Dynamics of hospitalizations in hemodialysis patients: results from a large US provider

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ABSTRACT

Background and objectives. In chronic hemodialysis (HD), patients’ hospitalizations result in significant costs and affect the quality of life. We aimed at understanding hospitalization rates before death and to identify patterns in clinical and laboratory parameters that precede the first hospitalization.

Design, setting, participants and measurements. We conducted two separate analyses in patients treated in the 51 US Renal Research Institute HD facilities. The first analysis involved hospitalizations before death in all HD patients who died between 1 January 2007 and 31 December 2011. In the second analysis, we studied the evolution of laboratory and treatment parameters before hospitalization in all patients with, at least, one hospital admission between 1 January 2007 and 31 December 2011. Patients were followed from up to 6 months prior to their first hospital admission. For comparison, we selected non-hospitalized patients and observed the evolution of their laboratory and treatment parameters.

Results. We studied 6262 patients in total. The first analysis encompassed 2058 deaths. In these patients, hospitalization increased from 0.32 admissions per patient-month 4 months before death to 1.85 in the month of death. In the second analysis, we studied the evolution of laboratory and treatment parameters before hospitalization in all patients with, at least, one hospital admission between 1 January 2007 and 31 December 2011. Patients were followed from up to 6 months prior to their first hospital admission. For comparison, we selected non-hospitalized patients and observed the evolution of their laboratory and treatment parameters.

Conclusions. Hospitalization rates increase sharply before death. Months before the first hospitalization changes in clinical and laboratory parameters ensued. These results suggest that models aiming at predicting hospitalization should include indicators capturing the dynamics of relevant parameters.

Keywords: epidemiology, hemodialysis, hospitalization, outcome, predictions

INTRODUCTION

Hospitalization rates in hemodialysis (HD) patients appear to have remained stable during the past decade, while a gradual improvement in mortality has been observed. Hospitalizations affect the quality of life in HD patients [1, 2] and have profound economic consequences. It has been estimated that approximately one-third of the total expenditure in end-stage renal disease patients results from hospital costs [1, 2]. Moreover, hospitalization heralds an increased probability of death for patients. A recent study showed that the risk of death during hospitalization was increased for patients with chronic kidney disease, and even more so for HD patients when compared with the general population [3, 4]. Clinical experience indicates that the number of hospitalizations increases before death. Therefore, the hospital admission rate is likely to be an important prognostic parameter for the outcome. However, in HD patients, the relationship between the rate of hospitalizations and mortality has not yet been addressed quantitatively.

Timely identification of dialysis patients at risk for hospitalization might aid preventive strategies. Various studies have analyzed risk factors for non-elective hospital admissions both in dialysis and in pre-dialysis patients using patient characteristics, laboratory and clinical parameters taken at a single point in time [5, 6]. Although this cross-sectional approach can identify which patients are at risk for future events, it cannot predict at which time the event will occur. By using a different approach, we were able to identify dynamic trends in important physiological and laboratory parameters before death [7, 8]. Using this methodology, death was used as the starting point, and the behavior of predictive variables was analyzed using a backward approach. Applying this approach, we...
observed an accelerated decline in key parameters such as albumin, systolic blood pressure (SBP) and inter-dialytic weight gain next to increases in C-reactive protein as early as 40 weeks before death [8]. We believe that studies of the dynamic behavior of clinical and laboratory markers before hospitalization, using the approach of our previous paper [8], may aid in the development of prediction systems to timely identify patients at risk. We hypothesize that changes in important patient parameters also occur before hospitalization.

The first aim of the present analysis was to study the dynamics of hospitalization rates before death and to describe the dynamics of selected clinical and laboratory parameters before death in a large cohort of US HD patients. The second goal was to identify dynamic patterns in clinical and laboratory parameters before the first hospitalization episode.

