

Demographic and Clinical Risk Factors of Hiccups

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Abstract

Background: The hiccup is a common somatic side effect of medication. Although hiccups rarely influence disease prognosis, they can reduce tolerance to medication regimens and decrease quality of life. Our previous analysis of the Japanese Adverse Drug Event Report Database identified male sex and height as factors related to hiccup risk. While the clinical features and pathogenesis of hiccups have been partially elucidated, there has been no analysis of the relation between hiccups and clinical variables, and to this end, we examined the relation among hiccups, patients' demographics and clinical risk factors.

Methods: In the present study, we conducted a more extensive examination of patient demographics, physical characteristics, primary disease, and other clinical characteristics to identify additional risk factors for medication-induced hiccups in patients hospitalized at Musashino Red Cross Hospital between April 2014 and December 2014. We conducted a statistical analysis of patient demographics, physical characteristics, and other clinical characteristics in patients with and without hiccups hospitalized at Musashino Red Cross Hospital between April 2014 and December 2014. In total, 7603 patients (> 40 years) and 2343 patients (≤ 40 years) were enrolled in the present study.

Results: In the patients > 40 years, 228 exhibited hiccups. Univariate analysis indicated that male sex, tall stature, low BMI, chemotherapy, and death within 24 hours of hospitalization were related to hiccup risk. Furthermore, a multivariable analysis identified male sex, chemotherapy, low BMI, and death within 24 hours of hospitalization as independent risk factors for hiccups. Neurovascular diseases and neoplasms (of renal pelvis, brain, bile duct, bladder, esophagus, and lung/bronchus) were also identified as independent risk factors in the patients > 40 years. In the patients ≤ 40 years, most with neonatal diseases, 28 exhibited hiccups. Sex was not a significant risk factor in the patients ≤ 40 years old.

Conclusions: We suggest that low BMI is a reliable physical index related to hiccup risk, while chemotherapy and certain malignant tumors are clinical risk factors. These results may assist in elucidating the underlying mechanisms and guiding therapy to reduce hiccup risk.

Keywords: Adverse Drug Reaction; Chemotherapy; Data Analysis; Drug Therapy; Hiccups

BMI : Body Mass Index

MDC : Main Disease Classifications

ICD-10 : International Statistical Classification of Diseases and Related Health Problems

Abbreviations

CNS : Central Nervous System

WHO : World Health Organization

Introduction

Hiccups are caused mainly by diaphragmatic myoclonus [1], a brief involuntary twitching of the diaphragmatic muscles, together with coordinated contraction of the glottic closure group of muscles. While transient hiccups rarely influence life or disease prognosis directly, persistent hiccups can disturb verbal communication, sleep, eating, and drinking, and in severe cases can result in weight loss, exhaustion, anxiety, and depression [2]. Thus, hiccup control may be clinically important, especially when hiccups arise as a side effect of lifesaving treatment.

Hiccups are classified based on duration as bout, persistent, or intractable [3]. Alternatively, hiccups are classified based on etiology as psychogenic, organic, or idiopathic [4]. No sex difference in the frequency of common hiccups has been found in healthy subjects, while onset of persistent or intractable hiccups shows male predominance [5]. Lee et al. reported that hiccups of non-Central Nervous System (CNS) origin are more common among males [6]. In our previous study, we investigated demographic and clinical characteristics contributing to hiccups using the large Japanese Adverse Drug Event Report Database [7]. That study suggested that male sex and tall stature are risk factors for hiccups. Chemotherapy-induced hiccups have also been reported, particularly during treatment with cisplatin [8,9]. In addition, dexamethasone often combined with anticancer drugs may increase the risk of hiccups. Lee et al. succeeded in decreasing induction of hiccups by substituting the antiemetic drug dexamethasone with methylprednisolone in the next course of treatment [10]. Thus, it is possible to define high-risk groups based on patient characteristics, but there are few reports on clinical factors influencing hiccup risk, such as specific primary disease and medication. While the clinical features and pathogenesis of hiccups have been partially elucidated, there has been no complete physical examination of the associations between hiccups and clinical variables such as primary disease. To this end, we examined the associations between hiccups and patient demographics, physical characteristics, primary disease, in-hospital events, and treatments received.

