Clinical features and practice patterns of treatment for adrenal crisis: a nationwide cross-sectional study in Japan

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Abstract

Context: Adrenal crisis is an endocrine emergency that requires prompt diagnosis and treatment. However, the clinical features and practice patterns of treatment for adrenal crisis are not completely understood.

Objective: To investigate patient characteristics, comorbidities and treatments of adrenal crisis.

Methods: We conducted a cross-sectional study of patients who received intravenous glucocorticoids for adrenal crisis at admission from 1 July 2007 to 31 March 2014, using a national inpatient database in Japan.

Results: Among approximately 34 million inpatients in the database, we identified 799 patients diagnosed with adrenal crisis and coexisting primary or secondary adrenal insufficiency at admission. The median (interquartile range) age was 58 (28–73) years, and the overall in-hospital mortality was 2.4% (19 of 799 patients). The most common comorbidity at admission was infections excluding pneumonia and gastroenteritis (15.0%). There were 68 (8.5%) patients with gastroenteritis, and no deaths occurred among these patients. The patients with secondary adrenal insufficiency showed significantly higher proportions of admission to ICU, extracellular fluid resuscitation, insulin therapy and catecholamine use than the patients with primary adrenal insufficiency. There were no significant between-group differences in mortality rate and variation in intravenous glucocorticoids (short-acting glucocorticoid, hydrocortisone; moderate-acting glucocorticoid, prednisolone or methylprednisolone; long-acting glucocorticoid, dexamethasone or betamethasone). Of the 19 dead patients, 15 were aged above 60 years, 12 had impaired consciousness at admission and 13 received insulin therapy.

Conclusions: Clinicians should be aware that older patients with impaired consciousness and diabetes mellitus are at relatively high risk of death from adrenal crisis.

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Introduction

Adrenal crisis is a life-threatening emergent manifestation of adrenal insufficiency that requires prompt management (1, 2, 3, 4). Currently, glucocorticoids are widely used in patients with various inflammatory or autoimmune diseases, as well as with primary or secondary adrenal insufficiency (5). Long-term glucocorticoid therapy leads to hypothalamic–pituitary–adrenal axis suppression, resulting in adrenal crisis, when insufficient endogenous

glucocorticoids are produced to meet the demand of physical or emotional stress (1, 2, 3, 4).

Adrenal crisis is characterized by several nonspecific symptoms such as hypotension, hypovolemia, diarrhea, vomiting, abdominal pain, severe fatigue and hypoglycemia (1, 2, 3, 4). However, validated diagnostic criteria for adrenal crisis have not been established owing to its rarity (1, 2, 3, 4). In previous studies, adrenal

Clinical Study	Y Ono and others	Clinical features of adrenal crisis	176:3	330
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crisis was defined as acute impairment of the general condition requiring hospital admission and intravenous glucocorticoid administration with or without fluid resuscitation (6, 7, 8, 9, 10). The most common precipitating factor for adrenal crisis was infectious gastroenteritis because of insufficient oral glucocorticoid absorption disturbed by diarrhea and vomiting (1, 3, 4, 6, 7, 8, 9, 11). Medications such as barbiturates, rifampicin and mitotane can also trigger adrenal crisis (1, 6, 12, 13).

The current standard treatment for adrenal crisis is intravenous administration of hydrocortisone together with appropriate fluid resuscitation including 0.9% saline (1, 2, 3, 4). Prednisolone can be an alternative if hydrocortisone is unavailable (3). Although there have been several reports regarding the incidence, mortality, risk factors and prevention strategies of adrenal crisis (6, 7, 8, 9, 10, 11, 14, 15, 16, 17), no studies have focused on describing the clinical practice patterns for treatment of this endocrine emergency owing to the lack of suitable databases. Furthermore, the differences in clinical features of adrenal crisis between primary and secondary adrenal insufficiency remain to be investigated.

To address these issues, the aims of the present study were to describe the clinical features and practice patterns of treatment for adrenal crisis including supportive measures, based on a national inpatient database in Japan.

