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Comparing the outcomes of treatment with INF-β 1-a (interferon beta-1a) and IFN-β 1-b (interferon beta-1b) among COVID-19 inpatients

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ABSTRACT

Background: IFNβs are known as one of the most promising drugs used for COVID-19 treatment. This study aimed to investigate the effects of treatment with INF-β 1-a (interferon beta-1a) and IFN-β 1-b (interferon beta-1b) on COVID-19 inpatients.

Methods: In this study, we retrospectively evaluated the clinical treatment outcomes of 100 patients with COVID-19 who received IFN-β 1-a and IFN-β 1-b during their hospitalization period. The rate of discharge from the hospital was considered equal to the clinical improvement and then evaluated as a primary outcome. Moreover, mortality, ICU admission and length of ICU stay, frequency of intubation and use of mechanical ventilation, duration of hospitalization, laboratory factors, and medications were assessed as secondary outcomes.

Results: The median discharge time of IFN-β 1a recipients was approximately equal to that of IFN-β 1-b recipients as 9 (5–10) days and 7 (5–11) days, respectively (HR = 2.43, P = 0.75).

Mortality rate was also estimated as 10% among IFN-β 1-a recipients and 14% among IFN-β 1-b recipients, which was not statistically significant (p = 0.190). ICU hospitalization rate for the IFN-β 1-a recipients and IFN-β 1-b recipients was 26% and 36%, respectively. In addition, no significant difference was found between these two intervention groups in terms of ICU length of stay (1 (0–2) vs. 1 (0–4.25(, respectively,) P = 0.357). There was no significant difference between the two study groups in terms of frequency of mechanical ventilation and length of hospital stay.

Conclusion: There was no significant difference between the two groups in terms of shortening the disease time, clinical improvements and other outcomes.

1. Introduction

The novel coronavirus 2019 (COVID-19) has firstly emerged in China in December 2019 [1]. Accordingly, it was indicated that it was caused by the acute respiratory syndrome-the coronavirus SARS-CoV-2, and hence was announced as a global pandemic on March 11, 2020 by the World Health Organization (WHO) [2].

Severe manifestations of COVID-19 were found to be associated with the combination of direct tissue damage by the virus's replication and cytokine storms [3].

Despite conducting many efforts to find a promising treatment worldwide, there is no proven effective treatment for this disease yet.

Up to now, several drugs, including antivirals, have been evaluated for their therapeutic efficacy. Accordingly, IFNs-α / β are broad-spectrum antivirals that have a direct inhibitory effect on virus replication and also help the immune system in clearing the virus [4].

In vitro studies of interferon type I (IFN I) have shown their inhibitory effects on SARS-CoV-2 replication and reduction of viral load [5]. In several clinical trials, interferons have been found to be effective on the treatment of COVID-19 [6,7]. Additionally, IFN-β is currently

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recommended as a promising treatment option in some severe cases of COVID-19 [8].

Recombinant IFN-β is produced in both animal and bacterial hosts known as IFN-β 1-a and IFN-β 1-b, respectively. Thus, IFN-β 1-a, not IFN-β 1-b, is glycosylated. Therefore, it can be said that IFN-β 1-a is less immunogenic [9].

SARS-CoV-2 infection has two-phase courses; viral proliferation and severe inflammatory syndrome characterized by a dramatic rise of circulating pro-inflammatory cytokines IFN-γ, TNF-α, IL-6, IL-1 in subgroup of patients with severe COVID-19 [10].

Type I IFNs are cytokines with innate anti-viral defense. Type I IFN includes IFN-α and IFN-β. IFN-β is produced by bronchial epithelial cells in response to viral infection.

Type I IFN binds the surface of infected cells and promotes the induction of more than 1,000 different IFN-inducible genes (ISGs) that prevent virus RNA synthesis or virion get together and release and virus protein trafficking [11].

The superiority of IFN-β 1-a over IFN-β 1-b has been demonstrated in the clinical improvement of COVID-19 disease [12]; however, the evidence for this superiority is very limited.

Based on the possible therapeutic effects of interferons as well as the administration of IFN-β in several cases in COVID-19 inpatients receiving two different IFN-β types, i.e. IFN-β 1-a and IFN-β 1-b, the challenge among our hospital physicians is about which type of interferon beta is better in the current study, we then decided to compare the effects of these two types of IFN-βs on patients with moderate to severe types of nCoV-2019 in a retrospective study.

