Unplanned Hemodialysis Initiation and Low Geriatric Nutritional Risk Index Scores are Associated with End-Stage Renal Disease Outcomes

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Abstract

Background

Patients with end-stage renal disease (ESRD) have low nutritional status, presenting a high mortality risk. The geriatric nutritional risk index (GNRI) is a predictive marker of malnutrition. However, it is unclear whether the association between unplanned hemodialysis (HD) and GNRI scores is related to mortality.

Methods

The 180 patients who underwent HD at our hospital were divided into two groups: unplanned initiation with a central venous catheter (CVC; n=73) or planned initiation with prepared vascular access (n=107).

Results

There were no significant differences in sex, age, malignant tumor, hypertension, and vascular disease, while there were significant differences in time from the first visit to HD initiation (0 vs. 7 times, p=0.012) and days between the first visit and HD (12 vs. 186 days, p<0.001). The CVC insertion group had significantly lower GNRI scores at initiation (85.5 vs. 98.8, p<0.001). The adjusted hazard ratios were 4.115 and 3.077 for the GNRI scores and frequency, respectively. Three-year survival was significantly lower in the CVC + low GNRI group (p<0.0001). GNRI after 1 month was significantly inferior in the CVC insertion group.

Conclusions

Inadequate general management due to late referral to the nephrology department is a risk factor for patients with ESRD.

Introduction

The number of patients with end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) is increasing worldwide [1, 2]. As the elderly population increases, a higher proportion of frail patients needing dialysis will appear globally. Although the development of hemodialysis (HD) management makes it possible to prolong patients' lifespans, it is well known that inadequate preparation such as an unplanned HD initiation needing central venous catheter (CVC) insertion affects their mortality [3]. Compared to arteriovenous fistulas, CVC insertion has a hazard ratio of 1.53 (95% confidence interval [CI] 1.41–1.67) for all-cause mortality [4], showing that HD with CVC is a risk factor for mortality. The arteriovenous fistulas should be performed 4 weeks before the scheduled HD initiation, as it takes at least 2 weeks before maturation [5]. This suggests that patients with chronic kidney disease (CKD) should be

referred to the nephrology department at the appropriate time, with access prepared before dialysis initiation [6], as late referral to nephrologists leads to unfavorable outcomes [7–9].

On the other hand, patients with ESRD and uremia can develop malnutrition [10], with a prevalence of 28–54% in patients undergoing HD [11]. Wei et al. showed that malnutrition could be associated with frailty, a geriatric syndrome that reflects multisystem physiological dysregulation [12]. Indeed, malnutrition in patients with ESRD and prefrailty/frailty is a significant risk factor for poor outcomes [11, 12].

Several prediction scores for mortality of malnutritional patients with ESRD have been broadly investigated. Biochemical indices such as serum albumin, C-reactive protein, and ferritin are well-known prediction markers. In contrast, the physical index described by a subjective global assessment, subjective global assessment-dialysis malnutrition scores, malnutrition inflammation scores, and geriatric nutrition risk index (GNRI) scores have also been studied and can be used to evaluate nutritional status [13–16]. GNRI was originally developed by Bouillanne [17] to recognize geriatric hospitalized patients at nutritional risk and is based on simple indices such as serum albumin and bodyweight. To date, several studies have shown that GNRI can be used to predict the mortality of frail patients undergoing HD [7, 8].

GNRI at the time of dialysis initiation is valuable for predicting mortality (GNRI Low, 22.2% vs. GNRI High, 12.6%, $p<0.001$) [18]. Although many studies have demonstrated the effectiveness of the GNRI as a predictive marker in the management of CKD or maintenance of patients with frailty and malnutrition undergoing HD, few have described whether GNRI scores at HD initiation could impact the outcome of unplanned HD initiation following inadequate preparation due to late referral. Thus, we investigated whether the association between unplanned dialysis and nutritional status affects patient outcomes.

