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Early plasma syndecan-1 dynamics and their prognostic value in major thoracic and abdominal surgery: a prospective observational study

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Abstract

Background Glycocalyx degradation, reflected by syndecan-1 shedding, is implicated in microcirculatory dysfunction and inflammatory responses. The present study aimed to assess early postoperative changes in plasma syndecan-1 levels following major thoracic and abdominal surgery, and their association with 30-days postoperative complications.

Methods A prospective, single-center observational cohort study included 107 patients. Syndecan-1 levels were measured preoperatively and two and 18 h after surgery. Associations with clinical and intraoperative variables were evaluated using univariate linear regression. The predictive performance of syndecan-1 for major complications and mortality within 30 days was assessed via receiver operating characteristic (ROC) analysis.

Results The median syndecan-1 values after two hours of surgery were 958 pg/mL (IQR 654–2665). No significant associations were found with comorbidities, surgical approach, intraoperative factors, or complications (all $p > 0.05$). Syndecan-1 showed poor predictive performance for major complications and mortality within 30 days (AUC 0.52; 95% CI: 0.40–0.63; $p = 0.765$).

Conclusion Syndecan-1 levels vary widely postoperatively and are not associated with key perioperative variables or outcomes. These findings suggest limited utility of syndecan-1 as a biomarker for perioperative risk stratification in this setting.

Keywords Endothelial glycocalyx, Syndecan-1, Postoperative complications, Major abdominal surgery, Major thoracic surgery

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Introduction

The endothelial glycocalyx is a key structural and functional component of the vascular barrier, contributing to fluid homeostasis, coagulation, immune modulation and antioxidant defense [1]. It is located on the luminal surface of the vascular endothelium, and composed of glycosaminoglycans, such as heparan sulfate and chondroitin sulfate, which bind to proteins like syndecans and hyaluronic acid [1, 2]. Beyond its role maintaining vascular integrity, the glycocalyx regulates transmembrane oncotic pressure, selectively filters solutes based on charge, and modulates vascular permeability. Albumin binding to the glycocalyx contributes to reduced hydraulic conductivity and protection against shear stress-induced damage [3, 4].

Glycocalyx degradation has been implicated in pathological conditions such as sepsis, trauma, ischemic and inflammatory events, hyperglycemia and atherosclerosis [2–5]. Loss of glycocalyx integrity enhances endothelial permeability, leukocyte adhesion, platelet aggregation, and prothrombotic states, and is associated with worse clinical outcomes, including acute kidney injury and increased mortality in critical illness [1, 6]. Surgical interventions, particularly those involving ischemia-reperfusion, have been associated with glycocalyx alterations, reflected by increased circulating levels of proteoglycans and syndecans. Procedures such as cardiac surgery with extracorporeal circulation, vascular interventions (particularly in aortic surgery), and liver transplantation, have demonstrated increased plasma concentrations of syndecan-1 and heparan sulfate correlating with markers of inflammation and organ dysfunction [7–9]. In contrast, limited data exist regarding glycocalyx degradation in surgeries without overt ischemic injury.

Direct visualization of the glycocalyx integrity remains challenging, as microscopy cannot visualize its components, and electron microscopy is limited by fixation artifacts. Moreover, its synthesis and assembly processes are complex, occurring simultaneously at multiple levels [10]. As a result, plasma biomarkers such as syndecan-1, hyaluronic acid, and heparan sulfate are used as indirect measures of its integrity [6, 7]. However, their interpretation is complicated by factors like renal clearance, which can confound the relationship between marker levels and glycocalyx damage [11–13].

The study aims to evaluate perioperative dynamic changes in plasma syndecan-1 levels as a representative marker of endothelial glycocalyx degradation during the first 24 h after elective major thoracic and abdominal surgery. Additionally, we explore their association between syndecan-1 levels and relevant clinical variables better understand the extent and implications of perioperative endothelial injury.

Materials and methods

A prospective, single-center observational cohort study was conducted at Vall d'Hebron University Hospital (Barcelona, Spain), between February 2021 and July 2022, including patients undergoing elective major thoracic and abdominal surgeries. Ethical approval was obtained from the hospital's Research Ethics Committee and the Research Projects Commission and following the principles of the Declaration of Helsinki and Spanish Organic Law 3/2018 referred to personal data protection. All participants provided written informed consent prior inclusion. The study was registered prior to patient enrollment at clinicaltrials.gov (NCT04900779).