2. Methods and materials

The present retrospective study was performed on 100 patients with moderate and severe types of COVID-19 admitted to Ayatollah Rouhani Hospital, Babol, Iran, from 22 September 2020 to 20 march 2021 (The second half of 1399 in the Persian Calendar).

Adult patients' data (≥18 years old) with positive PCR or clinical and radiological confirmation of the disease (clinical symptoms/signs of pneumonia, including dyspnea, cough, fever, and lung involvement in chest imaging), and those who received interferon, were recorded. A missing data was defined as the exclusion criterion of the study. The participants were selected via convenience sampling.

Fifty inpatients received a single dose of IFN-β 1-a (ReciGen, CinnaGen Co., Iran) with subcutaneous injections of 44 μg (12,000,000 IU) every other day during their hospitalization period for 5 days. Fifty other patients received IFN-β 1-b (Ziferon®, Zist Daru Daneh Co., Iran) with subcutaneous injections of 0.25 mg (8,000,000 IU), every other day for 5 days. National protocol of using drugs and other supportive care such as fluid therapy, prevention of deep vein thrombosis and stress ulcer, treatment of electrolyte disorders, and antibiotic therapy were considered in terms of the hospital protocols.

The included patients' demographic data, underlying diseases, symptoms at the time of onset of the disease, vital signs, laboratory and radiographic data upon the admission, and other medications received upon admission were recorded.

The parameter measured as the primary outcome was the clinical improvement of patients. In the present study, hospital discharge was considered as equal to clinical improvement.

Moreover, mortality, improvement in oxygen saturation level, frequency of mechanical ventilation use, length of hospital stay, and laboratory factors were evaluated as secondary outcomes.

2.1. Statistical analysis

To make a difference during these 2 days until clinical improvement with a power of 85%, with a 10-day estimation to reach clinical response, 50 patients were approximately designated in each group.

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right)^2 \left(\delta_1^2 + \delta_2^2\right)}{\left(\mu_1 - \mu_2\right)^2}$$

SD1, SD2 = 5 , μ1- μ2 = 2 ,Alfa = 0.05, Beta = 0.2 , Z1-a/2 = 1.96, Z1-B = 0.84

Continuous variables and categorical variables were expressed using median and interquartile range (IQR), as well as frequency and percentage, respectively. To compare continuous variables between the study groups, Mann-Whitney *U* test was used. While Chi-square test was utilized to compare categorical variables in SPSS Ver. 17.

Thereafter, Kaplan-Meier and Nelson-Aalen curves along with log rank test were used to compare the discharge rates between the two groups. We also used the Cox proportional hazard method, to estimate the hazard ratio of discharge and their confidence interval. Then, the Schoenfeld residual-based test and a graph showing the observed values of the discharge rate versus the predicted values were applied to examine the proportion of proportional hazards for the Cox model. Accordingly, all these analyses were performed in STATA software Ver. 15.

The present study was approved by the Ethics Committee of Babol University of Medical Sciences with the ID IR.MUBABOL.REC.1399.232.

2.1.1. Results

The median and interquartile range of the participants' age was calculated as 68 (51–76.25). Of note, 48% were males and 10% of them were smokers. In terms of demographic data, there was no significant difference between the study groups. The most common underlying comorbidities included hypertension, ischemic heart disease, and diabetes. In addition, shortness of breath, cough, and fever were the most common symptoms of this disease upon admission, respectively. (Table 1)

The median time of clinical improvement after intervention determined by discharge, was 9 days and 7 days in the two groups, respectively; however, this difference was not statistically significant (p = 0.346). (Table 2)

The number of deaths in the studied patients was 12 cases, of whom 5 and 7 were seen in the IFN-β 1-a and IFN-β 1-b groups, respectively.

Moreover, the median time of death in both the FN-β 1-a and IFN-β 1-b recipients was calculated as 7 and 12 days since the start of the interferon intervention, respectively. (p = 0.190)

The ICU admission number in the IFN-β 1-a and IFN-β 1-b groups was 13 and 18 patients, respectively (Mean: 2.81 ± 5.5 days). Accordingly, there was no significant difference between the two groups in terms of the length of ICU stay. (p = 0.357)

Fifteen of the a hundred patients and thirty-three of the same number of patients required invasive and non-invasive mechanical ventilation, respectively, and there was no significant difference between the two groups in terms of this factor.

