

Altered metabolism of serum Manganese is associated with Low levels of Hemoglobin in the patients with Chronic Kidney Disease

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Background

Manganese (Mn) is associated with iron deficiency or anemia. Although anemia is a common manifestation of CKD, it has barely been established whether blood Mn level have some effect on anemia in CKD patients or not. The purpose of this study is to analyze the relationship between blood Mn level and anemia in the patients with CKD

Method

This study was a cross-sectional study based on the patients with CKD. Total 426 patients with CKD were included in single center from March 2014 to January 2016. We excluded patients with missing values and evidence of acute illness like pneumonia, urinary tract infection or bleeding. They were divided into two groups by blood manganese level, 8.0 ug/L, according to the reference range of the hospital laboratory policy.

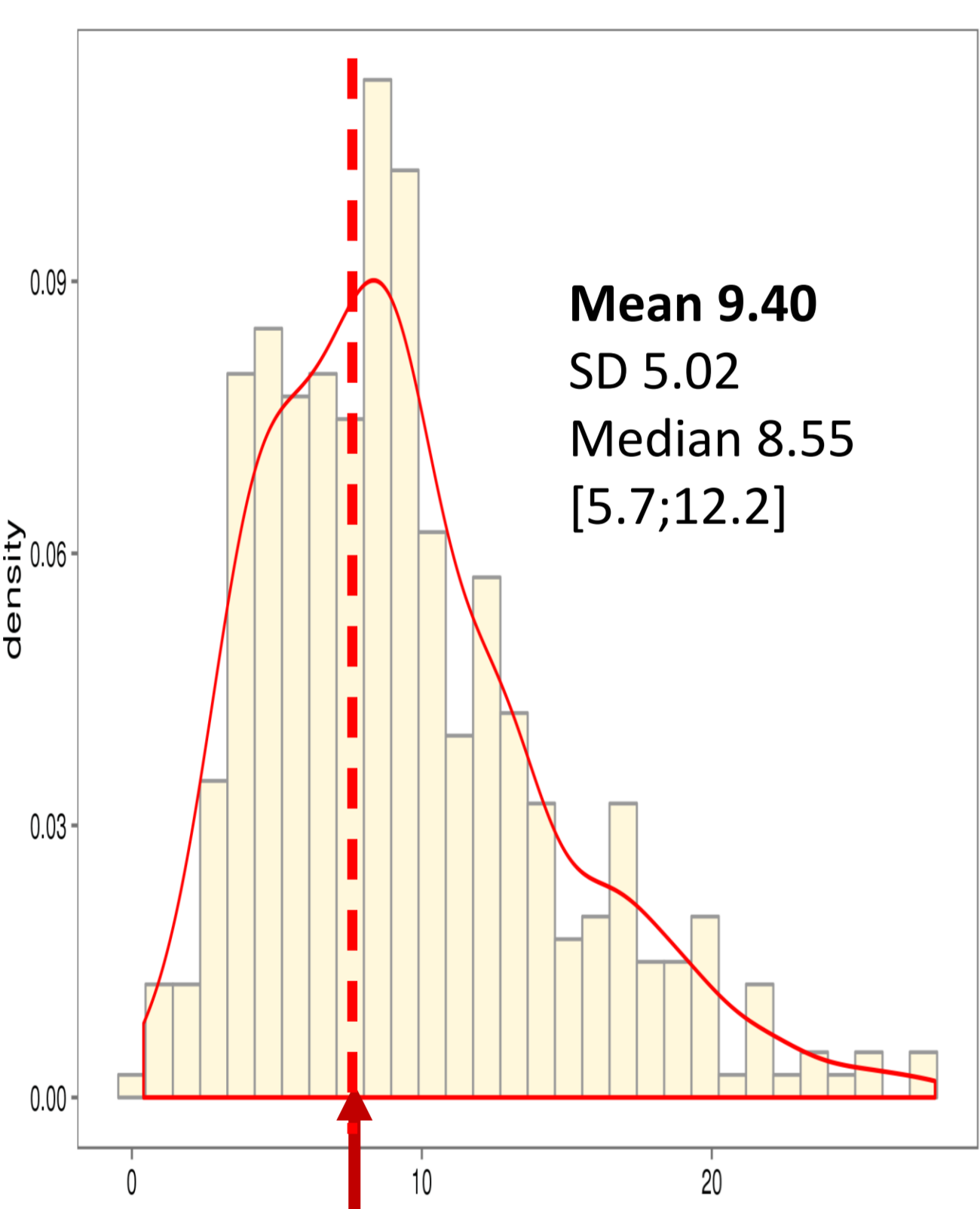


Figure 1. Distribution of blood Mn

Result

Table 1. Basal characteristics and comparison between Mn groups

Total number	Total (n=426)	Low Mn (<8 ug/L) (n=182)	High Mn (≥8ug/L) (n=244)	P value
Male, n(%)	199 (46.7)	99 (54.4)	100 (41.0)	0.008
Age	61.3 ± 18.2	64.4 ± 17.9	59.0 ± 18.2	0.002
BMI (kg/m ²)	23.9 ± 4.4	23.8 ± 4.6	24.0 ± 4.3	0.760
Smoking, n(%)	95 (22.3)	52 (28.6)	43 (17.6)	0.010
Hypertension, n(%)	292 (68.5)	137 (75.3)	155 (63.5)	0.013
Diabetes, n(%)	194 (45.5)	99 (54.4)	95 (38.9)	0.002
Cardiovasc. Dz, n(%)	49 (11.5)	23 (12.6)	26 (10.7)	0.642
PAD, n(%)	7 (1.6)	4 (2.2)	3 (1.2)	0.695
Chronic HF, n(%)	27 (6.3)	11 (6.0)	16 (6.6)	0.989
CVD, n(%)	61 (14.3)	32 (17.6)	29 (11.9)	0.128
Malignancy, n(%)	46 (10.8)	25 (13.7)	21 (8.6)	0.130
Hypothyroidism, n(%)	30 (7.0)	14 (7.7)	16 (6.6)	0.794
Medication				
ACEi or ARB, n(%)	192 (46.4)	85 (48.6)	107 (44.8)	0.505
CCB, n(%)	172 (41.5)	88 (50.3)	84 (35.1)	0.003
Beta blocker, n(%)	129 (31.2)	68 (38.9)	61 (25.5)	0.005
Diuretics, n(%)	175 (42.3)	93 (53.1)	82 (34.3)	<0.001
Aspirin, n(%)	68 (16.5)	29 (16.7)	39 (16.3)	1.000