Materials and Methods

Database

We selected patients hospitalized at Musashino Red Cross Hospital between April 2014 and December 2014. We retrospectively gathered patient physical examination information, clinical history, disease name, and disease classification from

the electronic medical chart system and identified those patients with hiccups during the research period. Data on hiccup patients were connected to all other patient data using their ID numbers to construct a data table (Figure 1). We removed duplicated data for patients readmitted during the research period.

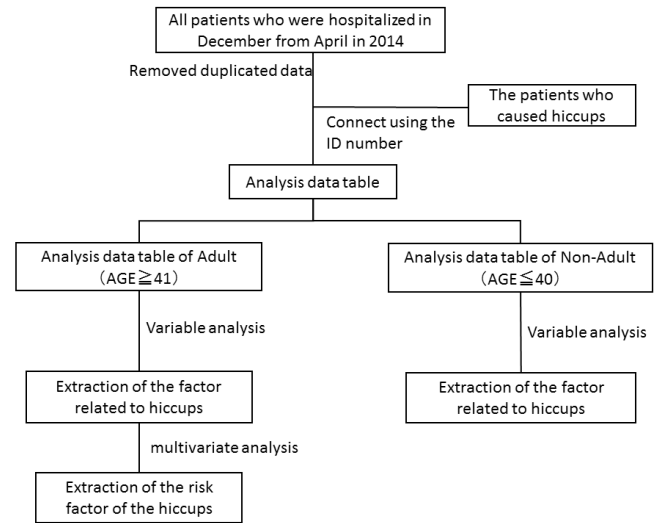


Figure 1: Flowchart for construction of the data analysis table.

We removed duplicated data for all patients readmitted using an ID number linking relevant clinicodemographic information with hiccup occurrence. Patients were classified into adult and non-adult groups for separate analysis.

Extraction of Patient Information

We investigated patient demographic and physical characteristics, chemotherapy (YES/NO, regimen), surgical treatment (YES/NO), death within 24 hours of admission (YES/NO), disease name according to the Japanese Major Diagnostic Categories (MDC), and International Classification of Disease (ICD-10).

Classification of Age

We classified all the patients into two groups based on age. Jacques VS et al. reported the association of age with the incidence of hiccups [11]. We focused on the patient's age and sex and assumed that age was related with hiccups. The incidence of hiccups suddenly increased after 40 years of age (Figure 2). From these results, we classified all patients into two groups: (1) patients group above 40 years old and (2) patients 40 years or younger.

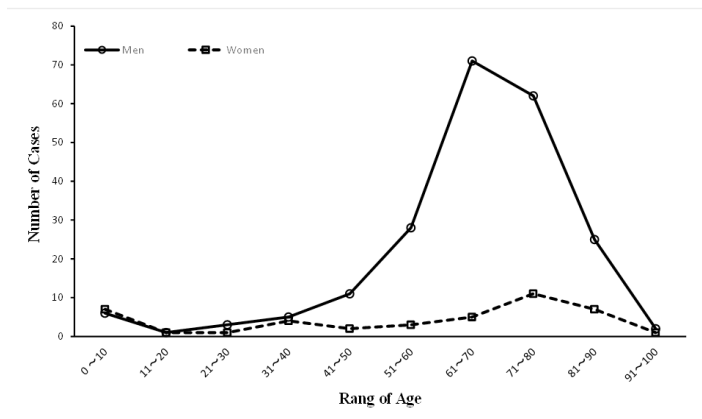


Figure 2: Distribution of patients by age and gender.

This figure shows the age and number of patients with hiccups.

Hiccups and Patient Information

We compared sex ratios between hiccup and non-hiccup groups for both the patients 40 years or younger and the patients above 40 years old using the Fisher exact test. Mean age, height, weight, and body mass index (BMI = weight in kg divided by height squared) [12] were compared using an independent samples t-test. Proportions of patients receiving chemotherapy (or not), treated surgically (or not), and deceased within 24 hours of hospitalization (or not) were compared using the Fisher exact test.

Hiccups and Disease Classification

Disease classification was performed at first hospitalization using MDC, consisting of 18 main categories based on the 22 categories of the ICD-10 established by the World Health Organization (WHO) [13]. Secondly, we compiled a cross-tabulation table of the patients above 40 years old based on two classifications, the presence or absence of hiccups and the presence or absence of a specific disease category. Proportions were compared using the Fisher exact test, and odds ratios (ORs) were calculated for each disease category. Similarly, we compiled a cross-tabulation table based on the presence or absence of hiccups and the presence or absence of a specific disease category

in patients 40 years or younger, and compared their proportions using the Fisher exact test.

