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Diagnosis Patterns of CKD and Anemia in the Japanese Population

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Introduction: Although early intervention for chronic kidney disease (CKD) and renal anemia are desirable, these conditions are often asymptomatic during their early stages and may be underdiagnosed.

Methods: We retrospectively analyzed Japanese administrative claims data for general and hospital populations. The data period for the general and hospital data ranged from January 2011 to December 2016 and from April 2008 to July 2017, respectively. CKD stage was determined by estimated glomerular filtration rate (eGFR). Anemia was defined per Japanese guidelines using hemoglobin (Hb) values. The proportion of patients who had eGFR-defined stages G3–G5 CKD without a CKD diagnosis, and Hb-defined anemia without an anemia diagnosis or treatment records, was estimated.

Results: Among 16,779 (general) and 68,161 (hospital) patients, a high proportion of G3 CKD patients did not have a CKD-related diagnosis (general: G3a, 95.0%; G3b, 68.4%; hospital: G3a, 89.2%; G3b, 67.9%); however, some patients were treated with antihypertensives. Among anemic patients, 75.7% (G3a) and 66.7% (G3b) of the general population, and 56.2% (G3a) and 47.5% (G3b) of the hospital population, did not have an anemia-related diagnosis or treatment. CKD and anemia were more likely to be diagnosed in patients with G4 and G5 CKD.

Conclusion: A high proportion of G3 CKD patients did not have a CKD-related diagnosis. Likewise, many anemic patients with G3 CKD did not have an anemia-related diagnosis. Despite the lack of a CKD-related diagnosis, some patients received appropriate treatment (e.g., antihypertensives). Further outreach to CKD and anemia patients at earlier stages may be warranted.

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In Japan, CKD prevalence has been increasing over time. This is especially true for stage G3–G5 CKD, which had a 3-fold and 2-fold prevalence increase in men and women, respectively, between 1974 and 2002.[1] As of 2005, the estimated prevalence of CKD in Japan reached approximately 13%.[2] CKD is associated with an increased risk of developing cardiovascular and metabolic disorders that, in turn, serve to exacerbate extant CKD. Furthermore, anemia is an independent risk factor for unfavorable events in CKD, such as left ventricular hypertrophy, congestive heart failure, and even mortality.[3–5] Given these factors, early detection of CKD and anemia, along with referral of these patients to a nephrologist, may help to slow the progression of CKD and its associated complications.[6–13]

Patients may fail to seek medical care because CKD and/or anemia is often asymptomatic, especially during its early stages, despite the fact that they are suffering from diminished kidney function and/or anemia.[14–17] Therefore, estimating the proportion of CKD and anemic patients who are undiagnosed in the field is challenging.[17–19] Even when a patient with diminished kidney function visits a hospital or clinic, healthcare professionals may overlook early signs of CKD, instead focusing on other symptoms or issues.

Here, we retrospectively investigated the diagnosis patterns of CKD and anemia patients in Japan using population-based and hospital-based real-world data in order to better understand the proportion of undiagnosed CKD/anemic patients. We also investigated the clinical and treatment characteristics of CKD and anemia patients by CKD stage.

METHODS

Study Design and Data Source

This study was a retrospective, cross-sectional analysis using 2 Japanese databases containing data from either

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the general population or a hospital population. The data for the general population was provided by the Japanese Medical Data Center (JMDC).[20–22] This database consisted of annual health checkup data for employees and their dependents, as well as monthly medical and prescription claims. At the time this study was conducted, the number of insurance beneficiaries was around 5.2 million (4% of the entire Japanese population); among them, approximately 2.2 million also provided annual health checkup data. The data available for patients aged ≥65 years are limited, and there are no data for patients aged >75 years.

The data for the hospital population were provided by Medical Data Vision.[22,23] This database consists of medical and prescription billing records for outpatients and inpatients visiting or admitted to member hospitals. At the time this study was conducted, this database consisted of data from more than 23.5 million patients from 359 acute diagnosis procedure combination hospitals nationwide; blood test results were provided by 35 of the 359 hospitals. Patients cannot be followed if they visited another hospital or clinic, even those among the panel hospitals. The data period for the general and hospital data ranged from January 2011 to December 2016 and April 2008 to July 2017, respectively.

Study Population

All data for subjects who had at least 2 serum creatinine (SCr) measurements between January 2015 and December 2016 (general population), or between August 2015 and July 2017 (hospital population), were extracted from each database for use in this analysis. Also, data for patients on dialysis, or those who had experienced kidney transplantation during the entire data period, were extracted. In this study, SCr values had to be measured before chronic dialysis started or before kidney transplantation. CKD stage was defined only by the eGFR value; albuminuria status was not taken into consideration in this study. Two eGFR values, at least 3 months apart, were estimated with the Japanese formula.[24] If the pair of eGFR values did not indicate the same CKD stage, the next possible pair was sought. If no pair indicated the same CKD stage, the subjects were excluded from the CKD cohort.

In the CKD cohort, the index date was defined as the second SCr measurement date, and the baseline period was defined as the period between the first and second SCr measurement dates, including the index date (Figure 1). The follow-up period was 1 year from the index date (inclusive), unless the subject was deceased. Subjects were excluded if they were <18 years of age at the index date, had <1 year of follow-up unless deceased (only for general population), or had no diagnosis code during the following year (only for hospital population; Figure 2).

The Hb cohort was developed as a sub-cohort of the CKD cohort; the Hb cohort included patients with at least one valid Hb value during the baseline period. If a patient had multiple Hb measurements, the closest one to the index date was used. Anemia prevalence was determined as the proportion of patients with low Hb levels, according to the guidelines for the Japanese population by age category and sex (Supplementary Table S1),[13] or as those receiving treatment for anemia (i.e., iron preparation, erythropoiesis-stimulating agent, phosphate binder, or red blood cell transfusion) within ±1 month of the index date. Treatment-required anemia was defined as subjects with an Hb value of <11.0 g/dl.[13] Self-reported anemia was defined as those who responded "yes" to the question of whether they have ever been diagnosed as anemic as part of the annual health checkup among those who responded to this question (i.e., excluding those who responded neither "yes" nor "no") in the general population.

Data Analyses

All analyses were performed separately for each population. Because this analysis focused only on non–dialysis-dependent patients with CKD stages G3a–G5, subjects with CKD stages G1–2, and those who started

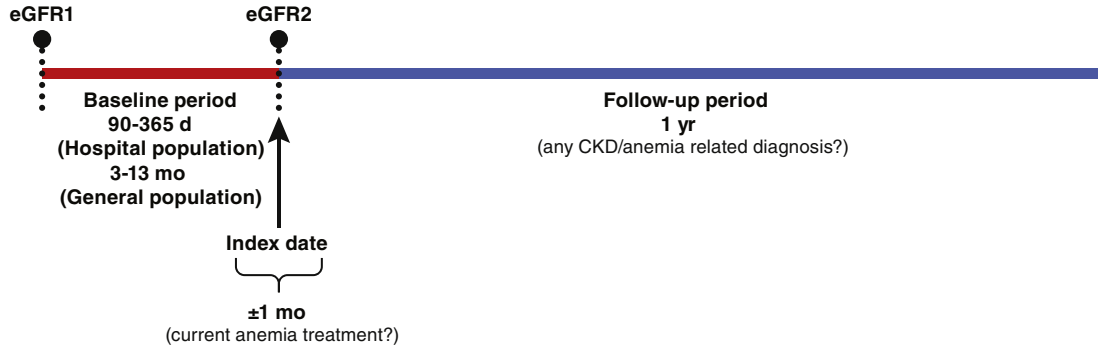

Figure 1. Study design. Estimated glomerular filtration rate (eGFR)1 and eGFR2 are categorized as same chronic kidney disease (CKD) stage.