Methods

Data source

The Diagnosis Procedure Combination (DPC) database is a national inpatient database including discharge abstract and administrative claims data in Japan. The data were collected for 6 months per year from 1 July to 31 December in the fiscal years 2007–2009, for 9 months per year from 1 July to 31 March in the fiscal year 2010, and for 12 months per year from 1 April to 31 March since the fiscal year 2011. The number of inpatient admissions in the fiscal year 2013 was approximately 7 million in 1061 hospitals and represented more than 50% of all inpatient admissions to acute-care hospitals in Japan. The database has been utilized for various fields of clinical research (18, 19, 20). The diagnoses of diseases are accurately recorded by the attending physicians. The database includes the following data: patients' sex and age; primary and secondary diagnoses; comorbidities at admission; admission to intensive care unit (ICU); medications and procedures; Japan Coma Scale (JCS) at admission and discharge status (alive

or dead). Diagnoses are recorded using International Classification of Diseases Tenth Revision (ICD-10) codes and text data in Japanese. The JCS scores comprise consciousness levels of 0 (alert consciousness), 1–3 (drowsy: wakefulness without any stimuli), 10–30 (somnolent: arousal by some stimuli) and 100–300 (comatose) (21). The JCS scores are well correlated with the Glasgow Coma Scale scores (22).

Ethical statement

The present study was approved by the Institutional Review Board at The University of Tokyo. Written informed consent was not required because of the anonymous nature of the data.

Patient selection

From the database, we retrospectively extracted the records for all patients who were diagnosed as adrenal crisis (ICD code, E27.2) with coexisting primary or secondary adrenal insufficiency at admission and received intravenous glucocorticoids from 1 July 2007 to 31 March 2014. Patients with a suspected diagnosis of adrenal crisis were excluded, because we considered that their data may not be well validated owing to the lack of detailed clinical information, such as symptoms, signs and biochemical findings, in the database.

Variables and main outcomes

We investigated patients' sex and age, JCS scores at admission, medications and requirements for supportive measures. Age was categorized into <20, 20–39, 40–59, 60–79 and ≥80 years. Etiology of adrenal insufficiency was categorized into the following two groups: (i) primary adrenal insufficiency (A18.7, tuberculous Addison disease; E24.1, Nelson syndrome; E25.0, congenital adrenogenital disorders associated with enzyme deficiency; E25.8, idiopathic adrenogenital disorder; E25.9, adrenogenital syndrome; E27.1, primary adrenocortical insufficiency; E27.3, drug-induced adrenocortical insufficiency; E27.4, other and unspecified adrenocortical insufficiency; E27.8, other specified disorders of adrenal gland (congenital adrenal hyperplasia as the Japanese-text diagnosis in the DPC database); E71.3, adrenoleukodystrophy; E89.6, postprocedural adrenocortical hypofunction; Q89.1, congenital malformations of adrenal gland);

Clinical Study	Y Ono and others	Clinical features of adrenal crisis	176:3	331
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Table 1 Clinical features of patients with adrenal crisis. Data are shown as *n* (%). All *P* values were obtained by chi-square tests or Fisher's exact tests.

	Overall (<i>n</i> =799)	Primary adrenal insufficiency (<i>n</i> =248)	Secondary adrenal insufficiency (<i>n</i> =551)	<i>P</i>
In-hospital death	19 (2.4)	9 (3.6)	10 (1.8)	0.12
Sex				0.71
Male	395 (49.4)	125 (50.4)	270 (49.0)	
Female	404 (50.6)	123 (49.6)	281 (51.0)	
Age (years)				<0.001
<20	164 (20.5)	106 (42.7)	58 (10.5)	
20–39	102 (12.8)	36 (14.5)	66 (12.0)	
40–59	156 (19.5)	21 (8.5)	135 (24.5)	
60–79	280 (35.0)	57 (23.0)	223 (40.5)	
≥80	97 (12.1)	28 (11.3)	69 (12.5)	
JCS score at admission				0.094
0 (alert)	562 (70.3)	184 (74.2)	378 (68.6)	
1–3 (drowsy)	137 (17.1)	42 (16.9)	95 (17.2)	
10–30 (somnolent)	55 (6.9)	9 (3.6)	46 (8.3)	
100–300 (comatose)	45 (5.6)	13 (5.2)	32 (5.8)	
Hormone replacement therapy				
Thyroid hormone	308 (38.5)	26 (10.5)	282 (51.2)	<0.001
Vasopressin	129 (16.1)	8 (3.2)	121 (22.0)	<0.001
Growth hormone	21 (2.6)	1 (0.4)	20 (3.6)	0.007
Testosterone	10 (1.3)	0 (0.0)	10 (1.8)	0.036

JCS, Japan Coma Scale; Thyroid hormone, levothyroxine sodium hydrate, liothyronine sodium or dried thyroid.

(ii) secondary adrenal insufficiency (E23.0, hypopituitarism; E23.6, other disorders of pituitary gland; E23.7, disorder of pituitary gland, unspecified; E89.3, postprocedural hypopituitarism). Hormone replacement therapy included thyroid hormone (levothyroxine sodium hydrate, liothyronine sodium and dried thyroid), vasopressin, growth hormone and testosterone. Medications that could possibly trigger adrenal crisis included inhibitors of adrenocortical steroid synthesis (mitotane, trilostane metyrapone),

rifampicin and barbiturate. We identified the number of repeat hospitalizations.