We also classified primary disease in patients above 40 years old at hospitalization according to the more detailed ICD-10 and constructed the same cross-tabulation table. Furthermore, we constructed a scatter plot (volcano plot) [14] of the negative log of the P-value ($-\log_{10}[P]$) from the Fisher exact test (y-axis) versus the log of the ROR ($\ln[OR]$) to identify disease categories most strongly influencing the onset of hiccups.

Multivariable Analysis

We performed multivariable logistic regression analysis to evaluate the importance of each factor for hiccup risk in the patients above 40 years old. The objective variable was hiccups (YES/NO) and explanatory variables were patient physical characteristics, clinical variables, and ICD-10 category that differed significantly in the univariable analysis.

Statistical Analyses

All analyses were performed using the JMP®Pro12 software (SAS Institute Inc. NC, U.S.A.). Continuous variables are presented as mean (\pm standard deviation). A P-value $< .05$ was considered statistically significant. In all individual analyses, patients with missing values were excluded. We estimated the internal correlation using the pair-wise method. When the square of the Spearman rank-order correlation coefficient [ρ^2] was greater than 0.9, we concluded that there was an internal correlation. When there was no internal correlation, we treated these items as independent factors.

Results

Influences of Patient-Clinic Demographic Variables and In-Hospital Events On Hiccup Risk

In total, 7603 patients (> 40 years) and 2343 patients (≤ 40 years) were hospitalized at Musashino Red Cross Hospital between April 2014 and December 2014. Hiccups were identified in 256 patients in the 41 years or older group and the 40 years or younger group. Table 1 summarizes patients' clinic demographic information and the results of univariable analysis for the non-hiccup and hiccup groups.

	AGE \leq 40 (N=2343)				AGE $>$ 40 (N=7603)			
	total	hiccups (n=28)	non-hiccups(n=2315)	P-value	total	hiccups (n=228)	non-hiccups(n=7375)	P-value
Gender Men/Women)	891/1452	15/13	876/1439	0.11570	4105/3498	199/29	3906/3469	$<0.0001^{###}$
AGE	2343	17.0 \pm 2.8	21.3 \pm 0.3	0.0612	7603	69.3 \pm 0.9	69.1 \pm 0.2	0.837
Height	2324	116.7 \pm 7.9	136.5 \pm 0.9	0.0128*	7520	164.2 \pm 0.6	159.5 \pm 0.1	$<0.0001^{***}$
Weight	2330	35.6 \pm 4.8	43.7 \pm 0.5	0.0885	7555	57.2 \pm 0.9	56.9 \pm 0.2	0.7514
BMI	2322	18.4 \pm 0.8	20.1 \pm 0.1	0.0504	7509	21.2 \pm 0.3	22.2 \pm 0.0	$<0.0001^{***}$
Chemotherapy	27	4	23	0.0002 ^{##}	390	42	348	$<0.0001^{###}$
Surgerv	1077	12	1065	0.6752	3845	87	3758	0.1091
The death within 24 hours	6	1	5	0.0697	256	21	235	$<0.0001^{###}$

Table 1: Patient physical characteristics and in-hospital events

#. Hiccup and non-Hiccup groups were compared using the Fisher exact test

*: Hiccup and non-Hiccup groups were compared using a t-test

###:***: p < 0.001

##:**: p < 0.01

*: p < 0.05

In the patients above 40 years old, more than 85% of hiccup group patients were male, while there was no difference in sex ratio in the patients 40 years or younger. Univariable analysis of the patients above 40 years old also revealed significant differences between non-hiccup versus hiccup groups in height (159.5 ± 0.1 cm vs. 164.2 ± 0.6 cm, respectively), and BMI (22.2 ± 0.0 vs. 21.2 ± 0.3, respectively), but no difference in age (69.1 ± 0.2 vs. 69.3 ± 0.9, respectively) and weight (56.9 ± 0.2 kg vs. 57.2 ± 0.9 kg, respectively) was observed. Univariable analysis of in-hospital events also indicated that there were significantly greater proportions of the patients above 40 years old receiving chemotherapy and of the patients above 40 years old who died within 24 hours of hospitalization exhibited hiccups.

