Supplemental Tables

Table S1. Definition of (A) cardiovascular mortality and (B) infectious mortality

(A)		**Cardiovascular Mortality**
	Death due to	acute myocardial infarction
		pericarditis (including cardiac tamponade)
		atherosclerotic heart disease
		cardiomyopathy
		cardiac arrhythmia
		cardiac arrest (cause unknown)
		valvular heart disease
		congestive heart failure
		pulmonary edema due to exogenous fluid
		pulmonary embolus
		cerebrovascular accident including intracranial hemorrhage and ischemic brain damage/anoxic encephalopathy
(B)		**Infectious Mortality**
	Death due to	septicemia due to internal vascular access
		septicemia due to vascular access catheter
		peritoneal access infectious complication (bacterial)
		peritoneal access infectious complication (fungal)
		peritonitis (complication of peritoneal dialysis)
		central nervous system infection (brain abscess, meningitis, encephalitis, etc.)
		septicemia due to peripheral vascular disease (gangrene)
		septicemia (other than cardiac infection [endocarditis])
		septicemia due to vascular access
		other infectious disease
		cardiac infection (endocarditis)
		pulmonary infection (pneumonia, influenza)
		abdominal infection (peritonitis [not component of peritoneal dialysis, perforated bowel, diverticular disease, gallbladder])

	genital-urinary infection (urinary tract infection, pyelonephritis, renal abscess)
	hepatitis B
	hepatitis C
	other viral hepatitis

Table S2. Linear regressions and correlations of baseline MCV with various laboratory data

Laboratory Variable	β Coefficient (95%CI)	Correlation (95%CI)	P
Serum Laboratory Values			
Albumin (per 5 g/dL)	-1.20 (-1.35, -1.05)	-0.047 (-0.053, -0.042)	<0.001
ALP (per 100 IU/L)	0.23 (0.18, 0.28)	0.028 (0.022, 0.034)	<0.001
B12 (per 100 pg/mL)	0.09 (0.05, 0.12)	0.040 (0.023, 0.058)	<0.001
Bicarbonate (per mEq/L)	-0.001 (-0.014, 0.012)	-0.001 (-0.006, 0.005)	0.877
Calcium (per mg/dL)	0.41 (0.34, 0.47)	0.038 (0.032, 0.044)	<0.001
Creatinine (per mg/dL)	-0.34 (-0.36, -0.33)	-0.135 (-0.141, -0.129)	<0.001
Ferritin (per 500 ng/mL)	0.79 (0.74, 0.83)	0.141 (0.135, 0.147)	<0.001
Folate (per 5 ng/mL)	0.36 (0.22, 0.51)	0.051 (0.031, 0.072)	<0.001
Hemoglobin (per g/dL)	0.18 (0.15, 0.21)	0.035 (0.029, 0.041)	<0.001
iPTH (per 250 pg/mL)	-0.29 (-0.32, -0.27)	-0.092 (-0.098, -0.086)	<0.001
Iron (per ug/dL)	0.056 (0.054, 0.058)	0.185 (0.18, 0.191)	<0.001
Iron Saturation (per %)	0.153 (0.149, 0.157)	0.230 (0.224, 0.235)	<0.001
KRU (per ml/min)	-0.14 (-0.16, -0.13)	-0.085 (-0.095, -0.074)	<0.001
LDH (per U/L)	0.004 (0.004, 0.005)	0.028 (0.023, 0.034)	<0.001
Lymphocyte (per 10 % WBC)	-0.35 (-0.40, -0.30)	-0.043 (-0.049, -0.037)	<0.001
nPCR (per g/kg/d)	-0.41 (-0.57, -0.24)	-0.015 (-0.021, -0.009)	<0.001
Phosphorus (per mg/dL)	-0.38 (-0.41, -0.35)	-0.073 (-0.079, -0.067)	<0.001
RDW (per %)	-0.17 (-0.19, -0.15)	-0.050 (-0.056, -0.044)	<0.001
Reticulocyte (per %)	0.04 (-0.05, 0.14)	-0.020 (-0.036, -0.004)	0.355
spKt/V (per 1 increment)	1.60 (1.49, 1.71)	0.086 (0.08, 0.092)	<0.001
TIBC (per 10 µg/dL)	-0.08 (-0.09, -0.07)	-0.066 (-0.072, -0.06)	<0.001
WBC count, (per $x10^3/\mu l$)	-0.02 (-0.03, -0.01)	-0.009 (-0.014, -0.003)	0.005
Medications			
ESA Use (per 1,000)	-0.002 (-0.005, 0.001)	-0.001 (-0.007, 0.005)	0.228
IV Iron (per 100 mg)	-0.069 (-0.074, -0.064)	-0.080 (-0.086, -0.075)	<0.001

Abbreviations: ALP, alkaline phosphatase; B12; vitamin B12; iPTH, intact parathyroid hormone; KRU residual renal urea clearance; LDH, lactate dehydrogenase; nPCR, normalized protein catabolic rate; RDW, red cell distribution width; spKt/V, single-pooled Kt/V; TIBC, total iron binding capacity; WBC, white blood cell count; ESA, erythropoiesis stimulating agent; IV, intravenous , MCV, mean corpuscular volume.

