



Clinical outcomes of stroke in hemodialysis patients: a retrospective single-center study

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Abstract

Purpose The incidence of stroke in patients undergoing hemodialysis (HD) is eight-to-ten times greater than that of the general population. However, data on the outcome of stroke in these patients are limited.

Methods In this retrospective observational cohort study, electronic medical records of all patients undergoing HD from 1.1.2014 to 31.12.2017 at Meir Medical Center, Israel, were reviewed. Stroke was defined as a focal neurological deficit of cerebrovascular origin, and confirmed as ischemic or hemorrhagic by computed tomography. Age- and sex-matched HD patients who did not experience a stroke (HD-NS) and hospitalized stroke patients with normal kidney function (NRF-S) served as the two control groups. Baseline demographic, clinical, and laboratory data were collected. Thrombolytic therapy, duration of hospital stay, and mortality were recorded. Functional status at discharge was assessed by the Modified Rankin Scale.

Results In the cohort study group (HD-S), 52 strokes occurred during 248.3 patient years, an incidence rate of 8.13%, and a stroke rate of 0.19% patients/month. Most strokes in HD patients were ischemic, and only four patients were administered tissue plasminogen activator. HD-S had longer hospitalization than did NRF-S (10.6 ± 9.9 vs. 5.96 ± 5.3 days, $p = 0.004$) and lower functional status at discharge (Rankin score 3.75 ± 1.57 vs. 2.29 ± 1.89 , $p < 0.001$). HD-S patients had a higher mortality than both HD-NS and NRF-S patients.

Conclusions Stroke outcome in these patients is dismal with prolonged hospital stay, poor functional status at discharge, very limited response to rehabilitation, and increased mortality.

Keywords Hemodialysis · Stroke · Prognosis · Outcome

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Introduction

Stroke is an important cause of disability and mortality. It is the third leading cause of death worldwide [1]. In the United States, the prevalence of stroke is about 3% of the adult general population. Approximately 87% of these strokes are ischemic infarctions and 13% are hemorrhagic (10% primary hemorrhages and 3% due to subarachnoid hemorrhage) [2].

Chronic kidney disease (CKD) is associated with an increased risk of vascular events, including stroke. There is a clear relationship between worsening renal function and stroke incidence, with patients on dialysis at the highest risk [1]. Patients with end-stage renal disease (ESRD) on hemodialysis have an eight-to-ten times greater incidence of stroke as compared to the general population [3]. The risk of stroke in these patients is greatest around the time dialysis is initiated. In a large cohort (> 20,000 patients) of Medicare-insured

hemodialysis patients, the incidence of stroke was found to be highest 1 month before and after dialysis initiation. The stroke rate was reported as 0.4–1.5% patients per month [4].

The increased risk in this unique population probably represents the interplay of the vascular comorbidities that cluster with renal impairment, as well as pathology inherent in uremia, such as accelerated vascular calcification, malnutrition, inflammation, and atherosclerosis. The hemodialysis procedure itself may contribute to decreased cerebral perfusion; thus, exacerbating the evolution of stroke [3, 4].

Despite the high frequency of stroke in the HD population, there are few randomized studies on its management and outcomes among these patients. Limited information is available about the prognosis of dialysis patients after various types of strokes.

Although both primary prevention and secondary prevention of stroke have been well studied and implemented in the general population, these issues are still debated regarding hemodialysis patients. Thus, stroke prevention either with anti-platelet or anti-coagulant therapy in dialysis patients is considered to be of lower efficacy and to have a less favorable safety profile [1].

Furthermore, although, in the general population, thrombolytic therapy for acute stroke with recombinant tissue plasminogen activator (tPA) is considered a viable option for suitable patients, the efficacy of such treatment in dialysis patients lacks reliable evidence.