In the patients 40 years or younger, there was no difference in sex ratio between the hiccup (15 males and 13 females) and non-hiccup groups (876 males and 1439 females). Univariable analysis revealed a significant difference between the non-hiccup and hiccup groups in height (136.5 ± 0.9 cm vs. 116.7 ± 7.9 cm, respectively), but not age (21.3 ± 0.3 vs. 17.0 ± 2.8 years, respectively), weight (43.7 ± 0.5 kg vs. 35.6 ± 4.8 kg, respectively), or BMI (20.1 ± 0.1 vs. 18.4 ± 0.8, respectively). Univariable analysis also indicated that a significantly greater proportion patient 40 years or younger receiving chemotherapy exhibited hiccups.

Associations Between Specific Disease Categories and Hiccups in The Group Patients ≤ 40 Years

a

Classification of disease name (MDC)	AGE≤40 (N=2343)				
	Total	Hiccups	non-Hiccups	P Value	Odd Ratio 95%CI
Diseases & Disorders of Blood, Blood Forming Organs, Immunologic Disorders	18	2	16	0.0187*	11.05 2.42 - 50.53
Diseases & Disorders of the Breast	10	1	9	0.1135	9.49 1.16 - 77.54
Diseases & Disorders of Newborns and congenital anomaly	209	9	200	0.0005**	5.01 2.24 - 11.22
Diseases & Disorders of the Nervous System	64	3	61	0.0392**	4.43 1.30 - 15.08
Diseases & Disorders of the Digestive System, the Hepatobiliary System & Pancreas	179	5	174	0.0573	2.67 1.00 - 7.12
Diseases & Disorders of the Kidney, Urinary Tract & the Male Reproductive System	103	2	101	0.3508	1.69 0.39 - 7.20
Diseases & Disorders of the Ear, Nose, Mouth & Throat	106	1	105	1	0.78 0.10 - 5.79
Diseases & Disorders of infants and young children	132	1	131	1	0.62 0.08 - 4.58
Diseases & Disorders of the Female Reproductive System and Pregnancy, Childbirth & the Puerperium	736	2	734	0.0035**	0.17 0.04 - 0.70
Burns, Injuries, Poisonings & Toxic Effects of Drugs	256	0	256	0.0654	0 - -
Diseases & Disorders of the Eye	2	0	2	1	0 - -
Diseases & Disorders of the Musculoskeletal System	67	0	67	1	0 - -
Diseases & Disorders of the Respiratory System	284	0	284	0.0411	0 - -
Diseases & Disorders of the Circulatory System	32	0	32	1	0 - -
Mental Diseases & Disorders	3	0	3	1	0 - -
Endocrine, Nutritional & Metabolic Diseases & Disorders	28	0	28	1	0 - -
Diseases & Disorders of the Skin, Subcutaneous Tissue & Breast	65	0	65	1	0 - -
Others	49	2	47	0.1149	3.71 0.86 - 16.09

The table 2a presents the result of univariable analysis for hiccup incidence according to MDC category regarding the patients 40 years or younger. There was a significantly disproportionate number of hiccup patients in the “Diseases & Disorders of Newborns and Congenital Anomaly,” “Blood Forming Organs, Immunologic Disorders,” “Diseases & Disorders of the Female Reproductive Systems and Pregnancy, Childbirth & the Puerperium,” and “Diseases & Disorders of the Newborns & Congenital Anomaly” categories. We did not scrutinize these correlations in greater detail using the ICD-10 owing to the small number of hiccup patients in the group of patients 40 years or younger.

Associations Between Disease Category and Hiccups in Patients > 40 Years of Age

Univariable analysis indicated significant differences in hiccup rates for the MDC categories “Diseases & Disorders of the Nervous System,” “Diseases & Disorders of Kidney, Urinary Tract & the Male Reproductive System,” “Diseases & Disorders of the Circulatory System,” “Burns, Injuries, Poisonings & Toxic Effects of Drugs,” “Diseases & Disorders of the Musculoskeletal System,” “Diseases & Disorders of the Female Reproductive System and Pregnancy, Childbirth & the Puerperium,” and “Others” (Table 2a). We also compiled a cross-tabulation table of hiccup rates according to the ICD-10 category and calculated P-values using the Fisher exact test as well as associated ORs. From the results of all categories with five or more patients (Table 2-b), we constructed a scatter plot of ORs and searched for significant differences to identify disease categories more strongly associated with hiccups (Fig. 3). The plot revealed particularly strong associations between hiccups in the patients above 40 years old and “Subarachnoid Hemorrhage from Anterior Communicating Artery,” “Malignant Neoplasm: Bronchus or Lung, Unspecified,” and “Intracerebral Hemorrhage in Hemisphere, Subcortical.” All analyses excluded patients with missing values.

