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Research Paper

Sex differences in cortisol levels and their relationship with memory and negative affectivity in patients with drug-resistant epilepsy

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ABSTRACT

Drug-resistant epilepsy can be considered a chronic stress condition characterized by uncontrollable seizures together with cognitive and affective alterations. Epilepsy and its treatments affect men and women differently, potentially due to interactions with sexual hormones that influence how they experience the condition. This study examines potential sex differences in cortisol levels (as the product of stress processes), affectivity, and memory in patients with drug-resistant epilepsy, and the relationships among these variables. The sample was composed of 96 adult patients with drug-resistant epilepsy ($M = 38.01 \pm 11.12$ years; 47 men and 49 women). Results show that men had higher evening cortisol levels and cortisol area under the curve (AUC_i) than women (for both, $p < .05$), especially in those with a left hemisphere focus. Men also showed higher trait anxiety, higher DDD and poorer memory than women. In the total sample, trait anxiety and the DDD significantly predicted poor immediate and delayed memory, controlling for the side of seizure focus and effects of epilepsy type ($p < .001$). When analyses were stratified by sex, cortisol AUC_i predicted poorer delayed memory in men but not in women, while DDD predicted memory performance only in women. These findings suggest that cortisol, trait anxiety and the DDD are reliable predictors of memory impairment in patients with drug-resistant epilepsy, with a sex-differential pattern of relationships. Our results highlight the importance of considering sex differences and clinical variables when developing tailored treatment approaches for this population.

1. Introduction

Epilepsy is a neurological disorder that encompasses cognitive impairments and mood comorbidities and has been proposed as a model of chronic stress in humans [1], particularly in its drug-resistant form, as it closely fits the most restrictive definitions of chronic stress [2]. It is characterized by a long-lasting predisposition to seizures and the associated neurobiological, cognitive, psychological, and social consequences [3]. From a psychosocial perspective, individuals with epilepsy often experience a perceived lack of control over seizure occurrence, unpredictability, and social stigma, along with restricted educational/employment opportunities and high psychiatric comorbidity, mainly depression and anxiety [4,5]. Regarding cognitive impairments, memory deficits have been widely reported in patients with temporal lobe epilepsy (TLE) [6]. However, such deficits are not exclusively limited to this epilepsy type [7]. Unlike other chronic neurological conditions, epilepsy uniquely combines unpredictable, uncontrollable ictal and interictal events that repeatedly engage the hypothalamic-pituitary-adrenal (HPA) axis and disrupt circadian organization, providing recurrent stressors. This supports the view of

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epilepsy as a persistent stress context with systemic implications. Although relatively few studies have directly quantified the epilepsy–-stress link, converging evidence indicates that stress can increase seizure frequency and occurrence [8,9], and may be associated with a higher risk of developing epilepsy [10]. Neurobiologically, epilepsy could affect key brain structures involved in the HPA axis regulation, such as the amygdala, hippocampus, and prefrontal cortex [11]. Recurrent seizures, especially those originating in the limbic system, have been reported to lead to sustained hyperactivation of the HPA axis, with elevated basal cortisol, blunted diurnal rhythms, and altered feedback regulation [12]. This disruption is not only a consequence of epileptic activity but may, in turn, exacerbate seizure susceptibility, contributing to a vicious cycle of stress and seizure exacerbation. The consequences of epilepsy have relevant implications, helping explain the marked impact on quality of life, especially in drug-resistant epilepsy [13].

Sex differences have been found in the prevalence of certain conditions involving cognitive and emotional impairments, such as neurodegenerative and mood disorders, which are more prevalent in women than in men [14,15]. This disparity could be attributed, at least in part, to the effects of sex hormones through their relationships with the hypothalamic-pituitary-adrenal (HPA) axis [16]. Cortisol, as a product of HPA-axis activation, modulates the activity of key structures for learning and emotion processing such as the hippocampus and amygdala [17]. Maintained cortisol levels are associated with memory deficits and negative affectivity, mainly anxiety and depression, in clinical and non-clinical populations [18,19].

Despite the extensive body of data available in healthy individuals and clinical populations, sex differences in cortisol levels remain a topic of ongoing debate. Evidence on sex differences in basal cortisol is mixed and depends on factors such as the biological matrix, age, or measurement timing [20–23]. Clinical findings linking cortisol with sex, cognition, and negative affectivity are likewise inconsistent [24–26].

A potential factor contributing to these heterogeneous results could be the influence of chronic stress. Long-term health conditions can negatively impact patients' quality of life, triggering ongoing stress responses and adaptive challenges. Individual and sex differences in coping with chronic stress may further affect the relationships among cortisol, cognition, and emotion. In turn, prolonged cortisol release produces structural and functional alterations in the hippocampus [27] that result in cognitive impairment [19]. Evidence suggests that stress may have a more pronounced effect on memory in men than women, with cortisol playing a significant role in this relationship, whereas in women stress–cognition relations appear to be more strongly modulated by circulating ovarian hormones than by cortisol, potentially reflecting a protective influence of estrogens [28]. Understanding these differential patterns between cortisol and cognition depending on sex may be crucial to identifying sex-specific vulnerability of men and women to developing cognitive and emotional disorders.

Surprisingly, research on cortisol levels in patients with epilepsy is scarce. The limited studies suggest that patients with epilepsy exhibit higher cortisol levels compared to healthy individuals and that elevated cortisol levels are positively correlated with depressive symptomatology [29], trait anxiety [30], and impaired memory function [29–31]. The scarce data are also extended to the sex issue where only partial results are available. Sex differences in memory functioning and negative affectivity have been explored but without considering the potential role of cortisol in these differences. Regarding memory, an advantage for women patients over men has been found in verbal memory [32]. Furthermore, better performance in women, regardless of side of seizure focus, has been demonstrated for facial recognition tasks [33]. The few studies of negative affectivity have found a greater vulnerability in women than in men [34], similar to the general population [15]. Chronic stress could differentially affect affective and cognitive performance in men and women. But, in turn, epilepsy could be differently experienced in men and women in aspects such as lactation, pregnancy, contraception, or potential interactions between sex hormones and antiseizure medications (ASMs).