Table S3. Five-year baseline all-cause mortality hazard ratios across MCV groups

				Unadjusted		Case-Mix		Case-Mix + MICS	
MCV [fL]	**n**	**mortality n [row %]**	**mortality rate per 1,000 person-years**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
<86	12,029	2,689 [22]	117 (113, 121)	0.76 (0.73, 0.80)	<0.001	0.99 (0.94, 1.04)	0.57	0.98 (0.94, 1.03)	0.51
86-<88	8,441	1,807 [21]	117 (112, 123)	0.76 (0.72, 0.81)	<0.001	0.92 (0.87, 0.97)	0.002	0.92 (0.87, 0.97)	0.002
88-<90	12,032	2,680 [22]	124 (120, 129)	0.81 (0.77, 0.85)	<0.001	0.93 (0.88, 0.97)	0.002	0.92 (0.88, 0.97)	0.002
90-<92	14,884	3,505 [24]	136 (132, 141)	0.89 (0.85, 0.93)	<0.001	0.96 (0.91, 1.00)	0.05	0.95 (0.91, 0.99)	0.03
92-<94	15,983	4,146 [26]	153 (148, 157)	1-referent		1-referent		1-referent	
94-<96	14,490	3,831 [26]	160 (155, 165)	1.05 (1.01, 1.10)	0.026	1.01 (0.96, 1.05)	0.82	1.00 (0.95, 1.04)	0.92
96-<98	11,366	3,364 [30]	186 (180, 193)	1.22 (1.17, 1.28)	<0.001	1.11 (1.06, 1.16)	<0.001	1.12 (1.07, 1.17)	<0.001
98-<100	8,081	2,520 [31]	200 (193, 208)	1.32 (1.25, 1.39)	<0.001	1.14 (1.08, 1.20)	<0.001	1.13 (1.07, 1.19)	<0.001
100+	12,195	4,432 [36]	250 (243, 257)	1.65 (1.58, 1.72)	<0.001	1.35 (1.29, 1.41)	<0.001	1.28 (1.22, 1.34)	<0.001

Table S4. Five-year time varying all-cause mortality hazard ratios across MCV groups

	Unadjusted		Case-Mix		Case-Mix + MICS	
MCV [fL]	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
<86	0.93 (0.87, 0.98)	0.011	1.05 (0.98, 1.11)	0.149	0.97 (0.92, 1.03)	0.351
86-<88	0.90 (0.84, 0.97)	0.004	0.99 (0.93, 1.06)	0.832	0.94 (0.88, 1.01)	0.099
88-<90	0.92 (0.86, 0.97)	0.004	0.96 (0.90, 1.02)	0.177	0.92 (0.87, 0.98)	0.006
90-<92	0.92 (0.88, 0.98)	0.005	0.95 (0.90, 1.00)	0.049	0.93 (0.88, 0.99)	0.014
92-<94	1-referent		1-referent		1-referent	
94-<96	1.05 (1.00, 1.10)	0.074	1.01 (0.96, 1.06)	0.746	0.99 (0.94, 1.04)	0.685
96-<98	1.14 (1.09, 1.20)	<0.001	1.09 (1.03, 1.14)	0.001	1.08 (1.03, 1.13)	0.003
98-<100	1.26 (1.20, 1.32)	<0.001	1.15 (1.10, 1.21)	<0.001	1.12 (1.07, 1.18)	<0.001
100+	1.79 (1.72, 1.87)	<0.001	1.54 (1.47, 1.60)	<0.001	1.39 (1.33, 1.45)	<0.001

Table S5. Five-year baseline cardiovascular mortality hazard ratios across MCV groups

