


Differences in hospitalisation between peritoneal dialysis and haemodialysis patients

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Abstract

Background: Dialysis is associated with frequent hospitalisations. Studies comparing hospitalisations between peritoneal dialysis (PD) and haemodialysis (HD) report conflicting results and mostly analyse data of patients that remain on their initial dialysis modality. This cohort study compares hospitalisations between PD and HD patients taking into account transitions between modalities.

Methods: The Dutch nocturnal and hoME dialysis Study To Improve Clinical Outcomes collected hospitalisation data of patients who started dialysis between 2012 and 2017. Primary outcome was hospitalisation rate, analysed with a multi-state model that attributed each hospitalisation to the current dialysis modality.

Results: In total, 695 patients (252 PD, 443 HD) treated in 31 Dutch hospitals were included. The crude hospitalisation rate for PD was 2.3 (\pm 5.0) and for HD 1.4 (\pm 3.2) hospitalisations per patient-year. The adjusted hazard ratio for hospitalisation rate was 1.1 (95%CI 1.02–1.3) for PD compared with HD. The risk for first hospitalisation was 1.3 times (95%CI 1.1–1.6) higher for PD compared with HD during the first year after dialysis initiation. The number of hospitalisations and number of hospital days per patient-year were significantly higher for PD. The most common causes of PD and HD hospitalisations were peritonitis (23%) and vascular access-related problems (33%).

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Conclusion: PD was associated with higher hospitalisation rate, higher risk for first hospitalisation and higher number of hospitalisations compared with HD. Since the PD hospitalisations were mainly caused by peritonitis, more attention to infection prevention is necessary for reducing the number of hospitalisations in the future.

KEYWORDS

end-stage kidney disease, haemodialysis, hospitalisation, peritoneal dialysis

1 | INTRODUCTION

Dialysis treatment for end-stage kidney disease (ESKD) is associated with high morbidity, frequently resulting in hospitalisation.¹⁻⁴ The hospitalisation rate of dialysis patients varies between 1.2 and 1.7 per patient-year, compared to 0.8 per patient-year for patients with a kidney transplant.^{2,5} Dialysis patients also have a higher risk of readmission, with a hazard ratio of 1.8 for readmission within one year compared with a control group of patients without kidney disease.^{2,6} Infections and cardiovascular diseases are the leading causes for hospitalisation in dialysis patients.^{2,7,8}

Hospitalisation is an indirect measure of morbidity in dialysis patients, as well as a risk factor for mortality.^{6,9} Also, hospitalisation negatively affects the quality of life and increases the costs of dialysis.^{7,10,11} Hospitalisation costs are one of the most expensive elements of dialysis treatment.¹⁰⁻¹² Therefore, prevention of hospitalisation of dialysis patients is of utmost importance.

Differences in hospitalisation between peritoneal dialysis (PD) and haemodialysis (HD) patients have been the subject of previous studies. However, there are several problems with these studies. First, they report conflicting results with studies describing an equal number and duration of hospital admissions for PD patients compared with HD patients,¹³⁻¹⁶ while other studies conclude that PD patients are more likely to be hospitalised.^{3,5,17-21} Second, most studies do not take into account the time on dialysis, which also seems to affect hospitalisation rates. The hospitalisation rate for HD patients is highest during their first year of dialysis with a decrease thereafter, while PD patients experience an increase in hospitalisation rate as their dialysis duration progresses, according to the 2018 report from the United States Renal Data System (USRDS).² Finally, and most importantly, most studies only analyse data from patients who remain on their initial dialysis modality or do not take transitions between dialysis modalities into account.^{3,13-15,18,19,21} However, a transition from one dialysis modality to another, for example from PD to HD, occurs frequently in daily practice. Analysing only the data of patients who continue their original dialysis modality

introduces selection bias in the results reported. Therefore, the aim of this study was to compare hospitalisations between incident PD and HD patients taking into account transitions between dialysis modalities and time on dialysis.

