



Short communication

Factors associated with death due to severe acute respiratory syndrome caused by influenza: Brazilian population study

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ARTICLE INFO

Article history:

Received 5 August 2022

Received in revised form 12 October 2022

Accepted 24 October 2022

Keywords:

Influenza

Severe acute respiratory syndrome

Risk factors

Vaccine

Infection control

ABSTRACT

Introduction: Influenza infection is characterized by acute viral infection of high transmissibility. Worsening of the case can lead to the need for hospitalization, severe acute respiratory syndrome (SARS) and even death.

Method: This is a cross-sectional population-based study that used secondary database from the Brazilian Influenza Epidemiological Surveillance Information System. Only cases of adults with diagnosis of influenza by RT-PCR and case evolution recorded were included.

Results: We identified 2273 adults with SARS by influenza, 343 of which had death as an outcome. The main risk factors for death were lack of hospitalization, not having cough and age, both with $p < 0.001$. In addition, without asthma, having black skin color, not receiving flu vaccine, having brown skin color and not having a sore throat ($p \leq 0.005$) were risk factors too.

Conclusion: Factors associated with death due to SARS caused by influenza in Brazil, risk factors and protective factors to death were identified. It was evident that those who did not receive the flu vaccine presented twice the risk of unfavorable outcome, reinforcing the need to stimulate adherence to vaccination adhering and propose changes in public policies to make influenza vaccines available to the entire population, in order to prevent severe cases and unfavorable outcomes.

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Introduction

Influenza cases have been reported worldwide for more than a century. Influenza is contagious and generates an important impact due to high morbidity and mortality [1]. It is an acute viral infection,

which attacks the respiratory tract several times throughout life, and can generate mild or severe symptoms in affected individuals. The virus transmission occurs through the airways, through secretions such as droplets, aerosols and contact with the mucosa.

Severe Acute Respiratory Syndrome (SARS) is an infectious respiratory syndrome, which can be caused by several etiological agents that infect the respiratory tract, including the influenza virus [2]. Its clinical presentation is characterized by a flu-like syndrome associated with symptoms of severe respiratory conditions such as

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dyspnea, tachypnea (respiratory rate equal to or above 20 breaths per minute) or hypoxia, with oxygen saturation (SpO_2) < 95% in room air [3]. SARS due to Influenza therefore follows the same characteristics of acute respiratory distress syndrome (ARDS) based on the Berlin definition. Patients who are suffering hypoxemia are classified as mild ($\text{PaO}_2/\text{FIO}_2 \leq 300$ mm Hg), moderate ($\text{PaO}_2/\text{FIO}_2 \leq 200$ mm Hg), or severe ($\text{PaO}_2/\text{FIO}_2 \leq 100$ mm Hg) [4], just like the COVID-19-associated respiratory distress syndrome (CARDS) [5]. SARS can progress to complications, which lead to an increased risk of hospitalization in the Intensive Care Unit (ICU), with the use of mechanical ventilation, and even death [6]. It is a disease of epidemiological importance that must be notified and investigated in order to prevent and monitor severe cases [7].

Since the 2000s, Brazilian regions have been receiving vaccine against the virus seasonally before autumn and winter [1]. The vaccine is the most efficient way of preventing influenza worldwide [8], since it contributes to decreasing the virus circulation, complications caused by the disease and death, especially in individuals with risk factors [9].

As for vaccination coverage (VC), for years it has been above the established goal, although it was not reached equally for all groups eligible for vaccination; however, it had good overall performance. However, since the beginning of the COVID-19 pandemic, all groups had VC below 90%, with the group of puerperal women with the highest coverage (85.1%), followed by indigenous peoples, with 78.2%, pregnant women, with 78%, and health workers, with the lowest performance among the eligible groups (68.4%) [10].

Thus, given the epidemiological and social importance of influenza, and the important drop in VC of the eligible Brazilian population, the present study investigated factors associated with death due to SARS caused by influenza in Brazilian adults.

Material and method

Study design

This is a cross-sectional population-based study that used secondary databases from the Influenza Epidemiological Surveillance Information System (IESI-Influenza). The INFLUD20-31-01-2022, INFLUD21-31-01-2022 and INFLUD22-31-01-2022 databases, made available by the Brazilian Ministry of Health (available in: <https://opendatasus.saude.gov.br/dataset?tags=SARS>), were accessed.

