Abstract: Anemia is a common complication for patients with chronic kidney disease (CKD) and is associated with cardiovascular comorbidities and reduced quality of life. The incidence of anemia increases as kidney function declines and affects approximately 32% of Japanese patients with stage 3–5 CKD. This review examined the current literature on anemia in CKD patients in Japan to provide an overview of the burden of anemia in CKD. Medline, Embase, and Igaku Chuo Zasshi databases were searched to identify relevant manuscripts and abstracts published from 2004 onward. The population included CKD patients with anemia, and the outcomes of interest were epidemiology, economic, humanistic, and treatment patterns. Observational studies, database analysis, and economic evaluation studies were included in the analysis. A total of 1151 references were identified, and 50 were eligible for final review. Economic burden was reported in most studies (n = 37) followed by treatment patterns (n = 26), and epidemiological (n = 25) and humanistic (n = 1) burdens. Prevalence of anemia varied largely (0–95%) based on the different definitions of anemia, and increased with CKD severity. Higher mortality was associated with erythropoiesis-stimulating agent (ESA) resistance and lower hemoglobin levels among patients treated with ESA. Drug dosage was the most reported economic burden (n = 33), followed by medical, and non-medical outcomes. Costs associated with anemia were considerable and depended on dialysis status and ESA treatment. Only one study reported data on quality of life, suggesting that further investigation on the humanistic burden of anemia in CKD is needed. Key Words: Anemia, Burden of illness, Chronic kidney disease, Japan, Review.

According to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines and the Japanese Society of Nephrology, chronic kidney disease (CKD) is defined as abnormality of the kidney structure or function that is present for >3 months. The criteria used to define CKD include the presence of markers of kidney damage (e.g. albuminuria, urine sediment abnormalities) or decreased glomerular filtration rate (GFR, <60 mL/min per 1.73 m²) (1,2). GFR is commonly estimated from serum creatinine levels using equations such as the isotope dilution mass spectrometry-standardized Modification of Diet in Renal Disease (IDMS-MDRD) or the Cockcroft-Gault equations. Since the IDMS-MDRD equation is less accurate when used to estimate GFR in Asian populations, additional correction coefficients are used for the Japanese population (3). Anemia is a common and serious complication of CKD that presents during the early phase of the disease and worsens as the kidney function deteriorates (4,5). The primary cause of anemia in CKD is a reduced ability of the failing kidneys to produce erythropoietin (EPO). Iron deficiency and inflammation are additional etiological factors that may contribute to anemia in CKD (6). Anemia is characterized by reduced blood hemoglobin (Hb) levels, and the

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Japanese Society for Dialysis Therapy (JSDT) has defined the reference values of Hb for the diagnosis of anemia in the general population to be <13.5 g/dL in adult males and <11.5 g/dL in adult females (7). The prevalence of anemia increases as kidney function declines and doubles as the estimated glomerular filtration rate (eGFR) decreases below a threshold value of 60 mL/min per 1.73 m² (4). Prevalence of anemia among Japanese patients with stage 3–5 CKD varies significantly among studies, and has been reported to be 10% or higher (8). Anemia in patients with CKD can increase the risk of several comorbidities, including cardiovascular disease, and is associated with activity impairment and reduced quality of life and work productivity (9,10). Furthermore, untreated anemia in CKD patients has been shown to result in negative effects on cardiac, cognitive, and immune functions, as well as survival, while appropriate treatment can significantly improve quality of life and slow disease progression (11).

To provide an overview of the current literature and to identify information gaps on anemia in CKD patients in Japan, a targeted literature review was conducted to describe the epidemiological, economic, and humanistic burdens, as well as the treatment patterns, associated with anemia in Japanese patients with CKD.

**MATERIALS AND METHODS**

**Information sources**

The following databases were searched to identify relevant studies: Medline (Epub Ahead of Print, In Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE, Ovid MEDLINE 1946 to Present), Embase (via Ovid 1974 to Present), and Igaku Chuo Zasshi (ICHUSHI: Japan’s largest medical-literature database established in 1903). Databases were searched for references dated from 2004 onward to align with the availability of the first published JSDT Guideline for Renal Anemia in Chronic Hemodialysis (HD); the date of the last search was January 24, 2017.

**Eligibility**

The search was carried out according to a pre-defined protocol with key words and queries based on the PICO(S) criteria (P: population, I: intervention, C: comparator, and O: outcomes). The population included CKD patients with anemia, with no limitations on age, stage of CKD, or dialysis status. No specific criteria for intervention or for comparator were applied. Outcomes of interest included epidemiology, economic, humanistic, and treatment patterns. Study design criteria included observational studies, database analyses, and economic evaluations (except modelling analyses that were not primary studies). No language restriction was applied. Details of the selection criteria are reported in Table 1.

**Study selection**

After all the identified references were imported into a joint database and duplicate references were removed, a review of titles and abstracts was conducted by two independent reviewers to identify publications that met the inclusion criteria. All references not excluded based on title or abstract had the full text reviewed by two independent reviewers. Titles, abstracts, and all full-text articles identified for review could be excluded for any of the following reasons: “not relevant population”; “not relevant country/setting”; “not relevant treatment (except erythropoiesis stimulating agent [ESA])”; “not relevant outcome”; “not relevant study design”; “not primary sources (all types of review articles and modelling study)”; “duplicate.”

