European Journal of Internal Medicine 64 (2019) 24–28

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

# Impact of underlying chronic adrenal insufficiency on clinical course of hospitalized patients with adrenal crisis: A nationwide cohort study

Masahiro Iwasaku, Shiro Tanaka, Maki Shinzawa, Koji Kawakami*

*Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Japan*

ARTICLE INFO

*Keywords:*
Adrenal insufficiency
Critical care
Mortality
Death risk
Glucocorticoids

ABSTRACT

*Background:* Chronic adrenal insufficiency (AI) is an established risk factor for adrenal crisis (AC). However, the proportion of patients with newly diagnosed chronic AI during admission for AC is unclear.

*Methods:* This retrospective cohort study used a Japanese claims database involving 7.39 million patients at 145 acute care hospitals between 2003 and 2014. Study patients with AC met these criteria: 1) newly coded in claims as AI; 2) glucocorticoid therapy administered; 3) admission; and 4) age ≥ 18 years. We investigated the prevalence of underlying chronic AI and assessed in-hospital mortality. Additionally, we explored risk factors for in-hospital mortality through multivariate analysis using a Cox proportional hazards model.

*Results:* Among 504 patients with AC, chronic AI was diagnosed before and during admission in 73 (14.5%) and 86 (17.1%) patients, respectively. In-hospital mortality rates were 1.4% and 5.8%, respectively, lower than that of the total population (14.1%). Significant risk factors for increased mortality were: age (hazard ratio [HR] 1.45/10 years; 95% confidence interval [CI] 1.17–1.78), requiring mechanical ventilation (HR 3.81; 95% CI 1.88–7.72), vasopressor administration (HR 2.05; 95% CI 1.16–3.64), sepsis (HR 3.79; 95% CI 1.57–9.14), AI-related symptoms (HR 2.00; 95% CI 1.02–3.93), and liver disease (HR 3.24; 95% CI 1.10–9.58).

*Conclusions:* Relative to patients without chronic AI, those diagnosed before admission tended to survive to discharge; however, the difference with those diagnosed during admission was not significant. Hospital admission due to nonspecific AI-related symptoms was associated with an increased risk of in-hospital mortality.

## 1. Background

Adrenal crisis (AC) is a life-threatening condition caused by an abrupt shortage of glucocorticoid hormone, which is essential for the maintenance of homeostasis [1,2]. An established risk factor of AC is chronic adrenal insufficiency (AI), i.e., impairment of the function of adrenocortical cells. The incidence of AC is rare and the onset of AC is difficult to investigate. However, a study involving patients with primary and central AI has played a major part in clinical research investigating AC [3–5]. A relative shortage of glucocorticoid hormone may occur in critically ill patients during the acute phase. This condition is termed critical illness-related corticosteroid insufficiency (CIRCI) [6]. Although the production and metabolism of glucocorticoids may alter the response during the acute phase, it may be inadequate considering the extent of the stress. Disruption of the hypothalamic–pituitary–adrenal axis, which regulates the secretion of glucocorticoid hormone, occurs in 10–20% of critically ill patients and 60% of patients with septic shock [7]. In addition to severe conditions (i.e., sepsis and acute respiratory distress syndrome [ARDS]), organ dysfunction in critical illness (i.e., renal failure and liver disease) influences the metabolism of glucocorticoid hormone during the acute phase [7–9].

The diagnosis of AC is challenging since it has various non-specific symptoms, and endocrinological testing for the diagnosis has not been established [10–13]. Underlying chronic AI may be a key factor for the diagnosis of AC. However, reaching a definitive diagnosis for chronic AI may exceed 6 months [14]. In clinical practice, treating physicians may not be able to recognize underlying chronic AI unless the patient's medical history is available [15,16]. Conversely, AC occasionally becomes an initial and important indicator for the diagnosis of underlying chronic AI [10,11].

