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Acute kidney injury patients primarily presented to Mansoura University Hospitals: One year observational study

Thesis

Submitted for Partial Fulfillment of the Master Degree in Internal Medicine

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"رَبِّ أَوْزِعْنِي أَنْ أَشْكُرَ نِعْمَتَكَ الَّتِي أَنْعَمْتَ عَلَيَّ وَعَلَى وَالِدَيَّ وَأَنْ أَعْمَلَ صَالِحًا تَرْضَاهُ وَأَدْخِلْنِي بِرَحْمَتِكَ فِي عِبَادِكَ الصَّالِحِينَ"

صَدَقَ اللّهُ الْعَظِيمِ

سورة النمل آية (19)

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Sherouk Salah Elnagar

Contents

List of abbreviations

AKI	Acute kidney injury
ACEI	Angiotensin converting enzyme inhibitors
NSAIDS	Non-steroidal anti-inflammatory
SLE	Systemic lupus erythromatosis
AGN	Acute glomerulonephritis
ATN	Acute tubular necrosis
PN	pyelonephritis
TLS	Tumour lysis syndrome
DM	Diabetes Mellitus
LCF	Liver cell failure
CHF	Chronic heart failure
GFR	Glomerular filtration rate
CKD	Chronic kidney disease
ESRD	End stage renal disease
RRT	Renal replacement therapy
CRRT	Continuous renal replacement therapy
CVVH	Continuous veno-venous hemofiltration
BUN	Blood urea nitrogen
IHD	Intermittent haemodialysis
Serum cr	Serum creatinine
CA-AKI	Community acquired acute kidney injury
HA-AKI	Hospital acquired acute kidney injury
ICU	Intensive care unit
KDIGO	Kidney disease improving global outcomes
RIFLE	Risk, injury, failure, loss, end stage renal disease
AKIN	Acute kidney injury network
HR	Hazard ratio
IQR	Interquartile ratio
MM	Multiple myeloma
APACHE	Acute Physiology and Chronic Health Evaluation

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Introduction

Introduction

Worldwide, acute kidney injury (AKI) is a major health problem with poor patient prognosis. Lately, establishing a unified definition for AKI allowed the investigators to provide more information about the epidemiology, natural history and outcomes of this disease ***(Lewington et al., 2013)***

Although severe AKI has existed throughout history, the natural course of AKI could not be defined until the introduction of acute dialysis. This was made possible because dialysis allowed for sufficient time for renal recovery to occur and for possible subsequent disease progression to develop ***(Brezis & Rosen, 1995)***.

Traditionally, the term acute renal failure was adopted to define cases with acute deterioration in their kidney function. However, the absence of consensus criteria for defining this condition represented a major flaw in studies addressing the problem of AKI. Consequently, in 2004, the Acute Dialysis Quality Initiative group created the RIFLE criteria for diagnosis and stratification of AKI ***(Bellomo et al., 2004b).*** Since then, other modifications were adopted to the RIFLE criteria three times. The first modification, the Paediatric RIFLE (pRIFLE) criteria, modified the RIFLE criteria for use in children ***(Akcan-Arikan et al., 2007)***. The second modified definition, the AKI Network (AKIN) criteria which expanded the diagnosis of AKI to include patients who had an increase in serum creatinine ≥0.3-mg/dl in a 48-hour period ***(Mehta et al., 2007b)***. The last modification, the Kidney Disease Improving Global Outcomes (KDIGO) classification system, harmonized RIFLE, AKIN, and pRIFLE.***(KDIGO, 2012)***.

The reported incidence of AKI varies significantly between different literatures. The explanation of this discrepancy might be explained by different used definitions for AKI, different types of the studied populations and different types of AKI (hospital acquired versus community acquired). About 7-18% of patients develop HA-AKI during their hospital admission. On the other hand, CA-AKI affects from 20–200 per million population in the community ***(Nash et al., 2002).*** Moreover, the aetiological spectrum differs distinctly between developed and developing countries. In low resources-societies, AKI is mainly community acquired disease, affecting young patients and caused by tropical infections such as malaria, diarrhoea, dehydration and herbal remedies ***(Daher et al., 1999).***

Many recent researches have been focused on detection and validation of novel biomarkers for early detection of AKI such as neutrophil gelatinase-associated lipocalin (NGAL), cystatin C (CysC), interleukin-18 and kidney injury molecule-1 (KIM-1). These biomarkers may also help in differentiating the cause of AKI, evaluation of the severity of AKI and assessment of response to treatment. ***(Koyner et al., 2010).***

The association between AKI and increased risk of mortality was addressed by many previous literatures. The risk of mortality remarkably increases with more severe forms of AKI; hence, patients requiring renal replacement therapy had the highest risk [50 –60%] ***(Cerdá et al., 2008).*** Additionally, several studies reported the increased risk of progression to CKD and ESRD after an episode of AKI ***(Coca et al., 2010).***

Many publications affirmed the importance of early nephrology consultation which may guide simple preventive and management measures (appropriate evaluation of volume status, reviewing the patient medications with dose adjustment or stopping of nephrotoxic drugs). Consequently, these measures help to decrease the incidence and severity of HA-AKI ***(Mehta et al., 2002)***.

Aim of the Work

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To study the natural history of community acquired AKI in patients presented to nephrology and dialysis unit in Mansoura University Hospitals during one year (from August 2015 to July 2016).

Review of Literature

Definition & Classification

A logical method to define "organ failure" is to define what it is that an organ does. In the case of the kidney, many of its functions are either shared with other organs (maintenance of acid-base with the lung) or involve other organs to require complex neurohormonal interactions (renin-angiotensin-aldosterone axis). Other kidney functions are small peptide excretion, tubular metabolism and hormonal production. Among these functions, production of urine and excretion of waste products of nitrogen metabolism are routinely and easily measured and are "unique" to the kidney. Thus, measurement of these functions help to define the existence of ARF ***(Bellomo et al., 2001)***.

Of the two waste products excreted by the kidney, extrarenal factors most markedly affect urea (gastrointestinal bleeding, changes in protein intake, changes in protein catabolism) .A more "reliable" marker of the glomerular filtration rate (GFR) is creatinine. However, creatinine is not a real-time descriptor of GFR because loss of nephron mass is not associated by proportionate changes in serum creatinine. Still, it seems practical and reasonable to use urea and creatinine to define ARF ***(Bellomo et al., 2001)***.

I. Types of AKI:

- **Community acquired acute kidney injury:**

Occurs in patients whose admission serum creatinine was sufficiently elevated to meet RIFLE criteria ***(Schissler et al., 2013)***. In low income societies, community acquired acute kidney injury is the main type of AKI. Many previous literatures have addressed the main causes for CA-AKI in these countries such as chest infections, diarrhea, sepsis, tropical infections such as malaria, leptospirosis, and dengue; acute glomerular

diseases; exacerbations of pre-existing kidney disease; nephrotoxicity caused by treatment with herbal remedies and other nephrotoxins, heart disease; and environmental poisoning such as snakebites ***(Ponce & Balbi, 2016)***.

- **Hospital acquired acute kidney injury:**

Occurs when serum creatinine increases twenty-four hours or longer after hospitalization ***(Schissler et al., 2013)***. Main type of AKI in industrialized countries. In such societies, HA-AKI was reported to occur in 7%–18% of patients during their hospital admission every year. Furthermore, the incidence of HA-AKI in these countries exceeds that of community acquired AKI by five to ten folds ***(Chertow et al., 2005; Jha & Parameswaran, 2013)***. Aetiological spectrum is similar in both developed and developing countries. Major causes of hospital acquired AKI include postsurgical complications, haemorrhage, infections, septic shock, and drug toxicity ***(Chertow et al., 2005; Schieppati et al., 2015)***.

II. Diagnosis of AKI:

For unifying the definition of ARF in clinical research, having too many essentially arbitrary biochemical "cut-off values" is a major hindrance. A review of 28 studies of postoperative ARF highlighted this point; each one used a different definition. Using different definitions, different mortality results are concluded, different preventive approaches are promoted or found useless. This continuous change in the entry criteria all the time makes one unable to come to any conclusions ***(Bellomo et al., 2001)***. For these reasons, in 2004, by the Acute Dialysis Quality Initiative (ADQI) group proposed the Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE) criteria for diagnosis and stratification of AKI ***(Bellomo et al., 2004a)***.

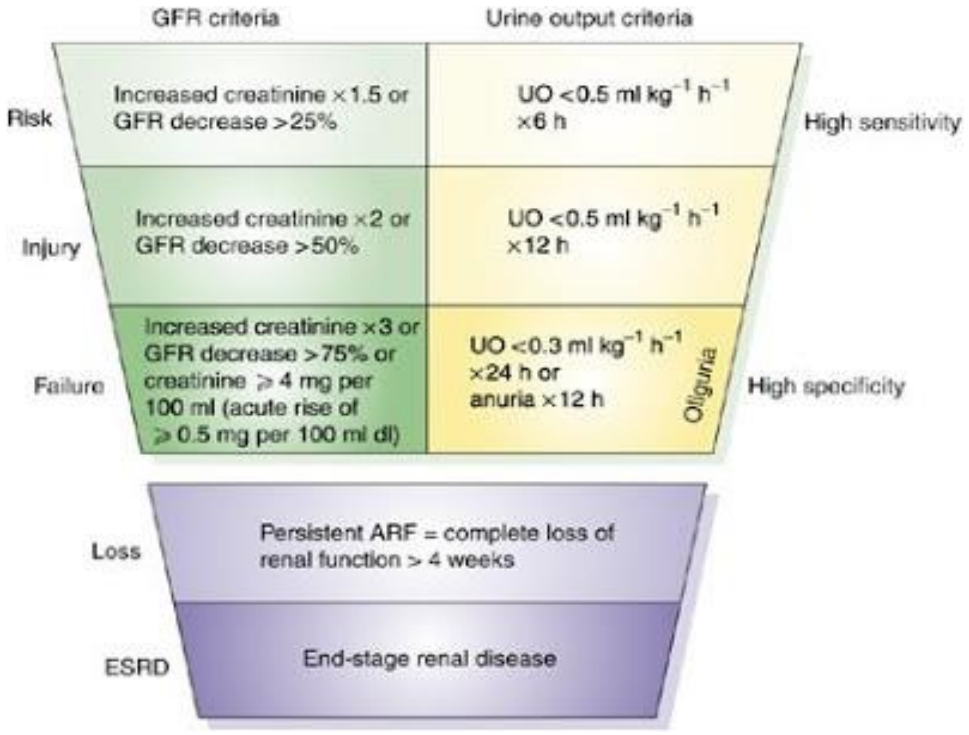


Figure (1): The RIFLE criteria for AKI. ARF, acute renal failure; GFR, glomerular filtration rate; Screat, serum creatinine concentration; UO, urine output**.** ***Source: (Bellomo, 2004)***

Important outcomes such as need for renal replacement therapy (RRT), length of hospital stay, and mortality have been linked to these criteria ***(Hoste et al., 2006b; Ricci et al., 2008)***. In fact, the RIFLE criteria are now well recognized and have been cited in more than 150 manuscripts. ***(Bellomo et al., 2007)***. However, these criteria have many limitations. Firstly, classifying AKI patients according to the RIFLE criteria requires to know the baseline serum creatinine and such data may not be available in many patients ***(Bagshaw et al., 2009)***. Secondly, within each RIFLE category, the relative changes for serum creatinine does not precisely reflect the equivalent change in glomerular filtration rate (GFR). Finally, although the concordance between UOP and serum creatinine level criteria is poor and urine output is often confounded by diuretic therapy, both criteria are given equal weighting for classification. ***(Chertow et al., 2005)***. For these reasons, some modifications were needed

to refine the RIFLE criteria ***(Mehta et al., 2007a)***. Modifications to RIFLE proposed by the AKIN includes: to classify AKI into 3 stages only; to ignore the GFR criteria and the outcomes 'loss' and 'end stage'; in order to define AKI, a minimum duration for abrupt changes in kidney function to occur is 48 hours and a minimum threshold for serum creatinine increase is ≥26.5 μmol/l; and to classify any patient receiving RRT, no matter how severe his AKI is, into stage 3. ***(Bagshaw, 2010)***.

Accordingly, Joannidis and his colleagues conducted a secondary analysis of the 16,784 critically ill patients to assess the validity of both RIFLE and AKIN criteria for AKI diagnosis, classification and prediction of in-hospital mortality ***(Joannidis et al., 2009)***. In total, 1,504 patients (10.5%) classified as having AKI by RIFLE criteria were missed by AKIN criteria. Most of the patients missed by AKIN criteria were categorized as RIFLE– risk, and none of them had an increase in serum creatinine of 26.5 μmol/l or more within 2 days. On the other hand, RIFLE criteria missed AKI diagnosis in 504 patients (3.5%) classified as having AKI by AKIN. With using either RIFLE or AKIN criteria for diagnosis, patients with higher stages of AKI had increased risk for in-hospital mortality. ***(Joannidis et al., 2009)***. For both systems, the mortality risk was obviously higher when AKI was classified according to serum creatinine criteria alone than when urine output or a composite of the worst of either serum creatinine or urine output was used. Remarkably, the risk of mortality in patients diagnosed as AKI patients by only one system (AKIN or RIFLE) was significantly higher than that of patients diagnosed as non-AKI by either system, which implies that frank misclassification occurred ***(Joannidis et al., 2009)***.

These data provided strong rationale for the KDIGO expert group to use a combination of both RIFLE and AKIN criteria to identify patients with AKI. AKI is defined as any of the following:

- Increase in serum creatinine by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 h.
- Increase in serum creatinine to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days.
- Urine volume <0.5 ml/kg/h for 6 h ***(Initiative, 2012)***.

Limitations of creatinine-based criteria for AKI

Serum creatinine is metabolized from creatine which is derived from the amino acids arginine and glycine in liver, kidneys and pancreas. In normal subjects, the rate of production of creatinine is balanced with the rate of excretion. However, serum creatinine is affected by multiple factors as dietary intake of red meats, muscle bulk, and the rate of production by liver pancreas and kidneys. Furthermore, in critically ill patients, persistent falls in creatinine production may occur ***(Clark et al., 1998; Doi et al., 2009)***.

Using serum creatinine as a marker for GFR is defiled by many limitations. Firstly, if the glomerular filtration rate (GFR) declines, the half-life of serum creatinine increases from 4 hours to 24–72 hours and serum level of creatinine may not rise except after 24–36 hours following sure renal insult. Moreover, serum creatinine is not an accurate marker for GFR in patients with sepsis, liver failure, and/or muscle wasting ***(Doi et al., 2009; Schetz et al., 2014; Thomas et al., 2015)***. Secondly, some drugs may affect serum creatinine level either by decreasing its tubular secretion or even disrupting the analytic assays used for serum creatinine quantification ***(Macedo et al., 2010; Liu et al., 2011)***. Thirdly, Variations

in volume status may affect serum creatinine level due to its measurement as a concentration. As a result, significant fluid shifts or fluid overload may delay the diagnosis of AKI. This notion was affirmed by Macedo and his colleagues in a post-hoc analysis of the Fluid and Catheter Treatment Trial ***(Macedo et al., 2010)***. Fourthly, all the proposed creatinine-based definitions need baseline creatinine value to describe the patient's steady-state kidney function just before the episode of AKI. However, basal renal function is not known in many patients with AKI ***(Thomas et al., 2015)***. Finally, the currently used creatinine-based definitions do not take in consideration the major differences in renal reserve between AKI patients with normal baseline renal function and AKI patients with pre-existing CKD. In patients with normal kidney function, a small increase in serum creatinine level by 0.3 mg/dl may indicate significant reduction in GFR. On the other hand, in patients with pre-existing CKD, a rise of serum creatinine by 0.3/mg/dl may be accepted as diurnal variation and simply reflect trivial change in GFR ***(Palevsky et al., 2013)***. Similar problems may occur when using the RRT criteria to define the third stage of AKI. Till now, there is no consensus about the optimal timing for initiation for RRT; thus, the initiation of RRT may be affected by the decision-making process of the clinician rather than the patient's underlying renal function ***(Ostermann & Joannidis, 2016)***.