While renal failure appears to be a risk factor for the development of stroke, its impact on prognosis after acute stroke is not clear. The outcomes of patients on HD who had a stroke were assessed in a small observational study which demonstrated longer hospitalization with, however, acceptable outcomes [5]. Other studies reported higher mortality rates among dialysis patients [6, 7]. Data on the efficacy of rehabilitation in the HD population after a stroke event are scarce. Most available studies assessed rehabilitation of dialysis patients in general without specifically alluding to rehabilitation after stroke. A single study that investigated rehabilitation after stroke demonstrated significantly lower functional independence measure (FIM) scores among end-stage renal disease (ESRD) patients compared to stroke patients without ESRD [8]. In contrast, Forrest reported inpatient rehabilitation in HD patients comparable to that of non-dialyzed patients [9].

The current study assessed the clinical approach to stroke among HD patients and focused on their functional status and efficacy of rehabilitation after stroke.

Materials and methods

Study design

For this retrospective, observational, case–control cohort study, the electronic medical records of all chronic HD patients at Meir Medical Center (MMC), Kfar Saba, Israel, from January 1, 2014 to December 31, 2017, were reviewed. Meir Medical Center is a university-affiliated hospital with a dialysis unit providing chronic hemodialytic care to 160–170 patients. Chronic HD was considered as maintenance HD for > 3 months. The Meir Medical Center Ethics Review Committee approved the study. Informed consent was waived.

Study population

The study cohort (HD-S) comprised all chronic HD patients at MMC admitted with stroke during the above specified period. None of our chronic HD patients with stroke were admitted to other hospitals. All chronic HD patients admitted with stroke comprised the study cohort (HD-S). Strokes were categorized as ischemic (IS) or hemorrhagic (HS). Stroke types were confirmed by computed tomography (CT). History of a stroke prior to the study period or prior to the start of HD was considered a comorbidity.

Chronic HD patients without stroke were designated as the HD-non-stroke (HD-NS) control group. A second control group was composed of patients admitted to an internal medicine department with stroke with normal renal function (NRF-S). Normal renal function (NRF) was defined as serum creatinine < 1.2 mg/dL on admission.

The two control groups were matched to the study cohort (HD-S) by group age and sex. NRF-S patients were also matched to HD-S patients according to type of stroke: IS or HS.

Demographic and clinical data

Demographic data gathered from electronic medical records included age, sex, comorbidities (such as diabetes mellitus and other chronic diseases), and baseline laboratory data.

Characteristics of the stroke—subtype, treatment before and after the onset of the stroke, hospital length of stay, functional status at discharge (according to Modified Rankin Scale) (detailed in Fig. 1) [10], in-hospital and 30-day mortality rates, were recorded. The efficacy of rehabilitation between the HD-S and NRF-S groups was assessed by FIM score at admission and at discharge.

Since some of the patients experienced a stroke several days after starting chronic hemodialysis treatments, dialysis vintage was measured from day of commencement of HD

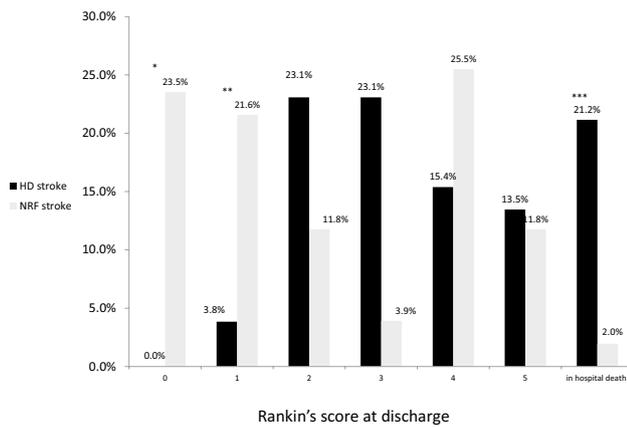


Fig. 1 Distribution of patients according to Rankin score in NRF-S versus HD-S. All patients were scored at discharge according to modified Rankin score: 0—no symptoms at all, 1—no significant disability despite symptoms; able to carry out all usual duties and activities, 2—slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance, 3—moderate disability requiring some help, but able to walk without assistance, 4—moderate disability requiring some help, but able to walk without assistance, and 5—severe disability: bedridden, incontinent, and requiring constant nursing care and attention

to eventuation of stroke in days. Stroke rate was calculated by dividing the number of new stroke by dialysis vintage of HD (months).

