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Impact of Medicare Reimbursement Policy Change on the Utilization, Risks, and Costs Associated with Erythropoiesis-Stimulating Agents in Cancer Patients with Chemotherapy-Induced Anemia

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IMPACT OF MEDICARE REIMBURSEMENT POLICY CHANGE ON THE UTILIZATION, RISKS, AND COSTS ASSOCIATED WITH ERYTHROPOIESIS-STIMULATING AGENTS IN CANCER PATIENTS WITH CHEMOTHERAPY-INDUCED ANEMIA

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ABSTRACT

Background: Erythropoiesis-stimulating agents (ESAs) are biological drugs used to stimulate the production of red blood cells. ESAs are commonly prescribed for cancer patients with chemotherapy-induced anemia and chronic kidney disease (CKD) patients with low levels of hemoglobin. Due to the increasing safety concerns, Centers for Medicare and Medicaid Services (CMS) issued a Medicare reimbursement policy change for ESAs in cancer patients to regulate the utilization of ESAs. For chemotherapy-induced anemia, when patients had solid tumors, multiple myeloma, lymphoma, or lymphocytic leukemia, ESA treatment is reimbursable by CMS only when the hemoglobin level is < 10g/dL.

Objectives: The objectives of this study were to (1) examine the utilization of ESAs and blood transfusions in cancer patients with chemotherapy-induced anemia before and after the implementation of Medicare reimbursement policy; (2) examine the impact of Medicare reimbursement policy change on the risks of myocardial infarction (MI), stroke, and venous thromboembolism (VTE) in incident users of ESAs with chemotherapy-induced anemia; and (3) examine the impact of Medicare reimbursement policy change on anemia-related and total medical costs in incident users of ESAs with chemotherapy-induced anemia.

Methods: This study used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. A repeated cross-sectional design was used in Aim 1 and a retrospective incident user cohort design was used in Aim 2 and 3. The treatment

group of the study was composed of Medicare beneficiaries with cancer and the control group of the study was composed of Medicare beneficiaries with CKD. In Aim 1, an interrupted time series design with a control group was used to examine the impact of Medicare reimbursement policy change on the utilization of ESAs and blood transfusions. In Aim 2, a logistic regression model was used to examine the impact of Medicare reimbursement policy change on the risks of MI, stroke, and VTE associated with ESAs. In Aim 3, a difference-in-difference design was used to examine the impact of Medicare reimbursement policy change on anemia-related and total medical costs associated with ESAs.

Results: After the implementation of Medicare reimbursement policy, the level in the monthly utilization of ESAs was reduced by 2.13% ($P < .0001$) but the trend in the monthly utilization of ESAs remained stable ($P = .1366$). After the implementation of Medicare reimbursement policy, the level in the monthly utilization of blood transfusions was increased by 0.10% ($P = .0186$) but the trend in the monthly utilization of blood transfusions remained stable ($P = .0524$). In the adjusted logistic regression analysis, we found that the implementation of Medicare reimbursement policy was not associated with the future development of MI (OR: 1.01; 95% CI: 0.74-1.39), stroke (OR: 0.99; 95% CI: 0.84-1.15), and VTE (OR: 0.93; 95% CI: 0.84-1.03). In the adjusted generalized linear regression analysis, we found that the implementation of Medicare reimbursement policy was associated with a 11.20% ($P = .0113$) reduction in anemia-related costs (a 9.83% reduction in Medicare payment ($P = .0310$) and a 18.40% reduction in patient cost-sharing ($P < .0001$)), and a 11.96% ($P = .0001$) reduction in total medical costs (a 11.59%

reduction in Medicare payment (P = .0003) and a 13.58% reduction in patient cost-sharing (P < .0001)).

Conclusion: Medicare reimbursement policy had a one-time only effect on the utilization of ESAs and blood transfusions (a relative 50% reduction in the monthly utilization of ESAs and a relative 10% increase in the monthly utilization of blood transfusions). Medicare reimbursement policy change had no impact on the risks of MI, stroke, and VTE associated with ESAs in cancer patients with chemotherapy-induced anemia. Medicare reimbursement policy change had an impact on the anemia-related and total medical costs associated with ESAs in cancer patients with chemotherapy-induced anemia (a 10% reduction in either anemia-related or total medical costs).

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LIST OF ABBREVIATIONS

ABN ..... Advance Beneficiary Notice of Noncoverage

ASCO ..... American Society of Clinical Oncology

ASH ..... American Society of Hematology

CCI ..... Charlson Comorbidity Index

CI ..... Confidence Interval

CKD ..... Chronic Kidney Disease

CMS ..... Centers for Medicare and Medicaid Services

CPI ..... Consumer Price Index

CPT ..... Current Procedural Terminology

ESA ..... Erythropoiesis-Stimulating Agents

ESRD ..... End-Stage Renal Disease

FDA ..... Food and Drug Administration

GLM ..... Generalized Linear Model

HCPCS ..... Healthcare Common Procedure Coding System

HMO ..... Health Maintenance Organization

ICD-9-CM .. International Classification of Diseases, Ninth Edition, Clinical Modification

MI ..... Myocardial Infarction

NCA ..... National Coverage Analysis

NCD ..... National Coverage Determination

NCI ..... National Cancer Institute

ODAC ..... Oncologic Drug Advisory Committee

OR ..... Odds Ratio

RCT ..... Randomized Control Trial

REMS ..... Risk Evaluation and Mitigation Strategies

SD ..... Standard Deviation

SEER ..... Surveillance, Epidemiology, and End Results

VTE ..... Venous Thromboembolism

CHAPTER 1

INTRODUCTION

1.1 Chemotherapy-Induced Anemia

Among individuals aged 65 years and older, the number of new cancer cases was 1.0 million in 2010 and it is expected to increase to 1.6 million in 2030 in the United States.[1] The most recent available data showed that about 30% to 90% of patients with cancer also had anemia.[2] Anemia is a prevalent complication of myelosuppressive chemotherapy and is associated with reduced quality of life.[3] Myelosuppressive chemotherapy could impair hematopoiesis in the bone marrow and decrease production of erythropoietin in the renal.[4] The type of malignancy is associated with the incidence and severity of chemotherapy-induced anemia.[5] Patients with lung tumors, gynecologic tumors, genitourinary tumors, lymphomas, and colorectal tumors have a high incidence of chemotherapy-induced anemia.[3,4]

Anemia can be treated with transfusion of red blood cells or administration of erythropoiesis-stimulating agents (ESAs). Transfusion of red blood cells is a rapid approach to increase hemoglobin and hematocrit levels in patients with anemia. The safety of blood transfusions (e.g. immunosuppression and transfusion reactions), however, is a significant concern.[6-11] In addition, transfusion of red blood cells is inconvenient and time-consuming to patients.

1.2 Erythropoiesis-Stimulating Agents

ESAs are commonly prescribed for cancer patients with chemotherapy-induced anemia or chronic kidney disease (CKD) patients with low levels of hemoglobin. ESAs are biological drugs used to stimulate the production of red blood cells. Epoetin alfa and darbepoetin alfa are two commercially available ESAs in the U.S. market. Epoetin alfa and darbepoetin alfa were first approved by the Food and Drug Administration (FDA) in 1993 and 2002, respectively, for the treatment of anemia associated with cancer chemotherapy. ESAs are injections for intravenous or subcutaneous administration. Epoetin alfa is a short-acting ESA and is administered one to three times a week; darbepoetin alfa is a long-acting ESA and is administered once every one to three weeks.

Among Medicare beneficiaries with cancer who received chemotherapy, the annual utilization of ESAs increased substantially from 5% to 50% in the past two decades.[12] In 2004, ESAs were the highest-expenditure drug in the Medicare system.[13] For cancer patients, Medicare expenditures for ESAs increased five-fold from $321 million in 1999 to $1.51 billion in 2004.[14]

ESAs are efficacious in increasing hemoglobin and hematocrit levels and reducing or avoiding future requirements of blood transfusions in cancer patients with chemotherapy-induced anemia.[15-25] However, ESAs are found to be associated with increased risks of tumor progression or recurrence, mortality, thrombovascular events, and cardiovascular events in several clinical trials.[22,26-39]

1.3 Safety Concerns

Emerging findings from clinical trials led to FDA's arrangements of two Oncologic Drug Advisory Committee (ODAC) meetings in 2004 and 2007 to assess the safety and efficacy profile of ESAs.[40,41] The 2007 ODAC recommended to add more restrictions on ESA labels and conduct additional clinical trials to understand more about the benefits and risks associated with ESAs.

Based on clinical information, the FDA issued a black-box warning on March 9, 2007 about the increased risk of death, myocardial infarction (MI), stroke, venous thromboembolism (VTE), thrombosis of vascular access, and tumor progression or recurrence associated with epoetin alfa and darbepoetin alfa in patients with cancer or CKD.[42,43] In the labeling of both epoetin alfa and darbepoetin alfa, the initiation of ESAs in patients on cancer chemotherapy is appropriate only if the hemoglobin level is < 10 g/dL.[42,43] The labeling, however, does not specify at which hemoglobin level the ESA treatment should be suspended.[42,43]

To better use current evidence to guide clinical practice, the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) published clinical practice guidelines on the use of epoetin alfa and darbepoetin alfa in adult patients with cancer in 2002, 2007, and 2010.[44-46] The ASCO/ASH guidelines recommended that ESAs should be initiated in cancer patients with chemotherapy-induced anemia when the hemoglobin level has been decreased to < 10 g/dL. When the hemoglobin level is ≥ 10 g/dL but < 12 g/dL, whether ESAs should be initiated cannot be definitively determined. The ASCO/ASH guidelines did not require monitoring the hemoglobin level in the maintenance administration of ESAs.

1.4 Medicare Reimbursement Policy Change

Due to the increasing safety concerns, Centers for Medicare and Medicaid Services (CMS) conducted a National Coverage Analysis (NCA) for ESAs in non-renal disease indications on May 14, 2007.[47] Prior to the NCA, CMS did not have a national policy to regulate ESA use in non-renal disease indications. However, based on the results of the NCA, CMS proposed a national policy to regulate ESA use in non-renal disease indications.

After reviewing public comments to the NCA, CMS issued a National Coverage Determination (NCD) for ESAs in cancer and related neoplastic conditions on July 30, 2007.[48-52] Specifically, for chemotherapy-induced anemia, when patients had solid tumors, multiple myeloma, lymphoma, or lymphocytic leukemia, ESA treatment was reasonable and necessary only when the hemoglobin level was < 10g/dL or the hematocrit level was < 30%.[53] Table 1.1 summarized details of the NCD requirements on ESA use in chemotherapy-induced anemia. Except for the requirements in the hemoglobin for initiation and starting dose, NCD requirements were generally more rigid than recommendations in the FDA labelling and ASCO/ASH guidelines for ESAs.

After the implementation of the NCD, when ESAs were used to treat chemotherapy-induced anemia in patients with solid tumors, multiple myeloma, lymphoma, or lymphocytic leukemia, Medicare denied payment of services if the hemoglobin level was ≥ 10 g/dL or the hematocrit level was ≥ 30%.[53] For patients who were not qualified for reasonable and necessary use of ESAs, they could still have access to ESA treatment. However, they needed to sign an Advance Beneficiary Notice of

Noncoverage (ABN) to be 100% liable for payment of services not covered under Medicare.[54]

Medicare reimbursement policy change on ESAs was only effective in cancer and related neoplastic conditions. ESA use in renal disease indications was not regulated by this policy. CMS does not have any NCD to regulate ESA use for CKD.

The NCD became effective on July 30, 2007. By January 1, 2008, providers have been required to use a modifier code attached to the Healthcare Common Procedure Coding System (HCPCS) codes indicating the purpose of ESA treatment (EA: chemotherapy-induced anemia; EB: radiotherapy-induced anemia; and EC: non-chemotherapy/radiotherapy induced anemia).[53] Based on these modifier codes, Medicare denied claims for non-renal ESA services when ESA use was considered unreasonable or unnecessary on or after January 1, 2008. The full implementation of the NCD was on April 7, 2008. Since then, Medicare contractors have been required to review claims to ensure the implementation of the NCD. Medicare retracted payment for claims that were considered not meeting the NCD requirements on or after April 7, 2008.[53]

Table 1.1: NCD requirements on the ESA treatment in chemotherapy-induced anemia

	Epoetin alfa	Darbepoetin alfa
Types of cancer	Solid tumors, multiple myeloma, lymphoma, and lymphocytic leukemia	
Hemoglobin for initiation	Only if hemoglobin is < 10 g/dL (or hematocrit is < 30%)	
Hemoglobin for maintenance	Only if hemoglobin is < 10 g/dL (or hematocrit is < 30%)	
Starting dose	150 U/kg three times per week or 40,000 U weekly	2.25 mcg/kg every week or 500 mcg every three weeks
Maintenance dose	Maintain the starting dose if hemoglobin increases ≥ 1 g/dL (or hematocrit increases ≥ 3%) four weeks after initiation and hemoglobin remains < 10 g/dL (or hematocrit remains < 30%).	
Dose reduction	Reduce dose by 25% if hemoglobin increases > 1 g/dL (or hematocrit increases > 3%) in any two-week period and hemoglobin remains < 10 g/dL (or hematocrit remains < 30%).	
Dose withhold	Withhold dose if hemoglobin is ≥ 10 g/dL (or hematocrit is ≥ 30%).	
Dose reinitiate	Reinitiate at a dose 25% below the previous dose when hemoglobin remains < 10 g/dL (or hematocrit remains < 30%).	
Dose increase	Increase dose once by 25% if hemoglobin increases < 1 g/dL (or hematocrit increases < 3%) after four weeks and hemoglobin remains < 10 g/dL (or hematocrit remains < 30%).	
Discontinue	Discontinue if hemoglobin increases < 1 g/dL (or hematocrit increases < 3%) after eight weeks.	
Treatment duration	Eight weeks following the final dose of chemotherapy in a chemotherapy course.	

NCD: National Coverage Determination; ESAs: erythropoiesis-stimulating agents

CHAPTER 2

CONCEPTUAL FRAMEWORK

Many factors could impact ESA prescribing and/or dispensing practices and patients' health outcomes. Based on the conceptual framework by Lipton *et al.*, these factors could be categorized into internal and external factors.[55] (Figure 2.1) The Lipton conceptual framework has been widely used to examine the impact of different factors on drug prescribing and/or dispensing practices and patients' health outcomes.[56-72]

This study used the adapted Lipton conceptual framework to understand factors influencing the utilization, risks, and costs associated with ESAs. Patient and prescriber factors are two internal factors. Patient factors (e.g. demographics, socio-economics, and clinical characteristics) could impact ESA prescribing and/or dispensing practices. For example, income is one of patient factors when using ESAs. Compare to those with high level of income, patients with low level of income are less likely to use ESAs because they could not afford the high costs. Prescriber factors (e.g. employment setting, degree type, and previous experience) could impact ESA prescribing and/or dispensing practices. Previous experience is one of prescriber factors when prescribing ESAs. Prescribers with successful previous experience in treating chemotherapy-induced anemia with ESAs are more likely to continue to prescribe ESAs. External factors, system factors (e.g. reimbursement, drug policies, and practice organization), could also impact ESA prescribing and/or dispensing practices. For example, Medicare reimbursement policy

change on ESAs is one of system factors. Due to the policy change, ESA prescribing and/or dispensing practices will be influenced because unreasonable and unnecessary ESA use in cancer patients with chemotherapy-induced anemia will not be reimbursed by CMS. The change in ESA prescribing and/or dispensing practices could impact patients' health outcomes (e.g. ESA utilization, adverse events, and medical costs). For example, when unsafe ESA prescribing is reduced, the utilization, adverse events, and medical costs associated with ESAs may also be reduced.

The policy evaluated in this study was Medicare reimbursement policy change for ESAs in cancer patients. The adapted Lipton conceptual framework is useful in identifying other factors influencing the utilization, risks, and costs associated with ESAs. This conceptual framework could guide us in identifying potential confounding factors that could influence the association between the policy change and health outcomes. We should control them in the study.

Based on the conceptual framework, Medicare reimbursement policy change (an external factor) could impact ESA prescribing and/or dispensing practices. Thus, health outcomes (including utilization, risks, and costs) associated with ESAs could change after the implementation of Medicare reimbursement policy in cancer patients with chemotherapy-induced anemia. To make sure that the change in health outcomes was due to Medicare reimbursement policy only, we need to control for potential confounding factors (other internal and external factors influencing patients' health outcomes) in the study. Internal factors considered in the study include demographics, socio-economics, clinical characteristics, tumor characteristics, and treatment characteristics. External factors such as guideline revisions and black box warnings should also be considered.

For instance, the FDA's black box warning on ESAs (an external factor) will be controlled in the study by incorporating a control group, because it is the first time for the FDA to add a black box warning on the labels of ESAs.[42,43] On the other hand, recommendations in the 2007 ASCO/ASH guidelines (an external factor) are not greatly different from recommendations in the 2002 ASCO/ASH guidelines with respect to ESA use, this study will not control for this external factor.[44,45]

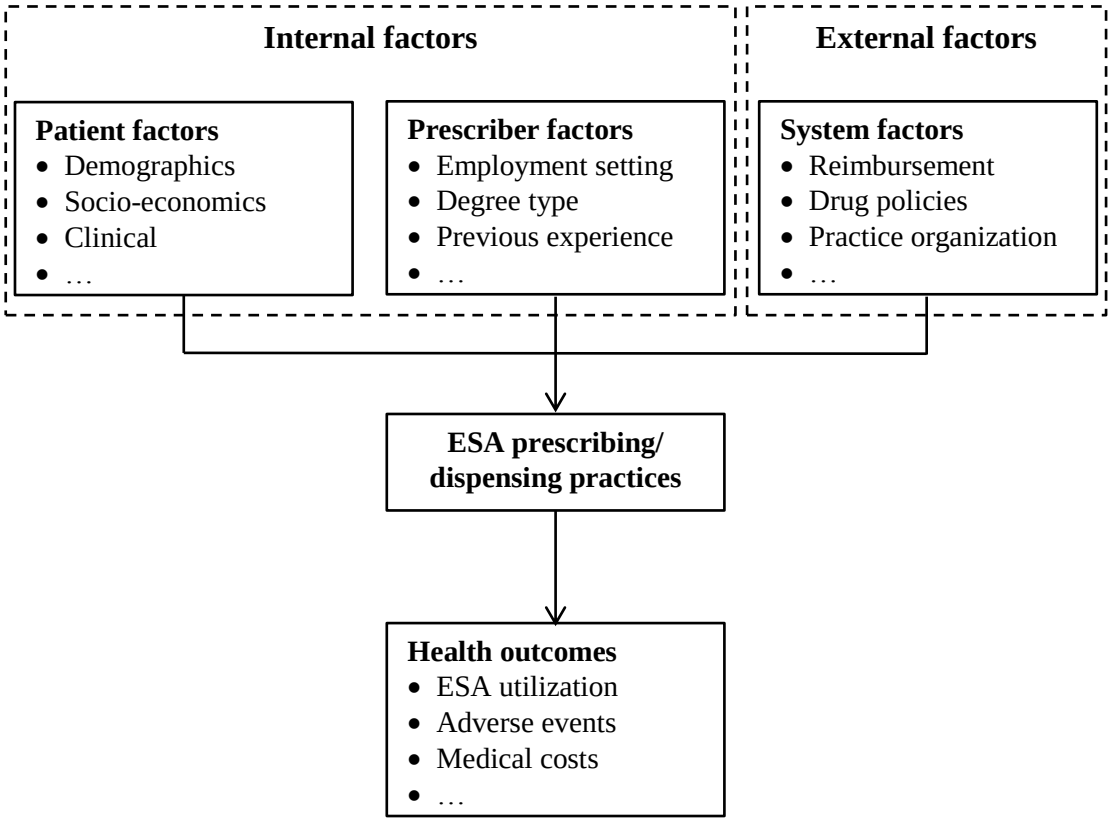

Figure 2.1: Impact of different factors on ESA prescribing/dispensing practices and health outcomes
(ESA: erythropoiesis-stimulating agents)

CHAPTER 3

RESEARCH QUESTIONS

3.1 Aim 1: Utilization

Aim 1.1: To examine the utilization of ESAs in cancer patients with chemotherapy-induced anemia before and after the implementation of Medicare reimbursement policy. Before the policy change, Medicare had no national restrictions on ESA use; after the policy change, however, Medicare restricted ESA use in cancer at the national level. We, therefore, hypothesized a reduction in ESA use following the policy change.