We identified the following comorbidities at admission: gastroenteritis; cardiovascular diseases; respiratory diseases including pneumonia; renal diseases; neuromuscular diseases; infections excluding pneumonia and gastroenteritis; rheumatic diseases; gastrointestinal diseases excluding gastroenteritis; hepatopancreatobiliary diseases; psychiatric diseases; cerebrovascular diseases; dementia; malignancy and trauma.

Table 2 Comorbidities at admission in patients with adrenal crisis. Data are shown as *n* (%). All *P* values were obtained by chi-square tests or Fisher's exact tests.

	Overall (<i>n</i> =799)	Primary adrenal insufficiency (<i>n</i> =248)	Secondary adrenal insufficiency (<i>n</i> =551)	<i>P</i>
Infections	120 (15.0)	45 (18.1)	75 (13.6)	0.097
Respiratory diseases	94 (11.8)	30 (12.1)	64 (11.6)	0.85
Gastroenteritis	68 (8.5)	32 (12.9)	36 (6.5)	0.003
Cardiovascular diseases	51 (6.4)	13 (5.2)	38 (6.9)	0.38
Gastrointestinal diseases	46 (5.8)	16 (6.5)	30 (5.4)	0.57
Neuromuscular diseases	45 (5.6)	10 (4.0)	35 (6.4)	0.19
Renal diseases	36 (4.5)	12 (4.8)	24 (4.4)	0.76
Malignancy	27 (3.4)	12 (4.8)	15 (2.7)	0.13
Psychiatric diseases	26 (3.3)	5 (2.0)	21 (3.8)	0.19
Cerebrovascular diseases	25 (3.1)	5 (2.0)	20 (3.6)	0.23
Hepatopancreatobiliary diseases	24 (3.0)	7 (2.8)	17 (3.1)	0.84
Rheumatic diseases	10 (1.3)	3 (1.2)	7 (1.3)	1.00
Dementia	8 (1.0)	1 (0.4)	7 (1.3)	0.45
Trauma	5 (0.6)	2 (0.8)	3 (0.5)	0.65

Clinical Study	Y Ono and others	Clinical features of adrenal crisis	176:3	332
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We investigated the practice patterns for treating adrenal crisis in terms of variation in intravenous glucocorticoid therapy (short-acting glucocorticoid, hydrocortisone; moderate-acting glucocorticoid, prednisolone or methylprednisolone; long-acting glucocorticoid, dexamethasone or betamethasone). We also examined the use of mineralocorticoid (fludrocortisone), extracellular fluid (normal saline or Ringer's solution), intravenous glucose, glucagon, insulin, catecholamines (dopamine, noradrenaline, adrenaline and dobutamine), immune globulin, albumin, antithrombin and blood transfusion (red blood cells, fresh-frozen plasma and platelets). Supportive measures included mechanical ventilation and hemodialysis (i.e. intermittent or continuous renal replacement therapy).

Statistical analysis

We compared the patient characteristics between the two groups with primary and secondary adrenal insufficiency using the chi-square test or Fisher's exact test as appropriate. All tests were two-tailed, and $P < 0.05$ was

considered statistically significant. All statistical analyses were performed using SPSS, version 22.0 (IBM).

Results

Clinical features of patients with adrenal crisis

Among approximately 34 million inpatient admissions during the study period, we identified 799 eligible patients. The clinical features of the patients in the subgroups are shown in Table 1. The median (interquartile range) age in the overall, primary adrenal insufficiency and secondary adrenal insufficiency groups was 58 (28–73), 29 (7–68), and 61 (41–73) years respectively. The ratio of females to males was 1.02. The overall in-hospital mortality was 2.4% (19 of 799 patients). The patients with primary adrenal insufficiency were more likely to be younger than the patients with secondary adrenal insufficiency. The proportions of patients receiving thyroid hormone, vasopressin, growth hormone and testosterone were significantly higher in the patients with secondary adrenal insufficiency.

Table 3 Clinical practice patterns for adrenal crisis. Data are shown as n (%). All P values were obtained by chi-square tests or Fisher's exact tests.

