Impact of fluid status and inflammation and their interaction on survival: a study in an international hemodialysis patient cohort

OPEN

Marijke J.E. Dekker[1,2], Daniele Marcelli[3], Bernard J. Canaud[3], Paola Carioni[3], Yuedong Wang[4], Aileen Grassmann[3], Constantijn J.A.M. Konings[2], Peter Kotanko[5,6], Karel M. Leunissen[1], Nathan W. Levin[5,6], Frank M. van der Sande[1], Xiaoling Ye[5], Vaibhav Maheshwari[5], Len A. Usvyat[5,7] and Jeroen P. Kooman[1]; for the MONDO Initiative

[1]*Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Center, Maastricht, Netherlands;* [2]*Department of Internal Medicine, Division of Nephrology, Catharina Hospital Eindhoven, Netherlands;* [3]*Fresenius Medical Care, Bad Homburg, Germany;* [4]*University of California, Santa Barbara, Santa Barbara, California, USA;* [5]*Renal Research Institute, New York, New York, USA;* [6]*Icahn School of Medicine at Mount Sinai Health System, New York, New York, USA; and* [7]*Fresenius Medical Care North America, Waltham, Massachusetts, USA*

In hemodialysis patients extracellular fluid overload is a predictor of all-cause and cardiovascular mortality, and a relation with inflammation has been reported in previous studies. The magnitude and nature of this interaction and the effects of moderate fluid overload and extracellular fluid depletion on survival are still unclear. We present the results of an international cohort study in 8883 hemodialysis patients from the European MONDO initiative database where, during a three-month baseline period, fluid status was assessed using bioimpedance and inflammation by C-reactive protein. All-cause mortality was recorded during 12 months of follow up. In a second analysis a three-month baseline period was added to the first baseline period, and changes in fluid and inflammation status were related to all-cause mortality during six-month follow up. Both pre-dialysis estimated fluid overload and fluid depletion were associated with an increased mortality, already apparent at moderate levels of estimated pre-dialysis fluid overload (1.1–2.5L); hazard ratio 1.64 (95% confidence interval 1.35–1.98). In contrast, post-dialysis estimated fluid depletion was associated with a survival benefit (0.74 [0.62–0.90]). The concurrent presence of fluid overload and inflammation was associated with the highest risk of death. Thus, while pre-dialysis fluid overload was associated with inflammation, even in the absence of inflammation, fluid overload remained a significant risk factor for short-term mortality, even following improvement of fluid status.

Kidney International (2017) **91,** 1214–1223; http://dx.doi.org/10.1016/j.kint.2016.12.008

KEYWORDS: body composition; fluid status; hemodialysis; inflammation

Correspondence: *Marijke Dekker, Department of Internal Medicine, Division of Nephrology, Maastricht University Medical Center, Post Box 5800, 6202 AZ Maastricht, Netherlands. E-mail: mje.dekker@gmail.com*

Received 28 July 2016; revised 14 November 2016; accepted 1 December 2016; published online 13 February 2017

In dialysis patients, the presence of extracellular fluid overload (FO) is associated with hypertension and left ventricular hypertrophy, while reversal of FO improves blood pressure (BP) and cardiac remodeling.[1,2] Recent studies have shown that severe FO, defined as an expansion of the extracellular fluid by more than 15% (around 2.5 L in a person weighing 70 kg), is associated with lower survival in both hemodialysis (HD) and peritoneal dialysis patients.[3–5] However, whether lower degrees of FO are also associated with mortality or the risk associated with FO increases incrementally with higher levels of FO has yet to be studied. Moreover, circumstantial evidence suggests that fluid depletion (FD) is also associated with adverse outcomes.[6] This is a highly relevant clinical question, because FD may contribute to intradialytic hypotension, impaired organ perfusion, and cardiac stunning.[7] Also, high ultrafiltration volumes required to normalize extracellular fluid volumes are associated with increased mortality[8] and can lead to postdialysis FD. The association between depleted fluid status and mortality has not been investigated previously.

Importantly, the hazards of abnormal fluid status may be modified by inflammation. Smaller studies have shown that inflammation, as reflected by increased C-reactive protein (CRP) levels, is associated with indicators of FO.[9,10] However, it is not known to what extent the concurrent presence of FO and inflammation is associated with an increased mortality risk, or whether the mortality risk of FO persists after adjustment for inflammation. Moreover, the nature and time line of this interaction has yet to be studied. Whereas FO might lead to inflammation (e.g., because of translocation of endotoxins through an edematous bowel[7]), inflammation might conversely precede FO (e.g., due to a reduction in lean body mass which, if undetected, may result in inadequate dry weight prescription).

This study in a multinational HD population had 3 goals. Firstly, to investigate the association between both moderate and severe FO and that of FD with all-cause mortality. Secondly, to assess the joint and separate effects of inflammation and fluid status on survival. Lastly, to identify the dynamic interaction of these parameters.

RESULTS

We included 8883 patients with a median age of 63 years, 57.2% male, and a median dialysis vintage of 3.6 years (Table 1 and Figure 1). Patient characteristics stratified by predialysis fluid status are presented in Table 2.

