Elevated serum galectin-1 concentrations are associated with increased risks of mortality and acute kidney injury in critically ill patients

Ruey-Hsing Chou
Taipei Veterans General Hospital

Chuan-Tsai Tsai
Taipei Veterans General Hospital

Ya-Wen Lu
Taipei Veterans General Hospital

Jiun-Yu Guo
Taipei Veterans General Hospital

Chi-Ting Lu
Taipei Veterans General Hospital

Yi-Lin Tsai
Taipei Veterans General Hospital

Cheng-Hsueh Wu
Taipei Veterans General Hospital

Shing-Jong Lin
Cheng Hsin General Hospital

Ru-Yu Lien
Taipei Veterans General Hospital

Shu-Fen Lu
Taipei Veterans General Hospital

Shang-Feng Yang
Cheng Hsin General Hospital

Po-Hsun Huang (✉ huangbsvgh@gmail.com)
Taipei Veterans General Hospital

Research

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Abstract

**Background:** Galectin-1 (Gal-1), a member of the β-galactoside binding protein family, is associated with inflammation and chronic kidney disease. However, the effect of Gal-1 on mortality and acute kidney injury (AKI) in critically ill patients remains unclear.

**Methods:** From May 2018 to March 2020, 350 patients admitted to the medical intensive care unit (ICU) of Taipei Veterans General Hospital, a tertiary medical center, were enrolled in this study. Forty-one patients receiving long-term renal replacement therapy were excluded. Serum Gal-1 levels were determined within 24 h of ICU admission. The patients were divided into three equally sized groups according to their serum Gal-1 levels (low, serum Gal-1 < 39 ng/ml; median, 39–70 ng/ml; high, ≥71 ng/ml). All patients were followed for 90 days or until death.

**Results:** Mortality in the ICU and at 90 days was greater among patients with elevated serum Gal-1 levels. In analyses adjusted for the body mass index, malignancy, sepsis, Sequential Organ Failure Assessment (SOFA) score, and serum lactate level, the serum Gal-1 level remained an independent predictor of 90-day mortality [median vs. low: adjusted hazard ratio (aHR) 2.11, 95% confidence interval (CI) 1.24–3.60, *p* = 0.006; high vs. low: aHR 3.21, 95% CI 1.90–5.42, *p* < 0.001]. Higher serum Gal-1 levels were also associated with a higher incidence of AKI within 48 h after ICU admission, independent of the SOFA score and renal function (median vs. low: aHR 2.77, 95% CI 1.21–6.34, *p* = 0.016; high vs. low: aHR 2.88, 95% CI 1.20–6.88, *p* = 0.017). The results were consistent among different subgroups with high and low Gal-1 levels.

**Conclusion:** Serum Gal-1 elevation at the time of ICU admission were associated with an increased risk of mortality at 90 days, and an increased incidence of AKI within 48 h after ICU admission.

**Background**

Galectin 1 (Gal-1) is a member of the galectin family that has one carbohydrate recognition domain. It is expressed throughout the body and involved in T-cell homeostasis, which in turn regulates the immune response and host–pathogen interaction [1]. Recombinant Gal-1 is expressed to ameliorate acute and chronic inflammation in patients with autoimmune encephalomyelitis and those with collagen-induced arthritis [2–4]. It also mediates the interaction of cancer cells with the extracellular matrix. [5] A recent review even suggested that Gal-1 is an emergent mediator of cardiovascular inflammation [6]. However, its role in critically ill patients remains poorly understood.

Sepsis, characterizes by uncontrolled infection and life-threatening organ dysfunction, is the leading causes of death among critically ill patients in medical ICUs [7]. Even non–infection-related systemic inflammatory response syndrome (SIRS) carry similar mortality risks in patients in the ICU [8]. In a previous study, 88.4% of patients in the intensive care unit (ICU) had at least two criteria of SIRS [9]. In this single-center observational study, we examined associations of the serum Gal-1 level with all-cause mortality and acute kidney injury (AKI) in septic or critically ill patients admitted to the ICU. We
hypothesized that patients with higher Gal-1 concentrations would have higher incidences of mortality and AKI.