**Data extraction process**

Data extraction was conducted using Excel software within four separate data grid sheets containing data specific to the given purpose. Sheets storing information about the publication and study were also developed. Information concerning each publication and study included ID number, first author and year of publication, language of publication, type of publication, title, sponsor, objective, study design, study location, follow-up period, enrollment, population, inclusion/exclusion criteria, details of study treatment, CKD classification, results availability (epidemiology, economic, humanistic, treatment patterns), key conclusions, limitations, and patient characteristics (sample size, mean age [SD], mean Hb [SD], mean eGFR [SD], sex, treatment with ESA, dialysis, CKD stage, cardiovascular disease, and diabetes). Data planned within the purpose included: epidemiology data (outcomes [mortality, incidence and prevalence of anemia in CKD patients]) and results; economic burden data (outcomes [cost, dosage, medical resource use, non-medical resource use]) and results; humanistic data (outcomes and results); and treatment patterns data (outcomes [ESA responsiveness and dialysis duration]) and results. For all studies, one reviewer completed a quality...
assessment as recommended by the guidance from the Centre for Reviews and Dissemination from the University of York (12).

RESULTS

Study selection

The literature search in the selected databases resulted in the retrieval of 1148 references (Fig. 1); three additional references were identified through a literature review publication (n = 1) and a hand search (n = 2). After 119 were identified as duplicates and removed, the remaining 1032 references were included in the title and abstract screening. A total of 940 records were excluded based on selection criteria, and 92 were selected for full-text analysis. The final analysis comprised 50 references (full-text articles, n = 47; conference abstracts, n = 3). Epidemiological outcomes were reported in 25 records, economic outcomes in 37, humanistic outcomes in one, and treatment patterns outcomes in 26.

Study characteristics

Epidemiological outcomes included cardiovascular and cerebrovascular events, inflammation rate, morbidity, mortality, and prevalence of anemia in CKD patients. Outcomes of economic burden included non-medical resource use, medical resource use, cost, and dosage. Non-medical resource use included time spent traveling for one hospital visit and rate of patients requiring caregivers for hospital visits. Medical resource use included frequency of hospital visits and treatment-related resource use. The results related to cost were divided into ESA treatment cost and other costs, including renal anemia management cost, ratio of drug cost to hospital income, ratio of EPO purchase cost to total drug purchase cost, cost saving associated with treatment change from recombinant human erythropoietin (rHuEPO) to darbepoetin (DA), and transportation expenses. Outcomes of treatment patterns included ESA responsiveness, dialysis duration, time to dialysis, and supplementary use of IV iron and ferrous citrate. The most frequent objectives were analysis of the changes in Hb levels in CKD patients treated with ESA (n = 11) and evaluation of anemia management (n = 9) (Table 2).

Target population

The target population in most of the identified studies (n = 27) were patients on dialysis. Patients with CKD were the target population in 19 studies, four of which enrolled patients on dialysis. In seven

| Criterion          | Inclusion                                                                                                                                                                                                 | Exclusion                                                                                     |
|--------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Population         | • CKD patients with anemia                                                                                                                                                                                | • Non-human subjects                                                                         |
|                    | • All ages and severity                                                                                                                                                                                   | • Non-Japanese patients                                                                        |
| Treatment          | No treatment (except ESA)                                                                                                                                                                                  | Any treatment (except ESA) or not reporting any outcomes of interest                          |
| Outcome            | Epidemiology: prevalence of anemia in CKD; morbidity/mortality of anemia CKD patients; hospitalization in anemia CKD patients; inflammation in anemia CKD patients; and anemia progression/evolution in CKD patients | Economic: cost of illness; resource use; health care use; productivity; work disability; medical leave; absenteeism; presenteeism; sick day; work day loss; caregivers; cost-effectiveness |
|                    | Humanistic: QoL; HRQoL; QALY; DALY; KDQ; KDQoL; PGIC; CGIC: FACT-An (T, F, and AnS); SF36; EQ-5D; utility, disutility, disability, functional status, physical function | Treatment patterns: different levels of ESA responsiveness (e.g. excessive, high, poor, etc.); time to dialysis; dialysis duration; IV iron use; use of iron replacement therapy; use of “ferrous citrate” |
| Study Design       | • Observational studies                                                                                                                                                                                   | Not the study type of interest (e.g. general review, SLR, letter, commentary, editorials, notes, opinions, case studies, PK studies, CTs); modelling study; RCTs |

*Review articles and modelling studies were excluded after references were checked during full-text screening. CGIC, clinical global impression of change; CKD, chronic kidney disease; CT, clinical trial; DALY, disability adjusted life year; ESA, erythropoiesis stimulating agent; FACT-An, functional assessment of cancer therapy-anemia (T, total; F, fatigue; AnS, anemia subscale); HRQoL, health-related quality of life; IV: intravenous; KDQ, kidney disease questionnaire; KDQoL, kidney disease quality of life; PGIC, patient global impression of change; PK, pharmacokinetics; QALY, quality adjusted life year; QoL, quality of life; RCT, randomized clinical trial; SF36, short-form 36; SLR, systematic literature review.

