Brief Report

DOI: 10.5582/ddt.2021.01085

Association of bleeding symptoms during influenza infection and administered drugs

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SUMMARY On March 1, 2019, the Ministry of Health, Labour and Welfare added bleeding symptoms to adverse reaction package inserts as a possible adverse event for a new anti-influenza drug, baloxavir marboxil, because 13 patients with bleeding symptoms were identified among influenza patients taking the drug. Nevertheless, aspects of the epidemiology of bleeding symptoms among influenza patients remain unclear. This study elucidated bleeding symptoms among influenza patients and hospitalized patients as severe cases. A survey was administered to all physicians in Japan during the 2019-2020 season for reporting of bleeding symptoms in influenza patients. The survey elicited information about outcomes, assuming associated underlying diseases and drugs in addition to administered drugs including acetaminophen and anti-influenza (antiviral) drugs. We received reports of 63 cases with bleeding symptoms, including 5 cases of hospitalized patients. Among all patients, 54% had been administered oseltamivir; 10% had been administered baloxavir marboxil. Among hospitalized patients, all had been administered acetaminophen; 40% of them had been administered oseltamivir, and one patient had been administered baloxavir marboxil. Accumulation of bleeding symptom cases is expected to be necessary to evaluate the association.

Keywords Acetaminophen, baloxavir marboxil, bleeding symptom, influenza, oseltamivir

1. Introduction

Since 13 cases of bleeding symptoms were reported to the Ministry of Health, Labour and Welfare (MHLW) from influenza patients using the newly launched anti-influenza virus drug endonuclease inhibitor, baloxavir marboxil, bleeding symptoms were added to instructions for drug package inserts on March 1, 2019. However, the epidemiology of bleeding symptoms among influenza patients, especially their association with anti-influenza virus drugs, was not well known then. The present study was conducted using a survey and a brief report of its results to elucidate epidemiological aspects of bleeding symptoms.

2. Methods

Under cooperation with MHLW, we surveyed all physicians throughout Japan about influenza patients with bleeding symptoms from November 1, 2019 through March 31, 2020. In addition to eliciting demographic information of patients such as gender and age, influenza-related information including the highest body temperature, vaccination history, rapid test results, onset date, administered drugs including acetaminophen, and anti-influenza virus drugs, we also asked about details of bleeding symptoms such as the following. (*1*) Clinical features: intracranial, conjunctiva, nose, intraoral, petechia, ecchymosis, hemarthrosis, hematemesis (upper gastrointestinal tract), sputum, hemoptysis, melena, stool, macroscopic hematuria, abnormal genital bleeding, and oozing. (*2*) Outcome: hemostasis (or arrest of bleeding symptoms) by pressure with no treatment, hemostatic by some treatment, hospitalization, and blood transfusion or fluid infusion. (*3*) Assumed associated underlying diseases: hemophilia, leukemia, thrombocytopenia, gastric ulcer and ulcerative colitis. (*4*) Assumed associated drugs: anticancer drugs (*1*), immunosuppressants, non-steroidal anti-inflammatory drugs such as antiplatelet agents (*2,3*), and

coagulation factor inhibitors such as anticoagulants (*3-6*).

After summarizing basic characteristics such as gender, age and the highest body temperature, we assessed bleeding sites and outcomes, with assumed associated and underlying diseases and drugs. Finally, we examined data related to administered anti-influenza virus drugs and acetaminophen before bleeding symptoms. Case groups of two types were analyzed: all reported bleeding symptoms cases and cases limited to those of hospitalized patients.

This study was approved by the Committee for Ethical Consideration, National Institution of Infectious Diseases, Japan: approval numbers were 261, 312, 375, and 462. Approval by the Kawasaki City Institution for Health and Safety, Committee for Ethical Consideration was 01-3.