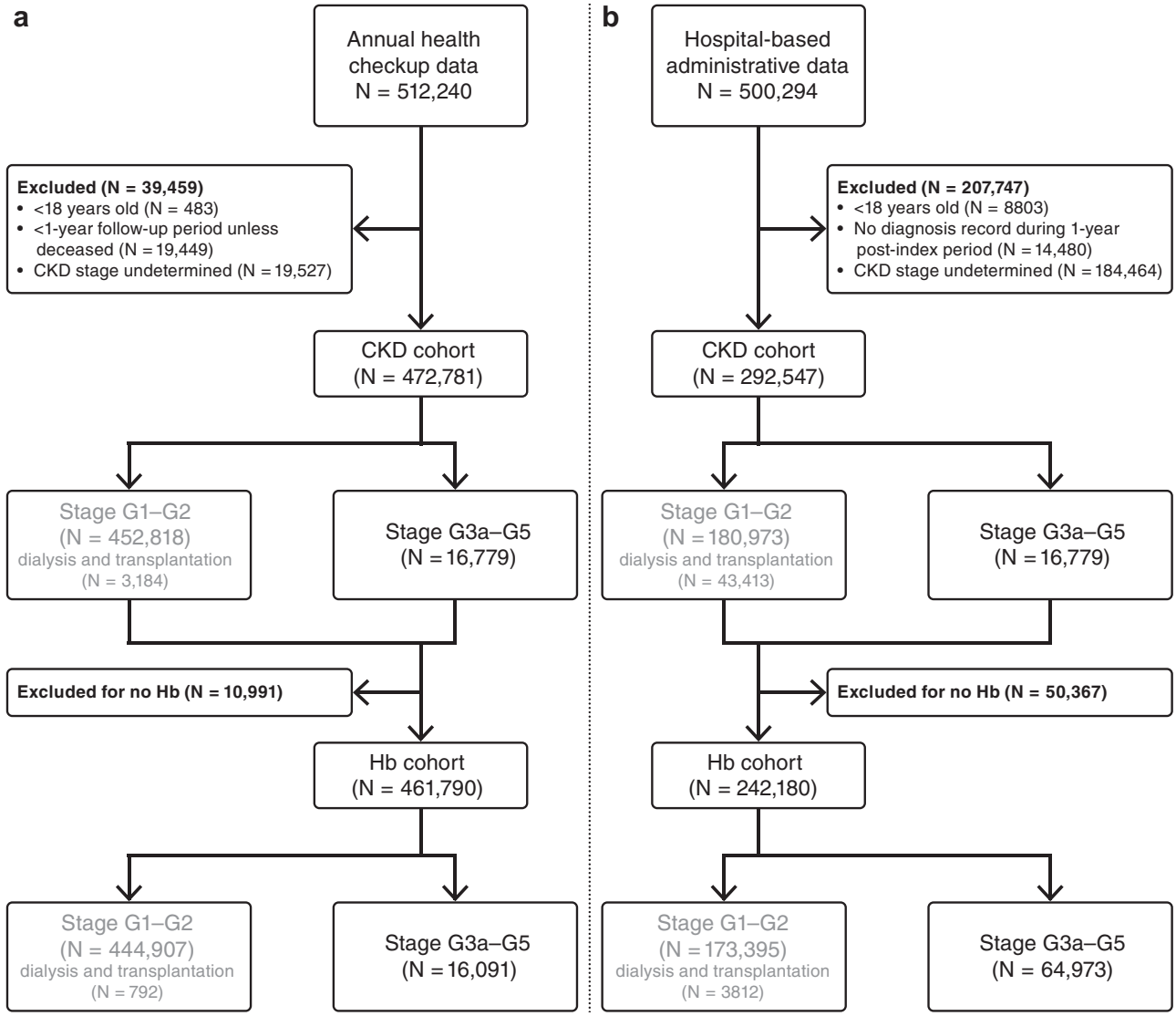

Figure 2. Flowchart of patients from the (a) hospital and (b) insurance claims databases. CKD, chronic kidney disease; Hb, hemoglobin.

dialysis or experienced kidney transplantation before providing any SCr values during the specified period, were not included in the analysis. Demographics at the index date, and the Elixhauser Comorbidity Index[25–28] during the baseline period, were descriptively summarized. CKD- and anemia-related diagnosis codes were prespecified using Japan-specific standardized disease and diagnosis codes (Supplementary Appendix S1). Among eGFR-defined CKD patients, CKD-related diagnosis codes given during the follow-up period were sought. Similarly, among Hb-defined anemia patients, anemia-related diagnosis codes given during the follow-up period or the anemia treatment given ±1 month from the index date were sought. The specialties that patients were treated under were categorized as nephrology, cardiology, diabetology (including endocrinology), general internal medicine, and others in the hospital population. Anemia treatment type was summarized among patients who received a prescription for anemia treatment ±1 month from the index date.

RESULTS

Patient Characteristics

In total, 472,781 (general population) and 292,547 (hospital population) patients were included in the CKD cohort; among them, 16,779 (general population) and 68,161 (hospital population) were included in the analysis (Figure 2). The general population was predominately male (Table 1[28]). The median age was highest in CKD stage G3b (60 years) and lowest in CKD stage G5 (52 years). In the hospital population, sex was well balanced, with the oldest median age in CKD stages G3b and G4 (79 years) and the youngest in G5 (72 years). In the general population data, 94% of

Table 1. Baseline characteristics of the CKD cohort by CKD stage (G3a–G5)