Table 2 Disease category and hiccups

Classification of disease name (MDC)	AGE>40 (N=7603)				
	Total	Hiccups	non-Hiccups	P Value	Odd Ratio 95%CI
Diseases & Disorders of Blood, Blood Forming Organs, Immunologic Disorders	179	10	169	0.0694	1.96 1.02 - 3.75
Diseases & Disorders of the Breast	147	0	147	0.0236*	0 - -
Diseases & Disorders of Newborns and congenital anomaly	6	0	6	1	0.00 - -
Diseases & Disorders of the Nervous System	693	46	647	<0.0001****	2.63 1.88 - 3.67
Diseases & Disorders of the Digestive System, the Hepatobiliary System & Pancreas	1923	68	1855	0.1215	1.26 0.95 - 1.69
Diseases & Disorders of the Kidney, Urinary Tract & the Male Reproductive System	500	28	472	0.0015**	2.05 1.36 - 3.07
Diseases & Disorders of the Ear, Nose, Mouth & Throat	168	3	165	0.4919	0.58 0.18 - 1.84
Diseases & Disorders of infants and young children	26	0	26	1	0.00 - -
Diseases & Disorders of the Female Reproductive System and Pregnancy, Childbirth & the Puerperium	534	2	532	<0.0001****	0.11 0.03 - 0.46
Burns, Injuries, Poisonings & Toxic Effects of Drugs	478	5	473	0.0054**	0.33 0.13 - 0.80
Diseases & Disorders of the Eye	68	0	68	0.2714	0.00 - -
Diseases & Disorders of the Musculoskeletal System	515	5	510	0.0029**	0.30 0.12 - 0.74
Diseases & Disorders of the Respiratory System	702	24	678	0.4854	1.16 0.76 - 1.79
Diseases & Disorders of the Circulatory System	1192	14	1178	<0.0001****	0.34 0.20 - 0.59
Mental Diseases & Disorders	6	0	6	1	0.00 - -
Endocrine, Nutritional & Metabolic Diseases & Disorders	225	5	220	0.6894	0.73 0.30 - 1.79
Diseases & Disorders of the Skin, Subcutaneous Tissue & Breast	82	2	80	1	0.81 0.20 - 3.30
Others	156	13	143	0.0008***	3.06 1.71 - 5.48

b

Classification of the disease name (ICD10)	Total	Hiccups	non-Hiccups	P Value	Odds Ratio	95%CI
Malignant neoplasm of renal pelvis	15	5	10	<0.0001****	16.51	5.60 - 48.71
Subarachnoid haemorrhage from anterior communicating artery	40	9	31	<0.0001****	9.74	4.58 - 20.70
Malignant neoplasm: Extrahepatic bile duct	36	5	31	0.0041**	5.31	2.05 - 13.79
Malignant neoplasm: Thoracic part of oesophagus	37	5	32	0.0046**	5.15	1.99 - 13.33
Intracerebral haemorrhage in hemisphere, subcortical	129	16	113	<0.0001****	4.85	2.82 - 8.33
Malignant neoplasm: Brain, unspecified	46	5	41	0.0117*	4.01	1.57 - 10.25
Malignant neoplasm: Bladder, unspecified	101	10	91	0.0009***	3.67	1.89 - 7.15
Malignant neoplasm: Bronchus or lung, unspecified	239	22	217	<0.0001****	3.52	2.22 - 5.58
Malignant neoplasm: Body of stomach	148	10	138	0.0133*	2.41	1.25 - 4.64

