Published in final edited form as:

Leuk Lymphoma. 2014 May ; 55(5): 1119–1125. doi:10.3109/10428194.2013.820286.

Health care utilization and risk of infection and bleeding among patients with myelodysplastic syndromes with/without transfusions, and with/without active therapy

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Abstract

This study utilized claims data from a national US commercial health insurer to examine rates of cytopenia-related complications (significant bleeding, infection) and health care utilization (emergency room visits, inpatient hospitalizations) among patients with myelodysplastic syndromes (MDS) within predefined periods of transfusion activity and active therapy. Periods with no transfusions, regardless of relationship to treatment intervention, were associated with lower rates of cytopenia-related complications. These data suggest that eliminating or reducing the need for transfusions may help to reduce MDS-related medical problems, and treatment toward that goal should be considered in patients with MDS needing transfusions.

Keywords

MDS; myelodysplastic syndromes; transfusion; outcomes; cytopenia; utilization

Introduction

Myelodysplastic syndromes (MDS) are a group of heterogeneous, clonal hematopoietic disorders characterized by morphologic dysplasia, aberrant hematopoiesis and a variable risk of progression to acute myeloid leukemia (AML). Clinical symptoms include fatigue from anemia and systemic cytokine production, recurrent infections from neutropenia and dysfunctional neutrophils, as well as bleeding and bruising from thrombocytopenia and/or dysfunctional platelets [1]. Patients with MDS commonly require chronic red blood cell (RBC) transfusions which can lead to iron overload resulting in eventual damage to the liver, heart and pancreas, and there is an increased risk of cardiac events for transfused patients when compared with non-transfused patients [2]. A 2007 Surveillance,

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Potential conflict of interest: Disclosure forms provided by the authors are available with the full text of this article at www.informahealthcare.com/lal.

Epidemiology and End Results (SEER) report [3] estimated that over 10 000 new cases of MDS were diagnosed in the USA between 2001 and 2003, but other studies have reported higher incidence estimates based on Medicare claims [4,5].

Traditionally, treatment options for MDS have depended on disease classification, prognostic stage, and the age and health status of the patient. The International Prognostic Scoring System (IPSS) for MDS assesses risk of AML evolution and overall survival, based on significant predictors that include percent of marrow blasts, number of peripheral blood cytopenias and cytogenetic subgroups [6]. Treatment for MDS based on IPSS risk groups can be generally described as directed at improving hematologic status for patients in the lower-risk groups versus altering the natural history of the disease for the higher-risk groups, which includes hematopoietic stem cell transplant (SCT). However, approaches such as SCT are often not feasible among older patients with MDS, and determining the best treatment option for these patients depends on several factors, including age and comorbidities.

Goldberg and colleagues [7] retrospectively studied Medicare claims and found that patients with MDS who received transfusions over a 3-year period (2002–2005) experienced more infectious complications and higher resource utilization when compared to patients with MDS who did not receive transfusions during the same period of time. However, Goldberg did not examine whether patients were also receiving active therapy for MDS. Many patients with MDS may not receive medical treatment for many different reasons, despite the availability of three Food and Drug Administration (FDA) approved drugs for the treatment of MDS: lenalidomide, azacitidine and decitabine. Lenalidomide is approved in the USA for the treatment of patients with transfusion-dependent anemia due to low- or intermediate-1-risk MDS associated with a deletion 5q cytogenetic abnormality, with or without additional cytogenetic abnormalities. Fenaux *et al.* [8] reported that 56.1% of patients with MDS receiving lenalidomide 10 mg/day achieved transfusion independence for 26 weeks, compared with only 5.9% of patients with MDS receiving placebo. Similarly, studies of the hypomethylating agents azacitidine and decitabine have reported clinical benefits, including transfusion independence, in patients with higher-risk MDS when compared with best supportive care [9,10].

