

Evaluation of Gender Differences in the Association between Hemoglobin and Survival among Hemodialysis Patients in the J-DOPPS

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Background / Goal

Background

- Female patients on dialysis experience mild anemia compared to male patients¹. The Japanese Society for Dialysis Therapy Renal Data Registry demonstrated that hemoglobin (Hgb) of male patients was 10.67 ± 1.29 g/dl, while Hgb of female patients was 10.47 ± 1.25 g/dl as of 2012².
- A study in non-dialysis patients with heart failure reported anemia was associated with 5 year mortality in male patients (odds ratio=1.76, 95%CI=1.15-2.70), but not female patients (odds ratio=1.15, 95%CI 0.65-2.05)³.
- Lower Hgb may be permissible among female patients without kidney diseases, but little is known about the gender-specific anemia management in hemodialysis patients.

Goal

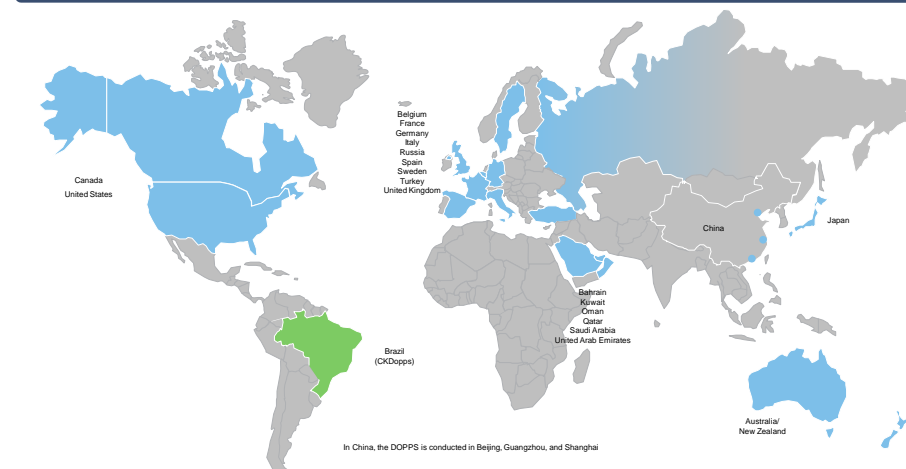
- We analyzed the Japan Dialysis Outcomes and Practice Patterns Study (J-DOPPS) data to explore the effect modification by gender of association between Hgb levels and all-cause mortality among maintenance hemodialysis patients.

¹ McDonald SP, Marshall MR, Kerr PG, et al. Erythropoietic agents, iron and hemoglobin—What happens beyond the trial setting: observational data from the ANZDATA registry. *Hemodial Int* 2004; 8(3):257-64.
² Nakai S, Hanafusa N, Masakane I, et al. An overview of regular dialysis treatment in Japan (as of 31 December 2012). *Ther Apher Dial* 2014; 18(6):535-602.
³ Ezekowitz JA, McAlister FA, Armstrong PW. The interaction among sex, hemoglobin and outcomes in a specialty heart failure clinic. *Can J Cardiol* 2005; 21(2): 165-71.

Methods

- Sample:** 6,891 maintenance hemodialysis patients from the J-DOPPS phases 3-5 (2005-2015)
- Analysis:**
 - Model:** Cox proportional hazards regression, adjusted for potential confounders
 - Outcome:** All-cause mortality rate
 - Exposure:** Baseline or time-varying Hgb values in five categories. Analyses were conducted with and without a 30-day lag between each Hgb measurement and the start of the associated time-at-risk, to account for possible effects of the death process on Hgb levels.
 - Adjustments:** age, comorbid factors, BMI, vintage, catheter use, interdialytic weight loss and labs (including albumin, calcium, creatinine, C-reactive protein, phosphorus, single pool Kt/V, ferritin, and TSAT)

