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March 6th, 2018

World Journal of Diabetes

Editor-in-Chief: Timothy R Koch, MD, Doctor, Professor

Fang-Fang Ji, MSc

Science Editor,

World Journal of Diabetes

Re: Manuscript entitled "Prevalence and Associated Factors of Hospitalization for Dysglycemia among Elderly Type 2 Diabetes Patients: A Nationwide Study"

Manuscript NO: 46457

Dear Prof. Koch, editorial team and Fang-Fang Ji,

Thank you for the thoughtful input and review of our manuscript. We believe as a result of this review, our study will have more value for your readers. We revised the manuscript based on the reviewers' suggestions. We have attached our point by point response.

Thank you for your time and consideration. If you have any additional questions or comments, please let us know.

With many thanks for your attention, I remain.

Sincerely yours,

Wisit Cheungpasitporn, MD

Division of Nephrology, Department of Medicine,

University of Mississippi Medical Center,

Jackson, Mississippi, USA

wcheungpasitporn@gmail.com

Response to Editor(s)' Comments to Author:

Recommendation Major Revision.

Response: We thank you for reviewing our manuscript and for your critical evaluation. We really appreciated your input and found your suggestions very helpful. We have now revised the manuscript comprehensively, based on the reviewers' suggestions. We have attached our point by point response.

Comment #1

In part of 'authors' affiliations', please offer the postcode! Thank you!

Response: We thank you for reviewing our manuscript. The postcode of each authors' address was added. The following text has been added in the authors' affiliations:

'Wisit Kaewput, Ram Rangsin, Department of Military and Community Medicine, Phramongkutklao College of Medicine, Bangkok 10400, Thailand
Charat Thongprayoon, Michael A Mao, Division of Nephrology and Hypertension, Department of Medicine, Mayo Clinic, Rochester, MN 55905, USA
Narittaya Varothai, Division of Geriatrics, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok 10400, Thailand
Anupong Sirirungreung, Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, CA 90095, USA
Tarun Bathini, Department of Internal Medicine, University of Arizona, Tucson, AZ 85721, USA
Wisit Cheungpasitporn, Division of Nephrology, Department of Medicine, University of Mississippi Medical Center, Jackson, MS 39216, USA'

Comment #2

In part of 'Institutional Review Board Approval Form or Document', please upload the primary version (PDF) of the Institutional Review Board's official approval, prepared in the official language of the authors' country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.

Response: We thank you for reviewing our manuscript. The primary version (PDF) of the Institutional Review Board's official approval, prepared in the official language of the authors' country, was uploaded to the system.

Comment #3

In part of 'Signed Informed Consent Form(s) or Document(s)', please upload the primary version (PDF) of the Informed Consent Form that has been signed by all subjects and investigators of

the study, prepared in the official language of the authors' country to the system; for example, authors from China should upload the Chinese version of the document, authors from Italy should upload the Italian version of the document, authors from Germany should upload the Deutsch version of the document, and authors from the United States and the United Kingdom should upload the English version of the document, etc.

Response: We thank you for reviewing our manuscript. The primary version (PDF) of the Informed Consent Form that has been signed by all subjects and investigators of the study, prepared in the official language of the authors' country, was uploaded to the system

Comment #4

In part of 'Conflict-of-interest statement', please upload the primary version (PDF) file.

Response: We thank you for reviewing our manuscript. The primary version (PDF) file of the conflict-of-interest statement was uploaded to the system.

Comment #5

In part of 'STROBE statement', please upload the primary version (PDF) file and write it with detail pages.

Response: We thank you for reviewing our manuscript. The primary version (PDF) file of the STROBE statement and written detailed pages were uploaded to the system.

Comment #6

In part of 'Correspondence to', only one author needed. Please revise.

Response: We thank you for reviewing our manuscript. Correspondence information has been revised. The following text has been added in the 'Correspondence to' part:

'Correspondence to: Wisit Kaewput, MD, Assistant Professor, Department of Military and Community Medicine, Phramongkutklao College of Medicine, Ratchathewi, Bangkok 10400, Thailand. wisitnephro@gmail.com Telephone: +66-23547600-93613 Fax: +6623547733'

Comment #7

In part of the 'ABSTRACT; background section', please write.

Response: We thank you for reviewing our manuscript. We apologize for this missing section. The following text has been added to the ABSTRACT part; background section:

'BACKGROUND: The prevalence of older individuals with type 2 diabetes mellitus (T2DM) is increasing due to the aging population and improved medical care. These

patients are very susceptible to disease and treatment-related hospitalizations, resulting in higher health care costs, morbidity, and decreased quality of life. However, data of treatment-related complications, especially dysglycemia-related hospitalizations, are lacking.'

