The importance of volume overload, hemodialysis access and duration of time on effective therapy during renal replacement modalities

PhD Thesis

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1. Introduction

Historically, an adequate Kt/V during hemodialysis was mediated by the combination of filter clearance and time spent on renal replacement therapy (RRT). With the evolution of RRT technology, identical Kt/Vs have been re-created but within a much shorter time, using larger dialysis filters and higher flow rates, leading to a potential deterioration of overall well-being and hemodynamical stability. The clearance of large-size uremic toxins is primarily dependent on time spent on RRT; not surprisingly, several true markers of uremia (phenylacetylglutamine, hippurate, indoxyl sulfate) maintain a markedly elevated level on chronic hemodialysis (x40-120), despite receiving what appears to be an adequate dialysis by small solute clearance criteria. The last one decade has witnessed re-emergence of a broader view in clinical nephrology, emphasizing the use of fistulas, pre-dialysis nephrology care, and maneuvers to preserve residual renal function during the care of these patients. Additional considerations are the length of effective dialysis received, the presence of inflammation with vascular access catheters and suboptimal compliance with dietary and fluid restrictions complicating effective therapy. Unlike chronic RRT patients, critically ill renal patients are much more heterogeneous with an acute component of renal dysfunction, further confounding the interpretation of serum creatinine. The practical value of creatinine is much limited in this setting and different cut-off values may apply to start renal replacement technologies in critically ill. In our former paper, we observed better outcomes in those with shorter wait-time before continuous renal replacement therapy (CRRT) and in those with impaired baseline creatinine. Further, the change in creatinine between admission and the initiation of CRRT was statistically different between survivors and non-survivors (1.6 vs. 2.6 mg/dL, p=0.023). Since the early 2000s, the early goal-directed therapy in sepsis has created a practice pattern of aggressive volume resuscitation in the Intensive Care Units (ICU). However, over-aggressive volume resuscitation is also harmful and indiscriminate fluid overload has been associated with increased morbidity and mortality in patients with acute respiratory distress syndrome, sepsis, in surgical ICU patients and those with abdominal compartment syndrome. Volume overload may also mask the rise of serum creatinine and markedly underestimate the degree of renal functional impairment. At first, pediatric studies indicated that fluid overload at the initiation of CRRT was associated with increased mortality. On the other hand, the impact of fluid overload for survival in adults was not well studied until recently and it remains uncertain whether CRRT can meaningfully influence prognosis, when compared with hemodialysis. Considering the above, there was a critical need to re-assess the impact of volume overload in critically ill patents, especially as it pertains to the trigger point of initiating RRT.

2. Objective

2.1 Volume-related weight gain study

Literature emerging around the middle of the first decade of the 21st century strongly suggested an adverse impact of volume overload in surgical settings for adults and in critically ill children with acute kidney injury (AKI). On the other hand, the impact of volume overload in adults with AKI was little explored at that time. Since fluid overload is associated with decreased survival in non-renal patients, we hypothesized that larger volume-related weight gain (VRWG) prior to RRT may be associated with higher mortality in critically ill AKI patients treated with CRRT.

Specific research goals:

1. To determine the degree of volume overload experienced in a cohort of critically ill patients before being started on CRRT.
2. To examine the association of VRWG with subsequent outcomes in these critically ill patients.

2.2 Dialysis prescription and inflammatory markers on dialysis study

Unlike in AKI patients, the source of fluid overload in end-stage renal disease (ESRD) patients is not exogenous IV fluid but represents the dietary intake of both salt (sodium-chloride) and water. Time spent on maintenance dialysis, both for the patients and providers' convenience, became progressively reduced in the era of high-flux dialyzers by the early 2000s and time itself turned into a relatively neglected clinical parameter. Since treatment time and ultrafiltration (UF) rate both correlate with patient survival, we hypothesized that long treatments with a slow UF rate may also influence the control of inflammation on dialysis.

Specific research goals:

1. To examine the association of time on chronic hemodialysis on serum C-reactive protein (CRP) and albumin.
2. To examine the association of hourly UF rate on chronic hemodialysis with serum CRP and albumin levels.

2.3 Vascular catheter access removal studies

Permanent or semi-permanent (long-term) intravascular access catheters became routine from 1990 on and escalated in the last two decades in dialysis patients. These foreign materials create a state of low-degree inflammation and contribute to excess infectious risk and mortality in ESRD patients. In such context, we wanted to examine the circumstances, indications and clinical success rate of an emerging

nephrology procedure, the bedside removal of these catheters. Our study hypothesis was that bedside removal of tunneled dialysis catheter (TDC) by a nephrologist is safe and effective, both for in- and outpatients and when performed by physicians during graduate medical education training. Our secondary objective was to examine the associations between select biomarkers (CRP, troponin-I) and clinical indications for TDC removals in our inpatient cohort.

Specific research goals:

1. To determine success rate with bedside removal of TDCs, including the safety and efficacy of such procedure in both inpatient and outpatient settings.
2. To examine the impact of vascular access catheters on certain serum biomarkers (CRP, troponin-I) in patients undergoing removal of semi-permanent vascular access catheters.

3. Methods

My proposed thesis will be supported by my existing publications on the subject. Herewith, I would like to review the Materials and Methods of the studies I have utilized to develop this thesis, including one study examining the importance of volume-related weight gain before CRRT, an another one examining the cross-sectional associations of inflammatory markers with treatment time during conventional hemodialysis and two studies on TDC removal.

3.1 Volume-related weight gain study

3.1.1 *Study population, definitions and variables of interest*

We prospectively collected data in 81 patients treated with CRRT at the University of Mississippi Medical Center (UMMC), Jackson, MS (United States of America) over an 18-month period from January 2003 to June 2004. The patients were considered to have AKI if their serum creatinine increased by 0.5 mg/dL (44.2 μmol/L) or greater from baseline or if they had an abnormal serum creatinine at the presentation with no known baseline value. Oliguria was defined as an average urine output of less than 20 mL/hour for at least 12 hours before enrollment. VRWG was defined as the difference between the initial (first available) weight and the weight at the initiation of CRRT. Weight gain percentage (%) was interpreted as a difference in percentage between the initial weight and weight obtained at the initiation of CRRT. The diagnosis of sepsis was a clinical diagnosis as stated on the medical record and Apache II scores were calculated at the time of the renal consult was obtained. The principal outcome was mortality on day 30.