DOPPS The Dialysis Outcomes and Practice Patterns Study



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The DOPPS is an international prospective cohort study of hemodialysis treatment and patient outcomes:

- DOPPS 1 (1996-2001):** 308 dialysis facilities and 17,034 patients in 7 countries (France, Germany, Italy, Japan, Spain, UK, and US)
- DOPPS 2 (2002-2004), DOPPS 3 (2005-2008), DOPPS 4 (2009-2011):** ≥300 facilities and 11,000 - 13,000 patients per study phase in 12 countries (DOPPS 1 countries + Australia, Belgium, Canada, New Zealand, and Sweden)
- DOPPS 5 (2012-2015), DOPPS 6 (2015-2017):** : ~500 facilities and 30,000 patients in nine new countries (Bahrain, China, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Russia, and Turkey) in addition to the 12 countries represented in DOPPS 4

COI Disclosure

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Results

Table 1: Patient characteristics by gender and hemoglobin levels

Characteristics	Female Hemoglobin, g/dL					Male Hemoglobin, g/dL				
	<9	9-9.9	10-10.9	11-11.9	12+	<9	9-9.9	10-10.9	11-11.9	12+
Patients, N	356 (14%)	601 (24%)	839 (34%)	532 (21%)	168 (7%)	517 (12%)	938 (21%)	1426 (32%)	1030 (23%)	484 (11%)
Patient age, years	68.0(12.9)	65.8(12.4)	64.7(12.0)	64.0(12.9)	63.8(12.5)	66.6(12.3)	65.6(11.9)	64.2(12.0)	62.4(12.5)	60.1(13.3)
Vintage, years	5.46(7.61)	7.62(7.96)	7.76(7.65)	7.67(7.38)	7.27(7.63)	4.09(6.26)	5.40(6.42)	6.20(6.98)	6.53(7.37)	6.36(7.37)
BMI, kg/m ²	20.7(4.1)	20.8(3.7)	20.5(3.6)	20.6(3.6)	20.4(3.4)	21.1(3.1)	21.6(3.4)	21.8(3.2)	21.8(3.1)	22.2(3.3)
Catheter, %	5%	1%	2%	1%	1%	7%	2%	1%	1%	1%
Comorbidities at baseline, %										
Coronary artery disease	32%	32%	27%	23%	28%	34%	36%	35%	35%	33%
Cancer, other than skin	9%	8%	9%	9%	9%	15%	14%	12%	11%	8%
Other CVD	27%	28%	27%	24%	27%	31%	27%	28%	28%	29%
Cerebrovascular disease	14%	10%	14%	11%	14%	17%	16%	14%	13%	13%
