ORIGINAL RESEARCH

Economic Burden of Anemia in an Insured Population

ALLEN R. NISSENSON, MD, FACP; SALLY WADE, MPH; L. TIM GOODNOUGH, MD; KEVIN KNIGHT, MD, MPH; and ROBERT W. DUBOIS, MD, PhD

ABSTRACT

OBJECTIVE: Anemia is a common hematological disorder characterized by reduced hemoglobin concentrations. Despite information on prevalence and associated outcomes, little is known about the impact of anemia on health care utilization and costs. This study examines anemia prevalence and associated medical costs and utilization, using administrative claims for adults newly diagnosed with anemia, including up to 12 months of follow-up.

METHODS: Patients predisposed to anemia, based on selected comorbid conditions (chronic kidney disease, human immunodeficiency virus, rheumatoid arthritis, inflammatory bowel disease, congestive heart failure, and solid-tumor cancers), were identified. Costs for anemic patients and a random sample of nonanemic patients with these conditions were compared. Associations were evaluated after adjustment for potential confounders using a regression model. Clinical care patterns were examined overall and by condition.

RESULTS: Anemia was observed in 3.5% (81,423) of approximately 2.3 million health plan members in 2000; 15% of anemic patients received an identified treatment, with transfusion being the most frequent intervention. Utilization and costs were significantly higher for anemic patients ($P < 0.001$). Average annualized per-patient costs were $14,535 for anemic patients (55% outpatient, 33% inpatient, 13% pharmacy), 54% higher than the $9,451 average cost for nonanemic patients (45% outpatient, 36% inpatient, 19% pharmacy). After adjustment for age, other comorbidities (e.g., chronic kidney disease and cancer), sex, and insurance type (indemnity, preferred provider organization/point of service, or health maintenance organization, in the Medstat MarketScan database), anemic patients had average costs that were more than twice the adjusted costs of nonanemic patients.

CONCLUSION: Medical costs for anemic patients are as much as twice those for nonanemic patients with the same comorbid conditions.

KEYWORDS: Anemia, Chronic conditions, Utilization, Medical costs

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Anemia is an important public health concern. It occurs commonly and is characterized by reduced concentrations of hemoglobin due to a variety of underlying causes.[1,2] Estimates of anemia prevalence vary considerably. The National Center for Health Statistics conservatively estimates that approximately 3.4 million individuals in the United States are anemic.[3]

The National Health and Nutrition Examination Survey (NHANES) provides an assessment of anemia prevalence based on laboratory testing. Results from NHANES III show anemia to be most prevalent in children through age 16, women aged 17 to 49 years, and the elderly (aged 75 years and older), especially elderly men.[4] Anemia prevalence is higher among individuals with certain chronic conditions, including chronic kidney disease (CKD), human immunodeficiency virus (HIV), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), congestive heart failure (CHF), and cancer.[2,5] In previous studies, anemia with chronic disease has been identified in 36% of patients with CKD[6] and 27% of patients with RA.[7] The increasing amount of information on the prevalence of anemia among individuals with such diseases supports the view that it is a condition of growing concern.[7-11]

Anemia has been shown to be associated with increased mortality and morbidity as well as with decreased physical functioning and quality of life.[2,12] Although anemia is often associated with disease progression or increased disease severity, evidence of its independent effect on these key outcomes is still accumulating.

Despite information on anemia prevalence and associated outcomes, little is known about the impact of anemia on health resource utilization and costs. Although the cost of anemia care has been examined using Medicare data for CKD,[13] cancer,[14,15] and heart failure,[16] the literature provides no data on anemia-related costs in other populations. Consequently, this study was undertaken to estimate the health care costs and treatment patterns of patients with anemia in a privately insured population.

Methods

This study is based on retrospective administrative claims data from commercially insured and Medicare plans represented in the Medstat MarketScan database, containing the combined administrative claims for more than 2 million health plan members for employers from across the country. The study population was selected only from those enrolled in plans with complete capture of facility-based and professional services, as well as outpatient prescription medications. The combined Medicare and commercial populations from which the study sample was