3.1.2 *Statistical methods*

The primary goal of the study was to examine the effect of various cut-off net fluid accumulations, that is VRWG ≥10% or ≥20% and oliguria as variables associated with mortality. Additional variables included age, sex, chart diagnosis of sepsis, Apache II scores, CRRT dose, creatinine level at the initiation of CRRT, absolute change form of creatinine, days waited and ICU location. A cross-sectional analysis of selected variables was conducted to identify correlates with mortality. Chi-square tests were used for bivariate analyses of correlations between selected variables and mortality. Independent *t*-tests were performed to assess the correlations of continuous variables with mortality. Multivariate logistic analyses were conducted for more complex correlations. The data were analyzed using SPSS version 16 (SPSS Inc., Chicago, IL) and Minitab (version 13; Minitab Inc., State College, PA).

3.2 Dialysis prescription and inflammatory markers on dialysis study

3.2.1 *Study population, definitions and variables of interest*

We have undertaken a cross-sectional study in a network of 12 hemodialysis centers including all Diaverum hemodialysis units in Hungary and the UMMC outpatient hemodialysis unit in Jackson, MS, USA. All patients receiving in-center maintenance hemodialysis three times a week were recruited for the study. Patient- and dialysis-related characteristics, comorbidity diagnoses, acute events, medication use, and other covariates were extracted in July, 2007. Treatment time was defined as the average length of dialysis sessions in minutes recorded during the index month. The UF rate was defined as the hourly volume removed in mL per kg of body weight (mL/kg/hour) and averaged over the index month. Serum albumin and CRP were measured as part of the routine care. Albumin was measured by Bromocresol green methods (Diagnosticum Zrt., Hungary; Spectra Laboratories, USA) and reported in gm/L or gm/dL. CRP was measured by immunoturbidimetric assay and reported as either < 5 mg/L, any numerical value above 5 mg/L (Spectra Laboratories, USA) or numerical values both below and above 5 mg/L (APTEC, Belgium).

3.2.2 *Statistical methods*

Data on patient characteristics are shown as mean ±SD for continuous variables or percentages for categorical variables. Serum albumin and CRP were used as continuous variables in the analysis of covariance (ANCOVA) models and categorized as bivariate during logistic regression. In our study, we *a priori* dichotomized albumin values at 40 gm/L (approximate mid-normal range value) with albumin > 40 gm/L designated as a favorable outcome for purposes of logistic regression analysis; conversely, albumin ≤ 40 gm/dL was designated as low albumin or failure to reach normal albumin levels. Similarly, CRP was dichotomized at 5 mg/L, with CRP ≤ 5 mg/L being designated as a favorable outcome, CRP > 5 mg/L as failure. Potential factors associated with inflammation were tested in ANCOVA models, with an initial 23 variables model narrowed down to 15 variables. Logistic regression models were constructed to calculate

Odds Ratio (OR) with 95% confidence intervals (CI) predicting favorable outcomes of CRP and albumin. Treatment time was dichotomized at four hours and entered into logistic regression modeling as a categorical variable of > 4 hours for "long" treatment time and ≤ 4 hours for "short" treatment time. The initial logistic regression model operated with the same 15 independent variables as the second ANCOVA model. Stepwise selection was applied in logistic regression modeling to assess the individual contribution of major predictors. All statistical analyses were performed using SPSS 16 (SPSS Inc., Chicago, IL).

3.3 Vascular access catheter removal studies

3.3.1 *Study population, definitions and variables of interest*

Our catheter removal experience consisted of two studies, Study A and Study B. Study A consisted of a retrospective cohort of a consecutive 3-year bedside TDC removal experience among hospitalized subjects at the UMMC (January 01, 2007 to December 31, 2009). Study B consisted of a review of mixed inpatient and outpatient bedside TDC removals from January 1, 2010 to June 30, 2013 at UMMC. For study A, we reviewed and collected data on multiple patient-related variables: age, ethnicity, sex and highest blood urea nitrogen (BUN), creatinine and blood coagulation tests within 24 hours of the procedure. Additionally, we collected data on certain other peri-procedure parameters up to three days before and after the procedure which consisted of peak and nadir white blood cell count (WBC); nadir hemoglobin, nadir platelet count and vital signs (temperature, heart rate, blood pressure). Two additional biochemical parameters associated with inflammation and myocardial stress, CRP and troponin-I were searched for and recovered from medical records, if available within 48 hours of TDC removal. Procedure-related variables, which included the indication for the procedure, the site and location of removal and any complications or difficulties during the procedure were recorded from the teaching log of the author of the present thesis. For study B, we collected data on similar variables but within three days before and after the procedure.

3.3.3 *Statistical methods*

Upon review of both electronic and paper-based medical records, pre-defined information was collected in Microsoft Excel data sheets. Data were analyzed using SPSS Statistics 19 (IBM Corporation, Armonk, NY) and reported with means ±SD or medians 25-75% IQR for descriptive data; Pearson's correlation and chi-square as well as independent-samples *t*-test were utilized for statistical comparisons.

