PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Comparison of emergency hospital admissions for drug poisoning and major diseases: a retrospective observational study using a nationwide administrative discharge database
AUTHORS	Okumura, Yasuyuki; Shimizu, Sayuri; Ishikawa, Koichi; Matsuda, Shinya; Fushimi, Kiyohide; Ito, Hiroto

VERSION 1 - REVIEW

REVIEWER	MD. Katarina Bilén Internal medicine, Södersjuhuset, Stockholm Department of clinical science and education, Karolinska Institutet, Södersjukhuset Sweden No competing interests.
REVIEW RETURNED	14-Aug-2012

THE STUDY	1. How many secondary and tertiary EMS were included in the study? In the method section the authors describe that 855 of 1558 DPC/PDPS hospitals participated and as shown in the setting method not all hospitals in Japan are included in the DPC/PDSP. The authors also describe that the study focus on secondary and tertiary EMS. Are all hospitals that participated in the survey (855) secondary and tertiary EMS? 2. Please clarify drugpoisoning. Are all cases of drugpoisoning included - deliberate and accidental? If so it would be good the clarify that there is a difference between deliberate self-poisoning and accidental drugpoisoning.
RESULTS & CONCLUSIONS	1. In the result section (also in the abstract) the authors point out that patients with drug poisoning were more likely to use ambulatory services (74,1%) which from table 2 is explained to be the use of ambulance service - it is better to use ambulance service in the text aswell. 2. Please clarify surgery - do the authors mean surgery in operating theatre or suturing in the emergency department? Drugpoisoning as main admission cause is not very likely to need surgery at all but in this material almost 2% needed surgery.

	3. The figure 1 is very difficult to understand. 4. The study shows that more than 26% of the drugpoisoning patients were in deep coma when admitted to hospital which can explain the use of ambulance service, tertiary EMS and emergency care resources. It might be good to further address this in more depth in the discussion section. 5. The high comorbidity of mental illness among drugpoisoning patients is ofcourse well known among deliberate selfpoisoning patients why it is of importance to clarify the definition of drugpoisoning patients (please see remark regarding this in the previous section) and also to address this in more depth.
GENERAL COMMENTS	I was interesed to read this paper and it shows what can be done with a national database to collect data from different hospitals.

REVIEWER	Gary Smith, MD, DrPH Professor of Pediatrics, Epidemiology and Emergency Medicine The Ohio State University I have no competing or conflicts of interest regarding this manuscript.
REVIEW RETURNED	13-Sep-2012

GENERAL COMMENTS	I believe that the title and focus of this study is off-target, that study findings are mis-interpreted, and therefore potentially misleading to readers. The article unfortunately needs a substantial re-orientation and re-write with an adequate focus on the intentionality of the drug ingestion, and not just on drug poisoning, and should interpret the findings in light of admission practices for cases of attempted suicide. Page 3, Line 15, Article Focus - this is not a nationally representative sample, although the authors claim that it is. Page 5, Methods, Data Source, line 20 - 855 hospitals participated in a survey, but there are no details about how this sample of hospitals was obtained, nor how the patients within those hospitals were selected for inclusion in the study. If it is not a probability sample, then it is a convenience sample, and cannot be claimed to be nationally representative. Page 6, lines 29-31 - The authors state that they "modified the disease code to separate drug poisoning from chemical and unspecified poisoning" - how certain is this method for identifying just the cases of drug-related poisoning? Is there a standard accepted procedure for doing this? Please provide more details. Page 6, Line 48 - Insomnia is included in the authors' definition of "mental illness." This does not make sense in my opinion. Please justify this decision. The high prevalence of mental illness exists in this study because of the association revealed later about most poisonings being suicide attempts. This fact is buried in this paper and therefore can be misleading to readers. The authors should