**Material And Methods**

**Study population**

This study was carried out in the noncoronary medical ICU of Taipei Veterans General Hospital, a tertiary medical center in Taipei, Taiwan. From May 2018 to March 2020, we screened 350 patients admitted to the medical ICU because of various critical illnesses, such as sepsis, pneumonia, massive gastrointestinal bleeding, and acute heart failure. Patients admitted for observation after surgery, those in the ICU for < 3 days, and those with pre-dialysis status before ICU admission (n = 41) were not included in the study. Patients were admitted from the emergency department or transferred from the ordinary ward. In total, 309 patients provided informed consent and participated in this study.

Trained personnel with data collection experience collected demographic and clinical data, including age, sex, body mass index, co-morbidities, drug exposure, etiologies of ICU admission, disease severity, and laboratory values at the time of ICU admission. The Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA) scores were calculated to assess disease severity at the time of ICU admission [10, 11]. Blood chemistry parameters were measured, and cell counts were determined by routine methods in the hospital's central laboratory on the day of ICU admission. The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation [12]. A flowchart of patient enrollment is provided as Fig. 1. This study was approved by the Research Ethics Committee of Taipei Veterans General Hospital (Num. 2018-02-009AC) and conducted according to the principles of the Declaration of Helsinki.

**Serum Gal-1 measurement**

Trained registered nurses obtained blood samples from participants within 24 h after ICU admission. Serum Gal-1 concentrations were determined using the commercially available Human Galectin-1 Quantikine ELISA Kit DGAL10 (R&D Systems, Inc., Minneapolis, MN, USA). The patients were divided into three equally sized groups according to the serum Gal-1 level.

To investigate the difference in the Gal-1 concentration between patients with and without critical illness, we compared the GAL-1 concentrations of patients admitted to the ICU with those of patients admitted for coronary angiography (CAG), measured in our previous study [13]. The CAG group consisted of 798 patients with (n = 400) and without (n = 398) significant coronary artery disease (CAD).

**Study outcomes and patient follow up**

We retrieved data on primary and secondary outcomes from the hospital's electronic medical records system. Primary outcomes were all-cause mortality in the ICU and at 90 days. Secondary outcomes were the durations of ICU admission and hospitalization, occurrence of AKI within 48 h after ICU admission, and dialysis dependency at the time of discharge. According to the Acute Kidney Injury Network criteria,
AKI was defined as the acute deterioration of renal function and requirement for renal replacement therapy [14, 15]. Dialysis dependency was defined as the requirement for renal replacement therapy (hemodialysis or peritoneal dialysis) after discharge due to irreversible kidney dysfunction [14].

Statistical analysis
Categorical variables are presented as numbers and percentages and were assessed using the Chi-Squared test. Continuous variables are expressed as medians and interquartile ranges and were analyzed using the Kruskal–Wallis test. Kaplan–Meier survival curves and the log-rank test were used to estimate 90-day mortality. Cox proportional-hazard regression analyses were used to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) for factors associated with 90-day mortality. Logistic regression analysis was performed to investigate the risk of AKI within 48 h after ICU admission. Variables with $p$ values $< 0.1$ in the univariate regression analysis were entered into a final forward stepwise multivariate regression model. To investigate the effect of Gal-1 modified by different conditions, we performed subgroup analyses with the cohort stratified by the presence of diabetes, proteinuria, initial eGFR, pneumonia, and septic shock. $P$ values $< 0.05$ were considered to be significant. All analyses were performed using SPSS software (version 19.0; IBM Corporation, Armonk, NY, USA).

Results

Baseline characteristics of study participants
In total, 309 patients admitted to the ICU with critical conditions were included in this study. The median age of the study population was 67 (range 57–78) years, and 68% of participants were male. Sepsis was the leading reason for ICU admission (87.4% prevalence) and pneumonia was the most common source of infection. The baseline characteristics of the study population are summarized in Table 1.
Table 1
Baseline characteristics of critically ill patients grouped by serum galectin-1 concentrations.

