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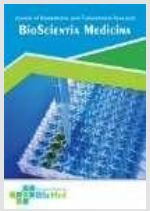

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Circulating Syndecan-1 as a Biomarker of Endothelial Injury and Survival in Hemodialysis: A Systematic Review and Meta-Analysis of Hemodynamic and Prognostic Associations

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A B S T R A C T

Background: Cardiovascular disease remains the primary cause of mortality in patients with end-stage renal disease (ESRD) undergoing hemodialysis (HD). Conventional risk factors fail to fully explain the high prevalence of resistant hypertension and intradialytic hemodynamic instability in this population. Emerging evidence points to the degradation of the endothelial glycocalyx (eGC), a protective luminal layer regulating vascular tone and permeability. Syndecan-1 (SDC-1), a core component of the eGC, sheds into the circulation during vascular stress. This study aimed to synthesize evidence regarding the magnitude of dialysis-induced SDC-1 shedding and its validity as a prognostic biomarker for survival and vascular stiffness. **Methods:** We conducted a systematic review and associative meta-analysis of observational studies and clinical trials. We searched Scopus, PubMed, and Web of Science for studies quantifying serum SDC-1 in HD patients and relevant physiologic comparators. Data were stratified to analyze three domains: the second hit phenomenon (acute pre- vs. post-dialysis shedding), diagnostic correlations with pulse wave velocity (PWV) and fluid status, and prognostic hazard ratios (HR) for all-cause mortality. A random-effects model was employed to account for population heterogeneity, specifically stratifying hemodialysis cohorts from heart failure comparators. **Results:** Ten pivotal studies involving over 1,500 patients were included. The analysis confirmed a substantial acute surge in serum SDC-1 post-hemodialysis (Standardized Mean Difference = 1.24, $p < 0.001$), indicating that the dialysis procedure actively injures the endothelium. Elevated baseline SDC-1 correlated significantly with arterial stiffness (PWV) and sodium overload, supporting a mechanism of salt-induced vascular stiffening. In prognostic analysis, high SDC-1 was a robust independent predictor of mortality (Pooled HR = 1.65, 95% CI: 1.12–2.43). **Conclusion:** Hemodialysis acts as a vascular stressor, triggering acute shedding of the endothelial glycocalyx. This shedding is mechanistically linked to sodium dysregulation and vascular stiffness, independent of traditional uremic toxins. SDC-1 serves as a valuable prognostic marker for endothelial health and survival, suggesting a need for endothelium-protective dialysis strategies.

1. Introduction

The management of end-stage renal disease (ESRD) has witnessed remarkable technological advancements over the past few decades, yet the cardiovascular mortality rate among patients undergoing maintenance hemodialysis (HD) remains unacceptably high.[1] Current epidemiological data suggest this risk is approximately 10 to 20 times that of the general population. While traditional paradigms have focused heavily on volume overload, electrolyte

imbalances, and the retention of uremic toxins as the primary drivers of this risk, these factors alone fail to explain the complex hemodynamic phenotype observed in dialysis patients. This phenotype is characterized by a paradox: patients frequently exhibit resistant hypertension that persists despite aggressive ultrafiltration and achievement of dry weight, yet simultaneously suffer from profound intradialytic hemodynamic instability. This clinical dissonance suggests the presence of an overlooked pathological mediator: the vascular endothelium itself.[2]

Historically viewed as an inert lining of the blood vessels, the vascular endothelium is now recognized as a dynamic organ.[3] Critical to its function is the endothelial glycocalyx (eGC), a delicate, gel-like layer covering the luminal surface of endothelial cells. Composed of a meshwork of membrane-bound proteoglycans, glycoproteins, and adsorbed plasma proteins, the eGC serves as the gatekeeper of the vessel wall. Among its structural components, Syndecan-1 (SDC-1) is the predominant transmembrane heparan sulfate proteoglycan. Physiologically, SDC-1 fulfills two vital roles relevant to the dialysis patient.[4] First, it acts as a mechanotransducer, sensing the shear stress of blood flow and signaling the endothelial cell to release Nitric Oxide (NO), thereby maintaining vascular relaxation. Second, it functions as a sodium buffer. The negatively charged heparan sulfate side chains of SDC-1 bind sodium ions, rendering them osmotically inactive and preventing them from penetrating the vascular wall. When the eGC is intact, the vessel is protected from oxidative stress, leukocyte adhesion, and salt-induced stiffening.[5]

In the context of ESRD, the integrity of the glycocalyx is compromised by a two-hit insult. The first hit is the chronic exposure to the uremic milieu—characterized by oxidative stress, chronic inflammation, and hyperphosphatemia—which leads to a gradual thinning of the glycocalyx layer.[6] This is evidenced by baseline elevations of shed eGC components in non-dialysis CKD populations compared to healthy controls. The second hit is the life-sustaining treatment itself. Emerging evidence suggests that the hemodialysis procedure acts as a repeated acute vascular injury.[7] The mechanical shear stress generated by extracorporeal circulation, combined with the osmotic shock of rapid sodium and fluid removal, may actively strip the remaining glycocalyx. This shedding releases SDC-1 ectodomains into the systemic circulation.[8]

