

REVIEWER'S REPORT

Manuscript No.: IJAR-59304

Title: TYPE 2 DIABETES MELLITUS AS A RISK FACTOR FOR DENGUE MORTALITY IN THE YEARS 2020-2024 IN THE OOAD SOUTH VERACRUZ,

Recommendation:

Accept as it is

Accept after minor revision.....

Accept after major revision ...YES.....

Do not accept (*Reasons below*)

Rating

Originality

Techn. Quality

Clarity

Significance

Excel.	Good	Fair	Poor
	☐		
		☐	
		☐	
	☐		

Reviewer's ID: JPR-094

Detailed Reviewer's Report

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Manuscript Title

“Type 2 Diabetes Mellitus as a Risk Factor for Dengue Mortality in the Years 2020–2024 in the OOAD South Veracruz”

Overall Assessment

The manuscript addresses an important public-health question concerning the association between type 2 diabetes mellitus (T2DM) and mortality among patients with dengue in the OOAD Veracruz Sur during 2020–2024. The use of a retrospective case-control design and routinely collected clinical, laboratory, and mortality data has potential value for understanding factors associated with dengue mortality in this regional population.

The study also reports potentially important associations between dengue mortality and thrombocytopenia, elevated SGOT/AST, elevated SGPT/ALT, hyperalbuminemia, leukopenia, abdominal pain, and persistent vomiting.

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However, the manuscript currently contains **major methodological, statistical, numerical, terminology, and presentation problems**. Several percentages and statements are internally inconsistent, the age eligibility criteria conflict with the age table, the analysis appears to rely primarily on unadjusted odds ratios, and important details concerning selection and comparability of cases and controls are insufficiently described.

Therefore, substantial revision is required before the scientific validity of the conclusions can be assessed.

1. STRENGTHS OF THE MANUSCRIPT

1.1 Relevant public-health topic

Dengue mortality remains an important clinical and epidemiological problem, and investigating whether T2DM is associated with mortality is clinically relevant.

1.2 Clearly defined study period

The study covers January 2020 to December 2024, providing a defined five-year observation period.

1.3 Case-control design

The retrospective case-control design is appropriate for investigating potential associations with a relatively uncommon outcome such as dengue-related death, provided that cases and controls are appropriately selected.

1.4 Reasonable sample structure

The study includes 93 cases and 279 controls using a 1:3 ratio, resulting in a total sample of 372 records. The use of three controls per case can provide greater statistical efficiency than a 1:1 design.

1.5 Laboratory and clinical variables are included

The manuscript examines several clinically relevant variables, including:

- Thrombocytopenia
- SGOT/AST elevation

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- SGPT/ALT elevation
- Hyperalbuminemia
- Hemoconcentration
- Leukopenia
- Mucosal bleeding
- Abdominal pain
- Persistent vomiting

This broad assessment is potentially useful for identifying clinical characteristics associated with fatal dengue.

1.6 T2DM finding is potentially informative

The reported association between T2DM and mortality is:

OR = 1.018; 95% CI: 0.604–1.716; p = 0.947.

This indicates that the study did not demonstrate a statistically significant association between T2DM and dengue mortality in this particular study population. A finding of no statistically significant association can itself be informative, particularly when previous studies have reported different results.

1.7 Regional epidemiological relevance

The focus on OOAD Veracruz Sur provides geographically specific information that may be useful for local epidemiological surveillance and healthcare planning.

1.8 Potentially important clinical observations

The reported strong crude associations involving elevated transaminases, hyperalbuminemia, thrombocytopenia, and abdominal pain may warrant further investigation and could have clinical relevance if the data and statistical methods are appropriately validated.

2. WEAKNESSES / MAJOR CONCERNS

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2.1 Major numerical inconsistency in the sex data

The manuscript states:

“Among the cases, men accounted for 13.4% (50 cases)”

There are 50 males among 93 cases.

Therefore:

$50/93 \times 100 = 53.8\%$, not 13.4%.

The value of 13.4% is:

$50/372 \times 100 = 13.4\%$.

Similarly, 43 females among 372 total participants equals 11.6%.

Thus, Table 1 appears to calculate percentages using the **total sample of 372**, whereas the accompanying text sometimes appears to interpret them as percentages within cases.