|                                | Low galectin-1 (< 39 ng/mL) | Median galectin-1 (39–71 ng/mL) | High galectin-1 (≥ 71 ng/mL) | P |
|--------------------------------|------------------------------|----------------------------------|-------------------------------|---|
| Age (years)                    | 64.0 (57.0–75.0)            | 68.0 (60.0–80.0)                 | 68.0 (55.0–80.0)              | 0.185 |
| Male gender                    | 73 (70.9)                   | 69 (67.0)                        | 69 (67.0)                     | 0.787 |
| Body mass index                | 22.3 (19.7–24.9)            | 23.6 (20.8–26.6)                 | 23.1 (20.1–27.0)              | 0.050 |
| Hypertension                   | 38 (36.9)                   | 60 (58.3)                        | 41 (39.8)                     | 0.004 |
| Diabetic mellitus              | 22 (21.4)                   | 31 (30.1)                        | 37 (35.9)                     | 0.069 |
| Heart failure                  | 8 (7.8)                     | 13 (12.6)                        | 16 (15.5)                     | 0.222 |
| Cirrhosis                      | 7 (6.8)                     | 6 (5.8)                          | 7 (6.8)                       | 0.948 |
| Malignancy (solid tumor)       | 42 (40.8)                   | 35 (34.0)                        | 38 (36.9)                     | 0.599 |
| ACEi / ARB exposure            | 17 (16.5)                   | 25 (24.3)                        | 23 (22.3)                     | 0.363 |
| Diuretics exposure             | 9 (8.7)                     | 22 (21.4)                        | 19 (18.4)                     | 0.036 |
| Nephrotoxic agents exposure    | 5 (4.9)                     | 11 (10.7)                        | 7 (6.8)                       | 0.268 |
| Etiologies of ICU admission    |                              |                                  |                               |     |
| Pneumonia                      | 77 (74.8)                   | 77 (74.8)                        | 73 (70.9)                     | 0.767 |
| Sepsis                         | 83 (80.6)                   | 91 (88.3)                        | 96 (93.2)                     | 0.023 |
| Acute heart failure            | 1 (1.0)                     | 3 (2.9)                          | 6 (5.8)                       | 0.140 |
| Massive bleeding               | 8 (7.8)                     | 5 (4.9)                          | 8 (7.8)                       | 0.631 |
| Disease severity               |                              |                                  |                               |     |
| APACHE II scores               | 22.0 (18.0–29.0)            | 26.0 (20.0–32.0)                 | 29.0 (24.0–35.0)              | < 0.001 |
| SOFA scores                    | 8.0 (6.0–10.3)              | 10.0 (8.0–12.0)                  | 11.0 (9.0–13.3)               | < 0.001 |
| Ventilator usage               | 94 (91.3)                   | 86 (83.5)                        | 99 (96.1)                     | 0.009 |
| Inotrope/ vasopressor usage    | 55 (53.4)                   | 46 (44.7)                        | 66 (64.1)                     | 0.020 |

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; eGFR, estimated glomerular filtration rate.
Patients with serum Gal-1 concentrations < 39 ng/ml were allocated to the low Gal-1 group, those with serum Gal-1 concentrations of 39–71 ng/ml were allocated to the median Gal-1 group, and those with serum Gal-1 concentrations ≥ 71 ng/ml were allocated to the high Gal-1 group. The prevalence of sepsis, septic shock, and proteinuria and the percentage of patients requiring ventilators and inotropes/vasopressors were greater among patients with high Gal-1 concentrations than among those with low and median Gal-1 concentrations. Patients with higher Gal-1 concentrations also had higher APACHE II and SOFA scores, and lactate concentrations, and lower hemoglobin levels, mean arterial pressure (MAP), and eGFRs. Gal-1 concentrations were significantly higher among patients admitted to the ICU than among those admitted for CAG (52.8 vs. 18.4 ng/mL, p < 0.001), and among patients with significant CAD relative to controls (19.4 vs. 17.4 ng/mL, p = 0.001; Additional file 1).

**Associations of the serum Gal-1 level with primary outcomes**

Participants’ clinical outcomes are summarized in Table 2. The ICU and 90-day all-cause mortality rates were greater in the high Gal-1 group than in the median and low Gal-1 groups (42.7% vs. 30.1% and 17.5%, and 66% vs. 50.4% and 35.9%, respectively; both p < 0.001). Accordingly, the 90-day survival rate was significantly lower in patients with high Gal-1 levels than in the other two groups (p < 0.0001; Fig. 2). In multivariate analysis adjusted for the body mass index, malignancy, sepsis, SOFA score, and serum...
lactate level, higher serum Gal-1 levels were associated with greater 90-day all-cause mortality [median vs. low: adjusted hazard ratio (aHR) 2.11, 95% CI 1.24–3.60, \( p = 0.006 \); high vs. low: aHR 3.21, 95% CI 1.90–5.42, \( p < 0.001 \); Table 3]. Subgroup comparisons according to the serum Gal-1 level are shown in Table 4. High serum Gal-1 levels were associated with greater 90-day mortality than were low serum Gal-1 levels across different subgroups.

