# Acute kidney injury and distant organ dysfunction–network system analysis



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**Acute kidney injury (AKI) occurs in about half of critically ill patients and is associated with high in-hospital mortality, increased long-term mortality postdischarge, and subsequent progression to chronic kidney disease. Numerous clinical studies have shown that AKI is often complicated by dysfunction of distant organs, which is a cause of the high mortality incidence associated with AKI. Experimental studies have elucidated many mechanisms of AKI-induced distant organ injury, which include inflammatory cytokines, oxidative stress, and immune responses. This review provides an update on evidence of organ crosstalk and potential therapeutics for AKI-induced organ injuries, and presents the new concept of a systemic organ network that balances homeostasis and involves multi-organ crosstalk beyond that of the kidney with a single distant organ.**

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Acute kidney injury (AKI) occurs in about half of critically ill patients, with high in-hospital mortality and morbidity.[1–3] AKI survivors still have increased risk of postdischarge mortality,[4–8] progression of proteinuria, and chronic kidney disease (CKD).[9–13] Although the mechanisms by which AKI leads to death, even when dialysis is available, remain incompletely understood, distant organ injury is considered an important cause, given that dysfunction of multiple organs is often observed in AKI patients, and that the number of injured organs is correlated with mortality.[14,15] AKI patients requiring intensive care and kidney replacement therapy still have a considerably higher mortality rate than patients with CKD stage 5D,[16] indicating that other factors rather than kidney dysfunction contribute to poor prognosis. These findings support the premise that AKI-induced distant organ dysfunction plays an important role in critically ill patients. To date, many studies have elucidated the mechanism by which AKI induces injury and dysfunction in distant organs, including the brain, heart, lung, liver, intestine, and spleen. These mechanisms include inflammatory cytokines, oxidative stress, and immune cell responses.

Previous reviews on this topic have heightened awareness and stimulated research regarding this important problem[17,18] More recently, mounting clinical and basic data in this field have led to identification of novel mechanisms; the current review provides an update on this work.

## Kidney–lung interactions

Respiratory complications are common in AKI patients. In a prospective observational study conducted in 18 French intensive care units, AKI developed more frequently in patients with acute respiratory distress syndrome (44%), compared with patients without this syndrome (27%).[19] This study also found that the combination of AKI with acute respiratory distress syndrome was associated with high mortality rates. These findings are consistent with a recent multicenter observation study of the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study, conducted in 459 intensive care units from 50 countries.[20] This study showed that patients with any AKI stage had a lower $PaO_2/FiO_2$ (P/F) ratio, a clinical indicator of oxygenation, and higher positive end-expiratory pressure, and that AKI was significantly associated with longer duration of invasive mechanical ventilation, longer hospitalization, and increased mortality.

These 2 clinical studies highlight the association of AKI and lung injury, although the injury in kidney and lung often occurs simultaneously, and therefore the conclusion could not be clearly drawn that AKI directly affects lung injury.

Respiratory dysfunction with AKI has been commonly believed to be due mainly to fluid overload and cardiogenic pulmonary edema.[21] However, several studies have demonstrated that additional mechanisms are involved in kidney–lung interactions, including inflammatory mediators, infiltrations of neutrophils and T cells, and enhanced microvascular permeability.[22–25] Experimental ischemic AKI in rats was shown to increase lung microvascular permeability, pulmonary edema, and microvascular leukocyte sludging with red blood cell rouleaux formation.[22] Lung injury also can be induced by bilateral nephrectomy, which suggests that acute uremia can cause lung injury.[26,27] In addition, interleukin 6 (IL-6), a cytokine increased in experimental and clinical AKI,[28–30] contributed to lung injury induced by kidney ischemia reperfusion or bilateral nephrectomy.[31] The induction of lung chemokine ligand 1 was involved in IL-6–related lung injury by AKI, and blockade of chemokine ligand 1 and IL-6 attenuated neutrophil infiltration and lung injury.[32] However, IL-6 also has an anti-inflammatory effect on the lung after AKI via IL-10 production from CD4 T cells.[33,34]

Signaling with Toll-like receptor (TLR) 4 and high mobility group box 1 (HMGB1) plays an important role in kidney–lung interactions. HMGB1, a damage-associated molecular pattern molecule (DAMP) released from apoptotic cells, interacts with TLR4 of target cells, leading to activation of nuclear factor kappa B and inducing immune responses.[35,36] Bilateral nephrectomy induced neutrophil infiltration to the lung, which was reduced in TLR4 mutant mice (C3H/HeJ strain). HMGB1 was elevated after nephrectomy, and HMGB1 blockade attenuated lung injury but only in wild-type mice.[27] However, HMGB1 blockade in an ischemic AKI model reduced pulmonary neutrophil infiltration independent from TLR4. These data suggest that the HMGB1–TLR4 pathway and other HMGB1-dependent pathways exist in parallel and contribute to lung injury induced by AKI.

Neutrophil extracellular traps (NETs) are also involved in AKI-induced lung injury. Activated neutrophils, via innate response to damage-associated molecular patterns produced from the injured organs, release granule proteins and histone. Extracellular histones derived from neutrophils activate TLR2, 4, and 9 expressed in neutrophils, resulting in an amplification of extracellular matrix formation in the distant organ, called NET formation.[37–39] After kidneys were subjected to ischemia, NETs were detected in the lung and promoted lung injury.[40] A recent study reported that recombinant thrombomodulin had high affinity for extracellular histone and prevented histone agglutination in the organs. Recombinant thrombomodulin administration either before or 6 hours after kidney ischemia reperfusion injury reduced histone accumulation in the lung and attenuated AKI-induced lung injury in a mouse model, indicating that recombinant thrombomodulin is has potential as a drug for treatment of respiratory failure with AKI.[41] Interesting to note is that the protective effect of recombinant thrombomodulin on the liver, but not on the lung, was observed in mice with intestinal ischemia reperfusion.[42]

Ligand–receptor pairing analysis is a relatively new technique using bulk or single-cell RNA sequencing to reveal cell–cell interactions.[43,44] This technique was used successfully to elucidate the fact that osteopontin released from injured tubular cells binds to lung macrophages, followed by neutrophil accumulation in the lung.[45] Kidney-derived osteopontin also triggered lung endothelial barrier dysfunction and vascular leak. Administration of osteopontin antibody reduced the infiltration of macrophages and neutrophils, protected lung endothelial barrier, and attenuated subsequent lung injury. Osteopontin is also a mediator for lung injury induced by intestinal ischemia.[46]

Metabolites may be a therapeutic target for AKI-induced lung injury and are a promising field of study. Metabolomic analysis revealed increased oxidative stress, a shift to alternative pathways for energy production (glycolysis, tricarboxylic acid cycle and pentose phosphate pathway) instead of oxidative phosphorylation, and adenosine triphosphate depletion in lungs after kidney ischemia.[47,48] As described below in the kidney–heart interaction section, metabolomic analysis was also reported during AKI-induced heart injury.[49] Because several organs, including kidney, heart, and liver, are known to have dynamic metabolic changes in response to insults,[49,50] metabolomic analysis is expected to help clarify the precise mechanisms of organ crosstalk in these organs.