Currently, the number of studies investigating the incidence of chronic AI in patients with AC is limited. Rushworth et al. reported that primary and central AI was present as underlying disease in 12.9% of patients with AC [17]. We previously reported that chronic AI (diagnosed before and during admission) was present in 31.5% of patients with AC [18]. However, the proportion of newly diagnosed chronic AI

* Corresponding author at: Yoshida-Konoe-cho, Sakyo-ku, Kyoto city, Kyoto 606-8501, Japan.
*E-mail addresses:* iwasaku.masahiro.87m@st.kyoto-u.ac.jp (M. Iwasaku), tanaka.shiro.8n@kyoto-u.ac.jp (S. Tanaka), shinzawa@kid.med.osaka-u.ac.jp (M. Shinzawa), kawakami.koji.4e@kyoto-u.ac.jp (K. Kawakami).

https://doi.org/10.1016/j.ejim.2019.04.001
Received 1 December 2018; Received in revised form 8 February 2019; Accepted 2 April 2019
Available online 10 April 2019

during admission for AC is unclear. In addition, the influence of underlying chronic AI along with comorbidity leading to CIRCI on the short-term prognosis remains undetermined.

This study compared data from Japanese patients with pre-existing chronic AI versus those with chronic AI diagnosed during admission for AC. Moreover, we explored risk factors of in-hospital mortality (i.e., pre-existing chronic AI, sepsis, liver dysfunction, and renal failure).

## 2. Materials and methods

### 2.1. Study design and setting

This retrospective cohort study analyzed data from a claims database, including information from 7.39 million patients in 145 acute phase hospitals across Japan between January 1, 2003 and April 30, 2014. This study was approved by the Kyoto University Graduate School and Faculty of Medicine, Ethics Committee (R1270). The requirement for informed consent was waived based on the Ethical Guidelines for Medical and Health Research Involving Human Subjects established by the Japanese Ministry of Health, Labour, and Welfare, and the Ministry of Education, Culture, Sports, Science and Technology. The details of this cohort and patient characteristics have been previously described [18].

### 2.2. Study populations and disease definition

Briefly, we identified patients with AC (including CIRCI) fulfilling all of the following criteria: 1) newly coded in claims as AI; 2) administration of glucocorticoid therapy (hydrocortisone equivalent dose ≥100 mg/day) within 3 days before or after the coding date; 3) admission within 3 days before or after the coding date; and 4) age ≥ 18 years at the coding date. With regard to the underlying disease, chronic AI was defined as consisting of primary and central AI [18]. Patients with primary AI met the following criteria: 1) presence of a disease considered to be the cause of primary AI or 2) presence of an adrenal disease for which an intervention involving the adrenal cortex was performed at least twice (since the adrenal organ is present bilaterally). Patients with central AI met the following criteria: 1) presence of central AI or 2) having undergone an intervention involving the hypothalamic–pituitary axis. We extracted disease data related to the indication for admission and comorbidity using the International Statistical Classification of Diseases and Related Health Problems 10th Revision. AI is characterized by diverse non-specific symptoms. Based on a previous study, we defined the following symptoms as AI-related: unspecified coma; unspecified hypotension; volume depletion; shock; anorexia; nausea; vomiting; unspecified fever: hyponatremia; and hypoglycemia [1].

We also checked the number of AC patients with insufficient glucocorticoid treatment (none or hydrocortisone equivalent dose < 100 mg/day) since not all such patients received appropriate glucocorticoid therapy in a clinical practice setting. A total of 616 patients were hospitalized for AC but may not have been treated with a suitable dosage of glucocorticoid (Supplementary Fig. S1). Compared with patients who received appropriate glucocorticoid therapy, patients without appropriate glucocorticoid therapy tended to be elderly (median age, 75 vs. 71 years), were less likely to be diagnosed with chronic AI before admission (6.0% vs. 14.5%), and were less likely to have received intensive therapeutic management (e.g. vasopressor administration, 7.8% vs. 24.4%). Conversely, they had a longer hospital stay (median, 22 vs. 14 days) and the in-hospital mortality was similar (12.0% vs. 14.1%; Supplementary Table S1).

### 2.3. Statistical analysis

The primary outcome of the study was in-hospital mortality, which was recorded in the database. Kaplan–Meier analysis was used to produce survival curves after hospital admission. Potential prognostic factors of in-hospital mortality were initially identified through a review of the literature [4,5,7–9,17–21]. Odds ratios (OR) or hazard ratios (HR) and 95% confidence intervals (CI) of prognostic factors were estimated using logistic regression and Cox regression analyses. The proportional hazards assumption was assessed using the Schoenfeld residuals test. We performed multivariate analyses using two models with different adjustment factors. Model 1 was adjusted for age, sex, intervention on the day of admission (i.e., mechanical ventilation and administration of a vasopressor), and indication for admission (i.e., sepsis, cardiovascular disease, AI-related symptoms, autoimmune disease). Model 2 was further adjusted for comorbidity (i.e., hypothyroidism, renal failure, chronic obstructive pulmonary disease and asthma, and liver disease) and cessation of glucocorticoid administration within 30 days before admission. Two-sided $p \leq .05$ denoted statistical significance. The statistical analysis was performed using the STATA ver. 13.1 software (StataCorp, College Station, TX, USA).