Statin, n(%)	88 (21.3)	45 (25.6)	43 (18.1)	0.085
Omega-3 agent, n(%)	10 (2.4)	4 (2.3)	6 (2.5)	1.000
Fenofibrate, n(%)	5 (1.2)	2 (1.1)	3 (1.3)	1.000
Laboratory findings				
Anemia, n(%)	192 (46.4)	155 (85.2)	146 (59.8)	<0.001
Hemoglobin (g/dL)	11.1 ± 2.3	10.0 ± 2.2	11.8 ± 2.1	<0.001
Hematocrit (%)	32.3 ± 6.8	29.0 ± 6.5	34.7 ± 5.9	<0.001
RDW (%)	13.7 ± 2.3	13.8 ± 1.8	13.6 ± 2.7	0.246
BUN (mg/dL)	45.1 ± 34.8	59.0 ± 38.5	34.7 ± 27.6	<0.001
Cr (mg/dL)	3.8 ± 3.4	4.8 ± 3.8	3.0 ± 2.9	<0.001
eGFR (ml/min/1.73m ²)	42.6 ± 41.9	30.6 ± 36.9	51.5 ± 43.2	<0.001
RRT, n(%)				0.001
No	327 (76.7)	151 (83.0)	176 (72.1)	
HD	66 (15.5)	14 (7.7)	52 (21.3)	
PD	18 (4.2)	12 (6.6)	6 (2.5)	
KT	15 (3.5)	5 (2.7)	10 (4.1)	
Serum total protein(g/dl)	6.4 ± 0.9	6.2 ± 1.0	6.6 ± 0.9	<0.001
Serum albumin (g/d)	3.5 ± 0.7	3.4 ± 0.7	3.7 ± 0.7	<0.001
Serum Manganese(ug/L)	8.6 [5.7; 12.2]	5.1 ± 1.7	12.6 ± 4.2	<0.001
Serum Zinc (ug/dL)	68.3 [56.9; 78.9]	62.6 ± 18.0	73.3 ± 30.1	<0.001
ft4 (ng/dL)	1.4 ± 5.0	1.1 ± 0.3	1.6 ± 6.6	0.261
TSH (uIU/mL)	7.3 ± 87.2	3.5 ± 8.0	10.2 ± 114.8	0.374
TC (mg/dL)	166.8 ± 60.1	162.9 ± 61.7	169.9 ± 58.8	0.238
TG (mg/dL)	146.0 ± 112.7	141.3 ± 100.1	149.5 ± 121.5	0.450
HDL (mg/dL)	39.6 ± 23.6	35.7 ± 15.9	42.6 ± 27.8	0.002
LDL (mg/dL)	94.3 ± 45.9	94.6 ± 50.7	94.1 ± 42.0	0.913
Fe (ug/dL)	59.4 ± 43.3	59.5 ± 36.1	59.3 ± 48.0	0.958
Ferritin (ng/ml)	300.5 ± 591.5	338.8 ± 608.9	271.3 ± 577.5	0.247
High ferritin (> 100)	298 (70.0)	147 (80.8)	151 (61.9)	<0.001
TIBC (ug/dL)	235.8 ± 67.0	216.8 ± 58.5	250.1 ± 69.5	<0.001
Transferrin (mg/dL)	193.7 ± 53.9	179.9 ± 49.9	204.1 ± 54.7	<0.001
TSAT	26.0 ± 17.0	28.4 ± 18.2	24.1 ± 15.9	0.010
High TSAT (> 20 %)	243 (57.0)	117 (64.3)	126 (51.6)	0.012
CRP (mg/L)	36.5 ± 74.3	38.6 ± 75.4	35.0 ± 73.6	0.624
HbA1c (%)	6.2 ± 1.5	6.2 ± 1.4	6.2 ± 1.5	0.833
ALP (IU/L)	263.8 ± 146.1	238.8 ± 103.4	282.5 ± 169.0	0.001
iPTH (pg/mL)	92.1 ± 165.9	109.4 ± 125.9	79.0 ± 190.0	0.050
1,25(OH)2 Vit.D (pg/mL)	19.6 ± 9.1	17.4 ± 7.6	21.3 ± 9.7	<0.001
25(OH)Vit.D (ng/mL)	12.8 ± 19.9	12.7 ± 28.8	12.8 ± 8.6	0.957