4. Results

4.1 Volume-related weight gain in critically ill patients with AKI and subsequent mortality

A total of 81 patients met inclusion criteria for the study, with mean age 51.4 years ±16.7 years, 24 of which were female (30%). The overall raw mortality rate for the cohort was 50.6%. Mean VRWG was 8.3 ±9.6 kg (range: -10.5 to +45.9 kg) and mean percent weight gain was 10.2 ±13.5% (range: -11 to +81%). Oliguria was present in 53 patients (65.4%) before CRRT commenced. Thirty-eight patients (46.9%) had VRWG ≥10% and thirteen patients (16%) had ≥20% VRWG. WRVG ≥10% (p=0.046) and oliguria (p=0.020) were significantly associated with death (**FIGURE 1.1**). Compared with the reference group of <10% VRWG, those gaining ≥10% before CRRT initiation had a more than doubled unadjusted risk of mortality in the cohort (OR 2.62, 95% CI: 1.07-6.44; p=0.046). When the patients were stratified using 20% VRWG as the cut-off point (**FIGURE 1.2**), the odds ratio for death in the patients with VRWG ≥20% was even higher, compared with the patients with VRWG <20% (OR 3.98, 95% CI: 1.01-15.75) albeit nominal significance was lost (p=0.067). Separating the cohort into three categories of VRWG (<10%; ≥10 but <20%; ≥20%) was associated with a stepwise progressive increase of mortality: 39.5% (17 of 43), 56% (14 of 25) and 76.9% (10 of 13). Accordingly, against a reference group of VRWG <10%, OR for death was increased to 1.95 (95% CI: 0.72–5.28; p = 0.191) in the group with intermediate weight gains (≥10 but <20%) and to 5.10 (95% CI: 1.22–21.25; p = 0.025) in the group with severe (≥20%) weight gains. Of the forty-one deceased patients 32 had oliguria with an unadjusted OR of death 3.22 (95% CI: 1.23-8.45, p=0.02) for oliguria. Finally, we performed a multivariate modeling to assess the correlations of other potential risk factors for death in these patients. When analyzed together, both oliguria (p=0.021) and ≥10 weight gain (p=0.042) maintained independent significance. When sepsis and Apache II scores were included in the modeling, once again, oliguria (OR 3.04, p=0.032) and ≥10% weight gain (OR 2.71, p=0.040) maintained significance in the more complex modeling. The effect of sepsis and Apache II scores remained non-significant on multivariate analysis. Altogether, the combined presence of oliguria and ≥10% weight gain explained approximately 12% of the observed mortality. Including into the logistic regression model creatinine level at CRRT initiation, CRRT dose and days waited for CRRT abolished the association of mortality with VRWG ≥10% (p=0.196; OR 0.71-5.29), but not with oliguria (OR 3.94; 95% CI 1.37-11.37; p=0.011) (R^2 0.16). As larger VRWG was also associated with lower serum creatinine (5.5 ±2.4 mg/dL vs. 4.5 ±1.8 mg/dL with lower creatinine in VRWG≥10%; p=0.039), adjusting for creatinine at CRRT start may have resulted in simultaneous adjustment for larger fluid gains in those with larger fluid gains and dilution of serum creatinine.
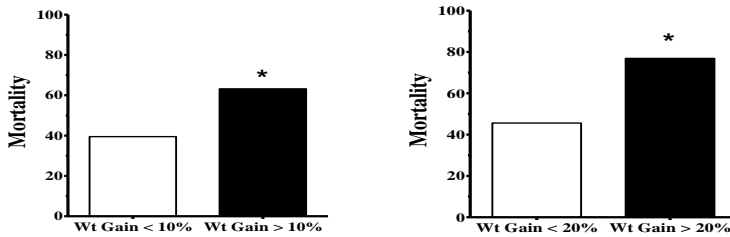
Figure 1.1 and 1.2. Association between VRWG and Mortality at different cut-offs of VRWG

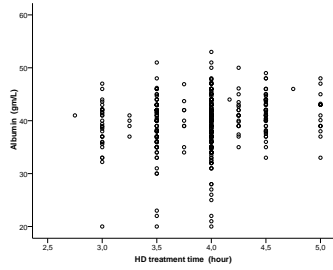Asterisk (*) indicating statistical significance (*p*<0.05)

4.2 Dialysis prescription and inflammatory markers during conventional hemodialysis

Of the 626 reviewed patients, 616 (98.4%) met our inclusion criteria for undergoing maintenance hemodialysis three times a week in the 12 participating centers and having at least one of the critical data (albumin or CRP) obtained during the data collection period available for further analysis. The distribution of serum albumin values by treatment time and UF rate is shown in **FIGURE 2.** and **FIGURE 3.**, respectively. CRP was highly variable with a wide range (undetectable to 146.8 mg/L) and ≤5 mg/L in 252 (41%) of the cohort. Mean albumin levels were 39.4 ±4.69 g/L among subjects receiving "short" (≤4 hours) treatment and 41.62 ±3.39 gm/L among those receiving "long" treatment (>4 hours). Stepwise selection was applied in logistic regression modeling to assess the individual contribution of major predictors. For albumin, failure to reach more than 40 g/L in Step 4 correlated with short treatment time, Caucasian ethnicity, dialysis vintage and the presence of acute infection. Treatment time of longer than 4 hours was associated with decreased odds of low albumin (OR 0.397, 95% CI: 0.235-0.672; p<0.001). Being Caucasian increased the likelihood of failing to reach the albumin target (OR 2.304, 95% CI: 1.462-3.630; p<0.0001), as did acute infection (OR 2.240, 95% CI: 1.327-3.780; p=0.003) and dialysis vintage (OR 0.995, 95% CI: (0.991-1.000), p=0.043). On the other hand, UF rate was not found to be a significant correlate of failure to reach > 40 gm/L albumin. Separating CRP according to treatment time, mean CRP in the short-treatment cohort was 12.05 ±18.78 mg/L and 11.23 ±15.62 mg/L in the long-treatment-time subgroup. Logistic regression demonstrated that factors correlating with high CRP were age, congestive heart failure (CHF), lower dry weight and vascular access type. During stepwise selection, only the presence of CHF (OR 1.634, 95% CI: 1.154-2.312; p=0.006) and acute infection (OR 1.799, 95% CI: 1.059-3.056, p=0.03) remained positive correlates of a high CRP level. The significance of age decreased (OR 1.014, 95% CI 1.002-1.026; p=0.02) while dry weight and vascular access type lost significance. UF rate was not found to be a significant correlate of either main outcomes.

