



Chronic kidney Disease Epidemiology and Diagnosis

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Agenda

- ✓ Introduction
- ✓ Epidemiology of CKD
- ✓ Definition of CKD
- ✓ Staging of CKD
- ✓ Referring the patients to nephrologists

Introduction

- Chronic kidney disease (CKD) is a worldwide public health problem.
- The number of patients enrolled in the end-stage renal disease (ESRD) Medicare-funded program has increased from approximately 10,000 beneficiaries in 1973 to 703,243 as of 2015



Introduction

Reasons for the growth of the ESRD

Under-
recognition of
earlier stages
of CKD and of
risk factors for
CKD

Differences in disease
burden among racial
groups

Changes in the
demographics of the
population

CKD

Epidemiology of CKD

- CKD, most commonly defined as an elevated Cr/decreased eGFR or moderately increased albuminuria:1-30 %.

Some Studies	Prevalence of CKD
Population-based study of Korean adults aged > 20 years	8.2 %
A report from Taiwan, the prevalence of an eGFR <60 mL/min/1.73 m ²	7 %
Overall prevalence of CKD in Norway	10.2%
Population-based study from West Malaysia	9%

Therapeutic Apheresis and Dialysis 2018

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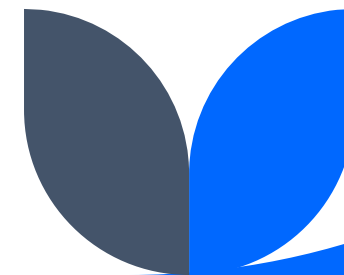
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Prevalence of Chronic Kidney Disease in Iranian General Population: A Meta-Analysis and Systematic Review

First Author	Year	Province	eGFR calculation method	Sampling method	Study period (years)	Setting	Sample size	Risk of bias
Gheissari et al.(24)	2013	Isfahan	MDRD	Multistage random cluster	1	School	712	Low
Hosseinpanah et al.(20)	2009	Tehran	MDRD	Multistage stratified random sampling	4	Hospital	10 063	Low
Khajehdehi et al.(8)	2014	Fars	MDRD	Simple random	2	Health Center	9404	Low
Mahdavi-Mazdeh et al.(21)	2010	Tehran	MDRD	Census	1	Health Center	31 999	Low
Malekmakan et al.(23)	2013	Fars	MDRD	Multistage stratified random sampling	3	Hospital	1190	Low
Naghibi et al.(25)	2015	Razavi Khorasan	MDRD	Multistage stratified random sampling	2	Health Center	1285	Low
Najafi et al.(22)	2010	Golestan	MDRD	Purposive	2	Health Center	3591	Low
Saber et al.(26)	2017	Kerman	MDRD	Single-stage cluster	1	Health Center	988	Low
Sepanlou et al.(7)	2017	Golestan	Schwartz	Simple random	4	Hospital	11 373	Low