| Table 2 | Clinical outcomes of critically ill patients grouped by serum galectin-1 concentrations. |
|---------|---------------------------------------------------------------------------------------|
|         | Low galectin-1 (< 39 ng/mL) | Median galectin-1 (39–71 ng/mL) | High galectin-1 (≥ 71 ng/mL) | \( P \) |
|         | n = 103                         | n = 103                           | n = 103                           |
| **Mortality during follow-up period** | | | | |
| Length of ICU stay (days) | 8.0 (5.0–14.0) | 9.0 (6.0–18.0) | 9.0 (5.0–14.0) | 0.265 |
| Length of hospitalization (days) | 25.0 (14.0–38.0) | 25.0 (12.0–38.0) | 20.0 (9.0–44.0) | 0.659 |
| Mortality, in ICU | 18 (17.5) | 31 (30.1) | 44 (42.7) | \(< 0.001\)|
| Mortality, 90-days | 37 (35.9) | 52 (50.4) | 68 (66.0) | \(< 0.001\)|
| **AKI within 48 hours after ICU admission** | | | | |
| AKI (total cases) | 18 (17.5) | 39 (37.9) | 52 (50.5) | \(< 0.001\)|
| Stage 1 | 10 (9.7) | 20 (19.4) | 15 (14.6) | \(< 0.001\)|
| Stage 2–3 | 8 (7.8) | 19 (18.4) | 37 (35.9) | |
| Dialysis-dependence after discharge | 0 (0) | 5 (4.9) | 7 (6.8) | 0.034 |

AKI, acute kidney injury; ICU, intensive care unit.
Table 3
Univariate and multivariate associations of factors with all-cause mortality within 90 days among critically ill patients.

|                                | Univariate | Multivariate* |
|--------------------------------|------------|---------------|
|                                | Crude HR (95% CI) | P       | Adjusted HR (95% CI) | P       |
| Age                            | 1.00 (0.99–1.01) | 0.488   | 0.94 (0.90–0.98)     | 0.006   |
| Male gender                    | 1.29 (0.92–1.83) | 0.145   |                     |         |
| Body mass index                | 0.96 (0.93–1.00) | 0.041   | 0.94 (0.90–0.98)     | 0.006   |
| Hypertension                   | 0.63 (0.46–0.87) | 0.005   |                     |         |
| Diabetic mellitus              | 0.74 (0.52–1.06) | 0.105   |                     |         |
| Heart failure                  | 0.82 (0.50–1.36) | 0.436   |                     |         |
| Cirrhosis                      | 1.16 (0.61–2.21) | 0.647   |                     |         |
| Malignancy (solid tumor)       | 1.48 (1.08–2.03) | 0.015   | 1.87 (1.27–2.75)     | 0.001   |
| ACEi / ARB exposure            | 0.89 (0.60–1.32) | 0.575   |                     |         |
| Diuretics exposure             | 1.15 (0.76–1.74) | 0.509   |                     |         |
| Nephrotoxic agents exposure    | 0.89 (0.50–1.61) | 0.706   |                     |         |
| Etiologies of ICU admission    |            |         |                     |         |
| Pneumonia                      | 0.91 (0.64–1.30) | 0.609   |                     |         |
| Sepsis                         | 1.99 (1.10–3.58) | 0.023   | 2.95 (1.07–8.11)     | 0.036   |
| Acute heart failure            | 0.52 (0.17–1.63) | 0.264   |                     |         |
| Massive bleeding               | 0.63 (0.31–1.27) | 0.195   |                     |         |
| Disease severity               |            |         |                     |         |
| APACHE II scores               | 1.06 (1.04–1.09) | < 0.001 |                     |         |
| SOFA scores                    | 1.16 (1.11–1.22) | < 0.001 | 1.11 (1.05–1.18)     | < 0.001 |
| Ventilator usage               | 2.23 (1.09–4.53) | 0.028   |                     |         |

*Adjusted for variables with \( p < 0.1 \) in the univariate analysis.