2 | MATERIALS AND METHODS

2.1 | Study population

The Dutch nocturnal and home dialysis Study To Improve Clinical Outcomes (DOMESTICO) is a multi-centre cohort study among dialysis patients in the Netherlands. For this analysis, retrospectively collected hospitalisation data from a cohort of patients from 31 hospitals were used. Eligible patients were adults (≥ 18 years) who started dialysis treatment (i.e. PD or HD) between 1 January 2012 and 1 January 2017 with a minimum dialysis treatment duration of 3 months. Patients were allowed to have had previous kidney replacement therapy in the form of (dialysis followed by) kidney transplantation. Follow-up of patients was conducted until after kidney transplantation, a patient's wish to stop dialysis, death, or the end of the study period on 1 January 2017. The study was approved by local medical ethics committees of the participating dialysis centres. Reporting of the study conforms to broad EQUATOR guidelines.²²

2.2 | Baseline characteristics

Baseline characteristics were collected at dialysis initiation. For the baseline data, patients were grouped according to their dialysis modality (i.e. PD or HD) at 3 months after dialysis initiation. Primary kidney disease was classified according to the European Renal Association—European Dialysis and Transplant Association (ERA-EDTA) codes and categorised into: glomerulonephritis/pyelonephritis, cystic kidney disease, renovascular kidney disease, diabetes mellitus and other/unknown.²³ Comorbidities were classified according to both the Charlson Comorbidity Index (CCI) and the Davies score.^{24,25} Kidney replacement therapy vintage and dialysis

vintage were presented as the months that patients received kidney replacement therapy (i.e. kidney transplantation and dialysis combined) or dialysis alone in the past. Residual glomerular filtration rate was calculated as the creatinine clearance (ml/min), using creatinine measurements in blood and 24 h urine collections. Patients were indicated as acute starters if they had never been under outpatient monitoring by a nephrologist prior to initiation of dialysis.

2.3 | Hospitalisation

Hospitalisation was defined as a hospital admission with a minimum duration of 24 h. The start and end dates of each hospitalisation were recorded along with the reason using ICD-10 codes.²⁶ The primary outcome was hospitalisation rate, which was defined as the number of hospitalisations per patient-year. Patient-years were defined as the number of years a patient performed a dialysis modality within the study period.

Secondary outcomes were risk for first hospitalisation, total number of hospitalisations per patient, number of hospital days per patient-year and causes of hospitalisation. Causes of hospitalisation were grouped into the following categories: access-related (including vascular access infection, fistula operation and PD catheter leakage, exchange or removal), peritonitis, fluid overload, cardiac disease (including myocardial ischaemia or infarction, cardiac arrest or arrhythmia, cardiac failure and haemorrhagic pericarditis), vascular disease (including pulmonary embolus, stroke, cerebrovascular haemorrhage, ruptured vascular aneurysm, mesenteric infarction and peripheral vascular disease), non-dialysis related infection, gastrointestinal disease (excluding PD peritonitis), malignancy, transplantation and other/unknown.

2.4 | Statistical analysis

Baseline characteristics were presented as mean with standard deviation (SD), median with interquartile range (IQR) or as number with percentages. Groups were compared with a chi-square test, an independent samples *t*-test or Mann–Whitney *U* test, where appropriate.

Since patients can transition between dialysis modalities over time (i.e. PD patients transition to HD or HD patients transition to PD), all analyses were performed with models that allow for such transitions. Hospitalisation rate was analysed with a multi-state model with recurrent events, which attributed every hospitalisation to the dialysis modality the patient performed at the time of admission. Patients who died were censored. The results of this model are presented with hazard ratios (HR).

The risk for first hospitalisation was analysed with a Cox regression model with dialysis modality as time-varying covariate. The proportional hazards assumption was tested, and if it was violated, data were presented for two different time periods. Number of hospitalisations and number of hospital days per patient-year were analysed with negative binomial regression. The last two outcomes were analysed in a multilevel model, in which dialysis modality was the first level and the patient the second level. This analysis thus corrected for the dependency of both dialysis modalities within the same patient.