Characteristic	General population				Hospital population			
	Stage G3a (n = 15,776)	Stage G3b (n = 804)	Stage G4 (n = 150)	Stage G5 (n = 49)	Stage G3a (n = 41,396)	Stage G3b (n = 17,087)	Stage G4 (n = 6566)	Stage G5 (n = 3112)
Sex								
Male	11,762 (74.6)	651 (81.0)	113 (75.3)	40 (81.6)	22,884 (55.3)	9109 (53.3)	3480 (53.0)	1916 (61.6)
Female	4014 (25.4)	153 (19.0)	37 (24.7)	9 (18.4)	18,512 (44.7)	7978 (46.7)	3086 (47.0)	1196 (38.4)
Age, yr								
Mean (SD)	55.9 (7.9)	59.2 (8.3)	55.7 (9.1)	52.4 (8.0)	74.1 (10.2)	77.2 (10.4)	76.7 (11.9)	70.7 (12.3)
Range	24–74	31–74	28–73	38–72	19–98	20–98	19–98	24–97
Median (Q1–Q3)	56 (51–61)	60 (54–66)	56 (49–62)	52 (47–57)	75 (68–82)	79 (72–85)	79 (70–85)	72 (64–80)
Age group, yr								
18–39	267 (1.7)	10 (1.2)	8 (5.3)	1 (2.0)	166 (0.4)	81 (0.5)	46 (0.7)	38 (1.2)
40–49	3005 (19.0)	99 (12.3)	30 (20.0)	16 (32.7)	738 (1.8)	240 (1.4)	179 (2.7)	150 (4.8)
50–59	7397 (46.9)	285 (35.4)	60 (40.0)	24 (49.0)	2474 (6.0)	687 (4.0)	354 (5.4)	344 (11.1)
60–69	4365 (27.7)	329 (40.9)	43 (28.7)	6 (12.2)	9006 (21.8)	2514 (14.7)	1020 (15.5)	825 (26.5)
70–74[a]	742 (4.7)	81 (10.1)	9 (6.0)	2 (4.1)	15,659 (37.8)	5606 (32.8)	1806 (27.5)	923 (29.7)
80–89	0	0	0	0	11,658 (28.2)	6491 (38)	2451 (37.3)	719 (23.1)
≥90	0	0	0	0	1695 (4.1)	1468 (8.6)	710 (10.8)	113 (3.6)
Treatment								
Antihypertensive	3992 (25.3)	499 (62.1)	124 (82.7)	38 (77.6)	16,880 (40.8)	9359 (54.8)	4264 (64.9)	1850 (59.4)
Oral antidiabetic	1064 (6.7)	158 (19.7)	37 (24.7)	9 (18.4)	7068 (17.1)	3434 (20.1)	1423 (21.7)	609 (19.6)
Antihyperuricemia	2423 (15.4)	382 (47.5)	111 (74.0)	38 (77.6)	5075 (12.3)	4206 (24.6)	2653 (40.4)	1220 (39.2)
Specialty								
Cardiology	—	—	—	—	6215 (15.0)	3298 (19.3)	1470 (22.4)	733 (23.6)
Diabetology	—	—	—	—	2437 (5.9)	1076 (6.3)	450 (6.9)	165 (5.3)
Nephrology	—	—	—	—	5043 (12.2)	3107 (18.2)	1964 (29.9)	1311 (42.1)
Internal medicine	—	—	—	—	14,787 (35.7)	6236 (36.5)	2341 (35.7)	776 (24.9)
Others	—	—	—	—	21,920 (53.0)	8071 (47.2)	2553 (38.9)	1228 (39.5)
Unknown	—	—	—	—	13 (0.0)	12 (0.1)	5 (0.1)	1 (0.0)
Weighted Elixhauser risk score								
Mean (SD)	2.0 (4.5)	4.7 (6.5)	8.5 (7.2)	11.3 (6.3)	7.4 (7.1)	9.4 (7.9)	11.7 (8.2)	12.4 (7.4)
Range	–7 to 44	–6 to 37	–2 to 32	–2 to 31	–7 to 52	–7 to 51	–5 to 52	–5 to 46
Median (Q1–Q3)	0 (0–2)	2 (0–9)	8 (3–13)	10 (8–15)	5 (2–12)	8 (4–14)	11 (5–17)	11 (7–17)
Elixhauser Comorbidity Index[b]								
Hypertension	5348 (33.9)	574 (71.4)	137 (91.3)	45 (91.8)	23,981 (57.9)	11,948 (69.9)	5152 (78.5)	2349 (75.5)
Diabetes, complicated	443 (2.8)	89 (11.1)	31 (20.7)	8 (16.3)	3443 (8.3)	2207 (12.9)	1306 (19.9)	940 (30.2)
Diabetes, uncomplicated	1818 (11.5)	195 (24.3)	37 (24.7)	9 (18.4)	12,270 (29.6)	5298 (31.0)	1942 (29.6)	779 (25.0)
Renal failure	173 (1.1)	113 (14.1)	90 (60.0)	44 (89.8)	2126 (5.1)	3501 (20.5)	3839 (58.5)	2750 (88.4)
Metastatic solid tumor	58 (0.4)	9 (1.1)	1 (0.7)	0	1983 (4.8)	840 (4.9)	216 (3.3)	72 (2.3)
Solid tumor without metastases	404 (2.6)	57 (7.1)	12 (8.0)	1 (2.0)	10,249 (24.8)	3725 (21.8)	1112 (16.9)	393 (12.6)
Blood loss anemia	3 (0.0)	0	0	0	123 (0.3)	76 (0.4)	51 (0.8)	32 (1.0)
Deficiency anemia	323 (2.0)	61 (7.6)	38 (25.3)	22 (44.9)	4442 (10.7)	2818 (16.5)	1746 (26.6)	967 (31.1)

CKD, chronic kidney disease; Q, quartile.
[a]70–79 in-hospital patients.
[b]Defined using Elixhauser Comorbidity Index (Quan *et al.*[28]). Entire Elixhauser Comorbidity Index is in Supplementary Table S2.
Values are n (%) unless otherwise indicated.

patients had CKD stage G3a, whereas patients with more-severe disease comprised the hospital data: 60.7% in CKD stage G3a, 25.1% in stage G3b, 9.6% in stage G4, and 4.6% in stage G5.

The median comorbidity score increased with CKD stage in both populations, but the median score for CKD stage G3b was 0 in the general population, whereas it was 5 in the hospital population at the same stage. In CKD stage G5, the median comorbidity score was similar between populations (10 in the general population and 11 in the hospital population; Supplementary Tables S2 and S3). More than half of the patients with CKD stage G3b or above received antihypertensives (range, 54.8%–64.9%), and around 20% received oral antidiabetics. Antihyperuricemia treatment was also prevalent, especially among the general population. Additional information regarding baseline characteristics in patients with and without CKD/anemia-related diagnosis codes can be seen in Supplementary Tables S4 and S5.

Diagnosis Pattern by CKD Stage

In the CKD cohort, 95% (general population) and 89.2% (hospital population) of eGFR-defined CKD stage