The discharge rate of the IFN-β 1-a recipients was approximately equal to that of the IFN-β 1-b recipients (HR = 2.34; P = 0.75). The results of Kaplan-Meier curve and Log-Rank test also showed no difference between the IFN-β 1-a recipients and IFN-β 1-b recipients in terms of their discharge rates. (P = 0.69) (Fig. 1).

The discharge rate in both groups was the same up to day 10, but the instant discharge rate rapidly decreased in the IFN-β 1-b group after the 10th day. On the other hand, the same rate in the IFN-β 1-increased approximately until day 17 and then decreased with a milder slope compared to the IFN-β 1-b group (Fig. 2).

Table 3 shows the results of the Cox regression model. In addition, the results of the Schoenfeld residual-based test and a graph showing the observed values of the discharge rate versus the predicted values showed that the presumption of proportional hazards for the Cox model was established.

Among the drugs used to treat COVID-19 in patients, remdesivir, atazanavir, dexamethasone, and plasma covid were found to be effective

Table 1
Baseline characteristics of patients.

Characteristics	Total (N = 100)	IFN-β 1-a (N = 50)	IFN-β 1-b (N = 50)	P-value
Age, median (IQR)—year	68(51.25–76)	68(55.25–78)	67(51–75.25)	0.506
Male sex—no. (%)	48	23 (46)	25 (50)	0.689
Smoking—yes. (%)	10	(8)4	(12)6	0.505
Symptoms at admission: n (%)				
Dyspnea	77	39(78)	38(76)	0.812
Fever	58	29(58)	29(58)	1
Cough	59	31(61)	28(56)	0.542
Diarrhea	8	5(10)	3(6)	0.461
Duration of symptoms before presentation, median (IQR)—day	3(1.73–7)	3(1.73–7)	4(1.25–7)	0.408
Underlying conditions—no. (%)				
Diabetes	35	19(38)	16(32)	0.529
Hypertension	45	23(46)	22(44)	0.841
Coronary heart disease	43	21(42)	22(44)	0.312
Chronic kidney disease	8	6(12)	2(4)	0.145
Malignancy	7	3(6)	(8)4	0.145
Body temperature (on admission), median (IQR)—°C	36.8(36.5–37.5)	36.8(36.5–37.1)	37(36.5–37.65)	0.188
Heart rate median (IQR)	84(78–99.75)	83.5(75–94.75)	85(80–100)	0.229
Respiratory rate median (IQR)	20(18–24)	20(18–24)	20(18–24)	0.504
Systolic blood pressure < 90 mm Hg—no. (%)	120(100–130)	115(100–130)	120(100–130)	0.789
Oxygen saturation (SpO2)—median (IQR)	95(92–97)	96(92–97)	95(91.75–97)	0.196
Venous PaO2, median (IQR)	33(25.5–46)	32.5(26.25–48.25)	33(25–44)	0.831
Venous PCO2, median (IQR)	45(39–52)	44.5(38.75–52)	46(40–53)	0.867
Venous HCO3, median (IQR)	25.9(23.1–30.35)	26.2(23.7–30.32)	25.4(21.1–30.6)	0.564
White blood cell count (×10 − 9/L)—median (IQR)	8600(5300–12400)	7300(5300–12400)	8800(5525–13300)	0.858
Lymphocyte count (×10 − 9/L)—median (IQR)	1100(800–1500)	1100(800–1500)	1150(825–1875)	0.363
Neutrophil count (×10 − 9/L)—median (IQR)	5900(3500–9250)	5800(3350–9750)	6150(3700–8875)	0.821
Platelet count ($\times 10^{-9}$/L)—median (IQR)	213000(155000–279500)	209500(148500–280000)	228000(162000–280000)	0.452
Hemoglobin (g/dl) median (IQR)	12.4(10.2–13.5)	12.1(9.9–13.75)	12.4(10.4–13.2)	0.925
Creatinine (mg/dl)—median (IQR)	1(0.35–1.5)	1.1(0.9–1.625)	1(0.8–1.3)	0.172
Aspartate aminotransferase (AST) (U/L)—median (IQR)	26(15–34)	35(25–56)	34(25–54)	0.561
Alanine Aminotransferase (ALT) (U/L)—median (IQR)	34.5(25–54)	30(17–41)	25(14–32)	0.242
Blood urea nitrogen (BUN) mg/dL—median (IQR)	22(14.25–46)	22(15–47)	22(14–29)	0.290
C-Reactive Protein (CRP) mg/L —median (IQR)	55(29–130.75)	48(21–90)	70(33–165)	0.176
Erythrocyte sedimentation rate (ESR)—median (IQR)	33.5(18.5–50)	30(15–50)	40(25–54)	0.172
Percentage of lung involvement—median (IQR)	30 (15–55)	32.5(15–55)	27.5(10–52.25)	0.280