All analyses were adjusted for potential confounders. In the first model, adjustments were made for age and sex, and in a second model, data were also adjusted for CCI, dialysis vintage and acute start of dialysis. Statistical analyses were conducted with IBM SPSS Statistics version 25 and R version 3.6.1.

3 | RESULTS

3.1 | Baseline characteristics

The study cohort consisted of 695 dialysis patients, of whom 252 (36%) were receiving PD and 443 (64%) HD at 3 months after dialysis initiation. Baseline characteristics are presented in [Table 1](#). Mean age was 63.0 (\pm 15.3) years for both groups, and the majority of patients were male. The comorbidity scores were similar between PD and HD patients. PD patients had a dialysis vintage of 16 months [IQR 9–41], whereas HD patients had a significantly longer dialysis vintage of 39 months [IQR 19–64]. PD patients less often had a previous kidney transplant compared with HD patients, 10% and 25%, respectively ($p < .001$). Only 4% of the PD patients had an acute start of dialysis, whereas 20% of HD patients did ($p < .001$). Just over half of the patients performed PD themselves; the rest were assisted by a nurse or other caregiver at home.

3.2 | Dialysis treatment and follow-up

The median dialysis duration for the entire study cohort was 22.0 months [IQR 11.1–36.4]. PD patients had a shorter dialysis duration [19.1 months, IQR 10.4–30.5] than HD patients [23.6 months, IQR 11.7–38.6] ($p = .001$). Patients transitioned more often from PD to HD (33%) than from HD to PD (11%) ($p < .001$).

3.3 | Hospitalisation rate

A total of 521 hospitalisations took place during PD, while 959 hospitalisations took place during HD. The crude

TABLE 1 Baseline characteristics according to dialysis modality at 3 months

Variable	Full sample <i>n</i> = 695	PD <i>n</i> = 252	HD <i>n</i> = 443
Age (yr), mean ± SD	63.0 ± 15.3	63.1 ± 14.9	62.9 ± 15.6
Sex (male), <i>n</i> (%)	418 (60)	160 (64)	258 (58)
Ethnic background, <i>n</i> (%)			
Caucasian	395 (57)	149 (59)	246 (56)
Other	123 (18)	30 (12)	93 (21)
Unknown	177 (25)	73 (29)	104 (23)
Primary kidney disease, <i>n</i> (%)			
Glomerulonephritis/pyelonephritis	141 (20)	39 (16)	102 (23)
Cystic kidney disease	38 (6)	19 (8)	19 (4)
Renovascular kidney disease	193 (28)	71 (28)	122 (28)
Diabetes mellitus	119 (17)	49 (19)	70 (16)
Other/unknown	204 (29)	74 (29)	130 (29)
BMI (kg/m ²), mean ± SD	26.8 ± 5.5	26.6 ± 4.7	26.9 ± 6.0
Smoking, <i>n</i> (%)			
Yes	117 (17)	42 (17)	75 (17)
Quit	172 (25)	67 (27)	105 (24)
Unknown	103 (15)	36 (14)	67 (15)
CCI score, <i>n</i> (%) ^a			
2	208 (30)	84 (33)	124 (28)
3–4	281 (41)	97 (39)	184 (42)
≥ 5	204 (29)	71 (28)	133 (30)
Davies score, <i>n</i> (%)			
0	182 (26)	77 (31)	105 (24)
1–2	370 (53)	125 (50)	245 (56)
≥ 3	141 (20)	50 (20)	91 (21)
KRT vintage (months), median [IQR] ^b	150 [64–212]	138 [44–181]	154 [69–230]
Dialysis vintage (months), median [IQR] ^c	35 [15–58]	16 [9–41]	39 [19–64]
Previous transplant, <i>n</i> (%)	138 (20)	26 (10)	112 (25)
Residual GFR (ml/min), median [IQR]	7.8 [4.6–11.6]	9.5 [6.7–12.9]	6.6 [3.3–10.4]
Residual diuresis (ml/day), mean ± SD	1459 ± 841	1708 ± 743	1317 ± 862
Acute start of dialysis, <i>n</i> (%)	98 (14)	11 (4)	87 (20)