Comment #8

AIM (no more than 20 words)

The purpose of the study should be stated clearly, with no or minimal background information, following the format of: "To investigate/study/determine..."

Please revise.

Response: We thank you for reviewing our manuscript. We apologize for this error. The following text has been added in the ABSTRACT part; AIM section:

'AIMs: To assess the prevalence and associated factors for dysglycemia-related hospitalizations among elderly diabetic patients in Thailand using nationwide patient sample.'

Comment #9

In part of 'Audio Core Tip', please offer the audio core tip, the requirements are as follows:

In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:

Acceptable file formats: .mp3, .wav, or .aiff

Maximum file size: 10 MB

To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

Response: We thank you for reviewing our manuscript. The audio file was uploaded to the system.

Comment #10

In part of 'citation numbers', the reference numbers should be superscripted in square brackets at the end of the sentence.

Please revise all.

Response: We thank you for your suggestion. We have revised all reference numbers so that they are superscripted in square brackets at the end of the sentence.

Comment #11

In part of 'reference', please add PubMed citation numbers and DOI citation to the reference list and list all authors. Please provide PubMed citation numbers for the reference list, e.g. PMID

and DOI, which can be found at <http://www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed> and <http://www.crossref.org/SimpleTextQuery/>, respectively. The numbers will be used in the E-version of this journal. Thanks very much for your co-operation.

Such as: 1 Nayak S, Rath S, Kar BR. Mucous membrane graft for cicatricial ectropion in lamellar ichthyosis: an approach revisited. *Ophthal Plast Reconstr Surg* 2011: e155-e156 [PMID: 21346670 DOI: 10.1097/IOP.0b013e3182082f4e]

Response: We thank you for reviewing our manuscript. We have added PubMed citation numbers and DOI citation to the reference list, and listed all authors.

Comment #12

In part of 'Table 1', please provide legend for all abbreviation names in this table.

Response: We thank you for reviewing our manuscript. We have added a legend for all abbreviation names in Table 1.

Comment #13

In part of 'Table 2', please provide legend for all abbreviation names in this table.

Response: We thank you for reviewing our manuscript. We have added a legend for all abbreviation names in Table 2.

Comment #14

In part of 'Table 3', please provide legend for all abbreviation names in this table.

Response: We thank you for reviewing our manuscript. We have added a legend for all abbreviation names in Table 3.

Response to Reviewer#1

Comment #1

This manuscript analyzed the prevalence and associated factors of hospitalization for dysglycemia among elderly type 2 diabetes patients using a nationwide study design. This is one of the most important problems of public health. The data source is excellent and the methods used are basically appropriate, and the interpretations of the results are reasonable. In order to improve the quality of the manuscript, the following clarifications and corrections should be made.

Specific comments:

Flow chart of selection of the study population is suggested.

Response: We thank you for reviewing our manuscript. We really appreciated your input and found your suggestions very helpful. We agree with the reviewer regarding the addition of a 'Flow chart of selection of the study population' (**Figure 1**).

Comment #2

In the Study Design and Population, the authors point out in a paragraph "This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health of Thailand". The authors have not specified what these procedures are. I believe that these, which are also part of the methodology and normally require considerable bureaucracy, should be reflected.

Response: We appreciated the reviewer input and found the comment very important. Due to the regulations of the bureaucratic systems in Thailand, the researchers and the people who participated in the study were both defense officers and civilians. This study had to be approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health of Thailand. The following text has been added in the discussion:

'This study was approved by both the Institutional Review Board of the Royal Thai Army Medical Department and the Ethical Review Committee for Research in Human Subjects, the Ministry of Public Health of Thailand due to the regulations of bureaucratic systems in Thailand'

Comment #3

From the epidemiologic viewpoint, there are many confounding factors in the evidenced-based researches. How did the authors deal with associated confounding factors in this study?

Response: We appreciated the reviewer input and found the comment very important. We included 18 variables composed of clinical characteristics, demographic information, medications, and laboratory data that might be confounders in our multivariable analysis using a backward (Wald) method to identify Independent associated factors of hypo/hyperglycemic admission in the old T2DM patients.

Comment #4

Why the authors did not consider the effects of alcohol consumption?