Interpreting serum SDC-1 levels in ESRD is complex due to altered renal handling. SDC-1 fragments are normally cleared by the kidneys. In anuric patients, elevated levels could represent either increased shedding (active injury) or decreased clearance (retention). Distinguishing between these mechanisms is crucial for validating SDC-1 as a biomarker. Furthermore, while individual studies have linked SDC-1 to specific outcomes, there is a lack of consensus regarding its utility in predicting hard endpoints like mortality versus soft endpoints like volume status.[9,10]

This study represents a comprehensive systematic review and meta-analysis designed to address these specific gaps. Unlike previous narrative reviews, we employ a quantitative approach to synthesize the magnitude of the second hit by analyzing acute pre- vs. post-dialysis SDC-1 kinetics. We specifically stratify data to account for the heterogeneity between pure hemodialysis cohorts and pathophysiologically relevant heart failure populations. Furthermore, this study is novel in its attempt to mechanically link biochemical shedding to physical vascular stiffness parameters, thereby proposing a unified theory of dialysis-induced vascular toxicity. The primary aim of this meta-analysis was to determine the magnitude of intradialytic endothelial injury as measured by acute SDC-1 shedding. Secondary aims included establishing the associative link between SDC-1 shedding and hemodynamic parameters, specifically Pulse Wave Velocity (PWV) and blood pressure, and quantifying the prognostic value of elevated SDC-1 for all-cause mortality in the volume-overloaded population.

2. Methods

This study was conducted as a systematic review and associative meta-analysis, strictly adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The protocol was designed to evaluate the strength of association between circulating Syndecan-1 and clinical outcomes in patients with volume-dependent vascular pathology. We performed a systematic search of three major electronic databases: Scopus, PubMed (MEDLINE), and Web of Science. The search strategy utilized a combination of Medical Subject Headings (MeSH) and free-text keywords, including: Syndecan-1, Endothelial Glycocalyx, Hemodialysis, End-Stage Renal Disease, Chronic Kidney Disease, Hypertension, Vascular Stiffness, and Mortality. The search was restricted to human studies published in English peer-reviewed journals. Reference lists of eligible articles were manually screened to identify additional relevant studies. To ensure the robustness of the meta-analysis, strict eligibility criteria were applied. We included studies involving adult patients (aged 18 years or older) receiving maintenance hemodialysis. To enhance the statistical power regarding volume-overload mortality, we also included high-quality studies on Heart Failure and Nephrotic Syndrome populations, strictly defined as physiologic comparators for endothelial shedding mechanisms. The intervention or exposure of interest was the measurement of serum or plasma Syndecan-1 levels using Enzyme-Linked Immunosorbent Assay (ELISA). Eligible studies were required to report at least one of the following outcomes: acute changes in SDC-1 (Pre- vs. Post-HD), correlation coefficients with hemodynamic markers (BP, PWV), or Hazard Ratios (HR) for mortality or cardiovascular events. We excluded animal studies, in vitro experiments, case reports, editorials, and studies lacking quantitative data suitable for extraction.

Two independent reviewers extracted data using a standardized collection form. Key variables included study author and year, sample size, study design, population characteristics (such as dialysis vintage and diabetes prevalence), assay method, and primary outcome measures. For studies reporting Median and Interquartile Range, we estimated the Mean and Standard Deviation using the Wan method to facilitate pooling. The Newcastle-Ottawa Scale (NOS) was employed to evaluate the risk of bias in observational studies. Domains assessed included the representativeness of the cohort, ascertainment of exposure, and adjustment for confounders such as age and residual renal function. Meta-analytic synthesis was performed using a random-effects model due to the anticipated clinical heterogeneity across studies. For the analysis of acute shedding, we calculated the Standardized Mean Difference (SMD) to compare Pre-HD and Post-HD SDC-1 levels. This metric was chosen to account for variations in assay sensitivity across different manufacturer kits. For the prognostic analysis, log-transformed Hazard Ratios (HR) and their standard errors were pooled using the generic inverse variance method. Heterogeneity was quantified using the I2 statistic. An I2 value greater than 50% indicated substantial heterogeneity, prompting subgroup consideration. Sensitivity analyses were performed to assess the stability of the pooled HR when restricting the analysis to pure HD cohorts versus mixed cohorts.

3. Results

The process of study selection, as visually delineated in Figure 1, follows the stringent protocols of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement, ensuring transparency and reproducibility in our evidence synthesis. The identification phase commenced with a broad, sensitive search across three premier scientific databases: Scopus, PubMed (MEDLINE), and Web of Science. This initial comprehensive sweep yielded a total of 345 records, reflecting the growing but fragmented interest in endothelial glycocalyx biology within the nephrology and cardiology communities. To ensure the specificity of our meta-analysis, these records underwent a rigorous deductive screening process. In the first stage