Hypothesis 1.1: In cancer patients with chemotherapy-induced anemia, the utilization of ESAs was reduced after Medicare reimbursement policy change.

Aim 1.2: To examine the utilization of blood transfusions in cancer patients with chemotherapy-induced anemia before and after the implementation of Medicare reimbursement policy. One of the important clinical benefits of ESA use is to reduce future needs of blood transfusions. When ESA use decreases, needs of blood transfusions could increase. However, the impact of the policy change on the potential increase in blood transfusions was indirect and unintended. We, therefore, hypothesized an increase in blood transfusions following the policy change.

Hypothesis 1.2: In cancer patients with chemotherapy-induced anemia, the utilization of blood transfusions was increased after Medicare reimbursement policy change.

3.2 Aim 2: Risks

Aim 2.1: To examine the impact of Medicare reimbursement policy change on the risks of cardiovascular events in incident users of ESAs with chemotherapy-induced anemia. The purpose of the policy change was to prevent potential harms associated with ESAs in Medicare beneficiaries with chemotherapy-induced anemia. MI and stroke are two of adverse cardiovascular events listed in the black box warning for ESAs. We hypothesized a decrease in the risks of MI and stroke following the policy change.

Hypothesis 2.1: In incident users of ESAs with chemotherapy-induced anemia, compared to patients who initiated ESAs before Medicare reimbursement policy change, those who initiated ESAs after the policy change were less likely to develop MI and stroke.

Aim 2.2: To examine the impact of Medicare reimbursement policy change on the risks of thrombovascular events in incident users of ESAs with chemotherapy-induced anemia. VTE is an adverse thrombovascular event listed in the black box warning for ESAs. We hypothesized a decrease in the risks of VTE following the policy change.

Hypothesis 2.2: In incident users of ESAs with chemotherapy-induced anemia, compared to patients who initiated ESAs before Medicare reimbursement policy change, those who initiated ESAs after the policy change were less likely to develop VTE.

3.3 Aim 3: Costs

Aim 3.1: To examine the impact of Medicare reimbursement policy change on anemia-related costs in incident users of ESAs with chemotherapy-induced anemia. Anemia-related costs include costs of ESAs, blood transfusions, and anemia treatments. After the policy change, the utilization of ESAs might decrease, the utilization of blood transfusions might increase, and the utilization of anemia treatments might remain stable. Hence, costs of ESAs might decrease, costs of blood transfusions might increase, and costs of anemia treatments might remain stable after the policy change. Because costs of ESAs are generally higher than costs of blood transfusions, we hypothesized a decrease in anemia-related costs following the policy change.

Hypothesis 3.1: In incident users of ESAs with chemotherapy-induced anemia, anemia-related costs were lower after Medicare reimbursement policy change compared to anemia-related costs before the policy change.

Aim 3.2: To examine the impact of Medicare reimbursement policy change on total medical costs in incident users of ESAs with chemotherapy-induced anemia. In addition to anemia-related costs, total medical costs (e.g. inpatient costs, outpatient costs, and emergency room costs) are another important factor to consider from CMS's perspective. After the policy change, adverse events (e.g. tumor progression or recurrence, mortality, thrombovascular events, and cardiovascular events) associated with

ESAs might decrease. We hypothesized a decrease in total medical costs following the policy change.

Hypothesis 3.2: In incident users of ESAs with chemotherapy-induced anemia, total medical costs were lower after Medicare reimbursement policy change compared to total medical costs before the policy change.

CHAPTER 4

LITERATURE REVIEW

4.1 Literature Review on the Utilization

To date, four studies have examined the change in the utilization of ESAs in cancer patients before and after the implementation of Medicare reimbursement policy.[73-76] Hess *et al.* used electronic medical records from seven practices, including 39 sites of care in seven states, and found that the utilization of ESAs significantly decreased from 41% between June 2006 and March 2007 to 30% between June 2007 and March 2008 (a 26% reduction, $p < .001$). Specifically, the utilization of ESAs significantly decreased by 29% ($p < .001$) and 24% ($p < .001$) among patients aged 65 years or older and younger than 65 years, respectively.[73] Through analyzing medical records at 49 community oncology clinics, Henry *et al.* found that the utilization of ESAs significantly decreased from 88% between January 2000 and July 2007 to 56% between August 2007 and January 2009 (a 36% reduction, $p < .0001$).[74] Arneson *et al.* used Medicare 5% sample data and focused on patients 66 years or older who had lung cancer, breast cancer, colorectal cancer, or lymphomas. Overall, the utilization of ESAs significantly decreased from 35% between September and November 2006 to 15% between September and November 2007 (a 57% reduction, $p < .0001$). Specifically, the utilization of ESAs significantly decreased by 51%, 55%, 69%, and 57% in patients with lung cancer, breast cancer, colorectal cancer, and lymphomas, respectively.[75] Hershman *et al.* used

Surveillance, Epidemiology, and End Results (SEER)-Medicare data and focused on patients 65 years or older. Annual utilization of ESAs increased from 12% in 2000 to 16% in 2006 and then decreased to 8% in 2008 (a 51% reduction).[76]

Table 4.1 summarized some characteristics of four studies examining the impact of Medicare reimbursement policy change on the utilization of ESAs. Hess *et al.* and Henry *et al.* used medical records and found that the utilization of ESAs had a 29% to 36% reduction after the policy change.[73,74] Using local medical records might not be able to measure the impact of the policy change on the utilization of ESAs at the national level. Arneson *et al.* and Hershman *et al.* used Medicare claims data and found that the utilization of ESAs had a 51% to 57% reduction after the policy change.[75,76] Using Medicare claims data could provide national estimates on the impact of the policy change on the utilization of ESAs. Medicare reimbursement policy change was released on July 30, 2007 and then fully implemented on April 7, 2008. The post-policy periods defined in four studies all included the policy implementation period.[73-76] Including part of the policy implementation period in the post-policy period could bias the estimate on the impact of the policy change on the utilization of ESAs.

In summary, previous studies found a 26% to 57% reduction in the utilization of ESAs after the implementation of Medicare reimbursement policy during different time periods or in different settings. These studies, however, lack control groups which cast doubt on the validity of the generated results. Furthermore, no studies have examined the utilization of ESAs during the complete pre- and post-policy periods. Therefore, the long-term effect of Medicare reimbursement policy change on the utilization of ESAs remains unknown.

Six studies have examined the change in the utilization of blood transfusions in cancer patients before and after the implementation of Medicare reimbursement policy.[73-78] Vekeman *et al.* conducted a simulation study and estimated that if the utilization of ESAs reduces by 25%, 50%, and 75%, requirements of blood supply will increase by 9%, 17%, and 26% in 2008, respectively.[77] Hess *et al.* found that the utilization of blood transfusions significantly increased from 8% between June 2006 and March 2007 to 9% between June 2007 and March 2008 (a 17% increase, p = .015). The increase in the utilization of blood transfusions was mainly driven by patients aged 65 years and older (a 31% increase, p = .007). Among patients aged less than 65 years, the utilization of blood transfusions did not change significantly (a 8% increase, p = .358).[73] Yu *et al.* reviewed medical records at the University of Illinois Medical Center and found that significantly more blood transfusions were given to patients between July 2006 and June 2007 than between July 2007 and June 2008 (18 in 55 versus 52 in 55, p = .004).[78] A study by Henry *et al.* found that compared to the period between January 2000 and July 2007, the period between August 2007 and January 2009 had more blood transfusions (odds ratio [OR]: 1.41; 95% confidence interval [CI]: 1.05-1.89) and required more blood supply (OR: 1.53; 95% CI: 1.15-2.04).[74] Arneson *et al.* found that compared to the period between September and November 2006, the utilization of blood transfusions did not change significantly in the period between September and November 2007 overall and in patients with different types of cancer.[75] Hershman *et al.* found that from 2000 to 2008, the annual utilization of blood transfusions remained constant, ranging from 9% to 10%.[76]

Table 4.2 summarized some characteristics of six studies examining the impact of Medicare reimbursement policy change on the utilization of blood transfusions. Vekeman *et al.* used data from published literature and conducted modeling simulation to predict the increase in blood supply based on the reduction in ESAs.[77] Hess *et al.*, Yu *et al.*, and Henry *et al.* used medical records and found that the utilization of blood transfusions had a small increase after the policy change.[73,74,78] Using local medical records might not be able to measure the impact of the policy change on the utilization of blood transfusions at the national level. Arneson *et al.* and Hershman *et al.* used Medicare claims data and found that the utilization of blood transfusions did not change after the policy change.[75,76] Using Medicare claims data could provide national estimates on the impact of the policy change on the utilization of blood transfusions. Medicare reimbursement policy change was released on July 30, 2007 and then fully implemented on April 7, 2008. The post-policy periods defined in six studies all included the policy implementation period.[73-78] Including part of the policy implementation period in the post-policy period could bias the estimate on the impact of the policy change on the utilization of blood transfusions.

In summary, previous studies are controversial regarding the change in the utilization of blood transfusions after the implementation of Medicare reimbursement policy during different time periods or in different settings. These studies, however, lack control groups which cast doubt on the validity of the generated results. Furthermore, no studies have examined the utilization of blood transfusions during the complete pre- and post-policy periods. Therefore, the long-term effect of Medicare reimbursement policy change on the utilization of blood transfusions remains unknown.

4.2 Literature Review on the Risks

To date, no studies have examined whether the risks associated with ESAs have been reduced after the implementation of Medicare reimbursement policy. This information is of great importance to CMS, as reducing potential risks associated with ESAs is the goal of the policy change. Therefore, empirical evidence is greatly needed to examine the effectiveness of the policy change in addressing safety concerns of ESAs.

4.3 Literature Review on the Costs

No studies have examined the impact of Medicare reimbursement policy change on medical costs associated with ESAs. In the U.S., CMS is the largest payer in healthcare. ESAs were the highest-expenditure drug in the Medicare system before the policy change. The economic consequence of the policy change should be of great interest to CMS. However, empirical evidence is currently lacking to evaluate the economic consequence of the policy change among users of ESAs.

4.4 Literature Gap

This study, therefore, filled three gaps in the literature by: (1) examining the utilization of ESAs and blood transfusions by containing a control group and including the complete pre- and post-policy periods; (2) evaluating the impact of Medicare reimbursement policy change on the risks associated with ESAs to determine if the goal of the policy change has been achieved; and (3) evaluating the impact of Medicare reimbursement policy change on the costs associated with ESAs to measure the economic consequence of the policy change.

Table 4.1: Studies examining the impact of Medicare reimbursement policy change on the utilization of ESAs

Author (Year)	Data source	Sample size	Pre-policy period	Post-policy period	Outcomes	Results
Hess[73] (2010)	Medical records from 7 practices	4,784 in the pre-policy period and 5,605 in the post-policy period	June 2006 to March 2007	June 2007 to March 2008	Utilization of ESAs in the study period	Changed from 41% in the pre-policy period to 30% in the post-policy period
Henry[74] (2012)	Medical records at 49 community oncology clinics	800 in the pre-policy period and 994 in the post-policy period	January 2000 to July 2007	August 2007 to January 2009	Utilization of ESAs in the study period	Changed from 88% in the pre-policy period to 56% in the post-policy period
Arneson[75] (2012)	Medicare 5% sample data	1,897 in the pre-policy period and 1,877 in the post-policy period	September 2006 to November 2006	September 2007 to November 2007	Utilization of ESAs in the study period	Changed from 35% in the pre-policy period to 15% in the post-policy period
Hershman[76] (2014)	SEER-Medicare data	Different in different years	2006	2008	Annual utilization of ESAs	Changed from 16% in 2006 to 8% in 2008

ESAs: erythropoiesis-stimulating agents; SEER: Surveillance, Epidemiology, and End Results

Table 4.2: Studies examining the impact of Medicare reimbursement policy change on the utilization of blood transfusions

Author (Year)	Data source	Sample size	Pre-policy period	Post-policy period	Outcomes	Results
Vekeman[77] (2009)	Simulation	Different in different assumptions	2004	2008	Incremental requirements of blood supply	If the utilization of ESAs reduces by 25%, 50%, and 75%, requirements of blood supply will increase by 9%, 17%, and 26% in 2008, respectively
Hess[73] (2010)	Medical records from 7 practices	4,784 in the pre-policy period and 5,605 in the post-policy period	June 2006 to March 2007	June 2007 to March 2008	Utilization of blood transfusions in the study period	Changed from 8% in the pre-policy period to 9% in the post-policy period
Yu[78] (2011)	Medical records at the University of Illinois Medical Center	55 in the pre-policy period and 55 in the post-policy period	July 2006 to June 2007	July 2007 to June 2008	Utilization of blood transfusions in the study period	More blood transfusions were given in the post-policy period (18 in 55 versus 52 in 55)
Henry[74] (2012)	Medical records at 49 community oncology clinics	800 in the pre-policy period and 994 in the post-policy period	January 2000 to July 2007	August 2007 to January 2009	Odds of receiving blood transfusions	Higher odds of receiving blood transfusions in the post-policy period (OR: 1.41; 95% CI: 1.05-1.89)
Arneson[75] (2012)	Medicare 5% sample data	1,897 in the pre-policy period and 1,877 in the post-policy period	September 2006 to November 2006	September 2007 to November 2007	Utilization of blood transfusions in the study period	No change in the post-policy period
Hershman[76] (2014)	SEER-Medicare data	Different in different years	2006	2008	Annual utilization of blood transfusions	No change in the post-policy period

ESAs: erythropoiesis-stimulating agents; OR: odds ratio; CI: confidence interval; SEER: Surveillance, Epidemiology, and End Results

CHAPTER 5

RESEARCH METHOD

5.1 Data Source

The SEER program is a large population-based cancer registry which collects information on cancer incidence and mortality.[79] The National Cancer Institute (NCI) developed and maintains the SEER program. Currently, the SEER program includes cancer registries across 14 states and covers 28% of the U.S. population. Population-based cancer registries of the SEER program include Alaska Native Tumor Registry, Arizona Indians, Cherokee Nation, Connecticut, Detroit, Georgia Center for Cancer Statistics, Greater Bay Area Cancer Registry, Greater California, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, Seattle-Puget Sound, and Utah. The information collected in the SEER program includes demographics, cancer type, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and follow-up for vital status.

Medicare is a national health insurance program administered by the U.S. federal government.[80] Medicare provides health insurance for Americans who are 65 years of age or older, under 65 years of age but with certain disabilities, or have end-stage renal disease (ESRD). Medicare provides hospital insurance (Part A) and medical insurance (Part B) to its beneficiaries. Since 2006, Medicare provides prescription drug coverage (Part D) to its beneficiaries. Medicare enrollment data include the eligibility and

demographic information of Medicare beneficiaries. Medicare claims are submitted by healthcare providers for services provided to Medicare beneficiaries. CMS then reviews Medicare claims and determines if these services should be reimbursed. The information available in Medicare enrollment and claims data includes eligibility, demographics, diagnosis, health service utilization, and payments for Medicare beneficiaries.

The enrollment and claims of Medicare beneficiaries in the SEER program can be identified and linked by a collaborative effort of NCI and CMS.[81] The SEER-Medicare linked data include two cohorts of people: cancer cohort and non-cancer cohort. The cancer cohort is defined as Medicare beneficiaries in the SEER program. The non-cancer cohort is defined as a random 5% sample of Medicare beneficiaries who do not have cancer but reside in the same SEER geographic areas. The non-cancer cohort is usually used for comparison purposes.

This study used the SEER-Medicare linked database. It is an appropriate dataset for this study because the linked database contains rich information on demographics, cancer incidence and mortality, health service utilization, diagnosis, and payments for Medicare beneficiaries with cancer. In addition, it allows us to incorporate a comparison group of non-cancer controls.

5.2 Study Design

This study used different study designs for different outcomes because units of analysis were different. When examining utilization, the unit of analysis was the group; when examining risks and costs, the unit of analysis was the individual.

This study used a repeated cross-sectional design in Aim 1. The repeated cross-sectional design enabled us to estimate the monthly utilization of ESAs and blood transfusions in the treatment and control group. The monthly utilization of ESAs and blood transfusions was compared before and after Medicare reimbursement policy change. In Aim 1, the period between January 1, 2003 and June 30, 2007 was defined as the pre-policy period; the period between July 1, 2007 and April 30, 2008 was defined as the policy period; and the period between May 1, 2008 and December 31, 2009 was defined as the post-policy period. We selected January 1, 2003 as the starting point because darbepoetin alfa was first approved by the FDA in 2002 and fully available on the U.S. market starting in 2003 for the treatment of anemia associated with cancer chemotherapy. We selected December 31, 2009 as the ending point because ESA Risk Evaluation and Mitigation Strategies (REMS), a policy change for ESAs by the FDA, came into effect after that.[82,83] The selection of the policy period was based on the timeline of Medicare reimbursement policy change. The NCD was released on July 30, 2007 and fully implemented on April 7, 2008. Thus, we selected the period between July 1, 2007 and April 30, 2008 as the policy period.

This study used a retrospective incident user cohort design in Aim 2 and 3.[84] The index date for the incident user of ESAs was the date of the first ESA prescription. The cohort design enabled us to estimate the incidence of cardiovascular and thrombovascular events in Aim 2. Incident users of ESAs before and after Medicare reimbursement policy change were followed up to one year since the index date for a diagnosis of MI, stroke, or VTE. Odds ratios of cardiovascular and thrombovascular events between the pre- and post-policy periods were estimated. In addition, the cohort design enabled us to estimate

anemia-related and total medical costs since the initiation of ESAs in Aim 3. Costs were measured in the treatment and control groups during the one-year follow-up period after the index date. Then the cost differences in the treatment and control groups between the pre- and post-policy periods were estimated. In Aim 2 and 3, individuals who initiated ESAs between May 1, 2005 and December 31, 2006 were considered as incident users in the pre-policy period; individuals who initiated ESAs between May 1, 2008 and December 31, 2009 were considered as incident users in the post-policy period. We selected the post-policy period first based on the timeline of Medicare reimbursement policy change and then selected the corresponding pre-policy period.

5.3 Control Group

Selecting an appropriate control group was essential to the success of this study. This study incorporated a CKD control group in Aim 1 and 3. The treatment group was composed of Medicare beneficiaries with cancer and the control group was composed of Medicare beneficiaries with CKD. We used CKD patients as the control group because ESAs can be used in CKD patients with low levels of hemoglobin and Medicare reimbursement policy change on ESAs was only applicable to cancer patients. ESA use in CKD patients have not been affected by this policy change. Furthermore, FDA's black box warning on ESAs applied to both conditions (cancer and CKD).[42,43] Therefore, using Medicare beneficiaries with CKD as the control group could eliminate possible threats to internal validity due to history (FDA's black box warning) when evaluating the utilization and costs associated with ESAs.

