Hematological indices as indicators of inflammation induced by exposure to pesticides

Miguel Alfonso Ruiz-Arias1,2 · Irma Martha Medina-Díaz1 · Yael Yvette Bernal-Hernández1 · Juan Manuel Agraz-Cibrián3 · Cyndia Azucena González-Arias1 · Briscia Socorro Barrón-Vivanco1 · José Francisco Herrera-Moreno1 · Francisco Alberto Verdín-Betancourt1 · José Francisco Zambrano-Zaragoza3 · Aurora Elizabeth Rojas-García1

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Abstract
Pesticide toxicity, both acute and chronic, is a global public health concern. Pesticides are involved in abnormal inflammatory responses by interfering with the normal physiology and metabolic status of cells. In this regard, inflammatory indices aggregate index of systemic inflammation (AISI), monocyte-to-high-density lipoprotein ratio, monocyte-to-lymphocyte ratio (MLR), neutrophil-to-lymphocyte platelet ratio (NLPR), neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune inflammation index, and systemic inflammation response index (SIRI) have been used as predictive markers of inflammatory status in several diseases and also in acute poisoning events. This study aimed to determine systemic inflammation indices and their relationship with pesticide exposure from urban sprayers in 302 individuals categorized into three groups (reference group and moderate and high exposure groups). The data suggest that the AISI, MLR, NLPR, and SIRI indices were significantly higher in the exposed groups compared with the reference group. In conclusion, this study proposes that inflammation indices warrant further attention in order to assess their value as early biomarkers of acute and chronic pesticide intoxication.

Keywords Pesticide · Occupational exposure · Inflammation index · Systemic inflammation · Urban sprayers · Inflammatory response

Highlights
• Significant differences were observed in clinical parameters in pesticide sprayers.
• AISI, MLR, NLPR, and SIRI indices were significantly higher in the exposed groups compared with the reference group.
• Significant higher inflammation indicators were observed in pesticide sprayers.

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Introduction
Exposure to pesticide mixtures has resulted in serious problems for human health and the environment. Several studies have confirmed the link between exposure to pesticides and the incidence of a large number of adverse outcomes, such as reproductive effects, endocrine disorders, birth defects, and neurological, hepatic, respiratory, hematopoietic, and immunological effects, as well as the development of various types of cancer, including multiple myeloma, leukemia, and non-Hodgkin’s lymphoma (Piccoli et al. 2019; Cestonaro et al. 2020; Mu et al. 2021). In addition, the incidence of diabetes, obesity, and cardiovascular diseases has also been associated with pesticide exposure (Dayton et al. 2010; Everett and Matheson 2010; Legler et al. 2011). The common pathogenic mechanisms of these diseases are an increase in oxidative stress and a general inflammatory state (Madani et al. 2016).
Pesticides may trigger an abnormal inflammatory response via interference with normal physiology and the metabolic state of immune cells (Block and Hong 2005; Kumar et al. 2014). In consideration of these, several inflammation and immune-based prognostic scores have been used for the recurrence of inflammatory processes and the prognosis of acute toxicity, such as neutrophil-to-lymphocyte ratio (NLR) (Dundar et al. 2014; Zhou et al. 2016; Cao et al. 2019; Jeong and Sun 2020; Lionte et al. 2021; Mu et al. 2021), monocyte-to-lymphocyte ratio (MLR) (Lionte et al. 2021), platelet-to-lymphocyte ratio (PLR) (Elhosary and Abdelbar 2018; Wang et al. 2019; Lionte et al. 2021; Ortiz-López et al. 2022), monocyte-to-high-density lipoprotein ratio (MHR), and neutrophil-to-lymphocyte platelet ratio (NLPR) (Kanbay et al. 2014; Fois et al. 2020).

In addition, numerous novel inflammatory markers that include three or more indicators have been developed to reflect the balance of host inflammatory and immune status, including the systemic immune inflammation index (SII) based on the number of lymphocytes, neutrophils, and platelets, is an indicator associated with inflammation and that can reflect the immune and inflammatory state (Hu et al. 2014; Meng et al. 2018). Also, some studies have associated the SII with the prognosis of diseases (Miyamoto et al. 2019; Li et al. 2020), and this parameter can properly represent the inflammatory and immune status in COVID-19 patients (Fois et al. 2020; Hamad et al. 2022). The systemic inflammation response index (SIRI, the quotient of neutrophils and monocytes, divided by lymphocyte count) has been used to predict that survival can fully evaluate the balance between host immune and inflammatory conditions in cancer (Chen et al. 2020).

