Comparison of Hemodiafiltration and Hemodialysis in Patients with End Stage Renal Disease

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Comparison of Hemodiafiltration and Hemodialysis in Patients with End-Stage Renal Disease

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Abbreviations

- ALP = Alkaline Phosphatase
- ALT = Alanine Transaminase
- APD = Automated Peritoneal Dialysis
- AST = Aspartate Aminotransferase
- AV = Arterio-Venous
- CAPD = Continuous Ambulatory Peritoneal Dialysis
- CKD = Chronic Kidney Disease
- CRP = C-reactive Protein
- Cu = Copper
- eGFR = estimated Glomerular Filtration Rate
- ESRD = End-stage renal disease
- Fe = Iron
- FDR = false discovery rate
- GGT = γ-Glutamyl Transferase
- GFR = Glomerular Filtration Rate
- h = hours
- HD = Hemodialysis
- HDF = Hemodiafiltration
- HDL = High-Density Lipoproteins
- HF = Hemofiltration
- Hgb = Hemoglobin
- IgA = Immunoglobulin A
- IgG = Immunoglobulin G
- IgM = Immunoglobulin M
- IL-6 = Interleukin 6
- KDIGO = Kidney Disease: Improving Global Outcome
- KRT = Kidney Replacement Therapy
- LD = Lactate Dehydrogenase
- LDL = Low-Density Lipoproteins
- LPS = Lipopolysaccharides
- MCHC = Mean Corpuscular Hemoglobin Concentration

- MCV = Mean Corpuscular Volume
- MW = Molecular Weight
- Mg = Magnesium
- min = Minutes
- ml = Milliliter
- m2 = Square meter
- NT-pro BNP = N-Terminal pro Brain-type Natriuretic Peptide
- nSTEMI = non-ST elevation myocardial infarction
- p = p value
- p.adj = adjusted p value
- RDW = Red Blood Cell Distribution Width
- stderr = standard error
- STEMI = ST elevation myocardial infarction
- TIBC = Total Iron Binding Capacity
- TMP = Transmembrane pressure
- TSH = Thyroid-Stimulating Hormone
- UIBC = Unsaturated Iron Binding Capacity
- VV = veno-venous

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1. Summary

TITEL: **Comparison of Hemodiafiltration and Hemodialysis in Patients with End Stage Renal Disease**

AUTHOR: **Nicola Michael Beat Willi Pohly**

The most common and widely used form of dialysis is hemodialysis. Throughout time new forms of dialysis and combinations out of existing methods were invented. The problem is where do the newer methods like hemodiafiltration fit in and which niche could they conquer. This study is a single center, case control study in a group of 68 patients with end stage renal disease (45 patients on hemodialysis, 25 patients on hemodiafiltration). We present structured analysis of in total 47 parameters, of which 43 were deemed essential for dialysis control and 4 counted as addition for an overview of inflammatory and cardiovascular biomarkers. The results indicate that hemodialysis and hemodiafiltration performed in our Department are equal methods regarding removal of uremic toxins, showing no significant differences in clearance ratios. Major differences were observed in N-Terminal pro Brain-type Natriuretic Peptide, which showed an increased net filtration in the patients treated with hemodiafiltration compared to hemodialysis (p.adj = 0.00073). Out of 68 patients, 53 of them had relevant comorbidities (68.8% in hemodialysis group and 92.0% in hemodiafiltration group), with no statistically significant difference between the groups.

Hemodiafiltration provides an alternative to hemodialysis regarding the removal of uremic toxins with similar clinical efficacy. There are potential benefits of performing hemodiafiltration in patients with end stage renal disease and comorbidities affecting the cardiovascular system compared to patients receiving hemodialysis. The outcome shown by NT-proBNP levels may lead to the suggestion that hemodiafiltration should be preferred in patients with active cardiovascular disease.

KEYWORDS: Hemodiafiltration, Hemodialysis, End Stage Renal Disease, Dialysis, Nephrology

2. Sažetak

NASLOV: **Usporedba hemodijafiltracije i hemodijalize u pacijenata s terminalnom bubrežnom bolesti**

AUTOR: **Nicola Michael Beat Willi Pohly**

Najčešće korišteni oblik dijalize je hemodijaliza. Tijekom vremena razvijali su se novi oblici dijalize te kombinirale već postojeće metode. Postavlja se pitanje gdje smjestiti novije metode kao što je hemodijafiltracija te koji postojeći oblik dijalize bi one mogle zamijeniti.
U ovom radu opisana je slučaj-kontrola studija u koju je uključeno 68 bolesnika s terminalnom bubrežnom bolesti liječenih dijalizom u KB Dubrava (45 bolesnika hemodijalizom, 25 bolesnika hemodijafiltracijom). Prikazani su podaci o ukupno 47 promatranih parametara od kojih se njih 43 smatra ključnim za kontrolu dijalize, a ostalih 4 pripada skupini inflamatornih i kardiovaskularnih biomarkera. Nakon analize dobijenih rezultata može se zaključiti kako su hemodijaliza i hemodijafiltracija u našoj ustanovi jednako uspješne metode za odstranjivanje uremijskih toksina (nije nađena statistički značajna razlika među klirensima). Najznačajnije razlike uočene su u koncentraciji NT-proBNP-a gdje se vidi veća neto filtracija kod bolesnika koji su liječeni hemodijafiltracijom u usporedbi s hemodijalizom (p.adj = 0.00073). Od ukupno 68 bolesnika njih 53 je imalo značajne komorbiditete (69.8% u skupini hemodijalize te 92.0% u skupini hemodijafiltracije), bez statistički značajne razlike između skupina. Hemodijafiltracija se pokazala kao alternativa hemodijalize s obzirom na uklanjanje uremijskih toksina s gotovo jednakim kliničkim ishodima. Postoje određene prednosti korištenja hemodijafiltracije kod bolesnika s terminalnom bubrežnom bolesti i komorbiditetima koji zahvaćaju srce i krvožilni sustav u usporedbi s hemodijalizom. Iz usporedbe razina NT-proBNP-a može se zaključiti kako bi metoda izbora kod tih bolesnika možda trebala biti hemodijafiltracija.

KLJUČNE RIJECI: hemodijafiltracija, hemodijaliza, terminalna bubrežna bolest, dijaliza, nefrologija

3. Introduction

Chronic kidney disease (CKD) is defined as any structural or functional abnormality of the kidney that lasts for more than three months with effects on the overall wellbeing (1). Clinical diagnostic criteria that physicians use daily for the diagnosis are pathologic findings in urinary sediment, imaging techniques or histology, and estimated glomerular filtration rate (eGFR) under 60 mL/min/173m^2. In most cases the eGFR is calculated by the CKD-EPI formula which is recommended by the Kidney Disease: Improving Global Outcome (KDIGO) considering the age, gender, ethnicity, blood creatinine. CKD is categorized into 5 stages (Table 1). Taking into account albumin concentrations and the degree of albuminuria further categorization could be performed (1).

Table 1 KDIGO chronic kidney disease stages

CKD - stages	eGFR (ml/min/1.73m2)	Levels of insufficiency
G1	≥ 90	Normal or high
G2	60 - 89	Mild insufficiency
G3a	45 - 59	Mild to moderate insufficiency
G3b	30 - 44	Moderate to severe insufficiency
G4	15 - 29	Severe insufficiency
G5	< 15	Kidney failure

Most common causes for CKD requiring dialysis in Croatia are arterial hypertension, diabetes mellitus and glomerulonephritis (focal segmental glomerulosclerosis, IgA glomerulonephritis, membranous glomerulonephritis as well as hereditary nephritis) (2–4).

The kidneys possess an excretory and endocrine function. Due to its complexity, damage to the kidney will result in organ dysfunction and in untreated cases will lead to a fatal outcome. The typical manifestations seen in renal disease patients are disturbances of water, electrolyte, and acid base homeostasis. Furthermore, damage to the renal endocrine function clinically manifests as anemia due to a lack of erythropoietin, and osteopathy due to lack of calcitriol and secondary hyperparathyroidism.

In an ideal world we would be able to prevent terminal renal failure from occurring in the first place but for now the medical field hasn't made such advancements yet, so the patients must undergo kidney replacement therapy (KRT). The two options at hand for patients with terminal

CKD are either kidney transplantation or dialysis. There are several established forms of dialysis such as hemodialysis (HD), hemofiltration (HF), peritoneal dialysis, and hemodiafiltration (HDF).

