Dear Editor,

We would like to resubmit the manuscript entitled "Elevated levels of fructosamine are independently associated with COVID-19 reinfection: A 12-month follow-up study" as an original article. We are grateful to you for giving us this chance to improve our manuscript and appreciate the insightful and constructive comments proposed by reviewers. All of these comments are valuable and helpful for improving the quality of our article, and they are of much guiding significance to our researches. The detailed point-by-point responses are listed below to acknowledge helps from the reviewers and denote where we made revisions, hoping to meet with your approval.

Responses to Reviewer 1:

1. *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-19 relapsed patients if it was administered).*

Response: Thank you for your professional comments on our article. We remarked the Table 1 Baseline characteristics of the study cohort which increased Diabetes mellitus, Corticosteroid therapy, and adjusted them in Table 2 Association of FMN levels with COVID-19 reinfection. After full adjustment, the elevated FMN group still showed an increased risk of reinfection (HR 6.249, 95% CI 1.377–28.351, *P* = 0.018; All *P* for trend 0.05).

We increased Appendix Table 1 Association of fructosamine levels with corticosteroid dose and Appendix Table 2 Association of fructosamine levels with corticosteroid duration, which show there have no statistical significance (all P＞0.05).

Table 1 Baseline characteristics of the study cohort

Variable	Total	Elevated FMN	Nonelevated FMN	*P*
Patients, n (%)	146	47 (68)	99 (32)	
Gender, n (%)				0.319
Male	72 (49)	26 (36)	46 (64)	
Female	74 (51)	21 (28)	53 (72)	
Age (yr)	49 (39–55)	53 (43–58)	47 (35–53)	0.008
Diabetes mellitus, *n* (%)	17 (12)	14 (82)	3 (18)	0.000
Hypertension, *n* (%)	18 (12)	8 (44)	10 (56)	0.023
Respiratory failure, *n* (%)	12 (8)	6 (50)	6 (50)	0.291
Corticosteroid therapy, *n* (%)	30 (21)	5 (17)	25 (83)	0.041
WBC (4.0×10^9–10.0×10^9/L)	4.64 (3.63–5.82)	5.06 (3.85–6.45)	4.58 (3.45–5.40)	0.067
CRP (<5 mg/L)	7.30 (5.0–25.60)	6.80 (5.0–34.90)	7.80 (5.0–23.60)	0.320
PNI	47.80 (44.26–50.58)	49.55 (46.05–50.95)	47.05 (44.05–49.55)	0.061
ALT (0–55 U/L)	20.50 (14.0–29.0)	22.00 (15.0–31.0)	19.00 (13.0–28.0)	0.138
AST (0–55 U/L)	23.00 (18.0–31.0)	25.00 (19.0–32.0)	22.00 (18.0–30.0)	0.016
SCR (45–84 μmol/L)	62 (50–74)	64 (55–73)	61 (50–75)	0.460
TC (3.60–5.70	4.24±0.77	4.11±0.79	4.30±0.76	0.176

mmol/L)				
TG (0.60–1.70 mmol/L)	1.16 (0.86–1.69)	1.22 (0.88–1.77)	1.14 (0.86–1.66)	0.239
HDL-C (1.09–2.27 mmol/L)	0.95 (0.80–1.16)	0.92 (0.76–1.16)	0.98 (0.83–1.16)	0.314
LDL-C (1.30–3.37 mmol/L)	2.30 (1.94–2.91)	2.22 (1.90–2.78)	2.32 (1.98–2.92)	0.242
Reinfection case, *n* (%)	11 (7.5)	8 (73)	3 (17)	0.008

Data presented as mean (SD) for normally distributed data and median (interquartile range) in non-normal distributed data. PNI = serum albumin (g/L) + 5× lymphocyte count (×10^9/L). *P* value was calculated using one-sample Kolmogorov–Smirnov test or *t*-test.

FMN: fructosamine; elevated FMN: upper third of FMN level; nonelevated FMN: lower two-thirds of FMN levels; CRP: C-reactive protein; PNI: Prognostic Nutritional Index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SCR: serum creatinine; TG: triglyceride; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol.

