Clozapine and Anemia: A 2-Year Follow-Up Study

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ABSTRACT

Objective: Clozapine's association with agranulocytosis led to the implementation of stringent and mandatory hematologic monitoring guidelines in most countries. Although other hematologic aberrations such as eosinophilia and neutropenia have been previously described, clozapine's impact on the erythroid lineage has not been studied. There is a suspicion that a higher rate of anemia is observed in patients receiving clozapine; therefore, we hypothesized that there would be a higher rate of anemia in patients receiving clozapine therapy.

Method: All individuals initiated on clozapine at our center from 2009 to 2010 were recruited. Information on age, gender, medical comorbidities, and smoking status was extracted from the medical records. Data from complete blood counts over a 2-year follow-up period were extracted, with anemia defined as a hemoglobin value below 120 g/L for women and 130 g/L for men. Time to anemia event was calculated and Cox regression was employed to identify predictors of anemia.

Results: We found a high incidence of anemia in the first 2 years following clozapine initiation; of the 94 individuals (68 men, 26 women) recruited, 23 (24.5%) developed anemia. Higher baseline hemoglobin level (hazard ratio [HR] = 0.86, $P = .002$) and smoking status (HR = 0.21, $P = .021$) were identified as significant protective factors against anemia in men but not in women (HR = 0.92, $P = .184$, and HR = 0.52, $P = .467$ for baseline hemoglobin and smoking, respectively).

Conclusions: Although smoking appears to lower the risk of anemia, we believe this is due to smoking's up-regulation of hemoglobin levels. Further studies are warranted in light of the present findings; for example, we cannot exclude the possibility that anemia was an epiphenomenon, characterizing instead a population with severe mental illness.

J Clin Psychiatry 2015;76(12):1642–1647
dx.doi.org/10.4088/JCP.14m09143

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Clozapine is a highly effective antipsychotic although it is generally relegated to a third-line pharmacologic agent, with specific indications for use in treatment-resistant schizophrenia.[1] It is associated with a series of noteworthy side effects (eg, neurologic, cardiac, gastrointestinal), but it is its association with agranulocytosis that has led to the implementation of stringent and mandatory hematologic monitoring guidelines for as long as an individual is prescribed clozapine.[2,3] Although health regulatory authorities and clozapine monitoring systems such as the Clozaril Support and Assistance Network in Canada require the monitoring of only white blood cell and neutrophil counts, frequently a complete blood count is ordered.

Although agranulocytosis is the hematologic side effect of greatest concern, it is a rare event that occurs at an incidence of less than 1%, mostly in the first 18 weeks after commencing clozapine.[4,5] Neutropenia is a far more common side effect, with an incidence of 2.7%.[5] Other hematologic aberrations in patients taking clozapine have been previously reported. Eosinophilia is a transient but commonly reported event, with a reported incidence of up to 61.7%[6]; of note, it has also been reported to be a potential marker for subsequent neutropenia.[7] Thrombocytosis and thrombocytopenia have similarly been reported in the literature, although their significance is not known.[8,9]

The exact pathophysiologic mechanism through which clozapine gives rise to the reported hematologic aberrations is unclear. Postulated mechanisms have included immune and nonimmune causes, with effects on circulating cells and possibly the bone marrow.[10] A prior in vivo study[11] found norclozapine and its metabolites to be toxic to hematopoietic precursors of the myeloid and erythroid lineages, and perturbations in the erythroid lineage could give rise to anemia. The clinical manifestations of anemia include lethargy and cognitive difficulties, both of which might be mistaken for, or compound, the negative symptoms and cognitive impairments seen in schizophrenia.[12] Anemia has been associated with an increased mortality in schizophrenia and has been known to impair cardiac function.[13,14] In light of the elevated cardiovascular mortality rates in schizophrenia, as well as the elevated cardiometabolic risks associated with clozapine, anemia is also of relevance when considering clozapine's hematologic side effects.[15,16]

In the extant literature, there has been only a single case report of aplastic anemia linked to clozapine use in an individual with Parkinson's disease.[17] No systematic studies have looked at anemia in individuals taking clozapine; accordingly, we set out to examine the incidence of anemia in the first 2 years after initiation of clozapine in a group of individuals with serious mental illness.

