Cohort profile: Alliance for Quality Assessment in Healthcare-Dialysis (AQuAH-D) prospective cohort study of patients on haemodialysis in Japan

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ABSTRACT

Purpose The global burden of kidney failure is increasing, but the treatment of kidney failure varies widely between patients, between dialysis facilities and over time. The Alliance for Quality Assessment in Healthcare-Dialysis (AQuAH-D) aims to conduct efficient and timely cohort studies on associations between those variations and clinical and patient-reported outcomes.

Participants Included are outpatients aged 20 years old or older who are undergoing haemodialysis and have consented to participate. A total of 2895 patients were enrolled from 25 facilities in Japan between August 2018 and July 2020 and are to be followed until 31 December 2026. Chart review and annual questionnaires are used to collect data on patient characteristics and on outcomes including quality of life. Data on medications, haemodialysis prescriptions and blood tests are obtained from existing electronic records. Data are collected retrospectively from 1 January 2017 to patient enrolment, and prospectively from patient enrolment until the end of December 2026.

Findings to date To date, the mean age is 68.3 (SD 12.2) years and 35.2% are female. The most common cause of kidney failure is diabetic nephropathy (37.4%). In January 2020, the facilities' median weekly doses of erythropoietin stimulating agent (ESA) and of intravenous vitamin D ranged from 1846 to 9692 IU (epoetin alfa equivalent) and 0.78 to 2.25 µg (calcitriol equivalent), respectively. The facilities' percentages of patients to whom calcimimetics are prescribed varied from 19% to 79%. During the retrospective period (averaging 1.85 years per participant), the incidence rates of any hospitalisation and of hospitalisation due to cardiovascular disease were 67.2 and 12.0 per 100 person-years, respectively.

Future plans AQuAH-D data will be updated every 6 months and will be available for studies addressing a wide range of research questions, using the advantages of granular data and quality-of-life measurement of ageing patients on haemodialysis.

Strengths and limitations of this study

- The Alliance for Quality Assessment in Healthcare-Dialysis, a multicentre prospective cohort of outpatients on haemodialysis in Japan. It will be updated every 6 months and will provide valuable data that can be used for timely studies on changing haemodialysis practice.
- With electronic records of highly granular, sequential practice-related data and data on outcomes including quality of life, a wide range of important research questions are expected to be addressed.
- Results from this cohort study are expected to inform approaches to the problems of ageing and multimorbidity of patients on haemodialysis, which are becoming more important worldwide.
- We are not attempting to construct a representative sample of dialysis facilities in Japan.
- We are unable to include data on prescriptions or examinations from facilities other than those participating in the study.

INTRODUCTION

Kidney failure is an important non-communicable disease. The number of people receiving kidney replacement therapy (KRT, either dialysis or kidney transplantation) worldwide was estimated to be 2.6 million in 2010 and is expected to reach 5.4 million by 2030.[1] Kidney transplantation is preferred because of its favourable effects on prognosis and on quality of life (QOL).[2] However, haemodialysis is currently the mainstay of KRT especially in eastern and southeastern Asia including Japan, where deceased-donor organ transplantation is relatively rare, probably due to cultural context.[3 4] In Japan, approximately 300 000 people were on maintenance haemodialysis in 2018 and the number is increasing.[5]

Variations in haemodialysis practice have been described in observational studies, and possible associations of patient outcomes with patient-level, institutional and temporal variations have been evaluated.[6–8] Management of kidney failure with haemodialysis requires

attention to anaemia,[9] mineral–bone disorder (MBD),[10] dialysis prescriptions,[11] vascular access,[12] comorbidities (diabetes mellitus, cardiovascular disease,[13 14] etc) and changes over time. A database allowing questions about management of kidney failure to be answered quickly and efficiently would be useful. Researchers lack information that is granular enough to facilitate investigation of those questions.

Because Japan's population is ageing faster than those in many other parts of the world, it is already dealing with the problems of ageing and multimorbidity of patients on haemodialysis that are starting to emerge in some other countries.[15] In addition to survival,[16] patient-reported outcomes (PROs), including QOL and symptoms, are important outcomes in this chronically ill and ageing population. In that context, we see an unmet need for a haemodialysis cohort database that includes both PROs and highly granular data, and for that database to be updated frequently and to be quickly available to researchers.

