Global Perspectives in Acute Kidney Injury: Japan

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Introduction
Since the establishment of widely recognized diagnostic criteria, Acute Kidney Injury (AKI) has become universally recognized as a major health problem worldwide. Many studies have reported that even a slight increase in serum creatinine can lead to a poor prognosis. Given our ability to correctly diagnose AKI, the next task facing physicians is effectively managing this condition. With this in mind, it will be useful to analyze the current situation in Japan regarding AKI management, so that these findings can be shared with physicians in other countries. Thus, in this mini review, we aim to present the epidemiology, circumstances, and features of AKI in Japan.

Epidemiology of AKI
On the basis of commonly recognized AKI diagnostic criteria, it is now possible to make meaningful comparisons of AKI epidemiology in various hospital settings, and researchers in Japan have published such studies. In this section, we focus on the epidemiology of AKI in patients with acute coronary syndrome (ACS), cardiac surgery–associated AKI, and in intensive care units (ICU) in Japan.

Kuji et al. performed a prospective multicenter trial (n=2798) that investigated the prognosis of patients with acute myocardial infarction (AMI) (1). They revealed that the cumulative incidence of AKI was 10% among patients with AMI who underwent urgent percutaneous coronary intervention. Ikemura et al. also analyzed the clinical prognosis of non-ST elevation ACS, using the Japan Cardiovascular Database–Keio Interhospital Cardiovascular Studies registry (n=16,564) (2). Their analysis showed that AKI occurred in 14% of the patients who were eligible. Given recent clinical studies from other developed nations have reported the AKI incidence in AMI patients ranged from 7% to 17%, the incidence of AKI in Japanese patients with ACS appears to be similar to that of other countries (3–6).

Meanwhile, Fuji conducted a multicenter prospective cohort trial (n=2421) to explore the AKI epidemiology in a mixed Japanese ICU (7). Their analysis showed the cumulative incidence of AKI was 45% among Japanese patients in the ICU. Another single-center trial (n=333), which examined the kidney prognosis of older patients who had undergone trauma and are in the ICU, reported an AKI incidence of 20% (8). The frequencies of AKI in these studies were comparable to those reported in international multicenter studies, although the studies in Japan included older patients (9). Regarding cardiac surgery–associated AKI, several observational studies in Japan have reported AKI incidence rates of 12%–55% (10–14). These rates were also similar to those of other countries (15), although the median age was >70 years in most of the studies in Japan, which was higher than that of other countries. Taken together, the AKI incidence in Japan appears to be comparable to that of other countries, despite the advanced age of patients in the Japanese studies.

Who Manages Apheresis and AKI?
Before discussing AKI management, it is necessary to explain the current medical management of patients who are critically ill in Japan. The Organization for Economic Co-operation and Development has analyzed medical services data for various countries (16). They found that although the number of acute care hospital beds in Japan is among the highest in the world, the number of ICU beds per capita is relatively low (Figure 1, A and B). These data indicate that some critical patients may have to receive medical treatments in an acute care hospital due to a shortage of ICU beds.

Meanwhile, the published data and our analysis revealed the ratio of nephrologists to the general population in Japan is relatively higher than that in other developed countries (Figure 1C) (17). Extracorporeal therapies performed outside the ICU are often handled by “blood purification divisions,” and nephrologists are often involved in these procedures. Blood purification divisions are responsible for various extracorporeal apheresis therapies, such as chronic hemodialysis, plasma exchange, and polymyxin B hemoperfusion. In Japan, blood purification divisions exist mainly in large hospitals, and are separate from the department of nephrology.

