Clinical outcomes of intracerebral hemorrhage in hemodialysis patients

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Introduction

Chronic renal failure (CRF) is a worldwide public health problem that is associated with a high risk of occurrence of cardiovascular events [9,19]. Hemodialysis (HD) is performed in more than 90% of patients in advanced stages of CRF. The number of HD patients in Japan has increased from 1624.1 per million at the end of 2000 to 2279.5 per million in 2009. The total number of HD patients exceeded 281,996 in 2009, the highest rate since 1983 [17]. The trend is similar in other countries, the total number of HD patients in the United States increasing from 281,355 in 2000 to 415,013 in 2010 (United States Renal Data System) [4,26]. Several studies have indicated that the incidence of ischemic and hemorrhagic events in the intracranial region (strokes) in CRF patients is high [1,7,8,10,12,14-16,18,21-23,27]. A single-center study in Japan showed that the frequency of intracerebral hemorrhage (ICH, 52% of 151 patients) in HD patients was higher than that of cerebral infarction (CI, 41%) between 1980 and 1996, while the rate of ICH (29%) between 1997 and 2002 was lower than that of CI (68%) [23]. Intensive control of hypertension, diabetes and hyperlipidemia may have reduced the incidence of ICH. However, the clinical status of HD patients with ICH remains severe, ICH being a common cause of death in HD patients. The incidence of death due to ICH is 2- to 3-fold higher than that due to CI [8,10,12,15].

Here, we retrospectively investigated 5 years worth of clinical data from ICH patients treated with or without HD at our institution. We reveal the differences in the clinical courses of HD and non-HD patients and identify the risk factors for poor outcomes in ICH patients undergoing HD.

Patients and Methods

We conducted a single-center retrospective study based upon a review of medical records.

The records of 366 consecutive patients with non-traumatic spontaneous ICH who were admitted to the neurosurgical department of Hitachi General Hospital between January 2007 and December 2011 were examined. Patients with ICH due to secondary causes, such as ruptured aneurysm, primary ischemic stroke, and arteriovenous malformation or tumor, were excluded from this study. In all cases, computed tomography (CT) scan was performed on admission. Magnetic resonance imaging (MRI) was performed on admission or after surgery for all patients with ICH except for deceased patients whose condition was rapidly deteriorating.

The following clinical information, including baseline characteristics, was collected: age, gender, location/side of the hematoma, volume of the hematoma, presence of intraventricular hemorrhage (IVH), microbleeds (MBs) on MRI scans, modified Rankin scale (mRS) scores at admission/discharge, type of surgical operation, use of antihypertensive and anti-diabetic drugs and antiplatelets/anticoagulants, primary renal disease, current history of HD, and the day of the week on which the ICH occurred in relation to HD. The hematoma volume in each case was determined by one of the authors (N.S.) from CT scans obtained at the onset as follows: the maximum transverse diameter × the maximal antero-posterior diameter × the maximal supero-inferior diameter × 1/2. Presence of IVH was also assessed using CT scans. Hematoma volume in the lateral ventricle was not included in the calculation of ‘volume of hematoma’ in this study.

The values are expressed as means ± SD. Differences in patient data were evaluated using univariate logistic analysis as well as χ^2 test, Fisher’s test or Student t test. P values less than 0.05 were considered to indicate statistical significance. All calculations were performed using JMP 5 software (SAA Corp., USA). Multivariate logistic analysis was performed for data in which p values were less than 0.1 on univariate logistic analyses. Differences were considered statistically significant if the p value was <0.05 in this analysis

as well. In the logistic analyses, continuous variables were dichotomized in terms of their mean or median values.