MCV [fL]	n	Mortality n [row %]	mortality rate per 1,000 person-years	Unadjusted HR (95%CI)	Unadjusted P	Case-Mix HR (95%CI)	Case-Mix P	Case-Mix + MICS HR (95%CI)	Case-Mix + MICS P
<86	12,029	1,007 [8.4]	44 (41, 47)	0.80 (0.74, 0.86)	<0.001	1.01 (0.93, 1.10)	0.810	0.99 (0.91, 1.07)	0.743
86-<88	8,441	701 [8.3]	45 (42, 49)	0.83 (0.76, 0.91)	<0.001	0.97 (0.89, 1.07)	0.569	0.96 (0.88, 1.05)	0.372
88-<90	12,032	985 [8.2]	46 (43, 49)	0.83 (0.77, 0.9)	<0.001	0.94 (0.86, 1.01)	0.106	0.93 (0.86, 1.01)	0.068
90-<92	14,884	1,252 [8.4]	49 (46, 51)	0.89 (0.82, 0.96)	0.002	0.95 (0.88, 1.02)	0.148	0.94 (0.87, 1.01)	0.099
92-<94	15,983	1,483 [9.3]	55 (52, 57)	1-referent		1-referent		1-referent	
94-<96	14,490	1,330 [9.2]	56 (53, 59)	1.02 (0.95, 1.1)	0.588	0.98 (0.91, 1.06)	0.625	0.98 (0.91, 1.05)	0.581
96-<98	11,366	1,114 [9.8]	62 (58, 65)	1.13 (1.05, 1.23)	0.002	1.04 (0.96, 1.12)	0.344	1.05 (0.97, 1.14)	0.195
98-<100	8,081	872 [10.8]	69 (65, 74)	1.28 (1.17, 1.39)	<0.001	1.13 (1.04, 1.23)	0.005	1.13 (1.04, 1.23)	0.005
100+	12,195	1,470 [12.1]	83 (79, 87)	1.53 (1.43, 1.65)	<0.001	1.30 (1.21, 1.39)	<0.001	1.27 (1.18, 1.36)	<0.001

Table S6. Five-year time varying cardiovascular mortality hazard ratios across MCV groups

	Unadjusted		Case-Mix		Case-Mix + MICS	
MCV [fL]	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
<86	0.93 (0.84, 1.02)	0.141	1.05 (0.95, 1.15)	0.358	0.96 (0.87, 1.06)	0.423
86-<88	0.87 (0.78, 0.98)	0.021	0.95 (0.85, 1.07)	0.417	0.90 (0.80, 1.01)	0.077
88-<90	0.94 (0.85, 1.04)	0.22	0.99 (0.89, 1.09)	0.766	0.95 (0.86, 1.04)	0.27
90-<92	0.83 (0.76, 0.91)	<0.001	0.85 (0.77, 0.93)	0.001	0.83 (0.76, 0.91)	<0.001
92-<94	1-referent		1-referent		1-referent	
94-<96	0.99 (0.91, 1.08)	0.844	0.96 (0.89, 1.04)	0.348	0.95 (0.87, 1.03)	0.196
96-<98	1.06 (0.97, 1.15)	0.178	1.01 (0.93, 1.10)	0.799	1.01 (0.93, 1.09)	0.893
98-<100	1.21 (1.12, 1.32)	<0.001	1.12 (1.03, 1.22)	0.007	1.10 (1.01, 1.20)	0.024
100+	1.62 (1.51, 1.74)	<0.001	1.42 (1.32, 1.52)	<0.001	1.32 (1.23, 1.42)	<0.001

Table S7. Five-year baseline cardiovascular mortality competing risk regression subhazard ratios across MCV groups for cardiovascular mortality with non-cardiovascular mortality as a competing event

	Unadjusted		Case-Mix		Case-Mix + MICS	
MCV [fL]	**SHR (95% CI)**	**P**	**SHR (95% CI)**	**P**	**SHR (95% CI)**	**P**
<86	0.83 (0.77, 0.90)	<0.001	1.01 (0.93, 1.09)	0.843	0.99 (0.91, 1.07)	0.8
86-<88	0.86 (0.79, 0.94)	0.001	0.99 (0.90, 1.08)	0.804	0.98 (0.89, 1.07)	0.615
88-<90	0.86 (0.79, 0.93)	<0.001	0.94 (0.87, 1.02)	0.165	0.94 (0.87, 1.02)	0.136
90-<92	0.9 (0.84, 0.97)	0.007	0.95 (0.88, 1.02)	0.169	0.94 (0.88, 1.02)	0.136
92-<94	1-referent		1-referent		1-referent	
94-<96	1.01 (0.94, 1.09)	0.781	0.98 (0.91, 1.05)	0.527	0.98 (0.91, 1.05)	0.505
96-<98	1.09 (1.01, 1.18)	0.029	1.01 (0.94, 1.09)	0.755	1.02 (0.94, 1.10)	0.649
98-<100	1.22 (1.12, 1.32)	<0.001	1.10 (1.01, 1.19)	0.032	1.09 (1.00, 1.19)	0.04
≥ 100	1.38 (1.28, 1.48)	<0.001	1.20 (1.12, 1.29)	<0.001	1.17 (1.09, 1.27)	<0.001