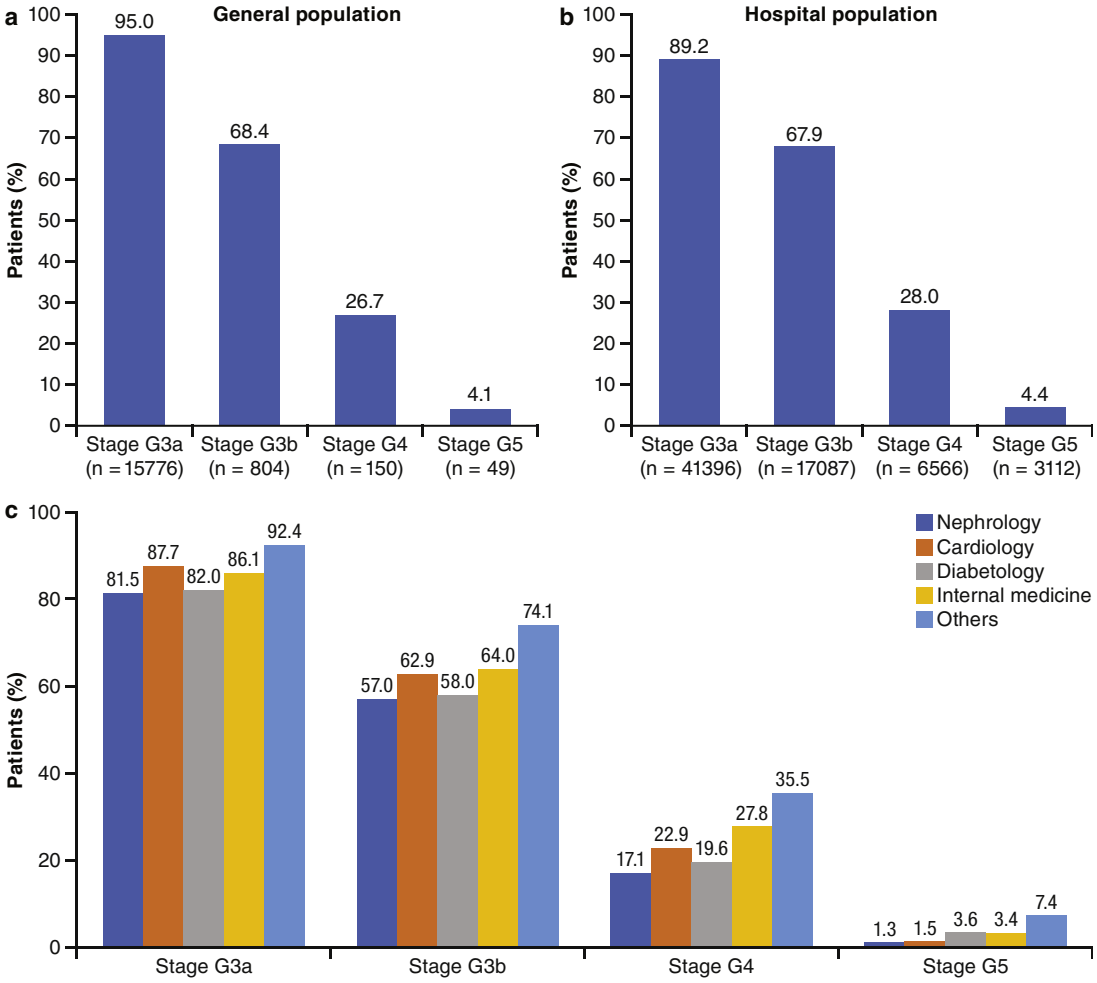

Figure 3. Prevalence of chronic kidney disease (CKD) patients without CKD-related diagnosis code by (a,b) CKD stage and (c) specialty in the hospital population.

G3a subjects did not have any CKD-related diagnosis code in the following year (Figure 3a and b). In CKD stage G3b, this proportion decreased to 68.4% (general population) and 67.9% (hospital population). Even for CKD stage G4, more than one-quarter of patients did not have a CKD-related diagnosis code. Almost all (>95%) of the CKD stage G5 patients had a CKD-related diagnosis code. Patients were more likely to receive a diagnosis code when receiving treatment from the nephrology and diabetology specialties (Figure 3c).

Prevalence of Anemia

The vast majority of subjects (95%–96%) in the CKD cohort were also included in the Hb cohorts, and patients with CKD stages G3–5 were analyzed (n = 16,091, general population; n = 64,973, hospital population; Table 2[28]). The baseline characteristics in the Hb cohort were similar to those in the CKD cohort across both the general and hospital populations. In both populations, Hb levels decreased as CKD severity increased (Figure 4). Overall, 764 (4.7%) and 14,286 (22.0%) patients either had a low Hb value according to Japanese guidelines or were currently under anemia treatment in the general and hospital populations, respectively. In both populations, the proportion of anemic patients increased with the severity of CKD, with a higher prevalence noted in the hospital population in patients with CKD stage G3 (Table 3). No meaningful differences were identified between sexes, except for the general population in CKD stage G4. The prevalence of treatment-required anemia (Hb < 11 g/dl) also increased with CKD severity and was higher in the hospital population overall. Females showed a higher prevalence of treatment-required anemia, except for the general population with CKD stage G5. In addition, more than one-quarter of low-Hb patients in CKD stage G4 or G5 were not treated. Among patients with Hb <11 g/dl, treatment rates increased as CKD stage increased, indicating resistance to treatment in higher CKD stages.

In the general population, approximately 90% of patients answered a question that asked whether they had ever been diagnosed with anemia; the prevalence

Table 2. Baseline characteristics of the Hb cohort by CKD stage (G3a–G5)