The Alliance for Quality Assessment in Healthcare-Dialysis (AQuAH-D), was established (1) to describe patient-level and facility-level variations in dialysis practice, (2) to investigate the factors explaining and predicting variations in dialysis practice and (3) to investigate associations between variations in dialysis practice and clinical outcomes including PROs among ageing patients on maintenance haemodialysis in Japan. To achieve those objectives, we have established a system to frequently collect highly granular data, and to share them with researchers without delay.

COHORT DESCRIPTION

Study design and Setting

This is a multicentre prospective cohort study of clinics and hospitals with outpatient haemodialysis centres in Japan. Facility recruitment started in September 2018 and participants are recruited from the time of facility participation until 30 June 2026. Follow-up is intended to continue until the end of December 2026.

Participants

Outpatients aged 20 years old or older, the age at which people in Japan are legally considered to be adults, who are undergoing maintenance haemodialysis and have consented to participate are being included. Patients who receive peritoneal dialysis are being excluded, because we have not established a sustainable method to collect sufficient data on peritoneal dialysis, due to the lack of facility-by-facility electronic data on variables relevant to research, such as daily dialysis prescriptions over time. This cohort is open: Patients who were attending a facility at the time of the start of that facility's participation and those who begin coming to the facility thereafter until 30 June 2026 are candidates for enrolment.

Data sources and data collection

In principle, the data come from three types of sources: existing electronic records of practice-related data, chart review and patient-completed questionnaires (figure 1). A unique application software called AQuAH-D app, installed on each facility's computer, is used to integrate the data by patient ID, to create the facility database and to transfer the participants' anonymised data to the central database every 6 months.

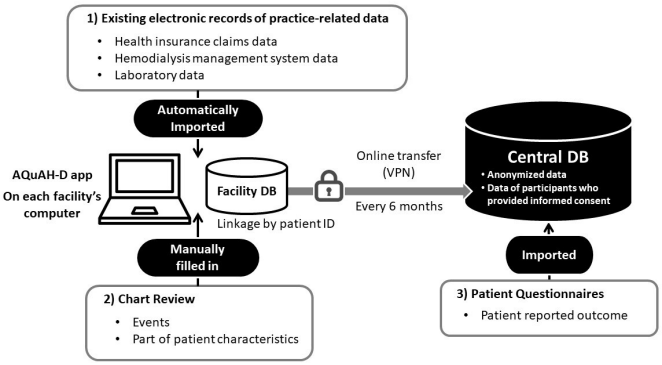

Figure 1 Data sources and data collection via the custom-made application software AQuAH-D app. Health insurance claims data are generated for reimbursement at each facility. Haemodialysis management systems are used by healthcare providers to manage haemodialysis prescriptions, to record the results of haemodialysis sessions, to hold data on patient characteristics and to hold data from each dialysis session. AQuAH-D, Alliance for Quality Assessment in Healthcare-Dialysis; DB, database, VPN, virtual private network.

Data source 1: existing electronic records of practice-related data

To minimise the burden of data collection, we use each facility's existing electronic records of practice-related data: health insurance claims data, haemodialysis management system data and laboratory data. Health insurance claims data are generated for reimbursement at each facility every month. Haemodialysis management systems are used by healthcare providers to manage haemodialysis prescriptions and to record the results of haemodialysis sessions. The systems hold data on patient characteristics and data from each dialysis session. Haemodialysis management systems marketed by NIPRO (Osaka, Japan), Nikkiso (Tokyo, Japan), TORAY (Tokyo, Japan), Green Information Systems (Okayama, Japan), MySystem (Okayama, Japan), MEDIBRAINS (Fukuoka, Japan) and SYSTEM RESEARCH (Hyogo, Japan) were either already able to create data files that can be imported into the AQuAH-D app, or such a function was added to them for this cohort. In principal, these existing electronic records of practice-related data are imported into the AQuAH-D app by medical staff once each month.

Data source 2: chart review

Event data and data on patient characteristics that are not in the existing electronic records are obtained by reviewing medical charts. The AQuAH-D app displays a data-entry form to the user, based on the data imported automatically into the facility database. The form is manually filled in by trained facility staff or clinical research coordinators.

