communications medicine

A Nature Portfolio journal

Article

https://doi.org/10.1038/s43856-025-01020-4

Association between blood cortisol levels and numerical rating scale in prehospital pain assessment

Raúl López-Izquierdo[1,2,3], Elisa A. Ingelmo-Astorga[1], Carlos del Pozo Vegas[2,4] ✉, Santos Gracia Villar[5,6,7], Luis Alonso Dzul López[5,6,7], Silvia Aparicio Obregón[5,8,9], Rubén Calderon Iglesias[5,8,10], Ancor Sanz-García[11,12,13,15] & Francisco Martín-Rodríguez[2,14,15]

Abstract

Background Nowadays, there is no correlation between levels of cortisol and pain in the prehospital setting. The aim of this work was to determine the ability of prehospital cortisol levels to correlate to pain. Cortisol levels were compared with those of the numerical rating scale (NRS).

Methods This is a prospective observational study looking at adult patients with acute disease managed by Emergency Medical Services (EMS) and transferred to the emergency department of two tertiary care hospitals. Epidemiological variables, vital signs, and prehospital blood analysis data were collected. A total of 1516 patients were included, the median age was 67 years (IQR: 51–79; range: 18–103) with 42.7% of females. The primary outcome was pain evaluation by NRS, which was categorized as pain-free (0 points), mild (1–3), moderate (4–6), or severe (≥7). Analysis of variance, correlation, and classification capacity in the form area under the curve of the receiver operating characteristic (AUC) curve were used to prospectively evaluate the association of cortisol with NRS.

Results The median NRS and cortisol level are 1 point (IQR: 0–4) and 282 nmol/L (IQR: 143–433). There are 584 pain-free patients (38.5%), 525 mild (34.6%), 244 moderate (16.1%), and 163 severe pain (10.8%). Cortisol levels in each NRS category result in $p < 0.001$. The correlation coefficient between the cortisol level and NRS is 0.87 ($p < 0.001$). The AUC of cortisol to classify patients into each NRS category is 0.882 (95% CI: 0.853–0.910), 0.496 (95% CI: 0.446–0.545), 0.837 (95% CI: 0.803–0.872), and 0.981 (95% CI: 0.970–0.991) for the pain-free, mild, moderate, and severe categories, respectively.

Conclusions Cortisol levels show similar pain evaluation as NRS, with high-correlation for NRS pain categories, except for mild-pain. Therefore, cortisol evaluation via the EMS could provide information regarding pain status.

Plain language summary

We aimed to determine the associations between prehospital cortisol levels and pain scores in pain assessment of nonselected patients with acute diseases treated by emergency medical services (EMS). This study was carried out in an ambulance referring to two hospitals in Spain A total of 1516 patients were ultimately enrolled in this work. Cortisol is an objective biomarker that could add value in pain assessment. The inclusion of this parameter in EMS pain assessment procedures along with the pain score could improve patients' care and optimize pain characterization.

As reported by the World Health Organization (WHO), pain is one of the most common causes of medical visits at all healthcare services and is one of the most frequent symptoms associated with multiple conditions[1]. Pain constitutes a common symptom in prehospital care, whether due to acute events (trauma, injuries, burns, chest pain), inadequate control of chronic pain, oncological processes, postoperative pain, etc., and is even a frequent reason for demanding emergency healthcare[2]. Over 30% of patients managed by emergency medical services (EMS) and transferred via ambulance to an emergency department (ED) presented moderate or severe pain[3].

However, the characterization of pain is particularly complex since the accompanying factors that can modulate this symptom are very heterogeneous, such as age (especially in children and the elderly), origin, acute or chronic, gender, previous experiences, cultural context, etc., ultimately, this is an interpersonal experience, difficult to define objectively and in a standardized way. In this sense, scales could help identify pain, showing EMS-providers the best way to pick up pain and guide the proper next steps[4].

EMSs should visualize, document and quantify pain as objectively as possible. This information may help in the decision-making process in the

A full list of affiliations appears at the end of the paper. ✉e-mail: cpozove@saludcastillayleon.es; carlosdelpozovegas@gmail.com

dynamic and ever-changing context of prehospital care, where critical moments need to be acted upon with very little data and in a diligent way. However, despite the availability of pharmacological and non-pharmacological solutions, operating procedures routinely involving the assessment of pain intensity and characteristics are rare in prehospital care[5].

Because pain is a totally subjective and interpersonal experience, this variability makes it essential to use specific validated scores to guide decision-making[6]. In this context, solutions such as the verbal rating score (VRS)[7] have rapidly expanded and started to be used in workflows as a regular practice[8]. However, pain assessment scales such as the VRS may not be sufficiently accurate as a single tool. Multiple factors could change the rating, like pain tolerance, previous use of painkillers or other drugs that change or suppress pain, acute poisoning from alcohol or drugs etc. So, clear as day, identifying and characterizing acute pain presents a challenge for EMS[9].

Research has shown that the hypothalamic–pituitary–adrenal axis is triggered in painful conditions, resulting in increased bioavailability of cortisol[10]. Cortisol testing in saliva, hair, or blood has proven to be valuable to detect elevated stress levels and chronic pain[11]. In addition, several studies have found high levels of cortisol prior to the diagnosis of life-threatening conditions, suggesting that cortisol is activated in response to serious disturbances in the normal regulation of biological and physiological processes[12].

There is a growing interest in identifying objective biomarkers that could provide information regarding pain assessment. Cortisol, a hormone released in response to stress via activation of the hypothalamic–pituitary–adrenal (HPA) axis, is associated with both acute and chronic pain. While cortisol is not specific to pain alone, its levels may reflect the physiological burden of pain in acute settings. Our hypothesis is that cortisol levels will increase in parallel with reported pain intensity and could serve as an objective indicator of pain severity, particularly in cases where subjective reporting may be unreliable or absent.

The primary aim of this study is to analyze the correlation between NRS and cortisol blood levels in patients with acute disease managed by EMS. The secondary aim consisted of an evaluation of the association between cortisol and NRS categorization. We find that there is a significant correlation between NRS ratings and cortisol. Cortisol measurements obtained for every NRS category are significant, as in the post-hoc analysis. Consequently, cortisol presents effective classification performance for pain-free, moderate and severe pain.