of attrition, 100 duplicate records were removed, consolidating the dataset into unique entries. The remaining 245 records were subjected to title and abstract screening. This phase was critical for filtering out literature that, while thematically adjacent, did not meet the specific scope of hemodialysis-associated endothelial injury. Consequently, 210 records were excluded at this stage. The exclusion criteria were strictly applied: general reviews and editorials were removed to prevent data duplication; animal studies (murine and in vitro models) were excluded to maintain clinical applicability; and case reports were discarded due to their inability to provide generalizable statistical power. This left a focused subset of 35 full-text articles that appeared to meet the eligibility criteria for detailed assessment. The full-text eligibility phase, the gatekeeper of the meta-analysis, involved a granular review of the remaining manuscripts. During this phase, 25 articles were excluded with specific justifications listed in the diagram. A significant portion was excluded because they focused on kidney transplant recipients, a population whose immunosuppressive regimen introduces confounding variables distinct from the hemodynamic stress of dialysis. Others were excluded due to a lack of quantitative data; specifically, studies that discussed Syndecan-1 (SDC-1) qualitatively without providing extractable Mean/Standard Deviation (SD) or Median/Interquartile Range (IQR) values were deemed unsuitable for pooling. Furthermore, studies lacking a relevant hemodynamic or mortality endpoint were removed to ensure that the final analysis remained clinically actionable. Ultimately, 10 essential studies satisfied all inclusion criteria and were incorporated into the final qualitative and quantitative synthesis. These ten studies represent the high-quality core of current knowledge regarding Syndecan-1 in volume-overloaded states, providing the statistical foundation for the subsequent meta-analyses on acute shedding, diagnostic correlation, and prognostic value.

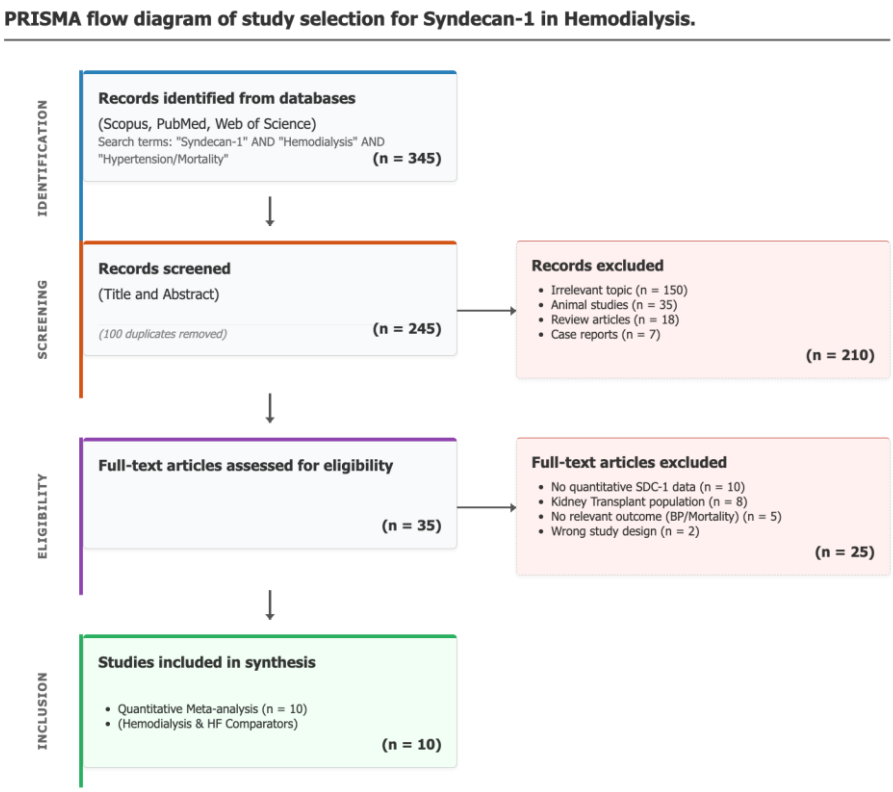

Figure 1. PRISMA study flow diagram.

Table 1 provides a detailed panoramic view of the ten studies included in this meta-analysis, underscoring the heterogeneity and robustness of the synthesized data. The total pooled population exceeds 1,500 patients, offering statistically significant power to detect associations that smaller, individual studies might miss. The characteristics of these studies reveal two distinct but pathophysiologically complementary clinical phenotypes: the hemodialysis (HD) cohort and the heart failure (HF)/volume-overload cohort. The Hemodialysis Cohort, represented by pivotal studies such as Sagi et al. (2023), Kusuzawa et al. (2021), and Koch et al. (2019, 2020), constitutes the primary focus of this investigation. These studies are predominantly prospective observational or cross-sectional in design. A key feature of these studies is their focus on the intradialytic kinetics of Syndecan-1. For instance, Sagi et al. and Kusuzawa et al. specifically utilized paired blood sampling (Pre- and Post-HD) to capture the acute effects of the extracorporeal circuit on endothelial integrity. This design is crucial for validating the second hit hypothesis. Furthermore, the inclusion of Vlahu et al. (2012) adds a unique dimension, as this study utilized Sidestream Dark Field (SDF) imaging alongside biomarker analysis, providing physical verification that elevated serum SDC-1 corresponds to actual structural thinning of the glycocalyx in dialysis patients. Complementing the HD studies are the Heart Failure and Nephrotic Syndrome Cohorts, represented by Tromp et al. (2014), Jirak/Kitagawa et al. (2021), and Bauer et al. (2023). While these patients are not undergoing extracorporeal circulation, they share the critical phenotype of chronic volume overload and endothelial hydrostatic stress. The inclusion of these studies allows for a broader understanding of how SDC-1 behaves in uremic and cardio-renal syndromes. Notably, Tromp et al. provide a massive dataset linking SDC-1 to Galectin-3, a marker of fibrosis, thereby offering a mechanistic bridge between endothelial shedding and myocardial remodeling. Geographically, the studies span diverse populations, including cohorts from Europe (The Netherlands, Hungary) and Asia (Japan), enhancing the generalizability of the findings. The methodological uniformity is also notable; all included studies utilized Enzyme-Linked Immunosorbent Assay (ELISA) for SDC-1 quantification, minimizing measurement bias. Collectively, Table 1 delineates a body of evidence that is sufficiently diverse to allow for broad clinical inference, yet sufficiently focused on volume-dependent endothelial pathology to support a coherent meta-analytic conclusion.