Results

Baseline characteristics

There was no significant between-group difference regarding sex, age, primary illness (such as active malignant tumors, diabetes mellitus, and hypertension), and past medical history, including ischemic heart disease, neurovascular disease, and peripheral artery disease. The medical history of RRT conducted prior to HD was similar between the two groups (Table 1). Visit frequency until ESRD requiring HD initiation was significantly lower in the CVC insertion group than in the vascular access initiation group (0 vs. 7, respectively; $p=0.012$). Similarly, the number of days between the first visit and HD (12 vs. 186 days, respectively; $p<0.001$) and between vascular access placement and HD were significantly lower in the CVC insertion group than in the vascular access initiation group (-15 vs. 71 days, respectively; $p<0.001$; the minus sign indicates that vascular access was created after HD initiation). Of note, there was a statistically significant between-group difference in GNRI scores at HD initiation (CVC insertion vs.

vascular access, 85.5 vs. 98.8%; p<0.001), similar to the visit frequency. Unplanned HD with CVC insertion and a low GNRI score were considered consequences of late referral to the nephrology department.

Table 1
Clinical characteristics of patients undergoing HD

	CVC insertion (n = 73)	Vascular access (n = 107)	p-value
Male, number (%)	70 (65.4%)	47 (64.4%)	0.886
Age [IQR]	69 [60–78]	70 [61–78]	0.726
Visit frequency until HD initiation	0 [0–3]	7 [4–12]	0.012
Days between first visit and HD initiation	12 [0–129]	186 [91–413]	<0.001
Days between VA preparing and HD initiation	-15 [-26– -7]	71 [20–143]	<0.001
Unexpected HD initiation, number (%)	56 (76.7%)	4 (3.7%)	<0.001
Pre-HD RRT, number (%)			
None	62 (84.9%)	100 (93.5%)	0.167
Peritoneal dialysis	7 (9.6%)	4 (3.7%)	
Kidney transplantation	4 (5.5%)	3 (2.8%)	
GNRI at HD initiation [IQR]	85.5 [79.4–97.7]	98.8 [94.0–106.5]	<0.001
Malignant tumor, number (%)	13 (17.8%)	12 (11.2%)	0.209
Diabetes, number (%)	36 (49.3%)	43 (40.2%)	0.226
Hypertension, number (%)	52 (71.2%)	82 (76.6%)	0.415
PAD, number (%)	8 (11.0%)	12 (11.2%)	0.957
PMH, ischemic heart disease, number (%)	14 (19.2%)	22 (20.6%)	0.820
PMH, neurovascular disease, number (%)	9 (12.3%)	12 (11.2%)	0.819
eGFR at initiation, mean	6.2±3.2	5.3±1.8	0.093

Abbreviations: CVC, central venous catheter; eGFR, estimated glomerular filtration rate; GNRI, geriatric nutritional risk index; HD, hemodialysis; IQR, interquartile range; PAD, peripheral artery disease; PMH, past medical history; RRT, renal replacement therapy; VA, vascular access.

Risk factors of patients' outcomes on time of HD initiation

Next, we analyzed the relationship between visit frequency and the incidence of CVC insertion using an established receiver operating characteristic (ROC) curve (area under the curve 0.780, p=0.0077), with the value of 1 (one visit) as that with the highest sensitivity and specificity (Fig. 1). Univariate Cox regression

analysis showed that GNRI (low vs. high) at HD initiation and visit frequency (≤1) were significant risk factors for poor outcomes (hazard ratio 3.888, 95% CI 1.800–8.398, p<0.001 vs. hazard ratio 4.266, 95% CI 1.884–9.661, p<0.001), in addition to age (>75 years old) and brain/cardiovascular disorders. Although age and brain/cardiovascular disorders are recognized as important factors for patients' outcomes in CKD (hazard ratio 3.220, 95% CI 1.496–6.931, p=0.003 vs. hazard ratio 2.368, 95% CI 1.110–5.050, p=0.026), the multivariate-adjusted Cox regression analysis also indicated that GNRI scores and visit frequency were significant risk factors for poor outcomes as well (hazard ratio 4.115, 95% CI 1.644–10.303, p=0.003 vs. hazard ratio 3.077, 95% CI 1.286–7.365, p=0.012; Table 2). Thus, these analyses revealed that nutritional status and visit frequency also had a critical impact on survival outcomes.

