

The Interconnected Landscape of Acute and Chronic Kidney Disease: Pathophysiology, Risk Factors, and Evolving Therapeutic Strategies. A Review

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Abstract

Chronic kidney disease (CKD) and its transition to end-stage kidney disease (ESKD) become a global burden identify by its complex pathophysiology and high rate of mortality word wide. This paper focuses on the transition of acute kidney injury (AKI) to chronic kidney injury (CKD), highlighting those factors which cause permanent organ damage like NLRP3 inflammasome and ferroptosis. This paper explains co-existent kidney diseases such as type 2 diabetes and heart failure and novel markers like NT-proBNP which improve predictive accuracy. Further, we discussed the impact of COVID-19 on this vulnerable population and those agents which cause nephrotoxicity like NSAID. At the end we discussed the newly discovered therapeutic agents like SGLT2 inhibitors and artificial intelligence, machine learning in modern nephrology. This paper explains the current challenges and future direction

in the field of nephrology.

Introduction:

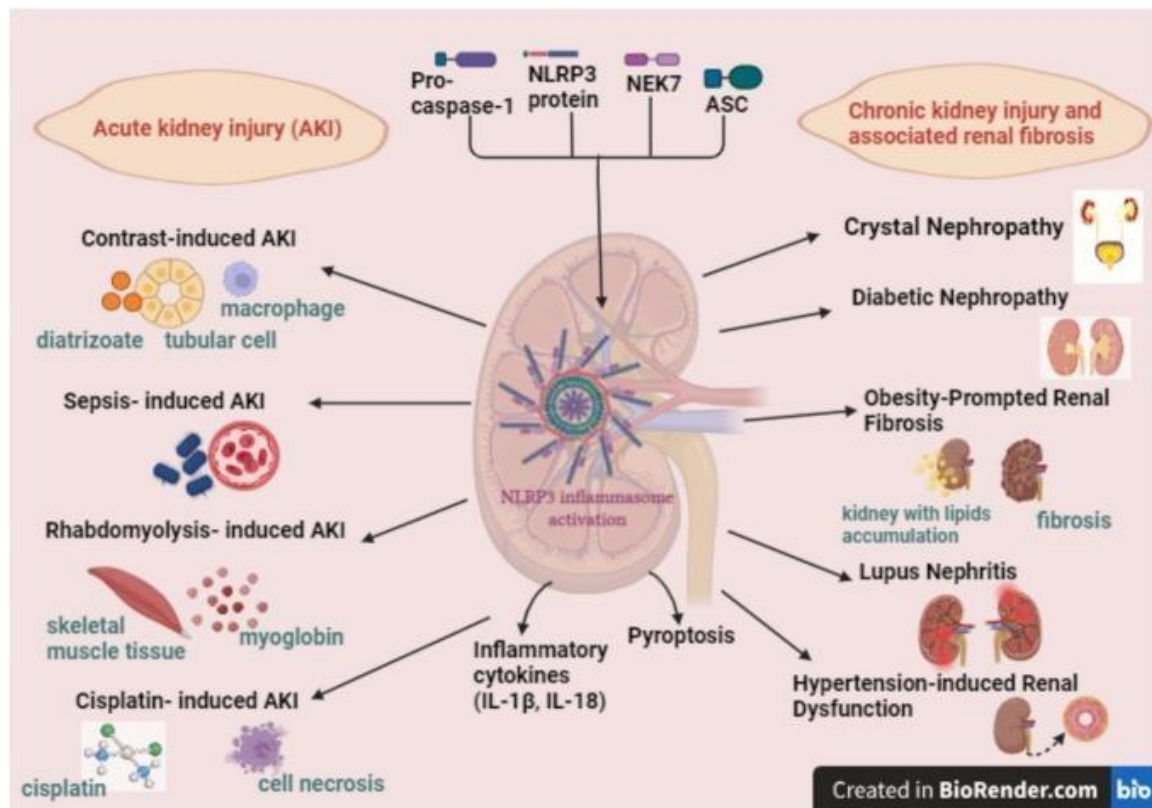
The field of renal medicine is significantly shifting as globally people are getting long term kidney diseases (CKD). The rising trend of CKD means developing better

