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Case Report

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# Cardio-Pulmonary-Renal Interaction (CPRI) - A Syndrome of Death

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**ABSTRACT**

Two deaths due to renal failure in the last 2 month led me to a review the current, state-of-the-art understanding of cardio-pulmonary-renal interactions and their related pathophysiology, perpetuating nature, and cycles of increased susceptibility and reciprocal progression. It indicates that Organ injury is the consequence of maladaptive neurohormonal activation, oxidative stress, abnormal immune cell signalling, and a host of other mechanisms that precipitate adverse functional and structural changes. This syndrome has many complex physiologic, biochemical, and hormonal abnormalities and its pathophysiology is not fully understood. The possible mechanisms include reduced kidney perfusion due to decreased forward flow, increased right ventricular and venous pressure, and neurohormonal adaptations. Assessment of biomarkers are valuable clinical strategies to screen and detect disease, assist in diagnosis, assess prognosis, and predict recovery or progression to chronic disease or even death. Reduced kidney function is associated with increased mortality in such patients.

Treatment options include inotropic medications; diuretics; ultrafiltration; and medications, such as β-blockers, inhibitors of the renin-angiotensin-aldosterone system, and more novel treatments. Recent observational studies suggest that treatments that result in a decrease in venous pressure and lead to haemoconcentration may be associated with improved outcomes.

I report here a male and female case who succumbed to Cardiac failure following renal failure in the last 2 months.

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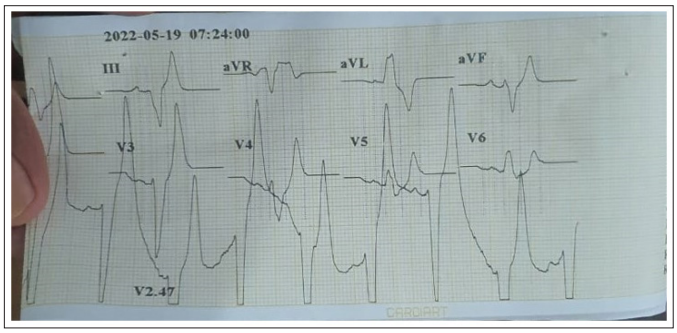
**Keywords:** ACS Acute coronary syndrome (ACS); acute heart failure (AHF); acute kidney injury (AKI); chronic kidney disease (CKD); cardiorenal syndrome (CRS); Cardio-pulmonary-Renal syndrome (CPRI) heart failure (HF); and left ventricular hypertrophy (LVH)

## Case Report 1

Our male patient is a 65-year-old man with known diabetes and hypertension for over 20 years. He was on a pilgrimage to Prayag, Uttar Pradesh was forced to be readmitted to a private hospital with the complaints of giddiness, breathless etc. by the tour operators. His medical history was significant for uncontrolled diabetes, severe hyperlipidaemia not treated and CKD with a baseline creatinine level of 3.5–5 mg/dl. Key laboratory investigations included i) Procalcitonin-7.39ng/ml indicative of high risk of progressing to severe systemic infections as against a referral range of <0.1ng/ml ii) TLC of19850 against a range of 4-11,000iii) Serum Urea-205mg/dl ,iv) serum creatinine 12.17 mg/dl, v) Serum Potassium 6.58 meg/l vi serum Calcium-8.3mg/ vii) Serum Uric acid-16.8mg/Dl viii) Serum Cholesterol 66.6/mg/dl, HDL-18.2mg/dl, LDL-22.02/dl and ix) Hb%-11.2 and x) Serum Troponin 2074.2ng/L as against an upper limit of 19 ng/L upper reference limit for 99 percentile . Repat tests after 6 hours showed worrisome situation indicating Myocardial Infarction. While systolic BP was stable the diastolic BP showed a bit of improvement up to 72 till 3 Am on 20/5 and started going down to around 40 mm of Hg and he finally was declared dead around 1000 hrs on 21/5 there after both systolic and diastolic BP and he died around 2200 hrs on 21 /5/ 22. Urinary output had gone below 100ml in 3 hours and though Physician was recommending Dialysis the general condition and BP did not allow the same. He was put on ventilator throughout the hospital stay. The medications included furosemide, 60 mg in the morning and 40 mg in the evening; carvedilol, 12.5 mg twice daily; hydrochlorothiazide, 25 mg daily; digoxin, 0.125 mg daily; aspirin, 75 mg daily; and warfarin, 3 mg daily.