TABLE 1 *Diagnosis Codes (ICD-9-CM) Used to Identify 6 Study Conditions*

Chronic kidney disease	
Malignant hypertensive renal disease (without renal failure)	403.00
Malignant hypertensive renal disease (with renal failure)	403.01
Benign hypertensive renal disease (without renal failure)	403.10
Benign hypertensive renal disease (with renal failure)	403.11
Unspecified hypertensive renal disease (without renal failure)	403.90
Unspecified hypertensive renal disease (with renal failure)	403.91
Malignant hypertensive heart and renal disease (with renal failure)	404.02
Malignant hypertensive heart and renal disease (with heart and renal failure)	404.03
Benign hypertensive heart and renal disease (with renal failure)	404.12
Benign hypertensive heart and renal disease (with heart and renal failure)	404.13
Unspecified hypertensive heart and renal disease (with renal failure	404.92
Unspecified hypertensive heart and renal disease (with heart and renal failure)	404.93
Nephrotic syndrome	581.0-581.9
Chronic glomerulonephritis	582.0-582.9
Nephritis (NOS as acute or chronic)	583.0-583.9
Chronic renal failure	585
Renal failure, unspecified	586
Renal sclerosis, unspecified	587
Chronic pyelonephritis (without lesion of renal medullary necrosis)	590.00
Chronic pyelonephritis (with lesion of renal medullary necrosis)	590.01
HIV infection	
HIV infection	042
Rheumatoid arthritis	
Rheumatoid arthritis	714.0
Felty's syndrome	714.1
Other rheumatoid arthritis with visceral or systematic involvement	714.2
Rheumatoid lung	714.81
Other	714.89
Inflammatory bowel disease	
Small intestine	555.0
Large intestine	555.1
Small intestine with large intestine	555.2
Unspecified site	555.9
Ulcerative (chronic) enterocolitis	556.0
Ulcerative (chronic) ileocolitis	556.1
Ulcerative (chronic) proctitis	556.2
Ulcerative (chronic) proctosigmoiditis	556.3
Left-sided ulcerative (chronic) colitis	556.5
Universal ulcerative (chronic) colitis	556.6
Other ulcerative colitis	556.8
Ulcerative colitis, unspecified	556.9
Congestive heart failure	
Congestive heart failure	428.0
Malignant hypertensive heart disease (with congestive heart failure)	402.01
Benign hypertensive heart disease (with congestive heart failure)	402.11
Unspecified hypertensive heart disease (with congestive heart failure)	402.91
Malignant hypertensive heart and renal disease (with congestive heart failure)	404.01
Malignant hypertensive heart and renal disease (with congestive heart failure and renal failure)	404.03
Benign hypertensive heart and renal disease (with congestive heart failure)	404.11
Benign hypertensive heart and renal disease (with congestive heart failure and renal failure)	404.13
Unspecified hypertensive heart and renal disease (with congestive heart failure)	404.91
Unspecified hypertensive heart and renal disease (with congestive heart failure and renal failure)	404.93
Cancer (primary only)	
Cancer diagnoses in the range of 140.0-199.x, excluding 173.0-173.9. For cancer patients, we required 2 outpatient diagnoses on separate service dates within 6 months or 1 diagnosis on an inpatient admission record.	

ICD-9-CM = International Classification of Diseases, 9th Revision, Clinical Modification; NOS = not otherwise specified.

drawn resided primarily in the southern, northern central, and northeastern regions of the United States, with a smaller representation from the western region.

Analyses were conducted to examine the prevalence of anemia and related utilization and health plan costs in an adult population. This paper presents results for the entire study population and separately for groups with specific conditions that are often associated with an increased occurrence of anemia or in which anemia presents particular clinical challenges. For condition-specific subgroup results, patients were identified based on the presence of diagnosis codes from the *International Classification of Diseases, 9th Revision, Clinical Modification,* (ICD-9-CM) for 6 conditions: CKD, HIV, RA, IBD, CHF, and solid-tumor cancer (Table 1). Patients who had multiple diagnoses during the study period were included in all condition-specific groups for which they qualified.

Since laboratory values such as hemoglobin levels are not generally available in medical claims data, anemia was identified by the presence of at least 1 diagnosis code for anemia (occurring in any position on a claim), 1 procedure code (*Current Procedural Terminology, 4th Edition* [CPT-4], ICD-9-CM, or Health Care Financing Administration Common Procedure Coding System [HCPCS]), or 1 drug code indicative of anemia treatment (e.g., blood transfusions, injections with recombinant erythropoietin. Diagnoses used for patient selection include iron deficiency anemia, pernicious anemia, anemia of chronic disease, nutritional anemia, other specified aplastic anemias, and other unspecified anemia. Codes for acute anemias were not included, and blood transfusion was only considered in the absence of a diagnosis of acute anemia (ICD-9-CM 285.1) (Table 2).

The study was divided into 2 components. The first component assessed anemia prevalence in the year 2000. The denominator included all adult health plan members who had continuous

TABLE 2 Diagnosis Codes (ICD-9-CM) and Procedure Codes (CPT-4, ICD-9-CM, HCPCS) Used to Identify Anemia

Iron deficiency anemia
280.x: Iron deficiency anemia

Anemia in chronic illness
285.2x: Anemia in chronic illness

Pernicious anemia
281.0 Pernicious anemia

Other anemia
The "other anemia" category includes patients with evidence of anemia diagnoses other than those listed above, plus patients with evidence of anemia treatment but no corresponding diagnosis.

281.1-281.9: Other nutritional anemias
285.9: Anemia, unspecified
284.8: Other specified aplastic anemias

Transfusion
V58.2, 99.0x (ICD-9-CM); 36430, 36440, 96400-96549 (CPT-4); P9010, P9011, P9012, P9013, P9016, P9017, P9018, P9019, P9020, P9021, P9022, P9023 (HCPCS)

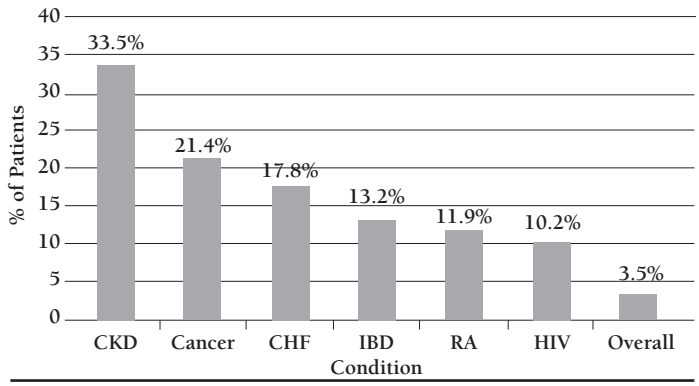
Note: Only patients with the above transfusion codes but no acute anemia (DX=285.1) in both the 12-month period preceding the transfusion and during the follow-up period were included in the anemic population.