Table 2
Risk factors affecting patient survival after HD initiation

	Univariate			**Multivariate**		
	Hazard ratio	95% CI	p-value	Hazard ratio	95% CI	p-value
Sex, male	0.809	[0.375, 1.743]	0.588			
Age, > 75 years old	3.220	[1.496, 6.931]	0.003	3.594	[1.586, 8.147]	0.002
Brain/Cardiovascular disorder	2.368	[1.110, 5.050]	0.026	3.475	[1.482, 8.150]	0.004
GNRI, Low vs. High	3.888	[1.800, 8.398]	<0.001	4.115	[1.644, 10.303]	0.003
Visit frequency ≤1	4.266	[1.884, 9.661]	<0.001	3.077	[1.286, 7.365]	0.012
*GNRI was calculated using the following formula: GNRI = (14.89 × sAlb) + 41.7 × (BW/IBW)						
Abbreviations: sAlb, serum albumin; BW, bodyweight; CI, confidence interval; GNRI, geriatric nutritional risk index; HD, hemodialysis; IBW, ideal body weight						

Association of unplanned HD initiation and malnutrition prior to initiation with patient mortality

We then investigated whether the combination of malnutrition and HD initiation with CVC insertion could lower all-cause mortality. Patients were divided into four groups according to GNRI and CVC insertion: with CVC + low GNRI, without CVC + low GNRI, without CVC + high GNRI, and with CVC + high GNRI. Although the 3-year patient survival in the "with CVC + low GNRI" group was inferior (53.9%, p<0.0001) to that of the other groups, the remaining three groups were not significantly different (84.0, 89.6, and 78.6%; p=0.5642; Fig. 2). Almost all events occurred within 48 weeks of initiation.

Furthermore, we analyzed the transition of GNRI scores during the adjustment period of HD between the CVC insertion and vascular access groups. The CVC insertion group had a lower GNRI (median,

interquartile range: 85.5 [79.4–97.7]) compared to the vascular access group (98.8, [94.0–106.4]; p<0.001) that persisted even after 1 month (85.4 [76.4–90.6]) compared to the vascular access group (93.6 [88.5–101.7]; p<0.001), showing that low GNRI scores persisted despite HD initiation (Fig. 3).

Discussion

We analyzed the association between malnutrition and inadequate preparation for HD and identified that unplanned HD initiation due to late referral to a nephrology department could lead to poor patient outcomes. In this retrospective cohort, although there was no significant between-group difference regarding age, sex, primary illness, and past medical history, visit frequency and GNRI were significantly different, showing that patients who underwent CVC insertion did not have sufficient time to have a vascular access prepared. Visit frequency ≤1 could be the cut-off value to denote CVC insertion and unplanned HD initiation. Three-year patient survival was significantly lower in the group with CVC and low GNRI scores than in the other combination groups. Furthermore, the GNRI scores of the CVC group also had a significantly lower value despite HD treatment.

The number of patients with ESRD is increasing worldwide, and more elderly patients are undergoing dialysis [1]. As the number of frail patients with CKD is increasing, physicians should manage the patients' health and consider their preferred choice [12]; if renal function decreases and patients wish to undergo RRT, they should be referred to experts. In a 2019 update, the Kidney Disease Outcome Quality Initiative (KDOQI) recommended that the ESRD life-plan be discussed with the patient within a multidisciplinary team framework. The nephrologist should at least discuss modality options with the patient, with referral to a vascular access surgeon for input on the appropriate dialysis access that corresponds to the chosen RRT modality [19]. In other words, vascular access should be prepared at an appropriate time to avoid the risk of CVC insertion. The Japanese Society for Dialysis Therapy guidelines describe that vascular access construction should be considered for CKD stages 4 or 5 while considering clinical conditions, and an arteriovenous fistulas should be constructed at least 2–4 weeks before the initial puncture [20].

A previous study showed that an unplanned start of dialysis was associated with poor survival. Roy et al. demonstrated that the survival rates at 3 and 12 months were 38.6% vs. 90.9% and 14.4% vs. 73.6% for unplanned vs. planned dialysis, respectively (p<0.001), showing that insufficient preparation is a risk for these patients [3]. Indeed, immature vascular access due to late referral could lead to unplanned dialysis [21]. However, there is no universal definition for referral timing in patients with CKD, and it varies between institutions [22–24]. Although the optimal cut-off value is still controversial, the most broadly accepted definition of late referral is the first encounter with an expert within 3–4 months prior to the diagnosis of ESRD [6, 25]. Our clinical data also showed that the vascular access group visited a physician to consider RRT, approximately 3 months or more (186 [range: 91–413] days) prior to the diagnosis of ESRD requiring HD initiation.

