

## Changes in Insulin-like Growth Factor-1 Level in Patients with Sepsis and Septic Shock

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**Background:** Despite many ongoing, prospective studies on the topic, sepsis still remains one of the main causes of death in hospital. The hormone insulin-like growth factor 1 (IGF-1) has a similar molecular structure to that of insulin. IGF-1 exerts anabolic effects and plays important roles in both normal physiology and pathologic processes. Previous studies have observed low serum IGF-1 level in patients with critical illnesses. Here, we evaluated changes in IGF-1 level based on survival of septic patients.

**Methods:** We evaluated 140 patients with sepsis and septic shock (21 with sepsis and 119 with septic shock) admitted to the intensive care unit of a university-affiliated hospital in Korea. Serum IGF-1 level was measured on days 0, 1, 3, and 7. Patients with liver disease were excluded from this study. All data were analyzed using SPSS version 20 (SPSS Inc., Chicago, IL, USA).

**Results:** Patients with septic shock had significantly lower serum IGF-1 level on days 1 and 3 than patients without septic shock ( $p = 0.002$  and  $p = 0.007$ , respectively). Generally, there was a negative relationship between IGF-1 and serum cortisol levels; however, this relationship was only significant on day 3 ( $p = 0.029$ ). Furthermore, renin showed significantly negative correlation with IGF-1 on day 3 ( $p = 0.038$ ). IGF-1 level did not show significant difference between survivors and non-survivors.

**Conclusions:** Our results showed that IGF-1 was associated with septic shock, and that the IGF-1 axis is severely disrupted in septic patients. Additionally, serum cortisol and renin levels were associated with IGF-1 level.

**Key Words:** insulin-like growth factor-1; sepsis.

### Introduction

Sepsis is one of the most common causes of death in the medical intensive care unit (ICU).[1] Recently, large-scale, prospective studies of early goal-directed therapy failed to demonstrate any improvement in the mortality.[2-4] Although many trials have been conducted, the global mortality rate remains high, ranging from 24.0% to 30.0% for sepsis and from 40.0% to 70.0% for septic shock.[5,6]

During sepsis, the hypothalamic-pituitary-adrenal axis (HPA) is activated, leading to the release of adrenocorticotrophic hormone. Activation of the HPA axis and release of cortisol are important steps in maintaining homeostasis in organs affected by sepsis.[7] Stress induced by critical illness leads to a sympathoadrenal response. In this type of response, the pituitary plays an important role in both im-

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munologic and metabolic homeostasis.[8] Stimulation of the pituitary gland by critical illness leads to the pulsatile release of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) into the plasma; however, prolonged sepsis gradually but significantly decreases the release of these hormones.[9] The more severe is the sepsis, the greater is the decrease in the levels of these hormones.[9] Previous studies showed mixed clinical results regarding the influence of GH/IGF-1. Some studies showed clinically positive effects of GH/IGF-1 administration in septic and surgical patients (improved nitrogen balance, maintenance of GH/IGF-1 level, increased bursting pressure of anastomosis, and prevention of gut barrier failure), whereas other studies reported no changes or even increased mortality in association with GH administration.[10-14]

Although the changes in serum GH/IGF-1 level under septic or surgical conditions have been studied previously, changes in these hormones over time have not been well-evaluated. Moreover, most previous studies regarding GH/IGF-1 were performed in Western countries. As such, additional studies are needed to investigate the role of GH in an Asian population. Furthermore, previ-

ous studies analyzed the interaction between IGF-1 and the cortisol or renin-angiotensin system in the context of diabetes mellitus or cardiovascular disease.[15-18]

