Original Article

Dynamic monitoring of kidney injury status over 3 days in the intensive care unit as a sepsis phenotype associated with hospital mortality and hyperinflammation

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**A B S T R A C T**

Background: Sepsis-associated acute kidney injury (AKI) often worsens with the deterioration of a patient’s condition. Therefore, we hypothesized that monitoring AKI dynamically from day 1 to day 3 was potential to predict hospital mortality. Specifically, we explored whether monitoring AKI dynamically in the intensive care unit (ICU) could be a sepsis phenotype predictive of mortality. A new classification was established based on the change in the AKI stage from admission day 1 and day 3. We compared the hospital mortality, cytokines, and immune response pattern between each group.

Methods: We retrospectively enrolled 523 patients with sepsis, and we calculated the AKI stages on day 1 and day 3 admission to ICUs.

Among these 523 people, 388 of them were assigned to normal, improved, and deteriorated groups according to the changes in the AKI stages. 263 of which did not develop AKI on day 1 and day 3 (normal group). The AKI stage improved in 68 patients (improved group) and worsened in 57 (deteriorated group). We compared the mortality rates between the groups, and identified the relationship between the dynamic AKI status, immune response patterns, and cytokine levels.

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Results: The hospital mortality rate in the deteriorated group was higher than that in the non-deteriorated group (combination of normal and improved group) \( (p = 0.004) \). Additionally, according to the Kaplan–Meier analysis, the non-deteriorated group had a distinct hospital survival curve \( (p = 0.004) \). Furthermore, both the overexpression of tumor necrosis factor-\( \alpha \) and decreased monocyte expression of human leukocyte antigen-DR were present in the deteriorated group.

Conclusions: The deteriorated group was associated with a higher hospital mortality rate, potentially resulting from an abnormal inflammatory response. Worsening AKI in the first 3 days of ICU admission may be a sepsis phenotype predictive of hospital mortality.

### At a glance of commentary

**Scientific background on the subject**

Acute renal injury is a warning sign of poor prognosis in the treatment of sepsis. By observing the deterioration of kidney function, physicians can predict the patient’s outcome earlier and give appropriate treatment individually.

**What this study adds to the field**

This article brings an idea that observing the changes in kidney function in the first three days could be closer to the clinical results than observing the kidney status on admission only. This article also gives a glance of cytokine changes between patients with normal, improved, or worsen kidney status.

### Material and methods

**Study design and setting**

This was a retrospective study conducted in three medical ICUs (34 beds total) at the Kaohsiung Chang Gung Memorial Hospital, a 2700-bed tertiary teaching hospital in Southern Taiwan. All patients admitted to the ICU between August 2013 and January 2016 were screened for the study. Patients were excluded if they met any of the following criteria: (1) <18 years of age, (2) no instance of sepsis during admission, and (3) those who died within 3 days of admission. Data from this study population were also analyzed for other specific aims determined beforehand \[10,12–18\].

**Definitions**

The criteria used to define sepsis were adopted from the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), which defines sepsis as an increase in the Sequential Organ Failure Assessment (SOFA) score by \( \geq 2 \) points \[3\]. The AKI stages were stratified based on the 2012 Kidney Disease Improving Global Outcomes Clinical Practice Guidelines for AKI \[19\], in which the stages are classified as follows: stage 1, an increase in serum creatinine level that is 1.5–1.9 times that taken at baseline or \( \geq 0.3 \text{mg/dL} \); stage 2, an increase in serum creatinine level that is 2.0–2.9 times that taken at baseline; and stage 3, an increase in serum creatinine level that is 3.0 times that taken at baseline or \( \geq 4.0 \text{mg/dL} \) or the initiation of renal replacement therapy. The first serum creatinine value measured on admission was considered the baseline level \[20\].

For patients who lacked serum creatinine data, urine output was used to determine the AKI stage, according to the following criteria: stage 1, urine output <0.5 mL/kg/h for 6–12 h; stage 2, urine output <0.5 mL/kg/h for >12 h; and stage 3, urine output <0.3 mL/kg/h for >24 h or the presence of anuria for >12 h. Chronic kidney disease (CKD) was defined as an abnormality in the structure or function of the kidney present for at least 3 months, with a glomerular filtration rate (GFR) < 60 mL/min/1.73 m\(^2\) (GFR categories: G3a–G5) \[21\].

Most patients in our study had complete creatinine data for levels and immune response patterns for each subgroup to predict mortality outcomes.
both admission days 1 and 3, and the AKI staging was verified by two licensed physicians to reduce the likelihood of misclassification bias.

