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Original Article

ORIGINAL ARTICLE

Syndecan-1 predicts hemodynamic instability in critically ill patients under intermittent hemodialysis

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ABSTRACT

Introduction. Up to 70% of intermittent hemodialysis (IHD) sessions in critically ill patients are complicated by hemodynamic instability. Although several clinical characteristics have been associated with hemodynamic instability during IHD, the discriminatory capacity of predicting such events during IHD sessions is less defined. In the present study, we aimed to analyse endothelium-related biomarkers collected before IHD sessions and their capacity to predict hemodynamic instability related to IHD in critically ill patients.

Methods. In this prospective observational study, we enrolled adult critically ill patients with acute kidney injury who required fluid removal with IHD. We screened each included patient daily for IHD sessions. Thirty minutes before each IHD session, each patient had a 5-mL blood collection for measurement of endothelial biomarkers—vascular cell adhesion molecule-1 (VCAM-1), angiopoietin-1 and -2 (AGPT1 and AGPT2) and syndecan-1. Hemodynamic instability during IHD was the main outcome. Analyses were adjusted for variables already known to be associated with hemodynamic instability during IHD.

Results. Plasma syndecan-1 was the only endothelium-related biomarker independently associated with hemodynamic instability. The accuracy of syndecan-1 for predicting hemodynamic instability during IHD was moderate [area under the receiver operating characteristic curve 0.78 (95% confidence interval 0.68–0.89)]. The addition of syndecan-1 improved the discrimination capacity of a clinical model from 0.67 to 0.82 ($P < .001$) and improved risk prediction, as measured by net reclassification improvement.

Conclusion. Syndecan-1 is associated with hemodynamic instability during IHD in critically ill patients. It may be useful to identify patients who are at increased risk for such events and suggests that endothelial glycocalyx derangement is involved in the pathophysiology of IHD-related hemodynamic instability.

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Keywords: critically ill, endothelium, hemodialysis, hemodynamic instability, syndecan-1

INTRODUCTION

Intermittent haemodialysis (IHD), delivered as a kidney replacement therapy (KRT) in a 3- to 12-h duration per session, is the original extracorporeal KRT [1]. IHD in the setting of acute kidney injury (AKI) is largely used in low-income countries as the only choice of initial KRT. It also continues to be used in highly developed centers for critically ill patients who are discontinuing continuous KRT [2].

However, a precise definition for hemodynamic instability related to IHD in critically ill patients is lacking. Up to 70% of IHD sessions are complicated by events such as discontinuation of session/reduction of target ultrafiltration (UF) for hemodynamic instability, initiation or increase of vasopressors or extreme blood pressure reduction [3].

Among several mechanisms underpinning hemodynamic instability related to IHD (failure to increase vascular tone and heart rate, "myocardial stunning"), reduction in intravascular volume, secondary to UF and rapid osmotic shifts, is believed to be the main pathophysiological process. The normal compensatory response is plasma refilling during IHD sessions by fluid in the extravascular space [4, 5].

However, in critically ill patients, several factors can reduce the plasma refilling rate and contribute to hemodynamic instability. Hypoalbuminemia is a known risk factor for hemodynamic instability related to KRT in general, and a recent randomized study demonstrated that albumin administration before IHD sessions reduces events related to hemodynamic instability [6]. Endothelium and its glycocalyx damage are suggested as another event related to reduced plasma refilling in critically ill patients [7, 8].

Several clinical characteristics have been associated with hemodynamic instability during KRT (lower systolic blood pressure before the hemodialysis session, vasopressor use and higher UF rates [9]). The discriminatory capacity of predicting hemodynamic events during IHD sessions is less defined. Hemodynamic instability during KRT is associated with a higher risk of death and lower probability of kidney function recovery [10–12], so better markers are necessary to predict and avoid such events. In the present study, we aimed to analyse endothelium-related biomarkers collected before IHD sessions and their capacity to predict hemodynamic instability related to IHD in critically ill patients. For this purpose, we evaluated vascular cell adhesion molecule-1 (VCAM-1), which is related to endothelial cell activation; angiopoietin-1 and -2 (AGPT1 and AGPT2), which interact with the same receptor Tie2, with equal affinity, whereas AGPT1 induces maturation and stabilization of the endothelium, AGPT2 causes destabilization and increases vascular permeability; and finally, syndecan-1, a newly explored marker of endothelial glycocalyx derangement [13].

