

Supplementary Materials

Table S1. Results of eligible articles.

Study	Aim(s)	Outcome Parameters	Nephro-cardiac Interplay	Uremic Toxin Changes	Cardiac Changes
Crespo-Salgado et al., 2016 [19]	<ul style="list-style-type: none"> - To assess the impact of ESKD on the intestinal microbiota of pediatric patients. - To evaluate how changes in the microbiome could influence the production and serum levels of bacterially derived uremic toxins. - To investigate the correlation between microbiota composition, C-reactive protein (an inflammation marker), and D-lactate (indirect marker of intestinal permeability). 	<ul style="list-style-type: none"> - Relative abundance of bacterial taxa and diversity within the gut microbiome - Serum levels of bacterially derived uremic toxins - Markers of systemic inflammation and intestinal permeability 	<ul style="list-style-type: none"> - The paper does not directly address the interplay between nephrological and cardiac disorders in pediatric CRS. 	<ul style="list-style-type: none"> - Serum levels of bacterially derived uremic toxins, IS and pCS, were significantly increased in pediatric patients with ESKD. - IS and pCS levels were significantly higher in patients undergoing PD and HD compared to the healthy controls and kidney transplant recipients. - There were no significant differences in IS and pCS levels between PD and HD patients. - The altered intestinal microbiota in these ESKD patients, characterized by bacterial population shifts and decreased bacterial diversity, was associated with increased production of these uremic toxins. 	<ul style="list-style-type: none"> - Although the primary focus of the paper was not on direct cardiac changes, the study implied a connection between increased uremic toxins and inflammation, which is a known contributor of CVD in ESKD patients.
Holle et al., 2019 [20]	<ul style="list-style-type: none"> - To investigate the association of uremic toxins (IS and pCS) with CV 	<ul style="list-style-type: none"> - cIMT - PWV - LVMI 	<ul style="list-style-type: none"> - The paper does not directly address the interplay between nephrological and cardiac disorders in pediatric CRS. 	<ul style="list-style-type: none"> - Serum levels of IS and pCS showed significant positive associations with urea levels 	<ul style="list-style-type: none"> - Only IS was significantly associated with a higher baseline cIMT and progression of PWV over 12

	surrogate parameters in children with CKD.		- However, the findings link renal dysfunction (through the accumulation of uremic toxins due to reduced renal clearance) with CV alterations.	and negative associations with eGFR and uric acid. - These associations indicated that as kidney function deteriorated, the levels of these toxins increased.	months, both surrogate markers of CV health.
Holle et al., 2020 [21]	- To assess the association of serum IS concentrations with the progression of CKD in children, specifically the potential predictive value of IS for disease progression.	- Progression of CKD, defined by a 50% loss of eGFR, eGFR < 10 ml/min/1.73m ² , or the initiation of renal replacement therapy.	- The paper does not directly address the interplay between nephrological and cardiac disorders in pediatric CRS. - It discussed the relationship between uremic toxins and kidney disease progression.	- Serum IS levels, but not serum pCS levels, were significantly associated with faster CKD progression, independent of other traditional risk factors such as baseline eGFR, proteinuria, and blood pressure.	- No findings about specific cardiac changes or the direct impact of uremic toxins on cardiac function.
Özdemir et al., 2015 [22]	- To investigate the functional and structural CV system changes in children receiving dialysis. - To explore any associations between these CV changes and the clearance of small water-soluble, middle molecule, and protein-bound uremic toxins.	- Clearance of uremic toxins in blood samples from HD patients with or without CVD - AIX - PWV - cIMT - LVMI	- The study does not explicitly mention CRS, but it examines the relationship between uremic toxin clearance and CV changes.	- There was no significant difference in the clearance of small water-soluble uremic toxins between patients with and without cardiac dysfunction. - The clearance of β 2M from the class of middle molecule uremic toxins and homocysteine from the class of protein-bound uremic toxins were significantly low in HD patients with CVD. - Between the two dialysis modalities, middle molecule	- Mean values of AIX, PWV, cIMT, and LVMI were significantly worse in the 40% of HD patients and 20% of PD patients compared to the control group. - Lower clearance of middle molecule and protein-bound uremic toxin classes was associated with worse CV outcomes in pediatric patients on HD.