	Overall ($n=799$)	Primary adrenal insufficiency ($n=248$)	Secondary adrenal insufficiency ($n=551$)	P
Admission to ICU	42 (5.3)	7 (2.8)	35 (6.4)	0.039
Variation in intravenous glucocorticoids				
Short-acting glucocorticoid ^a	736 (92.1)	230 (92.7)	506 (91.8)	0.66
Moderate-acting glucocorticoid ^b	89 (11.1)	26 (10.5)	63 (11.4)	0.69
Long-acting glucocorticoid ^c	35 (4.4)	13 (5.2)	22 (4.0)	0.43
Mineralocorticoid	76 (9.5)	70 (28.2)	6 (1.1)	<0.001
Extracellular fluid ^d	717 (89.7)	195 (78.6)	522 (94.7)	<0.001
Intravenous glucose	328 (41.1)	106 (42.7)	222 (40.3)	0.52
Glucagon	8 (1.0)	0 (0.0)	8 (1.5)	0.063
Insulin therapy	147 (18.4)	31 (12.5)	116 (21.1)	0.004
Catecholamine use	83 (10.4)	16 (6.5)	67 (12.2)	0.014
Variation in catecholamines				
Dopamine	56 (7.0)	9 (3.6)	47 (8.5)	0.012
Noradrenaline	27 (3.4)	7 (2.8)	20 (3.6)	0.56
Adrenaline	29 (3.6)	7 (2.8)	22 (4.0)	0.41
Dobutamine	15 (1.9)	2 (0.8)	13 (2.4)	0.17
Immune globulin	12 (1.5)	5 (2.0)	7 (1.3)	0.42
Albumin	25 (3.1)	5 (2.0)	20 (3.6)	0.23
Antithrombin	12 (1.5)	3 (1.2)	9 (1.6)	0.76
Blood transfusion				
Red blood cells	26 (3.3)	5 (2.0)	21 (3.8)	0.19
Fresh-frozen plasma	10 (1.3)	2 (0.8)	8 (1.5)	0.73
Platelets	17 (2.1)	4 (1.6)	13 (2.4)	0.60
Mechanical ventilation	34 (4.3)	10 (4.0)	24 (4.4)	0.83
Hemodialysis ^e	11 (1.4)	2 (0.8)	9 (1.6)	0.52

^ahydrocortisone; ^bprednisolone or methylprednisolone; ^cdexamethasone or betamethasone; ^dnormal saline or Ringer's solution; ^eintermittent or continuous renal replacement therapy.

Clinical Study	Y Ono and others	Clinical features of adrenal crisis	176:3	333
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In terms of medications possibly triggering adrenal crisis, three patients with primary adrenal insufficiency received inhibitors of adrenocortical steroid synthesis, one patient with secondary adrenal insufficiency received rifampicin and one patient with primary adrenal insufficiency received barbiturate. Among 248 patients with primary adrenal insufficiency, 20 (8.1%) were hospitalized twice, 6 (2.4%) were hospitalized three times and 4 (1.6%) were hospitalized more than four times. Similarly, among 551 patients with secondary adrenal insufficiency, 48 (8.7%) were hospitalized twice, 9 (1.6%) were hospitalized three times and 5 (0.9%) were hospitalized four times.

Comorbidities at admission

Infections were the most common comorbidity at admission, followed by respiratory diseases, gastroenteritis, cardiovascular diseases, gastrointestinal diseases and neuromuscular diseases (Table 2). The proportion of patients with gastroenteritis was significantly higher in

the patients with primary adrenal insufficiency than that in the patients with secondary adrenal insufficiency. Overall, 16 patients had both infections and respiratory diseases, and 3 patients had both infections and gastrointestinal diseases.

Clinical practice patterns for adrenal crisis

The clinical practice patterns for adrenal crisis are shown in Table 3. Overall, the rate of admission to ICU was 5.3% (42 of 799 patients). The proportions of patients with admission to ICU, extracellular fluid resuscitation, insulin therapy and catecholamine use were significantly higher in the patients with secondary adrenal insufficiency. In contrast, the patients with primary adrenal insufficiency were more likely to receive mineralocorticoid. Overall, 43 patients were treated with both short-acting and moderate-acting glucocorticoid, and 17 patients were treated with both short-acting and long-acting glucocorticoid. Among the 562 patients with alert consciousness (JCS score

Table 4 Details of the in-hospital deaths in 19 patients with adrenal crisis. Data are shown as *n* (%).