Methods

Study design and setting

A prospective observational study was performed. Adults with acute disease managed by EMS and transferred to the ED were prospectively included from the study "Clinical characterization of acute pain in prehospital critical care: novel biomarkers and therapeutic targets" (prePAIN study) between 1st January 2023 and 1st June 2024. The study included patients with acute disease with or without acute pain, ultimately aiming to analyze the association between NRS ratings and cortisol levels, using patients without pain as a control group. Starting hypothesis suggests that patients without pain should have shorter cortisol levels.

One advanced life support (ALS) unit and two university tertiary hospitals were involved in the study. ALS consists of two emergency medical technicians (EMTs), an emergency registered nurse (ERN) and a physician, operating 24/7/365 in urban and rural areas and providing coverage in Valladolid (Spain), with a population of 525,455 residents. Resources were fully pooled and managed by the Public Health System (SACYL).

The study was approved by the institutional review boards (IRB) of the Research Ethics Committee for Medicines (CEIm) of the Healthcare Area of Valladolid West, Spain (ref. 23:-PI110 protocol V_01) and was conducted in compliance with the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) guidelines.

Population

Adults (≥18 years old) with unselected acute diseases were included. To participate in the study, patients were mandatorily assessed by ALS physicians and subsequently evacuated to an ED, either in ALS or basic life support. Patients not requiring transfer to the hospital (discharge onsite) or who did not need an IV (always according to the ALS medical evaluation) were not eligible.

Minors, pregnant women (evident or probable), terminally ill patients (documented by specialist reports), absence of a blood sample (e.g., improper vascular access) or cases with an already established intravenous line, and those who provided no informed consent were excluded. Similarly, patients whose altered Glasgow Coma Scale (GCS) verbal response (score lower than 5 points) were also excluded. That is, all cases included in the final analysis demonstrated a normal verbal response (5-point rating), oriented in time, person and place. Additionally, stroke or transient ischemic attack cases were likewise excluded.

Informed consent was obtained during prehospital care by the ALS ERN and was applicable for the entire study, including the duration of follow-up for all participants. If, despite the previous attempt, authorization was not granted, an associate investigator from each ED was responsible for a second effort to obtain the document. Patients who provided non-informed consent were excluded.

Outcome

The primary outcome was the pain evaluation by using the NRS score collected during the first encounter of EMS providers with the patient and always prior to any type of intervention, obviously including analgesia or venous access. All NRS were performed obligatorily by the ALS physician and entered into the database set up for this purpose.

The score was determined and documented by the ERN or a physician from the ALS. The NRS is a validated tool employed in multiple clinical situations[13,14] including an adaptation and validation by Spanish[15].

NRS categorization

Long-standing efforts to provide a classification of reported pain levels have been made[16]. This way, the categorization suggested in this study is in line with previous study recommendations[17,18].

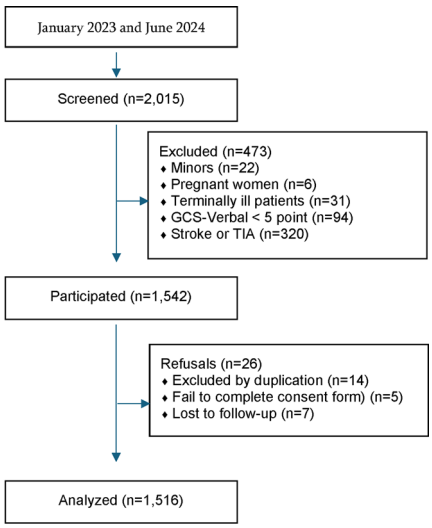
Pain intensity was assessed via a numerical rating scale (NRS), where patients were asked to rate their pain from 0 to 10, with 0 representing no pain and 10 representing the worst pain imaginable. This assessment was conducted by the ALS physician/ALS nurse during the first encounter with the patient prior to any intervention, including analgesia or venous access.

For analytical purposes, the continuous NRS scores were subsequently categorized into four pain severity groups following established clinical guidelines: pain-free (0 points), mild pain (1–3 points), moderate pain (4–6 points), and severe pain (≥7 points). This categorization was based on the one used for the verbal rating scale (VRS) categories and has been validated in previous emergency medicine research[4,19].

Note that "pain categories" or "NRS categories" will be used indistinctly throughout the text to refer to the above categorization.

Predictors and data abstraction

Epidemiological variables and vital signs were collected via the ALS ERN during the first contact with the patient. Prospectively, point-of-care cortisol measurements were conducted (extraction was performed in the ambulance but the analysis was done in another laboratory). Cortisol was measured with an Affias-6 (© Boditech Med, Inc., Gang-won-do, Korea), with a working range of 80–800 nmol/L. The EMS providers involved in the study attended mandatory face-to-face training for sample collection and storage. A four-step standardized operation is followed. First, 2 ml of whole blood was withdrawn from the venous line with the S-Monovette® EDTA K3 system (SARSTEDT AG & Co. KG, Nümbrecht, Germany). Arterial, venous, and capillary blood can be processed with these systems; however, only venous blood samples were tested in this study. Second, the S-Monovette® with the blood sample is labeled with the EMS



Abbreviations: GCS: Glasgow coma scale; TIA: transient ischaemic attack

Fig. 1 | Study flowchart. GCS Glasgow coma sale, TIA transient ischemic stroke.

incident ID code and refrigerated in the ambulance cooler, ranging in temperature from 4.5 to 8 °C. Third, the next day, an ambulance associate investigator transferred the samples (preserving the cold chain) to the Biomarker Laboratory (BioLab) of the School of Medicine (Valladolid University). Finally, a lab operator processed the sample, which was extracted by an electronic pipette with 100 µL of whole blood, which was deposited in the microwell of the test card. After 10 min, the result is displayed. Cortisol outcomes do not account for any on-scene or en-route intervention.

The ALS physician subsequently recorded the administration of opioid, opioid-free, and multimodal analgesia and suspected prehospital diagnoses, according to the International Classification of Diseases 11th Revision.