Selection criteria

The sample included cases of adults with SARS registered in the IESI-Influenza. Adults aged 18 years and over, aged less than 60 years, with laboratory confirmation of influenza by Real Time Polymerase Chain Reaction (RT-PCR), given the high sensitivity and specificity of the test [11,12], and with case evolution (death/cure) recorded were included. Cases with incomplete records or with inconsistent information were excluded.

Data collection

Data were obtained from the IESI-Influenza database, a Brazilian national system that records, monitors and provides data on SARS by respiratory pathogens, including influenza. The data used include all regions of Brazil, beginning in epidemiological week 8 (02/16–02/22) of 2020 until epidemiological week 4 (01/23–01/29) of 2022, with the final data collection performed in February 2022.

To construct the database and obtain the sample that answered the study questions, the following protocol was used: full databases available on 02/03/2022 were used; records of individuals aged 18 years or over and less than 60 years (931,591) with positive RT-PCR for influenza (2866) were selected; then cases with final evolution

recorded (2329) were filtered, since this was the outcome of interest (death/cure). After that, records with incomplete information were excluded, so that the proposed analysis would not be compromised, resulting in a final sample of 2273 cases. This is a non-probabilistic or convenience sample, since all cases of Influenza registered in the studied period were considered eligible to compose the sample of this study, and were included all cases that met the criteria established and cited in the above protocol.

The outcome investigated was death due to influenza (death/cure) in adults. The factors associated (independent variables) with the primary outcome studied were those related to socio-demographic and clinical variables, and signs and symptoms.

Ethical aspects

Data were extracted from a public secondary database, which provides anonymized data, in order to ensure that no participant can be identified. Therefore, all ethical precepts were complied with in accordance with Resolution 510 of the Brazilian National Health Council of April 7, 2016. Such resolution establishes in the single paragraph of its first article, item II, that research using publicly accessible information will not be registered by the Research Ethics Committee/Brazilian National Research Ethics Commission (REC/NREC), pursuant to Law 12,527 of November 18, 2011, and no appreciation of this study is necessary by a REC, being released from obtaining an informed consent form signed by participants [13].

Data analysis

Data were analyzed on softwares R version 4.1.1 and R Studio version 1.4.1106 (Integrated Development for R; RStudio, PBC, Boston, MA, United States), using the packages as follows: questionr, ResourceSelection and PROC. To identify the relationship between death due to SARS caused by influenza and the other variables studied, a bivariate analysis was performed using Fisher's exact test or chi-square test, when appropriate. Then, logistic regression was performed with significant variables using the bivariate analysis, in order to verify the association with outcome, and the Odds Ratio was estimated for each one. The significance level considered was alpha equal to 0.05.

Results

According to the study design, the final sample consisted of 2273 adults with SARS by influenza during the study period. Of these, 343 had death as outcome, recording a case fatality rate of 15.09% for the study group.

Table 1 shows the relationship between the case outcome (discharge/death) and other variables studied, highlighting the following associations: sex; education; pregnancy; respiratory distress; O_2 saturation below 95%; risk factors; chronic cardiovascular disease; chronic neurological disease; diabetes; received the flu vaccine; hospitalization; ICU admission; ventilatory support use; Chest X-ray; and influenza virus of subtypes A ($p \leq 0.001$). Furthermore, it is important to highlight the relationship between the outcome and variables used antiviral drug for flu ($p = 0.003$), antiviral drug used ($p = 0.003$), chronic kidney disease ($p = 0.035$), ethnicity/skin color ($p = 0.005$), asthma ($p = 0.007$) and obesity ($p = 0.011$).

Table 2 shows the association between the age of adults with SARS by influenza and the case outcome (discharge/death). It is worth mentioning that the group with a death outcome has a mean age higher than that of the survivors. Additionally, the median age is eleven (11) years higher in the former group. The first quartile is eight (8), and the third quartile, six (6) years more in the death group, compared to the discharge group.

Table 1

Association between outcome (discharge/death) and sociodemographic and clinical characteristics of adults with severe acute respiratory syndrome by influenza, Brazil, 2022 (n = 2273).