The authors must clearly specify whether percentages are calculated:

- within cases,
- within controls, or
- within the total study population.

This issue must be corrected throughout the manuscript.

2.2 Incorrect statement regarding mortality by sex

Line 143–144 states:

“higher mortality among men 50 (13.4%) compared to women 3 (11.6%).”

There are **43 women**, not 3, according to Table 1.

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Moreover, if the analysis concerns sex distribution among the 93 deaths:

Male: $50/93 = 53.8\%$

Female: $43/93 = 46.2\%$

The authors should not describe 50 versus 43 as a “higher mortality rate” without specifying the population denominator. A sex-specific mortality rate cannot be established from these counts alone unless the corresponding male and female populations at risk are available.

2.3 Case and control definitions require substantial clarification

The case definition is relatively detailed, but the control definition is insufficiently specific.

The authors need to clarify:

- Were controls patients hospitalized for dengue who survived?
- Were controls selected from the same hospitals as cases?
- Were controls selected from the same calendar years?
- Were controls matched to cases by age, sex, hospital, year, or another variable?
- Was the 1:3 ratio simply a sampling ratio or were controls individually matched?
- Could one patient appear more than once?
- How were controls selected from the eligible population?
- Was the control selection performed before examining diabetes status?

These issues are fundamental to evaluating selection bias.

2.4 No clear matching strategy is described

The manuscript repeatedly states that a 1:3 case-control ratio was used, but a **1:3 ratio does not itself constitute matching**.

If controls were matched to cases, the matching variables and matching procedure must be reported.

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If controls were not matched, the manuscript should explicitly state that this was an **unmatched case-control study**.

The statistical analysis must correspond to the actual study design.

2.5 Lack of multivariable analysis

This is one of the most important methodological concerns.

The manuscript reports crude ORs for T2DM and several clinical/laboratory variables. However, dengue mortality can be influenced by multiple potential confounders, including:

- Age
- Sex
- Year of infection
- Dengue severity
- Hospitalization characteristics
- Other comorbidities
- Hypertension
- Renal disease
- Cardiovascular disease
- Obesity
- Laboratory abnormalities
- Clinical warning signs

The reported OR of 1.018 for T2DM is therefore a **crude association** unless adjustment was performed.

The authors should consider an appropriate multivariable logistic regression model, provided the sample size and number of events support the model.

At minimum, the manuscript should discuss the potential for confounding and clearly state that the reported OR is unadjusted if no multivariable analysis was performed.

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2.6 The manuscript overstates the meaning of $p = 0.947$

The study concludes that:

“type 2 diabetes mellitus is not a risk factor for mortality.”

The data demonstrate that the study **did not find a statistically significant association** between T2DM and dengue mortality.

This is different from proving that T2DM has no effect.

The wide confidence interval:

0.604–1.716

includes both a potentially protective association and a potentially harmful association.

A more scientifically appropriate interpretation would be:

“No statistically significant association between T2DM and dengue mortality was observed in this study population.”

The conclusion should avoid claiming definitive absence of risk.

2.7 Important discrepancy in the Discussion: OR 1.18 versus OR 1.018

The manuscript reports:

- Abstract: **OR 1.018**
- Results: **OR 1.018**
- Table 4: **OR 1.018**
- Table 6: **OR 1.018**
- Discussion: **OR 1.18**

The correct crude OR from the displayed 2×2 table is:

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$67 \times 79 / (26 \times 200) =$ approximately **1.018**.

Therefore, the value **1.18 in the Discussion appears to be an error** and must be corrected.

2.8 Serious inconsistency in persistent vomiting data

Table 7 reports:

- Cases with persistent vomiting = 13
- Cases without = 80
- Controls with = 20
- Controls without = 80

However, the control numbers total:

$20 + 80 = 100$, not 279.

For the control group to contain 279 participants, the “No” category would need to be **259**, assuming 20 controls had persistent vomiting.

This is a major data-table error.

The reported OR of 2.104 also needs to be recalculated after correcting the underlying frequency.

The authors must return to the original database and verify this variable.