Statistical analysis

Data are expressed as mean \pm standard deviation for continuous variables and as numbers and percentage for non-metric parameters. Metric data were checked for normality with Shapiro–Wilk test. As some of the variables were not normally distributed, *t* test or Mann–Whitney nonparametric test was used to compare between the two groups for the different blood markers. Chi-square or Fisher's exact test was used to compare categorical parameters. Cox proportional hazard model was applied to estimate hazard ratios for mortality and survival curve in HD-S vs. NRF-S patients. A *p* value < 0.05 was considered statistically significant.

Results

During the study period, a total of 585 patients underwent hemodialysis in the unit. In the HD-S group, 52 patients developed stroke during a total of 248.3 HD patient years and a stroke rate of 0.017 patients/month. Their mean age was 67.92 ± 11.3 years with a male predominance (65.3%) (Table 1). 45 of strokes were ischemic and 7 were hemorrhagic.

Table 1 Demographic and clinical data of stroke patients with normal kidney function (NRF-S) vs. those on hemodialysis (HD-S)

Variable	NRF-S (N=52)	HD-S (N=52)	<i>p</i> value
Mean age at stroke	67.92 ± 11.34	67.4 ± 11.3	0.829
Male (%)	32 (65.3%)	30 (57.7%)	0.432
Ischemic heart disease	15 (29.4%)	22 (42.3%)	0.173
Congestive heart failure	0 (0%)	25 (48.1%)	0
Hypertension	43 (84.3%)	52 (100%)	0.003
Diabetes mellitus	26 (51%)	41 (78.8%)	0.003
Chronic lung disease	2 (3.9%)	13 (25%)	0.004
Stroke	18 (35.3%)	23 (44.2%)	0.354
Atrial fibrillation	5 (9.8%)	16 (30.8%)	0.008
Peripheral vascular disease	3 (5.9%)	15 (28.8%)	0.003
Left-ventricular hypertrophy	4 (11.1%)	23 (44.2%)	0.001
Smoking	21 (41.2%)	12 (23.5%)	0.057
Aspirin	20 (39.2%)	33 (67.3%)	0.005
Other anti-platelet therapy	9 (17.6%)	9 (18.4%)	0.925
Anti-coagulation	4 (7.8%)	2 (4.1%)	0.678
Beta blocker	23 (45.1%)	32 (65.3%)	0.042
Calcium blocker	18 (35.3%)	24 (49%)	0.166
ACEI/ARB	24 (47.1%)	24 (49%)	0.848
Alpha blocker	1 (2%)	11 (22.4%)	0.002
Statin	28 (54.9%)	26 (53.1%)	0.854

Medications in this table include only treatment before stroke

ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker

HD-S vs. NRF-S

After adjusting for age, sex, and stroke type, the HD-S group had significantly more comorbidities (congestive heart failure (CHF), hypertension, diabetes, chronic atrial fibrillation, chronic lung disease, peripheral vascular disease, and left-ventricular hypertrophy) compared to the NRF-S group (Table 1). HD-S patients were significantly more likely to be treated with aspirin, and alpha and beta blockers.

Four HD-S patients were administered tPA versus none of the NRF-S group ($p = 0.118$). None of the patients treated with tPA developed major bleeding or neurologic deterioration.

Mean hospital length of stay was significantly longer in HD-S group (10.6 ± 9.9 days) vs. 5.96 ± 5.3 days in the NRF-S group ($p = 0.004$).

Rankin scale score was 3.75 ± 1.57 in HD-S vs. 2.29 ± 1.89 in NRF-S ($p < 0.001$), reflecting a better functional status at discharge in NRF-S patients. More than 40% of NRF-S patients were independent at discharge (defined as able to carry out all usual duties and activities) compared with only 3.8% of HD-S patients (Fig. 1).