METHOD

Study Setting

Participants included in this study were patients from the Clozapine Registry at the Centre for Addiction and Mental Health (CAMH) in

Toronto, Canada. The Clozapine Registry is a centralized service that was initiated in 1994 and monitors all patients who were prescribed clozapine at CAMH. In this study, we included participants who were initiated on clozapine at CAMH within the study period January 2009 to December 2010. This period was chosen because of the initiation of electronic medical records in January 2009, permitting more comprehensive data collection. A 2-year follow-up period for all included participants was defined a priori. To be included, participants were required to have hemoglobin level measured at the CAMH before and after they were started on treatment with clozapine, and those with anemia identified prior to clozapine initiation were excluded from the analysis. This study was approved by the research ethics board at CAMH.

Data Collection

Data regarding age, gender, smoking status, psychiatric diagnoses, and all reported medical comorbidities at baseline were collected. Prescription data, including nonpsychotropics, were also noted. All complete blood count results performed at CAMH's clinical laboratory were extracted. Anemia was defined as a hemoglobin value below 120 g/L for women and 130 g/L for men, in accordance with the World Health Organization.[18] Date of first anemia occurrence was recorded, and number of days to anemia event was calculated.

Statistical Analyses

Baseline demographic and clinical variables of participants who did and did not develop anemia were compared using χ^2 or Fisher exact tests (for categorical variables) and Student *t* test or Mann-Whitney *U* test (for continuous variables). Cumulative incidence of anemia (defined as number of new cases divided by the population initially at risk) was computed. We employed a Cox proportional hazards model, in a time-to-anemia-event analysis, to identify predictors of anemia in this cohort. Participants who discontinued clozapine or had their care transferred out of CAMH prior to development of anemia were included as censors. Hazard ratios (HRs) and their confidence intervals (CIs) were reported. A $P < .05$ was taken to be statistically significant. Significant predictors identified in the unadjusted Cox regression analyses, including age and gender, were entered into the final model. Proportional hazards assumptions for significant predictors in the final model were tested. Baseline hemoglobin was identified as a potential predictor, and its analysis was stratified by gender in view of the significant gender differences. Significant predictors identified in the final Cox regression model were replicated and visualized in the Kaplan-Meier survival analysis by comparing the curves between the different factors. All statistical analyses were conducted on IBM SPSS version 20 (IBM Corp).

RESULTS

Of the 123 patients who were placed on the clozapine registry during the study inclusion period from 2009 to 2010, 94 were included in this study (Figure 1). Seven patients were found to have anemia prior to clozapine initiation, and no participant discontinued clozapine because of anemia. Table 1 displays the baseline clinical and demographic characteristics, as well as hemoglobin levels of the study sample. Diabetes mellitus, hyperlipidemia, hypertension, and hypothyroidism together accounted for 71% of all medical comorbidities. Other medical comorbidities reported in this sample included hepatitis C (n = 3), gastroesophageal reflux disease (n = 2), chronic obstructive pulmonary disease (n = 2), acne, incontinence, keratoconus, eczema, polycystic ovary disease, subarachnoid hemorrhage, osteoporosis, and tuberculosis (each n = 1).

There were 23 incident cases of anemia, giving a cumulative incidence of 24.5% over a 2-year follow-up period. Data from 33 participants who left the study prior to an observed anemia event were included as censored data in the survival analyses. Of the 33 participants, 19 discontinued clozapine, 12 had their care transferred out, and 2 were deceased. In the predictor analyses, as displayed in Table 2, smoking and medical comorbidities were significant predictors of anemia in the univariate analyses. However, only smoking emerged as statistically significantly associated with the absence of anemia in the final Cox regression model (HR = 0.23, $P = .005$).

The Kaplan-Meier plots for smoking and medical comorbidities are shown in Figure 2. Separations of the curves for smoking and medical comorbidities support the results of the Cox regression model. The log-rank *P* values for smoking and medical comorbidities were $P = .001$ and $P = .036$, respectively.

