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# Validation of a Clinical Scale for Early Detection of Infections at the Exit Site of Central Venous Catheters for Hemodialysis

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**Introduction:** Exit-site infections (ESI) of central venous catheters for hemodialysis (CVC-HD) has been associated with early catheter removal and an increased risk of CVC-HD related bacteremia. No specific clinical scales to predict ESI have previously been validated.

**Methods:** A multicenter prospective cohort study was performed to validate the proposed scale, which is based on the following 5 signs and symptoms: (i) pain at exit site during interdialytic period; (ii) hyperemia or erythema ≥2 cm from exit site; (iii) inflammation, induration, or swelling at exit site; (iv) fever ≥38 °C not attributable to other causes, and (v) obvious abscess or purulent exudate at the exit site. Adult patients with a tunneled CVC-HD for at least 1 month after insertion has been included. During each hemodialysis session, the exit site was assessed with the proposed scale by nurses. If any item was present, a peri-catheter skin swab culture was collected: positive results were gold standard. The scale was validated using receiver operating characteristic (ROC) curves and logistic regression analysis. For this purpose, the logit function was applied, and the ESI probability calculated, as elogit ESI/1 + elogit ESI.

**Results:** Three hundred thirty-seven CVC-HDs from 310 patients were analyzed, producing 515 cultures (117 infected and 398 healthy). The final version of the scale includes the following 3 signs and symptoms, which present the greatest predictive capacity: (i) pain at exit site during interdialytic period, (ii) hyperemia or erythema ≥2 cm from exit site, and (iii) abscess or purulent exudate at the exit site. The final version generated an area under the ROC curve (AUC) of 88.3% (95% confidence interval [CI]: 85.2%–91%; $P < 0.001$), Youden index 0.7557 ≈ 1, sensitivity 80.34% (95% CI: 71.36%–87.71%) and specificity 95.23% (95% CI: 92.73%–97%).

**Conclusions:** The validation shows that the scale has good predictive properties, detecting approximately 90% of ESI with very acceptable validity parameters.

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Worldwide, more than 800 million people suffer from chronic kidney disease and 3 million are receiving kidney replacement therapy; the global prevalence of chronic kidney disease is estimated to be 7% to 12%,[1,2] and the number of patients is expected to double by 2030.[3] The treatment approach most commonly used is that of hemodialysis.[4] In this context, the type of vascular access employed is closely related to patient morbidity and mortality. Thus, a patient receiving CVC-HD versus a fistula (whether autologous or prosthetic) is at 4 times greater risk of experiencing an infectious complication, and this risk is multiplied 10-fold when the sole vascular access is a CVC-HD.[5-8]

The incidence of CVC-HD-related bacteremia is highly variable (ranging from 0.56 to 6.18/1000 catheter-days for tunneled catheters and from 1.4 to 8.3/1000 catheter-days for nontunneled catheters).[9-11] Similarly, the incidence of ESI ranges from 0.31 to 8.3 per 1000 catheter-days for tunneled catheters and from 8.2 to 16.75 per 1000 catheter-days in nontunneled ones.[9,10,12] The total cost of hospitalization for a catheter-related infection ranges from $17,000 to $32,000,[1–13] depending on the causative agent and the duration of treatment and hospitalization. The majority of this cost is related to catheter-associated bloodstream infections and their sequelae.

At present, clinical practice guidelines on vascular access for hemodialysis do not provide a universal definition regarding ESI[4-16] and the 2019 update Kidney Disease Outcomes Quality Initiative of the vascular access guideline[13] merely states that "Further validation studies of diagnostic criteria for exit site and tunnel infections in HD patients" are required. To our knowledge, no validated scales have yet been proposed to evaluate the exit site of CVC-HD. Therefore, we deem it necessary and timely to design and validate a scale for assessing the exit site of tunneled CVC-HD, which supports the recommendations of clinical practice guidelines. The aim of this study is to validate a clinical scale for the early detection of ESI during the assessment of tunneled CVC-HD.

## METHODS

The EXIT site Assessment (EXITA) study is designed to validate an instrument for the early detection of ESI in tunneled CVC-HD: the study protocol[14] is based on the DeVellis recommendations.[15] The scale was developed in the following 2 phases:

1. Scale design. After conducting a scoping review of the literature[16] to identify clinical signs and symptoms, they were categorized by an international panel of experts in CVC-HD exit site care, using the Delphi technique.[17] The prioritization thus obtained was then used to develop the preliminary version of the proposed assessment scale.
2. Validation. A multicenter prospective cohort study was performed to determine the predictive properties of the ESI scale. The methodology of this validation phase and the results obtained are described below.

### Study Design

In the validation phase, a multicenter prospective cohort study was carried out on a population of chronic patients receiving hemodialysis at the following 9 Spanish hospitals (the corresponding autonomous community or region is given in parentheses): Hospital Universitario Reina Sofía de Córdoba (Andalusia), Hospital Universitario de Canarias (Canary Isles), Hospital Universitario Marqués de Valdecilla (Cantabria), Hospital Clínico Universitario de Valladolid (Castilla y León), Hospital Quironsalud A Coruña (Galicia), Hospital de Manacor (Balearic Isles), Hospital General Universitario Gregorio Marañón and Hospital Universitario Fundación Alcorcón (Madrid), and Complejo Hospitalario de Navarra (Navarra). The participating centers are representative of the various types of hemodialysis units: peripheral centers, university hospitals, tertiary referral hospitals, and regional hospitals.

The Cantabria Ethics Committee for Research with Medical Products approved the study protocol[14] in July 2019, under approval code 2019.146. A pilot study with version 1 of the scale was performed in May 2021. Patient recruitment took place from May 1, 2021, to June 30, 2022, during the validation period. The study data were analyzed, the predictive properties of the scale items reviewed, and the final version of the scale was decided upon from July to December 2022.