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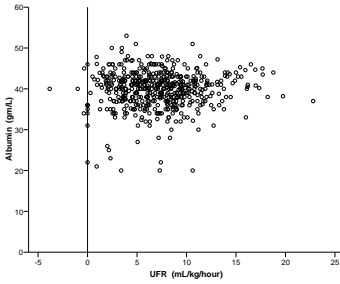
Figure 2. Distribution of serum albumin by treatment time

Figure 3. Distribution of serum albumin by treatment time

Abbreviations: UFR, ultrafiltration rate; HD, hemodialysis

4.3 Tunneled Dialysis Catheter removal success rate and biomarkers

4.3.1 *Results of the Inpatient Cohort*

Our Study A population consisted of 55 hospitalized patients. All TDCs were removed at the bedside and most cases (50/55 or 90.9%) completed by nephrology fellows under attending physician's supervision. Most cases had urgent indication for TDC removal with potential for harm with delays. These included proven (culture-positive) bacteremia in 36.4% of the cases, otherwise unexplained fever in 41.8% of the cases or clinical signs of sepsis with hemodynamic instability or respiratory failure in 20% of the cases. All removals were executed successfully without any retention of polyethylene ("Dacron") cuffs or catheter fracture observed. One patient had prolonged local bleeding which was controlled with extended local pressure. None of the cases required interventional radiology or general surgery consultation for assistance. Peak CRP (available in 63.6% of the cohort) was 12.9 ±8.4 mg/dL (reference range: <0.49 ml/dL), median troponin-I (34% available) was 0.127 ng/mL [25-75% IQR 0.03-0.9] (reference range: <0.034 ng/mL) and they did not correlate with each other (p=0.848). We did not observe any association between CRP and clinical indications for TDC removal. Additionally, clinical sepsis (as indication for TDC removal) correlated with systolic BP nadir (p<0.0001), temperature (p=0.002) and the lowest platelet count (p=0.016). Troponin-I had no association with systolic and diastolic BP or clinical sepsis as indication for TDC removal. However, troponin-I, as a continuous variable showed a trend with confirmed bacteremia (p=0.075); furthermore, the association of troponin-I as a bivariate variable (abnormal/normal) with bacteremia was statistically significant (Pearson's chi-square p=0.049).

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4.3.1 *Results of the Mixed Inpatient-Outpatient Cohort*

For study B, general cohort characteristics are shown in **TABLE 1.** The sites and indications for removals are listed in **TABLE 2.** Most of the outpatient removals took place due to access maturation (p<0.0001). Like in Study A, all removal procedures were successful and tolerated without tear of the catheter itself but, unlike in study A, we observed Dacron "cuff" separation and subcutaneous retention in 6.5% of cases, all in males. There was a significant association between cuff retention and outpatient removal (p=0.007) but not with the operators' training level, or the site of removal. Once again, similarly to study A, none of the patients required interventional radiology or general surgery consultation for assistance.

Table 1. Baseline Cohort Characteristics (N=138)

Age (years)	50 (15.9)
Gender *(%, female)*	49.3
Race *(%, African-American)*	88.2
Co-morbid Medical Conditions *(%)*	
Diabetes Mellitus	41
Systemic Lupus Erythematosus	6
Hypertension	85.1
Recent Renal Transplant	6.6
Biochemical Parameters	
Blood Urea Nitrogen, highest (mg/dL)[a] (n=109)	46.4 (18.9)
Creatinine, highest (mg/dL)[a] (n=109)	7.7 (3.9)
Platelet count, nadir (x10^3/mm^3)[a] (108)	223.4 (108.5)
Prothrombin Time International Normalized Ratio, highest[a] (n=56)	1.12 (0.31)
Partial Thromboplastin Time, highest (sec)[a] (n=58)	33.1 (8.5)
WBC count, peak (x10^3/mm^3)[a] (n=108)	9 (4.7)
Hemoglobin, nadir (gm/dL)[a] (n=108)	10.2 (1.5)

[a]obtained with 72 hours

Table 2. Procedure Location and Indications for Tunneled Dialysis Catheter
(TDC) Removal (N=138)

Location of TDC removed (%)	
Femoral vein *(left or right)*	8
Right Internal Jugular Vein	76.8
Left Internal Jugular Vein	15.2
Place of TDC Removal *(%, outpatient services)*	44.9
Indication for TDC Removal (%)	
Bacteremia	30.4
Fever (temperature >38 C°), Sepsis or Clinical Concerns for Infection	15.2
Exit Site Infection (as sole indication)	1.4
TDC "no longer needed" (renal recovery or access maturation)	52.2

5. Conclusions

5.1. In a single-center trial of eighty-one subjects, we found that fluid overload was common (46.9% had weight gain ≥10%) and an important prognostic factor for survival in critically ill AKI patients, subsequently treated with CRRT. Increasing VRWG had a graded adverse impact on 30-day survival, with mortality increasing by two and half times in those with VRWG ≥10% (OR 2.62, 95% CI: 1.07-6.44; p=0.046) and almost four times with VRWG ≥20% (OR 3.98, 95% CI: 1.01-15.75; p=0.067) in univariate analysis. Oliguria was also a strong predictor of death, with OR for mortality 3.22 (95% CI: 1.23-8.45; p=0.02). Both oliguria (OR 3.04, p=0.032) and VRWG ≥10% (OR 2.71, p=0.040) maintained respective statistically significant association with mortality in multivariate models that included sepsis and/or Apache II scoring. Therefore, among the first in adult medicine, we established fluid overload before CRRT to be an important prognostic factor for survival in critically ill patients with AKI.

5.2. We found that treatment time during conventional in-center HD had a significant cross-sectional association with serum albumin but not with CRP. In our study of >600 participants, treatment time longer than four hours was associated with a decreased risk of having low (< 40 gm/L) albumin levels with OR of 0.397 (95% CI: 0.235-0.672; p<0.001). For elevated CRP, significant correlates were congestive heart failure (OR 1.634, 95% CI: 1.154-2.312; p=0.006) and acute infection (OR 1.799, 95% CI: 1.059-3.056; p=0.03). However, we have not observed an association between UFR and either CRP or albumin. To our knowledge, this constituted the first report demonstrating an association between treatment time and albumin levels in hemodialysis patients. A large number of our patients, both from the European and North American cohorts achieved serum albumin and CRP targets, albeit with relatively long treatment times (237 ±24 vs. 236 ±24 minutes; approximately 15 minutes longer than the US average at that time). This study underlines and confirms the critical importance of time in good uremic control.

5.3. We have documented an excellent efficacy (100% success rate) and good safety profile during bedside removals of TDC from a combined cohort of two studies and 192 subjects. About one-third of the TDC removals took place urgently due to bacteremia, and elevated troponin-I had statistically significant associations with catheter-induced bacteremia in inpatients (p<0.05). Most (>50%) of the outpatient removals took place due to access maturation or cessation of indication for renal dialysis (p<0.0001). During outpatient removals, we observed subcutaneous retainer cuff separation in 6.5% of cases, all in males. There was a significant association between cuff retention and outpatient removal (p=0.007) but not with the operators' level of training, or the site of removal. However, we have not observed catheter body tear or frank complications (major vascular damage or air embolism). These studies underscore the potential for this procedure to enrich clinical nephrology training, contribute to timely care and improve clinical competency of practicing nephrologists.