Limitations of urine-based criteria for AKI:

Although urine output is a vital clinical sign, it is not renal specific and may persist even after renal function nearly stops ***(Prowle et al., 2011; Kellum et al., 2015)***. On the other hand, in normal kidneys, oliguria may occur in case of prolonged fasting, hypovolaemia, and following stress, pain or surgery as a part of physiological response ***(Zaloga & Hughes, 1990; Lehner et al., 2016)***. Also, the KDIGO criteria used to define AKI depend on the presence of oliguria for at least six hours. Nevertheless, the

accuracy of this arbitrary cut-off is uncertain ***(Lehner et al., 2016)***. To increase the specificity of these criteria, many literatures suggest to use either a longer minimum period (e.g. 12 h) or a lower threshold for urinary output [e.g. 0.3 ml/kg/h instead of 0.5 ml/kg/h] ***(Ralib et al., 2013; Ostermann, 2014)***. Finally, using weight to calculate urine output in AKI patients may not be an accurate estimate in obese patients. Thus, the European Renal Best Practice Guidelines (2012) recommend to use the ideal weight in weight based urine output criteria instead of using the true weight ***(Fliser et al., 2012)***.

Novel biomarkers of Acute Kidney Injury

Acute kidney injury (AKI) is a major clinical problem with a rising incidence and high mortality rate. Till now, the diagnosis of AKI is mainly dependent on serum creatinine. Serum creatinine as a marker of GFR is defiled by many limitations which in turn might afflict the proper management of AKI. Therefore, many recent researches have been focused on detection and validation of other novel biomarkers for early detection of AKI. Additionally, these biomarkers may help to differentiate between different types of AKI (pre-renal, intrinsic renal, or post-renal), identify different aetiologies of AKI (ischemia, toxins, sepsis, or a combination), evaluate the severity of AKI, and assess the response to treatment ***(Bellomo et al., 2007)***.

Ideal biomarker for diagnosis and prediction of AKI should preferably be non-invasive, easy to apply, rapid, reliable and with high sensitivity and specificity. This will almost certainly involve a combination of a panel of biomarkers, along with clinical information ***(Bellomo et al., 2007)***.

Novel biomarkers for acute kidney injury can be classified into markers principally assessing glomerular filtration (i.e. serum cystatin C),

glomerular integrity (i.e. albuminuria and proteinuria), tubular stress (i.e. insulin-like growth factor binding protein 7 [IGFBP-70]), tubular damage (i.e. neutrophil gelatinase-associated lipocalin [NGAL]), kidney injury molecule-1 (KIM-1) and intra-renal inflammation (i.e. interleukin-18) ***(Ostermann et al., 2012; Kashani et al., 2013)***.

III. Other diagnostic work up of AKI:

- **Urinalysis:**

Urinalysis is the most vital non-invasive test in the initial evaluation of patients with acute renal failure. Intrinsic renal glomerular pathology is highly suspected in patients with high positive protein values on reagent strip testing of their urine. A reagent strip positive for blood suggests the presence of red blood cells (> 5/high power field). Moreover, the presence of RBCs casts, dysmorphic RBCs and haematuria with proteinuria is typically suspicious for glomerular pathology ***(Favaro et al., 1997)***. On the other hand, other urinary tract pathologies may be associated with haematuria such as tumours and calculi, urinary tract infection or renal artery or renal vein thrombosis. Of note, rhabdomyolysis with myoglobinuria will cause a false positive reagent strip reaction for haematuria without evidence of red cells on microscopic examination ***(Lewington & Kanagasundaram, 2011)***. Increased numbers of white cells (> 5 per high power field) can be present in patients with acute interstitial nephritis, infection and glomerulonephritis. Eosinophiluria is typically helpful in excluding the presence of acute interstitial nephritis (negative predictive value > 90%). However, Eosinophiluria is not a very specific test for interstitial nephritis and has a very poor positive predictive value. ***(Rossert, 2001)***.

Urine microscopy can be useful in certain situations such as suspected poisoning. In patients with suspected ethylene glycol poisoning the presence of oxalate crystals in urine microscopy can help in the diagnosis, while the presence of urate crystals in patients treated with chemotherapy usually indicates the presence of tumour lysis syndrome. Some medications can cause AKI with crystalluria such as sulphonamides, acyclovir, triamterene, indinavir and cathartics high in phosphates ***(Fogazzi, 1996)***.

- **Complete blood count:**

The presence of haemolytic uremic syndrome or thrombotic thrombocytopenic purpura is typically suspected in patients with acute renal failure associated with coomb negative haemolytic anaemia with evidence of schistocytes in peripheral blood smear ***(Ostermann & Joannidis, 2016)***

- **Urine electrolytes:**

the measurement of analytes in urine (urea, creatinine, sodium, potassium) and/or the calculations of derived variables (fractional excretion of sodium, fractional excretion of urea) can be used to differentiate between preserved tubular function (which equates to pre-renal azotemia) or lost tubular function [which equates to ATN] ***(Miller et al., 1978; Langenberg et al., 2006)***. However, the measurement of these electrolytes should be interpreted cautiously in elderly patients, those with salt loosing nephropathy and patients treated with diuretics. In patients receiving diuretics, the resulting natriuresis may increase the value of fractional sodium excretion (FENa) to be more than one percent. In such cases, FENa is not considered a reliable diagnostic test of prerenal state and fractional excretion of urea may be more accurate, with values less than 35% indicating a prerenal cause. Additionally, fractional excretion of

sodium less than 1 % not necessarily indicates a prerenal cause because this measure can be confounded by other pathologies; such as contrast nephropathy, rhabdomyolysis and acute glomerulonephritis ***(Lewington & Kanagasundaram, 2011)***.

- **Imaging studies:**

Ultrasongraphic imaging of the kidneys is a mandatory diagnostic tool in patients with acute kidney injury, especially in older men, to exclude the presence of urinary tract obstruction (i.e., a post renal cause). The presence of residual urine more than 100 ml after voiding by bladder scan is usually suggestive of presence of urinary tract obstruction. In such cases, ultrasonography on both kidneys is mandatory to rule out hydronephrosis or outlet obstruction. Other imaging techniques such as computed tomography or magnetic resonance imaging may be helpful to exclude extrarenal causes of obstruction (e.g., pelvic tumours) ***(Ostermann & Joannidis, 2016)***.

- **Renal biopsy:**

Being invasive diagnostic tool, renal biopsy is typically specified to patients suspected to have intrinsic renal injury with exclusion of both prerenal and postrenal causes of AKI ***(Rahman et al., 2012)***. Moreover, Renal biopsy is indicated in patients with clinical and laboratory features suggestive of a disease that needs to be affirmed before institution of disease specific therapy (e.g., immunosuppressive medications). Urgent renal biopsy may be needed in patients with clinical features suggestive of rapidly progressive acute glomerulonephritis such as rapid deterioration of renal function and haematuria with red blood cell casts and dysmorphic RBCS. In such cases, in addition to indicating a diagnosis that requires immunosuppressive therapy, other special therapies may be instituted based on the biopsy results; such as plasmapheresis if Goodpasture syndrome is present ***(Rahman et al., 2012)***.

Epidemiology of AKI

Acute kidney injury (AKI) is a major global health problem, which imposes a negative effect on patient morbidity and is in charge of an estimated 1.4 million deaths per year. Even though the International Society of Nephrology has set a goal of eradicating preventable deaths due to AKI by 2025, there are major challenges in this project implementation in developing countries. Major limitations hampering AKI prevention in developing countries involve inadequate resources, poor quality data about the epidemiology and causes of AKI in these countries, the scares health care resources to diagnose and treat AKI, and the poor awareness of the impact of AKI on patient outcomes ***(Ponce & Balbi, 2016).*** These limitations signeficantly hindered research efforts aiming to adress the problem of AKI, which, in turn, represented a chief stimulus to expand the spectrum of acute renal failure by applying some modifecations to the RIFLE criteria and establish the AKIN criteria ***(Mehta et al., 2007b; Abdel-Kader & Palevsky, 2009)***.

Till now, the epidemiology of AKI worldwide is still vague. This indistinctness might be explained by the different used definitions for AKI and the different clinical backgrounds and geographical areas where the condition is managed ***(Xue et al., 2006)***. However, the global burden of AKI has been suggested to be up to 13.3 million cases per year, of which 11.3 million are in low- to middle-income countries and account for up to 1.4 million deaths per year. Moreover, AKI-related problems are responsible for up to 3% of hospital admissions in general health care facilities in LRSs ***(Schieppati et al., 2015)***. The epidemiology of AKI in developed countries, in which elderly patients predominate, differs from that of developing areas ***(Xue et al., 2006)***. In spite of the paucity of adequate knowledge about the epidemiology of acute kidney injury in low

income countries, it is fairly believed that the estimated prevalence of AKI in such countries is higher than that in high income countries ***(Susantitaphong et al., 2013; Mehta et al., 2015)***.

The aetiological spectrum of AKI can be generally classified into hospital acquired and community acquired. In developed countries, AKI is chiefly hospital-acquired disease. In such societies, HA-AKI was reported to occur in 7%–18% of patients during their hospital admission every year. Furthermore, the incidence of HA-AKI exceeds that of community acquired AKI by five to ten folds ***(Chertow et al., 2005)***. The chief causes of hospital acquired AKI in both low and high-income countries are almost similar; it comprises haemorrhage, obstetric complications, sepsis, and renal affliction by nephrotoxic drugs ***(Chertow et al., 2005; Schieppati et al., 2015)***. In contrast, in developing countries, AKI is chiefly a community acquired disease. However, the true prevalence of and the leading causes of AKI in these countries are not well defined. Limited registered data, insufficient health care resources and lack of awareness of the amplitude of the problem represent major challenges hindering efforts to prevent and manage the problem of AKI in developing countries ***(Chertow et al., 2005; Susantitaphong et al., 2013; Schieppati et al., 2015)***.

AKI in special populations:

1-critically ill patients:

The occurrence rate of acute renal failure (ARF) in critically ill patients varies widely in the literatures and is estimated to be between 1.1% and 31% ***(Chertow et al., 1998)***. Other previous literatures reported an increase in ICU admissions involving AKI ranging from 13% up to 78% ***(Paudel et al., 2012; Case et al., 2013)***. Additionally, in a published series of ICU admissions which included over17,000 patients (medical, surgical,

and mixed ICUs), Metnitz and his colleagues reported that 50.4% of medical admissions in ICUs involved patients with AKI ***(Metnitz et al., 2002)***. However, this discrepancy in reported rates reflects different used definitions of ARF and different studied populations rather than actual difference in AKI incidence ***(Chertow et al., 1998; Vivino et al., 1998)***. The incidence of ICU-related AKI over the last few decades has increased probably due to the increased incidence of sepsis related hospital admissions, increased prevalence of AKI risk factors such as chronic kidney disease (CKD) and diabetes mellitus, the increased use of intravenous radiocontrast agents.

Causes of AKI are classified as prerenal, intrinsic renal, and postrenal. This classification system oversimplifies the overlapping pathologic mechanisms underlying AKI. For example, hypovolemia or hypotension may initially cause renal parenchymal tissue hypoperfusion causing a reversible increase in serum creatinine level. As cellular dysfunction continues, ischemic injury of renal tubular cells may sustain even after correction of the initial hypoperfusion state, which in turn can change renal insult from prerenal azotaemia to acute tubular necrosis ***(Case et al., 2013)***. The most common form of intrinsic renal failure in the ICU is Acute tubular necrosis (ATN) comprising as much as 88% of all cases of AKI (***Hamdi et al., 2012)***. However, many causes of AKI in ICU patients likely have multifactorial aetiologies ***(Lia o et al., 1998)***.

AKI in itself is a life-threatening condition and can be a cause of mortality. Many previous literatures affirmed the independent association between AKI and increased risk for mortality, even after adjustment of all other determining variables ***(Metnitz et al., 2002)*** In harmony, many previous publications reported higher morbidity, mortality, and health care

costs in ICU patients with AKI in comparison to ICU patients without AKI .***(Waikar et al., 2008; Wijewickrama et al., 2014)***

2- Cancer patients:

Patients with cancer represent up to 20 % of actual ICU admissions. One of the chief contributing factors to AKI in cancer patients is their increased vulnerability to infectious and non-infectious complications either due to the primary malignancy itself or secondary to its treatment ***(Lameire et al., 2016)***. According to Dutch National Intensive Care Evaluation(NICE) database, the incidence of AKI in patients with haematological malignancies admitted to the ICU was19.4 %, which is comparable with incidence rates in patients with chronic liver cirrhosis and chronic heart failure, but higher than that in patients with solid tumours ***(van Vliet et al., 2014)***.

Particular risk factors for AKI in cancer patients include infection and sepsis ***(Rosolem et al., 2012; Heung & Koyner, 2015)***, tumour lysis syndrome (TLS) ***(Howard et al., 2016)***, immunosuppression induced kidney damage following hematopoietic stem cell transplantation (HSCT] ***(Kogon & Hingorani, 2010)***, and direct effects from the primary malignancy ***(Benoit et al., 2005)***.

AKI in cancer patients has many short and long-term consequences. Firstly, AKI in cancer patients impacts dosing of different chemotherapeutic agents according to the diminished creatinine clearance. Consequently, cancer patients with AKI are more prone for suboptimal dosing of chemotherapy. Secondly, AKI in cancer patients reduces the probability of achieving complete remission and increases health care costs due to increased length and frequency of hospitalization. Finally, cancer

patients with AKI have increased risk for CKD, ESKD and mortality compared to those without AKI ***(Olabisi & Bonventre, 2015)***.

3- AKI in geriatrics

Reported incidences of AKI in the elderly vary widely between different literatures. This difference might be attributed to different population studied, either community, hospitalized or ICU patients. In the USA, in a cohort involving 233,803 elderly hospitalized patients, a reported incidence of AKI was 3.1% ***(Ishani et al., 2009)***, while the incidence of AKI among Medicare beneficiaries between 1992 and 2001 was 2.38% ***(Xue et al., 2006)***. In addition, the reported incidence of community acquired non-dialysis requiring AKI in a previous cohort analysis was found to increase from 78 per 100,000 person-years in patients aged fifty years or less to 3,545 per 100,000 person-years in patients aged eighty or more ***(Hsu et al., 2007; Abdel-Kader & Palevsky, 2009)***

In Scotland, a reported incidence of AKI was 1,811 cases per million populations and a reported incidence of acute kidney injury on top of pre-existing CKD was 336 per million populations. Remarkably, the median age in patients with acute kidney injury was 76 years, while the median age in patients with acute on top of chronic kidney disease was 80.5 years (***Ali et al., 2007)***.

Risk Factors for developing Acute Kidney Injury in elderly patients:

Comorbidities are common among elderly patients ***(Anderson et al., 2011)***. In a previous analysis conducted on Medicare beneficiaries aged 65 and older, 65% of the participants had more than one chronic comorbid condition, 43% more than two chronic conditions and 24% had more than

three chronic conditions ***(Wolff et al., 2002)***.Contributing factors to AKI in geriatric populations include functional and structural changes in the kidney, other associated comorbidities (chronic kidney disease, cardiovascular disease, diabetes mellitus, abnormal lipid profile, increased liability for infections and malnutrition), using medications that can induce AKI (NSAIDS, diuretics, ACEIs, contrast nephropathy and nephrotoxic antibiotics) and oxidative stress [with increasing reactive oxygen species, free radicals, and advanced glycation end products] ***(Choudhury & Levi, 2011)***.

4-patients with diabetes mellitus:

About 10% of the general population suffer from Diabetes mellitus which is associated with high morbidity and mortality rates ***(Cowie et al., 2010)***. One of the most serious consequences of having diabetes mellitus is the risk of development of renal impairment ***(Shah & Hux, 2003; Laupland et al., 2004)***. The most common renal dysfunction pattern in diabetes is chronic kidney disease (CKD) which may progress to kidney failure ***(de Boer et al., 2011)***. In industrialized countries, the leading cause of end-stage kidney failure is diabetes-related CKD ***(de Boer et al., 2011)***. Furthermore, another literature reported that diabetic patients including those with earlier stages of chronic kidney disease are more susceptible to develop acute kidney injury during serious illnesses such as sepsis compared to non-diabetic ones ***(Hsu et al., 2008)***. Many previous publications reported that diabetes should be considered as an independent risk factor for AKI ***(Bagshaw et al., 2005; Vincent et al., 2010)***. Moreover, prolonged dialysis requirement, progression to ESRD, and death is associated with, acute-on-chronic kidney injury ***(Hsu et al., 2009)***.