3. Results and Discussion

We received 63 reports of bleeding symptoms associated with influenza, among which 34 cases (55%) were of female patients. Distributions of age and highest body temperature are presented respectively in Figures 1 and 2. These patients' average age was 18 years old, but the median was 8.5 years. The age distribution was skewed to a younger age, but patients of all age classes were

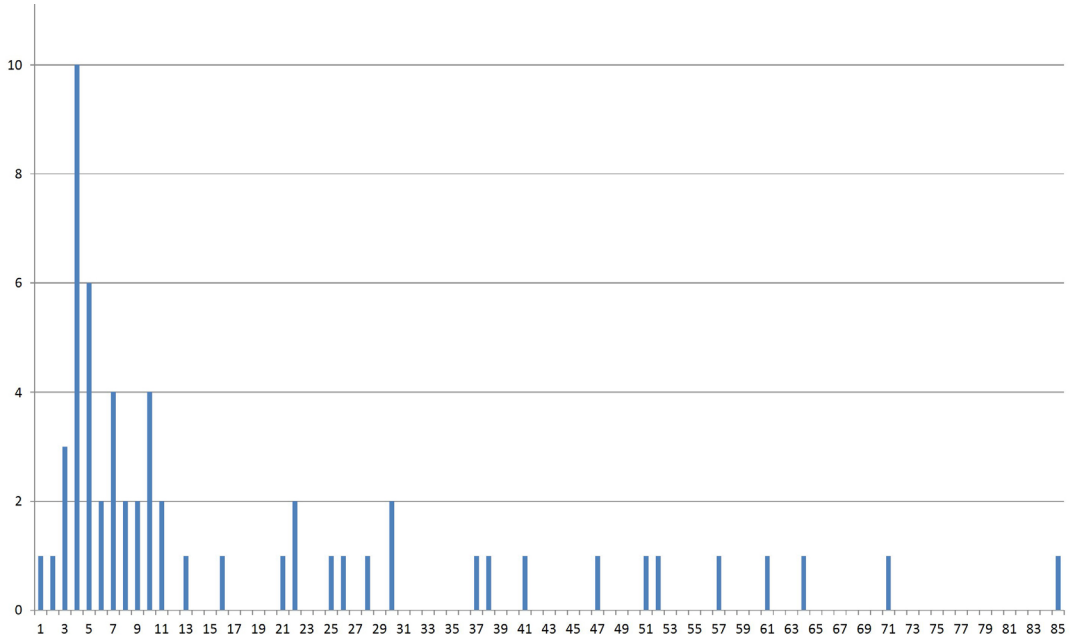

Figure 1. Age distribution in all bleeding symptom cases (*n* = 63). *Note*: Average age was 18 years old; median age was 8.5 years old.

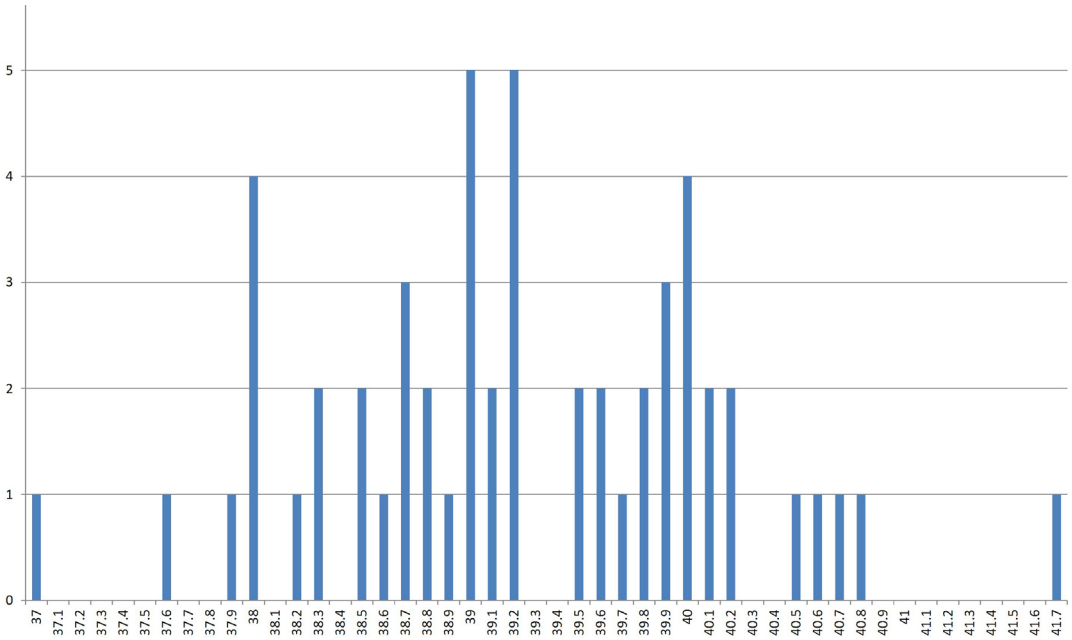

Figure 2. Distribution of the highest body temperature (*n* = 63). Note: Average and median of body temperature were 39.2°C.

reported. Both the average and median body temperature were 39.2°C. Regarding the vaccine history, 26 (58%) patients had received no influenza vaccination: those who had received one dose were 8 patients (19%); those with two doses were 11 patients (24%).