				and protein-bound uremic toxins were more efficiently cleared by PD compared to HD.	
Snauwaert et al., 2018 [23]	<ul style="list-style-type: none"> - To describe and compare the concentrations of various uremic toxins in healthy children and those with non-dialysis CKD stages 1–5. - To establish reference values for these toxins in the pediatric population. 	<ul style="list-style-type: none"> - Serum concentrations of small water-soluble, middle molecule, and protein-bound uremic toxins 	<ul style="list-style-type: none"> - The paper does not directly address the interplay between nephrological and cardiac disorders or reference pediatric CRS. - It discussed the analysis of uremic toxin levels in children with various stages of CKD compared to healthy controls. 	<ul style="list-style-type: none"> - Established reference values for a range of uremic toxins belonging to each class in healthy children and in children with non-dialysis CKD. - Concentrations of SDMA, CfD, β2M, HA, IAA, IS, pCS, and CMPF were significantly higher in the overall CKD group compared to healthy controls. - Concentrations of SDMA, CfD, β2M, IS, and CMPF were significantly higher in CKD stages 1–2 onwards compared to healthy controls. - Concentrations of pCS, pCG and IAA were significantly higher in CKD stages 3–4 onwards compared to healthy controls. - Concentrations of ADMA and HA were significantly higher only in CKD stage 5 	<ul style="list-style-type: none"> - No findings about specific cardiac changes or the direct impact of uremic toxins on cardiac function.

				compared to healthy controls.	
Snauwaert et al., 2019 [24]	- To investigate how RKF influences the concentrations of various uremic toxins in pediatric patients undergoing maintenance HD.	<ul style="list-style-type: none"> - Levels of protein-bound uremic toxins - Percentage of protein binding of these toxins - Residual urine volume 	<ul style="list-style-type: none"> - The paper does not directly address the interplay between nephrological and cardiac disorders or reference pediatric CRS. - It discussed the relationship between uremic toxin concentrations and RKF in pediatric HD patients. 	<ul style="list-style-type: none"> - 7.8-fold rise in IAA and 43-fold rise in HA in children on HD compared to healthy controls. - Levels of β2M, pCG, HA, IAA, and IS were significantly increased in children on HD compared to children with non-dialysis CKD stages 4-5. - There were no significant differences in UA, pCS, CMPF levels between children on HD and children with non-dialysis CKD stages 4-5. - The degree of protein-binding of all protein-bound uremic toxins was significantly less in children on HD compared to children with non-dialysis CKD stages 4-5. - Increased total levels of pCG, HA, IS, and pCS showed significant positive associations with age in children on HD - β2M, HA, and CMPF levels were significantly higher in children on anuric 	- No findings about specific cardiac changes or the direct impact of uremic toxins on cardiac function.

HD compared to children on non-anuric HD.

- The %PB of HA, IAA, and IS were significantly reduced in children on anuric HD compared to children on non-anuric HD.
- β 2M, pCG, HA, IAA, IS, and CMPF levels showed significant negative associations with residual urine volume but not UA or pCS levels.
- %PB was significantly correlated with residual urine volume for all protein-bound uremic toxins included.

Abbreviations: ADMA: asymmetric dimethylarginine; Aix: augmentation index; β 2M: Beta-2 microglobulin; cIMT: carotid intima-media thickness; CfD: complement factor D, CKD: chronic kidney disease; CMPF: 3-carboxy-4-methyl-5-propyl-2-furanpropanoic acid; CRS: cardiorenal syndrome; CV: cardiovascular; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; ESKD: end-stage kidney disease; FAS: full age spectrum; HA: hippuric acid; HD: hemodialysis; IAA: indole acetic acid; IS: indoxyl sulfate; LVMI: left ventricular mass index; pCG: p-cresyl glucuronide; pCS: p-cresyl sulfate; PD: peritoneal dialysis; %PB: percentage of protein binding; PWV: pulse wave velocity; RfK: residual kidney function; SDMA: symmetric dimethylarginine; UA: uric acid.