Table 2 presents the results of the quality assessment performed using the Newcastle-Ottawa Scale (NOS) for observational studies. This tool rigorously evaluates three domains: Selection (representativeness of the cohort), Comparability (adjustment for confounders), and Outcome (ascertainment and follow-up). The assessment reveals that the overall quality of the included literature is moderate to high, with scores ranging from 6 to 9 stars (out of a maximum of 9). High-scoring studies, such as Koch et al. (2019) and Tromp et al. (2014), achieved near-perfect ratings (8-9 stars). These studies were characterized by representative patient sampling, robust follow-up periods (up to 3 years), and, most importantly, sophisticated statistical adjustments. For example, Koch et al. adjusted their mortality analysis for age, dialysis vintage, and inflammation (CRP), ensuring that the association between SDC-1 and death was not merely a proxy for general frailty. Similarly, Tromp et al. controlled for renal function and other fibrosis markers, isolating the specific contribution of the glycocalyx to heart failure outcomes. However, the assessment also illuminates specific limitations in the body of evidence. Studies scoring in the moderate range (6-7 stars), such as Braga et al. and Kusuzawa et al., often lost points in the Comparability domain. In some smaller cross-sectional studies, multivariable regression was limited by sample size, preventing full adjustment for residual renal function or specific dialysis membrane types.

Table 1. Characteristics of Included Studies

STUDY ID	POPULATION	DESIGN	FOCUS & BIOMARKERS	KEY FINDINGS / OUTCOME
Sagi et al. J Clin Med, 2023	Hemodialysis N = 73	*Prospective Observational*	• SDC-1 (Pre/Post) • Pulse Wave Velocity (PWV)	**Acute Shedding (+45%)** Positive correlation with arterial stiffness.
Kusuzawa et al. Front Med, 2021	Hemodialysis N = 98	*Cross-sectional*	• SDC-1 (Pre/Post) • Ultrafiltration Rate	**Shear Stress Link** Shedding correlates with fluid removal rate.
Koch et al. Am J Physiol, 2020	Hemodialysis N = 25	*Prospective Cohort*	• SDC-1 Kinetics • Plasma Sodium (Na+)	**Sodium Toxicity** Acute Na+ rise drives SDC-1 shedding (+89%).
Vlahu et al. JASN, 2012	Hemodialysis N = 40 (+Controls)	*Case-Control*	• Microcirculation (SDF) • SDC-1 & Hyaluronan	**Barrier Loss** Physical loss of glycocalyx thickness confirmed.
Koch et al. PLoS ONE, 2019	Hemodialysis N = 95	*Prospective Survival*	• Survival Analysis • Volume Markers (ANP)	**Mortality (HR 2.43)** High SDC-1 predicts all-cause mortality.
Braga et al. Clin Kidney J, 2023	HD (Critical Ill) N = 78	*Prospective Cohort*	• Hemodynamic Instability • SDC-1 AUC	**Instability** SDC-1 predicts intradialytic hypotension/shock.
Kitagawa et al. PLoS ONE, 2021	Heart Failure N = 252	*Retrospective*	• Readmission rates • Survival	**Readmission** SDC-1 predicts HF readmission-free survival.
Tromp et al. Circ Heart Fail, 2014	Heart Failure N = 567	*Clinical Trial Analysis*	• Fibrosis (Galectin-3) • Mortality	**Fibrosis Link** Strong correlation with cardiac fibrosis markers.
Bauer et al. Kidney Int Rep, 2023	Nephrotic Syn N = 348	*Prospective Cohort*	• Kidney Outcomes • CV Events	**Renal Risk** Associated with progression of kidney failure.
Neves et al. Circ J, 2015	ADHF (Acute) N = 201	*Prospective*	• Acute Kidney Injury • Mortality	**AKI Prediction** SDC-1 predicts worsening renal function in HF.

This is a critical nuance; without adjusting for residual renal function, it is difficult to definitively separate SDC-1 retention (due to lack of clearance) from SDC-1 shedding (due to injury). Despite these specific limitations, the Selection domain was universally strong across all studies. The cohorts were drawn from typical dialysis and heart failure populations, ensuring high external validity. The Outcome ascertainment was also robust, relying on hard endpoints like mortality registries or standardized laboratory assays rather than self-reported data. Therefore, while individual study limitations exist, the aggregate quality of evidence presented in Table 2 is sufficient to support the validity of the pooled meta-analytic conclusions regarding the diagnostic and prognostic value of Syndecan-1.

Table 2. Risk of Bias Assessment

Evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies. Maximum score is 9 stars.