**MATERIALS AND METHODS**

As indicated in the study flow chart (Figure 1), we conducted two separate analyses:

**Hospitalization rates before death in relation to dynamics of clinical and laboratory parameters**

For the analysis of the hospitalization rates before death, we studied all in-center HD patients treated in 51 Renal Research Institute (RRI) clinics, who died between 1 January 2007 and 31 December 2011. Only the patients who were dialyzed, at least, 24 months prior to death were included in this analysis (Figure 1, left). Although this time frame is to some degree arbitrary, a longer time period was chosen in order to properly assess when the change in hospital admissions happens most precipitously. The averages of hospital admission rates were computed monthly in the 24 months prior to death. Hospitalizations related to kidney transplant procedures were excluded from the analysis ($N = 43$). Causes of death were classified based on ICD-9 documented diagnosis into four categories: cardiovascular disease (CVD), infection, neoplasm and other. Hospital admissions were categorized based on the primary discharge diagnosis as access related, fluid overload, CVD other than fluid overload, infections and other causes. Other CVD include hospitalizations for chest pain, hypo- and hypertension, cardiac arrest, atrial fibrillation and others.

Hospital admission rates were computed monthly prior to death based on the number of admissions and the number of patient-months. Averages of patient laboratory and treatment parameters were computed per patient per month prior to death [pre-dialysis systolic blood pressure (pre-dialysis SBP), pre-dialysis body temperature, intra-dialytic change in blood pressure, inter-dialytic weight gain, effective treatment time, average saline use, hemoglobin, albumin and neutrophil-to-lymphocyte ratio (NLR)].

**Dynamics in clinical and laboratory parameters before first hospitalization**

All in-center HD patients treated in the 51 RRI clinics who were hospitalized, at least, once between 1 January 2007 and 31 December 2011 were included in this analysis. First hospitalization per patient during the period was noted and patients’ laboratory and treatment parameters for the 6 months prior to this date of first hospitalization were obtained. Patients who had $<$70 treatments and who were transferred to a non-RRI clinic in any of the 26 weeks prior to hospitalization were excluded (Figure 1, Right). Causes of hospitalization were divided into five groups as was done in Part 1. Hospitalizations related to kidney transplantation were excluded ($n = 131$).

As a comparison group, we identified patients with vintage equal to the mean vintage of the hospitalized patients (mean = 4.1 years) and computed mean of patients’ laboratory and treatment parameters in a 6-month period between Months 43 and 49, i.e. the 6 months prior to the end of the 4.1 years. Only patients who had no hospitalization in this 6-month period were selected.

Laboratory results were automatically downloaded into the RRI data base from a central laboratory (Spectra Laboratories, Rockleigh, NJ). Blood pressure, body temperature and body weight were recorded by the dialysis clinic staff. No imputation of laboratory or treatment parameters was done if patients missed their treatments—only recorded data were used. A record of hospital admission is made by the clinic staff and those are required when a patient missed at least one treatment. Both automatic and manual procedures were put in place to identify and correct data entry errors. Monthly

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**FIGURE 1:** Study flowchart.
averages of individual patient laboratory and treatment parameters were computed prior to hospitalization. Linear mixed-effects models (LMMs) were constructed for each treatment and laboratory parameters with months to hospitalization as a predictor and fixed and random effects accounting for inter- and intra-patient variability. Penalized cubic B-spline functions were graphed for variables that changed significantly prior to hospitalization based on LMMs slopes; ninety-five percent confidence intervals for the spline functions are also presented to demonstrate which changes are significant [9]. The analyses were conducted in SPSS version 18 (IBM, Somers, NY) and SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Hospitalization rates before death in relation to dynamics of clinical and laboratory parameters

We analyzed 2058 deaths: 1366 (66%) were CVD-related, 301 (15%) were infection-related, 125 (6%) were due to neoplasms and 266 (13%) were for other causes. Hospital admission rates increased exponentially from 0.17 admissions per patient-month 24 months prior to death to 1.85 admissions per patient-month in the month of death, representing an 11 times increase in hospitalization rates (Figure 2, Left). This increase was independent of the cause of hospitalization (Figure 2, right) with the notable exception of vascular access interventions, which did not increase prior to death. Hospitalizations due to ‘other CVD’ causes increased >16 times from 0.03 to 0.55 admissions per patient-month between 24 months prior to death and the month of death. Hospitalizations due to infections, fluid overload and other reasons increased 9–11 times between 24 months prior to and the month of death. The increase in the number of hospital admissions was similar to patients who had 12 or more months of follow up before death (data not shown).

Analysis of hospital admissions by cause of death indicated comparable patterns: patients who died of CVD had the highest hospital admission rate before death (1.11 admissions per patient-month), while those who died of neoplasms had the lowest number of admissions (0.12 admissions per patient-month).