## 3. Results

### 3.1. Clinical course

A total of 504 patients with AC were identified. Table 1 shows the clinical course of the study population. Emergency hospital admission was reported for 42 patients (8.3%). Of note, 104 patients (20.6%) experienced AC during treatment with oral glucocorticoids. The median duration of oral glucocorticoid therapy was 75 days (interquartile range: 21–383 days). The median cumulative amount of continuously prescribed oral glucocorticoids was 1854 mg (interquartile range: 633–7795 mg). Admission within 30 days after cessation of glucocorticoid therapy was reported for 36 patients (7.1%). In terms of critical care management in the acute phase (within 2 weeks after admission), entry to the intensive care unit (ICU) and the high care unit was reported for 89 patients (17.7%) and 29 patients (5.8%), respectively, and 123 patients (24.4%) received treatment with a vasopressor. A requirement for mechanical ventilation was reported for 50 patients (9.9%), while endotracheal intubation due to the presence of more severe conditions was required in 31 patients (6.2%). Antibiotics were administered in 353 patients (70.0%). The levels of cortisol in the serum were measured in 258 patients (51.2%) during admission. The median duration of hospitalization was 14 days (interquartile range: 8–26 days). The incidence of in-hospital mortality was 14.1% (71 patients) in the total population with AC.

**Table 1**
Clinical characteristics of patients with adrenal crisis at admission.

| | All | |
|---|---|---|
| | ($n$ = 504) | |
| Median age (interquartile range) — yr | 71 | (59–80) |
| Male sex — no. (%) | 255 | (50.6) |
| Median body mass index (interquartile range)[a] | 21.1 | (19.0–24.1) |
| Emergency hospital admission — no. (%) | 42 | (8.3) |
| Therapeutic management[b] — no. (%) | | |
| Antibiotic administration | 353 | (70.0) |
| Vasopressor administration | 123 | (24.4) |
| ICU admission | 89 | (17.7) |
| Mechanical ventilation | 50 | (9.9) |
| Median duration of hospitalization — days (interquartile range) | 14 | (8–26) |
| In-hospital mortality — no. (%) | 71 | (14.1) |

Abbreviations: ICU, intensive care unit.

[a] The body mass index (BMI) is the weight in kilograms divided by the square of the height in meters. The BMI value was missing in 109 patients (21.6%).

[b] We counted the number of patients with therapeutic management within 2 weeks after admission.

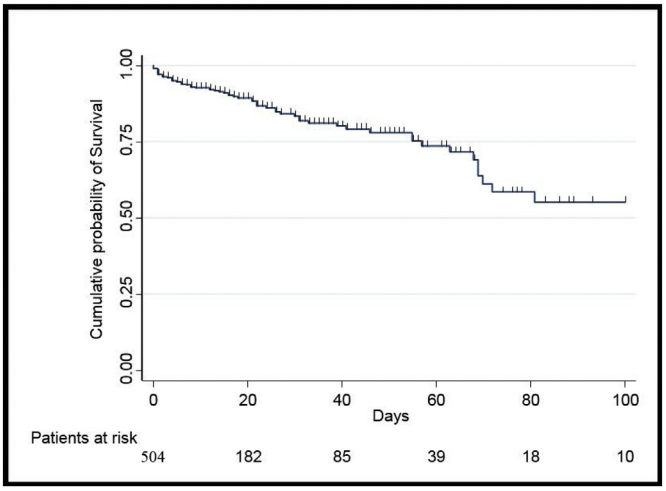


**Fig. 1.** Survival curve from admission to the 100-day follow-up.

### 3.2. Survival

Fig. 1 illustrates the survival curve of 504 patients from the time of hospital admission. Five, 31, 53, and 18 patients expired within the first day, 7 days, 28 days, and beyond 28 days after admission, respectively. The major causes of death in those who expired beyond 28 days after admission were as follows: malignancy (five patients); infection (two patients); and disseminated intravascular coagulation (two patients). Moreover, four patients (22.2%) expired due to in-hospital complications. From 2008 to 2014, there was no trend related to in-hospital mortality (Supplementary Table S2).

