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# Association of hyperglycemia episodes on long-term mortality in type 2 diabetes mellitus with vascular dementia: A population-based cohort study

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ABSTRACT

*Aim:* This study investigated the effect of severe hyperglycemia episodes on survival and associated factors related to risk of mortality in type 2 diabetes mellitus (DM) patients with dementia.
*Methods:* We enrolled all type 2 DM patients newly diagnosed as having dementia in Taiwan from 1998 to 2005. These patients were categorized into those who had hyperglycemia episodes and those who did not based on whether or not they had been hospitalized for hyperglycemia after dementia diagnosis. Factors independently associated with mortality were evaluated.
*Results:* Of 5314 patients identified, 303 (5.7%) had at least one hyperglycemia hospitalization. Patients with at least one hyperglycemia hospitalization had a 30% greater risk of mortality than those who had no such admissions (adjusted hazard ratio: 1.30, 95% confidence interval: 1.09–1.55). Other variables, including age, sex, geographical region, insurance amount, patient with congestive heart failure, cerebrovascular disease, renal disease, use of anti-hypertensive drugs, use of anti-lipid drugs, and use of insulin were independently associated with risk of mortality.
*Conclusion:* Severe hyperglycemia is common in type 2 DM patients with dementia and it substantially shortens their life. The findings of this study suggest a great need to improve care in DM patients with dementia.


## 1. Introduction

There were about 46 million people living with dementia worldwide in 2015.[1] Type 2 diabetes mellitus (DM) is one of the major risk factors for dementia,[2–4] so the primary goal of diabetes care is to maintain near normal blood glucose (hemoglobin A1c level below 7% of the total hemoglobin) to reduce other chronic diseases such as dementia.[5] Diabetes self-management, including nutritional management, adequate physical activity, and regular monitoring blood glucose, is essential to the prevention and delay in DM complications.[6,7]Although there are continuous improvements in the proportion of those meeting recommended glycemic control goals and reductions of hospital admissions due to poorly controlled glucose levels in general DM population,[8,9] there are important concerns regarding the capacity of dementia patients and there remains a need to assess care outcomes this vulnerable DM population.

Although it is understood that dementia patients often have a compromised capacity for self-management, it is unknown to what extent their inadequate control of diabetes affects their risk of mortality. Thus, this population-based study tapped a nationwide insurance claims database to evaluate mortality risk in type 2 DM patients with dementia who hospitalized for hyperglycemia episodes, including diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic

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state (HHS), in Taiwan. Factors influencing mortality were also explored.

## 2. Subjects, materials and methods

### 2.1. Database

This retrospective observational study was conducted using Taiwan's National Health Insurance Research Database (NHIRD) for the period between 1997 and 2008. Taiwan's National Health Insurance (NHI) program was established in 1995. In contracts with 97% of all medical providers in Taiwan, the NHI program provides compulsory universal health insurance to >99% of Taiwan's inhabitants. All contracted medical providers have been mandated to upload medical claims; the database contains comprehensive information on insured subjects, including dates of clinical visits, diagnostic codes, details of prescriptions, and expenditure amounts.[10] Taiwan's NHI Administration regularly performs reviews of the system to prevent waste, safeguard quality, and maintain the public's healthcare safety and quality.[11]

### 2.2. Definition of dementia with diabetes

We identified and included all patients with dementia who had been newly registered to receive the Catastrophic Illness Certificate for senile dementia [International Classification of Disease, 9th Revision (ICD-9-CM) code 290.X] from 1998 to 2005 in Taiwan. These senile dementia designations are based on rigid diagnostic criteria evaluated by medical board certified neurologists or psychiatrists. The index date used for this study was registry date found on the Catastrophic Illness Certificate. The dementia patients were defined as having comorbid diabetes if they had diagnostic ICD-9-CM code 250.XX listed on at least two ambulatory care claims records or one inpatient care claims record one year prior to the diagnosis of dementia. This study was approved by Institutional Review Board (IRB) Kaohsiung Medical University Hospital, Kaohsiung Medical University, Taiwan (KMUHIRB-SV(II)-20170053). All research procedures followed the directives of the Declaration of Helsinki. Because all identifying personal information was removed from the data files prior to analysis, the review board waived the requirement for informed written consent.