### Participants

The following inclusion criteria were established: patient on kidney replacement therapy with hemodialysis via a tunneled CVC-HD for at least 1 month after insertion, aged ≥18 years, and provision of signed informed consent to participate in the study. Recruitment was consecutive and convenience-based, until the preestablished sample size was obtained, and each patient was followed-up with during the study period.

The sample size was calculated taking as a reference the mean 20% incidence of ESI in Spain.[18-20] The expected sensitivity and specificity of the scale to be validated were 95% and 90%, respectively. Because no validation studies have been conducted of similar scales in vascular catheters, these expected properties are based on the parameters described by Eriguchi *et al.*[21] following their validation of the exit site scoring

system for peritoneal dialysis catheters, as recommended in the 2005 guidelines of the International Peritoneal Dialysis Society. We calculated that 92 patients should be included in the infection group to estimate the presence of ESI (92 exit sites with a positive culture), at a confidence level of 95% and a precision of ± 10 percentage units. We also calculated that 365 patients should be included in the noninfection group (365 exit sites with a negative culture), in order to estimate a healthy exit site (without infection), at a confidence level of 95% and a precision of ± 5 percentage units. The necessary sample size was calculated using Epidat 4.2 software.

## Variables

Version 1 of the scale was constructed from the 9 signs and symptoms prioritized by the panel of experts in the first phase of the EXITA study,[17] which our research team then grouped into the following 5 items:

- Pain at exit site during interdialytic period.
- Hyperemia or erythema ≥2 cm from exit site.
- Inflammation, induration, or swelling at exit site.
- Fever ≥38 °C not attributable to other causes.
- Obvious abscess or purulent exudate at the exit site.

The first version of the scale was piloted with 10 patients at each participating hospital, evaluated by 3 nurses in every case, in May 2021. This initial approach was intended to obtain linguistic validation of the instrument and thus evaluate its understandability and clarity. This piloting showed that no change in the items was needed.

ESI determined by microbiological culture of skin smears or pericatheter exudate was taken as the gold standard. In addition, the patients' clinical variables, catheter type, local CVC-HD maintenance policies and the outcomes of microbiological studies were recorded (Supplementary Table S1).

## Data Collection

Version 1 was taken as the exit site assessment method, which was applied before each hemodialysis session (in which the exit site treatment protocol remained unchanged). To evaluate the exit site, the nurses were provided with a millimeter ruler magnifying glass, the items to be assessed, and a QR code with access to the hospital's data collection record (Supplementary Figure S1). The nurses at the participating hospitals received training to ensure the unequivocal identification of the signs and symptoms to be validated, thus eliminating observer bias. For each CVC-HD, an initial control culture was obtained, upon the recruitment of each patient, based on a pericatheter skin smear from the healthy exit site (i.e., with no signs or symptoms of infection), as a control. When a relevant item was identified, a microbiological study of the pericatheter skin smear and/or exudate from the exit orifice (as appropriate) was performed. A pericatheter skin swab culture was repeated when the signs and symptoms disappeared, as a control. During the study period, each patient might present more than 1 positive or negative culture. If the patient had more than 1 CVC-HD during the study period, data corresponding to each catheter type were collected. Therefore, each catheter could have more than 1 culture during the follow-up period, always including a control culture (negative culture in the absence of signs and symptoms of infection). The cultures were collected by the nurse performing the hemodialysis session, before the session began. If patients were hospitalized due to an ESI or developed an ESI during hospitalization, the culture was collected in the same manner. A common protocol for culture collection was established across all centers. To obtain the samples, a dry cotton swab was rubbed over an area of 2 $cm^2$ around the exit orifice, immediately after removing the dressing, without disinfecting the skin.[22,23] If a local allergic reaction and/or bleeding were observed, no pericatheter skin smears were taken. ESI was assumed to be present when the culture results were positive, that is, ≥ 15 CFU/ml by the semiquantitative Maki technique or ≥ 1000 CFU/ml by the Cleri technique.[22,23] Skin contamination (microbiological growth in the culture ≤15 CFU/ml by the semiquantitative Maki technique or ≤ 1000 CFU/ml by the Cleri technique[22,23]) was not considered infection and was not included in the statistical analysis.

## Statistical Analysis

For each item present, 1 point was scored; its absence was scored as 0 points. The total score of the scale was calculated by adding the points for the presence or absence of the signs and symptoms to be validated (maximum 5 points in version 1). The total score was then subjected to exploratory descriptive analysis (central tendency, dispersion, skewness, and kurtosis) and univariate and multivariate tests of normality. For the decision validity analysis (predictive validity), the total score obtained was compared with the gold standard (microbiological culture of skin smears from the pericatheter or exit site exudate). The validity of the scale was assessed by calculating the specificity, the sensitivity, the positive and negative likelihood ratios (LH+, LH−), ROC curves, the AUC, and the 95% CI. An AUC value > 0.5 and close to 1 indicated a good level of predictability of the scale. In addition, the Youden index was calculated to optimize the cut-off point of the scale (Youden = sensitivity + specificity − 1).

**Table 1.** Baseline characteristics of patients and catheters included in the cohort

| Characteristic | *n* (%) |
|---|---|
| Patients (*n*) | 310 |
| Age (yr) | 67.78 ± 14.66 |
| Charlson Index for patients with kidney disease (score) | 5.1 ± 2.29 |
| Women, | 132 (39.4) |
| Etiology of kidney disease according to ERA/EDTA code | |
| Systemic | 166 (49.6) |
| Glomerular | 62 (18.5) |
| Other | 55 (16.4) |
| Tubulointerstitial | 20 (6.0) |
| Hereditary-family | 17 (5.1) |
| Various kidney disorders (nephrectomies. tumors, etc.) | 15 (4.5) |
| Number of catheters for patient (*n*) | 337 |
| 1 catheter | 314 (93.4) |
| 2 catheters | 14 (4.2) |
| 3 catheters | 3 (0.9) |
| 4 catheters | 4 (0.6) |
| 5 catheters | 1 (0.45) |
| 6 catheters | 1 (0.45) |
| Catheters design | |
| 1 exit site | 323 (96.4) |
| 2 exit sites | 12 (3.6) |
| Insertion vein | |
| Right jugular | 279 (83.3) |
| Left jugular | 34 (10.1) |
| Right subclavian | 8 (2.4) |
| Left subclavian | 7 (2.1) |
| Other | 7 (2.1) |
| Previous infections | |
| Infection of the exit site | 47 (14) |
| Bacteremia | 23 (6.9) |
| Tunnel infection | 7 (2.1) |

ERA/EDTA European Renal Association-European Dialysis and Transplant Association.