Collectively, as shown in Figure 1, basic studies indicate that AKI-induced lung injury is caused by inflammatory cytokines, TLR4 signaling, infiltration of immune cells, and NET formation, resulting in subsequent microvascular permeability and endothelial barrier dysfunction in the lung. This pathophysiology is partly supported by clinical studies showing that AKI worsens the respiratory state and is associated with higher mortality in acute respiratory distress syndrome patients.

### Kidney–heart interactions

The interactions between kidney and heart are well studied and are frequently lumped together as cardiorenal syndromes.[51,52] Cardiorenal syndrome is classified into 5 groups based on 2 factors—which organ has the primary dysfunction, and whether the primary organ dysfunction is acute or chronic. Cardiorenal syndrome type 1, in which AKI occurs with acute heart failure, has been reported in many studies, and AKI is considered an unfavorable prognostic factor.[53–56] However, cardiorenal syndrome type 3, in which acute cardiac dysfunction follows AKI, is less well known. Recent clinical studies demonstrated that AKI affects long-term cardiovascular disease and death.[57,58] A multicenter prospective matched cohort study (the Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury [ASSESS-AKI] trial) demonstrated that AKI is associated

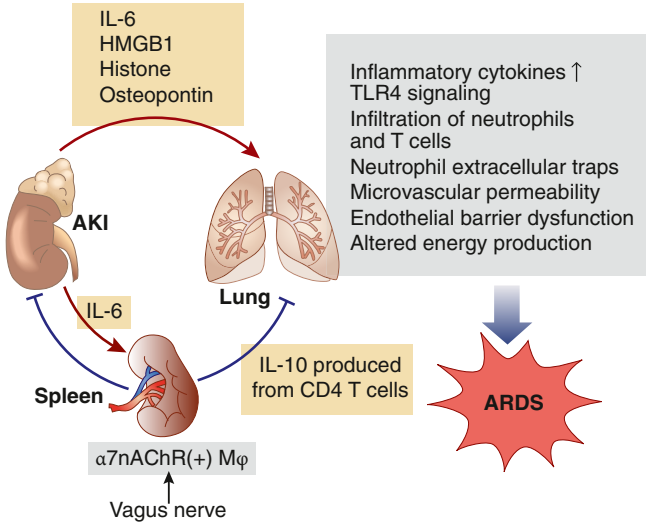


**Figure 1 | Crosstalk among kidney, lung, and spleen.** The injured kidney or acute kidney dysfunction produces inflammatory cytokines, including interleukin 6 (IL-6), damage-associated molecular patterns, such as high mobility group box 1 (HMGB1) and histone, and osteopontin. These mediators induce the production of inflammatory cytokines, Toll-like receptor 4 (TLR4) signaling, infiltration of neutrophils and T cells, neutrophil extracellular traps, microvascular permeability, and endothelial barrier dysfunction in the lung, resulting in acute respiratory distress syndrome (ARDS). Altered energy production in the lung induced by acute kidney injury (AKI) may be involved in ARDS. The indirect effect of AKI on the lung is that IL-6 stimulates CD4-positive T cells in spleen to produce interleukin-10 (IL-10), which attenuates AKI-induced lung injury. In addition, macrophage (Mφ) expressing α7 nicotinic acetylcholine receptors (α7nAChRs) stimulated by vagus nerve has a protective role in AKI.

with an increased incidence of heart failure and mortality.[59] This finding has been associated with an increased angiopoietin-2 level after AKI.[60] Angiopoietin-2 leads to vascular permeability and capillary loss, promoting interstitial fibrosis in kidney and heart.[61–63] Additional clinical studies have shown the association of AKI with major adverse cardiac events, including myocardial infarction, ischemic stroke, and peripheral artery disease.[64,65] However, this association was not significant when adjustment was made for estimated glomerular filtration rate and urine protein-to-creatinine ratio at the 3-month visit in the ASSESS-AKI study. This result suggests that failure of kidney recovery and persistent uremic toxins may be important in long-term cardiovascular risk after exposure to AKI.

When the kidney is injured, a systemic increase occurs in uremic toxins, such as indoxyl sulfate and p-cresyl sulfate, fibroblast growth factor 23 (FGF23), and many other molecules. *In vitro* experiments showed that uremic toxins can cause vascular inflammation and endothelial dysfunction,[66,67] which can contribute to cardiac dysfunction. FGF23 is a hormone that regulates phosphate dynamics and is elevated in AKI, due to inflammatory cytokines, such as IL-6.[68,69] FGF23 is secreted from bone in the steady state,[70] and it is also derived from liver via estrogen-related receptor-γ (ERR- γ) during inflammation or AKI.[71] An elevated FGF23 level induces left ventricular hypertrophy via the calcineurin-nuclear factor of activated T-cells (NFAT) pathway,[72] and it may impair immune function related to infection, such as pneumonia.[73,74] In clinical studies, an elevated FGF23 level in AKI is positively correlated with prolonged hospitalization, severe sepsis, and increasing mortality risk.[75–79] Thus, cardiac dysfunction induced by AKI may be due partially to liver FGF23 production stimulated by AKI.

Several lab studies have examined mechanisms underlying cardiac changes after AKI. An increase in tumor necrosis factor alpha (TNFα) and IL-1 expression and myeloperoxidase activity in the heart was observed after experimental kidney ischemia.[80] Myocardial apoptosis was also observed and attenuated by inhibition of TNFα. Another experimental study with kidney bilateral ischemia reperfusion injury showed mitochondrial fragmentation and release of cytochrome C in cardiomyocytes and reduced cardiac function. This study showed that mitochondrial fragmentation is due to increased dynamin-related protein 1, a guanosine triphosphatase that promotes mitochondrial fission. Dynamin-related protein 1 inhibitor,[81,82] and mitochondrial division inhibitor 1, reduced mitochondrial fragmentation and recovered cardiac function.[83]

A recent metabolomics analysis revealed that a decrease in amino acids, an increase in oxidative stress, and a shift to an anaerobic energy pathway, including glycolysis and a pentose phosphate pathway in the heart, occurred after kidney ischemia reperfusion injury.[49] These changes in metabolites induced adenosine triphosphate depletion in the heart and diastolic dysfunction. Supplementation or depletion of some metabolites may be therapeutic options.

The sympathetic nervous system and the renin–angiotensin–aldosterone system are involved in cardiac dysfunction after AKI.[51,52] The sympathetic nervous system and the renin–angiotensin–aldosterone system are activated during AKI,[84,85] and this activation can induce myocyte hypertrophy, apoptosis and necrosis, and upregulation of genes promoting fibrosis.[86,87] These results support the view that the activation of the sympathetic nervous system and the renin–angiotensin–aldosterone system contributes to cardiorenal syndrome, but direct evidence is still lacking. However, studies have demonstrated that the sympathetic nervous system plays a protective role against cardiorenal syndrome and AKI.[88,89]

A recent study showed that in mice with kidney ischemia reperfusion or unilateral urinary obstruction, cardiac dysfunction occurred with persistent cardiac inflammation and macrophage infiltration until 28 days. This phenomenon was dependent on galectin-3, as galectin-3 knockout or galection-3 inhibition prevented cardiac dysfunction after AKI.[90]

