# EARLY DIAGNOSTIC BIOMARKERS FOR ACUTE KIDNEY INJURY IN CRITICALLY ILL PATIENTS

*Essay*

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in Intensive Care Medicine

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# الدلائل الكيميائية المستخدمة فى التشخيص المبكر للإصابة الحادة للكلية فى مرضى الرعاية المركزة

# رسالـــة

**مقدمة للحصول علي درجة الماجستير في تخصص الرعاية المركزة**


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# Summary

The The incidence of acute kidney injury (AKI), previously referred to as acute renal failure, has reached epidemic proportions world-wide, affecting about ٧٪ of hospitalised patients. In the critical care setting, the prevalence of AKI requiring dialysis is about ٦٪, with a mortality rate exceeding ٦٠٪ (***Parikh and Devarajan, ٢٠٠٨).***

A significant increase in morbidity and mortality associated with AKI has been demonstrated in a wide variety of clinical situations, including exposure to radiocontrast dye, cardiopulmonary bypass, mechanical ventilation and sepsis. Once established, the treatment is largely supportive, at an annual cost surpassing $١٠ billion in the US alone ***(Parikh and Devarajan; ٢٠٠٨).***

The early diagnosis of AKI currently depends on detection of reduced kidney function by the rise in serum creatinine concentration and blood urea nitrogen(BUN), which are delayed and unreliable measures in the acute setting. In general, there are several non-renal factors influencing the serum creatinine concentration such as body weight, muscle mass, race, age, gender, total body volume, drugs, muscle metabolism and protein intake***(Parikh and Devarajan; ٢٠٠٨).***

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# List of Abbreviations

| | |
|---|---|
| **ABP** | Arterial blood pressure |
| **ACE** | *Angiotensin-converting enzyme* |
| **ACEIs** | angiotensin converting enzyme inhibitors |
| **ACTH** | *Adrenocortico trophic Hormone* |
| **ADF** | Actin depolymerizing factor |
| **ADH** | Anti diuretic hormons |
| **AIN** | Acute interstitial nephritis |
| **AKI** | Acute Kidney Injury |
| **AMP** | Adenosin monophosphate |
| **ANP** | Atrial natriuretic peptid |
| **ARBs** | angiotensin II receptor blockers |
| **ARDS** | Acute respiratory distress syndrome |
| **ARF** | Acute renal failure |
| **AT** | Angiotensin |
| **ATN** | Acute tubular necrosis |
| **ATP** | Adenosine triphosphate |
| **AUC** | Area under the curve |
| **BUN** | blood urea nitrogen |
| **CIN** | Contrast induced nephropathy |
| **CPB** | Cardiopulmonary bypass |
| **DCT** | The Distal Convoluted Tubule |
| **ECF** | *Extracellular Fluid* |
| **EDTA** | Ethylenediamine tetracetic acid |
| **EPO** | Erythro poietin |
| **$Fe_{Na}$** | *fractional excretion of sodium* |

| | |
|---|---|
| **FSGS** | Focal segmental glomerulosclerosis |
| **GFR** | Glomerular Filtration Rate |
| **Gro- α** | Growth related oncogene-α |
| **HCC** | Hydroxy cholecalciferol |
| **HRG** | Histidine rich glycoprotein |
| **HSCS** | Hematopoietic stem cells |
| **I cells** | Intercalated cells |
| **ICAM١** | Intercellular adhesion molecule ١ |
| **IL-١٨** | Interleukin-١٨ |
| **IRI** | Induced renal injury |
| **JG cells** | Juxtaglomerular cells |
| **JGA** | The Juxtaglomerular Apparatus |
| **KC** | keratinocyte-derived chemokine |
| **KC** | Chemokin |
| **$K_f$** | the capillary *filtration coefficient* |
| **KIM-١** | Kidney Injury Molecule-١ |
| **L-FABP** | Livre fatty acid binding protein |
| **LH** | The Loop of Henle |
| **MAC** | Minimum alveolar concentration |
| **MAP** | Monocyte activating polypeptide |
| **MIP** | Macrophage inflammatory protein |
| **NAG** | *N-acetyl*-β-D-glucosaminidase |
| **NAG** | N-acetyl-β-(D)-glucosaminidase |
| **NGAL** | Neutrophil gelatinase–associated lipocalin |
| **NHE٣** | Na+/ H+ Exchanger Isoform ٣ |
| **NO** | Nitric oxide |
| **NSAIDs** | nonsteroidal anti-inflammatory drugs |