	General population				Hospital population			
Characteristic	G3a (n = 15,142)	G3b (n = 762)	G4 (n = 139)	G5 (n = 48)	G3a (n = 39,221)	G3b (n = 16,333)	G4 (n = 6379)	G5 (n = 3040)
Sex								
Male	11,308 (74.7)	618 (81.1)	102 (73.4)	39 (81.3)	21,603 (55.1)	8667 (53.1)	3386 (53.1)	1869 (61.5)
Female	3834 (25.3)	144 (18.9)	37 (26.6)	9 (18.8)	17,618 (44.9)	7666 (46.9)	2993 (46.9)	1171 (38.5)
Age, yr								
Mean (SD)	55.6 (7.8)	58.9 (8.2)	54.9 (8.8)	52.4 (8.1)	74.3 (10.2)	77.4 (10.3)	76.8 (11.9)	70.7 (12.3)
Range	24–74	31–74	28–73	38–72	19–98	20–98	19–98	24–97
Median (Q1–Q3)	56 (51–61)	59 (54–65)	56 (48–61)	52 (47–57.5)	75 (68–82)	79 (72–85)	79 (70–85)	72 (64–80)
Age group, yr								
18–39	263 (1.7)	10 (1.3)	8 (5.8)	1 (2.1)	153 (0.4)	76 (0.5)	44 (0.7)	36 (1.2)
40–49	2946 (19.5)	96 (12.6)	30 (21.6)	16 (33.3)	673 (1.7)	221 (1.4)	169 (2.6)	147 (4.8)
50–59	7239 (47.8)	280 (36.7)	58 (41.7)	23 (47.9)	2239 (5.7)	638 (3.9)	336 (5.3)	335 (11.0)
60–69	4064 (26.8)	307 (40.3)	38 (27.3)	6 (12.5)	8345 (21.3)	2344 (14.4)	977 (15.3)	804 (26.4)
70–74[a]	630 (4.2)	69 (9.1)	5 (3.6)	2 (4.2)	14,892 (38.0)	5335 (32.7)	1749 (27.4)	896 (29.5)
80–89	0	0	0	0	11,252 (28.7)	6286 (38.5)	2402 (37.7)	710 (23.4)
≥90	0	0	0	0	1667 (4.3)	1433 (8.8)	702 (11.0)	112 (3.7)
Ferritin, ng/ml	—	—	—	—				
n	—	—	—	—	887	585	480	431
Mean (SD)	—	—	—	—	194.5 (452)	255.5 (929.7)	237.3 (525)	198.8 (222.9)
Range	—	—	—	—	1.9–5807	2–18,650.3	2–7515.5	5.3–1927.3
Median (Q1–Q3)	—	—	—	—	60 (27–147)	81.7 (33–190)	121.7 (51.5–248)	133 (67–237)
CRP, mg/dl	—	—	—	—				
n	—	—	—	—	19,543	8574	3459	1889
Mean (SD)	—	—	—	—	0.8 (2.0)	1.0 (2.4)	1.3 (2.8)	1.6 (3.3)
Range	—	—	—	—	0–34.7	0–26.8	0–27.3	0–38.4
Median (Q1–Q3)	—	—	—	—	0.1 (0.1–0.4)	0.2 (0.1–0.6)	0.2 (0.1–1.0)	0.3 (0.1–1.5)
Specialty	—	—	—	—				
Cardiology	—	—	—	—	6003 (15.3)	3198 (19.6)	1438 (22.5)	723 (23.8)
Diabetology	—	—	—	—	1848 (4.7)	869 (5.3)	407 (6.4)	155 (5.1)
Nephrology	—	—	—	—	4798 (12.2)	3003 (18.4)	1928 (30.2)	1281 (42.1)
Internal medicine	—	—	—	—	13,781 (35.1)	5897 (36.1)	2257 (35.4)	753 (24.8)
Others	—	—	—	—	21,242 (54.2)	7826 (47.9)	2505 (39.3)	1196 (39.3)
Unknown	—	—	—	—	12 (0)	12 (0.1)	5 (0.1)	1 (0)
Hemoglobin, g/dl								
Mean (SD)	14.7 (1.3)	14.2 (1.6)	12.8 (1.7)	11.4 (1.8)	13.1 (1.8)	12.3 (1.9)	11.2 (1.8)	10.7 (1.7)
Range	7.0–19.6	8.6–20.4	7.1–17.4	5.9–14.6	2.8–25.7	3.3–23.6	3.4–20.0	3.7–17.9
Median (Q1–Q3)	14.7 (13.8–15.6)	14.3 (13.3–15.2)	12.7 (11.8–13.8)	11.3 (10.5–12.8)	13.2 (12.0–14.3)	12.2 (11.0–13.5)	11.2 (10.1–12.4)	10.6 (9.5–11.7)
Weighted Elixhauser risk score								
Mean (SD)	2.0 (4.5)	4.7 (6.4)	8.4 (7.2)	11.3 (6.4)	7.6 (7.1)	9.5 (7.9)	11.8 (8.2)	12.4 (7.4)
Range	−7 to 44	−6 to 35	−2 to 32	−2 to 31	−7 to 52	−7 to 51	−5 to 52	−5 to 46
Median (Q1–Q3)	0 (0–2)	2 (0–9)	8 (3–13)	10 (8–15)	5 (2–12)	9 (4–14)	11 (5–17)	11 (7–17)
Elixhauser Comorbidity Index[b]								
Hypertension	5112 (33.8)	543 (71.3)	128 (92.1)	44 (91.7)	22,543 (57.5)	11,337 (69.4)	4988 (78.2)	2287 (75.2)
Diabetes, complicated	420 (2.8)	89 (11.7)	28 (20.1)	8 (16.7)	3003 (7.7)	1955 (12.0)	1236 (19.4)	910 (29.9)
Diabetes, uncomplicated	1735 (11.5)	179 (23.5)	36 (25.9)	9 (18.8)	11,395 (29.1)	5031 (30.8)	1889 (29.6)	761 (25.0)
Renal failure	167 (1.1)	104 (13.6)	81 (58.3)	43 (89.6)	2017 (5.1)	3382 (20.7)	3749 (58.8)	2685 (88.3)
Metastatic solid tumor	55 (0.4)	8 (1)	1 (0.7)	0	1953 (5.0)	831 (5.1)	215 (3.4)	71 (2.3)
Solid tumor without metastases	404 (2.7)	57 (7.5)	12 (8.6)	1 (2.1)	9983 (25.5)	3645 (22.3)	1095 (17.2)	384 (12.6)
Blood loss anemia	3 (0)	0	0	0	120 (0.3)	76 (0.5)	51 (0.8)	32 (1.1)
Deficiency anemia	304 (2.0)	60 (7.9)	35 (25.2)	22 (45.8)	4382 (11.2)	2783 (17.0)	1730 (27.1)	937 (30.8)

CKD, chronic kidney disease; CRP, C-reactive protein; Hb, hemoglobin; Q, quartile.
[a]70–79 for the hospital data.
[b]Defined using Elixhauser Comorbidity Index (Quan *et al.*[28]). Entire Elixhauser Comorbidity Index is in Supplementary Table S3.
Values are n (%) unless otherwise indicated.

of self-reported anemia was lower than the prevalence of Hb-defined or currently treated anemia, except in CKD stage G3 (7.1% and 3.8%, respectively).

Because of the limited number of patients, trends in prevalence by age were not clear in the general population, but the prevalence of anemia with CKD stages