**Categorization**

Patients with sepsis were categorized based on changes in renal function and AKI stage from day 1 to day 3 of ICU admission. Patients whose renal function and serum creatinine levels were normal with no AKI on both day 1 and day 3 were classified as the normal group. The improved group was comprised of patients whose AKI stage improved, and the deteriorated group was comprised of patients whose AKI stage worsened.

**Immune status and cytokine data**

In our prior studies, we investigated immune function and cytokine levels in sepsis [12,16]. We retrospectively reviewed the medical charts and excluded all those with missing data. A total of 74 patients were included in the immune function and cytokine data analysis.

Details regarding the laboratory procedures used have been reported in previous studies. In brief, after plasma and peripheral blood mononuclear cell preparation, the patients' immune status was determined by measuring the levels of monocyte expression of human leukocyte antigen-DR (HLA-DR) via flow cytometry. In this study, at least 30,000 peripheral blood mononuclear cells per 100 µL of peripheral blood were analyzed from each sample. The results are expressed as the percentage of HLA-DR-positive monocytes within the total monocyte population. We identified immune paralysis through monitoring the downregulation of HLA-DR expression [22].

The pro-inflammatory cytokine levels analyzed included tumor necrosis factor-α (TNF-α), interferon gamma (IFN-γ), and interleukin-6 (IL-6). TNF-α is a well-known pro-inflammatory cytokine. IFN-γ contributes to macrophage and T-cell activation and participates in anti-inflammatory processes such as the induction of anti-inflammatory molecules (e.g., interleukin-1 receptor antagonist [IL-1Ra]) and the modulation of pro-inflammatory cytokine production [23]. IL-6 acts as a pro-inflammatory cytokine with certain anti-inflammatory properties. Circulating IL-6 stimulates the production and
release of chemokines, resulting in the recruitment of neutrophils into the uninjured lung [24]. Simultaneously, IL-6 plays a role in interleukin-10 (IL-10) production and limits inflammation of the lungs [25].

IL-10 and IL-1Ra were selected for their anti-inflammatory effects. Both circulating IL-1Ra and IL-10 levels are significantly elevated in sepsis. IL-10 suppresses the production of proinflammatory mediators such as TNF-α, interleukin-1 (IL-1), IL-6, and IFN-γ in immune cells. IL-10 also mitigates AKI-associated lung inflammation [25]. IL-1Ra binds non-productively to the cell surface IL-1 receptor and prevents IL-1 from transmitting a signal to that cell. Therefore, IL-1Ra could potentially be used to predict sepsis mortality [26].

Vascular endothelial growth factor (VEGF) was also selected for its pro-inflammatory effects via cell-mediated immune inflammation and associated angiogenesis. Some studies have demonstrated the renal protective effect of VEGF through associated improvement in renal micro-perfusion [27].

Granulocyte colony-stimulating factor (G-CSF) is an immune modulator that acts on neutrophils to enhance their maturation, survival, and effector function [28]. The levels of selected cytokines were quantified using the MILLIPLEX MAP customized human cytokine/chemokine magnetic bead panel kit.

### Statistical analyses

Data analyses were performed using SPSS software (version 22.0; IBM Corp., Armonk, NY, USA), and statistical significance was set at a two-sided p value < 0.05. Patient demographics, clinical characteristics, and outcomes are summarized using frequencies and percentages for categorical variables and means ± standard deviations for continuous variables.

We performed a comparative analysis of 7-day, 14-day, 28-day, ICU, and hospital mortality between the groups using the Pearson chi-square test. Inter-group differences were analyzed using one-way analysis of variance followed by a post hoc test.
Bonferroni correction for repeated comparisons. A trend test was performed to examine the relationships between the groups. To analyze the survival curve, we compared time-to-event data using the log-rank test from the Kaplan–Meier survival analysis.

A univariate Cox regression analysis was performed to examine the impact of medical conditions on hospital survival. Several covariates, including mortality predictors (age, Acute Physiology and Chronic Health Evaluation II [APACHE II] score, and body mass index [BMI]) and potential confounders (gender, comorbidities, and progression of AKI stage) were included in the model. Multivariate Cox regression backward elimination (likelihood ratio) models were performed to analyze the association between mortality risk and medical conditions after adjusting for the relevant confounders.