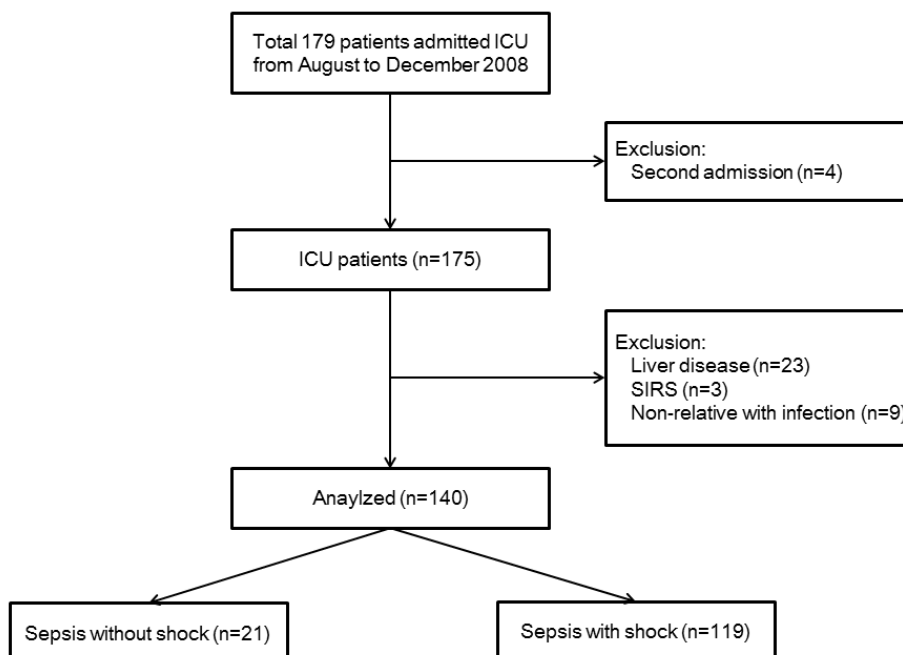
We aimed to investigate the differences and change over time in serum IGF-1 level in medical ICU patients with or without septic shock on days 0 (day of admission), 1, 3, and 7 to determine whether IGF-1 is associated with a better prognosis. Furthermore, we investigated the relationships of renin and cortisol with IGF-1 in patients with sepsis.

## Materials and Methods

### 1) Study populations

This study was performed in the medical ICU of Severance Hospital, a 2,500-bed university medical center in Seoul, South Korea. The medical ICU is a 30-bed closed unit, managed by certified ICU specialists who care only for ICU patients. The cardiac ICU is operated separately. All patients admitted to the medical ICU were enrolled in this study from August 2008 to December 2008.

In this study, sepsis was defined as a systemic response



**Fig. 1.** Flow chart of the study population. Initially, 179 intensive care unit (ICU) patients were enrolled from August to December 2008. The following patients were excluded: patients who were being admitted for a second time ( $n = 4$ ), patients with liver disease ( $n = 23$ ), patients diagnosed with systemic inflammatory response syndrome (SIRS) ( $n = 3$ ), and patients with noninfectious disease ( $n = 9$ ).

to infection that met three of the four criteria for systemic inflammatory response syndrome: (1) body temperature less than 36°C or greater than 38°C; (2) heart rate greater than 90 beats per minute; (3) respiratory rate greater than 20 breaths per minute or a PaCO<sub>2</sub> less than 32 mmHg; and (4) white blood cell count less than 4,000 cells/mm<sup>3</sup> or greater than 12,000 cells/mm<sup>3</sup>. Septic shock was defined as sepsis-related persistent hypotension, despite adequate fluid resuscitation.[19] A total of 179 ICU patients were initially enrolled. Patients were excluded if they were younger than 18 years of age, pregnant, or readmitted to the ICU during their hospital stay. Patients who required primary cardiac treatment, had liver disease (e.g., immune hepatitis, hepatitis B/C, liver cirrhosis, hepatocellular carcinoma), or did not meet the criteria for sepsis were also excluded. Finally, 140 ICU patients were analyzed; 21 patients had sepsis without shock, and 119 patients had sepsis with shock (Fig. 1).

