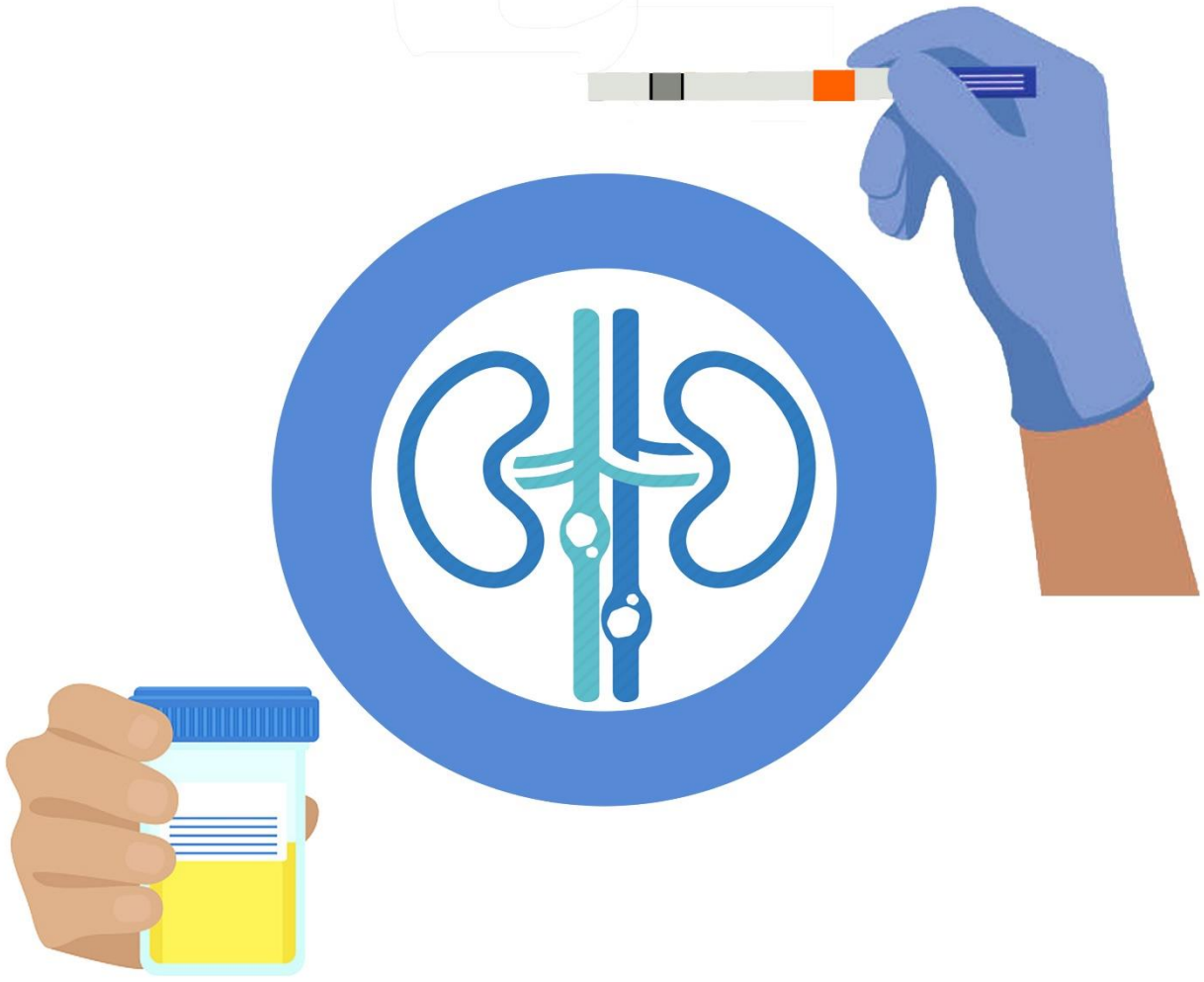
Health Technology Assessment in India (HTAIn)

HTA REPORT

Cost Effectiveness of Population-based screening for Chronic Kidney Disease among adults aged 40 years and above with Type 2 Diabetes Mellitus in Kerala and Puducherry



Health Technology Assessment Resource Centre (HTARC)

Department of Preventive and Social Medicine, JIPMER, Puducherry

HTA REPORT

On

COST EFFECTIVENESS OF POPULATION-BASED SCREENING FOR CHRONIC KIDNEY DISEASE AMONG ADULTS AGED 40 YEARS AND ABOVE WITH TYPE 2 DIABETES MELLITUS IN KERALA AND PUDUCHERRY

in Collaboration with HTARC,

Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST)

Principal Investigator
Dr. Sitanshu Sekhar Kar
Professor & Head
Department of Preventive and Social Medicine
JIPMER, Puducherry

Co-Principal Investigators
Dr. Biju Soman
Professor
Achutha Menon Centre for Health Science Studies
SCTIMST, Trivandrum

Dr. Kavitha Rajsekar
Scientist-E
Department of Health Research
Ministry of Health and Family Welfare
New Delhi

JIPMER HTAIn Team Members
Dr. Rajasulochana SR
Dr. S Mathan Kumar
Mr. Parthibane S
Mr. Saravanan E
Mrs. Jeyanthi Anandraj

SCTIMST HTAIn Team Members
Dr. Antony Stanley
Dr. Ashis Das

ABBREVIATIONS

ACR	Albumin Creatinine Ratio
AER	Albumin Excretion Rate
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
DKD	Diabetic Kidney Disease
ESRD	End-Stage Renal Disease
eGFR	estimated Glomerular Filtration Rate
ICER	Incremental Cost-effectiveness Ratio
ISN-KDDC	International Society of Nephrology's Kidney Disease Data Center
INR	Indian Rupee
KDIGO	Kidney Disease: Improving Global Outcome
MDRD	Modification of Diet in Renal Disease
NHSCDI	National Health System Cost Database for India
NPCDCS	National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke
NPV	Negative Predictive Value
OWSA	One way Sensitivity Analysis
PPV	Positive Predictive Value
PCR	Protein Creatinine Ratio
PSA	Probabilistic Sensitivity Analysis
QALY	Quality-Adjusted Life Years
SCORED	Screening for Occult Renal Disease
SRS	Sample Registration System

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Executive Summary

Chronic Kidney Disease (CKD) is emerging as a major public health issue in India, especially among persons with diabetes. CKD remains asymptomatic till late stage when intervention cannot halt the progression of the disease. Therefore, there is an urgent need to detect the disease early. Despite the high CKD prevalence among diabetic persons in states like Kerala and Puducherry, screening is still lacking. The objective of the HTA was to evaluate the cost effectiveness of annual population-based screening of CKD under two scenarios among normotensive people with diabetes aged 40 years and above compared with the current scenario. In scenario 1, primary screening of microalbuminuria was performed by the community health worker with dipstick, followed by referral for confirmatory tests (spot urine ACR and/or serum creatinine for eGFR estimation). In scenario 2, urine sample was collected by the community health worker and tested for spot urine ACR at the health care facility, followed by serum creatinine.

A decision tree combined with Markov model was utilized to depict the screening process and the changes in natural disease progression of CKD under different scenarios. The model was simulated for a cohort aged 40 years and above. The study adopted a societal perspective,taking into account direct and indirect medical expenditure along with income loss due to illness.The study assumed a lifetime horizon. The input parameters for the model were derived from thecross-sectional STEPS survey conducted in Puducherry, national sample survey, National Health System Cost Database for India (NHSCDI) and the relevant literature in the domain. The Incremental Cost-Effectiveness Ratio (ICER) estimates were generated for both scenarios, along with sensitivity analyses and budget impact analysis. Further, a review of equity issues surrounding the CKD prevalence, treatment and management in the Indian context was conducted.

The results of the study are as follows: The ICER per QALY gained estimated for CKD screening among the diabetic population in the Indian context were ₹ 27,279 and ₹ 23,519 for scenario 1 and 2, respectively. These ICER values were found to be cost-effective at the threshold of one-time per capita GDP of India. The budget impact analysis for Puducherry/Kerala showed that the scenario 1 and 2 would cost ₹ 67.8/1,638.5 crore and ₹ 142.9/3,453.8 crore, respectively, over a 4-year period.

1. INTRODUCTION

1.1 Chronic Kidney Disease (CKD)

CKD is defined as kidney damage for three months or longer, as defined by structural or functional abnormalitiesof the kidney, with or without decreased glomerular filtration rate (GFR), manifest either by pathological abnormalities or markers of kidney damage, including abnormalities in the composition of the blood, urine or imaging tests. (1)

1.2 Disease Burden

The incidence and prevalence of chronic kidney disease (CKD) are increasing and becoming a major public health problem. Various studies across India show that the prevalence of CKD ranges between <1% to 13% and a recent study from International Society of Nephrology's Kidney Disease Data Center (ISN-KDDC) conducted in 2016 statedprevalence to be 17%. (2) The prevalence of CKD in Kerala is 4.6% among the general populationand 45.3% in the diabetes population. (3) The prevalence of CKD in rural Puducherry is 24.2% among the age group more than 50 years. The majority of CKD falls under stage 2 CKD and nearlyhalf of the study participants have no history of type 2 diabetes mellitus and hypertension. (4) CKD gradually leads to end-stage renal disease (ESRD). Early detection of CKD followed by risk stratification and early treatment delays the progression and prevents the ESRD and other related complications. In India, about 2.2 Lakh people are diagnosed with ESRD every year. (5) Therefore, early screening and diagnosis of CKD would enable early treatment, which prevents and delay the progression of the disease to the ESRD. In India type 2 diabetes mellitus patients with renal complications spent ₹ 12,690 on disease management. (6) A study conducted by Satyavani K et al. reported direct cost associated with per day hospitalization for themanagement of CKD is around ₹ 12,664. (7) This is similar to the total median cost given above by Kumpatla et. al.. Further, the total median unit cost spent towards hemodialysis and kidney transplantation is around ₹ 61,170 and ₹ 3,92,920, respectively. (8)

The primary prevention of CKD is to identify the high risk population early and halt the progression of CKD. People have any one or more of the following risk factors, such as smoking habits, diabetes, hypertension, obesity, cardiovascular disease and family history of CKD, are susceptible to develop CKD which could be prevented by early screening. (9) Due to the rising CKD incidence, several national agencies recommend CKD screening in the general population for monitoring the disease progression and preventing the development of ESRD. However, the

early stages of kidney disease are usually asymptomatic which makes the CKD difficult to be detected in the early preclinical phases. The presence of proteinuria or albuminuria, i.e. increased level of protein/albumin excretion, in urine helps in identifying renal disease followed by assessing the disease progression through the reduction in glomerular filtration rate (GFR).

1.3 Etiologies of CKD

There are various causes for chronic kidney disease. Diabetic Nephropathy, Chronic Glomerulonephritis, Hypertension associated CKD, Cystic Kidney Disease, Tubulointerstitial Nephropathy are the common causes of CKD. (10) According to an Indian study reported by Parameshwaran et al conducted among CKD patients, the major cause of CKD is from unknown etiologies, followed by diabetic nephropathy, Chronic Glomerulonephritis and Chronic interstitial nephritis. (11) Due to poor availability of data on the unknown etiology of CKD, the current model focuses only the CKD caused due to Type 2 diabetes mellitus.

1.3.1 Diabetic kidney disease (DKD)

People with diabetes develop diabetic nephropathy (presented with microalbuminuria or macroalbuminuria) which further leads to CKD which is otherwise known as diabetic-induced CKD or diabetic kidney disease (DKD). (12) However, the proportion of DKD presented with non-albuminuric variant. (13) Type 2 diabetes patients are more than twice as likely as type 1 diabetic individuals to develop DKD. (14) In India, 40% of people with type 2 diabetes develop DKD. (15) DKD is the second most common cause of ESRD and the other major portion falls under unknown etiology. (16)

1.4 Screening and Diagnostic Tests for CKD

1.4.1 Proteinuria:

Proteinuria is a hallmark of CKD. Under physiological condition proteins such as immunoglobulins, albumins, Tamm-Horsfall mucoproteins, etc., are excreted at a basal level in urine. Excretion of protein above the normal range i.e. > 150 mg per day is suggestive of proteinuria which could be detected by several methods. (17) Classically protein excretion is quantified in the urine by Lowry's method from the urine specimen collected at different time intervals for 24hrs. Although it is a gold standard method for the detection of proteinuria, the major limitations of the method are the time taken for the test and inaccuracy due to handling errors. Another convenient method evolved which is the estimation of urinary protein-creatinine ratio

(PCR). The PCR could be done in a single voided urine sample which is well correlated with the estimates which are done with 24hrs urine specimens. (18–21) PCR is more accurate and it signifies a wide range of clinical conditions of renal disease. The PCR $\leq$ 0.2 mg/mg represents the normal range, whereas the ratio above 3.5 mg/mg is considered nephrotic range proteinuria and indicative of renal diseases. (22)

Dipstick test for proteinuria is a widely accepted test for mass screening and home-based monitoring of proteinuria. Dipstick results usually represent benign proteinuria whose association with CKD needs to be confirmed through diagnosis by PCR and other tests mentioned above. However, the accuracy of the dipstick test is well studied in comparison with both 24hrs urine specimen tests and PCR under various conditions and subjects. (23) The dipstick test cutoff values and sensitivity/specificity in predicting respective PCR. (24) Sensitivity and specificity of dipstick cut-off for detecting respective spot urine ACR and eGFR are well studied. (25)

1.4.2 Albuminuria:

Albuminuria is another condition where the abnormal excretion of albumin is detected in the urine. Unlike proteinuria, which represents whole protein excretion in the urine which includes all the proteins ranged from low to high molecular weight, albuminuria indicates only albumin. Estimation of albuminuria is another test that signifies only the excretion of urine albumin which is a high molecular weight protein whose abnormal secretion in urine is majorly associated with glomerular dysfunction. As like proteinuria, albuminuria could be assessed through albumin-creatinine ratio (spot urine ACR). Albuminuria can be classified into 3 stages, normal to mild (ACR < 30 mg/g), microalbuminuria or moderately elevated (ACR 30-300 mg/g) and macroalbuminuria or severely elevated (ACR > 300 mg/g). (26) There is no evidence on direct correlation and comparison with proteinuria and albuminuria especially in terms of cost-effectiveness. However, the diagnosis of CKD in diabetic, hypertensive and aging population by either measuring proteinuria or albuminuria followed by angiotensin converting enzyme inhibitor (ACEI) treatment intervention is cost-effective. However, based on the evidences, spot urine ACR shall be used to screen CKD in diabetics and PCR could be adopted for screening the non- diabetic population who are at risk of developing CKD. (27)

1.4.3. Estimated GFR:

On the other hand, estimation of **GFR** is done using either inulin or iothalamate infusions whose clearance in the plasma assesses the filtration capacity and function of the kidney. The GFR is estimated from the serum creatinine using a number of different formula. For adults, the four-variable Modification of Diet in Renal Disease (MDRD) formula has been widely adopted if eGFR is less than 60 ml/min/1.73m^2 which relies on creatinine, age, sex and race. The CKD-EPI equation is largely used for population-based screening were eGFR would usually be more than 60 ml/min/1.73m^2. (28) As per 'The Kidney Disease: Improving Global Outcomes (KDIGO)' clinical practice guidelines, stages and progression of CKD is defined by the level of eGFR (Figure 1). The recent guideline released in 2012 has included albuminuria along with eGFR in characterizing the severity and progression of CKD. As per the study conducted by Barai S et al., the eGFR threshold which is given by KDIGO as 60 mL/min/1.73 m^2 might not be appropriate for India. (29)

StatSensor is a strip-based handheld analyzer for whole blood creatinine testing could also be considered for population-based screening. (30) The StatSensor is also used to calculate eGFR using the MDRD equation. Diagnostic accuracy of StatSensor is reported as 90.2% and the difference between serum creatinine values tested using the StatSensor and laboratory test is not more than 0.3 mg/dl. (31) The sensitivity, specificity of testing serum creatinine in StatSensor is 100% and 89%, respectively, whereas the positive predictive and negative predictive value is 50% and 100%respectively. Accuracy for detecting patients with an estimated glomerular filtration rate < 45 ml/min/1.73 m^2 were subsequently calculated.