Table S8. Five-year baseline infectious mortality hazard ratios across MCV groups

				Unadjusted		Case-Mix		Case-Mix + MICS	
MCV [fL]	**n**	**Mortality n [row %]**	**mortality rate per 1,000 person-years**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
<86	12,029	207 [1.7]	9 (8, 10)	0.70 (0.59, 0.83)	<0.001	0.86 (0.72, 1.02)	0.091	0.87 (0.73, 1.03)	0.108
86-<88	8,441	131 [1.5]	8 (7, 10)	0.66 (0.54, 0.80)	<0.001	0.77 (0.63, 0.94)	0.012	0.77 (0.63, 0.95)	0.012
88-<90	12,032	204 [1.6]	9 (8, 11)	0.73 (0.62, 0.87)	<0.001	0.82 (0.69, 0.98)	0.027	0.82 (0.69, 0.98)	0.026
90-<92	14,884	284 [1.9]	11 (10, 12)	0.85 (0.73, 1.00)	0.047	0.91 (0.78, 1.07)	0.260	0.91 (0.78, 1.06)	0.240
92-<94	15,983	350 [2.2]	13 (12, 14)	1-referent		1-referent		1-referent	
94-<96	14,490	261 [1.8]	11 (10, 12)	0.85 (0.72, 1.00)	0.044	0.81 (0.69, 0.95)	0.011	0.80 (0.68, 0.94)	0.007
96-<98	11,366	271 [2.4]	15 (13, 17)	1.16 (0.99, 1.37)	0.059	1.06 (0.90, 1.24)	0.480	1.07 (0.91, 1.25)	0.413
98-<100	8,081	186 [2.3]	15 (13, 17)	1.15 (0.96, 1.37)	0.125	1.00 (0.83, 1.19)	0.974	0.99 (0.82, 1.18)	0.875
100+	12,195	351 [2.9]	20 (18, 22)	1.54 (1.33, 1.79)	<0.001	1.27 (1.09, 1.48)	0.002	1.18 (1.02, 1.38)	0.03

Table S9. Five-year time varying infectious mortality hazard ratios across MCV groups

	Unadjusted		Case-Mix		Case-Mix + MICS	
MCV [fL]	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**	**HR (95%CI)**	**P**
<86	1.06 (0.85, 1.30)	0.619	1.05 (0.95, 1.15)	0.358	1.12 (0.91, 1.39)	0.285
86-<88	0.92 (0.72, 1.19)	0.542	0.95 (0.85, 1.07)	0.417	0.97 (0.75, 1.26)	0.834
88-<90	1.08 (0.87, 1.33)	0.481	0.99 (0.89, 1.09)	0.766	1.10 (0.89, 1.35)	0.390
90-<92	0.92 (0.75, 1.13)	0.415	0.85 (0.77, 0.93)	0.001	0.93 (0.76, 1.13)	0.459
92-<94	1-referent		1-referent		1-referent	
94-<96	1.11 (0.92, 1.33)	0.265	0.96 (0.89, 1.04)	0.348	1.07 (0.89, 1.29)	0.444
96-<98	1.17 (0.98, 1.40)	0.091	1.01 (0.93, 1.10)	0.799	1.13 (0.94, 1.36)	0.183
98-<100	1.48 (1.24, 1.78)	<0.001	1.12 (1.03, 1.22)	0.007	1.39 (1.16, 1.66)	<0.001
100+	1.93 (1.66, 2.25)	<0.001	1.42 (1.32, 1.52)	<0.001	1.71 (1.47, 1.99)	<0.001

Table S10. Five-year baseline infectious mortality competing risk regression subhazard ratios across MCV groups for infectious mortality with non-infectious mortality as a competing event

MCV [fL]	Unadjusted		Case-Mix		Case-Mix + MICS	
	SHR (95% CI)	**P**	**SHR (95% CI)**	**P**	**SHR (95% CI)**	**P**
<86	0.74 (0.62, 0.87)	<0.001	0.86 (0.72, 1.03)	0.095	0.87 (0.73, 1.03)	0.110
86-<88	0.69 (0.56, 0.84)	<0.001	0.78 (0.64, 0.96)	0.018	0.78 (0.64, 0.96)	0.017
88-<90	0.76 (0.64, 0.90)	0.002	0.83 (0.70, 0.99)	0.042	0.84 (0.70, 0.99)	0.043
90-<92	0.87 (0.74, 1.02)	0.079	0.92 (0.79, 1.08)	0.292	0.92 (0.79, 1.08)	0.295
92-<94	1-referent		1-referent		1-referent	
94-<96	0.84 (0.71, 0.98)	0.029	0.81 (0.69, 0.95)	0.008	0.79 (0.67, 0.93)	0.004
96-<98	1.12 (0.95, 1.31)	0.168	1.04 (0.89, 1.22)	0.645	1.03 (0.88, 1.21)	0.675
98-<100	1.08 (0.91, 1.29)	0.387	0.96 (0.81, 1.15)	0.677	0.94 (0.79, 1.12)	0.497
≥ 100	1.37 (1.18, 1.59)	<0.001	1.16 (1.00, 1.35)	0.046	1.09 (0.93, 1.27)	0.288