TABLE 1. Inclusion and exclusion criteria applied to the targeted literature review
studies, the target population was patients with anemia. Among those studies, one study enrolled anemic patients on dialysis, and four studies enrolled CKD patients with anemia. Patients with anemia were examined as a subgroup in 23 studies. Patients treated with ESA represented the target population for 31 studies. Among the studies that specified the type of dialysis, hemodialysis was more frequent (n = 21) than peritoneal dialysis (PD) (n = 5). In seven studies, the type of dialysis was not reported, and in 10 studies the enrolled patients were not on dialysis. Out of 14 studies that reported whether the enrolled population were inpatient or outpatient, 12 studies enrolled outpatient, one study enrolled inpatient, and one study enrolled both outpatient and inpatient.
Study design

The most frequent study design among the identified studies was retrospective observational study \((n = 22)\), followed by prospective observational study \((n = 17)\), cross-sectional study \((n = 10)\), and database study \((n = 1)\). Economic outcome was the most frequently evaluated outcome \((n = 19)\) among retrospective observational studies, whereas epidemiological outcome \((n = 14)\) was the most frequent among prospective observational studies. Both epidemiological \((n = 6)\) and economic outcomes \((n = 6)\) were the most frequently evaluated types of outcome among cross-sectional studies. The only database study identified reported prevalence of anemia in CKD patients. Table 3 reports the number of studies identified for each study design type and outcome.

More than half of the studies included a single center \((n = 29)\), whereas a third were multicentric \((n = 16)\). The location of the study was not reported in four studies. The enrolled patients were from general hospital settings in 17 studies, from nephrology settings in 13 studies, from both hospital and nephrology settings in two studies, and from non-reported settings in 17 studies. Patient enrollment occurred before 2010 in 28 studies, and during or after 2010 in eight studies. The date of enrollment was not reported in 14 studies.

Outcome types

Economic outcomes were the most examined outcomes \((n = 37)\), followed by treatment patterns \((n = 26)\), epidemiological outcomes \((n = 25)\), and humanistic outcomes \((n = 1)\) (Table 3). Prevalence of anemia in CKD patients was the most assessed outcome within the epidemiological category \((n = 17)\), while ESA dosage was the most frequently assessed of all economic outcomes \((n = 33)\). Different ESA responsiveness \((n = 14)\) and dialysis duration \((n = 13)\) were both frequently assessed as treatment pattern outcomes. Quality of life (QoL) in HD patients was the only humanistic outcome evaluated, and was reported in only one of the 50 identified studies (Table 4).

SYNTHESIS OF RESULTS

Epidemiological burden

The prevalence of anemia was reported in 17 studies. These studies revealed a wide range of prevalence rates \((0-95\%)\) that were highly dependent on the definition of anemia as well as dialysis status (Table 5). As expected, prevalence rates increased with decreasing eGFR (8) and also tended to be higher among patients who were on HD (14,17,18,25,28,52,55,58) than those who were not on dialysis (13,15,23,50). Because most articles reported data from patients of varying treatment and dialysis status, anemia was defined using arbitrary criteria (Table 5) rather than the definition set forth by the 2008 JSDT guidelines, which applies to the general Japanese population (7). Only three studies defined anemia in accordance with any published guidelines. Among them, two studies of

| Table 2. Main objectives of included studies |
|--------------------------------------------|
| **Objective categories** | **No. studies** |
| To analyze changes in Hb level in CKD patients using ESA treatment | 11 |
| To evaluate anemia management | 9 |
| To investigate the association between anemia and adverse events/mortality risk | 8 |
| To examine ESA responsiveness | 7 |
| To examine the current situation of dialysis treatment | 5 |
| To compare the efficacy and cost-effectiveness between ESA treatments | 2 |
| To evaluate the prevalence of anemia in CKD patients | 2 |
| To investigate the impact of increasing dosing frequency of ESA treatments | 1 |
| To evaluate the frequency of anemia in diabetic patients | 1 |
| To compare the cost of peritoneal dialysis with that of hemodialysis | 1 |
| To evaluate the therapeutic and pharmacoeconomic outcomes of pharmacists actively managing erythropoietin therapy | 1 |
| To investigate the usefulness of new iron indicators | 1 |
| To examine the association between renal impairment and anemia | 1 |
| **Total** | **50** |

CKD, chronic kidney disease; ESA, erythropoiesis stimulating agents; Hb, hemoglobin.

| Table 3. Number of studies identified by study design and outcome |
|---------------------------------------------------------------|
| **Outcomes** | **Epidemiology** | **Economic** | **Humanistic** | **Treatment patterns** | **Reference** | **No. studies** |
| Study design | | | | | | |
| Prospective observational | 14 | 12 | 1 | 8 | (13–29) | 17 |
| Retrospective observational | 4 | 19 | — | 13 | (30–51) | 22 |
| Cross-sectional | 6 | 6 | — | 5 | (52–61) | 10 |
| Database | 1 | — | — | — | (5) | 1 |

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patients with acute myocardial infarction undergoing primary percutaneous coronary intervention (40), or untreated men aged 60–89 years undergoing a general health check-up (54), defined anemia according to the World Health Organization criteria (Hb <13 g/dL for men; Hb <12 g/dL for women) and reported a prevalence of 20.8–42.6%. A third study of men and women participating in a community-based health screening program (8) defined anemia according to the 2004 JSDT and Kidney Disease Outcomes Quality Initiative guidelines (Hematocrit [Het] <40% [men], <32% [women aged <50 years], <35% [women aged ≥50 years]), reporting a range of 8.4–82.9%, depending on kidney function.