6. Bibliography of the candidate's publications

6.1 Original publications utilized to develop the Thesis

Fülöp T, Pathak MB, Schmidt DW, Lengvárszky Z, Juncos JP, Lebrun CJ, Brar H, Juncos LA. (2010) *Volume-Related Weight Gain and Subsequent Mortality in Acute Renal Failure Patients Treated with Continuous Renal Replacement Therapy*. ASAIO J, 56: 333-337.

> **Impact Factor: 1.221** [Original Investigation]

*Zsom L, Zsom M, *__Fülöp T__, Wells C, Flessner MF, Eller J, Wollheim C, Hegbrant J, Strippoli FMG. (2010) *Correlation of Treatment Time and Ultrafiltration Rate with Serum Albumin and C-reactive Protein Levels in Patients with End Stage Kidney Disease Receiving Chronic Maintenance Hemodialysis: A Cross-Sectional Study*. Blood Purif, 30: 8-15.

*Authors contributed to the article equally; Dr. Fülöp corresponding Author

> **Impact Factor: 1.521** [Original Investigation]

Fülöp T, Tapolyai M, Qureshi NA, Beemidi VR, Gharaibeh KA, Szarvas T, Hamrahian SM, Csongrádi É. (2013) *The Safety and Efficacy of Bedside Removal of Tunneled Hemodialysis Catheters by Nephrology Trainees*. Ren Fail, 35: 1264-1268.

> **Impact Factor: 0.775** [Original Investigation]

Fülöp T, Rodríguez B, Kosztaczky BA, Gharaibeh KA, Lengvárszky Z, Dossabhoy NR, Tapolyai MB. (2015) *Tunneled Hemodialysis Catheter Removals by Non-Interventional Nephrologists: the University of Mississippi Experience*. Semin Dial, 28: E48–E52.

> **Impact Factor: 1.912** [Original Investigation]

6.2 Additional publications in support of the proposed Thesis or discussed therein

Zsom L, Zsom M, **Fulop T**, Flessner MF. (2008) *Treatment time, chronic inflammation, and hemodynamic stability: the overlooked parameters in hemodialysis quantification*. Sem Dial 21: 395-400.

> **Impact Factor: 2.671** [Review paper]

Fülöp T, Zsom L, Tapolyai MB, Molnar MZ, Rosiváll L. (2017) *Volume-related Weight Gain as an Independent Indication for Renal Replacement Therapy in the Intensive Care Units*. J Renal Inj Prev, 6: 35-42.

> **Impact Factor: 0** [Review paper]

Fülöp T, Tapolyai M, Agarwal M, Lopez-Ruiz A, Dossabhoy NR. (2016) *Tunneled Dialysis Catheter Removal by Nephrologists - A Lesson Learned from Nephrology Trainees*. Artif Organs (E-pub: 26 December 2016; DOI: 10.1111/aor.12869)

> **Impact Factor: 1.993** [Review paper]

Tapolyai M, **Fülöp T**, Uysal A, Lengvárszki Z, Szarvas T, Karim J, Ballard K, Dossabhoy NR. (2010) *Regional Differences in Nonadherence to Dialysis among Southern Dialysis Patients; a Comparative Cross Sectional Study to the DOPPS Study*. Am J Med Sci, 339: 516-518.

Impact Factor: 1.257 [Original Investigation]

Dossabhoy NR, Sangha B, Tapolyai MB, **Fülöp T**. (2016) *Outpatient Removal of Tunneled Dialysis Catheters by Nephrology Fellows in Training at a Veteran Administration Medical Center.* J Vasc Access 17:340-344.

Impact factor: 1.536 [Original Investigation]

Brar H, Olivier J, Lebrun CJ, Gabbard W, **Fulop T**, Schmidt DW. (2008) *Predictors of mortality in a cohort of intensive care unit patients with acute renal failure receiving continuous renal replacement therapy.* Am J Med Sci, 335: 342-347.

Impact Factor: 1.360 [Original Investigation]

Tapolyai MB, Faludi M, Berta K, Szarvas T, Lengvárszky Z, Molnar MZ, Dossabhoy NR, **Fülöp T**. (2016) *The Effect of Ambient Temperature and Humidity on Inter-Dialytic Weight Gains in End-Stage Renal Disease Patients.* Int Urol Nephrol, 48: 1171-1176.

Impact Factor: 1.292 [Original Investigation]

Fülöp T, Schmidt DW, Cosmin A, Islam N, Wells C, Lengvárszky Z, Bilbrew D, Zsom L. (2012) *Ambulatory blood pressure monitoring and peri-hemodialysis blood pressures in a Southeast U.S. hemodialysis unit.* Clin Nephrol, 77: 383-391.

Impact Factor: 1.288 [Original Investigation]

Abdul Salim S, Yougandhar A, Kandhuri S, Afshan S, Zsom L, Dixit MP, **Fülöp T.** (2016) *Successful Peritoneal Dialysis in Relatively Large Subjects (≥ 100 kg): Clinical Features and Comparison with Normal Weight (≤75 kg) Individuals.* Adv Perit Dial, 32: 61-67.

Impact Factor: 0 [Original Investigation]

Fulop T, Rule AD, Schmidt DW, Wiste HJ, Bailey KR, Kullo IJ, Schwartz GL, Mosley TH, Boerwinkle E, Turner ST. (2009) *C-reactive Protein among Community-Dwelling Hypertensives on Single-agent Antihypertensive Treatment.* J Am Soc Hypertens, 3: 260-266.

Impact Factor: N/A [Original Investigation]

Tapolyai M, Faludi M, Réti V, Lengvárszky Z, Szarvas T, **Fülöp T**, Bekő G, Berta K. (2013) *Volume estimation in dialysis patients: the concordance of Brain-type Natriuretic Peptide measurements and bioimpedence values.* Hemodial Int, 17: 406-412.