Epidemiology of AKI in diabetic patients was evaluated by several studies. A retrospective analysis was performed by Mehta and his colleagues, based on the Society of Thoracic Surgeons National Database, and included 449,524 patients between 2002 and 2004. the total prevalence of DM was 33%. after surgery., diabetes was diagnosed more frequently in individuals requiring dialysis than in those without renal replacement therapy [49 versus 33%] ***(Patschan & Müller, 2016)***.

Another retrospective survey of the General Practice Research Database (UK) compared type 2 DM patients with nondiabetic individuals. The yearly AKI incidence was 198 versus 27/100,000 subjects, and the difference remained statistically significant. At this point it is important to mention that diabetic patients generally displayed an overall higher cumulative morbidity. They differed in the following categories: obesity, congestive heart failure, hypertension, past AKI episodes, CKD prevalence, therapy with ACE inhibitors/angiotensin receptor blockers, therapy with other antihypertensive drugs, statin treatment, and NSAID use ***(Patschan & Müller, 2016)***.

It remains unclear whether the association between AKI and DM is attributable to the hyperglycaemic milieu per se or if it potentially results from end-organ damage such as generalized and intrarenal atherosclerosis ***(Vallon, 2014)***. DM should be recognized as "fast-acting" risk factor for kidney vulnerability to ischemia. The tissue susceptibility increases as a result of significant microvasculopathy and interstitial inflammation. The latter effects can occur even in nondiabetic patients in whom acute blood glucose deterioration is not efficiently controlled ***(Vallon, 2014).***

Among precipitating factors, sepsis is a major precipitating factor of AKI, which develops in one-fourth of all patients with sepsis and half of

patients with bacteraemia or shock ***(Murugan et al., 2012)***. Up to 70% of mortality rates were associated with Sepsis-related AKI ***(Neveu et al., 1996; Bagshaw et al., 2007; Bagshaw et al., 2008; Murugan et al., 2012)***. Whether diabetes increases the risk of AKI during sepsis is controversial ***(Yegenaga et al., 2004; Esper et al., 2009)***. However, it is widely known that diabetic patients are more prone to develop AKI and sepsis than non-diabetic ones ***(Shah & Hux, 2003; Laupland et al., 2004; de Boer et al., 2011)***. Moreover, previous study reported that diabetes mellitus is a risk factor for worsening of renal function after coronary computed tomography angiography (CCTA) even in patients with preserved renal function ***(Isobe et al., 2013)***. Deterioration of renal function has been found to be associated with elevated presurgical urinary microalbumin levels ***(Isobe et al., 2016)***. Possible pathophysiological mechanisms responsible for CIN in diabetic patients include endothelial dysfunction and altered nitric oxide-dependent vasodilatation, leading to reduced oxygen concentration at the renal medulla ***(Heyman et al., 2005)***. Furthermore, renal artery vasoconstriction and direct tubular toxicity owing to the use of contrast media may impair renal blood flow leading to worsening of medullary hypoxia ***(Isobe et al., 2016).***

Epidemiology in Egypt:

In Egypt, the epidemiology of AKI and its impact on morbidity and mortality has not been well studied. To the best of our knowledge, there are only paucity of literatures dealing with the problem of AKI and its cause in the general population. A Published prospective study by Talaat et al conducted on 3350 ICU patients stated that the prevalence of ICU-acquired acute kidney injury was 21.2% based on AKIN & RIFLE criteria. The age of the patients ranged from 17 years to 86 years (mean 50.6 ± 16.2). About 72% of patients were males. Ischemic acute tubular necrosis

representing the most common etiological diagnosis (35.3%), followed by prerenal causes (26.4%), sepsis induced AKI (13.9%) and toxic ATN (8.5%) retrospectively. There was an increase in the rates of in-hospital mortality with increasing both AKIN and RIFLE class. When comparing corresponding degrees of AKI according to AKIN and RIFLE (stage 1versus 'risk'; stage 2versus 'injury'; stage 3 versus 'failure'), no statistical difference in mortality was found [P value >0.05] ***(Talaat et al., 2014)***. In addition, Mohamed and his colleagues in a prospective observational study carried out in surgical intensive care in Cairo university hospital reported a higher prevalence of AKI in critically ill patients [35.7%]. The most common factor contributed to AKI is APACHE II score and sepsis. The overall mortality among patients studied was 53.5%. The mortality in AKI group was significantly higher than in non-AKI group 67.5% versus 45.8%, respectively. In multivariate analysis, APACHE II, AKI and needs for mechanical ventilation were independent risk factors for mortality ***(Mohamed et al., 2013)***.

Short and long-term outcomes of AKI

With the introduction of dialysis techniques capable of maintaining life in patients with impaired renal function, it was widely felt that the problem of acute reversible renal failure (ARF) had been solved ***(Stott et al., 1972)***.

More recently, interest has been rekindled by various workers attempting to define the pathophysiology of ARF, and by the growing suspicion that, somehow, dialysis has failed to make its expected impact on mortality from this condition. It became obvious that prognosis is hardly improved from what it was 20 years ago, and that many questions remain to be answered. Perhaps the major stimulus to further study of ARF has been the observation that despite improvements in dialysis techniques and in medical and surgical management of the critically ill patient, the mortality rate in patients with ARF remains around 50%, not significantly lower than 20 years ago. While such improvements are encouraging, prophylaxis is a more worthwhile aim than improved therapy. Better understanding of fluid and electrolyte management has undoubtedly contributed to reduction in incidence of ARF in less severely ill patients. However, specific prophylactic measures will only be developed when the pathophysiology of the condition is understood ***(Initiative, 2012)***.

Prognosis of AKI

AKI has many early and delayed outcomes. Early outcomes include longer duration of hospitalization, increased risk for short-term mortality and prolonged requirement of renal replacement therapy. On the other hand, long term outcomes include increased risk of progression to chronic kidney disease, development of cardiovascular disease, and increased risk of long-term mortality ***(Initiative, 2012)***.

- **Short-term prognosis of AKI:**

Many previous literatures have been focused on addressing short term outcomes of AKI. Chertow and his colleagues reported a very poor outcome for critically ill patients with AKI in their observational study. Modest changes in serum creatinine level were significantly associated with an increased risk for mortality. Moreover, an increase in serum creatinine levels by ≥ 0.5mg/dl was associated with a 6.5 fold increase in risk of death ***(Chertow et al., 2005)***. In harmony, many previous literatures reported that increasing RIFLE category is associated with corresponding increase in the risk of mortality in AKI patients ***(Abosaif et al., 2005; Bagshaw et al., 2007; Ricci et al., 2008)***. Same notion was reported by Hoste and his colleagues in a single-centre cohort study ***(Hoste et al., 2006a)***. Similarly, a previous literature reported that hospital mortality rates were 20.9 % with RIFLE-R, 45.6% with RIFLE-I, and 56.8% with RIFLE-F, compared to 8.4% among patients without AKI. An increased risk for mortality was significantly associated with older patients; higher APACHE II score recorded on admission to intensive care unit; presence of premorbid renal impairment; mechanical ventilation; multiple organ failure. Remarkably, renal replacement therapy was not associated with an increased risk of deaths among AKI patients ***(Ostermann & Chang, 2007)***. Despite that many literatures have been focused on scrutinizing the outcome of AKI patients, different types of populations, different places wherein the studies were carried out and different used definitions for AKI make it difficult to infer whether the outcome of AKI has been improved over the last years or not ***(Initiative, 2012)***. While some previous authors reported that mortality rates of AKI patients treated with RRT remained more or less constant between the years 1970-2004 ***(Ympa et al., 2005)***, other investigators found an improvement in outcomes following RRT over a ten year period after adjustment for severity of illness, age, and other

organ dysfunctions ***(Desegher et al., 2006)***. Even with improvement in mortality rates in AKI, the 2001 National Hospital Discharge Survey found that AKI was associated with prolongation of hospital length of stay (LOS) and greater requirement for posthospitalization care ***(Initiative, 2012)***.

Many previous literatures investigated the risk factors for mortality after an AKI episode. Higher mortality rates were observed in older patients with AKI ***(Schwilk et al., 1997; Chertow et al., 2005; Uchino et al., 2005; Bucuvic et al., 2011; Mehta et al., 2016)***. Previous studies reported that pre-existing CKD and CLD were associated with increased risk of mortality in AKI patients ***(Cosentino et al., 1993; Chertow et al., 2005)***. Other literatures reported that infection, sepsis and shock were independent predictors for mortality ***(Schwilk et al., 1997; Uchino et al., 2005; Lombardi et al., 2008)*.** As regard the need for RRT, many authors showed higher in-patient mortality rates in subjects with dialysis-requiring than the non-dialysis requiring AKI ***(Brivet et al., 1996; Liano et al., 1996; Mehta et al., 2004; Balbi et al., 2005; Lo et al., 2009)***. However, it is still controversial whether early initiation of RRT improves survival rates of AKI patients or not. An observational literature reported that starting RRT at urea values more than 27 mmol/L was associated with a two-fold increased risk of mortality ***(Liu et al., 2006)***. In harmony, a retrospective review of medical records of post traumatic patients who developed AKI and received CRRT reported that an earlier initiation of CRRT, pre-CRRT BUN less than 60 mg/dl, may improve the rate of survival of trauma patients who develop ARF ***(Gettings et al., 1999)***.

- **Long-term outcome of AKI:**

Long term survival after an episode of AKI

The longer-term outcomes of AKI have been less well-characterized than hospital outcomes ***(Initiative, 2012)***. Coca and his colleagues reviewed all literatures investigating long-term outcomes in AKI survivors, from 1985 to 2007 ***(Coca et al., 2009)***. The investigated long-term outcomes included long term mortality and the subsequent development of cardiovascular disease or CKD. Survivors with AKI had a two-fold increase in the incidence rate of long term mortality than survivors without AKI. Furthermore, multivariate adjustment in six studies revealed that AKI was an independent predictor for mortality ***(Coca et al., 2009)***. Similarly, another previous literature investigated the risk of long-term mortality after an episode of AKI during hospitalization after various cardiothoracic surgery procedures between 1992 and 2002. Ten-year survival was worse among patients with AKI and was proportional to its severity compared to patients without AKI. Interestingly, patients with complete renal recovery after AKI still had an increased adjusted HR for death compared to patients without AKI ***(Hobson et al., 2009)***.

Risk of progression to ESRD after an episode of AKI:

Although it is well known that chronic kidney disease is associated with increased risk for development of acute kidney injury on top of the pre-existing renal dysfunction, the impact of acute kidney injury on the outcome of patients with chronic kidney disease is still vague ***(Hou et al., 1983; Leblanc et al., 2005)***. Factors that improve renal recovery are sought in many researches confronting the problem of AKI. Nevertheless, the definition of renal recovery after an episode of AKI varied considerably in different studies. The difference in reported recovery rates in subjects who experienced AKI may actually reflect the difference in the used definitions

for renal recovery rather than the course of the disease. Multiple previous studies considered AKI patients who no longer need RRT at time of discharge as recovered. The majority of these studies included only critically ill patients requiring dialysis. However, many AKI patients are not critically ill, do not need renal replacement therapy, and may need alternative definitions for judging renal recovery ***(Macedo et al., 2008; Khwaja, 2012)***. On the other hand, renal recovery was determined in few previous studies using the last available serum creatinine measurement, and defined as complete if serum creatinine was equal to or lower than baseline or reference, partial if lower than diagnosis but not baseline or reference, and no-recovery if the serum creatinine did not decrease or if the patient remained on dialysis ***(Heung et al., 2012; Mehta et al., 2016)***

Although the data of previous literatures was suggestive of good long term prognosis of AKI ***(Liano et al., 2007)***. A meta-analysis by Coca and his colleagues involved more than 3000 patients in 13 studies reported that the risk of ESRD increases after AKI (hr: 3.10) ***(Coca et al., 2012)***. In harmony, Other previous publications showed a significant increase in the risk of ESRD after an episode of AKI ***(Ishani et al., 2009; Lo et al., 2009)***

Additionally, a previous report by Wald et al has addressed the complex complications and long-term risks of death and dialysis afflicting survivors of an episode of severe AKI requiring acute temporary dialysis during hospitalization. The authors analysed the data of patients during a 10-year period between 1996 and 2006 with identification of 15028 patients with a first hospitalization for AKI requiring dialysis. In harmony with the previous literatures addressing the prognosis of AKI, the recorded in-hospital mortality in these patients was 40%. Remarkably, about 50% of these patients had renal recovery for at least one month after hospitalization; reflecting the notable ability of the kidneys to repair and

regenerate even after aggressive forms of AKI. Even though 23% of patients were still requiring renal replacement therapy one month after discharge, it is not known whether these patients required chronic dialysis or not ***(Wald et al., 2009)***.

Many previous studies have addressed the risk factors for progression to chronic kidney disease after an episode of AKI. Chawla and his colleagues studied 5.351 AKI patients between 1999 and 2005 and compared them with 15.917 control subjects. About 13.6% of patients group developed stage-4 CKD compared to 8.5% of control group. Predictors for progression to CKD included advanced age, longer period of renal impairment, need for renal replacement therapy, higher risk, injury, failure, loss of kidney function, and End-stage kidney disease score and lower serum albumin levels ***(Coca, 2010)***.

Another previous literature evaluated nearly four thousand diabetic patients with history of acute kidney injury between 1999 and 2004. Patients were followed up till the end of 2008. Follow up involved the development of chronic kidney disease and all-cause mortality. Recurrence of AKI was documented in 530 patients during the follow up. Thirty percent of these patients had more than one attack of acute kidney injury during the follow up, while 70% of these patients had only one episode of AKI. Hospital acquired acute kidney injury, higher basal serum creatinine level, presence of proteinuria, hypertension, and female gender were significantly associated with increased risk for development of stage-4 CKD. Moreover, risk of chronic kidney disease was significantly higher in patients who were more frequent to experience recurrent attacks of AKI ***(Coca et al., 2009)***.

Finally, a published systematic review assessing the relation between AKI and chronic kidney disease inferred that, the risk for development of chronic kidney disease after an episode of AKI was significantly associated with the need for renal replacement therapy and/or recurrent episodes of AKI. Meanwhile, the association of advanced age, gender, origin of AKI (CA-AKI or HA-AKI) and associated comorbidities with increased risk for chronic kidney disease is still controversial ***(Gürsu et al., 2017)***.

Cardiovascular Risk after an episode of AKI:

A previous publication reviewed the data of patients who had AKI or myocardial infarction (MI) between 1999 and 2005. Patients were alienated into three groups: patients with history of acute kidney injury, patients with history of myocardial infarction and patients with history of acute kidney injury and myocardial infarction. Patients with estimated glomerular filtration rate below 45 mL/min/1.73 m2 were excluded. Primary end points were death and development of new reno-cardiac event. Recorded mortality was highest in patients with history of AKI and MI while patients with MI alone had the lowest mortality rates. Moreover, hospitalization due to cerebrovascular accidents, heart failure, and recurrent MI were reported more frequent in patients who had AKI. Accordingly, it can be inferred that AKI is independent predictor for increased risk for development of major cardiovascular event even in absence of history of a previous cardiovascular disease ***(Ali et al., 2007)***.

Subjects & Methods

Method and subjects

Type of study:

The present study is a prospective unicentric observational study that included all patients with AKI or acute on top of chronic kidney disease who presented to nephrology and dialysis unit in Mansoura university hospitals

Subjects:

This study included patients who presented to nephrology and dialysis unit in Mansoura university hospitals satisfying one of the following conditions:

(1) Elevation of serum creatinine at admission with normal baseline serum creatinine.
(2) Elevation of serum creatinine at admission followed by return to reference or baseline, or 50% improvement.
(3) Elevation of serum creatinine at admission in absence of a history suggestive of chronic kidney disease and with normal kidney by sonographic examination.
(4) Sudden rise in serum creatinine (50% or more) in patients known to have CKD in stages earlier than stage 5.

Method:

All patients were subjected to:

(1) Complete history taking and physical examination.
(2) Investigations including:

- Routine laboratory investigations that are routinely performed to AKI patient during their usual care in the hospital were

recorded with special stress on the following: complete blood count, arterial blood gases, liver function tests, serum creatinine, blood urea nitrogen, urine analysis, serum electrolytes

- Ultrasound on both kidneys
- Other investigations when needed according to the recommendation of the treating physicians.