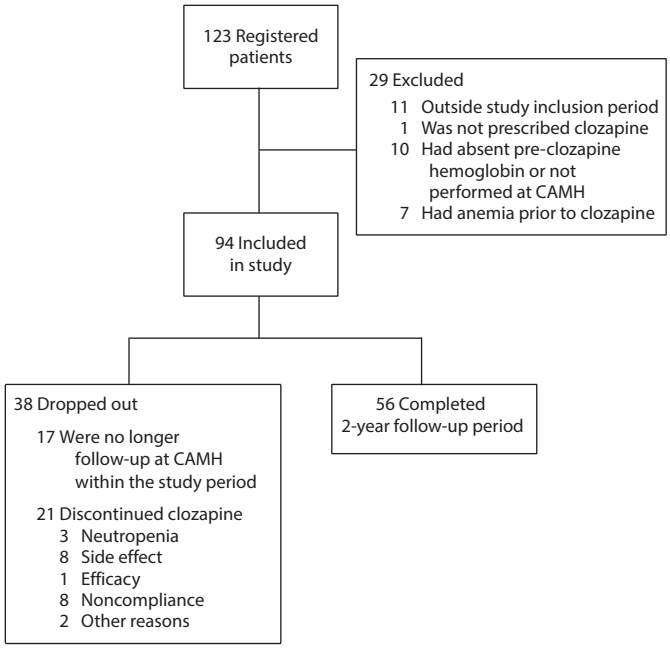
Higher baseline hemoglobin level (HR = 0.86, $P = .002$) and smoking status (HR = 0.21, $P = .021$) were identified as significant predictors of anemia in men but not in women (Table 3). Men and women were further categorized into 2 groups by a median split of their baseline hemoglobin level (less than 149 g/L and 134 g/L for men and women, respectively) to generate the respective Kaplan-Meier plots. The Kaplan-Meier curves (see Supplementary eFigure 1 at Psychiatrist.com) show clear separation for men, with a significant log-rank test ($P < .001$). All cases of anemia in the men have below-median hemoglobin levels prior to clozapine initiation. For women, the log-rank test was not significant ($P = .137$).

Of the 23 incident cases of anemia, 20 had either recurrent episodes of anemia or persistent anemia throughout the duration of follow-up. Normochromic, normocytic anemia

Clinical Points

- Anemia in schizophrenia might present with negative symptoms and cognitive impairment.
- There is a high incidence of anemia in patients with schizophrenia treated with clozapine.
- Clinicians need to be aware of risks of anemia in schizophrenia, perform the necessary workup, and institute the appropriate treatment for it.

Figure 1. Flowchart of Participants Included in Study



Abbreviation: CAMH = Centre for Addiction and Mental Health.

Table 1. Baseline Characteristics of Study Sample

Characteristic	Total, N = 94 (100%)		Anemia Absent, n = 71 (75.5%)		Anemia Present, n = 23 (24.5%)		*P* Value
	n	%	n	%	n	%	
Gender							
Male	68	72.3	54	76.1	14	60.9	.157
Female	26	27.7	17	23.9	9	39.1	
Smoking	51	54.3	46	64.8	5	21.7	<.001
Medical comorbidities	31	33.0	19	26.8	12	52.2	.024
Diabetes mellitus	10	10.6	5	7.0	5	21.7	.047
Hypertension	6	6.4	6	8.5	0	0	.330
Hyperlipidemia	10	10.6	5	7.0	5	21.7	.047
Hypothyroidism	3	3.2	2	2.8	1	4.3	1.000
Psychiatric diagnosis							
Schizophrenia	75	79.8	57	80.3	18	78.3	.330
Schizoaffective disorder	17	18.1	13	18.3	4	17.4	
Bipolar disorder	1	1.1	1	1.4	0	0	
Delusional disorder	1	1.1	0	0	1	4.3	
Concomitant medications[a]							
Antipsychotic	21	22.3	15	21.1	6	26.1	.774
Antidepressant	25	26.6	19	26.8	6	26.1	1.000
Mood stabilizer	25	26.6	20	28.2	5	21.7	.600
Benzodiazepine	13	13.8	10	14.1	3	13.0	1.000
Anticholinergic	18	19.1	15	21.1	3	13.0	.546
Others	44	46.8	29	40.8	15	65.2	.055
	Mean	SD	Mean	SD	Mean	SD	
Follow-up duration, d	521.1	290.1	480.8	304.7	645.5	197.2	.004
Age, y	35.9	12.1	34.9	12.2	38.9	11.6	.177
Baseline hemoglobin, g/L							
Male	150.3	10.4	152.8	10.0	140.9	5.7	<.001
Female	135.5	10.2	137.7	10.7	131.6	8.2	.150
Clozapine dose, mg[a]	355.7	134.4	350.0	140.0	373.4	117.5	.471
Plasma level, ng/mL[b]							
Clozapine	628.0	278.2	575.0	262.8	771.7	287.1	.135
Norclozapine	751.3	365.6	366.3	169.1	363.6	141.4	.866