Table 2 Association of FMN levels with COVID-19 reinfection

FMN dichotomy	B	SE	HR	95% CI	*P*
Model 1	1.827	0.677	6.214	1.647–23.438	0.007
Model 2	1.898	0.759	6.674	1.507–29.544	0.012
Model 3	1.832	0.772	6.249	1.377–28.351	0.018

Model 1: Unadjusted. Model 2: Adjusted for age, gender, diabetes mellitus, corticosteroid therapy and hypertension. Model 3: Adjusted for Model 2 and acute liver failure, acute kidney failure, white blood cell count, C-reactive

protein, Prognostic Nutritional Index, and blood lipids. *P* value for HR with 95% CI was calculated by Cox regression models to indicate a significant association. FMN: fructosamine; HR: hazard ratio; CI: confidence interval.

Appendix Table 1 Association of fructosamine levels with corticosteroid dose

Variable	Total	Elevated FMN	Nonelevated FMN	*P*
Corticosteroid dose, *n*	146	47	99	0.139
0 mg	117	42	75	
4 mg	1	0	1	
10 mg	1	0	1	
15 mg	1	0	1	
34 mg	2	0	2	
40 mg	3	1	3	
41 mg	1	0	1	
48 mg	1	0	1	
80 mg	5	5	5	
104 mg	1	0	1	
120 mg	1	0	1	
136 mg	1	0	1	
160 mg	1	0	1	
184 mg	1	0	1	
192 mg	1	0	1	
200 mg	2	2	2	
208 mg	3	3	3	
244 mg	1	1	1	
264 mg	1	1	1	
328 mg	1	1	1	

***P* value was calculated using Pearson's χ^2 test.**

Appendix Table 2 Association of fructosamine levels with corticosteroid duration

Variable	Total	Elevated FMN	Nonelevated FMN	*P*
Corticosteroid duration, *n*	**146**	**47**	**99**	**0.258**
0 d	**117**	**42**	**75**	
1 d	**5**	**1**	**4**	
2 d	**6**	**2**	**4**	
3 d	**2**	**0**	**2**	
4 d	**2**	**1**	**1**	
5 d	**2**	**0**	**2**	
6 d	**1**	**0**	**1**	
7 d	**1**	**0**	**1**	
8 d	**5**	**0**	**5**	
9 d	**2**	**0**	**2**	
10 d	**2**	**0**	**2**	
22 d	**1**	**1**	**0**	

***P* value was calculated using Pearson's χ^2 test.**

2 *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.*

Response: We appreciate your comments. Diabetes were not exclude in the inclusion criteria which is our limitation, but we adjusted for diabetes. We are sorry for the missing data of diabetes duration and treatment.

<u>Responses to Reviewer 2:</u>

1. *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.*

   Response: Thank you very much for your advice. We increased "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" in DISCUSSION paragraph 2.

2. *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.*

   Response: We appreciate your suggestion. We changed all the terminology of "COVID-19 relapse" to "COVID-19 reinfection".

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

Response: We are obliged to you for your suggestion. We increased "Disease-free survival was used as the time variable, and relapse was used as the state variable, adjusted for age, gender, influencing factors such as diabetes mellitus, hypertension and corticosteroid therapy, clinical significance index such as acute liver failure, acute kidney failure, white blood cell (WBC) count, C-reactive protein, Prognostic Nutritional Index (PNI), and blood lipids" in METHODS.

4. *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.*

Response: We appreciate your advice. We have omited Figure 2, and the HR for DFS rate as follow.

Association of FMN levels with DFS rate

FMN dichotomy	B	SE	HR	95% CI	*P*
	0.109	0.190	1.115	0.769–1.618	0.565

***P* value for HR with 95% CI was calculated by Cox regression models to indicate a significant association. FMN: fructosamine; HR: hazard ratio; CI: confidence interval.**

5. *In the discussion, justification is given as to why FMN levels are a better representation of recent blood sugar levels. 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.

Response: We appreciate your suggestion. We have moved "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" to to the introduction.

6. *However, further review by a native English speaker would help with sentence structure and clarity.*

Response: Thank you for your suggestion. We reviewed it by a native English speaker again.

Responses to Reviewer 3:

1 *Explain how the study size was arrived at. Give the inclusion-exclusion criteria, and the sources and methods of selection of participants.*

Response: We appreciate your advice. We remarked the Figure 1 Flowchart of the study cohort which can explain how the study size was arrived at and contain the inclusion-exclusion criteria, and the sources and methods of selection of participants.