Finally, 30 days after the index event (prehospital care), an associate investigator from each ED, by reviewing the electronic medical records, collected the following hospital follow-up data: admission rate; critical care unit-admission; 17 comorbidities required to compute the age-adjusted Charlson comorbidity index (aCCI); opioid, opioid-free, and multimodal analgesia; and 30-day mortality (all-cause). Electronic medical records contain info on both hospital and primary care, providing a very reliable and consistent source, both in- and out-of-hospital mortality.

Statistics and reproducibility

Descriptive results and the associations between the outcomes and the analyzed variables were assessed by a *t* test, the Mann–Whitney U test or the chi-square test, when appropriate. Absolute values and percentages were used for categorical variables, and median interquartile ranges (IQRs) were used for continuous variables because they did not follow a normal distribution. The data collection, missing value handling, and sample size calculations explained in supplementary material p5.

Three approaches were used to evaluate the association of cortisol with NRS: (i) analysis of variance (ANOVA), (ii) correlation, and (iii) classification capacity.

-(i) Considering NRS pain categories, an ANOVA, and subsequent post-hoc (Tukey's Honest Significant Difference (HSD) test), were used to analyze the differences in cortisol means across the categories of VRS (pain-free, mild pain, moderate pain, severe pain).

(ii) A Spearman correlation between cortisol and NRS was performed.

(iii) A multiclass classification approach was used by considering cortisol capacity to predict the aforementioned categories. The procedure was as follows. First, the cohort was split into training and validation cohorts by maintaining the proportion of the outcome in 2/3 and 1/3 of the patients, respectively. Second, a multinomial logistic regression was used to model the relationship between cortisol and NRS categories. Third, cortisol performance was assessed by the area under the curve (AUC) of the receiver operating characteristic (ROC) curve analysis, including the 95% confidence intervals (CIs). All 95% CIs were obtained by bootstrapping (2000 iterations). The following parameters of the ROC curve were assessed: specificity (sp), sensitivity (sen), positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio. The maximum potential effectiveness achieved by the score, the Youden index, was also reported. Since AUC, sp, and sen are typically computed for binary outcomes, a one-vs-all approach was used to evaluate each category against all others.

All calculations and analyses were performed by using our own codes, R packages and base functions in R, version 4.2.2 (http://www.R-project.org; the R Foundation for Statistical Computing, Vienna, Austria).

Ethics approval

This study was approved by the Health Research Ethics Board of all participating centers.

Results

Patient baseline

After the application of the exclusion criteria, 1516 patients were ultimately enrolled in the final analysis (see Fig. 1). The median age was 67 years (IQR: 51–79; range: 18–103), 42.7% (647 cases) were female, with median NRS and cortisol values of 1 point (IQR:0–4) and 282 nmol/L (IQR: 143–433) respectively, and the 30-day mortality rate was 5.3% (81 patients).

According to the NRS, severe pain (≥7 points) made up 10.8% (163 cases). This category had a median age of 59 years (46–74) with 28.8% younger than 49 years, the lowest age among participants ($p < 0.001$), and predominantly males. The primary EMS-related conditions were trauma and injuries (39.3%, 64 cases) and cardiovascular conditions (31.9%, 52 cases). The median cortisol level was 745 nmol/L (IQR: 654–800), and the rate of prehospital analgesia was the steepest in the analysis: 55.8% opioid-free, 63.2% opioid and 38% multimodal analgesia. As expected, this cluster displayed the worst rates of ICU admission and 30-day mortality, with reports of 35.4% (74 cases) and 8.6% (14 cases), respectively (see Table 1).

In contrast, the pain-free category (0 points) represented the bulk cases (38.5%, 584 cases), with a median age of 65 years (IQR: 48–78), highlighting diseases of medical origin (cardiovascular, neurological and infection), with only 0.5% (3 cases) experiencing trauma and injury. Mild pain (1–3 points) was 34.6% (525 cases) and moderate pain (4–6 points) was 16.1% (244 cases). From pain-free to severe pain, cortisol levels increased, as did analgesia utilization, ICU admission and 30-day mortality (see Table 1). The descriptive results of the variables according to each NRS point are in Supplementary Table S1.

Evaluation of the association between cortisol and the NRS

A statistically significant main effect was found for cortisol means across the categories of NRS ($F = 1283$, $df = 3$, $p = 2e{-}16$). Post-hoc comparisons revealed differences across all NRS categories (all $p = 1.2e{-}14$) (Fig. 2a). The correlation between the cortisol concentration and NRS was $R = 0.87$ ($p = 2e{-}16$) (Fig. 2b).

The results of the multinomial logistic regression used to model classification of cortisol into the four NRS categories are in Supplementary Table S2. The cortisol AUC for each NRS category was 0.882 (95% CI: 0.853–0.910), 0.496 (95% CI: 0.446–0.545), 0.837 (95% CI: 0.803–0.872), and 0.981 (95% CI: 0.970–0.991) for the pain-free, mild, moderate, and severe categories, respectively (Table 2). There were statistically significant differences between the classification capacity of all the categories ($p < 0.001$), except for the pain-free vs moderate categories. The results from further metrics of the AUC (Table 3) revealed that the cutoff points for each category were 230 (95% CI: 210–234), 150 (95% CI: 134–210), 345 (95% CI:

Table 1 | Baseline patient characteristics by NRS groups

	Numerical rating scale, points				
Characteristics[a]	**Pain-free (0)**	**Mild (1–3)**	**Moderate (4–6)**	**Severe (≥7)**	***p* value[b]**
No. (%)	584 (38.5)	525 (34.6)	244 (16.1)	163 (10.8)	NA
Epidemiological variables					
Sex, female	272 (46.6)	217 (41.3)	101 (41.4)	57 (35)	0.431
Age, year	65 (48–78)	72 (57–82)	63 (49–77)	59 (46–74)	1.6e−09
Age groups, year					
18–49	155 (26.5)	85 (16.2)	61 (25)	47 (28.8)	2.4e−06
50–74	238 (40.8)	212 (40.4)	108 (44.3)	78 (47.9)	
>75	191 (32.7)	228 (43.4)	75 (30.7)	38 (23.3)	
On-scene vital signs					
RR, breaths/min	18 (15–24)	19 (16–26)	18 (17–22)	22 (18–28)	2.1e−05
SpO2, %	97 (94–98)	97 (94–98)	97 (95–99)	96 (94–99)	0.024
SBP, mmHg	133 8114–153)	140 (121–159)	137 (120–158)	133 (111–148)	1.2e−04
DBP, mmHg	78 (64–91)	81 (67–93)	83 (68–95)	78 (67–91)	0.021
HR, beats/min	87 (70–109)	86 (70–105)	81 (70–96)	84 (71–103)	0.146
Temperature, °C	36.1 (35.8–36.7)	36.1 (35.9–36.7)	36 (35.8–36.3)	36 (35.7–36.5)	3.1e−04
GCS, points	15 (15–15)	15 (15–15)	15 (15–15)	15 (15–15)	0.458
Cortisol, nmol/L	133 (102–221)	287 (211–341)	469 (413–561)	745 (654–800)	3.7e−205
Prehospital analgesia					
Opioid-free	98 (16.8)	124 (23.6)	73 (29.9)	91 (55.8)	8.4e−23
Opioid	40 (6.8)	109 (20.8)	94 (38.5)	103 (63.2)	2.1e−58
Multimodal	12 (2.1)	31 (5.9)	31 (12.7)	62 (38)	6.3e−46
Prehospital diagnosis					
Cardiovascular	202 (34.6)	306 (58.3)	124 (50.8)	52 (31.9)	1.1e−16
Neurology	72 (12.5)	34 (6.5)	8 (3.3)	11 (6.7)	
Trauma	3 (0.5)	54 (10.3)	69 (28.3)	64 (39.3)	
Respiratory	52 (8.9)	38 (7.2)	11 (4.5)	1 (0.6)	
Poisoning	134 (22.9)	5 (1)	3 (1.2)	2 (1.2)	
Infection	67 (11.5)	50 (9.5)	5 (2)	8 (4.9)	
Digestive	10 (1.7)	26 (5)	23 (9.4)	22 (13.5)	
Endocrine	21 (3.6)	6 (1.1)	1 (0.4)	0 (0)	
Anaphylaxis	22 (3.8)	6 (1.1)	0 (0)	0 (0)	
Others[c]	0 (0)	0 (0)	0 (0)	3 (1.8)	
Hospital outcomes					
aCCI, points	4 (1–6)	5 (3–7)	3 (1–6)	3 (1–5)	1.3e−11
H. admission	182 (31.2)	230 (43.8)	132 (54.1)	122 (74.8)	3.9e−24
Hospital analgesia					
Opioid-free	110 (18.8)	171 (32.6)	90 (36.9)	62 (38)	4.1e−10
Opioid	17 (2.9)	44 (8.4)	45 (18.4)	64 (39.3)	4.1e−40
Multimodal	2 (0.3)	12 (2.3)	17 (7)	25 (15.3)	1.4e−19
ICU-admission	32 (5.5)	74 (14.1)	75 (30.7)	74 (35.4)	2.8e−12
30-day mortality	14 (2.4)	35 (6.7)	18 (7.4)	14 (8.6)	6.3e−04
In-hospital	9 (1.4)	26 (5)	13 (5.3)	10 (6.1)	0.003
Out-of-hospital	5 (0.9)	9 (1.7)	5 (2)	4 (2.5)	0.353

NA not applicable, *RR* respiratory rate, *SpO2* oxygen saturation, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HR* heart rate, *GCS* Glasgow Coma Scale, *aCCI* Age–Charlson comorbidity index, *H* hospital, *ICU* intensive care unit.

[a]Values are expressed as the total number (percentage in parenthesis) and median (25th percentile–75th percentile in parenthesis), as appropriate.

[b]The Mann–Whitney U test or chi-square test was used as appropriate.

[c]Other conditions: endocrine, genitourinary and disease of the blood and the immune system.

