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Emergencies in Nephrology - Renal Dysfunction a Sufficient Mortality Predictor?

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Introduction

Nowadays, even if a large number of diagnostic and laboratory tools are available for the benefit of patients long-term outcome, there are still many burden questions regarding the proper use of commonly known biomarkers and treatment strategies to avoid life-threatening complications in chronic kidney disease (CKD) patients.

The present review represents a short survey of the most frequent nephrology emergencies in daily practice and to make a statement of under-recognized diagnostic errors [1,2].

The renal function impairment is worldwide known to represent a pathological status often associated with a high prevalence of various major conditions with high risk of mortality: cardiovascular diseases (including acute ischemic stroke, sudden cardiac death) [3], neoplasia [4], diabetes [5-7], infections [8], hepatorenal syndrome[9-11]. Besides, to the traditional risk factors (e.g.: age, proteinuria, hypertension, diabetes, dyslipidemia, obesity and smoking), in the last decade, a new contributing factor in CKD progression has emerged: the periodontal disease [12]. Of course, other important problems are represented by different devastating complications of end-stage renal disease (ESRD), the type of renal replacement therapy and the right moment it should be performed.

Cardiovascular Complications

Cardiovascular (CV) diseases represent a common condition associated with CKD patients and several studies emphasized the clear correlation between renal dysfunction and development of ischemic stroke [13-16], myocardial infarction or heart failure [17-20]. Additionally, several reports showed that increased mortality incidence after acute ischemic stroke is linked to C-reactive protein (CRP) values, glucose levels, fibrinogen concentration, erythrocyte sedimentation rate, leukocyte count, uric acid and a low tri-iodothyronine rate on admission [16, 21-24]. Furthermore, other published researches noticed that a low serum creatinine concentration among patients on admission represented an independently predicted mortality tool [16,25,26].

Tsagalis et al. [16], in their study emphasized that even 10 years after ischemic stroke, kidney function on admission represents a powerful independent prognostic factor for mortality and cardiovascular morbidity. By measuring the glomerular filtration rate (GFR), they identified an important prevalence of kidney impairment in early admitted patients with acute stroke (<24 h). These findings could be explained by shared pathophysiological mechanisms involved in the development of renal, coronary and cerebral vessels atherosclerosis [16, 27] and also by a close correlation between renal function impairment and stroke caused by small vessel diseases [16, 28-31]. All these findings emphasize the importance of using GFR estimation formulas as routine laboratory tests in this group of patients, on admission day [32]. In addition, many studies showed the importance of using commonly laboratory tests on admission as sufficient death predictor markers [33-39], because high mortality was associated with important water-electrolyte imbalance and sever uremic status [40,41].

For this reason, in 1999, the Modification of Diet in Renal Disease (MDRD) formula appeared as an attempt to a better estimation of GFR [42]. Even if in the beginning, it was used in young stable CKD subjects, in time it had been validated in a variety of patients [43-46]. The formula uses six variables: age, race, gender, creatinine, urea and albumin, important factors in determining a thoroughly measure of GFR individual patient [47].

Chin et al. [47] study showed that an admission MDRD value below 60, increased death risk within 30-day death, considering that MDRD formula could be also used as mortality predictor. The same conclusion was reached in a previous study that observed a 10% increased death risk at every 10 mL/min/1.73m^2 decrease of GFR evaluated by MDRD [19].

Although MDRD formula represents a useful tool to predict death in ischemic stroke patients [48] and even in peripheral vascular disease patients [49], it cannot be usefully applied in patients with close to normal GFR (>60 mL/min/1.73m^2) [50]. For this reason a more refined equation was developed: Chronic Kidney Disease–Epidemiology Collaboration equation [51].

Sudden cardiac death (SCD) is another important CV complication in dialysed patients and it is associated to low survival rate in this group of patients [52,53]. Its pathophysiological mechanism is poorly understood and is considered to depend on various factors [54-57], such as: diabetes, hypertension, severe uremic condition and bone mineral imbalance [58-61].

Because several studies noticed that an increased α and β sympathetic activity – associated with myocardial fibrosis – develops a severe ventricle dysfunction in CKD patients [62-67], β-blockers therapy was proposed to prevent SCD, especially in patients with ischemic heart disease (IHD) [68]. A recent research provided useful information regarding this treatment strategy and concluded that β-blockers do not appear to be associated with SCD beneficial effects in dialysed patients without IHD, but may be associated with lower risk of SCD in those with preexisting IHD [69].

Another CV complication in daily practice is acute decompensated heart failure (ADHF) with the following clinical features: dyspnea, weight gain, jugular venous distension, lower-limbs and pulmonary edema [70]. Although the current guidelines recommendations point out the use of diuretics as primary-line treatment [71], they have been associated with high rates of mortality [72-74], renal dysfunction and heart failure progression [75-78].

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For this reason, in the last decade, extracorporeal ultrafiltration has been used in diuretic-resistant heart failure patients [79-89] with successful results [90,91].