	Overall (<i>n</i> = 19)	Primary adrenal insufficiency (<i>n</i> = 9)	Secondary adrenal insufficiency (<i>n</i> = 10)
Sex			
Male	11 (57.9)	6 (66.7)	5 (50.0)
Female	8 (42.1)	3 (33.3)	5 (50.0)
Age (years)			
<20	2 (10.5)	2 (22.2)	0 (0.0)
20–39	0 (0.0)	0 (0.0)	0 (0.0)
40–59	2 (10.5)	1 (11.1)	1 (10.0)
60–79	6 (31.6)	3 (33.3)	3 (30.0)
≥80	9 (47.4)	3 (33.3)	6 (60.0)
JCS score at admission			
0 (alert)	7 (36.8)	4 (44.4)	3 (30.0)
1–3 (drowsy)	4 (21.1)	2 (22.2)	2 (20.0)
10–30 (somnolent)	0 (0.0)	0 (0.0)	0 (0.0)
100–300 (comatose)	8 (42.1)	3 (33.3)	5 (50.0)
Hormone replacement therapy			
Thyroid hormone ^a	5 (26.3)	1 (11.1)	4 (40.0)
Vasopressin	4 (21.1)	2 (22.2)	2 (20.0)
Admission to ICU	5 (26.3)	3 (33.3)	2 (20.0)
Variation in intravenous glucocorticoids			
Short-acting glucocorticoid ^b	18 (94.7)	9 (100.0)	9 (90.0)
Moderate-acting glucocorticoid ^c	5 (26.3)	3 (33.3)	2 (20.0)
Long-acting glucocorticoid ^d	1 (5.3)	0 (0.0)	1 (10.0)
Intravenous glucose	18 (94.7)	9 (100.0)	9 (90.0)
Insulin therapy	13 (68.4)	6 (66.7)	7 (70.0)
Catecholamine use	12 (63.2)	6 (66.7)	6 (60.0)
Mechanical ventilation	11 (57.9)	5 (55.6)	6 (60.0)
Hemodialysis ^e	3 (15.8)	2 (22.2)	1 (10.0)

^alevothyroxine sodium hydrate, liothyronine sodium, or dried thyroid; ^bhydrocortisone; ^cprednisolone or methylprednisolone; ^ddexamethasone or betamethasone; ^eintermittent or continuous renal replacement therapy.

Clinical Study	Y Ono and others	Clinical features of adrenal crisis	176:3	334
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of 0) at admission, 19 were admitted to ICU, 35 were treated with catecholamines, 12 required mechanical ventilation and 4 required hemodialysis.

Details of in-hospital deaths

Details of the in-hospital deaths in 19 patients with adrenal crisis are shown in [Table 4](#). Given the small sample size of dead patients, statistical comparisons were not performed. Among the 19 dead patients, 15 (78.9%) were aged above 60 years, 12 (63.2%) had impaired consciousness (i.e., JCS score above 1) at admission and 13 (68.4%) received insulin therapy.

Discussion

We examined 799 patients with adrenal crisis using a national inpatient database in Japan. Our data suggest that the spectrum of adrenal crisis ranges widely from low to high risk. Furthermore, our results provide an overview of the practice patterns of treatment for this endocrine emergency. In particular, the proportions of older patients, patients with impaired consciousness at admission and patients with diabetes mellitus receiving insulin were relatively high among the dead patients. Overall, 92 patients (11.5%) with adrenal crisis had experienced previous repeat admissions. These findings highlight the clinical importance of aging, consciousness level and coexisting other endocrine disorder, as well as the need for ongoing patient education to prevent adrenal crisis in the management of patients with adrenal insufficiency. To the best of our knowledge, the present study is the first of its kind to describe the treatment patterns, including intensive therapies, for adrenal crisis. The strength of our study, compared with previous studies, is the large number of patients with adrenal crisis evaluated.

The large difference in mean age between the two types of adrenal insufficiency may have arisen because primary adrenal insufficiency, such as autoimmune Addison's disease and congenital adrenal hyperplasia, is commonly caused by gene mutations (2), and thus, develops earlier in life. In contrast, the common causes of secondary adrenal insufficiency were reported to be pituitary adenoma and other intracerebral tumors (6, 11). We therefore consider that the patients with secondary adrenal insufficiency were more likely to develop their disease later in life than the patients with primary adrenal insufficiency.

In the present study, the overall in-hospital mortality of adrenal crisis was 2.4%. In contrast, a recent prospective questionnaire survey in Germany showed that the adrenal crisis-related mortality of patients with primary or secondary adrenal insufficiency was 6.3% (four patients in 64 episodes of adrenal crisis) (11). This discrepancy may be explained by the differences in sample size and study design between the previous questionnaire survey and the present study. Our study represents a real-world clinical setting based on a national database.