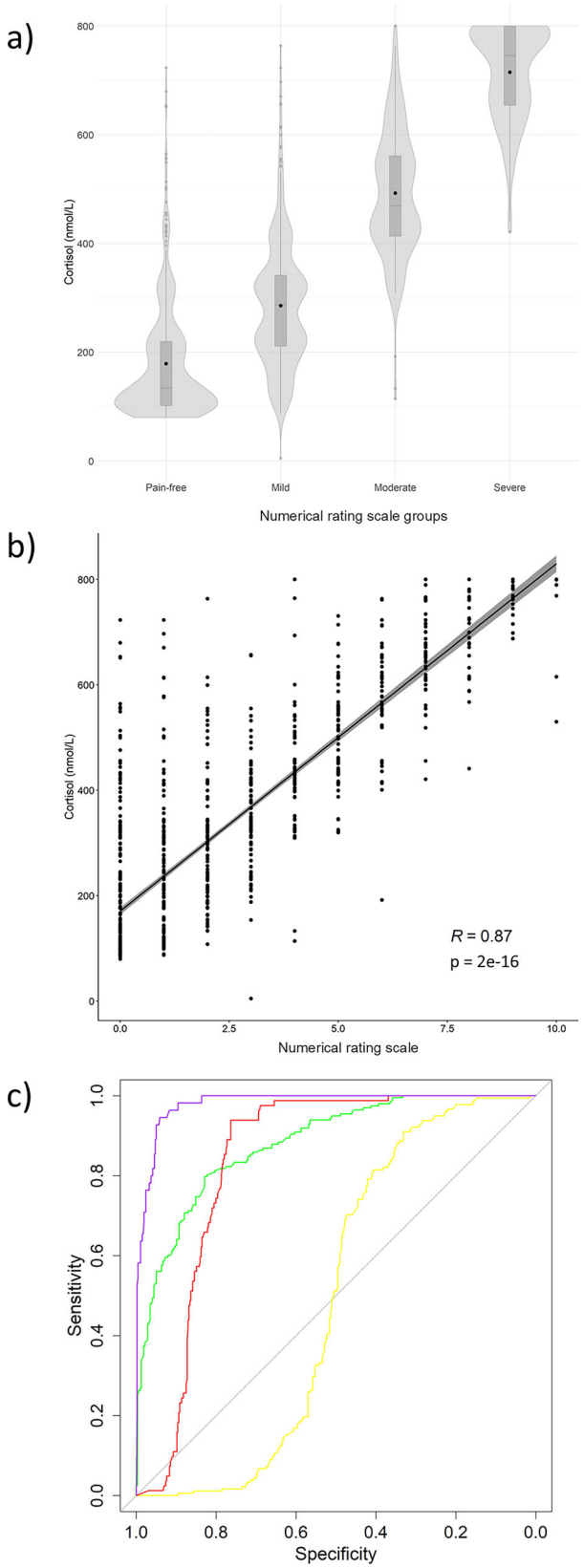


Fig. 2 | Evaluation of the association between cortisol and the NRS. a Boxplot of the cortisol distribution according to the VRS categories, **b** correlation between the cortisol level and NRS points, and **c** classification capacity of the cortisol level for each NRS category. Pain-free (green line), mild (yellow line), moderate (red line), and severe (purple line). $N = 1516$.

323–384), and 557 (95% CI: 515–588) for pain-free, mild, moderate, and severe patients, respectively.

Discussion

This prospective, observational ambulance-based study revealed a significant correlation between NRS ratings and cortisol point-of-care testing conducted in prehospital care in unselected adults with acute disease. Cortisol measurements obtained for every NRS category were significant, as in the post-hoc analysis; consequently, one could assume that cortisol levels are graded according to the NRS categories, with excellent classification performance for pain-free, moderate and severe pain.

Cortisol upregulation related to chronic pain, distress or prevalent comorbidities is well known[19]. Nonetheless, no study has analyzed cortisol upregulation in the acute pain phase and its association with the NRS score or other acute pain evaluation scores in prehospital critical care. Hao et al.[20] examined the effectiveness of several doses of corticosteroids administered by epidural injection in acute lumbar discogenic radicular pain by testing plasma levels of glucose, serum cortisol, and serum adrenocorticotropic hormone. Doses above 40 mg of corticosteroids resulted in pain relief, with serum cortisol triggers, thus indicating the role of cortisol as a reliable predictor of pain relief efficacy. Reyes Del Paso et al.[21] evaluated the role of hair cortisol levels in patients with fibromyalgia. Pain/intensive stress appears to acutely elevate cortisol levels in the early stages of fibromyalgia, decreasing levels in the longer term. Adachi et al.[22] conducted a study in which salivary cortisol and a low pulse-to-high pulse ratio were used to estimate perioperative pain in children. Salivary cortisol was strongly correlated with perioperative pain. Tanaka et al.[23] used three perioperative inflammatory biomarkers (interleukin-6, C-reactive protein, and cortisol levels) and the postoperative NRS to evaluate the effectiveness of analgesia in robot-assisted laparoscopic radical prostatectomy. In summary, despite the lack of evidence for the use of cortisol in acute diseases in prehospital care, blood cortisol appears to play a key role in the modulation of both chronic and acute pain, as attested by the studies cited above. Indeed, these studies are in line with our results, where it seems that an elevated intensity of pain is necessary to trigger a cortisol release, since there was a poor classification capacity of cortisol for those patients with mild pain.

The physiological pain-triggering response is well known. Faced with the unpleasant physiological and sensory experiences that lead to acute pain, the nociceptive system is immediately stimulated as an alarm signal and biological safeguard, despite the different capacities of individual patients to modulate this response (threshold). In this sense, pain can be evaluated by three different physiological activation pathways. Sympatho-adrenergic discharge is manifested mainly by gross alterations in heart rate and blood pressure. Activation of the hypothalamic-pituitary-adrenal axis causes sustained increases in blood cortisol and lactic acid. Finally, the immune response triggers an increase in the level of 6-interleukin[24,25] This array of signs, symptoms and biomarker alterations translates into a heterogeneous and diverse response, making quantification extremely challenging[26].

EMS providers routinely apply standardized scoring systems (e.g., the GCS and the modified Rankin Scale) and/or validated biomarkers such as glucose. Nonetheless, standardized and validated instruments for an objective assessment of pain in prehospital care are rarely adopted[27]. In this sense, a key challenge for EMS providers involves timely and consistent acute pain monitoring; and in a the second step, to objectively evaluate the intensity, in order to be able to implement the most appropriate response specifically tailored to each patient[28,29] To achieve this objective, two handicaps are detected. On the one hand, although pain is considered the fifth vital constant[30], no active research is carried out, resulting in a lack of standardized assessments with validated scoring systems; on the other hand, the poor perception of pain implies a scarcity of records and assessments of pain, resulting in an underestimation of this condition[31].

Cortisol has been shown to aid in the identification of acute, non-explicitly referred pain. EMS providers must make quick critical decisions,

Table 2 | Cortisol performance according to each NRS category

	Pain-free	Mild	Moderate	Severe
Pain-free	0.882 (0.853–0.910)	2.2e−16	0.052	2.9e−10
Mild		0.496 (0.446−0.545)	2.2e−16	2.2e−16
Moderate			0.837 (0.803–0.872)	2.3e−14
Severe				0.981 (0.970–0.991)

Delong's test results for the comparison between AUCs. The diagonal shows the AUC results and the 95% confidence intervals in parenthesis.