These results lead us to suspect sex differences in the relationships among cortisol levels, affectivity, and memory in patients with epilepsy – and these are probably modulated by clinical variables. This study aims to examine sex differences in cortisol levels, affectivity, and memory, as well as the existing pattern of relationships while considering clinical characteristics such as the side of the seizure focus or defined daily dose (DDD). In this sense, the variable sex was utilized, typically understood in a binary way as female or male, which encompasses a range of biological factors including physical, physiological, genetic, chromosomal, hormonal characteristics, and reproductive organs that are usually assigned at birth. Drawing insights from previous research, we hypothesized sex differences in afternoon salivary cortisol levels and that higher cortisol levels would be associated with poorer memory and greater negative affectivity [29–31]. We further hypothesized that these interrelations among cortisol, memory, and negative affectivity would show sex-specific patterns and be modulated by clinical variables such as side of seizure focus, seizure frequency, or DDD.

2. Materials and methods

2.1. Sample

Patients were recruited from the Refractory Epilepsy Unit at Hospital Universitario y Politécnico La Fe (Valencia, Spain) during the period from April 2015 to July 2023. All participants provided informed consent.

The inclusion criteria of the study were: (1) a diagnosis of drug-resistant focal epilepsy; (2) to be candidate for epilepsy surgery; (3) a minimum age of 18 years; and (4) undergoing a neuropsychological assessment before the surgical procedure. The exclusion criteria were as follows: (1) older than 65 years; (2) manifestation of severe cognitive impairment that impedes the administration of a reliable neuropsychological evaluation; (3) existence of an endocrine disorder; (4) lack of fluency in Spanish; and (5) the refusal to participate in the study.

2.2. Procedure

The present cross-sectional study has adhered to the guidelines and recommendations from the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [35] and to the principles stated in the Declaration of Helsinki. The procedure was approved by the Ethics Committee of the Hospital Universitario y Politécnico La Fe. Additionally, the study followed the SAGER (Sex and Gender Equity in Research) guidelines [36].

During the pre-surgical evaluation, the diagnosis of the type of epilepsy, the lateralization of the epileptogenic area, and the underlying etiology were determined. Sociodemographic characteristics of the patients (e.g., sex, age, marital status, educational level, employment status, or household members) were assessed. We collected data on the effects of menstruation on seizures in women, accounting for menopausal status, menstrual phase, and oral contraceptive use to control for their impact on cortisol levels. Clinical data (e.g., duration of epilepsy in years, age at epilepsy onset, seizure frequency per month, seizure type, and ASMs burden) were registered. The assessment was carried out by a multidisciplinary team, based on an extensive protocol including historical data collection, neurological examination, magnetic resonance imaging (MRI), video-electroencephalography (EEG) monitoring for five consecutive days, and in selected cases, positron emission tomography (PET), single photon emission computed tomography (SPECT), and intracranial EEG recording. Psychiatric and neuropsychological evaluations were performed on all the patients.

The pre-surgical neuropsychological assessment was carried out in a single session lasting approximately three hours, in which memory and negative affectivity (trait anxiety and depression) were evaluated. This session was conducted between 3 pm and 6 pm (late afternoon and

evening), to reduce possible hormone fluctuations in cortisol [37]. Participants were instructed to refrain from brushing their teeth, eating, smoking, or drinking stimulants for two hours before the assessment. In each session, nine saliva samples (C1-C9) were collected, maintaining approximately 20 min between samples.

ASMs burden was calculated in two ways: (a) the number of concurrent ASM; and (b) the computation of the DDD according to the Anatomical-Therapeutic-Chemical (ATC) classification index reported for drugs in use, which reflects the 'assumed average maintenance dose per day' [38]. For polytherapy, the DDD of individual concurrent drugs was added to the total DDD, allowing for inter-individual comparisons of total drug burdens [39].

2.3. Salivary cortisol

Saliva samples were collected using Salivette devices (Sarstedt, Nümbrecht, Germany). Participants were instructed to hold the cotton swab in their mouth for exactly 2 min without chewing. Samples were centrifuged at 3000 rpm for 15 min, yielding a clear, low-viscosity supernatant that was subsequently stored at -80 °C until analyses were performed at the Laboratory of Social Cognitive Neuroscience of the Faculty of Psychology, University of Valencia (Spain).

Salivary cortisol levels were measured in duplicate with the Salimetrics Salivary Cortisol Enzyme Immunoassay Kit (Newmarket, UK) with an assay sensitivity of < 0.007 μg/dL. For each patient, all samples were analysed in the same assay. Intra- and inter-assay coefficients of variation were less than 8 %, and cortisol concentrations were expressed in nmol/L.

2.4. Neuropsychological assessment

2.4.1. Memory

Memory was assessed using the Wechsler Memory Scale-Third Edition (WMS-III; [40]). The following subtests were employed: Logical Memory I and II (immediate and delayed verbal recall of short stories); Verbal Paired Associates I and II (immediate and delayed verbal recall of eight-word pairs); Faces I and II (immediate and delayed recognition of faces); and Family Scenes I and II (immediate and delayed recall for family scenes). These subtests provide material-specific memory indices (immediate auditory memory, delayed auditory memory, delayed auditory recognition, immediate visual memory, and delayed visual memory), two general memory indices (immediate memory and delayed memory), as well as indices of auditory processes (i.e., single-trial auditory learning, auditory learning slope, auditory retention index and auditory retrieval index). All indices were expressed in age-adjusted percentile or scalar scores. Test-retest reliability of this instrument is 0.87 [41].

2.4.2. Trait anxiety

Anxiety was assessed using the State-Trait Anxiety Inventory (STAI) questionnaire [42]. The trait anxiety scale (STAI-T) is composed of 20 items that assess relatively stable aspects of anxiety. Each item is ranked on a four-point Likert-type scale, from 0 ('hardly never') to 3 ('almost always'), with higher scores indicating higher anxiety. Total score was computed and transformed to percentile score. Cronbach's alpha for the Spanish adaptation of this inventory is 0.94 [43].

2.4.3. Depression

The depressive symptomatology was assessed using the Beck Depression Inventory-II (BDI-II; [44]) with 21 items rated on a four-point scale. The total direct score was computed, with higher scores indicating higher depression levels. Cronbach's alpha is 0.89 [45].

2.5. Statistical analyses

The Kolmogorov-Smirnov test was carried out to examine data normality. The distribution of the raw cortisol data was not normal, so a logarithmic transformation was performed.

Student's *t*-tests for independent samples were conducted to examine differences in continuous sociodemographic and clinical variables depending on sex and side of seizure focus. The chi-square test was used to evaluate the differences between the frequencies of categorical sociodemographic and clinical variables.