A previous study on adrenal crisis among inpatients aged above 20 years in Australia showed that the proportion of females was 62.5% (515 of 824 patients) (23). Several other studies also indicated that female patients with adrenal insufficiency were at higher risk for adrenal crisis (6, 11, 14, 15). In our study, the sex distribution of the patients with adrenal crisis was almost even, for unclear reasons.

Overall, approximately half of the patients with adrenal crisis were aged above 60 years, and older patients showed higher mortality. These findings highlight the importance of considering age when treating patients with adrenal insufficiency in the acute phase, because older patients are more likely to have several health problems and underlying comorbidities. For example, older patients with cognitive impairment may have difficulty in self-management of glucocorticoid stress doses when required (23). Moreover, older patients do not necessarily show typical symptoms of infectious diseases such as fever, and thereby delay self-management of glucocorticoid stress doses and intravenous administration of glucocorticoid by attending physicians. Thus, these problems can lead to the development of severe adrenal crisis with eventual lethality.

Patients with adrenal crisis and coexisting impaired consciousness at admission had relatively high mortality. One possible explanation is the existence of a point of no return in adrenal crisis, reflecting the point at which even optimum treatment will no longer prevent death from adrenal crisis (1). Consciousness level can be one of the criteria for determining the severity or grading of adrenal crisis. Notably, among the 19 dead patients, 7 patients (36.8%) had alert consciousness (JCS score 0) at admission. We speculate that these patients became worse after admission because they required supportive care including catecholamine, mechanical ventilation and hemodialysis. These findings indicate that if the diagnosis of adrenal crisis is missed, even

Clinical Study	Y Ono and others	Clinical features of adrenal crisis	176:3	335
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patients with alert consciousness in the early phases may possibly die.

Gastroenteritis, other infectious disease, diabetes insipidus and psychiatric disease were previously reported to be precipitating factors for adrenal crisis (6, 11, 15). In our study, 68 (8.5%) patients had gastroenteritis, and patients with primary adrenal insufficiency were more likely to have this comorbidity than patients with secondary adrenal insufficiency. No deaths were observed among the patients with gastroenteritis. We speculate that the patients with gastroenteritis were immediately treated with intravenous glucocorticoids because of apparent symptoms such as diarrhea and vomiting, resulting in prompt recovery. We further speculate that the diagnosis of gastroenteritis in adrenal crisis was potentially overestimated because the symptoms of this crisis, including nausea and vomiting, overlap with those of gastroenteritis and may be interpreted as acute gastroenteritis (23).

Interestingly, some patients with adrenal crisis were treated with moderate-acting or long-acting glucocorticoid combined with short-acting glucocorticoid. The reasons for the use of moderate-acting or long-acting glucocorticoid were not recorded in the database by the attending doctors. Previous European studies also described that some patients with adrenal insufficiency received prednisolone or dexamethasone (mostly combined with hydrocortisone, prednisolone or cortisone acetate) for unknown reasons (6, 8, 11). Additional studies are needed to clarify how physicians use different types of glucocorticoid in patients with adrenal crisis.

Compared with the patients with primary adrenal insufficiency, the patients with secondary adrenal insufficiency were more likely to receive intensive therapies including admission to ICU, extracellular fluid resuscitation, insulin therapy and catecholamine use. These findings suggest that the patients with secondary adrenal insufficiency may have developed more severe adrenal crisis than the patients with primary adrenal insufficiency. However, there were no significant between-group differences in mortality rate and variation in intravenous glucocorticoids. Moreover, our findings cannot provide recommendations regarding the optimal treatment for adrenal crisis because of the small number of deaths and the retrospective study design.

Among the 19 dead patients, 13 received insulin, 5 received thyroid hormone and 4 received vasopressin.

These findings suggest that the patients with adrenal insufficiency and coexisting multiple endocrine disorders may have developed severe adrenal crisis. This interpretation is supported by previous evidence that patients with autoimmune polyglandular syndrome were at higher risk for developing adrenal crisis (24).

Differences in the definition of adrenal crisis among studies can lead to heterogeneous results and interpretations. As a top priority, internationally uniform and validated diagnostic criteria for adrenal crisis should be established to serve as a platform for the advancement of research in this field. Although the present study did not include detailed endocrinological data, we believe that our findings based on large-scale data will provide clues toward better understanding of the clinical features of this impending crisis.