The most common discharge destination for HD-S was home despite their poorer functional status. Most (64.5%) were found suitable for home rehabilitation and 3.8% were referred to nursing homes. Only 7/52 (13.5%) HD-S patients versus 11/52 (21.2%) NRF-S patients ($p=0.084$) were referred for in-hospital rehabilitation. FIM score at the start of rehabilitation among HD-S patients was 52.57 ± 13.7 vs. 64.8 ± 31.63 in NRF-S patients, ($p=0.378$). It increased to 68.29 ± 26.11 and 84.2 ± 28.47 ($p=0.339$) at discharge, respectively. The average duration of rehabilitation was 63.8 ± 18.97 days in NRF-S vs. 45.7 ± 21.02 in HD-S patients, $p=0.158$. At discharge, successful rehabilitation to independent living at home was achieved by 60% of NRF-S patients vs. 14.3% of HD-S, $p=0.137$. Most HD-S patients were discharged from rehabilitation to a nursing home (42.9%) or to home, in a dependent state.

HD-S patients had significantly higher in-hospital mortality (21.2%) compared to NRF-S patients (5.8%) ($p=0.007$). The 30-day and 1-year mortality rates were significantly higher in the HD-S patients (30.8% vs. 15.4% and 51.9% vs. 17.3%, $p<0.05$, respectively; Fig. 2). Mean time from stroke to death was significantly shorter in HD-S patients (275.4 ± 412.2 days) vs. NRF-S (491.2 ± 289.1), $p=0.006$.

HD-S vs. HD-NS

All patients in the HD-S group had a previous diagnosis of hypertension. The only significant differences in comorbidities between HD-S and HD-NS were a higher prevalence of diabetes (78.8% vs. 59.6%, $p=0.034$) and a prior history of stroke (44.2% vs. 17.3%, $p=0.003$) in the HD-S patients. Atrial fibrillation did not differ significantly between the groups (Table 2).

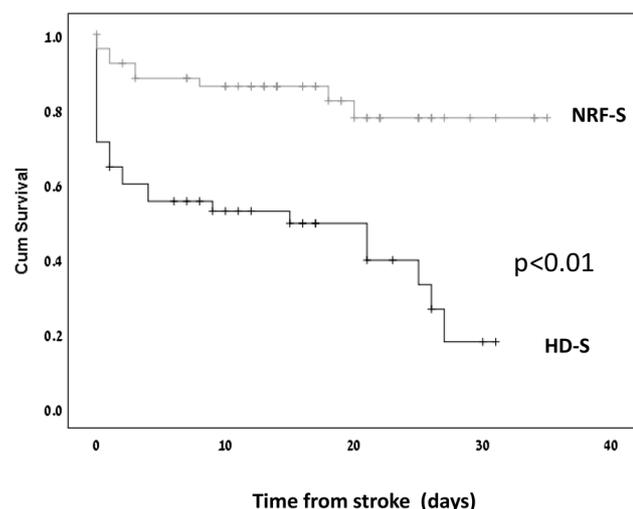


Fig. 2 Event-free survival curve for HD-S vs. NRF-S patients ($p=0.001$)

Table 2 Demographic and clinical data of hemodialysis patients without stroke (HD-NS) vs. those with stroke (HD-S)