The main principle of hemodialysis is draining blood from the body which then enters one compartment of a dialyzer while dialysate (dialyzing fluid) enters from the opposite side into another compartment. The compartments are separated by a semipermeable membrane which limits passage of certain molecules.

When retention of urinary waste products occurs, some of them may cause toxic effects. These substances are referred to as uremic toxins. There are over 140 known uremic toxins that have been defined by the European Uremic Toxin Work Group. The categorization of uremic toxins has been evolving over the last couple years due to the capabilities of newer dialyzing membranes allowing passage of larger molecules as before.

Uremic toxins may be divided according to their molecular weight in low molecular weight (MW) toxins (MW <500 D), middle MW toxins (MW 500-15'000 D), and large MW proteins (MW >15'000 D) (5).

Another, slightly different categorization describes uremic toxins into four groups. The first group are small, water soluble compounds like urea or hydrogen ions which tend to have no or minimal protein binding properties. The second would be small, lipid soluble compounds that have rather strong protein binding properties, such as tryptophan metabolites or phenyl acetic acid. Thereafter, there are middle MW molecules such as beta2-microglobulin. Regarding newer postulations of classifications another group has been added namely the large molecules. This novel category is defined as molecules with a MW above 58'000 Daltons, which is also known as the cut-off value for the permeability of the glomerular basement membrane. Included in this group are e.g., albumin and lipoproteins. Kidney insufficiency may not have a direct effect on the concentration of these substances, but it has been suggested that uremic conditions cause post-translational modifications to their structure (6,7).

Dialysis methods work by three major mechanisms namely passive diffusion, convection, and adsorption of solutes to the dialysis membrane. Passive diffusion takes place due to a concentration gradient that is created between the dialysate and the blood. In case of convection, differences in the hydrostatic pressure between two fluids forces water molecules out of the blood through a semipermeable membrane into the dialysate thereby exerting a force onto other molecules dragging them along with it creating an ultrafiltrate. This process is also known as ultrafiltration or solute drag. Adsorption of solutes on the dialysis membrane filters

is less well analyzed and understood and seems to play a minor role in kidney replacement therapy (8,9).

The main goal of any kidney replacement therapy is to prevent the accumulation of uremic toxins in the body.

3.1. Hemodialysis

The first dialyzer was created in 1943 by the Dutch physician Willem Kolff and has since been implemented into the medical field (10). Hemodialysis is a form of kidney replacement therapy which is being used in an everyday routine around the globe. As mentioned above the key function is to remove uremic toxins from the body. In hemodialysis this is mainly achieved by passive diffusion, the dialyzing machine creates a concentration gradient between blood and the dialysate (dialysis solution). Arterial, or oxygenated blood is being drained from the body and then enriched by heparin to prevent the blood from clotting. Thereafter, it enters a dialyzer which has two separate compartments, one for the blood and another for the dialysate (Figure 1). The compartments are separated by a semi permeable filter, which means that it only allows passage for certain molecules. In case of hemodialysis these most commonly are low MW molecules e.g., urea. The dialysate has lower concentrations thereby pulling the molecules out of the blood through the semipermeable membrane. Additionally, the blood flow and the dialysate flow in opposite directions thereby upholding a constant gradient over a certain distance. Finally, the dialyzed blood is brought back into the body.

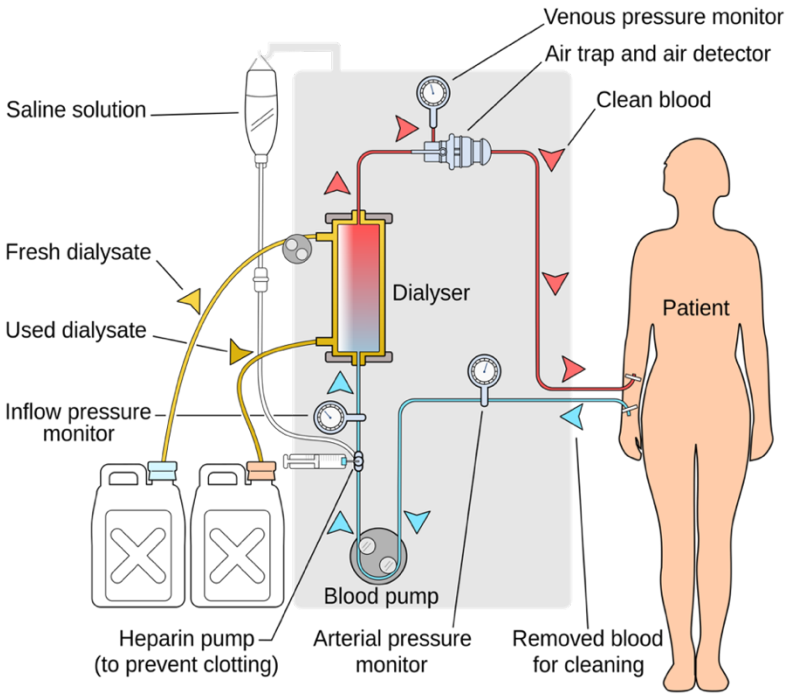

Figure 1 Schematic representation of Hemodialysis.
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3.2. Hemodiafiltration

Hemodiafiltration (HDF) is a rather new method compared to hemodialysis and is based on HD and HF. Leber et al. 1977 created the first combination of both methods and so HDF was born (11). HDF makes use of the diffusion properties of HD and the convective properties of HF thereby allowing the removal of not only low MW but also middle MW molecules. The downside to this is that with convection comes loss of water, so called ultrafiltrate. The loss of fluid volume must be subsidized or else we would end up having exsiccated patients. This is countered by the addition of substitution fluid, which usually is ultra-pure water that has undergone cleansing treatment with carbon filters, reverse osmosis, and sterilizing ultrafilters, thereby allowing substitution of fluid that is sterile and non-pyogenic. The substitution fluid may be added either before the dialyzer (pre-dilution) or after the dialyzer (post-dilution). Pre-dilution causes changes in blood concentrations before the dialyzer and thereby decreasing passive diffusion, called hemodilution. Additionally, portions of substitution fluid are lost in the ultrafiltrate. Post-dilution allows for a more controlled fluid substitution but carries the risk of hemoconcentration, if not performed accordingly. Referring to the scientific data up to now post-dilution is the more commonly applied method (12,13).

In HDF blood is being drained from the body like in HD but compared to HD the patient must have an arterio-venous (AV) or veno-venous (VV) access to allow flow of larger volumes of fluids that are being shifted. Like in HD, when blood is being drained from the body it is getting enriched with heparin by a pump before reaching the dialyzer. As in HD, the dialysate flows in the opposite direction and the two fluids are separated by a semipermeable membrane. Due to passive diffusion low MW molecules are filtered into the dialysate. Additionally hydrostatic pressure differences transport middle MW molecules through the filter into the dialysate, forming ultrafiltrate. After the dialyzer the filtered blood gets enriched by the substitution fluid before being brought back into the body (14–16). Isotonic sodium bicarbonate was initially used in substitution fluid but rather recently a trend has been set to fall back on ringer's lactate solutions and bicarbonate-based solutions. Acetate is a major component of these solutions which, in vivo, is being converted into bicarbonate (17).

3.3. Alternatives of dialysis

Other alternative methods of dialysis that we haven't mentioned but which find appliance in everyday medical practice are peritoneal dialysis and hemofiltration (HF). Peritoneal dialysis,

which is underused in many countries, provides a cost efficient and equally beneficial treatment as HD, as shown in many studies while allowing for a more home centered care of the patient. Peritoneal dialysis functions by using the peritoneum as a semipermeable membrane while dialysate flows into the abdomen by a catheter. This can either be done continuously throughout the day called continuous ambulatory peritoneal dialysis (CAPD) or at night assisted by a machine called automated peritoneal dialysis (APD). Frequent side effects of peritoneal dialysis are hernias, bleedings, and infections of the abdomen (18–21).