HLA-DR expression (%) is presented in a bar chart, and the distribution of cytokine levels (pg/dL) is shown using a box plot. We performed nonparametric statistics using the Kruskal–Wallis test to detect the statistical significance of each cytokine.

### Results

A total of 2295 patients were admitted to the three medical ICUs between August 2013 and January 2016. After excluding patients who did not develop sepsis and those who died within 3 days of admission, 523 patients remained. The new classification was adopted for 388 of these 523 patients. A total of 263 patients were included in the normal group, 68 in the improved group, and 57 in the deteriorated group. After excluding those with missing HLA-DR expression and cytokine level data, a total of 74 patients who had data for both day 1 and day 3 of admission were included (normal group = 48, improved group = 14, deteriorated group = 12) (Fig. 1).

The backgrounds and baseline characteristics of the patients are shown in Table 1. The variables, which include primary information (age, sex, and BMI), subscored items from the Charlson comorbidity index, and common possible infectious sources, were collected from the patients’ medical charts.

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| Table 2 Mortality outcomes of patients with sepsis. | Non-Deteriorated Group (n = 331) | Deteriorated Group (n = 57) | p value | p value for trend test |
|-----------------------------------------------|----------------------------------|-----------------------------|---------|------------------------|
| 7-day mortality | 28 (7.2) | 18 (5.4) | 10 (17.5) | 0.003 |
| 14-day mortality | 49 (12.6) | 36 (10.9) | 13 (22.8) | 0.017 |
| 28-day mortality | 88 (22.7) | 68 (20.5) | 20 (35.1) | 0.018 |
| ICU mortality | 78 (20.1) | 59 (17.8) | 19 (33.3) | 0.009 |
| Hospital mortality | 150 (38.7) | 120 (36.3) | 30 (52.6) | 0.027 |

1 Data expressed as n (%) for categorical variables.
2 Abbreviations: ICU: intensive care unit; AKI: acute kidney injury.
Determining whether dynamic monitoring of the AKI stage can be used to stratify patients’ hospital mortality

Significant differences in hospital mortality ($p = 0.027$) and all other mortality outcomes were found between the deteriorated and non-deteriorated groups (Table 2). The Kaplan–Meier analysis also revealed a significant difference in hospital mortality between the deteriorated and non-deteriorated groups ($p = 0.004$) (Fig. 2A).

Both univariate and multivariate Cox regression analysis were performed to analyze the association between the mortality and prognostic variables. Inclusion in the deteriorated group (HR: 1.702, $p = 0.004$), a history of stroke (HR: 0.671, $p = 0.011$), and cancer (HR: 2.225, $p < 0.001$) were the final independent and significant prognostic variables for hospital mortality after multivariate Cox regression analysis (Table 3).

Immune response patterns according to HLA-DR expression

The mean level of HLA-DR expression (%) is presented in a bar chart (Fig. 3A). Mean HLA-DR expression levels were highest in the deteriorated group on the first day, though the mean levels decreased from day 1 to day 3 in both the improved and deteriorated groups.

Expression of pro-inflammatory cytokines

The distribution of the cytokine levels is presented as a box plot (pg/dL) (Fig. 3B–F). The deteriorated group had the highest median TNF-$\alpha$ levels on day 1 (Fig. 3B) and the highest upper quartile and maximum TNF-$\alpha$ levels, which might suggest an overexpression of TNF-$\alpha$. Additionally, the TNF-$\alpha$ level in the deteriorated group was significantly higher than that in the normal group on both day 1 ($p < 0.001$) and day 3 ($p = 0.004$).

Similarly, the deteriorated group had the highest median and upper quartile IFN-$\gamma$ levels on both day 1 and day 3 (Fig. 3C). Additionally, the deteriorated group ($p = 0.001$) had significantly higher levels of IL-6 than the normal group on day 1 (Fig. 3D), and on day 3 ($p = 0.002$).

Expression of anti-inflammatory cytokines

The deteriorated group had the highest median IL-10 on both day 1 and day 3; however, the differences were not significant for either day (Fig. 3E). Similarly, no significant differences in IL-1Ra levels were found between the groups (Fig. 3F).

Other clinical variables

Essential clinical information associated with sepsis severity is compared in the Appendices. This includes kidney function (BUN, creatinine, fluid intake, urine output, and eGFR), liver function (bilirubin), inflammatory markers (C-reactive protein [CRP], and procalcitonin), and each subitem of the SOFA score. The G-CSF and VEGF levels are also available in the Appendices.

