Renal Replacement Therapy

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# Perimortem changes in clinical parameters in patients undergoing maintenance hemodialysis

Tadashi Yoshida[1*], Kohkichi Morimoto[1], Takashin Nakayama[2], Takuto Torimitsu[2], Shotaro Kosugi[2], Takuma Oshida[2], Nobuko Yamaguchi[1,3] and Mototsugu Oya[1,4]

## Abstract

**Background:** End-of-life medical care for patients receiving maintenance hemodialysis (HD) therapy has become an increasingly important issue worldwide. Thus far, no clear indicators and/or biomarkers exist regarding the timing of HD therapy withdrawal.

**Methods:** To clarify the perimortem circumstances, we examined temporal changes in multiple clinical parameters during the last 10 serial HD sessions of 65 terminal patients with end-stage renal disease who had undergone maintenance HD and died in our hospital.

**Results:** The results showed that, while most of the laboratory data were unaltered, the physical parameters, such as systolic blood pressure and consciousness levels, gradually and significantly deteriorated toward the last HD session prior to death. The frequency of the use of vasopressors and $O_2$ inhalation tended to increase. The accumulation of such severe conditions was observed at the last HD session. Of interest, the accumulation of severe conditions at the last HD session in patients with malignancies was significantly less than those with cardiovascular diseases or infectious diseases. The accumulation of severe conditions at the last HD session did not differ between patients who withdrew HD versus those who continued HD.

**Conclusion:** The results of the present study suggest that predicting the timing of maintenance HD therapy withdrawal is likely to be difficult and that the timing of maintenance HD therapy termination may differ among patient groups with distinct comorbid conditions.

**Keywords:** Hemodialysis, Forgoing, Withdrawal, Blood pressure

## Background

End-of-life medical care for patients receiving maintenance hemodialysis (HD) therapy has become an increasingly important issue worldwide [1–4]. This can be attributed, at least in part, to an increase in aging patients with end-stage renal disease (ESRD) [5, 6]. Many HD patients have serious complications, such as cardiovascular disease, and it is sometimes difficult to continue intermittent HD sessions during the final stage [7–9]. However, no clear indicators and/or biomarkers exist regarding the timing of HD therapy withdrawal.

The withdrawal of maintenance HD therapy is consequently related to death in ESRD patients. However, extracorporeal circulation occasionally leads to a severe reduction in blood pressure, and HD therapy itself can become life-threatening during a terminal stage [7]. Recently, the Japanese Society for Dialysis Therapy published a proposal for a shared decision-making process

*Correspondence: t-yoshida@keio.jp
[1] Apheresis and Dialysis Center, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan
Full list of author information is available at the end of the article

regarding the initiation and continuation of maintenance HD [3]. In this proposal, the withdrawal of maintenance HD therapy has been recommended under the following conditions: (1) when it is difficult to perform HD safely and when HD itself could be life threatening; and (2) when the patient's general condition becomes extremely poor and the patient's wish regarding the forgoing of HD has been specifically expressed, or when the family can assume the patient's wish definitely [3]. The medical team needs to evaluate these conditions objectively, but assessments have thus far been performed based on their individual experiences.

Previously, we collected data from deceased HD patients and showed that physical parameters (such as blood pressure and consciousness levels), the use of specific medical treatments (such as vasopressor use, oxygen inhalation and ventilator use), nursing care levels, and the activities of daily living (ADL) could be potential indicators to predict short-term prognosis in HD patients [10]. To clarify these perimortem circumstances in greater detail, we examined the temporal changes in multiple clinical parameters during the last 10 serial HD sessions in terminal patients with ESRD who had undergone maintenance HD and had died in our hospital.

## Methods

### Study subjects

This retrospective study was conducted at a single institution in Japan. The study protocol was approved by the institutional review board (IRB; Approval Number: 20190065). The IRB dismissed the need to obtain written informed consent from the family/relatives of the deceased patients, although the study protocol was disclosed and an opportunity to opt out was given. Between January 1, 2014, and December 31, 2018, 1525 ESRD patients underwent maintenance intermittent HD therapy while admitted to our hospital. Among them, 65 patients died during their hospital stay; these patients were recruited for the present study. In the present study, patients undergoing maintenance HD therapy were defined as those receiving intermittent HD therapy for more than 2 months. For patients whose dialysis modality changed from intermittent HD therapy to continuous hemodiafiltration therapy during their hospital admission, the last HD session was defined as the last session of intermittent HD.