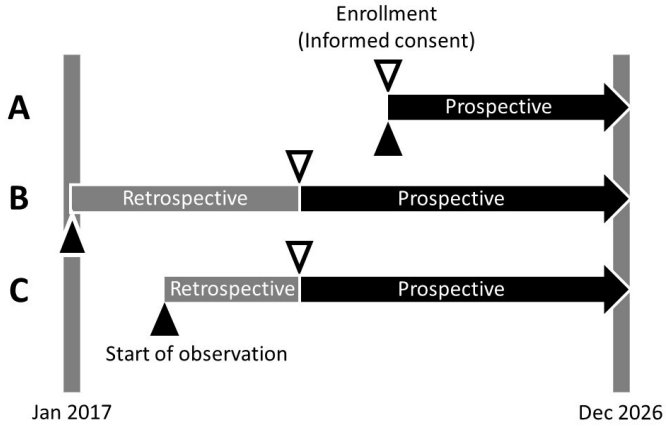

Figure 2 Observation period: retrospective period and prospective period. The start of observation (▲) is defined for each participant as 1 January 2017 or the patient's first day of haemodialysis in the facility, whichever is later. The retrospective period is from the start of observation to patient enrolment (▽, time of informed consent), and the prospective period is from patient enrolment to 31 December 2026. Case (A) participants who start haemodialysis on or after 1 January 2017 and provide informed consent when they start haemodialysis at the facility. No retrospective period. Case (B) participants who were already visiting the facility as haemodialysis patients on 1 January 2017. Retrospective period: 1 January 2017 to patient enrolment. Case (C) participants whose first visit to the facility as a haemodialysis patient was on or after 1 January 2017. Retrospective period: from the patient's first day of haemodialysis in the participating facility to the date of patient enrolment. In all cases, the prospective period is from patient enrolment through 31 December 2026.

Data source 3: patient questionnaires

Patient questionnaires, including those used to measure PROs, are distributed on paper once a year. The responses are converted into electronic form at the Institute for Health Outcomes and Process Evaluation Research (iHope International). The resulting electronic records are also imported to the central database and linked to other data.

Observation period

In principle, data acquisition starts at the time of patient enrolment and continues until the end of study, which will be the end of December 2026 (the prospective period, figure 2A). However, if a participant underwent outpatient haemodialysis at the same facility from January 2017 to enrolment, then data from existing electronic records, as well as data from chart review, were also obtained (the retrospective period, figure 2B,C). A participant's first day or 1 January 2017 of haemodialysis in the facility, whichever is later, is defined as the start of observation. The observation ends with death, kidney transplantation, withdrawal of consent, transfer to another facility, discontinuation of dialysis or transfer either to home dialysis or to peritoneal dialysis.

Variables

The measured variables, data sources and timing of measurements are summarised in table 1. Data on the patients' characteristics are collected primarily from existing electronic records, and are supplemented by chart review or patient questionnaires. Practice-related data and data on haemodialysis results from existing electronic records are recorded at the time of each dialysis visit, that is, about 13 days per month. Laboratory data measured as part of usual practice are recorded approximately one to four times a month.

Outcome data consist of PROs and events. PROs are measured at the time of patient enrolment and annually thereafter, and event data are collected when a predefined event occurs. Data on 7 kinds of events are collected: death, hospitalisation, kidney transplantation, vascular-access intervention, transfer to another facility, discontinuation of dialysis and transfer to peritoneal dialysis or to home dialysis. The plan is to measure QOL repeatedly by using the Quality of Life General-10,[17] the QOL Disease Impact Scale,[18] and the Kidney Disease Quality of Life instrument.[19] Details of other PROs to be measured will be revised. Table 1 shows the content of the first questionnaire, which is used at the time of facility enrolment.

Data availability

Data collected in the central database are converted into patient-level data with a format suitable for analysis. Participating facilities receive datasets generated from their own facility data, and are free to use them. All data from the AQuAH-D cohort are also available for use by participating institutions or third-party organisations under the following conditions: Each research question must be submitted to the publication steering committee, the committee must judge it to be relevant, and the committee must approve the validity of the study design.