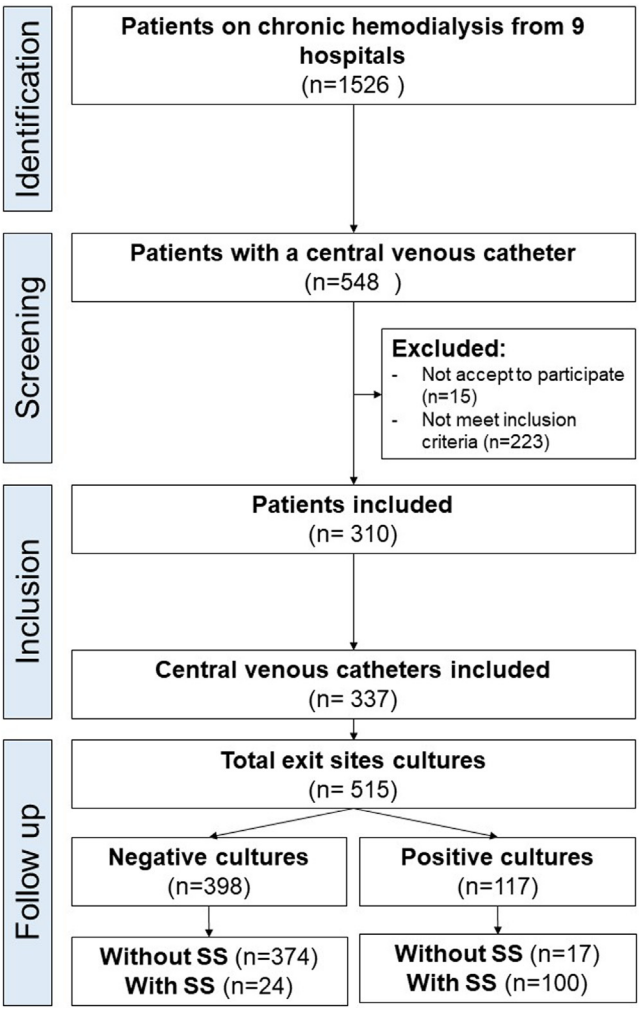


**Figure 1.** Summary participants and cultures flowchart. SS, Signs and symptoms.

The scale was validated by logistic regression analysis. The signs and symptoms of the scale in the multivariate analysis were selected according to a univariate analysis performed on each sign and symptom, following the selection criteria proposed by Hosmer, Lemeshow, and Sturdivant,[24] in which the variables with a significance level $< 0.25$ were considered. In addition, the clinical relevance of each sign or symptom was considered, regardless of the statistical significance obtained. The β coefficients for each item on the scale to be validated were estimated by logistic regression.

The formula

$$\text{Logit ESI} = \text{constant} + \beta_1 \times X_i + \beta_n \times X_n$$

was then applied.

To transform the logit ESI into the probability of ESI being present, the following formula was used:

$$\text{Probability of ESI} = e^{\text{logit ESI}}/1 + e^{\text{logit ESI}}$$

The above procedure enabled us to determine the probability, expressed as a percentage, of a patient with CVC-HD presenting ESI, according to the presence or absence of the items to be validated.[24,25] With this formula and the treatment approaches prioritized by the international panel of experts in phase 2 of the EXITA[17]study, an ESI risk calculator was generated (in Excel format), with the final version of the scale.

The statistical analyses were performed using IBM SPSS Statistics software (version 20.0) and MedCalc software (version 19.6).

## RESULTS

The study included 337 CVC-HDs, corresponding to 310 hemodialysis patients, of whom 39.4% were female, with a mean age of 67.78 ± 14.66 years (range 22–91 years) and a mean score on the modified Charlson comorbidity index for kidney disease of 5.1 ± 2.23 points (range 2–14 points). The characteristics of these CVC-HDs are detailed in Table 1. Five swabs had contamination and were excluded. A total of 515 exit site cultures were included; of these, 117 were positive and 398 were negative. Figure 1 shows a summary of the participants and cultures flow chart. Figure 2 shows