Definitions:

Risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury.

Contributing Factors are any behaviour, omission, or deficiency that sets the stage for an accident, or increases the severity of injuries

Comorbidity is the presence of one or more additional diseases or disorders co-occurring with (that is, concomitant or concurrent with) a primary disease or disorder.

We defined **baseline serum creatinine** as the lowest serum creatinine value closest to the time of admission within one year.

community-acquired acute kidney injury was defined if the patients developed rise in serum creatinine at the time of admission.

sepsis is defined as infection plus at least two signs of systemic inflammation ***(Melamed & Sorvillo, 2009)***:

- temperature >38˚c or <36˚c
- RR> 20/min or pco2 <32 mmHg
- WBCs >100000 or <4000 per microliter
- HR> 90/min

Statistical analysis:

-Data was presented using SPSS software version 21.

- categorical data were expressed as numbers and percentage and were analysed by chi-square test

- Scale data were expressed as means (SD) or medians, as appropriate. Parametric scale data were analysed using independent samples T test while non-parametric data were analysed using Mann Whitney test.

-Multivariate logistic regression was done to define the independent predictors for mortality

Results

Results

This study evaluated 199 patients (mean age 56.39±16.8 years ,51.8% females) admitted in Nephrology and Dialysis Unit in Mansoura University Hospitals over one year. These patients were diagnosed to have AKI or acute kidney injury on top of CKD according to the previously mentioned inclusion criteria. Table 1 show the age and gender of these patients.

Table 1: Description of age and gender of AKI patients:

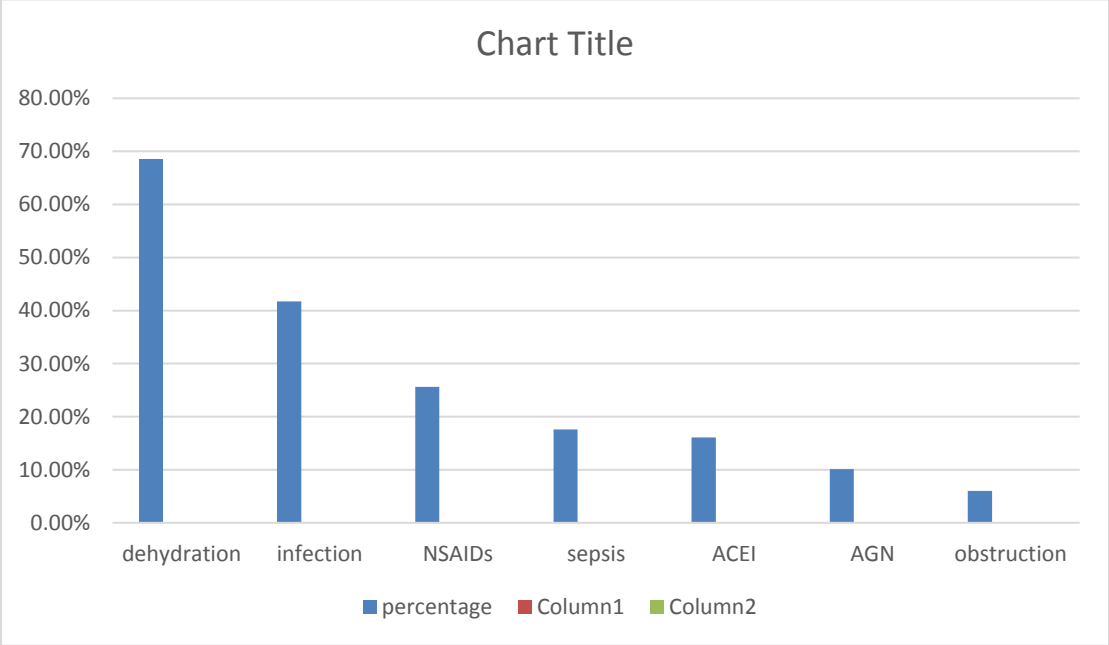
	Males	Females	Total	Statistics
Number	96	103	199	.901*
Age median	58	60	60	
(minimum-maximum)	20-88	18-86	18-88	

* Probability of Mann-Whitney U –test. Values of its variables are expressed as median (minimum-maximum).

As regards clinical data, Hypertension was present in 39.7 % of patients, while DM was present in 35.7 % of patients. Chronic kidney disease, chronic liver disease and chronic heart failure were also present but at lower percentages, (13.1 %, 12.1 % and 3 % respectively).

Dehydration was the commonest precipitating factor for AKI in these patients (68.8%) followed by infection (41.7 %), NSAIDS (25.6 %), sepsis (17.6 %), ACEI (16.1 %), AGN (10.1 %), and obstruction (6 %).

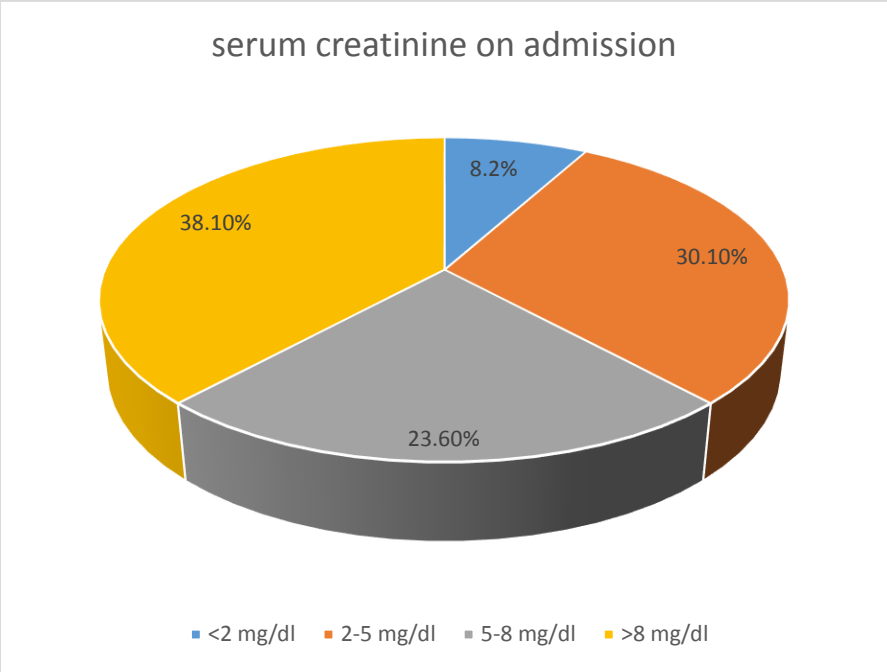
Figure 2: Bar chart; distribution of contributing factors in AKI patients.



Patients presented by different symptoms. Oliguria was present in 47.7 % of patients. infectious symptoms were present in 26.1 %. Other clinical symptoms as dysuria, hypotension, haematuria, and coma were also present but at lower frequencies.

Eight percent of patents had serum creatinine below 2mg/dl, 30.1% between 2 and5, 23.6 % between 5 and8 mg/dl and 38.1 % above 8 mg/dl.

Figure 3: Pie chart; distribution of serum creatinine on admission in AKI patients.



Regarding therapeutic modalities applied to patients: 65.8 % of patients received fluids, 22.6 % of patients received diuretics and 33.7 % received renal replacement therapy in the form of intermittent haemodialysis.

Serum creatinine among patients who received fluids was 5.2±0.8 mg /dl, 6.3 ±4 mg /dl in patients who received diuretics and 10.2 ±0.3mg/dl in patients who initiated haemodialysis.

About one and half percent of patients who initiated HD had serum creatinine below 2 mg /dl, 10.4 % between 2 and 5mg/dl, 11.9% between 5 and 8 mg /dl and 76.1% above 8mg /dl.

Outcomes were all-cause patient mortality, dialytic need and renal recovery. As regard mortality, 13.2 % of patients died during their admission.

As regard, renal recovery, relative improvement of serum creatinine at discharge was observed in 73% of patients with hospital stay less than one week, 44.7% of patients with hospital stay between one to two weeks and 54% of patients with hospital stay more than 2 weeks.

At discharge, 49.1 % of patients needed haemodialysis during their admission period were still on haemodialysis on discharge and 50.8 % were withdrawn from haemodialysis on discharge **(Table 2).**

Table 2: Description of clinical criteria of the patients:

Factor	Patient n= 199
Contributing factors: - **Dehydration n %** - **Infection n %** - **NSAIDs n %** - **Sepsis n %** - **ACEIs n %** - **AGN n %** - **Obstruction n %**	 137(68.8%) 83 (41.7%) 51(25.6%) 35 (17.6%) 32 (16.1%) 20 (10.1%) 12 (6%)
Presentation: - **Oliguria n %** - **Infection symptoms n %** - **Dysuria n %** - **Hypotension n %**	 95(47.7%) 44(22.1%) 38(19.1%) 35(17.6%)
Management: - **Fluids n %** - **Diuretics n %** - **RRT n %**	 131(65.8%) 45 (22.6%) 67(33.7%)
Outcome: - **Mortality n %** - **Recovery in patients with hospital stay <1-week n%** - **Recovery in patients with hospital stay (1-2) weeks n%** - **Recovery in patients with hospital stay >2weeks n%** - **No recovery n %**	 25 (13.2 %) 66 (73%) 42 (44.7%) 13 (54%) 69(36%)

Twenty two percent of patients were discharged with serum creatinine below 2 mg/dl, 43.9 % between 2 and 5 mg/dl, 22.5 % between 5 and 8 mg/dl and 10.9% above 8 mg /dl. Laboratory criteria of patients are shown in table 3.

Table 3: Description of laboratory criteria of the patients:

Factor	Patient n= 199
Serum Cr on admission* (mean± SD)	(7.51± 5.19)
Serum Cr on discharge* (mean± SD)	(4.42± 3.06)
Serum Cr on dialysis initiation* (mean± SD)	(10.2 ±0.3)
Haemoglobin$ (mean± SD)	(9.28± 2.352)
HCO_3# (mean± SD)	(16.36 ± 11.0)
pH (mean± SD)	(7.28 ± .09)
K^+# (mean± SD)	(4.6 ±1.2)
Ca* (mean± SD)	(8.21 ± 1.06)

Units of measurement: * mg/dl, $ g/l, # mEq/l

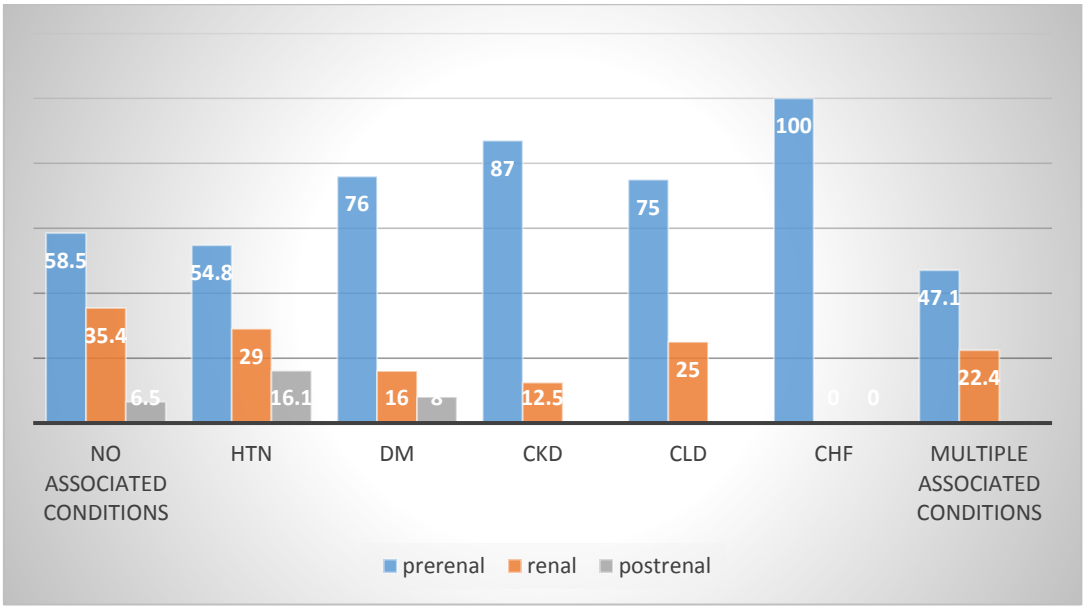
Patients were divided into 7 groups according to associated clinical conditions: patients without associated comorbidities, patients with DM, patients with HTN, patients with CLD, patients with CKD, patients with CHF, and patients with multiple associated comorbidities. Age and sex criteria in these groups are shown in table 4.

Table 4: Description of age and sex in different groups of AKI patients:

	No associated conditions n = 65	HTN n =31	DM n =25	CKD n =8	CLD n =8	CHF n =4	Multiple associated conditions n =58
Age	45.3±19	58.5±16	62.6±9.9	65.6±17	60.3±8.8	57±21	63±9.9
Gender Male female	29 (44.6%) 36 (55.4%)	16 (51.6%) 15 (48.4%)	15 (60%) 10 (40%)	4 (50%) 4 (50%)	6 (75%) 2 (25%)	4 (100%) 0	22 (37.9%) 36 (62.1%)

Dehydration, ACEI and NSAIDS were the commonest contributing factors in patients with CHF while Dehydration, infection and NSAIDS were the commonest contributing factors in all other groups **(Table 5).**

Figure 4: bar chart; frequency of prerenal, renal, postrenal AKI in different groups of AKI patients



While oliguria and infectious symptoms were the most frequent symptoms in patients with hypertension, diabetes and chronic kidney disease, oliguria and hypotension were the most frequent symptoms in

patients with chronic liver disease, congestive heart failure and multiple comorbidities **(Table 6).**

Regarding therapeutic modalities applied to the patients, the majority of patients in all groups received fluids and less number received diuretics or renal replacement therapy. Haemodialysis was more frequent in hypertensive patients than other groups **(Table 7).**

Table 5: Description of contributing factors to AKI in different groups of AKI patients:

	No associated conditions n = 65	HTN n =31	DM n =25	CKD n =8	CLD n =8	CHF n =4	Multiple associated conditions n =58
Dehydration	38 (58.5%)	17 (54.8%)	20 (80%)	7 (87.5%)	6 (75%)	4 (100%)	45 (77.6%)
Shock	6 (9.2%)	3 (9.7%)	3 (12%)	0	2 (25%)	0	4 (6.9%)
Infection	32 (49.2%)	10 (32.3%)	12 (48%)	2 (25%)	2 (25%)	1 (25%)	24 (41.4%)
Sepsis	13 (20%)	1 (3.2%)	7 (28%)	1 (12.5%)	1 (12.5%)	1 (25%)	11 (19%)
AGN	19 (21.5%)	2 (6.5%)	3 (12%)	0	0	0	1 (1.7%)
SLE	14 (21.5%)	2 (6.5%)	0	0	0	0	2 (3.4%)
AIN	1 (1.5%)	0	0	0	0	0	0
MM	2 (3.1%)	0	0	0	0	0	0
ACEI	1 (1.5%)	7 (22.6%)	7 (28%)	1 (12.5%)	0	2 (50%)	14 (24.1%)
NSAIDS	13 (20%)	9 (29%)	10 (40%)	1 (12.5%)	0	2 (50%)	16 (27.6%)
Contrast	0	0	0	0	1 (12.5%)	0	2 (3.4%)
Chemotherapy	3 (4.6%)	0	0	0	1 (12.5%)	1 (12.5%)	1 (1.7%)
TLS	0	0	0	0	0	0	1 (1.7%)
PN	3 (4.6%)	1 (3.2%)	2 (8%)	0	0	0	3 (5.2%)
Obstruction	4 (6.2%)	5 (16.1%)	2 (8%)	0	0	0	1 (1.7%)

Table 6: Description of clinical presentation in different groups of AKI patients:

	No associated conditions n = 65	HTN n =31	DM n =25	CKD n =8	CLD n =8	CHF n =4	Multiple associated conditions n =58
Dysuria	11 (16.9%)	3 (9.7%)	4 (16%)	1 (12.5%)	1 (12.5%)	2 (50%)	16 (27.6%)
oliguria	23 (35.4%)	14 (45.2%)	11 (44%)	6 (75%)	4 (50%)	3 (75%)	34 (58.6%)
hematuria	9 (13.8%)	3 (9.7%)	0	0	0	1 (25%)	1 (1.7%)
Infectious symptoms	15 (23.1%)	6 (19.4%)	9 (36%)	2 (25%)	2 (25%)	1 (25%)	9 (15.5%)
hypotension	13 (20%)	5 (16.1%)	5 (20%)	2 (25%)	2 (25%)	2 (50%)	6 (10.3%)

Table 7: Description of therapeutic modalities in different groups of AKI patients:

	No associated conditions n = 65	HTN n =31	DM n =25	CKD n =8	CLD n =8	CHF n =4	Multiple associated conditions n =58
fluids	36 (55.4%)	17 (54.8%)	19 (76%)	7 (87%)	5 (62.5%)	4 (100%)	43 (74.1%)
diuretics	19 (29.2%)	5 (16.1%)	3 (12%)	1 (12.5%)	2 (25%)	0	15 (25.9%)
dialysis	25 (38.5%)	12 (38.7%)	6 (24%)	1 (12.5%)	0	1 (25%)	22 (37.9%)

Mortality was more frequent in patients with DM and multiple co morbidities than in patients in other groups.