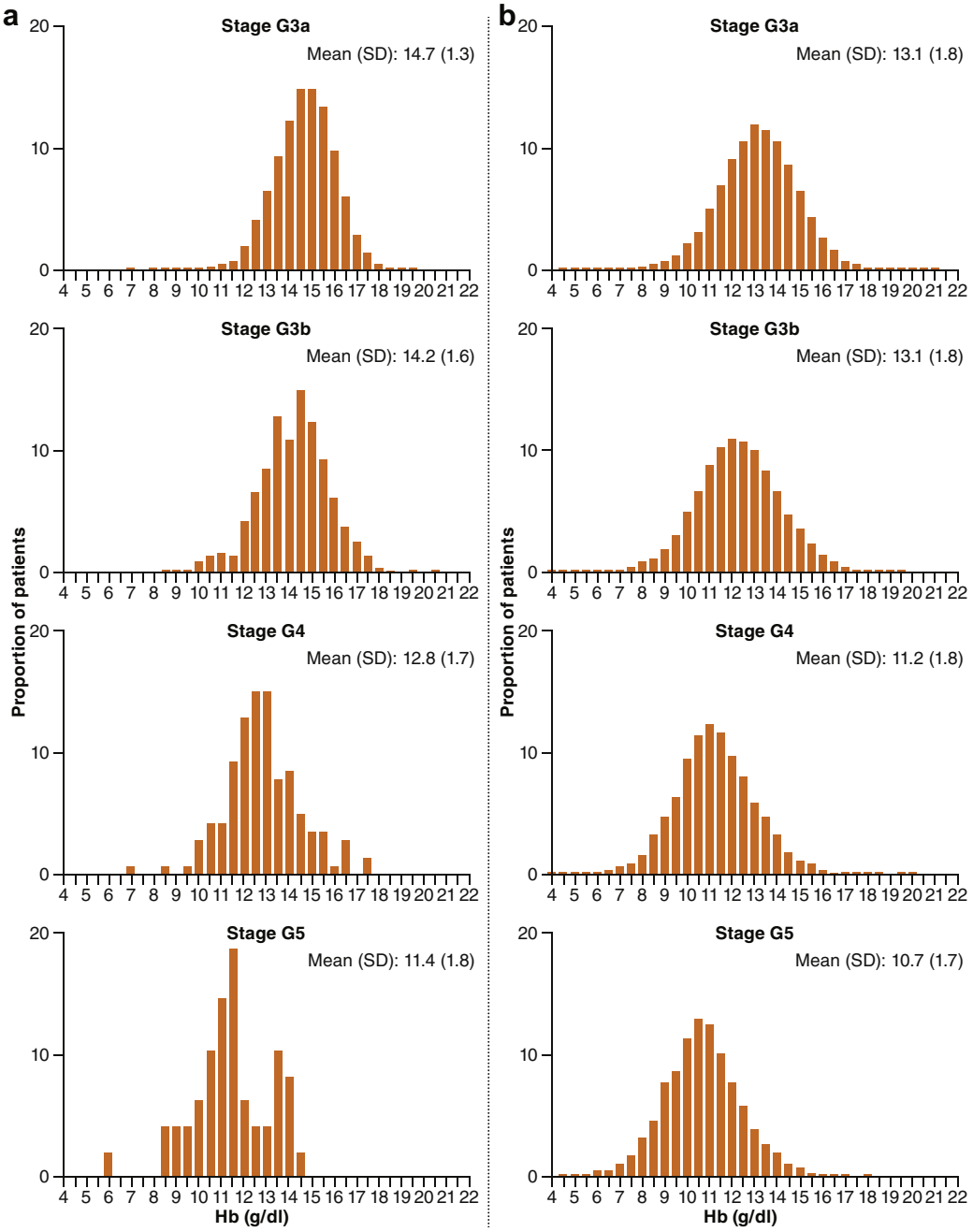

Figure 4. Distribution of hemoglobin (Hb) values by chronic kidney disease stage in the (a) general and (b) hospital populations.

G3a, G3b, and G4 tended to be lower in patients aged over 60 years (Figure 5). Interestingly, a J-curve trend was seen in the hospital population, in which the prevalence was lowest at age 60–79 years and increased thereafter (≥80 years old), across all stages of CKD.

Diagnosis and Treatment Pattern in Anemia Patients

Among patients with low Hb, a significant proportion of patients did not have an anemia-related diagnosis and were not treated, especially in the general population (Figure 6a and b). The anemia treatment rate increased as CKD stage increased. Compared with other specialties, the prevalence of patients without an anemia-related diagnosis code and not treated for anemia was higher for CKD stages G3a and G3b and was lowest for CKD stages G4 and G5 in the nephrology specialty (Figure 6c).

Oral iron preparation was the primary anemia treatment in CKD stage G3, whereas erythropoiesis-stimulating agents were more likely to be used in CKD stage G4 or above; IV iron was used sparingly across all stages/groups. Red blood cell transfusion was

Table 3. Prevalence of anemia and treatment by CKD stage (G3a–G5)

	General population				Hospital population			
	G3a (n = 15,142)	G3b (n = 762)	G4 (n = 139)	G5 (n = 48)	G3a (n = 39,221)	G3b (n = 16,333)	G4 (n = 6379)	G5 (n = 3040)
Low Hb or currently treated								
Total	568 (3.8)	91 (11.9)	66 (47.5)	39 (81.3)	4627 (11.8)	4107 (25.1)	3275 (51.3)	2277 (74.9)
Male	414 (3.7)	72 (11.7)	56 (54.9)	32 (82.1)	2605 (12.1)	2130 (24.6)	1732 (51.2)	1421 (76.0)
Female	154 (4.0)	19 (13.2)	10 (27.0)	7 (77.8)	2022 (11.5)	1977 (25.8)	1543 (51.6)	856 (73.1)
Low Hb and not treated	524 (3.5)	83 (10.9)	44 (31.7)	14 (29.2)	3158 (8.1)	2781 (17.0)	1813 (28.4)	780 (25.7)
Treatment-required anemia								
Total	115 (0.8)	23 (3.0)	16 (11.5)	17 (35.4)	4054 (10.3)	3840 (23.5)	2866 (44.9)	1749 (57.5)
Male	18 (0.2)	8 (1.3)	10 (9.8)	14 (35.9)	1642 (7.6)	1516 (17.5)	1254 (37.0)	997 (53.3)
Female	97 (2.5)	15 (10.4)	6 (16.2)	3 (33.3)	2412 (13.7)	2324 (30.3)	1612 (53.9)	872 (74.5)
Treatment-required anemia and not treated, n/N (%)	103/115 (89.6)	19/23 (82.6)	10/16 (62.5)	6/17 (35.3)	3374/4054 (83.2)	3059/3840 (79.7)	1844/2866 (64.3)	609/1749 (34.8)
Self-reported anemia								
N	13,311	672	116	44	—	—	—	—
n (%)	942 (7.1)	70 (10.4)	24 (20.7)	21 (47.7)				

CKD, chronic kidney disease, Hb, hemoglobin.
Values are n (%) unless otherwise indicated.

more common in the hospital population across each stage of disease (Figure 7).

DISCUSSION

This study demonstrates that, in Japanese administrative databases, a large proportion of patients with CKD stage G3 did not receive a CKD-related diagnosis code. Likewise, many patients with Hb-defined anemia in CKD stage G3 did not receive an anemia-related diagnosis or prescription record for anemia treatment. This tendency was observed in both the general and hospital populations. Nephrologists and diabetologists tended to diagnose CKD more frequently, suggesting