[a]Information obtained either at the point anemia occurred or from last known prescription. Two participants were on treatment with both clozapine and fluvoxamine.
[b]Plasma levels in the 4 weeks prior to study end date of event data were selected. Data were available for 26 individuals, of which 7 were from individuals who developed anemia and 19 were from individuals who did not.

was described in 18 cases, 3 had hypochromic microcytic anemia, and 2 had macrocytic anemia. One of the 23 incident cases of anemia had developed neutropenia before the onset of anemia, but the participant was continued on clozapine. There were no cases of agranulocytosis in the study.

DISCUSSION

Our study found a high incidence of anemia within the first 2 years in patients who were prescribed clozapine. To the authors' knowledge, this is the first report specifically examining anemia in a clozapine cohort. Individuals with low baseline hemoglobin level or who were nonsmokers tended to be at increased risk of anemia. Although there were more men initiated on clozapine during the study period, a higher proportion of women than men developed anemia while on clozapine.

Interestingly, we found that nonsmokers were at higher risk of developing anemia. This association was immediately apparent in the men, as illustrated in Figure 2A. Smoking has been known to reduce plasma clozapine levels[19]; if the pathophysiology of anemia were related to clozapine levels, then smoking, through reduction of plasma clozapine levels, would have conferred a reduced risk. However, a more plausible explanation might be the elevation of hemoglobin in smokers due to increased levels of carboxyhemoglobin.[20] Post hoc, we examined the baseline hemoglobin levels between smokers and nonsmokers for men and women separately and found that smokers indeed had higher hemoglobin levels at baseline (hemoglobin level in men: 153.0 g/L vs 146.3 g/L, $P = .006$) (hemoglobin level in women: 138.2 g/L vs 133.9 g/L, $P = .452$), prior to initiation of clozapine. As a consequence of smoking, the usual cutoffs for anemia will tend to underdetect cases of anemia, and the true rate of anemia is most likely higher than what is found in the present study. In addition, since smoking is highly prevalent in individuals with schizophrenia, this finding would have broader clinical implications beyond the group that was prescribed clozapine.

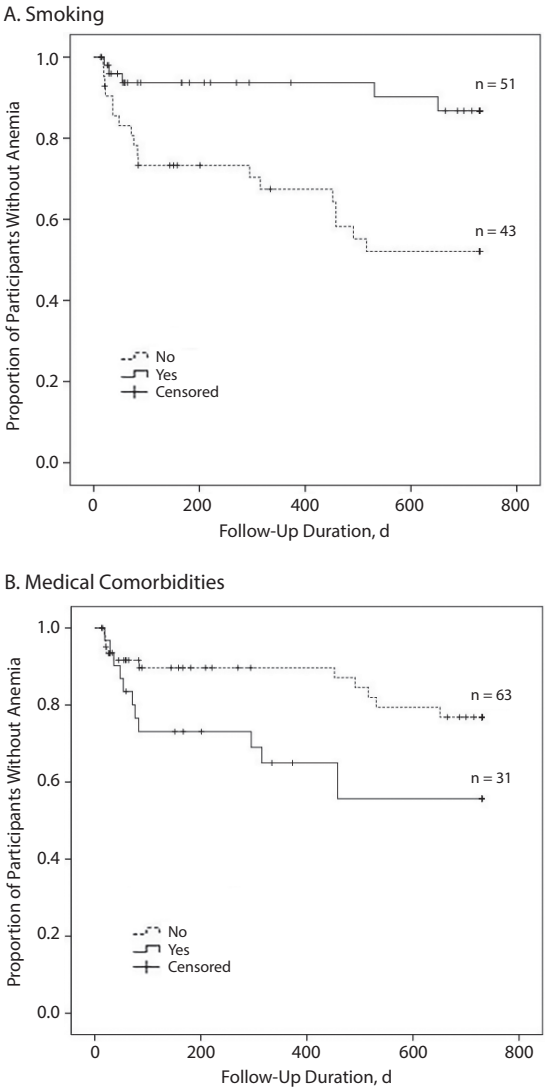
Although not statistically significant, it appears that individuals with medical comorbidities might be at elevated risk for anemia. Diabetes mellitus, even in the absence of kidney failure, has been associated with higher risk of anemia, but we did not find a significant association in our sample, likely because of low baseline rates of diabetes mellitus in this sample.[21] Individuals who were prescribed antihypertensive medications such as β-blockers and angiotensin-converting enzyme