Taken together, clinical studies have indicated the cardiorenal interaction that occurs in the acute and chronic phase. Basic studies have revealed that AKI is associated with subsequent inflammation, apoptosis, mitochondrial abnormality, and an altered energy pathway in the heart, resulting in cardiac dysfunction (Figure 2). Uremic toxins, including

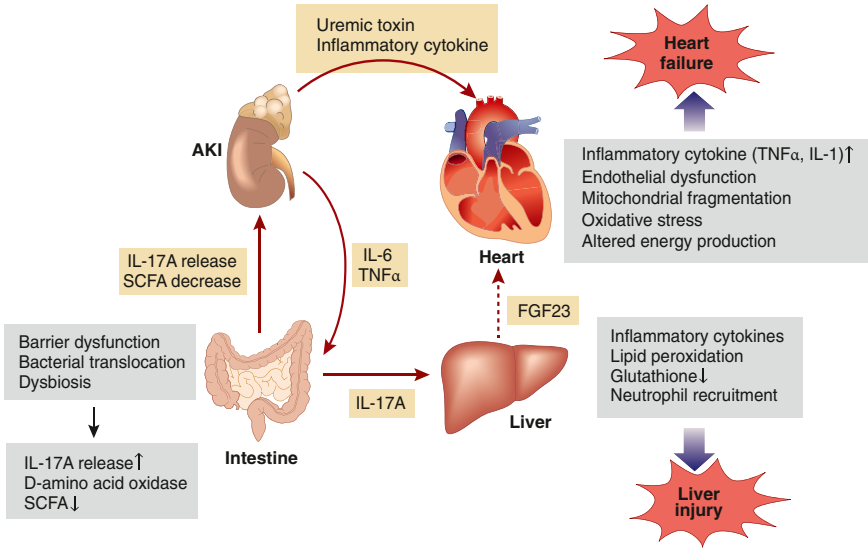


**Figure 2 | Crosstalk among kidney, heart, intestine, and liver.** Acute kidney injury (AKI) induces an increase in tumor necrosis factor alpha (TNFα) and interleukin 1 (IL-1) expression in the heart, myocardial apoptosis, and mitochondrial fragmentation, resulting in cardiac dysfunction. A shift to an anaerobic energy pathway including glycolysis and the pentose phosphate pathway in the heart occurs in AKI and is involved in diastolic dysfunction. Uremic toxins such as indoxyl sulfate and p-cresyl sulfate may cause vascular inflammation and endothelial dysfunction. Fibroblast growth factor 23 (FGF23), secreted from liver in AKI, may cause ventricular hypertrophy. Inflammatory cytokines cause the intestine barrier dysfunction and increased intestinal permeability, resulting in the changes in gut microbiome called dysbiosis. Dysbiosis is associated with an increase of IL-17A+ CD4+ T cells, which subsequently worsens the injury to kidney and liver. Dysbiosis may reduce the production of short-chain fatty acids (SCFAs), products of gut microbiota. SCFAs play a protective role in attenuating kidney injury by modulating the activity of histone acetyltransferase and deacetylase and inhibiting reduced nicotinamide adenine dinucleotide phosphate-oxidase signaling in T cells. Dysbiosis also decreased activity of D–amino acid oxidase and altered D-serine and D-alanine metabolism, which is associated with the degree of kidney injury. AKI directly cause liver injury via increased lipid peroxidation, reduced glutathione, and apoptosis in the liver.

FGF23, may cause vascular inflammation and endothelial dysfunction.

### Kidney–liver interactions

Clinical studies demonstrate that hepatic injury and dysfunction are often seen in AKI patients,[91,92] and *vice versa*.[93] Patients with both liver injury and AKI have a higher risk of mortality than those with either liver injury or AKI. However, whether AKI directly affects liver function remains unclear from clinical studies. Animal experiments indicate several possible mechanisms by which AKI affects liver function. Inflammatory cytokines have been reported to be involved in liver injury induced by AKI.[94] Knockout mouse studies have shown that IL-6 and TNFα induced during AKI contribute to liver injury.[95] IL-17A is also involved in kidney–liver interactions. IL-17A was found to be secreted from intestinal Paneth cells in mice with kidney ischemia reperfusion injury or nephrectomy, and IL-17A decreased in mice with genetically induced Paneth-cell deficiency.[96] IL-17A derived from intestinal Paneth cells recruits neutrophils in liver and kidney and causes both liver and kidney injury.[97] However, this study[97] unexpectedly found that intestinal Paneth cells could have a protective role against kidney and liver injury. Intestinal TLR9-deficient mice with renal ischemia had exaggerated kidney and liver injury, via the increase of IL-17A and other proinflammatory cytokines in the kidney, liver, and intestine, which demonstrates the complex role of the intestine in AKI.

Oxidative stress also participates in AKI-induced liver injury. Mice with kidney ischemia reperfusion or bilateral nephrectomy had increased lipid peroxidation, reduced glutathione, and apoptosis in the liver. Administration of glutathione attenuated liver injury induced by AKI.[98] Another study found that production of inflammatory cytokines, neutrophil infiltration, and apoptosis in the liver after kidney ischemia were suppressed by a genetic fusion protein consisting of human serum albumin and thioredoxin, of which the plasma half-life was 10-fold longer than that of thioredoxin, an antioxidative molecule.[99] Thioredoxin treatment also attenuates AKI and AKI-induced lung injury in addition to liver injury, suggesting that thioredoxin plays a protective role in multiple systemic biological actions, including reduction of circulating inflammatory cytokines (IL-6 and TNFα).

In summary, although clinical studies show that AKI and liver injury often occur simultaneously, and the causal effect of AKI on liver is not established in patients, laboratory studies demonstrated that AKI may cause liver injury directly, by increasing lipid peroxidation, reducing glutathione level, causing apoptosis in the liver, and indirectly, by the production of IL-17A from intestinal Paneth cells (Figure 2).

### Kidney–gut microbiome interactions

Several lab-based studies have explored the effect of AKI on gut microbiota. Increased inflammatory cytokines in septic

AKI cause injury to cell junctions, disrupt the gut barrier function, and increase intestinal permeability. This process leads to bacterial translocation, the expansion of inflammation, and subsequent immune responses.[100] In addition, crypt proliferation is decreased, and crypt and villous apoptosis occurs simultaneously via TLR4.[101] These changes can induce the changes in gut microbiome[102,103] called dysbiosis. Dysbiosis also can be observed in experimental ischemic and nephrotoxic AKI, particularly in the phyla Actinobacteria, Bacteroidetes, Firmicutes, Tenericutes, and Verrucomicrobia.[104] Of note, clear distinctions could be seen in the gut microbiota in ischemic AKI versus cisplatin-induced AKI at the same time points and with similar increases in serum creatinine. A recent study revealed that experimental kidney injury induced by ischemia reperfusion affects the intestinal microbiome by increasing *Enterobacteriacea* and decreasing *Lactobacilli* and *Ruminococacceae*, and increasing intestinal permeability and bacterial translocation.[105] These changes are associated with increase of IL-17A+ CD4+ T cells, and antibiotic-treated microbiome depletion reduces IL-17A+ CD4+ T cells with the expansion of regulatory T cells. Another study reported that kidney ischemia induced endotoxemia derived from gut microbiota and that endotoxin subsequently promoted inflammatory cytokines in the kidney. Norfloxacin pretreatment attenuated endotoxemia and improved kidney damage.[106]