2.9 Age eligibility is inconsistent with the age table

The Methods state that participants were aged:

“1 to 90 years”

However, Table 5 includes:

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“90 to 99 years old”

with one participant.

The authors must clarify whether:

- the upper age limit was 90 years, or
- patients older than 90 years were eligible.

The age category should also be correctly defined, for example:

- 1–9
- 10–19
- 80–89
- ≥ 90

if appropriate.

2.10 Age distribution is presented incorrectly

The manuscript states that the “70–79 age group” had 33 cases (8.9%).

But $33/372 = 8.9\%$.

Therefore, the percentage again appears to use the total study sample rather than the 93 cases.

Within the 93 cases:

$33/93 = 35.5\%$.

The authors must specify the denominator consistently.

2.11 Table numbering and descriptions are confused

The manuscript refers to:

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- Table 2 as mortality rate per year
- Table 3 as clinical/laboratory characteristics
- Table 4 as T2DM risk
- Table 5 as age
- Table 6 as T2DM risk again
- Table 7 as laboratory/clinical OR analysis

There appears to be duplication and misplaced table descriptions.

The authors should renumber all tables sequentially and ensure that every table is cited once and described correctly.

2.12 Duplication of T2DM analysis

The T2DM analysis is presented in both Table 4 and Table 6 with essentially identical data.

Unless the journal specifically requires separate tables, one table should be removed and the information consolidated.

2.13 SGOT and SGPT require clearer interpretation

The manuscript reports identical frequencies for SGOT and SGPT:

- Cases: 60
- Controls: 31
- OR: 14.545

Mathematically, identical 2×2 frequency distributions will produce identical crude ORs.

However, the authors should verify whether the database genuinely contains identical values or whether one variable was inadvertently copied from the other.

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The manuscript should also use standard terminology consistently:

- AST rather than SGOT
- ALT rather than SGPT

The older terminology can be retained in parentheses if appropriate.

2.14 Hyperalbuminemia requires clinical justification

The finding of hyperalbuminemia as a predictor of dengue mortality is potentially interesting, but the manuscript does not sufficiently explain:

- The laboratory reference range
- The threshold used to define hyperalbuminemia
- Whether albumin was measured at admission or later
- Whether timing differed between cases and controls
- Whether dehydration or hemoconcentration influenced the measurement

These details are important for interpreting the association.

2.15 Temporal relationship of laboratory variables is unclear

For a mortality case-control study, it is essential to know **when the laboratory measurements were obtained**.

For example:

- At admission?
- At first clinical evaluation?
- At the time of deterioration?
- Immediately before death?
- Maximum value during hospitalization?

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If measurements were obtained after severe disease had developed, these variables may be **markers of disease severity rather than independent predictors of mortality**.

The authors should explicitly define the timing of all clinical and laboratory variables.

2.16 Possible reverse causation / severity bias

The study aims to determine risk factors for mortality, but variables such as abdominal pain, thrombocytopenia, transaminase elevation, leukopenia, and albumin abnormalities may occur as manifestations of dengue severity.

Therefore, the manuscript should distinguish between:

- baseline risk factors,
- clinical warning signs,
- disease-severity markers, and
- complications occurring during hospitalization.

Calling all of these “risk factors” may be inappropriate unless temporality is demonstrated.

2.17 Dengue severity classification needs clarification

The Methods mention:

dengue with warning signs, dengue with alarm signs or severe dengue

There appears to be inconsistent terminology.

The authors should use an established dengue classification system and provide the precise operational definitions used.

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2.18 Important confounder: diabetes control

The authors appropriately acknowledge that they did not distinguish controlled versus uncontrolled diabetes.

However, additional diabetes-related variables should ideally be considered, such as:

- Duration of diabetes
- Antidiabetic treatment
- Glycemic control
- HbA1c, if available
- Diabetes complications
- Insulin use
- Renal complications

Without these data, the conclusion should be restricted to the presence/absence of recorded T2DM rather than the biological effect of diabetes itself.

2.19 Sample-size calculation is absent

The manuscript should provide a sample-size justification.

The authors should report:

- expected exposure prevalence,
- anticipated OR,
- alpha,
- power,
- case/control ratio,
- expected missing data,
- final sample size.

If all eligible cases during the study period were included and controls were selected retrospectively, this should be explicitly stated.