*Continuous variables are demonstrated as median (interquartile range (IQR)) and categorical variables as frequencies and percentages. Continuous variables were compared between the groups by Mann Whitney *U* test. The Fisher's exact test was applied for comparison of categorical variables

Table 2
Outcomes and complications.

Characteristics	IFN-β 1-a (N = 50)	IFN-β 1-b (N = 50)	P-value
All-cause mortality at day 28 no (%)	5(10)	7(14)	0.538
admission—no (%)ICU	13(26)	18(36)	0.280
Invasive mechanical ventilation—no (%)	6(12)	9(18)	0.401
Non-invasive ventilation (NIV) —no (%)	17(34)	16(32)	0.832
ICU stay—median no. of days (IQR)	1(0–3)	1(0–2)	1(0–4.25)
Hospital stay—median no. of days (IQR)	10(8–13)	10(7–14)	0.819
Time from enrollment to discharge (clinical response)—median no. of days (IQR)	9(5–10)	7(5–11)	0.346
Time from enrollment to death—median no. of days (IQR)	7(5.50–8.50)	12(6–25)	0.190

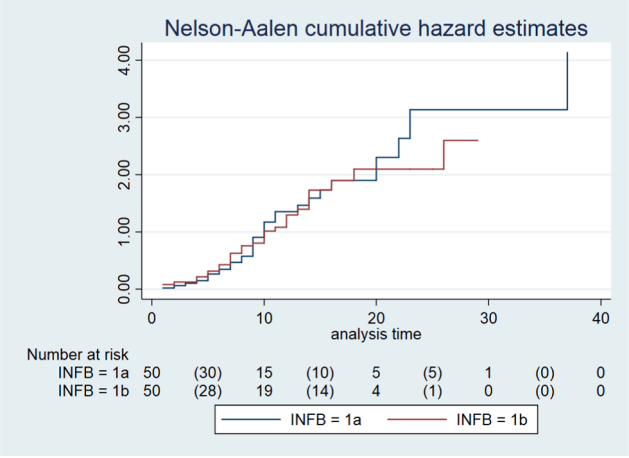

Fig. 1. Comparison of cumulative hazard estimates of discharging between COVID-19 patients receiving either IFN-β 1-a or IFN-β 1-b.

on the discharge rate of these patients. Notably, the discharge rate among the remdesivir recipients was twice the control group (HR = 2.34; P < 0.0001).

The same rate among the atazanavir recipients was 67% higher than that of the control group (HR = 1.67; P = 0.054).

On the other hand, the same rate was approximately 58% higher among the dexamethasone recipients compared to the control group (HR = 1.58; P = 0.009).

Finally, the discharge rate among the plasma covid recipients was 3 times more than that of the control group (HR = 3.67; P = 0.001).

Table 4 shows the number of the discharged patients, the discharge rate, and the 95% confidence interval. Correspondingly, these indicators were calculated according to the type of drug given to the patient.

According to this table, the highest discharge rate belonged to the IFN-β 1-a, remdesivir, and plasma recipients, respectively. While the lowest discharge rate was also related to the IFN-β 1-a + dexamethasone or IFN-β 1-b, remdesivir, and dexamethasone recipients, respectively.