MATERIALS AND METHODS

Patient and procedure selection

In this prospective observational study, we enrolled adult patients (>18 years) admitted to the intensive care unit (ICU) with AKI who required fluid removal with IHD. Patients were excluded if they had previous chronic kidney disease on maintenance KRT or severe dysnatremias—serum sodium <125 mEq/L or >150 mEq/L. We screened each included patient daily for IHD sessions. These sessions were prescribed according to the prevailing standard of care according to the nephrology attending physician. IHD was performed with NIPRO® DIAMAX FULL hemodialysis generators, NIPRO® ELISIO™-13 M dialysate membranes, and dialysate concentrate solutions with 136–142 mmol/L sodium, 2 mmol/L potassium, 1.75 mmol/L calcium and 0.5 mmol/L magnesium concentrations. Dialysis prescriptions were individualized for each patient (blood and dialysate flow rates, dialysate composition) to achieve a minimum urea reduction ratio of 65%. The attending nephrologist determined UF rates per hour to achieve the desired fluid balance for each session. Standard unit protocols were followed for hemodynamic instability in each session. These standards were individualized for each patient, depending on the severity and frequency of the event, including pausing the UF, reducing the UF target, giving 0.9% sodium chloride boluses, increasing vasopressor drugs, adjusting the dialysate sodium, and early session ending to reverse the episode of hypotension during IHD.

We added an IHD session if it had a duration of 4–8 h, an UF rate between 4 and 12 mL/kg/h, a mean blood pressure between 65 and 85 mmHg before the session and vasopressor dosage up to 0.5 µg/min/kg noradrenaline or equivalent. Each patient had a maximum of three IHD sessions included. To be included, a new IHD session for the same patients with a minimum 72-h interval from previous session inclusion was needed. The study was approved by the institutional review board (Ethical Committee of Instituto José Frota), and all participants or responsible signed free and informed consent before inclusion.

Clinical parameters

Demographic data (age, sex, height and ideal weight) were obtained from direct observation and medical records. Medications were screened for anti-hypertensive or vasopressor drugs. Thirty minutes before each IHD session, each patient had a 5-mL blood collection for measurement of endothelial biomarkers, as described below: serum hemoglobin, sodium, urea, lactate and albumin. Vital signs, vasopressor dosage and UF rate were recorded before and every 30 min during the IHD session. The dialysis nurse recorded in a standardized case report form all symptoms associated with hypotension as well as interventions during the session.

Biomarker measurement

Syndecan-1 was measured as a biomarker of endothelial glycocalyx injury (Abcam, Cambridge, MA, USA). The intra-assay coefficient of variation was 6.2%. ICAM-1, a marker of endothelial cell activation, was measured using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (Life Technologies Brasil, São Paulo, Brazil), with an intra-assay coefficient of 8.4%. Additionally, VCAM-1 was measured using a commercially available ELISA kit (Abcam, Cambridge, UK), with an intra-assay coefficient of 5.9%. AGPT 1 and AGPT2 were measured using an ELISA kit (R&D Systems, Minneapolis, MN, USA). The intra-assay coefficients of variation were 4.7 and 5.3%, respectively. All measurements were performed in duplicate.

Outcomes

None of the multiple operational definitions of KRT pointed to hemodynamic instability, specifically addressing issues relevant to critically ill patients. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) [14] defines intradialytic hypotension as "a decrease in systolic blood pressure by ≥20 mm Hg or a decrease in mean arterial pressure (MAP) by 10 mm Hg associated with symptoms that include abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety." The KDOQI definition does not account for KRT delivery in the ICU when symptoms may not be reported due to altered mental status or mechanical ventilation, nor does the KDOQI definition account for the use or increased need for vasopressor support to maintain systemic blood pressure during KRT. In the present study, we collected several classifications from clinical trials to define hemodynamic instability [15–17]:

(i) systolic blood pressure <90 mmHg or a 40 mmHg drop from the predialysis value or;
(ii) mean blood pressure <60 mmHg or;
(iii) interventions determined by nephrologist assistant to revert or prevent hemodynamic instability—initiation or increment in vasopressors; fluid bolus; reduction in UF rates; or early ending of session procedures.

Any of the abovementioned events during the IHD session were considered an outcome.