HR, hazard ratio; CI, confidence interval; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; eGFR, estimated glomerular filtration rate.
| Variable                                      | Univariate Multivariate* |
|-----------------------------------------------|--------------------------|
| Inotrope/ vasopressor usage                   | 1.69 (1.23–2.33)         |
| Mean arterial pressure (mmHg)                 | 0.98 (0.97–0.99)         |
| Septic shock                                  | 1.95 (1.39–2.75)         |
| White blood cells (K)                         | 0.99 (0.97–1.01)         |
| Hemoglobin (mg/dL)                            | 0.86 (0.79–0.93)         |
| Initial eGFR (mL/min/1.73 m2)                 | 1.00 (0.99-1.00)         |
| Proteinuria                                   | 1.15 (0.80–1.65)         |
| Glucose (mg/dL)                               | 1.00 (1.00–1.00)         |
| Lactate, 0 h (mg/dL)                          | 1.01 (1.01–1.02)         |
| Galectin-1 concentration low (< 39 ng/mL)     | Reference                |
| Median (39–71 ng/mL)                          | 1.64 (1.08–2.51)         |
| High (≥ 71 ng/mL)                             | 2.50 (1.67–3.74)         |

*Adjusted for variables with \( p < 0.1 \) in the univariate analysis.

HR, hazard ratio; CI, confidence interval; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; eGFR, estimated glomerular filtration rate.
Table 4
Stratified risk of 90-day mortality among patients grouped by the presence of diabetes, proteinuria, renal insufficiency, pneumonia, and septic shock.

| Subgroup                  | Median galectin-1 group* | High galectin-1 group* | P for interaction |
|---------------------------|--------------------------|------------------------|-------------------|
| (events/subjects)         | Adjusted HR (95% CI)     | Adjusted HR (95% CI)   |                   |
|                           | P                        | P                      |                   |
| Diabetes mellitus         |                          |                        |                   |
| Yes (40 / 90)             | 3.83 (0.92–15.90)        | 2.96 (0.78–11.23)      | 0.112, 0.898      |
| No (117 / 219)            | 1.83 (1.03–3.28)         | 3.41 (1.90–6.11)       | <0.001            |
| Proteinuria               |                          |                        |                   |
| Yes (119 / 228)           | 1.88 (1.00–3.54)         | 2.81 (1.51–5.23)       | 0.001, 0.726      |
| No (38 / 81)              | 3.69 (1.31–10.39)        | 3.40 (1.11–10.44)      | 0.032             |
| Initial eGFR < 45         |                          |                        |                   |
| Yes (88 / 172)            | 4.25 (1.58–11.48)        | 4.75 (1.80–12.48)      | 0.002, 0.120      |
| No (69 / 137)             | 1.59 (0.77–3.27)         | 2.83 (1.31–6.16)       | 0.008             |
| Pneumonia                 |                          |                        |                   |
| Yes (116 / 227)           | 2.07 (1.14–3.75)         | 3.33 (1.81–6.11)       | <0.001, 0.794     |
| No (41 / 82)              | 3.44 (0.99–12.04)        | 3.74 (1.06–13.24)      | 0.041             |
| Septic shock              |                          |                        |                   |
| Yes (48 / 73)             | 1.99 (0.64–6.24)         | 3.99 (1.48–10.74)      | 0.006, 0.287      |
| No (109 / 236)            | 2.17 (1.18–3.97)         | 2.56 (1.35–4.86)       | 0.004             |

*Compared with the low galectin-1 group.

Adjusted for the body mass index, malignancy, sepsis, Sequential Organ Failure Assessment score, and lactate concentration.

HR, hazard ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

**Associations of the serum Gal-1 level with secondary outcomes**

The durations of ICU admission and hospitalization did not differ according to the serum Gal-1 concentration (Table 2). The incidences of AKI within 48 h after ICU admission (50.5% vs. 37.9% and 17.5%; p < 0.001) and dialysis dependency (6.8% vs. 4.9% and 0%; p = 0.034) were greater among patients with high Gal-1 levels than among those with median and low Gal-1 levels. In multivariate analysis
adjusted for the SOFA score and renal function, the risk of AKI increased with the serum Gal-1 level (median vs. low: aHR 2.77, 95% CI 1.21–6.34, \( p = 0.016 \); high vs. low: aHR 2.88, 95% CI 1.20–6.88, \( p = 0.017 \); Table 5). Subgroup analysis revealed no significant difference in AKI according to the Gal-1 concentration (Table 6).
Table 5
Univariate and multivariate associations of factors with acute kidney injury within 48 h after intensive care unit admission

