

2021

# COVID-19病患急性腎損傷危機 與尿液檢驗之應用

臺北榮總病理檢驗部品保科 蔡慧思



## 01 PART

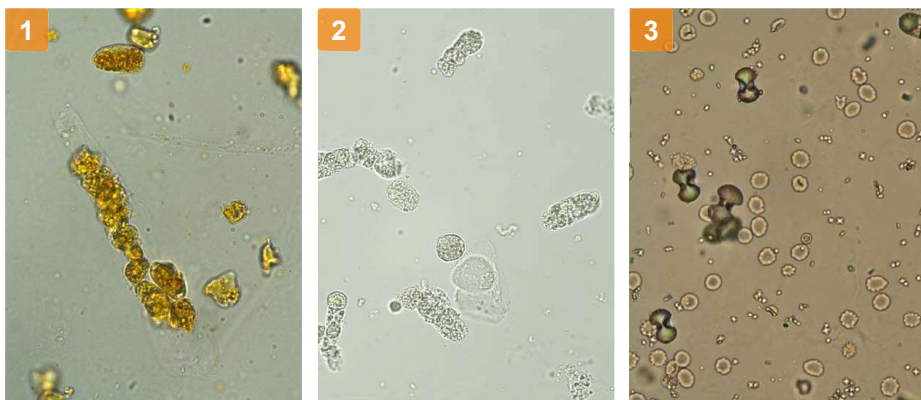
### 急性腎損傷 Acute Kidney Injury, AKI

#### Acute Kidney Injury (AKI)

- Also known as acute renal failure (ARF), is a sudden episode of kidney failure or kidney damage that happens within a few hours or a few days.
- Causes a build-up of waste products in your blood and makes it hard for your kidneys to keep the right balance of fluid in your body.
- Can also affect other organs such as the brain, heart, and lungs.
- Is common in patients who are in the hospital, in intensive care units, and especially in older adults.



## 下列尿沉渣像何者為AKI？



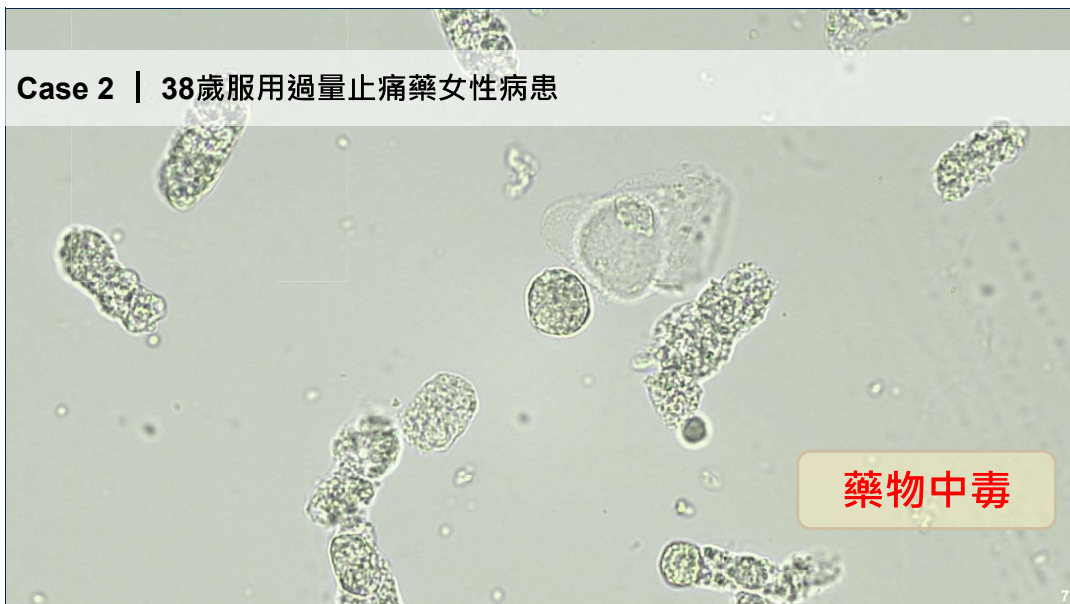
Case 1 | 64歲C型肝炎演進之肝硬化、肝細胞炎男性病患



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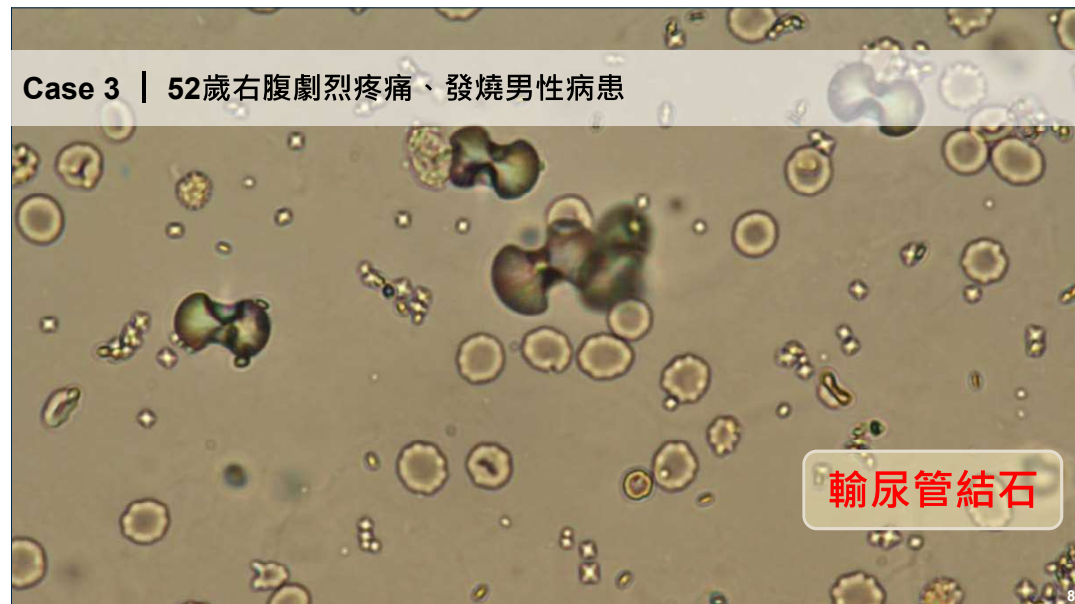
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Case 2 | 38歲服用過量止痛藥女性病患