Bleeding sites in all cases are shown in Figure 3, for which multiple answers were allowed. The highest frequency site was the nose (29 cases), followed by melena (7 cases). Outcomes in all cases are presented in Figure 4. Multiple answers were accepted. Almost half of

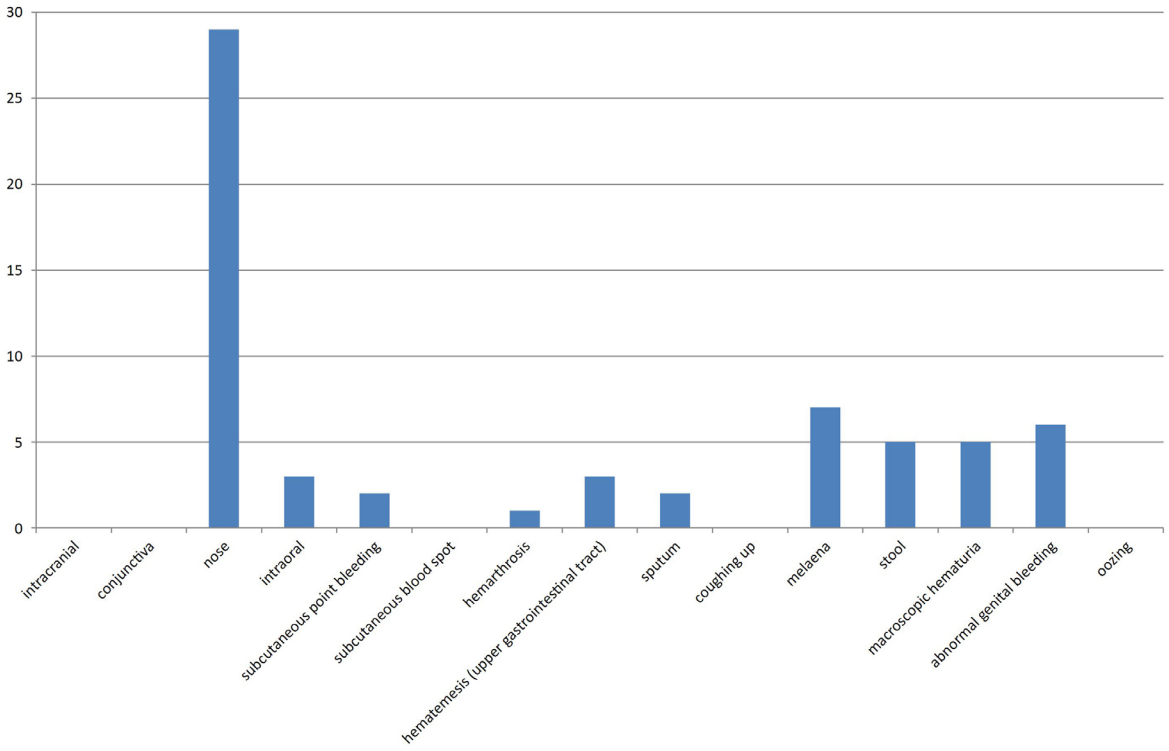

Figure 3. Bleeding site (*n* = 63). *Note*: Multiple answers were accepted.

