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Joint modeling of longitudinal and competing risks for assessing blood oxygen saturation and its association with survival outcomes in COVID-19 patients

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Abstract:

BACKGROUND: The objective of the present study is to evaluate the association between longitudinal and survival outcomes in the presence of competing risk events. To illustrate the application of joint modeling in clinical research, we assessed the blood oxygen saturation (SPO2) and its association with survival outcomes in coronavirus disease (COVID-19).

MATERIALS AND METHODS: In this prospective cohort study, we followed 300 COVID-19 patients, who were diagnosed with severe COVID-19 in the Rohani Hospital in Babol, the north of Iran from October 22, 2020 to March 5, 2021, where death was the event of interest, surviving was the competing risk event and SPO2 was the longitudinal outcome. Joint modeling analyses were compared to separate analyses for these data.

RESULT: The estimation of the association parameter in the joint modeling verified the association between longitudinal outcome SPO2 with survival outcome of death (Hazard Ratio (HR) = 0.33, $P = 0.001$) and the competing risk outcome of surviving (HR = 4.18, $P < 0.001$). Based on the joint modeling, longitudinal outcome (SPO2) decreased in hypertension patients ($\beta = -0.28$, $P = 0.581$) and increased in those with a high level of SPO2 on admission ($\beta = 0.75$, $P = 0.03$). Also, in the survival submodel in the joint model, the risk of death survival outcome increased in patients with diabetes comorbidity (HR = 4.38, $P = 0.026$).

CONCLUSION: The association between longitudinal measurements of SPO2 and survival outcomes of COVID-19 confirms that SPO2 is an important indicator in this disease. Thus, the application of this joint model can provide useful clinical evidence in the different areas of medical sciences.

Keywords:

Competing risk, COVID-19, joint modeling of longitudinal and survival, linear mixed effect model, time-dependent Cox regression model

Introduction

The coronavirus disease (COVID-19) caused by the novel coronavirus (SARS-CoV-2) broke out on March 11, 2020, and was declared a pandemic by the World Health Organization.[1]

The pathogenesis of the novel COVID-19 is still a matter of debate. Several predictors of mortality in COVID-19 patients have been studied since the beginning of the epidemic. These vary from vital parameters and measured laboratory tests, and demographic data to experimental biomarkers.[2-5] Also, in

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several studies, low blood oxygen saturation (SPO2) on admission has been reported as a strong predictor of hospitalization and mortality in COVID-19 patients.[6-10] Understanding changes in SPO2 outcome that may occur during hospitalization, assessing risk factors for this potential marker, and time to death outcome may improve diagnosis and management. In the COVID-19 dataset, estimating the effects of risk factors on the longitudinal outcome of SPO2 can be complicated by discharge or death events.

Previous studies have extensively used separate analyses for each of these outcomes extensively, for example, for time-to-event data, the Cox's proportional hazards model has been popular in survival data,[11-14] while the mixed effects model and the GEE method were widely used for longitudinal measurements.[15-17] but the two outcomes are known to be correlated, which may create nonignorable missing values for the SPO2 longitudinal outcome after death or discharge event.[18,19] When the outcome processes are correlated, joint modeling has been empirically demonstrated to lead to improved efficiency, reduced bias, and prediction improvement.[20]

There are few published studies that have looked at risk factors' effect on low SPO2 and survival outcome simultaneously and the association between the two outcomes.[21-23] In previous studies conducted on COVID-19, the joint statistical model only dealt with one type of event, for example, death or discharge,[21-23] but in fact, events occurring in COVID-19 data are competing risks. If the interest is to estimate the probability of discharge, death is a competing risk event and vice versa.[24]

Thus, we are interested in performing a more comprehensive joint model which links the two aspects together, and simultaneously assesses the effects of SPO2 changes on death as an event of interest in the presence of survivors as a competing risk event. Finally, we compare its results with separate longitudinal and survival models.

Materials and Methods

Study design and setting

In this prospective cohort study, COVID-19 patient data presented two different types of outcomes: (i) the longitudinal outcome was SPO2 that measured every day, and (ii) the time-to-event outcome composed of the follow-up time to the occurrence of death event as interested event and time to survive was considered as a competing event.