7

Case 3 | 52歲右腹劇烈疼痛、發燒男性病患



8

## AKI診斷標準與分期

System	Serum creatinine criteria	Urine output criteria
<b>RIFLE criteria</b>		
Risk	SCr increase to 1.5-fold or GFR decrease >25% from baseline	<0.5 mL/kg/h for 6 h
Injury	SCr increase to 2.0-fold or GFR decrease >50% from baseline	<0.5 mL/kg/h for 12 h
Failure	SCr increase to 3.0-fold or GFR decrease >75% from baseline or SCr $\geq 4$ mg/dL ( $\geq 354$ $\mu\text{mol/L}$ ) with an acute increase of at least 0.5 mg/dI (44 $\mu\text{mol/L}$ )	$\leq 0.3$ mL/kg/h x 24 h or anuria x 12 h
Loss	Persistent AKI = complete loss of kidney function >4 weeks	
End-stage renal disease	End stage kidney disease (>3 months)	
<b>KDIGO criteria</b>		
Stage 1	SCr increase $\geq 0.3$ mg/dL ( $\geq 26.5$ $\mu\text{mol/L}$ )* or increase to 1.5- to 2.0-fold from baseline <sup>‡</sup>	<0.5 mL/kg/h for 6–12 h
Stage 2	SCr increase >2.0- to 2.9-fold from baseline	<0.5 mL/kg/h for $\geq 12$ h
Stage 3	SCr increase >3.0-fold from baseline or serum creatinine $\geq 4.0$ mg/dL ( $\geq 354$ $\mu\text{mol/L}$ ) with an acute increase of at least 0.5 mg/dL (44 $\mu\text{mol/L}$ ) or initiation of RRT or, in patients <18 years, decrease in eGFR to <35 mL/min per 1.73 m <sup>2</sup>	<0.3 mL/kg/h for 24 h Anuria for $\geq 12$ h

RRT, renal replacement therapy; \*Within 48 h; ‡within the prior 7 days.

Contrib Nephrol. Basel, karger, 2018; 193: pp1-12.

9

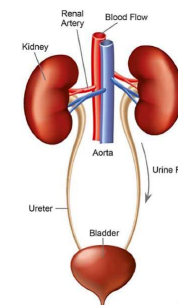
## AKI致病原因

### Prerenal

Sudden and severe reduction in blood pressure (shock) of interruption of blood flow to the kidneys from severe injury or illness

- Blood loss
- Dehydration
- Heart failure
- Sepsis
- Vascular occlusion

50~70%



### Intrinsic Renal

Direct injury to the kidneys by inflammation, drugs, toxins, infection, or reduced blood supply

- Acute tubular necrosis
- Drugs
- Toxins
- Prolonged hypotension
- Glomerulonephritis
- Acute tubular necrosis
- Autoimmune disease
- Infection
- Small-vessel vasculitis

25~45%

### Postrenal

Sudden obstruction of urine flow due to enlarged prostate, kidney stones, bladder injury or tumor

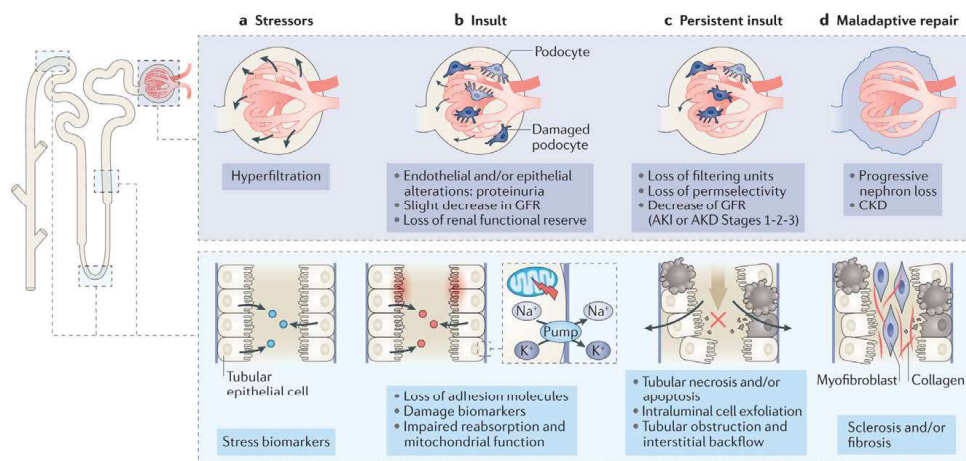
- Benign prostatic hyperplasia
- Cervical cancer
- Meatal stenosis/phimosis
- Retroperitoneal fibrosis
- Prostate cancer
- Urinary calculi

5%

J. Clin. Med. 2020; 9: 1104.  
ELSEVIER 腎臟醫學秘笈

10

## 腎性AKI組織變化

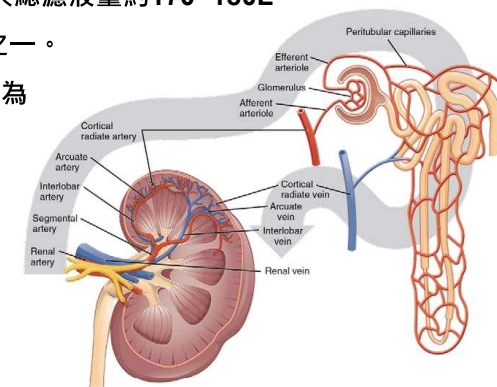


Nature Reviews Nephrology. 2021; 17: 493–502.

11

## 腎臟血流系統

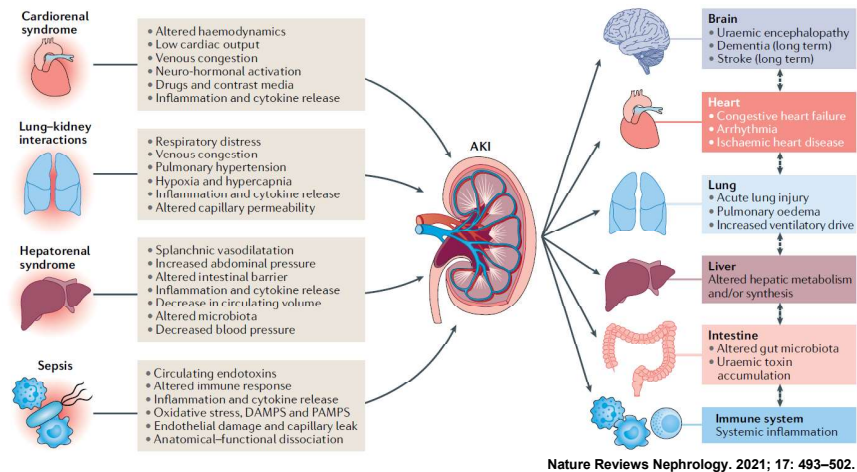
- 腎絲球濾液每分鐘約生成120mL，一天總濾液量約170~180L。
- 通過腎臟的血流約佔有總血量的四分之一。
- 急性腎衰竭中50~70%為腎前性，主因為腎臟血流動力異常，灌流不足所致。