Table S11. Sample size by subgroup

Subgroup	n
All Patients	109,501
Age <65 years	56,578
Age ≥65 years	52,923
African American	34,379
White	51,050
Hispanic	16,236
Female	47,690
Male	61,811
BMI ≥25 kg/m^2	66,537
BMI <25 kg/m^2	42,829
Diabetes	64,042
No Diabetes	45,459
CHF	40,294
No CHF	69,207
spKt/V ≥1.2	89,449
spKt/V <1.2	19,813
Albumin ≥4 g/dl	15,544
Albumin <4 g/dl	93,802
nPCR ≥0.79 g/kg/day	49,760
nPCR <0.79 g/kg/day	58,245
WBC ≥11 x10^3/µL	10,197
WBC <11 x10^3/µL	99,215
Lymphocyte ≥21 %	48,535
Lymphocyte <21 %	60,942
Hemoglobin ≥12 g/dl	24,990
Hemoglobin <12 g/dl	84,426
RDW ≥15.5 %	71,849
RDW <15.5 %	37,558
Ferritin ≥800 ng/ml	10,157
Ferritin <800 ng/ml	97,927
Iron ≥50 µg/dl	47,799
Iron <50 µg/dl	61,168
Iron Saturation ≥22 %	52,469
Iron Saturation <22 %	56,285
TIBC ≥200 µg/l	76,235
TIBC <200 µg/l	32,585
IV Iron >1,000 mg/month	57,040
IV Iron >0 to ≤1,000 mg/month	39,871
IV Iron =0 mg/month	12,590
ESA Use ≥5,000 U/week	53,273
ESA Use <5,000 U/week	56,263
B12 ≥620 pg/ml	6,358
B12 <620 pg/ml	6,333
Folate ≥9.6 ng/ml	4,697
Folate <9.6 ng/ml	4,596

Abbreviations: BMI, body mass index; CHF, congestive heart failure ; spKt/V, single-pooled Kt/V; nPCR, normalized protein catabolic rate; WBC, white blood cell count; RDW, red cell distribution width; TIBC, total iron binding capacity; IV, intravenous; ESA, erythropoiesis stimulating agent; B12, vitamin B12

Table S12. Tests for interaction between MCV ≥93 fL and subgroups in fully adjusted models

	All-Cause Mortality	Cardiovascular Mortality	Infectious Mortality
Subgroup	**P-int**	**P-int**	**P-int**
Age	0.1925	0.8171	0.4891
Race	0.0123	0.2416	0.0993
Sex	0.1126	0.2167	0.981
BMI	0.0144	0.1260	0.3328
Diabetes	0.0478	0.1411	0.0506
CHF	0.1563	0.0228	0.1518
Dialysis Dose	<0.001	0.0112	0.1108
Albumin	0.2286	0.691	0.7585
nPCR	0.8961	0.767	0.6297
WBC	0.0683	0.507	0.4089
Lymphocyte	0.8774	0.3559	0.3900
Hemoglobin	0.5433	0.4907	0.8191
RDW	0.7272	0.6088	0.0796
Ferritin	0.1474	0.2683	0.5457
Iron	0.1036	0.7858	0.5399
Iron Saturation	0.7272	0.7932	0.3003
TIBC	0.8494	0.8739	0.8809
IV Iron	0.6755	0.6504	0.7886
ESA Use	0.5644	0.8454	0.7129
B12	0.2018	0.0436	0.4851
Folate	0.4011	0.2344	0.9029

Abbreviations: BMI, body mass index; CHF, congestive heart failure; nPCR, normalized protein catabolic rate; RDW, red cell distribution width; TIBC, total iron binding capacity; IV, intravenous; ESA, erythropoiesis stimulating agent; B12, vitamin B12; and P-int, P-interaction

Supplemental Figures

Figure S1. Flow chart of patient selection for the cohort.