### 3.3. In-hospital mortality and relapse after discharge according to timing of diagnosis of underlying chronic AI

Of the 86 patients diagnosed with chronic AI during admission, five patients (5.8%) expired before discharge. Of the 73 patients diagnosed with chronic AI before admission, one patient expired (1.4%). Among the remaining 345 patients without chronic AI, 65 patients expired (18.8%; Table 2). We evaluated the risk of mortality according to the timing of the diagnosis of chronic AI using a logistic regression model. The risk of mortality was significantly lower among patients diagnosed with chronic AI before admission (OR 0.12; 95% CI 0.02–0.92) compared with that observed for patients without chronic AI. In contrast, the difference between patients diagnosed with chronic AI during admission and those without chronic AI was not significant (OR 0.51; 95% CI 0.19–1.41) (model 1; Table 3). The second model showed similar results (model 2; Table 3). Ten patients were newly diagnosed with chronic AI after discharge. Of the 433 patients who survived to discharge, 41 patients (9.5%) experienced AC relapse with a median follow-up period of 155 days (interquartile range: 32–473 days).

**Table 2**
In-hospital mortality and relapse rates of adrenal crisis after discharge among patients with or without chronic adrenal insufficiency.

| Timing of diagnosis of underlying chronic AI | In-hospital mortality | | Relapse after discharge[a] | |
|---|---|---|---|---|
| Chronic AI diagnosed before admission — no./total no. (%) | 1/73 | (1.4) | 12/72 | (16.7) |
| Primary AI | 0/9 | (0.0) | 1/9 | (11.1) |
| Central AI | 1/64 | (1.6) | 11/63 | (17.5) |
| Chronic AI diagnosed during admission | 5/86 | (5.8) | 6/81 | (7.4) |
| Primary AI | 2/14 | (14.3) | 1/12 | (8.3) |
| Central AI | 3/72 | (4.2) | 5/69 | (7.2) |
| Without chronic AI | 65/345 | (18.8) | 23/280 | (8.2) |

Abbreviations: AI, adrenal insufficiency
[a] Denominator is the number of patients who had survived to discharge.

**Table 3**
Risk of in-hospital mortality according to the period of diagnosis for chronic adrenal insufficiency.

| Timing of diagnosis of underlying chronic AI | Logistic regression: odds ratio (95% CI) | | | |
|---|---|---|---|---|
| | Model 1[a] | *p* value | Model 2[b] | *p* value |
| Chronic AI diagnosed before admission | 0.12 (0.02–0.92) | 0.041 | 0.10 (0.01–0.76) | 0.027 |
| Chronic AI diagnosed during admission | 0.51 (0.19–1.41) | 0.196 | 0.51 (0.18–1.43) | 0.200 |
| Without chronic AI (neither before nor during admission) | Reference | | Reference | |

[a] Multivariable-adjusted model 1 was adjusted for age, sex, and intervention on the date of admission: mechanical ventilation; vasopressor administration, and indication for admission: sepsis; cardiovascular disease; adrenal insufficiency-related symptoms; and autoimmune disease.
[b] Multivariable-adjusted model 2 was adjusted as for model 1 plus comorbidity: hypothyroidism; renal failure; chronic obstructive pulmonary disease and asthma; liver disease, and cessation of glucocorticoid administration within 30 days before admission.