Results

Comparisons between HD and non-HD patients

Table 1 shows the clinical characteristics of the patients in the study. A total of 366 patients were admitted to our hospital with a diagnosis of ICH during the study period. They were divided into two groups: 32 patients (9%) with CRF who received HD (HD group) and 334 patients who did not receive HD treatment (non-HD group). All the CRF patients in this study were on HD. Surgical hematoma evacuation was performed in 25% of the HD patients and in 13.5% of the non-HD patients, while a hematoma drain was inserted into the lateral ventricle of 6% and 7.5% of HD and non-HD patients, respectively. There were no differences in patient age, gender, laterality of hematoma and surgical procedure between the two groups. The HD group had higher rates of hematomas in the basal ganglia (84% in the HD group vs. 57% in the non-HD group, $p<0.05$), IVH (53% vs. 34%, $p<0.05$), use of antihypertensive drugs (72% vs. 32%, $p<0.01$), use of anti-diabetic drugs (41% vs. 20%, $p<0.01$) and use of antiplatelets/anticoagulants (41% vs. 17%, $p<0.01$). The mortality rate (mRS VI) was higher in the HD group (44%) than in the non-HD group (21%). There were no significant differences in the existence of cerebral MBs between the two groups, as seen on MRI ($p>0.1$, Fisher direct test). As seen in Table 1, univariate logistic analysis showed that hematoma location, presence of IVH, use of antihypertensive drugs, use of anti-diabetic drugs, use of antiplatelets/anticoagulants, patient mortality, and the number of patients with mRS ≥5 were significantly different between HD and non-HD groups. Similar results were also shown using the χ^2 test or Fisher's test (data not shown). Multivariate logistic analysis showed that

hematoma location, use of antihypertensive drugs, use of antiplatelets/anticoagulants, and number of patients with mRS ≥5 were different between the two groups (Table 1).

Analysis of patients who had died (mRS VI) in both groups indicated significant differences in the number of hematomas in the basal ganglia (86% vs. 45%, $p<0.01$), the use of antihypertensive drugs (50% vs. 21%: $p<0.01$) and the use of antiplatelets/anticoagulants (36% vs. 12%, $p<0.05$). There were no significant differences in the use of anti-diabetic drugs and incidence of IVH between the two groups.

Analyses of HD patients

Next, detailed data from the 32 patients on HD was analyzed. The causes of CRF were diabetic nephropathy (44%), glomerulonephritis (19%), cystic kidney disease (3%), sclerosis (3%), renal carcinoma (3%) and unknown etiology (28%). On admission, 13 patients (41%) received antiplatelets/anticoagulants for maintenance of shunt patency (31.2%), history of previous angina pectoris (2 cases), or history of previous cerebral infarction (1 case).

The condition of 24 of the patients (75%) was rated as being serious (mRS V) at the time of hospitalization, and antihypertensive drugs were administered to 23 of these patients. Mean systolic blood pressure values on admission in patients with and without antihypertensive drugs before admission were 190.0+/-43.2 and 166.3+/-53.1 mmHg ($p>0.05$, Student t test), respectively. Hematoma drain placement in the lateral ventricle was performed in 2 patients, both of who survived, while surgical hematoma evacuation was performed for 6 patients who survived and 2 patients who had a poor outcome (mRS VI). The final outcomes were mRS VI (44%) and V (25%). As shown in Figure 1, most patients' conditions did not improve throughout hospitalization. We analyzed the risk factors for poor outcomes (mRS VI). As shown in Table 2, univariate logistic analysis demonstrated significant differences between the patients who did and did not survive in terms of GCS

scores on admission, mRS scores on admission, hematoma volume, presence of IVH, and the use of antihypertensive drugs. Multivariate logistic analysis, however, showed no significant prognostic factor, indicating that the results of the analysis should only be used as an advisory, since the analyses were performed in a small sized sample. Older patients tended to have higher mortality rates than younger patients, although the difference between the two groups was not significant. There was no difference in systolic blood pressure between poor outcome patients and other HD patients (179.8+/- 59.8 mmHg (n=13) vs. 185.0+/- 35.0 (n=16), p>0.1, Student t test), or in HD duration between poor outcome patients and other HD patients (7.1 +/- 5.4 years (n=13) vs. 7.7 +/- 4.3 (n=15), p>0.1, Student t test).

As shown in Figure 2, no significant difference was observed between mortality (mRS VI) due to ICH on dialysis days (10 cases, 37%) and non-dialysis days (17 cases, 63%) in 27 cases with data regarding the timing of the ICH (p>0.05, Fisher's method). In these cases, 26% of the ICH occurred before the HD procedure on an HD day, which was a higher rate than during or after the HD procedure (11%) on the dialysis day.