Note: Abbreviations: CCI, Charlson comorbidity index; GFR, Glomerular filtration rate; HD, Haemodialysis; IQR, Interquartile range; KRT, Kidney replacement therapy; PD, Peritoneal dialysis; SD, Standard deviation.

^aBy definition, dialysis patients have a minimum CCI score of 2.

^bKRT vintage was only calculated for the 159 patients (23%) who received previous kidney replacement therapy: 33 PD patients (13%) and 126 HD patients (28%).

^cPrevious dialysis treatment was only calculated for the 148 patients (21%) who received dialysis before inclusion: 30 PD patients (12%) and 118 HD patients (27%).

hospitalisation rate for PD was 2.3 (± 5.0) hospitalisations per patient-year and for HD 1.4 (± 3.2) hospitalisations per patient-year. Using a multi-state model, the adjusted HR for hospitalisation rate was 1.1 (95% confidence interval (CI) 1.02–1.3) for PD compared with HD patients (Table 2).

3.4 | Risk for first hospitalisation, number of hospitalisations and number of hospital days per patient-year

Figure 1 shows the estimated cumulative incidence curves for the first hospitalisation for PD and HD patients

TABLE 2 Comparison of hospitalisation rate (hospitalisations per patient-year) and risk for first hospitalisation.

Dialysis modality	Crude HR (95% CI)	Adjusted* HR (95% CI)	Adjusted** HR (95% CI)
Hospitalisations per patient-year			
PD vs HD	1.1 (1.03–1.3)	1.1 (1.02–1.3)	1.1 (1.02–1.3)
Risk for first hospitalisation during first year after dialysis initiation			
PD vs HD	1.3 (1.1–1.6)	1.3 (1.1–1.6)	1.3 (1.1–1.6)
Risk for first hospitalisation ≥ 1 year after dialysis initiation			
PD vs HD	1.8 (1.4–2.5)	1.8 (1.4–2.5)	1.9 (1.4–2.5)

Note: The hospitalisation rate was calculated with a multi-state model with recurrent events, which attributed every hospitalisation to the dialysis modality the patient performed at the time of admission.

The risk for first hospitalisation was analysed with a Cox regression model with dialysis modality as time-varying covariate.

Abbreviations: HD, Haemodialysis; HR, Hazard ratio; PD, Peritoneal dialysis.

*Adjusted for age and sex

**Adjusted for age, sex, Charlson Comorbidity Index, dialysis vintage and acute start of dialysis

according to the Cox regression model. The model was adjusted for age, sex, CCI, dialysis vintage and acute start of dialysis.

Because the proportional hazards assumption was violated, HRs for risk for first hospitalisation were calculated separately for the first year after dialysis initiation and for the period thereafter, conditional on having survived the first year. The adjusted HR for risk for first hospitalisation during the first year was 1.3 (95% CI 1.1–1.6) for PD versus HD. For the period thereafter, the adjusted HR was 1.9 (95% CI 1.4–2.5) (Table 2).

TABLE 3 Comparison of number of hospitalisations and number of hospital days per patient-year.

Dialysis modality	Crude IRR (95% CI)	Adjusted* IRR (95% CI)	Adjusted** IRR (95% CI)
Number of hospitalisations			
PD/HD	1.3 (1.1–1.6)	1.7 (1.3–2.3)	1.7 (1.2–2.3)
Number of hospital days per patient-year			
PD/HD	1.6 (1.2–2.1)	1.6 (1.2–2.1)	1.5 (1.2–2.1)

Abbreviations: HD, Haemodialysis; IRR, Incidence rate ratio of PD relative to HD; PD, Peritoneal dialysis.