5.4 Study Population

The study population in Aim 1 was selected based on certain inclusion and exclusion criteria in each month. The study population of the treatment group in each month was selected from individuals who were aged 65 years or older, were eligible for Medicare because of age, had a primary diagnosis of breast cancer, colorectal cancer, lung cancer, lymphomas, ovarian cancer, or prostate cancer, and received chemotherapy after cancer diagnosis as recorded in the cancer cohort of the SEER-Medicare data. Individuals who enrolled in health maintenance organization (HMO) plans, did not have coverage of both Medicare Part A and B, were eligible for Medicare because of ESRD, or had a diagnosis of CKD were excluded from the treatment group in each month. The study population of the control group in each month was selected from individuals who were aged 65 years or older and were eligible for Medicare because of ESRD or had a diagnosis of CKD as recorded in the non-cancer cohort of the SEER-Medicare data. Individuals enrolled in HMO plans, did not have coverage of both Medicare Part A and B, or had a diagnosis of cancer were excluded from the control group in each month.

The study population in Aim 2 was selected from individuals who were aged 66 years or older, were eligible for Medicare because of age, had a primary diagnosis of breast cancer, colorectal cancer, lung cancer, lymphomas, ovarian cancer, or prostate cancer, received chemotherapy after cancer diagnosis, initiated ESAs after chemotherapy, and initiated ESAs during the study period as recorded in the cancer cohort of the SEER-Medicare data. Individuals who enrolled in HMO plans, did not have coverage of both Medicare Part A and B, were eligible for Medicare because of ESRD, had a diagnosis of CKD, or received ESAs one year before the index date were excluded from the study. To

identify the study population free of MI, we additionally excluded individuals who had a diagnosis of MI one year before the index date. To identify the study population free of stroke, we additionally excluded individuals who had a diagnosis of stroke one year before the index date. To identify the study population free of VTE, we additionally excluded individuals who had a diagnosis of VTE one year before the index date.

The study population of the treatment group in Aim 3 was selected from individuals who were aged 66 years or older, were eligible for Medicare because of age, had a primary diagnosis of breast cancer, colorectal cancer, lung cancer, lymphomas, ovarian cancer, or prostate cancer, received chemotherapy after cancer diagnosis, initiated ESAs after chemotherapy, and initiated ESAs during the study period as recorded in the cancer cohort of the SEER-Medicare data. Individuals who enrolled in HMO plans, did not have coverage of both Medicare Part A and B, were eligible for Medicare because of ESRD, had a diagnosis of CKD, or received ESAs one year before the index date were excluded from the treatment group. The study population of the control group in Aim 3 was selected from individuals who were aged 66 years or older, were eligible for Medicare because of ESRD or had a diagnosis of CKD, initiated ESAs after CKD diagnosis, and initiated ESAs during the study period as recorded in the non-cancer cohort of the SEER-Medicare data. Individuals who enrolled in HMO plans, did not have coverage of both Medicare Part A and B, had a diagnosis of cancer, or received ESAs one year before the index date were excluded from the control group.

5.5 Measurement

The utilization of ESAs was measured based on relevant HCPCS/Current Procedural Terminology (CPT) and revenue center codes from Medicare claims. The utilization of blood transfusions was measured based on relevant International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) and HCPCS/CPT codes from Medicare claims.

To measure cardiovascular and thrombovascular events, incident users of ESAs were followed up to one year for an event of MI, stroke, or VTE. The diagnosis of MI, stroke, or VTE was measured based on relevant codes in the ICD-9-CM and HCPCS/CPT from Medicare claims during the one-year follow-up period.

Medical costs in the study were measured from CMS's perspective. To measure anemia-related and total medical costs, incident users of ESAs were followed up to one year. Anemia-related and total medical costs were measured based on payment information from Medicare claims, including Medicare provider, carrier, outpatient, home health agency, hospice, and durable medical equipment, during the one-year follow-up period. Anemia-related costs included costs of ESAs, blood transfusions, and anemia treatments as recorded in Medicare claim. Total medical costs included all costs as recorded in Medicare claims. Anemia-related and total medical costs were composed of Medicare payment and patient cost-sharing. Consumer price index (CPI) of medical care services was used in the study to calculate the inflation rate and adjust medical costs occurred in different years to 2010 prices.[85] (Table 5.1)

Variables in the inclusion and exclusion criteria were measured based on the SEER registries and Medicare enrollment and claims. Chemotherapy was measured

based on relevant ICD-9-CM, HCPCS/CPT and revenue center codes from Medicare claims. Patients with breast cancer, colorectal cancer, lung cancer, lymphomas, ovarian cancer, or prostate cancer were identified from the SEER registries. Patients with CKD were identified from relevant ICD-9-CM codes from Medicare claims.

The main independent variable of the study was the policy change. Based on the conceptual framework, potential confounding factors included demographics, socio-economics, clinical characteristics, tumor characteristics, and treatment characteristics. Specifically, covariates considered in the regression model in Aim 2 were demographics (including age, sex, and race), socio-economics (including residence, region, education level, and poverty level), clinical characteristics (including Charlson comorbidity index (CCI) and vital status), tumor characteristics (including cancer type), and treatment characteristics (including surgery and radiation therapy). Covariates considered in the regression model in Aim 3 were demographics (including age, sex, and race), socio-economics (including residence, region, education level, and poverty level), and clinical characteristics (including CCI and vital status).

Covariates were measured based on the SEER registries and Medicare enrollment and claims. Specifically, education level was measured based on the percent of persons 25 years or older with less than 12 years of education in the area of residence. The study sample was divided into four quartiles based on education (first quartile: 0% to 10.4%; second quartile: 10.4% to 16.5%; third quartile: 16.5% to 26.1%; and fourth quartile: 26.1% to 100%). Poverty level was measured based on the percent of the population below the poverty level in the area of residence. The study sample was divided into four quartiles based on poverty (first quartile: 0% to 5.25%; second quartile: 5.25% to 9.1%;

third quartile: 9.1% to 15.5%; and fourth quartile: 15.5% to 100%). Because all individuals in the treatment group had a diagnosis of cancer and all individuals in the control group had a diagnosis of CKD, this study calculated the Deyo adaptation of the CCI excluding cancer and CKD.[86]

5.6 Statistical Analysis

In Aim 1, the monthly utilization of ESAs was calculated in Formula 5.1; the monthly utilization of blood transfusions was calculated in Formula 5.2. Percentages of patients received ESAs or blood transfusions in each month were compared before and after Medicare reimbursement policy change and plotted in graphs.

$$Monthly\ utilization\ of\ ESAs = \frac{Number\ of\ patients\ received\ ESAs\ in\ that\ month}{Total\ number\ of\ patients\ in\ that\ month}$$

(Formula 5.1)

$$Monthly\ utilization\ of\ blood\ transfusions = \frac{Number\ of\ patients\ received\ blood\ transfusions\ in\ that\ month}{Total\ number\ of\ patients\ in\ that\ month}$$

(Formula 5.2)

In Aim 1, with aggregate data, an interrupted time series design was used to examine the impact of Medicare reimbursement policy change on the utilization of ESAs and blood transfusions. A segmented regression analysis in Formula 5.3 was used in the interrupted time-series design.[87]

$$Y = \beta_0 + \beta_1\, Month + \beta_2\, Policy\ change + \beta_3\, Month\ after\ policy\ change + \beta_4\, Group\ assignment + \beta_5\, Month{\times}Group\ assignment + \beta_6\, Policy\ change{\times}Group\ assignment + \beta_7\, Month\ after\ policy\ change{\times}Group\ assignment$$

(Formula 5.3)

- Y indicates the monthly utilization;
- $Month$ is the number of months since the beginning of the pre-policy period (January 2003);
- $Policy\ change$ is a dummy variable indicating Medicare reimbursement policy change;
    - 0: pre-policy period
    - 1: post-policy period
- $Month\ after\ policy\ change$ is 0 if $Policy\ change$ equals to 0; or is the number of months since the beginning of the post-policy period (May 2008) if $Policy\ change$ equals to 1;
- $Group\ assignment$ is a dummy variable indicating the assignment of patients to either the treatment or control group;
    - 0: control group
    - 1: treatment group
- $Month{\times}Group\ assignment$ is an interaction term between $Month$ and $Group\ assignment$;
- $Policy\ change{\times}Group\ assignment$ is an interaction term between $Policy\ change$ and $Group\ assignment$;

- $Month\ after\ policy\ change \times Group\ assignment$ is an interaction term between $Month\ after\ policy\ change$ and $Group\ assignment$.

In Formula 5.3, β_0 estimated the base level in the monthly utilization in the beginning of the pre-policy period (January 2003) in the control group; β_1 estimated the base trend in the monthly utilization during the pre-policy period in the control group; β_2 estimated the difference in the level in the monthly utilization between the end of the pre-policy period (June 2007) and the beginning of the post-policy period (May 2008) in the control group; β_3 estimated the difference in the trend in the monthly utilization between the pre- and post-policy periods in the control group; β_4 estimated the difference in the base level in the monthly utilization in the beginning of the pre-policy period (January 2003) between the treatment and control groups; β_5 estimated the difference in the base trend in the monthly utilization during the pre-policy period between the treatment and control groups; β_6 estimated the difference in the difference in the level in the monthly utilization between the end of the pre-policy period (June 2007) and the beginning of the post-policy period (May 2008) between the treatment and control groups; β_7 estimated the difference in the difference in the trend in the monthly utilization between the pre- and post-policy periods between the treatment and control groups. Among them, β_6 and β_7 were two coefficients of interest. They indicated if there were any differences in the level and trend in the monthly utilization of ESAs or blood transfusions between the pre- and post-policy periods between the treatment and control groups. The monthly utilization of ESAs or blood transfusions during the policy period, the period between July 1, 2007 and April 30, 2008, were excluded in the segmented regression analysis.

In Aim 2 and 3, we conducted a descriptive analysis on characteristics of incident users of ESAs between the pre- and post-policy periods. Basic statistical tests (Chi-square or Fisher's exact test) were used to compare baseline characteristics of incident users of ESAs before and after Medicare reimbursement policy change. Significant factors associated with the policy change were identified. In Aim 3, we also compared the average medical costs in incident users of ESAs between the pre- and post-policy periods using the independent sample t-test. For all statistical tests in the study, a 5% level of significance was used.

In Aim 2, with individual data, a logistic regression model in Formula 5.4 was used to examine the impact of Medicare reimbursement policy change on the risks of MI, stroke, and VTE associated with ESAs.

$$ln(odds\ that\ Y = 1) = \beta_0 + \beta_1 Policy\ change + \beta_2 Demo + \beta_3 Socio + \beta_4 Clinical + \beta_5 Tumor + \beta_6 Treatment$$

(Formula 5.4)

- Y is a dummy variable indicating the diagnosis of MI, stroke, or VTE;
  - 0: not diseased
  - 1: diseased
- $Policy\ change$ is a dummy variable indicating Medicare reimbursement policy change;
  - 0: pre-policy period
  - 1: post-policy period
- $Demo$ includes a series of demographical variables;

- $Socio$ includes a series of socio-economic variables;
- $Clinical$ includes a series of variables indicating clinical characteristics;
- $Tumor$ includes a series of variables indicating tumor characteristics;
- $Treatment$ includes a series of variables indicating treatment characteristics.

In Formula 5.4, β_1 was the coefficient of interest. The odds ratio comparing the odds of having MI, stroke, or VTE in the post-policy period versus the pre-policy period among incident users of ESAs were measured as e^{β_1}.

In Aim 3, with individual data, a difference-in-difference design was used to examine the impact of Medicare reimbursement policy change on anemia-related and total medical costs associated with ESAs.[88] A generalized linear model (GLM) in Formula 5.5, with a log link and a gamma distribution, was used in the difference-in-difference design.

$$\mathrm{G}(\mu) = \beta_0 + \beta_1 Policy\ change + \beta_2 Group\ assignment + \beta_3 Policy\ change \times Group\ assignment + \beta_4 Demo + \beta_5 Socio + \beta_6 Clinical$$

(Formula 5.5)

- $\mathrm{G}(\mu)$ indicates log-transformed costs;
- $Policy\ change$ is a dummy variable indicating Medicare reimbursement policy change;
    - 0: pre-policy period
    - 1: post-policy period

- $Group\ assignment$ is a dummy variable indicating the assignment of patients to either the treatment or control group;
    - 0: control group
    - 1: treatment group
- $Policy\ change \times Group\ assignment$ is an interaction term between $Policy\ change$ and $Group\ assignment$;
- $Demo$ includes a series of demographical variables;
- $Socio$ includes a series of socio-economic variables;
- $Clinical$ includes a series of variables indicating clinical characteristics.

In Formula 5.5, β_1 estimated the difference in the log-transformed costs between the pre- and post-policy periods in the control group; β_2 estimated the difference in the log-transformed costs in the pre-policy period between the treatment and control groups; β_3 estimated the difference in the difference in the log-transformed costs between the pre- and post-policy periods between the treatment and control groups. Among them, β_3 was the coefficient of interest. It indicated if there were any differences in the log-transformed anemia-related and total medical costs associated with ESAs between the pre- and post-policy periods between the treatment and control groups.

All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Table 5.1 CPI and inflation rate of medical care services from 2005 to 2010

Year	CPI	Inflation rate (2010 prices)
2005	336.70	1.2213
2006	350.60	1.1729
2007	369.30	1.1135
2008	384.94	1.0682
2009	397.30	1.0350
2010	411.21	1.0000

CPI: consumer price index

CHAPTER 6

RESULTS

6.1 Results on the Utilization

After applying the inclusion and exclusion criteria in Aim 1, we identified the study sample of eligible cancer or CKD patients in each month. (Table 6.1 and 6.2) In the treatment group, the total number of eligible cancer patients in each month ranged from 55,719 to 109,646 from January 2003 to December 2009. In the control group, the total number of eligible CKD patients in each month ranged from 28,684 to 64,157 from January 2003 to December 2009.

6.1.1 Results on the Utilization of ESAs

Figure 6.1 illustrated the change in the monthly utilization of ESAs before and after the implementation of Medicare reimbursement policy. From visual inspection, we found that during the pre-policy period, the monthly utilization of ESAs changed from 5.23% in January 2003 to 3.15% in June 2007 in the treatment group; and the monthly utilization of ESAs changed from 5.68% in January 2003 to 4.66% in June 2007 in the control group. During the policy period, the monthly utilization of ESAs had a huge drop in the treatment group (from 3.21% in July 2007 to 1.24% in April 2008); and the monthly utilization of ESAs had a small drop in the control group (from 4.64% in July 2007 to 4.15% in April 2008). During the post-policy period, the monthly utilization of

ESAs changed from 1.23% in May 2008 to 0.79% in December 2009 in the treatment group; and the monthly utilization of ESAs changed from 4.11% in May 2008 to 3.57% in December 2009 in the control group.

To quantity the change in the monthly utilization of ESAs before and after the implementation of Medicare reimbursement policy, we conducted a segmented regression analysis in the interrupted time-series design. Table 6.3 summarized the results on the change in the monthly utilization of ESAs before and after the implementation of Medicare reimbursement policy. According to the segmented regression analysis, in the treatment group, the monthly utilization of ESAs in the end of the pre-policy period (June 2007) and the beginning of the post-policy period (May 2008) was estimated as 4.15% and 1.19%, respectively. The level in the monthly utilization of ESAs was estimated to be reduced by 2.96% after the policy change in the treatment group. In the control group, the monthly utilization of ESAs in the end of the pre-policy period (June 2007) and the beginning of the post-policy period (May 2008) was estimated as 4.93% and 4.10%, respectively. The level in the monthly utilization of ESAs was estimated to be reduced by 0.83% after the policy change in the control group. Thus, when including the control group in the interrupted time-series design, the level in the monthly utilization of ESAs was reduced statistically significantly by 2.13% ($P < .0001$) after the policy change.

According to the segmented regression analysis, in the treatment group, the trend in the monthly utilization of ESAs in the pre- and post-policy period was estimated as -0.03% and -0.02%, respectively. The trend in the monthly utilization of ESAs was estimated to be increased by 0.01% after the policy change in the treatment group. In the control group, the trend in the monthly utilization of ESAs in the pre- and post-policy

period was estimated as -0.01% and -0.02%, respectively. The trend in the monthly utilization of ESAs was estimated to be reduced by 0.01% after the policy change in the treatment group. Thus, when including the control group in the interrupted time-series design, the trend in the monthly utilization of ESAs was increased by 0.02% (P = .1366) after the policy change but was not statistically significant.

In summary, the utilization of ESAs in cancer patients with chemotherapy-induced anemia was reduced after the implementation of Medicare reimbursement policy. Specifically, the level (intercept) was reduced by 2.13% (about a relative 50% reduction) but the trend (slope) did not change. Because the trends before and after the policy change were similar, Medicare reimbursement policy had a one-time only effect on the utilization of ESAs.

6.1.2 Results on the Utilization of Blood Transfusions

Figure 6.2 illustrated the change in the monthly utilization of blood transfusions before and after the implementation of Medicare reimbursement policy. From visual inspection, we found that during the pre-policy period, the monthly utilization of blood transfusions changed from 1.29% in January 2003 to 0.91% in June 2007 in the treatment group; and the monthly utilization of blood transfusions changed from 1.14% in January 2003 to 0.90% in June 2007 in the control group. During the policy period, the monthly utilization of blood transfusions increased in the treatment group (from 0.88% in July 2007 to 1.02% in April 2008); and the monthly utilization of blood transfusions increased in the control group (from 0.83% in July 2007 to 1.02% in April 2008). During the post-policy period, the monthly utilization of blood transfusions changed from 1.01% in May

2008 to 0.96% in December 2009 in the treatment group; and the monthly utilization of blood transfusions changed from 1.04% in May 2008 to 0.95% in December 2009 in the control group.

To quantity the change in the monthly utilization of blood transfusions before and after the implementation of Medicare reimbursement policy, we conducted a segmented regression analysis in the interrupted time-series design. Table 6.4 summarized the results of the change in the monthly utilization of blood transfusions before and after the implementation of Medicare reimbursement policy. According to the segmented regression analysis, in the treatment group, the monthly utilization of blood transfusions in the end of the pre-policy period (June 2007) and the beginning of the post-policy period (May 2008) was estimated as 0.89% and 0.99%, respectively. The level in the monthly utilization of blood transfusions was estimated to be increased by 0.10% after the policy change in the treatment group. In the control group, the monthly utilization of blood transfusions in the end of the pre-policy period (June 2007) and the beginning of the post-policy period (May 2008) was estimated as 0.95% and 0.95%, respectively. The level in the monthly utilization of blood transfusions remained the same after the policy change in the control group. Thus, when including the control group in the interrupted time-series design, the level in the monthly utilization of blood transfusions was increased statistically significantly by 0.10% (P = .0186) after the policy change.

According to the segmented regression analysis, in the treatment group, the trend in the monthly utilization of blood transfusions in the pre- and post-policy period was estimated as -0.01% and 0.00%, respectively. The trend in the monthly utilization of blood transfusions was estimated to be increased by 0.01% after the policy change in the

treatment group. In the control group, the trend in the monthly utilization of blood transfusions in the pre- and post-policy period was estimated as 0.00% and 0.00%, respectively. The trend in the monthly utilization of blood transfusions was estimated to be the same after the policy change in the treatment group. Thus, when including the control group in the interrupted time-series design, the trend in the monthly utilization of blood transfusions was increased by 0.01% (P = .0524) after the policy change but was not statistically significant.

In summary, the utilization of blood transfusions in cancer patients with chemotherapy-induced anemia was increased after the implementation of Medicare reimbursement policy. Specifically, the level (intercept) was increased by 0.10% (about a relative 10% increase) but the trend (slope) did not change. Because the trends before and after the policy change were similar, Medicare reimbursement policy had a one-time only effect on the utilization of blood transfusions.

6.2 Results on the Risks

After applying the inclusion and exclusion criteria in Aim 2, we identified 17,382 incident users of ESAs during the pre- and post-policy periods, 12,892 (74.17%) and 4,490 (25.83%), respectively. (Figure 6.3) To understand the impact of Medicare reimbursement policy change on the risks of cardiovascular and thrombovascular events associated with ESAs, we additionally required the study samples in Aim 2 to be free of cardiovascular or thrombovascular events one year before the index date.