diagnostic and treatment strategies. The expert understands CKD is not a static condition, but it develops often once a person has experienced acute kidney injury (AKI) 3,6. The transition of AKI to CKD is a critical event if not properly resolved it led to maladaptive repair like fibrosis and eventually causes kidney failure 25. Ongoing research has identified some molecular pathways which play a pivotal role in the transition of AKI to CKD such as NLRP3 inflammasome and FOXO3 which provide good target for intervention 11,6. The comorbidities often lead toward complexity like cardiorenal syndrome which has direct impact on both kidney and heart which become difficult in the management and lead to hospitalization and poor outcome for the patients 20,21. Patients with type 2 diabetes has a high risk of cardiorenal complication but the emergence of NTproBNP biomarker and sodium glucose cotransporter-2 reduced the risk and organ transplantation protection 15,16,28. Furthermore, The gut microbiota dysbiosis has emerge novel area of interest, dysbiosis of gut microbiota lead to systemic inflammation and progression of CKD 2,4. The environmental and external factors also contribute in the development of renal diseases. As we have seen in covid-19 pandemic mortality of kidney transplant recipients and dialysis patients. 10,31,32. Further, the effect of common NSAID and immunosuppressive medicine in post liver transplant required vigilant monitoring because these medicines cause nephrotoxicity 12,29. The recent past development of AI, artificial intelligence can accurately predict the development of CKD to renal failure 1. Recently, novel therapeutic drugs have been investigated and are used like isloliquiritigenin and iron-targeted to reduce inflammatory and cell death 7,34. The paper provide the understanding of current science of renal and the longevity and quality life of patients.

Acute Kidney Injury (AKI)

Acute kidney injury (AKI) can be defined as a sudden reduction in the function of kidney, and which leads to the progression of chronic kidney disease (CKD) 3,5. AKI is notably high in critical ill patients, especially those undergoing sepsis and major surgeries 6,7,8. For a while, patients admitted to ICU with COVID-19, AKI requiring kidney transplant was observed in most of the patients 6. According to one study 54 OUT OF 481 ICU admitted positive patients with COVID19 developed AKI which required kidney replacement therapy (KRT) 9.

There are several factors which contribute to AKI. Sepsis is one of them which reduces blood flow and inflammatory markers which direct damage the nephron 6,10,8. Other causes include heart surgery, rhabdomyolysis, and intracranial brain hemorrhages or stroke 6. Therapy for cancer like radio-chemotherapy liver and respiratory complications also contribute to AKI development 6,10. Some medications also known that cause AKI like non steroid anti-inflammatory drug and antibiotic. For example, ibuprofen has high value in the development of AKI compared to other NASID in one of the analyses 8. Cisplatin, which is a chemotherapy drug contributing to cell necrosis which enhances the development of AKI 10,11.



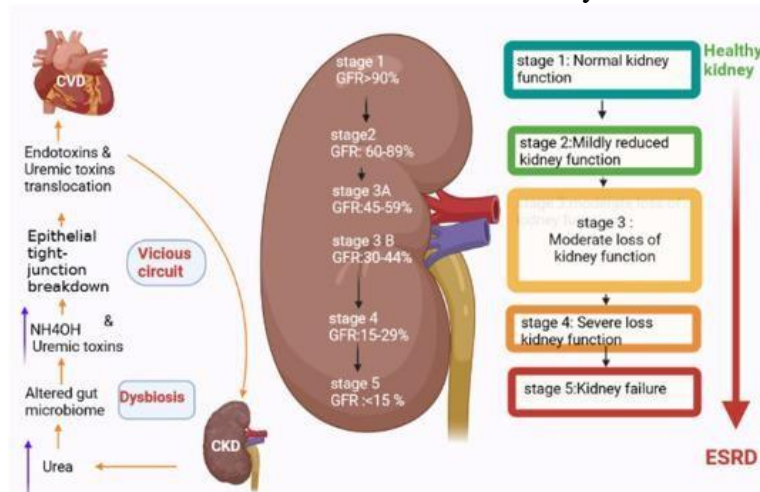
Source: 10

The diagram above illustrates that AKI is a tissue-specific inflammatory disorder linked to, a type of regulated cell death characterized by iron-dependent lipid peroxidation 10.

Additionally, NLRP3 is a complex protein involved in the development of AKI by responding to various stimuli through inflammatory responses and contrast agents, like sepsis, rhabdomyolysis, and cisplatin 12,13.