Differences in cortisol levels depending on sex and side of seizure focus were tested using repeated-measures analysis of covariance (ANCOVA) with 'sex' and 'side of seizure focus' as between-participant factors, 'moment' (C2 to C9) as the within-participant factor, and the C1 measurement (baseline levels) as a covariate. These analyses were repeated by including clinical and sociodemographic variables as covariates – such as educational level, insertion, duration of epilepsy in years, age of epilepsy onset, seizure frequency per month, age, affected lobe, and total DDD of ASM, according to previous studies [1]. In ANCOVAs, Greenhouse-Geisser correction was used to adjust for degrees of freedom where appropriate, and post-hoc comparisons were carried out using the Bonferroni test for *p*-values. We conducted independent samples *t*-tests and then univariate analyses of variance (ANOVAs) to assess the impact of sex, and the interaction between sex and the side of seizure focus on memory and negative affectivity. For trait anxiety, ANCOVAs were also repeated by including clinical and sociodemographic variables as covariates – such as educational level, insertion, duration of epilepsy in years, age of epilepsy onset, seizure frequency per month, age, affected lobe, and total DDD of ASM.

To explore the association of cortisol levels with sociodemographic and clinical variables, memory indices, trait anxiety, and depression, bivariate Pearson correlations were performed.

To estimate the magnitude of the evening variations in cortisol levels, the area under the curve to the ground (AUC_g) and the area under the curve to increase (AUC_i) were calculated following the trapezoid formula [46]. The AUC_g is an estimation of the total hormone secretion of cortisol throughout the nine samples of the evaluation, whereas the AUC_i, is a measure of the sensitivity of the system [46]. Student's *t*-tests were performed to explore the possible differences in AUC_g and AUC_i depending on sex and side of the seizure focus. Furthermore, univariate ANCOVAs were performed to analyse the differences among the groups in AUC_g and AUC_i, including as covariates the same variables used for the cortisol levels.

Hierarchical linear regression analyses were conducted to assess the potential predictive role of AUC_i and trait anxiety on memory, controlling the side of seizure focus, the affected lobe and the DDD. Immediate and delayed memory scores were entered as dependent variables. Three independent variables were included in three sequential blocks as follows: the first block includes the side of seizure focus,the affected lobe and the DDD; the second block includes AUC_i; and finally, the third block was composed of trait anxiety. These analyses were performed with the total sample and separately by sex.

A power analysis was conducted using G*Power version 3.1.9.7 to determine sample size [47]. Specifically, a prior power analysis indicated that a minimum of 24 participants would be required for a repeated-measures analysis of variance (ANOVA) with a within-between interaction, considering 'moment' (C2 to C9) as the within-subjects factor and 'sex' and 'side of seizure focus' as between-subjects factors ($f = 0.25$, $\alpha = 0.05$, power= 0.80, numerator $df = 21$, groups= 4, measurements= 8, nonsphericity correction $\varepsilon = 1$). Likewise, for a hierarchical multiple linear regression analysis with four predictors, the minimum required sample size was estimated at 85 participants ($f^2 = 0.15$, $\alpha = 0.05$, power= 0.80, numerator $df = 4$, total predictors= 4). Given the nature of all other analyses, no a-priori power analysis was conducted.

Data processing was performed with the SPSS version 28.0, and two-tailed tests with p set to 0.05 were considered significant.

3. Results

3.1. Patient characteristics

The study included 96 patients with drug-resistant epilepsy (M= 38.01 years, SD= 11.12; duration of epilepsy: M= 23.48 years, SD= 14.76) (Table 1). The sample was composed of 47 men and 49 women. Among the men, 19 had left-side seizure focus and 28 had right-side seizure focus. In the case of women, 28 had left-side seizure focus and 21 right-side seizure focus. The total DDD of ASMs differed between men and women (t= 2.21, p=.029; d= 1.19) with men taking higher doses of ASMs than women, so this variable was controlled for in subsequent analyses. No other significant differences were found in clinical and sociodemographic variables depending on sex and side of seizure focus. None of the 49 women were using oral contraceptives at the time of evaluation.

3.1.1. Sex differences in cortisol considering the side of the seizure focus

Repeated measures ANOVAs revealed a significant main effect of 'sex' on cortisol levels ($F_{(1,91)}$= 7.25, p= .008, η^2_p= 0.074), with higher levels in men than in women at C2, C4, C5, C7, C8 and C9 (for all, $p <$ .05), as well as a significant effect 'sex*side of seizure focus' interaction ($F_{(1,91)}$= 3.98, p= .049, η^2_p= 0.042). Specifically, in patients with the left seizure focus, men showed higher cortisol levels than women at C2, C3, C4, C5, C7, C8, and C9 (for all, $p <$ .05) (Fig. 1A), while no differences were found in patients with right seizure focus depending on sex (Fig. 1B). These effects were maintained even after controlling for sociodemographic and clinical covariates ($F_{(1,85)}$= 7.16, p= .009, η^2_p= 0.078 and $F_{(1,85)}$= 4.48, p= .037, η^2_p= 0.05, respectively). No other significant effects were found.

Significant differences were found in AUC_i according to sex ($F_{(1,92)}$= 5.24, p= .024, η^2_p= 0.054) (Fig. 2), with lower decreases in men than in women, even after controlling for sociodemographic and clinical covariates ($F_{(1,87)}$= 4.73, p= .032, η^2_p= 0.052). No significant differences were found depending on the side of seizure focus or 'sex*side of seizure focus' interaction. No significant effects were found for AUC_g.

3.1.2. Sex differences in memory and negative affectivity considering side of seizure focus

Univariate ANOVAs revealed significant differences in memory scores based on sex (Fig. 3), with men performing worse than women in the main indices of immediate and delayed memory, as well as delayed visual memory ($F_{(1,92)}$= 5.20, p= .025, η^2_p= 0.053; $F_{(1,92)}$= 4.46, p= .037, η^2_p= 0.046 and $F_{(1,92)}$= 4.64, p= .034, η^2_p= 0.048, respectively). A significant interaction effect of 'sex*side of seizure focus' was observed for auditory retention ($F_{(1,92)}$= 4.41, p= .038, η^2_p= 0.046), with men underperforming women in patients with right seizure focus. No significant main effects of the side of seizure focus on memory were found.