	distinguish between unintentional poisoning and intentional poisoning/suicide attempts in this study. Page7, line 29 - I am not familiar with the PCA biplot procedure - I suggest that a another reviewer/statistician verify that it is being correctly used here. Page 8, line 22 - "ranked in the top 41 causes..." is an awkward phrase; I suggest that the authors state that it ranked 41st, assuming that is what is meant here. Page 10, Discussion, line 7 - The authors cannot claim that this is a nationallly representative sample (see previous comment). Page 10, lines 40-47 - The authors state "Because most patients with drug poisoning have attempted suicide..." This explanation of the admitting practices for patients with attempted suicide to high-level EMS is very revealing and critical to interpretation of study results. And later in line 57, the information about ambulance officers having to contact more hospitals to transport patients with drug poisoning confirms that this is really not an issue about drug poisoning at all, it is an issue about admitting practices and the resources needed to manage attempted suicides. Many of these admissions were likely necessary to allow an assessment of whether the person was a continued threat to their own life. Presumably many of these admissions were for observation of behavior and not for monitoring and potential treatment of the toxicity of the ingestion. Therefore, the title and discussion of most of this paper misses the main point and can be misleading to the reader. The manuscript should be re-written as a paper about the resources used to manage patients following suicide attempts. The outcome measures of, for example, % requiring surgery, are irrelevant and should be omitted. In addition, in the US, the number of deaths, ED visits and hospital admissions due to unintentional opiod ingestion has dramatically increased. I am uncertain about any such trends in Japan. It would be informative if details regarding the type/class of drug was included in the analyses of this paper.

VERSION 1 – AUTHOR RESPONSE

To reviewer #1

We are grateful to reviewer #1 for the critical comments and useful suggestions that have helped us to improve our paper. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

Comment #1

How many secondary and tertiary EMS were included in the study? In the method section the authors describe that 855 of 1558 DPC/PDPS hospitals participated and as shown in the setting method not all hospitals in Japan are included in the DPC/PDSP. The authors also describe that the study focus on secondary and tertiary EMS. Are all hospitals that participated in the survey (855) secondary and tertiary EMS?

Response
Thank you for your suggestion. As suggested, we added information of number of tertiary EMS in the Setting paragraph as follows:
In Japan, the EMS system is divided into 3 categories:15 (1) primary EMS that provides care to patients who can be discharged without hospitalization; (2) secondary EMS that provides care to patients who require admission to a regular inpatient bed; and (3) tertiary EMS that provides care to severely ill and trauma patients who require intensive care. In 2008, there were 18 892 clinics and 963 hospitals for primary EMS, 3 053 hospitals for secondary EMS, and 214 hospitals for tertiary EMS.14 In the present study, we focused on secondary and tertiary EMS rather than primary EMS, because the DPC/PDPS database is an inpatient database. Among the 855 participating hospitals in the DPC/PDPS database, 130 provide tertiary EMS.

Comment #2
Please clarify drug poisoning. Are all cases of drug poisoning included - deliberate and accidental? If so it would be good the clarify that there is a difference between deliberate self-poisoning and accidental drug poisoning.

Response
Thank you for your helpful comment. We included all types of drug poisoning because data on external causes (ICD-10 codes V01–Y98) are not recorded in the DPC/PDPS database. We added information in the Limitation paragraph as follows:
Our study has several limitations. First, our results cannot be generalized and are limited to inpatient admissions to acute care hospitals rather than emergency outpatient admissions or emergency admissions to psychiatric hospitals, because we used the DPC/PDPS database. Second, we were unable to evaluate variables not included in the DPC/PDPS database. As a result, we could not assess other potentially important factors predicting the need for advanced treatments, such as acute physiology and chronic health evaluation (APACHE) scores at admission23 or clinical management and course during pre-hospital period.24 Third, we included all types of drug poisoning (i.e., deliberate, accidental, and undetermined intent) as in a previous study,7 because data on external causes (ICD-10 codes V01–Y98) are not recorded in the DPC/PDPS database. As a result, we could not distinguish between deliberate and accidental drug poisoning. Fourth, although the database included approximately 40% of all inpatient admissions in Japan, participation in the survey was voluntary for each hospital and the patient selection procedure was not based on a random sampling technique from all acute hospitals.
Comment #3
In the result section (also in the abstract) the authors point out that patients with drug poisoning were more likely to use ambulatory services (74,1%) which from table 2 is explained to be the use of ambulance service - it is better to use ambulance service in the text as well.