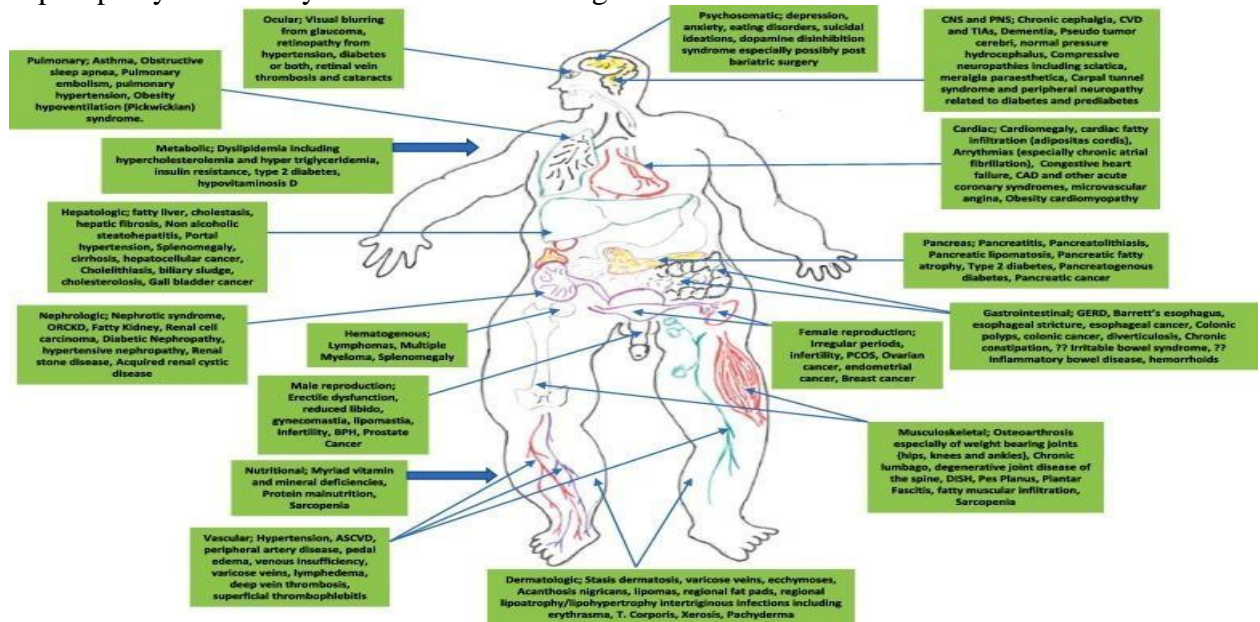
Chronic Kidney Disease (CKD)

CKD is a long-term condition of kidney in which the kidney loss their function consistently over months or years 3,2,4. It developed by various diseases like cardiovascular diseases diabetes mellitus, and hypertension 14,15,16. CKD has been divided into five stages by the value of GFR as shown in the figure. The peak of the GFR is <math>< 15 \text{ ml/min/ } 1.73 \text{ m}^2</math> which is a kidney failure 2.



Source 4:

The development of CKD is associated with structural and physiological changes, it includes reduction in kidney mass, weight, and cortical volume 17. Microscopic examinations: atherosclerosis, glomerulosclerosis, and interstitial fibrosis are the common findings 17. All these changes lead to kidney function impairment such as reduced GFR, blood flow and tubular transports 17. The risk factors for the development of CKD include Age, diabetes mellitus, hypertension, previous history, and obesity 17,18,16. Visceral obesity usually causes obesity related kidney disease (ORCKD) by the mechanisms of adiposopathy, diysglycemia, dyslipidemia and altered guts microbes which lead to renal inflammation, glomerular change like glomerulomegaly 16. The details of the diagram below show how obesity create different conditions like nephrotic syndrome, diabetic nephropathy, hypertensive nephropathy and kidney stones. Source of diagram 16.