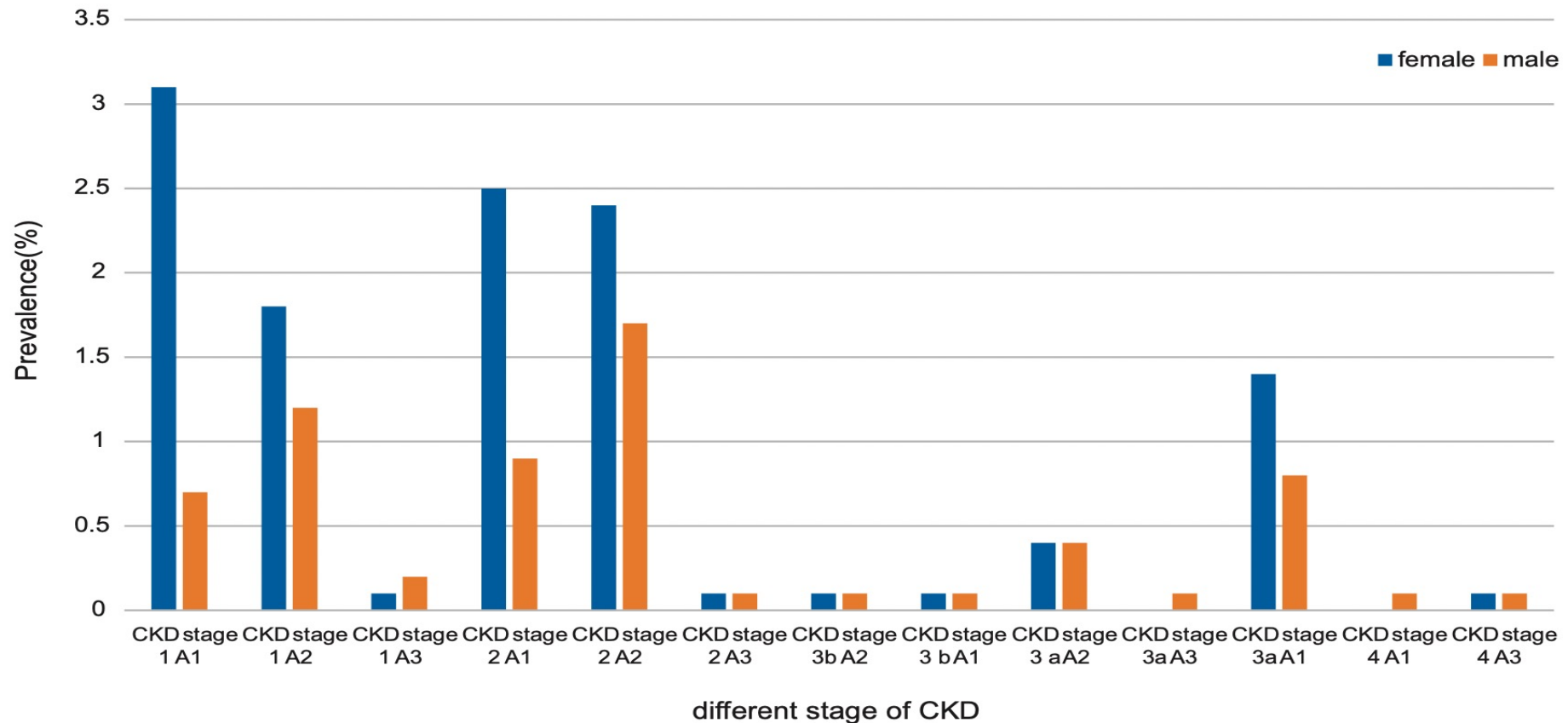
Prevalence of Chronic Kidney Disease in Iranian General Population: A Meta-Analysis and Systematic Review

- Overall prevalence of CKD in 70605 people was 15.14%
- The prevalence of CKD in female patients (18.80%) was 1.7 times higher than in male patients (10.83).
- The results of the this study indicate a higher than the global average prevalence of CKD in Iran and **the need for additional attention** of policy makers on better planning for control and implementation of screening programs in high-risk populations, such as patients with HTN & DM.



Chronic Kidney Disease in Isfahan Province, Action Plan for Screening in A Population-based Study