Study population

The study included patients over 18 years of age scheduled for elective major thoracic and abdominal procedures, anticipated to last more than two hours or to result in blood loss exceeding 500 milliliters (ml). These criteria were selected to capture surgeries with a significant physiological burden, where endothelial injury might be more pronounced. The study excluded patients with an American Association of Anesthesiologists (ASA) score equal or greater than IV, undergoing urgent or emergent procedures or preoperative hospitalization. Additional exclusion criteria included a history of acute or chronic kidney disease, chronic inflammatory conditions (e.g., autoimmune disease), acute infection before surgery or chronic use of corticosteroids or immunosuppressive therapy.

Study procedures

To assess changes in endothelial glycocalyx integrity, blood samples were collected at three predefined time points: immediately before the induction of anesthesia (baseline), two hours after the end of surgery, and 18 h postoperatively. The timing was selected based on existing literature [7, 9, 14, 15] describing biphasic or delayed peaks in syndecan-1 levels after endothelial insult. Plasma was processed and stored under controlled conditions. Syndecan-1 concentrations were measured using a commercially available ELISA kit (manufacturer: Human Syndecan-1 DuoSet ELISA, # DY2780, R&D Systems, Inc., a Bio-Techne Brand, MN, USA), and results were reported consistently in picograms per milliliter (pg/mL), including for sample size calculations and outcome reporting.

In terms of perioperative management anesthesia was administered following hospital protocols, typically using a balanced approach, combining intravenous drugs (like propofol and opioids) and inhaled anesthetics (such as sevoflurane or desflurane), to maintain stable vital signs and adequate anesthesia.

Data collection and follow-up

Clinical data were collected prospectively. Demographic information such as age, sex, was recorded, along with key preoperative comorbidities, preoperative hemoglobin and American Society of Anesthesiologists (ASA) classification score, used to assess preoperative risk. Detailed surgical information was also collected, including type of surgery (thoracic and abdominal), surgical approach (categorized as open, minimally invasive laparoscopic or robotic), type and maintenance of anesthesia (inhaled or intravenous anesthesia) and the duration of surgery. Intraoperative data included estimated blood loss, the number of red blood cell (RBC) units transfused, overall fluid balance and use of noradrenaline during surgery. Postoperative outcomes were collected, including intensive care unit (ICU) and hospital length of stay, mortality at 30 days and the occurrence of postoperative complications (renal failure, pulmonary complications and major adverse cardiovascular events). The definition of these complications was based on the guidelines of the European Society of Anesthesiology and Intensive Care (ESAIC) [16].

Sample size

The sample size was calculated based on the primary endpoint: detecting a change in plasma syndecan-1 levels before and after surgery. Reference values were based on the results of Wang et al. [17], who reported a

pre- and postoperative syndecan-1 concentration of 3.77 ± 3.15 ng/ml and 4.28 ± 3.30 ng/ml, respectively. For an alpha risk of 0.05, a beta risk of 0.02, and a correlation coefficient of 0.85 [18] in two-tailed testing, a total of 97 patients were required to detect a minimum difference of 0.51 ng/ml in two-tailed testing. Allowing for an estimated loss rate of 10%, an additional 10 patients were required, required the total sample size of 107 patients.

Statistical analysis

A descriptive analysis was conducted, with calculation of frequencies and percentages for quantitative variables. Likewise, measures of central tendency were reported as the mean or median, with the corresponding standard deviation (SD) or interquartile range (IQR) calculated, depending on whether the data exhibited a normal distribution.

A univariate linear regression analysis was performed to evaluate associations between perioperative variables and syndecan-1 levels at the 2-hour postoperative time points. These models were not adjusted for covariates and served to explore potential predictors for inclusion in multivariate modeling.

The discriminative ability of syndecan-1 to discriminate between patients who will experience morbidity and/or mortality was performed receiver operating characteristic (ROC) curve analysis. The area under the curve (AUC) was calculated with corresponding 95% confidence intervals. The statistical analysis was conducted using SPSS version 27.0 (IBM Corp., Armonk, NY). for Windows. Differences were considered statistically significant when $p \leq 0.05$.