### 2.3. Definitions of hyperglycemic episode and death

The dementia patients were assigned to the hyperglycemic group if they had been hospitalized for any of the following hyperglycemia-related diagnoses between 1997 and 2008: diabetes with ketoacidosis (ICD-9 code 250.1), diabetes with hyperosmolar coma (ICD-9 code250.2), diabetes with other coma (ICD-9 code250.3), secondary diabetes mellitus with ketoacidosis (ICD-9 code249.1), secondary diabetes mellitus with hyperosmolar coma (ICD-9 code249.2), or secondary diabetes mellitus with other coma (ICD-9 code249.3). Those without hyperglycemia-related hospitalizations were assigned to the control group. Date of death during observation period of year 1998–2008 was defined as the date of last patient inpatient record. Patients discharged in critical condition for whom no outpatient follow-up records existed were considered to have expired. Patients were traced from index date to date of death or the end of 2008, whichever came first. Mortality was the primary outcome of this study. Patients surviving till the end of study or withdrawn from NHI were censored. Follow-up time was calculated from index date to the last observed date a claims record was filed for the patient.

### 2.4. Covariates

We collected patients' sex, age, geographical region (northern, central, southern, and eastern Taiwan), urbanization level (urban and rural), insurance amount (dependent, < 20,000, and ≥20,000 New Taiwan dollars (~667 US dollars)). We also identified whether the patients had any major comorbidities indicated by ICD-9-CM codes for the various chronic disorders on their outpatient and inpatient claims records. These comorbidities included congestive heart failure, cerebrovascular disease, chronic pulmonary disease, peptic ulcer disease, mild liver disease, renal disease, hypertension, and hyperlipidemia (Table A in Appendix A). Disease severity was defined using Charlson comorbidity index scores.[12] The cofounding medicine were antihypertensive drugs, anti-lipid drugs, antiplatelet drugs, and insulin (Table B in Appendix A). Patients who used a prescribed medication for over 5% of the follow-up period were considered to have been treated with the drugs.

### 2.5. Sensitivity analysis

To ensure the robustness of our analysis, we further performed two sensitivity analyses. First, we stratified patients by main covariates including age of 75, sex, hypertension, renal disease, use of anti-lipid drugs, and use of insulin to explore the important factors potentially influencing the effect of hyperglycemia on mortality. In the other, we performed a propensity score-weighting analysis to reexamine the robustness of our main results.

### 2.6. Statistical analyses

Data presented as mean $\pm$ standard deviation (SD) for continuous variables and percentages for categorical variables. Differences between-group distributions were analysed using the independent *t*-test, and $\chi^2$ test. Cumulative survival rate was estimated using the Kaplan-Meier survival analysis and differences in the risk of mortality those who were hospitalized and those who were not was examined by log-rank test.

Cox proportional hazards regression model, adjusting for patients' characteristics (age, sex, urbanization level, insurance amount, major comorbidity, Charlson index, and medications) was used to compare risk of mortality between the two groups. All mortality risks were presented as hazard ratios (HR) along with 95% confidence intervals (CI). Multiple binary logistic regression was used to estimate propensity score of hyperglycemia by treating all covariates as independent variables. We recalculated HR of mortality by using inverse probability of treatment, stabilized inverse probability of treatment, and standardized mortality ratio weightings. All statistical operations and figures were performed using SAS (version 9.4, SAS Institute, Cary, N.C., USA), and GraphPad Prism 7.0 (GraphPad Software, San Diego, CA). All *p*-values were two-sided and considered significant if <0.05.

## 3. Results

### 3.1. Patient characteristics

We identified 28,807 patients newly diagnosed with dementia from 1998 to 2005. Patients whose ages were <18 years ($n = 125$), whose data were incomplete ($n = 16$), and those who did not have DM ($n = 23{,}352$) were excluded (Fig. S1 in Appendix A). After exclusion, we were left with 5314 patients to follow up. Three hundred and three of these dementia patients with DM had at least one hyperglycemia-related hospital admission during the observation period (equivalent to 303/22,754 = 13.3 per 1000 person-years) and 137 (45.2%) died. In the control group, which had no hospitalizations for hyperglycemia, only 38.2% (1915/5011) had died by the end of the observation period. Dementia patients with DM who had at least one hyperglycemia-related hospitalization were more likely to be female, have renal disease, and to be using insulin, compared to those not hospitalized (the controls) (Table 1).