Variable	HD-NS N=52	HD-S N=52	p value
Age	68.42 ± 11.14	67.44 ± 11.29	0.657
Male	33 (63.5%)	30 (57.7%)	0.547
Body mass index	29.59 ± 5.77	29.41 ± 11.29	0.882
Ischemic heart disease	24 (46.2%)	22 (42.3%)	0.693
Congestive heart failure	19 (36.5%)	25 (48.1%)	0.234
Hypertension	47 (90.4%)	52 (100%)	0.057
Diabetes Mellitus	31 (59.6%)	41 (78.8%)	0.034
Chronic lung disease	11 (21.2%)	13 (25%)	0.642
Prior stroke	9 (17.3%)	23 (44.2%)	0.003
Atrial fibrillation	11 (21.2%)	16 (30.8%)	0.263
Peripheral vascular disease	14 (26.9%)	15 (28.8%)	0.827
Left-ventricular hypertrophy	25 (48.1%)	23 (44.2%)	0.694
Smoking	17 (32.7%)	12 (23.5%)	0.301
Dialysis vintage (months)	50.46 ± 38.5	74.56 ± 183.1	0.355
Pre-stroke medications			
Aspirin	26 (50%)	33 (67.3%)	0.077
Other anti-platelet	7 (13.5%)	9 (18.4%)	0.5
Anti-coagulation	7 (13.5%)	2 (4.1%)	0.162
Beta blocker	34 (65.4%)	32 (65.3%)	0.993
Calcium channel blocker	30 (57.7%)	24 (49%)	0.38
ACEI/ARB	20 (38.5%)	24 (49%)	0.287
Alpha blocker	15 (28.8%)	11 (22.4%)	0.462
Phosphate binder	38 (73.1%)	18 (36.7%)	0.001
Statin	25 (48.1%)	26 (53.1%)	0.617
Laboratory values			
Kt/v	1.35 ± 0.32	1.30 ± 0.34	0.684
nPCR (g/kg/day)	1.08 ± 0.35	0.87 ± 0.26	0.067
Creatinine (mg/dL)	6.74 ± 2.21	5.79 ± 1.62	0.014
Albumin (g/dL)	3.66 ± 0.61	3.4 ± 0.55	0.023
Cholesterol (mg/dL)	157.9 ± 48.3	163.1 ± 48.4	0.585
Calcium (mg/dL)	8.6 ± 0.86	8.56 ± 0.78	0.807
Phosphor (mg/dL)	5.19 ± 1.45	5.16 ± 1.26	0.914
PTH (pg/mL)	355.9 ± 214.8	290.7 ± 166.7	0.116
HBA1C (%)	6.37 ± 1.56	6.9 ± 1.55	0.092
C-reactive protein (mg/L)	2.77 ± 3.55	7.72 ± 23.85	0.145
Hemoglobin (g/dL)	10.44 ± 1.29	10.48 ± 1.62	0.915

Medications include only treatment before stroke

ACEI angiotensin-converting enzyme inhibitor, ARB angiotensin receptor blocker

There were no significant differences in anti-platelet and anti-coagulation treatment. Serum albumin was lower in HD-S compared to HD-NS patients (3.4 ± 0.6 vs. 3.7 ± 0.6 , $p=0.023$) (Table 2). Mortality was significantly greater in HD-S vs. HD-NS (51.9 vs. 19.2%, $p=0.002$) (Fig. 3).

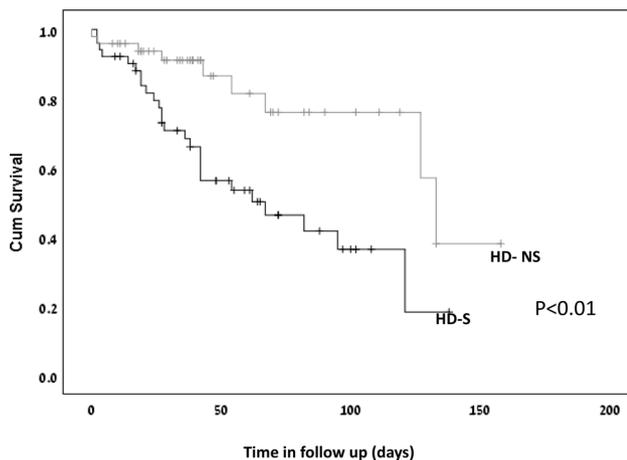


Fig. 3 Event-free survival curve for HD-S vs. HD-NS patients ($p=0.002$). The mortality rates were significantly higher in the HD-S patients compared with HD-NS