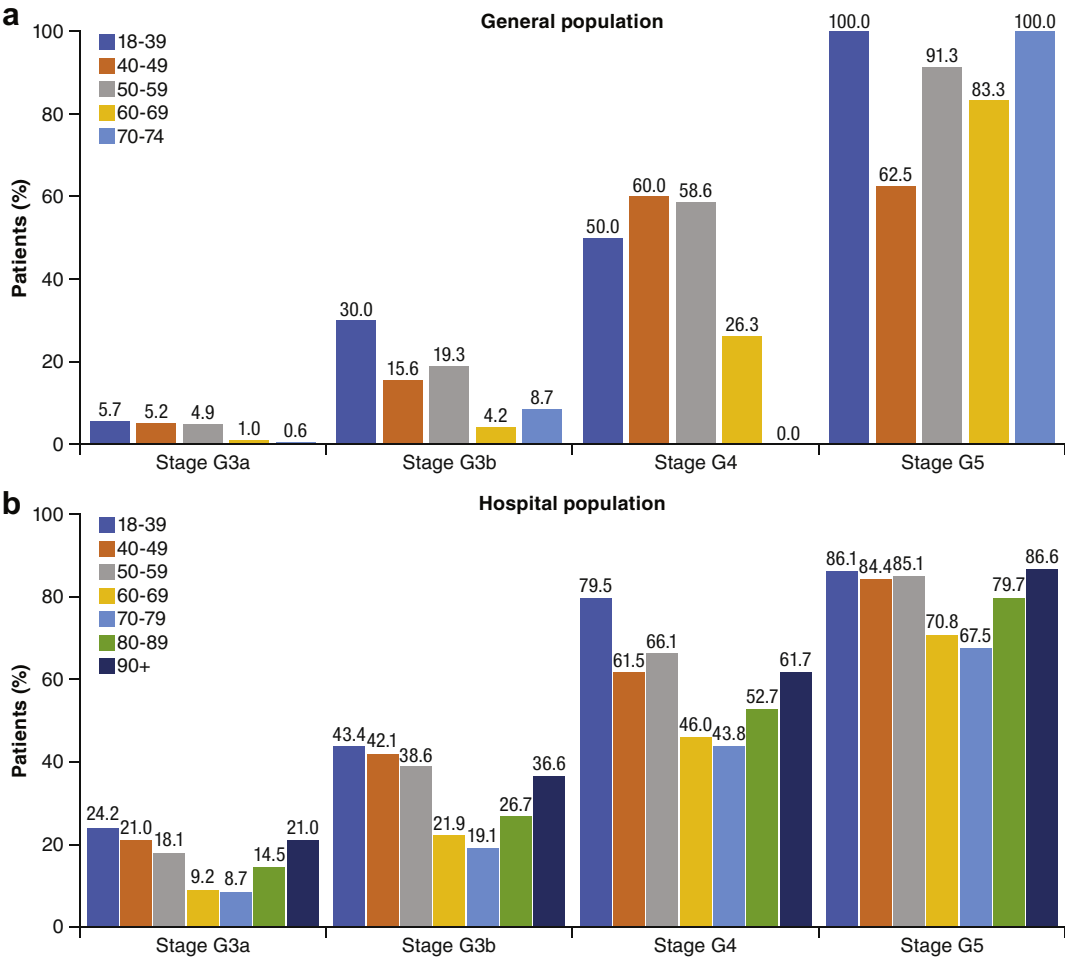

Figure 5. Prevalence of anemia by chronic kidney disease stage and age in the (a) general and (b) hospital populations.

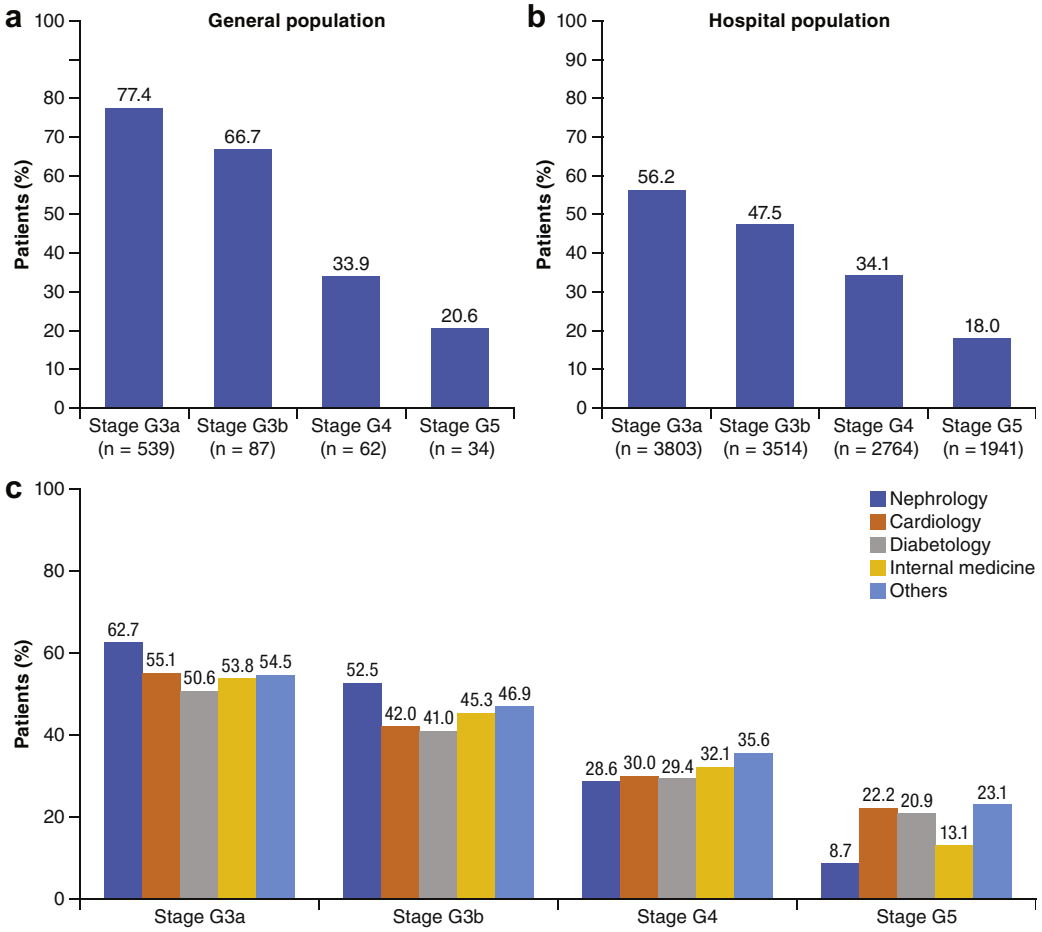

Figure 6. Prevalence of anemic patients without anemia-related diagnosis code or anemia-related treatment by (a,b) chronic kidney disease stage and (c) specialty in the hospital population. Treatment-required anemia defined as hemoglobin <11 g/dl.

that referral to these specialists by other healthcare providers may help diagnose CKD earlier. Patients with CKD- or anemia-related diagnosis codes were more likely to receive treatment and were more likely to present with comorbidities.

Diagnosis codes in claims data are used for reimbursement purposes and may not be perfectly reflective of clinical treatment in every instance; it is possible that patients who have CKD and/or anemia receive adequate care despite the absence of formal diagnosis codes associated with their claims. The current study was not performed in order to report on or estimate the prevalence or incidence of CKD and/or anemia in Japan. Rather, this study was performed in order to highlight the fact that some portion of patients who technically have signs of CKD and/or anemia do not have corresponding diagnosis codes, suggesting the existence of overlooked patients who could benefit from referral to and treatment from a specialist (e.g., a nephrologist). Indeed, the Japanese Society of Nephrology Guidelines suggest that early outreach to such patients is important; however, it is hard to estimate how many undiagnosed patients exist.[19] Notably, many CKD patients were treated for hypertension; it is established that rigorous blood pressure control is an effective means of delaying renal replacement therapy.[29–32] In this study, therefore, a noteworthy proportion of patients with early-stage CKD received appropriate treatment, even without CKD-related diagnosis codes. One reason for the low proportion of patients diagnosed with CKD could be that CKD-related diagnosis codes were not required for reimbursement purposes (e.g., when prescribing antihypertensive treatments). The proportion of CKD patients without a diagnosis code decreased as CKD stage increased. That is, the sensitivity of the diagnosis-based case definition increased with severity of CKD stage.[16,33,34] Given these findings, CKD studies using Japanese administrative data would benefit from using laboratory result–based case definitions, rather than diagnosis-based case definitions, unless the study focuses on a fairly advanced CKD population.