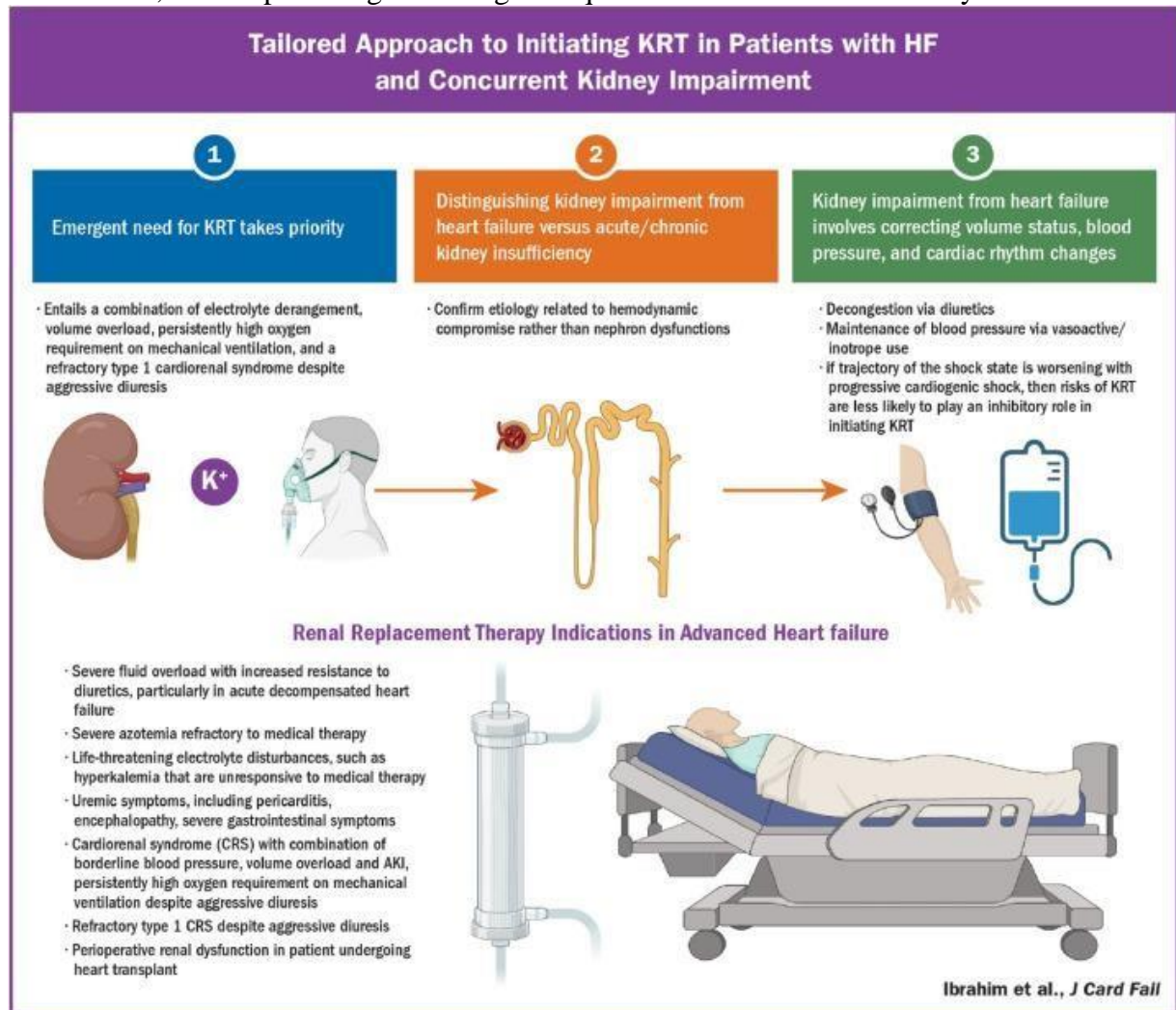


There is a strong relationship between CKD and CVD, the phenomenon referred to as cardiorenal syndrome 15,19,20. Heart Patients always develop acute kidney dysfunction which affects the prognosis of and increases the risk of mortality 22,19,21. Almost 50% of heart failure patients are also affected by CKD 19. Prominent level of uric acid is seen chronic kidney disease patients due to cardiovascular disease, hypertension atherosclerosis, and myocardial infarction 23. Leptospirosis also contributes to the development of acute and chronic kidney disease by infiltrating in the renal tubule and interstitial spaces of the kidney cells Which compromise the normal function of the kidney 24. Systemic erythematosis also damages the kidney by the mix nature of the disease and other contributing elements of factors 25.