Discussion

As expected, stroke prevalence rate among the HD patients (0.19% patients/month, incidence rate 8.13%) was more than tenfold that of the general population (based on data from the Israel Center for Disease Control and the Israel Neurological Association, which reported approximately 15,000 new cases of stroke every year in a population of about 8.5 million). Our stroke rate is lower than the 0.4–1.5% reported by Murray et al. [4], among a Medicare population on hemodialysis in the US. However, since our study included only prevalent dialysis patients, defined as being on chronic dialysis treatment for more than 3 months, the lower rate is to be expected. As mentioned above, stroke occurrence in hemodialysis patients is most common around the initiation of dialysis to the following month. The dissimilarity in rates might also be attributed to the different study populations and the bias inherent in the homogeneity of a single-center study. Our cohort population was almost exclusively Caucasian in comparison to the mixed Caucasian/Afro American cohort of Murray.

Our study demonstrated significantly more comorbidities among patients in the HD-S group as compared with patients in the NRF-S group. These included hypertension, diabetes, congestive heart failure, left-ventricular hypertrophy, atrial fibrillation, peripheral vascular disease, and pulmonary disease. This finding is not surprising, because many of these comorbidities represent either the basic renal disease leading to the initiation of dialysis or are inherent in the dialysis population (such as accelerated atherosclerosis, a state of chronic inflammation and fluid overload) [1, 3, 7, 11]. All types of anti-hypertensive medications were more prevalent among HD-S patients. This could be due to the underlying kidney disease and the higher prevalence

of both atrial fibrillation and left-ventricular hypertrophy (LVH). The influence of hypertension on the risk of stroke in dialysis patients is difficult to evaluate, as blood pressure measurements often reflect fluid overload. As such, inconclusive results have been reported in several studies.

In contrast to the study by Alqahtani et al. [7], atrial fibrillation was more prevalent among HD-S patients in our study, as compared to the NRF-S group. Considering their increased comorbidities, in all probability, HD-S patients had a higher CHAD VAS score. Despite this, only 4.1% of these HD-S patients were treated with anti-coagulants (apart from heparin administered during dialysis sessions). Most of these patients (67.3%) were maintained on low-dose aspirin, as well as other anti-platelet therapy. Although anti-coagulation is a well-established prophylactic measure for patients with atrial fibrillation and GFR > 30 mL/min, its use in HD patients is controversial. Most authorities will not treat these patients with warfarin [1, 6].

In support of this, anti-coagulant treatment policy is that the HD-NS group had similar prevalence of atrial fibrillation and no significant difference in prevalence of anti-coagulation. In fact, the only significant difference in chronic medications was higher use of phosphate binders in the HD-NS group. This may imply different pathogenetic mechanisms of stroke in dialysis patients as compared to NRF patients. Stroke evolution in dialyzed patients may be related primarily to renal osteodystrophy and could thus at least partly explain the low efficacy of anti-coagulation in preventing stroke in dialysis patients with AF. The pro-calcification effect of warfarin may also contribute to its decrease efficacy in this population [12].

Comparing the HD-S to the HD-NS groups, the only significant difference in comorbidities was a higher prevalence of diabetes and prior stroke in the former (Table 2). Serum albumin was significantly lower in HD-S patients. This coupled with a decreased need for, and therefore, use of phosphate binders, reduced nPCR, and higher CRP value (although the latter two did not reach statistical significance) indicate a higher degree of malnutrition–inflammation in the HD-S group. The critical role of malnutrition–inflammation as regards morbidity and mortality in HD patients was previously noted by Rambod et al. [13]. Other critical factors, such as age and hemoglobin level, were similar in HD-S vs. HD-NS patients.

Hemodialyzed stroke patients were hospitalized for a significantly longer period than their NRF-S counterparts. This finding has been previously reported and is a reflection of the higher comorbidity index among this population, leading to higher risk for sepsis and need for blood transfusion [5–7].

Due to their increased comorbidities and greater risk of bleeding, we expected that HD-S patients would be less likely to undergo thrombolytic therapy. However, contrary to our expectations, 4 HD-S patients were administered TPA

as compared to none of the NRF-S cohort. This is, in the main, attributed to delayed hospital admission of the NRF-S patients, exceeding the appropriate time interval. In contrast, the HD-S patients who received thrombolysis and the neurological symptoms of stroke evolution were witnessed during hospitalization or in-hospital dialysis session, allowing for prompt neurological assessment, CT imaging and consequent TPA administration. We found the thrombolytic treatment as effective (with resolution of symptoms) and safe, with no evidence of bleeding among these patients.