Baseline patient characteristics were age, sex, length of illness onset to hospitalization, signs and symptoms at study entry, comorbid diseases (such as hypertension, diabetes, cardiovascular diseases, cancer, and asthma), and vital signs (blood oxygen saturation on admission, respiratory rate, heart rate, systolic blood pressure, diastolic blood pressure, and temperature).

Study participants and sampling

In the present study, we followed 300 COVID-19 patients, who were diagnosed with severe COVID-19 disease in the Rohani Hospital in Babol, the north of Iran from 22 October 2020 to 5 March 2021. Inclusion criteria for severe patients were SPO2 $\leq$ 93%, respiratory rate >30 counts per minute, and having clinical symptoms related to the novel coronavirus, including fever, chills, cough, dyspnea, fatigue, etc., as well as the presence of para clinical measurements such as a computerized tomography scan of the chest, biochemical and laboratory tests, and RT-PCR that confirmed the COVID-19 infection,[25,26] and they were admitted to the hospital with the diagnosis by an infectious disease specialist. Also, we excluded the patients under 18 years of age, those with SPO2 follow-up less than three times, and those admitted to the intensive care unit at the time of hospital admission.

Data collection tool and technique

All statistical analyses were performed with SPSS (version 15), STATA (version 15), and R software (version 4.2.0). Descriptive statistics for continuous variables are presented as mean (SD), median (interquartile ranges (IQR)), and numbers and percentages for categorical variables. Comparisons of numerical data are evaluated using the independent sample *t*-test or non-parametric Mann–Whitney U test, and categorical variables with the Pearson Chi-square test or Fisher's exact when appropriate.

With the purpose of evaluating the relationship between SPO2 longitudinal measurements and death in the presence of the survive event as a competing risk, a joint model was implemented in R software by the fastJM package proposed by Li and colleagues (2022). We used this package to model the survival data using a (cause-specific) Cox proportional hazards regression and the longitudinal outcome modeling using a linear mixed-effects model. The association parameter was taken from shared random effects.[25,27]

Then, the parameter estimates and their standard errors using the joint modeling were compared to those obtained with the separate models, such as the linear mixed model[28] for the longitudinal outcome and the time-dependent Cox model[29] for the time-to-event outcomes. A two-sided *P* value of <0.05 was considered statistically significant.

Overview of joint competing risk and longitudinal outcome

Longitudinal submodel

For the joint model analysis[18,30] as we discussed in Section 2.2, a linear mixed effects model was assumed for the longitudinal SPO2 outcome, with evaluation in time for each patient defined as follows:

$$y(t) = m(t) + e(t)$$
$$= \beta_0 + \beta_1 sex + \beta_2 age + \beta_3 diabet + \beta_4 hypertension + \beta_5\ spo2\ baseline + \beta_6 time + b_0 + b_1\ time + \varepsilon(t)$$

m(t) is the mean of the longitudinal measures at time t, $\varepsilon(t)$ is the measurement error term with variance, σ^2 and $\beta_1, \beta_2, \ldots$ represent the parameters of the fixed-effects part composed by the main effect of sex, age…associated with the SPO2. respectively; b_0 and b_1 are random intercept and random slope terms for temporal variation.

Survival submodel

The competing risk survival outcome is modeled by a semiparametric cause-specific hazard model for each event defined as follows:

$$\begin{cases} \lambda_1(t) = \lambda_{01}(t) exp\left\{ \begin{matrix} \beta_{11} sex + \beta_{21} age + \beta_{31} diabet \\ + \beta_{41} hypertension + \alpha_1 m(t) \end{matrix} \right\} \\ \lambda_2(t) = \lambda_{02}(t) exp\left\{ \begin{matrix} \beta_{12} sex + \beta_{22} age + \beta_{32} diabet \\ + \beta_{42} hypertension + (\alpha_1 + \alpha_2) m(t) \end{matrix} \right\} \end{cases}$$

The parameters $\beta_{11}, \beta_{21}, \ldots$and denote the direct effects of sex, age, ... and SPO2, respectively, on the risk for death, and the parameters $\beta_{12}, \beta_{22}, \ldots$ and $\alpha_1 + \alpha_2$ denote the effects of sex, age,… and SPO2, respectively, on the competing risk event of surviving.