Several limitations to the present study should be acknowledged. First, the diagnoses of adrenal crisis recorded in our study may be less well-validated than those in prospective studies, because the database did not include detailed clinical information such as symptoms, vital signs and laboratory data. Second, the clinical outcomes might have been affected by unrecorded confounding factors as follows: dose and duration of glucocorticoid administration before admission; whether or not patients discontinued taking glucocorticoid before admission; severity and duration of stressful events and whether or not patients were educated to manage sick days to avoid adrenal crisis, and were equipped with a steroid emergency card to inform medical practitioners of the need for immediate parenteral glucocorticoid administration. Third, we were unable to confirm the causal relationship between the patient characteristics in our study and higher mortality in adrenal crisis because of the nature of the cross-sectional study. Fourth, although the DPC database included more than 50% of all inpatient admissions to acute-care hospitals in Japan, population representativeness may be limited because the patient selection was not based on a random sampling method. Fifth, age may be a confounding factor that should be adjusted when comparing the two types of patients. However, we could not perform a multivariable logistic regression analysis to evaluate the risk factors associated with in-hospital mortality, owing to the small number of non-survivors. This is because the ratio of the number of non-survivors to the number of candidate independent variables (i.e., sex, age, consciousness level, admission to ICU, variation in intravenous glucocorticoids and catecholamine use) was small (25, 26). Finally, it was

Clinical Study	Y Ono and others	Clinical features of adrenal crisis	176:3	336
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impossible to estimate the frequency of adrenal crisis in the study population with each etiology of adrenal insufficiency because the database did not include outpatient data. Despite these limitations, we believe that the present study serves to provide groundwork for future research in this field.

In conclusion, the present study suggests that clinicians should pay special attention to older patients with adrenal crisis and coexisting impaired consciousness and diabetes mellitus and treat them promptly and aggressively to prevent death from adrenal crisis. The necessary next steps are the establishment of internationally uniform and validated diagnostic criteria for adrenal crisis, and the establishment of a case registration system including detailed clinical information, with a view to achieving enhanced survival of this lethal endocrine emergency.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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References