HF is rather seen in acute clinical settings e.g., acute kidney failure or poisoning. HF uses transmembrane pressure (TMP) to create a force that filters molecules through a semipermeable membrane. As in HDF, HF makes use of convective forces but those are being created differently than in HDF. Instead of using a dialyzer, HF uses a hemofilter as a semipermeable membrane, over which blood is filtered by sheer pressure that is applied by an external pump. This causes plasma water to be filtered through forming an ultrafiltrate. Due to this transmembrane flow convection occurs thereby dragging molecules which can pass through the filter with the water. HF is mainly applied in acute kidney failure. This is on one hand due to its capability of rapidly influencing body volume and on the other hand due to its properties of filtering larger molecules compared to conventional HD that has better clearance properties of small molecules. The clearance of certain solutes depends on the ultrafiltration volume and on the sieving coefficient, which is 1 for small molecules, thereby making their clearance equal to the ultrafiltrate volume. The major downside of HF are the costs and poorer filtration rate of low MW molecules, thereby becoming somewhat irrelevant when talking about dialysis in terminal CKD (22–24).

3.4. Side effects of dialysis

Dialysis will only be a partial compensation for the loss of kidney function. Having said that, it is important to note that certain side effects can come along with it. Hypotension, low blood pressure, is one of the most common side effects seen in dialysis patients. Other major side effects are infections, including sepsis, necessity for precise anticoagulation, as well as muscle cramps and pruritus. A lot of these side effects come from variations in plasma volume during the dialysis sessions. This is where many have thought that HDF would be better than HD due to its capability of replenishing plasma volume by substitution fluid. Nevertheless in either intervention maintaining electrolyte homeostasis proves itself challenging (14,25).

4. Hypothesis

High dose hemodiafiltration might have advantages in comparison to conventional high flux hemodialysis in patients with end stage renal disease regarding cardiac function and side effects.

5. Objectives

The aims of this graduate thesis are as follows:

- To compare multiple variables in hemodialysis and hemodiafiltration patients and thereby allowing for a better comparison between these two methods in patients with end stage renal disease.
- To identify patients which could benefit from HDF treatment compared to hemodialysis.

6. Material and methods

We performed a single center case control study in a group of patients with end stage renal disease. The Data were kindly collected and provided by the dialysis department of the University Hospital Dubrava. Written consent was obtained along with provision of local regulations. All patients were treated in the same department by the same doctors and nurses. HD and HDF machines of Fresenius, Braun, Nikkiso, and Baxter were used.

6.1. Inclusion and exclusion criteria

Patients had to be over the age of 18 years to be eligible and had previously received the diagnosis of end stage renal disease (stage V) to be included into the study. Every patient received a minimum treatment of 3 months either with high-flux hemodialysis or hemodiafiltration in advance to the evaluation point. Written informed consent was provided about the procedure and the necessary adherence to willingly undergo dialysis sessions of three times per week. Participation for candidates was voluntary and in line with the current code of research ethics of the School of Medicine as well as all the institutions involved.
Exclusion criteria were the inability to adhere to dialysis procedure, follow up appointments and to medical prescriptions, as well as any evidence of other medical disease interfering with the future treatment, affecting the patient's compliance, or increasing the risk of an adverse complication.

Candidates fitting the inclusion criteria had been non-randomly and by discretion of an attending physician, assigned to either continue high-flux hemodialysis or receive high dose hemodiafiltration. Every participant received anticoagulation during dialysis and had a dialysis vascular access either by an AV fistula, graft, or catheter.
The preset for dialysis was the diagnosis of end stage renal insufficiency in all patients, which was defined by a glomerular filtration rate (GFR) <15 ml/min/1.73m^2.
In total 68 candidates were eligible, of which 43 (18 women, 25 men) were assigned to HD and 25 (7 women, 18 men) were assigned to HDF treatment. Before including the patients into the study all participants were deemed candidates for convective therapy of a minimum of 20 liters per session.
Multiple precautions were taken to minimize the bias and errors in this study; however, cost effectiveness of certain treatments and patient's wishes were considered limiting the

distribution to 43 (62.23%) HD and 25 (36.76%) HDF patients, thereby not achieving a 1:1 ratio.

6.2. Collected data

In total we measured 46 parameters. 39 of these where single measurements pre intervention, [namely Uric acid, Albumin, Phosphate, Creatin Kinase (CK), γ-Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), Iron (Fe), Unsaturated Iron Binding Capacity (UIBC), Total Iron Binding Capacity (TIBC), Vitamin B12, Folic Acid, Ferritin, Hemoglobin (Hgb), Mean Corpuscular Volume (MCV), Mean Corpuscular Hemoglobin Concentration (MCHC), Red Blood Cell Distribution Width (RDW), Thrombocytes, Leukocytes, Glucose, Total Protein, Bilirubin, Triglycerides, Cholesterol, High-Density Lipoproteins (HDL), Low-Density Lipoproteins (LDL), Chloride (Cl), Total Calcium, Ionized Calcium, Magnesium (Mg), Aspartate Aminotransferase (AST), Alanine Transaminase (ALT), Lactate Dehydrogenase (LD), Lipopolysaccharides (LPS), Copper (Cu), Thyroid-Stimulating Hormone (TSH), Immunoglobulin- A, G and M (IgA, IgG, IgM)]. Four other parameters were deemed necessary as control parameters for HD and HDF treatment which we measured pre and immediately (0h) post intervention, namely urea, creatinine, potassium (K), and sodium (Na). An additional four parameters were chosen to represent the effect of the two interventions on the heart as well as the inflammatory reaction. Those parameters were measured pre intervention as well as immediately (0h) post intervention, and 24h post intervention, namely troponin, NT-proBNP, Interleukin-6 (IL-6) and C-reactive protein (CRP).

Additionally, patients were evaluated for associated disease e.g., diabetes mellitus, hypertension, heart failure, cerebrovascular disease, coronary artery disease, peripheral artery disease, heart valvular disease, chronic inflammatory or autoimmune disease, and malignancies. For the 24h follow up visit data of troponin, NT-proBNP, IL-6 and CRP are missing in 13 (30.23%) HD candidates and 4 (16.00%) HDF candidates. Data of 48h and 72h follow ups were excluded due to the inability of too many patients to attend these follow up visits. For additional evaluation of further diseases 30 (69.77%) HD and 23 (92.00%) HDF were eligible.

6.3. Statistical analysis

All patient's data as well as laboratory results were registered in Microsoft Excel, where the aforementioned criteria were applied to perform exclusions of unfit candidates. We compared the pre intervention measurements between the HD and HDF groups by visualizing the absolute

measurements and testing for group differences using a two-sided Student's t-test. Post intervention measurements were visualized as ratio to the pre intervention measurement (Ratio = post intervention measurement / pre intervention measurement). Correspondingly, a ratio of 1.5 denotes a 50% increase relative to the pre intervention measurement, whereas a ratio of 0.5 corresponds to a 50% decrease relative to the pre intervention measurement. Pre and post intervention measurements were compared using a paired two-sided Student's t-test. To control the type I error rate (number of false-positive associations), we adjusted the raw p-values for multiple testing using Benjamin Hochberg procedure and report findings as significant at a false discovery rate (FDR) of <5% ($p.adj < 0.05$) (26). All statistical analysis was performed using the programming language R (27) and RStudio (28). For evaluation of patient's prevalence of their comorbidities we performed Chi-Square tests with a significance level set to <5% ($p < 0.05$)

7. Results

7.1. Single time point measurements

From the 39 parameters with single measurements, we found no significant differences by comparison of the mean values (Table 2). We decided to take a closer look at 14 of the 39 values which were mentioned in the literature as clinically relevant for patients with kidney replacement therapy (29–32).

In the 14 parameters with single measurements [for Uric acid, Albumin, Phosphate, CK, GGT, ALP, Fe, UIBC, TIBC, Vitamin B12, Folic Acid, Ferritin, Hgb, MCV] we found no major differences between the HD and HDF group whilst comparing the arithmetic mean, as seen in Table 2.

Some parameters had larger variability in the range of single measurements but with little to no effect on comparison of the mean, e.g., albumin, vitamin B12, folic acid, and more (Figures 2-13).

The most noticeable difference can be seen in UIBC (Figure 14) and TIBC (Figure 15) showing a higher median for HDF patients than for HD but without statistical significance when comparing the mean (Table 2).

Certain tendencies could be observed for specific parameters. As for albumin, HD patients showed a tendency for lower levels with large variations in the range of measured values, HDF patients on the other hand showed a tendency for smaller variation with an approach to higher absolute values. For vitamin B12 and ALP both groups showed a tendency for higher values in comparison to the median, but measurements in HD patients varied largely. For ferritin, folic acid and uric acid HD candidates showed a tendency for higher levels, while HDF candidates tended to the lower ranges, especially folic acid having a large variability in HD measurements (Figures 2-7).