6.2.1 Results on the Risk of MI

After excluding 146 Medicare beneficiaries who had a diagnosis of MI one year before the index date, we identified 17,236 incident users of ESAs free of MI in the pre- and post-policy periods, 12,791 (74.21%) and 4,445 (25.79%), respectively. (Figure 6.3 and Table 6.5)

Table 6.5 summarized baseline characteristics of incident users of ESAs free of MI one year before the index date between the pre- and post-policy periods. Except for age, sex, and the use of radiation therapy, all other baseline characteristics were statistically significantly different in incident users of ESAs between the pre- and post-policy periods. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period were more likely to be non-White, live in non-metropolitan areas, live in South, live in areas with low level of education, live in areas with low level of poverty, have one or more comorbidities, dead during the one-year follow-up period, have lung, ovarian, or prostate cancer, and not have surgery.

During the one-year follow-up period, 147 (1.15%) and 54 (1.21%) incident users of ESAs developed MI in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .7256). In the unadjusted logistic regression analysis, we found that the implementation of Medicare reimbursement policy was not statistically significantly associated with the future development of MI (OR: 1.06; 95% CI: 0.77-1.45).

In the adjusted logistic regression analysis, we controlled for potential confounding factors at the baseline. (Table 6.6) We found that the implementation of Medicare reimbursement policy was still not statistically significantly associated with the

future development of MI (OR: 1.01; 95% CI: 0.74-1.39). Factors statistically significantly associated with the future development of MI included age, education, comorbidity, and vital status. Compared to those aged 66 and 69, incident users of ESAs who were aged 75 and 79 were 64% more likely to develop MI (OR: 1.64; 95% CI: 1.10-2.43). Compared to those lived in areas with the highest level of education, incident users of ESAs who lived in areas with low level of education were 85% more likely to develop MI (OR: 1.85; 95% CI: 1.10-3.13). Compared to those without any comorbidity, incident users of ESAs who had a CCI of two were 70% more likely to develop MI (OR: 1.70; 95% CI: 1.14-2.55); and incident users of ESAs who had a CCI of three or more were 2.04 times more likely to develop MI (OR: 2.04; 95% CI: 1.26-3.31). Compared to those alive after the one-year follow-up period, incident users of ESAs who died during the one-year follow-up period were 2.40 times more likely to develop MI (OR: 2.40; 95% CI: 1.72-3.34).

In summary, the risk of MI associated with ESAs during the one-year follow-up period in cancer patients with chemotherapy-induced anemia was not changed after the implementation of Medicare reimbursement policy.

6.2.2 Results on the Risk of Stroke

After excluding 1,132 Medicare beneficiaries who had a diagnosis of stroke one year before the index date, we identified 16,250 incident users of ESAs free of stroke in the pre- and post-policy periods, 12,061 (74.22%) and 4,189 (25.78%), respectively. (Figure 6.3 and Table 6.7)

Table 6.7 summarized baseline characteristics of incident users of ESAs free of stroke one year before the index date between the pre- and post-policy periods. Except for age, sex, and the use of radiation therapy, all other baseline characteristics were statistically significantly different in incident users of ESAs between the pre- and post-policy periods. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period were more likely to be non-White, live in non-metropolitan areas, live in South, live in areas with low level of education, live in areas with low level of poverty, have one or more comorbidities, dead during the one-year follow-up period, have lung, ovarian, or prostate cancer, and not have surgery.

During the one-year follow-up period, 704 (5.84%) and 252 (6.02%) incident users of ESAs developed stroke in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .6719). In the unadjusted logistic regression analysis, we found that the implementation of Medicare reimbursement policy was not statistically significantly associated with the future development of stroke (OR: 1.03; 95% CI: 0.89-1.20).

In the adjusted logistic regression analysis, we controlled for potential confounding factors at the baseline. (Table 6.8) We found that the implementation of Medicare reimbursement policy was still not statistically significantly associated with the future development of stroke (OR: 0.99; 95% CI: 0.84-1.15). Factors statistically significantly associated with the future development of stroke included age, education, poverty, comorbidity, vital status, and cancer type. Compared to those aged 66 and 69, incident users of ESAs who were aged 80 and over were 42% more likely to develop stroke (OR: 1.42; 95% CI: 1.16-1.74). Compared to those lived in areas with the highest

level of education, incident users of ESAs who lived in areas with the lowest level of education were 88% more likely to develop stroke (OR: 1.88; 95% CI: 1.41-2.52). Compared to those lived in areas with the lowest level of poverty, incident users of ESAs who lived in areas with the lower level of poverty were 22% less likely to develop stroke (OR: 0.78; 95% CI: 0.62-0.98); and incident users of ESAs who lived in areas with the highest level of poverty were 30% less likely to develop stroke (OR: 0.70; 95% CI: 0.51-0.95). Compared to those without any comorbidity, incident users of ESAs who had a CCI of two were 25% more likely to develop stroke (OR: 1.25; 95% CI: 1.01-1.54). Compared to those alive after the one-year follow-up period, incident users of ESAs who died during the one-year follow-up period were 78% more likely to develop stroke (OR: 1.78; 95% CI: 1.53-2.07). Compared to those had a primary diagnosis of breast cancer, incident users of ESAs who had a primary diagnosis of lung cancer were 36% more likely to develop stroke (OR: 1.36; 95% CI: 1.05-1.77); and incident users of ESAs who had a primary diagnosis of lymphomas were 41% more likely to develop stroke (OR: 1.41; 95% CI: 1.06-1.89).

In summary, the risk of stroke associated with ESAs during the one-year follow-up period in cancer patients with chemotherapy-induced anemia was not changed after the implementation of Medicare reimbursement policy.

6.2.3 Results on the Risk of VTE

After excluding 3,158 Medicare beneficiaries who had a diagnosis of VTE one year before the index date, we identified 14,224 incident users of ESAs free of VTE in

the pre- and post-policy periods, 10,581 (74.39%) and 3,643 (25.61%), respectively. (Figure 6.3 and Table 6.9)

Table 6.9 summarized baseline characteristics of incident users of ESAs free of VTE one year before the index date between the pre- and post-policy periods. Except for age, sex, and the use of radiation therapy, all other baseline characteristics were statistically significantly different in incident users of ESAs between the pre- and post-policy periods. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period were more likely to be non-White, live in non-metropolitan areas, live in South, live in areas with low level of education, live in areas with low level of poverty, have one or more comorbidities, dead during the one-year follow-up period, have lung, ovarian, or prostate cancer, and not have surgery.

During the one-year follow-up period, 1,924 (18.18%) and 626 (17.18%) incident users of ESAs developed VTE in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .1748). In the unadjusted logistic regression analysis, we found that the implementation of Medicare reimbursement policy was not statistically significantly associated with the future development of VTE (OR: 0.93; 95% CI: 0.85-1.03).

In the adjusted logistic regression analysis, we controlled for potential confounding factors at the baseline. (Table 6.10) We found that the implementation of Medicare reimbursement policy was still not statistically significantly associated with the future development of VTE (OR: 0.93; 95% CI: 0.84-1.03). Factors statistically significantly associated with the future development of VTE included sex, race, region, poverty, vital status, and cancer type. Compared to females, incident users of ESAs who

were males were 15% less likely to develop VTE (OR: 0.85; 95% CI: 0.76-0.95). Compared to Whites, incident users of ESAs who were Black were 34% more likely to develop VTE (OR: 1.34; 95% CI: 1.12-1.61). Compared to those lived in West, incident users of ESAs who lived in Northeast were 19% more likely to develop VTE (OR: 1.19; 95% CI: 1.04-1.37); and incident users of ESAs who lived in South were 18% more likely to develop VTE (OR: 1.18; 95% CI: 1.04-1.33). Compared to those lived in areas with the lowest level of poverty, incident users of ESAs who lived in areas with the highest level of poverty were 25% less likely to develop VTE (OR: 0.75; 95% CI: 0.61-0.92). Compared to those alive after the one-year follow-up period, incident users of ESAs who died during the one-year follow-up period were 62% more likely to develop VTE (OR: 1.62; 95% CI: 1.47-1.79). Compared to those had a primary diagnosis of breast cancer, incident users of ESAs who had a primary diagnosis of colorectal cancer were 33% more likely to develop VTE (OR: 1.33; 95% CI: 1.12-1.57); and incident users of ESAs who had a primary diagnosis of lung cancer were 24% more likely to develop VTE (OR: 1.24; 95% CI: 1.06-1.46).

In summary, the risk of VTE associated with ESAs during the one-year follow-up period in cancer patients with chemotherapy-induced anemia was not changed after the implementation of Medicare reimbursement policy.

6.3 Results on the Costs

After applying the inclusion and exclusion criteria in Aim 3, in the treatment group, we identified 17,382 incident users of ESAs (12,892 (74.17%) in the pre-policy period and 4,490 (25.83%) in the post-policy period). (Figure 6.4 and Table 6.11) In the

control group, we identified 3,069 incident users of ESAs (1,763 (57.45%) in the pre-policy period and 1,306 (42.55%) in the post-policy period). (Figure 6.5 and Table 6.11).

Table 6.11 summarized baseline characteristics of incident users of ESAs between the pre- and post-policy periods in the treatment and control groups. In the treatment group, except for age and sex, all other baseline characteristics were statistically significantly different in incident users of ESAs between the pre- and post-policy periods. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period were more likely to be non-White, live in non-metropolitan areas, live in South, live in areas with low level of education, live in areas with low level of poverty, have one or more comorbidities, and dead during the one-year follow-up period. In the control group, except for region, all other baseline characteristics were similar in incident users of ESAs between the pre- and post-policy periods. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period were more likely to be live in South or West.

6.3.1 Results on the Anemia-Related Costs

Table 6.12 summarized average anemia-related costs (including Medicare payment and patient cost-sharing) in incident users of ESAs between the pre- and post-policy periods. In the treatment group, on average incident users of ESAs had anemia-related costs of $8,153.19 (standard deviation (SD): $10,391.06) and $7,843.67 (SD: $13,509.89) during the one-year follow-up period in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .1622). For Medicare payment of anemia-related costs, on average incident users of ESAs had $6,794.42 (SD:

$9,237.05) and $6,829.34 (SD: $12,544.48) during the one-year follow-up period in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .8642). For patient cost-sharing of anemia-related costs, on average incident users of ESAs had $1,358.76 (SD: $1,644.45) and $1,014.33 (SD: $1,442.35) during the one-year follow-up period in the pre- and post-policy periods, respectively. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period had statistically significant lower patient cost-sharing of anemia-related costs (P < .0001).

Similarly, in the control group, on average incident users of ESAs had anemia-related costs of $8,740.53 (SD: $13,761.47) and $9,282.03 (SD: $14,599.46) during the one-year follow-up period in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .2980). For Medicare payment of anemia-related costs, on average incident users of ESAs had $7,431.68 (SD: $12,424.46) and $8,084.79 (SD: $13,440.04) during the one-year follow-up period in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .1695). For patient cost-sharing of anemia-related costs, on average incident users of ESAs had $1,308.85 (SD: $1,768.06) and $1,197.24 (SD: $1,768.55) during the one-year follow-up period in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .0839).

In the unadjusted GLM analysis, we found that the implementation of Medicare reimbursement policy was statistically significantly associated with a 8.98% reduction in anemia-related costs (P = .0389). In the adjusted GLM analysis, we controlled for potential confounding factors at the baseline. (Table 6.13) We found that the

implementation of Medicare reimbursement policy was statistically significantly associated with a 11.20% reduction in anemia-related costs (P = .0113).

In Table 6.13, other factors statistically significantly associated with the change in anemia-related costs included age, sex, race, residence, region, education, poverty, comorbidity, and vital status. Compared to those aged 66 and 69, incident users of ESAs who were aged 70 and 74 on average had a 7.82% lower anemia-related costs (P = .0002); incident users of ESAs who were aged 75 and 79 on average had a 7.73% lower anemia-related costs (P = .0005); and incident users of ESAs who were aged 80 and over on average had a 16.99% lower anemia-related costs (P < .0001). Compared to females, incident users of ESAs who were males on average had a 8.62% higher anemia-related costs (P < .0001). Compared to Whites, incident users of ESAs who were Black on average had a 6.46% higher anemia-related costs (P = .0354). Compared to those lived in metropolitan areas, incident users of ESAs who lived in non-metropolitan areas on average had a 6.67% lower anemia-related costs (P = .0036). Compared to those lived in West, incident users of ESAs who lived in Northeast on average had a 4.92% higher anemia-related costs (P = .0349); and incident users of ESAs who lived in South on average had a 4.37% lower anemia-related costs (P = .0398). Compared to those lived in areas with the highest level of education, incident users of ESAs who lived in areas with the lower level of education on average had a 6.57% higher anemia-related costs (P = .0160) and incident users of ESAs who lived in areas with the lowest level of education on average had a 7.70% higher anemia-related costs (P = .0194). Compared to those lived in areas with the lowest level of poverty, incident users of ESAs who lived in areas with the higher level of poverty on average had a 5.78% lower anemia-related costs (P =

.0452). Compared to those without any comorbidity, incident users of ESAs who had a CCI of one on average had a 3.61% higher anemia-related costs (P = .0464); incident users of ESAs who had a CCI of two on average had a 8.44% higher anemia-related costs (P = .0005); and incident users of ESAs who had a CCI of three or more on average had a 15.14% higher anemia-related costs (P < .0001). Compared to those alive after the one-year follow-up period, incident users of ESAs who died during the one-year follow-up period on average had a 15.53% higher anemia-related costs (P < .0001).

When examining Medicare payment of anemia-related costs, we found that in the unadjusted GLM analysis, the implementation of Medicare reimbursement policy was not statistically significantly associated with Medicare payment of anemia-related costs (P = .1123). In the adjusted GLM analysis, we controlled for potential confounding factors at the baseline. (Table 6.14) We found that the implementation of Medicare reimbursement policy was statistically significantly associated with a 9.83% reduction in Medicare payment of anemia-related costs (P = .0310).

In Table 6.14, other factors statistically significantly associated with the change in Medicare payment of anemia-related costs included age, sex, race, residence, region, education, poverty, comorbidity, and vital status. Compared to those aged 66 and 69, incident users of ESAs who were aged 70 and 74 on average had a 8.74% lower Medicare payment of anemia-related costs (P < .0001); incident users of ESAs who were aged 75 and 79 on average had a 8.60% lower Medicare payment of anemia-related costs (P = .0002); and incident users of ESAs who were aged 80 and over on average had a 17.58% lower Medicare payment of anemia-related costs (P < .0001). Compared to females, incident users of ESAs who were males on average had a 8.81% higher

Medicare payment of anemia-related costs (P < .0001). Compared to Whites, incident users of ESAs who were Black on average had a 6.72% higher Medicare payment of anemia-related costs (P = .0338). Compared to those lived in metropolitan areas, incident users of ESAs who lived in non-metropolitan areas on average had a 8.16% lower Medicare payment of anemia-related costs (P = .0006). Compared to those lived in West, incident users of ESAs who lived in South on average had a 5.91% lower Medicare payment of anemia-related costs (P = .0071). Compared to those lived in areas with the highest level of education, incident users of ESAs who lived in areas with the lower level of education on average had a 7.16% higher Medicare payment of anemia-related costs (P = .0108) and incident users of ESAs who lived in areas with the lowest level of education on average had a 9.69% higher Medicare payment of anemia-related costs (P = .0043). Compared to those lived in areas with the lowest level of poverty, incident users of ESAs who lived in areas with the higher level of poverty on average had a 7.32% lower Medicare payment of anemia-related costs (P = .0139) and incident users of ESAs who lived in areas with the highest level of poverty on average had a 7.57% lower Medicare payment of anemia-related costs (P = .0357). Compared to those without any comorbidity, incident users of ESAs who had a CCI of one on average had a 3.96% higher Medicare payment of anemia-related costs (P = .0338); incident users of ESAs who had a CCI of two on average had a 9.81% higher Medicare payment of anemia-related costs (P < .0001); and incident users of ESAs who had a CCI of three or more on average had a 16.31% higher Medicare payment of anemia-related costs (P < .0001). Compared to those alive after the one-year follow-up period, incident users of ESAs who

died during the one-year follow-up period on average had a 19.71% higher Medicare payment of anemia-related costs (P < .0001).

When examining patient cost-sharing of anemia-related costs, we found that in the unadjusted GLM analysis, the implementation of Medicare reimbursement policy was statistically significantly associated with a 19.14% reduction in patient cost-sharing of anemia-related costs (P < .0001). In the adjusted GLM analysis, we controlled for potential confounding factors at the baseline. (Table 6.15) We found that the implementation of Medicare reimbursement policy was statistically significantly associated with a 18.40% reduction in patient cost-sharing of anemia-related costs (P < .0001).

In Table 6.15, other factors statistically significantly associated with the change in patient cost-sharing of anemia-related costs included age, sex, race, region, comorbidity, and vital status. Compared to those aged 66 and 69, incident users of ESAs who were aged 70 and 74 on average had a 3.96% lower patient cost-sharing of anemia-related costs (P = .0430); incident users of ESAs who were aged 75 and 79 on average had a 4.00% lower patient cost-sharing of anemia-related costs (P = .0494); and incident users of ESAs who were aged 80 and over on average had a 14.35% lower patient cost-sharing of anemia-related costs (P < .0001). Compared to females, incident users of ESAs who were males on average had a 8.48% higher patient cost-sharing of anemia-related costs (P < .0001). Compared to Whites, incident users of ESAs who were other races on average had a 7.22% lower patient cost-sharing of anemia-related costs (P = .0197). Compared to those lived in West, incident users of ESAs who lived in Northeast on average had a 9.90% higher patient cost-sharing of anemia-related costs (P < .0001); incident users of

ESAs who lived in Midwest on average had a 5.64% higher patient cost-sharing of anemia-related costs (P = .0252); and incident users of ESAs who lived in South on average had a 5.90% higher patient cost-sharing of anemia-related costs (P = .0026). Compared to those without any comorbidity, incident users of ESAs who had a CCI of three or more on average had a 8.70% higher patient cost-sharing of anemia-related costs (P = .0012). Compared to those alive after the one-year follow-up period, incident users of ESAs who died during the one-year follow-up period on average had a 7.75% lower patient cost-sharing of anemia-related costs (P < .0001).

In summary, anemia-related costs associated with ESAs during the one-year follow-up period in cancer patients with chemotherapy-induced anemia were reduced by 11.20% after the implementation of Medicare reimbursement policy. Specifically, Medicare payment of anemia-related costs were reduced by 9.83% and patient cost-sharing of anemia-related costs were reduced by 18.40%.

6.3.2 Results on the Total Medical Costs

Table 6.12 summarized average total medical costs (including Medicare payment and patient cost-sharing) in incident users of ESAs between the pre- and post-policy periods. In the treatment group, on average incident users of ESAs had total medical costs of $58,777.49 (SD: $41,369.36) and $55,850.92 (SD: $40,494.11) during the one-year follow-up period in the pre- and post-policy periods, respectively. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period had statistically significant lower total medical costs (P < .0001). For Medicare payment of total medical costs, on average incident users of ESAs had $48,845.85 (SD: $35,429.73) and $46,921.85 (SD: $34,962.77) during the one-year follow-up period in the pre- and post-

policy periods, respectively. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period had statistically significant lower Medicare payment of total medical costs (P = .0017). For patient cost-sharing of total medical costs, on average incident users of ESAs had $9,931.64 (SD: $7,365.37) and $8,929.06 (SD: $6,706.04) during the one-year follow-up period in the pre- and post-policy periods, respectively. Compared to those in the pre-policy period, incident users of ESAs in the post-policy period had statistically significant lower patient cost-sharing of total medical costs (P < .0001).