The guidelines of the Surviving Sepsis Campaign were used for management of the study population.[20] For each patient, age, sex, body mass index (BMI), PaO<sub>2</sub>/FiO<sub>2</sub> ratio, infection site, comorbidity, length of ICU stay, and 28-day mortality were investigated. Various laboratory parameters, including IGF-1 level, were analyzed on days 0 (day of ICU admission), 1, 3, and 7. Additionally, Acute Physiology and Chronic Health Evaluation (APACHE) II and Sequential Organ Failure Assessment (SOFA) scores were calculated.

## 2) Blood sampling and assays

After admission to the medical ICU (day 0), arterial catheterization was performed by a resident physician. Initial blood samples were obtained immediately using an indwelling arterial catheter. The remaining blood samples (days 1, 3, and 7) were obtained at 5:00 AM for all eligible patients. Serum IGF-1 level and renin were measured using a commercial radioimmunoassay kit (Diasorin, Stillwater, MN, USA). Cortisol level was measured with a competitive binding immunoenzymatic assay kit (Beckman Coulter, Miami, FL, USA).

## 3) Statistical analysis

The Mann–Whitney *U* test or Student's *t*-test was used for analysis depending on data distribution. Quantitative data are reported as median with interquartile range or mean ± standard deviation. Fisher's exact test or Pearson's 2 test was used for the analysis of categorical variables, which are reported as absolute frequencies and percentages. After adjusting for age, sex, and BMI, a linear mixed model was used to analyze changes in IGF-1 level over time in septic patients with or without shock. Pearson's correlation analyses were performed to evaluate relationships between cortisol, renin, aldosterone, glucagon, and IGF-1 level. The effect of IGF-1 on 28-day mortality after adjusting for age, sex, and BMI was analyzed using Cox proportional hazards regression models. All statistical analyses in this study were conducted using SPSS™ version 20 software (SPSS Inc., Chicago, IL, USA). An adjusted *p*-value < 0.05 was defined as statistically significant.

## 4) Ethics statement

The study protocol was reviewed and approved by the Institutional Review Board of Yonsei University Health Service, Severance Hospital (IRB approval No. 4-2008-0099). Written consent was obtained from the patients or their relatives.

## Results

Table 1 shows the baseline characteristics of the study population (*n* = 140) on the day of admission. The mean age of the enrolled patients was 62.3 ± 16.0 years, and the mean BMI was 23.1 ± 4.0 kg/m<sup>2</sup>. Age, sex, BMI, and length of ICU stay did not significantly differ between septic patients with shock and those without shock. Patients with septic shock had significantly elevated APACHE II and SOFA scores relative to those of sepsis patients without shock (*p* = 0.008 and < 0.001, respectively). The most common infection site was lung (83.6%) followed by abdomen (10.0%) in both groups, and the

**Table 1.** Baseline characteristics of patients at ICU admission (n = 140, day 0)

Variables	Sepsis without shock (n = 21)	Sepsis with shock (n = 119)	p-value
Age (yr)	58.2 ± 18.1	63.0 ± 15.5	0.203
Male	16 (76.2)	70 (58.8)	0.132
BMI (kg/m <sup>2</sup> )	23.0 ± 3.7	23.1 ± 4.1	0.962
Length of ICU stay (days)	7.0 [4.5, 14.5]	11.0 [5.0, 21.0]	0.147
APACHE II score	16.2 ± 6.6	19.7 ± 5.1	0.008
SOFA score	4.3 ± 2.1	8.2 ± 3.5	< 0.001
PaO <sub>2</sub> /FI <sub>O</sub> <sub>2</sub> (mmHg)	266.3 ± 136.6	212.8 ± 110.7	0.051
Infection site			0.932
Lung	17 (81.0)	100 (84.0)	
Urinary tract	1 (4.8)	4 (3.4)	
Abdomen	2 (9.5)	12 (10.1)	
Others	1 (4.8)	3 (2.5)	
Underlying diseases			
Diabetes mellitus	3 (14.3)	32 (26.9)	0.219
Chronic lung disease*	5 (23.8)	24 (20.2)	0.704
Chronic renal disease	4 (19.0)	17 (14.3)	0.522
Hypertension	10 (47.6)	47 (39.5)	0.485
Heart failure	5 (23.8)	12 (10.1)	0.137
Coronary artery disease	2 (9.5)	13 (10.9)	1.000
Mortality	1/20 (4.8)	62/57 (52.1)	< 0.001

Data are presented as mean ± SD or numbers (percentages).