Conversely, the role of the gut microbiome on AKI outcomes was first demonstrated by experiments using germ-free mice.[107] Germ-free mice with kidney ischemia-reperfusion injury had a higher number of natural killer T cells and increased CD8 T-cell trafficking and inflammatory cytokines, with worse kidney damage after ischemia reperfusion injury, compared to control mice. Reconstitution of germ-free mice using wild-type gut microbiota attenuated kidney injury after ischemia-reperfusion. The importance of gut microbiota on the course of AKI was also confirmed with experiments using antibiotic-induced microbiome depletion.[108] However, another study demonstrated that antibiotic-induced microbiome depletion improved kidney injury due to reduced levels of macrophages and inflammatory cytokines, including TNFα, IL-6, and monocyte chemoattractant protein-1.[109] The differences between these studies are not clear, although one possibility is that specific antibiotics can selectively deplete injurious bacteria while not depleting protective bacteria. In addition, the immune response in germ-free mice may not be the same as that in wild-type mice, because of the absence of germs since birth.[110]

The effect of gut microbiota on AKI is attributed partly to short-chain fatty acids (SCFAs), such as acetate, propionate, and butyrate. SCFAs are products of gut microbiota. SCFAs activate various G protein–coupled receptors including GPR43 and olfactory receptor-78,[111] which modulate the activity of histone acetyltransferase and deacetylase.[112] Treatment with acetate-producing bacteria protects against kidney ischemia.[112] SCFAs also modulate immune-cell function. In septic AKI, acetate inhibited reduced nicotinamide adenine dinucleotide phosphate (NADPH)-oxidase signaling in T cells and attenuated kidney injury.[113] *In vitro* experiments elucidated that SCFAs decreased dendritic cell maturation and inhibited CD4 and CD8 T cell proliferation.[112] D–amino acid oxidase is another factor in gut microbiota–kidney interaction. AKI induced gut dysbiosis with decreased activity of D–amino acid oxidase and altered D-serine and D-alanine metabolism.[114] Administration of D-serine or D-alanine to mice subjected to kidney ischemia reperfusion improved tubular injury.[114,115]

In summary, AKI causes intestine barrier dysfunction, an increase in intestinal permeability, and dysbiosis, resulting in activation of IL-17A+ CD4+ T cells, changes in SCFA levels, and activity of D–amino acid oxidase. These mechanisms modify injury responses in kidney and liver (Figure 2). However, information to date is limited on the interaction between the kidney and the gut in AKI patients.

### Kidney–brain interactions

The brain is an important target organ during AKI. A propensity-matched cohort study revealed that AKI was significantly associated with incident stroke long-term after kidney recovery.[116] The Atherosclerosis Risk in Communities (ARIC) study, which is a large prospective cohort study, showed the high incidence of dementia that occurred over the course of 10 years in AKI patients, and the significant association of AKI with incident dementia, after adjusting with various factors, including apolipoprotein E (APOE) genotypes.[117] A retrospective study demonstrated that AKI was independently associated with sepsis-associated encephalopathy.[118] A well-established finding is that AKI induces electrolyte and metabolic disorders in critical illness, which can cause encephalopathy.[119,120]

AKI leads to many changes in the brain. After severe ischemic AKI, mouse brains are characterized by increased neuronal pyknosis, increased microglial cells (brain macrophages), leakage in the blood–brain barrier, and inflammation in cortex and hippocampus.[121] In the same study, AKI also led to severe declines in locomotor activity. In another study, i.p. injection of indoxyl sulfate to unilateral nephrectomized mice caused behavioral disturbances with decreased neuronal survival, and neural stem-cell activity.[122] An *in vitro* study also demonstrated that indoxyl sulfate caused mitochondrial dysfunction and oxidative stress in astrocytes.[123] A recent study revealed that aryl hydrocarbon receptor in endothelial cells is involved in cognitive impairment by indoxyl sulfate,[124] and another study confirmed that p-cresyl sulfate had the same effect.[125]

However, unlike in CKD, the level of uremic solutes was measured as being low in AKI.[126] Thus, the encephalopathy by AKI could be from different factors, including proinflammatory cytokines, such as keratinocyte-derived chemoattractant and granulocyte colony stimulating factor (G-CSF).[121,127] AKI can lead to increased oxidative stress in the hippocampus and frontal area.[128] Kidney ischemia reperfusion injury also induces apoptosis and neutrophil infiltration in the brain. The brain

injury by AKI was attenuated by NETs and necrosis inhibitors, indicating that brain injury might involve NET formation, although NETs were not detected in the brain.[40] The blood–brain barrier can be also affected by AKI. Uremic solutes were found to modulate the expression of drug transporters, cellular receptors, and cellular tight junction in *in vitro* and *in vivo* experiments.[129] Kidney ischemia reperfusion decreased peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α levels in both the kidney and blood–brain barrier. PGC-1α transfection to ischemic AKI mice decreased brain vascular permeability via the restoration of mitochondrial function and tight junctions.[130]

In summary, clinical studies indicate that AKI is involved in brain functional changes both acutely and chronically. However, the pathophysiology is incompletely elucidated, although experimental studies suggest that the mechanisms include uremic toxins, mitochondrial abnormalities, and NET formation in the brain.

### Kidney–spleen crosstalk

The spleen is a large pool of immune cells, and splenocytes play an important role in experimental AKI models (Figure 1). In ischemic AKI, splenic macrophages with α7 nicotinic acetylcholine receptors were protective against kidney injury, whereas genetic or pharmacologic depletion of α7 nicotinic acetylcholine receptors, or splenectomy, removed the protective effects.[131,132] Activation of macrophage with α7 nicotinic acetylcholine receptors is dependent on a choline acetyltransferase-positive CD4+ memory T cell with β2 adrenergic receptor, which is stimulated by norepinephrine released from splenic nerve.[133] Stimulated macrophage expressing α7 nicotinic acetylcholine receptors reduced production of inflammatory cytokines and suppressed inflammation.[134,135] This anti-inflammatory pathway is elicited by electrical stimulation of the efferent vagus nerve[132] and is known as the cholinergic anti-inflammatory pathway (CAP). CAP also can be activated with the stimulation of C1 neurons,[136] located in the rostral ventrolateral medulla (RVLM), innervating sympathetic preganglionic neurons in the intermediolateral cell column of the spinal cord as well as neurons in the dorsal motor nucleus of the vagus (where most of the neurons of the efferent vagus nerve originate) and in the paraventricular nucleus of the hypothalamus (the primary driver of the hypothalamic–pituitary–adrenal axis).[137] A recent experiment using selective optogenetic stimulation (a method to target photosensitive proteins like channel rhodopsin by light) revealed that the protective effect of afferent vagus nerve stimulation for ischemic AKI was dependent on the C1 neurons–sympathetic nerve–splenic nerve axis.[138]

In an AKI-to-CKD transition model, splenic lymphocytes could contribute to the development of albuminuria after AKI.[139] The spleen is also involved in ischemic preconditioning during AKI.[140] Splenocytes also play a role in sepsis and septic AKI. Cecal ligation and puncture, one of the sepsis models, induced splenocyte apoptosis via TLR9.[141–143] Apoptotic splenocytes produced IL-12, IL-17A, and high mobility group box 1, which are proinflammatory cytokines causing tubular damage in sepsis.[142,144,145]

Splenocytes affect not only kidney but also other distant organs in AKI. Lung injury induced by AKI is partly attributable to IL-6, and is limited by IL-10, the production of which is stimulated by IL-6.[34] A recent study[33] found that IL-10 was produced from macrophage, B cells, and T cells. In experiments with CD4 knockout mice, the level of IL-10 was significantly reduced in the spleen, which induced the increase of serum and lung chemokine ligand 1 and lung injury. These studies emphasize the importance of splenocytes in the pathophysiology of lung injury induced by AKI.