Using health care claims databases to better understand the interplay between baseline disease activity, ongoing transfusion requirements, the various medical interventions available and cytopenia-related medical events may help to improve treatment approaches for patients with MDS. However, such databases typically do not allow for the accurate use of the available prognostic scoring systems, due to lack of clinical details of the MDS diagnosis. The objective of this study was to examine existing claims data to better discern how the occurrence of common cytopenia-related complications (i.e. clinically significant bleeding [gastrointestinal (GI) and intracranial] and infections), as well as health care utilization (i.e. emergency room [ER] visits and hospitalizations), relates to “MDS activity,” which was determined by developing predefined periods of transfusion activity with or without active therapy. The ultimate goal was to better understand the potential clinical benefit of active therapy with lenalidomide, 5-azacitidine or decitabine for patients with MDS not otherwise able to be classified using standard models.

Materials and methods

Data sources

Our retrospective claims database study utilized data from the Optum Research Database, which includes medical claims, pharmacy claims and eligibility information from a large national US health plan that offers both commercial and Medicare Advantage insurance to approximately 14 million commercial and 500 000 Medicare Advantage enrollees per year. The individuals covered by this health plan have both medical and pharmacy benefits, and they are geographically diverse across the USA, with the greatest representation in the South and Midwest US census regions. Medical (professional, facility) claims included International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) diagnosis codes, ICD-9 procedure codes, *Current Procedural Terminology, Version 4* (CPT-4) procedure codes, *Healthcare Common Procedure Coding System* (HCPCS) procedure codes and site of service codes. Outpatient pharmacy claims provided National Drug Codes (NDCs) for dispensed medications, quantity dispensed, drug strength and number of days of supply (days supply).

All study data were accessed using techniques compliant with the Health Insurance Portability and Accountability Act of 1996 [11], and no identifiable protected health information was extracted during the course of the study. Because this study involved analysis of pre-existing, de-identified data, it was exempt from Institutional Review Board approval.

Study subject identification

Patients were considered for inclusion if they had at least one medical claim with a MDS diagnosis (ICD-9-CM diagnosis codes 238.72-238.75) between 1 January 2007 and 31 December 2009. The index date was defined as the service date from the first medical claim with an MDS diagnosis during this period. Claims indicating diagnostic procedures from laboratory or diagnostic testing centers, or claims with codes for testing, were not considered for identifying patients with MDS, as these claims often indicate “rule out” testing before a definitive diagnosis can be made. Patients were also required to be at least 18 years old and be continuously enrolled in a commercial or Medicare Advantage plan with a medical and pharmacy benefit for 6 months before the index date (baseline period) and for a variable period of at least 30 days’ duration following the index date (follow-up period). The end of follow-up was determined by the earliest date of death, disenrollment from the health plan or the end of the study period on 30 June 2010.

Observed treatment periods

Each patient’s follow-up was examined and categorized into treatment periods, based on whether or not there was evidence that the individual was receiving active medical therapy for MDS and whether or not the individual was receiving RBC transfusion support. A treatment period with active medical therapy began on the earliest date of a medical or pharmacy claim for lenalidomide, decitabine or 5-azacitabine. Each active treatment period included only one active therapy agent and may or may not have included use of erythropoietic-stimulating agents (ESAs). Such treatment periods ended at the earliest of: (1)

a gap greater than 30 days after the last treatment with lenalidomide, decitabine or 5-azacitabine (where a 30-day gap for pharmacy prescription fills means 30 days after the run-out date), (2) the date prior to a switch in active therapy agent or (3) death, disenrollment or end of the study. Death data were obtained from Social Security Administration tapes.