### Data

Data regarding sex, age, ESRD etiology, HD vintage, the dates of admission, the last HD session and death, and the causes of admission and death were obtained from the patients' medical records. Laboratory data, including white blood cell counts, the levels of hemoglobin, total protein, albumin, urea nitrogen, creatinine, potassium, calcium, phosphate and C-reactive protein, as well as physical data, such as consciousness levels, systolic and diastolic blood pressure and heart rate, were collected. Data regarding the presence or absence of the oral intake of foods, vasopressor use, $O_2$ inhalation, surgery, and vascular access trouble were also collected. In the present study, the data regarding the presence or absence of the oral food intake were collected as a representative marker of ADL, because we previously showed that the abilities of patients to turn over in beds, change their clothes, eat, and perform oral care deteriorated significantly toward the death, and these abilities were well correlated each other [10].

### Statistical analyses

Normally distributed continuous variables were expressed as the mean ± standard deviation (SD), non-normal variables as the median and interquartile range (IQR), and categorized data as the percentage frequency. To test for differences between groups, a one-way ANOVA with a post hoc Fisher's protected least significant difference test was used for normally distributed variables, a Mann–Whitney test or a Kruskal–Wallis one-way ANOVA on ranks with Dunn's post hoc test was used for non-normal variables, and a $\chi^2$ test was used for categorical data. All the statistical analyses were performed using SigmaPlot/SigmaStat 9 (Systat Software Inc, San Jose, CA). A value of $P<0.05$ was considered significant.

## Results

### Characteristics of deceased HD patients

Sixty-five patients undergoing maintenance HD died in our hospital between January 1, 2014, and December 31, 2018 (Table 1). Fifty-three of them (82%) were male, whereas twelve (18%) were female. The median age at death was 73 (IQR: 65–79) years, and the HD vintage was 42 (IQR: 5–114) months. The patients had been admitted in the hospital for 33 (IQR: 16–114) days, and the duration from the last HD session until death was 2 (IQR: 1–4) days. In 5 patients, the dialysis modality was changed from intermittent HD therapy to continuous hemodiafiltration therapy at a terminal stage, but these patients all died within 2–12 days after the last intermittent HD session. The etiologies of ESRD were diabetes (29%), hypertension (20%), primary glomerular diseases (17%), polycystic kidney disease (8%), and others (26%). The reasons for hospital admission were cardiovascular diseases (34%), gastrointestinal disorders (20%), infectious diseases (18%), malignancies (17%), and others (11%). The causes of death were infectious diseases (45%), cardiovascular diseases (25%),

**Table 1** Characteristics of patients ($n = 65$)

| | |
|---|---|
| Male (%) | 82 |
| Age at death (years) | 73 (IQR: 65–79) |
| HD vintage (months) | 42 (IQR: 5–114) |
| Duration of admission (days) | 33 (IQR: 16–114) |
| Duration from last HD session until death (days) | 2 (IQR: 1–4) |
| *CKD etiology (%)* | |
| Diabetes | 29 |
| Hypertension | 20 |
| Primary glomerular diseases | 17 |
| Polycystic kidney disease | 8 |
| Others | 26 |
| *Causes of admission (%)* | |
| Cardiovascular diseases | 34 |
| Gastrointestinal diseases | 20 |
| Infectious diseases | 18 |
| Malignancies | 17 |
| Others | 11 |
| *Causes of death (%)* | |
| Cardiovascular diseases | 25 |
| Gastrointestinal diseases | 12 |
| Infectious diseases | 45 |
| Malignancies | 15 |
| Others | 3 |

The median values and interquartile ranges (IQR) or percentages are shown

malignancies (15%), gastrointestinal diseases (12%), and others (3%).

### Temporal changes in multiple clinical parameters before death

Temporal changes in laboratory data for the 65 deceased patients were examined over the last 10 serial HD sessions that were completed before death. As shown in Fig. 1, most of the laboratory data, including the white blood cell counts and the levels of hemoglobin, total protein, albumin, urea nitrogen, creatinine, potassium, and C-reactive protein were unaltered among the 10 time points before death. However, the serum phosphate level gradually increased toward the last HD session (Fig. 1H).

Changes in multiple physical parameters, including systolic blood pressure, diastolic blood pressure, heart rate, and consciousness levels, are shown in Fig. 2. The systolic blood pressure at the start of the HD session was the lowest at the last HD session (99 [IQR: 86–114] mmHg) among the 10 serial HD sessions (Fig. 2A). The diastolic blood pressure at the start of the HD session did not differ among the 10 serial HD sessions (Fig. 2B). The proportion of patients whose systolic blood pressure was less than 90 mmHg at the start of the HD session gradually increased over time (Fig. 2C), and the proportion of patients whose systolic blood pressure dropped to less than 90 mmHg during the HD session also increased toward the last HD session (Fig. 2D). On the other hand, the heart rate at the start of the HD session did not differ significantly among the 10 serial HD sessions (Fig. 2E). Regarding the consciousness levels, the proportion of patients with disturbed consciousness (i.e., Japan Coma Scale [JCS] $\geq 10$) gradually increased toward the last HD session (Fig. 2F) [11]. Indeed, 44% of the patients had disturbed consciousness at the last HD session.