Although none of the 10 studies reporting mortality data evaluated mortality rate due to anemia in CKD, seven studies reported all-cause mortality in HD patients. Mortality rate ranged from 7.2–13.3% in stage 5 CKD patients (14,24) (time to endpoint, 18–25 months) to 35.2% in CKD patients on dialysis receiving ESA treatment to maintain 10≤ Hb <11 g/dL (time to endpoint, 10 years) (45). Okazaki et al. reported that among HD patients, increased mortality was associated with ESA resistance (hazard ratio [HR], 4.204, highest [10.0–33.7] vs. lowest [2.0–5.0] erythropoietin resistance index [ERI] tertile; 95% CI 1.173–15.065) (24). Similarly, a study by Ishigami et al. showed that HD patients with Hb <10 g/dL after treatment with epoetin beta to achieve Hb <11 g/dL, showed a decreased survival rate (HR, 0.29, lowest Hb group [Hb <10 g/dL] vs. highest Hb group [Hb >11 g/dL]; 95% CI 0.10–0.83) (17). Data from a longitudinal study also revealed an association between increased mortality and lower baseline Hb levels (relative risk, 1.78, Hb <8 g/dL vs. Hb 11–11.99 g/dL) (14). Furthermore, among HD patients receiving ESA, those with lower baseline serum ferritin levels and TSAT >20% had a lower risk of death compared with those with higher baseline ferritin levels and TSAT ≤20% (HR, 0.16 [P = 0.004], 95% CI 0.05–0.55, TSAT >20% [serum ferritin 30–80 ng/mL] vs. TSAT ≤20%) (45). Similarly, a study by Kuragano et al. showed that among HD patients treated with ESA and iron over a 2-year period, the risk of death was higher for those who had an upward trend from low to high ferritin (HR, 6.18; 95% CI 1.99–19.12) during the study period or with

### TABLE 4. Summary of outcome types

| Outcome type       | Categories (citation)                     | No. (studies) |
|--------------------|-------------------------------------------|--------------|
| Epidemiology       | Cardiovascular and cerebrovascular events (19,21,23,26) | 4            |
|                    | Inflammation rate in anemia CKD patients (55) | 1            |
|                    | Morbidity of anemia CKD patients (26)      | 1            |
|                    | Mortality of anemia CKD patients (14–17,19,22,24,34,40,45) | 10           |
|                    | Prevalence of anemia in CKD patients (8,13–15,17,18,23,25,28,40,50,52–55,57,58) | 17           |
| Economic           | Cost (18,35,41,42,46,49,51,59,61)         | 9            |
|                    | Dosage (13,14,16,17,20,21,24,25,27–35,37–39,41–44,46–50,52,56,57,60) | 33           |
|                    | Medical resource use (18,19,30,33,51,61)   | 6            |
|                    | Non-medical resource use (61)              | 1            |
| Humanistic         | Kidney Disease Questionnaire (14)          | 1            |
| Treatment patterns | Supplementary IV iron use (18,20,24,49,52) | 5            |
|                    | Dialysis duration (16,24,27,37,39,41,42,45,46,48,56,58,60) | 13           |
|                    | Erythropoietin stimulating agent responsiveness | 14          |
|                    | (13,17,18,20,21,24,31,32,36,44,46,49,56,59) | 14           |
|                    | Renal survival (21,33,44)                  | 3            |
|                    | Supplementary ferrous citrate use (49)     | 1            |

### TABLE 5. Prevalence of anemia in CKD patients by anemia definition

| Definition of anemia | Prevalence rates                                      |
|----------------------|-------------------------------------------------------|
| Hb <10 g/dL          | HD: 13.8–60.0% (14,17,55)                             |
|                      | PD: 46.0% (57)                                       |
| Hb <11 g/dL          | HD: 67.6–95% (25,52)                                 |
|                      | Non-dialysis: 10.4–68.4% (13)                        |
|                      | Dialysis status unknown:                            |
|                      | 0–49.54% (53)                                       |
| TSAT ≤20% and/or serum ferritin ≤100 ng/mL | HD: 35.0–75.6% (18,28,52)                           |
| TSAT <20% or serum ferritin <50 ng/mL    | Non-dialysis: 15% (15)                               |
| Hematocrit <30%      | HD: 82.9% (18)                                      |
| Hb <13 g/dL for men; Hb <12 g/dL for women | Dialysis status unknown:                            |
| Hematocrit <40% (men); <32% (women aged <50 y); <35% (women aged ≥50 y) | 20.8–42.6% (40,54)                                |
|                      | Non-dialysis:                                        |
|                      | ≤20%                                              |
| ≤20% (women aged ≥50 y) | eGFR 45–59: 8.4% (8)                             |
| ≤35% (women aged ≥50 y) | eGFR 30–44: 18.1% (8)                        |
| ≤15% (women aged ≥50 y) | eGFR 15–29: 39.7% (8)                          |
| % HRC ≥10%           | HD: 34.7% (58)                                      |