12

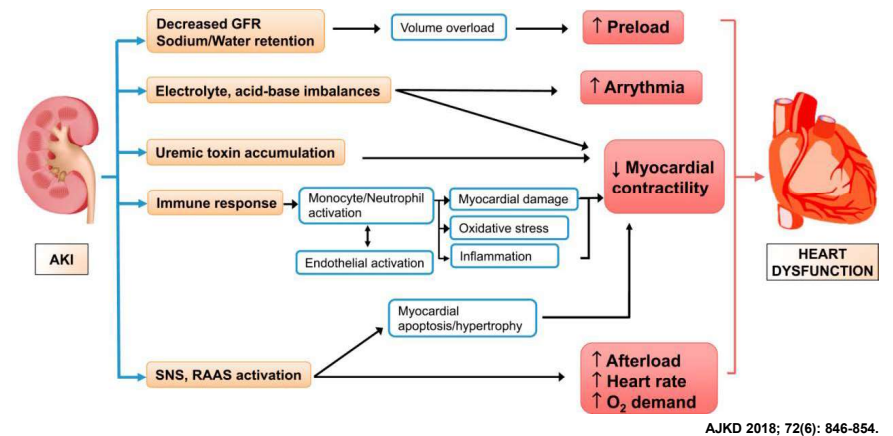


## AKI對遠端器官的影響



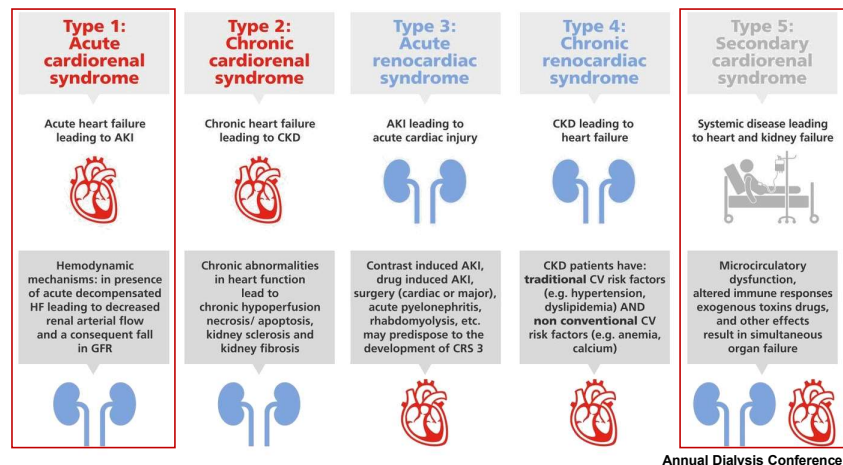
13

## 心肺腎 難兄難弟-1



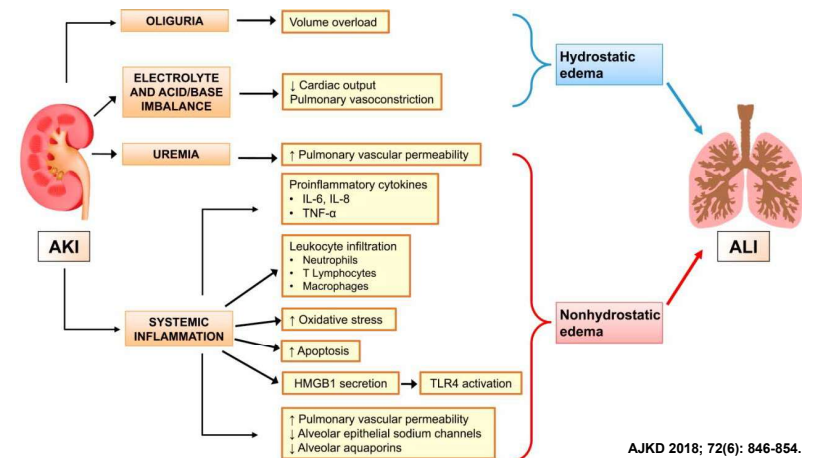
14

## 心腎症候群



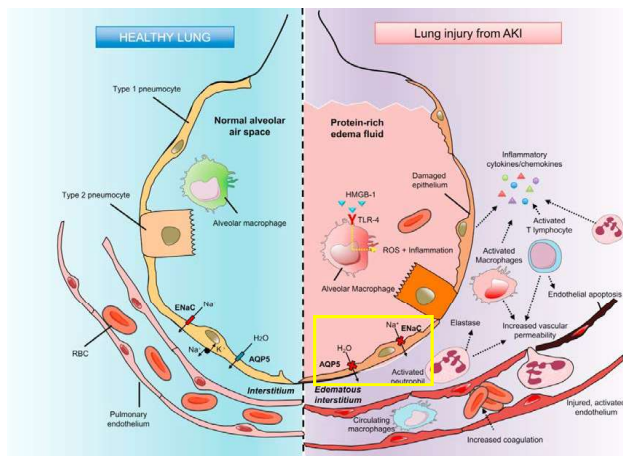
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## 心肺腎 難兄難弟-2



16

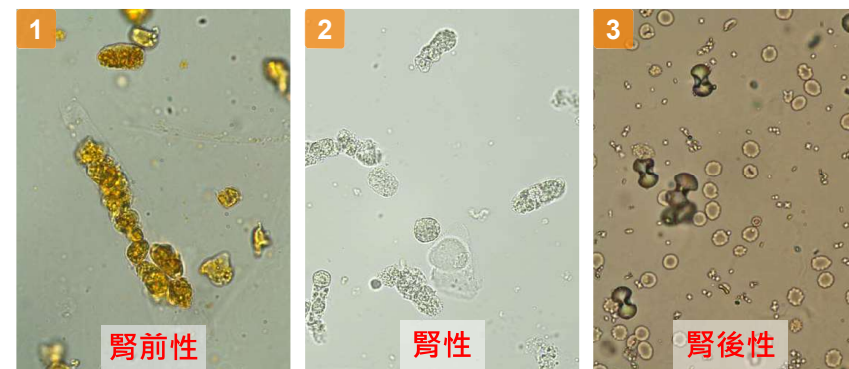
## 心肺腎 難兄難弟-3



AJKD 2018; 72(6): 846-854.