Treatment periods were also categorized based on whether or not patients received RBC transfusions. “Watch and wait” periods were defined where there was no evidence of active therapy, transfusions and no ESA use. These “watch and wait” periods began on the index date, and ended on the date prior to receipt of treatment, death, disenrollment or end of the study period. Thus, for the purpose of analysis, patient follow-up was divided into four unique observed treatment periods: (1) “watch and wait” periods of no active therapy and no transfusion needs and no ESAs; (2) active therapy ($\pm$ ESAs) with no transfusion needs; (3) active therapy ($\pm$ ESAs) with transfusion needs; and (4) no active therapy, no ESAs, but with transfusion needs. All treatment periods were required to be at least 8 weeks long, based on the recommended timeframe for assessing partial or complete remission in the International Working Group (IWG) criteria for MDS [12]. Active therapy included a combination of hypomethylating agents, as well as lenalidomide. Observed treatment periods with transfusion needs (period types 3 and 4) were a combination of periods with at least two RBC transfusion sessions on separate days during an 8-week period in addition to periods where transfusions occurred less frequently than every 8 weeks. Transfusions could have occurred in an inpatient or an outpatient setting. The two types of transfusion periods were aggregated into treatment periods 3 or 4 based on receipt of active therapy, and it was possible for patients to contribute more than once to either period 3 or 4 based on transfusion frequency. Also, although the four observation treatment periods were mutually exclusive, each patient could have contributed to more than one of the four observed treatment periods provided their active therapy or transfusion needs changed during the follow-up.

Study measures

Patient characteristics—Patient demographics were examined as of the index date and included: age, gender, geographic region in the USA (Northeast, Midwest, South, West) and insurance type. The baseline Charlson comorbidity index (CCI) [13] was captured for each patient and calculated based on the presence of diagnosis codes on medical claims during the 6-month period prior to the index date (date of the first claim with a diagnosis code of MDS). The CCI is commonly used in administrative claims data to assess case-mix or disease burden. In addition, patients with evidence of MDS during the 6-month baseline period prior to the index date were identified. Evidence of MDS included at least one claim with a diagnosis of MDS, at least one claim indicating receipt of active therapy or at least one claim indicating receipt of RBC transfusion.

Outcomes—The outcomes that were examined in the follow-up include health care resource utilization and clinical events. Health care resource utilization was focused on ER visits and inpatient hospitalizations and was defined as all ER visits and inpatient admissions with an MDS diagnosis. The clinical events that were examined in each of the follow-up treatment cohort periods included cytopenia-related complications such as infections and

significant bleeding events (GI, intracranial, hospitalized bleeding, bleeding deaths). See the Appendix for the codes used to identify infections and significant bleeding.

Statistical methods

Descriptive statistics (n [%]) were calculated for each of the follow-up treatment periods. Because the treatment periods varied with respect to length of follow-up, person-year incidence rates (IRs) are presented for each of the outcomes examined in order to better estimate the actual time-at-risk that all persons contributed to the study. The person-year IR is the estimated risk of an event occurring, and is calculated as the number of new persons who experience the event divided by the observed time at risk. Thus, the number of patients who experience the event are included in the numerator while the time at risk for experiencing the event is the denominator; patients who experience the event contribute time up until the event occurs, while patients who do not experience the event contribute the entire time observed during the period. Incidence rates were calculated using Stata's `stptime` (Stata1 version 9.2; StataCorp LP, Collegeville, TX). All event risks within each period are presented as "incidence per person-year."

Results

Demographic and clinical characteristics

A total of 4351 patients with MDS were represented in 4711 total follow-up periods. Figure 1 displays the MDS sample selection and treatment period assignment. The baseline patient demographics including age, gender, geographic region and insurance type for unique patients are shown in Table I. The mean age of the overall sample was 67.8 years (standard deviation [SD] = 14.8 years) and 52% were male. A larger portion of patients (44%) resided in the Southern region of the USA, and over two-thirds of patients (67%) were commercially insured. Approximately 25% of the study population had evidence of MDS during the 6-month baseline period prior to the index date.