**Table 1**
Baseline characteristics.

| | Control | | Hyperglycemia[a] | | *P*-value |
|---|---|---|---|---|---|
| | N | % | N | % | |
| Total | 5011 | | 303 | | |
| Sex | | | | | |
| Male | 1791 | 35.7 | 89 | 29.4 | 0.02 |
| Female | 3220 | 64.3 | 214 | 70.6 | |
| Age, years | 75.2 ± 7.9 | | 74.5 ± 8.1 | | 0.15 |
| <65 | 481 | 9.6 | 36 | 11.9 | 0.56 |
| 65–74 | 1823 | 36.4 | 112 | 37.0 | |
| 75–84 | 2248 | 44.9 | 130 | 42.9 | |
| ≥85 | 459 | 9.2 | 25 | 8.3 | |
| Geographical region | | | | | |
| North | 1973 | 39.4 | 111 | 36.6 | 0.34 |
| Central | 1087 | 21.7 | 79 | 26.1 | |
| South | 1762 | 35.2 | 101 | 33.3 | |
| East | 189 | 3.8 | 12 | 4.0 | |
| Urbanization level | | | | | |
| Urban | 1495 | 29.8 | 90 | 29.7 | 0.96 |
| Rural | 3516 | 70.2 | 213 | 70.3 | |
| Premium income, NTD | | | | | |
| Dependent | 2576 | 51.4 | 146 | 48.2 | 0.48 |
| <20,000 | 1859 | 37.1 | 117 | 38.6 | |
| ≥20,000 | 576 | 11.5 | 40 | 13.20 | |
| Major comorbidity | | | | | |
| Congestive heart failure | 364 | 7.3 | 23 | 7.6 | 0.83 |
| Cerebrovascular disease | 2248 | 44.9 | 144 | 47.5 | 0.37 |
| Chronic pulmonary disease | 896 | 17.9 | 51 | 16.8 | 0.64 |
| Peptic ulcer disease | 841 | 16.8 | 43 | 14.2 | 0.24 |
| Mild liver disease | 315 | 6.3 | 16 | 5.3 | 0.48 |
| Renal disease | 244 | 4.8 | 25 | 8.3 | 0.008 |
| Hypertension | 3315 | 66.2 | 192 | 63.4 | 0.32 |
| Hyperlipidemia | 856 | 17.1 | 46 | 15.2 | 0.39 |
| Charlson index | 3.3 ± 1.6 | | 3.4 ± 1.6 | | 0.27 |
| Medicine, % | | | | | |
| Antihypertensive drugs | 3976 | | 79.4 | | 233 |
| Anti-lipid drugs | 1039 | | 20.7 | | 73 |
| Antiplatelet drugs | 2523 | | 50.4 | | 155 |
| Insulin | 1001 | | 20.0 | | 99 |

Abbreviation: NTD, New Taiwan dollar.
Data represented as mean ± s.d. for continuous variables and percentages for categorical variables. Different between-group distributions were analysed using the independent *t*-test, and $\chi^2$ test. $P < 0.05$ was considered significant.
[a] Hyperglycemia includes diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic coma.

### 3.2. Cumulative mortality risk and independent factors of mortality

The patients hospitalized for hyperglycemia had a significantly higher 8-year cumulative mortality risk than the control group (52.9 *vs* 47.2%, $p = 0.02$ by Log-rank test) (Fig. 1). The mortality risk was more prominent in female patients (Fig. S2 and S3 in Appendix A). Table 2 shows the mortality risks in different stratifications of patient characteristics and factors associated with mortality. The patients who had

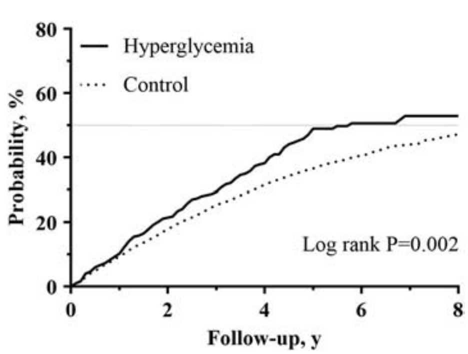


**Fig. 1.** Cumulative mortality rate by hyperglycemic episode. Kaplan Meier approached was used to estimate the mortality rates and the differences of mortality rate were examined by log-rank test. *P* value <0.05 was considered significant.