Statistical analysis

Continuous variables were described as medians (interquartile ranges) or means and standard deviations as appropriated, and categorical variables were described as proportions. Continuous variables were compared using a 2-sample *t*-test or Mann–Whitney test, and dichotomous variables were compared with the chi-square or Fisher's exact test. To evaluate the association of biomarkers with hemodynamic instability, we divided the cohort into two groups—with or without IHD-related hemodynamic instability. To evaluate the association between biomarkers and IHD-related hemodynamic instability, logistic regression models were used. We used the model adjusting for important covariates that predict IHD-related hemodynamic instability in the literature. These variables were also used to construct a clinical model to predict IHD hemodynamic instability. To avoid overfitting of the model, we used penalized maximum likelihood estimation, which yielded shrunk regression coefficients. The optimum penalty factor that maximized the modified Akaike information criterion was used.

The area under the curve receiver operating characteristic (AUC-ROC) values were calculated for biomarkers and for the clinical model. For syndecan-1, the optimal point was defined according to the highest Youden index, which was calculated as [1 − (1 − sensitivity) + (1 − specificity)]. After that, syndecan-1 was added to the clinical model, and the AUC-ROC values were compared using DeLong and colleagues' method [18]. Furthermore, we calculated the continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) for syndecan-1 regarding hemodynamic instability during IHD to evaluate its additional predictive value. The NRI is described as the percentage of patients whose stratification improves by adding the biomarker under assessment. It is determined by calculating the sum of differences in proportions of patients moving up minus the proportion moving down for patients who develop the event and the proportion of patients moving down minus the proportion moving up for patients who do not develop the event. NRI and IDI are recommended as sensitive tools for detecting the additional benefit of a predictive marker. Their sensitivity exceeds changes in AUC-ROC [19, 20]. IDI is calculated according to the same principle as NRI, using the changes in the model-based probabilities [20]. The calculation of NRI and IDI was made using the clinical model as a reference. The present study has a power of 80% to detect a difference of 0.15 between compared AUC-ROC, considering an incidence of outcome by 30%, a rank correlation coefficient in both positive and negative groups of 0.5 and a *P*-value of .05 [21]. To assess the robustness of our findings, we also performed a sensitivity analysis that included only the first IHD session for each patient. Analysis of the data was performed using SPSS 20.0 for Windows (SPSS Inc., Chicago, IL, USA) and R version 2.14.1 (R Development Core Team, Vienna, Austria).

RESULTS

Patients and procedures

Of 106 patients who were eligible during the study period, 87 (82.1%) gave their consent to participate. From these 87 patients, 270 IHD sessions were screened and 102 IHD sessions were included in the analysis. The majority of IHD sessions were excluded because the UF was below the minimum rate established in the inclusion criteria. A complete list of excluded IHD sessions is displayed in Fig. 1. Fifteen patients (17.2%) had two IHD sessions evaluated, and all remaining patients had only one session each. The main baseline characteristics of the patients are presented in Table 1. Most patients were male [$n = 71$ (81.6%)], and the mean age was 45.9 ± 18.5 years. Diabetes mellitus was present in 9 (10.3%) patients, and 51 (58.6%) patients had sepsis criteria at enrollment with at least 1 point on the nonrenal Sequential Organ Failure Assessment (SOFA).

Mean systolic and diastolic blood pressure at dialysis initiation were 124.6 ± 22.4 and 70.6± 18.4 mmHg, respectively, and 18 (17.6%) IHD sessions were initiated with at least one vasopressor. The media programed UF rate was 7.1 (4.7–12.4) mL/kg/h, and most IHD sessions ($n = 60$, 58.8%) had a 4-h duration. Hemodynamic instability occurred in 31 (30.4%) IHD sessions from 31 different patients (Table 2). The different definitions of episodes of hemodynamic instability and their frequency are shown in the Supplementary Table.

Association of endothelium-related biomarkers and hemodynamic instability

Median pre-hemodialysis levels of syndecan-1 and AGPT2 were higher before IHD sessions with hemodynamic instability [232.1 (168.3–748.3) vs 94.2 (49.0–187.5) ng/mL, $P < .001$ for syndecan-1 and 6686 (4662–9483) vs 5089 (3382–8332) ng/mL, $P = .046$] for AGPT2. No difference was observed in VCAM-1 levels, and there was a trend toward lower levels of AGPT1 in those with hemodynamic instability [2125 (880–5118) vs 4445 (2640–6923) ng/mL, $P = .061$]. Additionally, the AGPT2/AGPT1 ratio was higher in hemodialysis sessions with hemodynamic instability [1.70 (0.35–5.81) vs 0.71 (0.12–1.80), $P = .037$].