Outcomes

Descriptive statistics for transfusion activity, clinical events, inpatient hospitalizations and ER visits in the follow-up are presented stratified by transfusion activity (Table II) and then stratified by transfusion activity and active therapy (Table III). Both tables capture the event risk calculated as incidence per person-year (IR). Because of the limited sample sizes for patients receiving active therapy, we did not further stratify by ESA use. Consequently, periods with active therapy may or may not have included ESAs. Also, although patients did not receive whole/RBC transfusions during transfusion-free periods, a small percentage of patients did receive platelet transfusions (2–4%). Furthermore, 6% of the transfusion-free periods included the use of ESAs, and 7% included the use of granulocyte-colony stimulating factor/granulocyte macrophage-colony stimulating factor (G-CSF/GM-CSF). When stratified by transfusion activity and therapy (Table III), the use of ESAs was only associated with periods of active therapy, whereas the use of G-CSF/GM-CSF was associated with all four periods, although much less so (< 10%) with periods of no active therapy.

When compared to periods requiring RBC transfusion support, transfusion-free periods (Table II) were associated with a lower risk of infection (IR: 0.61, 95% confidence interval [CI]: 0.59–0.64 vs. IR: 1.57, 95% CI: 1.47–1.68; no transfusions vs. transfusions, respectively) and a lower risk of significant bleeding events (IR: 0.23, 95% CI: 0.21–0.24 vs. IR: 0.64, 95% CI: 0.59–0.70; no transfusions vs. transfusions, respectively). Similarly, when compared to periods with transfusions, periods with no transfusions were associated with a lower risk of hospitalization (IR: 0.37, 95% CI: 0.35–0.39 vs. IR: 1.91, 95% CI: 1.79–2.04; no transfusions vs. transfusions, respectively) and ER visits (IR: 0.51, 95% CI: 0.49–0.54 vs. IR: 1.59, 95% CI: 1.49–1.70; no transfusions vs. transfusions, respectively). Not surprisingly, patient groups in the transfusion-dependent periods also had higher baseline CCI scores (2.42 vs. 2.19, $p < 0.01$) and a higher percentage of platelet transfusions (29% vs. 2%, $p < 0.01$) (Table II), when compared with the periods without transfusions.

The association between transfusion-free periods and a lower risk of infections and significant bleeding remained when further stratifying by active therapy (Table III). As expected, the “watch and wait” periods, where patients were not receiving active therapy or RBC transfusion support, were associated with the lowest risk of infection (IR: 0.59, 95% CI: 0.56–0.62) and significant bleeding events (IR: 0.22, 95% CI: 0.20–0.24) compared with any other treatment period. The periods with active therapy and no transfusions were associated with the next lowest risk of infection (IR: 0.93, 95% CI: 0.79–1.09) and significant bleeding events (IR: 0.34, 95% CI: 0.26–0.43) and compared favorably with periods where patients were receiving transfusions with or without active therapy. The risk of infection and significant bleeding events for the two periods with transfusions were similar to each other (IR: 1.71, 95% CI: 1.45–2.00 and IR: 0.63, 95% CI: 0.49–0.79 vs. IR: 1.54, 95% CI: 1.43–1.66 and IR: 0.64, 95% CI: 0.58–0.70; infection and significant bleeding events for transfusion period cohorts with and without active therapy, respectively), suggesting that the potential toxicities associated with active therapy may not have increased the likelihood of experiencing cytopenia-related medical problems or increased the need for health care utilization. As expected, the group in “watch and wait” had the lowest CCI scores, possibly reflecting a low level of MDS activity.

The periods with transfusions were also associated with a higher risk of hospitalization and ER visits when compared with the periods without transfusions. Again, the “watch and wait” period was associated with the lowest risk of hospitalization and ER visits (IR: 0.35, 95% CI: 0.33–0.37 and IR: 0.47, 95% CI: 0.47–0.52, respectively) followed by the periods with active therapy and no transfusions (IR: 0.63, 95% CI: 0.52–0.76 and IR: 0.86, 95% CI: 0.73–1.01, hospitalization and ER visits, respectively). When looking at the two observation periods for patients who had evidence of RBC transfusions, periods of active therapy and transfusion support were associated with the highest risk of hospitalization and ER visits, and may have represented patients with the most severe disease as evidenced by twice as many transfusions per month occurring in this period (Table III). Still, there were an unexpectedly high number of periods with transfusions where patients were not receiving any therapy (886 periods from 886 patients), despite evidence that medical therapies commonly result in patients becoming transfusion-free [7].