1 Anemia definition based on The World Health Organization criteria. 2 Anemia definition based on the 2004 JSDT and KDOQI guidelines. 3 CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; Hb, hemoglobin; HD, hemodialysis; HRC, hypochromic red cells; PD, peritoneal dialysis; TSAT, transferrin saturation.
high-amplitude fluctuations in ferritin levels (HR, 3.75; 95% CI 1.15–12.28) compared with those with low ferritin levels (19). Mortality rate among HD patients receiving ESA who were part of the Dialysis Outcomes Practice Pattern Study in Japan was assessed over a 3-year period; risk increased with decreasing Hct levels, and was highest (80.4 per 1000 person-years) among patients with the lowest Hct level (Hct <27) (16). Maekawa et al. reported similar findings, showing that in patients without cardiovascular disease, elevated Hct levels were associated with longer survival; however, this relationship did not apply to patients with cardiovascular disease (22). All-cause mortality among stage 2–5 CKD patients who were not treated with ESA was higher among those with anemia who were not iron deficient (10.22 per 100 person-years) than those who were iron deficient but not anemic (5.13 per 100 person-years) (15). One study reported that the rate of cardiovascular-related mortality among HD patients who were treated with rHuEPO was 10.06%, and that the mortality rate did not significantly differ among those who were not treated with rHuEPO (34). Another study examined mortality data of anemic patients whose dialysis status was not reported, and evaluated in-hospital death among patients treated with percutaneous coronary intervention for acute myocardial infarction. The authors found that the risk of cardiac-related death was higher in patients with anemia compared with those without anemia (odds ratio, 2.085) (40).

Cardiovascular and/or cerebrovascular events associated with anemia were reported in four studies. The first study evaluated CKD outpatients who were treated with ESA for 12 weeks. Compared with good ESA responders (i.e. third tertile of change in Hb/week/ESA), patients who were poor ESA responders (i.e. first tertile) had a slightly higher rate (17.2% vs. 11.1%) of cardiovascular events (i.e. cardiac, cerebrovascular, and peripheral artery disease events), although this difference was not significant (21). The second study reported the adjusted HR for the occurrence of cardiovascular events in anemic patients stratified by iron status after 1 year of follow-up. Compared with patients without anemia or iron deficiency, cardiovascular risk was higher in patients with anemia (HR, 2.0; 95% CI 1.1–3.7) or with anemia and iron deficiency (HR, 2.7; 95% CI 1.1–6.5) (23). In a prospective observational study, 123 out of 2602 (0.047%) patients with CKD under regular nephrologist care developed cardiovascular events during a follow-up of 2.38 years (26). Kura-gano et al. examined the association between Hb levels and cardiovascular and cerebrovascular (CCV) risk, and reported that among HD patients, CCV risk was higher in patients who had Hb consistently below a target Hb level of 10–11 g/dL (HR, 3.78; 95% CI 1.12–12.8) and who had high fluctuations in Hb levels (HR, 3.94; 95% CI 1.12–13.87) compared with those who maintained the target Hb level; a greater CCV risk (HR, 6.02; 95% CI 1.1–32.86) was also associated with treatment with doses of intravenous iron ≥50 mg/week (19).

A single study evaluated the inflammation rate in anemic patients on dialysis, and reported that 28.94% of patients had serum C-reactive protein concentration >0.5 mg/dL (55).

One study reported morbidity outcomes. In a subgroup of patients with anemia (Hb <10 g/dL), 40.6% of whom were treated with ESA, the incident rate of end-stage kidney disease (ESKD) was 137.7 and 695.7 per 1000 person-years in stage 4 and stage 5 CKD patients, respectively (26). Compared with CKD patients with 10≤ Hb ≤12 g/dL, the risk for ESKD was higher in stage 4 (HR, 3.08; 95% CI 1.40–6.79; \( P < 0.05 \)) and stage 5 (HR, 1.43; 95% CI 1.01–2.05; \( P < 0.05 \)) CKD patients with Hb <10 g/dL. Moreover, patients with Hb <10 g/dL had an increased risk for the composite endpoint of cardiovascular events, all-cause mortality, and ESKD compared with patients with 10≤ Hb ≤12 g/dL (HR, 3.41; 95% CI 2.71–4.30; \( P < 0.05 \)); a significantly higher risk for all-cause mortality and cardiovascular events was observed for stage 3 patients with Hb <10 g/dL compared with those with 10≤ Hb ≤12 g/dL (HR, 4.49; 95% CI 2.06–9.80; \( P < 0.05 \)).

**Economic burden**

A total of 37 studies analyzed economic burden. The results from these studies were categorized as medical resource use, non-medical resource use, cost, and dosage. Among studies that examined medical resource use, three studies reported frequency of hospital visits, two studies reported treatment-related resource use, and one study reported risk of hospitalization. The average number of hospital visits per 6 months related to ESA administration for CKD patients was 8.4 for those treated with DA, and 6.3 for those treated with continuous erythropoietin receptor activator (CERA) in the period prior to initiation of dialysis (30). Hiramatsu et al. reported that approximately 50% of PD patients treated with rHuEPO had one hospital visit per 2 weeks, and this proportion was reduced to 30% and 24.1%, 3 and 6 months after patients were switched to DA, respectively (41). Among stage 3–5 CKD patients with anemia, 37.7% had one hospital visit per 2 weeks, and this proportion was reduced to 30% and 24.1%, 3 and 6 months after patients were switched to DA, respectively (41). Among stage 3–5 CKD patients with anemia, 37.7% had one hospital visit per 2 weeks, and this proportion was reduced to 30% and 24.1%, 3 and 6 months after patients were switched to DA, respectively (41).
visit/month, including those for other indications, whereas 27.4% had one hospital visit/2 months (61). Among the studies examining treatment-related resources, one study reported that the amount of EPO administered per month to stage 5 CKD patients at the study unit decreased from 915 000 IU to 624 000 IU 9 months after initiation of anemia management by a pharmacist (18). Kato et al. evaluated the mean medication period of rHuEPO, and found that stage 5 CKD patients with anemia (Hb <10.0 g/dL) and on dialysis had an average treatment period of 27.2 months (33). Kuragano et al. reported that the risk of hospitalization among HD patients was higher for those who were treated with high doses (≥50 mg/week) of intravenous iron (HR, 2.77; 95% CI 1.22–6.27), for those treated with high doses (≥4500 IU/week) for ESA (HR, 1.8; 95% CI 1.33–2.43), and for those who had high-amplitude Hb fluctuations (HR, 2.01, 95% CI 1.16–3.46) or low Hb levels with low-amplitude fluctuations (HR, 2.29; 95% CI 1.38–3.81) (19).