Similarly, in the control group, on average incident users of ESAs had total medical costs of $51,476.36 (SD: $53,823.64) and $55,219.84 (SD: $58,325.85) during the one-year follow-up period in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .0694). For Medicare payment of total medical costs, on average incident users of ESAs had $44,260.17 (SD: $47,398.36) and $47,602.76 (SD: $50,850.23) during the one-year follow-up period in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .0640). For patient cost-sharing of total medical costs, on average incident users of ESAs had $7,216.19 (SD: $7,440.38) and $7,617.09 (SD: $8,493.59) during the one-year follow-up period in the pre- and post-policy periods, respectively. The difference was not statistically significant (P = .1733).

In the unadjusted GLM analysis, we found that the implementation of Medicare reimbursement policy was statistically significantly associated with a 12.14% reduction in total medical costs (P < .0001). In the adjusted GLM analysis, we controlled for potential confounding factors at the baseline. (Table 6.16) We found that the

implementation of Medicare reimbursement policy was statistically significantly associated with a 11.96% reduction in total medical costs (P = .0001).

In Table 6.16, other factors statistically significantly associated with the change in total medical costs included age, sex, race, residence, region, education, poverty, comorbidity, and vital status. Compared to those aged 66 and 69, incident users of ESAs who were aged 70 and 74 on average had a 4.39% lower total medical costs (P = .0030); incident users of ESAs who were aged 75 and 79 on average had a 6.90% lower total medical costs (P < .0001); and incident users of ESAs who were aged 80 and over on average had a 15.31% lower total medical costs (P < .0001). Compared to females, incident users of ESAs who were males on average had a 5.41% higher total medical costs (P < .0001). Compared to Whites, incident users of ESAs who were Black on average had a 5.26% higher total medical costs (P = .0135); and incident users of ESAs who were other races on average had a 4.83% higher total medical costs (P = .0394). Compared to those lived in metropolitan areas, incident users of ESAs who lived in non-metropolitan areas on average had a 5.97% lower total medical costs (P = .0002). Compared to those lived in West, incident users of ESAs who lived in Northeast on average had a 3.56% higher total medical costs (P = .0286); and incident users of ESAs who lived in South on average had a 7.89% lower total medical costs (P < .0001). Compared to those lived in areas with the highest level of education, incident users of ESAs who lived in areas with the lower level of education on average had a 3.90% higher total medical costs (P = .0412). Compared to those lived in areas with the lowest level of poverty, incident users of ESAs who lived in areas with the lower level of poverty on average had a 4.82% lower total medical costs (P = .0046); and incident users of ESAs

who lived in areas with the higher level of poverty on average had a 5.34% lower total medical costs (P = .0084). Compared to those without any comorbidity, incident users of ESAs who had a CCI of three or more on average had a 20.58% higher total medical costs (P < .0001). Compared to those alive after the one-year follow-up period, incident users of ESAs who died during the one-year follow-up period on average had a 6.04% lower total medical costs (P < .0001).

When examining Medicare payment of total medical costs, we found that in the unadjusted GLM analysis, the implementation of Medicare reimbursement policy was statistically significantly associated with a 11.30% reduction in Medicare payment of total medical costs (P = .0003). In the adjusted GLM analysis, we controlled for potential confounding factors at the baseline. (Table 6.17) We found that the implementation of Medicare reimbursement policy was statistically significantly associated with a 11.59% reduction in Medicare payment of total medical costs (P = .0003).

In Table 6.17, other factors statistically significantly associated with the change in Medicare payment of total medical costs included age, sex, race, residence, region, education, poverty, and comorbidity. Compared to those aged 66 and 69, incident users of ESAs who were aged 70 and 74 on average had a 4.44% lower Medicare payment of total medical costs (P = .0036); incident users of ESAs who were aged 75 and 79 on average had a 6.33% lower Medicare payment of total medical costs (P < .0001); and incident users of ESAs who were aged 80 and over on average had a 14.32% lower Medicare payment of total medical costs (P < .0001). Compared to females, incident users of ESAs who were males on average had a 5.16% higher Medicare payment of total medical costs (P < .0001). Compared to Whites, incident users of ESAs who were Black

on average had a 5.47% higher Medicare payment of total medical costs (P = .0126); and incident users of ESAs who were other races on average had a 5.01% higher Medicare payment of total medical costs (P = .0380). Compared to those lived in metropolitan areas, incident users of ESAs who lived in non-metropolitan areas on average had a 7.09% lower Medicare payment of total medical costs (P < .0001). Compared to those lived in West, incident users of ESAs who lived in Northwest on average had a 3.46% higher Medicare payment of total medical costs (P = .0393); and incident users of ESAs who lived in South on average had a 8.45% lower Medicare payment of total medical costs (P < .0001). Compared to those lived in areas with the highest level of education, incident users of ESAs who lived in areas with the lower level of education on average had a 3.98% higher Medicare payment of total medical costs (P = .0431); and incident users of ESAs who lived in areas with the lowest level of education on average had a 4.93% higher Medicare payment of total medical costs (P = .0369). Compared to those lived in areas with the lowest level of poverty, incident users of ESAs who lived in areas with the lower level of poverty on average had a 4.92% lower Medicare payment of total medical costs (P = .0049); and incident users of ESAs who lived in areas with the higher level of poverty on average had a 5.66% lower Medicare payment of total medical costs (P = .0066). Compared to those without any comorbidity, incident users of ESAs who had a CCI of three or more on average had a 21.91% higher Medicare payment of total medical costs (P < .0001).

When examining patient cost-sharing of total medical costs, we found that in the unadjusted GLM analysis, the implementation of Medicare reimbursement policy was statistically significantly associated with a 16.06% reduction in patient cost-sharing of

total medical costs (P < .0001). In the adjusted GLM analysis, we controlled for potential confounding factors at the baseline. (Table 6.18) We found that the implementation of Medicare reimbursement policy was statistically significantly associated with a 13.58% reduction in patient cost-sharing of total medical costs (P < .0001).

In Table 6.18, other factors statistically significantly associated with the change in patient cost-sharing of total medical costs included age, sex, region, poverty, comorbidity, and vital status. Compared to those aged 66 and 69, incident users of ESAs who were aged 70 and 74 on average had a 4.26% lower patient cost-sharing of total medical costs (P = .0040); incident users of ESAs who were aged 75 and 79 on average had a 9.70% lower patient cost-sharing of total medical costs (P < .0001); and incident users of ESAs who were aged 80 and over on average had a 20.32% lower patient cost-sharing of total medical costs (P < .0001). Compared to females, incident users of ESAs who were males on average had a 7.46% higher patient cost-sharing of total medical costs (P < .0001). Compared to those lived in West, incident users of ESAs who lived in Northeast on average had a 4.22% higher patient cost-sharing of total medical costs (P = .0095); and incident users of ESAs who lived in South on average had a 4.63% lower patient cost-sharing of total medical costs (P = .0016). Compared to those lived in areas with the lowest level of poverty, incident users of ESAs who lived in areas with the lower level of poverty on average had a 4.18% lower patient cost-sharing of total medical costs (P = .0140). Compared to those without any comorbidity, incident users of ESAs who had a CCI of one on average had a 3.93% lower patient cost-sharing of total medical costs (P = .0019); incident users of ESAs who had a CCI of two on average had a 6.23% lower patient cost-sharing of total medical costs (P = .0002); and incident users of ESAs

who had a CCI of three or more on average had a 14.07% higher patient cost-sharing of total medical costs ($P < .0001$). Compared to those alive after the one-year follow-up period, incident users of ESAs who died during the one-year follow-up period on average had a 30.16% lower patient cost-sharing of total medical costs ($P < .0001$).

In summary, total medical costs associated with ESAs during the one-year follow-up period in cancer patients with chemotherapy-induced anemia were reduced by 11.96% after the implementation of Medicare reimbursement policy. Specifically, Medicare payment of total medical costs were reduced by 11.59% and patient cost-sharing of total medical costs were reduced by 13.58%.

Table 6.1: Total number of eligible cancer patients and percentage of patients received ESAs or blood transfusions in each month

Month	Total N	ESAs %	Blood transfusions %
2003			
January	55,719	5.23	1.29
February	56,503	5.02	1.14
March	57,412	5.23	1.29
April	58,206	5.31	1.19
May	59,077	5.53	1.25
June	60,002	5.53	1.14
July	60,979	5.76	1.24
August	61,750	5.60	1.17
September	62,621	5.60	1.18
October	63,551	5.64	1.26
November	63,974	5.16	1.08
December	64,592	5.46	1.17
2004			
January	65,367	5.28	1.23
February	66,022	5.13	1.17
March	67,031	5.63	1.26
April	67,814	5.42	1.11
May	68,458	5.48	1.09
June	69,308	5.81	1.14
July	70,141	5.59	1.14
August	70,982	5.65	1.19
September	71,821	5.54	1.05
October	72,537	5.14	1.16
November	73,185	4.97	1.12
December	73,762	4.99	1.03
2005			
January	74,521	4.77	1.04
February	74,990	4.70	1.05
March	75,780	5.04	1.15
April	76,264	4.98	1.03
May	76,942	5.02	1.08
June	77,674	5.14	1.06
July	78,381	5.02	1.11
August	79,161	5.19	1.11
September	79,593	4.96	0.96
October	80,152	4.75	0.99
November	80,775	4.85	0.92

December	81,177	4.66	0.97
2006			
January	81,405	4.60	0.98
February	81,786	4.54	0.96
March	82,514	4.83	1.03
April	82,805	4.66	0.94
May	83,471	4.95	0.97
June	84,004	4.86	0.97
July	84,700	4.71	0.98
August	85,463	4.87	1.01
September	85,895	4.53	0.90
October	86,700	4.63	0.98
November	87,348	4.57	0.95
December	87,861	4.24	0.83
2007			
January	86,999	4.39	0.91
February	87,604	4.04	0.89
March	88,364	3.93	0.95
April	88,810	3.55	0.95
May	89,548	3.50	0.98
June	90,187	3.15	0.91
July	90,967	3.21	0.88
August	91,898	2.08	1.06
September	92,464	1.68	0.92
October	93,400	1.78	1.00
November	93,988	1.60	0.98
December	94,664	1.49	0.89
2008			
January	94,045	1.47	0.94
February	94,532	1.42	0.91
March	95,192	1.36	1.02
April	95,761	1.24	1.02
May	96,385	1.23	1.01
June	97,135	1.23	0.98
July	98,005	1.27	1.01
August	98,774	1.10	0.95
September	99,629	0.97	1.01
October	100,608	1.06	1.01
November	101,167	0.91	0.96
December	101,875	0.97	0.97
2009			
January	101,269	0.85	0.96
February	101,773	0.86	0.89

March	102,573	0.91	1.05
April	103,247	0.95	1.02
May	103,967	0.91	1.00
June	104,807	0.90	1.03
July	105,751	0.85	1.04
August	106,590	0.84	0.96
September	107,333	0.79	0.96
October	108,298	0.79	1.02
November	108,914	0.75	0.94
December	109,646	0.79	0.96

ESAs: erythropoiesis-stimulating agents

Table 6.2: Total number of eligible CKD patients and percentage of patients received ESAs or blood transfusions in each month

Month	Total N	ESAs %	Blood transfusions %
2003			
January	28,684	5.68	1.14
February	28,952	5.54	1.03
March	29,275	5.60	1.02
April	29,570	5.53	1.00
May	29,944	5.49	1.09
June	30,232	5.50	0.93
July	30,672	5.64	0.94
August	31,055	5.58	0.99
September	31,481	5.51	0.97
October	31,903	5.60	1.06
November	32,234	5.44	0.95
December	32,572	5.50	1.12
2004			
January	32,892	5.47	1.09
February	33,138	5.46	0.96
March	33,531	5.63	1.12
April	33,825	5.63	1.05
May	34,168	5.56	0.92
June	34,546	5.57	0.96
July	34,899	5.58	0.99
August	35,339	5.50	0.93
September	35,732	5.62	0.96
October	36,175	5.42	0.96
November	36,457	5.45	0.95
December	36,872	5.38	1.10
2005			
January	37,265	5.40	1.06
February	37,510	5.35	0.98
March	37,848	5.39	1.04
April	38,093	5.36	1.07
May	38,433	5.33	1.04
June	38,783	5.41	1.00
July	39,133	5.32	0.91
August	39,569	5.43	0.98
September	39,517	5.34	0.91
October	40,211	5.28	0.99
November	40,913	5.21	0.96

December	41,516	5.16	0.93
2006			
January	41,916	5.19	1.05
February	42,392	5.14	1.01
March	43,021	5.24	1.06
April	43,372	5.10	0.97
May	44,000	5.19	0.98
June	44,583	5.17	1.03
July	45,167	5.06	0.91
August	45,830	5.17	0.98
September	46,322	5.03	0.85
October	47,018	5.09	0.93
November	47,505	5.06	0.86
December	48,049	4.96	0.92
2007			
January	47,790	5.06	1.05
February	48,168	4.96	0.89
March	48,618	4.88	0.96
April	49,023	4.76	1.01
May	49,581	4.74	1.05
June	50,128	4.66	0.90
July	50,726	4.64	0.83
August	51,363	4.51	0.94
September	51,852	4.42	0.85
October	52,462	4.41	0.87
November	52,959	4.30	0.89
December	53,548	4.16	0.92
2008			
January	53,670	4.28	1.07
February	54,073	4.09	0.95
March	54,507	4.05	1.03
April	54,786	4.15	1.02
May	55,238	4.11	1.04
June	55,653	4.09	0.87
July	56,281	4.03	0.90
August	56,806	4.01	0.95
September	57,366	3.94	0.88
October	57,939	3.97	0.96
November	58,375	3.77	0.87
December	58,916	3.81	0.98
2009			
January	58,679	3.83	1.07
February	59,051	3.81	0.88

March	59,490	3.88	0.97
April	59,856	3.88	0.96
May	60,376	3.75	0.86
June	60,933	3.77	0.96
July	61,634	3.81	0.88
August	62,132	3.63	0.94
September	62,738	3.72	0.85
October	63,244	3.69	0.92
November	63,679	3.49	0.90
December	64,157	3.57	0.95

CKD: chronic kidney disease; ESAs: erythropoiesis-stimulating agents

Table 6.3: Change in the monthly utilization of ESAs before and after the implementation of Medicare reimbursement policy

	Estimate	P
Intercept	5.73	<.0001
Month	-0.01	<.0001
Policy change	-0.83	<.0001
Month after policy change	-0.01	0.1905
Group assignment	0.06	0.5046
Month × Group assignment	-0.02	<.0001
Policy change × Group assignment	-2.13	<.0001
Month after policy change × Group assignment	0.02	0.1366

ESAs: erythropoiesis-stimulating agents

Table 6.4: Change in the monthly utilization of blood transfusions before and after the implementation of Medicare reimbursement policy

	Estimate	P
Intercept	1.03	<.0001
Month	0.00	0.0020
Policy change	0.00	0.9609
Month after policy change	0.00	0.9194
Group assignment	0.22	<.0001
Month × Group assignment	-0.01	<.0001
Policy change × Group assignment	0.10	0.0186
Month after policy change × Group assignment	0.01	0.0524

Table 6.5: Baseline characteristics of incident users of ESAs free of MI one year before the index date between the pre- and post-policy periods (N = 17,236)

	Pre-policy N = 12,791 %	Post-policy N = 4,445 %	P
Age			0.1429
66-69	26.77	25.94	
70-74	30.00	29.74	
75-79	23.84	25.53	
80+	19.39	18.79	
Sex			0.6545
Male	39.73	40.11	
Female	60.27	59.89	
Race			0.0062
White	88.34	86.68	
Black	6.67	7.22	
Other	4.99	6.10	
Residence			0.0008
Metropolitan	83.26	81.06	
Non-metropolitan	16.74	18.94	
Region			0.0020
Northeast	21.66	20.72	
Midwest	11.95	11.50	
South	27.53	30.55	
West	38.86	37.23	
Education			0.0062
1st quartile	25.37	24.03	
2nd quartile	25.31	23.91	
3rd quartile	25.22	25.51	
4th quartile	24.10	26.55	
Poverty			0.0273
1st quartile	25.42	24.58	
2nd quartile	25.47	23.86	
3rd quartile	24.74	25.22	
4th quartile	24.38	26.34	
CCI			<.0001
0	50.52	44.39	
1	31.69	35.21	
2	12.31	13.23	
3+	5.49	7.18	
Vital status			<.0001
Alive	56.19	52.13	
Dead	43.81	47.87	

Cancer type			<.0001
Breast cancer	19.97	18.74	
Colorectal cancer	15.44	10.66	
Lung cancer	38.12	42.18	
Lymphomas	12.70	12.64	
Ovarian cancer	4.66	5.76	
Prostate cancer	9.11	10.01	
Surgery			<.0001
Yes	50.35	42.25	
No	48.58	56.81	
Unknown	1.07	0.94	
Radiation therapy			0.1642
Yes	35.45	36.76	
No	62.61	61.08	
Unknown	1.94	2.16	

ESAs: erythropoiesis-stimulating agents; MI: myocardial infarction; CCI: Charlson comorbidity index

Table 6.6: Adjusted logistic regression analysis on factors associated with the future development of MI

	OR	95% CI	
Policy change			
Pre-policy period	Ref		
Post-policy period	1.01	0.74	1.39
Age			
66-69	Ref		
70-74	0.89	0.58	1.37
75-79	1.64	1.10	2.43
80+	1.31	0.84	2.05
Sex			
Male	0.96	0.69	1.33
Female	Ref		
Race			
White	Ref		
Black	1.20	0.68	2.10
Other	0.67	0.30	1.46
Residence			
Metropolitan	Ref		
Non-metropolitan	1.15	0.77	1.72
Region			
Northeast	0.96	0.63	1.47
Midwest	0.88	0.53	1.45
South	0.86	0.58	1.28
West	Ref		
Education			
1st quartile	Ref		
2nd quartile	1.53	0.97	2.41
3rd quartile	1.85	1.10	3.13
4th quartile	1.82	0.97	3.41
Poverty			
1st quartile	Ref		
2nd quartile	0.74	0.47	1.16
3rd quartile	0.61	0.36	1.06
4th quartile	0.63	0.33	1.19
CCI			
0	Ref		
1	1.11	0.78	1.57
2	1.70	1.14	2.55
3+	2.04	1.26	3.31
Vital status			
Alive	Ref		
Dead	2.40	1.72	3.34

Cancer type			
Breast cancer	Ref		
Colorectal cancer	0.69	0.36	1.34
Lung cancer	1.37	0.79	2.39
Lymphomas	1.18	0.62	2.25
Ovarian cancer	0.53	0.18	1.57
Prostate cancer	1.08	0.52	2.25
Surgery			
Yes	0.95	0.65	1.39
No	Ref		
Unknown	0.99	0.23	4.20
Radiation therapy			
Yes	0.81	0.59	1.11
No	Ref		
Unknown	0.82	0.25	2.69

MI: myocardial infarction; OR: odds ratio; CI: confidence interval; CCI: Charlson comorbidity index

Table 6.7: Baseline characteristics of incident users of ESAs free of stroke one year before the index date between the pre- and post-policy periods (N = 16,250)

	Pre-policy N = 12,061 %	Post-policy N = 4,189 %	P
Age			0.2760
66-69	27.05	26.21	
70-74	30.08	29.86	
75-79	23.82	25.28	
80+	19.05	18.64	
Sex			0.3507
Male	39.36	40.18	
Female	60.64	59.82	
Race			0.0098
White	88.39	86.99	
Black	6.64	6.85	
Other	4.97	6.16	
Residence			0.0002
Metropolitan	83.27	80.76	
Non-metropolitan	16.73	19.24	
Region			0.0006
Northeast	21.61	20.53	
Midwest	12.01	11.15	
South	27.41	30.72	
West	38.98	37.60	
Education			0.0029
1st quartile	25.37	24.29	
2nd quartile	25.43	23.82	
3rd quartile	25.24	25.10	
4th quartile	23.96	26.79	
Poverty			0.0307
1st quartile	25.46	24.82	
2nd quartile	25.35	23.69	
3rd quartile	24.85	25.08	
4th quartile	24.33	26.41	
CCI			<.0001
0	52.41	45.76	
1	31.27	34.95	
2	11.62	12.94	
3+	4.70	6.35	
Vital status			<.0001
Alive	56.78	52.90	
Dead	43.22	47.10	