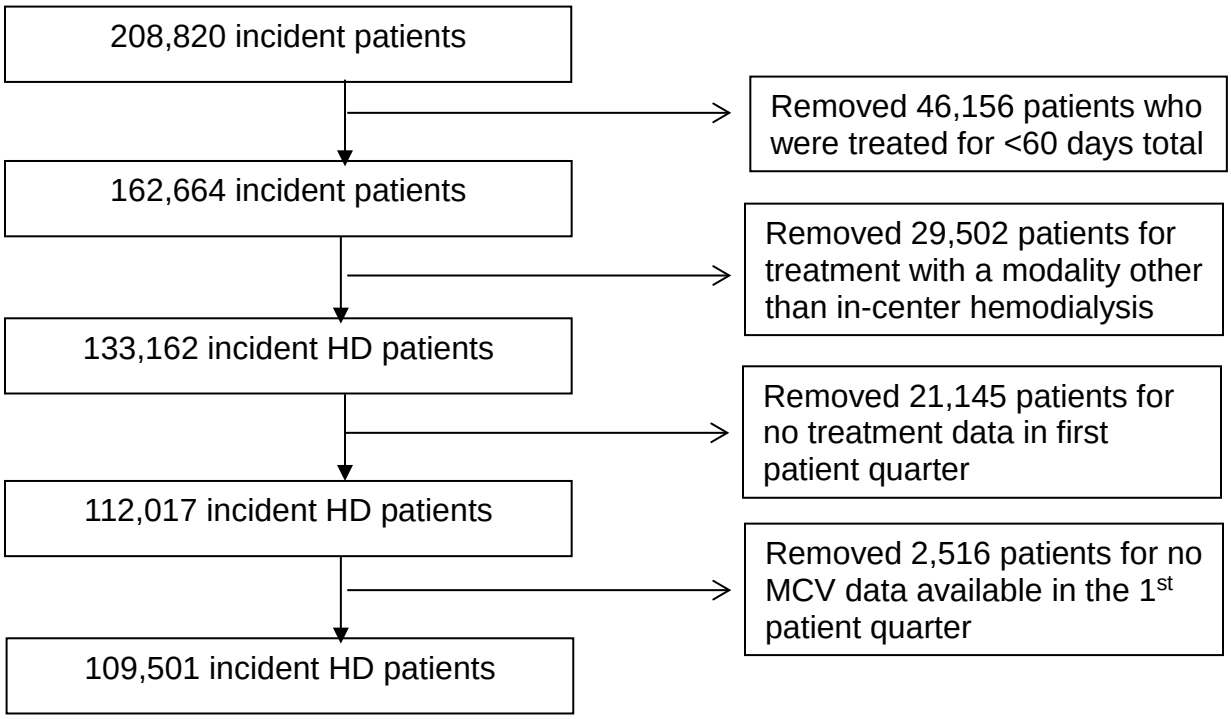

Figure S2. Trajectories of quarterly population mean MCV (fL) concentrations (A) across baseline serum MCV groups, (B) across baseline serum MCV groups with adjustment for weekly ESA dose and cumulative monthly IV iron dose, (C) stratified by 4 baseline weekly ESA dose groups, (D) stratified by 4 baseline weekly ESA dose groups with additional adjustment for weekly ESA dose per patient quarter, (E) stratified by 4 monthly cumulative IV iron dose groups, (F) stratified by 4 baseline monthly cumulative IV iron dose groups with additional adjustment for monthly cumulative IV iron dose per patient quarter during 20 patient quarters.