The spleen is involved in iron homeostasis. Iron is stored in hepatocytes as well as hepatic and splenic macrophages. Hepcidin is released from the liver and regulates systemic iron levels by degrading the iron exporter ferroportin, subsequently reducing the influx of iron into plasma from the stored cells.[146] In a kidney ischemia reperfusion model, circulating iron levels increase and the splenic iron level

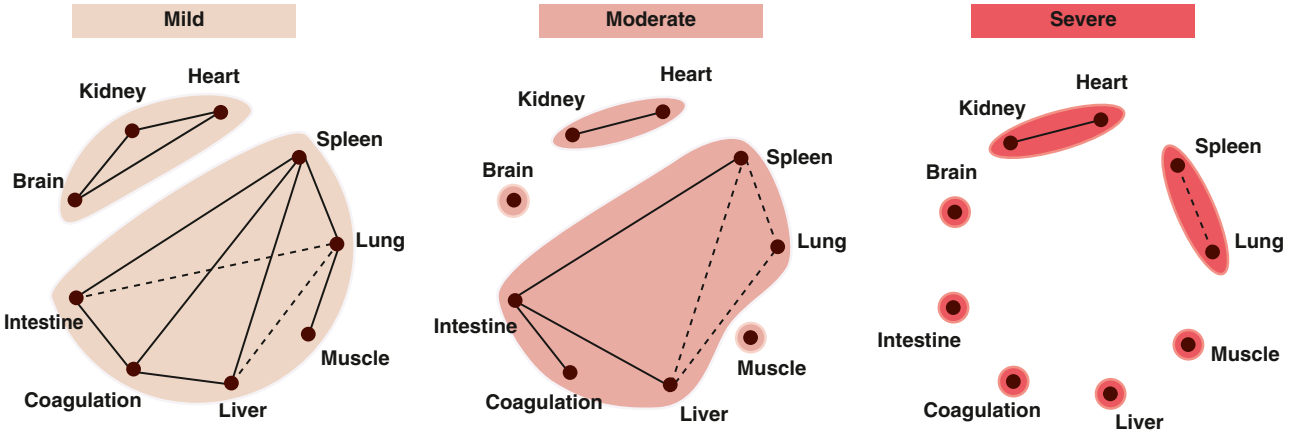


**Figure 3 | Organ network disruption.** The network analysis, the method to evaluate the connectivity among multiple nodes (organs), reveals whether interorgan associations are preserved or disrupted. This figure shows examples of mild, moderate, and severe disruption of the organ network that would be observed in critically ill patients.

**Table 1 | Representative clinical evidence on AKI-related organ injury**

| Organ | Study (reference) | Subjects | Results |
|---|---|---|---|
| Lung | Multicenter, observational study in France[19] | 8029 ICU patients without CKD | ARDS was independently associated with AKI (odds ratio, 11.01; 95% CI, 6.83–17.73).<br>AKI was associated with higher mortality in patients with ARDS (42.3% vs. 20.2% in patients without AKI). |
| | Multicenter, observational study in 60 countries[20] | 1974 ARDS patients with baseline eGFR ≥60 ml/min per 1.73 $m^2$ | The proportion of patients with severe ARDS increased with the severity of AKI.<br>FIO2, PEEP, and peak pressure in mechanical ventilator were higher in patients with AKI.<br>Mechanical ventilation-free days were lower in patients with AKI.<br>AKI was associated with higher mortality in ARDS patients. |
| Heart | A multicenter, prospective cohort study in multiple countries[53] | 927 patients with acute heart failure requiring i.v. diuretics | 72 patients (7.8%) had worsening kidney function, defined as a sustained increase in plasma creatinine level of 0.5 mg/dl or ≥50% above first value or initiation of acute RRT. |
| | Meta-analysis[56] | A total of 49,890 heart failure patients were included in 28 studies | 23% of the patients had worsening kidney function.<br>In multivariate analysis, worsening kidney dysfunction was an independent predictor of mortality (HR, 1.95; 95% CI, 1.45–2.62). |
| | A retrospective study with a large healthcare registry[57] | 146,941 hospitalized adults | 31,245 patients (9%) had AKI.<br>AKI was associated with hospitalization for heart failure (adjusted HR, 1.44; 95% CI, 1.33–1.56). |
| | A retrospective study with Swedish registry (SWEDEHEART)[58] | 24,018 patients who underwent coronary artery bypass grafting | The incidence of AKI was 12%. Mean follow-up was 4.1 years.<br>AKI was associated with hospitalization for heart failure (stage 1, HR 1.60 [95% CI, 1.34–1.92]; stage 2, HR, 1.87 [95% CI, 1.54–2.27]; stage 3, HR, 1.98 [95% CI, 1.53–2.57]). |
| | A multicenter, prospective cohort study[59] | 1538 hospitalized patients | 769 patients had AKI, with 39.8% having preexisting CKD.<br>Mean follow-up was 4.5 years.<br>AKI was associated with the incidence of heart failure (HR, 1.68; 95% CI, 1.22–2.31). |
| | A retrospective study with a health insurance registry[64] | 4869 AKI survivors requiring dialysis and 4869 non-AKI matches | The unadjusted rate of coronary events during follow-up was higher in the AKI group than in the non-AKI group (19.8 and 10.3 per 1000 person-years). AKI was associated with a higher long-term risk for coronary events (HR, 1.67; 95% CI, 1.36–2.04). |
| | A retrospective study in a single center[65] | 1030 patients with postcardiac surgery | 287 patients (27.9%) had AKI.<br>Five-year cumulative risk of myocardial infarction was 5.0% (95% CI: 2.9%–8.1%) among patients with AKI and 3.3% (95% CI: 2.1%–4.8%) among patients without AKI, which is not statistically significant (adjusted HR, 1.5; 95% CI: 0.7–3.2). |
| Liver | A multicenter, retrospective study[91] | 605 AKI patients | Liver failure was associated with mortality (HR, 3.09; 95% CI, 1.90–4.93). |
| | A prospective study in a single center[92] | 162 AKI patients requiring RRT | 30 patients (37%) had liver dysfunction. Higher level of plasma endogenous erythropoietin was associated with liver dysfunction. |
| Intestine | No data | | |
| Brain | A retrospective study with French multicenter database[118] | 2513 septic patients | 1341 (53%) had sepsis-associated encephalopathy (Glasgow coma scale <15 or delirium).<br>Acute renal failure was independently associated with encephalopathy. (adjusted odds ratio, 1.41; 95% CI, 1.19–1.67). |
| | A retrospective propensity score–matched study with a healthcare registry[116] | 1041 AKI patients and 1041 non-AKI matches | AKI was associated with increased risk of developing dementia (HR, 3.40; 95% CI, 2.14–5.40). |
| | Propensity score–matched study from ARIC study[117] | 854 AKI patients and 854 non-AKI matches | The cumulative incidence of dementia was 31.6% at 10 years.<br>AKI had a higher risk of dementia (cause-specific HR, 1.25; 95% CI, 1.02–1.52). |