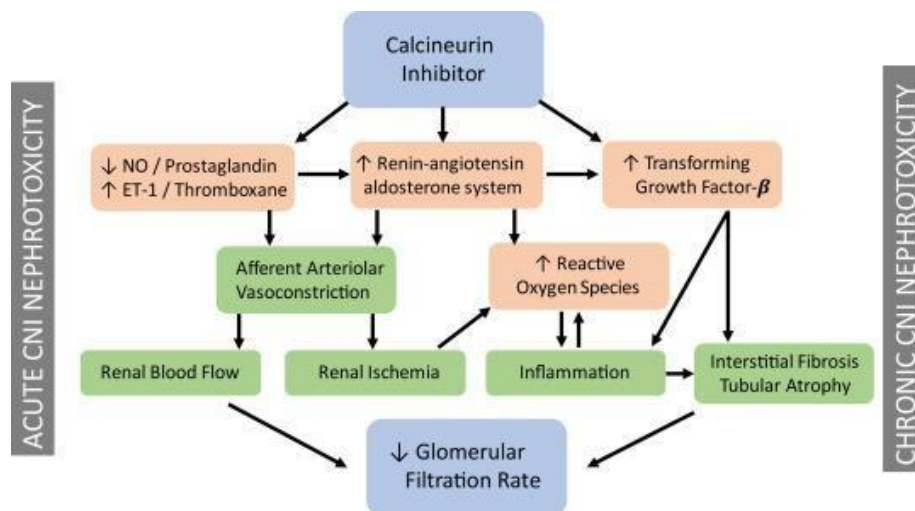
Management and Therapeutic Advances

Management of kidney failure is done by its severity and underlying cause. for acute kidney failure timely intervention is very important. The timing of the kidney replacement therapy (KRT) in acute kidney failure (AKI) has studied and suggested that there is no significant difference in early and delayed intervention in those who do not meet the emergency criteria 26. In heart failure patients' initiation of KRT required special attention, prioritizing all the emergent like fluid overload, vital electrolyte, or uremic symptoms 21.

The infographic diagram below shows approach while initiating KRT in patients with heart failure, also emphasizing the emergent requirements and causes of kidney failure.



For CKD, sodium glucose co-transporter 2 inhibitors (SGLT2is) have significant role in advance therapeutic. Initially it was developed for type 2 diabetes but now it plays a crucial role in the reduction of cardiovascular and renal complications in both diabetic and non-diabetic patients 27,15,28. SGLT2is has shown good effect in slowing the progression of kidney disease in some subgroups of type 2 diabetes and some rare conditions like ketoacidosis and amputation of lower limbs 28. In predicting cardiorenal events in type 2 diabetes N-terminal pro-B-type natriuretic peptide (NT-proBNP) has demonstrated, which is a good diagnostic marker than traditional one 14. During kidney transplant or liver transplantation management for rejection is necessary, immunosuppressives drugs calcineurin inhibitor are used but has the effect of nephrotoxicity in both acute and chronic kidney failure 29. Acute calcineurin inhibitor (CNI) constrict the afferent arterioles and reduce the blood flow which resulted in low GFR 29. Chronic calcineurin inhibitor (CNI) nephrotoxicity involved in the activation of renin angiotensin-aldosterone system (RAAS) which activates the production of reactive oxygen species (ROS) and inflammation which toward renal fibrosis and atrophy 29.



Source: 29

The above diagram shows the mechanism of acute and chronic nephrotoxicity caused by calcineurin inhibitors.