We next examined alterations in the eating status and various medical treatments during the last 10 serial HD sessions prior to death. The proportion of patients with oral intake did not differ significantly over time, although a trend toward a decrease in eating ability was observed (Fig. 3A). The proportions of patients who were treated with vasopressors and who inhaled oxygen, respectively, also tended to increase over time (Fig. 3B, C). Indeed, 29.2% of the patients were being treated with vasopressors at the last HD session, whereas only 11.4% of the patients had received treatment with vasopressors as of 10 sessions before the last HD session (Fig. 3B). Similarly, 64.6% of the patients required oxygen inhalation at the last HD session, while 40% of the patients had required oxygen inhalation as of 10 sessions before the last HD session (Fig. 3C). On the other hand, the proportion of patients who had undergone surgery within 7 days was unaltered across the 10 serial HD sessions (Fig. 3D). In addition, the proportion of patients with vascular access troubles was unaltered (Fig. 3E).

### Accumulation of severe conditions before death

We examined whether multiple severe conditions had accumulated before death. We counted the cumulative number of the following conditions over the last 10 serial HD sessions: (1) a systolic blood pressure of less than 90 mmHg at the start of the HD session; (2) a systolic blood pressure dropping to less than 90 mmHg during the HD session; (3) a disturbed consciousness level (JCS $\geq 10$); (4) an inability to consume food orally; (5) the

(See figure on next page.)

**Fig. 1** Temporal changes in white blood cell (WBC) counts (**A**), and the levels of hemoglobin (**B**), total protein (**C**), albumin (**D**), urea nitrogen (**E**), creatinine (**F**), potassium (**G**), phosphate (**H**), and C-reactive protein (**I**) were examined in 65 HD patients over 10 serial HD sessions prior to death. Data were collected from the 10th HD session before death (−10) until the last HD session (L). Differences were tested using a Kruskal–Wallis one-way ANOVA on Ranks (**A**–**G**, **I**) or a one-way ANOVA with a post hoc Fisher's protected least significant difference test (**H**). *$P < 0.05$ compared to the last HD session. **$P < 0.05$ compared to the −2 HD session prior to death. ***$P < 0.05$ compared to the −3 HD session prior to death