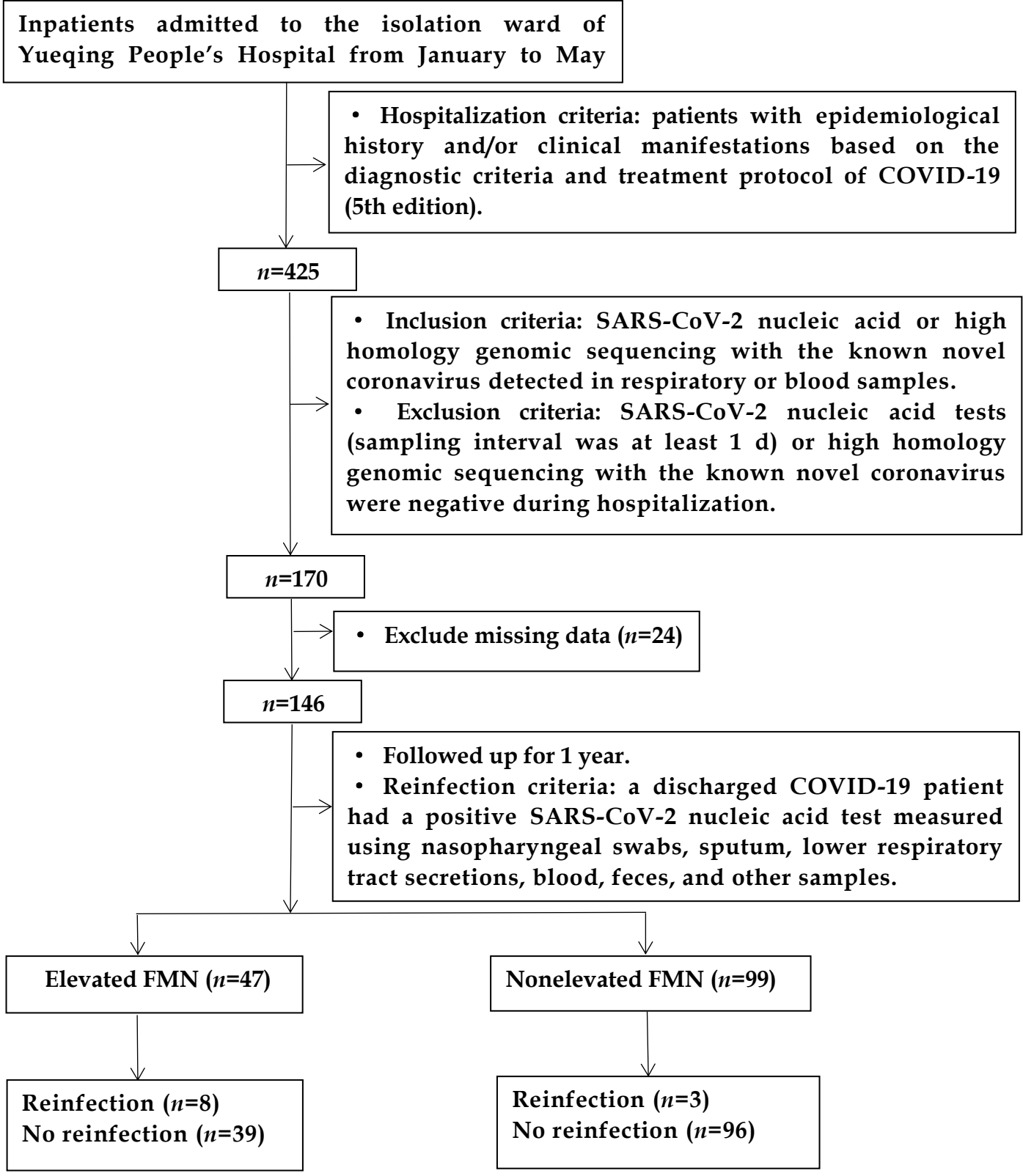

Figure 1 Flowchart of the study cohort.

2 *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.