Response: We appreciated the reviewer input and found the comment very important. One previous study had demonstrated an associated risk of hypoglycemia in T1DM patients with alcohol use. Conversely, another study did not show an association between alcohol consumption and risk of hypoglycemia in T2DM patients. Pietraszek, et al. reported that acute intake of alcohol does not increase hypoglycemic risk in diet-controlled T2DM subjects; an alcohol hypoglycemic effect only occurred when sulfonylurea is co-administered. Furthermore, long-term alcohol use seems to be associated with improved glycemic control in T2DM probably due to improved insulin

sensitivity. Although we do not have available data on alcohol consumption, we have added this into the limitations of study. The following text has been added in the discussion:

'Fourth, we did not adjust the final statistical models for several possible confounders such as alcohol consumption and former tobacco use as this data was unavailable. One previous study had demonstrated an associated risk of hypoglycemia in T1DM patients with alcohol use [40]. Conversely, another study did not show an association between alcohol consumption and risk of hypoglycemia in T2DM patients. Pietraszek, et al. [41] had instead reported that acute intake of alcohol does not increase hypoglycemic risk in diet-controlled T2DM subjects; an alcohol-related hypoglycemic effect only occurred when sulfonylurea was co-administered. Furthermore, long-term alcohol use seems to be associated with improved glycemic control in T2DM probably due to improved insulin sensitivity. Former tobacco use may have also affected our outcomes if patients had decided to quit smoking due to health conditions related to the dysglycemic admission.'

Comment #5

Regarding smoking, what proportion of subjects was excluded because of former smoker? If people decide to quit smoking due to some health conditions related to the outcomes of interest, the presented study results can be biased. The authors need to comment on this, in addition to what was currently mentioned.

Response: Thank you very much for your important suggestion. We have added this point in the revised manuscript. The following text has been added in the discussion; limitation part:

'Fourth, we did not adjust the final statistical models for several possible confounders such as alcohol consumption and former tobacco use as this data was unavailable. One previous study had demonstrated an associated risk of hypoglycemia in T1DM patients with alcohol use [40]. Conversely, another study did not show an association between alcohol consumption and risk of hypoglycemia in T2DM patients. Pietraszek, et al. [41] had instead reported that acute intake of alcohol does not increase hypoglycemic risk in diet-controlled T2DM subjects; an alcohol-related hypoglycemic effect only occurred when sulfonylurea was co-administered. Furthermore, long-term alcohol use seems to be associated with improved glycemic control in T2DM probably due to improved insulin sensitivity. Former tobacco use may have also affected our outcomes if patients had decided to quit smoking due to health conditions related to the dysglycemic admission.'

Comment #6

Describe any efforts to address potential sources of bias, if applicable.

Response: We appreciated the reviewer input and found the comment very important. We have added this point into the revised manuscript. The following text has been added in the discussion; limitation part:

'There are several limitations of this study. First, data collection was performed using retrospective medical record review; therefore, incomplete data records with missing diagnoses cannot be verified. Second, the study population does not include patients from university hospitals. Consequently, the prevalence of hypoglycemia and hyperglycemia-related hospitalization may be significantly underestimated. Third, we only measured hospitalization rates for dysglycemia. Dysglycemic events resulting in death prior to hospital admission were not captured. Fourth, we did not adjust the final statistical models for several possible confounders such as alcohol consumption and former tobacco use as this data was unavailable. One previous study had demonstrated an associated risk of hypoglycemia in T1DM patients with alcohol use [40]. Conversely, another study did not show an association between alcohol consumption and risk of hypoglycemia in T2DM patients. Pietraszek, et al. [41] had instead reported that acute intake of alcohol does not increase hypoglycemic risk in diet-controlled T2DM subjects; an alcohol-related hypoglycemic effect only occurred when sulfonylurea was co-administered. Furthermore, long-term alcohol use seems to be associated with improved glycemic control in T2DM probably due to improved insulin sensitivity. Former tobacco use may have also affected our outcomes if patients had decided to quit smoking due to health conditions related to the dysglycemic admission.'

Comment #7

Regarding to BMI, the authors need to cite papers describing the relevance of using BMI category in this population. If there are no such papers, the authors should not categorize the BMI variable. Instead, they should model as a continuous scale.

Response: Thank you very much for your important suggestions. BMI was stratified by using criteria for an Asian population. We have also provided the citation. The following text has been added in the data collection part:

'BMI was stratified by using criteria for an Asian population.'