Impact Factor: 1.363 [Original Investigation]

Tapolyai MB, Faludi M, **Fülöp T**, Dossabhoy NR, Szombathelyi A, Berta K. (2014) *Which fluid space is affected by ultrafiltration during hemodiafiltration?* Hemodial Int, 18: 384-390.

Impact Factor: 1.240 [Original Investigation]

Ferguson LM, Dreisbach AW, Csongrádi É, Juncos LA, **Fulop T**. (2013) *Recurring Extracorporeal Circuit Clotting during Continuous Renal Replacement Therapy in a Patient with Scedosporium prolificans Induced Fungal Sepsis: Successful Treatment with Argatroban.* Am J Med Sci, 345: 256-258.

Impact Factor: 1.515 [Case Report and Literature Review]

<u>**Fülöp T**</u>, Cosmin A, Juncos LA. (2011) *Recurring Extracorporeal Circuit Clotting During Continuous Renal Replacement Therapy Resolved after Single-Session Therapeutic Plasma Exchange*. J Clin Apheresis, 26: 214-215.

     Impact Factor: 1.933 [Case Report]

Elmahi N, Csongradi E, Kokko K, Lewin JR, Davison J, **Fulop T**. (2013) *Residual renal function in peritoneal dialysis with failed allograft and minimum immunosuppression*. World J Transplant, 3: 26-29.

     Impact Factor: 0 [Case Report and Literature Review]

<u>**Fülöp T**</u>, Zsom L. (2015) *On Poor Agreement between Dialysis Unit and Ambulatory Blood Pressures*. J Clin Hypertens, 17: 244.

     Impact Factor: 2.549 [Letter to the Editor; <u>non peer-reviewed</u>]

Fülöp T, Tapolyai M, Dossabhoy NR. (2013) *Timing of Continuous Renal Replacement Therapy Initiation in Septic Shock and Acute Kidney Injury*. Ther Apher Dial, 17: 642-643.

     Impact Factor: 1.532 [Letter to the Editor; <u>non peer-reviewed</u>]

6.3 Peer-reviewed publications unrelated to the proposed Thesis

Li M, Li Y, Weeks O, Mijatovic V, Teumer A, Huffman JE, Tromp G, Fuchsberger C, Gorski M, Lyytikäinen LP, Nutile T, Sedaghat S, Sorice R, Tin A, Yang Q, Ahluwalia TS, Arking DE, Bihlmeyer NA, Böger CA, Carroll RJ, Chasman DI, Cornelis MC, Dehghan A, Faul JD, Feitosa MF, Gambaro G, Gasparini P, Giulianini F, Heid I, Huang J, Imboden M, Jackson AU, Jeff J, Jhun MA, Katz R, Kifley A, Kilpeläinen TO, Kumar A, Laakso M, Li-Gao R, Lohman K, Lu Y, Mägi R, Malerba G, Mihailov E, Mohlke KL, Mook-Kanamori DO, Robino A, Ruderfer D, Salvi E, Schick UM, Schulz CA, Smith AV, Smith JA, Traglia M, Yerges-Armstrong LM, Zhao W, Goodarzi MO, Kraja AT, Liu C, Wessel J; CHARGE Glycemic-T2D Working Group,.; CHARGE Blood Pressure Working Group,.. Boerwinkle E, Borecki IB, Bork-Jensen J, Bottinger EP, Braga D, Brandslund I, Brody JA, Campbell A, Carey DJ, Christensen C, Coresh J, Crook E, Curhan GC, Cusi D, de Boer IH, de Vries AP, Denny JC, Devuyst O, Dreisbach AW, Endlich K, Esko T, Franco OH, **Fulop T**, Gerhard GS, Glümer C, Gottesman O, Grarup N, Gudnason V, Harris TB, Hayward C, Hocking L, Hofman A, Hu FB, Husemoen LL, Jackson RD, Jørgensen T, Jørgensen ME, Kähönen M, Kardia SL, König W, Kooperberg C, Kriebel J, Launer LJ, Lauritzen T, Lehtimäki T, Levy D, Linksted P, Linneberg A, Liu Y, Loos RJ, Lupo A, Meisinger C, Melander O, Metspalu A, Mitchell P, Nauck M, Nürnberg P, Orho-Melander M, Parsa A, Pedersen O, Peters A, Peters U, Polasek O, Porteous D, Probst-Hensch NM, Psaty BM, Qi L, Raitakari OT, Reiner AP, Rettig R, Ridker PM, Rivadeneira F, Rossouw JE, Schmidt F, Siscovick D, Soranzo N, Strauch K, Toniolo D, Turner ST, Uitterlinden AG, Ulivi S, Velayutham D, Völker U, Völzke H, Waldenberger M, Wang JJ, Weir DR, Witte D, Kuivaniemi H, Fox CS, Franceschini N, Goessling W, Köttgen A, Chu AY. (2017) *Two loci identified through large-scale exome chip meta-analysis, SOS2 and ACP1, show evidence for altered kidney development*. J Am Soc Nephrol, 28: 981-994.

     Impact Factor: 8.491

Akula YV, <u>**Fülöp T***</u>, Dixit MP. (2017) *Peritoneal Dialysis in Class 2-3 Obesity – A Single-Center Experience.* Am J Med Sci, 353:70-75. *Dr Fülöp corresponding Author

     Impact Factor: 1.575

Afshan S, Farah Musa AR, Lerant AA, Echols V, **Fülöp T**. (2017) *Persisting Hypocalcemia after Surgical Parathyroidectomy: The Differential Effectiveness of Calcium-Citrate vs. Calcium-Carbonate with Acid Suppression.* Am J Med Sci, 353: 82-86.

Impact Factor: 1.575

Molnar MZ, Nagy K, Remport A, Tapolyai MB, **Fülöp T**, Kama F, Kovesdy CP, Mucsi I, Mathe Z. (2016) *Inflammatory Markers and Outcomes in Kidney Transplant Recipients*. Transplantation (E-pub date: Oct 28, 2016; DOI: 10.1097/TP.0000000000001548)

Impact Factor: 3.690

Arany I, Carter A, Hall S, **Fulop T**, Dixit MP. (2017) *Coenzyme Q10 protects renal proximal tubule cells against nicotine-induced apoptosis through induction of p66shc-dependent antioxidant responses*. Apoptosis, 22: 220-228.