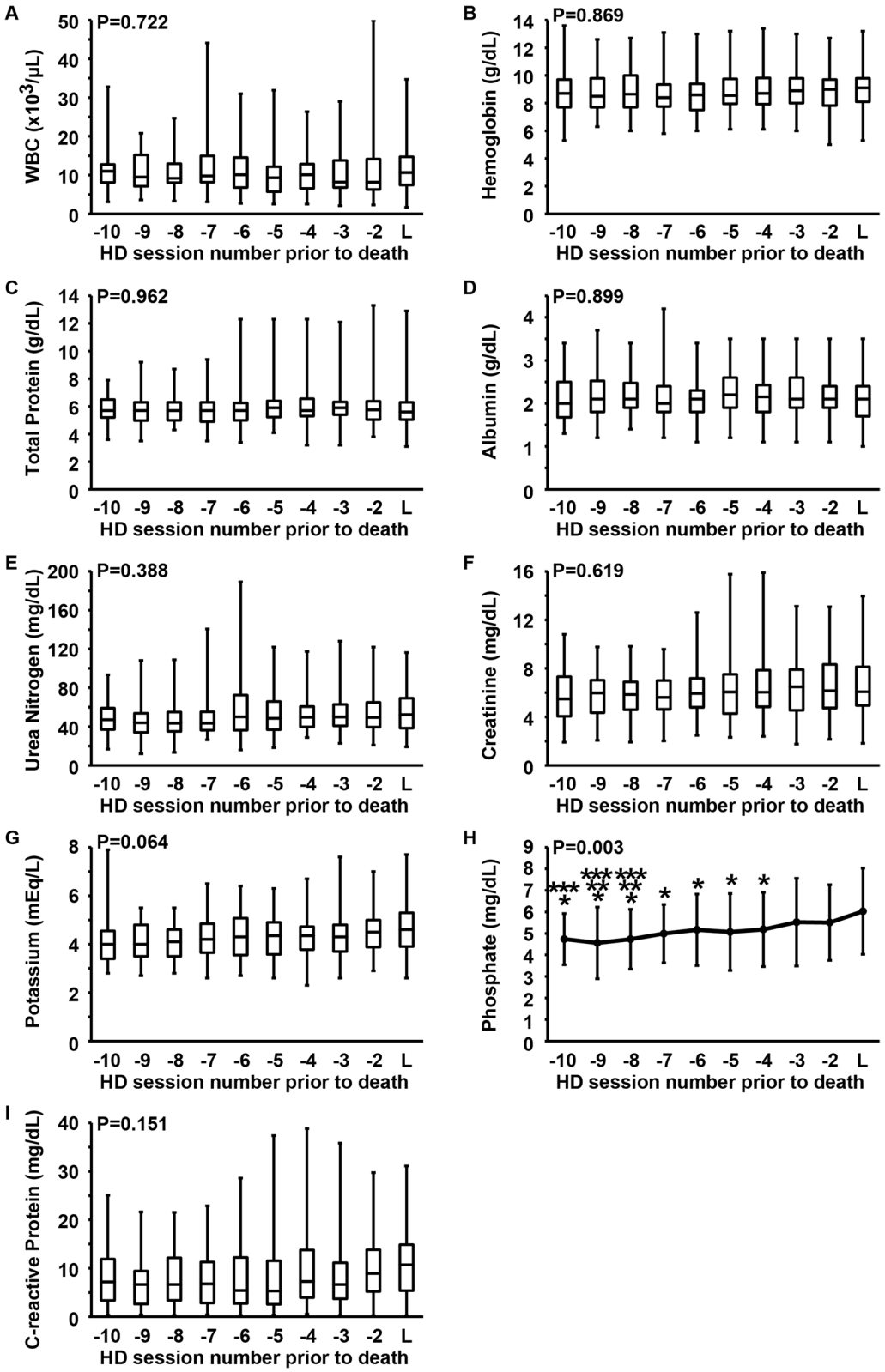


**Fig. 1** (See legend on previous page.)

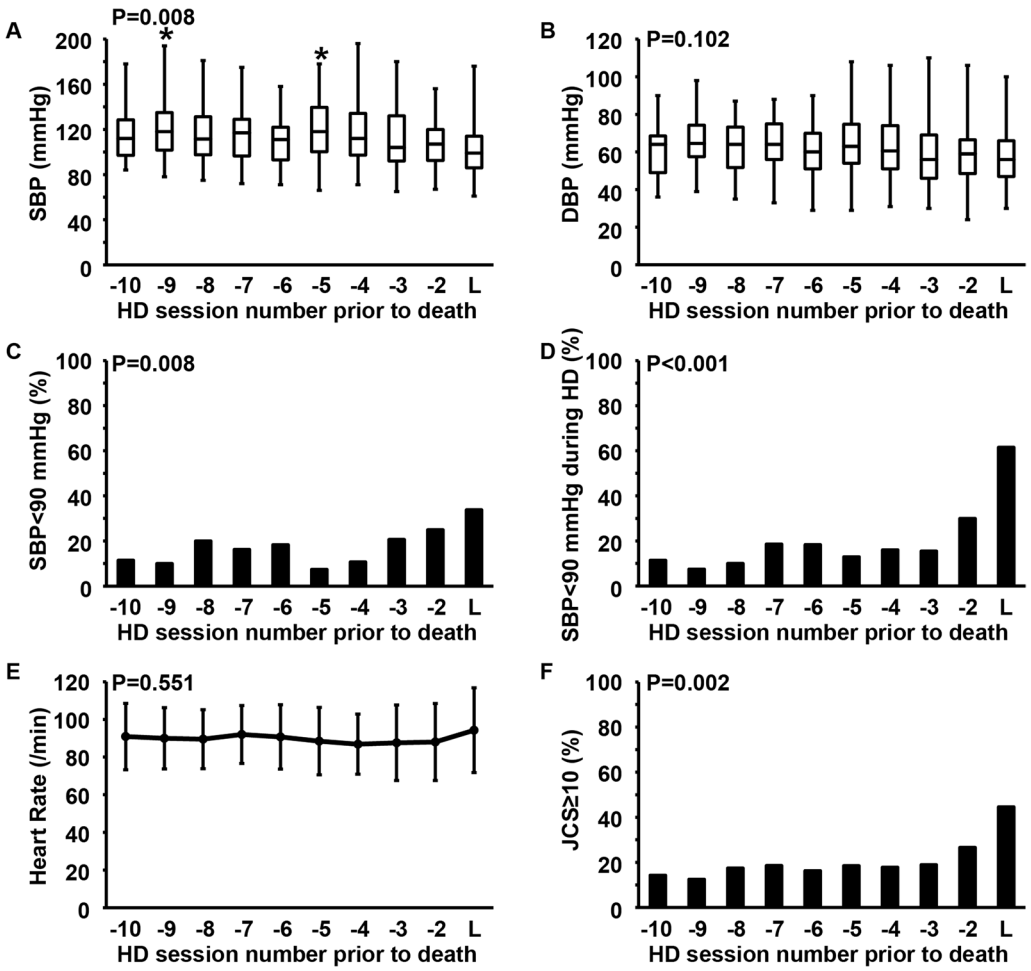


**Fig. 2** Changes in the systolic blood pressure (SBP) at the start of the HD session (**A**), the diastolic blood pressure at the start of the HD session (**B**), the proportion of patients with an SBP of less than 90 mmHg at the start of the HD session (**C**), the proportion of patients with an SBP of less than 90 mmHg during the HD session (**D**), the heart rate at the start of the HD session (**E**), and the proportion of patients with disturbed consciousness (JCS ≥ 10) were examined in 65 HD patients over 10 serial HD sessions prior to death. Data were collected from the 10th HD session before death (−10) until the last HD session (L). Differences were tested using a Kruskal–Wallis one-way ANOVA on Ranks with Dunn's post hoc test (**A**, **B**), a $\chi^2$ test (**C**, **D**, **F**), or a one-way ANOVA (**E**). *$P < 0.05$ compared to the last HD session

use of oxygen inhalation; and (6) the use of vasopressors. The median cumulative number was 1 or 2 conditions from 10 HD sessions before death until 2 HD sessions before death (Fig. 4A). However, a significant increase in the cumulative number of conditions was seen immediately before death. Indeed, the cumulative number of severe conditions was 3.0 (IQR: 2.0–4.0) at the last HD session. We further examined whether the cumulative number of severe conditions differed among patients with different causes of death (Fig. 4B). The cumulative number of severe conditions at the last HD session was 3.5 (IQR: 2.75–5.0) in patients who died of cardiovascular diseases and 4.0 (IQR: 2.0–4.0) in patients with infectious diseases. On the other hand, it was only 1.5 (IQR: 1.0–2.75) in patients who died of malignancies. Temporal changes in the cumulative number of severe conditions over the last 10 serial HD sessions in patients with malignancies and without malignancies are shown in Fig. 4C, D. These results suggest that the timing of maintenance HD termination may differ among patients with distinct comorbid conditions. However, the duration from the last HD session until death did not differ significantly among the groups (Fig. 4E). Finally, we examined whether the cumulative number of severe conditions at the last HD session differed between patients for whom HD was withdrawn ($n = 21$) and patients for whom HD was continued ($n = 44$). The accumulation of severe conditions was similar between both groups (Fig. 4F).