This approach focuses on the link between the two longitudinal and survival processes. Therefore, the association between these processes is represented through shared latent random effects, achieved through the inclusion of the longitudinal random intercept (b_0) and random slope (b_1) terms into the survival process.

Ethical consideration

The study protocol was approved by the Babol University of the medical science ethics committee (Ethic code: IR.MUBABOL.REC.1400.204). All patients had given written consent prior to participating in the study.

Result

Patients' demographic, clinical, and laboratory characteristics

A total of 300 severe patients with COVID-19 were included in the analysis. The overall median age was 58 (IQR, 44–68 years) years and females represented 142 (47.3%) of the total sample.

The most common comorbidities and symptoms were hypertension (79%), diabetes (69%), cardiovascular diseases (68%), dyspnea (64.4%), cough (63%), muscle pains) 60.9%), chills (51.9%), and anorexia (45.3%).

The median follow-up time (length of hospital stay) was 6 days (IQR: 4–8 days). Considering the longitudinal outcome, the number of measures of SPO2 varied among patients, with a minimum of 3 observations and a maximum of 25 observations. The median of observation per patient was 6 (IQR: 4–8 observations). The mean blood oxygen saturation score on admission (baseline SPO2) was 88.66 ± 5.70 for a total observation.

Considering the time-to-event outcome, 32 (10.7%) patients experienced the death event, and 251 (83.7%) survived those considered as competing risk events. Survival times were censored for 17 (5.7%) patients who did not experience any outcome until the end of the study.

The mean ± SD age in the death group (61.17 ± 18.95 years) was higher than in the surviving group (55.24 ± 17.49 years). However, there was no significant difference ($P = 0.086$). Also, a significant difference was observed in the proportion of patients with comorbid diseases, mainly diabetes (43.8% vs. 21.9%, $P = 0.007$), hypertension (43.8% vs. 25.9%, $P = 0.031$), and dyspnea asymptotic (87.5% vs 61.3%, $P = 0.004$) with higher frequencies in the death group. The other baseline information between the death and survivor groups is shown in Table 1. The baseline SPO2 was lower in dead patients compared to surviving patients (79.34% vs. 89.82%, $P < 0.001$). The other admission vital signs, such as Respiratory Rate (RR), Heart Rate (HR), Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), and temperature, showed worse outcomes in the death group [Table 2].

Exploratory analysis

A spaghetti plot showing the longitudinal response of the SPO2 for the different competing events is presented in Figure 1. In this figure, the mean of SPO2 differs slightly according to the different events that occurred, showing a possible association between longitudinal SPO2 and the survival endpoint. Thus, the analysis requires a joint modeling approach.

Figure 2 summarizes the cumulative incidence estimates for the two possible events, taking competing risks into account. The probability of surviving is always higher than the probability of death. For example, the probabilities of surviving by 10, 20, and 30 days after admission were 0.787, 0.870, and 0.884, respectively, and

Table 1: Demographic and clinical outcomes according to severe COVID-19 patients

Characteristics	Total (*n*=300)	Survivors (*n*=251)	Death (*n*=32)	*P*†
Age, mean±SD	59.07±17.59	55.24±17.49	61.17±18.95	0.086
Sex				
Male, *n* (%)	145 (51.2)	128 (51)	17 (53.1)	0.820
Female, *n* (%)	138 (48.8)	123 (49)	15 (46.9)	
Comorbidities				
Hypertension, *n* (%)	79 (27.9)	65 (25.9)	14 (43.8)	0.031
Diabetes n (%)	69 (24.4)	55 (21.9)	14 (43.8)	0.007
Cardiovascular diseases, *n* (%)	68 (24)	61 (24.3)	7 (21.9)	0.762
Cancer, *n* (%)	21 (7.4)	18 (7.2)	3 (9.4)	0.654
Asthma, *n* (%)	6 (3.2)	5 (3.1)	1 (4.2)	0.775
Signs and symptoms				
Fever, *n* (%)	104 (37.7)	91 (37.3)	13 (40.6)	0.715
Chill, *n* (%)	122 (51.9)	106 (52)	16 (51.6)	0.971
Cough, *n* (%)	174 (63)	154 (63.1)	20 (62.5)	0.946
Fatigue, *n* (%)	168 (60.9)	148 (60.7)	20 (62.5)	0.841
Dyspnea, *n* (%)	177 (64.4)	149 (61.3)	28 (87.5)	0.004
Headache, *n* (%)	48 (17.4)	43 (17.6)	5 (15.6)	0.779
Anorexia, *n* (%)	107 (45.3)	95 (46.3)	12 (38.7)	0.426
Chest pain, *n* (%)	23 (8.3)	19 (7.8)	4 (12.5)	0.364
Dizziness, *n* (%)	6 (2.2)	6 (2.5)	0 (0)	0.369
Diarrhea, *n* (%)	24 (8.7)	21 (8.6)	3 (9.4)	0.890
Nausea and vomiting, *n* (%)	39 (14.2)	35 (14.4)	4 (12.5)	0.772
Loss of smell, *n* (%)	27 (11.9)	22 (11.1)	5 (17.2)	0.341
Length of illness onset to hospitalization (day), median (IQR)	7 (5–10)	7 (5–10)	7 (5–10)	0.781
Length of hospital stay (day), median (IQR)	6 (4–8)	6 (4–7)	7 (4.25–11)	0.023