Echocardiography on admission had showed BP as 85/50 and pulse rate122/minute at 2200hrs on 19/5/2022. It showed an evidence of complete left Bundle Branch block (aVL, V6) and Sinus Rhythm an ejection fraction of 25% with moderate to severe global hypokinesis of the left ventricle. The right ventricle was normal in size, with normal thickness, and systolic function was mildly reduced. The left atrium was mildly dilated, and the right atrial size was normal.




## Case Report 2

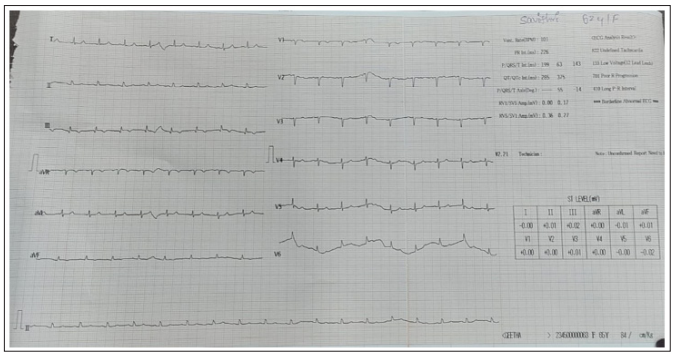
Our female patient was a 62-year-old retired Auxiliary Nurse midwife admitted on 30/03/22 to a private nursing home, with complaints of vomiting of 3 episodes, general weakness and breathlessness and loss of appetite for 3 days. Her past medical history revealed that she was diabetic for over 5 years and had a combination of surgical, chemo, radiation, and hormone therapy for breast cancer since 2018 and had 3 episodes of pleural effusion secondary to Cancer since 2020 and tapping of fluid is done for 3 occasions earlier.

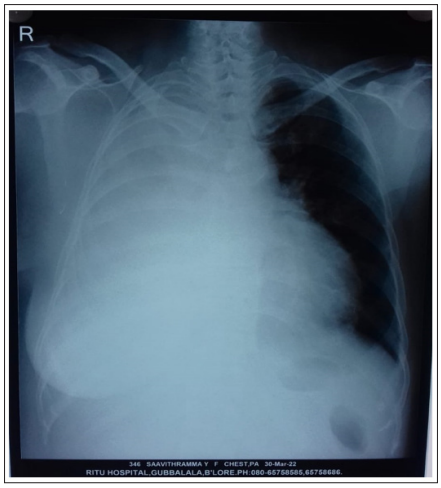
On examination, she was oriented, but dehydrated ad GRBS was 133mg/Dl CVS showed S1 and S2, Bilateral AE +CNS and per abdomen examination was normal. Her RR was 24/minutes, SPO2-95% on RA, pulse –826/min and BP=110/70. Normal temperature.

LFT parameters were all in normal ranges, Blood Urea=73mg/ dl against a referral range of 15-45mg/dl and Serum Creatinine was 1.7 (against 0.7-1.3), Sodium was 122 (113-145), Potassium=6.3 (3.5-5.5) and Choride-94 (95-110). WBC count was 13400 (4K-11K), Hb%-8G/dl (11.5-15), Platelets count was 2, 21,000 (150000-450000)

High frequency USG chest showed: Fluid in the Right pleural cavity about1200-1880 CC, along with some echogenic debris. Some clear fluid was seen left pleural cavity about 300-500 CC, suggestive of Bilateral pleural effusion due to Cancer secondaries.

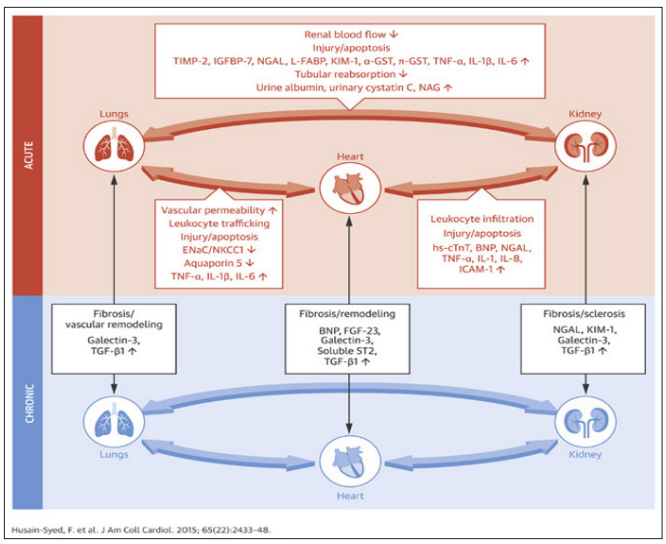
She was put on IV fluids and Pan-40 (antacid), Inj. Emeset an antiemetic and USG guided Thoracentesis. Done and maleroth tube was inserted and pleural effusion fluid withdrawn twice every day. Was shifted to oral feeding next day. On 31 /03 Blood urea came down to 49 and creatinine to 1.4 and Sodium to 126, on 2/4/22 Blood Urea reduced further to 58, creatinine e-1.5, Sodium -123 and Potassium-6.1. However, on 4/4 her urine output came down badly and BP was low enough not permitting for Dialysis and finally she died around 0300 AM of 5/4/22 due Cardiac arrest.