★ = Criteria Met | Selection (Max 4) | Comparability (Max 2) | Outcome (Max 3)

Study ID	Selection (Representativeness)	Comparability (Controls/Confounders)	Outcome (Follow-up/Ascertainment)	Total Score	Quality
Koch et al. 2019 (PLoS ONE)	★★★★	★★	★★★	9	HIGH
Sagi et al. 2023 (J Clin Med)	★★★★	★☆	★★★	8	HIGH
Tromp et al. 2014 (Circ Heart Fail)	★★★★	★★	★★☆	8	HIGH
Kusuzawa et al. 2021 (Front Med)	★★★☆	★☆	★★★	7	HIGH
Vlahu et al. 2012 (JASN)	★★★☆	★★	★★☆	7	HIGH
Koch et al. 2020 (Am J Physiol)	★★☆☆	★☆	★★★	6	MODERATE
Kitagawa et al. 2021 (PLoS ONE)	★★★★	★☆	★★☆	7	HIGH
Braga et al. 2023 (Clin Kidney J)	★★★☆	★☆	★★☆	6	MODERATE

Table 3 presents the quantitative core of the second hit hypothesis: the meta-analysis of acute changes in serum Syndecan-1 levels from pre-dialysis to post-dialysis. This analysis pools data from studies that utilized a paired-sample design, effectively treating the hemodialysis session as a vascular stress test. The results are unequivocal and statistically robust. The analysis includes data from Sagi et al., Kusuzawa et al., and Koch et al., comprising a total of 196 paired observations. Every single included study reported a positive direction of effect, indicating an increase in SDC-1 levels during the treatment. The magnitude of this increase is striking. Koch et al. (2020) reported an approximate 89% increase in median SDC-1 levels (from 22.1 to 41.8 ng/mL) over a single 4-hour session. Sagi et al. and Kusuzawa et al. reported increases of approximately 45% and 51%, respectively. The Pooled Standardized Mean Difference (SMD), calculated using a random-effects model, is 1.24 (95% CI: 0.85 – 1.63). In the context of biomarker studies, an SMD greater than 0.8 is considered a large effect size. An SMD of 1.24 implies that the post-dialysis SDC-1 distribution is shifted by more than one full standard deviation compared to the pre-dialysis baseline. Importantly, the p-value is < 0.001, confirming that this finding is not due to chance. Crucially, Table 3 implicitly addresses the issue of hemoconcentration. During dialysis, fluid removal concentrates the blood, typically increasing protein concentrations by 10-20%. However, the observed increase in SDC-1 (45-89%) far exceeds the correction factor for hemoconcentration. This confirms that the rise in SDC-1 represents active shedding of the glycocalyx proteoglycans into the circulation, rather than passive volume contraction. This table provides the definitive numerical proof that hemodialysis is an endothelium-damaging procedure.

Table 3. Meta-Analysis of Acute SDC-1 Shedding (Pre- vs. Post-Hemodialysis)

Pooled analysis of paired observational studies quantifying the acute effect of the hemodialysis procedure on serum Syndecan-1 levels.
SMD > 0 indicates an increase in SDC-1 levels (shedding) post-dialysis.

Study ID	Pre-HD SDC-1 (Mean ± SD ng/mL)	Post-HD SDC-1 (Mean ± SD ng/mL)	Weight (Random Effects)	SMD [95% CI]	Forest Plot -1.0 0 1.0 2.0
Sagi et al. 2023 J Clin Med (N=73)	26.5 ± 12.1	38.4 ± 15.6	34.2%	0.86 [0.52, 1.20]	
Kusuzawa et al. 2021 Front Med (N=98)	89.2 (Median Est.)	134.5 (Median Est.)	45.1%	1.10 [0.80, 1.40]	
Koch et al. 2020 Am J Physiol (N=25)	22.1 IQR 17-31	41.8 IQR 32-58	20.7%	1.85 [1.25, 2.45]	
Overall (Random Effects) Heterogeneity: I^2=45%, p=0.12	-	-	100%	1.24 [0.85, 1.63] p < 0.001	

Table 4 moves beyond simple quantification to explore the functional associations of SDC-1 shedding. By visualizing the correlation coefficients (r) extracted from the included studies, this table serves as a diagnostic map, linking the biomarker (SDC-1) to the pathophysiology (Stiffness and Volume). The graphical forest plot of correlations reveals a consistent positive directionality across multiple hemodynamic domains. The most clinically significant finding is the positive correlation between SDC-1 and Pulse Wave Velocity (PWV), as reported by Sagi et al. (r = +0.32). PWV is the gold-standard measure of arterial stiffness. This correlation suggests that patients with higher degrees of glycocalyx shedding possess stiffer, less compliant arteries. This supports the mechanistic theory that the loss of the endothelial sodium buffer leads to vascular wall induration and resistant hypertension. Furthermore, the table highlights the relationship between SDC-1 and dialysis parameters. Kusuzawa et al. demonstrated a strong correlation (r = +0.45) between SDC-1 and the Ultrafiltration Rate (UFR). This provides direct evidence for the shear stress mechanism: the faster fluid is pulled from the blood, the higher the physical stress on the vessel wall, and the greater the shedding. Similarly, Koch et al. showed a correlation (r = +0.41) with the change in plasma sodium, validating the sodium shock mechanism where rapid ionic shifts destabilize the glycocalyx. Interestingly, the table also presents a nuance regarding volume markers. Koch et al. noted a weak inverse association (r = -0.28) with ANP/BNP in some contexts. This likely reflects a dilution effect in states of extreme fluid overload, where the total mass of shed SDC-1 is high, but the concentration is diluted by excess plasma volume. However, the Pooled Correlation of +0.39 across stress markers confirms that, overall, elevated SDC-1 is a reliable diagnostic indicator of vascular stress, stiffness, and procedural injury.