Table 3 | Sensitivity and specificity combined with a better score (Youden's test) for the different analyzed pain categories

	Pain-free	Mild	Moderate	Severe
Youden's test	232 (210–234)	150 (134–210)	345 (323–384)	557 (515–588)
Sensitivity	0.80 (0.73–0.86)	0.91 (0.80–0.96)	0.95 (0.89–0.99)	0.96 (0.93–1.00)
Specificity	0.83 (0.78–0.88)	0.34 (0.27–0.46)	0.76 (0.68–0.80)	0.93 (0.88–0.97)
PPV	0.75 (0.69–0.81)	0.42 (0.40–0.45)	0.43 (0.37–0.48)	0.64 (0.49–0.76)
NPV	0 (0–0)	0 (0–0)	0 (0–0)	0 (0–0)
Likelihood ratio+	4.68 (3.30–7.31)	1.38 (1.09–1.77)	3.98 (2.80–5.01)	14.71 (7.58–28.63)
Likelihood ratio−	0.24 (0.16–0.34)	0.26 (0.10–0.75)	0.06 (0.02–0.16)	0.04 (0.01–0.08)

Bracketed numbers indicate 95% confidence intervals.
PPV positive predictive value, *NPV* negative predictive value.

sometimes with confounding data[32]. The use of standardized tools such as the NRS could assist in the decision-making process, with cortisol reinforcing the clinical characterization of acute pain[8,33] Pain experience is fully unique and is mediated by an innumerable list of distracting factors and comorbidities[34]. Faced with the same injury or acute disease, two patients may report different symptoms, or even the same patient, faced with a similar but recurrent ailment, may experience differences in the pain level. Therefore, reliable biomarkers that do not depend on personal experience, level of consciousness or cofounders to be able to objectify the degree of pain should be considered. In this sense, blood cortisol seems to be a good predictor of acute pain and may help EMS systems manage pain on scene or *en route*[35,36].

Our study was designed to explore whether cortisol levels, despite their broad reactivity, could still provide meaningful information in the specific context of acute pain assessment in prehospital care. In this particular scenario, where multiple stressors coexist, cortisol may serve as an objective measure capturing the overall physiological burden, and patients may be unable to communicate owing to altered consciousness, language barriers, or cognitive impairment or may deliberately underreport pain owing to fear of addiction stigma or desire for rapid transport. Additionally, healthcare providers may unconsciously bias their pain assessment on the basis of visible injuries, potentially missing internal pain sources. A recent study[37] revealed that 23% of EMS patients with significant pain were undertreated due to assessment limitations. To address this, we implemented several methodological safeguards: (i) Controlled timing of measurement: Cortisol levels were measured at the first EMS contact, prior to any intervention (e.g., analgesia, IV fluids), minimizing confounding from treatment-related stress responses. (ii) Exclusion criteria: We excluded patients with altered consciousness, stroke, or terminal illness and those without a reliable verbal response to reduce variability from nonpain-related stressors. (iii) Correlations with a validated pain scale: Despite the broad reactivity of cortisol, we found a strong correlation ($R = 0.87$, $p < 0.001$) between cortisol levels and the numerical rating scale (NRS), a validated subjective pain measure. These findings suggest that, in the acute setting, cortisol levels may reflect pain intensity with reasonable specificity. (iv) Differentiation by pain category: Cortisol demonstrated excellent classification performance for moderate and severe pain (AUC = 0.837 and 0.981, respectively) but not for mild pain (AUC = 0.496). This finding supports the idea that cortisol may be particularly useful in identifying clinically significant pain, where subjective reporting may be unreliable or unavailable. (v) Information role: We do not propose cortisol as a replacement for subjective pain assessment but rather as a tool, which is particularly valuable in cases where verbal communication is impaired or when providers face diagnostic uncertainty due to ambiguous or absent external signs of injury. In summary, while cortisol is indeed a broad marker of physiological stress, our findings suggest that in the prehospital setting, it can serve as a useful adjunct to traditional pain assessment tools, especially for identifying moderate to severe pain.

The study was not limitation-free. First, a single-center study involving a single ALS and two university tertiary hospitals was performed. To minimize bias, data from 24/7/365 cases in urban and rural areas were collected without filtering by condition group. Nevertheless, future multicenter studies in different EMS systems are needed to confirm the results obtained. Second, data extractors were not censored. To avoid cross-contamination, data collection was performed in two steps. In the first step, the EMS providers entered the prehospital variables into a database created for this purpose. In the second step, a hospital investigator collected the hospital follow-up data. The EMS providers did not have access to the hospital follow-up data; likewise, the hospital investigators did not know the prehospital care data. Only the PI and data manager had full access to the joint database. Third, prehospital NRS scores were available, but the same data were not available at the hospital level. A review of the electronic medical records revealed that the NRS score was recorded in only 32.2% of the patients under review. In subsequent research, the availability of this information would be highly recommended to be able to conduct a longitudinal comparison. Fourth, several factors such as stressful stimuli (not only physical but also emotional stress) have been shown to modify cortisol levels. Since these factors were not available in this work, our results should be interpreted considering this fact. Fifth, this study has shown the association between elevated cortisol levels and high NRS ratings. However, further research is needed to confirm whether cortisol is also involved in patients who cannot be tested for NRS. Sixth, the study would benefit from further analysis of nonsurvivors. Although the observed 30-day mortality rate was 5.3%, the NEWS scores in this population were generally low, indicating a low predicted risk of death. This discrepancy suggests that the mortality rate observed may be higher than expected for a population with such physiological profiles and warrants further investigation into potential contributing factors. Seventh, cortisol could be determined by salivary tests; however, we considered blood cortisol due to practical and methodological

considerations specific to the prehospital emergency setting: (i) In the dynamic and time-sensitive environment of prehospital care, the collection of saliva samples presents logistical challenges, including the need for patient cooperation, avoidance of contamination, and the requirement for specific storage conditions. In contrast, blood sampling is already a routine part of advanced life support (ALS) protocols; thus, integrating cortisol measurement into this workflow is more feasible and consistent. (ii) To mitigate the confounding effect of IV placement on cortisol levels, all blood samples were collected immediately upon vascular access and before any therapeutic intervention, including analgesia. While we recognize that venopuncture itself can increase cortisol, this effect is likely minimal compared with the physiological stress of acute illness or injury, particularly in patients with moderate to severe pain. (iii) Although salivary amylase has shown promise as a stress biomarker, it is more sensitive to sympathetic nervous system activation and may not reflect hypothalamic–pituitary–adrenal (HPA) axis activity as directly as cortisol is. Our study aimed to explore the HPA-mediated response to acute pain, for which cortisol remains a well-established marker. We agree that future studies should consider a multimodal biomarker approach, including salivary amylase, to increase diagnostic precision. (iv) Despite advances in salivary biomarker research, studies evaluating these markers in real-world EMS environments are lacking. Finally, portable, rugged and reliable small-sized cortisol analytical devices are not currently available, implying a technical and logistical complication. In addition, the implementation of these systems appears limited. However, the use of point-of-care testing is becoming widespread in multiple clinical scenarios, bringing blood tests for multiple biomarkers closer to the bedside.