In univariate analysis, syndecan-1 was the only biomarker associated with hemodynamic instability—odds ratio (OR) 1.89 [95% confidence interval (CI) 1.32–2.15] for each 100 ng/mL. AGPT1 and -2 had only a statistically significant trend in association with hemodynamic instability, and VCAM-1 had no

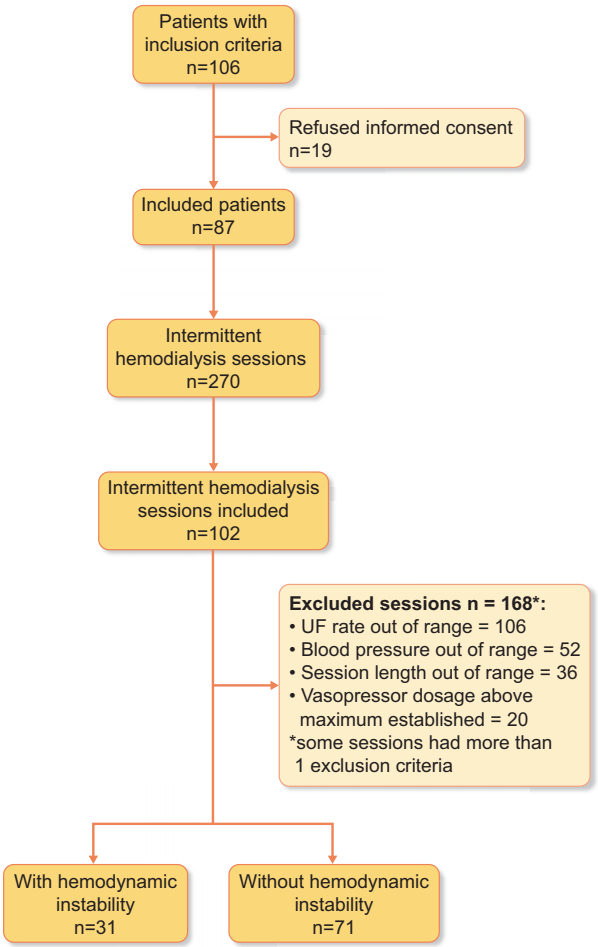

Figure 1: Flowchart of patients and hemodialysis sessions.

association. After adjusting for variables already known to be associated with hemodynamic instability—UF rate, central venous pressure (CVP), vasopressor use, mechanical ventilation, MAP before hemodialysis—syndecan-1 was the only endothelium-related biomarker associated with hemodynamic instability [OR 1.93 (95% CI 1.40–2.15) for each 100 ng/mL] (see Table 3).

Diagnostic testing

The AUC-ROCs for pre-hemodialysis syndecan-1, VCAM-1, AGPT2 and AGPT2/1 ratio are shown in Fig. 2. Although VCAM-1 showed no discrimination value for hemodynamic instability and AGPT1 and the AGPT2/1 ratio had significant but only poor prediction (AUC-ROC between 0.6 and 0.7), syndecan-1 had an AUC-ROC of 0.78 (95% CI 0.68–0.89). The syndecan-1 threshold value with maximal sensitivity and specificity was 151.2 ng/mL (sensitivity of 80% and specificity of 71%).

Added benefit of pre-hemodialysis syndecan-1 to predict hemodynamic instability above clinical prediction

The clinical prediction model with clinical variables—UF rate, CVP, vasopressor use, mechanical ventilation, MAP before IHD—for AKI hemodynamic instability had an AUC-ROC of only 0.67. Adding pre-IHD syndecan-1 as a biomarker to the clinical model improved discrimination by 0.82 ($P < .001$ for AUC-ROC comparison) (Fig. 3). Pre-IHD syndecan-1 also improved the classification accuracy of hemodynamic instability prediction. The continuous NRI resulting from syndecan-1 inclusion in a clinical model was amplified by both reclassification of nonevents (i.e. patients without hemodynamic instability) and events (i.e. patients with hemodynamic instability). The continuous NRI was 0.53 (95% CI 0.31–0.76). The IDI was 0.29 (95% CI 0.17–0.42).