Factors related to Hiccups (n= 7509)	Odds ratio	95%CI	P-value
Subarachnoid haemorrhage from anterior communicating artery	17.05*	7.13-37.67	<0.0001
Malignant neoplasm of renal pelvis	14.03*	3.87-46.22	0.0002
Malignant neoplasm: Brain, unspecified	7.80*	2.53-19.77	0.0011
Male	6.41*	3.96-10.69	<0.0001
Intracerebral haemorrhage in hemisphere, subcortical	5.83*	3.13-10.23	<0.0001
Malignant neoplasm: Extrahepatic bile duct	5.74*	1.85-14.75	0.0044
Malignant neoplasm: Bladder, unspecified	4.51*	2.13-8.60	0.0003
Chemotherapy	3.41*	2.26-5.04	<0.0001
Malignant neoplasm: Thoracic part of oesophagus	2.82	0.91-7.17	0.0708
Malignant neoplasm: Bronchus or lung, unspecified	2.47*	1.44-4.07	0.0015
The death within 24 hours	2.07*	1.19-3.43	0.0110
Malignant neoplasm: Body of stomach	2.00	0.94-3.81	0.0689
Height	1.35	0.27-6.70	0.7140
BMI	0.02*	0.003-0.16	0.0002

Table 3: Results of the multivariable analysis indicating independent risk factors for hiccups treated as variables that do not affect each other.

*: indicated a significant odds ratio

Discussion

In the current study, risk factors of hiccups were researched with clinical data from the Musashino Red Cross Hospital, a general hospital with many departments. Although the study was performed in the single institution, many cases were accumulated as in multi-center studies. We collected 256 cases of hiccups, surpassing the case-number of our previous study with the Japanese Adverse Drug Event Report Database including 160 cases of hiccups [7]. Furthermore, we were able to handle more clinic data by accessing the electronic medical record system. Thus, this study will be clinically important for it shows the way to control the symptom of hiccups.

Jacques VS et al. report the association of age with the incidence of hiccups [11]. However, there was no statistical clarification regarding the association between hiccups and age, gender, or disease. We supposed that age was related to the occurrence of hiccups; thus, we classified all patients into two age groups and analyzed the risk factors. We classified all the patients into two groups (patients ≤ 40 years of age and patients > 40 years) because the incidence of hiccups in male patients suddenly increased after 40 years of age (Figure 2). There were some different results between two groups regarding gender and classification of disease. These results suggest that it is the difference in the characteristics of hiccups between the younger group and others, and there is a difference in the mechanism of hiccups between the two groups. There were no reports that focused on gender, age, or classification of disease regarding hiccups. The present report is an important issue due to discussion about the disease-developing mechanism of hiccups.

The incidence of persistent or intractable hiccups is significantly higher in males than in females [5]. Lee et al. also indicated that hiccups tend to emerge in females at a younger age compared with males [6]. Our results showed that age was not an independent factor for hiccups in the both groups. In contrast to the patients above 40 years old, male sex was not a risk factor in patients 40 years or younger. Most cases of hiccups in the patients 40 years and younger group occurred in low-weight births, disorders of the blood, immune system, and disorders of the nervous system, suggesting that hiccups in younger patients are mainly due to organic disease. This male predominance has provided few clues to the underlying mechanism. It is possible that the stimulation threshold for hiccups is lower in males than in females owing to greater excitability of afferent or efferent nerves in the hiccup reflex arc [6]. Given the absence of male preponderance in patients 40 years or younger, we suggest different underlying mechanisms, such as possible sex differences in the development of respiratory apparatus or nervous system.

In our previous study, we identified tall stature as a risk factor for hiccups [7]. However, input to this database is voluntary

so parameters are often missing. Thus, our conclusions were drawn from group data. In contrast, the current study allowed for the investigation of hiccup risk factors using a smaller but more comprehensive hospital electronic medical chart system. Specifically, we could examine the influence of BMI as well as weight and height. In the univariable analysis, height and BMI were related to hiccups ($P < 0.001$), but only BMI was an independent risk factor for hiccups. The significance of height in the univariable analysis may reflect the strong association between height and sex in adults. We suggest that BMI is a suitable physical index for the evaluation of hiccup risk in adults. Furthermore, this relationship between low BMI and hiccup risk may provide clues to the underlying mechanisms.