Other reasons why physicians should refer patients with ESRD to a nephrology department is potential loss of appetite due to cytokine production, malabsorption due to gut edema, and difficulty in oral intake arising from general fatigue [26]. According to the 2020 KDOQI guidelines, CKD malnutrition care should be undertaken by multi-disciplinary teams [27]. To evaluate malnutrition status, the GNRI was originally developed by Bouillanne, and this simple marker represented by serum albumin and bodyweight has been proven useful for evaluating mortality of patients with CKD [8, 9, 17, 18]. One report stated that the GNRI was useful for predicting mortality in patients with CKD at the time of dialysis initiation [18]. In contrast, many studies have demonstrated that the GNRI could be an effective predictive marker in patients undergoing HD [7, 8, 28]. However, it remains unclear whether urgent HD initiation due to late referral and nutritional status is associated with patient outcomes. In our study, the CVC insertion group had a lower visit frequency until HD initiation than the vascular access group and had lower GNRI scores, which have been recognized as a predictor of mortality. The fact that the CVC + low GNRI group had the lowest 3-year survival demonstrated that inappropriate patient evaluation or late referral to a nephrology department lead to poor patient outcomes.

The major limitations of this study include the small patient cohort, the retrospective and short-term nature of the study, and the insufficient definition of the appropriate referral timing. Furthermore, unmeasured and residual confounding factors might have affected our results. Indeed, we did not compare the model performance of these nutritional indices with the malnutrition inflammation scores [14], a standard nutritional assessment tool frequently used in patients undergoing HD. Additionally, we could not retrospectively examine the rationale behind the visit frequency affecting GNRI scores. Further study is needed to investigate the causes of few visits in detail. Finally, because patients undergoing HD visited different HD clinics as outpatients after discharge, we did not consider residual bias that could exist in each clinic's management.

In conclusion, the combination of unplanned HD initiation with CVC insertion and low GNRI scores with low nutritional status was significantly associated with poor patient outcomes. Although this study had some limitations, our results support the critical role of managing patients with CKD who require RRT during the preservation period. We strongly recommend that non-nephrological experts refer such patients to the appropriate nephrology department to facilitate the early management of CKD. However, patient outcomes in ESRD may not be strictly associated with one nutritional factor, and further studies should focus on a larger number of patients, with detailed nutritional information, over longer follow-up periods.

Materials And Methods

This study was approved by the Osaka Medical and Pharmaceutical University ethics committee in accordance with institutional guidelines. The study conformed to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all the patients for publication.

Study population and clinical design

A total of 219 patients with ESRD who had started HD at Osaka Medical and Pharmaceutical University Hospital between January 2016 and December 2019 were retrospectively enrolled in this study. These patients were referred to our department from clinics or other departments to consider RRT. Among these patients, 39 were excluded due to a lack of clinical data or acute kidney injury. A total of 180 patients were finally included in this study and divided into two groups based on whether HD initiation was unplanned or planned (CVC insertion vs. vascular access; Fig. 4).

In our institute, patients with CKD are generally referred to our department to select RRT options. In this cohort, the patients who underwent planned HD received vascular access surgery in our department, and HD was subsequently initiated depending on their general condition. Unplanned HD initiation was defined as dialysis initiation when access was not ready for use, patients required hospitalization, or dialysis was initiated with a modality that was not the one initially selected for the patient (e.g., CVC insertion) [29]. The first visit refers to the day on which patients had a consultation or were referred to our department, and visit frequency is the time between the first visit and the first HD session.

The geriatric nutrition risk index

GNRI scores were calculated from the patients' serum albumin value and bodyweight using the following formula: GNRI = (14.89 × serum albumin [mg/dL]) + 41.7 × (bodyweight/ideal bodyweight) [17]. Bodyweight was measured in kg at the time of HD initiation and 1 month later. The ideal bodyweight was calculated from the patient's height and a body mass index of 22. The GNRI scores were used as both continuous and categorical variables. Here, we adopted a GNRI score of 91.2 as the cut-off for dividing the low and high GNRI groups in accordance with a previous study [27, 28].