Discussion

AKI is recognized not only as a comorbidity associated with sepsis, but also as a cause of mortality [29]. The development of AKI during sepsis has a significant effect on multiple organ function and is predictive of higher mortality [30]. Serial observations of a patient’s response to sepsis treatment is crucial and is associated with a better prediction of mortality than the use of static initial values [10], and our study further confirms this. Significantly different hospital survival curves were observed between the deteriorated and non-deteriorated groups ($p = 0.004$) (Fig. 2B). In our study, the progression of the AKI stage between days 1 and 3 (deteriorated group) is a potential predictor of hospital mortality (Table 3).

Monitoring dynamic changes in the AKI stage between days 1 and 3 is the cornerstone of our classification, which is easy to calculate and is clinically available information. Compared with the kinetic estimated glomerular filtration rate (KeGFR), initially designed as an easy bedside tool to dynamically assess a patient’s AKI status, our categorization is straightforward and can be applied in patients with sepsis.

### Table 3 Univariate and multivariate Cox regression analyses of the predictors of hospital mortality.

| Variable                      | Hazard ratio | 95% CI      | p value |
|-------------------------------|--------------|-------------|---------|
| **Hospital**                  |              |             |         |
| Age >65                       | 1.074        | 0.785–1.470 | 0.656   |
| Mortality                     |              |             |         |
| Gender, male                  | 0.882        | 0.660–1.180 | 0.398   |
| APACHE II                     | 0.994        | 0.978–1.011 | 0.494   |
| BMI                           | 0.990        | 0.962–1.019 | 0.490   |
| Coronary heart disease        | 0.753        | 0.527–1.077 | 0.121   |
| History of stroke             | 0.774        | 0.528–1.135 | 0.189   |
| Hypertension                  | 1.117        | 0.810–1.538 | 0.500   |
| COPD                          | 1.044        | 0.683–1.598 | 0.841   |
| Cancer                        | 2.032        | 1.511–2.731 | <0.001  |
| Liver cirrhosis               | 2.218        | 1.434–3.431 | <0.001  |
| Diabetes mellitus             | 0.928        | 0.688–1.253 | 0.627   |
| CKD                           | 0.937        | 0.608–1.442 | 0.766   |
| Deteriorated group (vs. all other groups) | 1.650 | 1.102–2.471 | 0.015   |

**Multivariate Cox regression analysis (likelihood ratio)**

| Hazard ratio | 95% CI | p value |
|--------------|-------|---------|
| 0.671        | 0.434–1.036 | 0.072   |
| 2.225        | 1.591–3.111 | <0.001  |
| 1.702        | 1.131–2.560 | 0.011   |

Abbreviations: APACHE II: Acute Physiology and Chronic Health Evaluation II; BMI: body mass index; COPD: chronic obstructive pulmonary disease; CKD: chronic kidney disease.
One major assumption of the KeGFR formula is the constant production of creatinine over the course of AKI, which may not be the case for patients with sepsis during fluid resuscitation [31].

Patients with severe chronic comorbidities often have poor outcomes. After adjusting for relevant confounders, our study also revealed other impactful factors, such as a history of cancer (Table 3). This suggests that sepsis outcomes may depend on multiple factors beyond the patient’s signs and symptoms. Clinical factors other than kidney condition are also important and should not be dismissed.

The decreased mean level of HLA-DR expression in both the improved and deteriorated groups might reflect HLA-DR downregulation during sepsis. However, the degree of

Fig. 3 HLA-DR expression and cytokine levels on day 1 and day 3. 1. Error bars in Fig. 3A represent the 95% confidence intervals; outliers in Fig. 3B–F are presented by the white circles above or below the box graphs. 2. The lowercase letters above or below the box graphs in the box plots in Figure 3B–F represent a significant difference (p-value < 0.05) between the two groups that are labeled with the same lowercase letters. 3. Abbreviations: HLA-DR, human leukocyte antigen-DR; TNF-α, tumor necrosis factor-α; IL, interleukin; IFN-γ, interferon-gamma.
fluid balance is not affected \cite{43}. Abnormal fluid accumulation late initiation of renal replacement therapy if the cumulative by associated malfunction of the heart and lungs. This may be driven by kidney failure, which can increase mortality over the first 72 h. The deteriorated group had relatively higher TNF-\(\alpha\) levels on the first day, possibly suggesting a more severe inflammatory status in the deteriorated group (Fig. 3B).