Among hospital events, chemotherapy, and death within 24 hours after hospitalization were identified as independent risk factors for hiccups in the patients above 40 years old using multivariable analysis. Several recent reports have documented hiccup risk owing to chemotherapy. Particularly, there are reports of hiccup cases induced by platinum-based drugs such as oxaliplatin and cisplatin [8,9]. A recent report also highlighted the possible involvement of dexamethasone, which is used as adjunct therapy to suppress nausea and allergic reactions [10]. In the present study, chemotherapy was an independent risk factor for hiccups and the strongest risk factor among in-hospital events. However, further investigation is required to determine whether hiccups are solely a response to chemotherapeutic drugs or are related to tumor pathophysiology.

Death within 24 hours of hospitalization was an independent risk factor for hiccups, although this relationship was not observed for patients within individual disease categories who died within 24 hours. Hiccups may occur at the end stage of cancer and in response to lifesaving measures. Twycross et al. suggested that the main causes of hiccups in terminal-phase patients are relaxation of the stomach, reflection of the stomach-esophagus, diaphragmatic excitement, excitation of the phrenic nerve, poisoning, and central nervous system cancers [15]. In addition, stimulation of the pharynx rear wall by intubation for lifesaving measures may induce hiccups [16]. However, there are no reports on the relationships among hiccups, intubation, and respiration. It is thought that hiccups in the terminal phase reduce QOL by disrupting conversation and sleep. Therefore, the investigation of hiccup treatments for terminal phase patients is urgently required.

We also analyzed associations between hiccup incidence and specific ICD-10 and Japanese MDC categories. Although limited numbers in some categories precluded analysis, we identified nine disease categories associated with hiccups, with several strongly associated categories according to volcano plot analysis (Figure 3). Multivariable analysis identified subarachnoid hemorrhage, intracerebral hemorrhage in hemisphere, and tumor of brain as

strong independent risk factors among patients with CNS diseases. It is known that the hiccups reflex center lies within the medulla oblongata, although the precise neurological mechanism is unclear [16]. We speculate that many brain tumor and hemorrhages in the above 40 years old group affected this brainstem hiccup center. Alternatively, hiccups may be induced by intubation for artificial respiration and gastric tube insertion during emergency treatment of these diseases. While cerebral hemorrhages were a significant risk factor in the present study, we could not identify the lesion sites. Hiccups disturb both treatment and rehabilitation following neurological diseases; therefore, prevention of hiccups may be particularly important for these patients. Further examination of available neuroimages is warranted to assess the relationship between lesion site and hiccup risk.