Statistical analysis

Demographic information is summarized using frequency counts or as the mean with standard deviation values and the median with interquartile range. The chi-square test with Fisher's exact test was used to compare categorical variables, and Student's t-test or one-way analysis of variance was used to compare continuous variables, as appropriate. ROC curve analysis was used to investigate whether visit frequency values could distinguish between CVC insertion and non-insertion at HD initiation. The frequency with the best accuracy was selected as the cut-off value. A multivariate Cox proportional hazard regression model was used to assess risk factors for all-cause mortality. The 3-year survival rate was initially estimated using Kaplan–Meier analysis. The population of kidney transplantation after HD initiation was considered censored in the survival analysis. Univariate analysis was used to examine prognostic factors for the final multivariate Cox regression analysis model. Factors that reached significance in the univariate analysis were subsequently included in the multivariate Cox model to determine the independent effects of each factor. Two-sided P-values <0.05 were considered statistically significant. All statistical analyses were performed using JMP Software 15 Pro version (SAS Institute, Cary, NC, USA).

Declarations

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Conflicts of interest

The authors declare that they have no conflicts of interest.

Author contributions

RM, DK, TM, and YY contributed equally to this work and performed the experiments, analyzed the data, and wrote the manuscript. ST, YF, KK, and HU performed and analyzed the experiments. MK, HH, TI, and HN analyzed the data and helped prepare the manuscript. HA designed and supervised the experiments and wrote and edited the manuscript.

Data availability statement

The data supporting this study's findings are available on request from the corresponding author (HA).

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Figures

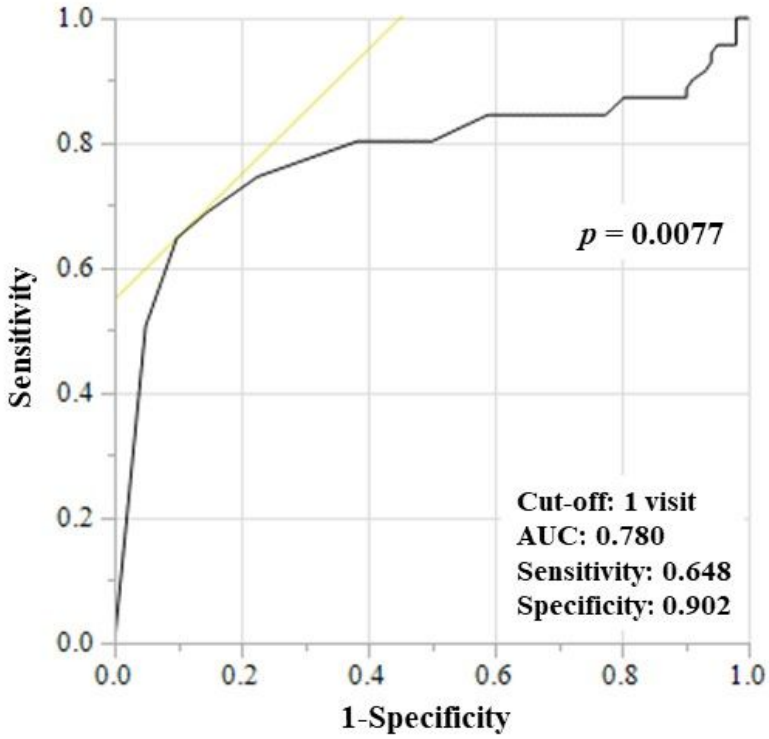

Figure. 1

Figure 1

ROC analysis based on visit time for CVC insertion at HD initiation. In this model, the cut-off value of visit time is 1; sensitivity and specificity were 64.8 and 90.2%, respectively; the AUC was 0.780, p=0.0077.

AUC, area under the curve; CVC, central venous catheter; HD, hemodialysis; ROC, receiver operating characteristic