Table 2 Comparison of the mean of all parameters with single measurements between the HD and HDF group pre dialysis, their p values (p), adjusted p values (p.adj), deltas (diff) and standard errors.

	Measurement	p	Diff	stderr	p.adj
1	Uric acid [µmol/L]	0.12446	-30.70140	19.60996	0.86421
2	Albumin [g/L]	0.67613	0.30884	0.73534	0.86421
3	Phosphate [mmol/L]	0.32589	0.13091	0.13182	0.86421
4	Creatine Kinase [U/L]	0.06820	88.63721	46.52219	0.86421
5	GGT [IU/L]	0.36535	8.56837	9.30758	0.86421
6	ALP [IU/L]	0.48863	-7.21953	10.36709	0.86421
7	Iron Fe [µmol/L]	0.52302	-0.61395	0.95564	0.86421
8	UIBC [µmol/L]	0.20810	2.93810	2.30021	0.86421
9	TIBC [µmol/L]	0.21985	2.82857	2.27369	0.86421
10	Vitamin B12 [pmol/L]	0.42870	-36.69860	46.00705	0.86421
11	Folic acid [nmol/L]	0.09687	-3.10327	1.83375	0.86421
12	Ferritin [ug/L]	0.14944	-81.35070	55.73223	0.86421
13	Hemoglobin [g/L]	0.38003	2.18233	2.46655	0.86421
14	MCV [fl]	0.71868	0.57516	1.58952	0.86998
15	Glucose [mmol/L]	0.66049	0.40260	0.91060	0.86421
16	Total protein [g/L]	0.68888	0.44372	1.10324	0.86421
17	Bilirubin [µmol/L]	0.54996	0.30391	0.50479	0.86421
18	Triglyceride [mmol/L]	0.44097	0.11460	0.14751	0.86421
19	Cholesterol [mmol/L]	0.53488	-0.16726	0.26716	0.86421
20	HDL [mmol/L]	0.28763	-0.07572	0.07041	0.86421
21	LDL [mmol/L]	0.52529	-0.13795	0.21528	0.86421
22	Chloride [mmol/L]	0.47618	-0.66140	0.92191	0.86421
23	Total Ca [mmol/L]	0.81074	0.00764	0.03176	0.90961
24	Ionized Ca [mmol/L]	0.68710	0.00906	0.02239	0.86421
25	Mg [mmol/L]	0.22370	0.05438	0.04412	0.86421
26	AST [U/L]	0.68718	0.59442	1.46875	0.86421
27	ALT [U/L]	0.54860	1.27349	2.11033	0.86421
28	LD [U/L]	0.39929	8.37953	9.84247	0.86421
29	AMS [IU/L]	0.97472	0.30698	9.64313	0.97472
30	LPS [IU/L]	0.80830	-2.30791	9.43907	0.90961
31	Cu [µmol/L]	0.62327	-0.41200	0.83292	0.86421
32	TSH [mIU/L]	0.32594	-0.33552	0.33899	0.86421
33	IgA [g/L]	0.92186	0.02921	0.29661	0.96377
34	IgG [g/L]	0.80642	-0.15944	0.64791	0.90961
35	IgM [g/L]	0.51611	0.05953	0.09105	0.86421
36	Leukocytes [x10^9/L]	0.55238	0.30912	0.51722	0.86421
37	MCHC [g/L]	0.62048	0.94140	1.88942	0.86421
38	RDW [%]	0.09052	0.92447	0.53427	0.86421
39	Thrombocytes [x10^9/L]	0.87887	2.59628	16.94678	0.96257

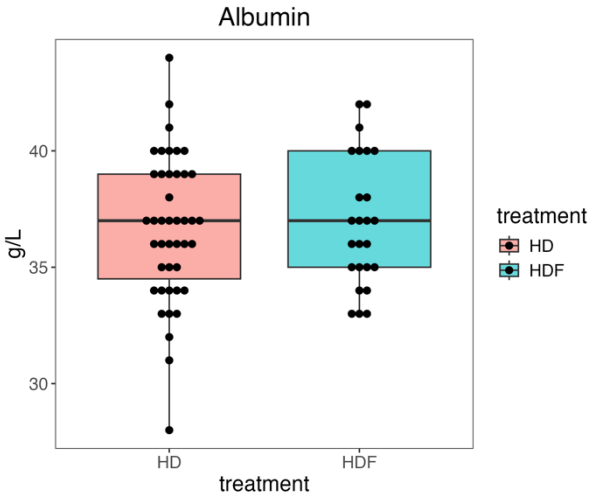

Figure 2 *Albumin concentrations [g/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

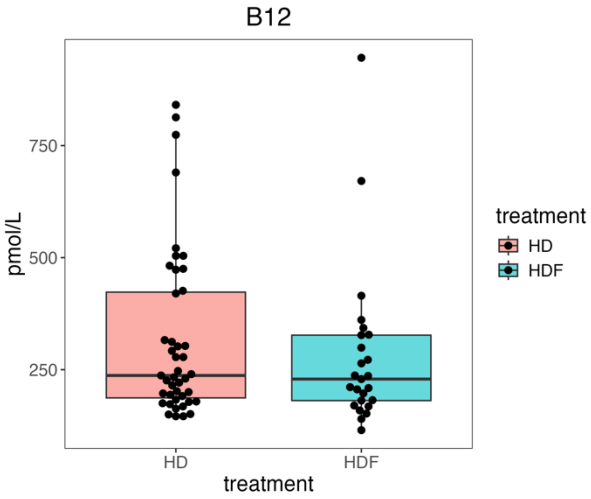

Figure 3 *Vitamin B12 concentrations [pmol/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

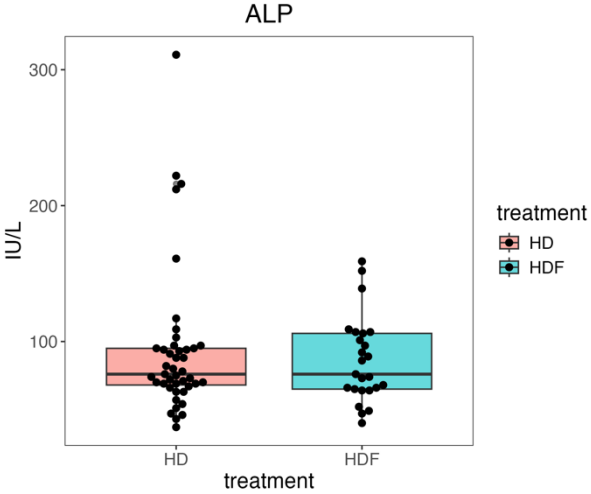

Figure 4 *Alkaline Phosphatase concentrations [IU/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

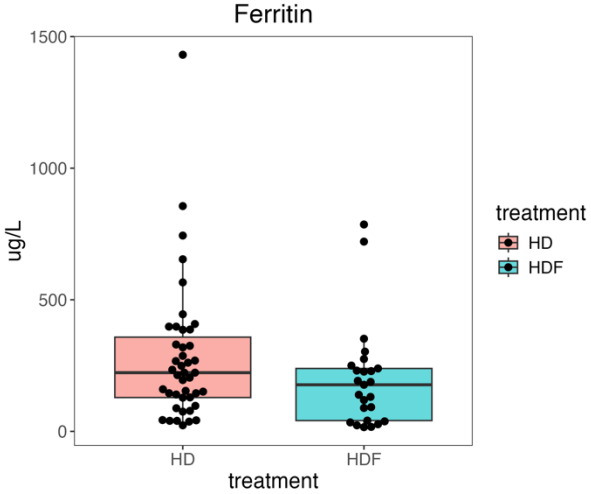

Figure 5 *Ferritin concentrations [ug/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

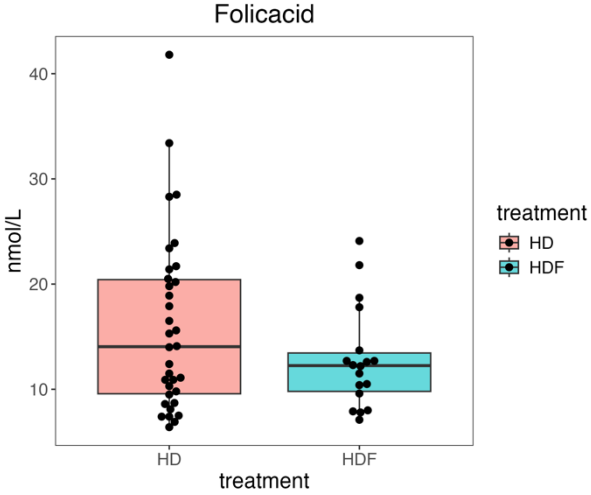

Figure 6 *Folic acid concentrations [nmol/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