## Discussion

Of late we are seeing complicated courses of hospitalization and the high mortality of patients with involvement of all 3 organs, needing an integrative approach to manage even at the specialist level. The current management by the general physicians/internal medicine, seeking consultations of respective super-specialists appears to failure and higher case fatalities even in metropolitan cities. The sequence of organ involvement varies depending on the acuity and nature of the underlying disorder. The interdependence mechanisms involved in the heart, lung, and kidney crosstalk, requires a descriptive classification of a syndrome, that may represent a framework for exploring epidemiology, pathophysiology, detection, and management. Majority of the patients I have seen dying in last 5 years with disorders of 1 organ (e.g., Diabetes with hypertension) die of complications of the other (e.g., Acute kidney failure) before the first organ's failure reaches its fullest extent. I assume that each dysfunctional organ can initiate and perpetuate mutual injury via hemodynamic, neurohormonal, and cell signalling feedback mechanisms. Multiple episodes of acute (on chronic) decompensation may lead to reciprocal end-organ disease progression. The multiple contributing factors and the time sequence of events in cardio-pulmonary-renal interactions (CPRI), pose challenges in identify the underlying pathophysiological mechanisms and develop a strategy for diagnostic and therapeutic intervention.




The lung is a highly immunologic organ, representing a gateway to the environment and it has critical pathophysiological connections to the failing heart and kidney.

In our second case due to Pleural effusion the gas exchange via 3 mechanisms: ventilation, diffusion, and perfusion got affected and led hyperventilation, greater oxygen extraction from blood by the tissues, and increased cardiac output, depending on the organ's functional reserve. Changes to the alveolar-capillary barrier induced an inflammatory cascade and oxidative stress of the pulmonary microcirculation, which results in cycles of alveolar wall injury predisposing and/or aggravating lung injury. The subclinical lung injury due to previous episodes of pleural effusion due toe secondaries of the breast cancer led to respiratory failure event.

In our recent (first) case circulating factors were implicated in the pathogenesis of pulmonary inflammation following renal injury. In ischemic AKI, pulmonary vascular permeability, cellular apoptosis, alveolar haemorrhage, and leukocyte trafficking due to the production and/or decreased clearance of mediators of lung injury increase. Pro-inflammatory cytokines produced by renal tubular cells as well as white blood cells include TNF-α and IL-1β and -6. Delayed recovery of kidney function may impair resolution of Cardiac injury. Mechanical ventilation increased intrathoracic pressure and produced adverse hemodynamic effects, compressing pulmonary vasculature, which resulted in increased right ventricular afterload and diminished cardiac output, leading to hypotension and fluid-responsive shock, and not allowing Dialysis. This scenario is commonly seen in the initial post-intubated period especially among person with diabetes and hypertension. The severest form of lung injury is acute respiratory distress syndrome (ARDS). It is defined as the onset of lung failure within 1 week of the onset of illness, and it is characterized by hypoxemia in the presence of bilateral infiltrates on the chest x-ray that cannot be explained by HF or fluid overload.

Cardiovascular diseases remain the major cause for hospitalization, disability, and mortality worldwide. Among those, Heart Failure (HF) is a pivotal and progressive condition that leads to a cascade sequence of interorgan crosstalk, including lung and kidney. HF is a heterogeneous group of syndromes leading to structural and functional alterations of myocardium.

During Acute Kidney Infections (AKI), the renal tubular epithelium responsible for regulation of inflammatory processes, is a major site of cell injury and death, catalysing circulating mediators in local and systemic inflammation by different mechanisms including epigenetic processes. Chronic Kidney Diseases (CKDs) accelerates coronary artery atherosclerosis, hypertension, dyslipidaemia, and abnormal calcium/phosphorus metabolism, associated with vascular remodelling and development of noncompliant vessels.