3. Discussion

The present study evaluated the treatment outcomes of IFN-β 1-a and

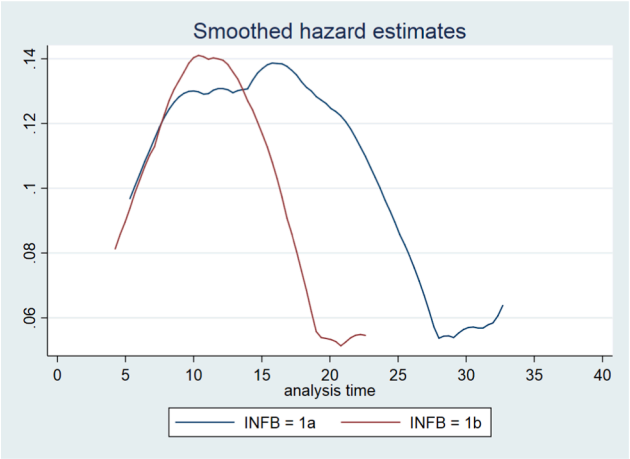

Fig. 2. Instantaneous hazard estimates for patients with COVID-19 receiving either IFN-β 1-a or IFN-β 1-b.

Table 3
Cox Regression model reveals the association of medication used by COVID-19 patients and discharging hazard.

Variables	Hazard Ratio	95% CI	P-value
IFN-β1b1a	Ref1.07	Ref0.71 to 1.61	0.75
RemdesivirNoYes	Ref2.34	Ref1.49 to 3.69	<0.0001
AtazanavirNoYes	Ref1.67	Ref0.99 to 2.83	0.054
DexamethasoneNoYes	Ref1.58	Ref1.39 to 1.87	0.009
Plasma COVIDNoYes	Ref3.67	Ref1.67 to 8.03	0.001

CI: Confidence Interval; Ref: Reference Category

IFN-β 1-b for the COVID-19 patients. The findings showed that no statistically significant difference exists between the two groups in terms of time of clinical improvement, survival rate, and discharge rate. Although the discharge rate among the IFN-β 1-a and IFN-β 1-b recipients was the same and ascending until day 10 from the tenth day onwards, the instantaneous discharge rate in FN-β 1-b rapidly decreased. However, the same rate almost increased in the IFN-β 1-a f group until day 17.

Type I IFNs play an important role in the antiviral response and modulate subsequent adaptive immune responses, although three major types of IFNs, type I, II and III, have been identified.

The antiviral activity of 22 agents including host-based IFNs (IFN β-1a, IFN β-1b, IFN α-2a and IFN γ-1B) was examined in Yuan et al.'s study. Based on the plaque reduction method, EC50 of these factors was determined. The strongest IFNs were IFN β-1b (EC50 = 31.2 IU / ml) and IFN β-1a (EC50 = 70.8 IU / ml) [10].

Based on this, it seems that the administration of IFN I (subgroup IFN-β) can be effective in COVID-19 disease. However, in the comparison of A and B in this study, no significant difference was found in the clinical improvement of patients, but this difference is in the availability of drugs and the cost of preparing these two types of interferons. Other researches have been conducted in Iran in this regard.

A clinical trial compared both IFNβ1-a and IFNβ1-b receiving groups with a control group at Loghman Hospital, Tehran, in April 2020. The results reported a significant difference between IFN-β 1-a recipients and the control group in terms of clinical recovery, as there was no significant difference between the IFN-β 1-b group and the control group [13] . Apart from the fact that the observed difference with the results of the present study may possibly be due to the studies' methodology, the present study also showed a difference in favor of IFNβ1-a; however, it was not statistically significant.

In another study with an IFN β-1-b group and a control group, the clinical recovery time in the IFN-β 1-a group was significantly shorter than that of the control group [6].

The present study found no significant difference between the two studied groups in terms of the number of ICU patients, length of ICU stay, and number of patients requiring invasive mechanical ventilation. The results of a previous study performed in Imam Khomeini Hospital in Tehran reported that the rate of ICU admission in the control group was significantly higher than that of the IFN group; however, there was no significant difference between these two groups in terms of lengths of hospital stay and ICU stay [6].

The present study also observed no significant difference between the IFN-β 1-a and IFN-β 1-b groups in terms of overall mortality on day 28; however, the number of deaths in the IFNβ-1a and IFN-β 1-b groups was 5 (10%) and 7 (12%), respectively. The median days between the start of interferon treatment to death among the deceased patients in the IFN-β 1-a and IFN-β 1-b groups were 7 and 12 days, respectively.