Discussion

On admission, the condition of ICH patients on HD in this study was frequently classified as being serious. The prognostic factors associated with mortality were GCS on admission <8, hematoma volume >50 ml, the presence of IVH, and lack of antihypertensive drug usage. In previous papers, the overall 30-day mortality rate in ICH patients with advanced CRF has been shown to be 30 - 83% [7,16]. In one of the studies, the prognostic factors independently associated with mortality were as follows: GCS scores, old age, systolic blood pressure, ICH volume ≥30 ml, presence of IVH, and high serum glucose [7]. In another

paper, additional factors indicating poor prognosis were level of consciousness on admission, the size and shape of the hematoma, prothrombin time, and fibrin degradation product level [14]. In general, cerebral MBs detected on T2-weighted MRI scans are closely related to ICH [11,13,20,24], although our results could not corroborate this since our data included only ICH patients. A previous paper showed that 35% of CRF patients had MBs. Factors associated with MBs were male sex, old age, hypertension and worsening of CRF, although MBs did not show a correlation with the duration of HD treatment [25].

In our study, antihypertensive drugs were used more frequently by CRF patients than non-CRF patients. CRF patients frequently have renal hypertension, which may cause ICH. The odds ratio for ICH was 2.44 in the CRF group when compared to the non-CRF group [22]. However, the use of antiplatelets/anticoagulants did not significantly predict poorer outcomes. Therefore, patients should strictly control their hypertension and should not hesitate to take antiplatelets/anticoagulants as they do not pose a risk for ICH. A limitation of the present study is that the results were obtained from retrospective and non-controlled data. However, various analyses, including univariate and multivariate logistic regression analyses showed similar results. Hence, we believe that these results are generally reliable.

As shown in Figure 2, ICH frequently occurred on a non-dialysis day. HD in CRF patients is usually scheduled three times a week, and some reports show that the occurrence of disease is related to the day of HD. For example, sudden cardiac death events occur more often on Mondays and Wednesdays [2]. The occurrence rates of acute myocardial infarction, heart failure and stroke are high when the interval between HD treatments is two days [5]. This suggests that medical practitioners should be careful to screen HD patients for ICH on non-dialysis days.

In our study, mortality in ICH patients on HD was associated with lack of antihypertensive drug usage. Most patients who do not use antihypertensive drugs are

patients with absent or mild hypertension, although there may be some cases of drug withdrawal in patients with severe hypertension. Interestingly, previous studies regarding risk factors for poor outcomes in non-traumatic ICH also did not contain a history of hypertension [3, 6]. For instance, one of these studies suggests that the factors independently associated with 30-day mortality are GCS scores, age ≥80 years, infratentorial origin of ICH, ICH volume and the presence of IVH [6]. In this previous study, the incidence of hypertension in the poor outcome group (43%) was lower than that in the other ICH group (73%) [6], similar to the present results. We speculate that severe ICH depends upon factors other than hypertension (such as existence of microaneurysms). Hence, the occurrence of severe ICH in both HD and non-HD patients should be considered independently of hypertension.

In conclusion, multivariate logistic analysis showed that hematoma location, use of antihypertensive drugs, use of antiplatelets/anticoagulants, and patient outcome were significantly different between HD and non-HD groups. On the other hand, use of antihypertensive drugs or antiplatelets/anticoagulants did not worsen the outcome of the ICH patients on HD. Thus, in HD patients, the possibility of severe ICH should be considered regardless of the use of antihypertensive drugs or antiplatelets/anticoagulants. In this study, ICH frequently occurred before the HD procedure on an HD day or on an interval day.

Conflict of Interest statement

All authors declare no conflicts of interest.

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Figure legends

Figure 1. Modified Rankin Scale scores in intracerebral hemorrhage (ICH) patients on admission and on discharge

Figure 2 Relationship between ICH occurrence and the timing of the hemodialysis (HD) procedure. Black and white bars indicate the frequencies of living and deceased patients, respectively.

