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# Blood Transfusions, Thrombosis and Mortality in Hospitalized Cancer Patients

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## Abstract

**Background—**Anemia is frequent in cancer patients, but there are concerns regarding treatment with erythropoiesis-stimulating agents (ESAs). Blood transfusions are commonly used as an alternative, but with little data regarding outcomes. We investigated the association between transfusions, venous thromboembolism (VTE), arterial thromboembolism (ATE) and mortality in hospitalized cancer patients.

**Methods—**We conducted a retrospective cohort study using the discharge database of the University HealthSystem Consortium. This included 504,208 hospitalizations of cancer patients between 1995 and 2003 at 60 United States medical centers.

**Results—**Of the patients included, 70,542 (14.0%) received at least 1 red blood cell (RBC) and 15,237 (3%) received at least 1 platelet transfusion. Among patients receiving RBC transfusions, 7.2% developed VTE and 5.2% developed ATE and this was significantly greater than rates of 3.8% and 3.1%, respectively, for the rest of the study population (P<0.0001 In multivariate analysis, both RBC [OR 1.60, (95%CI 1.53–1.67)] and platelet transfusion [OR 1.20(95% CI 1.11–1.29)] were independently associated with an increased risk of VTE. RBC [OR 1.53 (95%CI 1.46–1.61)] and platelet transfusion [OR 1.55 (95%CI 1.40–1.71)] were also associated with ATE (P<0.0001 for each). Transfusions were also associated with an increased risk of in-hospital mortality [OR 1.34 (95% CI 1.29–1.38) for RBC and 2.40 (95% CI 2.27–2.52) for platelets, p<0.0001].

**Conclusions—**RBC and platelet transfusions are associated with an increased risk of venous and arterial thrombotic events and mortality in hospitalized cancer patients. Further investigation is necessary to determine whether this relationship is causal.

## INTRODUCTION

Anemia is observed in 30–90% of cancer patients[1]. It is exacerbated by blood loss during surgery, myelosuppression related to chemotherapy and/or radiation therapy [2, 3]. Anemia can result in symptoms such as fatigue or angina in patients with coronary artery disease, and is associated with a reduction in quality of life. Erythropoiesis-stimulating agents (ESAs) are often used to treat anemia in cancer patients. However, recent reports suggest an increased risk of thromboembolic complications and decreased survival with the use of ESAs in cancer[4–6]. This has led to an FDA advisory restricting their use[7]. Red blood cell (RBC) transfusions are

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often used as an alternative treatment of anemia in cancer patients, and are recommended as therapeutic options by the American Society of Clinical Oncology/American Society of Hematology (ASCO/ASH) guidelines[2]. However, there are no randomized controlled trials demonstrating improved outcomes or quality of life in cancer patients receiving transfusions, and the safety profile of RBC transfusion in cancer patients has not been studied as rigorously as ESAs.

Studies attempting to assess the benefit of transfusions in non-cancer settings have reported conflicting findings. A randomized study found no benefits to transfusion of critically ill patients to maintain a hemoglobin level of 10 mg/dL compared to restricting transfusion to patients with a hemoglobin of 7 mg/dL or lower[8]. Indeed, patients with the more conservative transfusion indication had superior survival overall. A recent pooled analysis of clinical trials showed that patients with acute coronary syndromes receiving transfusion had a higher rate of myocardial infarction and death[9]. In contrast, blood transfusion in elderly patients with myocardial infarction has been associated with a lower 30-day mortality in more severely anemic patients although mortality was higher in transfused patients who were mildly anemic[10]. Blood transfusions have also been linked with an increased long-term risk of cancer[11]. Platelet transfusions have been linked with deep venous thrombosis (DVT) in critically ill patients[12], and with adverse outcomes, including stroke, following coronary artery bypass surgery[13]. There is a paucity of similar data in cancer patients, although perioperative transfusions of red cells and fresh frozen plasma were reported to be associated with VTE in a small cohort of patients undergoing gynecologic cancer surgery [14]. Similar preliminary findings have recently been reported in other surgical settings suggesting an association between perioperative transfusions, thrombosis[15, 16] and even survival[17].

The objective of this study was to determine the relationship between blood transfusion and outcomes in hospitalized cancer patients. We analyzed data from hospital discharge summaries of all cancer patients admitted to 60 United States academic medical centers between 1995 and 2003 to investigate the association between transfusions, thromboembolic events and in-hospital mortality.