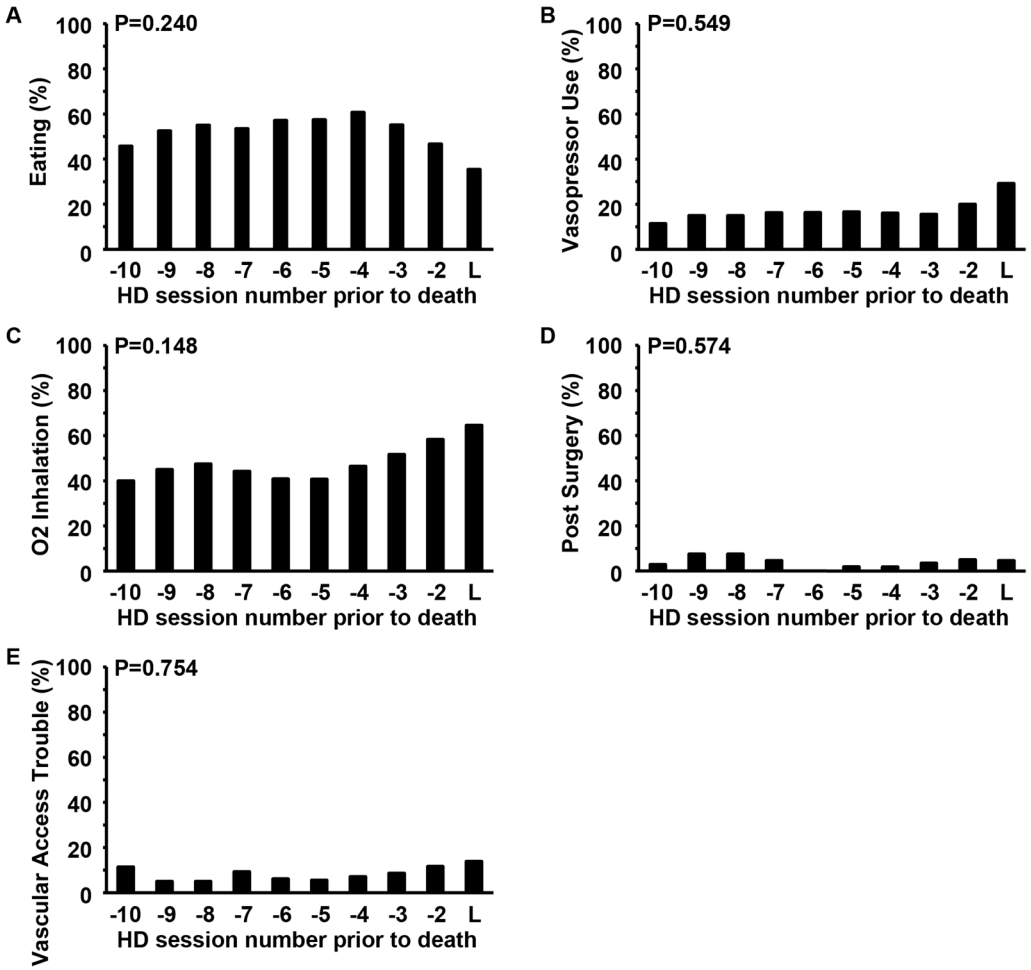


**Fig. 3** Changes in the proportion of patients who could eat orally (**A**), who were treated with vasopressors (**B**), who required $O_2$ inhalation (**C**), who had received surgery within 7 days (**D**), and who had vascular access troubles (**E**) were examined in 65 HD patients over 10 serial HD sessions prior to death. Data were collected from the 10th HD session before death (−10) until the last HD session (L). Differences were tested using a $\chi^2$ test

## Discussion

In the present study, we examined temporal changes in multiple clinical parameters, including laboratory data, physical data, the use of specific medical treatments, and the eating status of 65 ESRD patients who had undergone maintenance HD therapy prior to dying at our hospital. The results showed that most of the laboratory data, including serum albumin level, a marker of the nutritional status, were unaltered during the last 10 serial HD sessions prior to death. However, the physical parameters, such as the systolic blood pressure and consciousness levels, gradually and significantly deteriorated toward the last HD session before death. In addition, the frequency of the use of specific medical treatments, including vasopressor use and $O_2$ inhalation, tended to increase. The accumulation of severe conditions was observed at the time of the last HD session. Of interest, the accumulation of severe conditions varied according to distinct comorbidities. Indeed, the accumulation of severe conditions at the last HD session in patients with malignancies was significantly less than that in patients with cardiovascular diseases or infectious diseases. These results suggest that the timing of maintenance HD termination might differ among patients with distinct comorbid conditions. However, the duration from the last HD session until death did not differ significantly among the groups. Furthermore, we showed that the accumulation of severe conditions at the last HD session was not different between patients for whom HD was withdrawn and patients for whom HD was continued, suggesting that the withdrawal of HD in our hospital was executed at the very last moment in terminal HD patients.

Previously, we showed that physical parameters (blood pressure and consciousness levels), the use of specific medical treatments (vasopressor use, $O_2$ inhalation, and ventilator use), nursing care levels, and ADL,