1.5 Staging and Prognosis of CKD:

The rationale for staging of CKD is to stratify patients based on their risk of disease progression and development of complications. It also directs clinicians for appropriate monitoring and treatment planning. According to KDIGO guidelines 2012, the CKD staging is based on two major components, GFR and albuminuria as mentioned earlier. (26)

CKD patients can be broadly classified into 18 categories using the range of values of GFR and albuminuria (Figure 1). The heat map indicates 4 levels of risk (green-low, yellow-moderate, orange- high and red-very high risk) to predict the disease outcomes with respect to ESRD, CVD related mortality and other related complications.

Table: 1 Glomerular Filtration Rate categories in CKD

S. No.	GFR Category	GFR (ml/min/1.73 m^2)	Grade of severity
1.	Stage 1	≥90	Normal or high
2.	Stage 2	60-89	Mildly decreased*
3.	Stage 3a	45-59	Mildly to Moderately decreased
4.	Stage 3b	30-44	Moderately to severely decreased
5.	Stage 4	15-29	Severely decreased
6.	Stage 5	<15	Kidney failure

**Relative to young adult level.*
In case of no evidence of kidney damage, both grade 1 and grade 2 would not fulfill CKD criteria.

Table: 2 Albuminuria categories:

S. No.	Albuminuria category	AER (mg/24 hrs.)	ACR (mg/g)	Grade of severity
1.	A1	< 30	< 30	Normal to mild
2.	A2	30-300	30-300	Moderate*
3.	A3	>300	>300	Severe#

AER- Albumin Excretion Rate; spot urine ACR- Albumin Creatinine ratio.
**Relative to young adult level.*
#Nephrotic syndrome included (AER > 2200 mg/24 hrs. or spot urine ACR > 2220 mg/g)

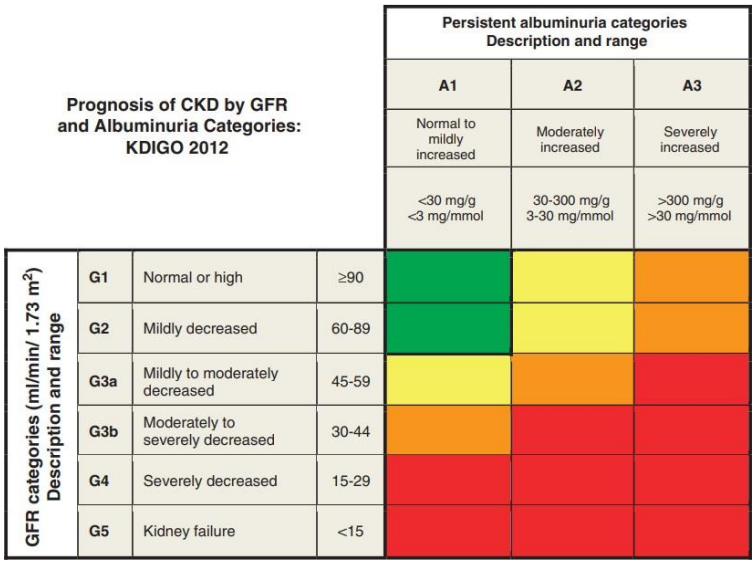


Figure: 1 GFR and albuminuria category of CKD (*Source: KDIGO guidelines 2012*)

The colored grids indicate the risk of CKD progression intensifies from low (Green) to very high (Red) risk.

1.6 Cost-effectiveness of CKD screening

There are no cost-effective studies conducted for CKD screening in India so far. Most of the cost-effective studies conducted in US and European countries identified that the screening of CKD using microalbuminuria or proteinuria among diabetes or/and hypertension population is cost- effective compared to CKD screening in general population. (32) However, screening the general population at multiple intervals is found to be cost-effective in some countries. (33) Screening of apopulation with a high incidence of CKD in the community may also be cost-effective provided effective screening tools and drug therapy. (34) Screening of adult population regardless of risk factors using proteinuria dipstick methods is cost-effective.

The present study is aimed to conduct cost-effectiveness analysis for the implementation of population-based screening intervention for CKD in the normotensive diabetic population above 40 years of age. Considering the feasibility of conducting CKD screening at the population level, the present study proposes two screening scenarios (Figure 2(a) and 2(b)). In scenario 1, primary screening of microalbuminuria is performed by the community health workers with dipstick, followed by referral for confirmatory tests (spot urine ACR, followed by serum creatinine - eGFR estimation). In scenario 2, urine samples are collected by community health workers and tested for spot urine ACR at the health care facility, followed by serum creatinine. Both the scenarios were compared with the no screening scenario for evaluating the cost- effectiveness of population-based CKD screening.

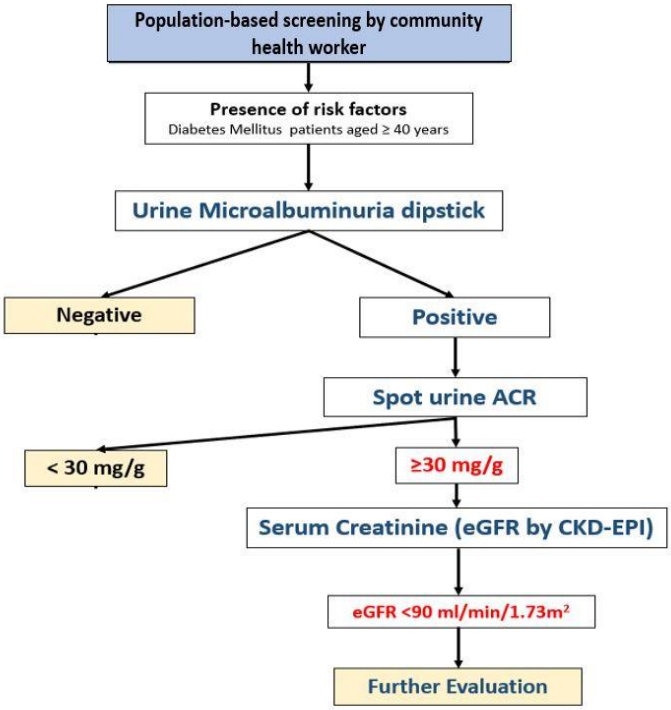


Figure 2(a). Scenario 1 population-based screening with dipstick microalbuminuria and urine ACR followed by GFR estimation

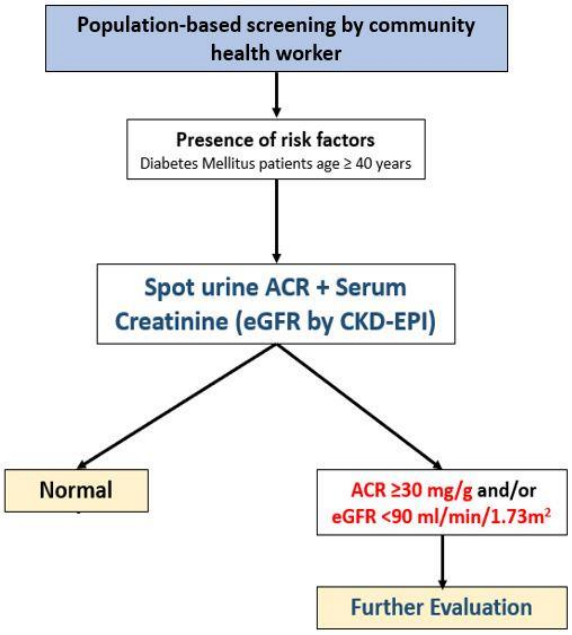


Figure 2(b). Scenario 2 population-based screening with simultaneous ACR Test and eGFR estimation

2. RESEARCH QUESTION

Whether annual population-based screening of CKD is cost-effective among adults with normotensive type 2 diabetes aged 40 years and above?

3. OBJECTIVE

To estimate the ICER per QALY (Quality Adjusted Life Years) gained with annual population-based CKD screening strategies among adults with normotensive type 2 diabetes aged 40 years and above compared with the current scenario.

4. METHODOLOGY

4.1 Economic Evaluation

4.1.1 Frame Work: PICO

P (Population) – Patients with normotensive type 2 diabetes aged 40 years and above

I (Intervention) – Population-based screening of CKD

C (Comparator) – Current scenario (No screening)

O (Outcome) – ICER (Incremental Cost-Effectiveness Ratio) per QALY gained and per life years saved

4.1.2 Study Perspective:

The present study was conducted from a societal perspective. The costs incurred by the provider (health system) and patients (direct & indirect medical costs along with income loss due to illness) for alternative interventions and comparator were included in the economic evaluation.

4.1.3 Time Horizon:

The cost and consequences associated with the alternative interventions and comparator were simulated for a lifetime horizon i.e. until the entire cohort was completely absorbed in the death state.

4.2 Study Setting

Puducherry is one of the four districts of the union territory of Puducherry located along the easterncoast, in southern India. The district's population is 9.8 lakhs with majority (69.16%) residing in urban areas. The district has sex ratio of 1,029, life expectancy of 68.35 years, and literacy rate of 85.44%. (35,36) Puducherry stands seventh in Human Development Index (HDI) compared to other Indian states. (37)

As in other states in the country, the care for DM and HTN in Puducherry is delivered through a three-tier system of healthcare facilities (primary, secondary and tertiary) comprising public and private establishments. In each public healthcare facility, at the level of PHC and above, NCD clinic is being conducted once a day of each week. At the clinic, diagnostic tests (including annualscreening for CKD), treatment initiation, and follow-up consultations are provided to the patientswith free monthly drug distribution. Further, community health workers (ANMs, ASHAs) are involved in screening, treatment initiation and follow-up for the patients. The private healthcare facilities include privately owned hospitals and medical colleges which follow independent NCD care delivery strategies.

Currently, the treatment for both DM and HTN is effective as well as inexpensive across healthcare facilities in the country. (38) However, in India, only a minority of patients having DM or HTN have ever been diagnosed, received recommended treatment and most importantly have achievedcontrol status which are crucial in preventing the development and progression of CKD among patients. For instance, in India, among adults having raised blood glucose, 52.5% are aware of their diagnosis, 40.5% received treatment and 24.8% achieved control status; (39) the corresponding proportions among individuals having raised blood pressure were 45%, 13% and 8% respectively. (40)

4.3 Current Scenario / Comparator

Currently, there is no population-based screening of CKD in India. Although the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseasesand Stroke (NPCDCS) recommends those diabetic and hypertensive patients currently under treatment to undergo an annual check-up for microalbuminuria through spot urine ACR test at healthcare facilities, it is not yet fully implemented in Kerala and Puducherry. Therefore, we considered no screening scenario as the comparator for the study.

4.4 Study Intervention

We assessed the cost-effectiveness of two point-of-care screening scenarios for CKD screening in the normotensive diabetic population at the population level: Scenario 1 - Spot urine dipstick microalbuminuria was done twice with the interval of three months followed by spot urine ACR test and/or serum creatinine; Scenario 2 - Spot urine ACR test and serum creatinine were done parallelly. In both scenarios, community healthcare workers (CHW) reach out to the households and screen all the adult household members aged ≥40 years for hypertension using digital blood pressure apparatus, followed by screening only those normotensive members for type 2 diabetes using glucometer. The normotensive members with random blood glucose >120mg/dL were confirmed for type 2 diabetes by fasting blood glucose test performed at the primary health center. The confirmed normotensive diabetic patients aged ≥40 were screened for CKD by either of the two aforementioned screening scenarios.

Screening scenario 1 ensured the feasibility of population-level CKD screening. On the other hand, screening scenario 2 was a mathematical scenario that assessed the effectiveness of intervention by considering missed out cohort from the scenario 1 due to either lack of diagnostic accuracy of the dipstick or non-albuminuric presentation of CKD. The threshold range used for screening or diagnosis was trace or 1+ for spot urine dipstick, <30 mg/g ACR and <90 ml/min/1.73m^2 eGFR. Based on the ACR estimates, the patients with ACR >30 mg/g and normal renal function were treated with ACEI /ARB. Patient with eGFR between 90 and 15 ml/min/1.73m^2 was treated with conservative medical management and patient with <15 ml/min/1.73m^2 eGFR were managed with hemodialysis or peritoneal dialysis (26). Both the ACEI and renal replacement therapy (hemodialysis and peritoneal dialysis) were provided at the tertiary care level.