ICU: intensive care unit; BMI: body mass index; APACHE II: Acute Physiology and Chronic Health Evaluation II; SOFA: Sequential Organ Failure Assessment.

\*Chronic lung disease includes asthma, chronic obstructive pulmonary disease, and structural lung diseases, such as bronchiectasis and interstitial lung disease.

differences between the groups were not significant ( $p = 0.932$ ). Comorbidities were not significantly different between the groups. Understandably, mortality was significantly higher in patients with septic shock ( $p < 0.001$ ).

Many of the laboratory results at admission are listed in Table 2. Hemoglobin level, platelet count, and renal function (blood urea nitrogen and creatinine levels) did not differ significantly between the groups ( $p = 0.741$ ,  $0.794$ ,  $0.457$ , and  $0.924$ , respectively). Among patients with sepsis, shock was associated with significantly elevated C-reactive protein level and significantly reduced albumin level ( $p = 0.007$  and  $0.004$ , respectively). A not significant difference in serum IGF-1 level was observed

between the groups. Furthermore, there were no significant differences in serum levels of many other hormones on the day of ICU admission.

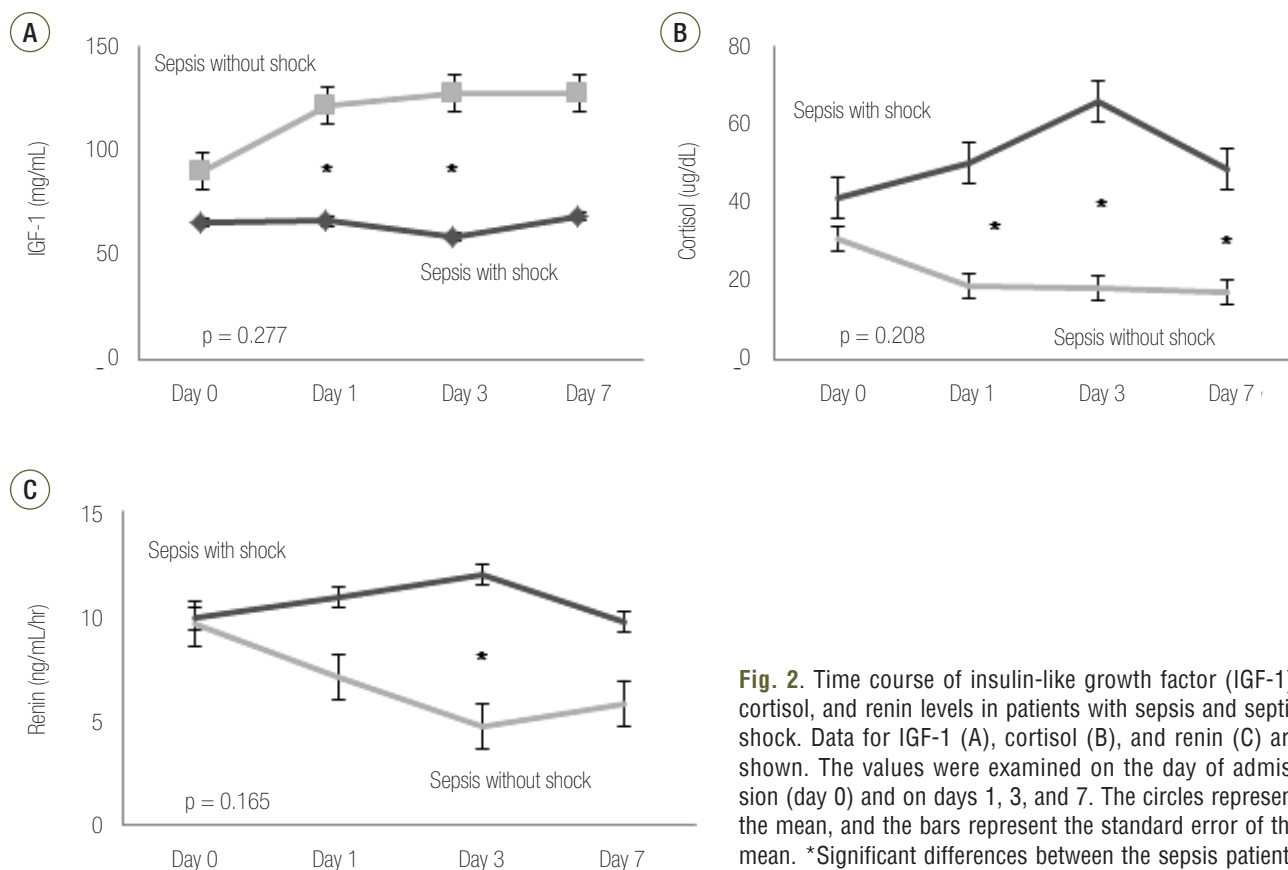
Fig. 2 shows the changes in serum IGF-1, cortisol, and renin levels over time from the day of ICU admission to ICU day 7. After adjusting for age, sex, and BMI, these changes did not differ significantly between septic patients with shock and those without ( $p = 0.277$ ,  $0.208$ , and  $0.165$ , respectively). However, significant differences in mean IGF-1 level were observed on days 1 and 3 ( $p = 0.002$  and  $0.007$ , respectively). In addition, the groups differed significantly in serum cortisol level on days 1, 3, and 7 and in serum renin level on day 3. A Cox pro-