The frequency of patients who were still on haemodialysis on discharge was more in patients with CHF followed by patients with HTN, multiple associated conditions, DM (25%, 22.6%, 15.5%, and 8% respectively).

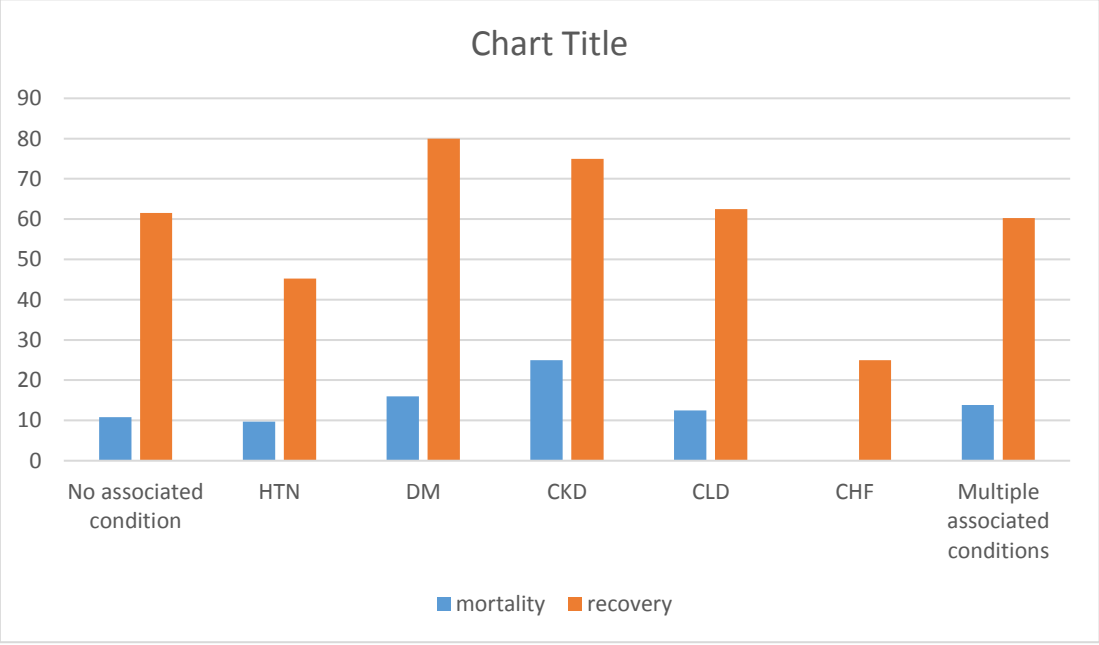
Partial or complete renal recovery by return of serum creatinine to baseline was more common in patients with DM followed by patients with CKD, CLD, no associated comorbidities, multiple comorbidities,

hypertension and CHF (80%, 75%, 62.5%, 61.5%, 60.3%, 45.2% and 25% respectively). Table 8 show clinical outcomes in different groups of patients **(table 8).**

Table 8: Description of outcome in different groups of AKI patients:

	No associated conditions n = 65	HTN n =31	DM n =25	CKD n =8	CLD n =8	CHF n =4	Multiple associated conditions n =58
Mortality	7 (10.8%)	3 (9.7%)	4 (16%)	2 (25%)	1 (12.5%)	0	8 (13.8%)
Recovery	39(61.5%)	14 (45.2%)	20 (80%)	6 (75%)	5 (62.5%)	1 (25%)	36 (60.3%)

Figure 5: Bar chart; Mortality and renal recovery in different groups of AKI patients.



Mean serum creatinine was highest in patients with diabetes. Mean HB level was lowest in patients with CKD. Mean serum albumin was lowest in

patients with CLD. Laboratory criteria of different groups of AKI patients are shown in **(table 9).**

Table 9: Description of laboratory criteria in different groups of AKI patients:

	No associated conditions n = 65	HTN n =31	DM n =25	CKD n =8	CLD n =8	CHF n =4	Multiple associated conditions n =58
Serum Cr on admission* (mean± SD)	7.7±6.2	8.7±5	8.4±4.7	7.2±3.8	4.4±1.8	7.4±4.7	7.1±4.4
Serum Cr on discharge* (mean± SD)	4.6±3.7	4.9±3.6	4 ± 2.2	3.4 ± 1.8	2.9 ± 2	5.7 ± 3.2	4.2±2.4
Haemoglobin (mean± SD) $	9 ± 2.6	9.4 ± 2	9.3 ± 1.9	7.2 ± 0.07	9.4 ± 1.4	8.7 ± 0.8	9.5 ± 2.5
PH (mean± SD)	7.2 ± 0.09	7.2 ± 0.1	7.2 ± 0.09	7.2 ± .07	7.3 ± 0.08	7.2 ± 0.08	7.2 ± 0.09
$HCO3^{-}$ #(mean± SD)	18.8 ± 17	13.9 ± 5	15.5 ± 4.7	14.2± 3.1	16.6 ± 2.6	17.4 ± 4.2	15.3 ± 3.5
K^{+}# (mean± SD)	4.4 ± 1.1	5 ± 1.3	4.1 ± 1.2	4.4 ± 1.1	4 ± 1	3.9 ± 0.4	5 ± 1.2
Serum albumin ^(mean± SD)	2.8 ± 0.7	3.1 ± 0.6	3.2 ± 1.2	2.9 ± 0.4	2.6 ± 0.7	3.1 ± 0.7	3 ± 0.6
Ca* (mean± SD)	8.2 ± 1.1	7.9 ± 0.9	8.1 ± 1	8 ± 0.9	8 ± 1.1	9.3 ± 1.1	8.3 ± 0.9

Units of measurement: * mg/dl, $ g/l, # mEq/l, ^gm/dl

Relations to mortality:

None of age, gender, or any of the associated conditions as DM, HTN, CKD, CHF and CLD was associated with mortality ($p > 0.05$) **(Table 10).**

Among contributing factors infection, sepsis and shock were associated with mortality ($p < 0.05$), while dehydration, obstruction, SLE, non-renal neoplasms, NSAIDS, chemotherapy and organ failure were not associated with mortality **(Table 11).**

As regards therapeutic modalities, dialysis, diuretics and fluids were not associated with mortality **(Table 12).**

Leucocytosis, low platelet count and high last available serum creatinine were associated with mortality **(Table 13).**

Multivariate logistic regression was done to examine the multiple variables associated with mortality. Analysis discerned shock and sepsis as the independent variables associated with mortality among AKI patients more than the other studied variables **(table 14).**

Table 10: Relation of different associated conditions to mortality in AKI patients during admission:

Associated condition	Present		Absent		P*
	Dead	Alive	Dead	Alive	
DM	9 (13%)	60 (87%)	16 (13.2%)	105 (86.8%)	.972
CKD	3 (10.7%)	22 (80%)	22 (13.6%)	143 (86.7%)	.854
HTN	11 (14.9%)	63 (85.1)	14 (12.1%)	102 (87.9%)	.578
CLD	4 (18.2 %)	18 (81.8%)	21 (12.5%)	147 (87.5%)	.458
CHF	1 (16.7%)	5 (83.3%)	24 (13%)	160 (87%)	.796

* Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage)

Table 11: Relation of different contributing factors of AKI to mortality (n=25) in AKI patients during Hospitalization:

Contributing factor	Present		Absent		P*
	Dead	Alive	Dead	Alive	
Prerenal	18 (12.9%)	122 (87.1%)	7 (14%)	43 (86%)	.504
Renal	6 (15%)	34 (85%)	19 (12.7%)	131 (87.3%)	.436
Postrenal	1 (9%)	9 (90%)	24 (13.4 %)	156 (86.6%)	.612

* Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage).

Contributing factor	Present		Absent		P*
	Dead	Alive	Dead	Alive	
Shock n=18	13 (72.2%)	5 (17.8%)	12 (7%)	160(93%)	.000
Infection	17 (21.3 %)	63 (78.8%)	8 (7.3 %)	102 (92.7%)	.005
Sepsis	12 (35.3 %)	22 (64.7%)	13 (8.3%)	143 (91.7%)	.000
ACEI	0 (0 %)	31 (100 %)	25 (15.7%)	134 (84.3%)	.018
Dehydration	17 (13 %)	114 (87%)	8 (13.6 %)	51 (86.4%)	.913
Hypotension	3 (9.4 %)	29 (90.6%)	22 (13.9 %)	136 (86.1%)	.354
Pyelonephritis	3 (33.3 %)	6 (66.7%)	22 (12.2)	159 (87.8%)	.067
SLE	2 (11.1 %)	16 (88.9%)	23 (13.4 %)	149 (86.6%)	.787
AGN	2 (10 %)	18 (90%)	23 (13.5 %)	147 (86.5%)	.659
NSAIDS	7 (13.7 %)	44 (86.3%)	18 (12.9 %)	121 (87.1%)	.889
Chemotherapy	1 (20 %)	4 (80%)	24 (13 %)	161 (87%)	.646
Postoperative	0 (0 %)	7 (100%)	25 (13.7 %)	158 (86.3%)	.294
Organ failure	4 (19 %)	17 (81%)	21 (12.4%)	148 (87.6%)	.397
Non renal neoplasm	1 (12.5%)	7 (87.5%)	24 (13.2%)	158 (86.8%)	.955
Obstruction	1 (9.1%)	10 (90.9%)	24 (13.4 %)	155 (86.6%)	.681

* Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage).

Table 12: Relation of different laboratory findings to mortality in AKI patients during admission:

Lab	Dead	Alive	P
Serum creatinine on admission@	6 (2.8-11)	6.6 (1.4-30.8)	**1.000***
Serum creatinine on dialysis@	8.1 ± 2.4	12.3 ± 6.2	**.002*****
Last available serum creatinine@	5.2 (1.4-11.4)	3.5 (0.6-18)	**.003***
Proteinuria	8 (32%)	60 (36%)	**.482****
Serum albumin^	3 (1.5-4.3)	3 (1.6-4.2)	**.81***
Serum bilirubin@	0.8 (0.5_15)	0.6 (0.3-39)	**.591***
WBCS	13.4 ± 6.2	10 ± 5.5	**.006*****
Hb$	9.8 ± 2.5	9.1 ± 2.2	**.181*****
Platelet count	162 (8-592)	206 (7-658)	**.053***
WBCs	13.4 ± 6.2	10 ± 5.5	**.006*****
PH	7.33 ± .08	7.28 ± .09	**.018*****
HCO3-#	24.7 ± 15.2	28.3 ± 4.3	**.113*****
K+#	4.2 (2.6-7.4)	4.6 (2.3-8.7)	**.341***
Ca@	7.9 ± 0.9	8.2 ± 1	**.216*****

* Probability of Mann-Whitney U –test. Values of its variables are expressed as median (minimum-maximum).

** Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage) ".

*** Probability of independent sample T–test. Values of its variables are expressed as mean ± standard deviation

Units of measurement: @mg/dl, $ g/l, # mEq/l, ^gm/dl

Table 13: Relation of different therapeutic modalities of AKI to mortality in AKI patients during admission:

Therapeutic modalities	Present		Absent		P *
	Dead	Alive	Dead	Alive	
Fluids	4 (9.5%)	38 (90.5%)	21 (14.2%)	127 (85.8%)	.430
Diuretics	8 (12.5%)	56 (87.5%)	17 (13.5%)	109 (86.5%)	.848
Haemodialysis	8 (12.3%)	57 (87.7%)	17 (13.6%)	108 (86.4%)	.803

* Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage).

Table 14: multivariate logistic regression to examine the multiple variables associated with mortality:

	B	S.E.	Wald	df	Sig.	Exp(B)
Age	.015	.019	.642	1	.423	**1.015**
Shock	3.303	.666	24.595	1	.000	**27.196**
Sepsis	1.390	.660	4.442	1	.035	**4.016**
ORGANFAILURE	-.378	.816	.214	1	.643	**.685**
Dialysis	.196	.613	.102	1	.749	**1.216**
WBCS	.055	.047	1.380	1	.240	**1.057**
PLT	-.003	.002	1.370	1	.242	**.997**
CKD	.371	.874	.180	1	.671	**1.449**
Constant	-3.975	1.319	9.084	1	.003	**.019**

In the present study, seventeen patients died without initiation of RRT. These patients were classified into 2 groups:

Group A: patients with low or improving serum creatinine before death.

Group B: patients with relatively high serum creatinine before death but with difficulty to initiate haemodialysis.

Laboratory and clinical criteria of both groups are shown in **(table 15).**

Table 15: laboratory and clinical criteria of patients who died without initiating haemodialysis:

	number of cases	Shocked or not	sepsis	Duration of hospital stay$	Creatinine at admission*	Creatinine before death*	Organ failure
Group A	12	7	7	7 (1-21)	6.01±3.1	4.2±1.8	2
Group B	5	3	4	2 (2-7)	5.3±0.5	6.8±1.8	1

Units of measurement$ days *mg/dl

Group A: patients with low or improving serum creatinine before death.

Group B: patients with relatively high serum creatinine before death but with difficulty to initiate haemodialysis

Relations to renal recovery:

In the present study, none of age, gender, or any of the associated conditions was associated with significant improvement of serum creatinine at discharge **(table16)**

Prerenal contributing factors showed a relatively more advantageous improvement of serum creatinine at discharge in comparison to other patients. On the other hand, intrinsic renal pathologies were associated with lack of recovery in patients at discharge. On more detailed analysis, patients presented with SLE or AGN were found to have worsening of serum creatinine or persistence on dialysis at the time of discharge, more

frequently than patients presented differently in the current study **(table 17).**

Patients treated with fluid therapy were more frequent to experience improved serum creatinine at discharge, whereas those treated with diuretics or renal replacement therapy were more frequent to show lack of renal recovery at discharge **(table 18).**

Higher creatinine values at admission and at dialysis initiation were associated with lack of recovery.at time of discharge **(table19).**

Table 16: Relation of different associated conditions to partial or complete renal recovery in AKI patients:

Associated condition	Present		Absent		P
	No recovery	Partial or complete recovery	No recovery	Partial or complete recovery	
DM	20 (29.4%)	48 (70.6%)	49 (40.2%)	73 (59.8%)	.140
CKD	5 (20.8%)	19 (79.2%)	64 (38.2%)	102 (61.8%)	.092
HTN	30 (41.1%)	43 (58.9%)	39 (33.3%)	78 (66.7)	.279
CLD	9 (40.9%)	13 (59.1%)	60 (35.7%)	108 (64.3%)	.634
CHF	3 (50%)	3 (50%)	66 (35.9%)	118 (64.1%)	.479

* Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage).

Table 17: Relation of prerenal, renal, and postrenal groups of AKI patients with recovery:

Contributing factor	Present		Absent		P*
	No recovery	Partial or complete recovery	No recovery	Partial or complete recovery	
Prerenal	45 (31.9%)	96 (68.1%)	24 (49 %)	25 (51%)	.025
Renal	21 (52.2%)	19 (47.8%)	48 (32%)	102 (68%)	..025
Postrenal	3 (33.3%)	6 (66.7%)	66 (36.4 %)	115 (63.6%)	.576

* Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage).