Reference: WHO Expert Consultation. Appropriate body-mass index for the Asian populations and its implications for policy and intervention strategies. Lancet. 2004; 363(9403):157-63. [PMID: 14726171], [DOI: 10.1016/s0140-6736(03)15268-3]

Comment #8

Please consider the comparison with the other epidemiological studies in other areas using table so make clear the significance of this study.

Response: Thank you very much for the recommendation. Thus, we added a comparison with other epidemiological studies in other areas by using Table 4 as the reviewer's suggested.

Comment #9

Discussion section was too simple. More discussion will be required based literature review of previous papers reporting and then, the authors should point will clarify the feature and novel findings of this study.

Response: Thank you very much for the recommendation. We have added more discussion to clarify the features and novel findings of this study. The following text has been added into the discussion part:

‘Our study revealed that age, female sex, hypertension, dementia, insulin use, low BMI, elevated HbA1C and low eGFR are associated with hypoglycemia-related hospitalizations. Older age and its association with severe hypoglycemia is consistent with several reports ^[19, 20]. The Korean cohort demonstrated that older patients, females, several comorbidities such as chronic kidney disease and dementia, and insulin use were associated with a high risk of hypoglycemia ^[19]. Another previous study found that in patients who are aged ≥ 80 years, severe hypoglycemia accounted for up to one in six hospital admissions ^[20]. Older patients may have multiple factors that can predispose them to develop hypoglycemia such as polypharmacy, age-related changes in pharmacokinetics and pharmacodynamics, decreased hormonal regulation and counter-regulation, suboptimal intake of water and/or food, decreased intestinal absorption, and cognitive impairment ^[21, 22]. They may also be burdened with diseases that affect their ability to effectively metabolize hypoglycemic agents or respond to hypoglycemia, such as heart failure, liver disease, sarcopenia ^[23] and kidney dysfunction ^[24]. Female sex is associated with hypoglycemia related hospitalizations, consistent with a Korean cohort ^[19]. Females are hypothesized to develop hypoglycemia more readily due to lower muscle mass, less tolerability of hypoglycemic symptoms, stricter diet control, and less access to medications than males ^[25, 26].

.....

Our study found that elderly T2DM patients with hypertension are associated with hypoglycemic admissions. This finding provides novel insights. A possible cause might be due to polypharmacy since these elderly T2DM patients with hypertension, had more comorbidities and more diabetic complications that affect hypoglycemic drugs metabolism.

.....

Insulin should be used with caution in older adults. The administration of insulin therapy requires good visual acuity, motor skills and cognitive ability in the patient, especially for regimens that require multiple daily injections. This may be too complex for patients with several comorbidities and limited functional status. Our study also demonstrated that low BMI is associated with hypoglycemia related hospitalizations as well. A low BMI in elderly patients may cause higher risk for hypoglycemia due to lower muscle mass, suboptimal nutrition status and low glycogen storage ^[36, 37]. Our study additionally demonstrated that an elevated HbA1C is associated with hypoglycemic admissions. An elevated HbA1C may increase hypoglycemic risk due to more aggressive blood glucose control resulting in labile blood sugars, or a higher association with polypharmacy. Our study also supported that a low eGFR is associated with severe

hypoglycemia in elderly T2DM patients, consistent with a prior report ^[19]. Impaired kidney function has been shown to significantly increase the risk of hypoglycemia ^[24]. The kidney may play an essential role in glucose metabolism and serve as a defense mechanism against hypoglycemia. Furthermore, impaired renal function limits insulin and other antidiabetic drugs clearance. Patients with advanced kidney disease may also have chronic inflammation and anorexia that leads to suboptimal nutrition and a reduction in glycogen stores ^[24]. Hence, in addition to their risk of polypharmacy, cognitive decline, dementia, sarcopenia, and frailty, older adults with diabetes and impaired renal function are at risk of hypoglycemia ^[24, 38].

.....

The American Diabetes Association (ADA) guidelines recognize the need to incorporate geriatric components into the assessment and management of diabetes ^[9]. By recognizing the multiple risk factors in elderly T2DM patients identified in our study, a multidisciplinary approach ^[9, 40, 41] to the individualization of a patient's optimal glucose level and its medical management can be performed. Future clinical practice improvements can then be compared to the prevalence rates identified in this study.'

Comment #10

If possible, please update the potential relevant publications.

Response: Thank you very much for your important suggestion. We have updated the potential relevant publications as the reviewer suggested.

Comment #11

If the above suggestions are incorporated and the paper is thoroughly edited, it will be a strong contribution to the literature.

Response: All authors thank the Editors and reviewers for their valuable suggestions. The manuscript has been improved considerably by the suggested revisions.