| Univariate Multivariate* | Crude OR (95% CI) | P       | Adjusted OR (95% CI) | P       |
|--------------------------|-------------------|---------|----------------------|---------|
| Age                      | 1.00 (0.99–1.02)  | 0.558   |                      |         |
| Male gender              | 1.04 (0.63–1.72)  | 0.884   |                      |         |
| Body mass index          | 1.02 (0.97–1.08)  | 0.363   |                      |         |
| Hypertension             | 1.67 (1.04–2.67)  | 0.032   |                      |         |
| Diabetic mellitus        | 1.52 (0.92–2.52)  | 0.102   |                      |         |
| Heart failure            | 1.66 (0.83–3.33)  | 0.151   |                      |         |
| Cirrhosis                | 1.24 (0.49–3.14)  | 0.648   |                      |         |
| Malignancy (solid tumor) | 0.80 (0.49–1.31)  | 0.380   |                      |         |
| ACEi / ARB exposure      | 1.40 (0.80–2.46)  | 0.236   |                      |         |
| Diuretics exposure       | 1.27 (0.68–2.37)  | 0.446   |                      |         |
| Nephrotoxic agents exposure | 1.76 (0.75–4.13)  | 0.195   |                      |         |
| Etiologies of ICU admission |                |         |                      |         |
| Pneumonia                | 1.15 (0.68–1.97)  | 0.604   |                      |         |
| Sepsis                   | 1.68 (0.79–3.59)  | 0.182   |                      |         |
| Acute heart failure      | 0.78 (0.20–3.08)  | 0.723   |                      |         |
| Massive bleeding         | 0.91 (0.36–2.33)  | 0.847   |                      |         |
| Disease severity         |                   |         |                      |         |
| APACHE II scores         | 1.06 (1.03–1.09)  | < 0.001 |                      |         |
| SOFA scores              | 1.23 (1.14–1.34)  | < 0.001 | 1.17 (1.06–1.29)     | 0.002   |
| Ventilator usage         | 0.80 (0.37–1.73)  | 0.569   |                      |         |
| Inotrope/ vasopressor usage | 1.26 (0.79–2.02)  | 0.329   |                      |         |

*Adjusted for variables with $p < 0.1$ in the univariate analysis.

OR, odds ratio; CI, confidence interval; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; eGFR, estimated glomerular filtration rate.
| **Univariate Multivariate*** |  |
|-----------------------------|---|
| Mean arterial pressure (mmHg) | 0.99 (0.97-1.00) | 0.098 |
| Septic shock                | 1.74 (1.02–2.97) | 0.043 |
| White blood cells (K)       | 1.02 (1.00-1.04) | 0.122 |
| Hemoglobin (mg/dL)          | 0.96 (0.86–1.07) | 0.483 |
| Initial eGFR (mL/min/1.73 m²) | 0.97 (0.96–0.98) | < 0.001 | 0.99 (0.98-1.00) | 0.020 |
| Proteinuria                 | 2.13 (1.19–3.80) | 0.011 |
| Glucose (mg/dL)             | 1.00 (0.99-1.00) | 0.077 |
| Lactate, 0 h (mg/dL)        | 1.01 (1.00-1.02) | 0.015 |
| Galectin-1 concentration    |  |
| Low (< 39 ng/mL)            | Reference | Reference |
| Median (39–71 ng/mL)        | 2.88 (1.51–5.49) | 0.001 | 2.77 (1.21–6.34) | 0.016 |
| High (≥ 71 ng/mL)           | 4.82 (2.54–9.12) | < 0.001 | 2.88 (1.20–6.88) | 0.017 |

*Adjusted for variables with \( p < 0.1 \) in the univariate analysis.