Table 18: Relation of prerenal, renal, and postrenal groups of AKI patients with recovery:

Contributing factor	Present		Absent		P*
	No recovery	Partial or complete recovery	No recovery	Partial or complete recovery	
Hypotension	5 (15.2 %)	28 (84.8%)	64 (40.8 %)	93 (59.2%)	.005
Shock n=18	7 (38.9%)	11 (61.1%)	62 (36%)	110(64%)	.811
SLE	10 (55.6%)	8 (44.4%)	59 (34.3%)	113 (65.7%)	.066
AGN	12 (60 %)	8 (40%)	57 (33.5 %)	113 (66.5%)	.020
Infection	25 (30.9%)	56 (69.1%)	44 (40.4 %)	65 (59.6%)	.178
Sepsis	11 (31.4%)	24 (68.6%)	58 (37.4%)	97 (62.6%)	.506
ACEI	10 (33.3 %)	21 (66.7 %)	59 (36.9%)	101 (63.1%)	.711
Dehydration	41 (31.1 %)	91 (68.9%)	28 (48.3 %)	30 (51.7%)	.023
Pyelonephritis	1 (11.1 %)	8 (88.9%)	68 (37.6)	113 (62.4%)	.107
NSAIDS	21 (41.2 %)	30 (58.8%)	48 (34.5 %)	91 (65.5%)	.399
Chemotherapy	3 (60 %)	2 (40%)	66 (35.7 %)	119 (64.3%)	.254
Postoperative	1 (14.3%)	6 (85.7%)	68 (37.2 %)	115 (62.8%)	.217
Organ failure	7 (33.3 %)	14 (66.7%)	62 (36.7%)	107 (63.3%)	.483
Obstruction	4 (36.4%)	7 (63.6%)	65 (36.3 %)	114 (63.7%)	.943

* Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage).

Figure 6: Bar chart; Mortality and renal recovery in prerenal, renal and postrenal groups of AKI patients

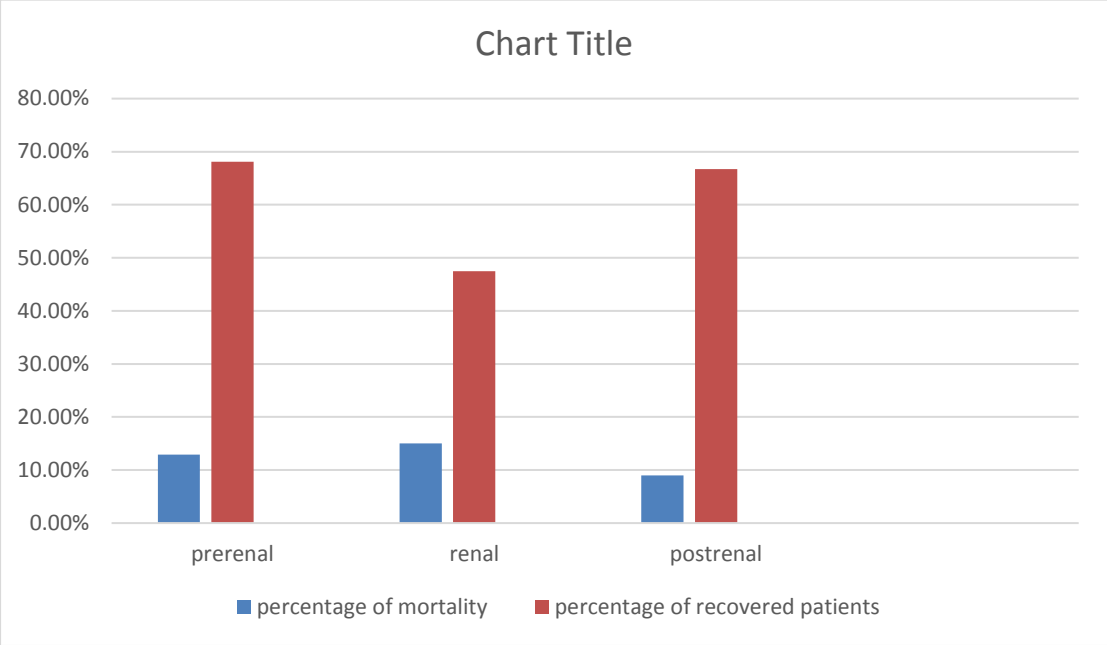


Table 19: Relation of different therapeutic modalities to partial or complete renal recovery in AKI patients:

Therapeutic modalities	Present		Absent		P *
	No recovery	Partial or complete recovery	No recovery	Partial or complete recovery	
Fluids	39 (31%)	87 (69%)	30 (46.9%)	34 (53.1%)	.031
Diuretics	22 (53.7%)	19 (46.3%)	47 (31.5%)	102 (68.5%)	.009
Haemodialysis	35 (55.6%)	28 (44.4%)	34 (26.8%)	93 (73.2%)	.000

* Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage).

Table 20: Relation of different laboratory criteria to partial or complete renal recovery in AKI patients:

Lab	No recovery	Partial or complete recovery	P
Serum creatinine on admission	8.8 ± 6.9	7 ± 3.7	**.043*** **
Serum creatinine on dialysis	4.4 ± 6.1	8.9 ± 4.5	**.000*** **
Last available serum creatinine	6.5 ± 3.6	3.2 ± 1.8	**.000*** **
Proteinuria	35 (51.5%)	35 (27.3%)	**.001** **
Serum albumin	2.8 (1.5-4.2)	3 (1.6-4.5)	**.427***
Serum bilirubin	0.8 (0.3_20)	0.8 (0.3-39)	**.875***
WBCS	13.4 ± 6.2	10 ± 5.5	**.250*** **
Hb	9.1 ± 2.1	9.2 ± 2.4	**.783*** **
Platelet count	221 ± 123	204 ± 111	**.346*** **
PH	7.30 (7.0-7.51)	7.30 (7.07-7.50)	**.838***
HCO3	14.5 (5.7-23)	15.9 (4.7-26)	**.448***
K	4.6 (2.7-7.9)	4.4 (2.3-8.7)	**.649***
Ca	8.2 ± 0.9	8.1 ± 1.1	**.891*** **

* Probability of Mann-Whitney U –test. Values of its variables are expressed as median (minimum-maximum).

** Probability of chi square χ 2-test. Values of its variables are expressed as n (%) number and (percentage) ".

*** Probability of independent sample T–test. Values of its variables are expressed as mean ± standard deviation

Discussion

Discussion

Acute kidney injury (AKI) is a major global health problem, and even though the International Society of Nephrology set a goal of eradicating preventable deaths due to AKI by 2025, there are major challenges in this project implementation in developing countries not only because of the inadequate resources, but also because of the limited data of epidemiology and causes of AKI in these countries, the scarce health care resources to diagnose and treat AKI, and the poor awareness of the impact of AKI on patient ***(Ponce & Balbi, 2016)***. Despite the paucity of quality data for the epidemiology of AKI in developing countries, the prevalence of AKI in this setting is estimated to be higher than that in developed countries. It has been suggested that the global burden of AKI is up to 13.3 million cases per year, 11.3 million of which are in low- to middle-income countries and responsible for up to 1.4 million deaths per year. Furthermore, AKI-related problems account for up to 3% of hospital admissions in general health care facilities in low resource societies ***(Schieppati et al., 2015)***.

AKI has harmful short-term consequences; longer hospital stays, greater disability after discharge, and greater risk of in-hospital mortality, as well as adverse long-term outcomes, such as progression to chronic kidney disease, development of cardiovascular disease, and increased risk of long-term mortality ***(Neves et al.; Ponce & Balbi, 2016)***.

In Egypt, the epidemiology of AKI and its impact on morbidity and mortality has not been well studied. To the best of our knowledge, there are only paucity of literature dealing with the problem of AKI and its cause in the general population. A published prospective study conducted on all patients who were admitted to intensive care units (ICUs) at Banha

University Hospitals stated that the prevalence of ICU-acquired acute renal failure was 21.2% based on AKIN & RIFLE criteria ***(Talaat et al., 2014)***. In addition, Mohamed and his colleagues in a prospective observational study carried out in surgical intensive care in Cairo university hospital reported a higher prevalence of AKI in critically ill patients [35.7%] ***(Mohamed et al., 2013)***

The aim of the current work is to study the clinical characteristics, risk factors, associated comorbidities, and outcomes of AKI patients admitted in nephrology and dialysis unit in Mansoura University Hospitals over one year.

In the current study, the median (IQR) age of AKI patients was 60 (47-70) years with 44% of patients aged above 60 years. Another study also reported a low frequency of AKI in patients above 60 years [35%] ***(Grams et al., 2011)***. In contrast, another previous study reported higher percentage of AKI patients above 60 years [65.2%] ***(Bucuvic et al., 2011)***. In the present study, 51.8% of patients were females. This lack of gender difference is in contrast to that reported by others where males were more frequent to have AKI ***(Gettings et al., 1999; Bucuvic et al., 2011; Mehta et al., 2016)***.

In dealing with epidemiology of AKI, it would be beneficial to identify both the contributing or precipitating factors as well as the associated comorbidities. Dehydration was found to be the commonest precipitating factor for AKI in the patients of the present study (68.8%), followed by infection (41.7 %), use of NSAIDS, sepsis, ACEI, AGN, and urinary obstruction. These findings cope with those of a previous study ***(Mehta et al., 2016)***. In harmony with the results of the present study, several previous studies reported that dehydration and sepsis constitute the

majority of contributing factors for AKI ***(Cole et al., 2000; Ali et al., 2007)***. In disagreement with these, some authors documented that sepsis was the first contributing factor for AKI ***(Uchino et al., 2005; Bagshaw et al., 2007)***. This difference might be attributable to the type of patients of these studies who were critically ill ICU patients.

The pathogenesis of renal affliction in volume depletion and sepsis is well known. Considerable dehydration leads to impaired renal perfusion with a resultant fall in glomerular capillary filtration pressure. In this setting, tubular function is typically normal, renal reabsorption of sodium and water is increased, and subsequently a concentrated urine is formed (urine osmolality >500 mOsm/kg). However, a marked reduction in renal perfusion may overwhelm autoregulation and precipitate an acute fall in GFR. This contrasts to AKI precipitated by infection. Severe infection contributes to AKI mainly by the sepsis-endotoxin-cytokine mediator system and superimposed disseminated intravascular coagulation. In this condition, the hemodynamic of this kidney is impaired even without systemic hypotension ***(Bone et al., 1992)***.

In the current study, the contributing factors affecting the patients were classified into 3 groups, according to the pathobiology at time of presentation: prerenal, renal and postrenal (73.4%, 21.1% and 5.5 % of AKI patients, respectively). This widely used conceptual classification assumes that prerenal azotaemia is diagnosed when rapidly reversible functional renal failure is triggered by events occurring ‘outside’ the kidney itself and do not include obstruction of the urinary tract. Additionally, it assumes that ischemic ATN cannot arise de novo but must by necessity be secondary to sustained or uncorrected functional injury which has progressed to the point of cell necrosis (hence the term ATN). Although this classification is widely used in studies dealing with the

epidemiological and clinical characteristics of ARF, in the clinical situations, there are no clear boundaries that can accurately differentiate between prerenal azotaemia and ATN and, till the current time, it is still difficult to know when a 'functional' AKI (pre-renal azotaemia) is changed into a 'structural 'AKI (ATN). Unfortunately, pre-renal azotaemia does not usually present with 'consensus criteria' that exclude the presence of ATN. Thus, it might be impossible to prove that a diagnosis of prerenal azotaemia coined by a given clinician is not the same as a diagnosis of ATN coined by another clinician.

In order to clearly define the latter confusion, either renal biopsy or scrutinizing the clinical course of the disease might be resorted to. However, both responses are flawed. Firstly, there is no enough published data on renal biopsy series from critically ill patients with clinically suspected ATN let alone 'pre-renal azotaemia'. Thus, the notion that ATN is the histopathological result of non-resolving AKI, is far from being supported by enough evidence. Secondly, adopting a diagnosis of 'ATN' to any AKI case with delayed recovery or a diagnosis of 'pre-renal' to any case with quick recovery is also not supported by significant evidence-based research ***(Bellomo et al., 2007)***.

Another published paradigm is the measurement of analytes in urine (urea, creatinine, sodium, potassium) and/or the calculations of derived variables (fractional excretion of sodium, fractional excretion of urea) can be used to accurately infer preserved tubular function (which equate to pre-renal azotaemia) or lost tubular function (which equates to ATN) ***(Miller et al., 1978; Langenberg et al., 2006)***. However, urinary electrolytes might be impaired in elderly patients, patients on loop diuretics and patients having salt loosing nephropathy. In addition, this paradigm would ideally

require histopathological confirmation that there is or there is not ATN for a given set of urinary findings ***(Bellomo et al., 2007)***.

Finally, no matter how flawed this classification is, it still works reasonably well in guiding clinicians to the right therapeutic measure "like an old map that does not accurately direct the driver to the right place the way a sophisticated electronic navigation system might, but is always better than no map at all" ***(Bellomo et al., 2007)***.

The majority of AKI patients in the present study had associated comorbidities as hypertension, DM, LCF or CHF, either in isolation or in combination. The same trend was also reported previously by others ***(Bucuvic et al., 2011; Wijewickrama et al., 2014)***; although the latters only studied ICU patients with AKI. In contrast, in another previous study, just under half of the patients (45.4%) had medical co-morbidities as DM , hypertension and ischemic heart disease ***(Wijewickrama et al., 2014)***. In the present study, the most common comorbidity was hypertension followed by DM, CLD, CKD and CHF; respectively, while another previous literature reported that hypertension was the most frequent comorbidity associated with AKI followed by CKD, DM, CHF and CLD respectively ***(Schissler et al., 2013)***.Although several epidemiologic studies of ARF have clearly indicated the importance of chronic premorbid conditions as congestive heart failure, chronic hypertension, diabetes mellitus and pre-existing renal disease in the development of kidney failure ***(Hsu et al., 2008; Okusa et al., 2009)***, the exact mechanism behind this association is not well identified yet.

One of the explanations is that renal insult associated with these chronic premorbid conditions might be attributed to impaired endothelium-derived vasorelaxation which is often present in diabetes mellitus,

hypertension, atherosclerosis, and heart failure, resulting in paradoxical vasoconstriction or reduced vasodilatation with regional hypoxia ***(Lüscher, 1993)***. Other underlying factors for increased risk of AKI in patients with CKD include disordered autoregulation, abnormal vasodilation, increased sensitivity to diuretics and nephrotoxic agents, age-related changes in renal physiology and associated heart failure which is common in CKD ***(Gürsu et al., 2017)***.

In the current study, the majority of AKI patients (62%) had serum creatinine above 5 mg/dl, while only 38 % of patients had serum creatinine below 5 mg/dl. The mean serum creatinine in all patients on admission was 7.5±5.1 mg/dl. Lower mean serum creatinine was reported by other previous studies ***(Liano et al., 1996; Schissler et al., 2013)***. This finding may be attributed to the fact that the patients of the current study had community acquired AKI and did not seek medical advice till they had severe symptoms. This late presentation might have an impact on the short and long-term outcomes of the patients.

In the current study, nearly half of the patients presented with oliguria, while other clinical presentations were also observed as infectious symptoms, dysuria, hypotension & hematuria, but at lower frequencies. Oliguria was also the most frequent observed presenting symptom in AKI patients previously ***(Liano et al., 1996)***.

Renal replacement therapy in the form of conventional haemodialysis was needed and applied in nearly one third of patients in the present study. On the other hand, the majority of patients received non-dialytic conservative treatment. According to the local working protocol in the unit where the present study was undertaken, haemodialysis is applied to the AKI patients essentially when they have severe volume overload, electrolyte disturbances resistant to medical treatment e.g. hyperkalaemia,

severe metabolic acidosis, symptoms suggestive of severe uremia e.g. uremic pericarditis, uremic encephalopathy and uremic asthma, and elevated serum creatinine above 8 mg/dl in absence of signs of recovery. Only few patients with deteriorated kidney functions did not initiate haemodialysis due to severe irreversible hemodynamic instability that made it difficult to instigate conventional haemodialysis. Additionally, three other patients, who were hemodynamically stable, had serum creatinine above 8 mg/dl but refused to initiate haemodialysis in our unit and preferred to move to private services.