Men also showed higher trait anxiety scores compared to women ($F_{(1,92)}$= 3.97, p= .049, η^2_p= 0.041) (Table 2), without differences in depression scores. These sex differences in trait anxiety were maintained even after controlling for sociodemographic and clinical covariates ($F_{(1,85)}$= 3.99, p= .049, η^2_p= 0.045).

3.2. Relationships among variables

In the total sample, AUC_i was related to poorer delayed auditory memory and auditory retention (r= -0.242, p= .018 and r= -0.259, p= .011, respectively). Trait anxiety was negatively associated with working memory, immediate auditory and visual memory, immediate memory, delayed auditory and visual memory, delayed memory, single-trial auditory learning, auditory learning slope and auditory retention (r= -0.264, p= .010; r= -0.342, p= .001; r= -0.407, $p <$ .001; r= -0.443, $p <$ .001; r= -0.329, p= .001; r= -0.432, $p <$ .001; r= -0.454, $p <$ .001; r= -0.289, p= .004; r= -0.221, p= .030; r= -0.232, p= .023, respectively). Nonetheless, no relationships were found between depression and any memory indices, nor between negative affectivity and cortisol levels. Regarding clinical variables, seizure frequency was not related to memory, cortisol levels, or negative affectivity. Conversely, the DDD was negatively associated with working memory, immediate visual memory, immediate memory, delayed visual memory, delayed memory and learning slope (r= -0.357, p= .001; r= -0.317, p= .002; r= -0.293, p= .004; r= -0.238, p= .020; r= -0.260, p= .011; r= -0.252, p= .013), but showed no association with any cortisol index or negative affectivity.

Hierarchical regressions were performed to determine the degree of contribution of each variable to memory performance, considering the side of seizure focus, the mainly affected lobe and the DDD (Table 3). In the total sample, higher immediate and delayed memory scores were predicted by lower trait anxiety and lower DDD, which explained more than 20 % of the variance. In sex-stratified analyses, the models were significant for both sexes, though predictive patterns differed. In men, better immediate memory was predicted by lower trait anxiety, while delayed memory was predicted by both lower trait anxiety and lower cortisol AUC_i. These models explained more than 30 % of the variance. In women, higher immediate and delayed memory were predicted by both lower trait anxiety and lower DDD, explaining over 20 % of the variance.

4. Discussion

In line with our hypotheses, the present study shows that men with epilepsy have higher cortisol levels and cortisol AUC_i than women with epilepsy. Consequently, in accordance with the circadian rhythm of cortisol, men demonstrate slower declining levels in the afternoon than women, especially when they have a left seizure focus. Men also show higher trait anxiety and DDD, as well as poorer performance in the main memory indices than women. Both trait anxiety, cortisol, and the DDD correlate with poor memory performance in the total sample. By contrast, associations between cortisol and negative affectivity were not significant. This study proposes a model in which lower trait anxiety and lower DDD significantly predicted memory performance in the total sample. However, the sex-related differences emerged in the pattern of predictors. In men, higher trait anxiety and higher cortisol AUC_i were significant predictors of poor delayed memory, whereas in women, both lower trait anxiety and lower DDD predicted general memory performance. It is worth noting that these results were found even controlling for sociodemographic and clinical variables.

We found differences in cortisol levels between men and women, with higher cortisol levels in men, in agreement with results obtained with healthy populations [22]. Studies that have compared basal cortisol levels between patients with epilepsy and healthy participants have found mixed results, possibly due to the lack of consideration of the modulatory role of sex in the results [1]. When examining the cortisol indices, significant sex differences emerged for AUC_i, with higher scores in men than women. However, differences in AUC_g did not reach statistical significance. It is important to note that AUC_i is a measure of the dynamic of the cortisol changes during the assessment and so is more related to the sensitivity of the system, whereas the AUC_g is an estimate of the total cortisol secretion [46]. Our findings suggest less ability of the HPA axis to descend during the daily circadian rhythm in men with epilepsy than in women. Considering drug-resistant epilepsy as a multifactorial model of chronic stress [1] together with the adversities of everyday life, higher cortisol levels in these patients could lead to high costs for their health and thus impact all dimensions of their lives. Interestingly, the impact of the ASMs on cortisol levels was not significant in the present study, as the inclusion or not of these variables in the analyses did not modify the results. Moreover, as none of the female participants were taking hormonal contraceptives at the time of evaluation, the observed sex differences in cortisol levels are unlikely to be confounded by exogenous hormonal influences.

In terms of memory, women exhibited superior immediate and

Table 1
Sociodemographic and clinical characteristics of the sample according to sex and the side of seizure focus (mean ± SD and n %)).