Characteristics	Discharge n (%)	Death n (%)	p-value
Sex			< 0.001*
Female	1137 (58.9)	156 (45.5)	
Male	791 (41.0)	187 (54.5)	
Not informed/ignored	2 (0.1)	0	
Ethnicity/skin color			
White	737 (38.2)	105 (30.6)	0.005*
Black	99 (5.1)	22 (6.4)	
Yellow	13 (0.7)	2 (0.6)	
Brown	732 (37.9)	161 (46.9)	
Indigenous	16 (0.8)	6 (1.7)	
Not informed/ignored	333 (17.3)	47 (13.7)	
Education			
No education/illiterate	25 (1.3)	17 (5.0)	< 0.001#
First cycle of elementary school	118 (6.1)	31 (9.0)	
Second cycle of elementary school	123 (6.4)	27 (7.9)	
High school	329 (17.0)	37 (10.8)	
Higher education	197 (10.2)	16 (4.7)	
Ignored	1138 (59.0)	215 (62.7)	
Pregnancy			
First trimester	28 (1.5)	1 (0.3)	< 0.001*
Second trimester	64 (3.3)	2 (0.6)	
Third quarter	150 (7.8)	3 (0.9)	
Gestational age ignored	8 (0.4)	0	
No	1680 (87.0)	337 (98.3)	
Fever			
Yes	1454 (75.3)	211 (61.5)	< 0.001#
No	476 (24.7)	132 (38.5)	
Cough			
Yes	1659 (86.0)	229 (66.8)	< 0.001#
No	271 (14.0)	114 (33.2)	
Sore throat			
Yes	686 (35.5)	63 (18.4)	< 0.001#
No	1244 (64.5)	280 (81.6)	
Dyspnea			
Yes	1108 (57.4)	263 (76.7)	< 0.001#
No	822 (42.6)	80 (23.3)	
Respiratory distress			
Yes	899 (46.6)	212 (61.8)	< 0.001#
No	1031 (53.4)	131 (38.2)	
Oxygen saturation < 95%			
Yes	721 (37.4)	221 (64.4)	< 0.001#
No	1209 (62.6)	122 (35.6)	
Risk factors			
Yes	899 (46.6)	227 (66.2)	< 0.001#
No	1031 (53.4)	116 (33.8)	
Chronic cardiovascular disease			
Yes	212 (11.0)	81 (23.6)	< 0.001#
No	1718 (89.0)	262 (76.4)	
Chronic neurological disease			
Yes	35 (1.8)	17 (5.0)	< 0.001#
No	1895 (98.2)	326 (95.0)	
Chronic kidney disease			
Yes	34 (1.8)	12 (3.5)	0.035#
No	1896 (98.2)	331 (96.5)	
Obesity			
Yes	80 (4.1)	25 (7.3)	0.011#
No	1850 (95.9)	318 (92.7)	
Diabetes			
Yes	162 (8.4)	75 (21.9)	< 0.001#
No	1768 (91.6)	268 (78.1)	
Asthma			
Yes	188 (9.7)	18 (5.2)	0.007#
No	1742 (90.3)	325 (94.8)	
Received the flu vaccine			
Yes	249 (12.9)	21 (6.1)	< 0.001#
No	1681 (87.1)	322 (93.9)	
Used antiviral drug for flu			
Yes	641 (33.2)	86 (25.1)	0.003#
No	1289 (66.8)	257 (74.9)	

Table 1 (continued)