Response: Thank you for your professional comments on our article. We remarked the Table 1 Baseline characteristics of the study cohort with CRP, Diabetes mellitus, Corticosteroid therapy, and adjusted them in Table 2 Association of FMN levels with COVID-19 reinfection. After full adjustment, the elevated FMN group still showed an increased risk of reinfection (HR 6.249, 95% CI 1.377–28.351, *P* = 0.018; All *P* for trend 0.05).

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Female	74 (51)	21 (28)	53 (72)	
Age (yr)	49 (39–55)	53 (43–58)	47 (35–53)	0.008
Diabetes mellitus, *n* (%)	17 (12)	14 (82)	3 (18)	0.000
Hypertension, *n* (%)	18 (12)	8 (44)	10 (56)	0.023
Respiratory failure, *n* (%)	12 (8)	6 (50)	6 (50)	0.291
Corticosteroid therapy, *n* (%)	30 (21)	5 (17)	25 (83)	0.041
WBC (4.0×10^9–10.0×10^9/L)	4.64 (3.63–5.82)	5.06 (3.85–6.45)	4.58 (3.45–5.40)	0.067
CRP	7.30 (5.0–25.60)	6.80 (5.0–34.90)	7.80 (5.0–23.60)	0.320

(<5 mg/L)				
PNI	47.80 (44.26–50.58)	49.55 (46.05–50.95)	47.05 (44.05–49.55)	0.061
ALT (0–55 U/L)	20.50 (14.0–29.0)	22.00 (15.0–31.0)	19.00 (13.0–28.0)	0.138
AST (0–55 U/L)	23.00 (18.0–31.0)	25.00 (19.0–32.0)	22.00 (18.0–30.0)	0.016
SCR (45–84 μmol/L)	62 (50–74)	64 (55–73)	61 (50–75)	0.460
TC (3.60–5.70 mmol/L)	4.24±0.77	4.11±0.79	4.30±0.76	0.176
TG (0.60–1.70 mmol/L)	1.16 (0.86–1.69)	1.22 (0.88–1.77)	1.14 (0.86–1.66)	0.239
HDL-C (1.09–2.27 mmol/L)	0.95 (0.80–1.16)	0.92 (0.76–1.16)	0.98 (0.83–1.16)	0.314
LDL-C (1.30–3.37 mmol/L)	2.30 (1.94–2.91)	2.22 (1.90–2.78)	2.32 (1.98–2.92)	0.242
Reinfection case, *n* (%)	11 (7.5)	8 (73)	3 (17)	0.008

Data presented as mean (SD) for normally distributed data and median (interquartile range) in non-normal distributed data. PNI = serum albumin (g/L) + 5× lymphocyte count (×10^9/L). *P* value was calculated using one-sample Kolmogorov–Smirnov test or *t*-test.

FMN: fructosamine; elevated FMN: upper third of FMN level; nonelevated FMN: lower two-thirds of FMN levels; CRP: C-reactive protein; PNI: Prognostic Nutritional Index; ALT: alanine aminotransferase; AST: aspartate aminotransferase; SCR: serum creatinine; TG: triglyceride; TC: total cholesterol; HDL-c: high-density lipoprotein cholesterol; LDL-c:

low-density lipoprotein cholesterol.

Table 2 Association of FMN levels with COVID-19 reinfection

FMN dichotomy	B	SE	HR	95% CI	*P*
Model 1	1.827	0.677	6.214	1.647–23.438	0.007
Model 2	1.898	0.759	6.674	1.507–29.544	0.012
Model 3	1.832	0.772	6.249	1.377–28.351	0.018

Model 1: Unadjusted. Model 2: Adjusted for age, gender, diabetes mellitus, corticosteroid therapy and hypertension. Model 3: Adjusted for Model 2 and acute liver failure, acute kidney failure, white blood cell count, C-reactive protein, Prognostic Nutritional Index, and blood lipids. *P* value for HR with 95% CI was calculated by Cox regression models to indicate a significant association. FMN: fructosamine; HR: hazard ratio; CI: confidence interval.

3 *I am wondering how many patients are receiving corticosteroid therapy (dosage and duration?).*

Response: Thank you for your professional comments on our article. We increased Appendix Table 1 Association of fructosamine levels with corticosteroid dose and Appendix Table 2 Association of fructosamine levels with corticosteroid duration, which show there have no statistical significance (all P＞0.05).