In addition to exponential increases in hospital admissions prior to death, other laboratory and patient treatment parameters showed notable patterns before death: the mean albumin levels dropped from 3.8 to 3.5 g/dL, pre-dialysis SBP dropped from 151 to 137 mmHg and NLR increased from 4.3 to 7.0 in the 24 months before death (Figure 3). Patient demographics are presented in Table 1.

Dynamics in clinical and laboratory parameters before the first hospitalization

The primary discharge diagnoses of the first hospital admission in 4204 patients were distributed as follows: access related 291 (7%), fluid overload 467 (11%), infections 820 (19%), CVD unrelated to fluid overload 858 (20%) and 1768 (42%) admissions occurred for other reasons.

Overall slopes of the treatment and laboratory parameters computed using LMMs in the 6 months prior to hospitalization are presented in Table 2. Hospitalization-cause-specific slopes are not presented.

While pre-dialysis SBP did not appear to follow significant trends prior to the first hospital admissions, the intra-dialytic decline in SBP, computed as pre-HD minus post-HD SBP, became less before hospital admission. This reduction was most apparent in patients admitted because of fluid overload (Figure 4). Average intra-dialytic SBP decline dropped from 11.5 to 10.2 mmHg during a 26-week period before hospitalization; the slope of the decline was significant using a LMM.

Inter-dialytic weight gain declined from 2.76 kg at 26 weeks prior to hospitalization to 2.67 kg in the month of hospital admission. The decline was most pronounced in the patients hospitalized for infections. The use of volume of saline administered during HD increased by 7 mL from 460 to 467 mL. The effective treatment time decreased from 215 min 6 months before admission to 213 prior to hospital admission.

While the pre-dialysis body temperature declined in general prior to hospitalizations, it rose from 36.5 to 36.7°C in the 3 weeks prior to hospital admission in patients hospitalized because of infections (data not shown). In the patients hospitalized for infections, an increase in NLR was observed from 3.5 to 5.2 in the 3 months prior to hospitalization. Albumin, however, decreased more gradually; the decline in
albumin was not significant during 6 months but was significant during 3 months prior to admission (data not shown for 3-month decline). In all patients, hemoglobin levels declined on average from 11.9 to 11.7 g/dL, particularly in patients hospitalized for fluid overload.

Patients with the same vintage as the mean vintage in the hospitalized patients (4.1 years), but no hospitalization between Months 43 and 49 served as a control group (n = 1116). In this cohort, no notable patterns in inter-dialytic weight gain, intra-dialytic change in SBP, NLR and Hgb were observed (Figure 4). Because some patients included in the hospitalized analysis above may also be in the non-hospitalized patient cohort of 1116 patients, we excluded patients who may not have been hospitalized at vintage of 4.1 years (n = 588); in a sensitivity analysis; without these patients the results were similar (data not shown). Patient demographic information for hospitalized and non-hospitalized patients is presented in Table 1.

**DISCUSSION**

The outcomes of our study in chronic HD patients are two novel findings: first, hospitalization rates rise sharply before death; second, distinct changes in clinical and laboratory indicators antedate the first hospitalization.

An increase in hospitalization rates before death was observed for most causes (fluid overload, infection related, CVD and other reasons) with the sole exception of non-infectious access-related interventions. In the final 4 months of life, hospitalization rates doubled every 5 to 6 weeks. Notably, the decline in SBP and serum albumin, and the increase in NLR preceded the sharp increase in the hospitalization rate by almost 1 year [7]. An important question beyond the scope of the present study is whether timely diagnostic and therapeutic interventions might prevent this increase in hospitalization rates and subsequent death within a ‘window of opportunity’. One of the possibilities is that at the inflection point indicating the sharp upward trend of the hospitalization rate, patients are already at a stage of irreversible homeostatic breakdown and decline in functional status, in which their ability to cope with external stressors is severely decreased. This would be analogous to an advanced stage of frailty as discussed in the geriatric literature [10]. The presence of frailty and a loss of functional status are strong predictors of mortality in dialysis patients [11].