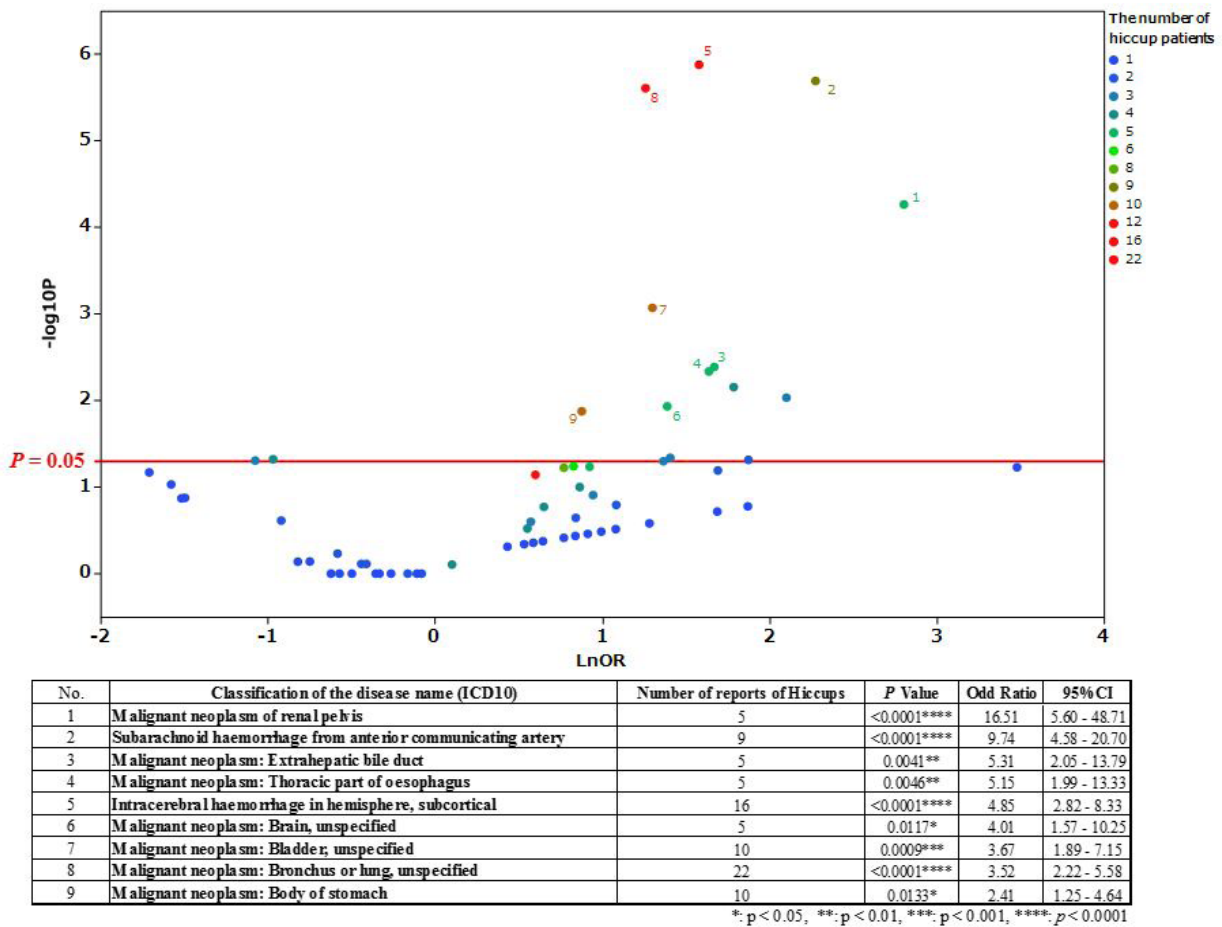


Figure 3: The volcano plot represents the relationship between hiccups and classification of disease (ICD10). Numbers with points in the figure correspond to the table under the figure. The x-axis represents the odds ratio (OR) in LnOR scale, and the y-axis represents the P value in a-log₁₀P scale. The red line demarcates the significance threshold $P = .05$. ORs were calculated using cross-tabulation. Different colors indicate the number of hiccup patients (from 5 in blue to 22 in red). Points in the upper right represent disease categories strongly associated with hiccups.

The volcano plot represents the relationship between hiccups and classification of disease (ICD10). Numbers with points in the figure correspond to the table under the figure. The x-axis represents the odds ratio (OR) in LnOR scale, and the y-axis represents the P value in a-log₁₀P scale. The red line demarcates the significance threshold $P = .05$. ORs were calculated using cross-tabulation. Different colors indicate the number of hiccup patients (from 5 in blue to 22 in red). Points in the upper right represent disease categories strongly associated with hiccups.

In addition to brain lesions, widely distributed neoplasms were also independent risk factors for hiccups according to the multivariable analysis (including renal pelvis, extrahepatic bile duct, neoplasms of bladder, and bronchus or lung). It is possible that these lesions damage nerves of the hiccup reflex arc. It was reported that the vagus nerve participates in both afferent and efferent coordination in the hiccup reflex [1,16], and malignant tumors of the aforementioned organs may stimulate the vagus nerve. In addition, the chemotherapy received in-hospital by

most cancer patients may induce hiccups independent of tumor-mediated nerve effects. However, we found no internal correlation between specific cancers and chemotherapy; therefore, it appears that both malignant tumors and the medications used for treatment induce hiccups. Further study of the associations between cancer type, chemotherapy regime, and hiccup risk is clearly warranted as hiccups can reduce treatment tolerance and quality of life. Moreover, such analysis may identify treatment regimens with lower risk.

The present study was based on a retrospective review of an electronic chart system from a single center and had some missing information. In addition, hiccups may not be reported by patients unless regarded as an unbearable symptom. Thus, our conclusions may be confounded by report bias.

Conclusion

We investigated risk factors for hiccups including patient age, physical characteristics, clinical variables, primary disease, and in-hospital events. We report for the first time that BMI is an independent risk factor for hiccups in patients above 40 years old. We also confirmed that chemotherapy, certain malignant tumors, and neurovascular diseases are risk factors. These results may enable the identification of high-risk patients and treatment regimens, thereby reducing risk and improving quality of life. Moreover, such information may help clarify the pathomechanisms of hiccups.

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