Epoetin alfa injection
HCPCS:
Q9920, Q9921, Q9922, Q9923, Q9924, Q9925, Q9926, Q9927, Q9928, Q9929, Q9930, Q9931, Q9932, Q9933, Q9934, Q9935, Q9936, Q9937, Q9938, Q9939, Q9940, Q0136

NDC:
55513014401, 55513047810, 55513047801, 55513028301, 55513026701, 55513014810, 55513082301, 55513014410, 55513028310, 55513012610, 55513012601, 05551326710, 05551314810, 05551314410, 05551312610, 55513014801, 55513026710, 55513082310, 59676031200, 00062740103, 00062740201, 00062740501, 00403489718, 59676740104, 59676740000, 59676034001, 59676032001, 54868252300, 59676031201, 59676031002, 59676031001, 59676030402, 59676030401, 59676030302, 00062740003, 59676030301, 59676740503, 59676030202, 59676030201, 54868252301

CPT-4=Current Procedural Terminology, 4th Edition; DX=Diagnosis; HCPCS=Health Care Financing Administration Common Procedure Coding System; ICD-9-CM=International Classification of Diseases, 9th Revision, Clinical Modification; NDC=National Drug Code.

FIGURE 1 Year 2000 Anemia Prevalence Overall and by Condition



Overall n=81,423 (out of overall Medstat MarketScan research database population=2,296,832); CKD=4,834; cancer=14,023; CHF=7,234; IBD=1,349; RA=1,885; HIV=151. Percentages for each condition are percentages of the anemic population.

N values for anemia prevalence by condition and age:

CKD:	*age 18-49=378;*	*age 50-64=771;*	*age 65+=1,160*
Cancer:	*age 18-49=1,201;*	*age 50-64=2,784;*	*age 65+=2,768*
CHF:	*age 18-49=216;*	*age 50-64=804;*	*age 65+=2,726*
IBD:	*age 18-49=296;*	*age 50-64=283;*	*age 65+=213*
RA:	*age 18-49=326;*	*age 50-64=550;*	*age 65+=572*
HIV:	*age 18-49=26;*	*age 50-64=7;*	*age 65+=2*

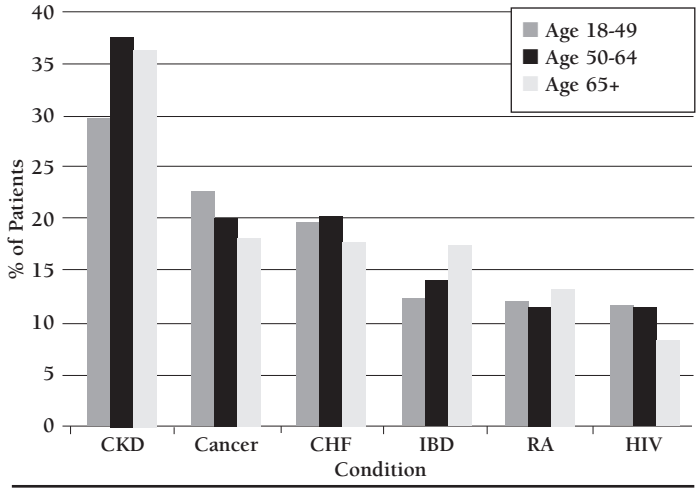
CKD=chronic kidney disease; CHF=congestive heart failure; HIV=human immunodeficiency virus; IBD=inflammatory bowel disease; RA=rheumatoid arthritis.

medical and drug benefits coverage during 2000, and the numerator included all members with evidence of a specified anemia diagnosis or treatment. The second component used administrative claims for dates of service between January 1, 1998, and June 30, 2001, to compare the health care cost and utilization patterns between anemic and nonanemic patients within the 6 study conditions. We captured the sequence of anemia-related services in the year following the initial diagnosis. For the second part of the study, we selected only those patients who were "newly diagnosed" with anemia, defined as those with at least 1 year of continuous medical and drug benefits coverage prior to their anemia index date (date of first anemia diagnosis or procedure in the study period [Table 2]) and no evidence of anemia diagnoses or treatment during this 1-year "history" period. For comparison, we selected patients who met the same health plan enrollment requirements as the anemic patients but had no evidence of anemia. We identified a comparison group for the overall anemic population and also constructed 6 condition-specific comparison groups using the same diagnostic criteria that we used for the anemic patients.

Since the objective of this study component was to characterize anemia care in the first year after diagnosis, follow-up data were examined for a maximum of 12 months after the anemia index date. Individual follow-up periods were determined by the amount of time that each patient had continuous benefits coverage following the anemia index date. To avoid skewing the study toward a sicker population, we did not require that patients remain in the health plan for the full 12 months of potential follow-up; this variable follow-up period was taken into consideration in the analyses.

For the cost model, we developed a variable to adjust for disease severity for each of the 6 conditions. Severity adjustment was based on specific ICD-9 codes, HCPCS codes for durable medical equipment, or pharmacy codes. Patients were separated into mild, moderate, and severe categories based on specific ICD-9 codes, HCPCS codes for durable medical equipment, or pharmacy codes. Cancer patients who were actively receiving chemotherapy were categorized as part of the moderate severity category, whereas those with evidence of metastasis were categorized as severe. CKD patients with 1 CKD hospitalization during follow-up were categorized as moderate while those with either more than 1 CKD hospitalization or with a kidney transplant were categorized as severe. Use of biologic therapies