*Adjusted for age and sex

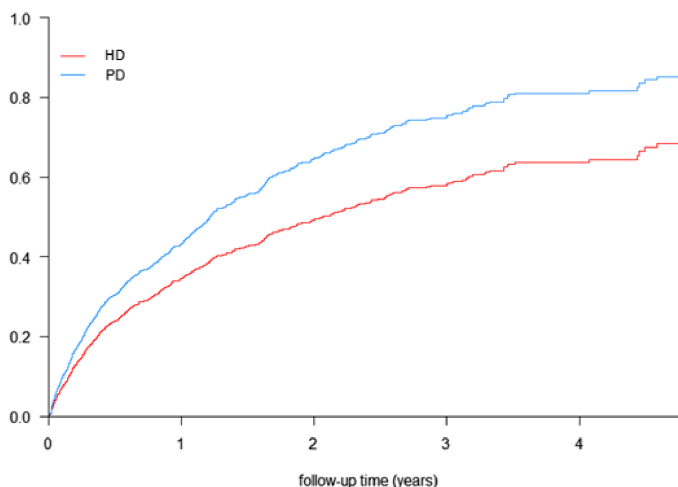
**Adjusted for age, sex, Charlson Comorbidity Index, dialysis vintage and acute start of dialysis

The number of PD hospitalisations, corrected for the total PD duration, was significantly higher than the number of HD hospitalisations, corrected for the total HD duration (crude incidence rate ratio of PD relative to HD 1.3; 95% CI 1.1–1.6). Additional adjustments for age, sex, CCI, dialysis vintage and acute start of dialysis resulted in a further increase in incidence rate ratio to 1.7 (95% CI 1.2–2.3) (Table 3).

The crude median number of hospital days per patient-year was 4.2 for PD patients [IQR 0–15.3] and 0.8 for HD patients [IQR 0–10.8]. The adjusted incidence rate ratio for number of hospital days per patient-year was 1.5 (95% CI 1.2–2.1) for PD compared with HD (Table 3).

3.5 | Causes

Causes of hospitalisations are presented in Table 4. The main cause for hospitalisations during PD treatment was

**FIGURE 1** Risk for first hospitalisation for PD and HD patients

PD= peritoneal dialysis; HD= haemodialysis. Estimated cumulative incidence curves for first hospitalisation for PD and HD patients derived from a multi-state Cox regression model. Model is adjusted for age, sex, Charlson Comorbidity Index, dialysis vintage, and acute start of dialysis.

TABLE 4 Causes of hospitalisations.

Causes	PD n = 521	HD n = 959
Access-related ^a	69 (13)	317 (33)
Peritonitis	117 (23)	N/A
Fluid overload	14 (3)	22 (2)
Cardiac disease ^b	57 (11)	87 (9)
Vascular disease ^c	28 (5)	50 (5)
Infection ^d	79 (15)	170 (18)
Gastrointestinal disease	46 (9)	94 (10)
Malignancy	9 (2)	25 (3)
Transplantation	13 (2)	25 (2)
Other/unknown	89 (17)	169 (18)

Note: Data are presented as n (%).

Abbreviations: HD, Haemodialysis; N/A, Not applicable; PD, Peritoneal dialysis.

^aAccess-related includes vascular access infection, fistula operation and PD catheter leakage/exchange/removal.

^bCardiac disease includes myocardial ischaemia/infarction, cardiac arrest/arrhythmia, cardiac failure and haemorrhagic pericarditis.

^cVascular disease includes pulmonary embolus, stroke, cerebrovascular haemorrhage, ruptured vascular aneurysm, mesenteric infarction and peripheral arterial disease.