Table 2. Cox Regression Analyses for Anemia

	Unadjusted			Adjusted for Age and Gender			Adjusted: Final Model		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Age	1.02	0.99–1.05	.185	1.02	0.99–1.05	.250	1.01	0.98–1.04	.615
Gender	1.72	0.74–4.00	.207	1.60	0.68–3.76	.280	1.33	0.56–3.16	.522
Smoking	0.22	0.08–0.60	.003	0.23	0.09–0.64	.004	0.23	0.09–0.64	.005
Medical comorbidities	2.34	1.03–5.30	.043	2.27	0.96–5.34	.063	2.22	0.93–5.34	.074
Diabetes	2.16	0.80–5.82	.129	1.68	0.56–5.02	.353			
Hyperlipidemia	2.40	0.89–6.48	.083	2.39	0.85–6.73	.099			

Abbreviation: HR = hazard ratio.

Figure 2. Kaplan-Meier Survival Plots for (A) Smoking (*P* = .001), (B) Medical Comorbidities (*P* = .036), and Time to Anemia Event



inhibitors have similarly been reported to develop anemia, but none of the cases with anemia were prescribed any of these antihypertensive medications.[22] Statins, employed in the treatment of hyperlipidemia, the second most common medical comorbidity in this sample, have not been reported to be associated with anemia and are unlikely to be a factor in this study.[23]

Although the association between clozapine and agranulocytosis has been known since 1975, the exact pathophysiology remains unclear and has been broadly categorized into immune and nonimmune factors.[24] Studies have also shown that clozapine could have cytotoxic effects on circulating neutrophils and on the bone marrow.[25,26] Although clozapine has also been shown to be toxic to erythroid precursors, this finding has its detractors.[11,27,28] In addition, the International Suicide Prevention Trial,[29] a trial in which participants taking clozapine and olanzapine were followed up over a 2-year period, did not identify anemia as a treatment-emergent adverse event. However, it should be noted that only 26.8% of participants in the trial were refractory to previous treatment and thus comparable to this study sample. Taken together, this leads us to consider possible alternative explanations for anemia other than clozapine.

Iron deficiency anemia is the most common form of anemia worldwide and emerges as a possible cause related to poor dietary habits in individuals suffering from treatment-refractory psychoses.[30] Its prevalence in schizophrenia has been reported to be 2.5%.[13] However, the predominant blood picture of normochromic, normocytic anemia (instead of the typical hypochromic, microcytic picture in iron deficiency anemia) and the much higher rates of anemia observed here suggest that iron deficiency anemia might not explain the majority of cases. The differential diagnoses for normochromic, normocytic anemia include anemia of chronic disease, renal failure, hypothyroidism, hypopituitarism, and bone marrow failure. No participant had a history of renal failure or hypopituitarism during follow-up. Although 3 participants had a history of hypothyroidism, their thyroid function values were within normal limits during the follow-up period. Anemia of chronic disease is immune driven and is the second most prevalent anemia after iron deficiency anemia.[30] Elevated inflammatory markers have been frequently reported in drug-naive and drug-treated schizophrenia patients[31]; therefore, we postulate that anemia in this group may represent an epiphenomenon of the underlying psychiatric illness rather than clozapine itself.