Because there is a clear association between cardiac and kidney failure, a new term has been developed for a better understanding of the pathophysiological interactions between these two conditions: Cardiorenal Syndrome [92]. It is considered to be a cardiac and renal dysfunction or the dysfunction in one organ may induce the impairment of the other organ, and it includes the following subtypes: acute cardiorenal syndrome (type 1), chronic cardiorenal syndrome (type 2), acute renocardiac syndrome (type 3), chronic renocardiac syndrome (type 4), secondary cardiorenal syndrome (type 5) [93]. The next figure (Figure 1) briefly presents the potential causes (insufficient understood) responsible for the cardiorenal syndrome [94].

Some recent data have reported that venous congestion and intra-abdominal hypertension could play an important role in cardiorenal syndrome genesis [95-98].

Freda et al study [99] proposed a list of advantages and disadvantages of using ultrafiltration for the benefit of ADHF patients (Table 1).

Even if all evidence reported favorable results regarding the use of ultrafiltration, there is still a selection and treatment protocol problem.

Another important group of patients is represented by those who underwent cardiac surgery with cardiopulmonary bypass (CPB) and consequently developed severe renal injury (~2% of patients and 60% mortality risk) [100,101]. An increase of serum creatinine above 25% to the normal-baseline was noticed to be linked to double mortality cases up to 10 years after the procedure [102].

Furthermore, new available data have shown that changes of serum creatinine values before and after surgery are associated with mortality risk and acute kidney injury (AKI) [103-105].

The same conclusion was presented in Ho et al. study [106], which revealed that a small increase in serum creatinine level (measured immediately after surgery) significantly improved prediction of AKI for this group of patients.

For the benefit of CKD patients associating or not CV diseases, recent evidence suggested the importance of high fiber diet [107], which was correlated to lower values of inflammation markers [107,108,109] and decreased mortality rate [107,110,111].

Hepatorenal Syndrome

Hepatorenal syndrome (HRS) (type 1 and 2), a devastating complication of liver cirrhosis, is accompanied by acute kidney failure and portal hypertension, and has high rate of mortality [112-114].

For this reason, many therapeutic strategies have been proposed and several systemic vasoconstrictors have been tested [115,116]. In Europe, terlipressin, a vasopressin receptor agonist, has been widely used [117], but in the largest randomized controlled trial, it failed to show effective benefits [118].

Recent reports noticed that an elevated mean arterial pressure (MAP) induced by terlipressin could have a higher probability in recovering renal function with encouraging results [119,120].

In addition, to support the new evidence, Velez et al. [121] observed a clear association between increased MAP in HRS patients and their therapeutic response. The study, also, emphasized that the improvement of kidney function was closely correlated with the magnitude of MAP elevation [121]. Considering that mammalian kidney starts losing its blood flow autoregulation below 75-80 mm Hg [122], the same research hypothesized that renal perfusion is optimized when MAP increases to approximately 80 mm Hg. However, there are a few studies, which failed to observe this correlation between systemic hemodynamics amelioration and HRS improvement [123-130]. Nevertheless, vasoconstriction therapy remains a useful treatment approach to the benefit of HRS patients.

Infections Complications

CKD is usually strongly associated with the risk of all-cause hospitalization [131]. This risk increases with 10%-50% in stage 3 CKD patients and with 110% for CKD stage 4 [131].

In addition, abnormal immune cell function is a common clinical complication of end-stage kidney disease, and it is proved by high rates of infection and infection-related death [132-134].

For this reason, different studies tried to determine the existence of a specific biological marker that prevents future infection complications. It was established that serum cystatin C could estimate more accurately adverse outcomes correlated with CKD compared with serum creatinine [135,136] and the conclusion was that even a mild renal dysfunction could be linked to higher infection risk (pulmonary, gastrointestinal, genitourinary, septicemia, soft tissue) [135,136].

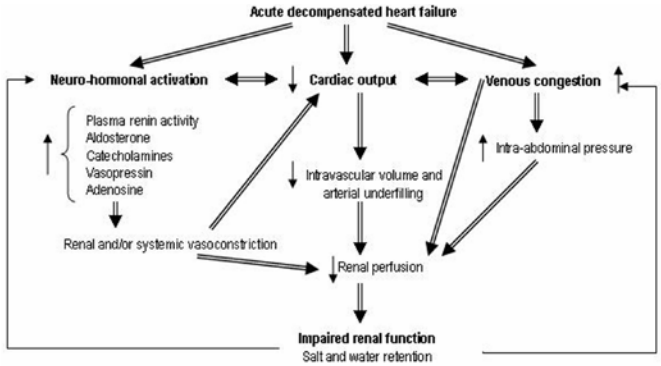

Figure 1: Potential causes for cardiorenal syndrome.