One study evaluated non-medical resource use and reported data on time spent for hospital visits and the proportion of patients requiring caregivers for hospital visits. Stage 3–5 CKD patients with anemia who were treated with ESA spent 31.4 min traveling to and 32 min traveling from the hospital, and spent 96.5 min waiting for ESA treatment; 44.5% of these patients required a caregiver for hospital visits (61).

The results related to cost were divided into treatment cost and other costs. Seven studies reported that monthly treatment management cost associated with anemia in CKD ranged from 4654–45 365 JPY (18,41,42,46,49,51,59). The overall average cost of rHuEPO treatment in HD patients was 16 122 JPY per month, and was lower (15 093 JPY) in a subgroup of good responders (Hb ≥10 g/dL per month), and higher (16 797 JPY per month) in poor responders (Hb <10 g/dL). Similarly, the cost of CERA treatment was lower in good responders (14 334 JPY per month) compared with poor responders (19 084 JPY per month) (46). Higher costs (approximately 45 365 JPY per month) were reported in the study by Kimura et al. for stage 5 CKD patients (18). Treatment costs ranged from 15 362 JPY to 29 313 JPY per 4 weeks for PD patients (41,51,59), and from 26 512 JPY to 36 572 JPY per 4 weeks for patients with unknown dialysis status, with the lowest cost observed 24 weeks after switching from epoetin beta to DA (35). Mean ESA (DA and CERA) treatment costs per month in predialysis/non-dialyzed patients ranged from 11 300 JPY (DA) to 13 600 JPY (CERA), with lower costs observed in patients treated with DA compared with patients treated with CERA (49). Other costs were reported in four studies. Furuta et al. reported that in HD patients who switched from rHuEPO to CERA, the ratios of drug cost to hospital income and of EPO drug purchase costs to total drug purchase costs changed from 12.1% to 14.2% and from 10.7% to 16.1%, respectively, when comparing mean costs for the 6 months before and after treatment change (46). Another study reported a cost saving of 1364.7 JPY per week per patient after switching from rHuEPO to DA in PD patients (41). Suzuki et al. reported that among stage 3–5 CKD anemic patients treated with ESA, the cost of transportation to and from the hospital was 2536.8 JPY for patients who travelled by train, and 132.3 JPY for those who travelled by car; the weighted average cost of transportation by both train and car was 1304.1 JPY (data extracted from a figure) (61). A total of 33 studies reported data related to dosage, and were categorized into iron dosage (n = 5), epoetin alfa dosage (n = 2), epoetin beta dosage (n = 6), epoetin kappa dosage (n = 3), epoetin alfa and beta dosage (n = 3), rHuEPO dosage (n = 13), epoetin beta pegol (CERA) dosage (n = 7), and DA dosage (n = 17). The results of the included studies that are related to dosage are summarized in Table 6.

An important consideration regarding the use of rHuEPO in Japan involves changes in the country’s reimbursement policy. The use of rHuEPO for the treatment of anemia was introduced in 1990 and subsequently resulted in a rise in Hb levels and a reduced need for blood transfusions among patients with CKD. During this time, the Japanese health insurance system reimbursed rHuEPO based on a fixed cost per dose. In 2006, a reimbursement policy was introduced where rHuEPO was bundled with other dialysis charges in an effort to reduce dialysis expenditures and also minimize morbidity and mortality risks associated with higher doses of rHuEPO. An analysis of HD patients from the Japanese Dialysis Outcomes and Practice Patterns Study revealed a reduction in the dose of rHuEPO (11.8%, P < 0.001) and an increase in the percentage of patients receiving IV iron (9.4%, P < 0.001) between the January before (2006) and after (2007) the policy change. There were no changes in mean iron dosage or in the percentage of patients who were prescribed rHuEPO between the pre-and post-policy cross-sections (52).

Humanistic burden

A prospective observational study examined the humanistic burden of anemia in patients on HD and
reported that patients with Hb <8 g/dL scored 1.6 points lower on the physical and mental component summaries of the Kidney Disease Quality of Life Instrument (62) than patients with 11 ≤ Hb <12 g/dL (14).