^dNon-dialysis related infections.

peritonitis (23%), while the second most common cause was non-dialysis related infections (15%). The main cause for hospitalisation during HD treatment was a vascular access-related reason (33%), such as a fistula operation or a dialysis access infection. The second most common cause for hospitalisation during HD treatment was non-dialysis related infections (18%). For both PD and HD, hospitalisations for fluid overload were rare (2%–3%).

4 | DISCUSSION

In this retrospective cohort study among 695 dialysis patients, PD treatment was associated with a higher hospitalisation rate, a higher risk for first hospitalisation, a higher number of hospitalisations and a higher number of hospital days per patient-year compared with HD treatment, when hospitalisations were attributed to the dialysis modality the patient was receiving upon admission. In addition, PD hospitalisations were mainly caused by peritonitis, while vascular access-related reasons were the main causes for HD hospitalisations.

A higher PD hospitalisation rate compared with HD is found in several other studies. Banshodani et al. retrospectively showed that emergency hospitalisation rates for cardiovascular diseases and infectious diseases

were significantly higher for 130 PD patients compared to 130 HD patients, with HRs of 2.70 (95% CI 1.53–4.77) and 4.16 (95% CI 2.59–6.68), respectively.^{3,21} Lafrance et al. also retrospectively showed that infection-related hospitalisation rates were significantly higher for PD patients compared with HD patients (HR 1.52, 95% CI 1.38–1.68).¹⁸ Besides the fact that Banshodani et al. had a smaller study population than our study and Lafrance et al. investigated younger patients (HD 58.5 ± 16.4 years and PD 58.8 ± 14.5 years) during the period 2001–2007, both studies did not take transitions in dialysis modality into account. Banshodani et al. censored all patients who changed dialysis modality, and Lafrance et al. attributed all hospitalisations of patients according to their dialysis modality at 90 days.^{3,18,21} These studies defined patients according to a single dialysis modality, which does not do justice to daily practice at all.

That it is important to take transitions from and to different dialysis modalities into account is also shown in a study by Murphy et al.¹⁷ In their prospective Canadian cohort, they showed that PD patients had a lower hospitalisation rate (defined as the total number of hospitalisation days relative to the survival of the patient) compared with HD patients (rate ratio 0.85, 95% CI 0.82–0.87) when hospitalisations were attributed to the dialysis modality at baseline, while they had a higher hospitalisation rate (rate ratio 1.31, 95% CI 1.27–1.34) when hospitalisations were attributed to the dialysis modality at 3 months.¹⁷ In addition, Murphy et al. performed an analysis in which hospitalisations were attributed to the dialysis modality the patient was receiving upon admission, which showed that PD treatment was associated with a higher hospitalisation rate than HD treatment, with a rate ratio of 1.10 (95% CI 1.07–1.13).¹⁷ This study advocated the use of treatment-received analyses in comparing hospitalisation rates, which we did, instead of intention-to-treat analyses. However, our study defined hospitalisation rate as the number of hospitalisations per patient-year, which is much more commonly used in studies, also investigated the risk for first hospitalisation and described a more recent study population.

In two Canadian cohorts, Quinn et al. and Oliver et al. used the number of hospitalisation days per patient-year for calculating their hospitalisation rates. In their analyses with dialysis as time-varying covariate, they showed equal hospitalisation rates for PD compared with (in-centre) HD (Quinn et al.: rate ratio 1.28, 95% CI 0.63–2.61. Oliver et al.: rate ratio 0.93, 95% CI 0.51–1.71).^{8,16} However, besides the fact that they used a different measure for hospitalisation rate, which makes comparison with our study difficult, they did not investigate the risk for first hospitalisation, and Oliver et al. only investigated patients on assisted PD.

Several other studies showed that hospitalisation rates of PD and HD patients are equal.^{13–15,19,27} However, these studies performed an intention-to-treat analysis by attributing hospitalisations of patients to their initial dialysis modality, which is not a valid analysis for the present research question, as argued above.