Sensitivity analysis

We performed a sensitivity analysis including only the first IHD session of each patient, and syndecan-1 remained independently associated with hemodynamic instability—OR 1.90 (95% CI 1.31–2.14) for each 100 ng/mL, after adjusting for UF rate, CVP, vasopressor use, mechanical ventilation and MAP before hemodialysis. The AUC-ROC was 0.77 (95% CI 0.65–0.89), and in this sensitivity analysis, adding pre-IHD syndecan-1 to the clinical model improved the discrimination from 0.65 to 0.81 ($P < .001$ for AUC-ROC comparison) (see Supplementary Figure).

Table 1: Cohort description of patients according to hemodynamic instability during intermittent hemodialysis status.

	All patients ($n = 87$)	Without hemodynamic instability ($n = 56$)	With hemodynamic instability ($n = 31$)	P
Age (years), mean ± SD	45.8 ± 19.0	44.8 ± 17.8	47.6 ± 18.1	.69
Male, *n* (%)	63 (72.4)	40 (71.4)	23 (74.2)	.78
Comorbidities				
Hypertension, *n* (%)	9 (10.3)	2 (3.6)	3 (9.7)	.24
Diabetes mellitus, *n* (%)	3 (3.4)	2 (3.6)	1 (3.2)	.93
Chronic kidney disease, *n* (%)	3 (3.4)	1 (1.8)	2 (6.4)	.25
Congestive heart failure, *n* (%)	4 (4.6)	2 (3.6)	2 (6.4)	.54
Main diagnosis at ICU admission				
Sepsis, *n* (%)	42 (48.3)	24 (42.9)	18 (58.1)	.17
Hemorrhagic shock, *n* (%)	18 (20.7)	12 (21.4)	6 (19.3)	.82
Acute respiratory failure, *n* (%)	12 (13.8)	10 (17.6)	2 (6.4)	.14
Coma, *n* (%)	9 (10.3)	5 (8.9)	4 (12.9)	.56
Other, *n* (%)	6 (6.9)	5 (8.9)	1 (3.2)	.31

SD: standard deviation.

Table 2: Cohort description of intermittent hemodialysis sessions according to hemodynamic instability status.

	All hemodialysis sessions ($n = 102$)	Without hemodynamic instability ($n = 71$)	With hemodynamic instability ($n = 31$)	P
Number of IHD session in the ICU, median (IQR)	4 (3–8)	4 (3–10)	3 (2–7)	.31
Nonrenal SOFA score on the IHD session, median (IQR)	6 (5–10)	6 (4–10)	7 (5–10)	.24
Parameters before IHD session				
Mechanical ventilation, *n* (%)	71 (69.6)	44 (61.9)	27 (87.1)	.01
Vasopressor use, *n* (%)	51 (50.0)	28 (39.4)	23 (74.2)	.001
Systolic blood pressure (mmHg), mean ± SD	124.6 ± 22.4	129.5 ± 23.2	113.4 ± 17.2	<.001
Diastolic blood pressure (mmHg), mean ± SD	70.6 ± 18.4	71.3 ± 18.6	69.0 ± 17.9	.56
IHD parameters, median (IQR)				
Duration (h)	4 (4–8)	4 (4–8)	4 (4–8)	.90
UF rate (mL/kg/h)	7.1 (4.7–12.4)	5.5 (3.4–9.2)	8.3 (5.8–14.4)	.02
Biomarkers before IHD session, median (IQR)				
Syndecan-1 (ng/mL)	136.7 (55.5–231.1)	94.2 (49.0–187.5)	232.1 (168.3–748.3)	<.001
VCAM-1 (ng/mL)	2320 (1337–3042)	2441 (1399–3102)	2016 (1273–3037)	.69
AGPT1 (ng/mL)	3840 (1867–6800)	4445 (2640–6923)	2125 (880–5118)	.06
AGPT2 (ng/mL)	5667 (3495–8466)	5089 (3382–8332)	6686 (4662–9483)	.04
AGPT2/1 ratio	1.06 (0.42–2.93)	0.71 (0.12–1.80)	1.70 (0.35–5.81)	.03

IQR: interquartile range; SD: standard deviation.