Response
Thank you for your helpful comment. The typos were corrected in the revised manuscript.

Comment #4

Please clarify surgery - do the authors mean surgery in operating theatre or suturing in the emergency department? Drug poisoning as main admission cause is not very likely to need surgery at all but in this material almost 2% needed surgery.

Response
In the first paragraph of Clinical and procedural characteristics subsection, we clearly described the definition of surgery and we changed the term 'surgery' to 'surgical procedures' as follows:
To describe clinical and procedural characteristics of emergency hospital admissions, we used the following study variables: (1) age; (2) gender; (3) major disease categories; (4) comorbidities at admissions; (5) level of consciousness assessed by the Japan Coma Scale (JCS);16 (6) use of ambulance service; (7) use of tertiary EMS; (8) requirement for surgical procedures that include both major surgery and suturing in an emergency department; (9) length of stay (days); and (10) in-hospital mortality.

Comment #5
The figure 1 is very difficult to understand.

Response
Thank you for your suggestion. In the revised manuscript, we added information of the figure caption as follows:
The predictive principal component biplot on data from the characteristics of the top 100 causes. Each dot represents one of the causes. Eight axes are positioned and calibrated so that the orthogonal projection of a dot onto an axis 'predicts' as best as is graphically possible the value of the corresponding disease on the corresponding variable. Ambulance, ambulance services; LOS, median length of stay; Mortality, in-hospital mortality; Surgery, surgical procedures; Tertiary, tertiary emergency medical services.

Comment #6
The study shows that more than 26% of the drug poisoning patients were in deep coma when admitted to hospital which can explain the use of ambulance service, tertiary EMS and emergency care resources. It might be good to further address this in more depth in the discussion section.

Response
Thank you for pointing out the potential explanation. We added information of potential reason of over-utilization. First, we added information of subarachnoid haemorrhage and ruptured cerebral aneurysm in the Results section as follows:
In terms of the percentage of patients admitted to tertiary EMS, subarachnoid haemorrhage and ruptured cerebral aneurysm (disease code 010020) ranked second (30.3%; 2nd; see the 46th row in Supplemental Table). Patients with subarachnoid haemorrhage and ruptured cerebral aneurysm were most likely to be admitted to hospitals with deep coma (33.9%; 1st) and most likely to use ambulance services (76.0%; 1st). They had a longer median length of stay (28 days; 4th), were more likely to require surgical procedures (73.2%; 11st), and were more likely to die during hospitalization (26.9%; 9th).

Second, we modified the Discussion as follows:
Another explanation for the potential over-utilization may relate to difficulties that confront ambulance officers. First, staff in secondary EMS hospitals might decline to manage patients with drug poisoning. A survey conducted in Osaka city revealed that ambulance officers contacted more hospitals to transport patients with drug poisoning than all patients (average number of contacted hospitals: 7.6 vs. 1.8, respectively).22 Second, ambulance officers might transport patients with drug poisoning to high-level EMS because of their deep coma. Drug poisoning ranked within the top 2 in terms of the percentage of patients with deep coma and percentage of patients admitted to tertiary EMS. However, patients with drug poisoning had a less severe clinical course than those with other causes. For example, subarachnoid haemorrhage and ruptured cerebral aneurysm had the second highest percentage of patients admitted to tertiary EMS and had a much more severe clinical course than drug poisoning. It would be of great value to investigate triage tools predicting the need for advanced treatments based on information not only from early admission factors,23 but also from pre-hospital factors.24

Comment #7
The high comorbidity of mental illness among drug poisoning patients is of course well known among deliberate selfpoisoning patients why it is of importance to clarify the definition of drug poisoning patients (please see remark regarding this in the previous section) and also to address this in more depth.