Characteristics	Discharge n (%)	Death n (%)	p-value
Antiviral drug used			
Oseltamivir	611 (31.7)	81 (23.6)	0.003*
Other	13 (0.7)	0	
Did not use/not reported	1306 (67.7)	262 (76.4)	
Hospitalization			
Yes	1780 (92.2)	287 (83.7)	< 0.001#
No	150 (7.8)	56 (16.3)	
ICU admission			
Yes	356 (18.4)	169 (49.3)	< 0.001#
No	1574 (81.6)	174 (50.7)	
Ventilatory support use			
Yes, invasive	75 (3.9)	176 (51.3)	< 0.001#
Yes, non-invasive	718 (37.2)	71 (20.7)	
No	1137 (58.9)	96 (28.0)	
Chest X-ray			
Normal	180 (9.3)	3 (0.9)	< 0.001#
Interstitial infiltrate	245 (12.7)	54 (15.7)	
Consolidation	39 (2.0)	12 (3.5)	
Mixed	26 (1.3)	10 (2.9)	
Other	74 (3.8)	28 (8.2)	
Not performed/not reported	1366 (70.8)	236 (68.8)	
RT-PCR for influenza			
Influenza A	1733 (89.8)	325 (94.8)	0.004#
Influenza B	197 (10.2)	18 (5.2)	
RT-PCR for influenza A - subtype			
Influenza A - H1N1	320 (16.6)	40 (11.7)	0.001#
Influenza A - H3N2	867 (44.9)	185 (53.9)	
Influenza A - not subtyped	438 (22.7)	86 (25.1)	
Influenza A - not subtypable	57 (3.0)	10 (2.9)	
Inconclusive	210 (10.9)	18 (5.2)	
Other	38 (2.0)	4 (1.2)	
RT-PCR for influenza B - subtype			
Victoria	31 (1.6)	0	0.027*
Yamagata	2 (0.1)	0	
Not performed	91 (4.7)	11 (3.2)	
Inconclusive	1806 (93.6)	332 (96.8)	

Caption: *Fisher's exact test; #Chi-square test; ICU – Intensive Care Unit.

Table 2

Association between outcome (discharge/death) and age of adults with severe acute respiratory syndrome by influenza, Brazil, 2022 (n = 2273).

Age	Discharge	Death	p-value
Minimum	18	18	< 0.001*
First quartile	27	35	
Median	36	47	
Mean (SD)	37.2 (± 12.033)	44.26 (± 11.39)	
Third quartile	48	54	
Maximum	59	59	

Caption: *Mann-Whitney test.

Adjusting a logistic model to estimate the risk of death (Table 3), considering as covariates those significant in the bivariate analyzes (Fisher's exact, chi-square, and Mann-Whitney tests), it can be stated that black adults have a 2.25-fold increased risk of death, as well as browns, with an almost 2-fold increased risk. Those who do not have cough and sore throat throughout the course of disease also have a higher risk of unfavorable outcome, as well as those who do not have asthma as a comorbidity. It is necessary to highlight that those who were not hospitalized had a higher risk of death, with an increase of almost 8 times, and those who did not receive the flu vaccine had twice the risk of an unfavorable outcome of the flu condition. For each 1-year increase in age, there is a 3.6% increase in the chance of death.

On the other hand, those who have complete high school or higher education, do not have dyspnea and O₂ saturation below 95%, do not have diabetes and chronic neurological disease, were not

Table 3

Logistic regression to estimate the risk of death due to severe acute respiratory syndrome by influenza in adults, Brazil, 2022 (n = 2273).

	Odds Ratio	95% CI	p-value
Intercept	0.132	0.029–0.581	0.008
Black skin color	2.253	1.155–4.237	0.014
Brown skin color	1.870	1.359–2.581	0.000
High school	0.559	0.341–0.894	0.018
Higher education	0.489	0.231–0.969	0.050
No cough	2.993	2.086–4.294	< 0.001
No sore throat	1.549	1.067–2.275	0.023
No dyspnea	0.659	0.456–0.949	0.026
No O ₂ saturation below 95%	0.619	0.430–0.889	0.009
No asthma	2.495	1.346–4.892	0.005
No diabetes	0.508	0.336–0.772	0.001
No chronic neurological disease	0.314	0.143–0.711	0.005
Did not receive the flu vaccine	2.182	1.238–4.038	0.009
No hospitalization	7.706	4.748–12.573	< 0.001
No ICU admission	0.581	0.397–0.857	0.006
Non-invasive ventilatory support	0.050	0.032–0.078	< 0.001
No ventilatory support use	0.041	0.024–0.067	< 0.001
Interstitial infiltrated chest X-ray	3.160	1.474–7.141	0.004
Not chest X-ray	3.998	1.612–10.200	0.003
Age	1.036	1.022–1.050	< 0.001

admitted to the ICU, required non-invasive ventilatory support or did not need this support are less likely to have a negative case outcome.