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**Table 1 |** (Continued) **Representative clinical evidence on AKI-related organ injury**

| Organ | Study (reference) | Subjects | Results |
|---|---|---|---|
| Spleen | No data | | |
| Muscle | A secondary analysis of multicenter, prospective observational study[156] | 462 AKI patients ≥65 years old | 141 (30.5%) patients had frailty at ICU admission. Frailty was associated with 90-day mortality (adjusted HR, 1.49; 95% CI, 1.11–2.01). |
| | A *post hoc* analysis of a multicenter prospective observational study[152] | 415 survivors who received dialysis for AKI | Health utility index at 60 days, a scale of general health state and quality of life, was low (0.40 ± 0.37). |

AKI, acute kidney injury; ARDS, acute respiratory distress syndrome; ARIC, Atherosclerosis Risk in Communities; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; $FiO_2$, fraction of inspiratory oxygen; HR, hazard ratio; ICU, intensive care unit; PEEP, positive end-expiratory pressure; RRT, renal replacement therapy; SWEDEHEART, the Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies.

decreases with upregulation of ferroportin in splenic macrophage, indicating that kidney injury induces the iron release from spleen.[147,148] Excessive iron causes production of reactive oxidative stress, lipid peroxidation, and subsequent ferroptosis, one of the emerging new mechanisms in AKI.[149,150] Hepcidin administration degraded the expression of ferroportin in splenic macrophage and attenuated acute kidney injury.[147]

In summary, recent basic studies indicate that spleen has multiple roles in AKI and distant organ injury, including both the protective effect of specific types of macrophages or T cells and the harmful effect of production of inflammatory cytokines and iron metabolism. Clinical data on spleen in AKI are limited. Further studies are necessary to elucidate the pathophysiology of immune responses and iron metabolism in spleen related to AKI.

### Kidney–muscle crosstalk

Recent clinical and experimental studies suggest that kidney and skeletal muscle interact. Skeletal muscle weakness and wasting occurs in critically ill patients with AKI, resulting in lower quality of life and lower levels of activity.[151,152] Although muscle wasting in AKI is less studied than that in CKD, suggested mechanisms include rapid activation of protein degradation and decrease of muscle synthesis. In experiments with bilateral ureteral obstruction or unilateral ischemia with contralateral nephrectomy, the level of phosphorylated Akt in muscle decreased, and expression of mediators of muscle wasting increased, indicating that muscle synthesis is inhibited during AKI. Muscle levels of IL-6, light chain 3B-II (LC3B-II), and the ubiquitin protease system are also increased in AKI, suggesting that AKI induces inflammation, autophagy, and protein degradation in muscle.[153,154] Muscle also may affect the progression of AKI to CKD. In experiments using mice with overexpression of PGC1α in skeletal muscle, kidney fibrosis was suppressed 7 days after folic acid nephropathy. PGC1α induced elevated circulating irisin, a myokine, inhibiting transforming growth factor beta signaling in tubular cells, and preventing fibrosis after kidney insult.[155] In clinical studies, preexisting frailty, a state of reduced physical reserve, is a factor for poor prognostic for short- and long-term mortality in AKI patients.[156] A point to note is that kidney function evaluation by serum

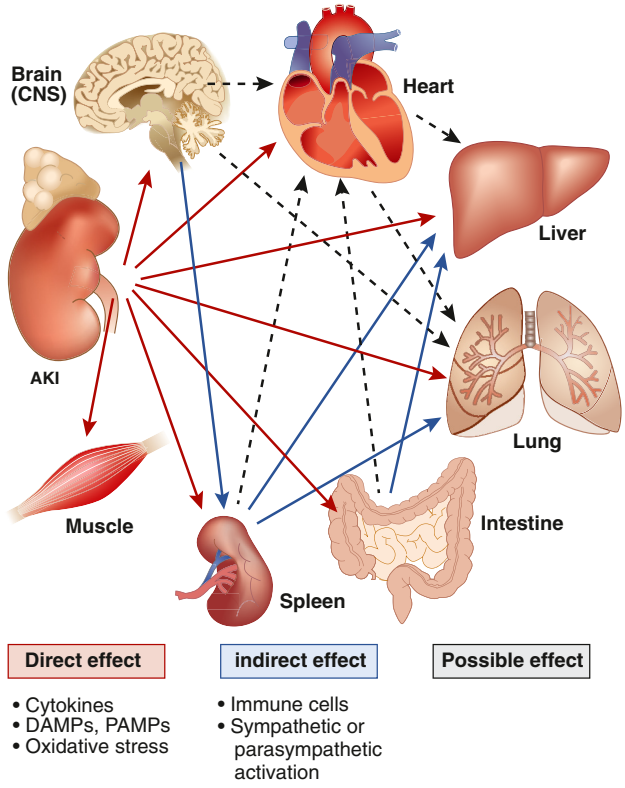


**Figure 4 | The impact of acute kidney injury (AKI) on distant organs.** AKI-induced injury to distant organs is mediated primarily by inflammatory cytokines, including interleukin 1 (IL-1), IL-6, monocyte chemoattractant protein-1, and tumor necrosis factor alpha, damage-associated molecular pattern molecules (DAMPs), and pattern-associated molecular patterns (PAMPs) released from the injured kidney. Immune cell infiltration to distant organs is also involved. In this model of direct damage by AKI (red arrow), the response originates directly from the injured kidney. Recent studies reveal that some distant organ injury can be affected by other distant organ injury induced by AKI. For example, the role of intestine-derived IL-17A production or immune cells modulated by AKI on liver injury has been elucidated.[96,97] The lung injury induced by AKI is regulated by splenocyte-derived IL-10, which is upregulated by AKI via the increase of circulating IL-6.[33] This type of distant organ damage is indirectly affected by AKI through other distant organ injury and can be called indirect damage by AKI (blue arrow). Moreover, clinical studies indicate that multiple organs mutually compensate the stress to each organ to survive and maintain the homeostasis,[158,159] although the precise mechanisms remain unknown (dotted arrow). CNS, central nervous system.