### 3.4. Risk factors associated with in-hospital mortality

We assessed clinical features associated with fatal outcome (Supplementary Table S2). Elderly patients, especially those aged ≥80 years, tended to have worse outcomes. Intensive treatments within the first day of admission (i.e., entry to the ICU, requirement of mechanical ventilation, administration of vasopressor agents, and administration of antibiotics) were linked to death. However, administration of glucocorticoid therapy during the day of admission did not affect the outcome. Moreover, the use of oral glucocorticoid therapy before admission did not influence in-hospital mortality. In contrast, cessation of glucocorticoid treatment within 30 days before admission was related to a favorable prognosis. Patients diagnosed with chronic AI before admission were linked to a high likelihood of survival. With regard to the indication for admission, cardiovascular disease and sepsis were the major indications among patients who died, whereas diseases associated with the hypothalamic–pituitary–adrenal axis were minor indicators. Of note, none of the five patients with traumatic head injury in need of admission expired. Renal failure was frequently observed in patients who died as a comorbidity. Significant risk factors of in-hospital mortality were age (HR 1.45 per 10 years; 95% CI 1.17–1.78, $p < .001$), a requirement of mechanical ventilation on the day of admission (HR 3.81; 95% CI 1.88–7.72, $p < .001$), the administration of a vasopressor on the day of admission (HR 2.05; 95% CI 1.16–3.64, $p = .014$), sepsis as an indication for admission (HR 3.79; 95% CI 1.57–9.14, $p = .003$), AI-related symptoms as an indication for admission (HR 2.00; 95% CI 1.02–3.93, $p = .044$), and liver disease as a comorbidity (HR 3.24; 95% CI 1.10–9.58, $p = .034$). In contrast, chronic obstructive pulmonary disease and asthma were significantly associated with a reduced risk of in-hospital mortality (HR 0.12; 95% CI 0.02–0.92, $p = .042$; model 2; Table 4). When covariates were limited to the essential ones, the results of the analysis were similar (model 1; Table 4).

## 4. Discussion

Among patients hospitalized for AC, the prevalence of underlying chronic AI diagnosed during and before admission was similar. Preexisting chronic AI is related to a favorable outcome. In contrast, having a critical condition on the day of admission (sepsis, liver disease, requiring mechanical ventilation or vasopressor support) and AI-related

**Table 4**
Univariate and multivariate analyses of risk factors associated with in-hospital mortality.

| Variables | Multivariate analysis (model 1[a]) | | | Multivariate analysis (model 2[b]) | | |
|---|---|---|---|---|---|---|
| | Hazard ratio | 95% CI | *p* value | Hazard ratio | 95% CI | *p* value |
| Age (per 10 yrs.) | 1.45 | 1.18–1.78 | < 0.001 | 1.45 | 1.17–1.78 | 0.001 |
| Male | 0.93 | 0.56–1.55 | 0.786 | 0.85 | 0.50–1.45 | 0.558 |
| Mechanical ventilation[c] | 4.44 | 2.19–9.02 | < 0.001 | 3.81 | 1.88–7.72 | < 0.001 |
| Vasopressor administration[c] | 2.48 | 1.40–4.38 | 0.002 | 2.05 | 1.16–3.64 | 0.014 |
| Chronic AI diagnosed before admission | 0.24 | 0.03–1.74 | 0.157 | 0.19 | 0.02–1.39 | 0.102 |
| Sepsis[c] | 3.14 | 1.33–7.42 | 0.009 | 3.79 | 1.57–9.14 | 0.003 |
| Cardiovascular[d] | 1.69 | 0.73–3.94 | 0.220 | 1.81 | 0.77–4.25 | 0.173 |
| AI-related symptoms[d] | 1.98 | 1.02–3.85 | 0.043 | 2.00 | 1.02–3.93 | 0.044 |
| Autoimmune disease[d] | 2.46 | 0.74–8.13 | 0.140 | 2.60 | 0.78–8.72 | 0.122 |
| Hypothyroidism[e] | | | | 0.78 | 0.27–2.23 | 0.640 |
| Renal failure[e] | | | | 1.99 | 0.97–4.08 | 0.061 |
| COPD and asthma[e] | | | | 0.12 | 0.02–0.92 | 0.042 |
| Liver disease[e] | | | | 3.24 | 1.10–9.58 | 0.034 |
| Cessation of glucocorticoid administration within 30 days before admission | | | | 0.25 | 0.03–1.86 | 0.176 |

Abbreviations: 95% CI 95%, confidence interval; AI, adrenal insufficiency; COPD, chronic obstructive pulmonary disease.

[a] The multivariable-adjusted model 1 was adjusted for age, sex, and intervention on the date of admission: mechanical ventilation; vasopressor administration, and indication for admission: sepsis; cardiovascular disease; adrenal insufficiency-related symptoms; autoimmune disease.

[b] The multivariable-adjusted model 2 was adjusted as model 1 plus comorbidity: hypothyroidism; renal failure; chronic obstructive pulmonary disease and asthma; liver disease, and cessation of glucocorticoid administration within 30 days before admission.

[c] Intervention on the date of admission.

[d] Indication for hospitalization.