However, recent data have suggested potentially modifiable risk factors for readmission after hospitalization. Dalrymple et al. [12] showed an increase in hospitalization for CVD causes within 90 days after an infection-related hospitalization procedure, suggesting that increased attention to cardiovascular risk factors, such as fluid overload, might prevent readmission. Chan et al. [2] showed that the optimization of hemoglobin therapy and the administration of vitamin D were associated with reduced risk for readmission. Whether interventions such as intensified dialysis treatment [13, 14], nutritional interventions [15], a meticulous search for infections and cardiovascular dysfunction, optimization of fluid status and active rehabilitation [16] would be able to reduce hospitalization rates needs to be addressed in future clinical trials.

In the second part of the study, we looked in greater detail into dynamic patterns of laboratory, treatment-related and clinical parameters before the first hospitalization. Apparent changes prior to the first hospitalization admissions were observed for a variety of clinical and laboratory parameters. While, in general, these changes were observed for all hospitalization categories, they were less apparent for access-related hospitalization. Body temperature increased 1 to 2 weeks before admission in patients admitted for infections, which is consistent with clinical experience [17]. More remarkable were...
the reduction in effective treatment time, inter-dialytic weight gain and the reduction in intra-dialytic blood pressure changes, as well as an increased volume of saline infusion. These changes were not only observed before infection and CVD-related hospitalizations, but also for hospitalization related to fluid overload. Although conjectural, hemodynamic deterioration related to an emergent illness might reduce tolerance to HD treatment, as indicated by a shortening of effective treatment time and the need for more saline infusions. A reduction in food and fluid intake due to loss of appetite might explain the reduction in inter-dialytic weight gain. In addition, body cell mass may decline due to the emergent illness resulting in fluid overload if dry weight is not adequately adjusted [18]. In turn, the presence of fluid overload combined with a lower ultrafiltration volume might explain the reduction in intra-dialytic blood pressure changes before hospitalization. These mechanisms might be mutually reinforcing, in the sense that the presence of fluid overload provides a further stimulus for cardiovascular and inflammatory events leading to hospitalization [19]. The latter hypothesis would fit with the higher risk for cardiovascular hospitalization following infection-related admissions observed by Dalrymple et al. [12].

With regard to the change in laboratory parameters, a decline in hemoglobin and albumin levels was observed 1 to 2 months before hospitalization. This analysis is more limited as

Table 2. Mean patient and laboratory parameters 6 months before and month of hospital admission and average monthly change in these parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Average 6 months before hospital admissions (units/month)</th>
<th>Average in the month of hospital admission (units/month)</th>
<th>LMM monthly slope (95% CI) (units/month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intra-dialytic change in SBP (mmHg)</td>
<td>11.4 (27.67)</td>
<td>10.2 (30.2)</td>
<td>−0.09 (−0.17 to −0.01)</td>
</tr>
<tr>
<td>Inter-dialytic weight gain (kg)</td>
<td>2.76 (1.5)</td>
<td>2.67 (1.51)</td>
<td>−0.009 (−0.013 to −0.005)</td>
</tr>
<tr>
<td>NLR</td>
<td>3.7 (3.48)</td>
<td>4.5 (4.17)</td>
<td>0.08 (0.04 to 0.13)</td>
</tr>
<tr>
<td>Hgb (g/dL)</td>
<td>11.87 (1.43)</td>
<td>11.65 (1.48)</td>
<td>−0.04 (−0.04 to −0.03)</td>
</tr>
<tr>
<td>Albumin (g/dL)</td>
<td>3.86 (0.4)</td>
<td>3.87 (0.38)</td>
<td>0.001 (−0.001 to 0.002)</td>
</tr>
<tr>
<td>Treatment time (min)</td>
<td>214.6 (30.9)</td>
<td>212.9 (33.2)</td>
<td>−0.19 (−0.26 to −0.12)</td>
</tr>
<tr>
<td>pre-dialysis SBP (mmHg)</td>
<td>149.6 (26.5)</td>
<td>149.5 (27.6)</td>
<td>0.03 (−0.06 to 0.12)</td>
</tr>
<tr>
<td>Pre-dialysis body temperature (°C)</td>
<td>36.48 (0.43)</td>
<td>36.48 (0.46)</td>
<td>−0.0016 (−0.0027 to −0.0005)</td>
</tr>
<tr>
<td>Saline use per treatment (mL)</td>
<td>460 (266.3)</td>
<td>467 (254.7)</td>
<td>1.43 (0.79 to 2.08)</td>
</tr>
</tbody>
</table>