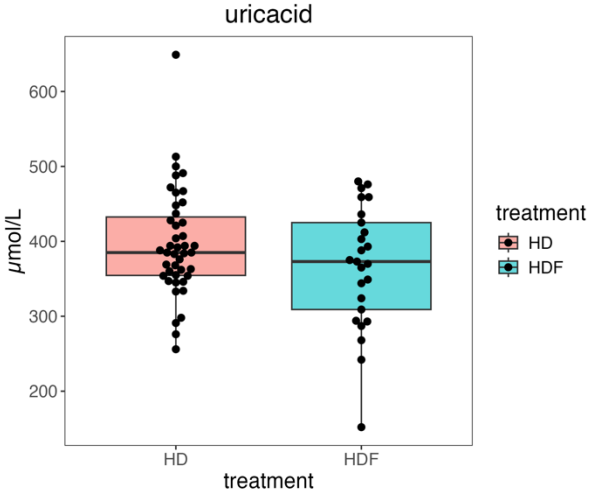

Figure 7 *Uric acid concentrations [µmol/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

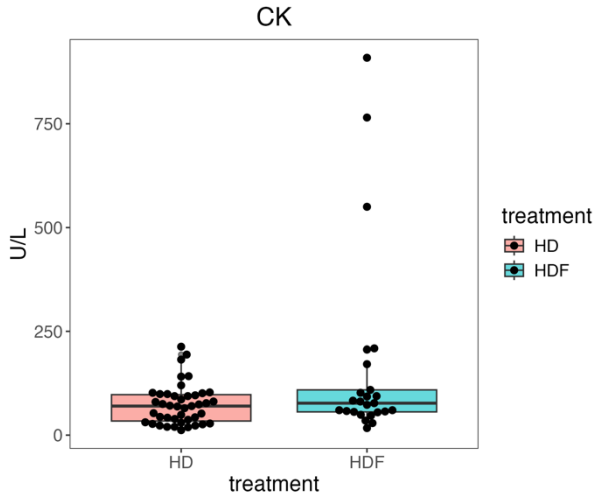

Figure 8 *Creatine kinase concentrations [U/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

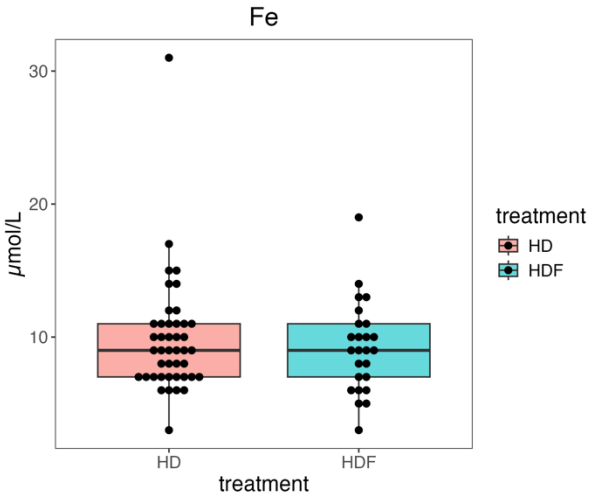

Figure 9 *Iron concentrations [µmol/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

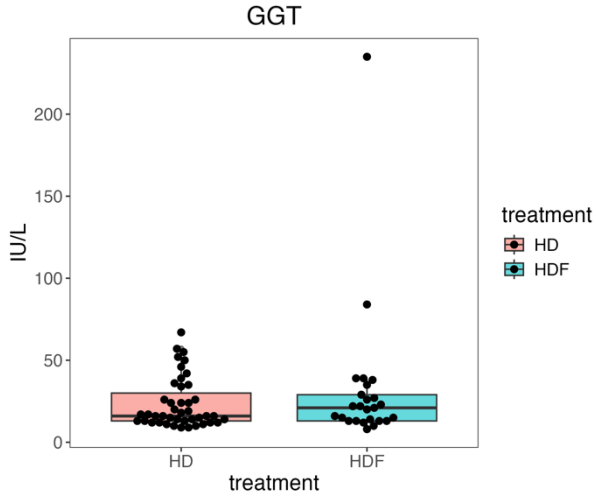

Figure 10 *γ-Glutamyl Transferase concentrations [IU/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

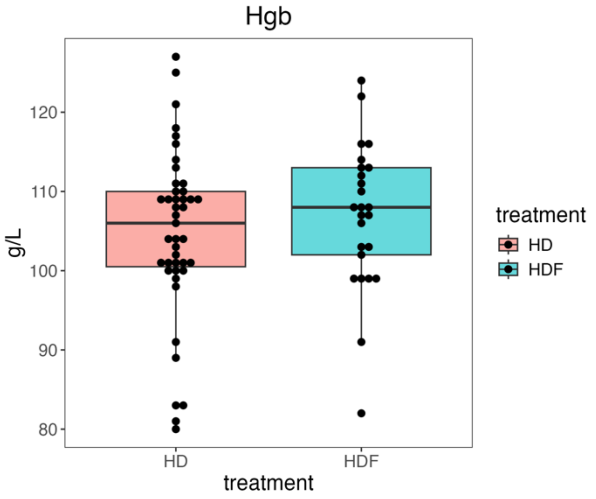

Figure 11 *Hemoglobin concentrations [g/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

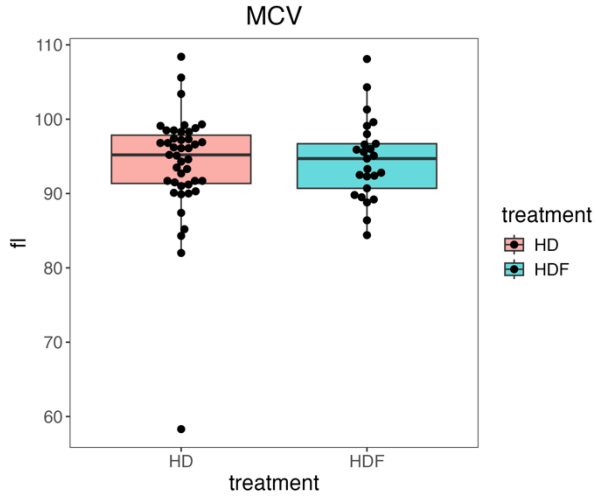

Figure 12 *Mean Corpuscular Volume [fl] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

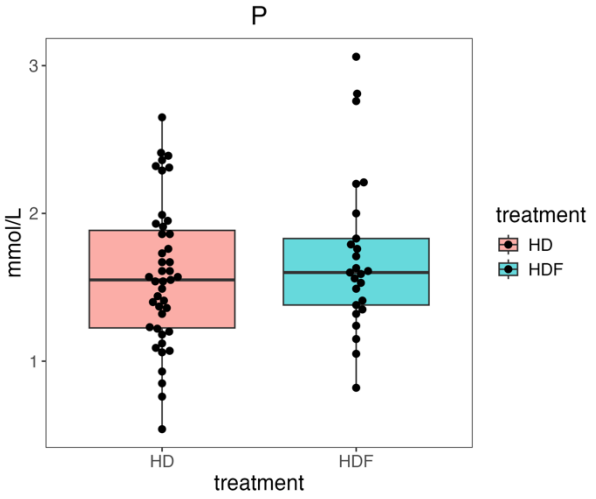

Figure 13 *Phosphate concentrations [mmol/Ll] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

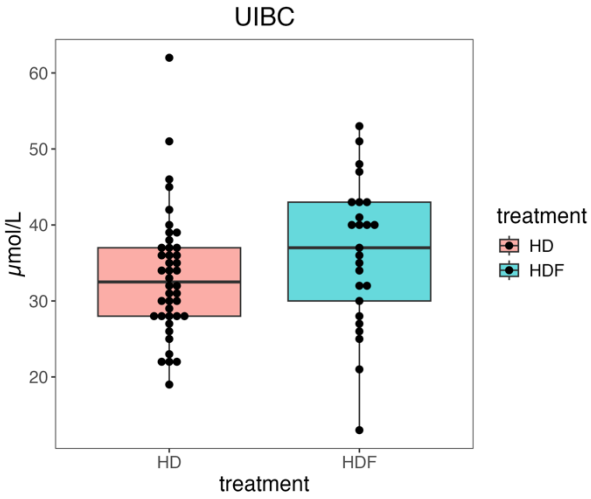

Figure 14 *UIBC levels [µmol/L] in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