**Treatment patterns**

Differences in the management of anemia in CKD have been observed among Japan and other regions. The treatment of anemia was generally less intensive in Japan than in Europe and the US and included lower target Hb levels and lower doses of ESA and IV iron (63). The JS DT guidelines recommend starting ESA treatment in HD patients when Hb is <10 g/dL and specify a target Hb level of 10–11 g/dL, whereas the recommended target Hb level in Europe and the US was between 11–13 g/dL before the 2012 KDIGO guidelines were published (7). In line with these recommendations, mean levels of Hb observed among HD patients were found to be lower in Japan (10.5 g/dL) than in Europe (11.3 g/dL) and the US (10.9 g/dL), and the median weekly dose of epoetin was lower in Japan (5000 units) than in Europe (7176 units) and the US (9000 units) (63). Similarly, the JS DT guidelines recommend lower limits for initiation of IV iron (ferritin ≤100 ng/mL and TSAT ≤20%) compared with guidelines in Europe and the US (ferritin <800 ng/mL; TSAT <50%) (7).

Treatment patterns were reported in 26 studies, 14 of which analyzed ESA responsiveness (Table 7). Two studies examined ESA responsiveness in patients treated with epoetin alfa (31,32), and six studies reported ESA responsiveness in patients treated with epoetin beta (17,20,24,39,43,46). One study reported that 8.9% of stage 5 CKD patients on dialysis were considered ESA hyporesponsive, defined as epoetin beta dose >93.3 IU/kg/week and Hb <10 g/dL (17), while another study reported that among HD patients treated with epoetin beta, the proportions of patients with ERI 2.0–5.0 (33.5%), 5.1–9.9 (33.5%), and 10.0–33.7 (33.1%) were equal (24). When defined as achieving a target Hct of >30%, the rate of target achievement increased from 17.1% to 78.0% within 9 months after initiation of anemia management by a pharmacist (18). A single study evaluated ESA hyper-responsiveness, defined as a continuous elevation of Hb and Hct after discontinuation of epoetin beta, and reported that one out of three patients on HD was considered hyper-responsive (36).

One study, which included stage 3–5 CKD patients not on dialysis, reported ESA responsiveness in patients treated with epoetin alfa/beta, and showed that higher eGFR was associated with
increased ESA responsiveness (13). The rate of ESA responsiveness in patients treated with DA was reported in six studies (20,31,32,36,49,59); among them, a single study reported that 41.7% of dialyzed patients were hyper-responsive to DA during treatment and after discontinuation (36). ESA responsiveness to epoetin beta pegol (CERA) was reported in three studies, whereas the ESA molecular name was not provided in three studies. A summary of ESA responsiveness by treatment and definition of responsiveness is presented in Table 7.

Dialysis duration in HD patients was reported in 10 studies (16,24,37,39,42,45,46,48,56,58), and ranged from 1.2 to 111.6 months. Time of dialysis appeared to be long among anemic patients treated with ESA (56.4–92.0 months). One study showed a significantly shorter dialysis history in patients with higher ESA responsiveness compared with those with lower responsiveness (P = 0.0164) (24) while another study did not find any significant difference between good responders (86 months) and poor responders (70 months) (46). Dialysis duration was reported in two studies (20–42.1 months) of PD patients (41,60), and in one study of patients with unknown dialysis status (7.3 years) (27).

Time to dialysis was evaluated in three studies. In one study, the one-year rate of renal survival, defined as the interval of time from the first examination detecting stage 5 CKD to the beginning of dialysis, was higher in patients treated with rHuEPO (90.5%) compared with those without rHuEPO treatment (66.7%). A similar trend was reported for the 2-year survival rate (47.6% vs. 28.6%) (33). Among CKD stage 2–4 patients treated with epoetin, renal survival was longer (13.6 months) among good responders (Hb ≥11 g/dL) compared with poor responders (Hb <11 g/dL) (7.7 months) (44). Similar findings were reported in a study by Kuwahara et al., where time from start of ESA treatment to initiation of dialysis ranged from 438 days (poor responders) to 637 days (good responders) (21).

The rate of supplementary IV iron use was reported in five studies, and varied between 0% for patients not on dialysis and 95.7% for HD patients who were treated with epoetin and who had Hct < 30% and iron deficiency (18,21,24,49,52). One study showed that patients with higher ESA resistance required more frequent supplementary IV iron administrations compared with patients with lower ESA resistance (24). The rate of oral administration of ferrous citrate was reported in one study, and ranged from 13.1% in patients treated with DA and 22.2% in patients treated with CERA (49).

### DISCUSSION

The data presented in this review provide an overview of the current body of knowledge on the burden of illness associated with anemia in CKD patients in Japan, and identifies information gaps that require further investigation.

Prevalence of anemia was one of the most frequently reported outcomes (n = 17) within the identified literature and varied from 0% to 95% depending on dialysis status and severity of CKD. As expected, a higher prevalence was reported among patients with lower eGFR (Table 5). The wide range in prevalence rates of anemia reported is likely due, in part, to the various criteria applied to define anemia and the heterogeneity of the patient populations among different studies. Because the patient populations were diverse in treatment and dialysis status, the 2008 JSDT definition of anemia was not applied in most studies, as this definition applies to the general population. As a result, we observed high variations in how anemia was defined. Given the impact that dialysis status, ESA treatment, and ESA resistance have on target Hb levels, it would be beneficial to consider these factors when assessing patients in order to define anemia by criteria that are more relevant to the patient’s condition and treatment. When anemia was defined according to the World Health Organization criteria or the 2004 JSDT and KDOQI