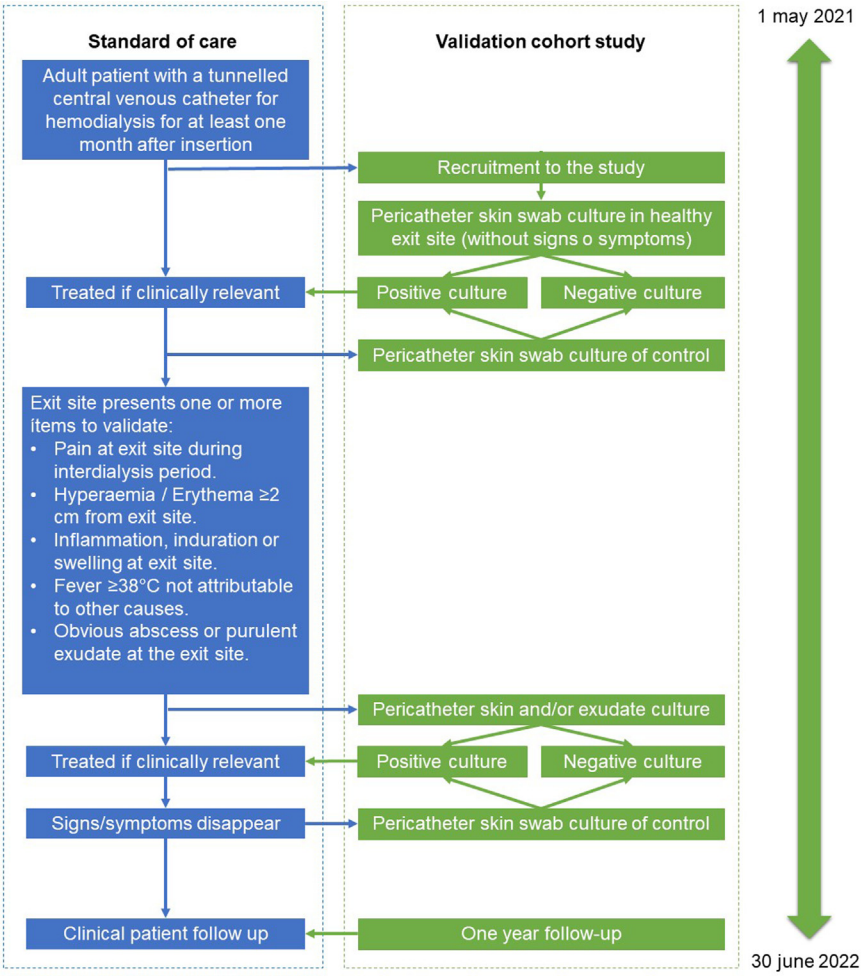


**Figure 2.** Individual patient participation in the study flowchart.

individual patient participation in the study flowchart. Table 2 shows the characteristics of swabs collected.

Supplementary Table S2 shows the variables related to exit site local policy of the CVC-HDs studied. In 63.3% of cases, the orifice was treated weekly, usually by washing with 0.9% physiological saline solution and followed (in 34.6% of cases) by the application of otic ciprofloxacin and covering it with a gauze dressing.

**Table 2.** Characteristics of swabs collected

| Characteristic | *n* (%) |
|---|---|
| Swabs (*n*) | 515 |
| Catheter's swabs frequency | |
| 1 swab | 238 (70.6) |
| 2 swabs | 54 (16) |
| 3 swabs | 26 (7.7) |
| 4 swabs | 10 (3) |
| 5 swabs | 5 (1.5) |
| 6 swabs | 3 (0.9) |
| 8 swabs | 1 (0.3) |
| Exit sites' swabs frequency | |
| Healthy exit sites (without signs or symptoms) | 391 (76) |
| Clinically suspicious exit sites | 124 (24) |

Of the 515 cultures performed, 75.9% presented no signs or symptoms and were taken as controls. The most common sign was hyperemia or erythema ≥ 2 cm from the exit site (15%), followed by obvious abscess or purulent exudate at the exit site (Supplementary Table S3). Supplementary Table S4 shows the frequency of combinations of signs and symptoms in the sessions in which cultures were collected. Among the 117 positive cultures, 18 different microorganisms were identified, the most common of which were *Staphylococcus epidermidis* (45.86%) and *Staphylococcus lugdunensis* (12.03%) (Supplementary Table S5).

Supplementary Table S6 shows the validity properties of each item on the initial version of the scale. The total score for this version, including the 5 items, presented the following characteristics: AUC 0.885 (88.5%; 95% CI: 85.4%–91.1%; standard error: 0.0191; bootstrap 95% CI: 84%–91.6%; z statistic: 22.953), Youden index 0.7557 ≈ 1, sensitivity 80.34% (95% CI: 72.0%–87.1%), specificity 95.23% (95% CI: 92.6%–97.1%), LR +: 16.83 (95% CI: 10.75–26.34), LR−: 0.21 (95% CI: 0.14 LR−:0.30). The ROC curve for the total score of version 1 of the scale is shown in

**Table 3.** Sensitivity, specificity, and likelihood ratios of versions 1, 2A, and 2B of scale for predicting exit site infection of central venous catheters for hemodialysis