OR, odds ratio; CI, confidence interval; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ICU, intensive care unit; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; eGFR, estimated glomerular filtration rate.
Table 6
Stratified risk of acute kidney injury in patients grouped by the presence of diabetes, proteinuria, renal insufficiency, pneumonia, and septic shock.

| Subgroup                  | Median galectin-1 group* | High galectin-1 group* | P for interaction |
|---------------------------|--------------------------|------------------------|-------------------|
|                           | Adjusted OR (95% CI)³   | P                      | Adjusted OR (95% CI)³ | P      |
| (events / subjects)       |                          |                        |                   |        |
| Diabetes mellitus         |                          |                        |                   |        |
| Yes (38 / 90)             | 2.72 (0.70-10.61)        | 0.149                  | 2.80 (0.70-11.22)  | 0.147  | 0.948 |
| No (71 / 219)             | 1.87 (0.77–4.56)         | 0.166                  | 1.81 (0.72–4.58)   | 0.210  |        |
| Proteinuria               |                          |                        |                   |        |       |
| Yes (90 / 228)            | 1.83 (0.78–4.26)         | 0.164                  | 1.92 (0.81–4.58)   | 0.140  | 0.871 |
| No (19 / 81)              | 2.46 (0.53–11.55)        | 0.253                  | 2.42 (0.43–13.54)  | 0.313  |        |
| Initial eGFR < 45         |                          |                        |                   |        |       |
| Yes (87 / 172)            | 1.16 (0.45–3.02)         | 0.763                  | 1.13 (0.43–2.95)   | 0.806  | 0.281 |
| No (22 / 137)             | 4.69 (1.28–17.14)        | 0.020                  | 3.68 (0.80-16.84)  | 0.093  |        |
| Pneumonia                 |                          |                        |                   |        |       |
| Yes (82 / 227)            | 1.88 (0.83–4.28)         | 0.133                  | 2.42 (1.02–5.75)   | 0.045  | 0.821 |
| No (27 / 82)              | 2.35 (0.44–12.60)        | 0.320                  | 1.54 (0.28–8.36)   | 0.618  |        |
| Septic shock              |                          |                        |                   |        |       |
| Yes (33 / 73)             | 3.50 (0.66–18.58)        | 0.142                  | 1.73 (0.38–7.87)   | 0.480  | 0.773 |
| No (76 / 236)             | 1.87 (0.82–4.30)         | 0.140                  | 2.35 (0.96–5.73)   | 0.061  |        |

*Compared with the low galectin-1 group.

³Adjusted for Sequential Organ Failure Assessment score and initial eGFR.

OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate.

ICU, intensive care unit; AKI, acute kidney injury.

Discussion

To our knowledge, this study is the first investigation of associations of the Gal-1 level with all-cause mortality and AKI in critically ill patients. It demonstrated that higher serum Gal-1 concentrations increase the risk of mortality in the ICU and at 90 days. This increase remained significant after controlling for the body mass index, malignancy, sepsis, SOFA score, and serum lactate level and was consistent across subgroups. The incidences of AKI and dialysis dependency after discharge were also greater in the high
Gal-1 group than in the low Gal-1 group. In multivariate analysis, the serum Gal-1 concentration remained an independent risk factor for AKI and renal replacement therapy dependency after controlling for the SOFA score and initial renal function.

Galectins are abundant in the skeletal, smooth, and cardiac muscles; motor and sensory neurons; thymus; kidney; and placenta [16, 17]. The function of galectin depends on the cellular location. Intracellular Gal-1 regulates cell growth via protein–protein interaction [18]. Secreted Gal-1 mediates cell aggregation and adhesion to the extracellular matrix, which are crucial for tumor invasion of surrounding tissues [19]. Gal-1 in CD8 T lymphocytes is a negative regulator of anti-tumor immunity. It helps tumors to escape immunosurveillance [20], and inhibits the immunosuppressive effects of mesenchymal stem cells. It stops cell proliferation in the G0 and G2 phases, when its concentration increases [21]. However, in chronic inflammation and autoimmune disorders, Gal-1 has immunosuppressive and anti-inflammatory effects [22, 23]. It prevents severe inflammation–induced neurodegeneration and improves neurogenesis after ischemic stroke [24]. Gal-1 is secreted early after acute myocardial infarction. It promotes the apoptosis of CD8, Th1, and Th17 lymphocytes, and is associated with adverse remodeling after acute coronary syndrome. Thus, Gal-1 upregulation may influence the resolution of cardiac inflammation and restore hemostasis. In an experimental study, mice lacking Gal-1 showed increased cardiac dilatation after acute myocardial infarction [6].