Cancer type			<.0001
Breast cancer	20.26	19.00	
Colorectal cancer	15.70	10.77	
Lung cancer	37.56	41.85	
Lymphomas	12.70	12.53	
Ovarian cancer	4.67	5.92	
Prostate cancer	9.10	9.93	
Surgery			<.0001
Yes	50.92	42.85	
No	48.06	56.17	
Unknown	1.02	0.98	
Radiation therapy			0.2718
Yes	35.34	36.50	
No	62.70	61.35	
Unknown	1.97	2.15	

ESAs: erythropoiesis-stimulating agents; CCI: Charlson comorbidity index

Table 6.8: Adjusted logistic regression analysis on factors associated with the future development of stroke

	OR	95% CI	
Policy change			
Pre-policy period	Ref		
Post-policy period	0.99	0.84	1.15
Age			
66-69	Ref		
70-74	1.15	0.95	1.39
75-79	1.08	0.88	1.31
80+	1.42	1.16	1.74
Sex			
Male	0.93	0.79	1.09
Female	Ref		
Race			
White	Ref		
Black	1.22	0.94	1.59
Other	0.88	0.63	1.23
Residence			
Metropolitan	Ref		
Non-metropolitan	1.04	0.85	1.26
Region			
Northeast	1.11	0.90	1.37
Midwest	1.22	0.97	1.55
South	0.99	0.82	1.20
West	Ref		
Education			
1st quartile	Ref		
2nd quartile	1.19	0.95	1.48
3rd quartile	1.25	0.97	1.61
4th quartile	1.88	1.41	2.52
Poverty			
1st quartile	Ref		
2nd quartile	0.78	0.62	0.98
3rd quartile	0.85	0.65	1.10
4th quartile	0.70	0.51	0.95
CCI			
0	Ref		
1	1.13	0.96	1.32
2	1.25	1.01	1.54
3+	1.27	0.95	1.69
Vital status			
Alive	Ref		
Dead	1.78	1.53	2.07

Cancer type			
Breast cancer	Ref		
Colorectal cancer	0.89	0.67	1.18
Lung cancer	1.36	1.05	1.77
Lymphomas	1.41	1.06	1.89
Ovarian cancer	0.95	0.63	1.41
Prostate cancer	1.25	0.89	1.77
Surgery			
Yes	1.05	0.87	1.25
No	Ref		
Unknown	0.91	0.45	1.84
Radiation therapy			
Yes	0.99	0.85	1.15
No	Ref		
Unknown	1.05	0.64	1.74

OR: odds ratio; CI: confidence interval; CCI: Charlson comorbidity index

Table 6.9: Baseline characteristics of incident users of ESAs free of VTE one year before the index date between the pre- and post-policy periods (N = 14,224)

	Pre-policy N = 10,581 %	Post-policy N = 3,643 %	P
Age			0.2463
66-69	27.03	25.94	
70-74	30.28	29.98	
75-79	23.51	25.09	
80+	19.18	19.00	
Sex			0.4584
Male	39.60	40.30	
Female	60.40	59.70	
Race			0.0115
White	88.49	86.77	
Black	6.40	6.97	
Other	5.11	6.26	
Residence			0.0015
Metropolitan	82.79	80.46	
Non-metropolitan	17.21	19.54	
Region			0.0129
Northeast	21.08	20.18	
Midwest	11.60	10.98	
South	27.85	30.69	
West	39.47	38.16	
Education			0.0099
1st quartile	24.88	24.08	
2nd quartile	25.73	23.82	
3rd quartile	25.12	25.24	
4th quartile	24.26	26.86	
Poverty			0.0430
1st quartile	24.88	23.91	
2nd quartile	25.51	24.25	
3rd quartile	25.29	25.21	
4th quartile	24.31	26.63	
CCI			<.0001
0	52.37	46.03	
1	31.41	35.44	
2	11.40	12.46	
3+	4.83	6.07	
Vital status			<.0001
Alive	57.89	53.34	
Dead	42.11	46.66	

Cancer type			<.0001
Breast cancer	21.41	19.74	
Colorectal cancer	13.17	9.61	
Lung cancer	39.17	42.44	
Lymphomas	12.68	12.46	
Ovarian cancer	4.24	5.30	
Prostate cancer	9.33	10.46	
Surgery			<.0001
Yes	49.98	41.61	
No	48.91	57.43	
Unknown	1.12	0.96	
Radiation therapy			0.1572
Yes	36.61	37.72	
No	61.48	60.01	
Unknown	1.91	2.28	

ESAs: erythropoiesis-stimulating agents; VTE: venous thromboembolism; CCI: Charlson comorbidity index

Table 6.10: Adjusted logistic regression analysis on factors associated with the future development of VTE

	OR	95% CI	
Policy change			
Pre-policy period	Ref		
Post-policy period	0.93	0.84	1.03
Age			
66-69	Ref		
70-74	1.03	0.92	1.16
75-79	1.11	0.98	1.26
80+	0.98	0.85	1.12
Sex			
Male	0.85	0.76	0.95
Female	Ref		
Race			
White	Ref		
Black	1.34	1.12	1.61
Other	0.88	0.71	1.10
Residence			
Metropolitan	Ref		
Non-metropolitan	0.93	0.82	1.06
Region			
Northeast	1.19	1.04	1.37
Midwest	1.10	0.94	1.28
South	1.18	1.04	1.33
West	Ref		
Education			
1st quartile	Ref		
2nd quartile	1.03	0.90	1.17
3rd quartile	0.99	0.85	1.16
4th quartile	0.98	0.81	1.18
Poverty			
1st quartile	Ref		
2nd quartile	0.96	0.84	1.10
3rd quartile	0.87	0.74	1.03
4th quartile	0.75	0.61	0.92
CCI			
0	Ref		
1	0.96	0.87	1.06
2	0.98	0.84	1.13
3+	1.05	0.85	1.28
Vital status			
Alive	Ref		
Dead	1.62	1.47	1.79

Cancer type			
Breast cancer	Ref		
Colorectal cancer	1.33	1.12	1.57
Lung cancer	1.24	1.06	1.46
Lymphomas	1.19	0.99	1.44
Ovarian cancer	1.16	0.91	1.47
Prostate cancer	1.17	0.93	1.46
Surgery			
Yes	1.05	0.93	1.19
No	Ref		
Unknown	1.12	0.73	1.74
Radiation therapy			
Yes	0.94	0.85	1.04
No	Ref		
Unknown	0.74	0.51	1.07

VTE: venous thromboembolism; OR: odds ratio; CI: confidence interval; CCI: Charlson comorbidity index

Table 6.11: Baseline characteristics of incident users of ESAs between the pre- and post-policy periods

	Treatment group N = 17,382			Control group N = 3,069		
	Pre-policy N = 12,892 %	Post-policy N = 4,490 %	P	Pre-policy N = 1,763 %	Post-policy N = 1,306 %	P
Age			0.1606			0.3033
66-69	26.72	25.75		14.97	15.16	
70-74	29.94	29.82		18.49	17.92	
75-79	23.95	25.55		24.33	21.82	
80+	19.39	18.89		42.20	45.10	
Sex			0.5843			0.5017
Male	39.87	40.33		45.09	43.87	
Female	60.13	59.67		54.91	56.13	
Race			0.0056			0.6113
White	88.37	86.70		75.53	74.00	
Black	6.65	7.22		13.57	14.65	
Other	4.97	6.08		10.90	11.35	
Residence			0.0007			0.0593
Metropolitan	83.20	80.96		85.41	82.91	
Non-metropolitan	16.80	19.04		14.59	17.09	
Region			0.0017			0.0293
Northeast	21.68	20.76		22.12	18.15	
Midwest	11.98	11.43		11.51	10.87	
South	27.54	30.58		27.96	31.09	
West	38.79	37.24		38.40	39.89	
Education			0.0055			0.5052
1st quartile	25.37	24.03		21.77	19.94	
2nd quartile	25.28	23.91		22.47	24.00	

3rd quartile	25.23	25.42		25.10	24.32	
4th quartile	24.13	26.64		30.66	31.74	
Poverty			0.0242			0.3630
1st quartile	25.43	24.59		22.76	20.10	
2nd quartile	25.45	23.82		23.23	23.92	
3rd quartile	24.72	25.23		23.99	24.32	
4th quartile	24.40	26.36		30.02	31.66	
CCI			<.0001			0.3625
0	50.16	43.96		21.10	19.60	
1	31.61	35.19		23.37	25.34	
2	12.46	13.41		23.60	21.98	
3+	5.77	7.44		31.93	33.08	
Vital status			<.0001			0.8719
Alive	56.14	51.94		76.97	76.72	
Dead	43.86	48.06		23.03	23.28	

ESAs: erythropoiesis-stimulating agents; CCI: Charlson comorbidity index

Table 6.12: Average anemia-related and total medical costs in incident users of ESAs between the pre- and post-policy periods

	Treatment group N = 17,382					Control group N = 3,069				
	Pre-policy N = 12,892		Post-policy N = 4,490		P	Pre-policy N = 1,763		Post-policy N = 1,306		P
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
Anemia-related costs	8,153.19	10,391.06	7,843.67	13,509.89	0.1622	8,740.53	13,761.47	9,282.03	14,599.46	0.2980
Medicare payment	6,794.42	9,237.05	6,829.34	12,544.48	0.8642	7,431.68	12,424.46	8,084.79	13,440.04	0.1695
Patient cost-sharing	1,358.76	1,644.45	1,014.33	1,442.35	<.0001	1,308.85	1,768.06	1,197.24	1,768.55	0.0839
Total medical costs	58,777.49	41,369.36	55,850.92	40,494.11	<.0001	51,476.36	53,823.64	55,219.84	58,325.85	0.0694
Medicare payment	48,845.85	35,429.73	46,921.85	34,962.77	0.0017	44,260.17	47,398.36	47,602.76	50,850.23	0.0640
Patient cost-sharing	9,931.64	7,365.37	8,929.06	6,706.04	<.0001	7,216.19	7,440.38	7,617.09	8,493.59	0.1733

ESAs: erythropoiesis-stimulating agents; SD: standard deviation

Table 6.13: Change in anemia-related costs before and after the implementation of Medicare reimbursement policy

	Estimate	P
Intercept	9.0831	<.0001
Policy change		
Pre-policy period	Ref	
Post-policy period	0.0512	0.1984
Group assignment		
Control group	Ref	
Treatment group	-0.0677	0.0234
Policy change × Group assignment		
Otherwise	Ref	
Post-policy period and treatment group	-0.1120	0.0113
Age		
66-69	Ref	
70-74	-0.0782	0.0002
75-79	-0.0773	0.0005
80+	-0.1699	<.0001
Sex		
Male	0.0862	<.0001
Female	Ref	
Race		
White	Ref	
Black	0.0646	0.0354
Other	-0.0187	0.5788
Residence		
Metropolitan	Ref	
Non-metropolitan	-0.0667	0.0036
Region		
Northeast	0.0492	0.0349
Midwest	-0.0048	0.8601
South	-0.0437	0.0398
West	Ref	
Education		
1st quartile	Ref	
2nd quartile	-0.0069	0.7694
3rd quartile	0.0657	0.0160
4th quartile	0.0770	0.0194
Poverty		
1st quartile	Ref	
2nd quartile	-0.0413	0.0887
3rd quartile	-0.0578	0.0452
4th quartile	-0.0622	0.0753

CCI		
0	Ref	
1	0.0361	0.0464
2	0.0844	0.0005
3+	0.1514	<.0001
Vital status		
Alive	Ref	
Dead	0.1553	<.0001

CCI: Charlson comorbidity index

Table 6.14: Change in Medicare payment of anemia-related costs before and after the implementation of Medicare reimbursement policy

	Estimate	P
Intercept	8.8665	<.0001
Policy change		
Pre-policy period	Ref	
Post-policy period	0.0734	0.0736
Group assignment		
Control group	Ref	
Treatment group	-0.0882	0.0042
Policy change × Group assignment		
Otherwise	Ref	
Post-policy period and treatment group	-0.0983	0.0310
Age		
66-69	Ref	
70-74	-0.0874	<.0001
75-79	-0.0860	0.0002
80+	-0.1758	<.0001
Sex		
Male	0.0881	<.0001
Female	Ref	
Race		
White	Ref	
Black	0.0672	0.0338
Other	-0.0099	0.7761
Residence		
Metropolitan	Ref	
Non-metropolitan	-0.0816	0.0006
Region		
Northeast	0.0416	0.0837
Midwest	-0.0165	0.5575
South	-0.0591	0.0071
West	Ref	
Education		
1st quartile	Ref	
2nd quartile	-0.0046	0.8504
3rd quartile	0.0716	0.0108
4th quartile	0.0969	0.0043
Poverty		
1st quartile	Ref	
2nd quartile	-0.0465	0.0626
3rd quartile	-0.0732	0.0139
4th quartile	-0.0757	0.0357

CCI		
0	Ref	
1	0.0396	0.0338
2	0.0981	<.0001
3+	0.1631	<.0001
Vital status		
Alive	Ref	
Dead	0.1971	<.0001

CCI: Charlson comorbidity index

Table 6.15: Change in patient cost-sharing of anemia-related costs before and after the implementation of Medicare reimbursement policy

	Estimate	P
Intercept	7.1513	<.0001
Policy change		
Pre-policy period	Ref	
Post-policy period	-0.0898	0.0143
Group assignment		
Control group	Ref	
Treatment group	0.0512	0.0619
Policy change × Group assignment		
Otherwise	Ref	
Post-policy period and treatment group	-0.1840	<.0001
Age		
66-69	Ref	
70-74	-0.0396	0.0430
75-79	-0.0400	0.0494
80+	-0.1435	<.0001
Sex		
Male	0.0848	<.0001
Female	Ref	
Race		
White	Ref	
Black	0.0386	0.1706
Other	-0.0722	0.0197
Residence		
Metropolitan	Ref	
Non-metropolitan	0.0161	0.4440
Region		
Northeast	0.0990	<.0001
Midwest	0.0564	0.0252
South	0.0590	0.0026
West	Ref	
Education		
1st quartile	Ref	
2nd quartile	-0.0110	0.6156
3rd quartile	0.0381	0.1333
4th quartile	-0.0315	0.3014
Poverty		
1st quartile	Ref	
2nd quartile	-0.0168	0.4559
3rd quartile	0.0205	0.4438
4th quartile	0.0064	0.8435

CCI		
0	Ref	
1	0.0272	0.1027
2	0.0068	0.7597
3+	0.0870	0.0012
Vital status		
Alive	Ref	
Dead	-0.0775	<.0001

CCI: Charlson comorbidity index

Table 6.16: Change in total medical costs before and after the implementation of Medicare reimbursement policy

	Estimate	P
Intercept	10.8772	<.0001
Policy change		
Pre-policy period	Ref	
Post-policy period	0.0648	0.0195
Group assignment		
Control group	Ref	
Treatment group	0.1914	<.0001
Policy change × Group assignment		
Otherwise	Ref	
Post-policy period and treatment group	-0.1196	0.0001
Age		
66-69	Ref	
70-74	-0.0439	0.0030
75-79	-0.0690	<.0001
80+	-0.1531	<.0001
Sex		
Male	0.0541	<.0001
Female	Ref	
Race		
White	Ref	
Black	0.0526	0.0135
Other	0.0483	0.0394
Residence		
Metropolitan	Ref	
Non-metropolitan	-0.0597	0.0002
Region		
Northeast	0.0356	0.0286
Midwest	-0.0092	0.6261
South	-0.0789	<.0001
West	Ref	
Education		
1st quartile	Ref	
2nd quartile	-0.0193	0.2419
3rd quartile	0.0390	0.0412
4th quartile	0.0441	0.0548
Poverty		
1st quartile	Ref	
2nd quartile	-0.0482	0.0046
3rd quartile	-0.0534	0.0084
4th quartile	-0.0352	0.1492

CCI		
0	Ref	
1	-0.0025	0.8412
2	0.0058	0.7306
3+	0.2058	<.0001
Vital status		
Alive	Ref	
Dead	-0.0604	<.0001

CCI: Charlson comorbidity index

Table 6.17: Change in Medicare payment of total medical costs before and after the implementation of Medicare reimbursement policy

	Estimate	P
Intercept	10.7021	<.0001
Policy change		
Pre-policy period	Ref	
Post-policy period	0.0693	0.0152
Group assignment		
Control group	Ref	
Treatment group	0.1600	<.0001
Policy change × Group assignment		
Otherwise	Ref	
Post-policy period and treatment group	-0.1159	0.0003
Age		
66-69	Ref	
70-74	-0.0444	0.0036
75-79	-0.0633	<.0001
80+	-0.1432	<.0001
Sex		
Male	0.0516	<.0001
Female	Ref	
Race		
White	Ref	
Black	0.0547	0.0126
Other	0.0501	0.0380
Residence		
Metropolitan	Ref	
Non-metropolitan	-0.0709	<.0001
Region		
Northeast	0.0346	0.0393
Midwest	-0.0157	0.4226
South	-0.0845	<.0001
West	Ref	
Education		
1st quartile	Ref	
2nd quartile	-0.0203	0.2314
3rd quartile	0.0398	0.0431
4th quartile	0.0493	0.0369
Poverty		
1st quartile	Ref	
2nd quartile	-0.0492	0.0049
3rd quartile	-0.0566	0.0066
4th quartile	-0.0368	0.1426

CCI		
0	Ref	
1	0.0049	0.7038
2	0.0185	0.2849
3+	0.2191	<.0001
Vital status		
Alive	Ref	
Dead	-0.0150	0.1932

CCI: Charlson comorbidity index

Table 6.18: Change in patient cost-sharing of total medical costs before and after the implementation of Medicare reimbursement policy

	Estimate	P
Intercept	9.0243	<.0001
Policy change		
Pre-policy period	Ref	
Post-policy period	0.0391	0.1591
Group assignment		
Control group	Ref	
Treatment group	0.3646	<.0001
Policy change × Group assignment		
Otherwise	Ref	
Post-policy period and treatment group	-0.1358	<.0001
Age		
66-69	Ref	
70-74	-0.0426	0.0040
75-79	-0.0970	<.0001
80+	-0.2032	<.0001
Sex		
Male	0.0746	<.0001
Female	Ref	
Race		
White	Ref	
Black	0.0390	0.0667
Other	0.0389	0.0963
Residence		
Metropolitan	Ref	
Non-metropolitan	-0.0014	0.9302
Region		
Northeast	0.0422	0.0095
Midwest	0.0225	0.2362
South	-0.0463	0.0016
West	Ref	
Education		
1st quartile	Ref	
2nd quartile	-0.0117	0.4803
3rd quartile	0.0364	0.0580
4th quartile	0.0179	0.4367
Poverty		
1st quartile	Ref	
2nd quartile	-0.0418	0.0140
3rd quartile	-0.0383	0.0600
4th quartile	-0.0254	0.3000

CCI		
0	Ref	
1	-0.0393	0.0019
2	-0.0623	0.0002
3+	0.1407	<.0001
Vital status		
Alive	Ref	
Dead	-0.3016	<.0001