| | |
|---|---|
| **P cells** | Principle cells |
| **PAH** | para-aminohippuric acid |
| $\boldsymbol{P_B}$ | the hydrostatic pressure in Bowman's capsule |
| **PCI** | Percutaneous intervention |
| **PCT** | The Proximal Convoluted Tubule |
| $\boldsymbol{P_G}$ | hydrostatic pressure inside the glomerular capillaries glomerular hydrostatic pressure |
| **PG** | Prostaglandins |
| **RBCS** | Red blood cells |
| **RBP** | retinol binding protein |
| **ROC** | Receiver operating characteristic |
| **ROS** | Reactive oxygen species |
| **ROS** | Reactive oxygen species |
| **RRT** | Renal replacement therapy |
| **SIRS** | systemic inflammatory response syndrome |
| **Sr.Cr.** | Serum Creatinine |
| **TNFα** | Tumor necrosis factor α |
| **VCAM** | Vascular cell adhesion molecule |
| $\boldsymbol{\pi_B}$ | the colloid osmotic pressure of the proteins in Bowman's capsule |
| $\boldsymbol{\pi_G}$ | the colloid osmotic pressure of the glomerular capillary plasma proteins |

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# Introduction

incidence of acute kidney injury (AKI), previously referred to as acute renal failure, has reached epidemic proportions world-wide, affecting about ٧٪ of hospitalised patients. In the critical care setting, the prevalence of AKI requiring dialysis is about ٦٪, with a mortality rate exceeding ٦٠٪.The treatment is largely supportive, at an annual cost surpassing $١٠ billion in the US alone.

The early diagnosis of AKI currently depends on detection of reduced kidney function by the rise in serum creatinine concentration and blood urea nitrogen(BUN), which are delayed and unreliable measures in the acute setting. Many potential markers have been studied. Promising injury markers in the urine include: Neutrophil gelatinase-associated lipocalin (NGAL), Interleukin ١٨ (IL-١٨), Kidney injury molecule ١ (KIM-١), Liver fatty acid binding protein (L-FABP), $\beta_{٢}$-microglobulin, $\alpha_{١}$-microglobulin, Retinol Binding Protein,Cystatin-C,Sodium/Hydrogen Exchanger Isoform and Fetuin A.

# Aim of the Work

The aim of this essay is to discuss the normal renal physiology,causes of acute kidney injury and the recent biomarkers for detection of acute kidney injury in critically ill patients.

# Physiology of the Kidney

The kidney is paired, reddish brown, solid organ, it is an ovoid in outline but the medial margin is deeply indented and concave at its middle. A wide, vertical cleft (the hilum) transmits the structures entering and leaving the kidney, and leads to space within the kidney, the *sinus of the kidney* ***(Romanes, ١٩٩١)***.

Each kidney consists of two distinct zones***(Jennette et al., ١٩٩٨)***:

**a) <u>An outer cortex</u>**:

This appears red because it is richly supplied with blood and granular because it contains renal glomeruli.

**b) <u>An inner medulla:</u>**

This is paler than the cortex because it is poorly supplied with blood, and is striated because it contains the loops of Henle and collecting ducts. It is formed of ١٠-١٥ triangular shaped wedges of tissue called the pyramids, the apecies of which form the renal papillae which drain into the calyces. The pyramids arbitrarily divide the kidney into lobes which are in turn subdivided into lobules.

# Functional divisions of the nephron

The functional unit of the kidney is called the *nephron*. Each kidney is composed of about ١,٣ million nephrons in each kidney, and each nephron is capable of forming urine by itself.The nephrons with glomeruli in the outer portions of the renal cortex have short loop of Henle (cortical nephron), whereas those with glomeruli in the juxtamedullary region of the cortex have long loops extending down into the medullary pyramids which represent about ١٥٪ of the nephrons**(figure ١)** ***(Romanes, ١٩٩٧)..***

## (١) The Proximal Convoluted Tubule (PCT):

Proximal convoluted tubule is about ١٥ mm long and ٥٥ μm in diameter. Its wall is made up of a single layer of cells that interdigitate with one another and is united by apical tight junctions. Between the bases of the cells, there are extensions of the extracellular space called the *lateral intercellular spaces*. The luminal edges of the cells have a striate *brush border* due to the presence of innumerable ٠,٧ μm microvilli. The proximal tubule terminates in the thin segment of the descending limb of the loop of Henle ***(Tisher and Brenner, ١٩٩٩)***.