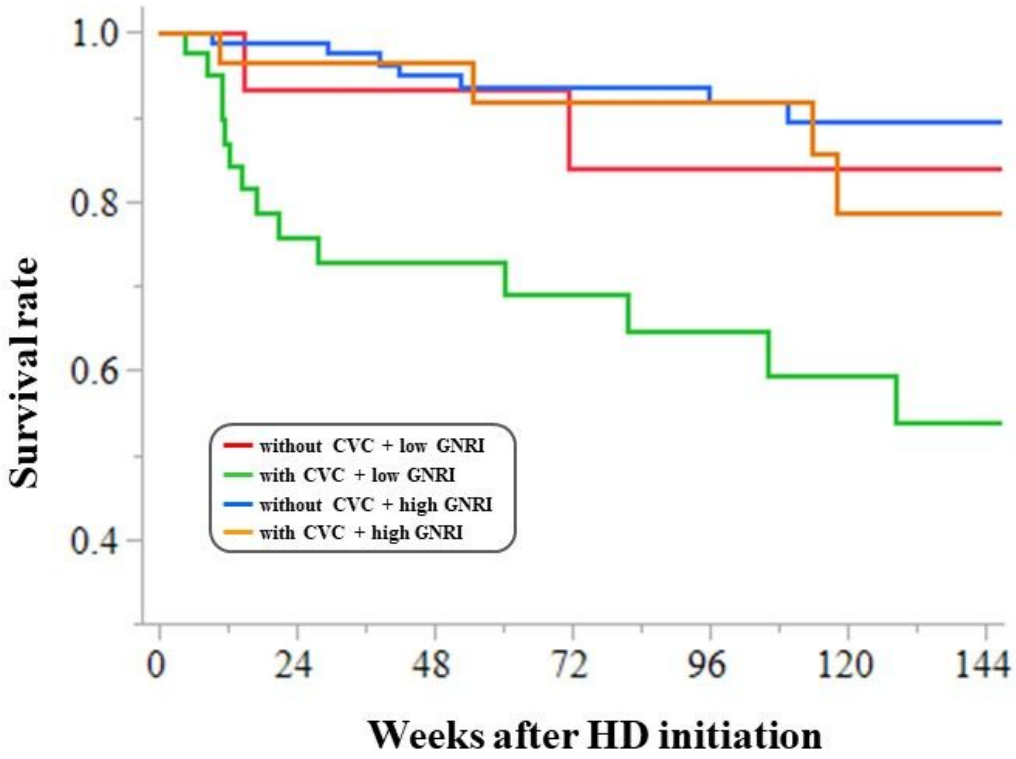

Figure. 2

Figure 2

The 3-year survival rates after HD initiation. We compared four groups based on two parameters: with CVC + low GNRI, without CVC + low GNRI, without CVC + high GNRI, and with CVC + high GNRI. Those who belonged to the “with CVC + low GNRI” had the lowest survival rate (53.9%, $p<0.0001$) compared to the other groups (84.9%, 89.8%, and 78.6%).

CVC, central venous catheter; GNRI, geriatric nutritional risk index; HD, hemodialysis