hyperglycemia-related hospitalization exhibited obviously higher mortality risk than the control group (the absolute risk increase from 8.87 to 11.79 per 100 person-year). After adjustment, those with hyperglycemia hospitalizations were found to be at significantly greater risk (30%) than those without (Adjusted-HR = 1.30, 95% CI = 1.09–1.55) (Table 2).

### 3.3. Sensitivity analysis

After stratifying by age (<75 and ≥75 years), sex, hypertension, renal disease, use of anti-lipid drugs, and use of insulin, we still found that dementia patients with hyperglycemia had a significantly higher mortality risk than the control group (range of adjusted HR = 1.20–1.76) (Fig. 2). After performing propensity score analysis, we found the hyperglycemia group to have an adjusted HR of 1.29 (95% CI = 1.22–1.38), 1.28 (95% CI = 1.08–1.53), and 1.32 (95% CI = 1.03–1.69) for mortality by using inverse probability of treatment, stabilized inverse probability of treatment, and standardized mortality ratio weightings, respectively (Table C in Appendix A).

## 4. Discussion

This study found an obvious increase in the mortality risk in dementia patients who had been hospitalized for hyperglycemia-related events. Compared to females, males were less likely to be hospitalized for hyperglycemia but more likely to die from their illnesses. Other variables, including age, sex, geographic region, insurance amount, comorbidities (congestive heart failure, cerebrovascular disease, and renal disease), and use of medication (anti-lipid drugs and insulin), were also associated with risk of mortality in patients with dementia.

One study has reported great improvement in DM population in meeting recommended glycemic control goals and reduction in hospital admissions for hyperglycemia.[9] However, little research attention has been paid to DM care and consequent outcomes in populations who are possibly less able to self-management their diseases. The present study found hospital admission for hyperglycemia in Taiwan's dementia population to be 13.3 per 1000 person-years, a rate obviously higher than that found in the all ages of elderly population with DM.[8] While the mechanisms underlying increased hospital admissions for hyperglycemia in dementia patients are complex and worthy of further study, it is reasonable to assume that severe decline in cognitive ability in patients with dementia results in a loss of ability to self-manage DM and maintain optimal blood glucose levels, which would more than likely put this population at greater risk of hyperglycemia. Prior to this study, this assumption had not been tested in Taiwan. One systemic review of the effect of disability in diseases like Parkinson's Disease found that barriers to adherence to regimens for use of mood disorder and cognition medications and lack of environmental support may contribute to the development of severe hyperglycemia in these patients.[13] The current study found that being female, having renal disease, using insulin increase the likelihood that dementia patients would have a hyperglycemic event. DM is prevalent in people with dementia and more attention is needed to prevent life-threatening DM-related episodes in this population. Thus, physicians may want to keep this knowledge in mind when treating DM in these patients.

With regard to mortality, much attention has been paid to the association between elevated glucose levels at admission and risk of mortality in different patient groups but not in dementia patients with DM.[14,15] We found a 30% increase in mortality risk in dementia patients hospitalized for hyperglycemia. The vascular injury caused by hyperglycemia can shorten a patient's life. One meta-analysis of ten cohort studies found an association between chronic hyperglycemia and an increased risk of cardiovascular disease.[16]

Notably, medication use in this study was significantly associated with mortality risk. Use of non-oral insulin by patients unable to administer injections to themselves many result in poorer glucose control. Both hypoglycemia and hyperglycemia have been associated with