Firouzeh Moeinzadeh,¹ Marjan Mansourian,² Mojgan Mortazavi,¹
 Shiva Seirafian,¹ Shahrzad Shahidi,¹ Zahra Tasdighi,³
 Sahar Vahdat,¹ Shahram Taheri,¹ Mohammad Hossein Rouhani,⁴
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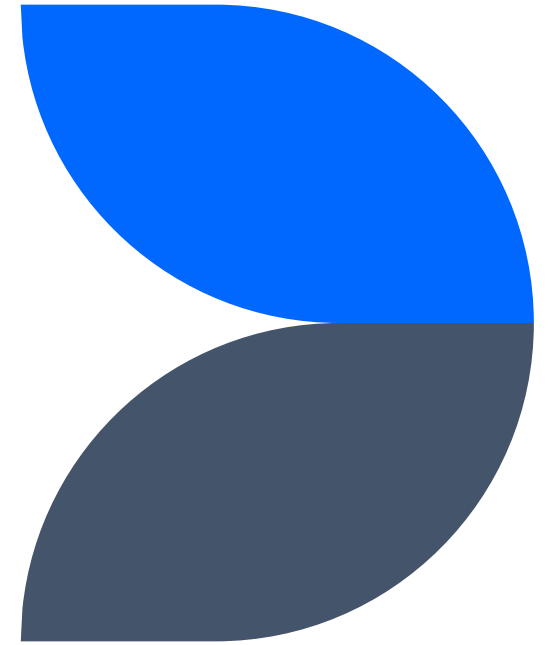
Chronic Kidney Disease in Isfahan Province, Action Plan for Screening in A Population-based Study

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- An overall CKD prevalence of 18.5% in Isfahan
- Smoking, older age, higher BMI and SBP, female sex, marital status, and low educational levels were significantly associated with higher risk of CKD.
- Increased risk of CKD is linked to decreased HDL and LDL levels and low waist-to-hip ratio and physical activity.



Definition and staging of CKD in adults



Definition of CKD

➤ Presence of kidney damage

➤ **or**

➤ Decreased kidney function

➤ **for three or more months**, irrespective of the cause

Kidney damage

Albuminuria

- Albuminuria reflects increased glomerular permeability to macromolecules.
 - Primary kidney disease
 - Kidney involvement in systemic disease
- The normal urine ACR in young adults is <10 mg/g

Kidney damage

Albuminuria

- Albumin-to-creatinine ratio (ACR) in an untimed "spot" urine

Reference Range

Category	Spot collection ACR	
	mg/g	mg/mmol
Normal	< 30	<3
Microalbuminuria	30-300	3-30
Clinical albuminuria	> 300	>30

“moderately increased”

“severely increased”

Kidney damage

Albuminuria

Factors other than CKD known to affect urinary albumin excretion:

- Urinary tract infection
- High dietary protein intake
- Congestive cardiac failure
- Acute febrile illness
- Heavy exercise within 24 hours
- Menstruation or vaginal discharge
- Drugs (especially NSAIDs, ACEIs, ARBs)

Albuminuria

Kidney damage

- A positive UACR test should be repeated to confirm persistence of albuminuria.
- CKD is present if 2 out of 3 tests (including the initial test) are positive.
- If the first positive UACR is a **random spot** (as it may be for opportunistic testing), then repeat tests should ideally be **first morning void** specimens

Albuminuria

Kidney damage

- Urine ACR >30 mg/g (or equivalent) have a significantly increased risk for **all-cause and cardiovascular mortality, ESKD, AKI and CKD progression** compared with those who have a lower ACR even when eGFR is normal.

Kidney damage

Albuminuria

Factor	Examples of effect
<i>Preanalytical factors</i>	
Transient elevation in albuminuria	Menstrual blood contamination Symptomatic UTI ¹⁸¹ Exercise ¹⁸² Upright posture (orthostatic proteinuria) ^{41,183} Other conditions increasing vascular permeability (e.g., septicemia)
Intraindividual variability	Intrinsic biological variability ¹⁸⁰ Genetic variability ¹⁸⁴
Preanalytical storage conditions	Degradation of albumin before analysis ^a
Non-renal causes of variability in creatinine excretion	Age (lower in children and older people) Race (lower in Caucasian than black people) Muscle mass (e.g., lower in people with amputations, paraplegia, muscular dystrophy) Gender (lower in women)
Changes in creatinine excretion	Non-steady state for creatinine (AKI)

Kidney damage

- Isolated non-visible (microscopic) hematuria with abnormal RBC morphology (anisocytosis): GBM disorders
- RBC casts: proliferative glomerulonephritis
- WBC casts: pyelonephritis or interstitial nephritis
- Oval fat bodies or fatty casts: diseases with proteinuria
- Granular casts and renal tubular epithelial cells: many parenchymal diseases, (non-specific)