Average change is computed from a LMM in the 6 months prior to hospitalization.
in RRI dialysis facilities, these laboratory parameters were assessed only once a month. In addition, a rise in NLR was apparent for all causes of hospitalization, except for access-intervention-related causes. NLR, a parameter of inflammation, was higher before hospitalization in patients admitted for fluid overload when compared with the other hospitalization categories. Fluid overload itself may result in barrier breakdown and subsequent translocation of endotoxins in the gut, and also predispose to pulmonary and skin infections [20]. Previous studies showed a complex relation between inflammation, fluid overload and body composition in dialysis patients [21, 22].

While there is no generally accepted methodology to compare trends in hospitalized and non-hospitalized ‘controls’, we observe no notable patterns in control patients, suggesting that dynamics in hospitalized patients are indeed different.

This study adds to the current body of the literature by analyzing dynamic trends in hospitalization rates and by exploring clinical and laboratory parameters before hospitalization. To the best of our knowledge, this is the first time that dynamic trends in clinical and laboratory parameters before hospitalization have been studied in the dialysis population.

Although the absolute changes in parameters of hospitalized patients are small, it is a mean change in a very large and highly variable group of patients, which was statistically significant. Our aim was to recommend that clinicians should follow trends in patient parameters in addition to its absolute values, even if those changes are small. Obvious limitations of the study are its retrospective nature and the fact that only a small number of clinical and laboratory parameters were assessed. Moreover, the broad categorization of hospitalization-causes may result in a loss of information. Given the structure of the RRI database, we cannot definitely distinguish elective and non-elective hospitalizations. LMMs can be used to further explore the statistical significance of changes before hospitalization at various time intervals; however, the time of the inflection point (the time when the slopes of the trajectories change significantly) needs to be further elucidated. Seasonality of patient parameters may play a role in patient trajectories before hospitalization and should be considered [23]. Finally, the dynamic change in parameters in the entire study population was based on aggregates of patients, not on individual trajectories. With respect to the number of hospital admissions before death, we required that patients had at least 24 months of treatment before their demise; this may introduce a bias because it excludes any patient who died within <24 months on dialysis. As a result, we conducted a sensitivity analysis in patients with 12 months before death and found increases in the number of admissions before death similar to patients who were around for 24 months prior to death.

In conclusion, we observed a sharp increase in hospitalization rates in the months before death, which was preceded by a gradual change in selected clinical and laboratory parameters within 1 year of death. Also, in the period preceding the first hospitalization, a change in clinical, dialysis-related and laboratory parameters was observed. Future studies should elucidate whether dynamic risk models can be developed, which aid the timely identification of patients at risk and which support daily clinical decision-making.

CONFLICT OF INTEREST STATEMENT

P.K., F.W.M. and N.W.L hold stock in Fresenius Medical Care.

(See related article by Fotheringham and Caskey. Predicting hospital admissions by looking backwards: an alternative perspective. *Nephrol Dial Transplant* 2014; 29: 225–227.)

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Children of non-Western origin with end-stage renal disease in the Netherlands, Belgium and a part of Germany have impaired health-related quality of life compared with Western children

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ABSTRACT

Background. Many children with end-stage renal disease (ESRD) living in Western Europe are of non-Western European origin. They have unfavourable somatic outcomes compared with ESRD children of Western origin. In this study, we compared the Health-related Quality of Life (HRQoL) of both groups.

Methods. All children (5–18 years) with ESRD included in the RICH-Q project (Renal Insufficiency therapy in Children- Quality assessment and improvement) or their parents were asked to complete the generic version of the Paediatric Quality-of-Life Inventory 4.0 (PedsQL). RICH-Q comprises the Netherlands, Belgium and a part of Germany. Children were considered to be of non-Western origin if they or at least one parent was born outside Western-European countries. Impaired HRQoL for children with ESRD of Western or non-Western origin was defined as a PedsQL score less than fifth percentile for healthy Dutch children of Western or non-Western origin, respectively.

Results. Of the 259 eligible children, 230 agreed to participate. One hundred and seventy-four children responded (response rate 67%) and 55 (32%) were of non-Western origin. Overall,