Table 2. Factors associated with Anemia

Risk factor	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Higher Mn level (≥8ug/L)	0.260 (0.160 – 0.420)	0.000	0.396 (0.221 – 0.710)	0.002
Smoking	0.872 (0.532 – 1.429)	0.587	0.565 (0.305 – 1.048)	0.070
Hypertension	3.130 (2.017 – 4.857)	0.000	1.337 (0.736 – 2.429)	0.341
Diabetes	3.582 (2.250 – 5.702)	0.000	1.723 (0.946 – 3.138)	0.075
Renal replacement therapy	0.876 (0.531 – 1.447)	0.606	3.753 (1.818 – 7.747)	<0.001
CKD stage				
- CKD grade 1 (eGFR > 90)	Reference		Reference	
- CKD grade 2 (60 < eGFR ≤ 90)	1.994 (0.967 – 4.111)	0.062	1.846 (0.854 – 3.988)	0.119
- CKD grade 3 (30 < eGFR ≤ 60)	3.404 (1.670 – 6.936)	0.001	2.789 (1.225 – 6.347)	0.015
- CKD grade 4 (15 < eGFR ≤ 30)	8.800 (3.995 – 19.384)	0.000	6.953 (2.736 – 17.668)	<0.001
- CKD grade 5 (eGFR ≤ 15)	17.506 (8.728 – 35.112)	0.000	20.586 (8.258 – 51.321)	<0.001
TSAT (>20%)	0.664 (0.432 – 1.021)	0.062	0.492 (0.291 – 0.832)	0.008
Ferritin (>100)	2.218 (1.428 – 3.446)	0.000	1.146 (0.649 – 2.023)	0.638

Table 3. Clinical data of RRT and non-RRT group analyzed by blood Mn level

(A) Patients who without receiving RRT

	No RRT (n=327)	Low Mn (N=151)	High Mn (N=176)	P value
Male	80 (53.0%)	79 (44.9%)	79 (44.9%)	0.177
Age	65.0 ± 18.4	56.8 ± 19.0	56.8 ± 19.0	<0.001
Zn	61.9 ± 18.1	72.6 ± 21.1	72.6 ± 21.1	<0.001
Smoking	44 (29.1%)	34 (19.3%)	34 (19.3%)	0.052
HBP	110 (72.8%)	97 (55.1%)	97 (55.1%)	0.001
DM	74 (49.0%)	60 (34.1%)	60 (34.1%)	0.009
Anemia, yes	129 (85.4%)	100 (56.8%)	100 (56.8%)	<0.001
Hb	9.9 ± 2.2	12.0 ± 2.2	12.0 ± 2.2	<0.001
Cr	4.3 ± 3.3	2.1 ± 2.1	2.1 ± 2.1	<0.001
eGFR	33.8 ± 38.3	64.5 ± 42.9	64.5 ± 42.9	<0.001
CKDGr5				<0.001
- 1	17 (11.3%)	55 (31.2%)	55 (31.2%)	
- 2	14 (9.3%)	36 (20.5%)	36 (20.5%)	
- 3	19 (12.6%)	31 (17.6%)	31 (17.6%)	
- 4	26 (17.2%)	25 (14.2%)	25 (14.2%)	
- 5	75 (49.7%)	29 (16.5%)	29 (16.5%)	
Total Protein	6.2 ± 1.0	6.6 ± 0.9	6.6 ± 0.9	<0.001
Albumin	3.4 ± 0.7	3.7 ± 0.7	3.7 ± 0.7	<0.001