Kidney damage

- Renal tubular acidosis
- Nephrogenic diabetes insipidus
- Renal potassium wasting
- Renal magnesium wasting
- Fanconi syndrome
- Non-albumin proteinuria
- Cystinuria

Renal tubular disorders

Kidney damage

Pathologic abnormalities detected by histology or inferred

- Glomerular diseases (diabetes, autoimmune diseases, systemic infections, drugs, neoplasia)
- Vascular diseases (atherosclerosis, hypertension, ischemia, vasculitis, thrombotic microangiopathy)
- Tubulointerstitial diseases (urinary tract infections, stones, obstruction, drug toxicity)
- Cystic and congenital diseases

Kidney damage

Structural abnormalities as markers of kidney damage detected by imaging

Ultrasound, CT/MRI +/-contrast, isotope scans, angiography

Polycystic kidneys

Dysplastic kidneys

Renal artery stenosis

Hydronephrosis due to obstruction

Small and hyperechoic kidneys

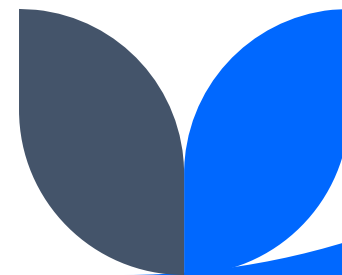
Renal masses or enlarged kidneys due to infiltrative diseases

Cortical scarring due to infarcts, pyelonephritis or associated with vesicoureteral reflux

Kidney damage

History of kidney transplantation

- Kidney biopsies in most kidney transplant recipients have histopathologic abnormalities even if GFR is >60 ml/min/1.73 m² and ACR is <30 mg/g (<3 mg/mmol)
- Kidney transplant recipients have an increased risk for mortality and kidney failure compared to populations without kidney disease
- Kidney transplant recipients routinely receive subspecialty care



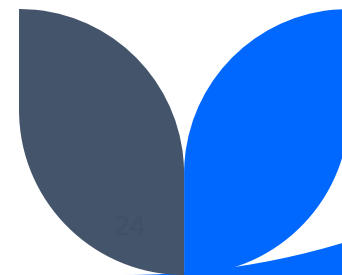
Decreased kidney function

- Creatinine measurement:
 - eGFR measurement: Cr or Cystatin-C

■ Cockcroft-Gault formula:

$$\text{creatinine clearance}_{(ml/min)} = \frac{(140 - \text{age}) \times W_{(kg)}}{72 \times Pcr_{(mg/dl)}}$$

- ✓ In women: multiple to 85%
- ✓ Not used in Cr > 5mg/dL
- ✓ Not used in very obese



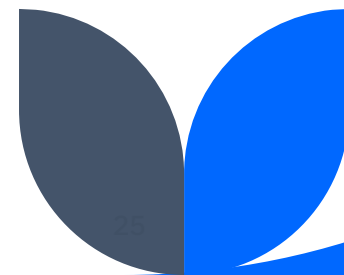
Cockcroft-Gault formula:

- For paraplegics, multiply by 0.8
- For quadriplegics, multiply by 0.6

The equation is not adjusted for body surface area.

Therefore to compare normal values, the calculation should be adjusted for BSA.

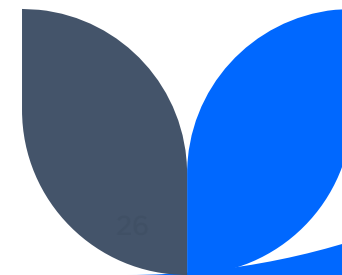
- **Applicable only when patient is in a steady state, not edematous and not obese.**



MDRD (modification of diet in renal disease)

$186 \times (\text{SCr})^{-1.154} \times (\text{Age})^{-0.203} \times (1.21 \text{ if African-American}) \times (0.742 \text{ if female})$

- Very difficult for measurement thus some calculators were designed.