Discussion

The study sample consisted of 2273 adults with SARS by influenza in the period from 02/16/2020 (8th epidemiological week of 2020) to 01/29/2022 (4th epidemiological week of 2022), with a lethality of 15.09%, which made it possible to study and identify factors associated with death from this disease.

A study conducted in a capital of northeastern Brazil analyzed SARS cases by influenza from 2012 to 2014 and recorded a lethality rate of 77.7% [14]. Another Brazilian study, conducted in southern Brazil, from 2009 to 2017, showed a lethality rate of 4% of the sample studied [15]. This variation can be justified by differences in access to health care, especially of high complexity, and vaccination. Moreover, the sample restrictions of these studies may have imposed the generalization of results, which differs from the present study, since it presents a national overview of SARS cases by influenza in adults.

In the second half of 2021, H3N2 infection cases, a subtype of influenza A, spread throughout Brazil and became epidemic in several states, with increased cases and hospitalizations. One of the reasons that explains this growth is the low VC against influenza, which reached 72.8% of the target audience that year, when the goal was to have 90% of each priority population vaccinated. The other is the population's lack of understanding that the vaccine prevents serious cases, reducing the occurrence of hospitalizations and death [9].

That same year, Brazil's influenza vaccination campaign began in April and lasted until September, due to low support. Among the priority groups of the 2021 influenza vaccination campaign (children, health workers, pregnant women, postpartum women, indigenous people and older adults), 39.41 million people were vaccinated, when it was expected to immunize 55.3 million. Among the entire target population, 67.98 million took the vaccine, compared to the 79.7 million expected to reach the goal [10].

The trivalent influenza vaccine used in Brazil in 2021 features three types of virus strains in combination (A/Victoria/2570/2019 (H1N1)pdm09, A/Hong Kong/2671/2019 (H3N2) and B/Washington/02/2019 (B/Victoria lineage)), according to the Resolution 4.184 of October 15, 2020 of the Brazilian National Health Regulatory Agency (ANVISA) – RE [16].

This study identified that black or brown adults have a higher risk of death due to SARS caused by influenza. For Lenzi et al., race did not affect the outcome of the disease [17], as in the work by Cavalieri, Lima, and Traebert, where the variable skin color did not show a statistically significant association in relation to reported cases [18]. On the other hand, Niquini et al. identified in their study a higher number of white patients hospitalized with SARS by influenza [19].

According to our results, when relating education to the outcome of the case (discharge/death), those with ignored education had a higher death rate, followed those with high school that represent more than 10% of death cases. However, as most of the results related to education were ignored at the time of case registration, these results are fragile. On the other hand, the study by Lenzi et al. showed that most of individuals who died were illiterate or with ignored education [17].

When reporting the existence of risk factors, our study identified that 66.2% of patients who reported having some risk factor evolved to death, with chronic cardiovascular disease being the most prevalent comorbidity, with a death rate of 23.6%. In the study conducted by Bedretchuk, Sakr and Cavalli, the most prevalent risk factor was pneumopathy [15].

When analyzing the main flu-like symptoms, fever was present in 75.3% of patients who were discharged and in 61.5% of those who died. Cough was present in 86% of individuals who were discharged, evidencing that, for the sample, patients who present these symptoms have a lower risk of death. Other common symptoms such as dyspnea and respiratory discomfort were present in 76.7% and 61.8%, respectively, in those who presented the negative outcome (death). These symptoms appear as the main and most frequently presented, according to the results of this study, corroborating the findings of previous studies [20,21]. On the other hand, Mazon et al. reported that cough was not a main symptom [22].

When verifying the records of chest X-ray results, it is noted that the main radiological pattern found was the interstitial infiltrate both in those who died (15.7%) and who were discharged (12.7%). This radiological pattern was also reported as the most frequent in the study by Silveira et al. [21].

This study showed that in the group of adults who died due to SARS caused by influenza, 93.9% had not received the vaccine against this viral infection and those who had not been vaccinated had a 2.182-fold increase in the risk of death. These findings reinforce previous results, such as the study by Araújo et al., where they analyzed SARS notifications in the state of Goiás (Brazil) and showed low vaccination compliance and higher chance of death in individuals not previously vaccinated [23]. Silveira et al. showed that 79.6% of patients in their study were not vaccinated [21], and 67.5% of participants in the study by Cavalieri, Lima, and Traebert, carried out in Santa Catarina, Brazil, had also not received the influenza vaccine [18].