**Table 2.** Laboratory data of patients at ICU admission (n = 140, day 0)

Variables	Sepsis without shock (n = 21)	Sepsis with shock (n = 119)	p-value
Hemoglobin (g/dL)	10.1 ± 2.7	9.9 ± 2.2	0.741
Platelets (10 <sup>3</sup> /mm <sup>3</sup> )	201.0 ± 118.8	191.6 ± 157.2	0.794
Blood urea nitrogen (mg/dL)	26.9 ± 20.4	31.3 ± 25.3	0.457
Creatinine (mg/dL)	1.9 ± 2.1	1.9 ± 2.2	0.924
CRP (mg/dL)	14.0 ± 7.1	19.5 ± 12.9	0.007
Albumin (mg/dL)	3.1 ± 0.7	2.6 ± 0.6	0.004
Cholesterol (mg/dL)	128.2 (112.5, 148.5)	97.1 (63.0, 120.0)	0.004
Triglyceride (mg/dL)	179.1 (62.0, 302.3)	106.8 (61.3, 130.3)	0.152
IGF-1 (ng/mL)	96.5 (46.6, 137.0)	47.9 (27.8, 89.9)	0.092
Cortisol (ug/dL)	29.8 (15.4, 37.7)	31.3 (20.2, 47.5)	0.213
Renin (ng/mL/hr)	2.9 (0.5, 13.9)	4.7 (0.9, 15.8)	0.941
Aldosterone (pg/mL)	82.4 (44.3, 170.3)	89.3 (42.9, 165.8)	0.962
Glucagon (pg/mL)	50.5 (45.3, 61.0)	67.0 (42.0, 132.0)	< 0.001

Data are presented as mean ± SD or median (interquartile range).

ICU: intensive care unit; CRP: C-reactive protein; IGF-1: insulin-like growth factor-1.



**Fig. 2.** Time course of insulin-like growth factor (IGF-1), cortisol, and renin levels in patients with sepsis and septic shock. Data for IGF-1 (A), cortisol (B), and renin (C) are shown. The values were examined on the day of admission (day 0) and on days 1, 3, and 7. The circles represent the mean, and the bars represent the standard error of the mean. \*Significant differences between the sepsis patients and the septic shock patients.