Table 3: Endothelial-related biomarker levels associated with increased risk of hemodynamic instability during intermittent hemodialysis.

	Univariate analysis OR (95% CI)	Multivariate analysis OR (95% CI)
Syndecan-1, for each 100 ng/mL	1.89 (1.32–2.15)	1.93 (1.40–2.15)
VCAM-1, for each 1000 ng/mL	0.99 (0.75–1.32)	1.01 (0.75–1.35)
AGPT1, for each 1000 ng/mL	1.09 (1.00–1.19)	0.89 (0.79–1.05)
AGPT2, for each 1000 ng/mL	0.89 (0.79–1.00)	1.06 (0.96–1.19)
AGPT2/AGPT1 ratio	1.00 (0.99–1.01)	1.00 (0.99–1.01)

Variables included in the multivariate analysis were UF rate, CVP, vasopressor use, mechanical ventilation and MAP before hemodialysis.

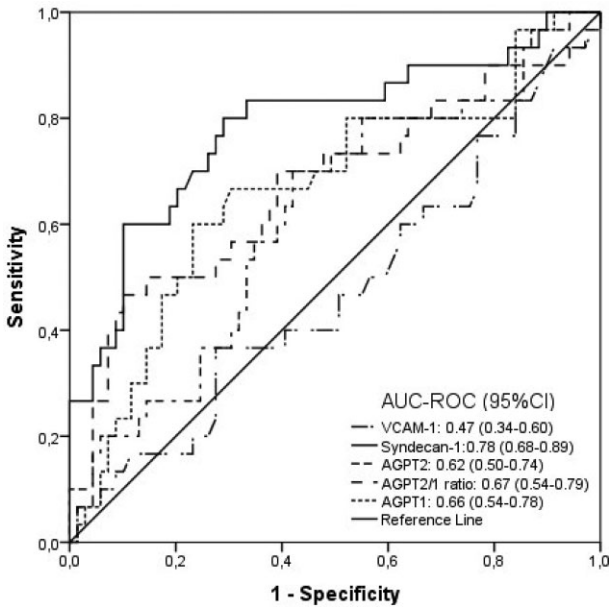

Figure 2: Diagnostic performance of the value of syndecan-1, VCAM-1, AGPT1 and -2, and AGPT2/1 ratio for the detection of hemodynamic instability during intermittent hemodialysis.

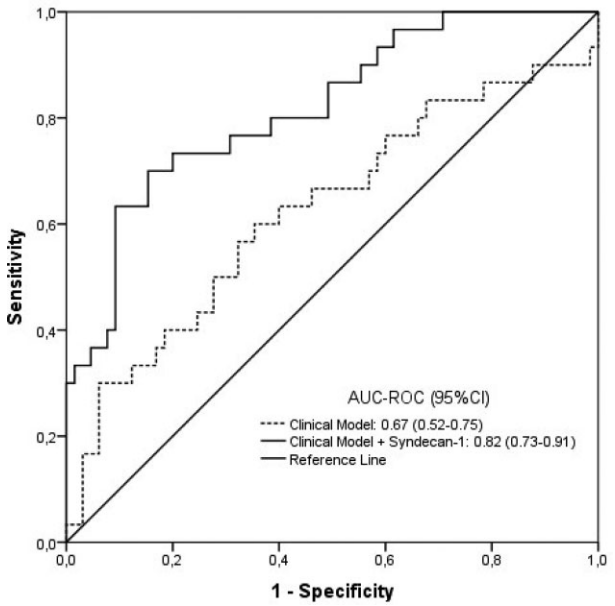

Figure 3: Diagnostic performance of a clinical model including—age, UF rate, CVP, vasopressor use, mechanical ventilation, mean blood pressure before intermittent hemodialysis adding or not adding the value of plasma syndecan-1.

DISCUSSION

In this study, we evaluated four endothelial biomarkers regarding their capacity to predict hemodynamic instability during IHD in critically ill patients. A better risk stratification of patients prone to hemodynamic instability can allow the physician to adopt adequate strategies to prevent their occurrence and reduce their negative consequences [22]. Although plasma VCAM-1 had no association and AGPT2 and the AGPT2/AGPT1 ratio were not independently associated with hemodynamic instability, syndecan-1 was strongly and independently associated with this outcome. Moreover, syndecan-1 alone had a good discriminatory capacity, and when added to a clinical setting, it was able to discriminate patients who did or did not develop hemodynamic instability.