Patient and public involvement

Patients and the public were not engaged in the design, conduct, or reporting of this study.

FINDINGS TO DATE

Facility and participant characteristics

From 1 September 2018 to 31 July 2020, 2895 participants from 25 facilities in Japan were enrolled in the study. Of those 25 facilities, 19 were clinics and 6 were hospitals (clinics are defined as having 19 or fewer inpatient beds, and hospitals are defined as having 20 or more inpatient beds). The patient volume, that is, number of visiting outpatients on haemodialysis at the time of facility enrolment, was less than 100 in five facilities, 100–149 in 12 facilities, 150–199 in six facilities and 200 or more in two facilities. The facilities are located in 11 prefectures, from Hokkaido in the north to Kyushu in the south. Facility recruitment is continuing, and by 7 March 2021 more facilities had begun participating in this cohort.

Table 1 Measured variables, data sources, and the timing of measurements

Variable	Data sources			Timing of measurement
	Electronic data	Chart review	Questionnaire	
Characteristics of patients				Start of observation*
Year and month of birth	✓			
Sex	✓			
Cause of kidney failure	✓	✓		
Date of haemodialysis initiation	✓	✓		
Height	✓	✓		
Type of vascular access	✓	✓		Start of observation and when status changes
Comorbidities	✓	✓		
Living status		✓		
Smoking status		✓		
Employment status			✓	Study enrolment
Alcohol consumption			✓	
Risk score for falls			✓	
Practice-related data				
Procedures (examinations, interventions, prescriptions)	✓			Every visit from start of observation
Haemodialysis prescription	✓			
Data on haemodialysis results				
Vital signs during haemodialysis	✓			Every session from start of observation
Body weight before and after haemodialysis	✓			
Laboratory data				
Items measured in daily practice	✓			
Outcomes				
Patient-reported outcomes				Study enrolment and annuall. Every measurementy
General QOL: QGEN-10			✓	
Disease-specific QOL: QDIS			✓	
Symptom scale in KDQOL			✓	
Events				When the outcome occurs from start of observation
Death		✓		
Hospitalisation		✓		
Vascular-access intervention		✓		
Kidney transplantation		✓		
Transfer to peritoneal dialysis or home haemodialysis		✓		
Transfer to another facility		✓		
Discontinuation of haemodialysis		✓		

Risk score for falls.[31]
*Start of observation is defined for each participant as 1 January 2017 or the participant's first day of haemodialysis, whichever is later (figure 2).
KDQOL, Kidney Disease Quality of Life instrument; QDIS, QOL Disease Impact Scale; QGEN-10, Quality of Life General-10; QOL, quality of life.

Participants' characteristics at the time of enrolment (figure 2) are shown in table 2 together with demographic information from the Japanese Society of Dialysis Therapy (JSDT) Registry in 2018. That registry includes survey results from 94.7% of all dialysis facilities, and thus, it covers nearly all patients on dialysis in Japan.[5] In the AQuAH-D cohort, the mean age was 68.3 (SD 12.2) years and 35.2% were female. The most frequent cause of kidney failure was diabetic nephropathy (37.4%), followed by glomerulonephritis (28.4%). These results were similar to those in the JSDT Registry.

Data from existing electronic records

As examples of existing electronic records of practice-related data, figure 3 shows the administration status of ESA for renal anaemia, intravenous vitamin D and calcimimetics for MBD management at each facility in January 2020, where data for the month is currently available.

Table 2 Baseline characteristics of participants in the AQuAH-D cohort and of Japan's dialysis population