(B) Patients who receiving RRT

	RRT patients (n=99)	Low Mn (N=31)	High Mn (N=68)	P value
Male	19 (61.3%)	21 (30.9%)	21 (30.9%)	0.008
Age	61.6 ± 14.8	64.8 ± 14.3	64.8 ± 14.3	0.312
Zn	66.3 ± 17.6	75.0 ± 46.1	75.0 ± 46.1	0.183
Smoking	8 (25.8%)	9 (13.2%)	9 (13.2%)	0.211
DM	6 (19.4%)	33 (48.5%)	33 (48.5%)	0.011
Anemia	26 (83.9%)	46 (67.6%)	46 (67.6%)	0.151
Hb	10.6 ± 1.8	11.3 ± 1.6	11.3 ± 1.6	0.059
Cr	7.6 ± 4.5	5.5 ± 3.4	5.5 ± 3.4	0.028
eGFR	15.1 ± 24.1	17.8 ± 19.2	17.8 ± 19.2	0.556
Total protein	6.2 ± 0.9	6.6 ± 0.7	6.6 ± 0.7	0.009
Albumin	3.3 ± 0.6	3.6 ± 0.6	3.6 ± 0.6	0.086

RRT	Low Mn	High Mn
HD	14 (45.2%)	52 (76.5%)
PD	12 (38.7%)	6 (8.8%)
PSKT	5 (16.1%)	10 (14.7%)