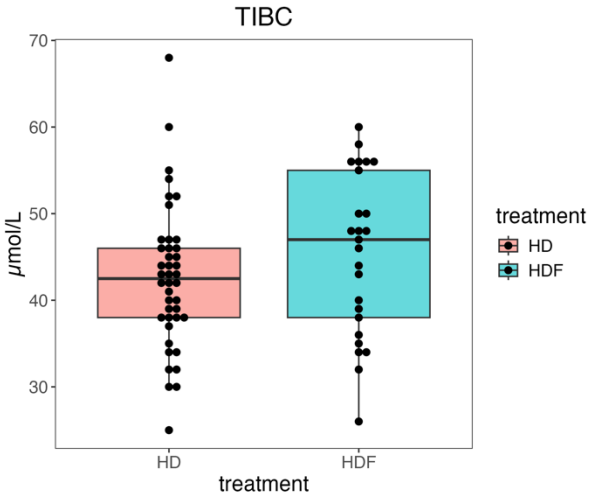

Figure 15 *TIBC levels [µmol/L in hemodialysis and hemodiafiltration patients, showing every measurement (•), median (——), and interquartile range (colored box).*

7.2. Two time point measurements

The results for parameters with two-point measurements [Urea, Creatinine, Na, K] pre and immediately (0h) post intervention, showed little to no differences between the two groups (Table 3). There was no sodium loss recorded in both groups (Figure 16) with no statistical significance in comparison with each other (Table 3). As for potassium, urea, and creatinine (Figures 17-19) we saw a net loss from pre to post intervention in all three parameters with deviations in the absolute numbers but equal ratios when comparing the HD and HDF group to each other, as represented by the adjusted p values seen in Table 3. There was a slight tendency in the HDF group for higher absolute creatinine levels at pre and 0h post intervention.

Table 3 Comparison of the mean of all first measurements (green) and comparison of the ratio adjusted to the first measurement for all the following test points, their p values (p), adjusted p values (p.adj), deltas (diff) and standard errors (stderr). The numbers represent the measurement time points 1 (pre intervention), 2 (0h post intervention), 3 (24h post intervention), 4 (48h post intervention), 5 (72h post intervention)

	Measurement	p	diff	stderr	p.adj
1	Troponin 1 [ng/L]	0.91160	1.13498	10.16021	0.96377
2	Troponin 2 [ng/L]	0.45226	-0.07790	0.10245	0.90452
3	Troponin 3 [ng/L]	0.35620	-0.23448	0.25121	0.83113
4	Troponin 4 [ng/L]	0.99711	0.00062	0.17082	0.99711
5	Troponin 5 [ng/L]	0.86506	0.01922	0.11252	0.99711
6	NTproBNP 1 [pg/mL]	0.93458	-641.75442	7782.33874	0.96888
7	NTproBNP 2 [pg/mL]	0.00005	-0.28229	0.06466	0.00073
8	NTproBNP 3 [pg/mL]	0.08476	-0.08862	0.05036	0.39556
9	IL6 1 [pg/mL]	0.37082	-2.75777	3.05833	0.86421
10	IL6 2 [pg/mL]	0.04247	-0.76933	0.36853	0.29729
11	IL6 3 [pg/mL]	0.12659	-0.34484	0.22154	0.44306
12	CRP 1 [mg/L]	0.69513	-1.30205	3.30095	0.86421
13	CRP 2 [mg/L]	0.91285	0.00515	0.04675	0.99711
14	CRP 3 [mg/L]	0.51986	-0.08647	0.13339	0.90975
15	urea 1 [mmol/L]	0.15215	-2.62326	1.80862	0.86421
16	urea 2 [mmol/L]	0.76996	0.00511	0.01738	0.99711
17	Creatinine 1 [µmol/L]	0.09412	110.50047	64.40881	0.86421
18	Creatinine 2 [µmol/L]	0.96153	0.00076	0.01566	0.99711
19	K 1 [mmol/L]	0.64684	0.07619	0.16542	0.86421
20	K 2 [mmol/L]	0.76730	0.00545	0.01830	0.99711
21	Na 1 [mmol/L]	0.94827	-0.06140	0.94091	0.96934
22	Na 2 [mmol/L]	0.28227	-0.00770	0.00707	0.79034

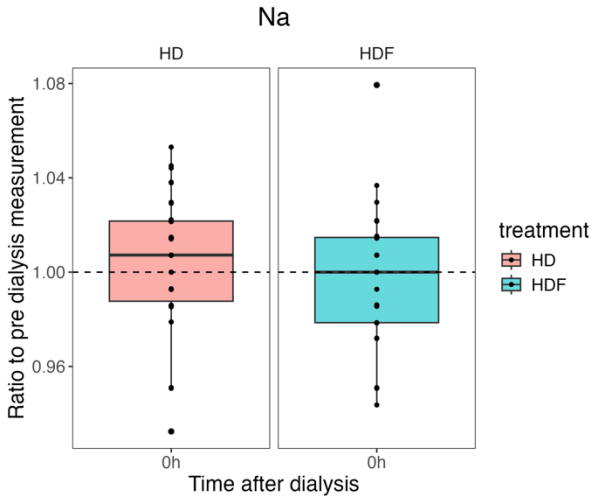

Figure 16 *Ratio of post intervention to pre intervention Sodium concentration [mmol/L] in hemodialysis and hemodiafiltration patients. Showing every post intervention measurement (•), ratio (- - -), median (——), and interquartile range (colored box).*

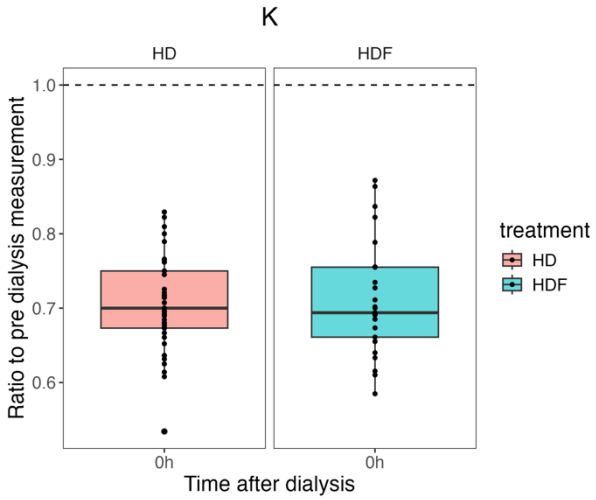

Figure 17 *Ratio of post intervention to pre intervention Potassium concentration [mmol/L] in hemodialysis and hemodiafiltration patients. Showing every post intervention measurement (•), ratio (- - -), median (——), and interquartile range (colored box).*

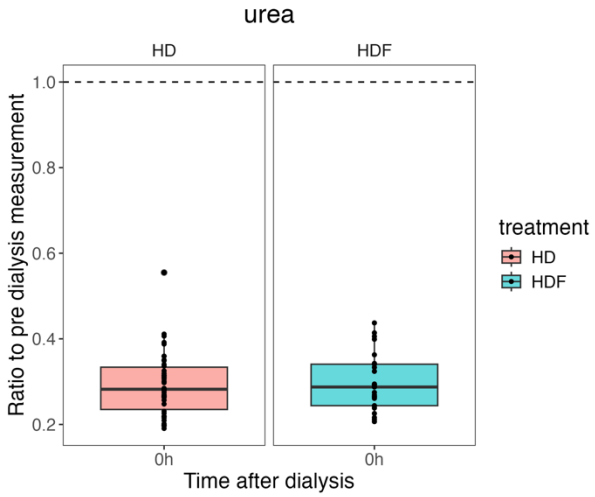

Figure 18 *Ratio of post intervention to pre intervention Urea concentration [mmol/L] in hemodialysis and hemodiafiltration patients. Showing every post intervention measurement (•), ratio (- - -), median (——), and interquartile range (colored box).*