Fig. 1

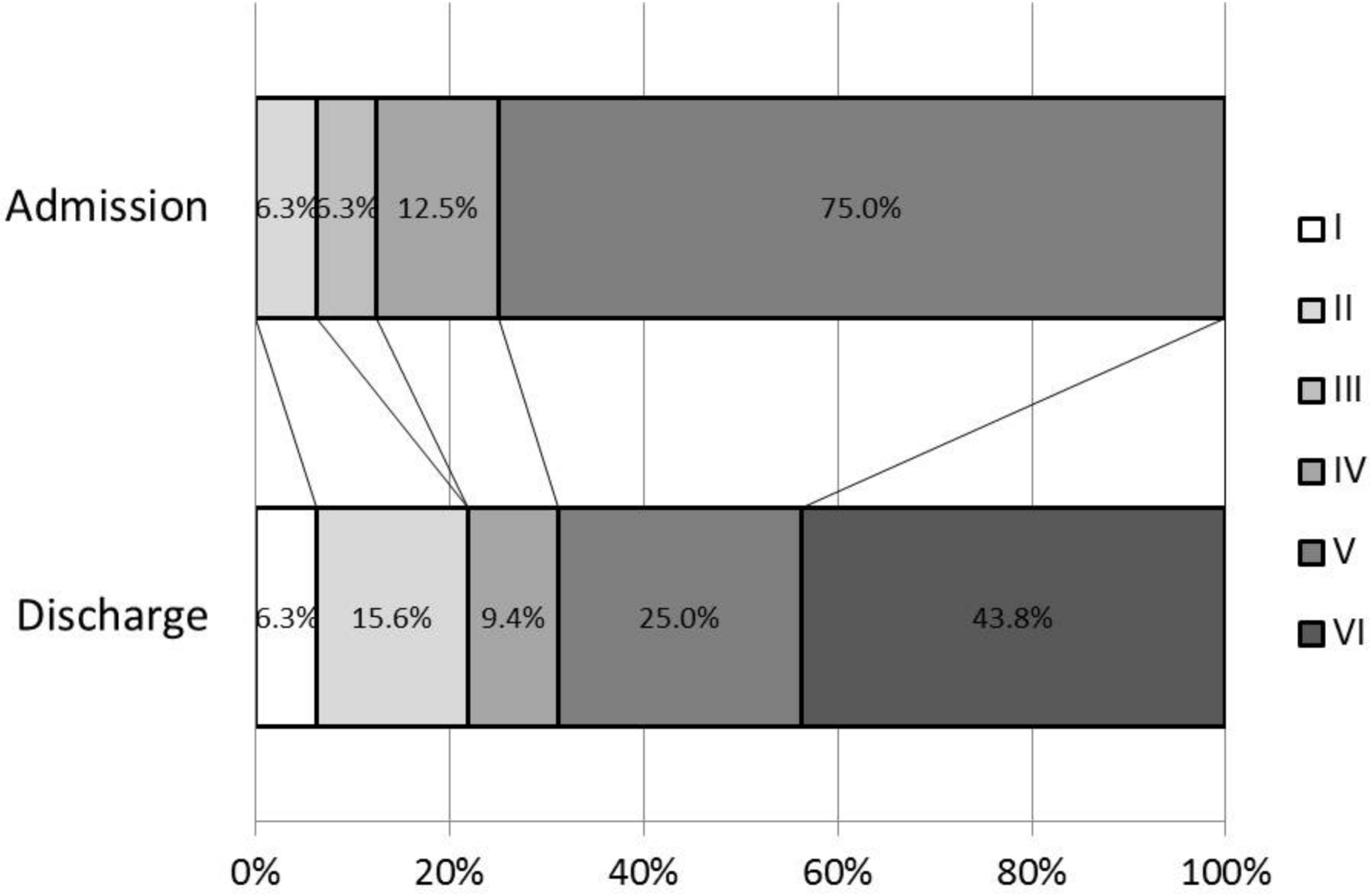
Admission
6.3%
6.3%
12.5%
75.0%
Discharge
6.3%
15.6%
9.4%
25.0%
43.8%
I
II
III
IV
V
VI
0%
20%
40%
60%
80%
100%