On the other hand, the aggregate index of systemic inflammation (AISI) has been proposed as a predictive tool that includes lymphocytes, neutrophils, platelets, and monocytes, which might be superior to simpler indexes as it better reflects the inflammatory status in the context of specific disease states (Zinellu et al. 2021).

Few studies have explored the relationship between pesticide exposure and hematological indices as indicators of inflammation. In most of these studies, only NLR, PLR, MLR, and SII indices were found to be determinate in acute intoxication (Dundar et al. 2014; Elhosary and Abdelbar 2018; Wang et al. 2019; Nejatifar et al. 2022). To the best of our knowledge, this is the first study in which eight inflammatory indices (AISI, MHR, MLR, NLPR, NLR, PLR, SII, and SIRI) are evaluated in a population chronically exposed to pesticides. This study aimed to determine the systemic inflammation indices and their relationship with pesticide exposure.

### Methodology

#### Study population

A cross-sectional study was carried out on a population of 302 individuals, of whom 181 were engaged in occupational pesticide spraying and the remaining 121 did not experience occupational exposure to pesticides. The inclusion criteria taken into account in the present study were individuals from Nayarit, Mexico, ≥ 18 years old, who decided to participate voluntarily in the present study, providing a signed written-informed consent letter. On the other hand, exclusion criteria were found: people who have constant exposure to x-rays or who taking immunosuppressants or corticosteroids. Each study participant donated a blood sample and completed a structured questionnaire designed to collect anthropometric and socioeconomic characteristics, age, harmful habits (smoking, consumption of drugs, and alcohol), medical history, as well as information on pesticide use and management, exposure time, and other variables. The study was approved by the Bioethics Commission of the State of Nayarit, Mexico (CEBN/0112017).

Peripheral blood samples were collected in EDTA tubes. Blood was drawn from the participants after fasting for 8–12 h. A certified laboratory carried out the blood work: a complete blood count and biochemical profile, including hemoglobin, hematocrit, platelets, glucose, urea, BUN, creatinine, total protein, albumin, total cholesterol, high-density lipoprotein (HDLC), triglycerides, and liver enzymes.

Blood was analyzed using an ADVIA 1650, Siemens Diagnostics, Marburg, Germany. In addition, the following formulas were used to determine the inflammatory indices:

**AISI** (neutrophils) (monocytes) (platelets) / lymphocytes

**MHR** monocytes / HDLC

**MLR** monocytes / lymphocytes

**NLPR** neutrophils / (lymphocytes)(platelet ratio)

**NLR** neutrophils / lymphocytes

**PLR** platelets / lymphocytes

**SII** (platelets)(neutrophils) / lymphocytes

**SIRI** (neutrophils)(monocytes) / lymphocytes

### Table 1 Formulas to determine inflammation indices

| Inflammation index | Formula |
|--------------------|---------|
| AISI               | (neutrophils) (monocytes) (platelets) / lymphocytes |
| MHR                | monocytes / HDLC |
| MLR                | monocytes / lymphocytes |
| NLPR               | neutrophils / (lymphocytes)(platelet ratio) |
| NLR                | neutrophils / lymphocytes |
| PLR                | platelets / lymphocytes |
| SII                | (platelets)(neutrophils) / lymphocytes |
| SIRI               | (neutrophils)(monocytes) / lymphocytes |

AISI, aggregate index of systemic inflammation; MHR, monocyte-to-high-density lipoprotein ratio; MLR, monocyte-to-lymphocyte ratio; NLPR, neutrophil-to-lymphocyte platelet ratio; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; SIRI, systemic inflammation response index; HDLC, high-density lipoprotein cholesterol (Kanbay et al. 2014 and Fois et al. 2020)
creatinine, uric acid, cholesterol, liver function tests, lipid profile, and absolute count of leukocytes, neutrophils, eosinophils, basophils, lymphocytes, and monocytes. Inflammation-related indices were calculated from the blood profile data, as presented in Table 1.