In the present study, the mean serum creatinine upon which the decision of haemodialysis initiation was taken was (10.2 ±0.3) mg/dl. with a creatinine level ranging from 8.3 to 15.3 mg/dl. Cole and his colleague in a multicentre study in Australia described a lower mean serum creatinine at time of initiation of RRT (3.5mg/dl). In their setting, critical care physicians and nurses fully control the management and renal replacement prescription and application for the majority of patients with severe AKI in their ICU. Nephrology unit opinion is sought in only a small group of patients. Such behavior suggests a strong desire to prevent, rather than simply treat, fluid overload and excessive uremia ***(Cole et al., 2000)***.

Mehta et al, in a well-designed recent study, analysed the data of various variables concerning AKI from 289 hospitals and centres distributed in different countries all over the world. They compared the frequency of initiation of dialysis in AKI patients between different countries classified according to the economic status. In their report, the fraction of patients treated with haemodialysis was 29%. and the median (IQR) of serum creatinine in their patients at time of initiation of haemodialysis was 7 (5.02-10.4) mg/dl in low income countries, while the corresponding data in high income countries were. 21.7 % and 5.3 (3.04-8.03) mg/dl. The fraction of patients requiring haemodialysis in the present

study is greater than that reported in both the high and low-income countries in the former report although the level of serum creatinine at the initiation of dialysis is higher in the present work. Had the two populations of both studies been similar, one would expect that the frequency of initiation of dialysis is lesser the higher the creatinine cut-off for dialysis initiation. However, this was not the case, denoting that there might have been significant differences between the population screened in the present study and those of Mehta et al (2016).

On carefully looking into this part of data of Mehta et al as well as the present work, one is tempted to infer that the fraction of patients initiating dialysis increases while the cut off value of plasma creatinine for dialysis initiation increases, when one moves from a higher income to a lower income country, considering that Egypt is currently suffering from a severe economic recession. It is also interesting to notice that the type of screened population in the present study and those of the two income level countries reported in Mehta et al (2016) are dissimilar regarding the type of AKI. In the present study, all of the screened population had community acquired AKI, screened population of the low-income countries of the former report contained 20% with hospital acquired AKI while those of high income countries contained 50% hospital acquired AKI ***(Mehta et al., 2016)***.

In the same context, the admission creatinine in the current study (median and IQR values of creatinine of 6.7 and 4-10 mg/dl) is higher than those reported in the low-income communities (3.2 and 2-5.8 mg/dl) and even much higher than those of the high income ones (2.4 and 1.6-4.1 mg/dl) ***(Mehta et al., 2016)***. This population differences might make appropriate inference from the collective patients' data unreliable.

Many previous publications highlighted many differences between hospital and community acquired AKI in term of severity and prognosis. In developed countries, in comparison with community acquired AKI, hospital acquired AKI was reported to have a more severe clinical course with subsequent greater need for dialysis and higher mortality rates ***(Liano et al., 1996; Obialo et al., 2000)***. This difference might be attributed to varied aetiological spectrum in both types of AKI; with volume depletion contributing to significantly more cases of CA-AKI, while ATN and drug-associated causes are more common in HA-AKI. Additionally, patients with HA-AKI are more likely to have underlying chronic illnesses, specifically coronary artery disease, congestive heart failure, and diabetes mellitus; and they are more likely to experience sepsis, respiratory failure, and pneumonia and to require ICU monitoring ***(Liano et al., 1996; Obialo et al., 2000; Cerdá et al., 2008; Schissler et al., 2013)***.

On the other hand, the majority of patients in low-income countries have community acquired AKI. People there often present late to hospital or large referral health care centres, which suggests more severe AKI at admission, greater need for dialysis, and an increased risk of death compared with higher-income countries. Since AKI is not associated with highly specific symptoms, and diagnosis is largely based on laboratory measurements, which are rarely available in remote areas of developing communities, it often goes unrecognized during the first examination by non-specialist health care providers ***(Cerdá et al., 2008; Mehta et al., 2016; Ponce & Balbi, 2016)***.

On the other hand, in low-income societies, patients with hospital acquired AKI are usually diagnosed at earlier and milder stage of disease even before the patient has symptoms in view of regular screening of in-hospital patients. Therefore, on comparing the data of different studies, the

type of studied population, their socioeconomic status, the type of AKI and the applied protocol for dialysis initiation, should be taken into consideration.

A critical decision in the support of critically ill patients with AKI is when to initiate RRT. There is sufficient evidence that earlier RRT initiation in patients with acidaemia, resistant hyperkalaemia, fluid overload, and systemic inflammation may attenuate kidney-specific and non-kidney organ injury. This in turn, may potentially translate into improved survival and earlier recovery of kidney function ***(Matson et al., 2004; Clark et al., 2006)***.

Nevertheless, in the absence of refractory acidaemia, toxic hyperkalaemia and intravascular fluid overload contributing to respiratory failure, there is limited evidence to guide clinicians on when to initiate RRT in critically ill patients with AKI ***(Karvellas et al., 2011)***.

An observational literature reported that starting RRT at urea values more than 27 mmol/L was associated with a two-fold increased risk of mortality ***(Liu et al., 2006)***.

In harmony, a retrospective review of medical records of post traumatic patients who developed AKI and received CRRT reported that an earlier initiation of CRRT, i.e. pre-CRRT BUN less than 60 mg/dl (21.4 mmol/L), may improve the rate of survival of trauma patients who developed ARF ***(Gettings et al., 1999)***.

In contrast, Wilson et al in a retrospective study concluded that dialysis was associated with increased survival when initiated in patients with AKI who have a more elevated creatinine level(≥ 3.8 mg/dl) but was associated with increased mortality when initiated in patients with lower

creatinine concentrations ***(Wilson et al., 2014)***. Additionally, a prospective randomised study of both dose and timing of initiation of CVVH did not show any survival advantage of early therapy ***(Bouman et al., 2002)***; an early start was defined as initiation within 12 hours of meeting the following criteria: a urine output <30 ml/hr for >6 hours and a measured urinary creatinine clearance <20 ml/min.

The lack of consensus criteria to define early and late dialysis, the heterogeneity in the population studied and the absence of adequate non-dialysed control groups make it difficult to determine whether the timing of RRT has an impact on patients' survival or not.

In a developing country like Egypt, the resources to support patients with AKI are unfortunately limited. Thus, the delay in starting RRT might be reasonable. In the unit where the present study was carried out, nearly 10-15 haemodialysis sessions are provided daily as emergency unscheduled sessions for emergency and critically ill patients, in addition to ~50 sessions provided for chronic patients on haemodialysis served by only 20 dialysis machines, 15 nurses, and 3 physicians. Undertaking more dialysis sessions of unproven benefit in such unit may impose physical and financial load on the provided dialysis service. So, in such situation, it might be prudent to adopt the policy of late dialysis. Debates between early and late dialysis are far from being completely settled and this area is in need for further extensive research.

In the present study, in-hospital mortality was recorded in 12.6% of AKI patients. However, such frequency may not be an accurate estimate to mortality in the present AKI cases as many severely ill patients might have been transferred to other services or were discharged upon their demands before completing their proposed course of medical follow-up. Thus, one

would not be able to tell whether they would have been living or dead if they had stayed under the study's observation. In contrast, multiple previous studies reported much higher rates of in-hospital mortality among AKI patients ***(Liano et al., 1996; Ali et al., 2007)***. The explanation of this discrepancy might reside in the fact that most of the latter publications were based on studies that included considerable proportion of intensive care or critically ill patients associated with an inherently higher mortality rate.

It might be logic to conceive that old age is an important risk factor for mortality in AKI patients. This concept has been affirmed by multiple previous studies that reported higher mortality rates in older patients with AKI ***(Schwilk et al., 1997; Chertow et al., 2005; Uchino et al., 2005; Bucuvic et al., 2011; Mehta et al., 2016)***. However, in the current research, patients' age was not found to influence the in-hospital mortality rates. Similar trend was also observed by previous authors ***(Van Den Noortgate et al., 2003)***.

This relatively favourable outcome in the elderly might be the consequence of a lower severity of the underlying disease. Obviously, the aging kidney is less capable to acclimatise to rapid hemodynamic changes and electrolyte imbalance. Thus, elderly patients are more susceptible to minor insults, that would not otherwise impose renal affliction in younger individuals, resulting in milder forms of AKI that develop earlier and more readily and could be less aggressive in these older patients.

In the current study, gender did not have a significant impact on mortality. The same finding was also reported in a previous study ***(Liano et al., 1996)***. In contrast, male gender reached borderline significance in association with increased risk of mortality in another previous study observing ICU patients with AKI ***(Cosentino et al., 1993)***.

None of the observed associated comorbidities in the present study (DM, hypertension, CKD, CLD and CHF) was accompanied with an increased risk for mortality. In harmony, other previous studies reported that DM, hypertension and premorbid renal impairment were not found to be independent predictors of mortality ***(Cosentino et al., 1993; Uchino et al., 2005)***. Surprisingly, another previous study reported that pre-existing CKD was associated with deceased risk for mortality ***(Mehta et al., 2015)***. However, other previous studies found that pre-existing CKD and CLD were associated with increased risk of mortality in AKI patients ***(Cosentino et al., 1993; Chertow et al., 2005)***.

In the current study, among the contributing factors, infection, sepsis and shock were associated with increased mortality. The same finding was reported by previous studies ***(Schwilk et al., 1997; Uchino et al., 2005; Lombardi et al., 2008)*.** On the other hand, dehydration, obstruction, SLE, non-renal neoplasms, NSAIDS, chemotherapy and associated failure of other organs were not associated with mortality. Contradictory previous studies reported that associated failure of other organs is associated with an increased risk for mortality in AKI patients ***(Cosentino et al., 1993; Mehta et al., 2016)*.**

Since 1992, sepsis has been defined by consensus as a systemic inflammatory response syndrome of infectious origin and the failure of one or more organ systems or the occurrence of hypoperfusion in conjunction with sepsis is considered to be severe sepsis, while severe sepsis accompanied by hypotension is considered septic shock ***(Melamed & Sorvillo, 2009)***. The burden of sepsis associated mortality has been reported by multiple previous literatures even in patients without AKI ***(Control, 1990; Martin et al., 2003; Dombrovskiy et al., 2007)***. Additionally, sepsis is the 10th leading cause of death in the United States

(Kung et al., 2008). Although the cause of death in septic patients has not been clarified by autopsy studies it has been suggested that associated failure of other organs is usually the cause of death in such cases ***(Melamed & Sorvillo, 2009)***.

The impact of laboratory data on mortality was also studied. In the present study, AKI patients with leukocytosis, lower platelet count or higher last observed serum creatinine had a higher risk of mortality than other patients. This finding might be explained by the fact that leukocytosis and lower platelet counts are laboratory variables possibly associated with sepsis which had been observed as an independent predictor for mortality ***(Melamed & Sorvillo, 2009)***.

It might be possible to postulate that many patients with AKI could die in consequence of any of the aggressive contributing illnesses that had inflicted the kidney injury rather than dying from the direct effect of AKI itself. Consequently, AKI could be viewed as a mere expression of an aggressive illness. On the other hand, many nephrologists believe that AKI in itself is a life-threatening condition and can be a cause of mortality. Consistent and strong evidence supports the notion that AKI has an independent impact on mortality, even after all other possible variables determining the outcome have been corrected for ***(Metnitz et al., 2002; Uchino et al., 2005; Xue et al., 2006)***.

It is well known that many patients could suffer from severe physiological perturbations in the form of volume overload, acid base and electrolyte disturbances and other systemic affliction by uremic toxins. Replacement of kidney function by manoeuvres that remove the noxious toxins and amend the disturbed physiology is expected to produce favourable effects on mortality and morbidity of AKI. However, there is

no current sufficient evidence that early RRT will improve the outcome. Given the multiple effects of AKI, efforts to prevent its development or hasten its recovery early in the course of the disease are expected to significantly improve survival in critically ill patients. ***(Hoste & Kellum, 2004)***.

In the present study, symptoms suggestive of infection were associated with increased risk for mortality, while other symptoms as oliguria, hypotension and coma were not significantly associated with mortality. However, other publications showed that oliguric AKI patients had higher mortality rates than non-oliguric patients ***(Liaño et al., 1993; Li et al., 2013; Mehta et al., 2016)***.

Oliguria, in the present study, was recorded on admission to the hospital which might reflect prerenal pathology that can be reversed by judicious fluid therapy, thus, mortality can be avoidable. Nevertheless, mortality in oliguric AKI patients is expected to be enhanced by aggressive fluid resuscitation regimens while wise fluid therapy that keeps fluid balance to the optimum standards, as much as possible, is believed to reduce mortality and morbidity ***(Grams et al., 2011)***. Previous published studies disagree with the present study in reporting conflicting findings of increased mortality rates in AKI patients with jaundice, sustained hypotension and coma ***(Barton et al., 1993; Liano et al., 1996; Paganini et al., 1996)***.

In the current study, there was no difference in mortality rates between patients treated with RRT and patients treated with conservative non-dialytic treatment. This result differs from those reported in previous studies which showed higher in-patient mortality rates in subjects with dialysis-requiring than the non-dialysis requiring AKI patients ***(Brivet et***

al., 1996; Liano et al., 1996; Mehta et al., 2004; Balbi et al., 2005; Lo et al., 2009). When comparing mortality rates between AKI patients who received RRT and patients who did not, one should consider two contradictory issues; firstly, the severity of AKI in dialysis requiring patients may be higher than the others. Secondly, dialysis therapy itself is usually a life rescuing manoeuver that would plausibly reduce mortality in the dialysis group. In the previous publications, the reported difference in mortality rates between dialysis versus non-dialysis patients was explained by an aggressive course of disease among the first group.

On the other hand, in the present study, as much as 29% of the mortality of the non-dialyzed patients occurred in patients who were actually dialysis requiring and yet dialysis therapy was not provided to them in view of their critical hemodynamic state. In this regard, it is noteworthy to mention that conventional hemodialysis was the only available mode of dialysis in the center wherein the present research was carried out. This relatively large fraction of patients would augment the rate of mortality in the non-dialyzed patients, although under hypothetically ideal circumstances they should have been allocated to the dialysis group, with their risk of mortality remaining high anyway.

In the present study, a more robust multivariate statistical analysis was performed to examine the multiple variables associated with mortality and their relative effect on it. Multivariate logistic regression discerned shock and sepsis as the independent variables associated with mortality among AKI patients more than the other studied variables.

Recovery is one of the most favorite targets of physicians dealing with AKI cases. Assessment of renal recovery is usually considered in most studies dealing with patients sustaining acute kidney damage. Renal

recovery is an important parameter that characterizes AKI when differentiating from CKD. Factors that improve recovery are almost always intensively sought in almost all researches confronting AKI. Nevertheless, the definition of renal recovery after an episode of AKI varied considerably in different studies. The difference in reported recovery rates in subjects who experienced AKI may actually reflect the difference in the used definitions rather than the course of the disease. Multiple previous studies considered renal recovery as dialysis independency at hospital discharge. The majority of these studies included only critically ill patients requiring dialysis. However, a significant proportion of AKI patients are not in the ICU, are not dialyzed, and may require alternate definitions for assessing renal recovery.***(Macedo et al., 2008; Khwaja, 2012)***. On the other hand, renal recovery was determined in few previous studies using the last available serum creatinine measurement. It was defined as complete if serum creatinine was equal to or lower than baseline or reference creatinine, and partial if it became lower than the creatinine at diagnosis but not down to baseline or reference. On the other hand, no-recovery was said to exist if the serum creatinine did not decrease or if the patient remained on dialysis ***(Heung et al., 2012; Mehta et al., 2016)***.

In the present study, relative improvement of serum creatinine at discharge was observed in 73% of patients with hospital stay less than one week, 44.7 % of patients with hospital stay between one to two weeks and 54% of patients with hospital stay more than 2 weeks. However, mere improvement of serum creatinine should not be viewed as definitive renal recovery because serum creatinine as a marker of GFR is defiled by many limitations. Serum creatinine is known to be secreted by the renal tubules and this secretion can be modified by pharmacological agents that are commonly used in severe illness. In addition, serum levels can be modified

by changes in volume status which often occurs especially in postoperative patients ***(Bosch, 1995)***. Another argument that defiles the validity of renal recovery in the present study is that the duration of hospital stay was not the same in all patients. Therefore, one would not be able to ascertain whether some prematurely discharged unrecovered patients would have been recovered had they stayed in hospital for a longer time under the study's observation. Despite these limitations, it was observed that age and gender were not associated with significant improvement of serum creatinine at discharge. The same finding was also reported by Lin and his colleagues in a previous published study assessing renal recovery in critically ill patients who required RRT ***(Lin et al., 2009)***.