A relatively wide distribution of IFN-\(\gamma\) levels were found in the normal group. The upper quartile IFN-\(\gamma\) level on day 1 was higher in the normal group than in the improved group, and the maximum on day 1 in the normal group was higher than that in the deteriorated group (Fig. 3C). This phenomenon might be explained by the complex role that IFN-\(\gamma\) plays in sepsis. IFN-\(\gamma\) is a macrophage and T-cell activating cytokine that also affects immunoregulation. IFN-\(\gamma\) inhibits renal fibrosis and plays a protective role in renal organ-specific autoimmunity \cite{33,34}. Furthermore, IFN-\(\gamma\) has been reported to reverse sepsis-induced immunoparalysis \cite{35}. Improved survival has been shown in patients with sepsis who also have decreased expression of HLA-DR when they are treated with recombinant IFN-\(\gamma\).

IL-10 acts as an anti-inflammatory cytokine; however, overexpression of IL-10 can be harmful since it can alternatively activate alveolar macrophages and decrease intracellular killing of bacteria, as demonstrated in a mouse model \cite{36}. However, whether the overexpression of IL-10 contributed to the high mortality rate in the deteriorated group in this study is not clear. Although the deteriorated group had higher upper quartile, median, and lower quartile levels of IL-10 compared to all other groups, there was no statistically significant difference in IL-10 levels between the subgroups. Indeed, the distribution of IL-10 levels varied considerably across the subgroups in our study.

Due to the heterogeneity of sepsis syndrome, correctly selecting the group of patients requiring optimal treatment must be approached carefully \cite{37}. Examining various sepsis phenotypes has potential treatment implications \cite{38}. This phenotype study of sepsis-associated AKI may improve our understanding of the complex pathophysiology of sepsis and help us to determine the appropriate application of these techniques. A conservative fluid strategy has been suggested as a treatment for patients with sepsis after the initial phase. Fluid balance and immune homeostasis play central roles in the resolution of inflammation \cite{10,39}. Our study demonstrated the positive association between an increase in cumulative fluid balance and mortality. The cumulative fluid balance in the deteriorated group was the highest over the first 72 h. The same phenomenon has also been observed in other studies \cite{40-42}.

Additionally, reversal may not be possible with the early or late initiation of renal replacement therapy if the cumulative fluid balance is not affected \cite{43}. Abnormal fluid accumulation may be driven by kidney failure, which can increase mortality by associated malfunction of the heart and lungs. This may suggest the need for a treatment strategy that first focuses on patients at high risk of kidney failure (e.g., dynamic AKI stage-based categorization) and then on an aggressive attempt to return the patient to a euvolemic state. However, this strategy requires validation from further randomized controlled trials.

Our study presented a new strategy of dynamically monitoring the AKI status of patients during their first 3 days of admission, and over-inflammation might explain the poor mortality outcomes in the deteriorated group. The difference in the survival curves between the deteriorated and non-deteriorated groups suggests this classification has the potential to be a useful sepsis phenotyping tool. We made a validation and compared the deteriorated group to non-deteriorated group in all the 523 patients; the survival curve remained distinct (\(p = 0.034\)) and the \(p\) value became 0.050 if we removed the patients with permanent renal replacement therapy prior to admission (Figure S3-S4).

Our study had some limitations. First, our categorization required AKI status information from day 3; therefore, patients who died before the third day of ICU admission were excluded. Nevertheless, most patients with sepsis admitted to the ICU survived for more than 3 days. Second, the number of patients in the subpopulation with immune profiles was relatively small, especially after they were categorized into subgroups. The likelihood that 74 patients can represent all potential immune responses may be questionable. A little investigation revealed that these 74 patients were relatively evenly distributed across groups (normal group: 48 (26.2%), improved group: 14 (27.9%), and deteriorated group: 12 (26.3%), \(p = 0.969\)). Third, since this study was conducted by retrospectively reviewing medical charts, the potential for selection bias must be considered. A multicenter, prospective validation study with clinical variables and immune profiles is warranted in the future.

Conclusions

The dynamic change in AKI status from day 1 to day 3 of ICU admission has the potential to be used as a sepsis phenotype to predict hospital mortality. AKI stage progression is associated with poor mortality outcomes and hyper-inflammatory responses.

Ethics approval and consent to participate

Written informed consent was obtained from the patients or their surrogates in the subpopulation with immune profiles. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital. All procedures were performed in accordance with the relevant guidelines and regulations.

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Conflicts of interest

The authors have no potential conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j bj.2021.08.006.

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