Response
Thank you for your suggestion. We added information in the Limitation paragraph. Please see the response for Comment#2.

Finally, we thank the reviewer #1 for his/her constructive comments that have hopefully helped to improve our manuscript. Looking forward to hearing from you.

Yours truly,

To reviewer #2
We are grateful to reviewer #2 for the critical comments and useful suggestions that have helped us to improve our paper. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper.

Comment #1
Page 3, Line 15, Article Focus - this is not a nationally representative sample, although the authors claim that it is.

Response

Thank you for raising this issue. In the revised manuscript, we use the term ‘multicenter’ or ‘a nationwide administrative discharge database’ rather than ‘representative sample’.

The Article focus in the Article summary now reads:
Only a few multicenter studies have compared resource use and clinical course of emergency hospital admissions. Our aim was to compare the clinical and procedural characteristics of emergency hospital admissions for drug poisoning and major diseases by using a nationwide administrative discharge database.

The Introduction section now reads:
Although a number of studies have examined the detailed epidemiology of drug poisoning,2-8 only a few multicenter studies have compared resource use and clinical course of emergency hospital admissions.10-12 It remains unknown whether drug poisoning imposes a greater burden on emergency care resources and has a less severe clinical course among major causes of admissions. We thus aimed to compare the clinical and procedural characteristics of emergency hospital admissions for drug poisoning and major diseases by using a nationwide administrative discharge database.

The Discussion section now reads:
To our knowledge, this is the first study that used a nationwide administrative discharge database to compare detailed clinical and procedural characteristics of emergency hospital admissions for drug poisoning and major diseases. We found that drug poisoning was unique among the top 100 causes of emergency admissions. Patients with drug poisoning had a less severe clinical course than those with other causes, although they had higher utilization of emergency care resources. Our findings suggest that drug poisoning imposes a higher burden on emergency care resources than other causes of emergency admissions.

Comment #2
Page 5, Methods, Data Source, line 20 - 855 hospitals participated in a survey, but there are no details about how this sample of hospitals was obtained, nor how the patients within those hospitals were selected for inclusion in the study. If it is not a probability sample, then it is a convenience sample, and cannot be claimed to be nationally representative.

Response
Thank you for your helpful comment. First, we used the term ‘multicenter’ or ‘a nationwide administrative discharge database’ rather than ‘representative sample’. Please see the response for Comment#1. Second, we added information of the Data source as follows:
We conducted an observational study using the nationwide discharge administrative database of the Diagnosis Procedure Combination/Per-Diem Payment System (DPC/PDPS), a Japanese case-mix classification system launched in 2002 by the Ministry of Health, Labour and Welfare of Japan.13 Every year, the DPC Research Group conducts a survey of DPC/PDPS hospitals. In 2008, 855 of 1 558 DPC/PDPS hospitals voluntarily participated in the survey. The DPC/PDPS database includes clinical and procedural information on all inpatients discharged from the participating hospitals between 1 July and 31 December. All the data for each patient were recorded at discharge. The database

includes 2.86 million admissions, representing approximately 40% of all inpatient admissions to acute care hospitals in Japan (excluding psychiatric and tuberculosis hospitals).14 In the present study, we included all emergency hospital admissions and excluded planned admissions to the DPC/PDPS hospitals.

Comment #3
Page 6, lines 29-31 - The authors state that they "modified the disease code to separate drug poisoning from chemical and unspecified poisoning" - how certain is this method for identifying just the cases of drug-related poisoning? Is there a standard accepted procedure for doing this? Please provide more details.

Response
Thank you for your helpful comment. Physicians recorded information on diagnoses using the ICD-10 codes. Drug related poisoning is defined as T360–T509 in the ICD-10 codes. In the revised manuscript, we clearly described the procedures as follows:
Physicians recorded information on diagnoses using the International Classification of Diseases 10th revision (ICD-10) codes. According to the ICD-10 codes, 506 major disease categories were defined in 2008 (see Supplemental Table). In the database, patients with drug, chemical, and unspecified poisoning (ICD-10 codes T360–T509, T510–T659, and T887, respectively) have the same major disease code (disease code 161070). In the present study, we modified the disease code to separate drug poisoning (modified disease code 161070a) from chemical and unspecified poisoning (modified disease code 161070b) according to their ICD-10 codes.