The normal heart, lung, and kidney permit a degree of physiological reserve that can maintain normal organ function for any given insult. Cardiac functional reserve is the ability of the myocardium to augment its cardiac output and tissue delivery of oxygen during stress of either diastolic dysfunction or overt systolic dysfunction. Pulmonary functional reserve is the ability of the lung to augment its respiratory minute volume during stress. The breathing reserve, expressed as the difference between the maximal voluntary ventilation and the maximum exercise ventilation. Similarly, the renal functional reserve represents the capacity of intact nephron mass to increase Glomerular Filtration Rate (GFR) in response to stress, indicating the difference between peak "stress" GFR induced by protein load (oral or intravenous) and the baseline GFR. The use of both functional (creatinine, cystatin C, Serum Sodium, Potassium, Calcium) filtration markers as well as renal tubular injury markers (TIMP-2, IGFBP-7, NGAL, etc) to both screen and detect AKI as well as to aid in the prognosis for important outcomes, including the need for dialysis and mortality are currently in use. But low Blood pressure did not allow for subjecting our patients for dialysis and making way for kidney transplantation leading to death

A population-based survey of Delhi and Chennai, India estimated overall, and age-, sex-, city-, and diabetes-specific prevalence of CKD. Of 12,271 participants, 80% had complete data on serum creatinine and albuminuria. The prevalence of CKD and albuminuria were 8.7% (95% confidence interval: 7.9 to 9.4%) and 7.1% (6.4 to 7.7%) respectively. Nearly 80% of patients with CKD had an abnormally high haemoglobin A1C (5.7 and above). Based on Kidney Disease Improving Global Outcomes guidelines, 6.0, 1.0, and 0.5% of study participants were at moderate, high, or very high risk for experiencing CKD-associated adverse outcomes. Thus, one in 12 persons living cities have evidence of CKD, with features that put them at high risk for adverse outcomes [1].

Prevalence of obesity, cardiovascular disease and type 2 diabetes mellitus is rising rapidly, and Prevalence of chronic kidney disease (CKD) is rising in parallel in India but have been infrequently studied and data on the burden of CKD in India remain scarce. Chronic kidney disease prevalence among participants with diabetes mellitus was 15.4%, substantially higher than that of participants without diabetes. Myocardial dysfunction leading to elevated left ventricular filling pressure and pulmonary venous hypertension is the predominant cause of PH in CKD. We know that CKD is associated with a two- to four-fold increase in the risk of death from cardiovascular causes, for patients who progress to end-stage renal disease, enormous economic costs, and early mortality [1]. Both of our cases spent nearly 7000 US$ in less than a week's hospitalization and finally succumbed.

**Creatinine Blood Test**

Creatinine is a waste product that forms when creatine, which is found in muscle, breaks down. Creatinine levels in the blood can provide your doctor with information about how well your kidneys are working. Each kidney has millions of small blood-filtering units called nephrons. The nephrons constantly filter blood through a very tiny cluster of blood vessels known as glomeruli. These structures filter waste products, excess water, and other impurities out of the blood. The toxins are stored in the bladder and then removed during urination. High levels of creatinine may indicate that your kidney is damaged and not working properly.

| Particulars | Normal | Risk | High risk |
|---|---|---|---|
| Creatinine level in men | 0.9 - 1.3 mg/dL | 2 - 4 | Above 4.5 |
| Creatinine level in women | 0.6 - 1.1 mg/dL | 2 - 4 | Above 4.5 |

Creatinine blood tests are usually performed along with several other laboratory tests, including a blood urea nitrogen (BUN) test and a basic metabolic panel (BMP) or comprehensive metabolic panel (CMP). A creatinine blood test to assess creatinine levels for signs of kidney disease. symptoms include fatigue and trouble sleeping, a loss of appetite, swelling in the face, wrists, ankles, or abdomen, lower back pain near the kidneys, changes in urine output and frequency, high blood pressure, nausea, and vomiting, as our both cases presented

Creatinine is measured in milligrams per decilitre of blood (mg/dL). In general, normal creatinine levels range from 0.9 to 1.3 mg/dL in men and 0.6 to 1.1 mg/dL in women who are 18 to 60

years old. Normal levels are roughly the same for people over 60. Levels of 2-4 indicate risk of kidney failure and that of over 4.5 indicate very high risk [2-4].

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