	Women (n = 49)	Men (n = 47)	p	Women with left focus (n = 28)	Women with right focus (n = 21)	Men with left focus (n = 19)	Men with right focus (n = 28)	p
Age	38.35 ± 11.04	37.66 ± 11.29	0.76	38.57 ± 10.95	38.05 ± 11.43	38.21 ± 9.48	37.29 ± 12.54	0.98
Menstrual cycle			0.001***					0.001***
Menstrual phase	7 (14.3 %)	0 (0.0 %)		2 (7.1 %)	5 (23.8 %)	0 (0.0 %)	0 (0.0 %)	
Follicular phase	10 (20.4 %)	0 (0.0 %)		8 (28.6 %)	2 (9.5 %)	0 (0.0 %)	0 (0.0 %)	
Ovulatory phase	4 (8.2 %)	0 (0.0 %)		4 (14.3 %)	0 (0.0 %)	0 (0.0 %)	0 (0.0 %)	
Luteal phase	3 (6.1 %)	0 (0.0 %)		2 (7.1 %)	1 (4.8 %)	0 (0.0 %)	0 (0.0 %)	
Missing data	11 (22.5 %)	0 (0.0 %)		5 (17.9 %)	6 (28.6 %)	0 (0.0 %)	0 (0.0 %)	
Menopausal	14 (28.6 %)	0 (0.0 %)		7 (25 %)	7 (33.3 %)	0 (0.0 %)	0 (0.0 %)	
Marital status			0.24					0.38
Single	22 (44.9 %)	25 (53.2 %)		12 (42.9 %)	10 (47.6 %)	8 (42.1 %)	17 (60.7 %)	
Married	22 (44.9 %)	21 (44.7 %)		12 (42.9 %)	10 (47.6 %)	10 (52.6 %)	11 (39.3 %)	
Divorced	5 (10.2 %)	1 (2.1 %)		4 (14.2 %)	1 (4.8 %)	1 (5.3 %)	0 (0 %)	
Educational level			0.19					0.33
Primary	15 (30.6 %)	23 (48.9 %)		6 (21.4 %)	9 (42.9 %)	9 (47.3 %)	14 (50 %)	
Secondary	16 (32.7 %)	11 (23.4 %)		9 (32.1 %)	7 (33.3 %)	4 (21.1 %)	7 (25 %)	
University	18 (36.7 %)	13 (27.7 %)		13 (46.5 %)	5 (23.8 %)	6 (31.6 %)	7 (25 %)	
Academic/employment insertion			0.31					0.63
Yes	20 (40.8 %)	24 (51.1 %)		10 (35.7 %)	10 (47.6 %)	10 (52.6 %)	14 (50 %)	
No	29 (59.2 %)	23 (48.9 %)		18 (64.3 %)	11 (52.4 %)	9 (47.4 %)	14 (50 %)	
Household members			0.41					0.64
Family	18 (36.7 %)	18 (38.3 %)		11 (39.3 %)	7 (33.3 %)	5 (26.3 %)	13 (46.4 %)	
Partner	27 (55.1 %)	28 (59.6 %)		15 (53.6 %)	12 (57.2 %)	13 (68.4 %)	15 (53.6 %)	
Alone	4(8.2 %)	1 (2.1 %)		2 (7.1 %)	2 (9.5 %)	1 (5.3 %)	0 (0 %)	
Epilepsy duration (years)	25.45 ± 14.91	21.42 ± 14.47	0.18	24.32 ± 14.24	26.96 ± 15.98	24.21 ± 15.48	19.53 ± 13.72	0.35
Age at epilepsy onset (years)	12.89 ± 10.15	16.23 ± 10.64	0.12	14.25 ± 10.04	11.08 ± 10.26	14 ± 10.78	17.75 ± 10.48	0.17
Epilepsy type			0.71					0.71
TLE[a]	33 (67.4 %)	29 (61.7 %)		20 (71.4 %)	12 (57.1 %)	11 (57.9 %)	18 (64.3 %)	
ETLE[b]	16 (32.6 %)	18 (38.3 %)		8 (28.6 %)	9 (42.9 %)	8 (42.1 %)	10 (35.7 %)	
Affected lobe			0.52					0.72
Frontal	8 (16.3 %)	12 (25.5 %)		4 (14.3 %)	4 (19.1 %)	5 (26.3 %)	7 (25 %)	
Temporal	33 (67.4 %)	29 (61.7 %)		21 (75 %)	12 (57.1 %)	11 (57.9 %)	18 (64.3 %)	
Parieto-occipital	8 (16.3 %)	6 (12.8 %)		3 (10.7 %)	5 (23.8 %)	3 (15.8 %)	3 (10.7 %)	
Seizures per month	20.96 ± 48.90	23.30 ± 37.10	0.79	29.48 ± 62.94	9.62 ± 12.47	25.37 ± 38.39	21.90 ± 36.84	0.45
Seizure type			0.24					0.29
FAS[c]	5 (10.2 %)	2 (4.2 %)		4 (14.3 %)	1 (4.8 %)	1 (5.3 %)	1 (3.6 %)	
FIAS[d]	22 (44.9 %)	15 (32 %)		10 (35.7 %)	12 (57.1 %)	4 (21 %)	11 (39.3 %)	
FBTCS[e]	0 (0 %)	2 (4.2 %)		0 (0 %)	0 (0 %)	0 (0 %)	2 (7.1 %)	
FAS[c] + FIAS[d]	9 (18.4 %)	8 (17 %)		5 (17.9 %)	4 (19.1 %)	3 (15.8 %)	5 (17.9 %)	
FAS[c] + FBTCS[e]	0 (0 %)	0 (0 %)		0 (0 %)	0 (0 %)	0 (0 %)	0 (0 %)	
FIAS[d] + FBTCS[e]	8 (16.3 %)	15 (32 %)		6 (21.4 %)	2 (9.5 %)	9 (47.4 %)	6 (21.4 %)	
FAS[c] + FIAS[d] + FBTCS[e]	5 (10.2 %)	5 (10.6 %)		3 (10.7 %)	2 (9.5 %)	2 (10.5 %)	3 (10.7 %)	
Total DDD[f]	3.01 ± 1.15	3.54 ± 1.22	0.03*	2.96 ± 1.13	3.08 ± 1.21	3.45 ± 1.39	3.62 ± 1.11	0.17
Number of ASMs[g]	2.78 ± 0.98	3.04 ± 0.85	0.16	2.64 ± 0.78	2.95 ± 1.2	3 ± 0.94	3.07 ± 0.81	0.34
Number of failed ASMs[g]	7 ± 3.22	7.25 ± 3.87	0.73	7.29 ± 3.17	6.61 ± 3.32	7.79 ± 4.24	6.89 ± 3.63	0.74
MRI[h] findings			0.44					0.53
Hippocampal sclerosis	17 (34.7 %)	9 (19.1 %)		10 (35.7 %)	7 (33.3 %)	5 (26.3 %)	4 (14.4 %)	
Focal cortical dysplasia	9 (18.4 %)	9 (19.1 %)		7 (25 %)	2 (9.5 %)	4 (21.1 %)	5 (17.9 %)	
Tumour	9 (18.4 %)	10 (21.3 %)		6 (21.4 %)	3 (14.4 %)	4 (21.1 %)	6 (21.4 %)	
Heterotopia	0 (0 %)	2 (4.3 %)		0 (0 %)	0 (0 %)	0 (0 %)	2 (7.1 %)	
Cavernoma	3 (6.1 %)	3 (6.4 %)		2 (7.2 %)	1 (4.8 %)	1 (5.2 %)	2 (7.1 %)	
Non-specific pathology	11 (22.4 %)	14 (29.8 %)		3 (10.7 %)	8 (38 %)	5 (26.3 %)	9 (32.1 %)	

Note. [a]TLE: temporal lobe epilepsy
[b] ETLE: extratemporal lobe epilepsy
[c] FAS: focal aware seizures.
[d] FIAS: focal impaired awareness seizures.
[e] FBTCS: focal to bilateral tonic-clonic seizures.
[f] Total DDD: defined daily dose.
[g] ASM: antiseizure medication.
[h] MRI: magnetic resonance imaging.