Results

A total of 107 patients were included in the study. Table 1 presents the demographic and clinical characteristics of the sample. Median age of included patients was 64 years (range 22 to 88) and the majority were male (63.6%). Comorbidities were common, including arterial hypertension (43%), smoking (21.5%), and diabetes mellitus (20.6%). Most patients were classified as ASA II (49.5%) or III (48.5%). Open surgery was the most common surgical approach (43.9%), followed by conventional laparoscopy (36.4%) and robotic surgery (19.6%). Most patients (91.6%) received balanced general anesthesia. The mean surgery duration was 253.3 ± 111.8 min. In 52.3% of the patients, regional anesthesia was used for postoperative pain management.

The median preoperative plasma syndecan-1 level was 740 pg/mL (IQR 520–2196), two hours after surgery 958 pg/mL (IQR 654–2665), and 18 h after surgery 924 pg/mL (IQR 635–2372). Raw data are shared in supplemental digital content (SDC) Table S1. This trend reflects a postoperative increase in syndecan-1 levels, with a peak

Table 1 Demographic and clinical characteristics of the study sample (n=107)

	Frequency (%)
Sex	
Male	68 (63.6%)
Female	39 (36.4%)
Comorbidities	
Smoking	23 (21.5%)
Arterial hypertension	46 (43%)
Heart disease	12 (11.21%)
Lung disease	27 (25.2%)
Obesity	21 (19.6%)
Diabetes mellitus	22 (20.6%)
ASA score	
I	2 (1.9%)
II	53 (49.5%)
III	52 (48.5%)
Surgical approach	
Open surgery	47 (1.4%)
Conventional laparoscopy	39 (36.4%)
Robotic surgery	21 (19.6%)
Maintenance of anesthesia	
Balanced general anesthesia	98 (91.6%)
Total intravenous anesthesia	9 (8.4%)
Surgery time (minutes)*	253.3 +/-111.8

*Expressed with mean and standard deviation

at 2 h post-surgery in most patients, suggestive of early endothelial glycocalyx injury. Levels remained elevated at 18 h, indicating a sustained or delayed shedding process. Of note, three patients exhibited markedly elevated preoperative syndecan-1 levels ($>20,000$ pg/mL), reflecting pre-existing endothelial injury or inflammation. To assess whether these extreme values influenced our findings, we performed a sensitivity analysis excluding these three patients (data not shown). The results remained consistent: none of the associations between preoperative or intraoperative variables and syndecan-1 levels at 2 h became statistically significant, and no associations were observed between syndecan-1 levels and postoperative complications.

The linear regression analysis did not identify any significant association between preoperative clinical variables and syndecan-1 concentrations measured 2 h after surgery. Neither age >70 , sex, smoking, nor comorbidities such as arterial hypertension, diabetes mellitus, or obesity had a statistically significant influence (Table 2).

In case of intraoperative variables as shown in Table 3, type of surgery (thoracic vs. abdominal), surgical technique, anesthesia type, fluid administration, and use of vasopressors, were not significantly associated with syndecan-1 levels at 2 h postoperatively. No intraoperative factor emerged as a significant predictor in the linear model.

Finally, in case of Syndecan-1 and Postoperative Outcomes, no significant correlation was found between syndecan-1 plasma levels (at any time point) and major postoperative morbidity or mortality within 30 days (Table 4). The ROC curve analysis for syndecan-1 as a predictor of major postoperative complications yielded an area under the curve (AUC) of 0.52 (95% CI: 0.40–0.63, $p=0.765$), indicating no discriminative ability (Fig. 1).