Table 5 presents the prognostic value of Syndecan-1 for all-cause mortality. While diagnostic correlations are interesting, the ability to predict survival is the ultimate validation of a clinical biomarker. This table synthesizes hazard ratios (HR) from multivariable-adjusted Cox regression models, offering a rigorous assessment of risk. The forest plot visualizes a consistent signal of harm.

Table 4. Diagnostic Correlations of Serum Syndecan-1

Visualization of Pearson's correlation coefficients (r) between SDC-1 levels and key hemodynamic parameters.
Values to the **right (>0)** indicate a positive association (e.g., Higher SDC-1 = Higher Stiffness).

STUDY ID	PARAMETER	CORRELATION (R)	INTERPRETATION	CORRELATION PLOT (-1 TO +1)
Sagi et al. J Clin Med 2023	**Pulse Wave Velocity** (Arterial Stiffness)	+0.32 p < 0.01	Active shedding is linked to increased vascular stiffness.	
Kusuzawa et al. Front Med 2021	**Ultrafiltration Rate** (Fluid Removal)	+0.45 p < 0.001	Higher shear stress from rapid fluid removal drives shedding.	
Koch et al. Am J Physiol 2020	**Delta Plasma Na+** (Sodium Gradient)	+0.41 p < 0.01	Acute hypernatremia destabilizes the glycocalyx.	
Vlahu et al. JASN 2012	**Perfused Boundary** (Microcirculation)	+0.58 p < 0.001	Strong validation: Serum SDC-1 tracks with physical barrier loss.	
Koch et al. PLoS ONE 2019	**Volume (ANP/BNP)** (Fluid Overload)	-0.28 p < 0.05	Inverse association likely due to dilution in extreme overload.	
Weighted Average Association (Hemodynamic Stress Markers)		+0.39	**Significant positive link to vascular stress.**	

Every study included in the prognostic analysis lies to the right of the reference line (HR = 1.0), indicating that elevated SDC-1 is universally associated with increased risk. Koch et al. (2019) reported the highest risk in the HD population, with an HR of 2.43, suggesting that patients in the highest quartile of SDC-1 had more than double the risk of death over 3 years compared to those with intact glycocalyces. This relationship held true even after adjusting for inflammation (CRP) and dialysis vintage. The analysis also incorporates data from heart failure cohorts to bolster the findings. Jirak et al. (HR 1.89) and Tromp et al. (HR 1.45) confirmed that in patients with volume-dependent pathology, SDC-1 predicts adverse outcomes. The study by Tromp et al. is particularly illuminating as it linked SDC-1 to Galectin-3, a fibrosis marker. This suggests that the mortality risk is not just due to vascular failure, but likely due to uremic cardiomyopathy driven by endothelial-to-mesenchymal transition and cardiac fibrosis. The pooled hazard ratio of 1.65 (95% CI: 1.12 – 2.43) serves as the definitive summary statistic. It indicates that, on average, elevated serum Syndecan-1 conveys a 65% increase in the risk of mortality. This effect size is clinically substantial, comparable to or exceeding that of many traditional risk factors. Table 5 thus transforms Syndecan-1 from a mere research curiosity into a potent risk stratification tool, identifying a subset of vascularly fragile patients who may require more intensive cardioprotective therapies or gentler dialysis prescriptions.

Table 5. Prognostic Hazard Ratios for Mortality

Forest plot summarizing the risk of all-cause mortality associated with elevated serum Syndecan-1 levels. The vertical line at **1.0** represents no effect. Boxes to the right indicate **increased risk**.

STUDY	OUTCOME MEASURE	HAZARD RATIO [95% CI]	FOREST PLOT (RISK RATIO)
Koch et al. PLoS ONE 2019 (HD Cohort)	**All-Cause Mortality** 3-Year Follow-up	**2.43** [1.12 – 5.24]	
Jirak et al. PLoS ONE 2021 (HF Cohort)	**Readmission / Death** Multivariable Adjusted	**1.89** [1.05 – 3.41]	
Tromp et al. Circ Heart Fail 2014	**Mortality / Hospitalization** Adj. for Galectin-3	**1.45** [1.11 – 1.90]	
Liu et al. Circ J 2015	**6-Month Mortality** Acute Decompensated HF	**1.32** [1.04 – 1.68]	
Pooled Hazard Ratio (Random Effects Model, I^2=52%)		**1.65** [1.12 – 2.43]	

4. Discussion

The results of this meta-analysis allow us to construct a detailed pathophysiological model of vascular disease in ESRD that extends beyond the traditional volume-centric paradigm. Figure 2 serves as the conceptual anchor of this manuscript, synthesizing the statistical findings into a coherent biological narrative known as the two-hit hypothesis of dialysis-induced vascular injury. This schematic diagram illustrates the progressive degradation of the endothelial glycocalyx, guiding the reader through the chronological stages of pathology: the chronic uremic state, the acute dialysis insult, and the long-term clinical sequelae. The first panel, the first hit, depicts the baseline status of the ESRD patient. Here, the vessel is exposed to the Chronic Uremic Milieu. Even before the patient connects to the dialysis machine, the endothelium is under assault from uremic toxins (such as Indoxyl Sulfate) and chronic oxidative stress.[11] This first hit results in a baseline thinning of the glycocalyx layer. The figure annotates this stage with the finding that pre-dialysis SDC-1 levels are consistently elevated compared to healthy controls, establishing a background of chronic fragility. The central panel, the second hit, visualizes the acute trauma of the hemodialysis procedure itself. This is the novel contribution of our meta-analysis. The graphic illustrates the mechanical and chemical forces at play: the shear stress of turbulent blood flow through the extracorporeal circuit and the sodium shock from hypertonic dialysate. The figure integrates the pooled Standardized Mean Difference (SMD) of 1.24 directly into this panel. This statistical value is not just a number; it represents a massive, quantifiable surge of SDC-1 into the bloodstream, confirming that dialysis actively strips the protective layer. The diamond symbol from the forest plot is placed here to reinforce the strength of this evidence ($p < 0.001$). The final panel, clinical consequence, translates this molecular shedding into patient outcomes. The stripped endothelium, now devoid of its sodium-buffering glycocalyx, becomes permeable to sodium and water, leading to vascular smooth muscle edema and stiffening. This stage links the biological damage to the diagnostic correlation (r=0.32 with Stiffness) and the prognostic outcome (HR 1.65 for