| Total score | Sensitivity (95% CI) | Specificity (95% CI) | Positive likelihood ratio (95% CI) | Negative likelihood ratio (95% CI) | Positive predictive value (95% CI) | Negative predictive value (95% CI) |
|---|---|---|---|---|---|---|
| Version 1 | | | | | | |
| ≥ 0.053822444 | 100.00 (96.9–100) | 0.00 (0.0–0.9) | 1.00 (1.00–1.00) | | 22.7 (22.7–22.7) | – |
| > 0.053822444 | 100.00 (96.9–100) | 1.26 (0.4–2.9) | 1.01 (1.00–1.02) | 0.00 (-) | 22.9 (22.7–23.1) | 100.0 |
| > 0.065018712[a] | 80.34 (72.0–87.1) | 95.23 (92.6–97.1) | 16.83 (10.75–26.34) | 0.21 (0.14–0.30) | 83.2 (76.0–88.6) | 94.3 (91.9–96.0) |
| > 0.202270873 | 77.78 (69.2–84.9) | 95.48 (92.9–97.3) | 17.20 (10.84–27.29) | 0.23 (0.17–0.33) | 83.5 (76.1–88.9) | 93.6 (91.2–95.4) |
| > 0.705746946 | 76.07 (67.3–83.5) | 95.73 (93.2–97.5) | 17.81 (11.06–28.67) | 0.25 (0.18–0.35) | 84.0 (76.5–89.4) | 93.2 (90.8–95.0) |
| > 0.710928773 | 58.97 (49.5–68.0) | 97.49 (95.4–98.8) | 23.47 (12.50–44.09) | 0.42 (0.34–0.52) | 87.3 (78.6–92.8) | 89.0 (86.7–91.0) |
| > 0.746177556 | 55.56 (46.1–64.7) | 97.74 (95.8–99.0) | 24.57 (12.62–47.82) | 0.45 (0.37–0.56) | 87.8 (78.8–93.4) | 88.2 (85.9–90.2) |
| > 0.782316442 | 28.21 (20.3–37.3) | 98.99 (97.4–99.7) | 28.06 (10.15–77.60) | 0.73 (0.65–0.81) | 89.2 (74.9–95.8) | 82.4 (80.7–84.0) |
| > 0.897385536 | 27.35 (19.5–36.4) | 98.99 (97.4–99.7) | 27.21 (9.82–75.38) | 0.73 (0.66–0.82) | 88.9 (74.3–95.7) | 82.3 (80.6–83.8) |
| > 0.899672339 | 26.50 (18.8–35.5) | 98.99 (97.4–99.7) | 26.36 (9.50–73.16) | 0.74 (0.67–0.83) | 88.6 (73.6–95.6) | 82.1 (80.4–83.6) |
| > 0.929097431 | 22.22 (15.1–30.8) | 99.75 (98.6–100.0) | 88.44 (12.13–644.87) | 0.78 (0.71–0.86) | 96.3 | 81.4 (79.8–82.8) |
| > 0.991996851 | 21.37 (14.3–29.9) | 99.75 (98.6–100.0) | 85.04 (11.65–620.99) | 0.79 (0.72–0.87) | 96.2 | 81.2 (79.7–82.6) |
| > 0.992193546 | 15.38 (9.4–23.2) | 100.00 (99.1–100.0) | – | 0.85 (0.78–0.91) | 100.0 | 80.1 (78.8–81.3) |
| > 0.997792258 | 12.82 (7.4–20.3) | 100.00 (99.1–100.0) | – | 0.87 (0.81–0.93) | 100.0 | 79.6 (78.4–80.7) |
| > 0.997846828 | 0.00 (0.0–3.1) | 100.00 (99.1–100.0) | – | 1.00 (1.00–1.00) | – | 77.3 (77.3–77.3) |
| Version 2A | | | | | | |
| ≥ 0.06606743 | 100.00 (96.9–100) | 0.00 (0.0–0.9) | 1.00 (1.00–1.00) | – | 1 (1.0–1.0) | – |
| > 0.06606743[a] | 77.78 (69.2–84.9) | 95.48 (92.9–97.3) | 17.20 (10.84–27.29) | 0.23 (0.17–0.33) | 17.20 (10.8–27.3) | 0.23 |
| > 0.724269589 | 57.26 (47.8–66.4) | 97.49 (95.4–98.8) | 22.79 (12.12–42.87) | 0.44 (0.36–0.54) | 22.79 (12.1–42.9) | 0.44 |
| > 0.803532537 | 22.22 (15.1–30.8) | 99.75 (98.6–100) | 88.44 (12.13–644.87) | 0.78 (0.71–0.86) | 88.44 (12.1–644.9) | 0.78 |
| > 0.993458263 | 0 (0.0–3.1) | 100.00 (99.1–100) | – | 1.00 (1.00–1.00) | – | 1 |
| Version 2B | | | | | | |
| ≥ 0.064863578 | 100.00 (96.9–100.0) | 0.00 (0.0–0.9) | 1.00 (1.00–1.00) | – | 22.7 (22.7–22.7) | – |
| > 0.064863578[a] | 80.34 (72.0–87.1) | 95.23 (92.6–97.1) | 16.83 (10.75–26.34) | 0.21 (0.14–0.30) | 83.2 (76.0–88.6) | 94.3 (91.9–96.0) |
| > 0.203391964 | 77.78 (69.2–84.9) | 95.48 (92.9–97.3) | 17.20 (10.84–27.29) | 0.23 (0.17–0.33) | 83.5 (76.1–88.9) | 93.6 (91.2–95.4) |
| > 0.710357369 | 58.97 (49.5–68.0) | 97.49 (95.4–98.8) | 23.47 (12.50–44.09) | 0.42 (0.34–0.52) | 87.3 (78.6–92.8) | 89.0 (86.7–91.0) |
| > 0.778239804 | 28.21 (20.3–37.3) | 98.99 (97.4–99.7) | 28.06 (10.15–77.60) | 0.73 (0.65–0.81) | 89.2 (74.9–95.8) | 82.4 (80.7–84.0) |
| > 0.900276331 | 26.50 (18.8–35.5) | 98.99 (97.4–99.7) | 26.36 (9.50–73.16) | 0.74 (0.67–0.83) | 88.6 (73.6–95.6) | 82.1 (80.4–83.6) |
| > 0.928150249 | 22.22 (15.1–30.8) | 99.75 (98.6–100.0) | 88.44 (12.13–644.87) | 0.78 (0.71–0.86) | 96.3 (78.1–99.5) | 81.4 (79.8–82.8) |
| > 0.992005419 | 15.38 (9.4–23.2) | 100.00 (99.1–100.0) | – | 0.85 (0.78–0.91) | 100.0 | 80.1 (78.8–81.3) |
| > 0.997815416 | 0.00 (0.0–3.1) | 100.00 (99.1–100.0) | – | 1.00 (1.00–1.00) | – | 77.3 (77.3–77.3) |

CI, confidence interval.
[a]Associated criterion.
Version 1: Pain at exit site during interdialytic period; hyperemia or erythema ≥ 2 cm from exit site; inflammation, induration or swelling at exit site; fever ≥ 38 °C not attributable to other causes; obvious abscess or purulent exudate at the exit site.
Version 2A: Hyperemia or erythema ≥ 2 cm from exit site and obvious abscess or purulent exudate at the exit site.
Version 2B (Final version): Pain at exit site during interdialytic period; hyperemia or erythema ≥ 2 cm from exit site and obvious abscess or purulent exudate at the exit site.

Supplementary Figure S2, and its characteristics in Tables 3 and 4.

Table 5 shows the weights of each item considered to predict the presence of ESI in a univariate analysis, by calculating the β coefficients. These calculations show that the signs that presented the greatest weight and which were statistically significant were the items "hyperemia or erythema ≥ 2 cm from exit site" ($\beta = 51.68$, $P < 0.001$) and "obvious abscess or purulent exudate at the exit site" ($\beta = 35.366$, $P < 0.001$). The item "pain at exit site during interdialytic period" presented $\beta > 1$ but lacked statistical significance ($\beta = 3.646$, $P = 0.138$). In the logistic regression analysis, the same 2 signs ("hyperemia or erythema ≥ 2 cm from exit site" and "obvious abscess or purulent exudate at the exit site"), which remained until the last step, were the main predictors of ESI (Table 6). The symptom "pain at exit site during interdialytic period" was eliminated in the penultimate step, with $\beta > 1$ ($\beta = 1.303$, $P = 0.132$).