In summary, blood cortisol has been demonstrated to be associated with pain, as shown by its correlation with NRS, and the capacity to classify patients according to pain categories, except for mild pain. This evidence suggests that blood cortisol could provide information regarding patient pain in acute conditions, such as that observed in the EMS environment.

Data availability

Complete data from this study is available from the corresponding author upon reasonable request. Source data underlying the results and figures are available in the Supplementary Data 1 file.

Code availability

R Code details are available in the Supplementary Methods.

Received: 17 October 2024; Accepted: 8 July 2025;
Published online: 23 July 2025

References

1. Raja, S. N. et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. *Pain* **161**, 1976–1982 (2020).
2. Lindbeck, G. et al. Evidence-based guidelines for prehospital pain management: recommendations. *Prehosp. Emerg. Care.* **27**, 144–153 (2023).
3. Schaller, S. J. et al. Differences in pain treatment between surgeons and anaesthesiologists in a physician staffed prehospital emergency medical service: a retrospective cohort analysis. *BMC Anesthesiol.* **19**, 18 (2019).
4. Karcioglu, O., Topacoglu, H., Dikme, O. & Dikme, O. A systematic review of the pain scales in adults: which to use? *Am. J. Emerg. Med.* **36**, 707–714 (2018).
5. Hewes, H. A., Dai, M., Mann, N. C., Baca, T. & Taillac, P. Prehospital pain management: disparity by age and race. *Prehosp. Emerg. Care.* **22**, 189–197 (2018).
6. Ferreira, G. E. et al. General practitioners' decision-making process to prescribe pain medicines for low back pain: a qualitative study. *BMJ Open.* **13**, e074380 (2023).
7. Atisook, R., Euasobhon, P., Saengsanon, A. & Jensen, M. P. Validity and utility of four pain intensity measures for use in international research. *J. Pain. Res.* **14**, 1129–1139 (2021).
8. Wennberg, P., Pakpour, A., Broström, A., Karlsson, K. & Magnusson C. Alfentanil for pain relief in a swedish emergency medical service - an eleven-year follow-up on safety and effect. *Prehosp. Emerg. Care* 1–6, https://doi.org/10.1080/10903127.2024.2363509) (2024).
9. Nimmaanrat, S., Thepsuwan, A., Tipchatyotin, S. & Jensen, M. P. Measuring pain intensity in older patients: a comparison of five scales. *BMC Geriatr.* **24**, 556 (2024).
10. Bindellini, D. et al. A quantitative modeling framework to understand the physiology of the hypothalamic-pituitary-adrenal axis and interaction with cortisol replacement therapy. *J. Pharmacokinet Pharmacodyn.* https://doi.org/10.1007/s10928-024-09934-7 (2024).
11. Ciubotariu, D. et al. Hair cortisol as a marker of stress in mild traumatic brain injury: a challenging measure. *Sci. Rep.* **15**, 9373 (2025).
12. Faresjö, T. et al. Elevated levels of cortisol in hair precede acute myocardial infarction. *Sci. Rep.* **10**, 22456 (2020).
13. Price, D. D., McGrath, P. A., Rafii, A. & Buckingham, B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain* **17**, 45–56 (1983).
14. Delgado, D. A. et al. Validation of digital visual analog scale pain scoring with a traditional paper-based visual analog scale in adults. *J. Am. Acad. Orthop. Surg. Glob. Res Rev.* **2**, e088 (2018).
15. Ferrer-Peña, R. et al. Adaptation and validation of the Spanish version of the graded chronic pain scale. *Reumatol. Clin.* **12**, 130–138 (2016).
16. Hjermstad, M. J. et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. *J. Pain. Symptom Manag.* **41**, 1073–1093 (2011).
17. Moore, R. A. et al. Comparing pain intensity rating scales in acute postoperative pain: boundary values and category disagreements. *Anaesthesia* **79**, 139–146 (2024).
18. He, S., Renne, A., Argandykov, D., Convissar, D. & Lee, J. Comparison of an Emoji-based visual analog scale with a numeric rating scale for pain assessment. *JAMA* **328**, 208–209 (2022).
19. Bijur, P. E., Latimer, C. T. & Gallagher, E. J. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. *Acad. Emerg. Med.* **10**, 390–392 (2003).
20. Jesin, J. A. & Walton, D. M. Cortisol as a marker of pain and distress after acute musculoskeletal trauma. *Clin. J. Pain.* **40**, 157–164 (2024).
21. Hao, C. et al. Pain reduction and changes in serum cortisol, adrenocorticotropic hormone, and glucose levels after epidural injections with different doses of corticosteroid. *Pain Phys.* **27**, E119–E129 (2024).
22. Reyes Del Paso, G. A. et al. A two-component model of hair cortisol concentration in fibromyalgia: Independent effects of pain chronicity and severity. *Eur. J. Pain.* **28**, 821–830 (2024).
23. Adachi, A. et al. Evaluating perioperative stresses in children by noninvasive modalities using salivary cortisol and autonomic reactivity. *Pediatr. Surg. Int.* **40**, 1 (2024).
24. Tanaka, N. et al. Effect of nociception level-directed analgesic management on opioid usage in robot-assisted laparoscopic radical prostatectomy: a single-center, single-blinded, randomized controlled trial. *J Anesth.* https://doi.org/10.1007/s00540-024-03365-x (2024).
25. Timmers, I. et al. Fear of pain and cortisol reactivity predict the strength of stress-induced hypoalgesia. *Eur. J. Pain.* **22**, 1291–1303 (2018).
26. Jayasinghe, S. U. et al. Hypothalamo-pituitary adrenal axis and sympatho-adrenal medullary system responses to psychological stress were not attenuated in women with elevated physical fitness levels. *Endocrine* **51**, 369–379 (2016).
27. Russell, G. & Lightman, S. The human stress response. *Nat. Rev. Endocrinol.* **15**, 525–534 (2019).