Congestive heart failure	30%	22%	20%	20%	29%	29%	21%	21%	18%	24%
Diabetes mellitus	38%	32%	29%	29%	39%	49%	45%	43%	43%	40%
Gastrointestinal bleeding	6%	2%	4%	2%	4%	10%	5%	5%	4%	4%
Hypertension	77%	77%	77%	71%	71%	81%	82%	81%	80%	78%
Lung disease	4%	2%	3%	2%	2%	5%	6%	3%	3%	3%
Neurologic disorder	14%	10%	12%	10%	13%	14%	6%	7%	7%	7%
Psychological disorder	6%	6%	5%	5%	9%	5%	4%	4%	4%	3%
Peripheral vascular disease	17%	12%	14%	13%	16%	22%	19%	18%	16%	17%
Recurrent cellulitis	3%	4%	3%	3%	4%	7%	4%	4%	3%	4%
Laboratory data at baseline										
Hemoglobin, g/dL	8.17(0.71)	9.51(0.28)	10.4(0.3)	11.4(0.3)	12.6(0.7)	8.21(0.66)	9.50(0.29)	10.5(0.3)	11.4(0.3)	12.7(0.7)
Albumin, g/dL	3.40(0.61)	3.65(0.45)	3.75(0.43)	3.78(0.40)	3.73(0.43)	3.37(0.61)	3.61(0.50)	3.73(0.45)	3.81(0.42)	3.84(0.39)
Creatinine, mg/dL	7.87(2.49)	9.07(2.36)	9.40(2.47)	9.45(2.55)	9.38(2.64)	9.11(3.21)	10.3(3.1)	10.9(3.1)	11.2(3.1)	11.4(3.5)
C-reactive protein, mg/mL	13.6(33.8)	4.72(13.61)	3.74(10.92)	3.16(11.36)	5.94(21.19)	14.2(27.5)	8.48(22.43)	6.45(64.41)	4.08(13.17)	3.30(6.86)
Serum Phosphorus, mg/dL	5.07(1.47)	5.28(1.30)	5.37(1.26)	5.43(1.40)	5.64(1.36)	5.07(1.61)	5.30(1.45)	5.44(1.41)	5.57(1.38)	5.70(1.59)
Single Pool Kt/V	1.41(0.37)	1.48(0.31)	1.53(0.28)	1.51(0.29)	1.50(0.25)	1.19(0.31)	1.24(0.26)	1.26(0.25)	1.26(0.26)	1.24(0.27)
TSAT, %	22.6(13.2)	23.9(12.9)	25.0(12.2)	25.3(11.6)	26.1(11.7)	24.1(14.2)	23.1(11.4)	24.8(11.3)	25.1(11.7)	26.2(13.4)
Ferritin, ng/mL	105 [44,230]	94.3 [36.0,194.0]	79.5 [38.2,185.1]	83.9 [34.3,180.5]	88.7 [38.6,180.1]	156 [59,311]	99.0 [39.6,213.0]	85.3 [36.0,185.8]	72.1 [31.0,157.2]	62.0 [32.2,165.0]
Anemia treatment at baseline										
ESA use (yes/no)	97%	93%	91%	88%	75%	95%	90%	86%	82%	62%
EPO dose (units/kg)	750(537)	541(323)	518(376)	453(370)	481(402)	699(551)	506(389)	419(351)	391(367)	352(275)
IV Iron use (yes/no)	38%	31%	36%	36%	38%	38%	33%	31%	36%	33%