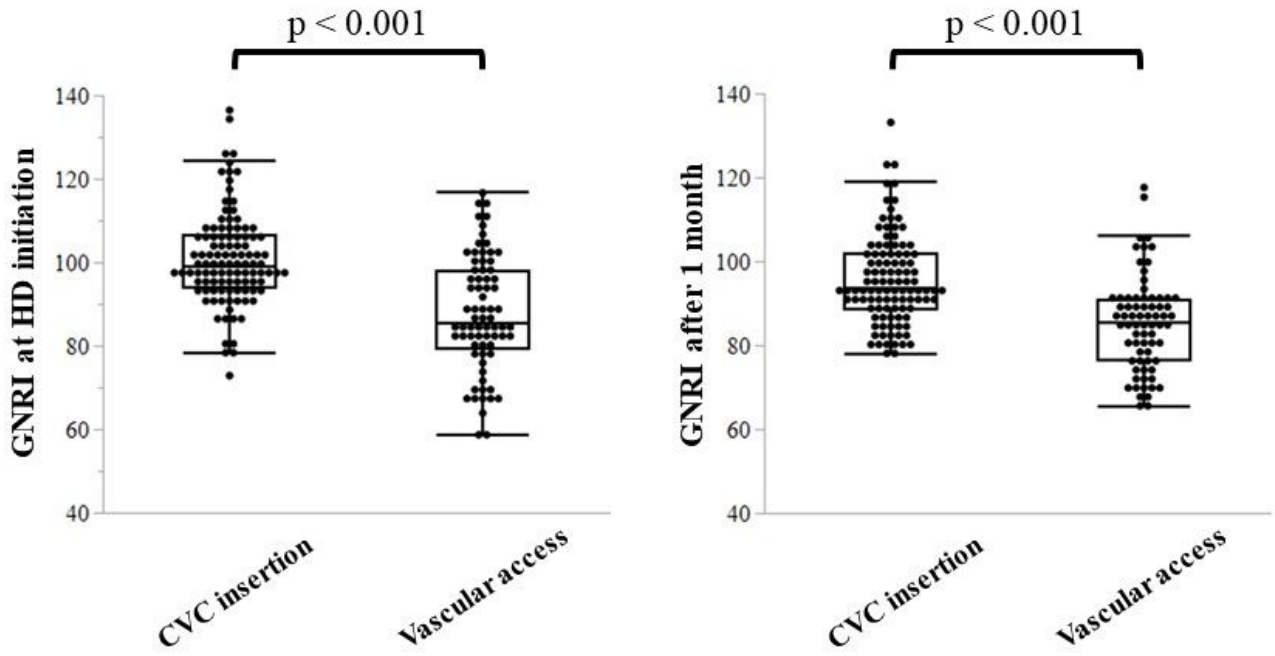

Figure. 3

Figure 3

The transition of GNRI between HD initiation and 1 month after initiation. At the time of initiation, GNRI was significantly lower in the CVC group compared to the vascular access group. Similarly, at 1 month after initiation, the low value of GNRI persisted in the CVC insertion group.

CVC, central venous catheter; GNRI, geriatric nutritional risk index; HD, hemodialysis

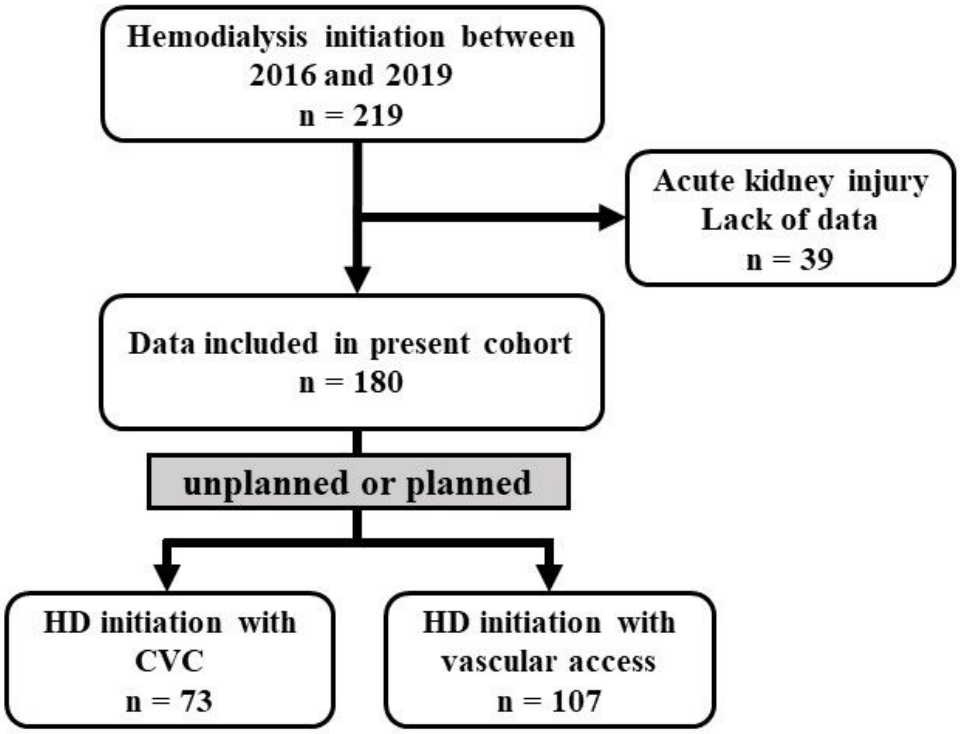

Figure. 4

Figure 4

Flowchart of patient selection. Out of 219 patients screened between January 2016 and December 2019, we excluded 39 due to acute kidney injury and lack of data. Ordinarily, patients are referred to our department from other departments or clinics to prepare vascular access and HD initiation. Of the 180 patients, the CVC group contained 73, and the vascular access group contained 107 patients in this cohort study.

CVC, central venous catheter; HD, hemodialysis