Sepsis remains a significant challenge in medicine and is the most common cause of death in critically ill patients admitted to the ICU [25]. SIRS, another common reason for ICU admission, is a clinical syndrome that results from deregulation of the inflammatory response to infections or non-infectious insults, such as acute pancreatitis, vasculitis, and autoimmune disorders [26]. Biomarkers have been developed to diagnose, predict, or influence the disease severity of sepsis or SIRS. In this study, the risk of mortality increased with the serum concentration of Gal-1, a regulator of the inflammatory response. Additionally, serum Gal-1 concentrations were higher in patients with critical illnesses than in those who underwent CAG. These findings may reflect the severity of infection or inflammation and the host response to it. A complicated and overwhelming host response that involves immune, inflammatory, metabolic, and neuroendocrine factors leads to multiorgan dysfunction [27], thereby increasing mortality [28].

AKI occurs in up to 5.7% of critically ill patients during their ICU stays [29]. Its causes include sepsis, inflammation, hepatorenal and cardiorenal syndromes, and nephrotoxic agents. AKI is associated with increased morbidity, mortality, and duration of hospitalization [30]. At the time of hospital discharge, 9–14% of patients in whom AKI occurred during hospitalization are dependent on renal replacement therapy [31]. Galectin has been associated with progressive renal fibrosis, and its absence may protect against renal failure [32]. GAL-1 was reported to regulate podocin production and podocyte damage [33]. GAL-1 elevation has been associated with diabetic nephropathy [34] and renal function decline [13]. Our findings further strengthen the association of GAL-1 with AKI.

Patients with solid tumors comprised 40% of our study population. With recent progress in intensive chemotherapeutic regimens and hematopoietic stem cell transplantation, the cancer-related mortality rate
has declined gradually. Thus, ICUs are required to provide life-sustaining treatments for infection or chemotherapy-related toxicity events to patients with cancer [35]. Corapi et al. [20] found that the absence of Gal-1 in the T lymphocytes of patients with prostate cancer potentiated anti-tumor immune responses. In patients with cancer, high levels of Gal-1, most likely secreted from tumor cells, may help tumor cells to evade immune responses.

**Limitations**

This study has several limitations. First, it was conducted at a single-center with relatively few patients. Second, given the lack of a reference Gal-1 range, we could only divide patients into three equally sized serum Gal-1 groups. Third, co-morbidities and disease severity differed significantly among groups, indicating the presence of selection bias. Although we performed adjusted analyses, some confounding factors may not have been accounted for. Finally, the study was observational and the causality of relationships could not be established.

**Conclusions**

Elevation of the serum Gal-1 concentration was associated with high ICU and 90-day mortality rates. The risks of AKI were also increased in patients with high Gal-1 levels. Serum Gal-1 concentrations may be a prognostic predictor for sepsis or SIRS. These findings provide indirect evidence of Gal-1’s involvement in acute inflammation.

**Abbreviations**

Acute kidney injury, AKI; Acute Physiology and Chronic Health Evaluation II, APACHE II; coronary angiography, CAG; coronary artery disease, CAD; confidence interval, CI; estimated glomerular filtration rate, eGFR; galectin 1, Gal-1; hazard ratio, HR; intensive care unit, ICU; mean arterial pressure, MAP; Sequential Organ Failure Assessment, SOFA; systemic inflammatory response syndrome, SIRS.

**Declarations**

**Ethics approval and consent to participate**

This study was approved by Research Ethics Committee of Taipei Veterans General Hospital (Num. 2018-02-009AC).

**Consent for publication**

Not applicable.

**Availability of data and materials**

The datasets generated and analyzed are available from the corresponding author on reasonable request.
Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

Research idea and study design: RH Chou, CT Tsai, PH Huang; data acquisition: YW Lu, JY Guo, CT Lu, RY Lien, SF Lu; data analysis/interpretation: RH Chou, CT Tsai, YL Tsai; statistical analysis: RH Chou, CH Wu, SF Yang; supervision or mentorship: SJ Lin, SF Yang, PH Huang. All authors read and approved the final manuscript.

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Figures

350 cases admitted to medical ICU (May 2018-Mar 2020)

Exclusion
41 cases of pre-dialysis

Check serum galectin-1 concentration

Low galectin-1 (<39 ng/mL)
103 cases

Median galectin-1 (39-71 ng/mL)
103 cases

High galectin-1 (≥71 ng/mL)
103 cases

Analysis for AKI within 48 hrs after ICU admission, and all-cause mortality with 90 days

Figure 1

flow chart
Figure 2

90-day survival rate

Supplementary Files

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