17

## 下列尿沉渣像何者為AKI？



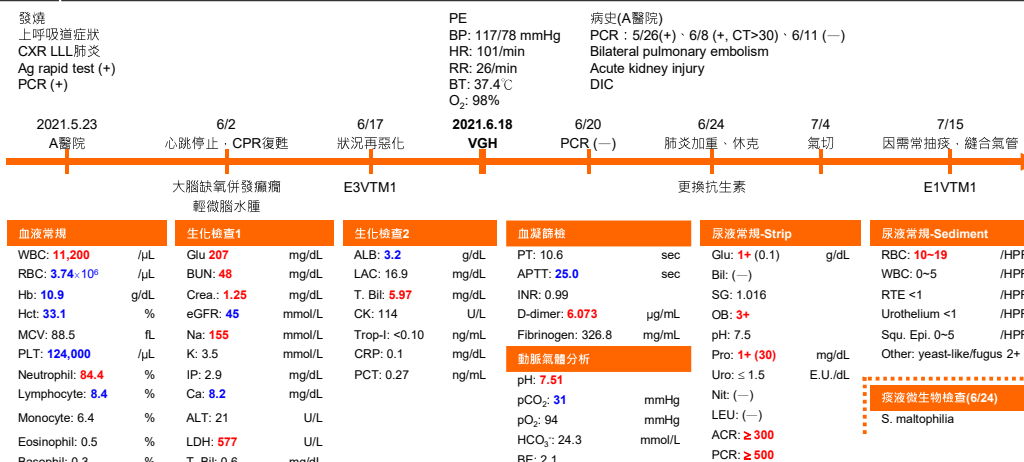
Ans：以上皆是！

18

## 02 PART

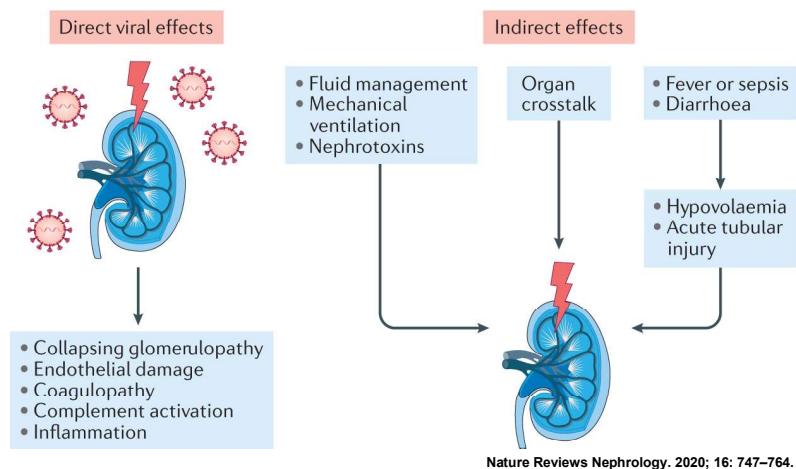
## 新冠肺炎相關急性腎損傷 COVID-19-associated AKI

## Case 4 | 53歲女性COVID-19病患



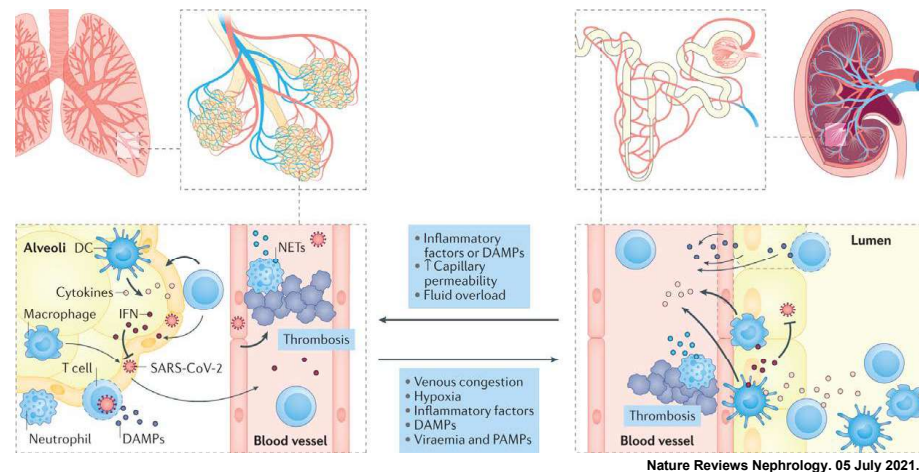
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## SARS-CoV-2直接、間接對腎臟的影響



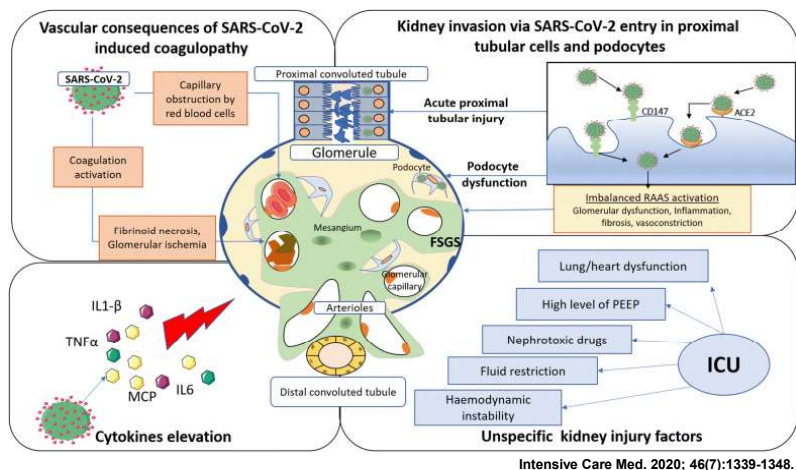
21

## SARS-CoV-2對肺臟與腎臟的影響



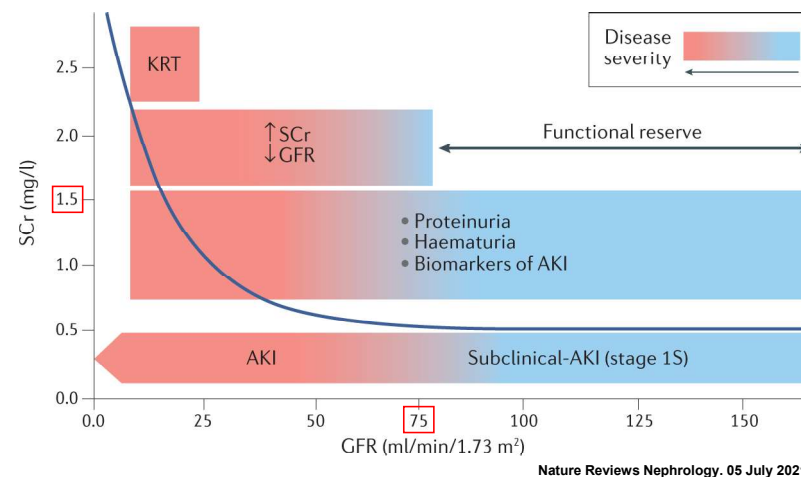
22

## SARS-CoV-2引發AKI機轉



23

## COVID-19-associated AKI嚴重度分期



24

## COVID-19-associated AKI促進因子

Etiology	Etiopathology
Acute tubular injury	<ul style="list-style-type: none"> <li>Regional inflammation</li> <li>Direct viral infection</li> <li>Renal compartment syndrome</li> <li>Tissue hypoxia hypoperfusion leading to hypoxaemia, hypotension, hypovolaemia and heart failure</li> <li>Nephrotoxic-induced injury (potentially associated with the use of antibiotics (vancomycin, aminoglycosides, colistin) or antivirals (remdesivir, ritonavir))</li> <li>Rhabdomyolysis</li> </ul>
Vascular injury	<ul style="list-style-type: none"> <li>Endothelitis</li> <li>Microthrombi</li> <li>Thrombotic microangiopathy</li> </ul>
Glomerular injury	<ul style="list-style-type: none"> <li>Collapsing glomerulopathy (potentially caused by interferon-associated podocyte injury)</li> <li>Glomerulonephritis</li> </ul>
Interstitial injury	<ul style="list-style-type: none"> <li>Acute interstitial nephritis; infiltration by immune cells</li> <li>Interstitial oedema</li> </ul>

Nature Reviews Nephrology. 05 July 2021.