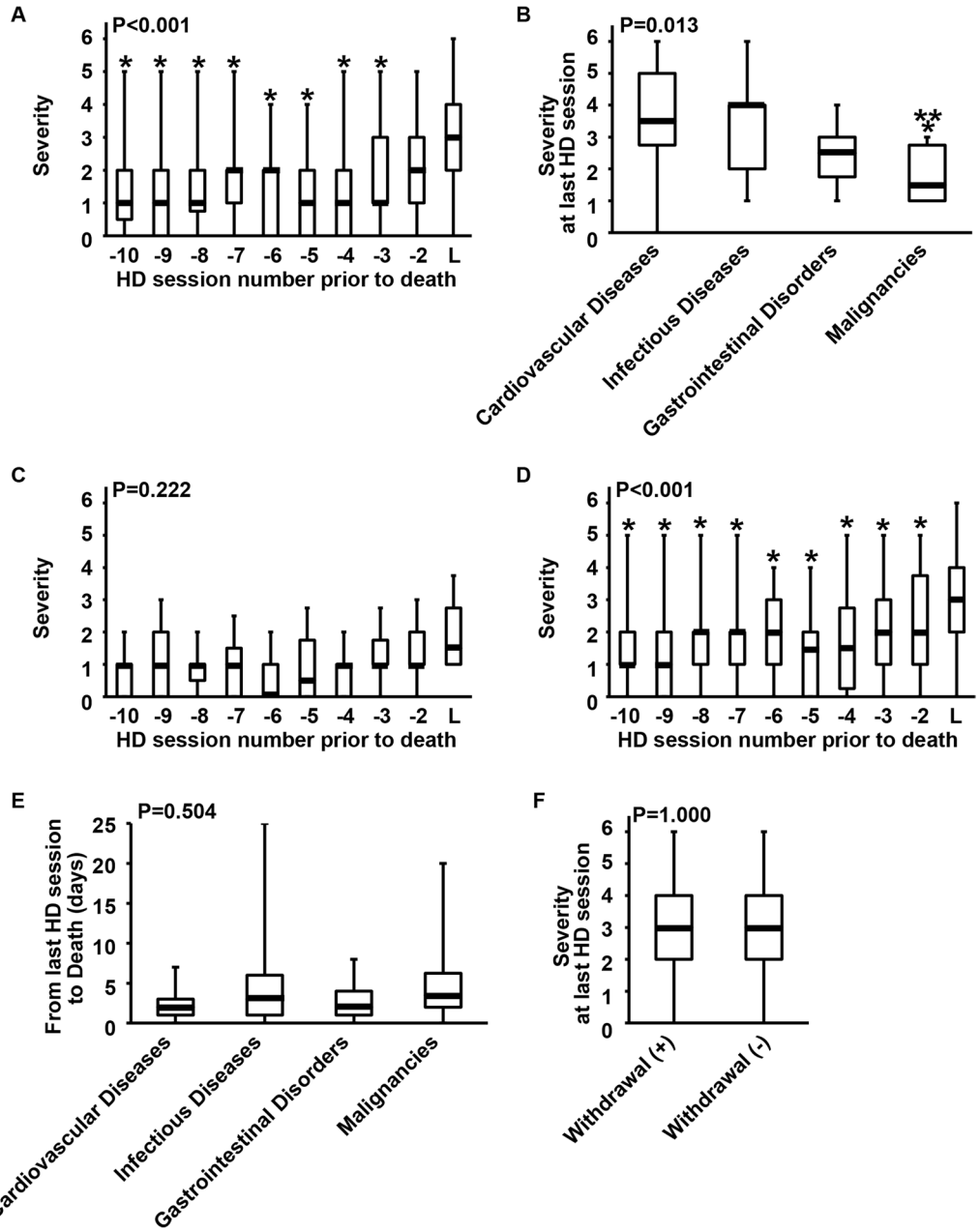


**Fig. 4** **A** Changes in the cumulative number of severe conditions, including (1) a systolic blood pressure of less than 90 mmHg at the start of the HD session; (2) a systolic blood pressure that dropped to less than 90 mmHg during the HD session; (3) a disturbed consciousness level (JCS ≥ 10); (4) an inability to consume food orally; (5) the use of oxygen inhalation; and (6) the use of vasopressors, were examined in 65 HD patients over 10 serial HD sessions prior to death. Data were collected from the 10th HD session before death (−10) until the last HD session (L). *$P < 0.05$ compared to the last HD session. **B** Cumulative numbers of severe conditions at the last HD session for patients classified according to the cause of the death. *$P < 0.05$ compared to patients with cardiovascular diseases. **$P < 0.05$ compared to patients with infectious diseases. **C**, **D** Changes in the cumulative number of severe conditions were examined in HD patients with malignancies (**C**, $n = 10$) and without malignancies (**D**, $n = 55$) over 10 serial HD sessions prior to death. Data were collected from the 10th HD session before death (−10) until the last HD session (L). *$P < 0.05$ compared to the last HD session. **E** The duration from the last HD session until death was examined in 65 HD patients. **F** The cumulative number of severe conditions at the last HD session was compared between patients for whom HD was withdrawn and patients for whom HD was continued. **A**–**F** Differences were tested using a Mann–Whitney test (**F**) or Kruskal–Wallis one-way ANOVA on Ranks with Dunn's post hoc test (**A**–**E**)

but not laboratory data, could be potential predictors of the short-term prognosis of terminal HD patients. These results were obtained after examining data from 47 deceased patients at 4 time points, including time of hospital admission, 2 weeks before death, last HD session, and day of the death [10]. The aim of the present study was to confirm and to extend these previous findings and to clarify how these factors change over 10 serial HD sessions prior to death. Basically, the results of the present study were consistent with those of our previous study [10], but the present study clarified that the deterioration in the parameters and the conditions occurred abruptly at the time of the last HD session. For example, the systolic blood pressure at the start of the HD session did not differ significantly from the 10th HD session to the 2nd HD session prior to death. However, it had decreased and reached its lowest value at the last HD session. The cumulative number of severe conditions at the last HD session was significantly higher than that at the 10th to the 3rd HD session prior to death. These results suggest that the timing of HD withdrawal might be difficult to predict in advance. On the other hand, the results of the present study also suggest that an increase in the cumulative number of severe conditions from 2 to 3 may reflect dangerous changes in the patient's physical condition immediately before death. Physicians should consider withdrawing maintenance HD therapy under such conditions.

When the cumulative number of severe conditions increases from 2 to 3 in a terminal HD patient, one may think that changing the dialysis modality from intermittent HD to others gives an advantage to long-term survival. However, we do not recommend this option. Indeed, 5 out of 65 patients in our study population changed the dialysis modality from intermittent HD to continuous hemodiafiltration therapy at a terminal stage, but they all died within 2–12 days after the last intermittent HD session. Conservative kidney management is probably the most appropriate option under such conditions.