Although it is tempting to speculate that patients already known to have CKD are less liable to benefit from recovery after an episode of AKI in view of the limited expected regeneration capacity of the diseased kidney. However, in the present study as well as in a previous study the preexisting CKD did not have a major harm on renal recovery in AKI patients ***(Bagshaw et al., 2006)***. Also, none of the associated other comorbidities (DM, HTN, CLD and CHF) was associated with lack improvement of serum creatinine at discharge in the present study. The same notion was also reported by Bagshaw and his colleague in a previous study ***(Bagshaw et al., 2006)***.

In the present study, patients with prerenal contributing factors showed a relatively more advantageous improvement of serum creatinine at discharge in comparison to the others. Similarly, patients who presented with hypotension showed the same trend; this in turn may reflect its association with the prerenal pathological categories. A parallel finding was reported by another published study ***(Magden et al., 2013)***. On the other hand, intrinsic renal pathologies were associated with lack of

recovery in patients at discharge. On more detailed analysis, patients presented with SLE or AGN were found to have worsening of serum creatinine or persistence on dialysis at the time of discharge, more frequently than patients presented differently in the current study. In harmony, other published studies reported lower rates of renal recovery after AKI due to renal parenchymatous causes ***(Bhandari & Turney, 1996; Magden et al., 2013)***.

In the present study, higher creatinine values at admission and at dialysis initiation were associated with lack of recovery.at time of discharge. In agreement with these results, Lin and his colleagues reported higher rates of recovery in AKI patients with lower serum creatinine at intensive care admission ***(Lin et al., 2009)***. Additionally, other authors reported that lower serum creatinine at the time of starting dialysis was associated with higher recovery rates in AKI patients ***(Bagshaw et al., 2006)***. This observation might reflect the fact that lower serum creatinine values at admission may indicate lower severity of the disease, while higher serum creatinine values at dialysis initiation might denote possible delay in management, at least in some cases.

In the present study, patients treated with fluid therapy were more frequent to experience improved serum creatinine at discharge, whereas those treated with diuretics or renal replacement therapy were frequent to have worsening of serum creatinine at discharge. Other previous literatures reported that the use of diuretics and fluid overload at initiation of RRT were associated with lack of renal recovery in patients with AKI ***(Mehta et al., 2002; Heung et al., 2012)***. The lack of recovery in patients treated with diuretics might reflect presence of volume overload or at least absence of prerenal pathologies that carry favorable prognosis; thus, at least good number of these cases may be attributable to intrinsic renal disease.

Having said that, it is noteworthy to mention that the definition of recovery was not unified in the previously mentioned studies. Some studies defined recovery as dialysis independency ***(Bellomo et al., 2007; Lin et al., 2009)***. Other studies determined renal recovery using the last available serum creatinine measurement ***(Mehta et al., 2002; Heung et al., 2012)***. Although the differences between the used variable definitions in these studies are not great, drawing inferences by comparing data originating by different definitions might be implausible.

Taking the aforementioned discussion points together, AKI is as common in this study as it has been reported in many previous studies. Despite initiation at higher serum creatinine concentrations, significant proportion of patients received RRT, higher than that previously published, reflecting higher severity of the CA-AKI patients of the present study. In harmony with a general consensus, dehydration is the commonest contributing factor while shock and sepsis are found to be associated with increased risk of mortality. On investigating the issue of recovery, prerenal contributing factors are significantly associated with signs suggestive of recovery. On the other hand, other factors are found to be associated with non-recovery or relatively prolonged dialysis dependency, like direct renal affliction, high serum creatinine at admission, use of diuretics, need for RRT, and late initiation of haemodialysis. However, accurate understanding of the ideal management of AKI may need individualization for each case and is still far from being completely comprehended.

Summary & Conclusions

Summary and conclusion

Acute kidney injury (AKI) is a major global health problem, which imposes a negative effect on patient morbidity and is responsible for an estimated 1.4 million deaths per year. Even though the International Society of Nephrology has set a goal of eradicating preventable deaths due to AKI by 2025, there are major challenges in this project implementation in developing countries. Major limitations hampering AKI prevention in developing countries involve inadequate resources, limited data of epidemiology and causes of AKI in developing countries, the scarce health care resources to diagnose and treat AKI, and the poor awareness of the impact of AKI on patient outcomes ***(Ponce & Balbi, 2016).***

This study evaluated 199 patients with AKI or AKI on top of CKD (mean age 56.39±16.8 years, 51.8% females) admitted in Nephrology and Dialysis Unit in Mansoura University Hospitals over one year.

In this cohort of patients, hypertension was present in 39.7 %, while DM was present in 35.7 %. CKD, chronic liver disease and chronic heart failure were also present but at lower percentages. Dehydration was the commonest precipitating factor for AKI in these patients (68.8%) followed by infection (41.7 %), NSAIDS (25.6 %), sepsis (17.6 %), use of ACEI (16.1 %), AGN (10.1 %), and urinary tract obstruction (6 %). Oliguria was a presentation symptom in 47.7 % of patients, infectious symptoms were present in 26.1 %, while other clinical symptoms as dysuria, hypotension, haematuria, and coma were also present but at lower frequencies. Eight percent of patients had serum creatinine below 2mg/dl, 30.1% between 2 and 5mg/dl, 23.6 % between 5 and 8 mg/dl, and 38.1 % above 8 mg/dl.

Regarding therapeutic modalities applied to the patients: 65.8 % received fluids, 22.6 % received diuretics and 33.7 % received renal

replacement therapy in the form of intermittent haemodialysis. About one and half percent of patients who received HD had serum creatinine below 2mg/dl, 10.4 % between 2 and 5mg/dl, 11.9% between 5 and 8 mg /dl and 76.1% above 8mg /dl.

The outcomes studied in the present research included all-cause mortality, dialytic need and improvement of serum creatinine. About 12.6% of patients died during their hospital stay; none of the associated comorbidities as DM, HTN, CKD, CHF or CLD was associated with mortality. Infection, sepsis and shock were associated with mortality, while dehydration, obstruction, SLE, use of NSAIDS, recent exposure to chemotherapy and associated organ failure were not associated with mortality. Dialysis, diuretics and fluids were not associated with mortality

In the present study, relative improvement of serum creatinine at discharge was observed in 73% of patients with hospital stay less than one week, 44.7% of patients with hospital stay between one to two weeks and 54% of patients with hospital stay more than 2 weeks. Neither age, gender nor any of the associated comorbidities were associated with significant improvement of serum creatinine at discharge, whereas, prerenal contributing factors and hypotension were associated with relative improvement of serum creatinine at discharge. On the other hand, SLE, AGN and intrinsic renal pathology were associated with worsening of serum creatinine or persistence on dialysis at the time of discharge.

Limitations of the study

Unfortunately, the current study had the following restrictive limitations:

- Unavailability of basal kidney function (basal creatinine) in large proportion of patients in the present study might have increased the susceptibility of erroneous inclusion of some chronic cases as having acute kidney injury.
- The judgment of recovery might have been defiled by two issues: firstly, renal recovery was defined using serum creatinine which is not considered an optimal marker for GFR. Secondly, the duration of hospital stay was not subjected to predefined rules, which precluded proper assessment of recovery.
- The reliance on conventional haemodialysis as the only mode of RRT in the centre wherein this study was carried out may be another limitation of the study Thus, a fraction of non-dialyzed patients could have been dialyzed if more advanced modes as CRRT or HDF were available.

In conclusion, community acquired acute kidney injury is a major health problem in our locality that is precipitated commonly by prerenal followed by intrinsic renal pathologies. It is attended by significant mortality and morbidity; that could be affected by some comorbidities and can be modifiable by proper conservative and, when needed, renal replacement therapy.

Recommendations

Recommendations of the study

- The field of AKI epidemiology, causes and outcome in EGYPT is in need for further extensive research.
- Early nephrological consultation can alleviate the prognosis in AKI patients.
- Further studies are needed that should include cases of hospital-acquired-AKI beside the cases of community acquired AKI and AKI in critical care settings, with accessibility to different modes of RRT and clearly predefined rules for discharge of cases after stabilization.
- Further research relying on long term follow up of AKI cases is desirable to examine the long-term outcomes regarding future development of CKD and ESRD following an episode of AKI
- Collaborative efforts should be implemented in order to raise the awareness of AKI and how to avoid its preventable precipitating factors. This is expected to result in decreasing the heavy burden of AKI problem in Egypt
- It is mandatory that the management of AKI patients be individualized regarding the choice of either conservative or dialytic therapy.
- There should be consensus on optimal timing for starting renal replacement therapy that suits the socioeconomic capacity of our locality.

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Arabic Summary

الملخص العربي

تعد إصابة الكلى الحادة مشكلة صحية كبيرة على مستوى العالم، والتي تفرض أثرا سلبيا على الحالة المرضية للمرضي ; كما أنها مسؤولة عما يقدر ب ١,٤مليون حالة وفاة سنويا ورغم أن الجمعية الدولية لأمراض الكلى وضعت هدفا للقضاء على الوفيات التي يمكن الوقاية منها بسبب إصابة الكلى الحاد بحلول عام ٢٠٢٥، الا ان هناك تحديات كبيرة في تنفيذ هذا المشروع في البلدان النامية. وتشتمل القيود الرئيسية التي تعرقل الوقاية من الإصابات الكلوية الحادة في البلدان النامية عدم كفاية الموارد، ومحدودية البيانات الخاصة بانتشار ومسببات الإصابة الكلوية الحادة، اضافة الى نقص موارد الرعاية الصحية لتشخيص وعلاج إصابات الكلى الحادة، وكذلك نقص التوعية بأثر إصابة الكلى الحادة على مصائرالمرضى.

لقد قيمت هذه الدراسة ١٩٩ مريضاً مصابين بإصابات كلوية حادة أو تدهور حاد لمرض الكلى المزمن في وحدة أمراض الكلى والغسيل الكلوي في مستشفيات جامعة المنصورة على مدى عام كامل.

وقد صاحب اصابة الكلي الحادة ارتفاع ضغط الدم في ٣٩,٧٪ من المرضي، وُوجد داء البول السكري في ٣٥,٧٪. منهم بينما كانت أمراض الكلى المزمنة، وأمراض الكبد المزمنة وفشل القلب المزمن موجودة أيضا ولكن بنسب مئوية أقل. وكان الجفاف هو العامل الأكثر تأثيراً للإصابة الكلوية الحادة لدى هؤلاء المرضى (٦٨,٨%)، ثم العدوى (٤١,٧٪)، والعقاقير المضادة للالتهاب غير الستيرويدية (٢٥,٦٪)، وتسمم الدم (١٧,٦٪)، واستخدام مثبطات إنزيم تحويل الأنجيوتنسين (١٦,١٪)، والتهاب كبيبات الكلى الحاد (١٠,١٪)، واخيرا انسداد المسالك البولية (٦٪).

وكان قلة البول هو العرض الأكثر شيوعا لدي المرضي يليه الأعراض الدالة علي وجود عدوي بالجسم، في حين كانت الأعراض السريرية الأخرى كعسر البول، انخفاض ضغط الدم، بول دموي، والغيبوبة موجودة أيضا ولكن في عدد اقل من المرضي.

وكان مستوي الكرياتينين في الدم أقل من ٢mg / دل في ثمانية في المئة من المرضى، بين ٢ و٥ مغ / دل في ٣٠,١٪، بين ٥ و٨ملغ / دل في ٢٣,٦%، وفوق ٨ ملغ / دل.في ٣٨,١٪. وفيما يتعلق بالطرق العلاجية المطبقة على المرضى: تلقى ٦٥,٨٪ من المرضي السوائل، و٢٢,٦% تلقوا مدرات البول، و٣٣,٧٪ تلقوا العلاجات البديلة عن الكلى في شكل غسيل الكلى المتقطع. ولقد كان مستوي الكرياتينين أقل من ٢mg / دل في حوالي واحد ونصف في المئة من المرضى الذين تلقوا غسيل الكلى، بين ٢ و٥ مغ / دل في ١٠,٤٪ بين ٥و ٨ مغ / دل في ١١,٩٪ وفوق ٨mg / دل في. ٧٦,١٪ .

شملت النتائج التي تمت دراستها في هذا البحث الوفيات الناجمة عن كل الأسباب، والحاجة الملحة للاستصفاء الكلوي وتحسن مستوي الكرياتينين في الدم. توفي حوالي ١٢,٦٪ من المرضى أثناء إقامتهم في المستشفى؛ فى حين لم ترتبط أي من الأمراض المصاحبة لإصابة الكلي الحادة مثل مرض السكري، وارتفاع ضغط الدم، وأمراض الكلى المزمنة، وفشل القلب الاحتقاني أو مرض الكبد المزمن مع تلك الوفيات. ولقد ارتبطت العدوى وتسمم الدم والصدمة بحدوث الوفاة، في حين أن الجفاف، وانسداد المسالك البولية، ومرض الذئبة الحمراء، واستخدام العقاقير غير الستيرويدية المضادة للالتهابات، والتعرض القريب للعلاج الكيماوي وفشل الاعضاء المتعدد لم تكن مرتبطة مع هذه الوفيات. كذلك لم يرتبط غسيل الكلى ومدرات البول والسوائل بحدوث الوفيات.

في هذه الدراسة، لوحظ تحسن نسبي في مستوي الكرياتينين في الدم في ٧٣٪ من المرضى الذين أقاموا في المستشفى لمدة لا تتجاوز أسبوع واحد و٤٤,٧٪ من المرضى الذين أقاموا في المستشفى بين أسبوع لأسبوعين و٥٤٪ من المرضى الذين أقاموا في المستشفى أكثر من اسبوعين. ولم يوجد ارتباط لأي من العمر أو الجنس أو أي من الأمراض المصاحبة مع تحسن كبير في الكرياتينين في الدم وقت خروج المرضي. في حين ارتبط انخفاض ضغط الدم والعوامل المساهمة ما قبل الكلوية مع التحسن النسبي للكرياتينين في الدم وقت خروج المرضى، ومن الناحية الاخرى ارتبط مرض الذئبة الحمراء، والتهاب كبيبات الكلى الحاد وامراض الكلى الذاتية مع تدهور مستوي الكرياتينين في الدم أو استمرار احتياج المريض للاستصفاء الكلوي.

ومما يؤسف له أن الدراسة الحالية قد عانت من بعض العيوب التالية: • عدم توفر تحاليل وظائف الكلى المبدئية (الكرياتينين المبدئى) في نسبة كبيرة من المرضى في هذه الدراسة مما قد يزيد من قابلية الإدراج الخاطيء لبعض الحالات المزمنة على انها إصابات حادة في الكلى

• قد يكون الحكم بشفاء المرضي يشوبه بعض القصور: أولا، تم تعريف االشفاء الكلوي باستخدام مستوي الكرياتينين في الدم والذي لا يعتبر المقياس الأمثل لمعدل الترشيح لكبيبات الكلى. وثانيا، لم تخضع مدة الإقامة في المستشفى لقواعد محددة سلفا مما حال دون إجراء تقييم سليم لتحسن المرضي.

• الاعتماد على غسيل الكلى التقليدي باعتباره الوسيلة الوحيدة المتاحة في المركز الذي أجريت فيه هذه الدراسة.

في الختام، إصابة الكلى الحاد هي مشكلة صحية رئيسية في منطقتنا تنتج بشكل رئيسي عن العوامل ما قبل الكلوية يتبعها امراض الكلى الذاتية. ويحضر ذلك حدوث تفاقم كبير في اعداد الوفيات والمرضى؛ التي يمكن أن تتأثر ببعض الأمراض المصاحبة والتي يمكن أن تكون قابلة للتعديل عن طريق العلاج التحفظي او العلاجات البديلة عن الكلى.

الملخص العربي

جامعة المنصورة
كلية الطب
قسم امراض الباطنة

مرضي القصور الكلوي الحاد المترددين لأول مرة على وحدة الكلي بمستشفى المنصورة الجامعي: دراسة وصفية لمدة عام

رسالة مقدمة من

شروق صلاح الدين النجار

طبيب مقيم أمراض باطنة

توطئة للحصول على درجة الماجستير في الباطنة العامة

المشرفون

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