FIGURE 2 Year 2000 Anemia Prevalence in Females by Condition and Age



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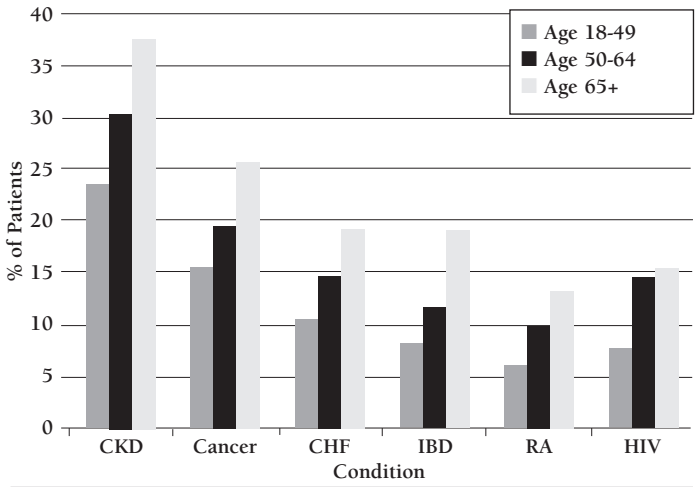
RA:	*age 18-49=326;*	*age 50-64=550;*	*age 65+=572*
HIV:	*age 18-49=26;*	*age 50-64=7;*	*age 65+=2*

CHF=congestive heart failure; CKD=chronic kidney disease; HIV=human immunodeficiency virus; IBD=inflammatory bowel disease; RA=rheumatoid arthritis.

FIGURE 3 Year 2000 Anemia Prevalence in Males by Condition and Age



N values for anemia prevalence by condition and age:

CKD:	*age 18-49=280;*	*age 50-64=763;*	*age 65+=1,482*
Cancer:	*age 18-49=298;*	*age 50-64=1,774;*	*age 65+=5,198*
CHF:	*age 18-49=105;*	*age 50-64=708;*	*age 65+=2,675*
IBD:	*age 18-49=152;*	*age 50-64=211;*	*age 65+=194*
RA:	*age 18-49=55;*	*age 50-64=167;*	*age 65+=215*
HIV:	*age 18-49=64;*	*age 50-64=43;*	*age 65+=9*

CHF=congestive heart failure; CKD=chronic kidney disease; HIV=human immunodeficiency virus; IBD=inflammatory bowel disease; RA=rheumatoid arthritis.

and selected nonbiologic therapies indicated moderate RA while joint surgery indicated severe RA. For IBD, more advanced medications, surgery, and multiple hospitalizations were indicators of severe disease. For CHF, the severity increased as the number of concomitant CHF medications and hospitalizations increased.

The Charlson Comorbidity Index (CCI) was used to quantify burden of illness in the study population based on claims incurred during the 6 months before each patient's index date.[17]

In order to assess treatment patterns, we identified specific procedures and medications that are commonly used in the management of anemia. These included blood transfusions, erythropoietin injections, B12 injections, iron injections, and use of testosterone, nandrolone, folate, or folic acid. It is important to note that the study database captured information only on outpatient prescription medications and did not include utilization of any inpatient or over-the-counter medications. Anemia treatment regimens were assessed for up to 1 year following patients' anemia index dates; follow-up periods ended either at the conclusion of the study period or when patients left the health plan. All relevant therapies provided on or after the anemia index date were counted.

The costs evaluated in this study were the payments made by the health plan, after subtraction of member cost-share, as reported on the final adjudicated version of each claim. No adjustments were made to standardize costs across the study period. Unfortunately, the structure and level of detail of administrative claims precluded us from simply summing up payments in order to determine the cost of anemia. As is common in cost studies such as this one, we created an algorithm to estimate the direct health plan payments attributable to anemia.[14-16] For inpatient and outpatient (nonpharmacy) services, claims with either a primary or secondary diagnosis resulted in the attribution of a portion of the costs to anemia. In general, if anemia was listed as the primary diagnosis, 50% of the costs on the claim were attributed to anemia. If anemia was listed only as a secondary diagnosis, 25% of the costs were attributed to anemia.

Allocations for individual claims ranged from 0% to 100%, depending on whether the anemia diagnosis was primary or secondary, how many additional diagnoses were on the claims, and whether anemia-specific services (e.g., erythropoietin injection) appeared on the claim. In addition, costs for anemia-specific procedure codes were attributed to anemia even when anemia was not listed explicitly as a diagnosis (e.g., transfusion). For outpatient pharmacy claims, all erythropoietin costs were attributed to anemia.

Pairwise comparisons were performed for each variable according to the nature of the data involved: continuous variables were compared using *t* tests or nonparametric equivalents, and categorical variables were compared using chi-square tests. A multivariate analysis was also conducted to estimate cost

TABLE 3 Number of Patients and Average Follow-Up Months by Condition and Anemia Status Based on Claims Incurred January 1, 1998, to June 30, 2001