Data are *n* (%). non-normal distributed data are median (IQR). †*P*-values were calculated by the Chi-square test and Mann–Whitney *U*-test

Table 2: Comparison of the mean of vital signs between survivors and death at baseline admission

Vital signs	Total (*n*=300)	Survivors (*n*=251)	Death (*n*=32)	*P*
Oxygen saturation on admission (%)	88.66±5.70	89.82±3.36	79.34±10.39	<0.001
Respiratory rate (breaths/minute)	19.32±5.88	16.25±6.17	19.88±2.81	0.607
Heart rate (bpm)	88.07±18.78	87.49±18.20	91.72±22.18	0.297
Systolic blood pressure (mmHg)	118.03±16.91	117.72±16.96	120.00±16.77	0.533
Diastolic blood pressure (mmHg)	76.39±10.73	76.01±10.96	79.11±8.70	0.265
Temperature (°C)	37.05±0.81	37.05±0.82	37.04±0.78	0.938

Mean±SD reported in table. †*P*-values were calculated by the independent sample *t*-test

by the same time points, the probabilities of death were 0.084, 0.103, and 0.112. This curve gives a global idea about the survival process.

Comparison of joint modeling with the presence of competing risk and separates modeling

The parameter estimates and *P* values from the joint modeling and the separate approaches (linear mixed model and extended Cox model) are presented in Table 3. In a separate extended Cox analysis, the negligible effect of age was significant for both events (death event: HR = 1.04, *P* = 0.00; and surviving event: HR = 0.99, *P* = 0.024). While in the joint model, logically, the effect of age with HR = 1.03 (*P* = 0.281) for the death event and HR = 0.99 (*P* = 0.711 for the surviving event was not significant.

The results of the longitudinal submodel in the joint model in Table 3 showed that longitudinal outcome (SPO2) decreased in hypertension patients (β = -0.28, *P* = 0.581) and the separate longitudinal model gave a positive effect and an illogical result (β = 0.04, *P* = 0.930). Also, the same conflicting result was observed in the separately extended Cox model for the evaluation of hypertension comorbidity and the survival outcome of death (HR = 0.60, *P* = 0.003), implying a lower risk of death in patients with hypertension comorbidity. Considering the appropriate results obtained from the joint model, according to the survival submodel, the association parameter verifies an association between SPO2 and risk of death (HR = 0.33, *P* = 0.001), meaning that a unit increase in the SPO2 decreases the risk of a death event by approximately 0.7 and also improves the time to survive, which is a competing risk event, by 4.18 times. Using the longitudinal submodel in the joint model, we observed that the high level of SPO2 admission (β = 0.75, *P* < 0.001) and time (β = 0.65,

Table 3: Comparison of parameter estimates of the separate model and joint model for longitudinal and survival outcomes in the presence of competing risk