**Table 2 | Suggested mediators and potential therapeutic targets**

| Organ | Mediators or mechanisms (reference) | Potential therapeutic |
|---|---|---|
| Lung | Macrophage[22] | An inhibitor of macrophage activation, CNI-1493, attenuates pulmonary vascular permeability and congestion induced by AKI. |
| | Infiltration of neutrophil[24] | Neutrophil infiltration in the kidney and lung after kidney ischemia reperfusion is observed. Adenosine A2A agonist, which reduces inflammatory cell recruitment, attenuates lung vascular permeability and neutrophil infiltration. |
| | Neutrophil elastase[25] | The increase of neutrophil elastase activity in the lung after bilateral nephrectomy induces cytokine production and lung injury. Neutrophil elastase inhibitor suppresses the expression of inflammatory cytokine and lung injury. |
| | IL-6[31] | In IL-6 knockout mice subjected to kidney ischemia perfusion, lung inflammation and capillary leak are reduced compared to wild-type mice. Anti-IL-6 antibody also attenuates lung injury induced by AKI. |
| | CXCL1[32] | AKI induces CXCL1 production in lung endothelial cells stimulated by circulating IL-6. Anti-CXCL1 antibody administration or CXCR2 (a receptor for CXCL1) knockout improves lung injury while kidney function is not affected. |
| | TLR4–HMGB1 pathway[27] | The experiment using TLR4-mutant mice reveals that TLR4 is involved in lung injury including neutrophil infiltration, increased neutrophil elastase activity, and vascular permeability caused by bilateral nephrectomy. Blockade of HMGB1 (one TLR4 agonist) by neutralizing antibody reduced neutrophil infiltration in TLR4-wild-type. |
| | NETs formation[40] | Histone secretion from injured tubules induces the formation of neutrophil extracellular traps in the *in vitro* experiment. Kidney ischemia reperfusion increases the levels of circulating histones, and NET formation is detected in the lung after the renal injury. NETs inhibition or anti-Histone antibody administration reduced the injury to the lung. |
| | NETs formation[41] | The lung injury by kidney ischemia reperfusion is caused by histone and NETs formation. Recombinant thrombomodulin, which binds to circulating histone, attenuates the lung injury. |
| | Osteopontin[45] | Ligand-receptor pairing analysis using kidney and lung single-cell RNA sequencing identifies osteopontin released from kidney as a cause of lung injury following kidney ischemia reperfusion. Osteopontin-knockout or anti-osteopontin antibody attenuates lung injury caused by AKI. |
| | Altered energy production[47] | Kidney ischemia reperfusion alters the lung metabolic pathway to the fatty acid oxidation pathway. This change is correlated with the extracellular accumulation of the mitochondrial damage–associated molecular patterns (mtDAMPs). |
| | Altered energy production[48] | Metabolomics analysis elucidates increased oxidative stress, a shift to anaerobic energy production and depleted level of adenosine triphosphate. |
| Heart | TNFα, IL-1[80] | Kidney ischemia reperfusion affects the increase expression of IL-1 and TNFα, increased apoptosis in the heart and systolic dysfunction. Blockade of TNFα decreases the apoptotic area in the heart. |
| | Mitochondrial fragmentation by DRP1[83] | Cardiac dysfunction and mitochondrial fragmentation in the heart are observed after AKI. Mitochondrial fragmentation is regulated by DRP1, and mdivi1, a DRP1 inhibitor, decreased mitochondrial fragmentation in the heart, and improved cardiac function. |
| | Altered energy production[49] | Metabolomics analysis revealed amino acid depletion, increased oxidative stress, and a shift to anaerobic energy production in the heart 24 hours after kidney ischemia reperfusion. These changes lead to decreased adenosine triphosphate level in the heart and diastolic dysfunction. |
| | Galectin 3[90] | Kidney ischemia reperfusion induces cardiac systolic dysfunction, whereas galectin 3 knockout attenuates cardiac dysfunction by renal injury. Further experiments using chimeric mice reveal that galectin 3 from bone marrow–derived cells is responsible for cardiac dysfunction. Modified citrus pectin, a galectin 3 inhibitor, attenuates cardiac dysfunction by renal injury. |
| Liver | IL-6, MCP-1, TNFα[94] | Kidney ischemia reperfusion induces the increase of inflammatory cytokines (IL-6, MCP-1, TNFα) in the liver. The increase of NF-kB/DNA binding activity is also confirmed by EMSA. |

(*Continued on following page*)

**Table 2 |** (Continued) **Suggested mediators and potential therapeutic targets**

| Organ | Mediators or mechanisms (reference) | Potential therapeutic |
|---|---|---|
| | IL-6, IL-17A, TNFα[95] | Kidney ischemia reperfusion or bilateral nephrectomy induces the increase of liver enzymes, hepatic vascular permeability, and neutrophil infiltration in the liver. Neutralizing antibodies against TNF-α, IL-17A, or IL-6 or gene depletion of TNF-α, IL-17A, IL-17A receptor, or IL-6 are protected against hepatic injury. |
| | IL-17A[96] | Small intestinal Paneth cells increases the synthesis and release of IL-17A after kidney ischemia reperfusion or bilateral nephrectomy. Intestinal macrophages transport IL-17A released from Paneth cell granule and induce hepatic injury. Genetic or pharmacologic depletion of Paneth cells decreases small intestinal IL-17A secretion and attenuates hepatic and kidney injury after AKI. |
| | Interleukin 17A[97] | Intestinal TLR9 deletion induces higher expression of IL-17A in the intestine and worsens the injury to kidney and liver after kidney ischemia reperfusion. Administration of anti-IL-17A antibody attenuates the injury to kidney and liver after ischemia reperfusion. |
| | Oxidative stress[98] | Kidney ischemia and bilateral nephrectomy induce the increase of malondialdehyde, an index of lipid peroxidation, while total glutathione is decreased in the liver. Hepatic apoptosis also increases. Infusion of reduced glutathione improves liver architecture and is associated with a reduction in hepatic malondialdehyde and serum alanine transaminase levels. |
| | Oxidative stress[99] | A long-acting thioredoxin, a fusion protein of albumin and thioredoxin (anti-oxidative protein), attenuates lung and liver injury caused by kidney ischemia. |
| Intestine | Gut microbiota[105] | Kidney injury by ischemia induces dysbiosis with increase of *Enterobacteriacea* and decrease of *Lactobacilli* and *Ruminococacceae* and decreases the level of short chain fatty acids in stool. Deletion of microbiota protects against renal ischemia reperfusion, with the expansion of regulatory T cells and M2 macrophages in kidney, spleen, and intestine. |
| | Gut microbiota[108] | Deletion of gut microbiota by broad-spectrum antibiotics attenuates kidney injury after ischemia reperfusion, which is attributed to immature F4/80+ kidney resident macrophages and bone marrow monocytes with low expression of CX3CR1 and CCR2. |
| | Short-chain fatty acids[112] | Administration of acetate-producing bacteria (B. longum or B. adolescentis) attenuated kidney injury caused by ischemia reperfusion. Short-chain fatty acids inhibit histone deacetylase activity. SCFAs decrease the maturation of dendritic cells and inhibit the capacity of these cells to induce CD4(+) and CD8(+) T cell proliferation. |
| | D-serine[114] | Gut microbiota protect against kidney ischemia in the experiment using germ-free mice. AKI-induced gut dysbiosis alters the balance of D/L-amino acids in the intestine, and D-serine was increased in the injured kidney. D-serine supplementation reduced tubular injury after ischemia reperfusion. |
| | D-alanine[115] | This study is relevant to reference 111. D-alanine is increased in feces and plasma after kidney ischemia reperfusion. D-alanine supplementation protected against kidney ischemia with the recovery of mitochondria function, probably via N-methyl-D-aspartate (NMDA) receptor signaling. |
| Brain | Indoxyl sulfate[123] | In *in vitro* experiments with human astrocyte–treated IS, IS stimulates the release of reactive oxygen species, increases nuclear factor (erythroid-derived 2)–like 2 levels, and reduces mitochondrial membrane potential. IS also triggers astrocyte apoptosis. |
| | Uremic toxin[124] | Using SPECT-CT, uremic toxin disrupts the blood–brain barrier. In mice with knockout of aryl hydrocarbon receptor (AhR), the receptor of indoxyl sulfate, the blood–brain barrier is protected against IS-induced disruption. |
| | p-cresol sulfate[125] | The unilateral nephrectomized mice with p-cresol sulfate administration developed depression-like, anxiety-like, and cognitive impairment behaviors with accumulation of p-cresol sulfate in brain. Increased apoptosis, oxidative stress, and neuroinflammation occur in the prefrontal area. AST-120, a regent chelating uremic toxin, attenuates neurologic disorders. |
| | Uremic toxin[129] | The *in vitro* and *in vivo* experiments show that uremic toxins such as indole-3-acetic acid and IS change the expression of drug transporters (Abcb1b, Abcc1, Abcg2). |
| | Keratinocyte-derived chemoattractant and G-CSF[121] | Kidney ischemia increases neuronal pyknosis and microgliosis in the brain and induces increased levels of the proinflammatory chemokines such as keratinocyte-derived chemoattractant and G-CSF in the cerebral cortex and hippocampus. |