[e] Comorbidity at admission.

symptoms are significantly associated with an increase in in-hospital mortality.

AC may be an initial indicator for the diagnosis of chronic AI [20]. The present study demonstrated that patients hospitalized for AC have the potential to be diagnosed with chronic AI during admission. Consistently with previous reports [4], this study showed that 11.8% of patients with AC and chronic AI experienced AC relapse after discharge. Otherwise, some patients reached a diagnosis of chronic AI after discharge and were associated with a risk of AC relapse. The present estimation was limited to patients who received follow-up; thus, the incidence rate of AC relapse may be higher. It is plausible that physicians treat AC considering the possibility of underlying chronic AI, especially in patients requiring the administration of glucocorticoid therapy. Treating physicians refer to the guidelines for the treatment of sepsis and CIRCI, even if the condition is not diagnosed before admission [11,22].

Ono et al. reported that the in-hospital mortality rate of AC among patients with previously diagnosed chronic AI was 2.4% [5]. In patients with newly diagnosed AI admitted to non-ICU wards, the in-hospital mortality rate was 8.3% [9]. Guidelines for CIRCI, mostly based on data from patients hospitalized in the ICU, indicated that the in-hospital mortality rate was > 25% [11]. Similarly, the present study showed that in-hospital mortality among patients diagnosed with chronic AI before admission was lower compared with that reported in those not diagnosed with chronic AI at admission (1.4% vs. 16.2%, respectively). In addition, we conducted a comparison of the three groups (i.e., diagnosed with chronic AI before admission, during admission, and without chronic AI), divided by the time of diagnosis of underlying chronic AI. The results showed that the in-hospital mortality rate in patients diagnosed with chronic AI before admission was significantly lower than that observed in patients without AI. Moreover, the difference in in-hospital mortality between patients diagnosed with chronic AI before admission and those diagnosed during admission was not statistically significant.

Patients diagnosed with chronic AI before admission are considered at high risk of AC. Such patients tend to be treated in the early stages of the disease, resulting in a reduction of mortality. Furthermore, patient education is important for those with chronic AI requiring prompt lifesaving treatment with glucocorticoids [13]. Conversely, in patients not diagnosed with chronic AI until admission, AC may emerge due to severe conditions (i.e., sepsis and ARDS). Insufficient secretion of glucocorticoid hormone is a principal mechanism involved in chronic AI. However, AC due to critical illness (i.e., CIRCI) also influences the metabolism and clearance of glucocorticoid hormone [8]. Following the diagnosis of chronic AI after admission, it is recommended to initiate immediate treatment with glucocorticoids. When chronic AI is not diagnosed before admission, appropriate treatment is not initiated unless the presence of a severe condition (e.g., respiratory failure or refractory shock) is detected [10,11,22]. A trend toward a higher risk of in-hospital mortality was observed in patients not diagnosed with chronic AI throughout admission. This included cases with early death after admission and those with an unverified diagnosis of chronic AI due to insufficient medical care resources. Recently, guidelines for the management of AC in patients with chronic AI and CIRCI have become available [10,11]. According to these guidelines, prompt treatment is necessary coupled with consideration of the pathophysiological mechanism.

Currently, studies investigating the risk of mortality in the acute phase of AC are limited and important predictors of mortality are undetermined. This study showed that advanced age, a requirement for mechanical ventilation, the administration of a vasopressor, and liver disease were significant risk factors for in-hospital mortality. A descriptive study previously identified advanced age as a potential risk factor for mortality [5]. Respiratory, cardiovascular, and hepatic dysfunction was determined using indicators of organ dysfunction [19]. In particular, ARDS and liver disease are risk factors of CIRCI, with a powerful predictive ability for mortality [7]. In addition, we identified sepsis and AI-related symptoms as significant risk factors for in-hospital mortality. Sepsis may also be a risk factor of CIRCI and lead to secondary immunosuppression [7,23]. Impaired consciousness and hypoglycemia have been previously suggested as risk factors for mortality [5]. These non-specific symptoms related to AI may be a significant risk for death. Therefore, physicians identifying clinical symptoms indicative of AI in critical care settings, should consider a differential diagnosis of AC. Prompt management may result in the reduction of mortality associated with non-specific clinical symptoms.