CKD-EPI Equations for Glomerular Filtration Rate (GFR)

Equation

- 2021 CKD-EPI Creatinine
- 2021 CKD-EPI Creatinine-Cystatin C
- 2009 CKD-EPI Creatinine
- 2012 CKD-EPI Cystatin C
- 2012 CKD-EPI Creatinine-Cystatin C



Sex

Female Male

Age

Norm: 0 - 0 years

Serum creatinine

Norm: 0.7 - 1.3 mg/dL ↔

Race

Black Non-black

Race may/may not provide better estimates of

GFR: optional
6/11/1401

Equation



- 2021 CKD-EPI Creatinine
- 2021 CKD-EPI Creatinine-Cystatin C
- 2009 CKD-EPI Creatinine
- 2012 CKD-EPI Cystatin C
- 2012 CKD-EPI Creatinine-Cystatin C

Sex

Female Male

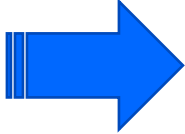
Age

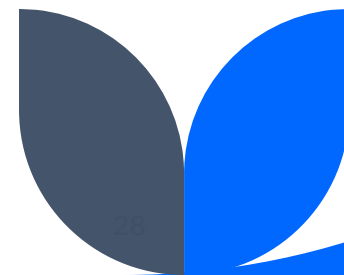
Norm: 0 - 0 years

Serum creatinine

Norm: 0.7 - 1.3 mg/dL ↔

Cystatin C

- Is a cysteine protease that is produced by nucleated cells, into bloodstream and then completely filtered by the glomerulus.
- Cystatin C **is not affected** by conditions that alter muscle mass such as sex, age and chronic disease (cancer, liver disease)  may be more reliable than Cr.



Cystatin- C:

Normal value: Adult : 0.5-0.97 mg/L

Table 13. Sources of error in GFR estimating using cystatin C

Source of error	Example
Non-steady state	Acute kidney injury
Non-GFR determinants of serum cystatin C that differ from study populations in which equations were developed	
Factors affecting cystatin C generation	<ul style="list-style-type: none">• Race/ethnicity other than US and European black and white• Disorders of thyroid function• Administration of corticosteroids• Other hypothesized factors based on epidemiologic associations (diabetes, adiposity)
Factors affecting tubular reabsorption of cystatin C	None identified
Factors affecting extra-renal elimination of cystatin C	Increased by severe decrease in GFR
Higher GFR	
Interference with cystatin C assay	Heterophilic antibodies

When we use cystatin-c?

- Measuring cystatin C in adults with eGFR_{creat} 45-59 ml/min/1.73m² who do not have markers of kidney damage **if confirmation of CKD is required.**
 - If eGFR_{cys}/eGFR_{creat-cys} is also <60 ml/min/ 1.73 m², the diagnosis of CKD is confirmed.
 - If eGFR_{cys}/eGFR_{creat-cys} is >60ml/min/1.73m², the diagnosis of CKD is not confirmed.

eGFR by Cystatin-C

Equation	<ul style="list-style-type: none">2021 CKD-EPI Creatinine2021 CKD-EPI Creatinine-Cystatin C2009 CKD-EPI Creatinine2012 CKD-EPI Cystatin C2012 CKD-EPI Creatinine-Cystatin C
Sex	<input type="radio"/> Female <input type="radio"/> Male
Age	Norm: 0 - 0 years
Serum creatinine	Norm: 0.7 - 1.3 mg/dL ↔
Serum cystatin C	Norm: 0.51 - 0.98 mg/L
Race <small>Race may/may not provide better estimates of GFR; optional</small>	<input type="radio"/> Black <input type="radio"/> Non-black