	Newly Diagnosed Anemic Patients			Nonanemic Comparison Patients		
	N (Average Follow-up Months)	Average Age	% Female	N (Average Follow-up Months)	Average Age	% Female
Overall population	118,332 (8.9)	56.9	66.3	35,948 (9.3)	61.6	53.0
Condition-Specific Populations						
Chronic kidney disease	7,545 (9.0)	65.8	49.3	5,814 (9.3)	62.7	44.4
Human immunodeficiency virus	354 (8.7)	45.9	31.9	232 (9.1)	44.5	29.7
Rheumatoid arthritis	3,852 (9.1)	61.2	76.1	3,303 (9.2)	59.8	71.6
Inflammatory bowel disease	2,538 (9.3)	55.9	61.5	2,139 (9.3)	53.8	55.1
Congestive heart failure	14,985 (8,7)	72.5	53.5	11,886 (9.2)	71.3	49.5
Cancer	22,030 (8.7)	65.7	51.6	17,542 (9.3)	65.3	53.0

differences between anemic and nonanemic patients, adjusting for factors likely to influence health care utilization and expenditures. An exponential model was fit using a generalized linear modeling technique, with patient age and gender, coverage type (e.g., preferred provider organization, indemnity), predisposing condition (i.e., the 6 study conditions), and disease severity for each predisposing condition as covariates and a binary indicator variable for presence or absence of anemia. Due to the skewed nature of distributions of payment data, a gamma variance function was chosen using the Park test, and bootstrap standard errors were estimated. All analyses were conducted using SAS software version 8.02 (Cary, NC) and STATA version 7.0 (College Station, TX).

Results

Based on data for the 2,296,832 adult health plan members with continuous benefits coverage during 2000, the overall anemia prevalence was 3.5% (81,423) (Figure 1). Although statistical comparisons cannot be made because the condition groups were not mutually exclusive, it is clear that the prevalence of anemia varied significantly by condition, with CKD defining the upper end. Within each of the 6 study conditions, the relationship between anemia and age among females was not consistent. However, among males, anemia prevalence increased with age (Figures 2 and 3).

Overall, 118,332 anemic patients and a random sample of 35,948 nonanemic patients were identified for inclusion in the cost and utilization component of the study (Table 3). (Case-matching was determined to be unnecessary in order to provide reasonably precise adjusted measures of association since the size of the study population was large). The number of patients in the condition-specific subgroups ranged from 354 anemic patients and 232 nonanemic patients in the HIV subgroup to 22,030 anemic patients and 17,542 nonanemic patients in the cancer subgroup (Table 3). Females made up the majority of both the overall anemic and control populations (66% and 53%, respectively), and the proportion of females in the anemic population was statistically higher ($P<0.001$). With the exception of the HIV population, females were more common in the anemic populations for all study conditions ($P<0.01$).

Overall, nonanemic patients were nearly 5 years older on average compared with the anemic patients (61.6 years vs. 56.9 years, $P<0.001$). The opposite was true in the condition-specific populations: anemic patients were older, on average, than nonanemic patients in all of the condition-specific populations except for HIV ($P<0.002$). With respect to the CCI, the overall population of anemic patients did not differ statistically from nonanemic comparison subjects ($P=0.22$). However, in each of the 6 condition-specific populations, anemic patients had a statistically higher burden of illness as evidenced by higher CCI scores ($P<0.001$). The difference in CCI scores was greatest in patients with CKD (1.6 for anemic vs. 0.98 for nonanemic) and those with cancer (1.6 for anemic and 0.56 for nonanemic).

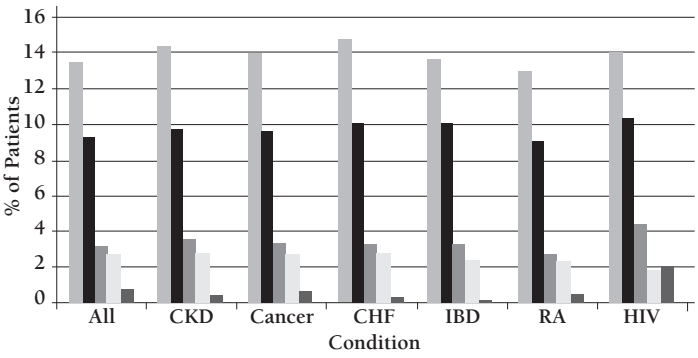
Anemia Management

The average follow-up period for patients in this study was approximately 9 months.

Overall Population

In the overall population, the majority of anemic patients (86.5%) did not receive any of the therapies evaluated in this study (Figure 4). Among therapies evaluated, transfusion was the most commonly used, with nearly 1 out of every 10 anemic patients (9.3%) receiving at least 1 blood transfusion during the follow-up period. These patients averaged 1.1 transfusions per month. For most transfused patients, transfusion was the only therapy used; approximately 1 in 5 also received erythropoietin, which was nearly always given after the transfusion.

FIGURE 4 Anemia Management Strategies by Condition



Treatment	All	CKD	Cancer	CHF	IBD	RA	HIV
Any	118,322	7,545	22,030	14,985	2,539	3,852	354
Transfusion	11,017	738	2,130	1,528	257	349	37
EPO	3,743	271	739	527	86	109	16
B12 injections	3,146	213	599	438	61	94	6
Iron injections	238	11	40	22	1	6	2

CHF = congestive heart failure; CKD = chronic kidney disease; EPO = erythropoietin; HIV = human immunodeficiency virus; IBD = inflammatory bowel disease; RA = rheumatoid arthritis.

TABLE 4 Average Annualized Utilization of Key Services per Patient Based on Claims Incurred January 1, 1998, to June 30, 2001

Service	Total Population: Anemic N = 118,332 (Average Follow-up Months = 8.9)	Total Population: Nonanemic N = 35,948 (Average Follow-up Months = 9.3)	*P* Value (2-Tailed Student's *t* Test)
Outpatient visits	6.1	5.3	<0.001
Emergency room visits	0.2	0.1	<0.001
Inpatient admissions	0.4	0.3	<0.001
Hospital days	3.1	2.0	<0.001
Laboratory tests	5.3	2.6	<0.001

Condition-Specific Populations

As in the overall population, the majority of patients (85.2%-86.9%) in each of the 6 condition-specific populations had no documented anemia treatment. In these populations, the pattern of anemia treatment was similar to that in the overall population. Anemic HIV patients had the highest transfusion use (10.5% with at least 1 transfusion), but they also had the lowest average number of transfusions per patient per month (0.8). Therapy involving both transfusion and erythropoietin was most common among anemic HIV patients (27.0% of transfused patients) and least common among anemic RA patients (15.5% of transfused patients). Nearly 1 in 5 transfused CKD patients (19.1%) and cancer patients (19.2%) also received erythropoietin.