Discussion

Understanding the impact of medical intervention for diseases such as MDS with highly variable clinical courses and outcomes can be a significant challenge. This retrospective analysis helps to align the impact of the highly variable clinical courses of MDS and medical interventions by defining periods of disease activity and studying the patterns of health care utilization and outcomes for patients in those periods.

Like Goldberg *et al.* [7], we found that transfused patients with MDS had significantly more hospitalizations and ER visits and experienced a higher percentage of infectious complications when compared with non-transfused patients with MDS. However, we further examined the potential impact of active therapy, and also found differences in utilization and infectious complications based on receipt of active therapy. Further stratifying periods based on receipt of active therapy showed that periods without transfusions and with active therapy were associated with a lower risk of infection and significant bleeding events compared with either of the treatment periods with transfusions, and may allay concerns that therapy-related toxicities would negatively impact these treatment-defined periods. Moreover, these results suggest that active therapy may help to lower supportive care requirements, and may also help to reduce disease-specific resource utilization by lowering the risk of MDS-related adverse clinical events. Interestingly, recent data suggest that active therapy, and not supportive care [14,15], may in fact alter the natural history of these bone marrow failure malignancies [8,16,17]. It appears that both transfusion needs and active therapy may contribute to the utilization of disease-specific medical resources by this group of patients.

The highest risk of ER visits and hospitalization occurred during periods of active therapy with ongoing transfusion needs and while these outcomes were not significantly higher than those among periods with transfusions and no active therapy, the contribution of active therapy to these events remained unclear. It is possible that these periods capture those patients with the most severe disease activity and/or disease that is poorly responsive to medical therapy, although the medical claims data do not include the specific clinical data necessary to confirm this possibility. However, receipt of active therapy during periods without transfusions was associated with a lower risk of infection, significant bleeding, ER visits and hospitalization, when compared to periods with transfusions, suggesting that active therapy may be associated with a reduced need of transfusions which may be associated with better outcomes for some patients.

It is important to highlight that the baseline CCI was highest among patients who contributed to periods with receipt of transfusions and no active therapy – periods in which the activity of MDS would be expected to be the greatest. It may be possible that this group of patients were generally sicker, with comorbidities that limited doctors' initiation of active therapy. However, a medical chart review would be needed to confirm this possibility, as medical claims do not include information about treatment decisions. Noting that periods with no transfusions and active therapy were associated with a much lower risk of infection when compared with either of the transfusion periods, the decision to offer treatment must be weighed carefully against the patient's general medical condition, as treatment may ultimately lower the medical problems associated with the patient's MDS.

In addition to the lack of specific clinical information (i.e. ability to determine IPSS for individual patients), there are important limitations that are associated with retrospective studies, the first of which is that claims data are collected for the purposes of payment and not research. Such studies are also limited to the degree to which claims data can accurately capture an individual's medical history. The presence of a diagnosis code on a medical claim is not a perfect predictor of the presence of disease, as the diagnosis code may be incorrectly coded, or not recorded at all. The retrospective nature of claims analyses does not allow the assignment of a causal direction to any of the relationships found in this study. These data are from a managed care population, and the results are primarily applicable to patients with MDS in managed care settings and may not be applicable to patients who were uninsured or receiving Medicaid. An extension of this limitation is the finding that the claims database used in this study primarily reflects a commercially insured population rather than Medicare Advantage enrollees, and the mean age of our patients (67.77 years) is younger than that found in other studies (77 years) that used only Medicare claims [4,5,10]. It may be possible that our patients with MDS were healthier than those found in other studies of older patients with MDS. Also, we did not explicitly consider ESA use in this study because of limited sample size among the periods with active therapy, and it would be useful to examine ESA utilization in future analyses. Finally, the number of patients who contributed to multiple study periods was low (a total of 4351 patients contributed to the 4711 periods identified), and therefore limited the ability to assess outcomes and medical resource utilization in patients moving between the predefined groupings, and did not permit for substantial observation of patients in multiple stages.