Supplementary Figure S3 shows the ROC curve and Table 4, the AUC characteristics for version 2A, with the sum of "hyperemia or erythema ≥ 2 cm from exit site" and "obvious abscess or purulent exudate at the exit site." These 2 signs jointly predict 87.2% of ESI, with a sensitivity of 77.78% and a specificity of 95.48%, given the presence of at least 1 of these signs (Youden index 0.7326 ≈1, $P < 0.001$).

Figure 3 shows the ROC curve and Table 4 shows the AUC characteristics for version 2B of the scale, with the sum of "pain at exit site during interdialytic period", "hyperemia or erythema ≥ 2 cm from exit site" and

**Table 4.** Area under the ROC curve and Youden index values of version 2A and 2B of scale for predicting exit site infection of central venous catheters for hemodialysis

| EXITA scale | Version 1 | Version 2A | Version 2B |
|---|---|---|---|
| Area under the ROC curve (AUC) | 0.885 | 0.872 | 0.883 |
| Standard error[a] | 0.0191 | 0.0201 | 0.0193 |
| 95% Confidence interval[b] | 0.854–0.911 | 0.840–0.899 | 0.852–0.910 |
| 95% Bootstrap CI[c] | 0.840–0.916 | 0.726–0.819 | 0.821–0.904 |
| z statistic | 20.156 | 18.511 | 19.865 |
| Significance level *P* (Area = 0.5) | < 0.0001 | < 0.0001 | < 0.0001 |
| Youden index J | 0.7557 | 0.7326 | 0.7557 |
| Associated criterion | > 0.0650187212 | > 0.06606743 | > 0.064863578 |
| Sensitivity | 80.34 | 77.78 | 80.34 |
| Specificity | 95.23 | 95.48 | 95.23 |

AUC, area under the ROC curve; ROC, receiver operating characteristic curve.
[a]DeLong *et al.*,[26] 1988.
[b]Binomial exact.
[c]$BC_a$ bootstrap confidence interval (1000 iterations; random number seed: 978).
Version 1: Pain at exit site during interdialytic period; hyperemia or erythema ≥ 2 cm from exit site; inflammation, induration or swelling at exit site; fever ≥ 38 °C not attributable to other causes; obvious abscess or purulent exudate at the exit site.
Version 2A: Hyperemia or erythema ≥ 2 cm from exit site and obvious abscess or purulent exudate at the exit site.
Version 2B (Final version): Pain at exit site during interdialytic period; hyperemia or erythema ≥ 2 cm from exit site and obvious abscess or purulent exudate at the exit site.

"obvious abscess or purulent exudate at the exit site." The combination of these 3 signs and symptoms predict 88.3% of ESI, with a sensitivity of 80.34% and a specificity of 95.23%, based on the presence of 1 of these signs (Youden index 0.7557 ≈ 1, $P < 0.001$). In view of the properties of the combination of these 3 signs and symptoms, this was taken as the optimum version of the scale (final version, version 2B).

According to the corresponding formula, the values of final version (version 2B) of the scale were calculated as:

Logit ESI= −2.668 + Pain at exit site during interdialytic period × 1.303 + Hyperemia or Erythema ≥ 2 cm from exit site × 3.924 + Obvious abscess or purulent exudate at the exit site × 3.566

By applying this formula in the presence of signs and symptoms, we obtain a numerical value that can be transformed into probability using the equation:

**Table 5.** Univariate analysis of the β coefficients for each of the items of version 1 of the scale

| Item | β | 95% CI | | *P*-value |
|---|---|---|---|---|
| | | Lower limit | Upper limit | |
| Pain at exit site during interdialytic period | 3.646 | 0.661 | 20.113 | 0.138 |
| Hyperemia or erythema ≥2 cm from exit site | 51.680 | 22.557 | 118.404 | 0.000 |
| Inflammation, induration or swelling at exit site | 0.818 | 0.124 | 5.389 | 0.835 |
| Fever ≥ 38 °C not attributable to other causes | 0.975 | 0.085 | 11.233 | 0.984 |
| Obvious abscess or purulent exudate at the exit site | 35.366 | 14.310 | 87.406 | 0.000 |
| (Constant) | 0.070 | | | 0.000 |

CI, confidence interval.

**Table 6.** Logistic regression with exit site infection as dependent variable and signs and symptoms from version 1 of the scale as predictor variables

| Variables in the equation | | | | | | |
|---|---|---|---|---|---|---|
| Recommendation | | β | Standard Error | Wald | df | *P* |
| Step 1 | Pain at exit site during interdialytic period | 1.294 | 0.871 | 2.205 | 1 | 0.138 |
| | Hyperemia or erythema ≥2 cm from exit site | 3.945 | 0.423 | 86.988 | 1 | 0.000 |
| | Inflammation, induration, or swelling at exit site | −0.201 | 0.962 | 0.044 | 1 | 0.835 |
| | Fever ≥ 38 °C not attributable to other causes | −0.025 | 1.247 | 0.000 | 1 | 0.984 |
| | Obvious abscess or purulent exudate at the exit site | 3.566 | 0.462 | 59.660 | 1 | 0.000 |
| | (Constant) | −2.666 | 0.201 | 176.046 | 1 | 0.000 |
| Step 2 | Pain at exit site during interdialytic period | 1.292 | 0.869 | 2.212 | 1 | 0.137 |
| | Hyperemia or erythema ≥ 2 cm from exit site | 3.945 | 0.423 | 86.993 | 1 | 0.000 |
| | Inflammation, induration, or swelling at exit site | −0.201 | 0.962 | 0.044 | 1 | 0.834 |
| | Obvious abscess or purulent exudate at the exit site | 3.563 | 0.440 | 65.626 | 1 | 0.000 |
| | (Constant) | −2.666 | 0.201 | 176.060 | 1 | 0.000 |
| Step 3 | Pain at exit site during interdialytic period | 1.303 | 0.865 | 2.270 | 1 | 0.132 |
| | Hyperemia or erythema ≥ 2 cm from exit site | 3.924 | 0.409 | 92.124 | 1 | 0.000 |
| | Obvious abscess or purulent exudate at the exit site | 3.566 | 0.440 | 65.778 | 1 | 0.000 |
| | (Constant) | −2.668 | 0.201 | 176.973 | 1 | 0.000 |
| Step 4 | Hyperemia or erythema ≥ 2 cm from exit site | 4.057 | 0.402 | 101.615 | 1 | 0.000 |
| | Obvious abscess or purulent exudate at the exit site | 3.614 | 0.436 | 68.762 | 1 | 0.000 |
| | (Constant) | −2.649 | 0.199 | 176.926 | 1 | 0.000 |