This study was characterized by several limitations. We enrolled patients treated with sufficient glucocorticoid therapy in the acute

phase. Thus, patients with AC who received inadequate glucocorticoid therapy in the acute phase are not represented in this study. The precise proportion of the AC population these patients make up is unknown, but may be more than that of those who received sufficient glucocorticoid therapy in the acute phase. As previously reported, > 70% of patients with relative AI were not treated with glucocorticoids [21,24]. Consequently, this limitation may decrease the validity of the prognosis based on the timing of a chronic AI diagnosis. This study analyzed data extracted from a claims database, raising questions regarding the validity of the diagnosis. More than half of the study patients had undergone measurement of the levels of serum cortisol. This is a relatively high proportion in clinical practice settings, considering that a major clinical trial measured the levels of serum cortisol in approximately 70% of the population [25]. However, the use of data from a multihospital claims database permits an assessment across hospital departments/practice groups and provides an overview of patients with AC. Earlier studies were exclusively based on patients admitted to the ICU or those with previously diagnosed chronic AI [5,24]. The conditions in clinical settings differ from those of the present study; therefore, the interpretation of the results was challenging. However, abolishing the exclusion criteria related to clinical settings enables researchers to observe all patients with AC in need of hospitalization. Currently, etomidate is not available in Japan. Thus, we were unable to estimate its effect, potentially leading to AC. Patients receiving glucocorticoid therapy within the first day of admission were linked to the presence of more severe conditions and the effect of glucocorticoid therapy may be attenuated.

## 5. Conclusions

Among patients with AC, 17.1% and 14.5% were diagnosed with chronic AI during and before admission, respectively. Previously diagnosed chronic AI was associated with lower in-hospital mortality. Conversely, patients hospitalized due to AI-related non-specific symptoms were linked to a higher risk of mortality. Appropriate follow-up management is necessary in patients diagnosed with chronic AI to avoid delay in treatment administration and prevent death. Moreover, a differential diagnosis of AC in the acute phase is encouraged.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejim.2019.04.001.

## Financial support

This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

## Conflict of interest and source of funding

The authors declare no conflicts of interest directly relevant to the content of this article within 36 months of submission.

Koji Kawakami received research funds from Dainippon Sumitomo Pharma, Stella Pharma, Pfizer, CMIC, Bayer Yakuhin; honorarium from Astellas Pharma, Daiichi Sankyo Pharm, Eisai, Mitsubishi Tanabe Pharma, Abbie, Takeda Pharmaceutical Company Limited; and consult fees from Kyowa Hakko Kirin and Kaken Pharmaceutical. There are no patents, products in development or marketed products to declare, relevant to these companies. Other authors declare that they have no conflict of interest.

## Acknowledgements

We thank Mr. Masaki Nakamura, staff of Medical Data Vision Co. Ltd. (Tokyo Japan), for his technical support in using the healthcare database. This study did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