## METHODS

All discharge summaries of adult cancer patients admitted between 1995 and 2003 to one of 60 academic medical centers in the United States were reviewed using the discharge database of the University HealthSystem Consortium (UHC). To avoid centers not reporting or inconsistently reporting transfusion data, only hospitals reporting packed red cell transfusions in at least 2% of admissions and platelet transfusions in at least 0.1% of admissions during every year of the study were included in this analysis. These criteria correspond to the lowest quartile of all UHC institutions. Patients were identified using ICD-9-CM codes that contained at least one diagnosis of malignant disease (ICD-9-CM 140–208). Patients who received transfusions were identified with procedure codes for packed red cells (99.04), platelets (99.05) and autologous whole blood (99.02). Patients with VTE were identified using codes for venous thrombosis (451,452,453) and pulmonary embolism (415.1–415.19). Patients with ATE were identified using codes for arterial embolism (444), acute cerebrovascular disease (433–434, 436), and acute coronary arterial disease (410, 411.1–411.8). Patients on active therapy were identified using codes for chemotherapy (99.25, V58.1, V67.2), high-dose interleukin-2 (00.15), biologic therapy (99.28), adverse events from chemotherapy (E930.7, E933.1) and neutropenia (288.0). Selected surgical oncologic procedures included mastectomy or lumpectomy (85.21–85.23, 85.34, 85.36, 85.4), unilateral or bilateral radical cervical lymph node dissection (40.4), partial or total pancreatectomy (52.5–52.7) neurosurgery (01.1–01.39, 01.5–01.59) and spinal surgery (03.0, 03.09, 03.3, 03.32, 03.39, 03.4). Patients with catheters were identified using codes 38.93, 86.06 or 86.07. Comorbidities and risk factors included

infection (001–139.8, 480–486, 9966.2), pulmonary disease (487–519), hypertension (401), renal disease (580–593), diabetes mellitus (250–250), congestive heart failure (428–428), hepatic disease (570–576), anemia (280–285) and obesity (278.0).

### Statistical analysis

Patients with multiple hospitalizations were identified and only a single randomly chosen hospitalization per patient was included in analysis. Binary clinical covariates were created based on the presence or absence of the relevant diagnostic code. The chi-square test was used to compare dichotomous outcomes for categorical variables. Variables associated with a higher risk of thromboembolism were identified using multivariate logistic regression. The fixed set of medically relevant covariates was chosen prior to analysis. The cancer type was included in the model with all disease categories first. After adjusting for the additional covariates, cancer types associated with an increased risk of VTE were kept as separate categories and the rest were grouped into the reference category. The final multivariate analysis included cancer type, age, gender, ethnicity and clinical variables that were statistically significantly associated with risk of event in the full model. The omission of not significant variables only slightly influenced model coefficients. Twenty one observations with unknown gender were excluded from the multivariate analysis. For ethnicity, the group “other/unknown” was created. Association of transfusion variables with mortality was also similarly tested in the multivariate analysis. To address VTE or ATE events that occurred at admission, patients with a primary diagnosis of VTE or ATE were excluded from the respective multivariate analysis. To address large sample size and multiple testing, only P values less than 0.001 were considered significant. Statistical analysis was performed using SAS, version 9.1.3 (SAS Institute, Cary, NC).

## RESULTS

### Patient Characteristics

The study population comprised 504,208 cancer patients admitted between 1995 and 2003 at 60 medical centers (Table 1). Over one-third of patients were age 65 years or older. Over two-thirds of the population was white, with Blacks representing 12.3% and Hispanics 4.6%. VTE occurred in 21,040 patients (4.2%), including 17,613 patients (3.5%) with DVT and 5,547 patients (1.1%) with PE. ATE events occurred in 16,651 patients (3.3%).

### Transfusions

Of the study population, 74,051 patients (14.7%) received either packed red cell or platelet transfusions. Of these, 70,542 (14.0%) received at least 1 red cell transfusion and 15,237 (3%) received at least 1 platelet transfusion (Table 1). Only 3,509 patients (0.7%) received solely platelet and no RBC transfusions and 11, 728 (2.3%) received both platelet and RBC transfusions. An additional 2,939 patients (0.6%) received autologous whole blood or red cell transfusions. For further analysis, patients receiving both platelet and RBC transfusions were included in the platelet transfusion category whereas patients receiving only RBC transfusion were included in the RBC transfusion category.

VTE occurred in 4,234 patients (7.2%) receiving RBC transfusions only, 770 patients (6.6%) receiving both red cells and platelet transfusions and 223 patients (6.4%) receiving only platelet transfusions. These rates were substantially higher than the VTE rate of 3.7% in hospitalized cancer patients not receiving transfusions ($P<0.0001$). ATE occurred in 3,034 patients (5.2%) receiving RBC transfusions only, 524 patients (4.5%) receiving both RBC and platelet transfusions and 108 patients (3.1%) receiving only platelet transfusions. Again, these rates were significantly higher than the ATE rate of 3.0 % in hospitalized cancer patients not

receiving transfusions (P<0.0001). Both VTE (0.9%) and ATE rates (0.6%) were low in the small number of patients (N=2,939) receiving whole blood autologous transfusions.

### Multivariate Analysis

In a multivariate logistic regression analysis, both RBC transfusions (OR 1.60 95% CI 1.53–1.67, p<0.0001) and platelet transfusions (OR 1.20 95% CI 1.11–1.29) were independently associated with VTE. Other variables significantly associated with VTE included age ≥ 65 years, female gender, use of chemotherapy, primary site of cancer, use of venous catheters, and the presence of comorbidities (including anemia, infection, renal and lung disease) (Table 2). RBC transfusions [OR 1.53, 95% CI (1.46–1.61), P<0.0001] and platelet transfusions [OR 1.55 95%CI (1.40–1.71), P<0.0001] were also independently associated with ATE in a separate multivariate analysis. Other variables associated with ATE included age ≥ 65 years, male gender, primary site of cancer (including prostate, colon, lung, gastrointestinal, lymphoma and leukemia), use of venous catheters and presence of comorbidities (including congestive heart failure, hypertension, diabetes mellitus, pulmonary and renal disease and tobacco abuse).