Table 2 Effect of preoperative variables on syndecan-1 levels two hours after surgery

	B (SE)	CI 95% B	p-value
Age above 70-years-old	-786.65 (964.26)	-2698.61–1125.31	0.416
Sex	843.99 (899.03)	-938.61–2626.59	0.350
Smoking	-1313.71 (1.049.92)	-3.395.51–768.09	0.214
Arterial hypertension	-651.84 (875.36)	-2387.52–1083.84	0.458
Heart disease	-843.64 (1374.50)	-3569.02–1881.73	0.541
Lung disease	-10.07 (1000.34)	-1993.56–1973.42	0.992
Obesity	-1599.26 (1082.81)	-3746.26–547.74	0.143
Diabetes mellitus	-1608.05 (1063.60)	-3716.97–500.86	0.134
Preoperative anemia	596.81 (906.07)	-1199.77–2393.38	0.512

SE Standard error, CI Confidence interval

^Bunstandardized regression coefficient

Table 3 Effect of intraoperative variables on syndecan-1 levels two hours after surgery

	B (SE)	CI 95% B	p-value
Type of surgery (thoracic vs. abdominal)	-654.33 (975.44)	-2588.44–1279.78	0.504
Surgical approach	-175.75 (572.02)	-1309.95–958.45	0.759
Surgery time	-1.02 (3.90)	-8.76–6.72	0.794
Type of anesthesia	-1569.31 (1557.94)	-4658.42–1519.81	0.316
Fluid administration during surgery	61.10 (95.07)	-127.40–249.61	0.522
Blood transfusion	-1143.35 (1213.29)	-3549.08–1262.38	0.348
Noradrenaline during surgery	1171.66 (1069.01)	-948.00–3291.32	0.276

SE Standard error, CI Confidence interval

^Bunstandardized regression coefficient

Discussion

The present study showed a high degree of variability in preoperative plasma syndecan-1 levels among patients undergoing major thoracic and abdominal surgery, with

Table 4 Effect of syndecan-1 levels two hours after surgery on morbidity and mortality within the first 30 days

	Frequency	B (SE)	CI 95% B	p-value
Renal failure	15 (14%)	308.29 (1251.15)	-2172.51–2789.09	0.806
Pulmonary complications	11 (10.3%)	-1673.92 (1421.32)	-4492.14–1144.30	0.242
Need for ventilatory support	6 (5.6%)	-1482.32 (1883.04)	-5216.04–2251.41	0.433
Cardiovascular events	2 (1.9%)	-1925.18 (3202.72)	-8275.58–4425.22	0.549
Need for reoperation	9 (8.4%)	-345.11 (1565.09)	-3448.40–2758.17	0.826
Surgical wound infection	16 (15%)	-982.78 (1214.63)	-3391.17–1425.61	0.420
ICU length of stay **	1.49 +/- 2.24	-125.64 (194.71)	-511.72–260.43	0.520
Length of hospital stay (days) **	7.73 +/- 6.65	-62.93 (65.39)	-192.58–66.73	0.338
Readmission to ICU	2 (1.9%)	-721.18 (3207.45)	-7080.96–5638.61	0.823
Mortality	1 (0.9%)	-694.33 (2631.19)	-2.288,72–1306.83	0.589