- 1 Allolio B. Extensive expertise in endocrinology. Adrenal crisis. *European Journal of Endocrinology* 2015 **172** R115–R124. (doi:10.1530/EJE-14-0824)
- 2 Charmandari E, Nicolaides NC & Chrousos GP. Adrenal insufficiency. *Lancet* 2014 **383** 2152–2167. (doi:10.1016/S0140-6736(13)61684-0)
- 3 Bornstein SR, Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer GD, Husebye ES, Merke DP, Murad MH, Stratakis CA *et al.* Diagnosis and treatment of primary adrenal insufficiency: an Endocrine Society clinical practice guideline. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 364–389. (doi:10.1210/jc.2015-1710)
- 4 Puar TH, Stikkelbroeck NM, Smans LC, Zelissen PM & Hermus AR. Adrenal crisis: still a deadly event in the 21(st) century. *American Journal of Medicine* 2016 **129** 339.e1–339.e9. (doi:10.1016/j.amjmed.2015.08.021)
- 5 Marik PE & Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. *Archives of Surgery* 2008 **143** 1222–1226. (doi:10.1001/archsurg.143.12.1222)
- 6 Hahner S, Loeffler M, Bleicken B, Drechsler C, Milovanovic D, Fassnacht M, Ventz M, Quinkler M & Allolio B. Epidemiology of adrenal crisis in chronic adrenal insufficiency: the need for new prevention strategies. *European Journal of Endocrinology* 2010 **162** 597–602. (doi:10.1530/EJE-09-0884)
- 7 Reisch N, Willige M, Kohn D, Schwarz HP, Allolio B, Reincke M, Quinkler M, Hahner S & Beuschlein F. Frequency and causes of adrenal crises over lifetime in patients with 21-hydroxylase deficiency. *European Journal of Endocrinology* 2012 **167** 35–42. (doi:10.1530/EJE-12-0161)
- 8 Smans LC, Van der Valk ES, Hermus AR & Zelissen PM. Incidence of adrenal crisis in patients with adrenal insufficiency. *Clinical Endocrinology* 2016 **84** 17–22. (doi:10.1111/cen.12865)
- 9 White K & Arlt W. Adrenal crisis in treated Addison's disease: a predictable but under-managed event. *European Journal of Endocrinology* 2010 **162** 115–120. (doi:10.1530/EJE-09-0559)
- 10 Nagesser SK, van Seters AP, Kievit J, Hermans J, Krans HM & van de Velde CJH. Long-term results of total adrenalectomy for Cushing's disease. *World Journal of Surgery* 2000 **24** 108–113. (doi:10.1007/s002689910020)
- 11 Hahner S, Spinnler C, Fassnacht M, Burger-Stritt S, Lang K, Milovanovic D, Beuschlein F, Willenberg HS, Quinkler M & Allolio B. High incidence of adrenal crisis in educated patients with chronic adrenal insufficiency: a prospective study. *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 407–416. (doi:10.1210/jc.2014-3191)
- 12 Elansary EH & Earis JE. Rifampicin and adrenal crisis. *British Medical Journal* 1983 **286** 1861–1862. (doi:10.1136/bmj.286.6381.1861-a)
- 13 Kyriazopoulou V, Parparousi O & Vagenakis AG. Rifampicin-induced adrenal crisis in Addisonian patients receiving corticosteroid replacement therapy. *Journal of Clinical Endocrinology and Metabolism* 1984 **59** 1204–1206. (doi:10.1210/jcem-59-6-1204)
- 14 Thompson SK, Hayman AV, Ludlam WH, Deveney CW, Loriaux DL & Sheppard BC. Improved quality of life after bilateral laparoscopic adrenalectomy for Cushing's disease: a 10-year experience. *Annals of Surgery* 2007 **245** 790–794. (doi:10.1097/01.sla.0000251578.03883.2f)
- 15 Omori K, Nomura K, Shimizu S, Omori N & Takano K. Risk factors for adrenal crisis in patients with adrenal insufficiency. *Endocrine Journal* 2003 **50** 745–752. (doi:10.1507/endocrj.50.745)
- 16 Repping-Wuts HJ, Stikkelbroeck NM, Noordzij A, Kerstens M & Hermus AR. A glucocorticoid education group meeting: an effective strategy for improving self-management to prevent adrenal crisis. *European Journal of Endocrinology* 2013 **169** 17–22. (doi:10.1530/EJE-12-1094)
- 17 Hahner S, Hemmelmann N, Quinkler M, Beuschlein F, Spinnler C & Allolio B. Timelines in the management of adrenal crisis – targets, limits and reality. *Clinical Endocrinology* 2015 **82** 497–502. (doi:10.1111/cen.12609)
- 18 Ono Y, Ono S, Yasunaga H, Matsui H, Fushimi K & Tanaka Y. Factors associated with mortality of thyroid storm: analysis using a national inpatient database in Japan. *Medicine* 2016 **95** e2848. (doi:10.1097/MD.0000000000002848)
- 19 Hamada T, Yasunaga H, Nakai Y, Isayama H, Horiguchi H, Matsuda S, Fushimi K & Koike K. Continuous regional arterial infusion for acute pancreatitis: a propensity score analysis using a nationwide administrative database. *Critical Care* 2013 **17** R214. (doi:10.1186/cc13029)
- 20 Ono S, Ishimaru M, Matsui H, Fushimi K & Yasunaga H. Effect of hospital volume on outcomes of surgery for cleft lip and palate. *Journal of Oral and Maxillofacial Surgery* 2015 **73** 2219–2224. (doi:10.1016/j.joms.2015.04.003)
- 21 Todo T, Usui M & Takakura K. Treatment of severe intraventricular hemorrhage by intraventricular infusion of urokinase. *Journal of Neurosurgery* 1991 **74** 81–86. (doi:10.3171/jns.1991.74.1.0081)
- 22 Ono K, Wada K, Takahara T & Shirohata T. Indications for computed tomography in patients with mild head injury. *Neurologia Medico-Chirurgica* 2007 **47** 291–298. (doi:10.2176/nmc.47.291)
- 23 Rushworth RL & Torpy DJ. A descriptive study of adrenal crises in adults with adrenal insufficiency: increased risk with age and in

Clinical Study	Y Ono and others	Clinical features of adrenal crisis	176:3	337
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- those with bacterial infections. *BMC Endocrine Disorders* 2014 **14** 79. ([doi:10.1186/1472-6823-14-79](https://doi.org/10.1186/1472-6823-14-79))
- 24 Meyer G, Badenhoop K & Linder R. Addison's disease with polyglandular autoimmunity carries a more than 2.5-fold risk for adrenal crises: German Health insurance data 2010–2013. *Clinical Endocrinology* 2016 **85** 347–353. ([doi:10.1111/cen.13043](https://doi.org/10.1111/cen.13043))
- 25 Harrell FE, Lee KL, Matchar DB & Reichert TA. Regression models for prognostic prediction: advantages, problems, and suggested solutions. *Cancer Treatment Reports* 1985 **69** 1071–1076.
- 26 Peduzzi P, Concato J, Kemper E, Holford TR & Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *Journal of Clinical Epidemiology* 1996 **49** 1373–1379. ([doi:10.1016/S0895-4356\(96\)00236-3](https://doi.org/10.1016/S0895-4356(96)00236-3))

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