Table: 3 Intervention Scenarios

Screening scenarios	Target population	Dipstick micro albuminuria	Spot urine ACR	Serum creatinine
Scenario 1	Normotensive Diabetic Population (≥ 40 years)	All Cohort	Dipstick positive Cohort	Spot urine ACRpositive Cohort
Scenario 2	Normotensive Diabetic Population (≥ 40 years)	--	All Cohort	All Cohort

4.5 Model Overview and Cost-effectiveness Analysis

The study involved a decision tree combined with the Markov model for simulation of population-based screening strategies, as shown in figure 3. The cohort (N=1) enters into Markov simulation in any of the five health states (Normoalbuminuria, Microalbuminuria, Macroalbuminuria or Elevated Serum Creatinine (Elevated Sr. Cr.) and ESRD) in case of diabetic kidney disease with albuminuria or three health states (Normal, Elevated Serum Creatinine and ESRD) for the non- albuminuric type of chronic kidney disease among patients with diabetes. In addition, there is oneabsorbing state (Death).

- In scenario 1, the initial cohort undergoes the dipstick microalbuminuria (MA) twice, the second test was conducted three months after the first test. The tested positive cohort was subjectedto spot urine ACR and those found to have microalbuminuria >30 mg/g are further subjected to serum creatinine test. Others were not considered for further evaluation and hence this strategy misses out on a proportion of the cohort due to false-positive results. Likewise, in the second arm of the first scenario, the cohort was classified as true negative and false negative based on the dipstick MA test and assumed to present themselves with late diagnosis.
- In scenario 2, the entire cohort undergoes simultaneous spot urine ACR and serum creatinine tests. The cohort was classified into two subgroups i.e. albuminuric CKD and non-albuminuric CKD. In this scenario, there are four possible outcomes i) ACR (>30 mg/g) and elevated serum creatinine, ii) ACR (>30 mg/g) and normal serum creatinine, iii) ACR (<=30 mg/g) and elevated serum creatinine, and iv) ACR (<= 30 mg/g) and normal serum creatinine. Here the subgroups (i) and (ii) enter the albuminuric CKD arm of scenario 2 and the other two subgroups enter the non-albuminuricCKD arm.
- The cohort in the no screening scenario entered the Markov simulation according to the natural disease progression. The model assumed the cohort enter into the health states of Elevated Sr. Cr. and ESRD as late presentation.

The intervention model under both scenarios assumed that those diagnosed with microalbuminuriawith normal serum creatinine would be treated with ACEI. Benefits of ACEI was applied for reversing the ‘microalbuminuria’ and delaying the progression of ‘micro to macroalbuminuria’based on the evidence reported by Strippoli GFM et al. (41). On the other hand, the current scenario was not included with benefits of ACEI.

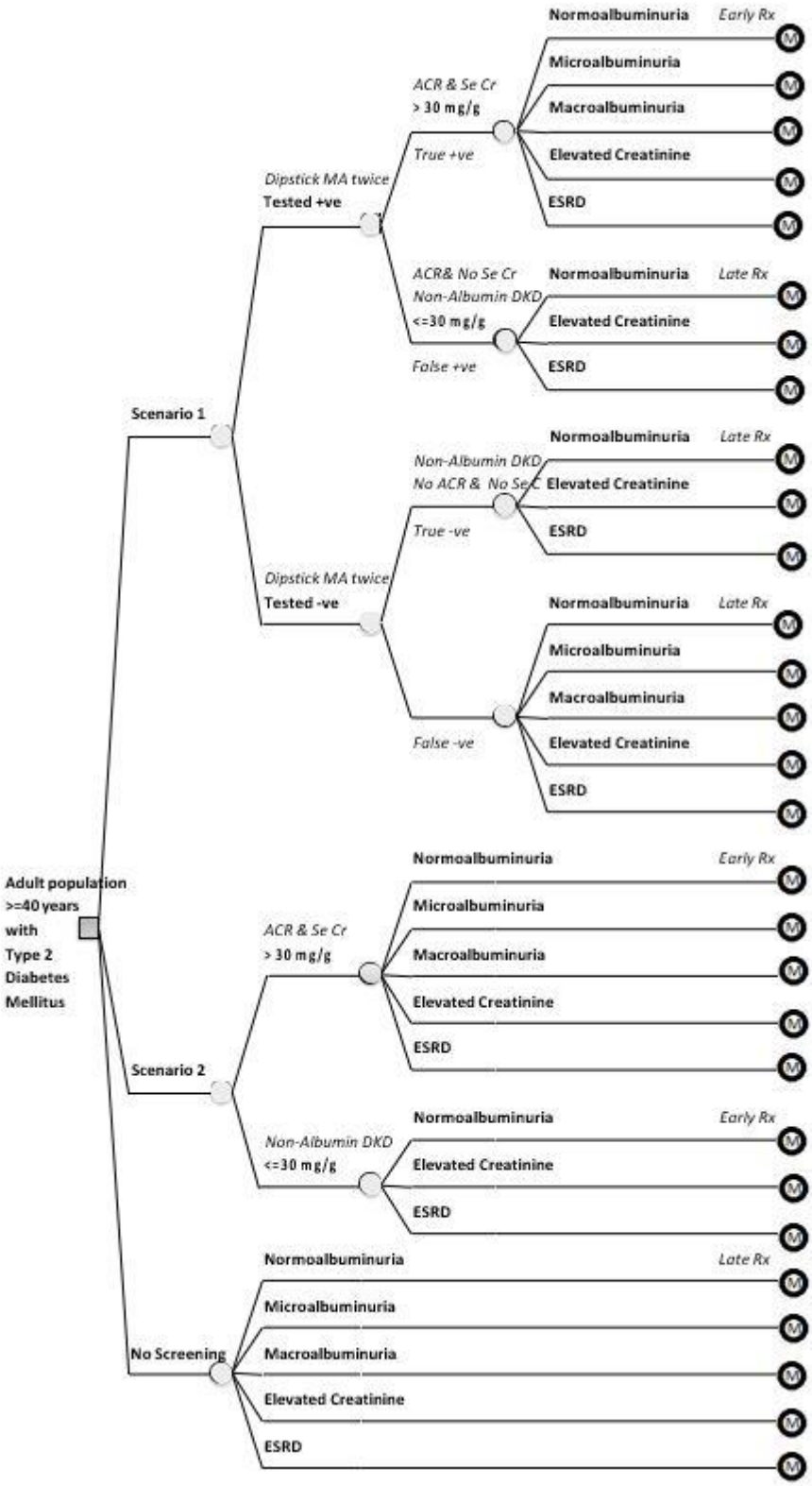
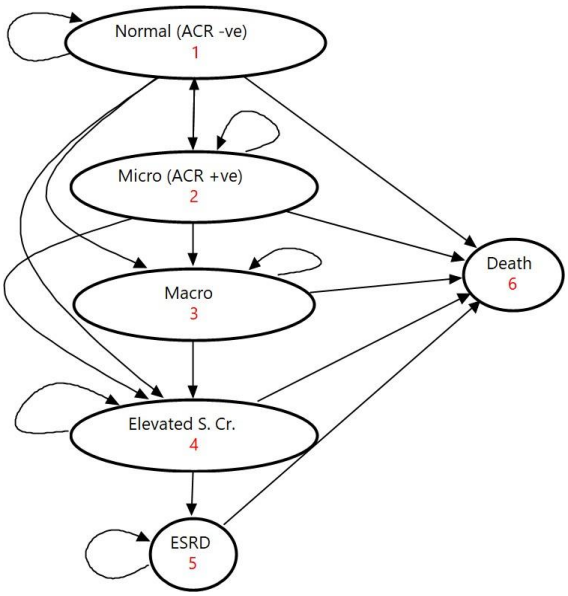


Figure: 3 (a) The Decision tree model



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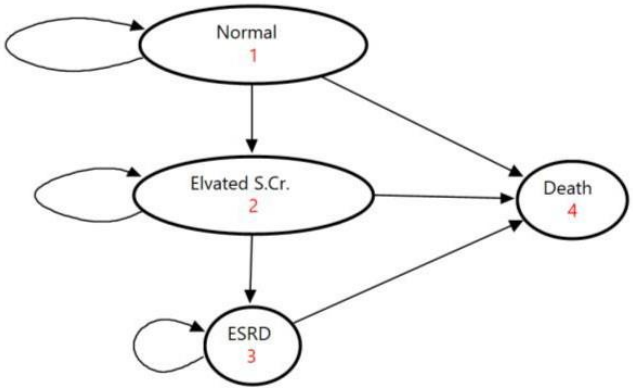

Figure: 3 (b) Albuminuric CKD

Figure: 3 (c) Non Albuminuric CKD

4.5 Data Collection and Model Inputs

Table 4 and 5 show the source of data for different components of the model. The diagnostic accuracy of the dipstick test was obtained from the literature. (42) Other clinical data related to the prevalence of CKD stages and transition probabilities were obtained from the targeted literature search. (43,44) All-cause mortality rates were collected from life table published by Sample Registration System (SRS) (45) and the diabetic specific mortality rate was taken from Mohan et al. (46)

4.6.1 Unit cost estimates

The unit costs for screening and treatment of CKD were compiled from multiple sources such as Government's current expenditure/ health system cost and based on market prices. These unit costs were adjusted for inflation and converted into 2021 prices. Different cost components (shown in table 5) are described as follows:

a. Cost for diabetes screening

A previous HTA report on population-based screening for diabetes computed the pooled unit cost (Haryana and Tamil Nadu) to be Rs 38.40 at the sub-centre level. We assumed the same for the model.

b. Microalbuminuria (MA) dipstick cost

The cost of MA dipstick applies only to scenario 1. It was assumed that the hypothetical screening strategy would be integrated with the NPCDCS. This implies that no additional manpower would be recruited and no duplication of cost on referral card, contingency and travel etc. Only the training cost of CHW and the recurring cost of MA screening would add into the ongoing NPCDCS. The unit cost would include the overhead cost of annual training of community health workers, per head consumables like urine container and personnel protective equipment such as disposable gloves, mask, sanitizer etc7 and Roche Test Kit with 30 dipsticks for 100 persons for the first-time screening and for 47.1 persons for the second time screening. The unit cost of conducting 1st time dipstick MA and 2nd time dipstick MA test ranged between ₹ 116 and ₹ 121 and ₹ 51 respectively in 2021 prices in Kerala and Puducherry. The details of costing are shown in appendix Table 1.

c. Diagnosis cost of spot urine ACR and Serum Creatinine

The unit cost of ACR and Serum creatinine was compiled from the market prices quoted online by different vendors across different parts of the country. The median price of ACR and Serum creatinine was found to be ₹ 506.5 and ₹ 135 respectively. In scenario 1, those tested positivewith MA dipstick twice would undergo ACR (72.8% of the eligible population) and those tested ACR >30 mg/g would be tested for Serum creatinine (43.2% of the eligible population) sequentially incurring outpatient cost twice. In scenario 2, all 100% of the eligible population would undergo ACR and Serum creatinine simultaneously in one time outpatient consultation.

d. ACEI cost

It is assumed that those diagnosed with microalbuminuria with normal serum creatinine would be treated with ACEI under both scenarios. On the other hand, the comparator strategy would not include the benefits of timely ACEI treatment. The unit cost of Angiotensin Converting Enzyme Inhibitor (ACEI) was taken from the National Health System Cost Database for India (NHSCDI).

Assuming ACEI is given twice a dayand the cost per dose to be ₹ 1.34 (NHSCDI), the annual cost for the treatment was estimated to be ₹ 978. Also, the drug cost for diabetes (Metformin, 500mg; Sulfonylurea, 1mg)per day was ₹ 6,613 (NHSCDI). The eligible population would be expected to make follow-up visits four times, incurring an outpatient consultation inclusive of income loss. From the NSSO data, we get the OOPE related to outpatient visits (₹ 695 per visit x 4 times) as ₹ 2,780. Adding up both, the unit cost for ACEI treatment would be ₹ 9,883.

e. Medical management of CKD stages

The cost associated with the medical management of CKD stages was taken from the paper by Ahlawat et al 2017 conducted in a public tertiary care setting. These costs were converted into 2021 prices accounting for inflation adjustments. This was multiplied with the proportion of patients in each of the CKD stages, to arrive at an expected unit cost of ₹ 20,222. Also, the drug cost for diabetes (Metformin, 500mg; Sulfonylurea, 1mg) per day was ₹ 6,613 (NHSCDI). Further, the OOPE related to outpatient visits (₹ 695 per visit x 12 times) was derivedfrom NSSO as ₹ 8,340. The unit cost of medical management of CKD stages is ₹ 35,176.

f. Dialysis cost

The proportion of people undergoing hemodialysis and peritoneal dialysis were taken from Parameshwaran et al. 2011. (16) The health system cost as well as the OOPE borne by patients due to hemodialysis was obtained from Kaur et al 2018. The cost of per session was ₹ 4,917 at 2021 prices) per year. Assuming 156 sessions, the unit cost of hemodialysis was ₹ 12, 72, 886. Likewise, the cost data for peritoneal dialysis was derived from Jeloka et al 2012. Further, the drug cost for diabetes (Metformin, 500mg; Sulfonylurea, 1mg) per day was ₹ 6613 (NHSCDI). The mean monthly cost of peritoneal dialysis was ₹ 27,569 which translated into ₹ 330,822 in 2021 prices.

Table: 4 Overview of Data Source for the Model

COST DATA	Health System and Patient (Direct and Indirect cost)	Screening and Diagnosis (Annual Unit Cost)	*Market Price, Literature and NSSO Data*
		Treatment (Annual Unit Cost)	
CLINICAL DATA	Diagnostic Accuracy	Screening Tests	*Literature* (42)
	Transition Probabilities	Across Health States	*Targeted Literature Search*
	Relative Risk	Treatment	
	Utilities and Life Expectancies	Each Health State	

4.6.2 Utility estimates

Utility indices for normo, micro / macro albuminuria health states were obtained from a HTA study. (47) Health utilities for hemodialysis and peritoneal dialysis were obtained from the primary study conducted in tertiary health care at Puducherry using EQ-5D-5L questionnaire and Indian specific health-related-quality of life tariff. (48) The utility associated with the health states of elevated serum creatinine was obtained from a Thailand study by Srisubat et al. 2014. (49) Based on demographics, the Thailand-specific health-related quality of life was assumed to be similar to the quality of life experienced by the population in India.