| Treatment (number of studies) | Hb level under ESA treatment (g/dL) | Proportion of patients (%) |
|-------------------------------|------------------------------------|-----------------------------|
| **Epoetin alfa (n = 2)** (31,32) | <10 41.9 | 10–11 38.7–61.5 |
|                               | ≥11 19.4 |                           |
| **Epoetin beta (n = 6)**      | <10 30.4–60.4 | 10–11 30.4–41.8 |
|                               | (17,18,20,24,36,46)                  |
| **Epoetin alfa/beta (n = 1)** | ≥11 28.1–42.3 |                           |
|                               | (20,31,32,36,49,59)                  |
| **Darbepoetin alfa (n = 6)**  | <10 25.4–35.5 | 10–11 27.4–42.7 |
|                               | (20,31,32,36,49,59)                  |
| **CERA (n = 3)** (20,49,59)   | <9 9.8–14.7 | 9–10 13.4–18.3 |
|                               | 10–11 26.8–32.9 | 11–12.9 63.9 |
| **ESA (unspecified)**        | <10 28–62.1 | 10–37.9–71.0 |
| (n = 3) (21,44,56)           |                                      |

1 Stage 2–5 CKD not on dialysis. 2 Dialysis status not reported. 3 Patients not on dialysis. 4 Patients on HD. 5 Stage 3–5 CKD, not on dialysis, eGFR <15. 6 Stage 3–5 CKD, not on dialysis, eGFR 30–45. 7 Including 10 ≤Hb ≤12, 11 ≤Hb ≤12.1, 11.5 ≤Hb ≤12.9, Hb ≥11 g/dL. 8 Continuous Erythropoietin Receptor Activator; ESA, erythropoiesis stimulating agents; Hb, hemoglobin.
guidelines, prevalence ranged from 20.8% to 42.6% and 8.4% to 82.9%, respectively. Non-Japanese epidemiological studies conducted in Korea, China and the US reported more consistent prevalence rates when anemia was defined according to World Health Organization criteria (i.e. Hb <13 g/dL for men; Hb <12 g/dL for women). Prevalence rates were reported as 45.0% in Korea (4) and 51.5% in China (64); prevalence rates in the US had a greater variation and were reported to be between 15.4% and 46% (5,65).

Data on mortality were reported in 10 studies, most of which did not indicate the specific CKD stage. Among HD patients, higher mortality was associated with ESA resistance, lower Hb levels, and elevated or fluctuating ferritin levels among patients treated with ESA, and with lower Hb and Hct levels among patients not treated with ESA. This is consistent with conclusions from a 2013 review article on mortality risk associated with anemia management in CKD. The authors noted that poor response to ESA treatment was a substantial challenge in anemia management and increased the risk of poor outcomes (66). Information on cardiovascular-related mortality was limited to only one study (34).

The economic burden analyses revealed limited data on medical and non-medical resources, while several studies (n = 33) reported information related to treatment dosage. Most data were related to DA dosage (n = 17), while dosage information for epoetin alfa was reported in only two studies (Table 6). Costs, including treatment cost, renal anemia management cost, ratio of drug cost to hospital income and ratio of EPO purchase cost to total drug purchase costs, and transportation expenses for hospital visits, were reported in nine studies and revealed a substantial cost associated with anemia. Overall, these data reveal that cost varies depending on dialysis status, ESA treatment, and anemia management. Implementation of anemia management by a pharmacist was shown to decrease the cost of anemia management. None of the studies examined the impact of anemia on indirect medical costs such as productivity loss, work disability, and absenteeism.

Information related to humanistic burden was very limited; only one study reported data on QoL in a subgroup of CKD patients with anemia (14). Overall, there is a lack of information regarding different humanistic aspects associated with anemia in Japanese CKD patients, including the assessment of QoL using different specific instruments such as the Functional Assessment of Cancer Therapy-Anemia scale, the assessment of QoL in patients with different types of dialysis, or the evaluation of other types of outcomes such as fatigue, depression, anxiety, and pain. Furthermore, information regarding the impact of CKD severity and of ESA treatment on the humanistic burden of anemia in CKD patients is lacking. A paucity of humanistic data was also reported in a similar burden of illness review of US studies (67). Of 16 articles that reported QoL data, only one directly measured QoL associated with anemia in patients with CKD not on dialysis using the Short Form-36. The authors noted that a need exists for a health-related QoL instrument that is specific to anemia.

Several studies reported treatment patterns that included ESA responsiveness, dialysis patterns, and supplementary treatment patterns. DA and epoetin beta were the most evaluated ESA for responsiveness, while responsiveness for epoetin alfa was reported in only two studies. ESA responsiveness was generally low, and varied widely depending on the specific ESA treatment, dialysis status, and definition of responsiveness; the highest rate of patients achieving Hb target was 62.1%. Studies reporting duration of dialysis in HD patients showed a wide range (1.2 and 111.6 months), and treatment with ESA appeared to be associated with longer dialysis duration. Three studies reported renal survival and showed that treatment with rHuEPO and ESA responsiveness were associated with longer renal survival. Only a few studies reported the proportion of patients treated with IV iron and ferrous citrate. However, most of them did not clearly define anemia, suggesting that information on supplementary treatment patterns is lacking.

CONCLUSIONS

Overall, this review of literature revealed a high variation of prevalence rates, indicating the need for adherence to the definition provided in the 2008 JSDT guidelines. The greatest burden of anemia in Japanese patients appears to be related to cost, and is dependent, in part, on dialysis status and ESA responsiveness. The humanistic burden of anemia remains underdetermined and reveals the need for further investigation of this outcome.

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