Longitudinal sub-model	Joint model		Separate model	
	Coefficient (SE)	*P*	Coefficient (SE)	*P*
Fixed effects				
Intercept	21.49 (2.89)	<0.001	11.95 (2.88)	<0.001
Sex (Female vs male)	-0.13 (0.40)	0.751	-0.10 (0.34)	0.768
Age (year)	-0.006 (0.02)	0.733	-0.003 (0.01)	0.786
Diabetes (yes vs no)	-0.09 (0.47)	0.839	-0.10 (0.42)	0.812
Hypertension (yes vs no)	-0.28 (0.51)	0.581	0.04 (0.41)	0.930
Blood oxygen saturation on admission (%)	0.75 (0.03)	<0.001	0.86 (0.03)	<0.001
Time (day)	0.65 (0.03)	<0.001	0.69 (0.06)	<0.001
Survival sub-model	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Event of interest (Death)				
Sex (Female vs Male)	0.94 (0.33–2.72)	0.281	0.91 (0.69–1.21)	0.525
Age (Year)	1.03 (0.98–1.08)	0.281	1.04 (1.02–1.05)	<0.001
Diabetes (yes vs no)	4.38 (1.88–6.16)	0.026	3.88 (2.82–5.35)	<0.001
Hypertension (yes vs no)	1.38 (0.42–4.53)	0.594	0.60 (0.43–0.84)	0.003
Association parameter	0.33 (0.17–0.65)	0.001	0.99 (0.99–1.00)	<0.001
Event of interest (Survivors)				
Sex (Female vs Male)	1.07 (0.70–1.66)	0.732	0.92 (0.83–1.02)	0.111
Age (Year)	0.99 (0.97–1.02)	0.711	0.99 (0.99–1.00)	0.024
Diabetes (yes vs no)	1.06 (0.58–1.95)	0.837	1.26 (1.10–1.46)	0.001
Hypertension (yes vs no)	0.68 (0.39–1.17)	0.992	0.87 (0.76–0.98)	0.032
Association parameter	4.17 (2.67–6.48)	<0.001	1.01 (1.01–1.02)	<0.001

Longitudinal outcome (SPO2); survival outcome (time to death); competing risks (time to survive). Separate model: longitudinal model (linear mixed model); survival model (extended Cox model)

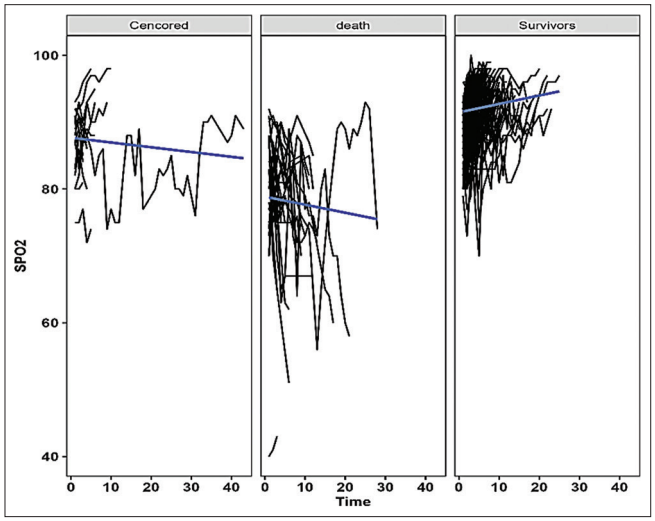

Figure 1: Smooth spline empirical mean of SPO2 evaluation for the three subsets of events: censored, death, and survivors

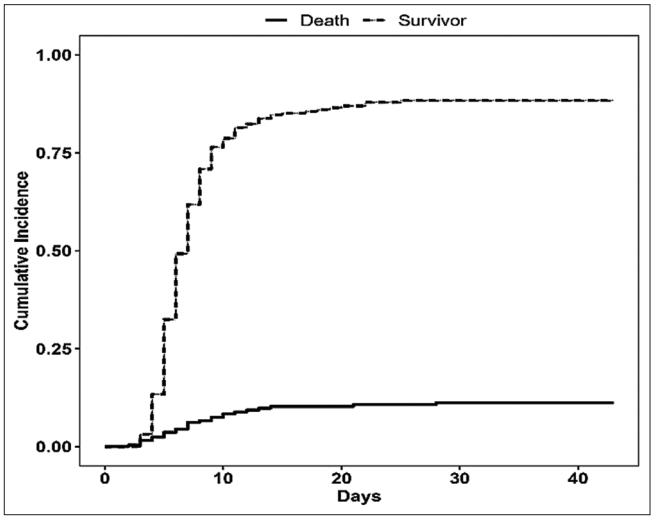

Figure 2: Cumulative incidence curve for death (solid line) and for survived (dotted line)

$P < 0.001$) were significantly associated with the increase of the SPO2 longitudinal outcome.

