



PEER-REVIEW REPORT

Name of journal: *World Journal of Diabetes*

Manuscript NO: 73854

Title: Elevated levels of fructosamine are independently associated with SARS-CoV-2 reinfection: A 12-mo follow-up study

Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05445949

Position: Editorial Board

Academic degree: MD, PhD

Professional title: Assistant Professor, Chief Physician, Research Associate

Reviewer's Country/Territory: Serbia

Author's Country/Territory: China

Manuscript submission date: 2021-12-08

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-12-16 17:29

Reviewer performed review: 2021-12-16 17:50

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



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Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

The paper is well-organized and well-written. But the main obstacle is omitting of markers of glucose metabolism presence (morning glycemia, occurrence of diabetes or not, the effects of corticosteroid treatment in COVID relapsed patients if it was administered). I try to find several times the inclusion criteria and did not find the levels of glycemia, the data about diabetes presence, diabetes duration and treatment. It is non-sense to have a data about increased or decreased FMN levels, but have no info about diabetes presence or its treatment in such patients...



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Provenance and peer review: Unsolicited manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05420398

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: United States

Author's Country/Territory: China

Manuscript submission date: 2021-12-08

Reviewer chosen by: Jia-Qi Zhu

Reviewer accepted review: 2022-03-02 03:48

Reviewer performed review: 2022-03-02 20:36

Review time: 16 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



Peer-reviewer statements	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
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SPECIFIC COMMENTS TO AUTHORS

The authors present a retrospective, observational study of 146 Chinese patients that aimed to assess the association of serum fructosamine (FMN) levels and various COVID-19 related outcomes including the rate of reinfection with COVID-19 and overall mortality. The study topic is novel and very little or no literature has been published on the link between fructosamine and COVID-19 outcomes. The authors found that elevated FMN levels were associated with an increased risk of COVID-19 reinfection and increased mortality. The findings are indeed novel, but their clinical significance remains less clear. There were few total cases of reinfection, and the HR confidence intervals for reinfection were very wide, likely owing to a small sample size. However, these data are still potentially valuable and hypothesis generating at the least. I do, however, disagree with the authors conclusion about how to use these data. I do not think that trending FMN levels is practical, financially reasonable or of much clinical utility, to prognosticate COVID-19 reinfection risk. However, these data do support the notion that targeting euglycemia is of more acute importance, particularly in the post-COVID clinical course, since it appears that FMN levels may predispose individuals to reinfection. Thus, the clinical focus should be on maintaining consistent euglycemia, using standard point-of-care glucose checks. Recommend modifying the discussion/conclusion to reflect these comments.

Specific Comments - Advise changing the terminology of "COVID-19 relapse" to "COVID-19 reinfection". Relapse is confusing because it suggest that the virus has a chronic or latent stage, which it does not. Reinfection makes it clear that the virus was cleared and the patient was reinfected.

- The authors say that they used a "multivariate" cox regression analysis. While the



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variables included in the model are listed in the results section, these should first be stated in the methods section. The authors should also provide an explanation for why these variables were included - The following sentence belongs in the methods section: "In the COX regression model, disease-free survival (DFS) was used as the time variable, and relapse was used as the state variable" - It is unclear if the DFS analysis used a multivariate approach; please clarify. This is important because patients with elevated FMN were older, and this could be a major confounder. If a multivariate approach was used, please provide the results either as an expansion of table 2 or as a new table - Please provide HR for DFS rate - Figure 2 is not necessary, consider omitting; this information is already stated in the text - In the discussion, justification is given as to why FMN levels are a better representation of recent blood sugar levels; "In the COX regression model, disease-free survival (DFS) was used as the time variable, and relapse was used as the state variable." HbA1c reflects overall glycemic control over the past 2-3-months, while FMN reflects the overall glycemic control over the past 2-3-weeks. General blood glucose monitoring and HbA1c levels can not accurately contribute to a prediction index for recent glycemic control. But FMN is rapid and better reflects recent glycemic control." - I recommend moving part of this justification to the introduction to better frame the relevance of your study - Overall, the authors did a great job of conveying their findings. However, further review by a native English speaker would help with sentence structure and clarity



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Peer-review model: Single blind

Reviewer's code: 05429346

Position: Peer Reviewer

Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Turkey

Author's Country/Territory: China

Manuscript submission date: 2021-12-08

Reviewer chosen by: Jia-Qi Zhu

Reviewer accepted review: 2022-03-03 09:39

Reviewer performed review: 2022-03-15 11:44

Review time: 12 Days and 2 Hours

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input checked="" type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Re-review	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No



Peer-reviewer statements	Peer-Review: [<input checked="" type="checkbox"/>] Anonymous [<input type="checkbox"/>] Onymous Conflicts-of-Interest: [<input type="checkbox"/>] Yes [<input checked="" type="checkbox"/>] No
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SPECIFIC COMMENTS TO AUTHORS

Dear authors, Your study, 'Elevated Levels of Fructosamine are Independently Associated with Coronavirus Disease 2019 Relapse: a 12-month Followed-up Study 'is carefully reviewed. That's a good investigation, but there are some deficits have to be corrected: 1. Explain how the study size was arrived at 2. Give the inclusion-exclusion criteria, and the sources and methods of selection of participants. • Why were important parameters such as comorbid diseases, hs-CRP level not included in the study? In general, hs-CRP and glucose levels show a positive correlation. Therefore, patients with high hs-CRP levels may also have high fructosamine levels. • It is unclear whether the patients included in the study had diabetes mellitus or a disease causing hyperglycemia. • Corticosteroid therapy is an important initial therapy in COVID-19 treatment regimens. The treatment regimens received by the patients were not included in the study. I am wondering how many patients are receiving corticosteroid therapy (dosage and duration?). It is known that hyperglycemia and diabetes mellitus develop due to corticosteroid therapy. Depending on this, the expectation of a high level of fructosamine may be due to taking corticosteroid therapy. 3. Are the patients ICU (Intensive care unit) or non-ICU patients? How are their respiratory conditions? It is obvious that severe hypoxemia will impair blood glucose regulation. 4. Did patients with relapse have clinical symptoms? Is PCR positivity alone enough to say relapse? 5. The study was presented as a 12-month follow-up study and appears to have been conducted prospectively However, in the limitations of the study, it was written retrospectively. ('First, the study was a retrospective, single-center, and a small cohort study.') If the study was done retrospectively, why was the fructosamine level taken



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from these patients while being followed up for COVID-19? It's been a confusing situation.



RE-REVIEW REPORT OF REVISED MANUSCRIPT

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Academic degree: MD, PhD

Professional title: Assistant Professor, Chief Physician, Research Associate

Reviewer's Country/Territory: Serbia

Author's Country/Territory: China

Manuscript submission date: 2021-12-08

Reviewer chosen by: Jing-Jie Wang

Reviewer accepted review: 2022-05-01 07:56

Reviewer performed review: 2022-05-01 09:46

Review time: 1 Hour

Scientific quality	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
Language quality	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
Conclusion	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
Peer-reviewer	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous



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statements

Conflicts-of-Interest: [] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

The authors investigated potential relationship between blood levels of fructosamine and COVID-19 reinfection. They concluded that elevated levels of fructosamine are independently associated with COVID-19 reinfection. Please, think about omitting of paragraph as it is not linked with the topic...In addition, FMN levels are positively associated with the risk of periprosthetic joint infection and negatively associated with cancer risk. A previous study also demonstrated that FMN is a valuable marker for predicting adverse outcomes following total hip arthroplasty [16]. After the corrections are being made according to the reviewers questions and connotations, the paper is to me ready to be published.