Comment #4
Page 6, Line 48 - Insomnia is included in the authors' definition of "mental illness." This does not make sense in my opinion. Please justify this decision. The high prevalence of mental illness exists in this study because of the association revealed later about most poisonings being suicide attempts. This fact is buried in this paper and therefore can be misleading to readers. The authors should distinguish between unintentional poisoning and intentional poisoning/suicide attempts in this study.

Response
First, we included insomnia as one of mental illness according to the global burden of disease study. In accordance with this comment, we tried to exclude insomnia and conduct re-analysis. However, insomnia was seldom recorded as comorbidities (0.2%) and results were virtually the same. So we did not change the definition of mental illness. Second, we included all types of drug poisoning because data on external causes (ICD-10 codes V01–Y98) are not recorded in the DPC/PDPS database. We added information in the Limitation paragraph as follows:
Our study has several limitations. First, our results cannot be generalized and are limited to inpatient admissions to acute care hospitals rather than emergency outpatient admissions or emergency admissions to psychiatric hospitals, because we used the DPC/PDPS database. Second, we were unable to evaluate variables not included in the DPC/PDPS database. As a result, we could not assess other potentially important factors predicting the need for advanced treatments, such as acute

physiology and chronic health evaluation (APACHE) scores at admission23 or clinical management and course during pre-hospital period.24 Third, we included all types of drug poisoning (i.e., deliberate, accidental, and undetermined intent) as in a previous study,7 because data on external causes (ICD-10 codes V01–Y98) are not recorded in the DPC/PDPS database. As a result, we could not distinguish between deliberate and accidental drug poisoning. Fourth, although the database included approximately 40% of all inpatient admissions in Japan, participation in the survey was voluntary for each hospital and the patient selection procedure was not based on a random sampling technique from all acute hospitals.

Comment #5
Page7, line 29 - I am not familiar with the PCA biplot procedure - I suggest that a another reviewer/statistician verify that it is being correctly used here.

Response
We think this issue is at the discretion of the Managing Editor.

Comment #6
Page 8, line 22 - "ranked in the top 41 causes..." is an awkward phrase; I suggest that the authors state that it ranked 41st, assuming that is what is meant here.

Response
Thank you for your comment. As suggested, we corrected the phrase as follows:
During the study period, there were a total of 1 157 893 emergency hospital admissions to 855 hospitals. Characteristics of these admissions are presented in Table 1. The majority (51.7%) of admissions were for patients aged ≥ 65 years. Patients aged 0–14 years accounted for less than one-sixth (15.3%) of the admissions. The most prevalent diagnosis was pneumonia, accounting for 10.2% of all admissions, followed by stroke (5.5%) and heart failure (2.8%). Drug poisoning ranked 41st among causes of admissions. Less than 5% of patients used tertiary EMS. Of those patients, 88.3% stayed for more than 3 days. About 7% of patients died during hospitalization.

Comment #7
Page 10, Discussion, line 7 - The authors cannot claim that this is a nationally representative sample (see previous comment).

Response
Thank you for your helpful comment. We used the term ‘multicenter’ or ‘a nationwide administrative discharge database’ rather than ‘representative sample’. Please see the response for Comment#1.