**Table 2 |** (Continued)

| Organ | Mediators or mechanisms (reference) | Potential therapeutic |
|---|---|---|
| | NET formation[40] | Histone secretion from injured tubules induces the formation of neutrophil extracellular traps in the *in vitro* experiment. Kidney ischemia reperfusion increases the levels of circulating histones, and neutrophil infiltration and TUNEL-positive cells are detected in the brain after the renal insult. NETs inhibition or the administration of anti-Histone antibody reduced the injury to the brain. |
| | Oxidative stress[128] | Lipid and protein oxidation was higher in the hippocampus in kidney ischemia reperfusion. Lipid oxidation in the frontal cortex is also higher. |
| | PGC1α[130] | Kidney ischemia reperfusion induces the decrease in the expression of PGC1α in the brain. PGC1α overexpression decreases the blood–brain barrier and increases the protein expression of tight junction. |
| Spleen | Vagus nerve stimulation and α7nAChR-positive splenocytes[132] | Stimulation of vagus nerve alleviates kidney injury after ischemia reperfusion. This protective effect of vagus nerve stimulation is involved in α7nAChRs-positive splenocytes. |
| | C1 neuron and α7nAChR-positive splenocytes[136] | C1 neuron consists of glutamatergic and catecholaminergic neurons and mediates adaptive autonomic responses to physical stressors. Optogenetic C1 neuron stimulation protected from kidney ischemia-reperfusion injury. This protection is involved in subdiaphragmatic vagal nerve and α7nAChR-positive splenocytes. |
| | TLR9[141,142] | The experiment using TLR9 inhibitor or genetic deletion of TLR9 reveals that TLR9 is involved in kidney dysfunction in the sepsis model. TLR9 is activated by mitochondrial DNA. Splenic apoptosis is potentially involved in this mechanism. |
| Muscle | Downregulated Akt phosphorylation[153,154] | Kidney ischemia or nephrectomy induces the decrease of Akt phosphorylation and protein synthesis in muscle. Muscle level of IL-6, LC3B-II, and ubiquitin protease system elevated. Inflammation and the increase of autophagy and protein degradation may be involved in AKI-induced muscle atrophy. |
| | PGC1α, irisin[155] | Overexpression of muscle PGC1α attenuated folic acid nephropathy. A myokine, irisin, alleviated TGF-β signaling in tubule cells. |

BM, bone marrow; CX3CR1, C-X3-C motif chemokine receptor 1; CCR2, C-C motif chemokine receptor 2; CXCL1, chemokine ligand 1; DRP1, dynamin-related protein 1; EMSA, electrophoresis mobility shift assay; G-CSF, granulocyte colony stimulating factor; HMGB1, high mobility group box 1; IL, interleukin; IS, indoxyl sulfate; LC3B-II, light chain 3B-II; MCP1, monocyte chemoattractant protein 1; NET, neutrophil extracellular trap; NF-kB/DNA, nuclear factor kappa beta/DNA; PGC1, peroxisome proliferator-activated receptor-gamma coactivator; SCFA, short-chain fatty acid; SPECT-CT, single-photon emission computed tomography; TGF, transforming growth factor; TLR4, Toll-like receptor 4; TNF, tumor necrosis factor; TUNEL, terminal deoxynucleotidyl transferase biotin-dUTP nick end labeling; α7nAChR, α7 nicotinic acetylcholine receptor.

creatinine levels will be less reflective of glomerular filtration rate, given muscle reduction in AKI. Significant falls in serum creatinine level that persisted to hospital discharge were reported particularly in survivors of AKI.[157] Taken together, basic and clinical data suggest that AKI and skeletal muscle changes are linked.

## Multiple-organ crosstalk in AKI

AKI patients often have multiple organ dysfunction, rather than single-organ injury. This finding suggests a model in which AKI induces systemic responses in inflammatory and immune systems and subsequently causes other organ injuries. Recent studies have demonstrated this concept of crosstalk among multiple organs, using a new approach called organ network analysis. The network analysis aims to evaluate the connectivity among multiple nodes (organs). When connectivity among some nodes is strong, these nodes are treated as a cluster. A larger number of clusters indicates that the network is disrupted and fragmented, and smaller numbers indicate that the nodes are tightly connected (Figure 3). This network analysis was applied to adult critically ill patient data and revealed that 2 organ-system networks exist in critically ill patients—the respiratory–renal–inflammatory and the cardiovascular–hepatic–coagulation. These 2 organ networks were found to be balanced and connected to each organ in survivors, whereas in nonsurvivors, these networks are disrupted.[158,159] These finding support the view that death will occur when organs lose their ability to respond concordantly to stress and fail to maintain systemic stability. However, data are limited regarding the precise mechanisms by which single-organ injury such as AKI leads to multiple-organ injury and death.

## Summary and perspectives

AKI is a major morbidity and mortality multiplier in critically ill patients, and an unacceptably high mortality rate of severe AKI has been reported, even with the availability of dialysis. This finding indicates that AKI may not be just a single-organ injury but may amplify multiple-organ injuries. Representative clinical evidence on AKI-related organ injury is shown in Table 1. Increasing experimental data are revealing the pathophysiology of the interactions between kidney and other involved organs (Figure 4) and identifying possible mediators and potential therapeutic targets

(Table 2). A point to note is that many different mechanisms are contributing to many different organ injuries both simultaneously and one after another. Comprehensive and integrated analysis for the disease trajectory of multiple-organ failure will be the next step for future research. Network analysis recently identified that organ-network disruption might be associated with death in critically ill patients; however, data supporting this concept reported to date are limited. Future studies are needed to elucidate the mechanism of not only 2-organ crosstalk but also crosstalk with the organ network. Recent studies on the single-cell transcriptome of human peripheral blood cells in septic patients revealed that specific types of monocytes or neutrophils are associated with illness severity and may be involved in the pathophysiology of multiple-organ injury.[160,161] Further studies targeting inflammatory reactions by immune cells are necessary to elucidate organ-network mechanisms. Such studies will help in development of therapeutic strategies against AKI and distant organ injury.

## DISCLOSURE

All the authors declared no competing interests.

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