	AQuAH-D cohort		JSDT Renal Data Registry (2018)*	
No of patients	2895		339 841	
Age (years)	68.3	(12.2)	68.8	(12.5)
Sex, female	1019	35.2%	–	34.6%
Cause of kidney failure				
Diabetic nephropathy	1083	37.4%	127 745	39.0%
Glomerulonephritis	823	28.4%	87 598	26.8%
Nephrosclerosis	347	12.0%	35 495	10.8%
Other diseases	642	22.2%	–	–
Duration of dialysis (years)	5.4	(2.0, 11.2)	–	–
	8.3	(9.1)	7.3	(7.7)
Body mass index (kg/m^2)	22.2	(4.1)	–	–
Type of vascular access				
Arteriovenous fistula	2532	87.6%	–	–
Arteriovenous graft	224	7.7%	–	–
Others	135	4.7%	–	–
Comorbidity				
Cardiovascular disease	1505	52.0%	–	–
Diabetes mellitus	1297	44.8%	–	–
Lung disease	178	6.1%	–	–
Liver disease	219	7.6%	–	–
Malignancy	499	17.2%	–	–
Haemodialysis prescription				
Type of dialysis treatment				
Haemodialysis	1433	49.5%	177 718	57.6%
Haemodiafiltration	1285	44.3%	119 959	38.9%
Missing	177	6.1%		
Single pool Kt/V†	1.62	(0.36)	–	–
Laboratory data				
Haemoglobin (g/L)	112	(12)	–	–
Serum albumin (g/dL)	3.6	(0.4)	–	–
Serum phosphorus (mEq/L)	5.3	(1.4)	–	–
Corrected serum calcium‡ (mg/dL)	9.1	(0.6)	–	–

Continuous variables are described by the mean (SD) or the median (IQR), and categorical variables are described by the number and percentage.
*Results of a survey carried out by the Japanese Society for Dialysis Therapy, in December 2018.[5] The JSDT registry includes about 9000 patients on peritoneal dialysis. Percentages were calculated among participants without missing data.
†Single pool Kt/V values were calculated using the equation by Daugirdas.[32]
‡Serum calcium values were corrected for albumin concentration using a modified version of Payne's formula.[33]
AQuAH-D, Alliance for Quality Assessment in Healthcare-Dialysis; JSDT, Japanese Society for Dialysis Therapy.

The median doses of ESA and of intravenous vitamin D ranged from 1846 to 9692 IU per week and from 0.78 to 2.25 µg per week, respectively. The percentage of patients to whom calcimimetics were prescribed varied by facility, from 19% to 79%.

Incidence of hospitalisations and vascular-access interventions in the retrospective period

During the retrospective periods, the total observation time was 5356 person-years (an average of 1.85 years). The incidence rate of any hospitalisation was 67.2 per 100 person-years, and the most common cause of hospitalisation was vascular-access complication, followed by cardiovascular disease (19.8 and 12.0 per 100 person-years, respectively). The incidence rate of vascular-access intervention, which can be done as an outpatient treatment, was 60.6 per 100 person-years. Details are shown in online supplemental table 1.

STRENGTHS AND LIMITATIONS

The AQuAH-D is a multicentre cohort of outpatients on haemodialysis in Japan. With electronic records of practice-related data and data on outcomes including