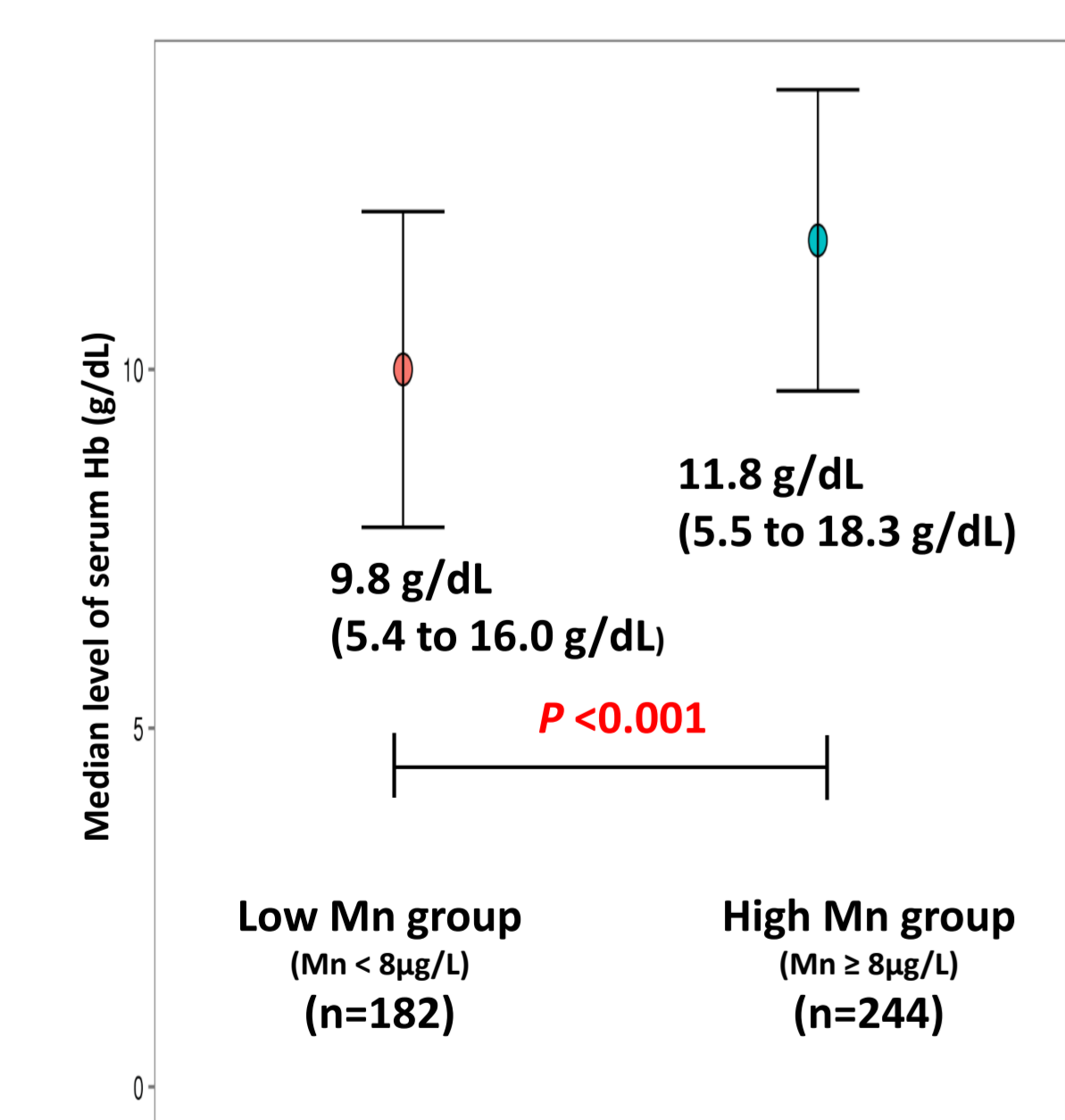


Fig 2. Comparison of median level of serum Hb between Mn groups

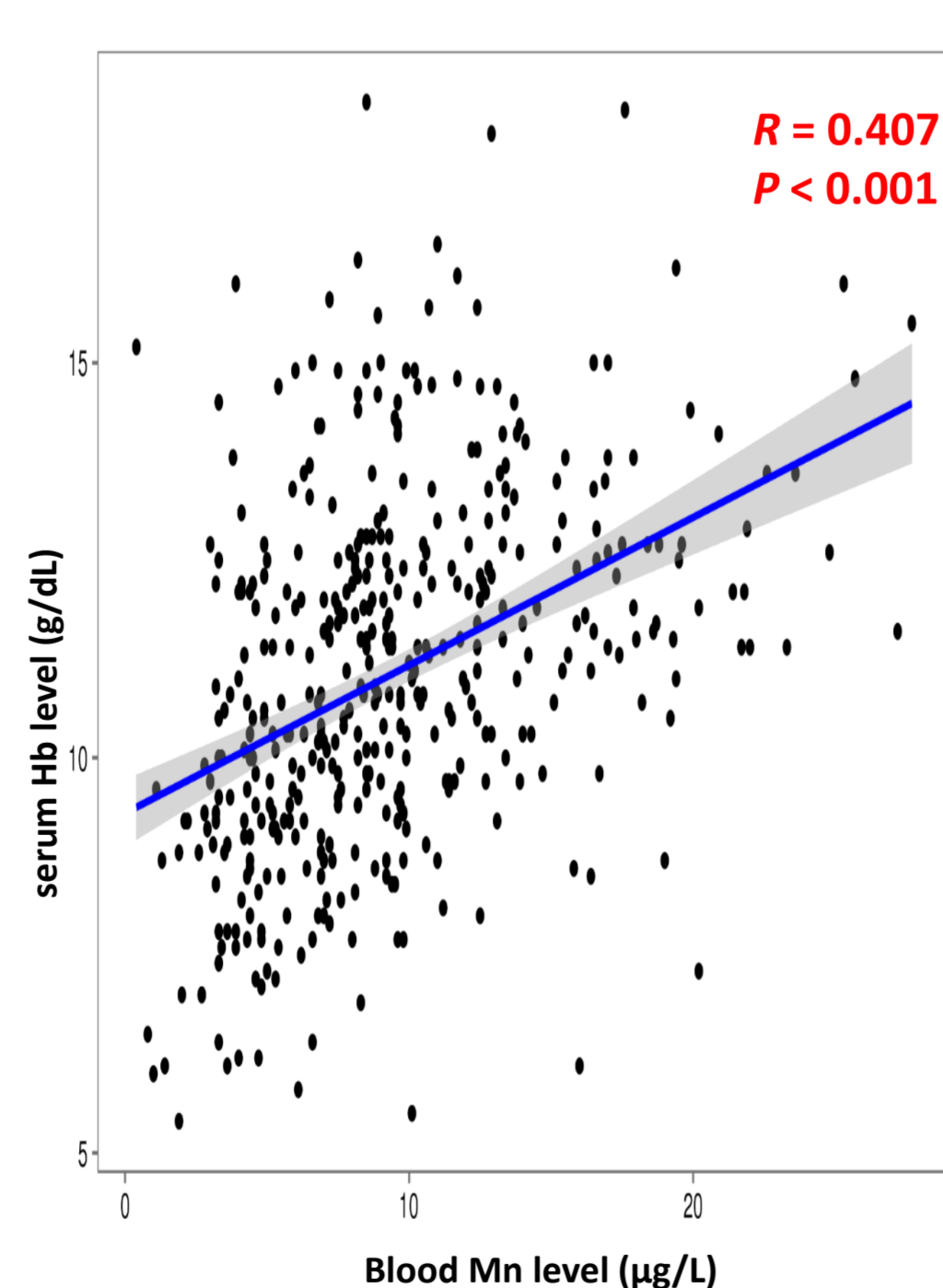


Fig 3. Association of blood Mn and serum Hb