It is noteworthy that, although influenza vaccination is a public health measure that helps reducing hospitalizations and deaths [23], this immunobiological agent is not available free of charge to the entire Brazilian population, only to priority groups established by the Ministry of Health.

In the group with the discharge outcome, hospitalization was necessary in 92.2% of cases and in 83.7% of those who had the death outcome. A study carried out in Australia showed that, among adults, the rate of hospitalization for influenza was 42.2%, and the rate of those who had the outcome of death was 12.3% [24]. Another study showed a higher hospitalization rate, 98.7% [18], as well as in the research of Silveira et al., who analyzed the profile of SARS cases in the state of Goiás, identifying the need for hospitalization in 93.1% of cases [21].

When analyzing the results of viral typing by RT-PCR, influenza A is the most frequent, being associated with discharge in 89.8% of

cases, but also present in 94.8% of patients with death outcome, as well as in the study by Muscatello et al., which also found a higher prevalence of influenza A, with a rate of 70% [24]. In addition, the influenza A subtype most found in the patients of this study was H3N2, of which 53.9% died, as in the study by Fielding et al., which reported most cases of H3N2 subtype influenza [25]. On the other hand, the results of Araújo et al., Rossetto and Luna, and Silveira et al. [20,21,23] showed that the predominant subtype of influenza A was H1N1, as well as the Australian study, which analyzed influenza outbreaks, showing that H1N1 was predominant [26]. The study by Muscatello et al. also found the most recorded influenza A in the studied period with a rate of 70%, but did not analysis the specific subtype [24].

This study is extremely relevant, since it allows to know and analyze deaths due to influenza in the period and population studied. Moreover, it demonstrates the importance of planning actions to promote and prevent diseases by facing a pandemic, denoting the importance of adopting contingency plans and joint actions so that VC is achieved even in the presence of a health emergency, since low compliance by the population for vaccination has contributed to increased influenza cases in Brazil. This demonstrates the importance of implementing national strategies, monitoring results and seeking alternatives that enable the goals and objectives established by WHO in the Global Influenza Strategy [27], in order to ensure safety and universal health coverage to the population.

The study's limitations are due to the fact that it deals with secondary data analysis, which has data quality issues, especially regarding the heterogeneity and lack of standard in data recording in the IESI-Influenza.

It is important to highlight that in the sample studied it is not possible to affirm whether unvaccinated individuals were included in the National Immunization Program (NIP) to receive the influenza vaccine or not, since the database used does not contain this data. However, it is important to reinforce that, in Brazil, the groups of adults considered eligible for influenza vaccination are restricted, leaving a considerable portion of this population without adequate protection to the disease.

Another limitation to be highlighted is the difficulty experienced as a notifying professional, due to the instability of the system, since there are times of "peak" access, especially during business hours, which generates delay of the web site in loading the recorded information and greater risk of bias in the quality of records.

Conclusion

The results of this study showed factors associated with death due to SARS caused by influenza in Brazil and identified risk factors and protective factors for death in the sample studied.

The main risk factors for death are no hospitalization, no cough and age. Also, black and brown individuals and people who did not receive the flu vaccine also have a higher risk of death.

Those who have complete high school or higher education, do not have dyspnea and O₂ saturation below 95%, do not have diabetes and chronic neurological disease, were not admitted to the ICU, required non-invasive ventilatory support or did not need this support are less likely to have a negative case outcome.

These findings reinforce the need to propose changes in public policies to make influenza vaccines available to the entire population and encourage vaccination compliance, in order to prevent severe cases, hospitalization and unfavorable outcomes, which translates into quality of life for the population and economy to the public health system.

Author contributions

The design the study was established by R.B.M., P.M.S.S., M.T., K.R.N.H., and P.H.B.S. Data were collected by R.B.M., P.M.S.S. and T.M.G. All authors have participated in data analysis, wrote the first draft, revised and approved the final version of the manuscript.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgements

This study was financed in part by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior - Brasil (CAPES) - Finance Code 001" and by the Grant #2021/04492-1, São Paulo Research Foundation (FAPESP).

We are grateful to Cintia Yurie Yamachi for her contribution to the statistical analysis of the data.

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