25

## COVID-19-associated AKI風險因子

Demographic	for AKI at admission	for AKI during hospitalization
<ul style="list-style-type: none"> <li>Older age</li> <li>Diabetes mellitus</li> <li>Hypertension</li> <li>Cardiovascular disease or congestive heart failure</li> <li>High body mass index</li> <li>Chronic kidney disease</li> <li>Genetic risk factors (e.g. APOL1 genotype; ACE2 polymorphisms)</li> <li>Immunosuppressed state</li> <li>Smoking history</li> </ul>	<ul style="list-style-type: none"> <li>Severity of COVID-19</li> <li>Degree of viraemia</li> <li>Respiratory status</li> <li>Non-respiratory organ involvement, e.g. diarrhoea</li> <li>Leukocytosis</li> <li>Lymphopaenia</li> <li>Elevated markers of inflammation, e.g. ferritin, C-reactive protein, D-dimers</li> <li>Hypovolaemia/Dehydration</li> <li>Rhabdomyolysis</li> <li>Medication exposure, e.g. angiotensin-converting-enzyme (ACE) inhibitors and/or angiotensin-receptor blockers (ARBs), statins, nonsteroidal anti-inflammatory drugs (NSAIDs)</li> </ul>	<ul style="list-style-type: none"> <li>Nephrotoxins (medications, contrast exposure)</li> <li>Vasopressors</li> <li>Ventilation, high positive end-expiratory pressure</li> <li>Fluid dynamics (fluid overload or hypovolaemia)</li> </ul>

Nature Reviews Nephrology. 2020; 16: 747–764.

26

## COVID-19-associated AKI原因與檢驗數據變化

分類/細項	常見原因
腎前性 (pre-renal)	體液缺乏、敗血症、心臟衰竭、藥物(NSAID, ACEI/ARB)、系統性發炎、細胞激素風暴症候群
腎性 (intrinsic renal)	腎小管上皮細胞與足細胞感染、急性腎小管壞死(ATN)、藥物(NSAID, proton pump inhibitor, antibiotics)
腎後性 (post-renal)	無

台灣醫界2021. Vol. 64, No.4



Material	Abnormal Parameter	Elevated/Lowered
Urine samples	<ul style="list-style-type: none"> <li>Proteinuria</li> <li>Hematuria</li> </ul>	Elevated
Blood count	<ul style="list-style-type: none"> <li>WBC</li> <li>Neutrophils</li> <li>Platelets</li> <li>Lymphocytes</li> </ul>	Elevated Lowered
Pro-inflammatory markers	<ul style="list-style-type: none"> <li>Ferritin</li> <li>IL-2R</li> <li>IL-6</li> <li>hsCRP</li> <li>LDH</li> </ul>	Elevated
Coagulation markers	<ul style="list-style-type: none"> <li>D-dimer</li> </ul>	Elevated
Renal markers	<ul style="list-style-type: none"> <li>Creatinine</li> <li>Blood urea nitrogen</li> <li>eGFR</li> </ul>	Elevated Lowered

Int. J. Mol. Sci. 2021; 22: 7082.

27



## 尿液檢驗於急性腎損傷應用 Urinary tests applied to AKI



## 哪些檢驗項目可用於AKI診斷與評估？

BUN

sCr

uCr

sNA

uNA

SG

Sediment

uAlbumin

sAlbumin

Posmo

Uosmo



## AKI檢驗要求

Property	Explanation
<b>Easily measured</b>	Reliable quantification of a biomarker requires that the biomarker is stable during collection and processing and the test distinguishes the gene product from its metabolic product
<b>'Rapid on, rapid off' kinetics</b>	Biomarker expression must be upregulated shortly after the injurious stimulus and downregulated after termination of stimulus
<b>Dose-dependent response</b>	The quantity of the biomarker must be proportional to the number of injured nephrons or the severity of the injured nephrons. Hence, a biomarker must be sensitive to the injury of a small number of nephrons but also demonstrate a broad dynamic range to respond to widespread injury
<b>Tubular origin</b>	In acute renal failure caused by tubular injury, the biomarker must be expressed at sites of tubular damage. Specific An ideal biomarker should be able to distinguish the injury induced by different types of acute renal failure, such as volume depletion versus tubular damage and potentially proximal tubular from distal tubular injury
<b>Essential to homeostasis, injury or repair</b>	An ideal biomarker should reflect the injury process, a property called 'biological plausibility', e.g. KIM1 is needed to remove cellular debris, whereas NGAL defends the urinary system from infection
<b>Distinct from functional marker</b>	Analysis with an 'injury' biomarker should interact in a synergistic fashion with analysis by a 'functional' biomarker

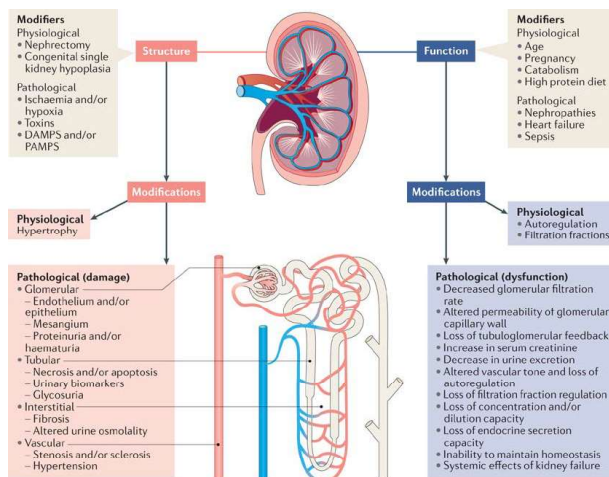
KIM1, kidney injury molecule 1; NGAL, neutrophil gelatinase-associated lipocalin.

Nature Reviews Nephrology. 2019, 15:599–612.

29

30

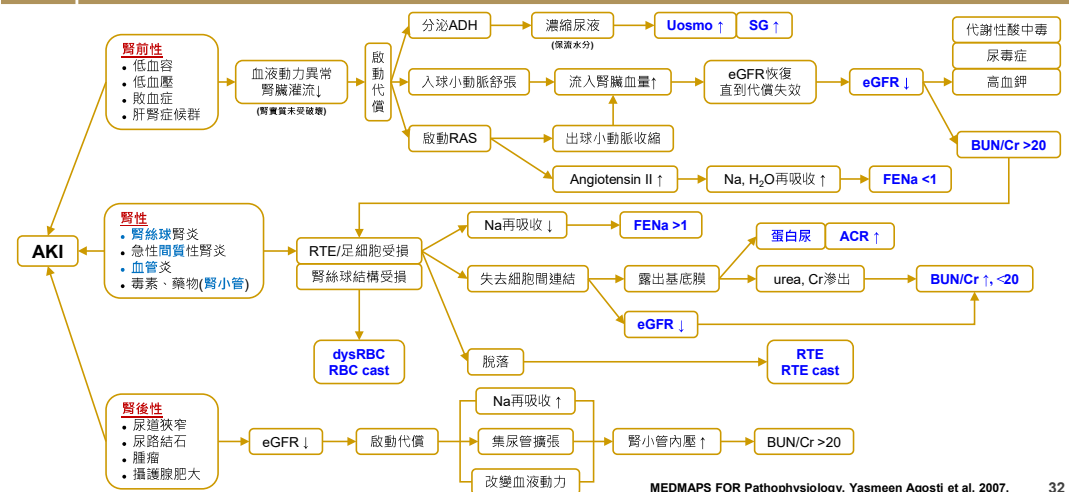
## 結構損傷vs.功能損傷



Nature Reviews Nephrology. 2021, 17:493–502.