Comment #8
Page 10, lines 40-47 - The authors state "Because most patients with drug poisoning have attempted

suicide..." This explanation of the admitting practices for patients with attempted suicide to high-level EMS is very revealing and critical to interpretation of study results. And later in line 57, the information about ambulance officers having to contact more hospitals to transport patients with drug poisoning confirms that this is really not an issue about drug poisoning at all, it is an issue about admitting practices and the resources needed to manage attempted suicides. Many of these admissions were likely necessary to allow an assessment of whether the person was a continued threat to their own life. Presumably many of these admissions were for observation of behavior and not for monitoring and potential treatment of the toxicity of the ingestion. Therefore, the title and discussion of most of this paper misses the main point and can be misleading to the reader. The manuscript should be re-written as a paper about the resources used to manage patients following suicide attempts. The outcome measures of, for example, % requiring surgery, are irrelevant and should be omitted.

Response
We agree that most patients of drug poisoning deliberately poisoned themselves for suicidal purpose. First, we included all types of drug poisoning because data on external causes (ICD-10 codes V01–Y98) are not recorded in the DPC/PDPS database. Please see the response for Comment#4.

Second, as suggested, we changed the title as follows:
Comparison of emergency hospital admissions for drug poisoning and major diseases: a retrospective observational study using a nationwide administrative discharge database

Third, to frame research question, we changed the objective. The Abstract now reads:
Objective: To compare the clinical and procedural characteristics of emergency hospital admissions for drug poisoning and major diseases.
Design: Retrospective observational study.
Setting: Discharged patients from 855 acute care hospitals from 1 July to 31 December in 2008 in Japan.
Results: There were a total of 1 157 893 emergency hospital admissions. Among the top 100 causes, drug poisoning was ranked higher in terms of the percentage of patients using ambulance services (74.1%; 2nd) and tertiary emergency medical services (37.8%; 1st). Despite higher utilization of emergency care resources, drug poisoning ranked lower in terms of the median length of stay (2 days; 100th), percentage of requirement for surgical procedures (1.7%; 91st), and in-hospital mortality ratio (0.3%; 74th).
Conclusion: Drug poisoning is unique among the top 100 causes of emergency admissions. Our findings suggest that drug poisoning imposes a greater burden on emergency care resources but has a less severe clinical course than other causes of admissions. Future research should focus on strategies to reduce the burden of drug poisoning on emergency medical systems.

The Article focus in the Article summary now reads:
Only a few multicenter studies have compared resource use and clinical course of emergency hospital admissions. Our aim was to compare the clinical and procedural characteristics of emergency hospital admissions for drug poisoning and major diseases by using a nationwide

administrative discharge database.

The Introduction section now reads:
Although a number of studies have examined the detailed epidemiology of drug poisoning,2-8 only a few multicenter studies have compared resource use and clinical course of emergency hospital admissions.10-12 It remains unknown whether drug poisoning imposes a greater burden on emergency care resources and has a less severe clinical course among major causes of admissions. We thus aimed to compare the clinical and procedural characteristics of emergency hospital admissions for drug poisoning and major diseases by using a nationwide administrative discharge database.

The Discussion section now reads:
To our knowledge, this is the first study that used a nationwide administrative discharge database to compare detailed clinical and procedural characteristics of emergency hospital admissions for drug poisoning and major diseases. We found that drug poisoning was unique among the top 100 causes of emergency admissions. Patients with drug poisoning had a less severe clinical course than those with other causes, although they had higher utilization of emergency care resources. Our findings suggest that drug poisoning imposes a higher burden on emergency care resources than other causes of emergency admissions.

Comment #9
In addition, in the US, the number of deaths, ED visits and hospital admissions due to unintentional opiod ingestion has dramatically increased. I am uncertain about any such trends in Japan. It would be informative if details regarding the type/class of drug was included in the analyses of this paper.