Conclusions

Transfusion dependence remains a significant problem for patients with MDS. This database analysis used clinically predefined periods to attempt to define the activity level of the MDS and better understand the burden of transfusions. The clinically predefined follow-up periods tracked well with the expected biology of MDS, with follow-up periods with transfusions being associated with higher numbers of medical events compared with periods without transfusions. This benefit was seen in periods without transfusions on active therapy, as well as in the “watch and wait” periods without transfusions or active therapy, suggesting that active therapy was not associated with worse outcomes and may be associated with reduced supportive care requirements, resource utilization, and risk of MDS-related medical events. It was noted that there were an unexpectedly large number of patients who were receiving transfusions and not receiving active therapy, suggesting that there may be potential cohorts of MDS patients who could benefit from medical intervention.

Appendix

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Figure 1. MDS sample selection and treatment period assignment. Abbreviations: AT = active therapy; Trans = transfusion.

Table I

Baseline patient demographics.

Demographics	Total unique patients who contributed to periods (<i>n</i> = 4351)	
	Mean	SD
Age (continuous)	67.77	14.84
Gender	<i>n</i>	%
Male	2244	51.57
Female	2107	48.43
US region		
Northeast	558	12.82
Midwest	1292	29.69
South	1903	43.74
West	598	13.74
Insurance type		
Commercially insured	2922	67.16
Medicare Advantage	1429	32.84
Baseline evidence of MDS	1106	25.42

SD, standard deviation; MDS, myelodysplastic syndromes.

Table II

Study outcomes stratified by transfusion activity.

	Periods of transfusions*	
	No transfusions (<i>n</i> = 3515)	Transfusions (<i>n</i> = 1196)
Number of unique patients	3515	1105
Mean (SD) Charlson comorbidity index score [†]	2.04 (2.19)	2.72 (2.42)
Mean duration, days (SD)	465 (352)	356 (323)
Mean (SD) number of whole/RBC transfusions	0 (0)	0.53 (0.64)
Number (%) of patients with platelet transfusions	77 (2)	349 (29)
Number (%) of periods with ESA [‡]	215 (6)	156 (13)
Number (%) of periods with G-CSF/GM-CSF [‡]	255 (7)	218 (18)
Events	<i>n</i> (%)	<i>n</i> (%)
Infection	1715 (49)	829 (69)
Significant bleeding	838 (24)	500 (42)
Inpatient hospitalization	1234 (35)	919 (77)
ER visit	1538 (44)	840 (70)
	Incidence per person-year (95% CI)	
Infection	0.61 (0.59–0.64)	1.57 (1.47–1.68)
Significant bleeding	0.23 (0.21–0.24)	0.64 (0.59–0.70)
Inpatient hospitalization	0.37 (0.35–0.39)	1.91 (1.79–2.04)
ER visit	0.51 (0.49–0.54)	1.59 (1.49–1.70)

SD, standard deviation; RBC, red blood cell; ESA, erythropoietic-stimulating agent; G-CSF/GM-CSF, granulocyte-colony stimulating factor/granulocyte macrophage-colony stimulating factor; ER, emergency room; CI, confidence interval.

* Periods of therapy may or may not have included ESAs.

[†] Reflects baseline Charlson comorbidity index score.

[‡] $p < 0.05$.

Table III

Study outcomes stratified by transfusion activity and therapy.