**Table 2**
Independent predictors of death among dementia patients with diabetes.

| Parameter | No. of death | Person-year | Mortality rate (95% CI) | Adjusted hazard ratio (95% CI) |
|---|---|---|---|---|
| Hyperglycemia[a] | | | | |
| No | 1915 | 21,591 | 8.87 (8.48–9.28) | 1.00 [reference] |
| Yes | 137 | 1162 | 11.79 (9.97–13.94) | 1.30 (1.09–1.55) |
| Sex | | | | |
| Male | 800 | 7811 | 10.24 (9.55–10.97) | 1.00 [reference] |
| Female | 1252 | 14,942 | 8.38 (7.93–8.86) | 0.80 (0.73–0.88) |
| Age, per 10 years increase | 2052 | 22,754 | 9.02 (8.64–9.42) | 1.40 (1.31–1.48) |
| Geographical region | | | | |
| North | 768 | 9475 | 8.11 (7.56–8.7) | 1.00 [reference] |
| Central | 456 | 4833 | 9.44 (8.61–10.35) | 1.19 (1.05–1.35) |
| South | 761 | 7573 | 10.05 (9.36–10.79) | 1.32 (1.19–1.46) |
| East | 67 | 872 | 7.68 (6.04–9.76) | 0.95 (0.74–1.23) |
| Urbanization level | | | | |
| Rural | 625 | 6530 | 9.57 (8.85–10.35) | 1.00 [reference] |
| Urban | 1427 | 16,223 | 8.8 (8.36–9.27) | 0.91 (0.82–1.01) |
| Insurance amount, NTD | | | | |
| ≥20,000 | 108 | 2916 | 3.7 (3.06–4.47) | 1.00 [reference] |
| <20,000 | 882 | 8143 | 10.83 (10.14–11.57) | 2.30 (1.88–2.81) |
| Dependent | 1062 | 11,695 | 9.08 (8.55–9.64) | 2.49 (2.03–3.05) |
| Major comorbidity | | | | |
| Congestive heart failure | 181 | 1462 | 12.38 (10.7–14.32) | 1.23 (1.04–1.44) |
| Cerebrovascular disease | 982 | 10,000 | 9.82 (9.22–10.45) | 1.13 (1.03–1.25) |
| Chronic pulmonary disease | 410 | 3862 | 10.62 (9.64–11.7) | 1.02 (0.91–1.15) |
| Peptic ulcer disease | 358 | 3717 | 9.63 (8.68–10.68) | 1.02 (0.90–1.15) |
| Mild liver disease | 118 | 1439 | 8.2 (6.85–9.82) | 0.92 (0.76–1.12) |
| Renal disease | 149 | 897 | 16.61 (14.15–19.5) | 1.70 (1.41–2.05) |
| Hypertension | 1331 | 14,839 | 8.97 (8.5–9.47) | 0.93 (0.84–1.02) |
| Hyperlipidemia | 273 | 3889 | 7.02 (6.23–7.9) | 0.91 (0.79–1.04) |
| Charlson index | 2052 | 22,754 | 9.02 (8.64–9.42) | 1.02 (0.98–1.06) |
| Medication | | | | |
| Antihypertensive drugs | 1641 | 1,7957 | 9.14 (8.71–9.59) | 1.15 (1.02–1.29) |
| Anti-lipid drugs | 292 | 5152 | 5.67 (5.06–6.36) | 0.68 (0.59–0.77) |
| Antiplatelet drugs | 995 | 11,724 | 8.49 (7.98–9.03) | 0.93 (0.85–1.02) |
| Insulin | 466 | 4679 | 9.96 (9.1–10.91) | 1.24 (1.12–1.38) |

Abbreviation: CI, confidence interval; NTD, New Taiwan Dollar.
Incidence rate (per 100 person-year).
Cox proportional hazard model was used for hazard ratio and 95% CI estimation after adjusting for all covariates.
[a] Hyperglycemia includes diabetic ketoacidosis and hyperglycemic hyperosmolar state.