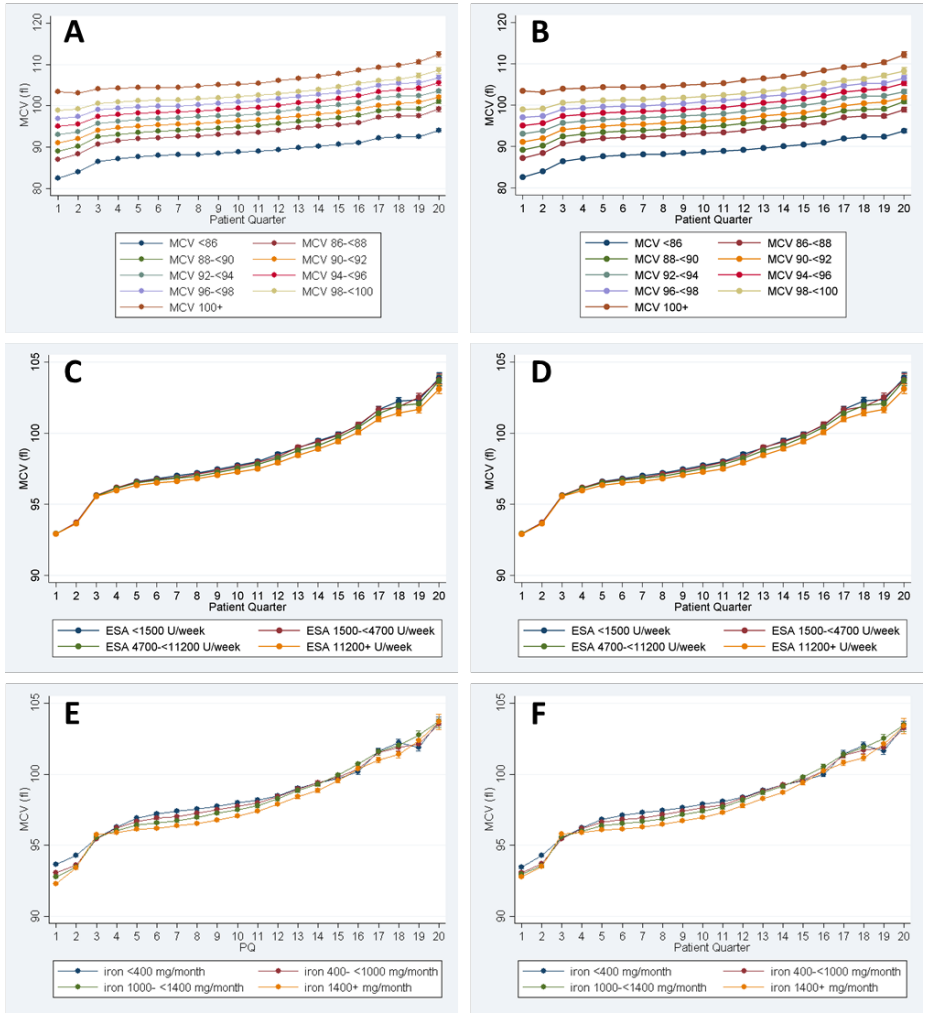

Figure S3. Baseline all-cause mortality hazard ratios (and 95%CI error bars) by MCV levels across four levels of multivariable adjustment (A) in 9,293 patients with folate and MCV measurement at baseline, (B) 12,691 patients with B12 and MCV measurement at baseline, and (C) 36,334 patients with KRU and MCV measurement at baseline.

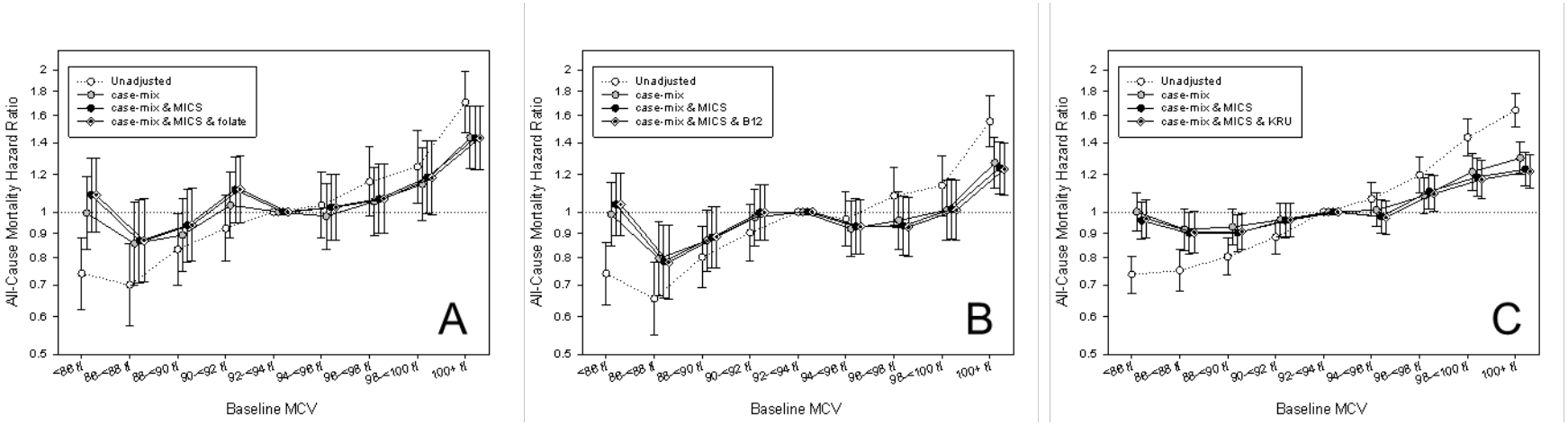

Figure S4. Restricted cubic splines of baseline all-cause mortality (A) unadjusted, (B) case-mix, and (C) case-mix plus MICS, baseline cardiovascular mortality (D) unadjusted (E) case-mix, and (F) case-mix plus MICS, and baseline infectious mortality (G) unadjusted, (H) case-mix, and (I) case-mix plus MICS hazard ratios (and 95%CIs) with MCV, over histograms of MCV distribution.

