Table 2 Hematocrit levels and prevalence of anemia by clinical characteristics

	All ($N = 94,602$)			Men ($N = 39,754$)			Women ($N = 54,848$)		
	Number	Hematocrit (%)	Anemia, number (prevalence)	Number	Hematocrit (%)	Anemia, number (prevalence)	Number	Hematocrit (%)	Anemia, number (prevalence)
BMI (kg/m^2)									
≥26	24367	42.3 ± 4.0 (ref)	664 (2.7)	10422	45.5 ± 3.0 (ref)	317 (3.0)	13945	40.0 ± 2.8 (ref)	347(2.5)
24–26	20942	41.9 ± 4.0*	921 (4.4)	96651	44.9 ± 3.0*	489 (5.1)	11281	39.4 ± 2.9*	432 (3.8)
22–24	22287	41.3 ± 4.1*	1325 (5.9)	9645	44.4 ± 3.2*	726 (7.5)	12642	38.9 ± 2.9*	599(4.7)
<22	26241	40.3 ± 4.0*	2429 (9.3)	9754	43.4 ± 3.6*	1471(15.0)	16487	38.5 ± 3.0*	958(5.8)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$
Age (years)									
20–29	5423	42.8 ± 4.3 (ref)	53(1.0)	2773	46.1 ± 2.7 (ref)	32(1.2)	2650	39.4 ± 2.6 (ref)	21(0.8)
30–39	11802	41.9 ± 4.7*	294 (2.5)	5746	46.7 ± 2.8*	99 (1.7)	6056	38.3 ± 3.0*	195(3.2)
40–49	17612	41.3 ± 4.7*	671 (3.8)	7723	45.3 ± 2.9*	210 (2.7)	9889	38.2 ± 3.3*	461(4.7)
50–59	19996	41.6 ± 3.7*	811 (4.1)	7684	44.7 ± 3.0*	340 (4.4)	12312	39.7 ± 2.7#	471(3.8)
60–69	22446	41.5 ± 3.6*	1306 (5.8)	9035	44.0 ± 3.2*	833 (9.2)	13411	39.7 ± 2.7§	473(3.5)
≥70	17323	40.5 ± 3.8*	2320 (13.4)	6793	42.6 ± 3.8*	1542 (22.7)	10530	39.2 ± 3.1	778(7.4)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$
Estimated GFR (ml/min per 1.73 m^2)									
≥90	25258	41.4 ± 4.4 (ref)	1084 (4.3)	10709	45.0 ± 3.0 (ref)	459 (4.3)	14549	38.7 ± 3.1 (ref)	625 (4.3)
60–89	54042	41.7 ± 4.0*	2836 (5.3)	24100	44.6 ± 3.3*	1741 (7.2)	29942	39.4 ± 2.9*	29942 (3.7)
45–59	13287	40.8 ± 3.8*	1115 (8.4)	4360	43.6 ± 3.8*	642 (14.7)	8927	39.4 ± 2.9*	473 (5.3)
30–44	1829	39.6 ± 4.0*	331 (18.1)	524	41.9 ± 4.5*	174 (33.2)	1305	38.7 ± 3.4	157 (12.0)
15–29	151	37.4 ± 5.0*	60 (39.7)	47	39.2 ± 5.9*	27 (57.5)	104	36.6 ± 4.5*	33 (31.7)
<15	35	31.5 ± 4.9*	29 (82.9)	14	31.6 ± 4.8*	13 (92.9)	21	31.5 ± 5.0*	16(76.2)
ANOVA		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$		$P < 0.0001$	$P < 0.0001$

* <0.0001, # <0.05, § <0.0005

(eGFR 60–89 ml/min per 1.73 m^2), 5.9% (eGFR 45–59 ml/min per 1.73 m^2), 12.3% (eGFR 30–44 ml/min per 1.73 m^2), 32.7% (eGFR 15–29 ml/min per 1.73 m^2), and 81.0% (eGFR <15 ml/min per 1.73 m^2) when JSDT anemia criteria were applied.