The functional status at discharge (as reflected by the Modified Rankin score) was markedly better in NRF-S patients as compared to HD-S patients. A significantly larger percentage of NRF-S vs. HD-S patients were independent at discharge from hospitalization (45.1% vs. 3.8%, $p=0.015$). It might be argued that the functional status prior to stroke was not assessed in our patients. Given their increased number of comorbidities and the impact of dialysis itself (cumulative asymptomatic brain injury) [14], HD-S patients, despite being age and sex matched to NRF-S patients, might have started with lower functional capacity before stroke eventuation. Furthermore, we did not compare infarct size or brain CT scans. Nevertheless, our study does show the poor outcome of stroke in HD patients, rendering most as functionally dependent.

Similar percentages of HD-S and NRF-S patients (45.1% and 52%, respectively) were referred for rehabilitation. However, whereas NRF-S patients were almost equally assigned to trial rehabilitation at home (23.5%) or at hospital (21.6%), many HD-S patients (38.5%) received rehabilitation in a home setting. Although at times, patients may prefer a home environment with familiar surroundings, hospital rehabilitation is considered more intensive and is usually reserved for patients whose chance for improved functional status is deemed good. It is speculated that the referral of most HD-S patients to home rehabilitation is a reflection of their poorer functional status and lower likelihood of recovery.

Data on the specific functional outcomes of hemodialysis patients after stroke are limited. Cowen et al. [15] reported significantly lower motor FIM scores among patients with ESRD after rehabilitation following stroke as compared to those without ESRD.

More recently, El Husseini et al. [15] found that dialysis patients older than age 65 years had a lower likelihood of home discharge following acute ischemic stroke (OR 0.86; CI 0.79–0.94, $p < 0.001$) versus younger patients did.

Mortality was significantly higher in HD-S cohort compared to both NRF-S and HD-NS groups ($p=0.001$ and $p=0.002$, respectively). The higher mortality in HD-S vs NRF-S patients has been reported previously [6, 7] and is probably due to the increased comorbidities of the former group. It may also be the result of the stroke severity itself (not examined in this study). The mortality rate was higher

during the hospitalization phase, at 30 days and at 1 year after the stroke. The OR for death in HD-S vs. NRF-S was 2.53 (CI 1.4–4.58). The higher mortality of HD-S patients compared to age- and sex-matched dialysis patients (HD-NS group) highlights stroke as a major factor responsible for mortality in these patients.

The current study aimed to assess the outcome of stroke in HD patients. Apart from the recently published work by Alqahtani et al. [7], this issue has rarely been addressed in the literature. The previous studies mainly focused on associated risk factors and comorbidities. Similar to Alqahtani et al., who used a large, nationwide, representative sample, we found longer hospitalization and higher mortality in HD stroke patients. Neither the Rankin scale nor FIM assessment was employed by Alqahtani. These measures of functional status and efficacy of rehabilitation, respectively, revealed markedly lower functional status at discharge among HD-S patients. Response to rehabilitation was poor, with most HD-S patients discharged in a functionally dependent state.

This study had a few limitations. Despite achieving statistically significant results, the number of patients in each group was small. The Rankin score at discharge was determined retrospectively, based on the description of the patient's condition as written in the discharge summary. The pre-admission Rankin score was not available for comparison before and after stroke in HD patients. The study population was heterogeneous in their age, dialysis vintage, and comorbidities, which could influence the etiology and pathogenesis of stroke.

The strengths of this study are that the diagnosis of stroke was confirmed by CT in all patients. The use of the modified Rankin scale and FIM score to evaluate the severity of stroke and the effectiveness of rehabilitation reinforce the prognostic value of our findings.

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Compliance with ethical standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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