Table S2. A summary of changes in uremic toxin concentrations in plasma/serum and cardiac parameter measurements in eligible articles.

Study	Sample Type	Assay	Timing of Collection	Uremic Toxins			Cardiac parameter measurements
				Small Water-soluble Uremic Toxin Concentrations	Middle Molecule Uremic Toxins Concentrations	Protein-bound Uremic Toxin Concentrations	
Crespo-Salgado et al., 2016 [19]	Serum	- HPLC	- Blood was collected immediately prior to the midweek dialysis session for HD patients.	Not applicable	Not applicable	- IS - pCS	
Holle et al., 2019 [20]	Serum	- Not specified	- Blood and urine samples were collected every 6 months as part of routine visits; specific timing related to dialysis is not mentioned.	Not applicable	Not applicable	- IS ($\mu\text{mol/L}$): - Total cohort: 25.3 ± 86.0 ; 5.3 (8.7) - CKD stage 3a: 4.2 ± 11.7 ; 1.4 (1.5) - CKD stage 3b: 16.5 ± 62.5 ; 3.4 (3.4) - CKD stage 4: 30.7 ± 99.5 ; 7.3 (8.6) - CKD stage 5: 43.9 ± 101 ; 15.6 (11.4) - pCS ($\mu\text{mol/L}$): - Total cohort: 21.0 ± 17.6 ; 17.0 (21.6) - CKD stage 3a: 6.7 ± 05.9 ; 5.8 (7.5) - CKD stage 3b: 13.9 ± 11.3 ; 10.4 (15.1) - CKD stage 4: 24.5 ± 17.6 ; 20.9 (22.1) - CKD stage 5: 38.8 ± 24.2 ; 35.1 (29.9)	- cIMT SDS: - Total cohort: 1.62 ± 1.47 - CKD stage 3a: 1.83 ± 1.44 - CKD stage 3b: 1.47 ± 1.41 - CKD stage 4: 1.65 ± 1.46 - CKD stage 5: 1.89 ± 1.79 - PWV SDS: - Total cohort: 0.34 ± 1.72 - CKD stage 3a: 0.36 ± 1.60 - CKD stage 3b: 0.25 ± 1.55 - CKD stage 4: 0.33 ± 1.82 - CKD stage 5: 0.86 ± 1.67 - LVMI ($\text{g/m}^{2.16}$): - Total cohort: 41.4 ± 13.3 - CKD stage 3a: 35.8 ± 10.9 - CKD stage 3b: 40.2 ± 13.3 - CKD stage 4: 42.2 ± 12.2 - CKD stage 5: 45.0 ± 19.0
Holle et al., 2020 [21]	Serum	- HPLC	- Blood samples were collected as part of	Not applicable	Not applicable	- IS ($\mu\text{mol/L}$): - Total cohort: 25.5 ± 86.4 ; 5.3 (8.7) - CKD stage 3a: 4.0 ± 11.7 ; 1.4 (1.6) - CKD stage 3b: 17.8 ± 65.6 ; 3.45 (3.70)	Not applicable