**Table 3.** Survival analysis for IGF-1, cortisol, and renin adjusting for age, sex, body mass index, and Sequential Organ Failure Assessment score

Variables		Median (IQR)	Hazard ratio	95% CI	p-value
Day 0	IGF-1	55.3 (30.7, 96.9)	1.004	0.996-1.011	0.327
	Cortisol	31.1 (19.5, 46.2)	0.997	0.990-1.004	0.422
	Renin	3.8 (0.7, 15.2)	0.998	0.974-1.022	0.871
Day 1	IGF-1	57.8 (30.6, 104.2)	1.001	0.994-1.007	0.805
	Cortisol	27.4 (17.6, 47.2)	1.001	0.996-1.006	0.718
	Renin	4.0 (1.2, 14.4)	1.025	1.001-1.049	0.042
Day 3	IGF-1	51.4 (29.8, 91.9)	0.996	0.987-1.005	0.402
	Cortisol	23.2 (15.0, 74.5)	0.998	0.994-1.003	0.523
	Renin	3.1 (0.8, 20.7)	1.023	0.997-1.049	0.084
Day 7	IGF-1	65.7 (46.1, 95.5)	1.000	0.991-1.009	1.000
	Cortisol	23.9 (17.1, 49.2)	0.995	0.984-1.006	0.381
	Renin	2.2 (0.5, 15.1)	1.106	1.055-1.160	< 0.001

IGF-1: insulin-like growth factor-1; IQR: interquartile range; CI: confidence interval.

**Table 4.** Correlations between IGF-1 level and serum concentrations of cortisol and renin in ICU patients with sepsis

	Variable	Correlation (rho)	p-value
Day 0	Cortisol	-0.052	0.647
	Renin	0.044	0.700
	Aldosterone	-0.015	0.896
	Glucagon	-0.159	0.218
Day 1	Cortisol	-0.215	0.066
	Renin	0.005	0.965
	Aldosterone	-0.087	0.456
	Glucagon	-0.136	0.317
Day 3	Cortisol	-0.271	0.029
	Renin	-0.258	0.038
	Aldosterone	-0.052	0.684
	Glucagon	0.000	0.998
Day 7	Cortisol	-0.221	0.140
	Renin	-0.135	0.382
	Aldosterone	0.068	0.659
	Glucagon	0.199	0.253

IGF-1: insulin-like growth factor-1; ICU: intensive care unit.

portional hazards model was used to evaluate the effects of IGF-1, cortisol, and renin levels on survival (Table 3). This analysis of days 0, 1, 3, and 7 was adjusted for age, sex, BMI, and SOFA score. With the exception of renin, the hormones did not significantly affect survival. How-

ever, renin only affected survival on days 1 and 7, losing statistical significance on days 0 and 3.

We further investigated the correlative relationship between IGF-1 level and cortisol, renin, aldosterone, and glucagon levels (Table 4). Serum cortisol level consistently showed a negative correlation with IGF-1 level, and this was significant on day 3 ( $p = 0.029$ ). The other hormones showed no distinct correlation with IGF-1 level.

## Discussion

This study investigated changes in serum IGF-1, cortisol, and renin levels over time in a Korean population with sepsis or septic shock. Serum IGF-1 level was lower in patients with septic shock than in septic patients without shock. Furthermore, IGF-1 level tended to have a negative relationship with serum cortisol level.