Statistical analysis

The geometric means (GM) with a 95% confidence interval (95% CI) in nonparametric variables and arithmetic means ± standard deviation (±SD) in parametric variables were calculated, and the proportions were analyzed via the Chi-square test. ANOVA with post hoc Bonferroni test and Kruskal–Wallis with post hoc Dunn’s test were applied to the parametric and nonparametric data, respectively. Statistical significance was considered at p values of <0.05. Statistical analysis was performed with Stata version 14 (Stata Statistical Software, Stata Corporation, College Station, Texas, USA) and GraphPad Prism version 6.02 (GraphPad software, San Diego, California, USA).

Results

Characteristics of the study population

The participants were categorized into three groups: (a) reference group, i.e., individuals without activities related to the use of pesticides, either permanent or temporary (office workers and others); (b) moderate exposure group, i.e., individuals who carried out spraying activities occasionally; and (c) high exposure group, i.e., individuals who participated in permanent fumigation activities. The GM of exposure to pesticides in the moderate exposure group (b) was 6.3 years (95% CI: 4.71–7.82), while in the high exposure group (c) was 6.7 years (95% CI: 5.02–8.45). Previously, our working group reported differences in some pesticide biomarkers of exposure among the study groups (Zepeda-Arce et al. 2017; Herrera-Moreno et al. 2021).

The population consisted of 36.75% women and 63.25% men, and the GM of the participants’ age was 34.80 years (95% CI: 33.64–35.99). With respect to body mass index (BMI), 35.10% of the participants were overweight, according to the World Health Organization (WHO) classification (2022), and 39.74% were obese. Table 2 presents the general characteristics of the study population for the exposition group (n = 302). A significant difference was observed in age, BMI, and educational level between the study groups. Regarding the BMI observed in the study population, overweight and obesity are mainly linked to cardiovascular diseases (WHO 2021), which could have negative implications for the health of the participants, in addition to the damage caused by occupational exposure to pesticides.

As shown in Fig. 1, organophosphates (OP), pyrethroids (PYR), and carbamates (CB) were the most used pesticides (by frequency) by the moderate and high exposure groups. In addition, temephos was the most used pesticide in the OP group, followed by chlorpyrifos and malathion. In the PYR group, the most used pesticides (by frequency) were deltamethrin, lambda-cyhalothrin, and permethrin. Bendiocarb is the most widely used pesticide in the case of CB.

Table 2 General characteristics of the study population

| Characteristics          | Group          | Reference | Moderate exposure | High exposure | p value   |
|-------------------------|--------------|-----------|-------------------|--------------|-----------|
| Total [n(%)]            |              | 121 (40.07) | 121 (40.07)       | 60 (19.87)   |           |
| Sex                     |              |           |                   |              | 0.10      |
| Male [n(%)]             |              | 73 (60.33) | 73 (60.33)        | 45 (75.00)   |           |
| Female [n(%)]           |              | 48 (39.67) | 48 (39.67)        | 15 (25.00)   |           |
| Age [years (95% CI)]    |              | 32.63 (30.81–34.56) | 37.17 (35.32–39.12) | 34.68 (32.48–37.04) | <0.01 |
| BMI (kg/m²)             |              |           |                   |              | <0.001    |
| Underweight [n(%)]      |              | 1 (100)   | –                 | –            |           |
| Normal weight [n(%)]    |              | 43 (57.33) | 17 (22.67)        | 15 (20.00)   |           |
| Overweight [n(%)]       |              | 43 (40.57) | 42 (39.62)        | 21 (19.81)   |           |
| Obesity [n(%)]          |              | 34 (28.33) | 62 (51.67)        | 24 (20.00)   |           |
| Education* [years (95% CI)] | 16.04 (15.47–16.64) | 11.52 (11.01–12.06) | 11.50 (10.89–12.14) | <0.001 |

*Values are presented as geometric means
95% CI, 95% confidence interval

Body mass index (BMI) according to the World Health Organization (WHO 2022): underweight (≤18.5 kg/m²), normal weight (>18.5 kg/m², ≤25 kg/m²), overweight (>25 kg/m², ≤30 kg/m²), and obesity (>30 kg/m²)
The main symptomatology reported by the study population exposed to pesticides included headache (68.51%), skin discomforts such as burning or itching (53.89%), weakness (50.83%), constant thirst (49.16%), burning in the eyes (48.07%), and abnormal tiredness (46.61%).