Table: 5 Model input parameters

Parameters	Base case	Lower limit	Upper limit	References
Prevalence of microalbuminuria using ACR	0.471	0.377	0.565	Grey Literature *(PhD Thesis)*
Prevalence of CKD in non-albuminuria population (NA)	0.062	0.050	0.075	
Sensitivity of dipstick microalbuminuria	0.917	0.734	1.000	(42)
Specificity of dipstick microalbuminuria	0.440	0.352	0.528	
Probability of normal	0.563	0.450	0.676	(50)
Probability of microalbuminuria	0.377	0.302	0.452	
Probability of macroalbuminuria	0.038	0.030	0.046	
Probability of elevated serum creatinine among NA	0.055	0.044	0.066	Estimated
Probability of ESRD among NA	0.007	0.006	0.009	
Probability of elevated serum creatinine	0.016	0.013	0.019	(50)
Probability of ESRD	0.081	0.065	0.097	(51)
Death due to microalbuminuria	0.117	0.094	0.141	
Death due to macroalbuminuria	0.228	0.182	0.273	

Death due to elevated serum creatinine	0.262	0.209	0.314	(52,53)
Death due to ESRD	0.513	0.410	0.615	
Normoalbuminuria to microalbuminuria	0.020	0.016	0.024	
Normoalbuminuria to macroalbuminuria	0.001	0.001	0.001	
Normoalbuminuria to elevated serum creatinine	0.001	0.001	0.001	
Microalbuminuria to normoalbuminuria	0.030	0.024	0.036	
Microalbuminuria to macroalbuminuria	0.028	0.022	0.034	
Microalbuminuria to elevated serum creatinine	0.003	0.002	0.004	
Macroalbuminuria to elevated serum creatinine	0.023	0.018	0.028	
Elevated serum creatinine to ESRD	0.140	0.112	0.168	
Relative risk of microalbuminuria to macroalbuminuria	0.013	0.010	0.015	
Relative risk of microalbuminuria to normoalbuminuria	0.092	0.073	0.110	
Probability of hemodialysis	0.514	0.411	0.617	(50)
Probability of peritoneal dialysis	0.073	0.058	0.087	
Utility of normal	0.800	0.770	0.590	(47)
Utility of microalbuminuria	0.640	0.590	0.700	
Utility of macroalbuminuria	0.640	0.590	0.700	
Utility of elevated serum creatinine	0.560	0.448	0.672	(53)
Utility of hemodialysis	0.396	0.208	0.584	Grey Literature *(MPH Thesis)*
Utility of peritoneal dialysis	0.608	0.450	0.766	
Case identification followed by screening (Scenario-1)	227	173.73	669	Market price (internet) (54,55)
Case identification followed by screening (Scenario-2)	680	540.00	1153	
Cost of ACR	507	409.00	546	
Cost of serum creatinine	135	108.00	165	
Cost of ACEI	10372	8297.60	12446	
Cost of medical management	35176	28140.81	42211	
#Cost of hemodialysis	12.7	10.1	15.3	
#Cost of peritoneal dialysis	4.9	3.9	5.9	

**per person, shown in detail in Appendix table 1, #Lakh Indian rupees*

4.6 QALY Estimation

Using the formula given below, the overall health gain in the form of QALY from the utilities and life-years saved at each arm and its associated health states were estimated. Other estimates such as the number of CKD cases detected and the number of life-years saved in both the comparator and intervention arms were calculated. We applied half-cycle correction while estimating QALY and cost.

QALY = Utility X Life Expectancies

4.7 ICER Estimation

The present economic model aimed to estimate the Incremental Cost-Effectiveness Ratio (ICER) per life-years saved/ QALY gained related to population-basedCKD screening as follows:

Incremental Cost = Annual Unit Cost of Intervention − Annual Unit Cost of Comparator

Incremental Effect
QALY/ Life years Saved (LYS) = QALY/LYS/CD (Intervention) − QALY/LYS/ CD (Comparator)

Incremental Cost-effectiveness Ratio (ICER) = **Incremental Cost** / **Incremental Effect**

4.8 Systematic Review and Meta-analysis

In the present study, a systematic review was conducted to obtain diagnostic accuracy of dipstick microalbuminuria screening for the detection of CKD in the targeted population. The systematic review protocol and results are given in Annexure I.

4.9 Sensitivity Analysis

The robustness of the model and parameters used in the model were assessed through one-way sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). Both analyses were carried out in MS excel. PSA was done using macros through visual basic coding for simulating the results (over 1000 times) obtained from the Monte Carlo method. The results of OSWA and PSAwere represented in the tornado graph and cost-effective plane, respectively.

4.10 Budget Impact Analysis

The budget impact analysis (BIA) model was based on the decision analytics model for both CKD screening scenarios 1 and 2, as compared with the current scenario of no screening. We estimated the financial costs and budgetary implications associated with annual population-based CKD screening and its treatment in Puducherry and Kerala.

Identification of the Target population

The target population for the hypothetical screening program was identified using a "top-down approach". The demographic information on the size and age composition (population aged 40 years and above) were taken from the census 2011 and census 2021 (projected population). The prevalence of diabetes among adults aged 40 and higher was obtained from WHO STEPS survey conducted in Puducherry. Owing to similar socio-demographic characteristics and NCD prevalence, in Kerala and Puducherry, we applied the same prevalence of diabetes in both states. For the current no screening scenario, the health seeking behavior was assumed to be 90% owing to high literacy rate in the southern states of Puducherry and Kerala. For the hypothetical CKD screening scenario 1 and 2, the coverage parameters of 20%, 40%, 60%, 80% and 100%. Table 6 displays the eligible target population for alternative screening scenarios.

Table 6 Top-down approach for identification of eligible population

	Kerala	**Puducherry**
No Screening		
Estimated population (Census, 2021)	34698876	1692000
Proportion of population 40 years and above (Census, 2011)	0.378	0.3208
Population aged 40 years and above	13116175	542794
Prevalence of Diabetes among 40 years and above (WHO STEPS survey in Puducherry)	0.337	0.337
Total Diabetic population	4420151	182921
Population seeking health care (90%)	3978135	164629
Screening 1 & 2		
Coverage parameter		
Eligible target population		
20%	884030	36584
40%	1768060	73169
60%	2652091	109753
80%	3536121	146337
100%	4420151	182921

Perspective

The study takes multiple payer perspective based on government's current expenditure, out of pocket expenses borne by patients and market prices for drugs and diagnostics (outsourced) to the private player.

Unit cost

The unit costs for the CEA model described in the previous section was used for the BIA.

Time Horizon

The time frame for the budget impact analysis is four years.

4.11 Equity Review

Primary evidences from India related to CKD prevalence, treatment and management were compiled, using the equity lens framework of PROGRESS (56) and its expanded version PROGRESS-Plus. (57) The acronym represents Place of residence; Race/ethnicity/ culture/ language; Occupation; Gender/ sex; Religion; Education; Socio-economic status; Social capital/ networks. The 'Plus' component includes context-specific factors disability, sexual orientation and age. This spot urine acronym has been endorsed by the Campbell and Cochrane Equity Methods Group to guide the analysis and reporting of equity focused research. (58)

We conducted a targeted literature search to identify relevant studies to assess the equity and ethical issues in the management and treatment of CKD for the Indian population. Online databases like PubMed, Cochrane Database of Systematic Reviews (CDSR) and EMBASE were searched using PROGRESS acronym, for obtaining research articles published between 2010 and 2021. Databases were searched using the terms: 'India', 'health status disparities', 'healthcare disparities', 'equity', 'social marginalization', 'poverty', 'socioeconomic factor', 'social status', 'social capital', 'occupation', 'education', 'discrimination', 'Chronic kidney disease', 'Microalbuminuria', 'kidney failure', 'kidney transplantation' and 'end stage renal disease'. We further searched Google scholar for relevant literature and reports on Government websites. We excluded pregnancy-related acute renal failure and acute kidney injury. We found 17 articles that provided relevant information on disparities in CKD prevalence, treatment and related ethical issues from the Indian context.

5. RESULTS

5.1 Base Case Results

The results shown in tables 7.1 & 7.2 are for an individual having normotensive diabetes mellitus aged 40 years and above. The study evaluated the cost-effectiveness of annual population-based screening of CKD in scenarios 1 & 2 as compared with the non-screening scenario. The discounted total cost incurred was ₹ 40,927 for non-screening, ₹ 62,368 for screening scenario 1 and ₹ 64,282 for screening scenario 2. The discounted total QALY for non-screening, screening scenario 1 and screening scenario 2 were 6.10, 6.88 and 7.09, respectively. All the three scenarios - non-screening, screening scenario 1 and screening scenario 2, resulted in respective total life years of 10.22, 11.59 and 11.65. The discounted incremental cost and QALY for screening scenario 1/scenario 2 were ₹ 21,441 /₹ 23,355 and 0.79/0.99, respectively, compared with the non-screening scenario. The life-years saved under screening scenario 1 was 1.37 and screening scenario 2 was 1.43 compared with the non-screening scenario. Discounted ICER/QALY gained and discounted ICER/Life year saved with screening scenario 1 was ₹ 27,279 and ₹ 15,600, respectively, whereas with screening scenario 2 the discounted ICER/QALY gained was ₹ 23,519 and discounted ICER/Life year saved was ₹ 16,294 when compared with the non-screening scenario. Table 7.2 represents the corresponding net monetary benefit (NMB) associated with both scenarios, assuming the threshold value (λ) as one-time GDP per capita income of ₹ 1,63,450 in April 2021. The NMB for scenario1 and scenario 2 were found to be ₹ 1.07 and ₹ 1.38 Lakhs, respectively.

5.2 Sensitivity Analyses

5.2.1 One-way sensitivity analysis

Variations in the ICER concerning the higher and lower base case parameter values are presented in figures 4 and 5. In scenario, 1, Cost of ACEI and Relative Risk of Micro to Normoalbuminuria had the highest variations in the ICER when assessed with ±20% change in the bases case values. Other parameters that influenced ICER values were ‘Prevalence of Microalbuminuria’, ‘Cost of Case Identification and Screening’, ‘Death Due to Microalbuminuria’ and so on, as given in the figure. Likewise, in scenario 2, ‘Cost of ACEI’, ‘Relative Risk of Micro to Normoalbuminuria’, ‘Utility of Microalbuminuria’ and ‘Prevalence of Microalbuminuria’ had the highest influence on the ICERs. However, the changes in sensitivity of the dipstick test caused lesser variation in the base case ICER of scenario 2 than the scenario 1. The influence of other parameters on the ICER is presented in the figures.

Table 7.1 Base Case Results (N=1)

	No screening	Screening scenario I	Screening scenario II
Undiscounted estimates			
Total cost	₹ 45,407	₹ 69,469	₹ 71,715
Total QALYs	7.62	8.87	9.13
Total life years	10.22	11.59	11.65
Incremental cost	-	₹ 24,062	₹ 26,308
Incremental QALYs	-	1.25	1.51
Incremental life years	-	1.37	1.43
ICER/QALY gained	-	₹ 19,317	₹ 17,424
ICER/Life Year saved	-	₹ 17,507	₹ 18,355
Discounted estimates			
Total cost	₹ 40,927	₹ 62,368	₹ 64,282
Total QALYs	6.10	6.88	7.09
Total life years	-	-	-
Incremental cost	-	₹ 21,441	₹ 23,355
Incremental QALYs	-	0.79	0.99
Incremental life years	-	-	-
ICER/QALY gained	-	₹ 27,279	₹ 23,519
ICER/Life year saved	-	₹ 15,600	₹ 16,294

Table 7.2 Net Monetary Benefits associated with CKD screening (N=1)

	Incremental cost	Incremental benefit	Net Monetary Benefit
Screening scenario 1	₹ 21,441	₹ 1,28,471	**₹ 1,07,030**
Screening scenario 2	₹ 23,355	₹ 1,62,308	**₹ 1,38,953**

Note: Assuming threshold (λ) = ₹ 1, 63,450 (US$ 2190 @ 1US$= ₹ 74.6)