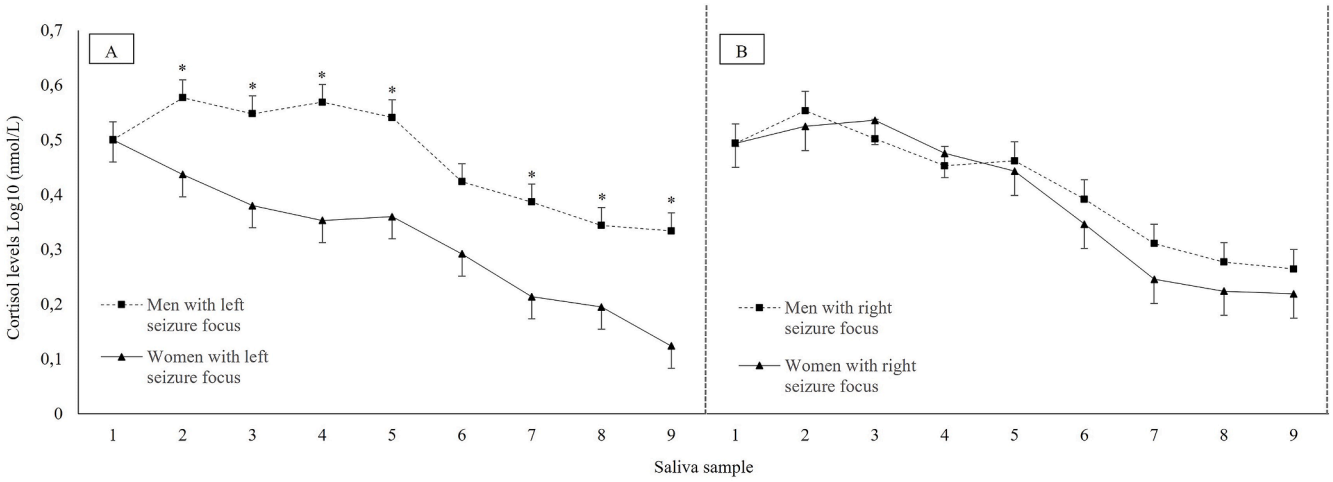

Fig. 1. Cortisol levels depending on sex and side of the seizure focus, controlling for baseline cortisol levels. A) Patients with left seizure focus. B) Patients with right seizure focus. Error bars represent 95% confidence intervals; *: significant 'sex*side of seizure focus' interaction.

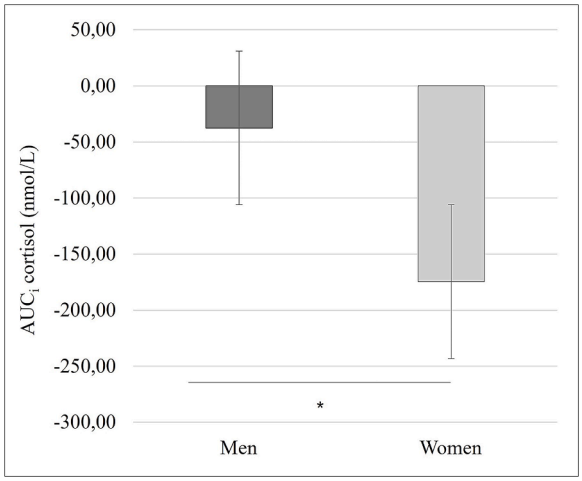

Fig. 2. AUC_i of cortisol depending on sex. Error bars represent 95% confidence intervals; *: $p < 0.05$.

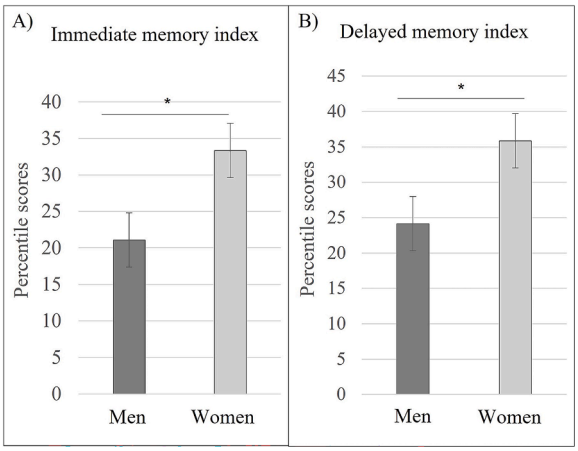

Fig. 3. Differences in the main memory indices (percentile scores) depending on sex. Error bars represent 95% confidence intervals; *: $p < 0.05$.

delayed recall, as well as enhanced delayed visual memory than men. Our findings are aligned with previously reported sex differences in episodic memory among patients with TLE [32] and are consistent with evidence of better performance by women in face recognition tasks, regardless of the side of seizure focus [33]. Indeed, in our study the visual memory tasks consisted of face recognition and recall of familiar scenes, which could explain the observed female superiority in delayed visual memory.

Our results indicated that men exhibited higher levels of trait anxiety than women; however, no significant differences were observed in depression scores. It should be noted that we considered trait anxiety and depression scores, which are not clinical measures, and this does not enable establishing a diagnostic criterion. These findings contrast with those found using clinical measures, where higher rates of mental health diagnoses were observed in women than men [34], similarly to the results found in the general population [15]. One plausible explanation is that the higher DDD observed in men —which may be indicative of disease burden— could contribute to elevated anxiety levels in this sample. However, the persistence of this sex difference after controlling for sociodemographic and clinical variables, including DDD, suggests that other factors are also involved (e.g., coping strategies, gender roles, or neurobiological differences in stress regulation). Furthermore, Witt et al. [48] reported that drug load bears only marginal links to markers of clinical severity, suggesting it should be interpreted primarily as treatment exposure and disease chronicity. Future studies should investigate these mechanisms further. In this context, it is important to consider the potential role of estradiol, which has been understudied, despite being associated with beneficial effects on mood and cognition [49]. Our findings underline the importance of considering sex

Table 2
Memory scores and negative affectivity depending on sex and side of seizure focus (mean ± SD).