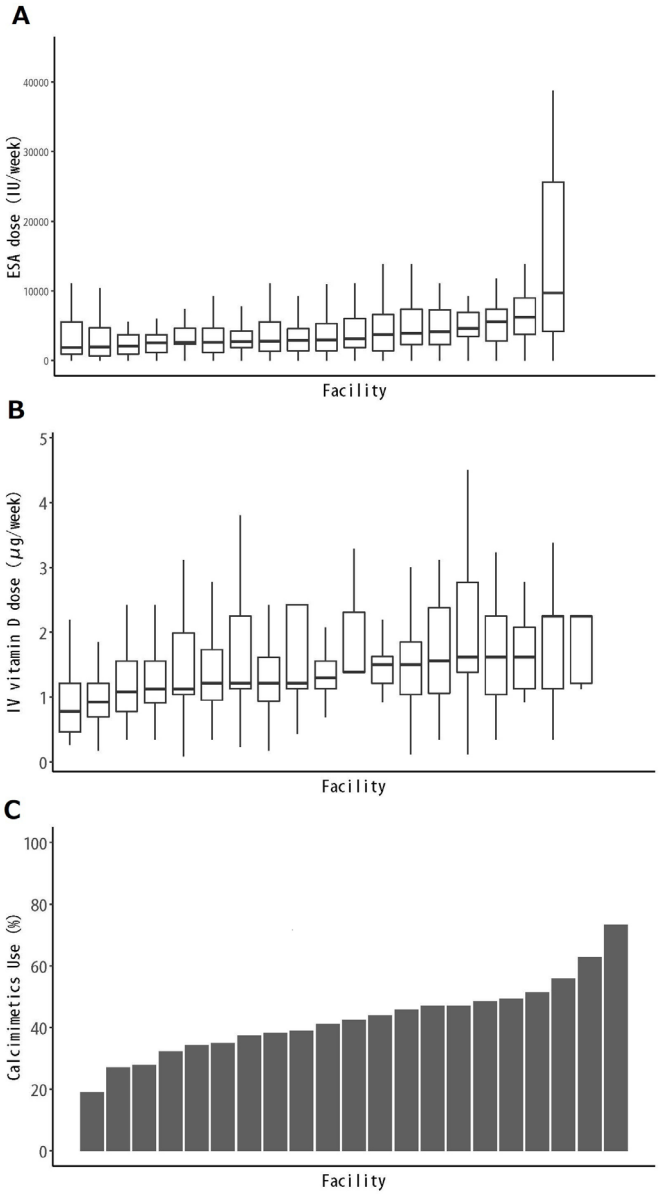

Figure 3 Prescription status of the three medications in each facility in January 2020. Boxplots indicate medians and IQRs of the doses of erythropoietin stimulating agent (ESA) (A), and of intravenous vitamin D (B). The percentages of patients who received calcimimetics (C) are shown in the bar chart. The doses of ESA and of intravenous vitamin D were converted into erythropoietin alfa dose (erythropoietin alfa:darbepoietin alfa:epoetin beta pegol=1:200[34]:225[35] and calcitriol dose (maxacalcitoriol:calcitriol=1:7,[36] respectively).

QOL, a wide range of important research questions are expected to be addressed.

To clarify the strengths and limitations of this cohort, online supplemental table 2 shows a summary of some major characteristics of the AQuAH-D together with those of four other registries: the US Renal Data System database,[20–22] the European Renal Association-European Dialysis and Transplant Association Registry,[23–25] the JSDT Renal Data Registry[5 26] and the Dialysis Outcomes and Practice Patterns Study.[27–29]

Strengths

This study has several strengths. First, our unique software (the AQuAH-D app) enables us to automatically import patient data and thus minimise the administrative burden on facility staff. This advantage will contribute to cohort sustainability. In addition, the availability of highly granular, sequential, patient-level data is expected to allow researchers to address a wide range of research questions, including questions about the impact of various exposures on patient outcomes. The AQuAH-D-app can import data in a variety of formats. If each facility enters more of its data into electronic health records, then we will be able to collect data on more variables. Second, data from medical chart reviews are incorporated to address two common limitations of existing databases: missing data and misclassification.[22 25 30] For example, one major limitation of some existing large databases is a lack of accurate data on comorbidities, but in this cohort those data are collected (by chart review) (online supplemental table 2). Third, measuring QOL provides important information about patients with kidney failure,[16] and the plan here is to measure QOL repeatedly. Fourth, this cohort will provide information about problems that are emerging worldwide as a result of ageing and multimorbidity of patients on haemodialysis. Fifth, we consider the participating facilities to constitute a research consortium, and we encourage healthcare professionals there to use these data. We believe that will motivate participating facilities, which will help to sustain the cohort and will facilitate research on clinically relevant questions.

Limitations

There are several limitations. First, we are not attempting to construct a representative sample of dialysis facilities in Japan. In addition, only those participants who give their informed consent are included, which might result in the participants being healthier or younger than Japan's haemodialysis population as a whole. Especially in descriptive studies, researchers should recognise that generalisability of the results is limited. Second, we are unable to include data on prescriptions or examinations from facilities other than those participating in the study. Third, data pertaining to the retrospective period (1 January 2017 to the time of patient enrolment) come from participants who survive until the time of enrolment, so inferences from those data can be affected by selection bias.

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Contributors SS took responsibility for the work and the conduct of the study, had access to the data, controlled the decision to publish, the integrity of the data, and the accuracy of the data analysis. Concept and design: ShiF and ShuF. Acquisition, analysis or interpretation of data: SS, YO, KK, JW and ShuF. Drafting of the manuscript: SS, YO and KK. Critical revision of the manuscript for important intellectual content: all authors. All authors meet the full authorship criteria.