Among condition-specific anemic populations, erythropoietin was used most commonly by HIV patients (4.5%) and least commonly by RA patients (2.8%). The majority of erythropoietin use in these populations was in conjunction with (usually following) blood transfusion.

Utilization and Costs

Utilization of selected key services was significantly higher for anemic patients ($P<0.001$ in all cases), as presented in Table 4. Similarly, per-patient payments for health care services (Tables 5 and 6) were higher for anemic patients than for nonanemic patients, both overall and within each of the 6 study conditions ($P<0.001$). With the exception of outpatient pharmacy-based prescription drugs, anemic patients exhibited higher costs than did nonanemic patients for all types of care, including inpatient, outpatient, emergency room, and outpatient laboratory ($P<0.001$). With the exception of outpatient facility care for HIV patients, this pattern of higher costs (including, in this case, higher outpatient prescription costs) among anemic patients persisted in the condition-specific populations ($P<0.03$).

Among anemic patients, average total annualized costs were $14,535 per patient. Outpatient care, including physician office visits, accounted for more than half ($7,927, 54.5%) of the average total costs. Inpatient care accounted for nearly one third ($4,775, 33%) of the average total costs. Payments for pharmacy-based outpatient prescriptions averaged $1,833. In the nonanemic population, average total annualized costs were $9,450 per patient. Outpatient care accounted for 45% ($4,262) of the total average costs, while inpatient care accounted for 36% ($3,375). Outpatient pharmacy payments averaged $1,813 (19%). Cost differences between anemic and nonanemic patients were statistically significant ($P<0.001$) for all types of care except outpatient pharmacy ($P=0.24$).

Table 7 presents adjusted and unadjusted differences in average annualized per-patient costs. Cost differences persisted after adjusting for differences in patient gender and age, coverage type (e.g., preferred provider organization, indemnity), predisposing condition (i.e., the 6 study conditions), and disease severity for each predisposing condition. The average annualized total cost per anemic patient was more than twice the average for nonanemic patients. Both outpatient and inpatient costs were more than twice as high for anemic patients as for nonanemic patients.

Services that we could attribute to anemia, based on our algorithm (i.e., claims for anemia treatment or claims containing a

diagnosis of anemia), accounted for only 5% to 11% of the cost differential between anemic and nonanemic patients. Most of the difference was accounted for by services without an anemia diagnosis code or another unambiguous relationship to anemia. Average annualized anemia-attributed payments, using our algorithm, were $563 per patient. Outpatient care accounted for the largest share of anemia-attributed expenditures (which included a proportion of costs for services with either an anemia diagnosis or anemia-specific procedure such as erythropoietin administration), averaging $412 per patient annually (73% of total anemia-attributed costs). The costs of inpatient care attributable to anemia, based on our algorithm, were slightly lower than those for professionally administered outpatient medications, $90 and $99 per patient annually. Anemia-attributed outpatient prescription costs (i.e., costs for anemia-related medications) averaged $61 per patient annually.

TABLE 5 Average Annualized Health Care Payments by Type of Care for Anemic and Nonanemic Patients Based on Claims Incurred January 1, 1998, to June 30, 2001

Type of Care	Payments ($) per Anemic Patient N = 118,332 (Average Follow-up Months = 8.9)	Payments ($) per Nonanemic Patient N = 35,948 (Average Follow-up Months = 9.3)	*P* Value (2-Tailed Student's *t* Test)
Total	14,535	9,451	<0.001
Inpatient care	4,775	3,375	<0.001
Emergency room	137	$101	<0.001
Outpatient care	7,927	4,262	<0.001
Pharmacy-based outpatient medications	1,833	1,813	0.238
Professionally administered outpatient medications	157	0.13	<0.001

Discussion

For this study, we examined anemia prevalence, current treatment patterns, and associated costs of care in a privately insured population in order to determine the impact of anemia on the use of health care resources. In general, anemia occurred with noticeable frequency even in a relatively healthy privately insured population and resulted in higher health care utilization and costs.

Overall, 3.5% of the study population was anemic at some point during the study year. It is somewhat challenging to compare this estimated anemia prevalence with estimates from previous studies, given that no standard definition of anemia is currently used and that reported and actual prevalence vary widely depending on the nature of the population studied. It is likely that the prevalence estimates of anemia in this study underestimate the true prevalence since, in order to be considered anemic, a patient was required to have a diagnosis of anemia recorded on a claim during the study period or to have received one of the specified anemia therapies.

These results underscore the fact that anemia is common enough to merit attention, even outside the context of those conditions with which it has historically been associated. Nearly 4% of the overall study population had anemia that was serious enough to be recorded as a diagnosis on a medical claim, to receive an anemia-related prescription medication, or to require an anemia-related procedure.

In general, these results highlight the importance of understanding the demographic and clinical risk factors that increase the likelihood that a particular individual will be anemic. From both public health and provider perspectives, such profiles of "at-risk" populations are critical for improving anemia screening, detection, and treatment. This study suggests that anemia merits particular attention in routine clinical care for women and the elderly.