Impact Factor: 3.592

Molnar MZ, Nagy K, Remport A, Gaipov A, **Fülöp T**, Czira ME, Kovesdy CP, Mucsi I, Mathe Z. (2017) *Association between Serum Leptin Level and Mortality in Kidney Transplant Recipients.* J Ren Nutr, 27: 53-61.

Impact Factor: 2.090

Fülöp T, Zsom L, Rodríguez B, Afshan S, Davidson JV, Szarvas T, Dixit MP, Tapolyai MB, Rosivall L. (2017) *Preserved Effectiveness of Potassium-Sparing Diuretics in Peritoneal Dialysis Patients to Maintain Normal Serum Potassium*. Perit Dial Int, 37: 63-69.

Impact Factor: 1.298

Young BA, Katz R, Boulware E, Kestenbaum B, de Boer I, Wang W, **Fülöp T**, Bansal N, Robinson-Cohen C, Griswold M, Correa A. (2016) *Risk Factors for Rapid Renal Function Decline and Incident Chronic Kidney Disease (CKD) among African Americans: The Jackson Heart Study (JHS).* Am J Kidney Dis, 68: 229-239.

Impact Factor: 6.269

Humayun Y, Ball KC, Lerant AA, Lewin JR, **Fülöp T**. (2015) *Acute Oxalate Nephropathy Associated with Orlistat*. J Nephropathol, 5: 79-83.

Cade BE, Gottlieb DJ, Lauderdale DS, Bennett DA, Buchman AS, Buxbaum SG, DeJager PL, Evans DS, **Fülöp T**, Gharib SA, Johnson WC, Larkin EK, Lim AS, Punjabi NM, Saxena R, Tranah GJ, Weng J, Zee PC, Patel SR, Zhu X, Redline S. (2016) *DRD2 is Associated with Sleep Duration: The CARe Consortium.* Hum Mol Genet, 25: 167-79.

Impact Factor: 5.985

Zsom L, Wagner L, **Fülöp T**. (2015) *Minimization vs. Tailoring - Where Do We Stand with Personalized Immunosuppression during Renal Transplantation in 2015?* World J Transplant, 5: 73-80.

Farah Musa AR, **Fülöp T**, Kokko K, Kanyicska B, Lewin JR, Csongrádi É. (2015) *Cytomegalovirus Colitis in a Critically Ill, Dialysis-dependent Acute Kidney Injury Patient without Immunosuppressive Therapy.* Clin Nephrol, 84: 44-49.

      Impact Factor: 1.065

Humayun Y, Sanchez P, Norris LT, Monga D, Lewin J, **Fülöp T**. (2015) *Kidney Biopsy for Renal Tubular Acidosis: When Tissue Diagnosis Makes a Difference.* Clin Nephrol – Case Studies 5: 79–83.

Wang W, Griswold ME, Young BA, de Boer IH, Katz R, **Fülöp T**, Correa A, Boulware E. (2015) *Effects of Serum Creatinine Calibration on Estimated Renal Function in African Americans: the Jackson Heart Study.* Am J Med Sci, 349: 379-384.

      Impact Factor: 1.575

Fülöp T, Csongrádi É, Lerant AA, Lewin M, Lewin JR. J Nephropathol. (2015) *Resolution of C1q Deposition but not of the Clinical Nephrotic Syndrome after Immuno-modulating Therapy in Focal Sclerosis.* J Nephropathol, 4: 54-58.

Gharaibeh KA, Brewer JM, Agarwal M, **Fülöp T**. (2015) *Risk Factors, Complication and Measures to Prevent or Reverse Catastrophic Sodium Overcorrection in Chronic Hyponatremia.* Am J Med Sci. 2015, 349: 170-175.

      Impact Factor: 1.575

Gottlieb DJ, Hek K, Chen Th, Watson NF, Eiriksdottir G, Byrne EM, Cornelis M, Warby SC, Bandinelli S, Cherkas L, Evans DS, Grabe HJ, Lahti J, Li M, Lehtimaki T, Lumley T, Marciante KD, Perusse L, Psaty BM, Robbins J, Tranah GJ, Vink JM, Wilk JB, Stafford JM, Bellis C, Biffar R, Bouchard C, Cade B, Curhan GC, Eriksson JG, Ewert R, Ferrucci L, **Fulop T**, Gehrman PR, Goodloe R, Harris TB, Heath AC, Hernandez D, Hofman A, Hottenga JJ, Hunter DJ, Jensen MK, Johnson AD, Kahonen M, Kao L, Kraft P, Larkin EK, Lauderdale DS, Luik AI, Medici M, Montgomery GW, Palotie A, Patel SR, Pistis G, Porcu E, Quaye L, Raitakari O, Redline S, Rimm EB, Rotter JI, Smith AV, Spector TD, Teumer A, Uitterlinden AG, Vohl MC, Widen E, Willemsen G, Young T, Zhang X, Liu Y, Blangero J, Boomsma DI, Gudnason V, Hu F, Mangino M, Martin NG, O'Connor GT, Stone KL, Tanaka T, Viikari J, Gharib SA, Punjabi NM, Raikkonen K, Volzke H, Mignot E, Tiemeier H. (2014) *Novel loci associated with usual sleep duration: the CHARGE Consortium Genome-Wide Association Study.* Mol Psychiatry, 20: 1232–1239.

      Impact Factor: 13.314

Tapolyai M, Faludi M, Barna I, Dossabhoy NR, Lengvárszky Z, Szarvas T, Berta K, **Fülöp T**. (2014) *Diuretics and bioimpedance-measured fluid spaces in hypertensive patients.* J Clin Hypertens, 16: 895–899.

      Impact Factor: 2.851

Fülöp T, Alemu B, Dossabhoy NR, Bain JH, Pruett DE, Szombathelyi A, Dreisbach AW, Tapolyai, M. (2014) *The Safety and Efficacy of Percutaneous Renal Biopsy by Physician-in-Training in an Academic Teaching Setting.* South Med J, 107: 520-525.

      Impact Factor: 0.927

Csongrádi É, Shoemaker-Moyle M, Zsom L, Wells C, Lengvárszky Z, Tapolyai M, **Fülöp T**. (2014) *Investigation of the Efficacy of Intravenous versus Subcutaneous Recombinant Erythropoietin in Obese African-American patients in a Southeast U.S. Dialysis Cohort.* Br J Med Medic Res, 4: 184-193.