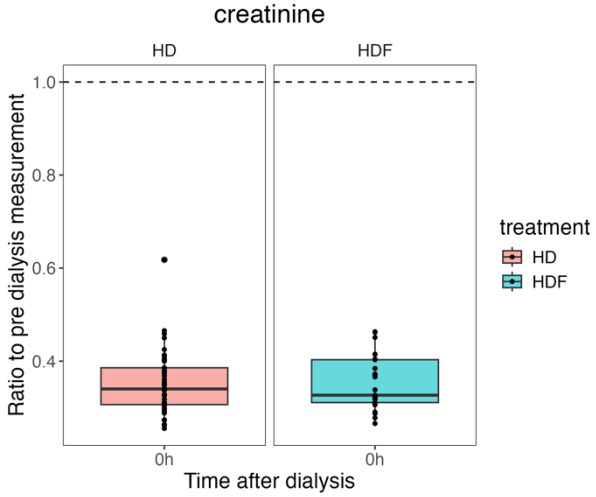

Figure 19 *Ratio of post intervention to pre intervention Creatinine concentration [µmol/L] in hemodialysis and hemodiafiltration patients. Showing every post intervention measurement (•), ratio (- - -), median (——), and interquartile range (colored box).*

7.3. Three time point measurements

Parameters that had three-point measurements [Troponin, NT-proBNP, CRP, IL-6] were collected pre, 0h post and 24h post intervention. The CRP results showed that absolute CRP levels from all three measurements were lower in HDF patients in comparison to the HD group, but comparison of the ratios adjusted to the first measurements revealed no statistical significance at 0h and 24h post intervention (Table 3 & Figure 20). However, for both groups an increase in CRP was seen post intervention. For IL-6 we did see an increase in levels for both groups 0h post intervention as shown in Figure 21. 24h post intervention results showed a drop in IL-6 for the HDF patients while HD patients continued to increase on average. Important to note are the interquartile ranges (IQRs) which show narrow variability in the measurements of both HD and HDF groups. Troponin tends to increase 0h post intervention in the HD group while the HDF group showed a rather equal ratio to the pre intervention levels with a slight tendency to decrease (Figure 22). 24h post interventional both groups showed a tendency to increase in troponin. For CRP, IL-6, and troponin neither 0h post intervention nor 24h post intervention values revealed statistical significance (Table 3).

On the other hand, NT-proBNP showed a major difference in levels directly post intervention (Figure 23). NT-proBNP levels dropped significantly (p.adj = 0.00073) more in the HDF group compared to the HD group after dialysis (Table 3). While 24h post intervention absolute values were lower for HDF patients there was no significant difference when comparing their ratios. Additionally, results showed that NT-proBNP levels were more variable with a larger range in the 24h post intervention outcomes of the HD group compared to the HDF group with a trend towards higher levels of NT-proBNP for HD patients and rather lower levels in the HDF group. Comparing the ratios, HDF patients have a NT-proBNP level which is lower than the pre intervention levels throughout 0h and 24h post intervention measurements. While in HD patients the 24h post intervention NT-proBNP surpasses the pre intervention levels.

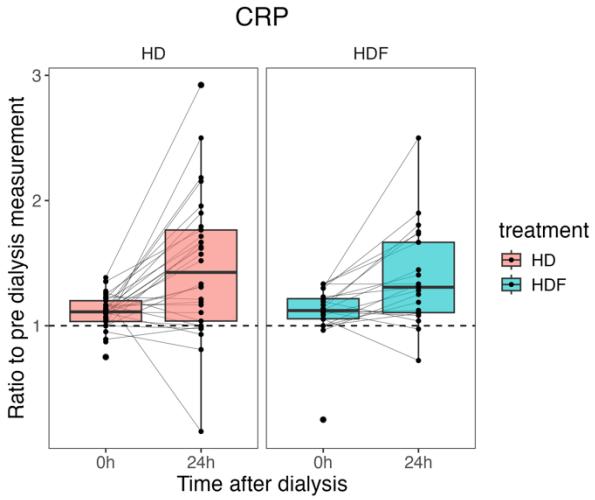

Figure 20 *Ratio of post- and 24h post intervention to pre intervention C-reactive protein concentration [mg/L] in hemodialysis and hemodiafiltration patients. Showing every post and 24h post intervention measurement (•), ratio (- - - -), median (——), and interquartile range (colored box).*

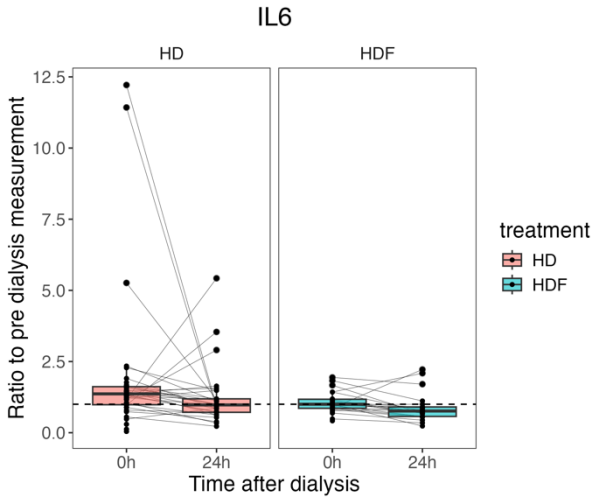

Figure 21 *Ratio of post- and 24h post intervention to pre intervention Interleukin-6 concentration [pg/mL] in hemodialysis and hemodiafiltration patients. Showing every post and 24h post intervention measurement (•), ratio (- - - -), median (——), and interquartile range (colored box).*

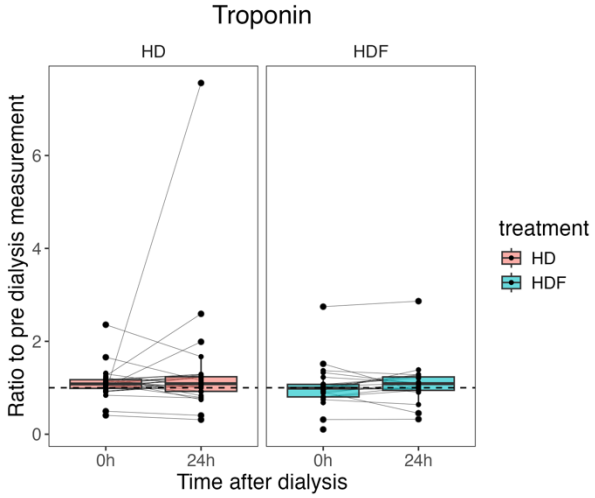

Figure 22 *Ratio of post- and 24h post intervention to pre intervention Troponin concentration [ng/L] in hemodialysis and hemodiafiltration patients. Showing every post and 24h post intervention measurement (•), ratio (- - - -), median (——), and interquartile range (colored box).*

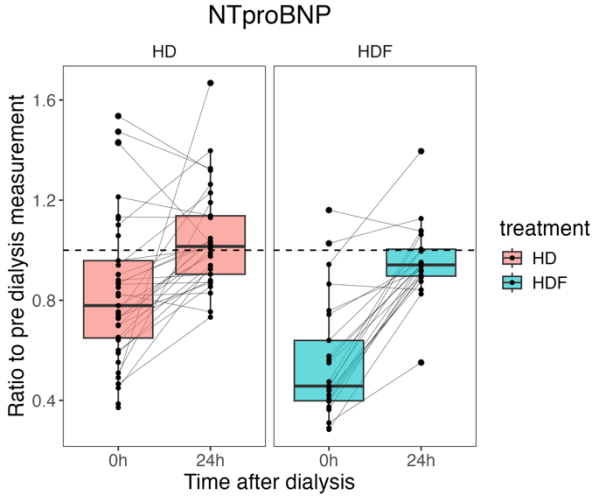

Figure 23 *Ratio of post- and 24h post intervention to pre intervention NT-proBNP concentration [pg/mL] in hemodialysis and hemodiafiltration patients. Showing every post and 24h post intervention measurement (•), ratio (- - - -), median (——), and interquartile range (colored box).*

7.4. Clinical Data

From the 68 patients, comorbidities were registered in 30 out of 45 HD (69.8%) and 23 out of 25 HDF (92.0%) patients. 90 % of HD patients and 100% of HDF patients were diagnosed with hypertension, 53% HD and 43% HDF with diabetes mellitus, 43% HD and 35% HDF patients with heart failure (Table 4). No significant difference could be found in the prevalence when comparing the two groups, represented by the Chi-Square test (p.diabetes = 0.48; p.heartfailure = 0.53; p.hypertension = 0.12).