CCI: Charlson comorbidity index

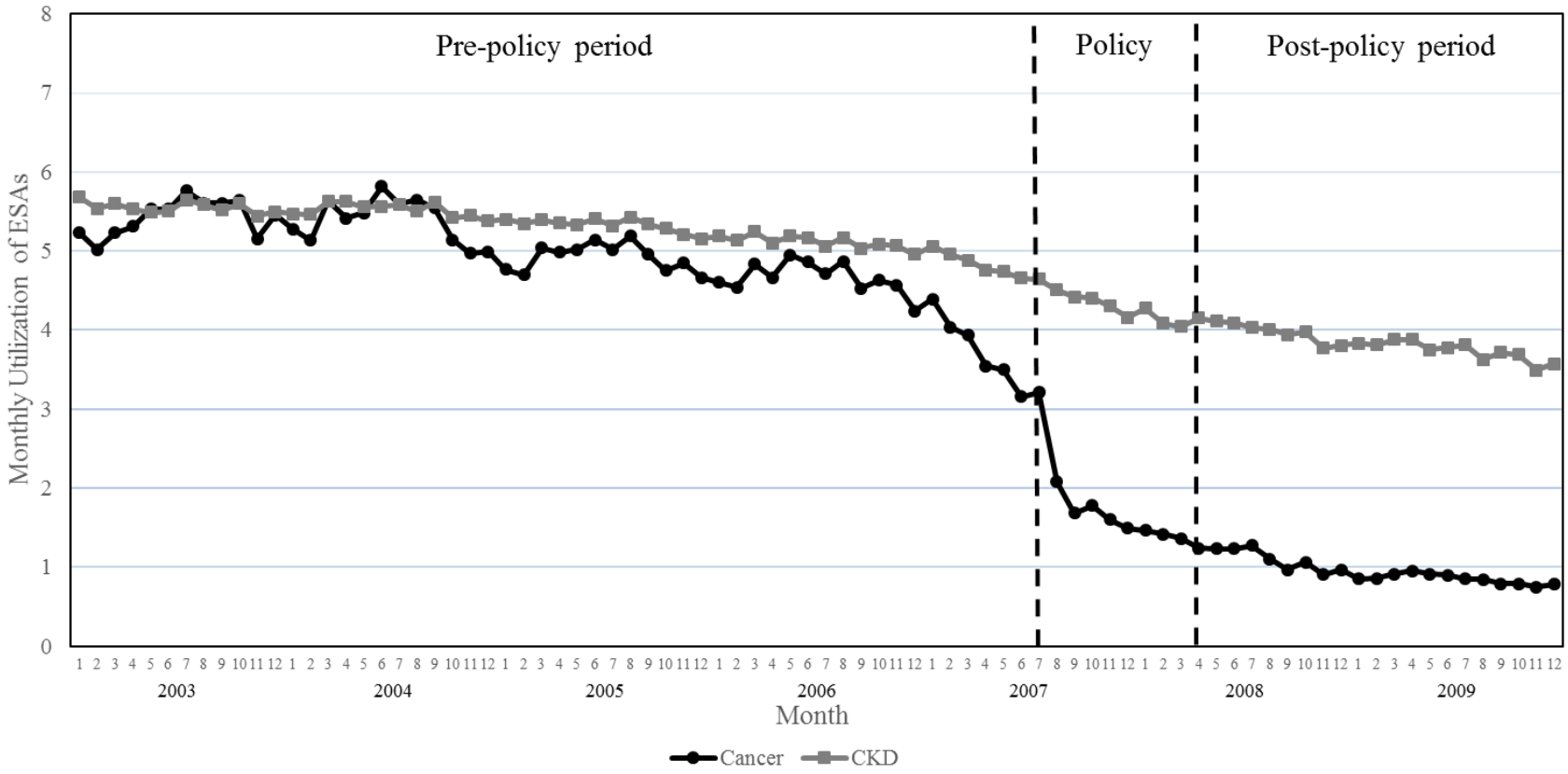

Figure 6.1: Change in the monthly utilization of ESAs before and after the implementation of Medicare reimbursement policy (ESAs: erythropoiesis-stimulating agents; CKD: chronic kidney disease)

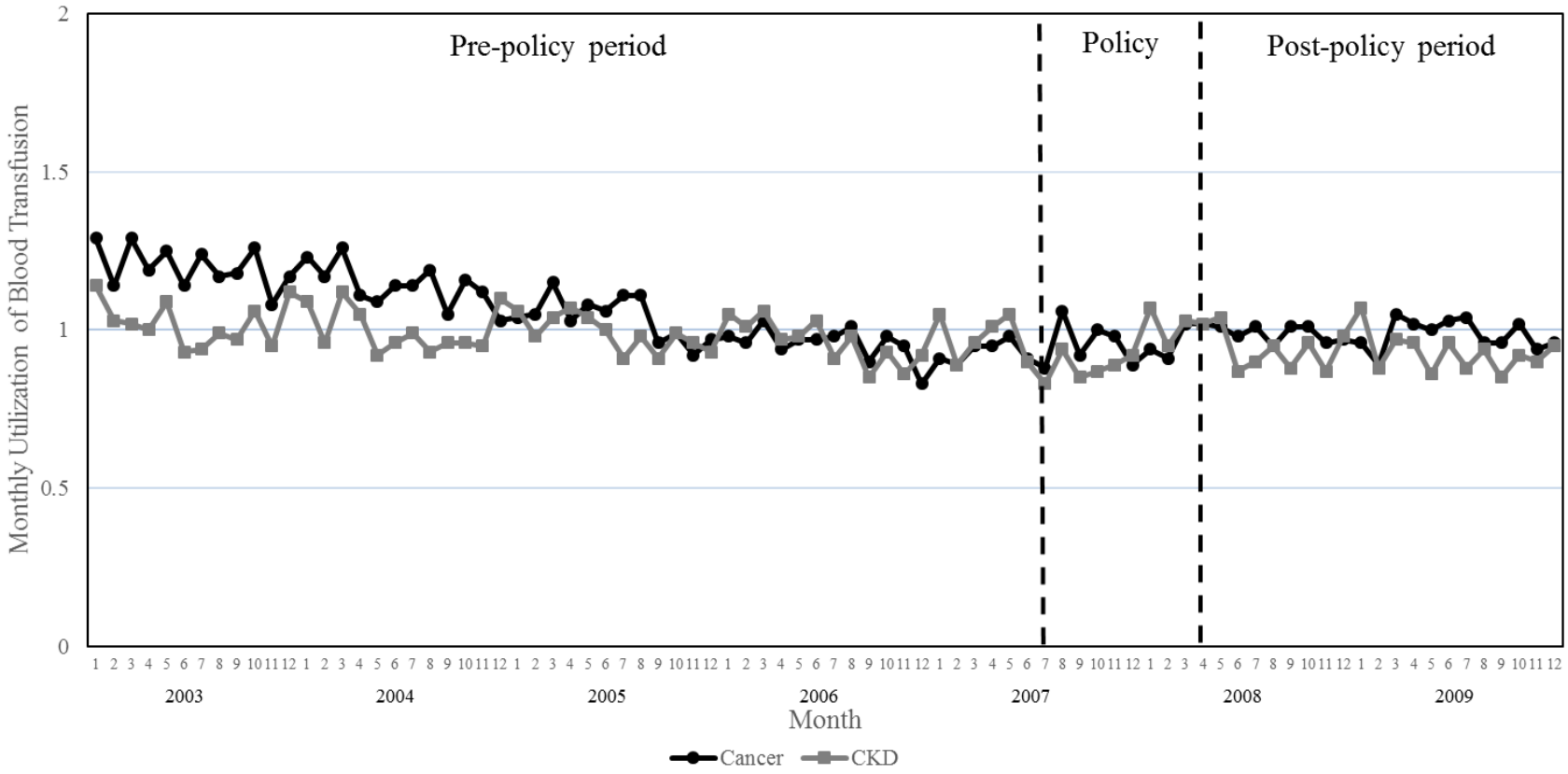

Figure 6.2: Change in the monthly utilization of blood transfusions before and after the implementation of Medicare reimbursement policy
(CKD: chronic kidney disease)

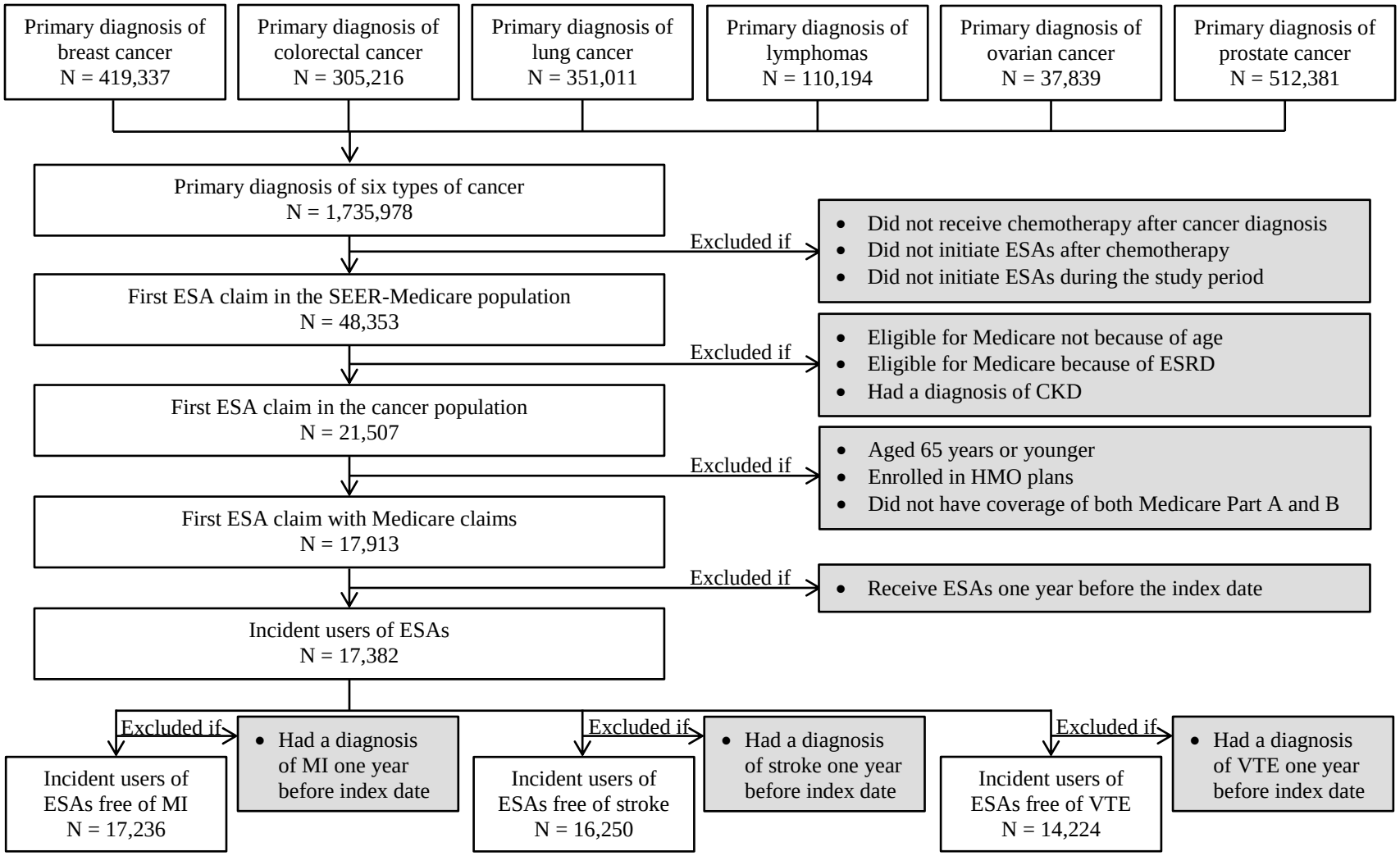

Figure 6.3: Flow chart of sample selection in Aim 2

(ESAs: erythropoiesis-stimulating agents; SEER: Surveillance, Epidemiology, and End Results; ESRD: end-stage renal disease; CKD: chronic kidney disease; HMO: health maintenance organization; MI: myocardial infarction; VTE: venous thromboembolism)

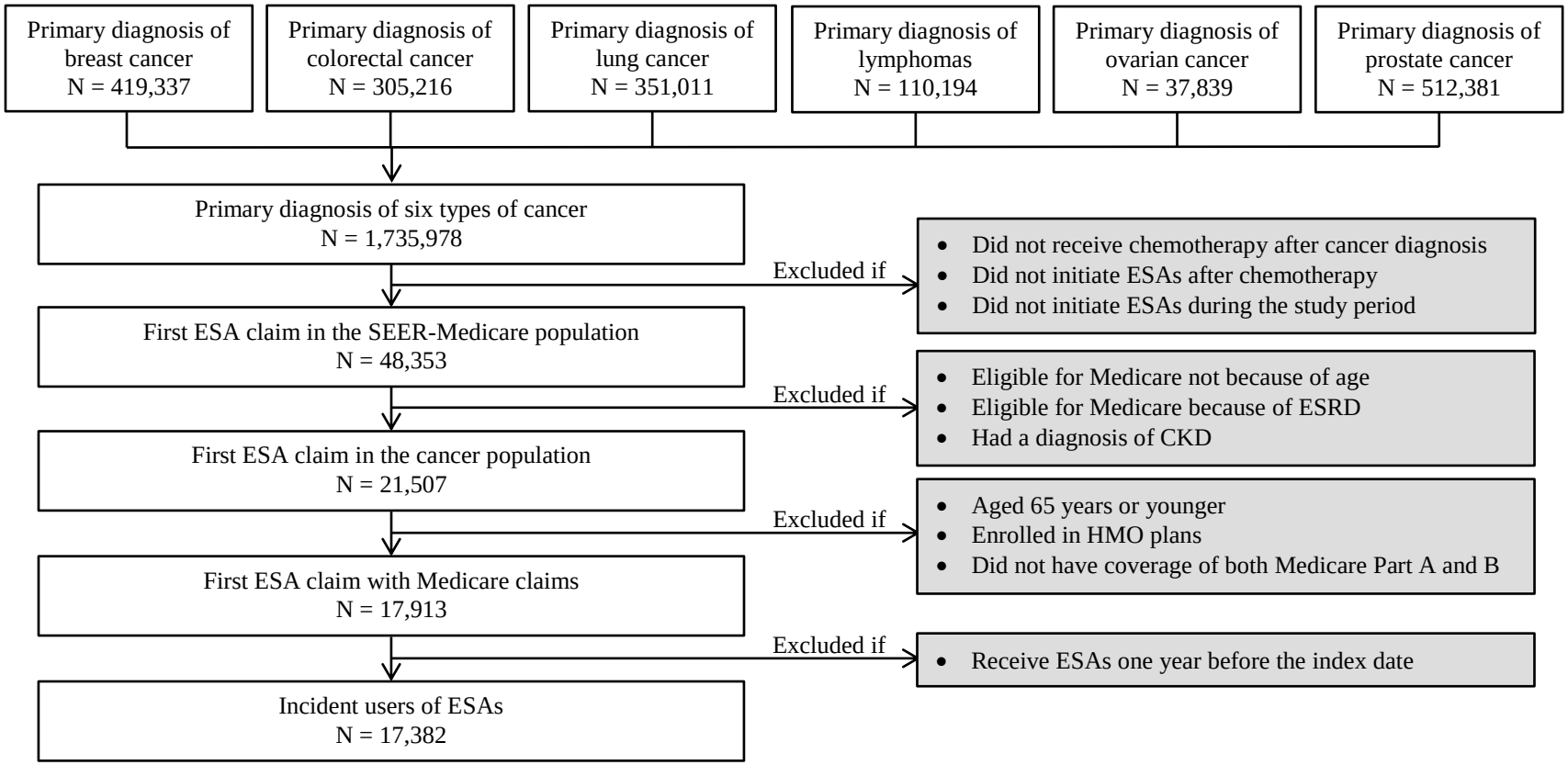

Figure 6.4: Flow chart of sample selection of the treatment group in Aim 3
(ESAs: erythropoiesis-stimulating agents; SEER: Surveillance, Epidemiology, and End Results; ESRD: end-stage renal disease; CKD: chronic kidney disease; HMO: health maintenance organization)

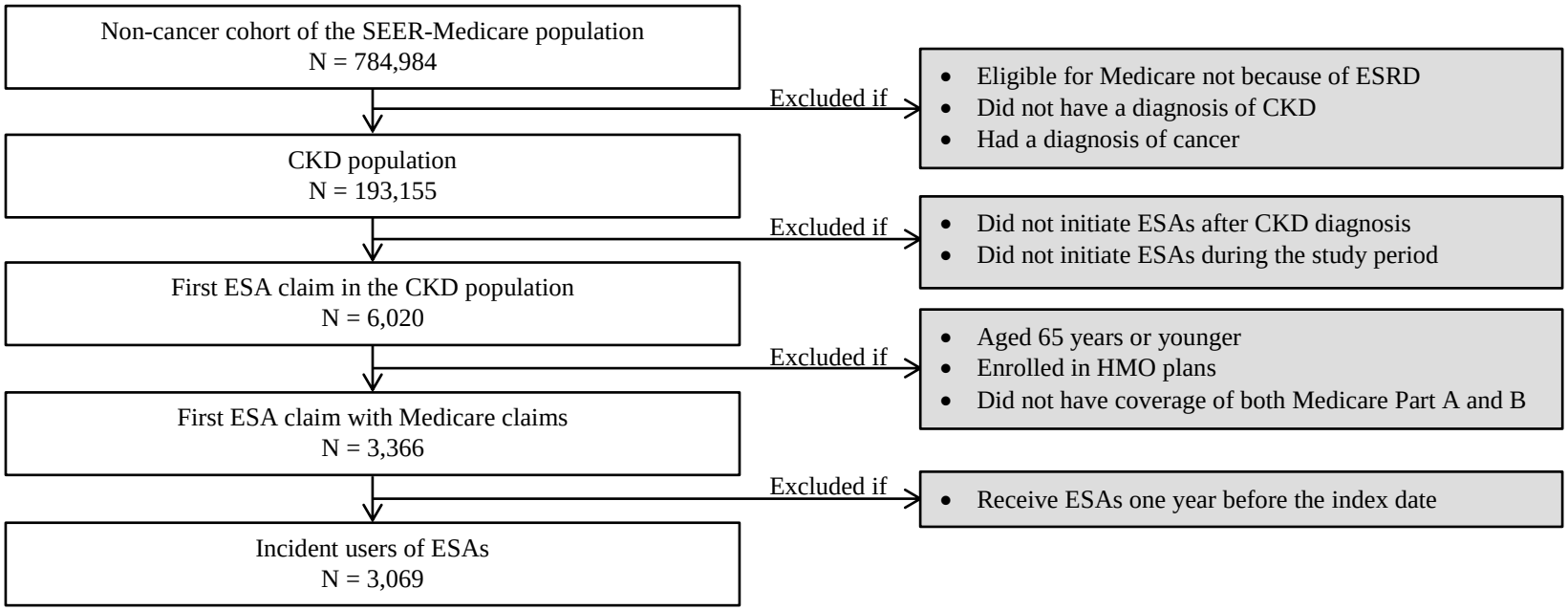

Figure 6.5: Flow chart of sample selection of the control group in Aim 3
(SEER: Surveillance, Epidemiology, and End Results; ESRD: end-stage renal disease; CKD: chronic kidney disease; ESAs: erythropoiesis-stimulating agents; HMO: health maintenance organization)

CHAPTER 7

DISSCUSION

7.1 Discussion on the Utilization

Results on the impact of Medicare reimbursement policy change on the utilization of ESAs in cancer patients with chemotherapy-induced anemia found in the study were similar to findings in some of previous studies. Through analyzing Medicare claims data, Arneson *et al.* and Hershman *et al.* found that the utilization of ESAs had a 51% to 57% reduction after the implementation of Medicare reimbursement policy, which were similar to the 50% reduction found in this study.[75,76] Studies conducted by Hess *et al.* and Henry *et al.* analyzed medical records and found that the utilization of ESAs had a 29% to 36% reduction after the implementation of Medicare reimbursement policy, which were lower than the 50% reduction found in this study.[73,74] Using medical records in local settings might only reflect the impact of the policy change at the local level instead of the national level. This study used the SEER-Medicare linked database (a nationally representative database) and could provide national estimates on the impact of Medicare reimbursement policy change on the utilization of ESAs.