	Periods of active therapy and transfusions*			
	"Watch and wait," no AT/no trans (n = 3028)	AT/no trans (n = 487)	AT/trans (n = 310)	No AT/trans (n = 886)
Number of unique patients	3028	337	253	886
Mean (SD) Charlson comorbidity index score [†]	2.00 (2.17)	2.28 (2.26)	2.33 (2.23)	2.86 (2.47)
Mean duration, days (SD)	516 (350)	153 (130)	431 (340)	143 (105)
Mean (SD) number of whole/RBC transfusions	0	0	0.88 (0.79)	0.40 (0.52)
Number (%) of patients with platelet transfusions	57 (2)	20 (4)	130 (42)	219 (25)
Number (%) of periods with ESA [‡]	0	215 (44)	156 (50)	0
Number (%) of periods with G-CSF/GM-CSF [‡]	115 (4)	140 (29)	128 (41)	90 (10)
Events	n (%)	n (%)	n (%)	n (%)
Infection	1561 (52)	154 (32)	149 (48)	680 (77)
Significant bleeding	775 (26)	63 (13)	68 (22)	432 (49)
Inpatient hospitalization	1120 (37)	114 (23)	180 (58)	739 (83)
ER visit	1398 (46)	140 (29)	164 (53)	676 (76)
	Incidence per person-year (95% CI)			
Infection	0.59 (0.56–0.62)	0.93 (0.79–1.09)	1.71 (1.45–2.00)	1.54 (1.43–1.66)
Significant bleeding	0.22 (0.20–0.24)	0.34 (0.26–0.43)	0.63 (0.49–0.79)	0.64 (0.58–0.70)
Inpatient hospitalization	0.35 (0.33–0.37)	0.63 (0.52–0.76)	2.25 (1.94–2.60)	1.84 (1.71–1.98)
ER visit	0.47 (0.47–0.52)	0.86 (0.73–1.01)	2.01 (1.73–2.35)	1.51 (1.40–1.63)

SD, standard deviation; RBC, red blood cell; ESA, erythropoietic-stimulating agent; G-CSF/GM-CSF, granulocyte-colony stimulating factor/granulocyte macrophage-colony stimulating factor; ER, emergency room; AT, active therapy; trans, transfusion; CI, confidence interval.

* Periods of therapy may or may not have included ESAs.

[†] Reflects baseline Charlson comorbidity index score and global $p < 0.01$.

[‡] $p < 0.05$.