Fig. 2

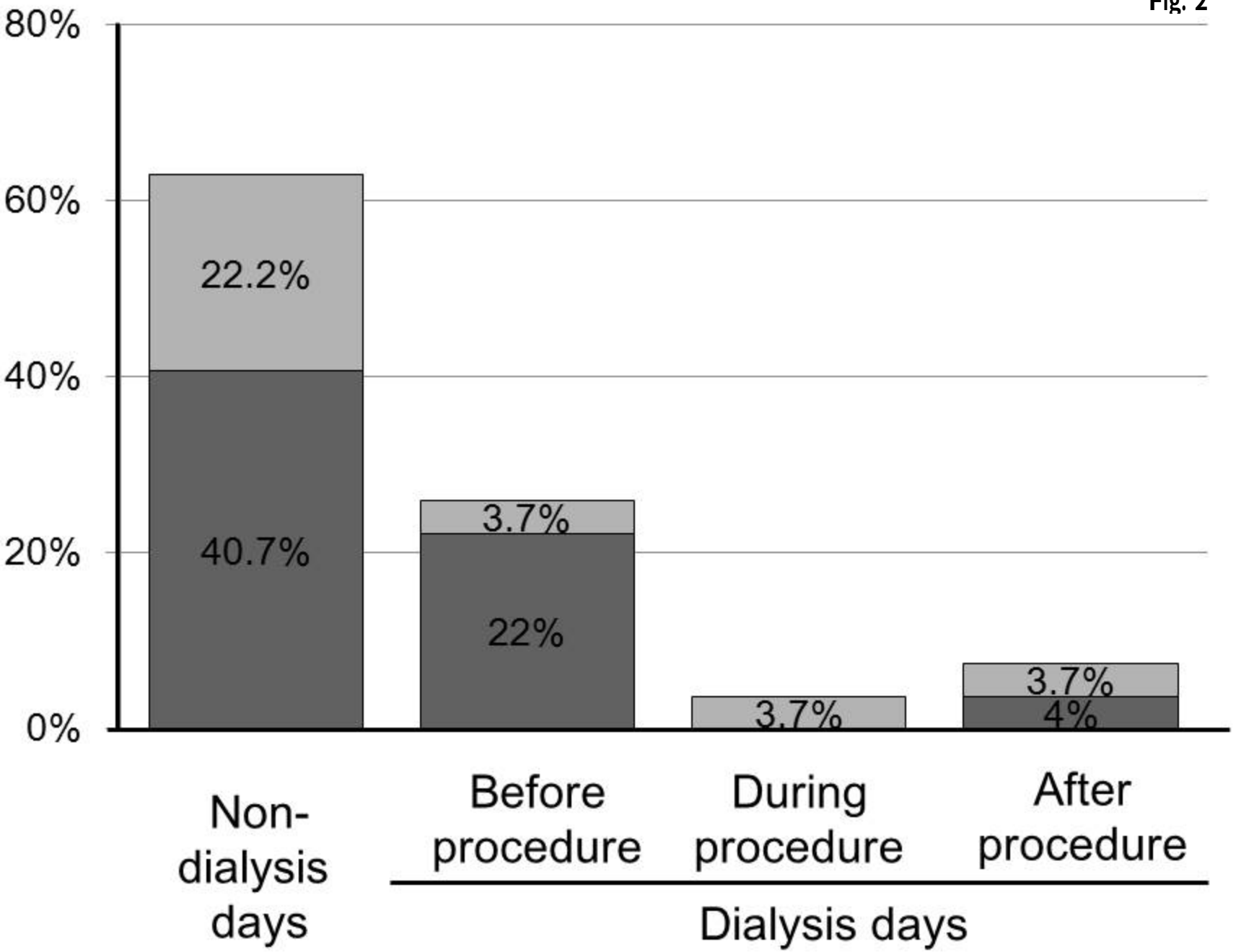
80%
60%
40%
20%
0%
22.2%
40.7%
3.7%
22%
3.7%
3.7%
4%
Non-dialysis days
Before procedure
During procedure
After procedure
Dialysis days

Table 1: Characteristics of ICH patients (n=366)