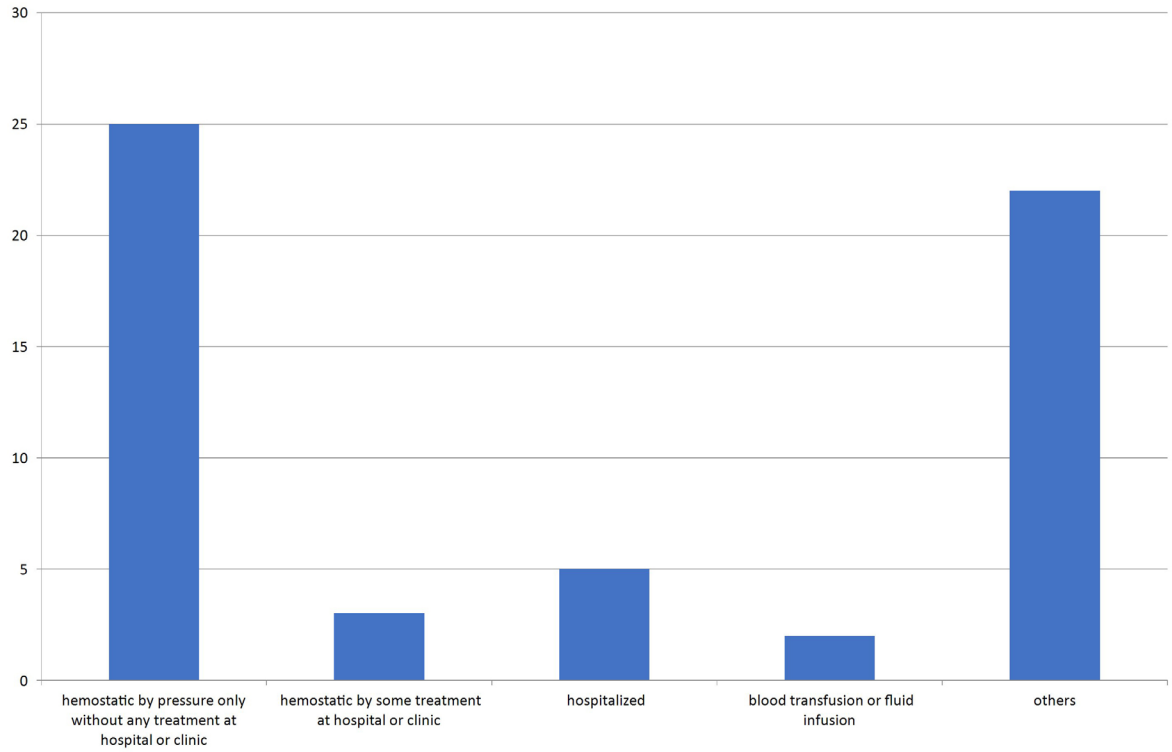

Figure 4. Outcome (*n* = 63). *Note*: Multiple answers were accepted.