Anemic patients used significantly more health care services and had higher costs ($14,535 vs. $9,451, $P < 0.001$), even compared with patients with the same underlying condition who were not anemic. Since it is often assumed that anemia may simply be a marker for the severity of a key underlying disease (e.g., RA) and that disease severity would therefore be the primary driver for any observed cost differences, our multivariate analysis was designed to adjust for the presence of key conditions and the severity of those conditions as well as for other factors that could influence costs (i.e., patient age, gender, and coverage type). Our results indicate that costs of anemic patients were more than twice those of nonanemic patients even after adjusting for these other potential confounders.

The majority of the anemic patients (85%) did not receive any of the therapies assessed. This is quite striking since these patients were primarily identified through the presence of explicit anemia diagnoses on the medical claims and, therefore, those with mild anemia may be underrepresented. One possible explanation is the use of oral iron, which was not captured in the study database because it is an over-the-counter medication. Nonetheless, the finding that only 15% of patients received any apparent treatment raises serious concern that anemia is inadequately managed. It is possible that physicians in general do not attribute much clinical importance to anemia, especially in patients who do not have medical conditions that may be exacerbated by anemia, and/or for whom anemia management is part of the standard of care. If that is the case, then efforts to increase awareness of anemia's risk factors and consequences are needed, along with practical clinical treatment guidelines.

It may not be surprising that anemia in the overall health plan population appears to be either undertreated or minimally treated. It is surprising, however, that despite explicit guidelines

TABLE 6 Average Annualized Health Care Payments for Anemic and Nonanemic Patients

Condition	Anemic Patients		Nonanemic Patients		Payment ($) Difference	Anemia-Attributed Payment ($) per Patient (% Difference)
	N	Average Payment ($) per Patient	N	Average Payment ($) per Patient		
All	118,332	14,535	35,948	9,451	5,084*	563 (11%)
Chronic kidney disease	7,545	41,292	5,814	12,535	28,757*	2,324 (8%)
HIV	354	37,424	232	13,579	23,845*	1,300 (5%)
Rheumatoid arthritis	3,852	17,186	3,303	7,777	9,409*	502 (5%)
Inflammatory bowel disease	2,538	19,113	2,139	7,678	11,435*	676 (6%)
Congestive heart failure	14,985	29,703	11,886	12,459	17,244*	1,141 (7%)
Cancer	22,030	34,009	17,542	9,034	24,975*	1,480 (6%)

** P<0.001 based on 2-tailed Student's t test.*
HIV=human immunodeficiency virus.

TABLE 7 Unadjusted and Adjusted Differences* in Average Annualized Health Care Payments for Anemic and Nonanemic Patients

	Average Total Payments ($) per Patient†	Average Inpatient Payments ($) per Patient	Average Outpatient Payments ($) per Patient
Unadjusted costs for anemic patients (N=118,332)	14,535	4,775	7,927
Unadjusted costs for nonanemic patients (N=35,948)	9,451	3,375	4,262
Adjusted costs for nonanemic patients	7,106	1,996	3,297
Unadjusted cost differences	5,084	1,400	3,665
Adjusted cost differences‡	7,429	2,779	4,630

** Costs for the nonanemic patients were standardized using the covariate levels in the anemic population. Covariates included age, sex, coverage type (preferred provider organization), presence and severity of 6 study conditions, Charlson Comorbidity Index.*
† Total payments include inpatient, outpatient, and outpatient pharmacy costs.
‡ P values for differences were all <0.001 based on 2-tailed Student's t test.

emphasizing aggressive anemia management in CKD[18] and cancer,[19] such patients are not receiving adequate or appropriate care.[19,20]

These results also suggest that when anemia treatments are employed, their usage is remarkably similar across the 6 study conditions. The one exception is HIV, where the use of erythropoietin is more commonly observed than in the other conditions. This pattern suggests that the presence of underlying conditions may not play a significant role in clinical judgments about which anemia treatment is most appropriate or even about how aggressively to manage anemia.

Some of the observed treatment patterns also highlight specific quality-of-care considerations. Despite growing concern about the risks associated with transfusions and a wide array of initiatives to promote blood conservation, transfusions represented the predominant treatment among patients with newly diagnosed anemia in the study database. There is a clear gap between current practice relative to blood conservation and recommendations for transfusion alternatives. For example, current recommendations for use of blood products list iron, folate, B12, and erythropoietin therapy as specific therapies that should be administered instead of blood transfusions if the patient's condition permits time for these agents to be utilized.[21] Since the current study focused only on use of injectable drugs, further analysis is necessary to understand the full extent to which these recommended first-line pharmaceutical therapies are used.

Limitations

Administrative claims data are one of the richest sources of information on health care utilization and cost and have historically served as the foundation for many areas of health services research. Like any data source, claims data present limitations: the most important is that the level of detail available is limited to that required for claims adjudication and internal and external health plan reporting. This limitation may lead to underidentification of anemia in the study population since the anemia diagnosis codes and anemia-related procedures and pharmaceutical therapies used for patient selection are only proxy indicators of anemia. The lack of actual hemoglobin levels for the patients in the study population also precludes the assessment of anemia severity. While claims data do present a reasonable amount of clinical information, no simple standard methodology was available to stratify patients by severity for

the 6 study conditions. Finally, although the costs presented in this paper may differ from those experienced by another health plan due to differing fee schedules, the more critical finding is the statistically higher health care costs associated with anemia.