	HD		Non-HD		Logistic analysis (p value, Exp)			
	(n=32)		(n=334)		Univariate		Multivariate	
Background								
Median age (years)	64 (28-84)		69 (8-95)		(> 0.1, Student t)			
Age (≤65 years)	16	50%	134	40%	0.2801	(1.493)	-	-
Gender (Female)	16	50%	135	40%	0.2952	(1.474)	-	-
Use of AHD (Y)	23	72%	108	32%	0.0001	5.348	0.0009	4.934
Use of ADD (Y)	13	41%	66	20%	0.0080	2.778	0.1880	(1.846)
Use of AP/AC (Y)	13	41%	58	17%	0.0023	3.256	0.0068	3.299
One drug / Two drugs	*9 / 4*		*45 / 13*					
After ICH								
Location (BG)	27	84%	192	57%	0.0055	3.994	0.0087	4.130
BG (putamen, thalamus)/ Lobar (subcortical) / Others (cerebellum, brainstem)	*27 / 3 / 2*		*192 / 70 / 72*					
Laterality (Left sided)	18	58%	166	56%	0.4800	(1.300)	-	-
Presence of IVH	17	53%	114	34%	0.0357	2.187	0.7968	(1.127)
Operation (Y)	10	31%	70	21%	0.2128	(1.654)	-	-
Surgical hematoma evacuation / Hematoma drain placement in the lateral ventricle	*8 / 2*		*45 / 25*					
Patient Outcome								
Outcome (mRS) (VI)	14	44%	71	21%	0.0054	2.881	0.3150	(1.741)
(V+VI)	22	69%	122	37%	0.0008	3.823	0.0093	4.338
I / II / III / IV / V / VI	*2 /5 /0 /3 /8 /14*		*51/92/22/47/51/71*					

ADD, anti-diabetic drugs; AHD, anti-hypertensive drugs; AP/AC, antiplatelets or anticoagulants; BG, Basal ganglia; HD, hemodialysis; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin scale; Y, yes

Table 2: Characteristics of ICH patients with HD (n=32)

	Dead (n=14)	Alive (n=18)	Logistic analysis (p value, Exp) Univariate		Multivariate	
Background						
Age (years)	70.3+/-10.2	62.1+/-12.7	*(0.0591, Student t)*			
Age >65 years	64%	39%	0.1590	(2.825)		
Gender (Female)	57%	44%	0.4773	(1.667)		
HD duration until ICH (years)	7.1 +/- 5.4	7.7 +/- 4.3	*(>0.1, Student t)*			
HD duration < 7.5 years	62%	47%	0.4331	1.828		
Use of AHD (N)	50%	11%	0.0240	8.000	0.9864	-
Use of ADD (N)	64%	56%	0.6185	(1.441)		
Use of AP/AC (N)	64%	56%	0.6185	(1.441)		
After ICH						
GCS on admission (median)	4	13.5	*(0.0001, MWU)*			
GCS <8 (Y)	93%	17%	0.0006	65.00	0.9480	-
mRS on admission (median)	5	5	(0.0356, MWU)			
mRS = 5	93%	61%	0.0649	8.273	0.9999	
sBP (mmHg)	179.8+/- 59.8	185.0+/- 35.0	*(>0.1, Student t)*			
sBP <180	38%	38%	0.9577	(1.042)		
ICH location (BG)	86%	78%	0.5709	(1.714)		
ICH laterality (non-left sided)	54%	33%	0.2578	(2.333)		
ICH volume	74.3+/-16.4	24.0+/-6.2	*(0.0027, Student t)*			
Volume >50 ml (Y)	58%	17%	0.0240	6.993	0.9612	-
Presence of IVH (Y)	79%	33%	0.0152	7.353	0.9856	-
Operation (N)	86%	56%	0.0810	4.808	0.9496	-
Patient Outcome						
GOS (median)	5	3	*(0.0001, MWU)*			
mRS (median)	6	4	*(0.0001, MWU)*			

ADD, anti-diabetic drugs; AHD, anti-hypertensive drugs; AP/AC, anti-platelets or anti-coagulants; BG, basal ganglia; GCS, Glasgow Come Scale; GOS, Glasgow Outcome Scale; ICH, intracerebral hemorrhage; IVH, intraventricular hemorrhage; mRS, modified Rankin scale; MWU, Mann-Whitney U test; N, no; sBP, Systolic Blood pressure on admission; Y, yes.