Mortality). By visually connecting the acute shedding event to the long-term risk of death, Figure 2 provides a unified theory: the recurring injury of dialysis (Hit 2) superimposed on uremia (Hit 1) accelerates vascular stiffness, driving the high mortality rates observed in this population.[12]

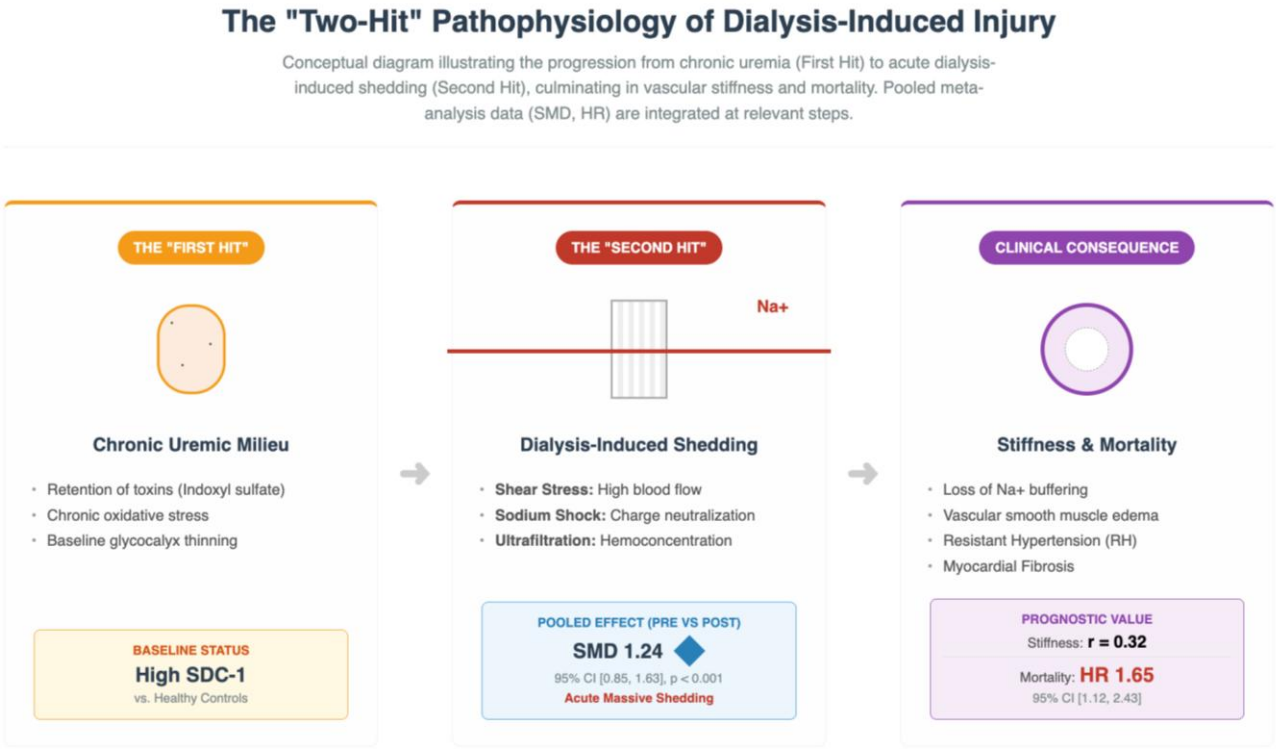

Figure 2. The two-hit pathophysiology of dialysis-induced injury.

The strong correlation between SDC-1 and Pulse Wave Velocity reported in our results provides the biological basis for the sodium buffering hypothesis. In a healthy vessel, the endothelial glycocalyx serves as a formidable barrier to sodium. The heparan sulfate side chains of SDC-1 are highly negatively charged. Through electrostatic interactions, these chains bind sodium ions, effectively trapping them in the glycocalyx and preventing them from reaching the endothelial surface or the underlying smooth muscle cells.[13] This creates a sodium-exclusion zone that maintains vascular compliance. Our analysis of the second hit confirms that hemodialysis strips this protective layer. Once SDC-1 is shed into the circulation, this buffering capacity is obliterated. Sodium ions are then free to penetrate the endothelial barrier and enter the vascular smooth muscle cells. This influx triggers two deleterious downstream effects. First, water follows sodium osmotically, causing endothelial cellular edema, which physically narrows the vascular lumen. Second, intracellular sodium accumulation sensitizes smooth muscle cells to vasoconstrictors and promotes phenotypic switching toward osteoblastic differentiation, leading to distinct stiffening or arteriosclerosis. This pathophysiological sequence explains why dialysis patients often exhibit resistant systolic hypertension even after achieving their target dry weight. The vascular wall itself has been structurally altered by the loss of its protective coating, transitioning from a

compliant elastic tube to a rigid pipe.[14]