IGF-1 is a single-chain polypeptide hormone mainly produced by the liver and stimulated by pituitary GH. It has an anabolic effect that slows the catabolic response. [21] IGF-1 also plays an important role in multiple aspects of immunity (both innate and acquired) and inflammatory disorders.[22]

In our study, serum IGF-1 level was consistently lower in patients with septic shock than in sepsis patients without shock; however, this was not significant on the day of admission or on day 7. In pro-inflammatory conditions like sepsis, expression of many cytokines, including interleukin-1 and tumor necrosis factor- $\alpha$ , increases and can induce metabolic changes. As a result, GH and IGF-1 levels are decreased.[23] Altered pulsatile release and blood sampling at a non-standard time on the day of admission might explain the nonsignificant difference between sepsis and septic shock patients on day 0.[24] The significant difference in IGF-1 level on days 1 and 3 might indicate that this level increased toward normal in patients without shock, while it remained low in patients with shock. Ashare et al.[25] reported that pretreatment with IGF-1 or replacement of IGF-1 12 hours after infection improved hepatic bacterial clearance and overall survival in a mouse model. Therefore, the difference in IGF-1 level between the two groups in the present study suggests that early IGF-1 treatment could be a beneficial component of infection control in septic patients.

Previous studies showed mixed results when assessing the effect of GH on mortality. Some studies showed that a high GH level was significantly associated with increased mortality, while other studies did not.[26-29] Papastathi et al.[9] showed that mortality was not related with IGF-1, IGF-binding protein-3, or GH level. Furthermore, they reported that GH was not a prognostic marker of survival. Similarly, our study showed that IGF-1 level on day 0, 1, 3, or 7 was not associated with survival.

However, we did observe that renin was significantly associated with mortality on days 1 and 7. Previous studies showed that the renin-angiotensin-aldosterone system (RAAS) is activated in sepsis patients, and that activated RAAS mediators were associated with microvascular dysfunction and organ disorders.[30,31] Salgado et al.[31] reported that administration of RAAS antagonists in the early phase of sepsis could protect against endothelial damage and organ failure and eventually reduce the mortality rate. Further studies are needed to examine the role of renin in sepsis.

Low-dose hydrocortisone is usually administered in the ICU to patients with septic shock who are unresponsive to volume trial and vasopressor administration. However, Volbeda et al.[32] conducted a systematic review and meta-analyses of 35 trials, including 4,682 patients, and reported no statistically significant effects of steroid therapy on mortality or adverse events in patients with systemic inflammatory response syndrome, sepsis, severe sepsis, or even septic shock. Our study supports those earlier findings. Although serum cortisol level was significantly different between sepsis patients and septic shock patients on days 1, 3, and 7, cortisol level was not significantly associated with mortality.

A previous study showed that IGF-1 level was negatively correlated with cortisol level and sepsis severity.[9] IGF-1 also reduces angiotensin level and apoptosis.[33] In our study, IGF-1 level was significantly negatively correlated with both cortisol and renin levels on day 3; however, on the other days, these correlations were not significant. This could be explained by different blood sampling times on the day of admission and disruption of hormone homeostasis within approximately 1 week in sepsis patients.

This study has some limitations. First, we did not evaluate hormones that are closely related to IGF-1. GH and IGF-binding protein-3 levels are closely associated with IGF-1 level. An analysis of these hormones might have provided additional information about the changes in IGF-1 level in sepsis patients. Second, the duration of sepsis before ICU admission was not evaluated in this study. Hormone levels are severely affected by the severity and duration of sepsis. Therefore, the duration of infection before ICU admission might have affected the results of our study. Well-designed prospective studies that consider the severity of sepsis and the duration of infection before ICU admission are therefore needed. Third, although we excluded patients with liver disease, we did not exclude those who had recently been prescribed corticosteroids or those with malignant disease or diabetes mellitus. While this could have affected our results, all of the study population was treated with an insulin protocol



with a targeted glucose level of 100 to 140 mg/dL, and their diet was managed by a specialized nutrition team.

In conclusion, we investigated whether the severity of sepsis was associated with changes in hormone levels in Korean ICU patients. Although IGF-1 level was lower in septic shock patients, this factor was not significantly associated with mortality. Septic shock patients also exhibited higher cortisol and renin levels relative to sepsis patients. Furthermore, renin level was significantly related with mortality on days 1 and 7. Prospective large-scale studies are needed to confirm the roles of these hormones in ICU patients.

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