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2.20 Missing-data handling is insufficient

The manuscript states that incomplete clinical records were eliminated, but does not report:

- how many records were initially identified,
- how many were excluded,
- reasons for exclusion,
- number of incomplete records,
- whether missingness differed between cases and controls.

A participant selection flow diagram would substantially improve transparency.

3. KEY POINTS FOR THE AUTHORS

Correct all numerical inconsistencies before publication.

- Recalculate and verify every OR, 95% CI, and p-value from the original dataset.
 - Correct the T2DM OR discrepancy (**1.018 vs 1.18**).
 - Correct the persistent vomiting control denominator.
 - Correct sex percentages and clarify denominators.
 - Correct the age-group eligibility discrepancy.
 - Clearly define how controls were selected.
 - State whether the case-control design was matched or unmatched.
 - Consider multivariable logistic regression to account for important confounders.
-
- Avoid interpreting a non-significant result as proof that T2DM has no effect.
 - Define exactly when laboratory measurements were obtained.
 - Distinguish mortality predictors from markers of established severe dengue.
 - Clarify the diagnostic and severity classification criteria.
 - Provide an appropriate sample-size justification.
 - Provide the ethics committee/IRB approval number if available.

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- Improve English grammar, spelling, punctuation, and scientific terminology throughout.
- Correct duplicated tables and renumber the tables.
- Verify all references, especially references 25, 26, 30, 31, and 33.
- Ensure all cited studies actually support the statements made in the Discussion.
- Follow an appropriate reporting guideline such as **STROBE for observational studies**.

4. SIGNIFICANCE OF THE STUDY

The study has **potential scientific and regional significance** because it evaluates T2DM in relation to dengue mortality using data from OOAD Veracruz Sur over a five-year period.

The regional focus is potentially valuable because associations observed in one healthcare system or geographic population may not necessarily be identical to those observed elsewhere.

The reported lack of a statistically significant association between T2DM and mortality is also potentially informative, particularly because other published studies have reported different associations.

However, the current manuscript does not yet establish whether the observed result is attributable to a true absence of association, limited statistical precision, residual confounding, exposure misclassification, differences in diabetes severity, or characteristics of the selected control group.

Consequently, the significance of the findings will depend substantially on correction of the methodological and numerical problems.

5. SPECIFIC STATISTICAL COMMENTS

T2DM

The reported 2×2 table is:

Cases Controls

T2DM Yes 67 200

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Cases Controls

T2DM No 26 79

The crude OR is approximately:

OR = 1.018

This agrees with the value reported in Tables 4 and 6.

The 95% CI crosses 1 and $p = 0.947$; therefore, the study does not demonstrate a statistically significant crude association.

The authors should report this as a **lack of statistically significant association**, rather than definitively stating that T2DM is not a risk factor.

Thrombocytopenia

Reported:

OR 3.967; 95% CI 2.393–6.575; $p < 0.001$

The frequency data appear internally compatible with this crude OR. However, the interpretation should be cautious because thrombocytopenia may represent a manifestation of dengue severity rather than an independent pre-existing risk factor.

SGOT/AST and SGPT/ALT

Reported:

OR 14.545; 95% CI 8.263–25.606; $p < 0.001$

These are very large crude associations. The authors should verify the original data and laboratory definitions.

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If these laboratory abnormalities were measured after clinical deterioration, the interpretation should be changed from “risk factor” to “factor associated with mortality” or “marker associated with fatal disease,” depending on the timing.

Hyperalbuminemia

Reported:

OR 12.675; 95% CI 7.290–22.038; $p < 0.001$

The threshold for defining hyperalbuminemia and timing of measurement must be reported.

Hemoconcentration

Reported:

OR 1.260; 95% CI 0.785–2.022; $p = 0.337$

This does not demonstrate a statistically significant association.

Leukopenia

Reported:

OR 2.082; 95% CI 1.269–3.415; $p = 0.003$

This demonstrates a statistically significant crude association in the presented data, but confounding and temporality need consideration.

Mucosal bleeding

Reported:

OR 1.113; 95% CI 0.534–2.321; $p = 0.082$

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The manuscript should consistently describe this as **not statistically significant**.