Clinical parameters

Table 3 shows data on the clinical parameters of the study population. Significant differences were observed between the groups in the following parameters: urea, uric acid, cholesterol, GOT, GPT, GGT, globulin, and hematocrit. A significant increase in the values of leukocytes, neutrophils, basophils, and lymphocytes was observed in the high exposure group.

Inflammation parameters

The AISI and MHR indices were analyzed with respect to the exposure groups (Fig. 2). The results show that AISI was significantly higher in both the moderate and high exposure groups compared with the reference group. In contrast, no significant difference was found in the values of the MHR index among the different groups.

As shown in Fig. 3, the values of the indices MLR and NLPR are plotted by exposure group. The results show an increasing trend of MLR values with respect to occupational exposure to pesticides. A significant difference in NLPR values is evident in the moderate and high exposure groups compared with the reference group.

In the case of NLR values, no significant difference was found between the exposure groups (Fig. 4). However, PLR values were significantly different in the moderate exposure group compared with the reference group. Interestingly, the individuals with the highest exposure did not show statistically significant differences in PLR values compared with the reference group.

Figure 5 shows the SII and SIRI values with respect to the exposure groups. The SII values were not influenced by the study population’s exposure to pesticides; however, differences were observed in the SIRI values in the moderate and high exposure groups when compared with the reference group.

Discussion

The threat of disease-transmitting vectors has led to the use of pesticides as the main strategy for pest control in many Latin American countries, including Mexico (Gómez-Arroyo et al. 2013). Personnel who apply pesticides or who handle different formulations in closed environments are at risk, and the severity of risk depends upon (among other factors) the duration of handling or application; in many cases, this is nearly constant throughout the year (Benitez-Trinidad et al. 2018).

Inflammation is essential for effective immunity, including tissue repair and the return to homeostasis (Afonina et al. 2017; Eming et al. 2017; Gong et al. 2020). However,
in unregulated conditions, inflammation is regarded as an unwanted response, particularly as it can lead to serious consequences, such as immune dysfunction, further tissue damage, sepsis, organ failure, or even death (Iqbal et al. 2017). The complexity of the process is reflected in the large number of cells involved in the molecular patterns associated with damage, mainly monocytes/macrophages, dendritic cells, neutrophils, mast cells, natural killer cells, and eosinophils (Gong et al. 2020). Accordingly, there is keen interest among researchers in characterizing diverse parameters of inflammation that can serve as prognostic tools in a broad array of diseases (Li et al. 2018; Aydin et al. 2022; Kara et al. 2022). Indices based on cell counts have been used to detect inflammatory events that are triggered by exposure to