Equation	<ul style="list-style-type: none">2021 CKD-EPI Creatinine2021 CKD-EPI Creatinine-Cystatin C2009 CKD-EPI Creatinine2012 CKD-EPI Cystatin C2012 CKD-EPI Creatinine-Cystatin C
Sex	<input type="radio"/> Female <input type="radio"/> Male
Age	Norm: 0 - 0 years
Serum creatinine	Norm: 0.7 - 1.3 mg/dL ↔
Serum cystatin C	Norm: 0.51 - 0.98 mg/L

Duration of CKD

- In people with GFR <60 ml/min/1.73 m² or markers of kidney damage, review past history and previous measurements to determine duration of kidney disease.
- If duration is >3 months, CKD is confirmed. Follow recommendations for CKD.
- If duration is not >3 months or unclear, CKD is not confirmed.
- Patients may have CKD or acute kidney diseases (including AKI) or both and tests should be repeated accordingly.

Staging of CKD

GFR category	GFR (ml/min/1.73 m ²)	Terms
G1	≥ 90	Normal or high
G2	60–89	Mildly decreased*
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	< 15	Kidney failure

Category	AER (mg/24 hours)	ACR (approximate equivalent)		Terms
		(mg/mmol)	(mg/g)	
A1	< 30	< 3	< 30	Normal to mildly increased
A2	30–300	3–30	30–300	Moderately increased*
A3	> 300	> 30	> 300	Severely increased**

**Prognosis of CKD by GFR
and Albuminuria Categories:
KDIGO 2012**

				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min/1.73m ²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	<15			

Confirming the chronicity of damage or decreased function

- It can be obtained by one of the following:
 - Review of past measurements or estimates of GFR
 - Review of past measurements of albuminuria or proteinuria
 - Review of past urine dipstick and sediment examinations
 - Imaging findings, such as reduced kidney volume and reduction in cortical thickness, or presence of multiple cysts
 - Obtaining repeat measurements within and beyond the three-month point



چند مثال برای تعیین CKD در بیماران

○ خانم ۴۴ ساله با آزمایشهای زیر:

- BUN=22mg/dL Cr=1.2mg/dL
- U/A: Pr= Trace Blood=Neg cast= Neg
- eGFR= 57mL/min/1.73m²
- **Steps?**



چند مثال برای تعیین CKD در بیماران

○ آقای ۵۵ ساله سابقه دیابت از ۵ سال قبل سابقه رتینوپاتی دیابتی و آزمایشات زیر

- BUN=28mg/dL Cr=1.4mg/dL
- U/A: Pr= + Blood=Neg cast= Neg
- ACR=100mg/g
- eGFR=60ml/min/1.73m²
- CKD? Stage?

چند مثال برای تعیین CKD در بیماران

○ خانم ۳۴ ساله مورد پیوند کلیه از ۵ سال قبل با آزمایشات زیر

- BUN=13mg/dL Cr=0.8mg/dL
- U/A: Pr=Neg Blood=Neg

When to refer to the Nephrologist?

- Patients who have an eGFR less than 30 mL/min per 1.73 m²
- Urine ACR \geq 300 mg/g
- Hematuria not secondary to urological conditions
- Inability to identify a presumed cause of CKD
- eGFR decline of >30 % in fewer than 4 months without an obvious explanation

When to refer to the Nephrologist?

- Difficult to manage complications such as anemia requiring EPO, and abnormalities of BMD requiring phosphorus binders or vitamin D preparations
- Serum potassium greater than 5.5 mEq/L
- Difficult to manage drug complications
- Patients under the age of 18 years

When to refer to the Nephrologist?

- Resistant hypertension
- Recurrent or extensive nephrolithiasis
- Confirmed or presumed hereditary kidney disease, such as polycystic kidney disease, Alport syndrome, or autosomal dominant interstitial kidney disease

Take home messages

- CKD is defined as abnormalities of kidney structure or function, present for >3 months
- Presence of kidney damage including: Albuminuria, abnormal urine sediment, abnormal kidney imaging, abnormal pathology of kidney, Renal tubular disorders, Kidney transplantation.
- Loss of kidney function, as: low eGFR < 60 ml/min/1.73m²