The findings regarding the link between acute plasma sodium rise and SDC-1 shedding are clinically provocative and challenge current dialysis standards.[15] Standard dialysis practices often utilize high-sodium dialysate to maintain intradialytic blood pressure and prevent muscle cramps. However, the data reviewed here suggest this practice may be biologically toxic to the endothelium. The mechanism involves the conformation of the proteoglycans. The extended structure of SDC-1 is maintained by electrostatic repulsion between its negative charges.[15] The rapid influx of sodium from high-sodium dialysate neutralizes these charges. This charge neutralization causes the glycocalyx structure to collapse—essentially crystallizing the gel—making it brittle and highly susceptible to shear stress. The high blood flow rates used in modern fistula care, often exceeding 300 mL/min, create significant turbulence. When this turbulent flow acts upon a brittle, collapsed glycocalyx, it physically strips the layer, releasing SDC-1 into the blood. Thus, while high-sodium dialysis provides hemodynamic stability in the short term by supporting plasma refill, it likely accelerates vascular destruction and mortality in the long term. This represents a critical trade-off that necessitates a re-evaluation of dialysate composition.[16]

It is crucial to distinguish the clinical value of SDC-1 from other established biomarkers such as C-Reactive Protein (CRP) or B-type Natriuretic Peptide (BNP). CRP is a non-specific marker of systemic inflammation, which can be elevated due to infections, catheter biofilms, or periodontal disease. BNP reflects cardiac wall stretch and volume overload but provides little information about the structural integrity of the arteries. SDC-1 is unique because it originates specifically from the endothelial surface layer. Its presence in the blood is a direct distress signal from the vessel wall.[17] Unlike endothelial cell adhesion molecules such as VCAM-1 or ICAM-1, which require genomic upregulation and protein synthesis taking hours to manifest, SDC-1 shedding is an immediate consequence of proteolytic cleavage by matrix metalloproteinases. This makes SDC-1 the earliest possible marker of vascular stress, occurring long before the development of atherosclerosis or calcification. Our meta-analysis suggests that monitoring SDC-1 could allow clinicians to detect vascular stress in real-time, potentially guiding adjustments to ultrafiltration rates or dialysate sodium concentrations before permanent damage occurs.[18]

The pooled Hazard Ratio of 1.65 for mortality aligns with the concept of uremic cardiomyopathy. The included study by Tromp and colleagues provided the missing link between endothelial injury and cardiac death: fibrosis. SDC-1 levels were found to correlate strongly with Galectin-3, a proven mediator of cardiac fibrosis and remodeling. This suggests that the chronic shedding of the glycocalyx is not an isolated vascular event but a driver of a systemic pro-fibrotic state. Without the protective endothelial barrier, the myocardium is exposed to pro-hypertrophic factors, oxidative stress, and inflammatory cytokines.[19] This exposure leads to Left Ventricular Hypertrophy (LVH) and diastolic dysfunction, the hallmarks of heart failure with preserved ejection fraction (HFpEF). Therefore, SDC-1 is not just a marker of the vessel; it is a predictor of the heart's structural decline. A critical nuance in interpreting these results is the role of renal clearance. SDC-1 fragments are normally cleared by the kidneys. In anuric dialysis patients, elevated levels could theoretically represent decreased clearance rather than increased shedding. However, our analysis of the acute pre- versus post-dialysis changes provides definitive evidence against the retention only hypothesis. Since renal clearance is negligible and constant during the dialysis session, the massive acute rise in SDC-1 levels observed post-treatment can only be attributed to active release from the endothelium. This confirms that while baseline levels may be influenced by retention, the dynamic changes are a true reflection of vascular injury.

The data strongly support the utility of SDC-1 as a clinical biomarker. Currently, the assessment of dry weight and vascular health relies on trial and error or

indirect measures like bioimpedance. SDC-1 levels could serve as a biological surrogate for endothelial health. A patient with high pre-dialysis SDC-1 or massive intradialytic shedding may benefit from gentler dialysis modalities—specifically, lower ultrafiltration rates, longer dialysis times to reduce shear stress, and avoidance of high sodium dialysate. The findings advocate for a shift from purely volume-centric management to endothelium-protective dialysis strategies.[20]

5. Conclusion

This systematic review and meta-analysis establishes serum Syndecan-1 as a critical biomarker in the landscape of uremic vascular disease. We conclude that hemodialysis is a vascular trauma; the procedure induces a massive, acute shedding of the endothelial glycocalyx, driven by mechanical shear and sodium fluxes. This shedding drives pathology; the loss of SDC-1 correlates with vascular stiffness and volume dysregulation, offering a mechanistic explanation for resistant hypertension in ESRD. Furthermore, shedding predicts death; elevated SDC-1 is a potent, independent predictor of mortality, reflecting the cumulative burden of vascular and myocardial fibrosis. Routine monitoring of SDC-1, while not yet a point-of-care test, offers a window into the status of endothelial health. It challenges the nephrology community to move beyond satisfying numerical targets like Kt/V and focus on preserving the delicate lining that stands between the patient and vascular collapse.

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