Results on the impact of Medicare reimbursement policy change on the utilization of blood transfusions in cancer patients with chemotherapy-induced anemia found in the study were different from findings in previous studies. Through analyzing Medicare claims data, Arneson *et al.* and Hershman *et al.* found that the utilization of blood

transfusions did not change after the implementation of Medicare reimbursement policy, which were different from the 10% increase found in this study.[75,76] Unlike the utilization of ESAs, the impact of the policy change on the utilization of blood transfusions was indirect and unintended. The policy change might have a delayed effect on the utilization of blood transfusions. Arneson *et al.* and Hershman *et al.* only examined the utilization of blood transfusions until November 2007 and December 2008, respectively.[75,76] Their post-policy periods might be not long enough to observe the delayed effect of the policy change on the utilization of blood transfusions. This study included the complete pre- and post-policy periods which enabled us to examine both the short-term and long-term effects of the policy change. The study conducted by Hess *et al.* analyzed medical records and found that the utilization of blood transfusions had a 31% increase after the implementation of Medicare reimbursement policy, which was higher than the 10% increase found in this study.[73] Using medical records in local settings might only reflect the impact of the policy change at the local level instead of the national level. This study used the SEER-Medicare linked database (a nationally representative database) and could provide national estimates on the impact of Medicare reimbursement policy change on the utilization of blood transfusions.

After the implementation of Medicare reimbursement policy, we found that the increase in the utilization of blood transfusions was smaller than the decrease in the utilization of ESAs. Three reasons can be used to explain this finding. First, unreasonable or unnecessary use of ESAs was reduced after the policy change. The goal of Medicare reimbursement policy change was to reduce unsafe use of ESAs. Patients receiving unreasonable or unnecessary ESA treatments did not require blood transfusions to treat

anemia. Second, some patients eligible for the administration of ESAs were not eligible for the transfusion of red blood cells. For example, when patients were severely ill, even though they did not have access to ESA treatment, they would not seek for blood transfusions. Third, some patients were worried about adverse events (e.g. immunosuppression and transfusion reactions) associated with blood transfusions. When physicians recommended blood transfusions to them, they might refuse to get transfusion of red blood cells.

This study clearly distinguished among the pre-policy, policy, and post-policy periods. The post-policy periods defined in the previous studies were problematic.[73-76,78] All of them included some months of the policy period, the period between July 2007 and April 2008, in their post-policy periods. Even though Medicare reimbursement policy change was issued on July 30, 2007, it was not fully implemented until April 7, 2008. During the policy period, Medicare contractors were not required to review ESA claims and Medicare would not deny payment of ESA services. Thus, we would still have some claims of unreasonable or unnecessary ESA use (when the hemoglobin level was $\geq$ 10 g/dL or the hematocrit level was $\geq$ 30%) during the policy period. Including part of the policy implementation period in the post-policy period in the analysis might underestimate the true impact of the policy change on the utilization of ESAs and blood transfusions. Thus, by defining the pre-policy, policy, and post-policy periods correctly, results of this study were more valid than the previous studies.

A policy could cause two types of change on the utilization of ESAs or blood transfusions: the change in the level and the change in the trend. A policy might have both, either, or neither of these two types of change. Previous studies examined the

average monthly or annual utilization of ESAs and blood transfusions in the pre- and post-policy periods.[73-76] These studies examined the change in the level of utilization only; the change in the trend of utilization was not captured. This study used the interrupted time series design, which enabled us to examine two types of change. By using the segmented regression analysis, the change in the level of utilization could be measured by the difference in the intercepts and the change in the trend of utilization could be measured by the difference in the slopes.

This study incorporated a control group when examining the impact of Medicare reimbursement policy change on the utilization of ESAs and blood transfusions. All published studies did not include control groups and thus subjected to threats to internal validity.[73-76,78] In this study, after including the control group, we concluded that the level in the monthly utilization of ESAs was reduced by 2.13% (about a relative 50% reduction) after the policy change. If the control group was not included, on the other hand, we could have concluded that the level in the monthly utilization of ESAs was reduced by 2.96% (about a relative 70% reduction) after the policy change. Thus, without the control group, we could have overestimated the impact of Medicare reimbursement policy on the utilization of ESAs.

7.2 Discussion on the Risks

Results on the impact of Medicare reimbursement policy change on the risks of cardiovascular and thrombovascular events associated with ESAs in cancer patients with chemotherapy-induced anemia found in the study were different from what we hypothesized. We hypothesized that in incident users of ESAs with chemotherapy-

induced anemia, compared to patients who initiated ESAs before the policy change, those who initiated ESAs after the policy change were less likely to develop MI, stroke, and VTE. However, this study found that the risks of MI, stroke, and VTE associated with ESAs during the one-year follow-up period in cancer patients with chemotherapy-induced anemia was not changed after the implementation of Medicare reimbursement policy.

Several factors should be considered to interpret the results. First, the clinical evidence on the association between the hemoglobin level and the risks of cardiovascular and thrombovascular events in incident users of ESAs with chemotherapy-induced anemia was not clear. According to individual randomized control trials (RCTs) and literature-based meta-analyses, a target hemoglobin level completely free of increased risks of cardiovascular and thrombovascular events could not be identified.[16,22,28,29,36,37,89-91] CMS, FDA, and ASCO/ASH had different requirements on the appropriate hemoglobin level of ESA treatment in cancer patients. FDA labeling required to initiate ESA treatment only when the hemoglobin level was < 10 g/dL; but the hemoglobin level in the following administration of ESAs was not specified.[42,43] The ASCO/ASH guidelines recommended to initiate ESA therapy when the hemoglobin level was < 10 g/dL; but could not determine whether to initiate ESA therapy when the hemoglobin level was ≥ 10 g/dL but < 12 g/dL; and the target hemoglobin level of ESA therapy was not specified.[44-46] CMS's requirements on the appropriate hemoglobin level of ESA treatment were more rigid than recommendations in the FDA labelling or ASCO/ASH guidelines. As specified in Medicare reimbursement policy change, ESA treatment was reasonable only when the hemoglobin level was < 10 g/dL.[53] Different requirements on the

appropriate hemoglobin level of ESA treatment between Medicare reimbursement policy and the FDA labeling or ASCO/ASH guidelines might explain why the implementation of Medicare reimbursement policy did not have an impact on the risks of cardiovascular and thrombovascular events in incident users of ESAs with chemotherapy-induced anemia.

Second, older adults are underrepresented or not included in some clinical trials examining the risks associated with ESAs. Current knowledge on the association between the hemoglobin level and the risks of cardiovascular and thrombovascular events in incident users of ESAs with chemotherapy-induced anemia are based on findings from clinical trials. Even though older adults are often included in some clinical trials, sample sizes of these clinical trials are usually not large enough for the subgroup analysis on the risks associated with ESAs in different age groups.[92,93] The risks of cardiovascular and thrombovascular events associated with ESAs might be different between older adults and young or middle aged adults. If that is true, the association between the hemoglobin level and the risks of cardiovascular and thrombovascular events in incident users of ESAs with chemotherapy-induced anemia based on clinical trials of the adult population might not be the same in the older adult population. In addition, individuals who are 75 years or older are not included in most clinical trials.[94] The association between the hemoglobin level and the risks of cardiovascular and thrombovascular events in incident users of ESAs with chemotherapy-induced anemia identified in these clinical trials might not be generalizable to those who are 75 years or older. In this study, about half of the study population were 75 years or older. We had little knowledge on the association between the hemoglobin level and the risks of cardiovascular and thrombovascular events

in this population. The demographics of the study population in this study might explain why the implementation of Medicare reimbursement policy did not have an impact on the risks of cardiovascular and thrombovascular events in incident users of ESAs with chemotherapy-induced anemia.

7.3 Discussion on the Costs

Results on the impact of Medicare reimbursement policy change on anemia-related and total medical costs associated with ESAs in cancer patients with chemotherapy-induced anemia found in the study were similar to what we hypothesized. We hypothesized that in incident users of ESAs with chemotherapy-induced anemia, anemia-related and total medical costs were lower after Medicare reimbursement policy change compared to those before the policy change. The impact of the policy change on anemia-related costs (a 11.20% reduction) and total medical costs (a 11.96% reduction) in incident users of ESAs was similar. However, the impact of the policy change on different components of medical costs was different. In anemia-related costs, a greater cost saving was observed in patient cost-sharing (a 18.40% reduction) than Medicare payment (a 9.83% reduction). In total medical costs, cost savings in patient cost-sharing (a 13.58% reduction) and Medicare payment (a 11.59% reduction) were similar.

Medicare reimbursement policy change was effective in reducing medical costs associated with ESAs in cancer patients with chemotherapy-induced anemia from CMS's perspective. How the policy change could impact the expenses by patient, third-party payers, and the whole society was not examined in this study. Medicare beneficiaries could sign an ABN for ESA services not reimbursed under CMS and be liable of paying

100% of the treatment expenses.[54] When Medicare beneficiaries have supplemental insurances, they could seek reimbursement of ESA services from other insurers. If that is true, expenses from third-party payers might increase. When Medicare beneficiaries do not have any supplemental insurances, they need to pay ESA services out-of-pocket. If that is true, expenses from patient might increase. From the societal perspective, additional information is needed to understand the impact of Medicare reimbursement policy change on medical costs associated with ESAs in cancer patients with chemotherapy-induced anemia.

This study examined medical costs in incident users of ESAs with chemotherapy-induced anemia during the one-year follow-up period. The impact of the policy change on medical costs in the long-term (more than one year) was not examined in this study. Some medical costs associated with ESAs (e.g. costs used to treat long-term adverse events) might occur one year after the index date. If that is true, we might be not able to observe all medical costs associated with ESAs during the one-year follow-up period. With a longer follow-up period, we might be able to have a complete picture of all medical costs associated with ESAs and thus better understand the long-term impact of Medicare reimbursement policy on medical costs in incident users of ESAs with chemotherapy-induced anemia.

7.4 Significance

This study has the following three policy significance. First, through examining the utilization of ESAs and blood transfusions before and after the implementation of Medicare reimbursement policy, it could help CMS understand both the short-term and

long-term effects of the policy change. Based on the current evidence in the literature, the effect of the policy change on the utilization of ESAs and blood transfusions during the complete pre- and post-policy periods was unknown. An understanding of the short-term and long-term effects of Medicare reimbursement policy on the intended change in ESAs and the possible unintended change in blood transfusions could help decision makers at CMS make appropriate policy decisions in the future to better meet the goal of CMS while considering both the intended and possible unintended policy consequence. Aim 1 of the study was the first to examine the change in the utilization of ESAs (intended consequence) and blood transfusions (unintended consequence) after the implementation of Medicare reimbursement policy including the complete pre- and post-policy periods.

Second, this study could help CMS understand whether the goal of Medicare reimbursement policy change, reducing potential harms caused by unreasonable or unnecessary ESA use, has been reached. In the U.S., the safety of ESAs is a significant concern for patients, healthcare providers, payers, and society. Understanding how the risks associated with ESAs changed after the implementation of Medicare reimbursement policy is critical for CMS to assess if the goal of the policy change has been achieved. Based on the current evidence in the literature, among users of ESAs, how risks would change after the implementation of Medicare reimbursement policy was unknown. Aim 2 of the study enabled us to evaluate, for the first time, if Medicare reimbursement policy change reached its intended goal of reducing potential risks of cardiovascular and thrombovascular events associated with ESAs.

Third, this study could help CMS understand the economic consequence of Medicare reimbursement policy change by examining the difference in medical costs

before and after the policy change. This information is of great significance to CMS because "smarter spending: lowering the total cost of care due to reduced monthly expenditures for Medicare beneficiary by improving care" is one of CMS's top missions.[95] As the highest-expenditure drug in the Medicare system before the policy change, medical costs associated with ESAs accounted for a significant proportion of CMS budget. CMS should find "new ways to pay for and deliver care that can lower costs and improve care".[95] By restricting unsafe use of ESAs, medical costs associated with ESAs would decrease. The issue, however, is that some other medical costs (e.g. costs of blood transfusions) might increase. Based on the current evidence in the literature, among users of ESAs, how anemia-related and total medical costs would change after the implementation of Medicare reimbursement policy was unknown. Therefore, it is critically important for CMS to understand both the intended and potential unintended economic consequence of the policy change when making policy decisions. Aim 3 of the study was the first to evaluate the economic consequence of Medicare reimbursement policy change among users of ESAs.

In summary, the findings of this study are of great significance not only for evaluating the impact of Medicare reimbursement policy change, but also for providing critical empirical evidence for CMS's future policy considerations.

7.5 Innovation

This study is innovative in the following five areas. First, this study was the first to assess the impact of Medicare reimbursement policy change on the risks and costs associated with ESAs. No previous studies have examined these issues in the literature.

Currently, the empirical evidence on the differences in the risks and costs associated with ESAs between the pre- and post-policy periods was not available. CMS, however, needs policy evaluation studies to assess if the goal of Medicare reimbursement policy change for ESAs in cancer patients has been achieved; and if the policy change generated cost savings among users of ESAs with chemotherapy-induced anemia.

Second, this study was the first to incorporate a control group when assessing the impact of Medicare reimbursement policy change on the utilization of ESAs and blood transfusions. Previous studies examined the change in the utilization of ESAs and blood transfusions after the implementation of the policy only in cancer patients.[73-78] Using the single group design in these published studies, however, was subject to threats to internal validity (e.g. history). Incorporating a control group in the design could eliminate multiple possible threats to internal validity, thus enhancing internal validity of the study. We also incorporated a control group when assessing the impact of Medicare reimbursement policy change on the costs associated with ESAs in cancer patients with chemotherapy-induced anemia.

Third, better design and advanced statistical methodologies were used in the study to control for potential biases. (1) This study used an interrupted time series design to examine the changes in the utilization of ESAs and blood transfusions after the implementation of Medicare reimbursement policy.[87] The interrupted time series design is a particularly strong quasi-experimental design with a high degree of internal validity when evaluating the impact of the policy change. This study design will allow us to control for confounding omitted variables and autocorrelation. (2) This study employed an incident user design to examine the risks and costs associated with ESAs, which

further enhanced the interval validity of the study.[84] When events vary with time, the traditional prevalent user design could introduce bias because some early events are not measured. The incident user design, which is similar to clinical trials, could avoid this bias because all users have their own starting index dates and all the subsequent events during the follow-up period could be observed. Prior treatment could affect risk factors of future events. By using the incident user design, potential confounding variables were all measured at the beginning of each follow-up. (3) A difference-in-difference design was used in the study to examine the impact of Medicare reimbursement policy change on medical costs associated with ESAs.[88] The underlying assumption of using a simple pre-post design is that there is nothing associated with the outcome and that happened at the same time as the policy change. The difference-in-difference design does not require such an assumption because it has a comparison group which is not subject to the policy change.

Fourth, this study examined the changes in the utilization of ESAs and blood transfusions including the complete pre- and post-policy periods. Previous studies have only examined the change before and after the implementation of Medicare reimbursement policy and found that after the policy change, the utilization of ESAs decreased by 26% to 57% and the utilization of blood transfusions remained constant or increased slightly.[73-78] However, the latest information available in the literature regarding the utilization of ESAs and blood transfusions during the post-policy period was 2008.[74] This study provided complete information on the utilization of ESAs and blood transfusions during the post-policy period until December 2009, before ESA REMS was implemented.

Fifth, this study used a large population-based dataset. Most of previous studies of Medicare reimbursement policy change reviewed medical records in local settings only.[73,74,77,78] Many of these studies usually had small sample sizes and were not powered to detect the difference between the pre- and post-policy periods. In addition, their findings would likely not be generalizable to the U.S. population. Given that some risks associated with ESAs are not common, only population-based database, such as the SEER-Medicare database (a nationally representative database), would enable us to identify rare events.

7.6 Limitation

Three possible limitations of the study should be considered. First, an ideal control group should be similar to the treatment group in all aspects but not subject to Medicare reimbursement policy change. Specifically, the ideal control group for the study should be Medicare beneficiaries with cancer who used ESAs to treat chemotherapy-induced anemia but not subject to the policy change. However, finding a perfect control could be challenging. Our control group consisted CKD patients who used ESAs when they had low levels of hemoglobin. The advantage of this control group is that it is not subject to the policy change; while, the limitation is that this control group may not be similar to the treatment group in all aspects.

Second, some potential confounding variables were not observed in the study. In the conceptual framework, we identified some internal factors that could influence the association between the policy change and health outcomes. However, some of them, which were potential confounding variables, were not controlled for in the study. The

SEER-Medicare database contain little information on physician characteristics (e.g. employment setting and previous experience), behavioral factors (e.g. smoking and alcohol use), and patient risk factors (e.g. obesity and family history of cancer), thus limiting our ability to measure and control for these potential confounding variables in the study. However, this study incorporated a control group in the study design, which enabled us to control for biases caused by confounding variables common to the treatment and control groups, even when they were unobserved.

Third, the utilization of ESAs under Medicare Part D was not measured in the study. ESAs are covered under Medicare Part B when administered in physician's offices and are covered under Medicare Part D when administered outside physician's offices. Because Medicare Part D claims were first available in the SEER-Medicare database in 2007, the pre-policy period did not have ESA treatment information under Medicare Part D. For a fair comparison between the pre- and post-policy periods, we chose to not measure the utilization of ESAs under Medicare Part D in this study. However, the impact of missing Medicare Part D information on the validity and accuracy of study results should be minimum because this study included a control group and ESA use under Medicare Part D only accounted for a small proportion of all ESA use.[96]

In summary, because we have incorporated a control group in the study design, the impact of limitations on the internal validity of study results should be minimal.

CHAPTER 8

CONCLUSION

This study found that Medicare reimbursement policy change had an impact on the utilization of ESAs and blood transfusions in cancer patients with chemotherapy-induced anemia. Medicare reimbursement policy had a one-time only effect on the utilization of ESAs. After the policy change, the monthly utilization of ESAs had a relative 50% reduction. Medicare reimbursement policy also had a one-time only effect on the utilization of blood transfusions. After the policy change, the monthly utilization of blood transfusions had a relative 10% increase. The goal of Medicare reimbursement policy change was to reduce potential harms caused by unreasonable or unnecessary ESA use. So, the impact of the policy change on the utilization of ESAs was intended but the impact on the utilization of blood transfusions was indirect and unintended. For CMS's future policy considerations, in addition to predict and study the intended changes caused by the policy, the possible unintended changes should also be studied.

This study found that Medicare reimbursement policy change had no impact on the risks associated with ESAs in cancer patients with chemotherapy-induced anemia. The risks of MI, stroke, and VTE associated with ESAs during the one-year follow-up period in cancer patients with chemotherapy-induced anemia was not changed after the implementation of Medicare reimbursement policy. Further studies are needed to understand why Medicare reimbursement policy change did not reach its goal of reducing

potential risks associated with ESAs. CMS should reevaluate the appropriateness of Medicare reimbursement policy change and make necessary changes on the current regulations if future studies confirm our findings.

This study found that Medicare reimbursement policy change had an impact on the costs associated with ESAs in cancer patients with chemotherapy-induced anemia. Anemia-related and total medical costs associated with ESAs during the one-year follow-up period in cancer patients with chemotherapy-induced anemia were reduced by about 10% after the implementation of Medicare reimbursement policy. This study provided evidence on the economic consequence of the policy change in cancer patients with chemotherapy-induced anemia. ESAs were the highest-expenditure drug in the Medicare system before the implementation of Medicare reimbursement policy. This policy change was effective in lowering CMS expenditures.

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