df, degree of freedom.

$$e^{\text{logit IOS}}/1 + e^{\text{logit IOS}}$$

This procedure obtains the probability, expressed as a percentage, of a patient with CVC-HD presenting ESI, according to the presence or absence of these 3 signs and symptoms.

EXITA scale calculator is available in this link: https://goo.su/HU64JM, which can be used to calculate the probability of a patient presenting ESI according to the presence or absence of each of the items in final version, together with the best treatment approach to be taken, as established in phase 2 of the study.[17] This probability ranges from 6.49% (when all the items are absent, and corresponds to the mere existence of a CVC-HD) to 99.78% (when all the items are present).

Figure 4 shows final version of the scale (version 2B), together with the treatment approach determined in phase 2 of the study,[17] upon the appearance of each sign and symptom.

## DISCUSSION

To our knowledge, the multicenter cohort study we describe is the first to develop a predictive model of ESI by CVC-HD, validating the EXITA scale. With 3 very

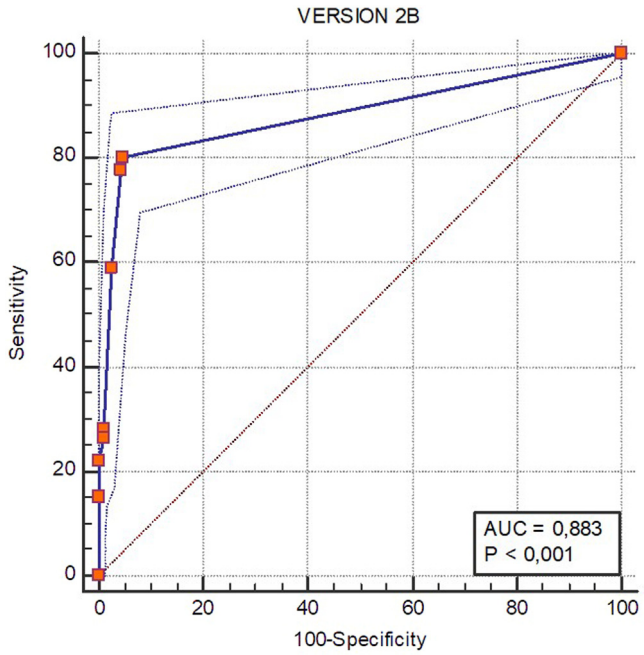


**Figure 3.** ROC curve and AUC characteristics of the scale, for final version (2B version) (pain at exit site during interdialytic period; hyperemia or erythema ≥ 2 cm from exit site and obvious abscess or purulent exudate at the exit site). AUC, area under the ROC curve; ROC, receiver operating characteristic curve.

simple items to assess, it also guides the treatment approach to be adopted, according to the presence or absence of each item. It is the first instrument of its kind, it has been robustly validated, and predicts almost 90% of ESI, with high sensitivity and specificity.

In the present study, version 1 of the instrument (with 5 items) was subjected to clinical validation in a predictive capacity study. The very specific prioritization of these 5 signs and symptoms by the expert panel was endorsed during the clinical validation phase, which highlighted the excellent predictive properties of this first version of the scale. With the presence of just 1 of the items, the scale had a sensitivity of 85.47% and a specificity of 93.97%.

The calculation of the β coefficients in the univariate analysis showed that the items with the greatest predictive capacity were "hyperemia or erythema ≥ 2 cm from exit site" ($\beta = 51.68$, $P < 0.001$) and "obvious abscess or "purulent exudate at the exit site." This conclusion was confirmed by logistic regression. For our research team, however, the presence of pain at the exit site during the interdialytic period is sufficiently significant to merit attention. In this respect, Harwood *et al.*[27] observed an association between the presence of pain and ESI. For this reason, pain was included in the final version of the scale. This improved the predictive characteristics of the instrument, raising the AUC from 87.2% to 88.3%, and the sensitivity from 77.8% to 80.34%, while maintaining good specificity (which fell from 95.5% to 95.23%). In all cases, the Youden index was close to 1, and so the mere presence of 1 of the items allows the early identification of ESI. The precision obtained with these items reflects the good work done by the panel of experts and their expertise in the phenomenon under study. These values are similar to those presented by the initial 5 items, improving efficiency in the application of the scale. The fact that the final version of the scale has only 3 items, all of which can be straightforwardly determined in each hemodialysis session, facilitates its immediate transfer to clinical practice. Moreover, the development of the ESI risk calculator will facilitate its implementation at the point of care, enabling its integration into clinical information systems, as part of the daily assessment