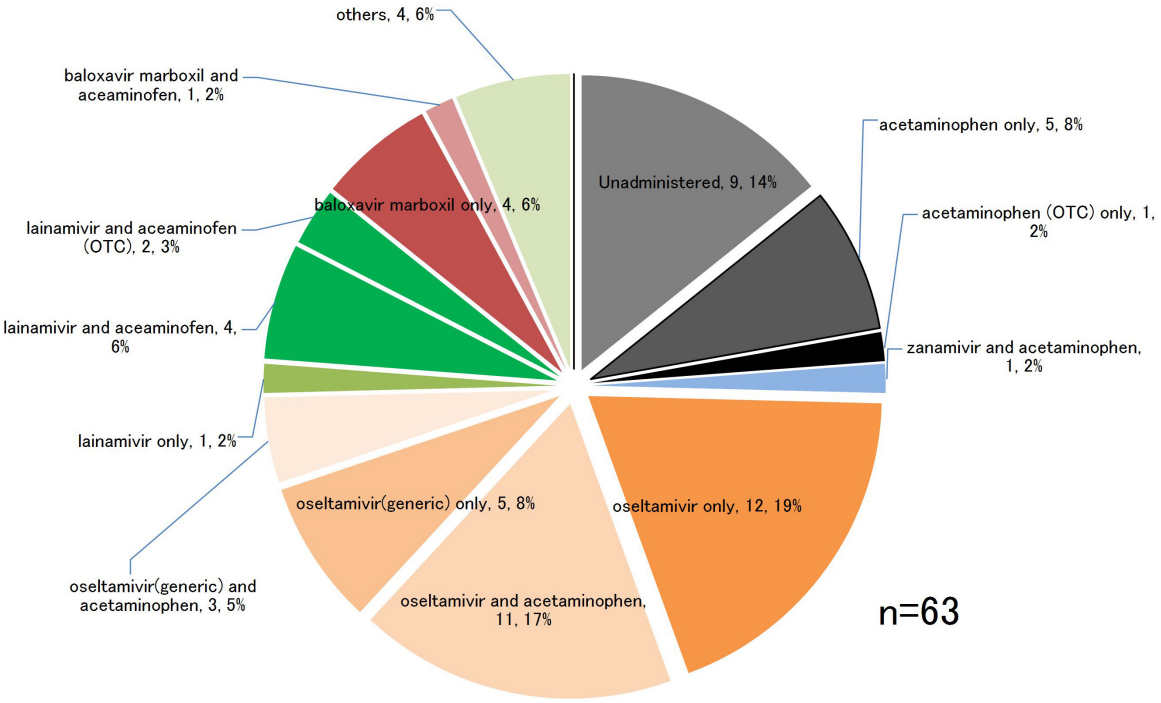

Figure 5. Combinations of administered acetaminophen and anti-influenza virus drugs in all cases (*n* = 63). *Note*: Others included four cases with oseltamivir + acetaminophen + peramivir, oseltamivir (generic) + peramivir, oseltamivir (generic) + acetaminophen + peramivir and baloxavir marboxil + peramivir + acetaminophen.

the cases, 25, were resolved with no treatment other than pressure. However, others were 22 cases. Stomach ulcers were reported for two cases, presumably associated with underlying diseases. For 52 cases, no drug among the assumed associated drugs was reported. They were recorded as lacking drug treatment.

Figure 5 shows combinations of administered acetaminophen and anti-influenza virus drugs for all cases. The proportion of no considered drug administered was 14%. That of acetaminophen including its over-the-counter (unprescribed) formulations was 10%. Oseltamivir accounted for 54%. Baloxavir marboxil accounted for only approximately 10%.

We administered all of the hospitalized patients reported at our site. One patient among them (case C in Tables 1 and 2) was not hospitalized for bleeding symptoms. Actually, she had asthma and had received steroid treatment before bleeding symptoms. Subsequently, she showed upper gastrointestinal tract bleeding during the hospital visit.

Table 1 presents age, gender, blood transfusion or fluid infusion, vaccine history, and the highest body temperature, assuming associated underlying diseases, drugs, and bleeding sites for hospitalized patients. No particular pattern was apparent for age or gender. No patient had been vaccinated. Two patients had received blood transfusion or fluid infusion. No assumption was made of associated underlying diseases and drugs, although they were not reported in four cases.

Table 2 shows findings for administration of acetaminophen and anti-influenza virus drugs among hospitalized patients. All patients had been administered acetaminophen. All patients were administered acetaminophen before bleeding symptoms. Three patients were administered oseltamivir. One patient took peramivir and baloxavir marboxil. However, no patient used zanamivir or laninamivir.

Even though 8.5 years old was the median age, people older than 80 years old were reported to have experienced bleeding. Therefore, patients were not only younger people. Moreover, bleeding symptoms were severer for female patients than for male patients. This finding differs from those related to abnormal behavior among influenza patients, for whom the incidence of abnormal behavior among younger male patients was higher than among others. Even for hospitalized patients, no particular pattern was found for age or gender. Most patients reported no associated underlying disease or related drug. That was true even among hospitalized patients.

Regarding the combinations of administered acetaminophen and anti-influenza virus drugs, the remarkable proportion of patients who had not been administered these drugs or who had been administered acetaminophen without anti-influenza virus drugs was similar to that of patients exhibiting abnormal behavior (*7-9*). The share of patients receiving oseltamivir might be higher than reported from an earlier study examining abnormal behavior among influenza patients. Even among hospitalized patients, 2 of 5 patients used

Table 1. Fundamental characteristics assuming associated underlying diseases and drug and bleeding site in hospitalized cases (n = 5)

Case	Age (years old)	Blood transfusion or fluid infusion	Gender	Vaccine history	Highest body temperature (°C)	Assuming associated underlying diseases	Assuming associated drug	Bleeding site			
								hematemesis (upper gastrointestinal tract)	melena	sputum	stool
A	52	-	N.A.	–	N.A.	N.A.	N.A.	-	-	+	-
B	1	-	Male	N.A.	40.0	–	N.A.	+	-	-	-
C	4	+	Male	–	40.8	N.A.	–	+	+	-	-
D	85	+	Female	N.A.	39.7	N.A.	N.A.	-	+	-	-
E	16	-	Female	N.A.	38.7	N.A.	N.A.	-	-	-	+

Note: "+" denotes yes; "-" represents no. No leading site other than hematemesis (upper gastrointestinal tract), melena, sputum, and stool was reported. Assumed associated underlying diseases were hemophilia, leukemia, thrombocytopenia, stomach ulcer and ulcerative colitis. Assumed associated drugs were anticancer drugs, immunosuppressants, non-steroidal anti-inflammatory drugs such as antiplatelet agents and coagulation factor inhibitors such as anticoagulants. Case C was administered steroids for asthma treatment before bleeding symptoms.