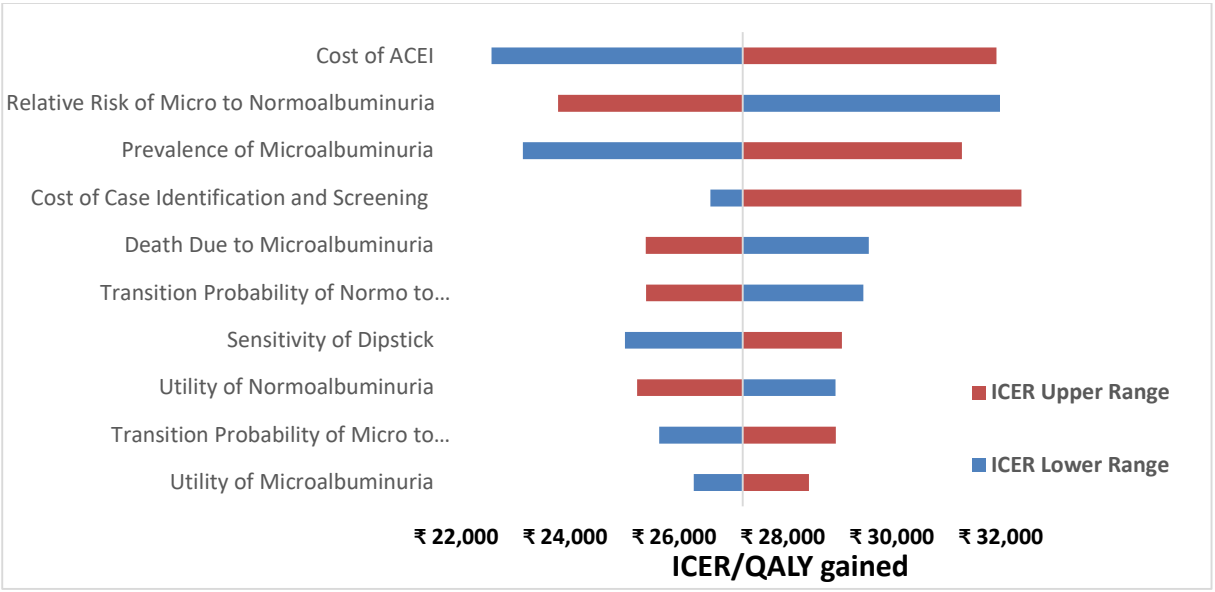

Figure. 4 One-way sensitivity analysis for scenario 1

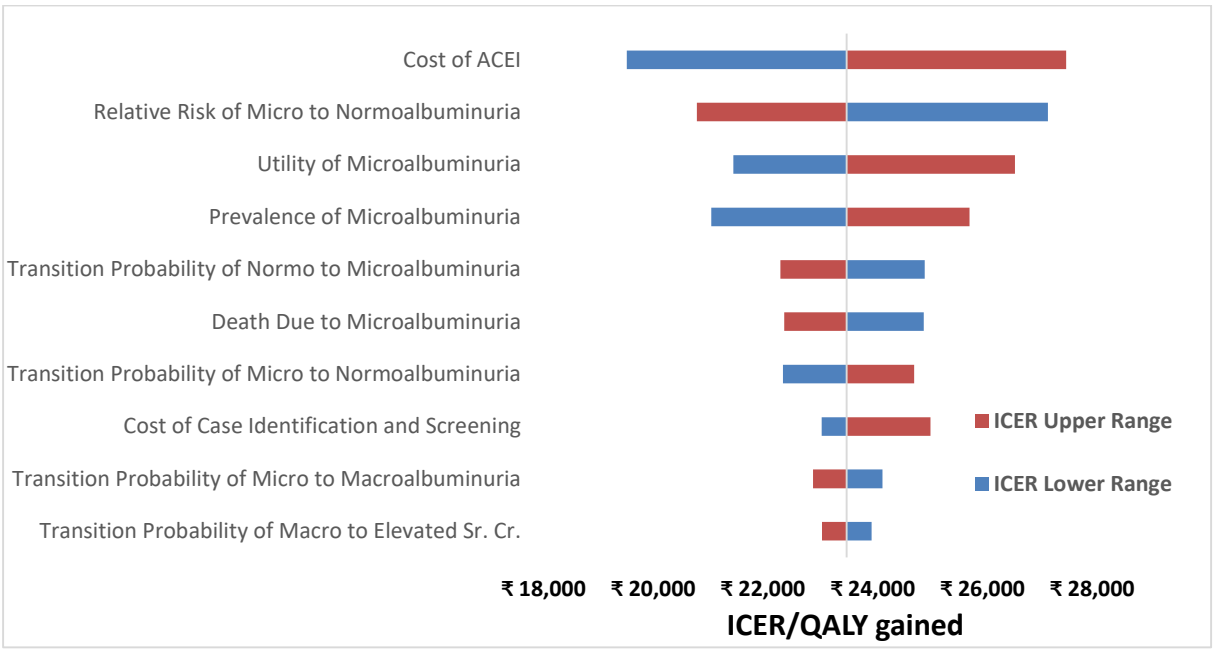

Figure 5. One-way sensitivity analysis for scenario 2

5.2.2 Probabilistic sensitivity analysis (PSA)

The PSA with thousand iterations of the cost-effectiveness model showed clustering of ICERs around the base case results in both the scenarios indicating less uncertainty on the estimates. The differences in the incremental costs and incremental outcomes between the two screening scenarios in comparison to the current scenario are presented in the cost-effectiveness plane given in Figure 6. Based on the position of incremental costs and QALYs on the northeast quadrant of the cost-effectiveness (CE) plane, both scenarios were found to be cost-effective. The results obtained from 1000 simulations were fallen on the same quadrant of the CE plane.

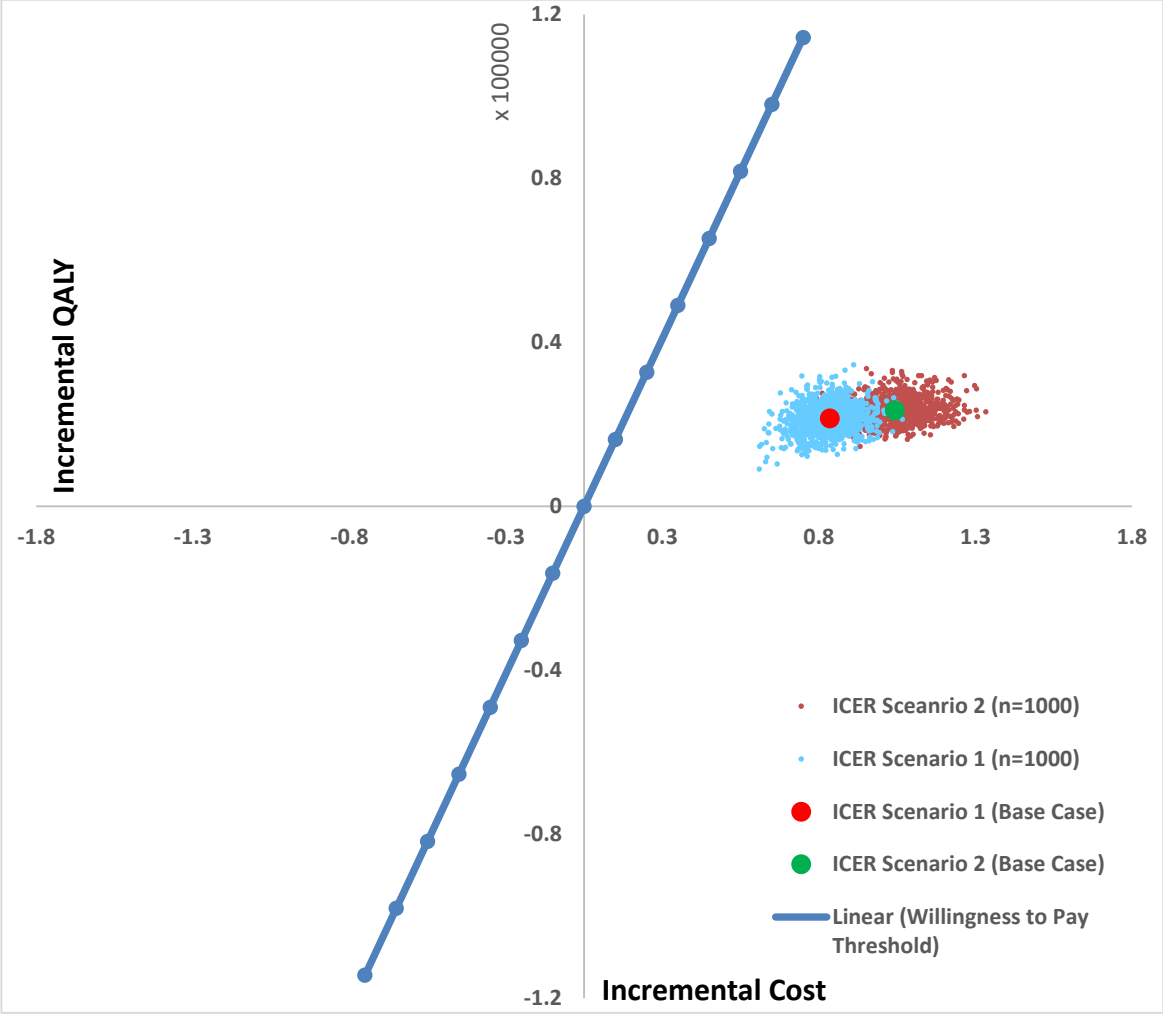

Figure 6. Probabilistic sensitivity analysis for scenarios 1 & 2

5.2.3 Cost-Effectiveness Acceptability Curve

Compared to the non-screening scenario, the ICER estimates, i.e., ₹ 27,279/QALY gained for scenario 1 and ₹ 23,519/QALY gained for scenario 2, were lower than one-time per capita GDP (₹ 1, 63,450), which was assumed to be the willingness-to-pay threshold for India. According to the assumed willingness topay, the probability that scenario 1 / scenario 2 to be cost-effective is 100% (Figure 7)

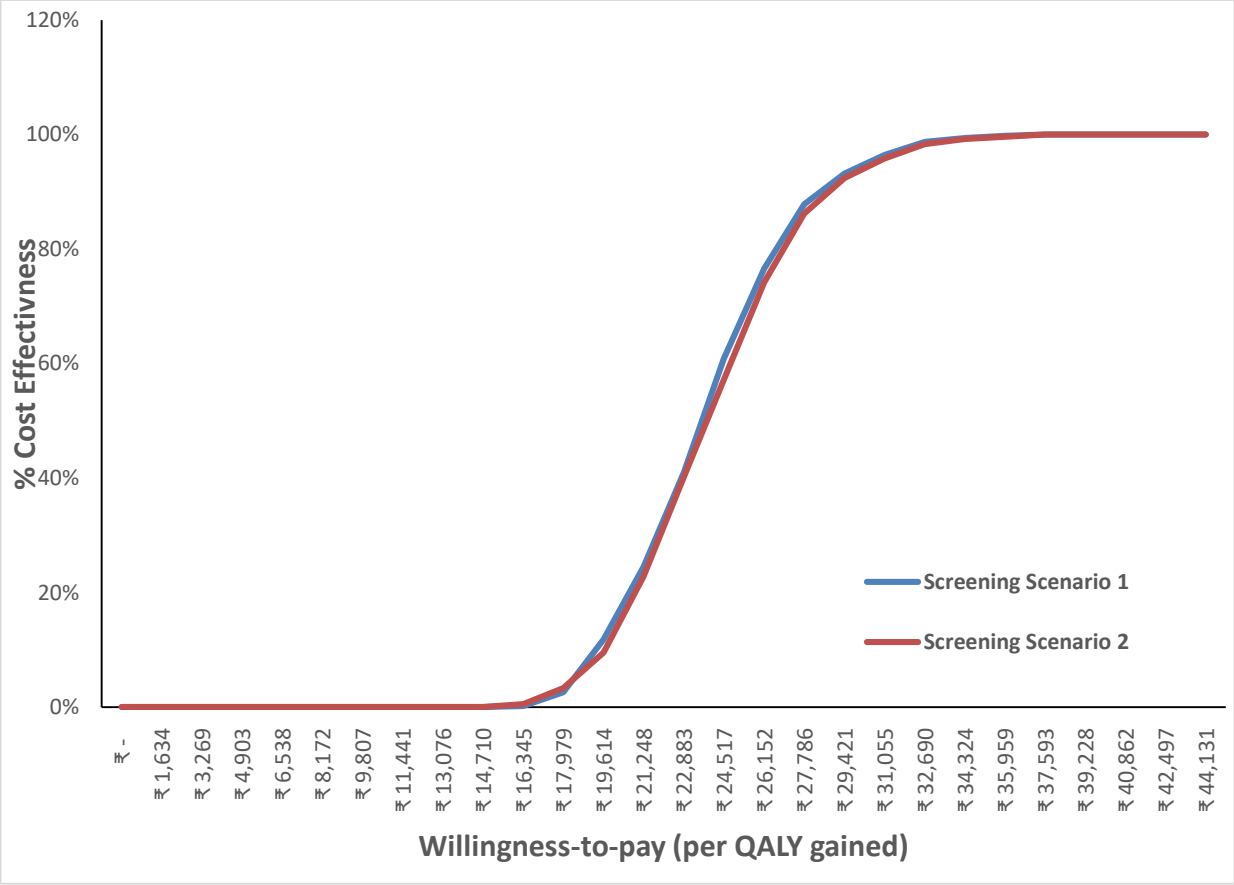

Figure 7 Cost-Effectiveness Acceptability Curve

5.3 Reduction of ESRD cases

As per the model, the reduction of ESRD cases over ten years in screening scenario 1 and scenario 2 per 1,00,000 population (hypothetical cohort) were 179 and 193 cases respectively compared with no-screening scenario (Figure 8). This reduction in ESRD cases resulted in cost saving of ₹ 12.3 crores in screening scenario 1 and ₹ 13.3 crores in screening scenario 2 (Table 8).

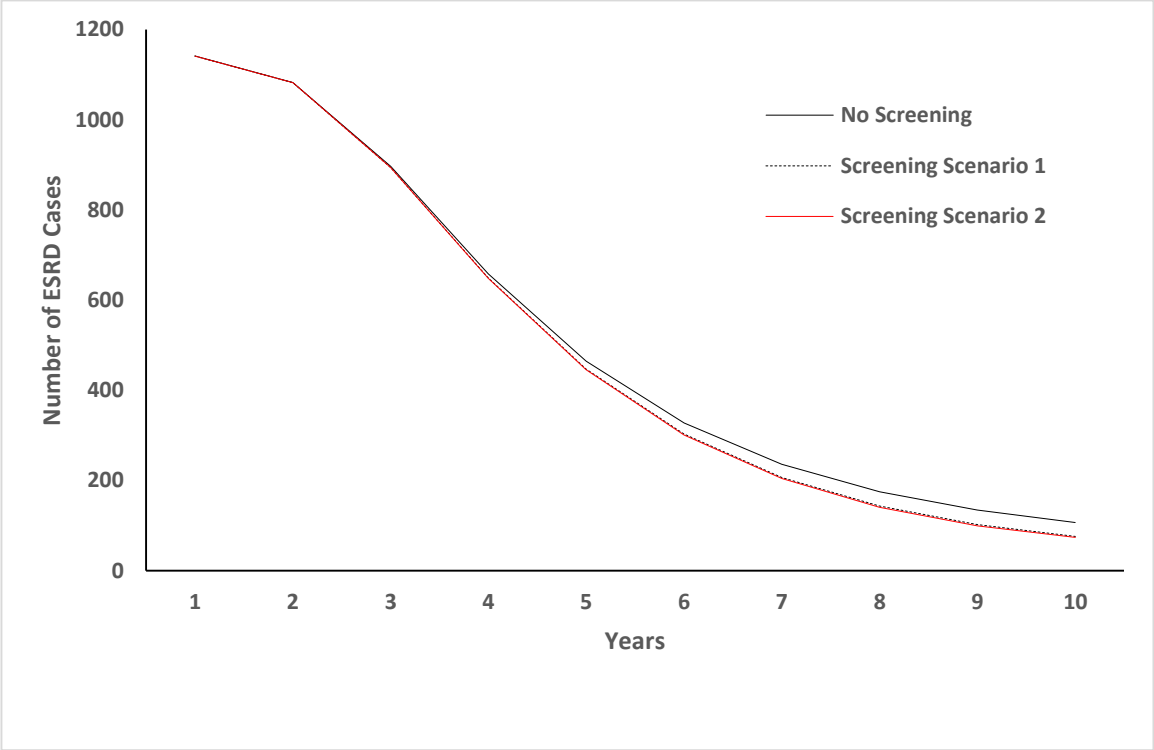

Figure 8 Reduction of ESRD cases per 1,00,000 population over ten years.
(The curve of scenarios 1 and 2 are overlapping)

Table 8: Impact of population-based screening for CKD on the number of ESRD cases and the associated treatment cost over the ten years per lakh population

Year	Number of ESRD cases			Number of cases prevented in scenario 1 vs no screening	Treatment cost saved in scenario 1 vs no screening (₹ Lakh)
	No screening	Screening scenario 1	Screening scenario 2		
1	1142	1142	1142	0	0
2	1083	1083	1083	0	0
3	897	894	894	3	18.2
4	658	649	648	9	64.8
5	465	447	446	18	121.0
6	328	303	301	25	170.0
7	236	207	204	30	203.8
8	175	143	141	32	220.3
9	135	102	100	32	221.7
10	107	76	74	31	212.5

5.4 Budget Impact Analysis (BIA)

Table 9 displays the year-wise disaggregated distribution of budget estimates for the target population over four years' time horizon for both screening strategies under 20% coverage. CKD Screening for the diabetic population for aged 40 and above at 20% coverage under scenario 1 costs Rs 67.81crore and scenario 2 costs Rs 142.93 crore for Puducherry. Likewise, the cost of CKD screening under 20% coverage in Kerala under scenario 1 and scenario 2 are Rs 1,638.47 crore and Rs 3,453.84 crore, respectively. In both states, the financial cost related to screening scenario 1 under 20% coverage was found to be much lower than that of cost under current no screening scenario (i.e, Rs 385 crore in Puducherry and Rs 9,303.17 crore in Kerala). The budget estimates for the actual population of the states of Puducherry and Kerala at different coverage levels of 20%, 40%, 60%, 80% and 100% are displayed in Appendix table 3.