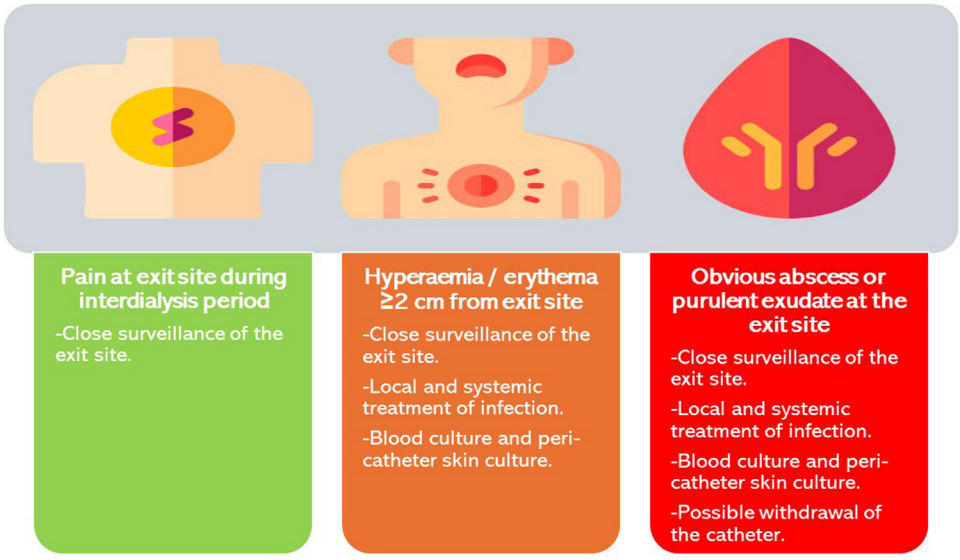


**Figure 4.** Final version of the EXITA scale, with the recommended treatment approach. EXITA, EXIT site Assessment.

recommended by the corresponding clinical practice guidelines.[13,23,28]

To our knowledge, the only scale of this type currently available is the REDS scale (published in 2021, after the start of the present research). However, it has not been subjected to validation or a study of its predictive capacity.[29] The REDS scale evaluates the presence of 4 items: redness, edema, and exudate at the exit site; and systemic symptoms of infection that might indicate catheter-related bacteremia.

In another study, Porazko *et al*.[29] reported that with the implementation of the REDS scale, the 2-year cumulative incidence of ESI was significantly reduced (log rank $P < 0.001$) from 0.89 episodes/1000 catheter days (53.5%, 95% CI: 35.9%–66.2%) in the period before the use of the REDS scale, to 0.26 episodes/1000 catheter days (18.6%, 95% CI: 6.1%–29.4%) with its application. These authors also observed a significant decrease in complicated ESI with catheter-related bacteremia that required removal of the tunneled CVC-HD (0.6 episodes/1000 catheter days; 18.6%, 95% CI: 6.1%–29.4%; vs. 0.3 episodes/1000 catheter days; 4.7%, 95% CI: 0.0%–10.7%; log-rank $P = 0.04$, in the periods before and after implementation of the REDS scale, respectively.[29] In our opinion, the use of such a scale could reduce the rates of local and systemic infection, by enabling the early detection of signs and symptoms indicative of ESI, and the prompt application of measures to inhibit its progression and prevent the intraluminal contamination of the CVC-HD, with the risk of bacteremia. Nevertheless, we do not believe this improvement would be of the magnitude indicated by Porazko *et al*.[29] Accordingly, an implementation study of the EXITA scale should be conducted to determine the real impact (both clinical and economic) of its use in clinical practice.

The limitations and strengths of our study should be considered in order to properly interpret the results obtained. For example, a significant consideration is that the ethnicity of the patients was not considered in our analysis, although most patients were of Caucasian origin. However, Rigo *et al*.[30] observed differences in the results obtained when the Twardowski scale was used to assess the exit site of peritoneal dialysis catheters, according to the race of the patient, in the sense that ESI was underdiagnosed in the case of African Americans. Accordingly, we suggest the scale we propose should be validated for use with African-American and sub-Saharan populations in order to verify its behavior in this respect. Nevertheless, in general terms we believe the presentation of the phenomenon under study is universal and that our scale is generally applicable in any health care context. Positive exit site cultures in the absence of exudate may represent contamination rather than ESI.

The implementation of the EXITA scale in the clinical environment may reduce early ESI and catheter-related bacteremia and therefore reduce morbidity and mortality among patients with chronic kidney disease with CVC-HD, because colonization by microorganisms of the catheter surface and of the exit orifice is the main source of contamination of this type of vascular device.[13]

In conclusion, we have successfully developed the first clinically-validated ESI prediction scale for CVC-HD. This instrument has good predictive properties, and only requires the straightforward evaluation of 3 items before each hemodialysis session. According to the predictive model developed, the presence of just 1 of these items has a high predictive power for ESI. The use of this scale facilitates the early detection and treatment of ESI, before its microbiological confirmation. Furthermore, its use would improve observational objectivity by ensuring uniformity of classification, thus facilitating the comparison of results, the continuity of care, cost savings, patient education, and the comparison of research studies on measures for prevention and/or treatment.

## DISCLOSURE

All the authors declared no competing interests.

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## SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

**Figure S1.** A millimeter ruler with magnifying glass showing the signs and symptoms to be evaluated together with the QR code to access the data collection notebook used by nurses to assess the exit site(s) in each hemodialysis session.

**Figure S2.** ROC curve and AUC characteristics of version 1 of the scale (pain at exit site during interdialytic period; hyperemia or erythema ≥ 2 cm from exit site; inflammation. induration or swelling at exit site; fever ≥

38 °C not attributable to other causes and obvious abscess or purulent exudate at the exit site).

**Figure S3.** ROC curve and AUC characteristics of version 2A of the scale (hyperemia or erythema ≥2 cm from exit site and obvious abscess or purulent exudate at the exit site).

**Table S1.** Variables included in the study of predictive capacity.

**Table S2.** Variables related to exit site local policy for CVC-HD maintenance ($n = 335$).

**Table S3.** Frequency of each sign and symptom in the sessions in which cultures were collected ($n = 515$).

**Table S4.** Frequency of combinations of signs and symptoms in the sessions in which cultures were collected ($n = 515$).

**Table S5.** Frequency of occurrence of microorganisms responsible for culture-positive exit site infections.

**Table S6.** Validity properties of each item of the scale.

**STROBE Statement.**

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