In the secondary outcomes of our study, such in the primary outcome, there was no significant difference between the two groups.

In another study, a total of 19 patients died during the study. Additionally, in-hospital mortality rate was lower in both IFN-β 1-a (20%) and IFN-β 1-b (30%) groups compared to the control group (45%), which was not statistically significant [12].

The mortality rate due to all causes on day 28 in Imam Khomeini Hospital in Tehran was reported as 6.06% and 18.18% in the interferon and control groups, respectively [6].

In the present study, there was no difference between the IFN-β 1-a and IFN-β 1-b groups in terms of median length of hospital stay.

Table 4
Rate and number of discharged patients with COVID-19 based on medications strata.

IFN-β	Remdesivir	Atezonovir	Dexamethasone	Plasma COVID	Discharge	TDT	Rate	95% CI
1a	No	No	No	No	26	294	0.09	0.06 to 0.13
1a	No	No	No	Yes	2	10	0.20	0.05 to 0.80
1a	No	No	Yes	No	5	78	0.06	0.03 to 0.15
1a	No	Yes	No	No	5	35	0.14	0.06 to 0.34
1a	Yes	No	No	No	3	17	0.18	0.06 to 0.55
1a	Yes	No	No	Yes	1	2	0.50	0.07 to 3.50
1a	Yes	Yes	Yes	No	1	7	0.14	0.02 to 1.00
Total	–	–	–	–	45	463	0.097	0.07 to 0.13
1b	No	No	No	No	27	288	0.09	0.06 to 0.14
1b	No	No	Yes	No	3	38	0.08	0.02 to 0.24
1b	No	Yes	No	No	4	45	0.09	0.03 to 0.24
1b	No	Yes	No	Yes	1	4	0.25	0.04 to 1.80
1b	No	Yes	Yes	No	1	10	0.10	0.01 to 0.71
1b	Yes	No	No	No	2	13	0.15	0.04 to 0.61
1b	Yes	No	Yes	No	1	16	0.06	0.01 to 0.44
1b	Yes	Yes	Yes	No	1	5	0.20	0.03 to 1.40
Total	–	–	–	–	43	453	0.094	0.07 to 0.13

TDT: Total Discharge Time; CI: Confidence Interval.

In a previous study conducted at Loghman Hospital, there was no difference between the IFN-β 1-a and IFN-β 1-b groups in terms of the median days of hospital stay; however, a significant difference was found between the groups receiving interferon and the control group [6].

There was no difference among vital signs, laboratory, and ABG findings of the IFN-β 1-a and IFN-β 1-b recipients.

It is noteworthy that plasma covid, remdesivir, atazanavir, and dexamethasone had the greatest effects on the rate of discharge and clinical improvement of the COVID-19 patients, respectively. Among the various drug combinations, the highest discharge rates were observed among the patients receiving IFN-β 1-a, remdesivir, and plasma covid.

There are studies conducted on the efficacy of using the improved plasma of SARS-CoV-2 survivors [14], remdesivir [15], atazanavir [16], and dexamethasone [17] for the treatment of COVID-19 patients. Correspondingly, they revealed that the above-mentioned drugs can improve clinical outcomes in patients with moderate to severe types of COVID-19.

One of the limitations of our study was the retrospective design of the study, which led to the following:

Inferior level of evidence compared with the prospective studies.

Control subjects were recruited by convenience sampling.

In conclusion, although there was no significant difference between the two study groups in terms of shortening the disease time and clinical improvement, the discharge rate in the IFN-β 1-b had rapidly decreased. However, the same rate had almost increased in the IFN-β 1-a f group until day 17. The patients receiving concomitant IFN-β 1-a, remdesivir, and plasma covid had the highest discharge rates.

CRediT authorship contribution statement

Shahram Seyfi: Writing – original draft, Software, Validation. **Kayvan Latifi:** Conceptualization, Methodology, Software, Data curation. **Parviz Amri male:** Visualization, Investigation. **Mahmoud Sadeghi Haddad Zavareh:** Supervision. **Khadijeh Ezoji:** Writing – review & editing. **Mousa Mohammadnia-Afrozi:** Supervision.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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