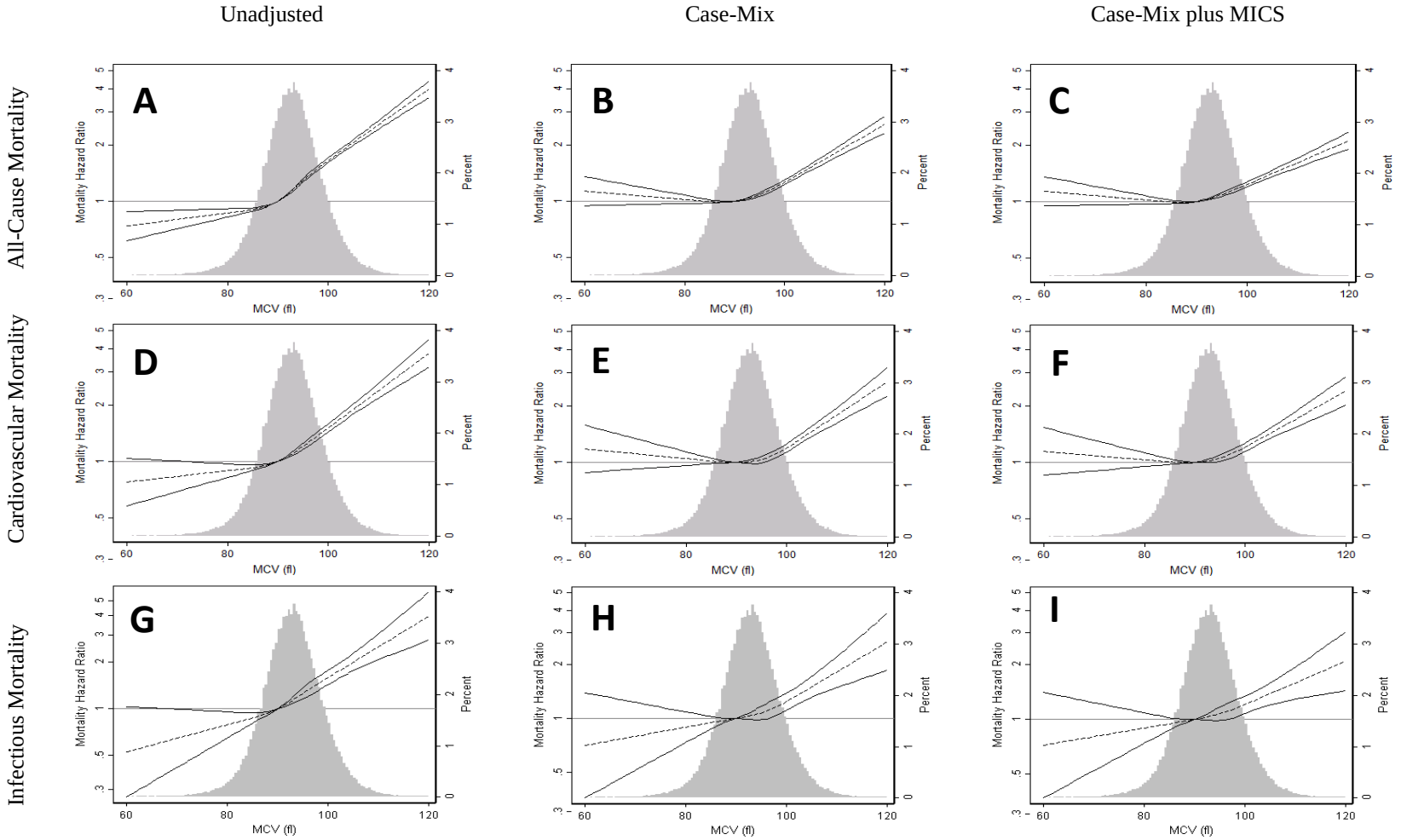

Figure S5. Restricted cubic splines of time-varying all-cause mortality (A) unadjusted, (B) case-mix, and (C) case-mix plus MICS, time-varying cardiovascular mortality (D) unadjusted, (E) case-mix, and (F) case-mix plus MICS, and time-varying infectious mortality (G) unadjusted, (H) case-mix, and (I) case-mix plus MICS hazard ratios (and 95%CIs) with MCV.