Values with $\pm$ are expressed as mean $\pm$ standard deviation

SE Standard error, CI Confidence interval

^Bunstandardized regression coefficient

**Expressed with mean and standard deviation

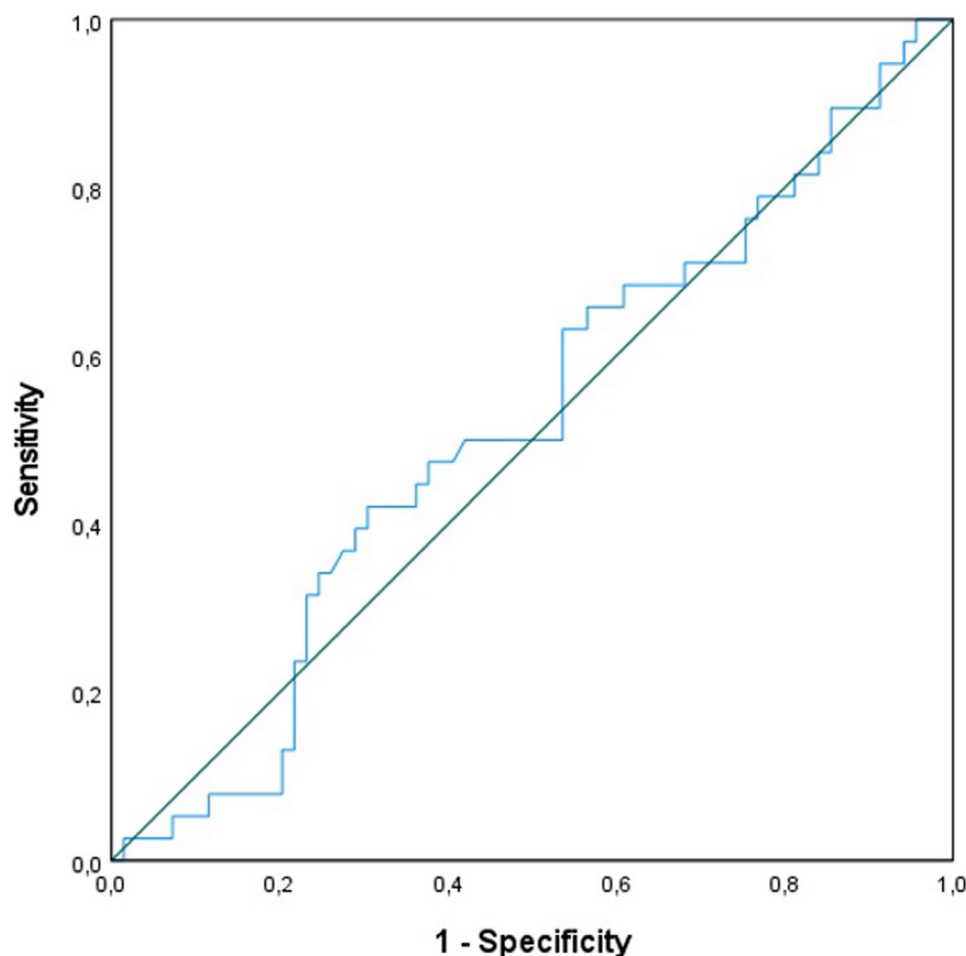


Fig. 1 Analysis of syndecan-1 cut-off point for predicting major postoperative morbidity and mortality within 30 days

values ranging from 242 pg/ml to 25.020 pg/ml. Notably, seven patients exhibited markedly elevated baseline values, contributing to the nearly 100-fold variation across the cohort. Similarly, Pesonen et al. observed up to a 247-fold variation in preoperative syndecan-1 levels among patients undergoing cardiac surgery [7]. Such variability is likely attributable to underlying comorbidities known to upregulate syndecan-1 expression, including cardiovascular disease, liver dysfunction and diabetes mellitus [19–22]. Clinically, the presence of such elevated baseline syndecan-1 levels may identify patients at higher risk of endothelial dysfunction or major perioperative vulnerability. Thus, further investigation of the underlying factors leading to these elevations, such as chronic inflammatory states, cardiovascular comorbidities, or prior endothelial injury, may provide valuable insights for risk stratification and targeted perioperative management. Contrary to initial expectations, no consistent postoperative trend was observed, as some patients exhibited syndecan-1 concentrations lower than their baseline values. This heterogeneous pattern highlights the complexity of syndecan-1 dynamics in the perioperative period and suggests that

multiple biological and clinical factors likely influence its circulating concentrations.

Firstly, while syndecan-1 is a key component of the endothelial glycocalyx, it is also expressed in various other tissues throughout the body, such as epithelial layers, pre-B cells, and plasma cells in their non-circulating (attached) states. Therefore, circulating syndecan-1 does not exclusively reflect endothelial glycocalyx degradation [23]. Direct visualization techniques, such as electron microscopy, provide more definitive assessment of glycocalyx integrity but are impractical for routine clinical use. Measurement of the perfused boundary region (PBR) offers a non-invasive alternative; however, its availability is limited due to cost and technical requirements, including in our institution [24, 25].

Another important consideration is the role of renal clearance in syndecan-1 metabolism. Impaired renal function significantly increases its plasma concentration independently of endothelial injury, with documented perioperative variations reaching up to six-fold in patients undergoing abdominal surgery, burn patients, and even healthy volunteers [11, 12]. Given the relatively

rapid turnover of circulating syndecan-1, reported to occur within approximately 15 h, minor fluctuations in renal clearance can significantly impact plasma levels [12].