Table 9 Budget Impact Assessment across time horizon of four years (₹ crore) at 20%coverage

Puducherry			
Coverage 20%	**Current scenario** (₹ crore)	**Scenario 1** (₹ crore)	**Scenario 2** (₹ crore)
Year			
2022	104.83	28.87	43.00
2023	106.27	16.77	39.97
2024	97.82	12.54	34.02
2025	76.08	9.63	25.94
Total	**385.00**	**67.81**	**142.93**
Kerala			
Coverage 20%	**Current scenario** (₹ crore)	**Scenario 1** (₹ crore)	**Scenario 2** (₹ crore)
Year			
2022	2533.13	697.69	1038.98
2023	2568.00	405.13	965.93
2024	2363.72	302.98	822.16
2025	1838.32	232.67	626.77
Total	**9303.17**	**1638.47**	**3453.84**

5.4 Equity Review

We report inequity and ethical issues associated with the management and treatment of CKD in India using the PROGRESS framework as follows: to be very cost effective

Place of Residence:

Epidemiological studies show prevalence of CKD of unknown etiology (CKDu), are unusually high ranging from 10 to 20%, in specific regions (hotspots) as compared to other parts of India. Some of the identified "hotspots" include coastal Uddanam region of Andhra Pradesh, (59) south eastern coastal region of Tondaimandalam covering Tamil Nadu and Puducherry; (11) Cuttack district of the Odisha state; (60) Nainakuppam village in Villupuram district of Tamil Nadu; tribal village of Supebeda, Chhattisgarh. (61) Several factors are associated with CKD such as prolonged dehydration leading to heat stress, poor sanitation, pollutants, watercontamination, heavy metal toxicity, pesticide exposure, snake bite etc.

There are differences in clinical characteristics of subjects with CKD between northern and southern states of India. CKD due to diabetes and unknown origin were more prevalent in Southern India while chronic interstitial nephritis was more prevalent in Northern regions of India. (62)

There are wide disparities in the availability of facilities and expertise for CKD management and treatment across the country. There are about 7 nephrologists per lakh population who are unequally distributed and are mostly concentrated in urban centres. In urban areas hemodialysis (HD) is more common, whereas peritoneal dialysis (PD) are more common in the rural areas. Timely supply of PD fluid to remote regions (mountainous terrains and villages) without adequate road, lack of access to clean water and access to hospital for evaluation and treatment of PD-related infections are important issues that needs to be addressed. (2)

Race/Ethnicity/Culture/Language/Religion:

We did not find any evidence on CKD prevalence, specifically associated with race/ethnicity/culture/language/religion in the Indian context.

Use of complementary and alternative medicine (CAM), especially ayurvedic medication, is widespread among CKD subjects attending nephrology outpatient clinic, although accurate data on its utilization is lacking. These medications being naturally sourced are perceived to be safer and free from undesirable side effects by patients. (63,64)

Occupation/Lifestyle:

Several studies show that CKD prevalence is higher among unskilled occupations and manual laborers/farmers than the general population. (59,62,64) Farmers had 20% more prevalence of CKD compared to non-farmers. Alcohol consumption, and chewing tobacco were found to be independent predictors of CKD. (59,65,66) High CKD prevalence has been attributed to occupations requiring significant physical activity; It has been hypothesized that working in hot and humid climate shrunken echogenic kidneys with minimal proteinuria, which presents itself as presumably minimally symptomatic or asymptomatic early stages of CKD. (11)

Gender/Sex:

Most studies from India report higher prevalence of CKD among males as compared to females (59,60,64,66–68) Several studies have noted gender imbalance in living donor (LD) for renal transplantation in India. (69) The majority of the recipients were male while female donors were predominant among living donors in renal transplant programme. (70) Womenare having 78.5% higher incidence of donation. Among them, mothers, wives, sisters, anddaughters were the major participants. (71) Financial factors such as greater income of men, and psychosocial issues like heightened female sense of obligation, altruism, or even coercion explainthis phenomenon of gender bias in live kidney donation. Also, men are more likely to be excludedas donors because of a higher incidence of diabetes, hypertension and ischemic heart disease than their female counterparts.

Education:

Illiteracy or low levels of education where associated with CKDu prevalence especially in "hot-spot" regions in India (59–61,67). However, no clear evidence is observed between education and CKD prevalence in the rest of India.

Socioeconomic status/ OOPE:

The prevalence of CKD was higher among lower socioeconomic groups than among general population. (60) Affordability of CKD treatment is a huge concern; over 90% of patients requiring RRT in India die because of inability to afford care, and even in those who initiate RRT, 60% quit the treatment for financial reasons. Among patients who undergo kidney transplantation, unexpected complications have the potential to impose serious financial hardships. Lack of health

insurance coverage and expensive recurring costs are deterrents. (2) Some patients are able to access RRT under government health insurance schemes (where available) that provide twice weekly HD, PD, or transplantation for the underprivileged. The Indian Government, in its Healthcare Union Budget 2016, announced the plan for stand-alone HD centers for patients with ESRD, and the National Dialysis Services.

Regulatory environment:

Living donor kidney transplantation far exceeds deceased donor transplantation. The imbalance between availability of organs and the need for transplantation has led to the unregulated practice of illegal living donor transplants in India. There are ethical concerns raised about legalizing compensated transplantation under strict government rules and regulations. (72) Further due to lack of transparency and accountability in the implementation of the Transplantation of Human Organs Act (THOA) have considerably curtailed commercial transplantation. The unequivocal and universal implementation of the United Nations Trafficking Protocol may eliminate this bane from society. The THOA has led to organ sharing partnerships between private and government hospitals in some states, and this has revolutionized deceased donor transplantation. The Tamil Nadu Cadaver Transplant Program is an example, having done 5092 organ transplants, including 1655 kidney transplants, in under a decade. This is a direct result of education and promoting awareness in the community (73)

6 DISCUSSION

We found that annual population-based CKD screening among adults aged 40 years and above with normotensive type 2 diabetes in India was cost-effective at the ICERs of ₹ 27, 279 and ₹ 23, 519 per QALY gained and ₹ 15, 600 and ₹ 16, 294 per life years-saved for the screening scenarios 1 and 2, respectively, compared with the no screening scenario. In both the intervention scenarios, the cost of ACEI and the relative risk of micro to macroalbuminuria had the highest influence on the ICER values obtained, and the probability of both interventions being cost-effective was 100% at the one-time per capita GDP threshold of India.

In line with the current study findings, several studies from other Asian, US, and European countries have shown that the population-based screening for MA among diabetic populations uses dipstick as a cost-effective strategy in preventing ESRD development and progression. As reported by Wu et al., the screening for microalbuminuria in newly diagnosed type 2 diabetes patients was a cost-saving option for the prevention of CKD in the Chinese population. (74,75) Studies from other Asian countries like Japan, (76) Thailand, (44) and Korea (54) also found CKD screening using either proteinuria or albuminuria dipstick to be cost-effective in high-risk populations, especially among diabetics. Studies from US and European countries on CKD screening using microalbuminuria or proteinuria among diabetes or/and hypertension populations have found the intervention to be cost-effective. However, CKD screening among the general population is found to be cost-ineffective, as reported from studies across the world. (34)

The estimated ICER per QALY gained for screening CKD in diabetic patients from the present study for scenario 1 ($ 363) and 2 ($ 313) are higher than the estimates from Thailand ($ 97). However, the estimates were lower than those estimated in Korea ($37,812) as well as those estimated in US and European countries ($5,298- $54,943). (34) Studies employing proteinuria screening exhibited a higher ICER than studies involving microalbuminuria screening. This could be due to the comparatively lower diagnostic accuracy of the proteinuria in determining CKD when compared to MA. Poor diagnostic accuracy leads to the loss of patients with corresponding clinical presentations and misleads the wrong population for the therapy. Hence, the variance in the ICER estimates obtained in the study when compared to other regional studies could be attributable to the prevalence and clinical presentation of microalbuminuria/proteinuria in the diabetic population. The preceding assertion was further supported by OWSA findings, which revealed that the

prevalence of microalbuminuria and the sensitivity of the dipstick microalbuminuria test had considerable influence on the ICER estimates. The results were consistent with that reported by Sisrubat et al., where the positive predictive value of dipstick microalbuminuria was found to be one of the most influential parameters of the model estimates. (44)

The choice of dipstick or ACR for microalbuminuria screening in the diabetic population decides the ICER estimates. As reported by Lepore et al., the use of screening tests such as dipstick and ACR to screen microalbuminuria in the diabetic population resulted in ICERs of $2,607 and $8,902, respectively. (78) The lower ICER in scenario 2 in the present study might be due to the parallel screening with ACR and serum creatinine, which includes the non-albuminuric diabetic population who would nonetheless progress to CKD.

The major strength of the study was the assessment of interventions, one based on the feasibility (scenario 1) and the other based on clinical validity (scenario 2), which enabled us to appreciate the extent of benefit derived from scenario 1. Unlike other cost-effectiveness studies, modeling of non-albuminuric CKD made the disease model more realistic and novel. Further, we used local evidence on the prevalence of microalbuminuria among diabetic patients estimated from a WHO STEPS survey conducted in Puducherry during 2019-2020. But, the prevalence was based on a single-time estimation of microalbuminuria (whereas as per standard guidelines, the prevalence should have been estimated from a two-time estimation with an interval of three months between each test). However, the estimates were congruent with the national-level prevalence data.

The shortcomings of the study were data limitations in the Indian setting. The natural progression and transition probabilities for different stages of CKD were derived from a UK-based study, which may represent disease progression among the Indian population to a lesser extent. As the population undergoing renal transplantation is negligible in India, we did not incorporate parameters relevant to renal transplantation in the model. The CVD complications associated with CKD were also not incorporated as the intervention was already cost-effective. Other limitation includes the cost estimates used in the study, which were based on secondary sources. Side effects of ACEI were not incorporated in the model. The cohort of non-albuminuric CKD was not assigned with the benefit of early detection due to the complex nature of the etiologies other than diabetes and treatment effectiveness. The screening coverage was assumed to be 100% in the model; therefore, lower coverage may impact the ICER estimation.

Budget and financial implications

The BIA results for actual population at 20% coverage showed that the financial cost of CKD screening was Rs 67.80 crore (scenario 1) for Puducherry and Rs 1638.47 crore (scenario 1) for Kerala. These budget estimates roughly constitute 20% of state health budget of Puducherry and Kerala. The budget estimates for medical and public health & family welfare for the year 2021- 22 in Puducherry was Rs 332.7 crore (Puducherry budget website) and Rs 7615 crore (Kerala budget website). Clearly, population-based CKD screening programs are not feasible given the current levels of health expenditures in respective state governments.

The funding of NCD-related programs in India is inadequate in relation to the NCD disease burden. The NCD programs including NPCDCS are funded under two centrally sponsored schemes, viz the NRHM Flexible pool for NCD, Injury and Trauma (NCDI) and the tertiary care programs for prevention and control of NCD. The flexible pool for NCDI constitutes around 1.4 % of the approved outlay for NHM in the year 2020-21 and it is around 2.3% of the budget estimates for 2021-22. (See the table 9). However, the share of NCD in total disease burden in India has been rising rapidly. It was 46.4% in 2006 and is projected to increase to 51% in 2026 and 57.4% in 2051. The health-care expenditure on the non-communicable diseases from ₹ 45,735 crores to 114,413 crores during the same duration. (79) A budget-based study shows that the state level spending on NCDI is grossly inadequate compared against disease burden using DALYs and there is a need to step up funding to address the increasing disease burden of NCDIs and to reduce the high out-of-pocket expenditure on NCDI. (55)

Table 9: Public Health Expenditure towards NCD (₹ crore)

	2019-2020 (Actual) ₹	2020-2021 (Budget) ₹	2020-2021 (Revised) ₹	2021-2022 (Budget) ₹
1. Health Budget	62397.08	65011.80	78866.00	71268.77
2. NRHM Budget	29986.82	27039.00	28366.75	30100.00
Centrally Sponsored Schemes under NRHM				
a) NRHM-Flexible Pool for NCD, Injury and Trauma (NCD & IT)	674.78	717.00	403.51	717.00
b) Tertiary Care Programs-NPCDCS	150.02	175.00	133.86	175.00

Source: Notes on Demands for Grants, 2021-2022

Equity considerations

Previous studies show considerable financial and societal burden associated with kidney failure. The treatment cost for ESRD and CKD management remains exorbitantly high, despite ongoing public health insurance schemes. In the event of renal failure, women face disproportionately higher incidence of 78.5% live kidney donation than men (5). Thus, there are negative externalities associated with the rising incidence of CKD in India. Given the lower level utilization of NCD outpatient clinic by patients with diabetes, population-based screening for microalbuminuria seems suitable to detect diabetic nephropathy, before onset of symptoms. Such a one-size-fits-all approach is likely to reduce health inequalities across all social groups, including the affluent and the poor. To promote equity, there is a need for targeted screening and awareness program to identify the cases of poorly controlled diabetes especially among lower socio-economic status groups, particularly among males.