Appendix Table 1 Association of fructosamine levels with corticosteroid dose

Variable	Total	Elevated FMN	Nonelevated FMN	*P*
Corticosteroid dose, *n*	146	47	99	0.139
0 mg	117	42	75	
4 mg	1	0	1	
10 mg	1	0	1	

15 mg	1	0	1
34 mg	2	0	2
40 mg	3	1	3
41 mg	1	0	1
48 mg	1	0	1
80 mg	5	5	5
104 mg	1	0	1
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136 mg	1	0	1
160 mg	1	0	1
184 mg	1	0	1
192 mg	1	0	1
200 mg	2	2	2
208 mg	3	3	3
244 mg	1	1	1
264 mg	1	1	1
328 mg	1	1	1

P value was calculated using Pearson's χ^2 test.

Appendix Table 2 Association of fructosamine levels with corticosteroid duration

Variable	Total	Elevated FMN	Nonelevated FMN	*P*
Corticosteroid duration, *n*	146	47	99	0.258
0 d	117	42	75	
1 d	5	1	4	
2 d	6	2	4	
3 d	2	0	2	
4 d	2	1	1	
5 d	2	0	2	

6 d	**1**	**0**	**1**
7 d	**1**	**0**	**1**
8 d	**5**	**0**	**5**
9 d	**2**	**0**	**2**
10 d	**2**	**0**	**2**
22 d	**1**	**1**	**0**

***P* value was calculated using Pearson's χ^2 test.**

4 *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.*

Response: We appreciate your suggestion. They are not ICU patients. We increased the respiratory failure in table 1 and there was significant difference in respiratory failure with different group of fructosamine (all *P* < 0.05) (Table 1). We adjusted it in Table 2 Association of FMN levels with COVID-19 reinfection. After full adjustment, the elevated FMN group still showed an increased risk of reinfection (HR 6.249, 95% CI 1.377–28.351, *P* = 0.018; All *P* for trend 0.05).

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Diabetes mellitus, *n* (%)	**17 (12)**	**14 (82)**	**3 (18)**	**0.000**
Hypertension,	**18 (12)**	**8 (44)**	**10 (56)**	**0.023**

n (%)				
Respiratory failure, *n* (%)	**12 (8)**	**6 (50)**	**6 (50)**	**0.291**
Corticosteroid therapy, *n* (%)	**30 (21)**	**5 (17)**	**25 (83)**	**0.041**
WBC (4.0×10^9–10.0×10^9/L)	**4.64 (3.63–5.82)**	**5.06 (3.85–6.45)**	**4.58 (3.45–5.40)**	**0.067**
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TG (0.60–1.70 mmol/L)	**1.16 (0.86–1.69)**	**1.22 (0.88–1.77)**	**1.14 (0.86–1.66)**	**0.239**
HDL-C (1.09–2.27 mmol/L)	**0.95 (0.80–1.16)**	**0.92 (0.76–1.16)**	**0.98 (0.83–1.16)**	**0.314**
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Model 1: Unadjusted. Model 2: Adjusted for age, gender, diabetes mellitus, corticosteroid therapy and hypertension. Model 3: Adjusted for Model 2 and acute liver failure, acute kidney failure, white blood cell count, C-reactive protein, Prognostic Nutritional Index, and blood lipids. *P* value for HR with 95% CI was calculated by Cox regression models to indicate a significant association. FMN: fructosamine; HR: hazard ratio; CI: confidence interval.

5 *Did patients with relapse have clinical symptoms? Is PCR positivity alone enough to say relapse?*

Response: We appreciate your suggestion. We increased Appendix Table 3 Number of clinical manifestations between different fructosamine levels as follow.

Appendix Table 3 Number of clinical manifestations between different fructosamine levels

Variable	Total	Elevated FMN	Nonelevated FMN
Clinical manifestations, n	11	8	3
weakness	1	1	0
cough	3	2	1
asymptomatic	3	2	1
chest tightness	2	2	0
sore throat	2	1	1

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

Response: Thank you very much for your reminding. We are sorry for the mistake, the study was prospectively.

Responses to Revision Reviewer:

1 *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.*

Response: Thank you very much for your reminding. We will omit the paragraph.

2 *After the corrections are being made according to the reviewers questions and connotations, the paper is to me ready to be published.*

Response: We appreciate your suggestion. We have provided point to point answer to all reviewers.