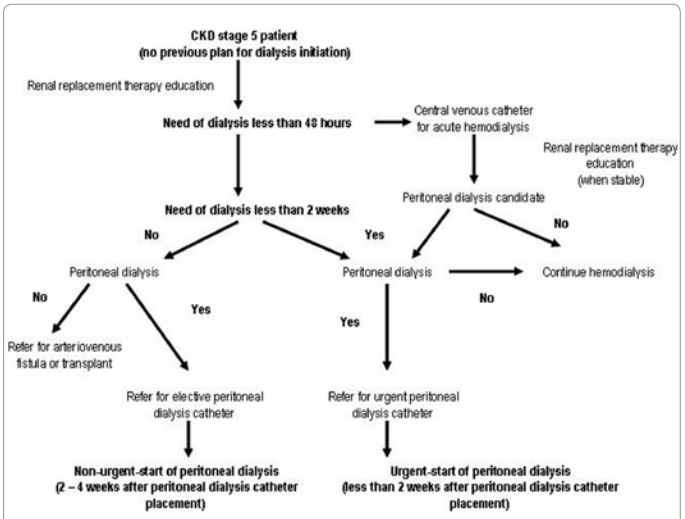

Figure 2: Urgent-start PD algorithm.

	Advantages	Disadvantages
Diuretics	symptomatic control of extracellular fluid volume overload decrease cardiac filling pressures	electrolyte disturbances possible association with mortality risk intravascular volume depletion ototoxicity neuro-hormonal activation ineffective in patients with diuretic resistance decreased kidney function.
Ultrafiltration	decreased re-hospitalization rate more sodium removal than diuretic controlled removal of volume avoidance of electrolyte disturbances effective in patients with diuretic resistance	systemic anticoagulation recommended vascular access related complications intravascular volume depletion decreased kidney function costs

Table 1: Theoretical advantages and disadvantages of diuretic and ultra filtration in ADHF treatment.

Except for common infection complications in CKD patients, recent evidence suggested a strong correlation between periodontal disease and CKD progression [137]. Periodontal disease, a chronic bacterial infection resulting in inflammatory damage of connective tissue and teeth bone [138], presents elevated levels of interleukin 1 (IL-1), IL-6, and tumor necrosis factor [139,140]. These proinflammatory immune mediators could enter the systemic circulation and produce distant organ dysfunction [140]. Furthermore, this could be a plausible explanation of renal function impairment in patients, to whom all traditional cardiovascular disease and CKD risk factors were previously adjusted [141,142].

Renal Replacement Therapy Approach

When dealing with a patient with poor renal function who could, in addition, associate different comorbidities, a difficult question arises: 'To initiate or not dialysis and which type of renal replacement therapy (RRT) should be approached for an immediately favorable outcome?'. Furthermore, it is possible that dialysis procedure itself or vascular access may contribute to a poor outcome due to adverse cardiac effects, vascular access related complications and accelerated loss of residual kidney function. In addition, in case of aged patients more other questions regarding the right treatment strategy should be taken into account.

There are studies that suggested that early dialysis initiation or starting RRT in long-term care facilities patients are associated with poor survival rate and deteriorated quality of life [143,144]. A number of reports noticed that CKD severity could be overdiagnosed in elderly patients due to an improper eGFR measurement, leading to unrequired RRT initiation [145].

Recent data have shown that elderly patients with associated comorbidities could be managed using conservative management protocols without dialysis and better outcomes [146-153].

Considering all this, Renal Physicians Association clinical practice guidelines recommended to assess the balance of the benefit versus the burdens of dialysis for each individual [154], because an earlier initiation of RRT in the elderly may accelerate loss of residual kidney function.

Another burden problem is whether starting hemodialysis (HD) or peritoneal dialysis (PD) in acute emergency cases. There are several reports that conclude there is a high rate of patients without a plan at the time of RRT initiation (up to 80%) who start dialysis therapy with a central venous catheter (CVC) [155] and consequently, there is a significant prevalence of CVC related complications [156-158]. Furthermore, there are studies suggesting that, in the first 90 days since RRT has been initiated, the high rate of using CVC in new dialysate patients is an important risk factor of high mortality [159-163].

Considering these important facts, Ghaffari [164] proposed a new RRT protocol for cases that could be initiated as urgent-start PD (Figure 2).

His innovative algorithm was sustained by various reports that observed an early survival benefit for PD patients versus HD individuals in the first 2 years, with similar prognostic even after 5 years [165-169].

Conclusion

To sum up, there is a worldwide increasing interest in using laboratory data as predictors not only of CKD evolution, but also as mortality predictors. This new concept was extrapolated from the fact that virtually all patients admitted with an acute medical condition underwent renal function tests that are easily to be accessed and interpreted. In this manner, a simultaneous multidisciplinary approach can be performed to the patients' benefit.

In addition, the use of laboratory findings as possible mortality risk predictors could also improve the standards of the diagnostic test accuracy in establishing a correct medical diagnosis, supported by clinical and laboratory features.

Probably the answer to the question: 'Renal dysfunction a sufficient mortality predictor?' could be affirmative, considering the large number of evidence that suggest a clear correlation between kidney function impairment and high rate of mortality in patients associating or not different pathological conditions.

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