Response
Thank you for your comment. But, it is not our focus. In addition, average consumption of opioid was much lower in Japan than those in the United States. The International Narcotics Control Board reported that the consumption level reached nearly 40,000 S-DDD (defined daily doses for statistical purposes) per million inhabitants per day in the United States; on the other, the consumption level reached 1,023 S-DDD per million inhabitants per day in Japan.

cf: Report of the International Narcotics Control Board on the Availability of Internationally Controlled Drugs: Ensuring Adequate Access for Medical and Scientific Purposes (http://www.incb.org/pdf/annual-report/2010/en/supp/AR10_Supp_E.pdf)

VERSION 2 – REVIEW

REVIEWER	Katarina Bilén, MD Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden Competing interest none

REVIEW RETURNED	02-Nov-2012

THE STUDY	The authors describe that 855 hostpitals participated and 130 provided tertiary EMS. Are all other hospitals secondary EMS? The authors describe that they focus on secondary and tertiary EMS so my previous comment remain - are all 855 hospitals secondary and tertiary EMS and included in the study or are some of the 855 hospitals primary EMS and not included?
GENERAL COMMENTS	Comment # 1: figure 1 is still difficult to overview. Comment #2: In the discussion sections the authors describe that subarachnoid hemorrahage and ruptured cerebral aneurysm had a much more severe clinical course than drug poisoning. The point of comparing these diseases which are so different and ofcourse has very different clinical courses is not clear!

VERSION 2 – AUTHOR RESPONSE

To reviewer #1

We are grateful to reviewer #1 for useful suggestions that have helped us to improve our paper. As indicated in the responses that follow, we have taken all these comments and suggestions into account in the revised version of our paper. Blue text indicates where changes to the revised manuscript have been made.

Comment #1
The authors describe that 855 hostpitals participated and 130 provided tertiary EMS. Are all other hospitals secondary EMS? The authors describe that they focus on secondary and tertiary EMS so my previous comment remain - are all 855 hospitals secondary and tertiary EMS and included in the study or are some of the 855 hospitals primary EMS and not included?

Response
Thank you for your suggestion. As suggested, we added information of number of secondary and tertiary EMS in the Setting paragraph as follows:
In Japan, the EMS system is divided into 3 categories:15 (1) primary EMS that provides care to patients who can be discharged without hospitalization; (2) secondary EMS that provides care to patients who require admission to a regular inpatient bed; and (3) tertiary EMS that provides care to severely ill and trauma patients who require intensive care. In 2008, there were 18 892 clinics and 963 hospitals for primary EMS, 3 053 hospitals for secondary EMS, and 214 hospitals for tertiary EMS.14 In the present study, we focused on secondary and tertiary EMS rather than primary EMS, because the DPC/PDPS database is an inpatient database. Among the 855 participating hospitals in the DPC/PDPS database, 725 provide only secondary EMS and the other 130 provide tertiary EMS. Although some of the participating hospitals also provide primary EMS, data on emergency outpatient admissions are not included in the database.

Comment #2
figure 1 is still difficult to overview.

Response
Thank you for your helpful comment. In the revised manuscript of Figure 1, we added the label of subarachnoid haemorrhage and ruptured cerebral aneurysm to increase interpretability.

Comment #3
In the discussion sections the authors describe that subarachnoid hemorrahage and ruptured cerebral aneurysm had a much more severe clinical course than drug poisoning. The point of comparing these diseases which are so different and of course has very different clinical courses is not clear!

Response
Thank you for your helpful comment. We added the point of comparing these diseases as follows: Another explanation for the potential over-utilization may relate to difficulties that confront ambulance officers. First, staff in secondary EMS hospitals might decline to manage patients with drug poisoning. A survey conducted in Osaka city revealed that ambulance officers contacted more hospitals to transport patients with drug poisoning than all patients (average number of contacted hospitals: 7.6 vs. 1.8, respectively).22 Second, ambulance officers might transport patients with drug poisoning to high-level EMS because of their deep coma. Drug poisoning ranked within the top 2 in terms of the percentage of patients with deep coma and percentage of patients admitted to tertiary EMS. However, patients with drug poisoning had a less severe clinical course than those with other causes. For example, in terms of the percentage of patients admitted to tertiary EMS, drug poisoning ranked first, followed by subarachnoid haemorrhage and ruptured cerebral aneurysm, which had a much more severe clinical course than drug poisoning. It would be of great value to investigate triage tools predicting the need for advanced treatments based on information not only from early admission factors,23 but also from pre-hospital factors.24