Kidney function and the odds ratio of anemia

We performed multiple logistic analyses adjusted for older age (70 years and older) and BMI category to further assess the effect of decreased kidney function on anemia. Lower eGFR was found to be significantly associated with higher prevalence of anemia below eGFR of 90 ml/min per 1.73 m^2 in men and of 45 ml/min per 1.73 m^2 in women (Fig. 2). The odds ratios (ORs) of eGFR categories (ref, eGFR ≥90 ml/min per 1.73 m^2) overall, in men, and in women were as follows: eGFR 60–89 ml/min per 1.73 m^2: 1.150 (1.067–1.240, $P = 0.003$), 1.536 (1.374–1.717, $P < 0.0001$), and 0.857 (0.772–0.950, $P < 0.0001$); eGFR 45–59 ml/min per 1.73 m^2: 1.526 (1.385–1.681, $P < 0.0001$), 2.278 (1.979–2.622, $P < 0.0001$), and 1.076 (0.940–1.233, $P = 0.2885$); eGFR 30–44 ml/min per 1.73 m^2: 2.976 (2.564–3.454, $P < 0.0001$), 5.117 (4.072–6.431, $P < 0.0001$), and 2.265 (1.843–2.783, $P < 0.0001$); eGFR 15–29 ml/min per 1.73 m^2: 11.346 (7.909–16.276, $P < 0.0001$), 24.404 (12.710–46.857, $P < 0.0001$), and 8.234 (5.269–12.867, $P < 0.0001$); and eGFR ≤15 ml/min per 1.73 m^2: 104.250 (41.632–261.049, $P < 0.0001$), 288.024 (36.039–2301.922, $P < 0.0001$), and 65.386 (23.265–183.767, $P < 0.0001$). The OR of older age (over 70 years) was 2.772 (2.597–2.959, $P < 0.0001$) overall, 3.850 (3.531–4.198, $P < 0.0001$) in men, and 1.698 (1.530–1.884, $P < 0.0001$) in women. Additionally, the ORs of BMI categories (ref. BMI ≥26 kg/m^2) overall, in men, and in women were as follows: BMI 24–26 kg/m^2: 1.565 (1.412–1.735, $P < 0.0001$), 1.552 (1.339–1.798, $P < 0.0001$), and 1.580 (1.367–1.826, $P < 0.0001$); BMI 22–24 kg/m^2: 2.159 (1.960–2.377, $P < 0.0001$), 2.305 (2.007–2.648, $P < 0.0001$), and 1.959 (1.710–2.244, $P < 0.0001$); BMI <22 kg/m^2: 3.571 (3.264–3.907 $P < 0.0001$), 4.543 (3.991–5.171, $P < 0.0001$), and 2.466 (2.172–2.800, $P < 0.0001$).

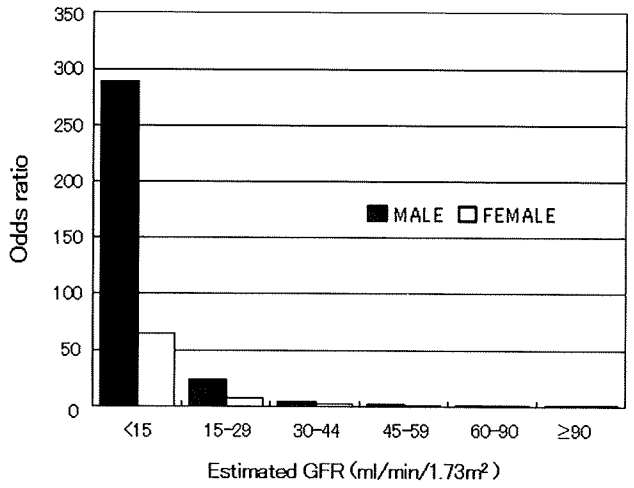

Fig. 2 Odds ratio of anemia by sex, adjusted for body mass index category and older age (>70 years) according to estimated glomerular filtration rate category in both sexes. Reference is eGFR ≥90 ml/min per 1.73 m^2

Prevalence of stage 3–5 CKD complicated with anemia

The result of the present study showed that 10% of subjects with stage 3–5 CKD were complicated with anemia. Since it has been estimated that there are 10,000,000 Japanese people with stage–3–5 CKD by using a new Japanese equation: eGFR (ml/min per 1.73 m^2) = 194 × serum creatinine$^{1.094}$ × age$^{0.287}$ × 0.739 (if female) [18], there could be as many as 1,000,000 Japanese people with stage 3–5 CKD complicated with anemia.

Discussion

Anemia is often associated with decreased eGFR. However, previous reports have suggested that the relationship between decreased kidney function and anemia varies across countries and races [15, 16, 23]. In the present study, which was conducted among a general Japanese population, the effect of decreased kidney function on anemia was significantly prevalent below eGFR of 90 ml/min per 1.73 m^2 in men and 45 ml/min per 1.73 m^2 in women.