Anemia was not a reason for clozapine discontinuation, and, hence, there was no censoring of data attributable to this effect. This study included only hemoglobin results processed by a single laboratory, thereby reducing the technical variations that might occur in determining levels. Collection of data was comprehensive, as we restricted the

Table 3. Cox Regression Analyses for Anemia Looking at Baseline Hemoglobin as a Predictor for Men and Women

	Unadjusted			Adjusted: Final Model		
Variable	HR	95% CI	*P* Value	HR	95% CI	*P* Value
Men						
Baseline hemoglobin	0.86	0.79–0.93	< .001	0.86	0.79–0.95	.002
Age				1.03	0.97–1.09	.385
Medical comorbidities				1.54	0.50–4.78	.451
Smoking				0.21	0.05–0.79	.021
Women						
Baseline hemoglobin	0.91	0.82–1.01	.084	0.92	0.81–1.04	.184
Age				1.01	0.96–1.07	.685
Medical comorbidities				4.68	0.78–28.03	.091
Smoking				0.52	0.09–2.98	.467

Abbreviation: HR = hazard ratio.

study inclusion period to a period when electronic medical records were available. All patients who were prescribed clozapine were from a single setting and were monitored via a central registry on site, ensuring inclusion of all eligible participants.

One of the main limitations was the lack of a comparator control group, without which we cannot confidently attribute the observed cases of anemia to clozapine. However, we were unable to find a comparable control group with complete blood count sampled as intensely over a 2-year period as in the case of clozapine in order to circumvent the issue of detection bias. Nevertheless, it is undeniable that the rates of anemia reported here are high and persistent. The study is likely underpowered to detect significance in women since only a quarter of the sample comprised women. However, the hazard ratios were congruent with those observed in men, leading us to postulate that the risk factors might be similar. The risk factors considered here, such as medical comorbidities and smoking, were at baseline only. Conditions such as diabetes mellitus and hyperlipidemia might arise during the course of treatment with clozapine and could modify risk subsequently. We did not have specific information on serum clozapine levels prior to the anemia event to examine if there was a relationship. We were unable to reliably determine if participants with anemia experienced symptoms in the chart review. The exact types of anemia could not be determined because a detailed anemia workup was not performed for all cases. As this was a retrospective study, we were unable to examine the potential confounding effect of menstruation in women on the development of anemia. Lastly, this being a single-center study limits its generalizability to other centers, and findings here would need to be replicated.

In conclusion, we found a high incidence of anemia in individuals initiated on clozapine; moreover, this most likely represents an underestimate of the true incidence of anemia because of the effect of smoking on hemoglobin levels. The potential 3-way relationship between schizophrenia, clozapine, and anemia warrants further study and could have implications regarding clozapine monitoring and physical health guidelines for this unique group. For now, clinicians should be aware of and monitor for development of anemia, especially in individuals with hemoglobin in the lower range of normal.

Submitted: March 18, 2014; accepted September 24, 2014.

Online first: August 18, 2015.

Drug names: clozapine (Clozaril, FazaClo, and others), fluvoxamine (Luvox and others), olanzapine (Zyprexa and others).

Potential conflicts of interest: **Dr Bies** is a consultant for INC research and has received funds through the Indiana Clinical and Translational Sciences Institute (CTSI) as a result of a gift from Eli Lilly and Company to Indiana University. **Dr Remington** has received research support, consulting fees, or speaker's fees from the Canadian Diabetes Association, the Canadian Institutes of Health Research, Hoffman-La Roche, Laboratorios Farmacéuticos Rovi, Medicure, Neurocrine Biosciences, Novartis Canada, Research Hospital Fund–Canada Foundation for Innovation, and the Schizophrenia Society of Ontario. **Ms Powell** has received a speaker's honorarium from Novartis. **Dr Lee** and **Ms Bhaloo** have no potential or other conflicts of interest to report.

Funding/support: Dr Lee is supported by the Singapore Ministry of Health's National Medical Research Council under its Transition Award (grant no: NMRC/TA/002/2012). Dr Bies is supported by the Campbell Family Foundation as well as the Indiana CTSI. Dr Remington is supported through an Academic Health Science Center (Ontario, Canada) Alternate Funding Plan Innovation Fund Award.