Hemodynamic instability during KRT is not only associated with higher in-hospital mortality [12] but may also be associated with decreased kidney recovery [10]. Although determination of risk factors and predictive models for KRT-related hemodynamic instability could help clinicians to identify patients in whom initiation of KRT should be judicious, factors associated with hemodynamic instability in such situations remain poorly explored. Recently, hemodynamic parameters demonstrated conflicting results regarding volemic status for critically ill patients before IHD in predicting related hemodynamic instability. Chimot *et al*. [23] revealed that echocardiographic parameters, including higher inferior vena cava collapse, were only weakly associated with hemodynamic instability. In contrast, another study [24] demonstrated that a passive leg raising test–induced increased cardiac index predicted intradialytic hypotension with an AUC-ROC of 0.89, although only 39 patients were included in this last study.

To the best of our knowledge, this is the first study to evaluate an endothelial biomarker to predict hemodynamic instability during KRT in critically ill patients. In comparison with a suggested clinical model developed to predict hemodynamic instability in critically ill patients, the SOCRATE (cardiovascular SOFA, index CRT and lactATE) score [25], syndecan-1 alone, showed at least a similar performance. In our cohort, a clinical model using known risk factors for hemodynamic instability and incorporating almost all variables of the SOCRATE score (see below in limitations) was built up but had only moderate discriminatory capacity, and syndecan-1 significantly increased the discrimination performance of this clinical model.

In addition to the potential use of syndecan-1 in risk stratification for IHD tolerance, our study also highlights the importance of glycocalyx damage in the pathophysiology of IHD-related hemodynamic instability. The glycocalyx constitutes a structural portion of the endothelium, which contributes substantially toward maintaining its integrity [26]. From a functional perspective, the glycocalyx acts as a protective layer of the endothelial cell; it also regulates the permeability of various molecules into and out of the endothelial cell, as well as the permeability to water and solutes. Using special enzyme and dextran application techniques to degrade the glycocalyx, van Haaren *et al*. [27] showed that this structure is responsible for changes in water permeability caused by tension forces, and when intact, it is responsible for protecting against edema and protein filtration. Moreover, Henrich *et al*. [28] demonstrated that some proinflammatory cytokines may injure the glycocalyx, thus increasing vascular permeability and affecting tissue perfusion. Likewise, this inflammatory response favors movement of albumin toward the interstitial space, leading to reduced plasmatic oncotic pressure.

Several means are implicated in the mechanism for hemodynamic instability during KRT, and hypovolemia is considered to be a key mechanism. KRT can predispose hypovolemia because UF and/or fluid shifts related to osmolality changes, and plasma refilling from fluid is expected in the interstitial and intracellular compartments compensates for fluid removal with UF. However, a damaged glycocalyx can hinder plasma refilling, worsen hypovolemia, reduce cardiac output and lead to hemodynamic instability [3]. Another potential linkage is glycocalyx damage causing reduced vasoreactivity to endogenous or administered catecholamines; however, this remains only in the field of speculation.

Our study has several limitations. First, it is a monocentric study, and the results need to be confirmed in a multicenter study. Second, our study focused on patients receiving IHD. Future studies also including patients receiving continuous KRT are needed to test whether syndecan-1 could help to identify patients at risk of hemodynamic instability regardless of the modality of KRT. Third, because the great majority of our patients had dark skin, we did not include capillary refilling time (a validated parameter in the SOCRATES score) in our clinical model. Fourth, it is known that the syndecan-1 level can vary after an IHD session [29], and there is no study about its kinetics in the interdialytic interval. Because our patients had different interdialytic intervals, it is possible that the syndecan-1 level before IHD can be influenced by the previous session. Finally, because syndecan-1 levels are increased in AKI [30], we excluded patients with chronic kidney disease on maintenance KRT, so our results cannot be extrapolated to such situations.

In conclusion, the syndecan-1 level before IHD is independently associated with and is a useful marker to predict hemodynamic instability. Adding pre-IHD syndecan-1 to a clinical model that already incorporates variables known to be associated with hemodynamic instability during IHD results in significant improvement in the capacity to predict IHD intolerance (Fig. 3).

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article will be shared on reasonable request to the corresponding author.

CONFLICT OF INTEREST STATEMENT

None declared.

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