## References

[1] Charmandari E, Nicolaides NC, Chrousos GP. Adrenal insufficiency. Lancet 2014;383:2152–67. doi https://doi.org/10.1016/S0140-6736(13)61684-0.
[2] Rushworth RL, Torpy DJ, Falhammar H. Adrenal crises: perspectives and research directions. Endocrine 2017;55:336–45. doi https://doi.org/10.1007/s12020-016-1204-2.
[3] Hahner S, Spinnler C, Fassnacht M, et al. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. J Clin Endocrinol Metab 2015;100:407–16. doi https://doi.org/10.1210/jc.2014-3191.
[4] Smans LC, Van der Valk ES, Hermus AR, Zelissen PM. Incidence of adrenal crisis in patients with adrenal insufficiency. Clin Endocrinol (Oxf) 2016;84:17–22. doi https://doi.org/10.1111/cen.12865.
[5] Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K, Tanaka Y. Clinical features and practice patterns of treatment for adrenal crisis: a nationwide cross-sectional study in Japan. Eur J Endocrinol 2017;176:329–37. doi https://doi.org/10.1530/EJE-16-0803.
[6] Mesotten D, Vanhorebeek I, Van den Berghe G. The altered adrenal axis and treatment with glucocorticoids during critical illness. Nat Clin Pract Endocrinol Metab 2008;4:496–505. https://doi.org/10.1038/ncpendmet0921.
[7] Annane D, Pastores SM, Arlt W, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a multispecialty task force of the society of critical care medicine (SCCM) and the european society of intensive care medicine (ESICM). Crit Care Med 2017;45:2089–98. doi https://doi.org/10.1097/CCM.0000000000002724.
[8] Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. N Engl J Med 2013;368:1477–88. https://doi.org/10.1056/NEJMoa1214969.
[9] Ben-Shlomo A, Mirocha J, Gwin SM, et al. Clinical factors associated with biochemical adrenal-cortisol insufficiency in hospitalized patients. Am J Med 2014;127:754–62. https://doi.org/10.1016/j.amjmed.2014.03.002.
[10] Bornstein SR, Allolio B, Arlt W, et al. Diagnosis and treatment of primary adrenal insufficiency: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2016;101:364–89. doi https://doi.org/10.1210/jc.2015-1710.
[11] Annane D, Pastores SM, Rochwerg B, et al. Guidelines for the diagnosis and management of critical illness-related corticosteroid insufficiency (CIRCI) in critically ill patients (part I): society of critical care medicine (SCCM) and european society of intensive care medicine (ESICM) 2017. Crit Care Med 2017;45:2078–88. https://doi.org/10.1097/CCM.0000000000002737.
[12] Yanase T, Tajima T, Katabami T, et al. Diagnosis and treatment of adrenal insufficiency including adrenal crisis: a Japan endocrine society clinical practice guideline [opinion]. Endocr J 2016;63:765–84. https://doi.org/10.1507/endocrj.EJ16-0242.
[13] Hahner S, Hemmelmann N, Quinkler M, Beuschlein F, Spinnler C, Allolio B. Timelines in the management of adrenal crisis - targets, limits and reality. Clin Endocrinol (Oxf) 2015;82:497–502. https://doi.org/10.1111/cen.12609.
[14] Papierska L, Rabijewski M. Delay in diagnosis of adrenal insufficiency is a frequent cause of adrenal crisis. Int J Endocrinol 2013;2013:482370https://doi.org/10.1155/2013/482370.
[15] Husebye ES, Allolio B, Arlt W, et al. Consensus statement on the diagnosis, treatment and follow-up of patients with primary adrenal insufficiency. J Intern Med 2014;275:104–15. doi https://doi.org/10.1111/joim.12162.
[16] Wass JA, Arlt W. How to avoid precipitating an acute adrenal crisis. BMJ. 2012;345:e6333. https://doi.org/10.1136/bmj.e6333.
[17] Rushworth RL, Torpy DJ. A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in those with bacterial infections. BMC Endocr Disord 2014;14. https://doi.org/10.1186/1472-6823-14-79. 79-6823-14-79.
[18] Iwasaku M, Shinzawa M, Tanaka S, Kimachi K, Kawakami K. Clinical characteristics of adrenal crisis in adult population with and without predisposing chronic adrenal insufficiency: a retrospective cohort study. BMC Endocr Disord 2017;17. https://doi.org/10.1186/s12902-017-0208-0. 58-017-0208-0.
[19] Vincent JL, Moreno R. Clinical review: scoring systems in the critically ill. Crit Care 2010;14:207. https://doi.org/10.1186/cc8204.
[20] Bancos I, Hahner S, Tomlinson J, Arlt W. Diagnosis and management of adrenal insufficiency. Lancet Diabetes Endocrinol 2015;3:216–26. doi https://doi.org/10.1016/S2213-8587(14)70142-1.
[21] Freund Y, Jabre P, Mourad J, et al. Relative adrenal insufficiency in critically ill patient after rapid sequence intubation: KETASED ancillary study. J Crit Care 2014;29:386–9. doi https://doi.org/10.1016/j.jcrc.2013.12.018.
[22] Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med 2017;45:486–552. https://doi.org/10.1097/CCM.0000000000002255.
[23] van Vught LA, Klein Klouwenberg PM, Spitoni C, et al. Incidence, risk factors, and attributable mortality of secondary infections in the intensive care unit after admission for sepsis. JAMA. 2016;315:1469–79. doi https://doi.org/10.1001/jama.2016.2691.
[24] Elsouri N, Bander J, Guzman JA. Relative adrenal insufficiency in patients with septic shock; a close look to practice patterns. J Crit Care 2006;21:73–7. [doi:S0883-9441(05)00191-7 [pii].
[25] Annane D, Renault A, Brun-Buisson C, et al. Hydrocortisone plus fludrocortisone for adults with septic shock. N Engl J Med 2018;378:809–18. https://doi.org/10.1056/NEJMoa1705716.