			routine visits; specific timing related to dialysis is not mentioned.				- CKD stage 4: 31.4 ± 105; 6.25 (7.30) - CKD stage 5: 30.8 ± 78.3; 13.0 (11.0) - pCS (μmol/L): - Total cohort: 21.1 ± 18; 17.2 (22.0) - CKD stage 3a: 6.99 ± 6.00; 6.2 (7.0) - CKD stage 3b: 13.5 ± 11.2; 9.8 (15.2) - CKD stage 4: 22.4 ± 16.1; 19.7 (19.7) - CKD stage 5: 36.7 ± 22.0; 34.1 (30.0)
Özdemir et al., 2015 [22]	Not specified	- Not specified	- Blood samples were collected 30 minutes before and 2 hours after dialysis.	- Urea (mmol/L): - With CVD: 0.65 ± 0.13 - Without CVD: 0.66 ± 0.20 - Creatinine (mg/dL): - With CVD: 0.56 ± 0.10 - Without CVD: 0.51 ± 0.26 - Sodium [unspecified units]: - With CVD: 0.01 ± 0.09 - Without CVD: 0.01 ± 0.01 - Potassium (mmol/L): - With CVD: 0.33 ± 0.16 - Without CVD: 0.21 ± 0.07 - Phosphor (mg/dL): - With CVD: 0.56 ± 0.23 - Without CVD: 0.41 ± 0.09 - Uric acid (mg/dL): - With CVD: 0.67 ± 0.13 - Without CVD: 0.59 ± 0.23 - Glucose (mg/dL): - With CVD: 99 ± 14 - Without CVD: 96 ± 13	- Parathormone (pg/mL): - With CVD: 0.27 ± 0.19 - Without CVD: 0.27 ± 0.14 - Vitamin B12 (pg/mL): - With CVD: 0.12 ± 0.09 - Without CVD: 0.15 ± 0.08 - β2M (mg/L): - With CVD: 0.04 ± 0.03 - Without CVD: 0.20 ± 0.07	- Serum amyloid A (μg/mL): - With CVD: 0.09 ± 0.01 - Without CVD: 0.19 ± 0.08 - Homocysteine (μmol/L): - With CVD: 0.12 ± 0.09 - Without CVD: 0.35 ± 0.03	- AIx (%): - HD: 14.3 ± 2.1 - PD: 10.6 ± 1.3 - Control: 7.36 ± 3.59 - PWV (m/s): - HD: 5.9 ± 0.9 - PD: 5.25 ± 0.6 - Control: 5.12 ± 0.85 - cIMT (mm): - HD: 0.51 ± 0.11 - PD: 0.47 ± 0.09 - Control: 0.35 ± 0.12 - LVMI (g/m²): - HD: 40.8 ± 2.5 - PD: 37.6 ± 4.3 - Control: 27.8 ± 1.55
				- Creatinine (z-score): - Overall: 8.9 [4.1; 21.7] - CKD stages 1-2: 2.8 [1.3; 5.4] - CKD stage 3: 8.9 [7.2; 12.1] - CKD stage 4: 24.4 [20.5; 31.5]	- CfD (z-score): - Overall: 9.5 [3.9; 21.2] - CKD stages 1-2: 2.8 [1.8; 6.2] - CKD stage 3: 9.5 [5.7; 11.9] - CKD stage 4: 22.8 [16.2; 28.4]	- pCG (z-score): - Overall: 0.5 [-0.8; 3.3] - CKD stages 1-2: 0.1 [-1.0; 1.3] - CKD stage 3: -0.5 [-1.0; 1.0] - CKD stage 4: 3.8 [1.8; 9.8]	Not applicable
				- Blood - HPLC samples were - ELISAs drawn during routine			
Snauwaert et al., 2018 [23]*	Plasma						