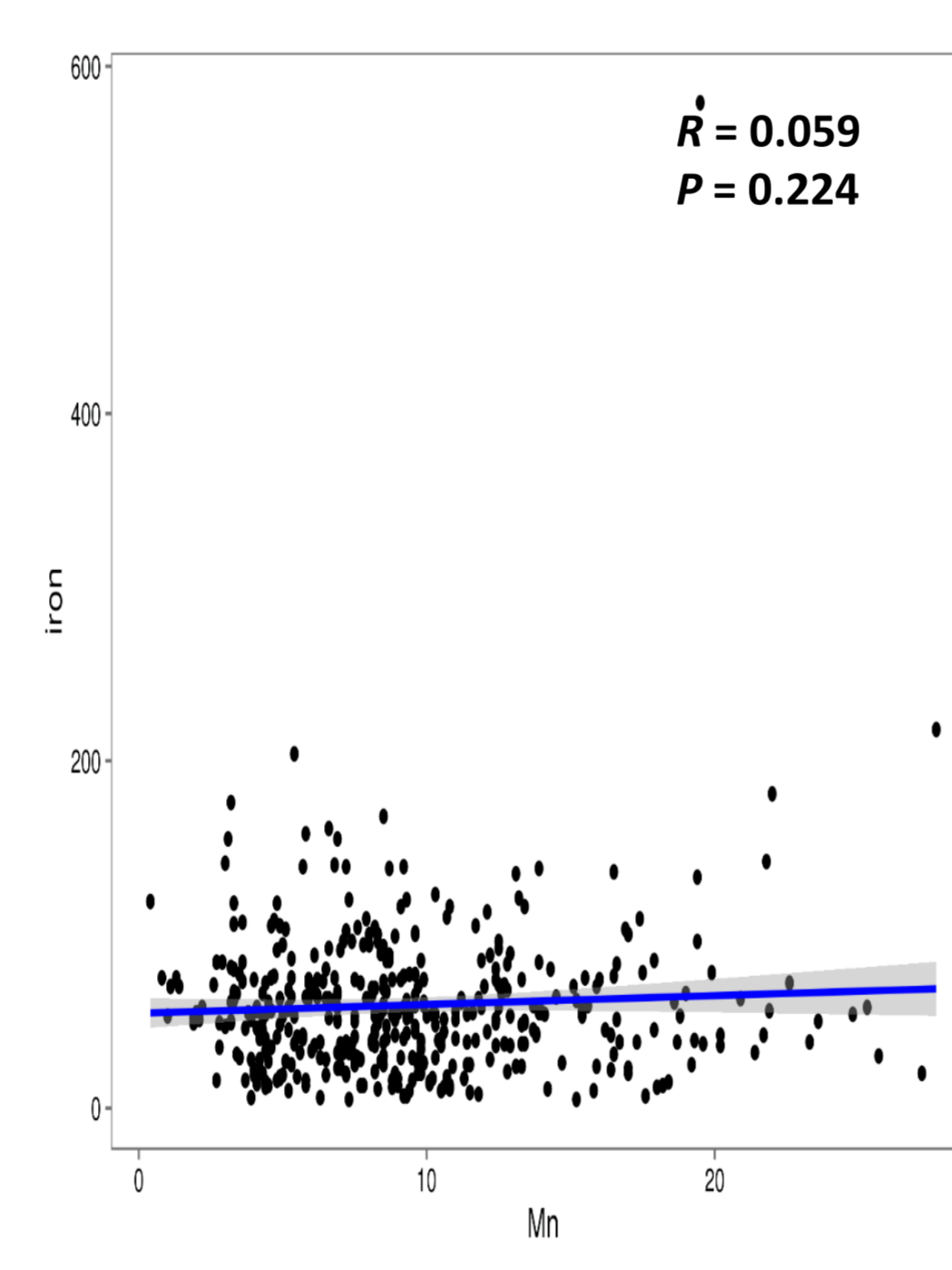


Fig 4. Blood Mn and serum Iron

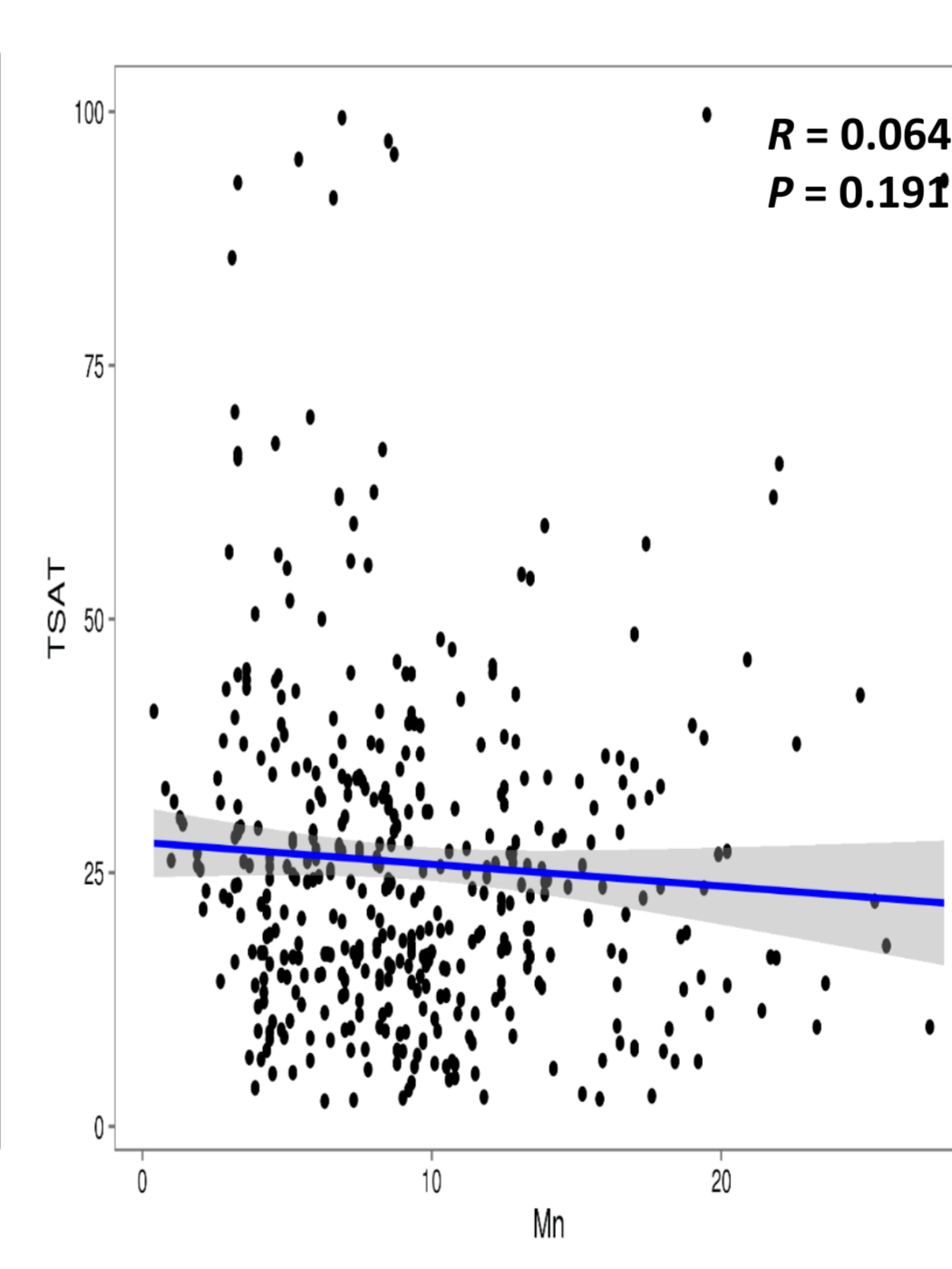


Fig 5. Blood Mn and TSAT