As the previous study demonstrated [12], the distribution of eGFR among the general Japanese population is shifted to the lower side compared with that of the general US population [17]: the mean eGFR value was approximately 79 ml/min per 1.73 m^2 in our cohort, while it is reported to be 93 ml/min per 1.73 m^2 in the USA [17]. The higher incidence of aged subjects might be responsible for the lower eGFR value in Japan. Alternatively, the normal kidney function of the Japanese population might be fundamentally less than that of Caucasian populations due to the relatively smaller size of kidney and lower intake of protein. Regardless of its cause, a cutoff value of eGFR for clinical relevance is yet to be determined for the Japanese population. Some researchers have argued that it would be approximately 50 ml/min per 1.73 m^2 since the risk of end-stage renal disease (ESRD) increases significantly at this level [25]. In the present study, the OR of anemia increased to more than twice at eGFR values of less than approximately 50 ml/min per 1.73 m^2. According to the present study, the adjusted OR of stage 3 CKD for anemia in the Japanese general population has been shown to be around

two, which is similar to that in the general US population [16]. In terms of risk for complicating anemia, the clinical eGFR value in Japan might be similar to that of the general US population.

In the US population in the Third National Health and Nutrition Examination Survey (NHANES III), it was shown that African–Americans had a significantly higher OR (2.5) for anemia than Caucasians [16]. In another study from Italy conducted among patients whose mean age was about 75 years, the threshold of kidney function as a risk factor of anemia was found to be 30 ml/min per 1.73 m^2, which is lower than that of Japanese and US populations [24]. Although age might be responsible for the difference in the threshold level of kidney function in the Italian study, we found no such difference between subjects 70 years and older, and those under 70 years old (data not shown). Some factors, including differences in the definition of anemia and/or race, may affect this discrepancy.

In addition to racial differences, there might also be gender differences in the rate of complication with anemia at the same degree of kidney function. In the present study, men had a higher incidence and OR for anemia compared with women at eGFR values below 60 ml/min per 1.73 m^2; this is consistent with the previous report by Hsu et al. [25]. Differences in the cause of CKD between genders [26] and the effect of sex hormones on erythrogenesis might be responsible for this gender difference [27, 28].

The combination of anemia and CKD is reported to have a significant impact on survival compared with either anemia alone or CKD alone [29]. Since anemia has been identified not only as a nonclassical cardiovascular risk factor but also as a progressive factor in decreasing kidney function, anemia might play a significant role in the association between CKD and CVD. Accordingly, intervention for anemia could be an effective approach to prevent CVD in CKD subjects. However, large randomized intervention studies [30, 31] and a meta-analysis [32] have shown a slight but significant benefit of lower hemoglobin levels; it would thus be better to maintain these lower levels rather than attempt to improve outcome by achieving higher hemoglobin levels in CKD patients. Since the higher hemoglobin target group showed itself to have a higher risk of poorly controlled blood pressure [32], the clinical benefits of correction of anemia via an erythropoiesis-stimulating agent should be determined under strict control of blood pressure. Considering the substantial number of patients complicated with CVD and related death before starting hemodialysis therapy, intervention during ESRD might be too late to effectively prevent CVD. The incidence of anemia appears to increase from an eGFR of less than 60 ml/min per 1.73 m^2, as shown in previous studies [16] as well as in the present study. Therefore, intervention for anemia in the early stages of CKD could be an effective method of preventing CVD among CKD subjects.

In Japan, incidence of CKD is predicted to be much higher than that in the US population [12, 17]. Furthermore, it will increase since the number of elderly people is predicted to increase in Japan, at least during the next two decades. According to the present study, an association of kidney function with anemia was similar to that in the US population. Therefore, it is critical to screen CKD subjects for anemia.

The present study has a number of important limitations. First, we were unable to identify any causal association between decreased kidney function and anemia due to the cross-sectional design of the study. It was not clear how long-term CKD contributes to anemia at each CKD stage. We cannot exclude the possibility that other factors such as iron deficiency, malnutrition, and chronic disease might affect anemia. Second, one-third of the total cohort was excluded because of lack of data for Scr and Ht. It is possible that those with known kidney diseases and/or comorbid individuals are selected. However, the total number of subject is more than 90,000 and therefore it is subtle as a community-based cohort. Third, the results might vary according to the definition of anemia. The assessment of anemia by hematocrit may not be always precise and may be affected by volume status. Previous studies investigating the relationship between renal function and anemia have used the World Health Organization (WHO) criteria to define anemia [15, 16]. The WHO defines anemia as hemoglobin concentration of less than 12 g/dl for women and less than 13 g/dl for men. However, these criteria have physiological correlates in younger individuals. Therefore, it has been suggested that it might be inappropriate to apply these criteria to the present cohort, which included a substantially high number of older subjects [33]. Thus, it might be preferable to use the definition of anemia, which takes both age and sex into account [20, 21].

In conclusion, the threshold level of kidney function, below which there is an increased risk of more than twice for complicating anemia, was found to be an eGFR of approximately 50 ml/min per 1.73 m^2 in a general Japanese population. Therefore, there is expected to be a substantial number of CKD subjects with anemia who could have a higher risk for CVD as well as ESRD. Further information is needed to determine how and when intervention should be initiated in patients with both CKD and anemia.

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