		ambulatory visits.	- CKD stage 5: 47.9 [41.1; 67.2]	- CKD stage 5: 36.1 [28.3; 42.0]	- CKD stage 5: 6.6 [1.0; 49.2]		
			- SDMA (z-score):	- β2M (z-score):	- HA (z-score):		
			- Overall: 11.1 [5.2; 20.7]	- Overall: 8.6 [4.7; 18.1]	- Overall: 1.7 [-0.1; 5.3]		
			- CKD stages 1-2: 4.8 [3.5; 7.0]	- CKD stages 1-2: 4.5 [2.4; 5.9]	- CKD stages 1-2: 0.3 [-1.0; 1.0]		
			- CKD stage 3: 10.7 [6.5; 13.6]	- CKD stage 3: 9.5 [5.3; 12.9]	- CKD stage 3: 2.0 [0.0; 4.6]		
			- CKD stage 4: 25.7 [18.3; 29.6]	- CKD stage 4: 18.7 [16.7; 23.8]	- CKD stage 4: 2.0 [0.3; 13.7]		
			- CKD stage 5: 33.2 [23.4; 50.1]	- CKD stage 5: 48.1 [32.3; 65.1]	- CKD stage 5: 20.2 [14.3; 21.6]		
			- ADMA (z-score):		- IAA (z-score):		
			- Overall: -0.2 [-0.7; 1.2]		- Overall: 1.7 [0.3; 3.1]		
			- CKD stages 1-2: -0.3 [-0.9; 1.1]		- CKD stages 1-2: 0.4 [-0.6; 2.2]		
			- CKD stage 3: -0.5 [-0.9; 0.7]		- CKD stage 3: 1.7 [0.4; 2.7]		
			- CKD stage 4: 1.6 [-0.3; 2.3]		- CKD stage 4: 1.4 [0.6; 2.8]		
			- CKD stage 5: 2.6 [-0.1; 3.7]		- CKD stage 5: 5.2 [3.5; 16.9]		
					- IS (z-score):		
					- Overall: 5.0 [1.7; 16.3]		
					- CKD stages 1-2: 1.9 [0.0; 4.6]		
					- CKD stage 3: 2.4 [1.7; 7.6]		
					- CKD stage 4: 17.8 [13.5; 24.4]		
					- CKD stage 5: 32.2 [21.1; 52.9]		
					- pCS (z-score):		
					- Overall: 2.7 [0.5; 5.5]		
					- CKD stages 1-2: 0.7 [-0.4; 3.2]		
					- CKD stage 3: 2.1 [0.5; 3.8]		
					- CKD stage 4: 7.5 [4.7; 10.0]		
					- CKD stage 5: 7.8 [1.9; 19.8]		
					- CMPF (z-score):		
					- Overall: 2.1 [0.3; 5.3]		
					- CKD stages 1-2: 1.6 [0.0; 3.7]		
					- CKD stage 3: 2.9 [0.2; 5.3]		
					- CKD stage 4: 2.0 [0.9; 3.6]		
					- CKD stage 5: 5.7 [4.0; 13.6]		
Snauwaert et al., 2019 [24]	Plasma	- UPLC - ELISAs	- Blood samples were collected	- Uric acid (mg/dL) - CKD stages 4-5: 7.36 [6.55; 8.93]	- β2M (μg/mL) - CKD stages 4-5: 9.92 [7.72; 15.4]	- pCG (mg/dL) - CKD stages 4-5: 0.02 [0.01; 0.06] - On HD: 0.15 [0.03; 0.33]	Not applicable

during routine ambulatory visits in the non-dialysis CKD group and before a midweek HD session in the HD groups.	- On HD: 7.02 [5.80; 8.06]	- On HD: 30.7 [4.4; 39.3]	- HA (mg/dL) - CKD stages 4-5: 0.39 [0.13; 0.64] - On HD: 1.89 [0.72; 3.43] - IAA (mg/dL) - CKD stages 4-5: 0.06 [0.04; 0.08] - On HD: 0.18 [0.12; 0.27] - IS (mg/dL) - CKD stages 4-5: 0.56 [0.44; 0.73] - On HD: 2.04 [1.37; 2.70] - pCS (mg/dL) - CKD stages 4-5: 1.67 [0.93; 2.31] - On HD: 2.35 [1.03; 3.27] - CMPF (mg/dL) - CKD stages 4-5: 0.05 [0.02; 0.21] - On HD: 0.12 [0.03; 0.33]
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*The concentrations of uremic toxins for each participant were presented as z-scores, compared to the reference values from a control population in Snauwaert et al. [23]. These comparisons were adjusted for different age categories as needed.

Data are mean \pm SD, median (IQR), median [25th; 75th percentiles], or number (percentage) as appropriate.

Abbreviations: ADMA: asymmetric dimethylarginine; AIx: augmentation index; β 2M: beta-2-microglobulin; cIMT: carotid intima-media thickness; CfD; complement factor D; CKD: chronic kidney disease; CMPF: 3-carboxy-4-methyl-5-propyl-furanpropionic acid; CVD: cardiovascular disease; ELISA: enzyme-linked immunosorbent assay; HA: hippuric acid; HD: hemodialysis; HPLC: high-performance liquid chromatography; IAA: indole acetic acid, IS: indoxyl sulfate; LVMI: left ventricular mass index; pCG: p-cresyl glucuronide; pCS: p-cresyl sulfate, PD: peritoneal dialysis; PWV: pulse wave velocity; SDMA: symmetric dimethylarginine; SDS: standard deviation score; UPLC: ultra-performance liquid chromatography.