### Table 3 Clinical parameters of the study population

| Parameter                  | Reference       | Moderate exposure | High exposure | p value |
|----------------------------|-----------------|-------------------|--------------|---------|
| Glucose [mg/dL (95% CI)]   | 84.16 (82.43–85.94) | 95.59 (85.47–95.23) | 84.50 (79.63–89.65) | 0.22<sup>a</sup> |
| Urea [mg/dL (95% CI)]      | 23.99 (22.92–25.11) | 22.25 (21.02–23.54) | 22.29 (20.76–23.94) | 0.03<sup>b</sup> |
| BUN [mg/dL (95% CI)]       | 11.21 (10.71–11.73) | 10.39 (9.82–11.00) | 10.81 (9.83–11.88) | 0.05<sup>a</sup> |
| Creatinine [mg/dL (95% CI)]| 0.76 (0.73–0.79) | 0.73 (0.70–0.77) | 0.76 (0.71–0.80) | 0.09<sup>a</sup> |
| Uric acid [mg/dL (± SD)]   | 5.32 (1.31) | 5.80 (1.66) | 5.97 (1.77) | 0.02<sup>b</sup> |
| Cholesterol [mg/dL (± SD)] | 182.62 (39.25) | 200.23 (37.64) | 182.59 (35.68) | <0.001<sup>b</sup> |
| GOT [UI/L (± SD)]          | 24.42 (20.96) | 30.99 (32.25) | 23.54 (12.11) | <0.001<sup>b</sup> |
| GPT [UI/L (95% CI)]        | 21.09 (18.96–23.47) | 30.17 (26.42–34.44) | 25.11 (21.58–29.22) | <0.001<sup>a</sup> |
| GGTP [UI/L (± SD)]         | 26.04 (23.17–29.25) | 40.11 (34.85–46.16) | 32.73 (26.90–39.82) | <0.001<sup>a</sup> |
| Albumin [g/dL (95% CI)]    | 4.70 (4.65–4.75) | 4.75 (4.69–4.81) | 4.77 (4.69–4.85) | 0.06<sup>a</sup> |
| Globulin [g/dL (± SD)]     | 2.72 (0.33) | 2.83 (0.34) | 2.83 (0.43) | 0.04<sup>b</sup> |
| Hemoglobin [g/dL (± SD)]   | 15.06 (1.41) | 14.79 (1.48) | 14.80 (1.40) | 0.27<sup>b</sup> |
| Hematocrit [% (± SD)]      | 44.50 (3.83) | 44.65 (3.91) | 44.83 (3.36) | 0.84<sup>b</sup> |
| Leukocytes [/mm³ (± SD)]   | 6702.31 (1592.33) | 7769.01 (1775.91) | 8187.33 (2219.47) | <0.001<sup>b</sup> |
| Neutrophils [/mm³ (95% CI)]| 3471.52 (3241.85–3717.46) | 4097.15 (3868.08–4339.78) | 4284.46 (3815.55–4810.98) | <0.001<sup>a</sup> |
| Eosinophils [/mm³ (95% CI)]| 258.00 (218.52–304.61) | 309.71 (265.18–361.73) | 293.72 (235.54–366.27) | 0.17<sup>a</sup> |
| Basophils [/mm³ (95% CI)]  | 67.59 (61.08–74.81) | 73.53 (63.49–85.17) | 99.94 (80.30–124.39) | <0.01<sup>a</sup> |
| Lymphocytes [/mm³ (95% CI)]| 2216.34 (2115.63–2321.85) | 2470.69 (2333.91–2615.48) | 2393.40 (2192.15–2613.13) | <0.01<sup>a</sup> |
| Monocytes [/mm³ (± SD)]    | 326.12 (173.78) | 468.49 (186.97) | 224.34 (244.34) | <0.001<sup>b</sup> |
| Platelets [/mm³ (± SD)]    | 264,644.6 (61,745.16) | 258,289.3 (63,096.15) | 254,916.7 (65,862.8) | 0.56<sup>b</sup> |

Fig. 2 AISI and MHR index values of the three exposure groups. AISI, aggregate index of systemic inflammation; MHR, monocyte/high-density lipoprotein cholesterol ratio. (a) Reference group individuals; (b) moderate exposure group individuals; (c) high exposure group individuals. Statistical analysis included ANOVA, Bonferroni test (ASI), and Kruskal–Wallis and Dunn’s test (MHR). Significant differences are indicated with the letters a, b, and c (p < 0.05).
Fig. 3 MLR and NLPR index values of the three exposure groups. MLR, monocyte-to-lymphocyte ratio; NLPR, neutrophil-to-lymphocyte platelet ratio. (a) Reference group individuals; (b) moderate exposure group individuals; (c) high exposure group individuals. Statistical analysis included ANOVA, Bonferroni test (MLR), and Kruskal–Wallis and Dunn’s test (NLPR). Significant differences are indicated with the letters a, b, and c ($p < 0.05$).

Fig. 4 NLR and PLR index values of the three exposure groups. NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. (a) Reference group individuals; (b) moderate exposure group individuals; (c) high exposure group individuals. Statistical analysis included Kruskal–Wallis and Dunn’s test (NLR and PLR). Significant differences are indicated with the letters a, b, and c ($p < 0.05$).