The Japanese National University Hospital Association for Blood Purification Divisions has annually surveyed the situation of blood purification in 42 Japanese university hospitals. Using the survey data in 2020, we examined how Japanese nephrologists are involved in extracorporeal apheresis therapy. We classified these university hospitals into three groups depending on

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Figure 1. The number of intensive care beds, acute care hospital beds, and nephrologists in Japan from a global perspective. (A) Capacity of intensive care beds in selected Organization for Economic Co-operation and Development (OECD) countries, 2020 or nearest year. (B) Acute care hospital beds in OECD countries in 2017 or nearest years. The OECD defines acute care hospital beds as “beds
the involvement of nephrologists in the blood purification divisions: (1) hospitals in which the blood purification division is administered primarily by nephrologists, (2) hospitals in which blood purification division is administered partially by nephrologists, and (3) hospitals in which blood purification division is not administered by nephrologists. Our analysis showed that 26 hospitals (62%) had blood purification divisions administered primarily by nephrologists, 11 (26%) partially by nephrologists, and five (12%) where nephrologists are not involved in the blood purification divisions. These data reveal that nephrologists in Japan are deeply engaged in blood purification procedures outside the ICU. As the number of nephrologists in Japan has increased, more involvement in blood purification can be expected.

Furthermore, the association reported that continuous RRT (CRRT) sessions were performed in ICUs of 42 Japanese university hospitals. The total number of CRRT sessions performed in these hospitals was 20,387 in 2020, and 41% of these sessions were managed by blood purification divisions that included nephrologists. These data indicate that nephrologists in Japan play an essential role in AKI management in ICUs, alongside intensivists. Meanwhile, in most developed countries, intensivists rather than nephrologists are mainly responsible for CRRT in the ICU, according to a global survey (18,19). Therefore, the engagement of nephrologists in Japan in CRRT appears to be relatively higher than in other countries.

Methodology of AKI Diagnosis
The Japanese Society of Nephrology (JSN) has published AKI management guidelines that recommend using the Kidney Disease Improving Global Outcomes (KDIGO) AKI criteria (20). These public promotions raised awareness of AKI diagnosis among general physicians and other health care workers. Perhaps not surprisingly, the diagnosis of AKI, and even severity staging, is often made by non-nephrologists in Japan.

Urinary biomarkers have become recognized as an important tool for early AKI detection. Our government health insurance approves using some biomarkers for AKI management, including urine neutrophil gelatinase-associated lipocalin (NGAL) and liver-type fatty acid–binding protein. Several published clinical studies from Japan have investigated the clinical significance of such urine biomarkers (21). The AKI guidelines of the JSN also suggest using biomarkers for severity assessment, prognosis prediction, and differential diagnosis of AKI (20).

Prophylactic Intervention for AKI in Patients Who are High Risk
Since 2012, the JSN has also issued guidelines for contrast-associated AKI together with other societies (22). These societies have advocated the importance of contrast-associated AKI prevention to various health care workers. Saline administration or oral water intake for the prevention of AKI is common in clinical practice in Japan.

Additionally, the JSN has drawn attention to the dangers of AKI in patients with cancer through the publication of relevant guidelines (23). They have suggested various prophylactic AKI interventions for patients with cancer, such as risk assessments, dose adjustment of anticancer drugs, and hydration to prevent cisplatin nephrotoxicity. Reflecting these efforts, “onc nephrology” has been recognized as an emerging topic in Japan.

Another prophylactic intervention for AKI is the administration of atrial natriuretic peptide (ANP). ANP induces natriuresis, vasodilation, and suppression of circulating renin, angiotensin II, and aldosterone. These pharmacological effects are widely applied to the treatment of congestive heart failure in Japan. Low-dose ANP has been occasionally administered to prevent AKI, particularly in patients who are postcardiovascular surgery, or those with heart failure. However, a recent systematic review does not necessarily support the administration of low-dose ANP for AKI prevention, and raised concerns about the high risk of bias and insufficient sample sizes of the studies involved (24). In fact, the AKI guidelines from the JSN also make no clear recommendation on low-dose ANP administration (20).