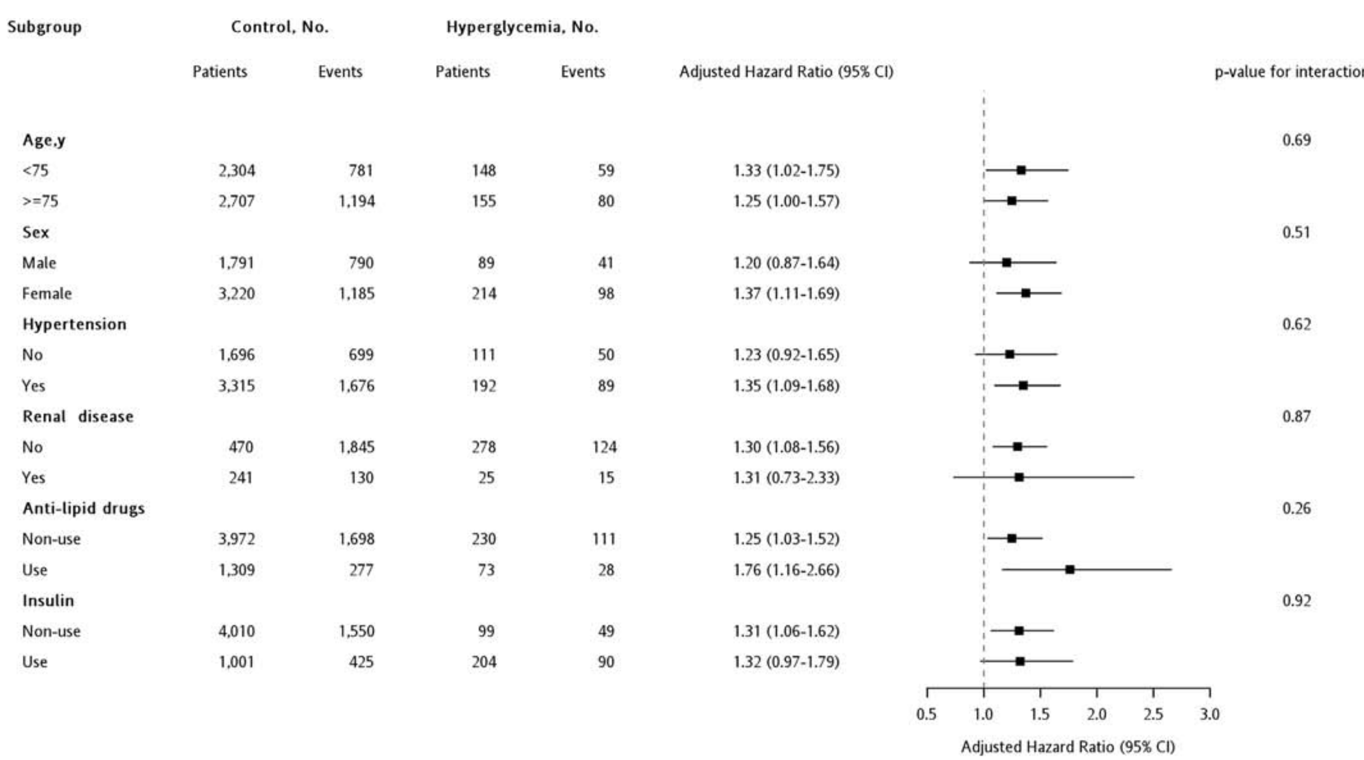


**Fig. 2.** Multivariable stratified analyses for the association between hyperglycemia and mortality (reference of hazard ratio for each stratification is the control group). CI = confidence interval.

increased all-cause mortality and cardiac events in patients with DM.[17] Previous studies of community-dwelling frail older patients and our study of those with dementia found that use of anti-lipid medications improved survival.[18] Further study of larger populations is needed to reconfirm these relationships.

This study has several limitations. One limitation is that the definitions of hyperglycemia, DM and any other comorbid conditions were based on diagnostic codes used on insurance claims. Some misclassification is possible, though the effect may be small or random. Previous studies of these sources have repeatedly found high agreement of diagnosis codes used in database and medical charts for several chronic diseases.[19,20] Another limitation is that, like other studies using claims data, we were unable to obtain lifestyle data, body mass index, or specific DM control status, factors that may be associated with admission for hyperglycemia and risk of mortality in our study population. Nonetheless, given the magnitude and statistical significance of the observed effects in this study, this limitation was unlikely to have compromised our results. Still another limitation is that our study is of dementia population in Taiwan. Our results may not be generalizable to other races, ethnic groups, or countries.

In conclusion, admission for hyperglycemia is common in dementia patients with type 2 DM and associated with long-term mortality. These results suggest a need for more appropriate diabetic care for patients with dementia.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2018.10.014.

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