Although the data collected are not sufficient to explain why health care costs are higher among anemic patients, we would like to suggest a few possible explanations. First, despite our best efforts to control for disease severity and comorbidity burden in this analysis, it is possible that anemic patients are simply sicker than the controls and therefore use more health care services. It is also possible that the presence of anemia may contribute to a higher rate of detection of comorbidities in these patients or that anemic patients with comorbidities may be more likely to have their anemia detected, resulting in an association that is not causal.

These adjusted cost comparisons should also be considered in light of our examination of anemia-attributed costs (e.g., costs due to specific anemia visits, tests, and therapies). Although these anemia-attributed costs certainly contributed to overall health care costs in the study population, they represented only a small percentage of the total costs per patient. These results suggest that anemia may be responsible for excess costs in areas that cannot be captured by our algorithm or, alternatively, that the association is a marker for disease severity associated with increased costs (i.e., that the association is not causal).

Conclusions

The results of this study demonstrate that the elevated clinical burden that anemia imposes at the patient level in turn increases the resource burden at the health plan level. As anemia gains greater recognition as both an important clinical and public health issue, careful consideration should be given to determining the most cost-effective approaches to anemia screening in high-risk populations and efforts to improve anemia diagnosis and treatment. Given the challenges inherent in isolating the true costs of anemia, future research should examine the economic impact of more aggressive anemia treatment to determine if expected short-term cost increases incurred by earlier treatment would be offset by savings from fewer admissions, shorter lengths of stay, and less use of other expensive services in the treatment of anemia-related outcomes. Target research should also examine the extent to which patient care is consistent with current guidelines.

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Nissenson served as principal author of the study. Study concept and design were contributed by all authors. Analysis and interpretation of data were contributed by Wade and Knight. Drafting of the manuscript was primarily the work of Wade and Dubois, and its critical revision was the work of all authors. Statistical expertise was contributed by Knight.

REFERENCES

1. Dallman PR, Yip R, Johnson C. Prevalence and causes of anemia in the United States, 1976 to 1980. *Am J Clin Nutr.* 1984;39:437-45.

2. Goodnough LT, Dubois RW, Nissenson AR. Anemia: not just an innocent bystander? *Arch Intern Med.* 2003;163:1400-04.

3. Adams PF, Hendershot GE, Marano MA. Current estimates from the National Health Interview Survey, 1996. *Vital Health Stat 10.* 1999:1-203.

4. Guralnik JM, Eisenstaedt RS, Ferrucci L, Klein HG, Woodman RC. Prevalence of anemia in persons 65 years and older in the United States: evidence for a high rate of unexplained anemia. *Blood.* 2004;104:2263-68.

5. Goodnough LT, Dubois RW, Nissenson AR. Anemia: not just an innocent bystander? [correction]. *Arch Intern Med.* 2003;163:1820.

6. Kausz AT, Steinberg EP, Nissenson AR, Pereira BJG. Prevalence and management of anemia among patients with chronic kidney disease in a health maintenance organization. *Dis Manag Health Outcomes.* 2002;10:505-13.

7. Baer AN, Dessypris EN, Krantz SB. The pathogenesis of anemia in rheumatoid arthritis: a clinical and laboratory analysis. *Semin Arthritis Rheum.* 1990; 19:209-23.

8. Knight K, Wade S, Balducci L. Prevalence and outcomes of anemia in cancer: a systematic review of the literature. *Am J Med.* 2004;116(suppl 7A):11S-26S.

9. Belperio PS, Rhew DC. Prevalence and outcomes of anemia in individuals with human immunodeficiency virus: a systematic review of the literature. *Am J Med.* 2004;116(suppl 7A):27S-43S.

10. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. *Am J Med.* 2004;116(suppl 7A):44S-49S.

11. Wilson A, Yu HT, Goodnough LT, Nissenson AR. Prevalence and outcomes of anemia in rheumatoid arthritis: a systematic review of the literature. *Am J Med.* 2004;116(suppl 7A):50S-57S.

12. Weiss G, Goodnough LT. Anemia of chronic disease. *N Engl J Med.* 2005; 352:1011-23.

13. Collins AJ, Li S, Ebben J, Ma JZ, Manning W. Hematocrit levels and associated Medicare expenditures. *Am J Kidney Dis.* 2000;36:282-93.

14. Berndt E, Crown W, Kallich J, et al. The impact of anaemia and its treatment on employee disability and medical costs. *Pharmacoeconomics.* 2005; 23:183-92.

15. Lyman GH, Berndt ER, Kallich JD, et al. The economic burden of anemia in cancer patients receiving chemotherapy. *Value Health.* 2005;8:149-56.

16. Nordyke RJ, Kim JJ, Goldberg GA, et al. Impact of anemia on hospitalization time, charges, and mortality in patients with heart failure. *Value Health.* 2004;7:464-71.

17. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol.* 1992;45:613-19.

18. NKF-DOQI clinical practice guidelines for the treatment of anemia of chronic renal failure. National Kidney Foundation-Dialysis Outcomes Quality Initiative. *Am J Kidney Dis.* 1997;30:S192-S240.

19. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst.* 1999;91:1616-34.

20. Nissenson AR, Collins AJ, Hurley J, et al. Opportunities for improving the care of patients with chronic renal insufficiency: current practice patterns. *J Am Soc Nephrol.* 2001;12:1713-20.

21. American Association of Blood Banks, America's Blood Centers, and the American Red Cross. Circular of information for the use of human blood and blood components. Available at: http://www.aabb.org/All_About_Blood/COI/coi0702.pdf. Accessed June 15, 2005.