Epidemiology of RRT
The situation for RRT for AKI in Japan has been covered by several studies that analyzed multicenter trials or national databases (Table 1) (7,25–27). These analyses showed that CRRT accounts for 70%–80% of all RRT modalities in the ICU in Japan. In comparison with reports from other countries, which showed that the rate of CRRT performed in the ICU is 30%–90%, the CRRT rate in Japan appears to be similar (28–31).

Table 1 also shows the causes of AKI in patients who are critically ill and required RRT. Sepsis and cardiovascular diseases were present in more than half of all patients who underwent RRT, which is similar to other developed countries (32).

Prescriptions and Cost of RRT
Japan’s CRRT procedures have two distinguishing features compared with other countries. The first is that nafamostat mesylate, a synthetic serine protease inhibitor, is one of the most frequently used anticoagulants. The advantage of nafamostat mesylate is that it inhibits coagulation and platelet aggregation with an extremely short half-life of 8 minutes. Therefore, it is mainly administered to patients receiving RRT who are at the highest risk of bleeding, such as patients who are postoperative or have undergone trauma, as the JSN
guidelines recommend (20). Unfractionated heparin is also widely used as an anticoagulant not only for CRRT, but also for intermittent hemodialysis. Meanwhile, citrate, although strongly recommended in the KDIGO guidelines, is seldomly administered in Japan due to the unavailability of applicable dialysate to citrate anticoagulation.

The second unique point about CRRT procedures in Japan is that the CRRT prescription dose is lower than the international standard dose. On the basis of various randomized controlled trials that investigated the effectiveness of a higher CRRT dose, the KDIGO AKI guidelines recommend a standard dose of 20–25 ml/kg per hr. Unfortunately, this standard dose prescription is not necessarily accepted by the Japanese government health insurance system, which seeks to reduce health care costs for Japan’s aging society. Therefore, in practice, the average CRRT dose in Japan is 10–15 ml/kg per hr, as mentioned in several Japanese guidelines (20,33).

Meanwhile, the influence of this lower CRRT dose on prognosis has been questioned. Uchino et al. compared the prognosis of patients with severe AKI in the international ICU database (n=1006, 20–25 ml/kg per hr) with that of patients in the Japanese ICU database (n=343, 10–15 ml/kg per hr) (34). Their multivariable logistic and sensitivity analyses demonstrated that a lower dose of CRRT did not significantly influence hospital mortality of patients who are critically ill. Table 1 shows the hospital mortality of patients with AKI who underwent RRT using larger Japanese databases. The mortality rates in Japan were not higher than those of patients who were critically ill with RRT in the Initiation of Dialysis Early Versus Delayed in the Intensive Care Unit (IDEAL-ICU), STandard versus Accelerated Initiation of Renal Replacement Therapy in Acute Kidney Injury (STARRT-AKI), Early versus late initiation of renal replacement therapy in critically ill patients with acute kidney injury (ELAIN) studies, which was 30%–60% (32), although there may be confounding factors other than the dose of CRRT.

As for the payment of RRT costs, Japan has adopted a universal health insurance system. Therefore, patients’ financial situation does not influence physicians’ decisions on medical interventions and RRT induction.

### Future Perspectives

In conclusion, researchers in Japan have published epidemiologic studies of AKI treatment on the basis of large databases, which summarize data on the health conditions and treatments of major segments of the Japanese population. However, there is no nationwide registry specific to AKI. The JSN has established a nationwide multicenter electronic health record-based chronic kidney disease database (35). Establishing a similar database for patients with AKI would be useful and desirable.

Also, following-up patients who are post-AKI is not widely performed by non-nephrologist physicians, despite its importance (36). In the future, efforts must be made to raise awareness among general physicians and other health care workers about how AKI can easily progress to CKD without appropriate treatment (37).

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### Author Contributions

H. Yamada was responsible for the investigation and wrote the original draft; M. Yanagita conceptualized the study, provided supervision, and reviewed and edited the manuscript.

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