Data shown as mean (standard deviation), median [interquartile range], or prevalence

Summary / Conclusions

- The patients with lower Hgb tended to be female and older. They also had shorter vintage, higher comorbidities, inflammation, wasting, ferritin levels and ESA doses
- The association between Hgb and survival might differ between genders in Japanese HD patients
- Only male patients showed a “U-shaped” association between Hgb and survival, while a moderate and inverse linear relationship was observed in females
- The detailed investigations in the male patients with higher Hgb levels might lead to better understanding of the gender differences in anemia management and of anemia management in whole dialysis population as well

Figure 1: Hemoglobin distribution by gender

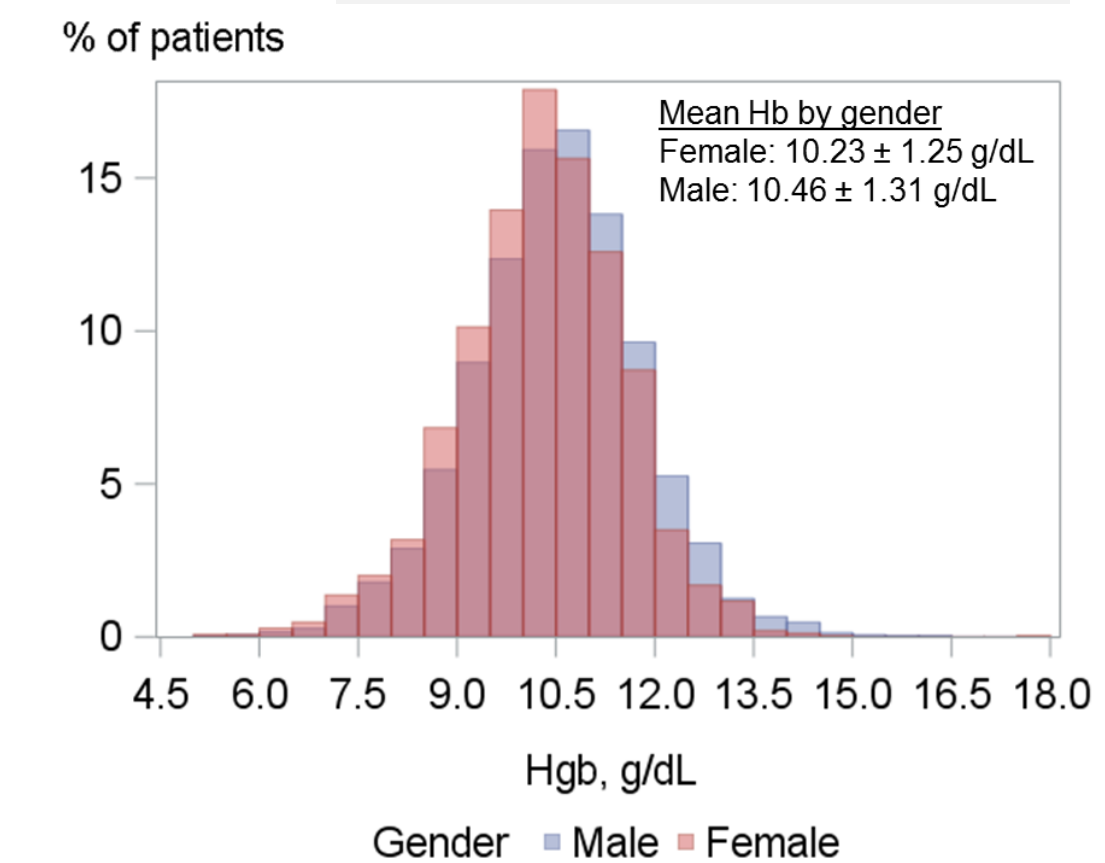


Figure 2: Adjusted HR of all-cause mortality, by baseline hemoglobin (lagged 30 days) and gender