Gharaibeh KA, Craig MJ, Koch CA, Lerant AA, **Fülöp T**, Csongrádi É. (2013) *Desmopression is an Effective Adjunct Treatment for Reversing Excessive Hyponatremia Overcorrection.* World J Clin Cases 1: 155-158.

Fülöp T, Iboaya BU, Avusula R, Csongrádi É, Juncos LA. (2013) *Recalcitrant Hypoglycemia Resolved with 2.5% Dextrose Containing Replacement Fluid during Hemodiafiltration.* Ren Fail, 35: 1035–1037.

Hui X, Matsushita K, Sang Y, Ballew SH, **Fülöp T**, Coresh J. (2013) *CKD and Cardiovascular Disease in the Atherosclerosis Risk in Communities (ARIC) Study: Interactions with Age, Sex, and Race.* Am J Kidney Dis, 62: 691-702.

Impact Factor: 5.756

Agarwal M, Csongrádi É, Koch CA, Juncos LA, Echols V, Tapolyai M, **Fülöp T**. (2013) *Severe Symptomatic Hypocalcemia after Denosumab Administration in an End-Stage Renal Disease Patient on Peritoneal Dialysis with Controlled Secondary Hyperparathyroidism.* Br J Med Medical Res, 3: 1398-1406.

 Avusula R, Shoemaker-Moyle M, Pathak MB, Csongrádi É, **Fülöp T**. (2013) *Bacterial Peritonitis following Esophagogastro-duodenoscopy in a patient on peritoneal dialysis.* Br J Med Medical Res, 3: 784-789.

Patel SR, Goodloe R, De G, Kowgier M, Larkin E, Young T, Buxbaum S, **Fulop T**, Gharib S, Gottlieb DJ, Johnson C, Lauderdale D, Punjabi NM, Zee P, Cade B, Laird N, Mukherjee S, Palmer L, Zhu X, Redline S. (2012) *Association of genomic loci with sleep apnea in European Americans and African-Americans: The Candidate Gene Association Resource (CARe).* PLoS ONE, 7: e48836.

Impact Factor: 3.730

Gharaibeh KA, Csongrádi É, Shoemaker-Moyle M, Lerant AA, Tapolyai M, **Fülöp T**. (2012) *Pulmonary Embolization in Face of Tunneled Catheter-Associated Blood Stream Infection; the Perils of Systemic Anticoagulation.* Nephrol Rev, 4: e17.

***Fulop T**, *Hickson DM, Wyatt SB, Bhagat R, Rack N, Gowdy O, Jr., Flessner MF, Taylor HA. (2012) *Sleep-Disordered Breathing Symptoms among African-Americans in the Jackson Heart Study.* Sleep Med, 13: 1039-1049. *Authors contributed to the article equally; Dr Fülöp corresponding Author

Impact Factor: 3.487

Hamrahian M, Pitman KT, Csongrádi É, Bain J, Kanyicska B, **Fülöp T**. (2012) *Symmetrical Craniofacial Hypertrophy in Patients with Tertiary Hyperparathyroidism and High-dose Cinacalcet Exposure.* Hemodial Int, 16: 571-576.

Impact Factor: 1.440

Chandrashekar KB, **Fulop T**, Juncos LA. (2012) *Medical Prevention of Nephrolithiasis*. Am J Med, 125: 344-347.

Impact Factor: 4.768

Zsom M, **Fülöp T***, Zsom L, Baráth Á, Maróti Z, Endreffy E. (2011) *Genetic Polymorphisms and the Risk of Progressive Renal Failure in Elderly Hungarian Patients*. Hemodial Int, 15: 501-8. *Dr. Fülöp corresponding Author

Impact Factor: 1.543

Csongrádi É, Nagy B, Jr, **Fulop T**, Varga Z, Karányi Z, Magyar MT, Oláh L, Papp M, Facskó A, Kappelmayer J, Paragh G, Káplár M. (2011) *Increased level of platelet activation markers is positively associated with carotid wall thickness in obese patients.* Thromb Haemost, 106: 567–752.

Impact Factor: 5.044

Akoudad S, Szklo M, McAdams MA, **Fulop T**, Hong W, Kao L, Coresh J, Köttgen A. (2010) *Correlates of kidney stone disease in a multi-ethnic middle aged population: The ARIC Study.* Preventive Med, 51:416-420.

Impact Factor: 3.299

Tapolyai M, Uysal A, Dossabhoy NR, Zsom L, Szarvas T, Lengvárszky Z, **Fülöp T***. (2010) *High Prevalence of Liddle's Syndrome Phenotype Among Hypertensive U.S. Veterans in Northwest Louisiana.* J Clin Hypertens, 12: 856-860. *Dr. Fülöp corresponding Author

Impact Factor: 2.230

*Islam N, ***Fulop T**, Zsom L, Miller E, Mire CD, Lebrun CJ, Schmidt DW. (2010) *Do Platelet Function Analyser-100 Testing Results Correlate with Bleeding Events after Percutaneous Renal Biopsy?* Clin Nephrol, 73: 229-237. *Authors contributed to the article equally; Dr. Fülöp corresponding Author

Impact Factor: 1.058

Fulop T, Olivier J, Meador RS, Hall J, Islam N, Mena L, Henderson H, Schmidt DW. (2010) *Screening for Chronic Kidney Disease in the Ambulatory HIV Population*. Clin Nephrol, 73: 190-196.

Impact Factor: 1.058

Flessner MF, Wyatt SB, Akylbekova EL, Coady S, **Fulop T**, Lee F, Taylor HA, Crook E. (2009) *Prevalence and awareness of CKD among African Americans: the Jackson Heart Study.* Am J Kidney Dis, 53: 238-247. Erratum in: Am J Kidney Dis (2009) 53: 721.

Impact Factor: 5.152

Bash LD, Coresh J, Köttgen A, Parekh RS, **Fulop T,** Wang Y, Astor BC. (2009) *Defining Incident Chronic Kidney Disease in the Research Setting: The ARIC Study.* Am J Epidemiol, 170: 414-424.

Impact Factor: 5.589