The underdiagnosis of CKD in the general population may suggest that some patients did not actively seek medical help because of the asymptomatic nature of their condition.[12] Previous work has found that earlier diagnosis of CKD can help delay renal

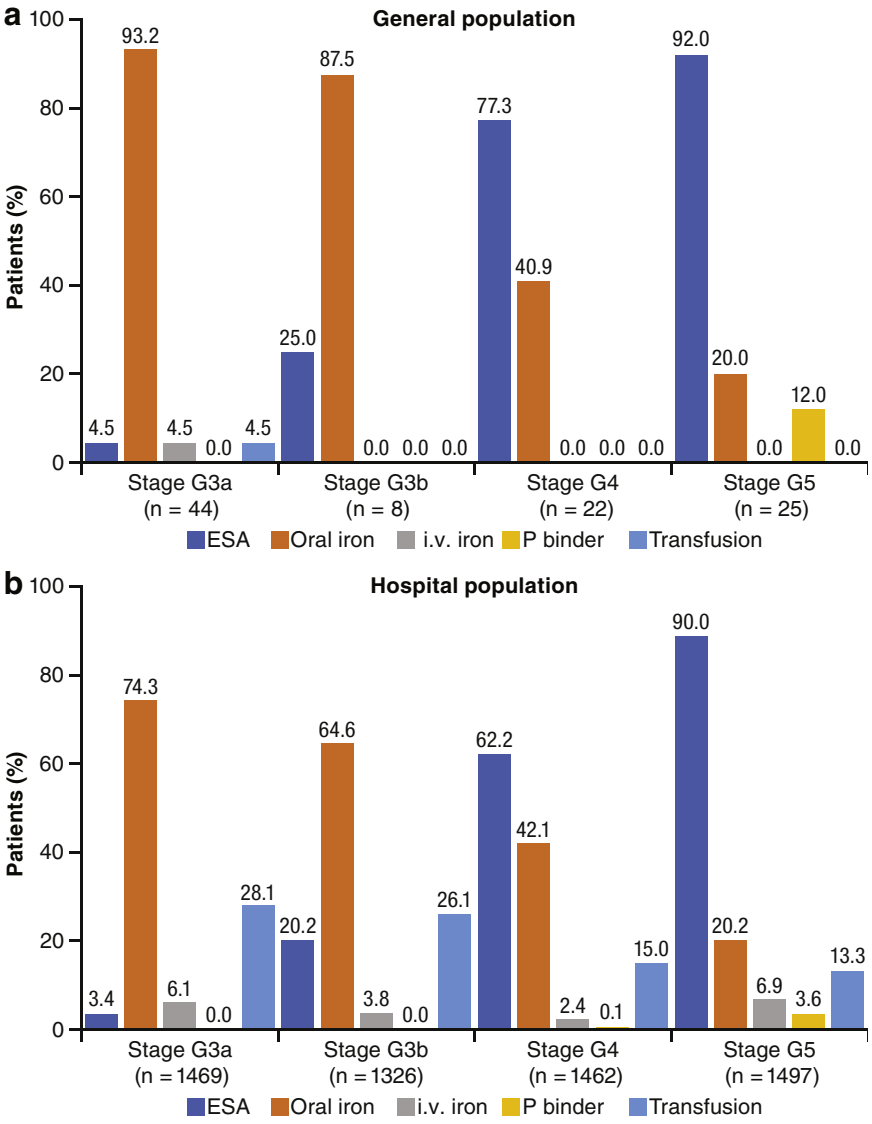

Figure 7. Anemia treatment type by chronic kidney disease stage. (a) General population and (b) hospital population. ESA, erythropoiesis-stimulating agent; P binder, phosphate binder.

replacement therapy in a portion of these patients.[6,9–11] This notion is further supported by evidence that creative integration of care pathways led to improved outcomes in patients with CKD, both renal-related and otherwise.[9,10,35–37] Currently, SCr measurement is not mandatory during special annual health checkups, but is done at the discretion of the insurer. It may be worthwhile to investigate whether the mandated measurement of SCr at annual health checkups could be cost effective for the government.

The prevalence of anemia in patients with CKD stage G3a was slightly lower in the general population in the current study (3.8%), relative to previously reported data.[14,15] This difference may be due to the higher proportion of males in this study population, although the difference between sexes in the current study was not clear. Another reason may be the various anemia definitions used across different studies. It should also be noted that Hb values in the current study may have been obtained several months before the index date in some cases and can be affected by subsequent treatment and/or other factors. Therefore, caution should be exercised when interpreting these results.

In this study, the prevalence of self-reported anemia was higher in CKD stage G3a and lower in CKD stage G5 compared with Hb-defined anemia, suggesting that once they were diagnosed or treated, most patients remained aware of their condition, even if it was transient, whereas patients with severe CKD may not necessarily be aware of their anemic condition, even if treated with erythropoiesis-stimulating agent.

The anemia treatment patterns were similar to those in previous studies,[38,39] in which oral iron was the most common anemia treatment in CKD stage G3, and erythropoiesis-stimulating agents are more likely to be used in CKD stage G4 or above; IV iron was used sparingly across all groups and stages. Red blood cell transfusion was far more common in the hospital

population, suggesting that patients either were sicker or were treated for a condition requiring surgery or for blood loss–related anemia.

The proportion of Hb-defined anemia patients without anemia diagnosis or treatment decreased from CKD stages G3a (hospital: 56.5%; general: 77.4%) to G5 (hospital: 18.1%; general: 20.6%). This decrease may be because as CKD progresses, anemia symptoms may become more prominent, thereby increasing the likelihood that a patient will seek medical care. On the other hand, the prevalence of anemic patients without an anemia-related diagnosis code or anemia treatment was higher for CKD stages G3a and G3b in the nephrology specialty versus other specialties, and lower for CKD stages G4 and G5. This difference could be because nephrologists are more apt to monitor Hb levels as they worsen (e.g., <11 g/dl).[40] By the time patients had CKD stage G5, nephrologists were most likely to diagnose and treat anemia, relative to the other specialties examined in this study.

The generalizability of our findings is limited: data for the general population do not capture subjects aged >75 years, and the hospital population is limited to diagnosis procedure combination hospitals. Also, the hospital data do not capture anemia treatment that may have been provided elsewhere and could therefore be underestimating anemia-related treatment in this population.

In conclusion, the current study highlights the noteworthy proportion of CKD stage G3 patients who may not necessarily be recognized as having early CKD, although some were treated for hypertension. Even in CKD stage G4, one-quarter of patients still did not receive any CKD-related diagnosis code. A significant proportion of anemic patients with CKD stage G3 also did not receive diagnosis and treatment. The regular assessment of SCr level and monitoring of eGFR and Hb values will help to identify patients who have early-stage CKD and anemia. Referral of patients who have symptoms associated with early-stage CKD to specialists may also offer a promising solution to these issues. These study results can help healthcare professionals understand trends related to the diagnosis and treatment of CKD and anemia, thereby helping them to identify opportunities for earlier intervention in these conditions.

DISCLOSURE

TK, RS, and KN are employees of Astellas Pharma, Inc.

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For the Astellas criteria on data sharing, see https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Table S1. Anemia definition by hemoglobin level (g/dl) for the Japanese population.

Table S2. Elixhauser Comorbidity Index in CKD cohort by CKD stage.

Table S3. Elixhauser Comorbidity Index in Hb cohort by CKD stage.

Table S4. Baseline characteristics of the CKD cohort by CKD stage and with or without CKD diagnosis codes.

Table S5. Baseline characteristics of the Hb cohort by CKD stage and with or without anemia diagnosis codes.

Appendix S1. Japan-specific standardized disease and diagnosis codes.

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