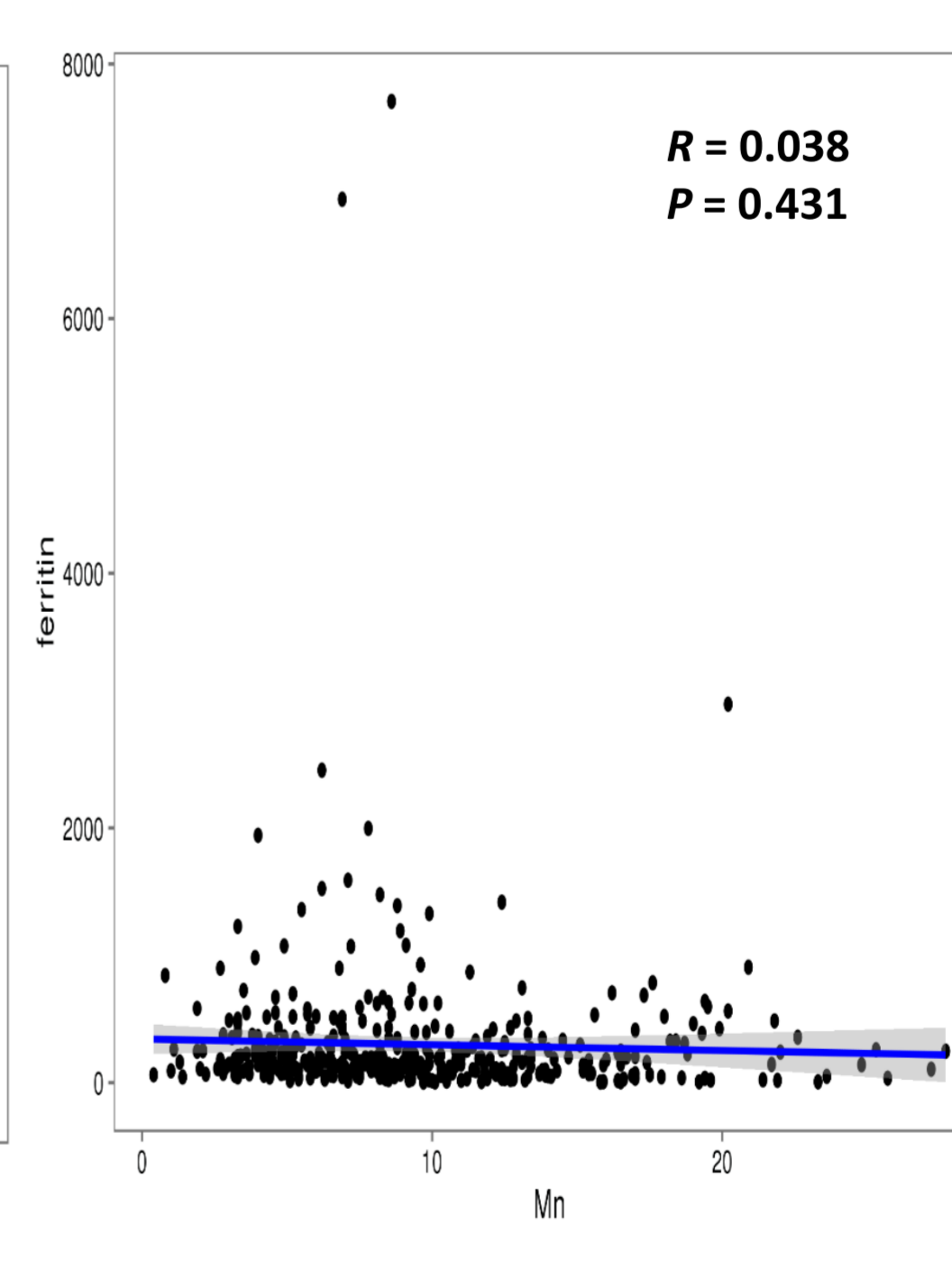


Fig 6. Blood Mn and serum ferritin

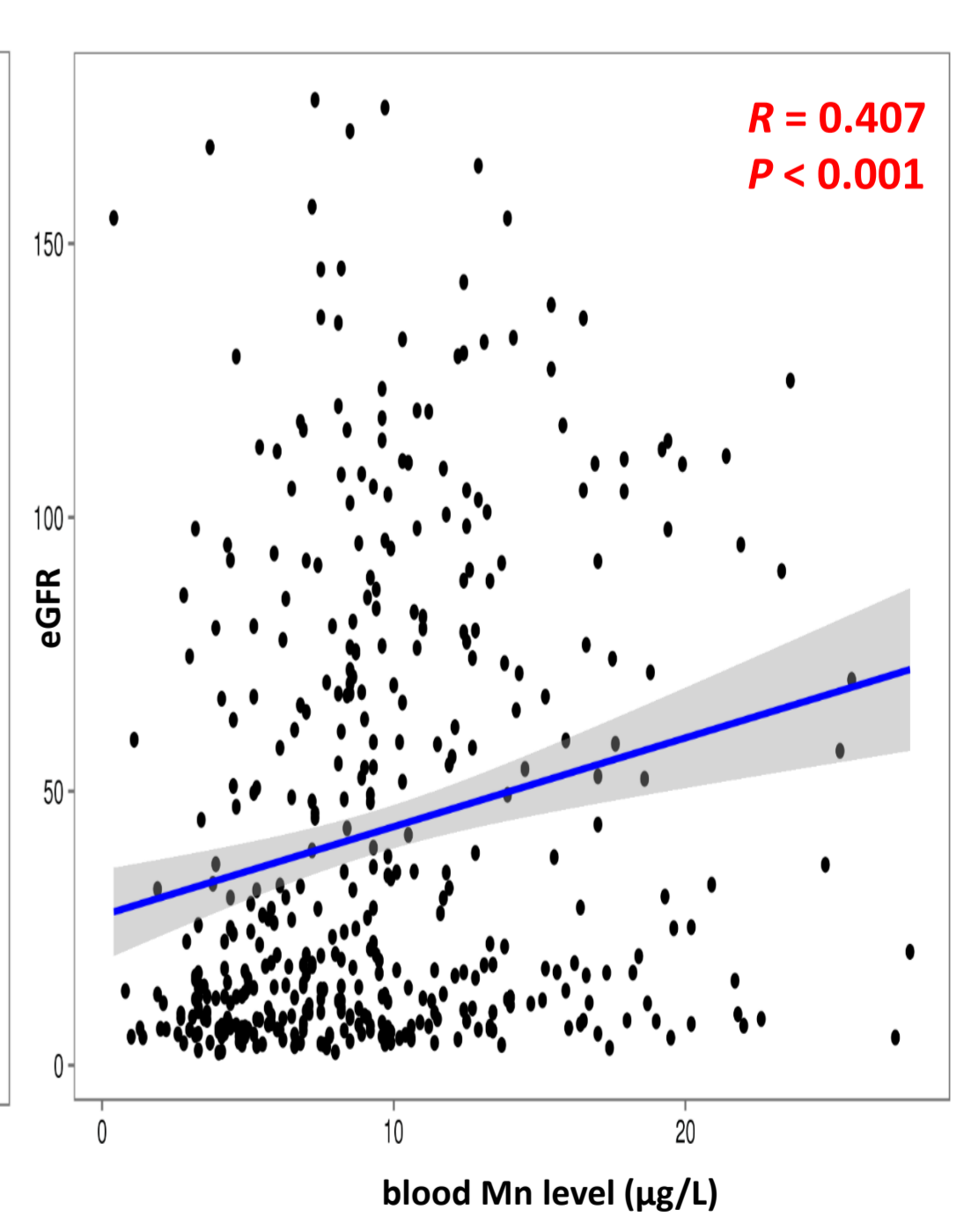


Fig 7. Association of blood Mn and estimated GFR

Conclusion

The current data suggest that the determination of the blood Mn levels would be appropriate for risk stratification and guidance of anemia management in patients with CKD.