Fig. 5 SII and SIRI index values of the three exposure groups. SII, systemic inflammatory index; SIRI, systemic inflammatory response index. (a) Reference group individuals; (b) moderate exposure group individuals; (c) high exposure group individuals. Statistical analysis was performed with the Kruskal–Wallis and Dunn’s test (SII and SIRI). Significant differences are indicated with the letters a, b, and c ($p < 0.05$).
pesticides, and NLR is one of the most widely used indices (Dundar et al. 2014; Nejatifar et al. 2022). In the present study, we found significant differences in hematological parameters between the different exposure groups (moderate and high pesticide exposure compared to the reference group). These results are similar to those published recently by Nejatifar et al. (2022), who observed that NLR and other hematologic parameters, such as platelet count, red blood cell distribution, and the number of white blood cells, neutrophils, basophils, and eosinophils, in a group exposed to pesticides were significantly higher than in the unexposed group.

Moreover, the prognostic value of NLR, PLR, and other hematologic parameters measured in patients intoxicated with pesticides (within the first 24 h of admission to the emergency department) shows that the value of NLR and PLR was significantly higher in patients suffering from severe poisoning (Dundar et al. 2014). However, our data suggest that individuals subjected to high (occupational) exposure did not show significant differences in these index values compared with the control subjects. Therefore, in cases of pesticide intoxication, it is important to evaluate whether the degree of intoxication—based on the NLR and PLR indices—could be masked in subjects with chronic exposure. In addition, in the clinical studies mentioned above, patients requiring mechanical ventilation were found to have significantly higher leukocyte and neutrophil counts, as well as higher values of NLR and PLR and lower lymphocyte counts compared to non-ventilated patients (Dundar et al. 2014). Wang et al. (2019) determined that PLR is not a predictor for patients with acute paraquat poisoning; however, our data indicate that there is a decrease in PLR values compared to the reference group, similar to the results of a study in Egypt of patients with acute pesticide poisoning, in which it was shown that NLR and PLR were statistically elevated in the group of individuals who died compared to the group. These results are similar to those published recently by Nejatifar et al. (2022), who observed that NLR and other hematologic parameters, such as platelet count, red blood cell distribution, and the number of white blood cells, neutrophils, basophils, and eosinophils, in a group exposed to pesticides were significantly higher than in the unexposed group.

The main groups of pesticides (OP, CB, and PYR) to which urban sprayers are exposed can generate considerable alterations in many cellular structures, culminating in tissue-specific or system-wide damage (Le Couteur et al. 1999; Kirby et al. 2001; Barlow et al. 2005; Hirschfeld et al. 2010; Astiz et al. 2012; Cave et al. 2012; MacFarlane et al. 2013; Wong et al. 2017, 2021; Petrescu et al. 2018; Chen et al. 2019; Vilas-Boas et al. 2019). The mechanisms of pesticide uptake, the inflammatory environment, and their relationship. Pesticides induce oxidative stress through the generation of reactive oxygen species and reactive nitrogen species (RNS) by the activation of NADPH oxidases (NOX). This could induce the oxidation of lipids, proteins, and DNA damage. Continuous stress triggers inflammation and apoptosis. Additionally, these stressors lead to the activation of TNFR1/TNF-α, MAPK, NF-κB, and mitochondrial apoptosis.
pathways. Moreover, increased levels of nitric oxide (NO) and increased Ca\textsuperscript{2+} uptake stimulate the production of RNS. Intracellular Ca\textsuperscript{2+} induces an inflammatory stage through NF-κB activation, promoting the increase in the levels of proinflammatory cytokines (TNF-α and IL-6). Lastly, the inflammatory environment is associated with several chronic diseases, such as endocrine disorders, cancers, and deleterious effects on the neurological, immunological, and respiratory systems; all of these effects have been linked with pesticide exposure.

The main limitation of this study was not evaluating diseases that could interfere with hematological indices; however, this was in all the study groups. Our recommendation is that in future studies, cytokines as well as C-reactive protein could complement the inflammatory status.

In conclusion, we propose that inflammation indices warrant more attention in order to evaluate their value as early biomarkers of both acute and chronic pesticide poisoning and to explore the link between pesticide exposure and the development of inflammatory-related diseases.

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**Data availability** The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.
Declarations

Ethics approval The study was approved by the Bioethics Commission of the State of Nayarit, Mexico (CEBN/0112017).

Consent to participate All individuals voluntarily participated in the study and gave their informed written consent.

Consent for publication Written informed consent was obtained from all participants.

Competing interests The authors declare no competing interests.

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