Result for further comorbidities showed 9 HD (30%) and 5 HDF (22%) patients were diagnosed with atrial fibrillation. 8 HD (27%) and 3 HDF (13%) patients suffered from cerebrovascular disease which were divided into transitory ischemic attacks (2 HD, 1 HDF) and strokes (6 HD, 2 HDF). Coronary artery disease was evident in 9 HD (30%) and 10 HDF (43%) patients which included stable angina (2 HD, 1 HDF), unstable angina with ST-elevation myocardial infarct (STEMI) or non-STEMI (nSTEMI) (4 HD, 6 HDF), and previous stenosis with percutaneous coronary intervention (3 HD, 3 HDF). Peripheral artery disease was documented in 3 HD (10%) and 2 HDF (9%) patients divided into claudication (0 HD, 1 HDF), claudication with ulceration (0 HD, 0 HDF) and amputation (3 HD, 1 HDF). 5 HD (17%) and 5 HDF (22%) were diagnosed with heart valve diseases. 0 HD (0%) and 2 HDF (9%) suffered from chronic or autoimmune inflammatory disease. Malignancies (either in remission or under current treatment) were documented in 3 HD (10%) and 0 HDF (0%).

Table 4 showing absolute and percentages of HD and HDF patients, their cardiovascular comorbidities, and their p values

	Number of patients	Diabetes mellitus	Heart failure	Hypertension
HD	30	16 (53%)	13 (43%)	27 (90%)
HDF	23	10 (43%)	8 (35%)	23 (100%)
Total	53	26 (49%)	21 (40%)	50 (94%)
p values		0.48	0.53	0.12

8. Discussion

The single measurement parameters revealed no significant difference between the two groups after receiving a minimum of three months of dialysis treatment prior to the study.

Absolute numbers and their variability could be misleading in the interpretation of their results. Therefore, we decided to compare two- and three-point parameters by performing ratios of the pre and post intervention measurements. This allowed us to achieve clearer results and perform a more realistic comparison of the patients in and between either group. The advantage was best demonstrated by the creatinine concentrations. The absolute numbers showed a net average of 755 μmol/L in HD and 865 μmol/L in HDF pre intervention, and 267 μmol/L in HD and 305 μmol/L in HDF post 0h intervention. Viewing only these numbers one would assume HD has better properties due to reaching lower absolute values post intervention. When comparing the ratios adjusted to the pre intervention values, the results show a larger net filtration in the HDF group. Even though the absolute average post intervention is higher there is more creatinine filtered due to HDF patients having a larger absolute average pre dialysis. Additionally, this can be shown by the net loss (ΔHD = 488 μmol/L, ΔHDF = 560 μmol/L).

For a better evaluation of the dialysis function and international comparison in the two forms of intervention the Kt/v ratio could have been calculated, which is a measurement based on urea clearance. However, since the patients had been under treatment for a minimum of three months with the same staff, same clinical setting, positive outcomes, and due to up-to-date literature referring to the Kt/v ratio as outdated we deemed the calculations not necessary. Although these analyses could be subsequently performed (33).

The large variation seen in certain parameters like albumin, vitamin B12, UIBC and TIBC could be linked to comorbidities of the patients as well as nutrition of the patients. For the latter we did not have the data collected.

The two-point measurement parameters are important indicators for the viability of the dialysis procedures. Urea and creatinine count as uremic toxins which should always be removed by any procedure of dialysis. On the other hand, sodium counts as one of the most important electrolytes for the body's homeostasis. Sodium should be kept in equilibrium during the procedure of hemodialysis or hemodiafiltration e.g., by adding substitution fluid. As the results

show there was no significant net loss of sodium (ΔHD = -0.7 mmol/L, ΔHDF = 0.9 mmol/L) throughout the procedures allowing for a stable sodium concentration. Potassium is a very difficult electrolyte as either hyperkalemia or hypokalemia may be life threatening. Therefore, close attention should be paid to maintaining its concentration in the physiological ranges. The average for pre intervention potassium values combined was 5.1 mmol/L (5.06 mmol/L HD, 5.13 mmol/L HDF) and post 0h intervention 3.6 mmol/L (3.54 mmol/L HD, 3.62 mmol/L HDF), with the lowest levels, in three HD patients, reaching 3.0 mmol/L. These results show that the patients moved right in between the physiological levels pre and post intervention. These are important characteristics to keep in mind for dialysis since we don't want chronic kidney replacement patients coming to the dialysis center only when they are hyperkalemic, nor should they leave in a hypokalemic state after a session of dialysis.

By the net loss of urea and creatinine we were able to demonstrate the efficiency of removing uremic toxins by the applied HD and HDF methods. Therefore, assuring that the procedures resulted in the attainable therapeutic effect.

The three-point measurement parameters were the focus of this trial with inflammatory markers and indicatory biomarkers of cardiac strain and damage. The results of our group of patients showed no relevant difference regarding CRP, IL-6, and troponin. On one hand this may be due to HD filters having undergone such innovation that they allow for better clearance of multiple uremic toxins compared to former trials, when HDF and HD were firstly compared to each other (9). On the other hand, it might be due to the specific care that CKD patients receive these days under well-trained staff and implementation of specific dialysis centers. We can say regarding our results that hemodialysis provides equal filtration capacities for almost all tested parameters, except one namely NT-proBNP (34).

The results may lead to the conclusion that there is no major difference of performing HDF over HD. When looking at the protein NT-proBNP which has a shorter half-life than troponin (NT-proBNP $t_{1/2}$ = 25 min, troponin $t_{1/2}$ = 90-120 min) (35,36), there are clear signs that indicate a HDF intervention may be more beneficial for patients suffering from end stage renal disease. These findings are in concordance with previously published results (37–40). However, cutoff values for NT-proBNP, troponin and other markers are still discussed. Suitability and reliability of cardiac and inflammatory biomarkers for optimal surveillance are also still being reviewed.

In our trial it was shown that there are potential benefits of performing HDF in patients with ESRD and comorbidities affecting the cardiovascular system compared to patients receiving HD. This is demonstrated by the NT-proBNP results, even when considering a higher production of NT-proBNP in patients suffering from cardiovascular disease. Results show the net filtration of the HDF group exceeds that of the HD patients by an absolute average difference of 7’000 pg/L. Additionally, the slow and variable rise in troponin levels in comparison to NT-proBNP is one of the reasons why we highlight the use of NT-proBNP as a cardiac biomarker compared to troponin levels, as in concordance with previously published results regarding troponin, being not an ideal choice for the use as biomarker for early diagnosis of acute myocardial infarction or after percutaneous coronary intervention (41,42).

9. Conclusion

Hemodiafiltration is an ever-growing modality of dialysis that has been introduced to all dialysis wards routine work throughout the last 25 years. It is a promising and capable intervention with an ability to remove uremic toxins fast and efficiently while allowing for more control over the patient's volume homeostasis by the physician due to the use of substitution fluid. Hemodialysis on the other hand provides an excellent alternative as it is fast, simple, and cheaper than hemodiafiltration, due to not being dependent on a substitution fluid. Also, this brings HD more in line with the principle of green nephrology since it has significantly less water consumption.

After performing our pilot trial, we can conclude that hemodiafiltration may offer a benefit to patients with end stage renal disease especially when diagnosed with comorbidities affecting the cardiovascular system. There are no clear indications that hemodiafiltration provides an additional beneficial outcome in patients without cardiovascular comorbidities when compared to hemodialysis.

Additional research is necessary to gain further comprehensive understanding of hemodiafiltration in patients with end stage renal disease in Croatia. The intention of this study was to provide a starting point for years of follow up to come. Further parameters and tests like quality-of-life patient surveys, detailed follow up of comorbidities, and longitudinal evaluation of patients' laboratory values will be performed in the future.

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12. Biography

My name is Nicola M. B. W. Pohly. I am currently a sixth-year medical student at the School of Medicine, University of Zagreb. I was born and raised in Berlin, Germany in 1997. I come from a physician family with both my parents being medical doctors and academics. After my brother finished his degree in medicine, I followed in his footsteps to become a physician myself. During my childhood I was fortunate enough to travel through multiple exotic countries and continents seeing different cultures that allowed me to broaden my horizon with every new adventure. The second country I call home is Switzerland since I have been living there for most of my teenage years due to my parents deciding to become independent and creating their own clinic back in 2008. So, when the opportunity came around which allowed me to become a medical student at the University of Zagreb the decision was an easy one, even without having any roots or ties with the beautiful country of Croatia that I learned to love and cherish over the years.