In our study, the main cause of PD hospitalisations was peritonitis, while HD hospitalisations were mainly vascular access-related. Also in a Japanese survey among 89,748 patients, these were most common causes for PD and in-centre HD hospitalisations.²⁰ Several other studies have identified infections and specifically peritonitis as an important cause for PD hospitalisations.^{16,18,21,28}

Apparently, PD patients have a higher risk for hospitalisation than HD patients. This could be attributed to the dialysis modality per se, or could be the result of circumstantial factors. A possible explanation could be that the threshold for hospitalisation is lower for PD than for HD patients. In-centre HD patients frequently visit the hospital for dialysis, in most cases at least three times a week for four hours. If, for example, they develop an infection, assessment and (start of) antibiotic treatment can easily be performed during the dialysis session in hospital. Moreover, the effect of the antibiotic treatment can be evaluated during the next scheduled dialysis session and adapted based on culture results. On the contrary, PD patients are treated at home and visit the hospital much less frequently. If they develop an infection, they must visit the hospital for evaluation. In addition, they have to attend the hospital again for evaluation of the treatment effect. It is conceivable that this need for frequent hospital visits could lead to a lower threshold for hospitalisation in PD patients. Finally, we cannot exclude residual confounding as possible or additional explanation for finding a higher hospitalisation risk in PD compared with HD.

To our knowledge, this is the first European study to describe several important hospitalisation outcomes of PD and HD, taking into account transitions between dialysis modalities and thus properly showing the risk for hospitalisation of the different dialysis modalities. Almost one-fifth of our population changed dialysis modality, underscoring that a model allowing this is superior to models evaluating hospitalisations on an intention-to-treat basis. Besides the fact that we used a multi-state model in a relatively large cohort of patients, we also describe a recent dialysis population, which is relevant because the composition of the dialysis population has changed in previous years, for example with respect to age.^{29,30} However, our study has some limitations. First, all types of admissions with a minimum duration of 24 h were analysed, possibly including admissions for PD training and vascular access procedures. Consequently, both PD and HD admissions might be overrated. Second, no centre correction has been

conducted, while the decision to admit a patient might differ between centres. Third, it should be noted that a very small number of HD patients were treated with home HD ($n = 45$) and hospitalisations during this treatment ($n = 57$) were counted among HD hospitalisations, which may have affected the results. Finally, the model we used, which allows transitions between dialysis modalities over time, was not compatible with competing risk regression models, whereas death should be considered a competing event. However, in our population, only 17 patients died without being hospitalised, while 140 patients died during or after at least one hospitalisation. Thus, we do not think that accounting for competing risks would have altered our results.

In conclusion, our study shows that, when hospitalisations are attributed to the type of dialysis treatment upon admission, PD is associated with a higher hospitalisation rate, a higher risk for first hospitalisation, a higher number of hospitalisations and a higher number of hospital days per patient-year compared with HD. Since the PD hospitalisations were mainly caused by peritonitis, more attention to infection prevention is necessary for reducing the number of hospitalisations in the future.

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CONFLICT OF INTEREST

A.E.S. and A.C.A. have received speaker honoraria from Baxter Healthcare. All other authors declare no conflict of interest. The results in this article have not been published previously in whole or part, except in abstract format.

AUTHOR CONTRIBUTIONS

A.E.S., A.A.B., B.C.J. and A.C.A. designed the research question. A.E.S., A.A.B. and V.A.W. collected data. A.E.S., A.A.B., V.A.W. and B.I.L. performed the statistical analyses. A.E.S., A.A.B., V.A.W., B.C.J. and A.C.A. interpreted the data. T.H., F.W.D., F.J.I. and M.C.V. provided intellectual content of critical importance to the work described. A.E.S. drafted the manuscript. All authors critically edited the manuscript and approved the final version.

DATA AVAILABILITY STATEMENT

The data underlying this article will be shared upon reasonable request to the corresponding author after approval of the DOMESTICO steering group.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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