Discussions

It is very common that both longitudinal measurements and event time to occur during follow-up. In this study, the longitudinal outcome is the level of SPO2 at 25 days of hospitalization for COVID-19 patients, the desired survival outcome is the time to death, and the competing risk event is the survivors.

In the current study, non-negligible missing values in longitudinal SPO2 measurements occurred after discharge for one of the reasons, death or survivor outcomes, so these two outcomes are known to be correlated. Joint models are an appropriate approach that can be used to simultaneously assess the effects of factors of interest on both outcomes as well as examine the association between the survival outcome and the longitudinal outcome.[18,19,31]

Several simulation studies have shown that the joint model could be substantially more efficient than the separate

analysis methods and reduce the biases of parameter estimates by accounting for the association between the longitudinal and time-to-event outcomes.[32-35] Also, this method has been applied in several medical areas, such as AIDS studies,[36] cancer,[33,37,38] and COVID-19.[21,23,39,40]

In the published studies conducted related to COVID-19, the common assumption of most of the studies in the survival submodel of the joint model was based on a single failure type, while dropout occurs due to the death event as well as the presence of a survivor competitive risk event, and this issue should not be ignored. We illustrated in this paper how the joint model extends to competing risks to fit survival responses and may influence the results compared to separate analyses. Analysis of the joint model with competing risk was performed with the fastJM package proposed by Li and colleagues (2022) that survival data were modeled using a (cause-specific) Cox proportional hazards regression model, and the longitudinal outcome was modeled using a linear mixed-effects model. The association parameter was taken from shared random effects.[25,27]

Based on the results, for joint analyzes, the effects of non-significant covariates became significant when a separate analysis approach was performed. This can be due to the variability that was overestimated in a separate analysis, which was due to ignoring the association between the longitudinal and survival.

Also, it was a contradictory result that patients with hypertension comorbidity were at low risk to have mortality, as shown in the separate model 0.60 (0.43–0.84), which was different in the hazard ratio from the joint model 1.38 (0.42–4.53). The result of the joint model is in agreement with previous research.[41–44] Also, the wrong result has been observed in the evaluation of the effect of this covariate on the SPO2 measurements in the separate longitudinal submodel, which indicates an increase in SPO2 in patients with hypertension comorbidity and it is contrary to the studies.[45]

Our main findings of this joint model analysis, which is association between longitudinal outcome and survival outcome, showed that the patients, were at more risk to have a death event when SPO2 abruptly decreased during hospitalization 95% Confidence Interval (CI) (0.33 (0.17-0.65)) and patients with a high level of SPO2 measurements were more likely to have survived event because of association parameter was significantly positively correlated and the hazard ratio was 95% CI (4.17 (2.67–6.48)). These findings are similar to previous research findings that identified SPO2 as a potential indicator in the outcomes related to COVID-19 disease.[6,9,46,47] Subsequently, the results of the joint model reveal that diabetes is associated with the mortality of the patients by 4.38 times (95% CI: 1.88–6.16), and many research studies reported similar results.[48-51] Also, based on the longitudinal submodel in the joint model, a high oxygen saturation level on admission has a positive effect on SPO2 measurements during hospitalization (β = 0.75, P = 0.001), which is in accordance with the previous studies.[46,52,53]

Our suggestion for future studies is to include other types of applications in this model for medical field data. For example, consider applying the survival submodel considering recurrent events with univariate or multivariate longitudinal submodels. The non-cooperation of some patients was one of the limitations of the study.

Conclusion

In conclusion, joint modeling for longitudinal outcomes and time-to-event in the presence of competing risks is useful in different areas of medicine when the goal is to assess the relationship between these two types of outcomes. This result from the joint model with competing risks provides useful guidelines for clinical practice.

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Conflicts of interest
There are no conflicts of interest.

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