				Women		Men		
	Women ($n = 49$)	Men ($n = 47$)	p	Left focus ($n = 28$)	Right focus ($n = 21$)	Left focus ($n = 19$)	Right focus ($n = 28$)	p
Memory[a]								
Immediate auditory	40.32 ± 33.87	30.55 ± 22.46	0.06	33.32 ± 33.31	49.66 ± 33.11	29.46 ± 23.43	31.28 ± 22.20	0.22
Immediate visual	32.37 ± 25.20	21.81 ± 23.30	0.07	33.16 ± 24.99	31.32 ± 26.08	29.29 ± 25.35	16.73 ± 20.76	0.29
Immediate memory	33.26 ± 29.94	21.19 ± 19.78	0.025*	30.04 ± 29.92	37.55 ± 30.18	24.56 ± 22.78	18.90 ± 17.53	0.22
Delayed auditory	42.50 ± 31.85	32.78 ± 25.04	0.07	35.66 ± 30.28	51.62 ± 32.33	32.74 ± 28.34	32.80 ± 23.09	0.18
Delayed visual	36.70 ± 29.98	23.42 ± 25.21	0.037*	34.01 ± 28.26	40.29 ± 32.49	32.74 ± 27.24	17.09 ± 22.04	0.06
Delayed memory	35.72 ± 29.98	24.30 ± 21.88	0.037*	31.06 ± 27.85	41.93 ± 32.25	28.89 ± 23.62	21.19 ± 20.47	0.09
Delayed auditory recognition	60.64 ± 127.04	40 ± 26.19	0.22	40.54 ± 29.61	87.44 ± 190.34	41.92 ± 27.71	38.71 ± 25.55	0.19
Single-trial auditory learning	43.53 ± 28.24	39.23 ± 20.10	0.38	41.64 ± 29.38	46.05 ± 27.15	39.47 ± 21.81	39.07 ± 19.26	0.64
Auditory learning slope	53.10 ± 32.08	50.26 ± 28.46	0.51	46.46 ± 34.58	61.95 ± 26.68	48.84 ± 29.77	51.21 ± 28.04	0.30
Auditory retention	51.12 ± 35.50	39.79 ± 26.95	0.06	41.75 ± 33.92	63.62 ± 34.42	42.79 ± 29.55	37.75 ± 25.39	0.038*
Auditory retrieval	47.86 ± 28	51.45 ± 32.89	0.53	45.14 ± 30.29	51,48 ± 24.87	56.95 ± 30.62	47.71 ± 34.39	0.22
Letter-Number Sequencing	7.92 ± 2.78	7.85 ± 2.36	0.88	7.86 ± 3.14	8 ± 2.28	7.83 ± 2.47	7.86 ± 2.33	0.91
STAI-T[b]								
Trait anxiety	54.73 ± 31.24	68.08 ± 28.40	0.049*	56.50 ± 31.73	52.38 ± 31.22	59.63 ± 28.94	73.82 ± 27.06	0.14
BDI[c]								
Depressive symptoms	12.06 ± 9.71	12.47 ± 8.94	0.83	13.36 ± 10.70	10.33 ± 8.15	12 ± 8.83	12.79 ± 9.15	0.71

[a] WMS-III: Wechsler Memory Scale, percentile scores are provided for all subscales except for the letter-number sequencing subscale, which includes scalar scores.
[b] STAI-T: Trait-State Anxiety Questionnaire, percentile scores of trait version.
[c] BDI-II: Beck Depression Inventory-II, direct scores.

hormones when studying the cognitive and emotional aspects of epilepsy. Although other clinical factors to explain these results cannot be discarded [50], the effects of variables such as younger age, seizure frequency, educational level, or younger age at epilepsy onset were controlled for throughout the different statistical analyses and results were maintained.

Regarding the relationships among variables, cortisol AUC_i was associated with poor memory, suggesting that elevated evening cortisol levels could result from an inability of the HPA axis to adequately inhibit itself, thus negatively impacting cognitive performance in these patients [29–31]. No significant associations were found between negative affectivity and cortisol, according to previous studies [30,31]. Contrary to expectations, seizure frequency showed no association with cortisol levels, memory, or negative affectivity [1,51,52]. Nonetheless, the DDD was negatively associated with memory performance, in line with evidence that greater ASM load relates to poorer objective memory and cognitive outcomes in epilepsy [53,54].

Our study proposes a model in which lower trait anxiety and lower DDD of ASMs were reliable predictors of immediate and delayed memory in the total sample, according to Cano-López et al. [31] and Höller et al. [55].

When analyzing sexes separately, distinct patterns emerged. In men, poorer immediate and delayed memory were predicted by higher trait anxiety, while poorer delayed memory was also predicted by higher cortisol AUC_i. In women, poorer immediate and delayed memory were predicted by higher trait anxiety and higher DDD, but not by cortisol. These findings underscore sex-specific pathways linking epilepsy-related variables, neuroendocrine function, and cognition. In women, trait anxiety and especially ASM burden—as reflected by DDD—appear to play a prominent role, potentially via pharmacokinetic and hormonal influences that can amplify ASM cognitive side effects in females (e.g., interactions with estrogen and progesterone) [56–58]. In men, the combination of heightened anxiety and impaired cortisol regulation appears particularly detrimental for memory. The absence of an association between cortisol and memory in women may relate to neuroprotective effects of female sex hormones in the presence of chronic stressors [1] and in HPA axis regulation [28,49,59]. Animal studies likewise show that, under chronic stress, memory performance can improve in females but worsen in males [60]. Thus, the effects of cortisol on memory likely depend on a complex interplay between brain region specificity, timing, and chronicity of exposure. Given the characteristics of these patients, a larger sample would be valuable to better profile differences, especially considering the side of seizure focus, as no significant differences were found when analyzing sex and seizure focus together in the present study.

Apart from sex differences in cortisol levels, the side of the seizure focus has also been considered and only cortisol levels and retention scores showed significant effects. With regards to cortisol levels, men have higher cortisol levels than women only in the left seizure focus group. In our study, comorbidities and cognitive performance are not significantly different in the group of men with left seizure focus which could contribute to explaining the cortisol differences. Previous studies have found functional hemispheric asymmetry in patients with brain damage, in which the right hemisphere plays an important role in the processing of negative emotions and in the regulation of cortisol secretion in emotional situations [61]. Despite this, left hemisphere could be also involved in regulating the time course of affective responses via inhibitory actions upon the right hemisphere, making necessary a healthy balance between both hemispheres for emotional processing [62]. However, previous research on this point is unclear and the underlying mechanisms are not yet fully understood. Future studies should examine the molecular, structural, and physiological implications of structures involved in the activation of the HPA axis, including the cognitive and behavioural consequences, considering variables such as sex or the side of seizure focus. Finally, we only found a significant interaction between sex and seizure focus side in auditory retention

Table 3
Hierarchical regressions.