Strengths and limitations of the study:

First, this is first of its kind study in the Indian context on the CKD screening strategies at the population level. Second, the study uses local evidence on the prevalence of microalbuminuria among diabetic patients, collected through a district-wide representative cross-sectional survey (34) in Puducherry.

Limitations of the study are due to data constraints in the Indian context. The prevalence of CKD estimated from WHO STEPS was based on single time estimation of microalbuminuria. (34) However, the definition recommends two times estimation of microalbuminuria in an interval of three months. This deviation from the definition might have overestimated the prevalence of CKD used in the model. Further, the prevalence of CKD was estimated for the population aged between 40 and 69 years. As the current model is meant for the population aged ≥40 years, and diabetes induced renal impairment happens at later stages in life, the prevalence of CKD estimated from this age restricted study population could underestimate the prevalence derived for use in the model. Another limitation of the study stems from lack of empirical evidences related to diagnostic accuracy of dipstick albuminuria and CKD progression in the Indian context. Hence the model in the study is informed by effectiveness estimates of sensitivity and specificity of the dipstick from the manufacturer's product catalogue. Being a marketing tool, the product catalogue may be biased about the information on sensitivity and specificity of the urine dipstick. Likewise, the natural progression and transition probabilities for different stages of CKD were derived from a UK study, which may represent disease progression among Indian population to a lesser extent. The benefit of ACEIs among the diabetic population having CAD was also not accounted in the current model due to lack of data.

A third set of limitation is that the study is based on cost estimates derived from secondary sources, since primary data collection using standard bottom-up micro-costing approach and cost of illness methodology, was not possible due to COVID-19 scenario. Hence the cost estimates are likely to be accurate to a lesser extent. Fourth, the effectiveness of ACEI and drug side effects have been ignored in the model. Cohort of non-albuminuric CKD were not assigned with the benefit of early detection due to complex nature of the etiologies other than diabetes and treatment effectiveness. This will influence the ICER reported for the scenario 2. The CVD complications associated with CKD is not incorporated as the intervention is already cost effective. The coverage of screening is assumed to be 100% and the lower coverage may have impact on the ICER estimation. Future scope of HTA study can extend the economic evaluation with the support of micro or dynamic model and estimation of ICER values associated with the frequency of screening (twice or thrice) in a year.

7 CONCLUSIONS

To conclude, both scenarios of population-based screening for CKD were cost-effective with ICER of ₹ 27, 279 (scenario 1) and ₹ 23, 519 (scenario 2) per QALY gained, which were below the threshold value of GDP per capita (₹ 1, 63,450). The programmatic cost of screening for CKD (scenario 1) can be reduced if it is effectively integrated with the population-based screening for diabetes under the NPCDCS program. Such integration would reduce the overhead cost of administration, training and human resources cost.

Implementing the population-based screening with spot urine dipstick- microalbuminuria followed by ACR test and serum creatinine has the potential to reduce ESRD cases and its related expenditure borne by the health system as well as patients. Early CKD detection through population-based screening can promote kidney health and prevent dialysis over time, thereby can reduce the expenditure incurred under the Pradhan Mantri National Dialysis Programme.

ANNEXTURE – I

AI. SYSTEMATIC REVIEW AND META-ANALYSIS PROTOCOL

OBJECTIVE

To evaluate the diagnostic accuracy of microalbuminuria screening.

METHODOLOGY

Framework for Systematic Review: PIRD (Population, Index test, Reference Test, Disease Condition)

- Population – Persons with type 2 diabetes who are aged 40 years and above
- Index Test – Dipstick Microalbuminuria
- Reference Test – Spot urine ACR
- Disease Condition – Diabetic nephropathy

Database and literature search:

We systematically searched the databases of PubMed and Embase to source articles published in English language from the year 2000 to January 2021. A combination of free key words and Medical Subject Heading terms related to point of care testing, Chronic Kidney disease, mass screening, and microalbuminuria were utilized. Synonyms of key search terms were listed and they were combined using 'AND' operator for the search. All relevant articles identified were hand searched for additional articles by reviewing its references.

Table A1: Search Strategy

PUBMED
((((((((((((((((((((((((((((((((((("india"[MeSH Terms] OR "india"[All Fields]) OR "indias"[All Fields]) OR "indias"[All Fields]) OR "Kerala"[All Fields]) OR "Tamil Nadu"[All Fields]) OR "Andaman and Nicobar"[All Fields]) OR "Arunachal Pradesh"[All Fields]) OR"Assam"[All Fields]) OR "Bihar"[All Fields]) OR "Chandigarh"[All Fields]) OR "Chattisgarh"[All Fields]) OR "Dadra and Nagar Haveli"[All Fields]) OR "Daman and Diu"[AllFields]) OR "delhi"[All Fields]) OR "Goa"[All Fields]) OR "Gujarat"[All Fields]) OR "Haryana"[All Fields]) OR "Himachal Pradesh"[All Fields]) OR "Jammu and Kashmir"[All Fields]) OR "Jharkhand"[All Fields]) OR "Karnataka"[All Fields]) OR "Lakshadweep"[All Fields]) OR "Madhya Pradesh"[All Fields]) OR "Maharashtra"[All Fields]) OR "Manipur"[All Fields]) OR "Meghalaya"[All Fields]) OR "Mizoram"[All Fields]) OR "Nagaland"[All Fields]) OR "Odisha"[All Fields]) OR "Orissa"[All Fields]) OR "Puducherry"[All Fields]) OR

"Punjab"[All Fields]) OR "Rajasthan"[All Fields]) OR ("sikkim"[MeSH Terms] OR "sikkim"[All Fields])) OR "Telangana"[All Fields]) OR "Tripura"[All Fields]) OR "Uttar Pradesh"[All Fields]) OR "West Bengal"[All Fields]) OR ((((((("Aged"[Mesh] OR "Adult"[Mesh] OR "Middle Aged"[Mesh] OR "Adult"[Mesh]) OR ((((((((("diabete"[All Fields] OR "diabetes mellitus"[MeSH Terms]) OR ("diabetes"[All Fields] AND "mellitus"[All Fields])) OR "diabetes mellitus"[All Fields]) OR "diabetes"[All Fields]) OR "diabetes insipidus"[MeSH Terms]) OR ("diabetes"[All Fields] AND "insipidus"[All Fields])) OR "diabetes insipidus"[All Fields]) OR "diabetic"[All Fields]) OR "diabetics"[All Fields]) OR "diabets"[All Fields])) OR "diabet*"[All Fields]) OR "hypertens*"[All Fields]) OR (((((((("hypertense"[All Fields] OR "hypertension"[MeSH Terms]) OR "hypertension"[All Fields]) OR "hypertension s"[All Fields]) OR "hypertensions"[All Fields]) OR "hypertensive"[All Fields]) OR "hypertensives"[All Fields]) OR "hypertensives"[All Fields])) OR "blood pressure"[All Fields])) AND (((("Rapid Test"[All Fields] AND ((((((((((("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields]) OR "screening"[All Fields]) OR "mass screening"[MeSH Terms]) OR ("mass"[All Fields] AND "screening"[All Fields])) OR "mass screening"[All Fields]) OR "early detection of cancer"[MeSH Terms]) OR (("early"[All Fields] AND "detection"[All Fields]) AND "cancer"[All Fields])) OR "early detection of cancer"[All Fields]) OR "screen"[All Fields]) OR "screenings"[All Fields]) OR "screened"[All Fields]) OR "screens"[All Fields])) OR (("dipstick"[All Fields] OR "dipsticks"[All Fields]) AND ((((((((((("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields]) OR "screening"[All Fields]) OR "mass screening"[MeSH Terms]) OR ("mass"[All Fields] AND "screening"[All Fields])) OR "mass screening"[All Fields]) OR "early detection of cancer"[MeSH Terms]) OR (("early"[All Fields] AND "detection"[All Fields]) AND "cancer"[All Fields])) OR "early detection of cancer"[All Fields]) OR "screen"[All Fields]) OR "screenings"[All Fields]) OR "screened"[All Fields]) OR "screens"[All Fields]))) OR ("Microalbuminuria"[All Fields] AND ((((((((((("diagnosis"[MeSH Subheading] OR "diagnosis"[All Fields]) OR "screening"[All Fields]) OR "mass screening"[MeSH Terms]) OR ("mass"[All Fields] AND "screening"[All Fields])) OR "mass screening"[All Fields]) OR "early detection of cancer"[MeSH Terms]) OR (("early"[All Fields] AND "detection"[All Fields]) AND "cancer"[All Fields])) OR "early detection of cancer"[All Fields]) OR "screen"[AllFields]) OR "screenings"[All Fields]) OR "screened"[All Fields]) OR "screens"[All Fields])))) AND ((("Serum Creatinine"[All Fields] “Creatinine clearance” [All Fields] OR ("creatinine"[All Fields] AND "clearance"[All Fields]) OR “Creatinine clearance test” [All Fields] OR OR “Insulin clearance” [All Fields] OR ("insulin"[All Fields] AND "clearance"[All Fields]) OR “Insulin clearance test” [All Fields] OR (("glomerular filtration rate"[MeSH Terms] OR (("glomerular"[All Fields] AND "filtration"[All Fields]) AND "rate"[All Fields])) OR "glomerular filtration rate"[All Fields])) OR "eGFR"[All Fields]) OR "estimated glomerular filtration rate"[All Fields])) AND ((((((((((((((((((((("Renal Insufficiency"[All Fields] OR "Kidney Diseases"[All Fields] OR "Chronic Renal Failure"[All Fields]) OR "Renal Insufficiency, chronic"[All Fields]) OR "Diabetic Nephropathy"[All Fields]) OR "Diabetic Glomerulosclerosis"[All Fields]) OR "Rapidly Progressive glomerulonephritis"[All Fields]) OR "Chronic Glomerulonephritis"[All Fields]) OR "IgA Nephropathy"[All Fields]) OR "End stage renal disease"[All Fields]) OR "End stage kidney disease"[All Fields]) OR "reduced eGFR"[All Fields]) OR "Chronic Kidney Disease"[All Fields]) OR "ESRD"[All Fields]) OR "ESKD"[All Fields]) OR "CKD"[All Fields]) OR "high serum creatinine"[All Fields]) OR "Microalbuminuria"[All Fields]) OR ("albuminuria"[MeSH Terms] OR "albuminuria"[All

Fields])) OR "Kidney Function Tests"[All Fields] OR (("proteinuria"[MeSH Terms] OR "proteinuria"[All Fields]) OR "proteinurias"[All Fields])) OR "Macroalbuminuria"[All Fields]) OR "stage 5 CKD"[All Fields]) OR "Hypertensive nephrosclerosis"[All Fields]) OR "CKD of unknown etiology"[All Fields]) OR "Glomerular disease"[All Fields]) OR "Chronic Interstitial nephritis"[All Fields])

EMBASE

('diabetes mellitus'/exp OR 'diabetes mellitus'/ta OR 'diabetes mellitus':ti,ab OR 'diabetes mellitus' OR 'hypertension/exp' OR 'hypertension':ti,ab OR 'hypertension') AND ([adult]/lim OR [aged]/lim)

Population:

'India'/exp OR 'India'/ta OR 'India':ti,ab OR 'Indian'/exp OR 'Indian'/ta OR 'Indian':ti,ab OR 'Indian ink'/exp OR 'Indian ink'/ta OR 'Indian ink':ti,ab OR 'Kerala'/exp OR 'Kerala'/ta OR 'Kerala':ti,ab OR 'Tamil nadu'/exp OR 'Tamil nadu'/ta OR 'Tamil nadu':ti,ab OR 'Andaman and Nicobar'/exp OR 'Andaman and Nicobar'/ta OR 'Andaman and Nicobar':ti,ab OR 'Arunachal Pradesh'/exp OR 'Arunachal Pradesh'/ta OR 'Arunachal Pradesh':ti,ab OR 'Assam'/exp OR 'Assam'/ta OR 'Assam':ti,ab OR 'Bihar'/exp OR 'Bihar'/ta OR 'Bihar':ti,ab OR 'Chandigarh'/exp OR 'Chandigarh'/ta OR 'Chandigarh':ti,ab OR 'Dadra and Nagar'/exp OR 'Dadra and Nagar'/ta OR 'Dadra and Nagar':ti,ab OR 'Daman and Diu'/exp OR 'Daman and Diu'/ta OR 'Daman and Diu':ti,ab OR 'Delhi'/exp OR 'Delhi'/ta OR 'Delhi':ti,ab OR 'Goa'/exp OR 'Goa'/ta OR 'Goa':ti,ab OR 'Gujarat'/exp OR 'Gujarat'/ta OR 'Gujarat':ti,ab OR 'Haryana'/exp OR 'Haryana'/ta OR 'Haryana':ti,ab OR 'Himachal Pradesh'/exp OR 'Himachal Pradesh'/ta OR 'Himachal Pradesh':ti,ab OR 'Jammu and Kashmir'/exp OR 'Jammu and Kashmir'/ta OR 'Jammu and Kashmir':ti,ab OR 'Jharkhand'/exp OR 'JharkhandJharkhand'/ta OR 'Jharkhand':ti,ab OR 'Karnataka'/exp OR 'Karnataka'/ta OR 'Karnataka':ti,ab OR 'Lakshadweep'/exp OR 'Lakshadweep'/ta OR 'Lakshadweep':ti,ab OR 'Madhya Pradesh'/exp OR 'Madhya Pradesh'/ta OR 'Madhya Pradesh':ti,ab OR 'Maharashtra'/exp OR 'Maharashtra'/ta OR 'Maharashtra':ti,ab OR 'Manipur'/exp OR 'Manipur'/ta OR 'Manipur':ti,ab OR 'Meghalaya'/exp OR 'Meghalaya'/ta OR 'Meghalaya':ti,ab OR 'Mizoram'/exp OR 'Mizoram'/ta OR 'Mizoram':ti,ab OR 'Nagaland'/exp OR 'Nagaland'/ta OR 'Nagaland':ti,ab OR 'Odisha'/exp OR 'Odisha'/ta OR 'Odisha':ti,ab OR 'Puducherry'/exp OR 'Puducherry'/ta OR 'Puducherry':ti,ab OR 'Punjab'/exp OR 'Punjab'/ta OR 'Punjab':ti,ab OR 'Rajasthan'/exp OR 'Rajasthan'/ta OR 'Rajasthan':ti,ab OR 'Sikkim'/exp OR 'Sikkim'/ta OR 'Sikkim':ti,ab OR 'Telangana'/exp OR 'Telangana'/ta OR 'Telangana':ti,ab OR 'Tripura'/exp OR 'Tripura'/ta OR 'Tripura':ti,ab OR 'Uttar Pradesh'/exp OR 'Uttar Pradesh'/ta OR 'Uttar Pradesh':ti,ab OR 'West Bengal'/exp OR 'West Bengal'/ta OR 'West Bengal':ti,ab