Appendix

Event type	Code
Bleeding death	ICD-9 diagnosis codes: 798.1, 798.2, 798.9
Intracranial bleed	ICD-9 diagnosis codes: 430, 431, 432.0, 432.1, 432.9
GI bleed	ICD-9 diagnosis codes: 456.0, 456.20, 530.21, 530.7, 530.82, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.60, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 535.71, 537.83, 537.84, 562.02, 562.03, 562.12, 562.13, 569.3, 569.85, 569.86, 578.0, 578.1, 578.9, 784.8; CPT codes: 43227, 43255, 43501, 44366, 44378, 44391, 45317, 45334, 45382, 46614 ICD-9 procedure codes: 44.43, 44.44, 44.49
Hospitalized bleed	ICD-9 diagnosis codes: 246.3, 363.72, 364.41, 372.72, 374.81, 376.32, 377.42, 423.0, 430, 431, 432.0, 432.1, 432.9, 456.0, 456.20, 459.0, 530.82, 531.00, 531.01, 531.20, 531.21, 531.40, 531.41, 531.60, 531.61, 532.00, 532.01, 532.20, 532.21, 532.40, 532.41, 532.61, 533.00, 533.01, 533.20, 533.21, 533.40, 533.41, 533.60, 533.61, 534.00, 534.01, 534.20, 534.21, 534.40, 534.41, 534.60, 534.61, 535.01, 535.11, 535.21, 535.31, 535.41, 535.51, 535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, 578.9, 596.7, 599.7, 602.1, 620.1, 719.10, 719.11, 719.12, 719.13, 719.14, 719.15, 719.16, 719.17, 719.18, 719.19, 782.7, 784.7, 784.8, 786.3, 360.43, 362.43, 362.81, 363.61, 363.62, 379.23
Infections	ICD-9 diagnosis codes: Sepsis: 003.1, 020.2, 022.3, 036.2, 038.0, 038.10, 038.11, 038.12, 038.19, 038.2, 038.3, 038.40, 038.41, 038.42, 038.43, 038.44, 038.49, 038.8, 038.9, 054.5, 670.20, 670.22, 670.24, 670.30, 670.32, 670.34, 995.91, 995.92; Bacteremia: 790.7; Cellulitis: 035, 040.0, 376.01, 380.10, 380.11, 380.12, 380.13, 380.14, 380.15, 380.16, 478.21, 478.71, 528.3, 607.1, 614.3, 614.4, 681.00, 681.01, 681.02, 681.10, 681.11, 681.9, 682.0, 682.1, 682.2, 682.3, 682.4, 682.5, 682.6, 682.7, 682.8, 682.9; Pneumonia: 003.22, 011.60, 011.61, 011.62, 011.63, 011.64, 011.65, 011.66, 020.3, 020.4, 020.5, 021.2, 022.1, 041.3, 052.1, 055.1, 055.1, 073.0, 073.0, 112.4, 114.0, 115.05, 115.15, 115.95, 130.4, 136.3, 480.0, 480.1, 480.2, 480.3, 480.8, 480.9, 481, 482.0, 482.1, 482.2, 482.30, 482.31, 482.32, 482.39, 482.40, 482.41, 482.42, 482.49, 482.81, 482.82, 482.83, 482.89, 482.9, 483.0, 483.1, 483.8, 484.1, 484.3, 484.5, 484.6, 484.7, 484.8, 485, 486, 487.0, 517.1, 997.31; Urinary tract/bladder infection: 098.19, 099.40, 099.41, 099.49, 590.00, 590.01, 590.10, 590.11, 590.2, 590.3, 590.80, 590.81, 590.9, 597.0, 597.80, 599.0, 601.3, 646.6, 646.60, 646.61, 646.62, 646.63, 646.64, 996.64; Cystitis: 032.84, 098.11, 098.31, 595.0, 595.1, 595.2, 595.4, 595.81, 595.89, 595.9, 601.3; Sinusitis: 461.0, 461.1, 461.2, 461.3, 461.8, 461.9, 473.0, 473.1, 473.2, 473.3, 473.8, 473.9; Meningitis: 003.21, 013.00, 013.01, 013.02, 013.03, 013.04, 013.05, 013.06, 036.0, 047.0, 047.1, 047.8, 047.9, 049.0, 049.1, 053.0, 054.72, 072.1, 090.42, 091.81, 094.2, 098.82, 100.81, 112.83, 114.2, 115.01, 115.11, 115.91, 320.0, 320.1, 320.2, 320.3, 320.7, 320.81, 320.82, 320.89, 320.9, 321.0, 321.1, 321.2, 321.3, 321.4, 321.8, 322.0, 322.1, 322.2, 322.9; Myocarditis: 032.82, 036.43, 074.23, 093.82, 130.3, 391.2, 398.0, 422.90, 422.91, 422.92, 422.99, 429.0; Colitis: 006.2, 009.0, 009.1, 540.0, 540.1, 540.9, 541, 542, 562.11, 562.13; Otitis media: 381.00, 381.01, 381.02, 381.03, 381.10, 381.19, 381.20, 381.29, 381.3, 381.4, 382.00, 382.01, 382.02, 382.1, 382.2, 382.3, 382.4, 382.9; Enteritis: 003.0, 008.5, 008.61, 008.62, 008.63, 008.64, 008.65, 008.66, 008.67, 008.69; Malaria: 084.0, 084.1, 084.2, 084.3, 084.4, 084.5, 084.6, 084.7, 084.9, 647.40, 647.41, 647.42, 647.43, 647.44, 961.4, E931.4; Fungemia: 117.9; Thrombophlebitis: 325, 451.0, 451.11, 451.19, 451.2, 451.81, 451.82, 451.83, 451.84, 451.89, 451.9, 453.1, 670.30, 670.32, 670.34, 671.20, 671.21, 671.22, 671.23, 671.24; Influenza: 038.41, 041.5, 482.2, 487.0, 487.1, 487.8, 488.0, 488.1; Parainfluenza: 480.2; HIV: 042, 079.53, V08; West Nile virus: 066.40, 066.41, 066.42, 066.49;