Total sample						
	β	Lower limit	Upper limit	ΔR^2	R^2	F
Immediate memory index						
Block 1				.058		
Side of seizure focus	.04	-7.05	11.7			
Affected lobe	.03	-6.7	8.98			
DDD	-0.23*	-8.89	-1.1			
Block 2				.069		
AUC_i	-0.15	-0.03	.001			
Block 3				.24	.28	6.82**
Trait anxiety	-0.42**	-0.54	-0.22			
Delayed memory index						
Block 1				.04		
Side of the seizure focus	.06	-6.4	12.9			
Affected lobe	-0.05	-10.2	6.0			
DDD	-0.20*	-8.51	-0.48			
Block 2				.05		
AUC_i	-0.15	-0.03	.003			
Block 3				.23	.27	6.69**
Trait anxiety	-0.44**	-0.54	-0.22			
Men						
	β	Lower limit	Upper limit	ΔR^2	R^2	F
Immediate memory index						
Block 1				-0.03		
Side of the seizure focus	-0.03	-12.1	9.4			
Affected lobe	-0.02	-8.9	7.8			
DDD	-0.13	-6.23	2.12			
Block 2				-0.04		
AUC_i	-0.19	-0.02	.004			
Block 3				.25	.34	4.12*
Trait anxiety	-0.55**	-0.57	-0.20			
Delayed memory index						
Block 1				.02		
Side of the seizure focus	-0.09	-15.4	7.9			
Affected lobe	-0.08	-12.0	6.0			
DDD	-0.07	-5.7	3.2			
Block 2				.001		
AUC_i	-0.26*	-0.03	-0.001			
Block 3				.29	.36	4.7**
Trait anxiety	-0.55**	-0.62	-0.22			
Women						
	β	Lower limit	Upper limit	ΔR^2	R^2	F
Immediate memory index						
Block 1				-0.09		
Side of the seizure focus	.13	-8.52	23.9			
Affected lobe	.02	-12.9	15.4			
DDD	-0.31*	-15.1	-0.77			
Block 2				.09		
AUC_i	-0.13	-0.05	.02			
Block 3				.15	.24	2.71*
Trait anxiety	-0.28*	-0.53	-0.01			
Delayed memory index						
Block 1				.10		
Side of the seizure focus	.19	-5.02	27.3			
Affected lobe	-0.06	-17.0	11.2			
DDD	-0.31*	-15.1	-0.78			
Block 2				.09		
AUC_i	-0.06	-0.04	.03			
Block 3				.16	.25	2.8*
Trait anxiety	-0.29*	-0.54	-0.02			

Note. AUC_i: the cortisol area under the curve to increase; *, $p < .05$; **, $p < .001$.

scores, with worse results in right-focused males than in right-focused females; however, no relationships were found with cortisol levels.

This study has some limitations. First, the sample size might influence the limited results obtained regarding the impact of the interaction between the side of seizure focus and sex, despite a prior power analysis suggested that a sample size of 96 participants would have been sufficient to conduct the main statistical analyses. Second, it is possible that the neuropsychological assessment process acted as a stressful stimulus influencing cortisol levels. However, this does not explain the sex differences found to the extent that men and women performed the same procedure. Third, the focus on a specific population with focal epilepsy might have influenced the findings or limited the generalisability of the results to other epilepsy types, such as generalised epilepsies. Nonetheless, focal epilepsy is the most prevalent epilepsy type, accounting for approximately 61 % of all epilepsy cases [63]. These results facilitated a more precise exploration of the neuropsychological and endocrinological differences in this population. Fourth, data on the time elapsed between the last seizure and cortisol collection were not available, and its potential impact on cortisol levels cannot be ruled out [1,12]. Moreover, reliance on a single-day cortisol measurement may introduce variability, further limiting the interpretation of individual cortisol values. Nevertheless, we observed no significant association between cortisol levels and seizure frequency in our sample. Future research should control for this variable to strengthen the validity of cortisol-related findings. Fifth, the absence of a healthy control group limits the ability to determine whether the observed cortisol and anxiety levels are specific to individuals with epilepsy or reflect a sex-related pattern in the general population. The inclusion of such a group in subsequent investigations would improve interpretation regarding the nature of these differences. Finally, potential interactions of sex hormone fluctuations, as a result of phases in the menstrual cycle or menopause, cannot be discarded. Nevertheless, not enough data are available for robust analysis. Future studies should systematically collect data on sex hormones and menstrual cycle phases to address this issue. As multiple statistical comparisons were conducted, the possibility of type I error cannot be entirely ruled out, and results should be considered exploratory.

5. Conclusion

Overall, our results suggest that chronic stress may trigger a dysregulation of the HPA axis leading to a corticosteroid-dependent hippocampal damage mechanism, which may underlie cognitive impairments in these patients. Men show greater vulnerability to the effects of cortisol and trait anxiety on delayed memory than women. Women were more vulnerable to the effects of ASMs load (DDD) and also trait anxiety on general memory performance. Surprisingly, cortisol levels, the DDD and trait anxiety were not related. Our findings suggest that hormonal, cognitive, and affective dimensions are involved in drug-resistant epilepsy, a condition that is both complex and multifactorial and must be carefully considered from a sex-specific view. Therefore, it is crucial to further elucidate the affective-cognitive profiles within this clinical population to enhance disease management and significantly improve patients' quality of life. Our results also suppose a significant contribution to the field of neuroscience as it is one of the few works that examines sex differences in cortisol levels and their correlation with affectivity and memory in this population. This study also highlights the importance of including both sexes in future research to mitigate sex bias in neurosciences.

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CRediT authorship contribution statement

Paula Tormos-Pons: Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Irene Cano-López:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Conceptualization. **Judit Catalán-Aguilar:** Methodology, Investigation, Data curation. **Alejandro Lozano-García:** Methodology, Investigation, Data curation. **Kevin G. Hampel:** Writing – review & editing, Resources, Methodology. **Vanesa Hidalgo:** Writing – review & editing, Methodology. **Alicia Salvador:** Writing – review & editing. **Vicente Villanueva:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Funding acquisition. **Esperanza González-Bono:** Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

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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Data availability

Data will be made available on request.

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