Table 2. Administered acetaminophen and anti-influenza virus drug in hospitalized cases (n = 5)

cases	acetaminophen	oseltamivir	baloxavir marboxil	peramivir
A	+	-	-	-
B	+	+	-	-
C	+	+	-	-
D	+	-	+	+
E	+	+	-	-

Note: "+" represents administered and "-" denotes drug not-administered before bleeding symptoms. No patient was administered zanamivir or laninamivir.

oseltamivir.

The proportions of influenza patients administered acetaminophen or anti-influenza virus drug or not administered acetaminophen and anti-influenza virus drugs is not known precisely. However, accompanying research investigating abnormal behavior administered a questionnaire survey contemporaneously with the report described herein: 352 non-life-threatening abnormal behavior cases were identified (*10*). In those cases, 99 (28%) patients had been administered acetaminophen including its over-the-counter formulations; 129 cases (37%) had been administered oseltamivir. In addition, 72 cases (6%) were not administered acetaminophen or any anti-influenza virus drug. These proportions do not resemble those of the entire population of all influenza patients. Especially, most influenza patients with abnormal behavior were male and younger than 19 years old. Their characteristics might bias the proportions of administered acetaminophen and/or anti-influenza virus drugs. However, their magnitude cannot be evaluated precisely. At least, the proportions of acetaminophen administered among bleeding and hospitalized cases and of oseltamivir administered among all bleeding cases were higher than those of cases of reported abnormality. For several reasons, these differences cannot be evaluated statistically.

These findings indicate that acetaminophen and oseltamivir might be associated with higher likelihood of bleeding symptoms than other anti-influenza virus drugs. To evaluate these associations, adequate data of bleeding symptoms among influenza patients must first be accumulated. Then the total amounts of prescriptions for these drugs must be controlled. The incidence rate among people using these drugs must also be considered.

During the study period, the influenza patients nationwide were estimated as approximately nine million based on Prescription Surveillance (*11-13*) (*http://prescription.orca.med.or.jp/syndromic/kanjyasuikei/*). Therefore, approximately 7.5% of all residents in Japan were infected by influenza. When this number was used for influenza patients, the total number of bleeding symptoms cases, 63, represents 7 cases per million influenza patients, with hospitalization bleeding symptom cases as 0.56 per million influenza patients. The sample

size might be too small to analyze differences in the incidence of bleeding symptom cases according to the administered drug.

Influenza itself might be associated with thrombocytopenia or aberrant coagulation, especially in severe cases with systemic inflammatory response syndrome, including avian influenza (*14-17*). Unfortunately, these were not considered in any association with administered drugs, especially anti-influenza virus drugs. Results of this study demonstrated that even patients with mild seasonal influenza might show bleeding symptoms, even though most incidents were self-limited. In fact, 14% of all reported patients were not administered acetaminophen or any anti-influenza virus drug. Influenza can cause mucosal inflammation and thrombocytopenia. Therefore, influenza with mild symptoms might play some role in the occurrence of bleeding symptoms. Results of the present study indicate that bleeding symptoms can be associated with influenza.

This study has some limitations. First, although we identified 63 cases in all and 5 cases among hospitalized cases, the sample is expected to be very small. Findings related to their characteristics might differ when sufficient data are accumulated. Therefore, the results obtained from the present study must be understand as merely interim findings. Secondly, although we summarized bleeding symptom epidemiology descriptively, the symptoms must be analyzed statistically with an incidence ratio, as in an abnormal behavior study (*6-9*). Application of that methodology remains as a challenging subject for future research. Thirdly, even though we combined questions about blood transfusion and fluid infusion in our questionnaire, great differences were found among treatments of blood transfusion and fluid infusion. A revised questionnaire must be administered in a later study.

Funding: This research was supported financially by the Japan Agency for Medical Research and Development (19mk0101141 in 2019).

Conflict of Interest: The authors have no conflicts of interest to disclose.

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Received September 15, 2021; Revised October 18, 2021; Accepted October 24, 2021.

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Released online in J-STAGE as advance publication October 29, 2021.