31

## AKI病生理與檢驗項目



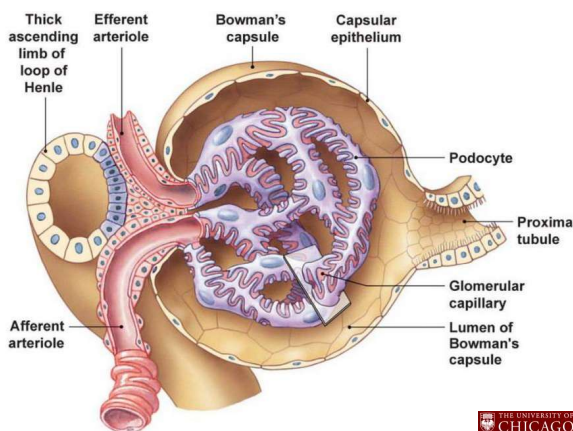
MEDMAPS FOR Pathophysiology. Yasmeen Agosti et al. 2007.

32



## eGFR

- 腎臟”功能”最重要指標
- 利用入球-出球小動脈血壓差將含氮廢物濾出至尿液
- 參考值100~120 ml/min/1.73m<sup>2</sup>  
以一位65公斤健康成年人來說，其血液量約5,000 mL，若eGFR為100 ml/min/1.73m<sup>2</sup>，5,000/100=50，意即，每50分鐘，腎臟為全身”消毒”一次。

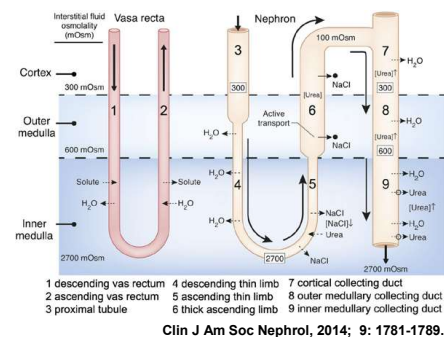


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33

## BUN/Cr. ratio

- BUN
  - ✓ 蛋白質代謝產物於肝臟合成尿素，送至腎臟由尿液排出。
  - ✓ 腎小管再吸收率48.4%。
- Creatinine
  - ✓ 肌肉代謝產物，受性別、年齡、肌肉量影響Cr濃度。
  - ✓ 腎小管再吸收率0%，但會主動分泌。
- BUN/Cr. Ratio
  - ✓ 正常大約為10。
  - ✓ 比值大於20，可能為prerenal azotemia。

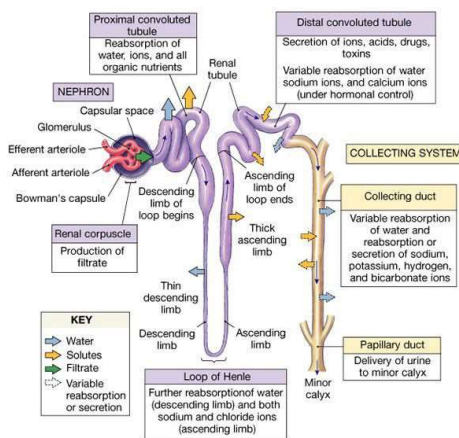


物質	血漿濃度(mg/dL)	再吸收率(%)	清除值(ml/min)
BUN	24	48.4	57.3
Cr.	1	0.0	110.0

34

## Urine osmolality / SG

- Uosmo
  - ✓ 尿液中所有可溶性粒子的濃度。
  - ✓ 評估腎小管的濃縮能力、電解質與水份之間的平衡狀態。
  - ✓ 配合血清滲透壓，可更瞭解患者體內水分與電解質狀態。
- SG
  - ✓ 評估腎小管的濃縮能力，與尿液滲透壓意義相同。
  - ✓ Functional range: 1.015~1.025。
  - ✓ 腎前性：>1.018；腎性：<1.012。



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35

## Fractional excretion of sodium, FENa

- 腎臟過濾的鈉在尿液中排泄的百分比
- 評估腎小管再吸收能力
- 區分AKI發生原因

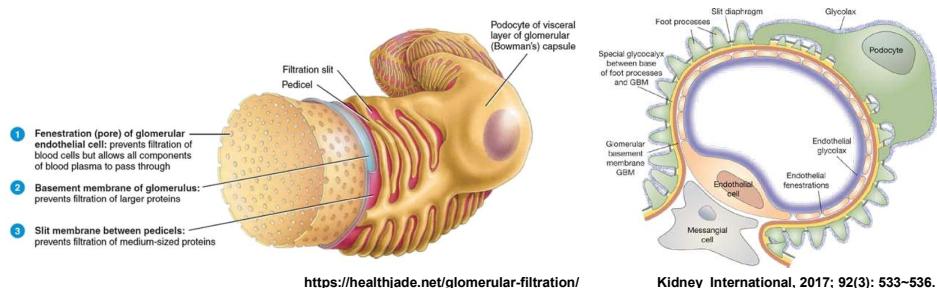
$$FENa = \frac{U_{Na} \times P_{Cr}}{P_{Na} \times U_{Cr}} \times 100$$

腎前性	腎性
<1%	>1%

36

## ACR / Proteinuria

- 評估血管內皮細胞-基底膜-足細胞結構完整性
- Albumin (負電)是第一個漏出的蛋白



## COVID-19-associated AKI患者蛋白尿陽性

Variables	AKI (n = 17)	Non-AKI (n = 331)	p value
<b>Proteinuria, n(%)</b>			
Negative	6 (35.3)	315 (95.2)	<.001
1 +	6 (35.3)	7 (2.1)	
2-3 +	5 (29.4)	9 (2.7)	
<b>Albumin/creatinine ratio (mg/g), n(%)</b>			
<30	4 (23.5)	291 (87.9)	<.001
30-300	8 (47.1)	35 (10.6)	
>300	5 (29.4)	5 (1.5)	
<b>Protein/creatinine ratio (mg/g)</b>			
<150	3 (17.6)	275 (83.1)	<.001
150-500	7 (41.2)	41 (12.4)	
>500	7 (41.2)	15 (4.5)	
<b>Haematuria with urine dipstick, n(%)</b>	<b>11 (64.7)</b>	<b>143 (43.2)</b>	<b>.08</b>
Positive with red blood cells > 5 with automated urine microscopy, n(%)	6 (35.3)	38 (11.5)	.013