Role of the sponsors: The sponsors were not involved in the design and conduct of this study; analysis and interpretation of the data; and preparation, review, or approval of the manuscript.

Supplementary material: Available at PSYCHIATRIST.COM

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Supplementary Material

Article Title: Clozapine and Anemia: A 2-Year Follow-Up Study

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DOI Number: 10.4088/JCP.14m09143

List of Supplementary Material for the article

1. eFigure 1 — Kaplan-Meier survival plots comparing high and low baseline hemoglobin groups for (a) males ($p<0.001$), (b) females ($p=0.137$) and time to anemia event

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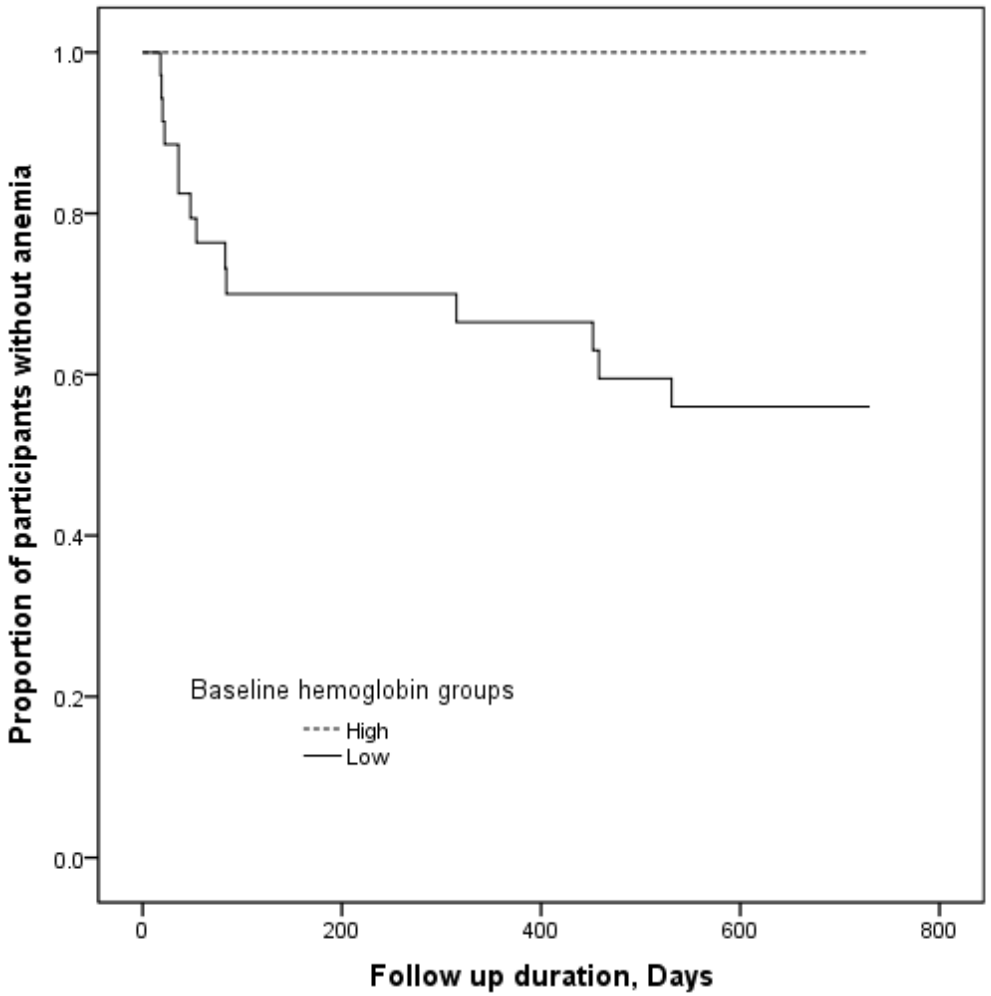
Supplementary Figure 1. Kaplan-Meier survival plots comparing high and low baseline hemoglobin groups for (a) males ($p<0.001$), (b) females ($p=0.137$) and time to anemia event.

(a)



(b)