The results of the present study showed that the cumulative number of severe conditions at the last HD session in patients with malignancies was significantly smaller than that in patients who died of cardiovascular diseases or infectious diseases. In such patients, the withdrawal of maintenance HD therapy might be determined, based on the score of survival prediction tools for terminally ill cancer patients [12–14]. Although the right to die with dignity has not been established by law in Japan, the Japanese Society for Dialysis Therapy has proposed that the presence of an incurable malignant disease should prompt a review of whether HD should be withdrawn [3]. The timing of maintenance HD termination might be slightly earlier among patients with malignancies at our hospital. In our cases, the median duration from the last HD session until death was 2 (IQR: 1–4) days. Even if the median survival time is only 2 days, the medical team, together with the patient's family, should make a palliative care plan. Indeed, among the 65 patients, 2 patients survived for more than 20 days after the last HD session. Conservative kidney management, including effective palliative care, should be provided to patients in whom HD therapy is withdrawn.

Withdrawal of maintenance HD therapy occurs frequently and has been recognized as an appropriate treatment option in Western countries [5–7, 15]. For example, dialysis withdrawal is the second or third leading cause of death in patients with ESRD in North America and Australia [5, 6, 15]. In "shared decision-making in the appropriate initiation of and withdrawal from dialysis", a clinical practice guideline published by the Renal Physician Association in the United States of America [4], it has been described that patients with two or more of the following characteristics may have a particularly poor prognosis: (1) elderly (age 75 years and older); (2) patients with high comorbidity scores (e.g., modified Charlson Comorbidity Index score of 8 or greater); (3) marked functional impairment (e.g., Karnofsky Performance Status Scale score of less than 40); and (4) severe chronic malnutrition (e.g., serum albumin level less than 2.5 g/dL). It has also been described that patients in this population should be informed that dialysis may not confer a survival advantage or improve functional status over medical management without dialysis and that dialysis entails significant burdens that may detract from their quality of life. Although these points are important information for making a decision to not initiate or to discontinue dialysis, they are not the description about the timing to withdraw dialysis at the terminal stage. Prediction of the timing of maintenance HD withdrawal is likely to be difficult.

The present study had several limitations. First, all 65 patients were hospitalized in a single institution. Although the composition of the causes of death and the age of the patients were similar to those of the entire HD patient population in Japan [16], the patient population examined in the present study might have been unique, and the presently obtained results might contain some biases that would prevent the results from being generalizable. Because our institution is a university hospital, HD patients who undergo aggressive treatment tend to stay in our hospital until the final stage, whereas those who decline such treatment tend to move to other hospitals prior to death. Consequently, the mortality rate of HD patients in our hospital was extremely low. Further data from deceased

HD patients who had been admitted to various types of clinics, hospitals, and hospices are needed. The retrospective nature of the analysis and a small number of Japanese patients were also limitations in this study. However, prospective studies of this topic are quite difficult. Further studies are required to confirm and extend our findings.

## Conclusion

In conclusion, the results of the present study showed that many clinical parameters, including blood pressure and consciousness levels, deteriorated gradually and significantly toward the last HD session in terminal HD patients. The accumulation of multiple severe conditions was observed at the time of the last HD session, but predicting the timing of maintenance HD withdrawal is likely to be difficult. Further studies are required to establish a scoring system for evaluating the short-term prognosis of these patients.

### Abbreviations

HD: Hemodialysis; ESRD: End-stage renal disease; ADL: Activities of daily living; IRB: Institutional review board; SD: Standard deviation; IQR: Interquartile range; JCS: Japan Coma Scale.

### Authors' contributions

TY: principal project leader, conceived study, participated in design and coordination, drafted manuscript, read and approved the final manuscript; KM, TN, TT, SK, TO, NY, MO: collected and analyzed the data, read and approved the final manuscript. All authors read and approved the final manuscript.

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### Availability of data and materials

The dataset used during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

The study protocol was approved by the IRB (Approval Number: 20190065). The IRB dismissed the need to obtain written informed consent from the family/relatives of the deceased patients, although the study protocol was disclosed and an opportunity to opt out was given.

### Consent for publication

Not applicable.

### Competing interests

The authors declare no conflict of interest.

### Author details

[1]Apheresis and Dialysis Center, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, Japan. [2]Division of Endocrinology, Metabolism and Nephrology, Department of Internal Medicine, Keio University School of Medicine, Tokyo, Japan. [3]Department of Nursing, Keio University Hospital, Tokyo, Japan. [4]Department of Urology, Keio University School of Medicine, Tokyo, Japan.

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## Publisher's Note