Nephrology. 2021; 1-9.c

37

38

## ACR於AKI檢驗具高度敏感性與專一性

	AUC 95%CI	Cut-off value	Sensitivity (%) 95%CI	Specificity 95%CI	PLR 95%CI	NLR 95%CI	Accuracy 95%CI
Cystatin C	0.96 (0.90-1.0)	1.00	90.0 (55.5-99.75)	88.5 (84.6-91.7)	7.84 (5.45-11.2)	0.11 (0.02-0.71)	88.56 (84.7-91.7)
Albumin/creatinine ratio	0.95 (0.91 to 0.98.9)	30	90.0 (55.5-99.7)	87.9 (83.9-91.2)	7.45 (5.22-10.6)	0.11 (0.02-0.71)	87.9 (84.0-91.2)
Protein/creatinine ratio	0.88 (0.72-0.95)	150	80.0 (44.3-97.4)	83.0 (78.6-86.9)	4.73 (3.2-6.9)	0.24 (0.07-0.83)	82.9 (78.5-86.8)
CRP	0.89 (0.82-0.96)	5	90.0 (55.5-99.7)	69.7 (64.5-74.6)	2.98 (2.29-3.88)	0.14 (0.02-0.90)	70.3 (65.1-75.1)
D-dimer	0.94 (0.89-0.98)	0.5	90.0 (55.5-99.75)	86.7 (82.6-90.2)	6.77 (4.8-9.55)	0.12 (0.02-0.77)	86.8 (82.7-90.2)
Fibrinogen	0.88 (0.79-0.98)	328	90.0 (55.5-97.5)	67.9 (62.5-72.9)	2.81 (2.17-3.64)	0.15 (0.02-0.96)	68.6 (63.4-73.5)
Ferritin	0.72 (0.55-0.88)	36.5	80 (44.3-97.5)	53.1 (47.6-58.6)	1.71 (1.23-2.38)	0.38 (0.11-1.32)	53.9 (48.5-59.3)
LDH	0.68 (0.45-0.92)	260	70.0 (34.7-93.3)	81.2 (76.6-85.3)	3.74 (2.35-5.95)	0.37 (0.14-0.95)	76.3 (76.3-85.0)

Nephrology. 2021; 1-9.c

39

## SARS-CoV-2對腎臟的傷害不容小覷！

	On hospital admission	28th day of hospital admission	p value
Patient with acute kidney injury (n = 16), mean ± SD			
Cr (mg/dl) <sup>a</sup>	1.3 ± 0.50	1.4 ± 1.1	.278
BUN (mg/dl) <sup>a</sup>	27.6 ± 14.6	39.9 ± 29.7	.109
GFR (ml/min per 1.73 m <sup>2</sup> ) <sup>b</sup>	56.3 ± 21.0	58.8 ± 22.4 <sup>a</sup>	.111
Cystatin C (mg/L) <sup>a,c</sup>	1.46 ± 0.5	1.51 ± 0.45	.929
Albumin/creatinine ratio (mg/g) <sup>a,c</sup>	185 ± 177.9	97 ± 108.9	.075
Protein/creatinine ratio (mg/g) <sup>a,c</sup>	486.2 ± 375.5	611.0 ± 544.6	.286
Patient without acute kidney injury (n = 147), mean ± SD			
Cr (mg/dl) <sup>b</sup>	0.74 ± 0.16	0.77 ± 0.48	.419
BUN (mg/dl) <sup>a</sup>	12.7 ± 3.70	12.8 ± 3.40	.605
GFR (ml/min per 1.73 m <sup>2</sup> ) <sup>a</sup>	88.7 ± 5.25	88.8 ± 4.9	.852
Cystatin C <sup>a,d</sup>	0.84 ± 0.19	0.82 ± 0.21	.284
Albumin/creatinine ratio (mg/g) <sup>a,d</sup>	39.8 ± 119.2	26.5 ± 10.1	<.001
Protein/creatinine ratio (mg/g) <sup>a,d</sup>	222.5 ± 475.5	124.2 ± 178.4	<.001

Nephrology. 2021; 1-9.c

40

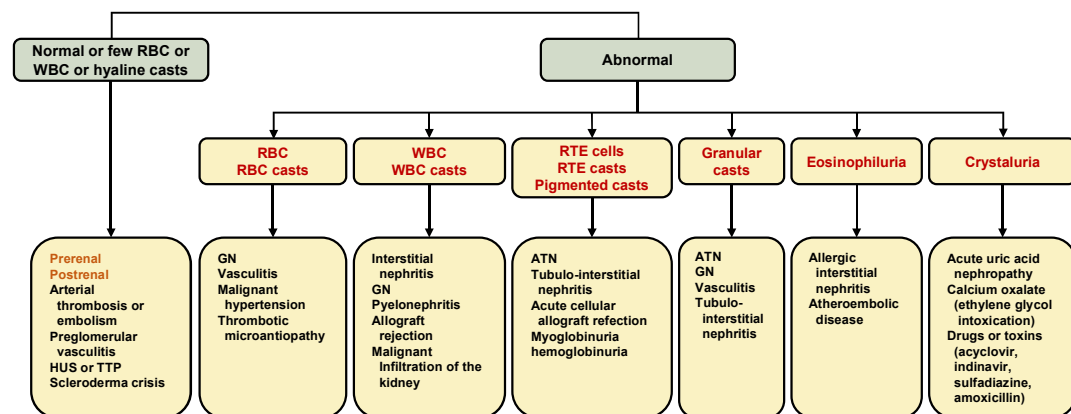
## 腎前性vs.腎性AKI檢驗指標差異

Clinical and Laboratory Variables in the Differential Diagnosis Between Prerenal and Renal AKI		
	Prerenal	Renal
<b>History</b>	GI, urinary, skin volume loss, blood loss or third spacing	Drugs or toxin exposure, hemodynamic change
<b>Clinical presentation</b>	Hypotension or volume depletion	No specific symptoms or signs
<b>Laboratory studies</b>		
BUN/SCr	>20	<20
Sediment	Normal to few casts	"Muddy brown" casts
U <sub>osm</sub> (mmol/kg)	>500	<350
Proteinuria	None to trace	Mild to moderate
U <sub>Na</sub> (mmol/l)	<20	>40
FE <sub>Na</sub> (%)	<1	>1
FE <sub>Urea</sub> (%)	<35	>35
U <sub>Cr</sub> /S <sub>Cr</sub>	<20	>40
Novel biomarkers	None	KIM-1, cystatin C, NGAL, CYR61, others

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41

## Urinary sediment in AKI



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42

## 常見腎性AKI原因與尿沉渣鏡檢

疾病	急性腎小管壞死 ATN	急性間質性腎炎 AIN	急性腎絲球腎炎 AGN	結晶性腎病 CN
發生原因	缺血(60~70%) 敗血症(50~60%) 腎毒物(30~40%)	藥物(NSAIDs) 感染 全身性疾病	全身性疾病 原發性腎(絲球)病	結石 藥物 腫瘤溶解症候群
沉渣發現	RTE Granular cast 	RBC WBC/Eosinophil WBC cast 	Dysmorphic RBC RBC cast 	Crystal: Calcium oxalate Uric acid Drug 