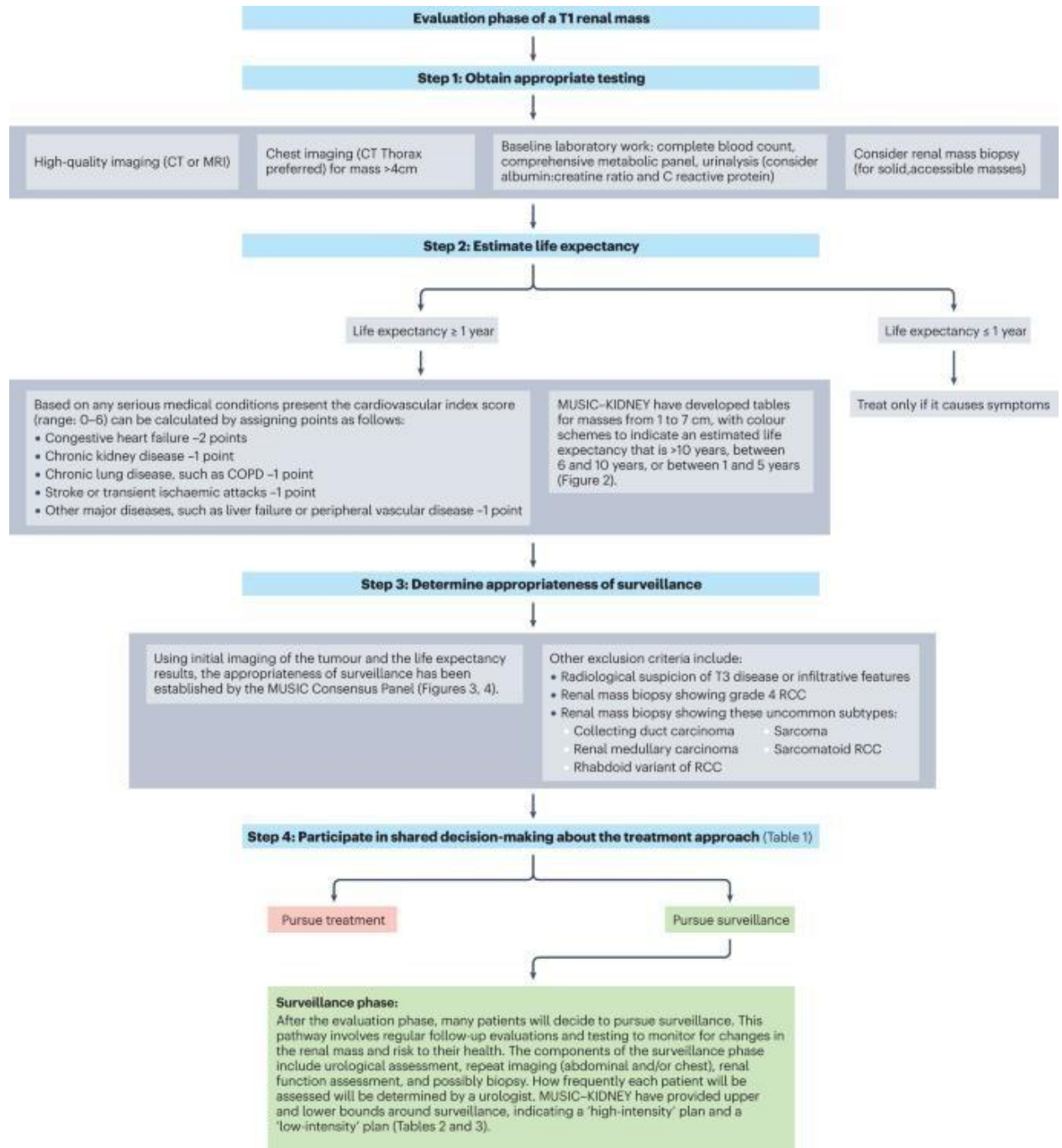
Multiple donors for a single patient are very beneficial because they save the expenses and time of patient on dialysis 30. Because of COVID-19, a lot of patients are waiting for transplant, resources must be dedicated to streamline the donors because it is more important than ever 30.

Emerging Concepts and Future Directions

The relationship between AKI and CKD is well understood, but AKI is a prominent risk factor for the development of CKD 3,5. Ongoing research is explaining the transition of AKI to CKD, finding insight like hypoxia and tubular epithelial regeneration 5.

Some systemic infections like SARS covid-2 which directly affect the kidney leading to various abnormalities like development of the AKI, proteinuria, hematuria 31. The kidney transplant recipient community is vulnerable and increases mortality rate when infected by covid-19 32. This threat highlights the need of urgent vaccination of the dialysis community 32. Newly therapeutic drugs are under investigation in critically ill patients and in acute kidney for example, iron hemostasis in ferroptosis 6,12. Isoliquiritigenin is a bioactive compound derived from licorice and exhibit an anti-inflammatory activity which could be beneficial in both acute and chronic renal injuries 34.

Artificial intelligence (AI) and Machine learning (ML) are the emerging technologies in the field of medicine, which identify different variables and predict by those variables, whether the CKD is going toward renal failure or not 1. The chances of nephrectomy of small renal masses are reduced, despite surgery active surveillance is done 35. This involved various processes like high quality imaging (MRI or CT) laboratory tests, life expectancy, one the bases of all these treatment strategies are made 35.



Source 35:

The above diagram shows the management of T1 renal masses which focus on imaging, lab tests and life expectancy of the patient and then decision making.

Conclusion

Kidney failure, whether it is acute or chronic, imposes burden on global healthcare system. Deeper understanding of pathophysiology of the acute and chronic kidney failure it includes, inflammation, oxidative stress, cellular death like ferroptosis, fibrosis and necrosis, all these interventions can reduce the number 13,10,36. Advancement in pharmacological treatments like SGLT2 inhibitor and change in kidney replacement therapy strategies improved the patient’s outcome 27,21,28. The intervention of various discipline of medicine in the management of kidney failure are very crucial like early diagnosis, prevention, and target therapies. The continuous

discovery of novel therapeutic drugs and introduction of artificial intelligence (AI) and machine learning (ML) mitigating the burden of kidney failure globally 1.

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