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Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Ethical Review Committee of iHope International (Approval number: 2017A0102). It is being conducted in accordance with the Declaration of Helsinki and with Japan's ethical guidelines for medical and health research involving human subjects (https://www.mhlw.go.jp/content/10600000/000757206.pdf).

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Supplementary Table 1. Incidence of hospitalizations and vascular-access intervention in the retrospective period. (n = 2,895)

	The number of events [a]	Incidence rate (per 100 person-years)
Any hospitalization	3,598	67.2
Cause-specific hospitalization [b]		
Vascular-access complications	1,061	19.8
Cardiovascular diseases	643	12.0
Infection	357	6.7
Bone fracture	117	2.2
Malignancy	116	2.2
Hemorrhage	116	2.2
Vascular-access intervention	3,244	60.6

The retrospective period is defined as the period from January 1, 2017 or from the patient's first day of hemodialysis in the facility, whichever is later, to patient enrollment (Figure 2). No deaths or events that cause censoring (kidney transplantation, transfer to peritoneal dialysis or home hemodialysis, transfer to another facility, discontinuation of hemodialysis) occur during this period.

The total observation time in the retrospective period was 5,356 person-years (an average of 1.85 years).

[a] Events might occur multiple times in one person.

[b] In some cases, there were more than two causes of a hospitalization.

Supplementary Table 2. Comparison of the characteristics of five databases that include patients on maintenance hemodialysis.

	AQuAH-D	USRDS[21-23]	ERA-EDTA registry[24-26]	JSDT Renal Registry[5,27]	DOPPS[28,29]
Setting	- Japan - 32 facilities willing to participate in 2020	- United States - Nearly complete inclusion of the US ESRD population	- Europe and countries bordering the Mediterranean Sea - 37 countries in 2017 - Covered 81.8% of Europe's general population in 2017	- Japan - 4,222 (94.7%) facilities in 2018	- 16 countries in DOPPS 6 (2015-2018)
Number of patients	- 2,895 on HD in 2020 and still recruiting	- 468,086 on HD in 2018	- 592,779 on RRT in 2017 (HD 57%)	- 339,841 on RRT (HD 88.0%) in 2018	- About 20,000 on HD - 1,440 on HD in Japan (DOPPS7)
Data sources	- Existing electronic records from facilities - Chart review - Patient questionnaires	- Claims data (Medicare) and other sources	- 32 national or regional renal registries in 17 countries - Aggregated data from 21 countries	- Questionnaire for medical staff	- Questionnaire for medical staff and patients
Strengths	- Relatively large size for Japanese sample - Granular data from electronic practice data - Detailed data on	- Size - Representativeness - Granular data from claims data	- Size - Representativeness - Multinational	- Size - Representativeness	- Representativeness (Random sampling) - Multinational - Detailed data on patient characteristics

	patient characteristics from chart review - Patient-reported outcomes				- Patient-reported outcomes - Facility-specific variables
Limitations	- Lack representativeness - Only patients with consent - Missing data on practice at other facilities - Limited use of the retrospective period	- Continuous validation of its methods - Lack of complete comorbidity and laboratory data - Lack of accuracy of cause of death	- Missing data, especially on comorbidities - Variable heterogeneity between registries - Absence of a central laboratory	- Low granularity in data (small number of variables and annual measurement)	- Small number of patients in Japan
Burden on facility staff of data administration	- Burden reduced by utilizing electronic practice data and a custom application	- Burden reduced by utilizing claims data	- Depends on the registries	- Burden of completing questionnaire is on medical staff	- Burden of completing questionnaire is on medical staff
Data availability	- Participating facilities can use their own facility's dataset - The dataset of all facilities is available if application is approved	- Need to request and obtain approval	- Not mentioned on the website	- Not mentioned on the website	- Need to request and obtain approval

USRDS: U.S. Renal Data System; ERA-EDTA: the European Renal Association–European Dialysis and Transplant Association; JSDT: Japanese Society for Dialysis Therapy; DOPPS: The Dialysis Outcomes and Practice Patterns Study; HD: hemodialysis; RRT: renal replacement therapy.