ELSEVIER 腎臟醫學秘笈

43

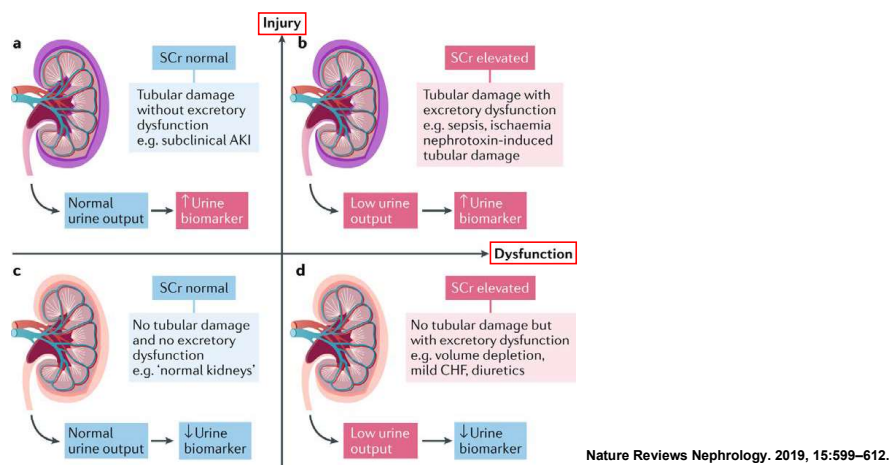
## 尿沉渣與腎臟疾病的相關性

Kidney Lesions/Syndrome	Urine Sediment	Urine Dipstick
Prerenal azotemia	Bland, hyaline casts, few finely granular casts, occasional RTECs	-/+ protein
Acute tubular injury	RTECs, RTEC casts, coarse granular casts, "muddy brown" Casts	-/+ protein
Acute interstitial nephritis	WBCs, WBC casts, RTECs, RTEC casts, RBCs, occasional RBC casts	-/+ protein, +/++ LE, +/++ blood
Nephritic syndrome	Dysmorphic RBCs (acanthocytes), isomorphic RBCs, WBCs, RBC casts, WBC casts	+/++ protein, ++/+++ blood
Nephrotic syndrome	Lipid droplets, oval fat bodies, birefringent Maltese cross, lipid laden casts, cholesterol crystals	+++ /++++ protein
Crystalline nephropathy	Various endogenous or drug-related crystals, RTECs, RBCs, WBCs, some WBCs engulfing crystals	-/+ blood, -/+ LE
Osmotic nephropathy	Swollen RTECs with cytoplasmic vacuoles, RTEC/granular Casts	-/+ protein

Am J Kidney Dis. 73(2): 258-272.

44

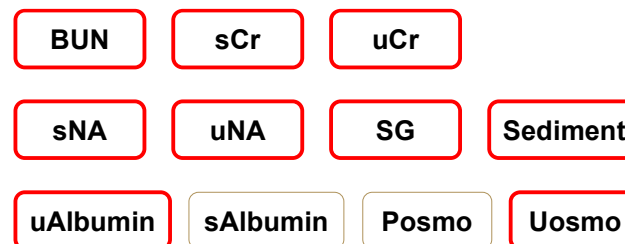
## 腎臟結構與功能損傷評估



45

## 哪些檢驗項目可用於AKI診斷與評估？

Ans :



46

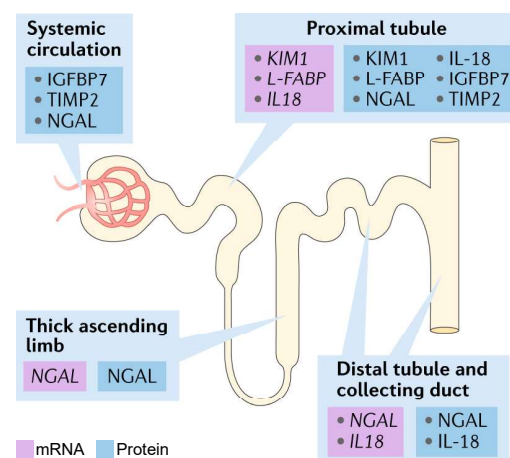
## AKI新興檢驗項目

Biomarker	Type	Origin
NGAL	Damage	Distal tubule
KIM1	Damage	Proximal tubule
L-FABP	Damage	Proximal tubule
TIMP2	Stress	Distal tubule
IGFBP7	Stress	Proximal tubule
IL-18	Inflammation	Multiple cell types throughout the body
TNFR1 and TNFR2	Inflammation	Ubiquitous membrane receptors
EGF	Cell growth and differentiation	Salivary and other glands
UMOD	Unclear	Loop of Henle
CHI3L1	Repair?	Multiple cell types throughout the body
CCL14	Persistence (of AKI)	Multiple cell types throughout the body

Nature Reviews Nephrology. 2021, 17:493–502.

47

## 各段腎小管損傷檢驗項目

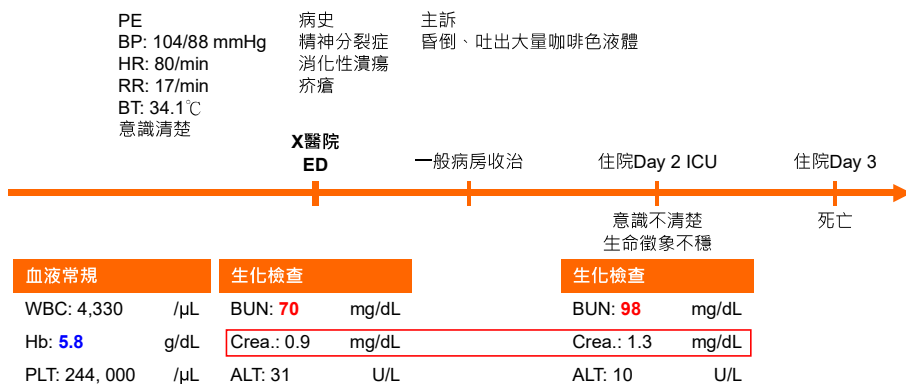


Nature Reviews Nephrology. 2019, 15:599–612.

48



## 請問這位81歲男性病患有AKI嗎？



49

## Take Home Message



AKI為患者短時間內發生腎臟功能異常的情形，意即患者血清Creatinine於48小時內上升高於0.3 mg/dL，原因可分為腎臟結構或功能損傷。



AKI病因分為腎前性(50~70%)、腎性(25~45%)與腎後性(5%)，常見原因分別為[腎前]低血容、低血壓、敗血症，[腎]腎小管壞死，[腎後]尿流阻塞。



SARS-CoV-2可直接或間接引發COVID-19-associated AKI，病毒能直接侵犯腎臟，或因為肺炎(肺臟損傷)遠端影響腎臟功能。



eGFR、BUN/Cr、Uosmo、FENa、ACR、Sediment等檢驗項目常應用於AKI原因診斷。簡便的尿液常規檢查可早於腎臟功能異常前提早偵察結構的損傷！

謝謝

THANK YOU