Categorical analysis of mortality risk associated with different levels of fluid state

In the adjusted analysis, levels of predialysis FO were associated with risk of death. Compared to normovolemia, hazard ratios (HR) for mortality increased from 1.64 (95% confidence interval [CI]: 1.35–1.98) in the group with moderate FO to 4.23 (95% CI: 3.16–5.65) in patients with extreme FO (Figure 2a). In addition, predialysis FD was also associated with increased mortality (HR: 2.03, 95% CI: 1.32–3.12). The association between fluid status and mortality was confirmed in a second analysis in which predialysis fluid status was divided by normohydration weight on a patient base level. The association with mortality was assessed via quantiles, and the same trend of incrementally increased risk of death with higher levels of fluid overload and with fluid depletion was observed (data not shown).

Predialysis systolic BP increased incrementally with fluid status. It was lowest in the predialysis FD group, and highest in patients with the most extreme FO (Table 2). CRP was lowest in the normovolemia group, and increased incrementally with both FO and FD. Serum albumin levels decreased with increasing FO. Inter-dialytic weight gain (IDWG) and ultrafiltration rate (UFR) were the lowest in predialysis normovolemic patients and increased with both predialysis FO and FD, with the longest treatment time in the group with extreme FO predialysis (Table 2). The number of baseline multifrequency bioimpedance spectroscopy (MF-BIS) measurements did not materially affect the results (data not shown).

Table 1 | Demographic characteristics at baseline for the total cohort ($N = 8883$) and subgroup ($N = 5450$)

Variable	Total cohort Mean (SD)	Dynamic cohort Mean (SD)
Age (yr)	63 (14.8)	61.7 (15.6)
Males	57.2%	56.7%
Dialysis vintage (yr)	3.6 (1.6–6.9)	3.7 (1.8–7.2)
Diabetes Mellitus	17.1%	17.7%
Catheter access	18.6%	15.5%
Northern Europe[a]	21 (0.2%)	3 (0.1%)
Eastern Europe[a]	4145 (46.7%)	3116 (57.2%)
Western Europe[a]	333 (3.7%)	133 (2.4%)
Southern Europe[a]	4384 (49.4%)	2198 (40.3%)

[a]Stratification for the 4 regions within Europe was based on the United Nations geographic scheme.

When the calculated postdialysis fluid status was analyzed, the same trend of an increasing risk of death by increasing levels of postdialysis FO was observed (Figure 2b). With regard to BP, the same trend of increasing BP with higher level of fluid overload was observed both before and after dialysis (Table 2). However, postdialysis FD was associated with significantly *better* survival compared with postdialysis normovolemia (HR: 0.74, 95% CI: 0.62–0.90) (Figure 2b). The majority of patients with postdialysis FD were normovolemic before dialysis, but a small percentage of patients also originated from the predialysis moderate and extreme FO groups (Figure 3).

Concurrent presence of FO and inflammation

Concurrent presence of inflammation and FO increased the risk of death in a dose-dependent fashion. Predialysis FD concomitant with inflammation was also associated with a higher mortality risk. In patients with predialysis severe FO in whom no inflammation was present, the HR was 3.09 (95% CI: 2.20–4.36); the HR increased to 6.02 (95% CI: 4.41–8.23) when inflammation was present (Table 3). Also in the normovolemia group, an increased risk was observed when inflammation was present (HR: 2.53, 95% CI: 1.81–3.53).

Dynamic interactions between fluid and inflammatory status

In this part of the study we included 5450 patients, 56.7% female, 17.7% with diabetes, and 84.5% with an arterio-venous fistula (Table 1). The highest percentage of patients (40.9%, $n = 2228$) was categorized into the FO^-/inflammation not present (I^-) group and the lowest percentage (13.4%, $n = 732$) into the FO^+/I^- group (Figure 4). Patients in the FO^-/I^- group were younger, more often female, and had higher hemoglobin, albumin, creatinine, and normalized protein catabolic rate (nPCR). They were also less likely to have diabetes, and their predialysis BP was lower than patients categorized into any of the FO^+ groups. A subset analysis in patients in the first year of dialysis showed materially identical results, with equal distribution over all groups (Supplementary Material B).

Changes in fluid and inflammation status between the first and second baseline periods. Figure 4 depicts patients switching between the different groups. In general, the majority of patients remained in the same group throughout the study period. Of the 773 patients in the FO^+/I^+ group, 10.7% changed to the FO^-/I^- group in the second period. Of the 1717 patients in the FO^-/I^+ group in baseline period 1, 12.5% experienced FO in the subsequent period (switched to the FO^+/I^+ group and FO^+/I^- groups), whereas of the 732 FO^+/I^- patients, 26.8% experienced inflammation during follow-up.

In a subset analysis with patients stratified by access type, starting in the FO^-/I^- group was significantly less frequent in patients with catheter access (32.1%) compared to those with an arteriovenous fistula (42.5%) ($P < 0.001$). They also more frequently remained in 1 of the inflammation groups (Supplementary Material C).

Change in fluid and inflammation status and its association with mortality. Patients who continued to experience inflammation and FO were at highest risk of death (HR: 9.44,