Although postoperative syndecan-1 levels increased in our cohort, the rise was modest, approximately 1.3-fold at two hours post-surgery. This contrasts with conditions involving pronounced endothelial injury, such as sepsis, where syndecan-1 levels can increase 9- to 50-fold above baseline [14, 26, 27]. The comparatively small elevation observed in our study is likely attributable to the magnitude of surgical stress, as the procedures included generally did not involve ischemic injury or major hemodynamic compromise. Mild to moderate surgical stress, such as thoracic or abdominal procedures without ischemic compromise, may not substantially disrupt the glycocalyx to the degree required for marked syndecan-1 shedding. More severe clinical conditions, including trauma or septic shock, appear necessary to induce the substantial glycocalyx disruption reflected by large syndecan-1 elevations [25]. Supporting this, Rovas et al. reported a 10-fold increase in syndecan-1 levels among septic patients, with a moderate correlation between plasma syndecan-1 concentrations and PBR values ($r = 0.51$, 95% CI: 0.22 to 0.72), reinforcing the role of syndecan-1 as a marker of endothelial glycocalyx degradation in more critical conditions [27].

Interpretation of perioperative syndecan-1 levels is further complicated by the fact that several studies have observed little or no postoperative change in syndecan-1 despite significant elevations in other endothelial biomarkers, such as heparan sulfate, hyaluronan, or angiopoietins [6–11, 17, 28]. These discrepancies may reflect differences in assay sensitivity, biomarker turnover kinetics, or the specific pathways activated by different types of surgical injury. Thus, focusing on syndecan-1 alone may not fully capture the spectrum of endothelial alterations occurring during surgery.

Substantial inter-individual variability, both at baseline and in response to surgery, limits the utility of syndecan-1 for predicting postoperative outcomes. Our ROC curve analysis did not identify meaningful thresholds. This differs from the findings of Kim et al., who reported that postoperative syndecan-1 levels above 48 ng/mL were associated with an increased risk of reoperation following robotic esophagectomy [29]. Notably, that study examined a more homogeneous surgical population and used absolute values rather than relative changes, limiting direct comparability.

Our findings highlight that syndecan-1 levels do not follow a consistent perioperative trajectory; in some patients, levels decreased after surgery, and baseline values differed by over 40-fold across the cohort. Such variability reduces the predictive value of both absolute and relative changes in

syndecan-1 when applied across diverse surgical contexts. Given the range of clinical and biological factors that may influence syndecan-1, such as pre-existing inflammation, liver disease, and fluid management, its role as a reliable standalone biomarker for risk stratification remains unconvincing in its current form.

Finally, methodological heterogeneity across studies further complicates the interpretation of syndecan-1 levels. Variations in assay kits, units' measurement, and the absence of standardized quantification protocol slow down inter-study comparability and limit the clinical applicability of syndecan-1 as a biomarker [6–11, 17, 28, 29]. Without accepted and validated reference standards, harmonized methodology and standardized reporting, the broader clinical implementation of syndecan-1 as a biomarker remains challenging. Until such standardization is achieved, and biomarker performance is confirmed in independent and stratified cohorts, syndecan-1 remains a promising but unproven biomarker for perioperative risk assessment.

Strengths and limitations

Strengths of this study include a prospective design, standardized sample collection, and inclusion of a heterogeneous surgical population, enhancing generalizability. Limitations include a relatively small sample size, lack of external validation, and absence of standardized reference ranges or adjustment for potential confounders affecting syndecan-1 levels.

Conclusion

Plasma syndecan-1 levels exhibit substantial inter-individual variability and show limited association with perioperative variables, reducing their utility for risk stratification. While these knowledge-generating findings provide important insights, they do not support routine clinical use of syndecan-1 without further validation in larger, well-stratified cohorts in the non-urgent surgical population.

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13741-025-00642-5>.

Supplementary Material 1

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Authors' contributions

Study conception: LL, MdM, MdN. Data acquisition and curation: LL, MA, JPD. Data analysis: LL, JP, MdM, EP, MdN. Writing of the manuscript, critical revision, approval of the final version and agreement to be accountable for data: all authors.

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Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethical approval was obtained from the Research Ethics Committee and the Research Projects Commission of Vall d'Hebron University Hospital and following the principles of the Declaration of Helsinki and Spanish Organic Law 3/2018 referred to personal data protection. All participants provided written informed consent prior inclusion.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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