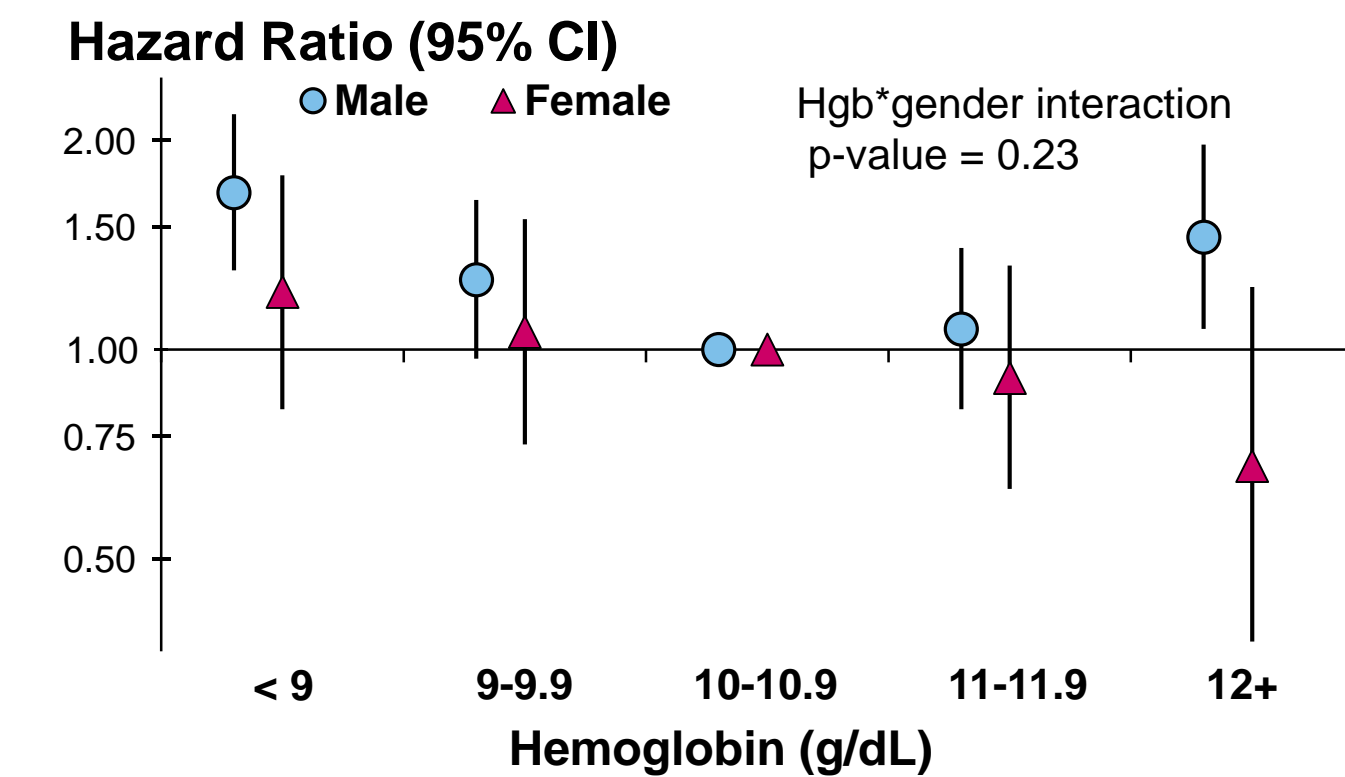


Table 2: Association of hemoglobin (without 30 day lag) and all-cause mortality, by gender and adjustment level

		Hemoglobin category, g/dL					p-value for interaction
		<9	9-9.9	10-10.9	11-11.9	12+	
Model 0	Female	2.07(1.48-2.89)	1.11(0.76-1.61)	1 (ref)	0.88(0.62-1.23)	0.79(0.46-1.39)	0.28
	Male	2.46(1.90-3.20)	1.42(1.11-1.81)	1 (ref)	0.93(0.72-1.20)	1.10(0.82-1.46)	
Model 1	Female	1.70(1.23-2.35)	1.06(0.74-1.52)	1 (ref)	0.90(0.64-1.26)	0.83(0.46-1.49)	0.49
	Male	2.18(1.68-2.83)	1.30(1.01-1.66)	1 (ref)	1.02(0.80-1.31)	1.44(1.07-1.93)	
Model 2	Female	1.79(1.29-2.47)	1.13(0.78-1.63)	1 (ref)	0.94(0.66-1.34)	0.73(0.41-1.29)	0.61
	Male	1.96(1.50-2.56)	1.28(0.98-1.67)	1 (ref)	1.07(0.82-1.39)	1.42(1.06-1.91)	
Model 3	Female	1.79(1.30-2.48)	1.13(0.78-1.63)	1 (ref)	0.94(0.66-1.34)	0.73(0.41-1.30)	0.60
	Male	1.96(1.50-2.55)	1.28(0.98-1.67)	1 (ref)	1.07(0.82-1.39)	1.43(1.06-1.91)	
Model 4	Female	1.34(0.96-1.87)	1.04(0.72-1.50)	1 (ref)	0.91(0.64-1.29)	0.70(0.39-1.24)	0.77
	Male	1.58(1.22-2.04)	1.23(0.94-1.61)	1 (ref)	1.11(0.85-1.46)	1.53(1.12-2.08)	

Model 0: hemoglobin, sex and the interaction between sex and hemoglobin

Model 1: Adjust for age

Model 2: Model 1 + comorbid factors, BMI, vintage, catheter use, etc.

Model 3: Model 2 + interdialytic weight loss

Model 4: Model 3 + labs (including albumin, calcium, creatinine, C-reactive protein, phosphorus, single pool Kt/V, ferritin, and TSAT)