Intervention:

'Microalbuminuria'/exp OR 'Microalbuminuria'/ta OR 'Microalbuminuria':ti,ab OR 'Urine test strip'/exp OR 'Urine test strip'/ta OR 'Urine test strip':ti,ab OR 'Urine reagent strip test'/exp OR 'Urine reagent strip test'/ta OR 'Urine reagent strip test':ti,ab OR 'Screening test'/exp OR 'Screening test'/ta OR 'Screening test':ti,ab OR 'Mass screening'/exp OR 'Mass screening'/ta OR 'Mass screening':ti,ab

Reference:

'creatinine blood level'/exp OR 'creatinine blood level'/ta OR 'creatinine blood level':ti,ab OR 'Glomerulus filtration rate'/exp OR 'Glomerulus filtration rate'/ta OR 'Glomerulus filtration

rate':ti,ab OR 'Estimated glomerular filtration rate'/exp OR 'Estimated glomerular filtration rate'/ta OR 'Estimated glomerular filtration rate':ti,ab

Disease:

'kidney failure'/exp OR 'kidney failure'/ta OR 'kidney failure':ti,ab OR 'End stage renal disease'/exp OR 'End stage renal disease'/ta OR 'End stage renal disease':ti,ab OR 'Macroalbuminuria'/exp OR 'Macroalbuminuria'/ta OR 'Macrooalbuminuria':ti,ab OR 'diabetic nephropathy'/exp OR 'diabetic nephropathy'/ta OR 'diabetic nephropathy':ti,ab OR 'albuminuria'/exp OR 'albuminuria'/ta OR 'albuminuria':ti,ab OR 'Proteinuria'/exp OR 'Proteinuria'/ta OR 'Proteinuria':ti,ab

Study Selection

We included studies from Indian settings on screening for CKD by the following criteria.

Inclusion Criteria:

- All the original research conducted and published after the year 2000.
- Studies that assessed diagnostic accuracy (sensitivity, specificity) of microalbuminuria using a point of care device (Index text) through a population based cross-sectional approach
- Studies that reported data from which diagnostic accuracy (true positive, true negative, false positive, false negative) could be calculated
- Studies that used laboratory based ACR estimation as reference test (reference standard)
- Conducted among patient groups such as diabetes, hypertension or for whom national treatment guidelines recommend periodic screening for CKD by early detection of albuminuria

Exclusion Criteria:

- Experimental studies, randomized clinical trials, reviews, meta-analysis, conference proceedings and letters/editorials/commends were excluded
- Studies on other diseases independent with microalbuminuria, decreased eGFR, CKD and ESRD

Title and abstract screening

Title and abstract of each article was reviewed by three of the study authors independently. Articles were reviewed based on pre-determined inclusion and exclusion criteria in order to retain or exclude articles for the study. The review was carried out in the RAYAAN software to ensure blinding of each reviewer in their decision on inclusion/exclusion. Discrepancies between reviewers in inclusion/exclusion of articles were resolved based on the decision of the principal investigator. All articles included were reviewed for full text

Quality Assessment of included studies

The articles selected for the review were assessed for its quality using QUADAS (Quality Assessment of Diagnostic Accuracy Studies) tool (Tran K, et al. 2006).

Data extraction

Following are the major data or information which were searched in literature selected from the above protocol.

- Sensitivity and Specificity
- Positive predictive value and negative predictive value.
- Prevalence of microalbuminuria, reduced GFR, CKD and ESRD among general population and other risk groups

RESULTS

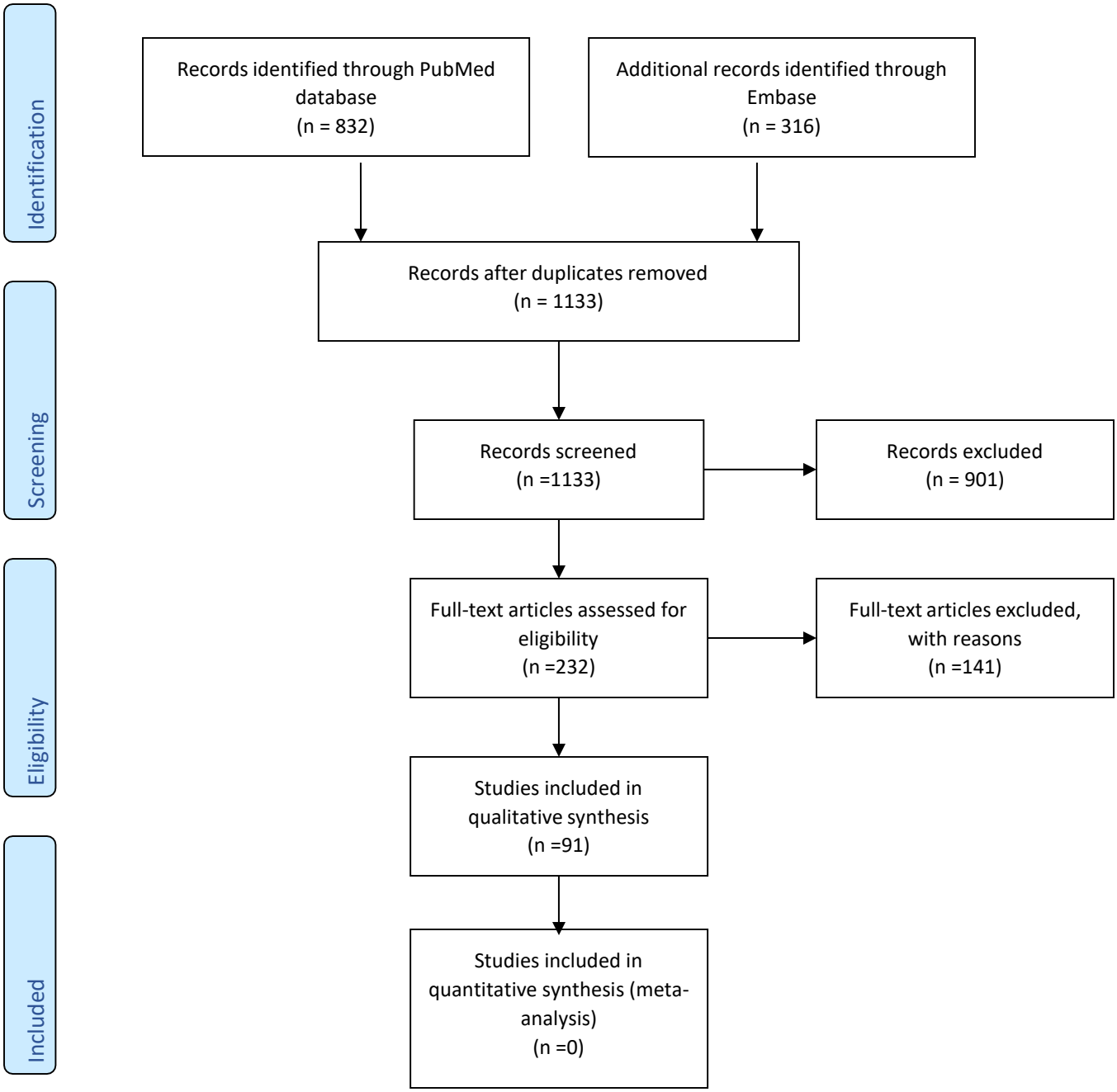

Figure A1: PRISMA Flow Diagram for Systematic Review

AII. COST AND BUDGET ESTIMATIONS

Appendix Table 1a: Cost estimates for population-based CKD Screening

Thematic Training of CHW for CKD Screening – 4 days X 4 rounds	
Nos. of Participants per batch	30
Sub-centre Batch Size	5
Venue of Training: Theoretical training at Block PHC/ CHC level Field training to be imparted at SC Level.	
Per Batch Cost	INR
1. Perdiem @ Rs. 100 X 4 days X30 nos = Rs. 12000/-	12000
2. T.A @ Rs. 100/- X 30 nos (subject to actual) = Rs. 3000/-	3000
3. Contingency (Lunch, Tiffin, tea, stationery & field visit expenses) @ Rs. 100/- X 4 days X 30 nos	12000
4. Honorarium to Resource Persons @ Rs. 100/- per X 6 nos. X 4 days	2400
5. Training materials	1500
Training cost per round	30900
4 Rounds Training in a year	4
(a) Total Training Cost for four round training	**123600**
(b) Number of CHW trained (4*30 CHW)	**120**
(c) Training cost per CHW (a) divided by (b)	**1030**

Target population to be covered by CHW in a year		
	Kerala	**Puducherry**
Households covered by 1 CHW in a year	2000	2000
Average household size (Census, 2011)	4.2	4.1
Population covered by CHW per year	8400	8200
Proportion of population 40 years and above (Census, 2011)	0.378	0.321
Annual target population to be covered by CHW (twice a week)	3175.2	2630.56
Number of persons to be screened first time by CHW (in 108 days)	**29**	**24**
Number of persons to be screened second time by CHW (in 108 days)	**13.85**	**11.47**

CHW Salary component	
Manpower (1CHW)	
Annual Salary	36000
working days (6 days *54 weeks)	324
Community Screening days	108
Apportioning factor	0.33333333
Apportioned salary	12000

Appendix Table 1b: Microalbumiuria dipstick cost applies only for Scenario 1

		Per patient cost (₹)	
		Kerala	**Puducherry**
1st time			
Ice box per person		1.59	1.92
Consumables - urine container+PPE (Disposable gloves, mask, sanitizer etc)- per head		10.00	10.00
Plastic 12 Months Micral 30 Roche Test Kit, 20 mIU/mL (30 dipsticks)- Rs 2450- 1 stick (First time @ per stick Rs 81.66 for 100 persons = Rs 8166 & Second time for 47.1 persons =Rs 3846)		81.66	81.66
CHW Training (per head)	1030	35.03401	42.28757
2nd time			
Ice box per person		3.38	4.08
Consumables - urine container+PPE(Disposable gloves, mask, sanitizer etc)- per head		10.00	10.00
Plastic 12 Months Micral 30 Roche Test Kit, 20 mIU/mL (30 dipsticks)- Rs 2450- 1 stick (First time @ per stick Rs 81.66 for 100 persons = Rs 8166 & Second time Rs 81.66 for 47.1 persons =Rs 3846)		38.46	38.46

Appendix Table 1c: Treatment cost

Treatment Cost	**INR**
ACEI Treatment cost	10,372
Annual cost of medical management	35,176
Annual cost of Hemodialysis	12,72,886
Annual cost of Peritoneal Dialysis	4,93,892

Note: Costs have been computed from different sources and adjusted for 2020-21 prices

Appendix Table 2: Model estimates of Budget Impact for actual eligible population

Puducherry	Coverage										
		20%		40%		60%		80%		100%	
Year	Current scenario (₹)	Scenario 1 (₹)	Scenario 2 (₹)	Scenario 1 (₹)	Scenario 2 (₹)	Scenario 1 (₹)	Scenario 2 (₹)	Scenario 1 (₹)	Scenario 2 (₹)	Scenario 1 (₹)	Scenario 2 (₹)
2022	1048296780	288726965	429966329	577453930	859932657	866180895	1289898986	1154907859	1719865314	1443634824	2149831643
2023	1062728002	167658633	399735132	335317267	799470264	502975900	1199205396	670634534	1598940528	838293167	1998675660
2024	978191205	125383461	340240379	250766922	680480758	376150383	1020721137	501533844	1360961517	626917305	1701201896
2025	760762551	96288722	259379600	192577444	518759200	288866166	778138800	385154888	1037518400	481443610	1296897999
Total (₹)	**3849978538**	**678057781**	**1429321440**	**1356115563**	**2858642879**	**2034173344**	**4287964319**	**2712231125**	**5717285758**	**3390288906**	**7146607198**
Kerala	**Coverage**										
		20%		40%		60%		80%		100%	
Year	Current scenario (₹)	Scenario 1 (₹)	Scenario 2 (₹)	Scenario 1 (₹)	Scenario 2 (₹)	Scenario 1 (₹)	Scenario 2 (₹)	Scenario 1 (₹)	Scenario 2 (₹)	Scenario 1 (₹)	Scenario 2 (₹)
2022	25331256953	6976857198	10389793956	13953714397	20779587912	20930571595	31169381868	27907428793	41559175824	31395857392	46754072802
2023	25679975941	4051337374	9659281162	8102674747	19318562325	12154012121	28977843487	16205349495	38637124649	18231018182	43466765231
2024	23637211544	3029791496	8221637835	6059582992	16443275670	9089374487	24664913505	12119165983	32886551340	13634061731	36997370257
2025	18383221272	2326740293	6267701493	4653480586	12535402985	6980220878	18803104478	9306961171	25070805970	10470331317	28204656716
Total (₹)	**93031665710**	**16384726361**	**34538414446**	**32769452721**	**69076828891**	**49154179082**	**103615243337**	**65538905442**	**138153657783**	**73731268622**	**155422865006**

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