Abdominal pain

Reported:

OR 8.955; 95% CI 5.240–15.304; $p < 0.001$

This is a strong crude association, but the authors should verify whether abdominal pain was recorded before progression to severe dengue and whether its clinical assessment was standardized.

6. MAJOR REVISION JUSTIFICATION

The manuscript requires **Major Revision** for the following reasons:

1. Data integrity concerns

Multiple discrepancies exist between frequencies and percentages, raising concerns about the accuracy of the reported results.

2. Incorrect or inconsistent denominators

Sex and age percentages appear to use the total sample denominator, while the text sometimes presents them as case-specific percentages.

3. Persistent vomiting table error

The control-group frequencies in Table 7 total only 100 rather than 279, requiring verification of the underlying data and recalculation of the OR and p-value.

4. T2DM OR inconsistency

The manuscript reports both 1.018 and 1.18 for the study's T2DM OR.

5. Inadequate control-selection description

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The manuscript does not sufficiently establish that controls represent the appropriate source population for the cases.

6. Insufficient adjustment for confounding

The analysis appears to rely mainly on crude ORs and does not adequately address potential confounders such as age, sex, severity, and other comorbidities.

7. Causal interpretation is too strong

A non-significant association should not be interpreted as definitive evidence that T2DM is not a risk factor.

8. Timing of exposure/clinical variables is unclear

Without knowing when laboratory and clinical variables were measured, it is difficult to establish whether they preceded mortality or merely reflected severe disease.

9. Methodological reporting is incomplete

Sample-size justification, participant selection, missing-data handling, control selection, and ethical approval details require improvement.

10. Scientific writing requires extensive correction

Numerous grammatical, spelling, terminology, formatting, and citation problems reduce clarity and reproducibility.

7. MINOR COMMENTS

Title

The title should be grammatically revised. A clearer version would be:

“Association Between Type 2 Diabetes Mellitus and Dengue Mortality in OOAD Veracruz Sur, Mexico, 2020–2024”

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This is preferable because the study ultimately reports an association analysis rather than establishing T2DM as a risk factor.

Abstract

The abstract should be rewritten to include:

- study design,
- study population,
- number of cases and controls,
- principal OR,
- 95% CI,
- p-value,
- main conclusion.

Keywords

The current keywords are insufficient. Consider:

Dengue; dengue mortality; type 2 diabetes mellitus; diabetes; case-control study; mortality; Veracruz; Mexico.

Introduction

The introduction should more clearly establish:

- what is already known about diabetes and dengue outcomes;
- what remains uncertain;
- why OOAD Veracruz Sur requires specific investigation;
- the precise research hypothesis.

Methods

The authors should provide enough information for another researcher to reproduce the study.

Results

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Avoid repeating the same results in the text and multiple tables.

Discussion

The discussion should distinguish:

- the current study's findings,
- findings from previous studies,
- possible explanations for differences,
- methodological limitations.

Conclusion

The conclusion should not claim that T2DM definitively has no effect on dengue mortality.

8. RECOMMENDATION

Recommendation: MAJOR REVISION

Rationale

The manuscript addresses a relevant clinical and epidemiological question and contains potentially useful regional data. The 93-case/279-control dataset and assessment of T2DM together with clinical and laboratory characteristics provide a potentially valuable contribution.

However, the current version contains **substantial numerical inconsistencies, an apparent error in the persistent-vomiting table, inconsistent denominators, inadequate description of control selection, insufficient consideration of confounding, unclear temporal relationships between clinical/laboratory variables and mortality, and overly strong interpretation of a non-significant T2DM association.**

The manuscript should **not be accepted in its present form**. The authors should first verify the original dataset, correct all tables and statistical calculations, clarify the study design and control selection,

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strengthen the statistical analysis, revise the interpretation, and undertake comprehensive language and reference editing.

If the authors satisfactorily address these issues and the corrected analyses support the reported findings, the manuscript could be reconsidered for publication.

Reviewer's key recommendation: The strongest issue is not the topic itself but **data/reporting reliability**. I would specifically ask the authors to provide the corrected raw 2×2 frequencies and recalculate **all ORs, CIs and p-values before the manuscript can be reconsidered.**