28. Oberholzer, N. et al. Factors influencing quality of pain management in a physician staffed helicopter emergency medical service. *Anesth. Analg.* **125**, 200–209 (2017).
29. Nugent, S. M., Lovejoy, T. I., Shull, S., Dobscha, S. K. & Morasco, B. J. Associations of pain numeric rating scale scores collected during usual care with research administered patient reported pain outcomes. *Pain. Med.* **22**, 2235–2241 (2021).
30. Rugg, C., Woyke, S., Voelckel, W., Paal, P. & Ströhle, M. Analgesia in adult trauma patients in physician-staffed Austrian helicopter rescue: a 12-year registry analysis. *Scand. J. Trauma Resusc. Emerg. Med.* **29**, 28 (2021).
31. Levy, N., Sturgess, J. & Mills, P. Pain as the fifth vital sign" and dependence on the "numerical pain scale" is being abandoned in the US: Why? *Br. J. Anaesth.* **120**, 435–438 (2018).
32. Pierik, J. G. J., IJzerman, M. J., Gaakeer, M. I., Vollenbroek-Hutten, M. M. R. & Doggen, C. J. M. Painful discrimination in the emergency department: risk factors for underassessment of patients' pain by nurses. *J. Emerg. Nurs.* **43**, 228–238 (2017).
33. Arimon, M. P. et al. A communicative intervention to improve the psychoemotional state of critical care patients transported by ambulance. *Am. J. Crit. Care.* **30**, 45–54 (2021).
34. Lord, B. A. & Parsell, B. Measurement of pain in the prehospital setting using a visual analogue scale. *Prehosp. Disaster Med.* **18**, 353–358 (2003).
35. Brown, M. E. L. et al. Exploring the perceptions of senior medical students on gender and pain: a qualitative study of the interplay between formal and hidden curricula. *BMJ Open.* **14**, e080420 (2024).
36. Shah, K., Kumari, R. & Jain, M. Unveiling stress markers: a systematic review investigating psychological stress biomarkers. *Dev. Psychobiol.* **66**, e22490 (2024).
37. Larsson, G., Wennberg, P. & Wibring, K. Pain assessment and management of adult patients in the Swedish EMS: a nationwide registry study. *Scand. J. Trauma Resusc. Emerg. Med.* **33**, 22 (2025).

Acknowledgements

This work was supported by the Institute of Health Carlos III (Spain) and co-financed by the European Union [grant numbers DTS23/00010] for F.M.-R. and by the Gerencia Regional de Salud, Public Health System of Castilla y León (Spain) [grant number GRS 2693/B/2023] for F.M.-R. Sponsor role: None.

Author contributions

CRediT authorship contribution statement: Elisa A. Ingelmo-Astorga and Francisco Martín-Rodríguez conceptualized the project, managed, and coordinated the project, assisted with the design of the methodology, analyzed the data, and prepared the initial and final drafts of the manuscript. Ancor Sanz-García and Raúl López-Izquierdo takes responsibility for the data and their analysis. Carlos del Pozo Vegas, Santos Gracia Villar, Luis Alonso Dzul López, Rubén Calderon Iglesias and Silvia Aparicio Obregón contributed to the management and coordination of the project, assisted with the design of the methodology, and helped review the manuscript. Elisa A. Ingelmo-Astorga, Raúl López-Izquierdo, Ancor Sanz-García, and Francisco Martín-Rodríguez conceptualized the project and helped review and comment on the initial and final drafts of the manuscript. All the authors performed a critical review and approved the final manuscript for interpretation of the data and important intellectual input.

Competing interests

The authors have no disclosures to declare. On behalf of the other authors, the corresponding author guarantees the accuracy, transparency, and honesty of the data and information contained in the study; that no relevant information has been omitted; and that all discrepancies between authors have been adequately resolved and described.

Additional information

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43856-025-01020-4.

Correspondence and requests for materials should be addressed to Carlos del Pozo Vegas.

Peer review information *Communications Medicine* thanks James R. Miner and the other, anonymous, reviewer(s) for their contribution to the peer review of this work. [A peer review file is available].

Reprints and permissions information is available at http://www.nature.com/reprints

Publisher's note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

[1]Emergency Department. Hospital Universitario Rio Hortega, Gerencia Regional de Salud de Castilla y León, Valladolid, Spain. [2]Faculty of Medicine. Universidad de Valladolid, Valladolid, Spain. [3]CIBER of Respiratory Diseases (CIBERES), Institute of Health Carlos III, Madrid, Spain. [4]Emergency Department. Hospital Clínico Universitario. Gerencia Regional de Salud de Castilla y León, Valladolid, Spain. [5]Universidad Europea del Atlántico, Santander, Spain. [6]Universidad Internacional Iberoamericana, Campeche, México. [7]Universidad Internacional Iberoamericana, Arecibo, PR, USA. [8]Universidad de La Romana, La Romana, República Dominicana. [9]Fundación Universitaria Internacional de Colombia, Bogotá, Colombia. [10]Universidade Internacional do Cuanza, Cuito, Bié, Angola. [11]Faculty of Health Sciences, University of Castilla la Mancha, Talavera de la Reina, Spain. [12]Technological Innovation Applied to Health Research Group (ITAS Group), Faculty of Health Sciences, University of de Castilla-La Mancha, Talavera de la Reina, Spain. [13]Evaluación de Cuidados de Salud (ECUSAL), Instituto de Investigación Sanitaria de Castilla-La Mancha (IDISCAM), Toledo, Spain. [14]Prehospital Critical Care, Emergency Medical Services. Gerencia Regional de Salud de Castilla y León, Valladolid, Spain. [15]These authors jointly supervised this work; Ancor Sanz-García, Francisco Martín-Rodríguez. ✉e-mail: cpozove@saludcastillayleon.es; carlosdelpozovegas@gmail.com