### In-Hospital Mortality

Data regarding in-hospital mortality were available for 503,185 patients (99.8% of the study population). Death during hospitalization occurred in 33,924 patients (6.7%). In-hospital mortality rates were higher in patients receiving RBC transfusions (11.9%) and platelet transfusions (23.1%). In-hospital mortality was also significantly higher among patients with VTE (16.7%) and ATE (19.3%). In a multivariate analysis, RBC [OR 1.34 95% CI (1.29–1.38) P<0.0001] and platelet transfusions [OR 2.40, 95% CI(2.27–2.52) P<0.0001] continued to be independently associated with an increased risk of in-hospital mortality after adjusting for other known risk factors for mortality. Other variables significant in this analysis included older age, primary site of cancer, non-white ethnicity, VTE, ATE and presence of comorbidities.

## DISCUSSION

Using a large nationwide database of hospitalized cancer patients, we found that 7.2% of patients receiving RBC transfusions had VTE and 5.2% had ATE, and these rates were significantly higher than 4.2% and 3.3% rates of VTE and ATE, respectively, in the general study population. In multivariate analysis, use of RBC and platelet transfusions was significantly associated with VTE, ATE and in-hospital mortality after adjusting for other covariates.

There are a number of possible mechanisms that might explain the associations reported here, if eventually proven causal. A major effect of transfusion is the delivery of large amounts of redox-active iron, which has been linked to cardiovascular disease because of increased iron-catalyzed free radical-mediated oxidative stress[18]. Indeed, several variables associated with vascular events in this analysis including age, ethnicity and comorbidities, have been linked to increased body iron stores as well[19]. Alternatively, red cell transfusions, by increasing the circulating red cell mass, may improve hemostasis, with one consequence being an increased risk of thrombosis[20]. Stored red cells are severely depleted in nitric oxide, which may lead to vasoconstriction and increase the risk of thrombosis due to vascular rheologic changes and increased platelet activation[21]. Furthermore, non-leukoreduced red cells and all platelet transfusions contain pro-inflammatory and pro-thrombotic soluble mediators such as sCD40L, platelet microparticles and activated platelets which could contribute to the prothrombotic state in cancer patients[22–24]. Other risk factors for VTE reported here including age, site of cancer, presence of comorbidities and chemotherapy are consistent with prior reports[5, 25, 26].

It is noteworthy that all of the platelet transfusion recipients and many of the red cell transfusion recipients were likely thrombocytopenic to some degree, the platelet transfusion recipients severely so. This suggests that severe thrombocytopenia may not protect against VTE and ATE, a novel and somewhat counterintuitive finding. However, this is consistent with recent data suggesting that patients with hematologic malignancies, who are often myelosuppressed, have an elevated risk for VTE similar or even greater than observed in solid tumor patients[27]. The role of platelets in the multifactorial etiology of cancer-associated thrombosis is, however, unclear.

Limitations of this analysis include its reliance on administrative coding. However, codes for venous thromboembolism as well as comorbidities have been validated in prior reports and are considered to be accurate[28–31]. The diagnostic criteria to identify VTE included superficial thrombophlebitis, but <1% of patients fell into this category and therefore did not substantially influence the analysis. We controlled for under-reporting of transfusion by excluding hospitals that did not report transfusions or were in the lowest quartile of hospitals reporting transfusions. This dataset does not allow us to identify patients concomitantly receiving ESAs as part of outpatient therapy, a potential confounding factor. Data regarding compliance with appropriate thromboprophylaxis were also not available. A major limitation of this analysis is the inability to determine the time of administration of transfusion in relation to development of thromboembolic events, or to identify patients admitted with VTE who subsequently required transfusions. In order to account for this, however, we excluded patients with a primary diagnosis of VTE or ATE from the multivariate analyses. Finally, it is possible that anemia is a surrogate for aggressive tumor biology, more intense chemotherapy or “sicker” patients; although, in our analysis, transfusions continued to be associated with poor outcomes even after adjusting for type of cancer and comorbidities.

Currently, controversy exists regarding treatment of anemia in cancer with ESAs because of potential adverse effects including thromboembolism and worsened survival. The data presented here suggest caution in using transfusions as an alternative to ESAs, since these may carry a similar risk of adverse thrombotic and survival outcomes. Our findings suggest that rigorous studies evaluating the risks and benefits of blood transfusion in cancer patients are necessary.

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**Table 1**

Characteristics Of The Study Population

| | All Patients 1995–2003 | |
|---|---|---|
| | N | % |
| **All** | **504,208** | **100** |
| **Age** | | |
| ≥ 65 | 218,901 | 43.4 |
| **Gender** | | |
| Female | 249,094 | 49.4 |
| **Ethnicity** | | |
| White | 357,608 | 70.9 |
| Black | 61,882 | 12.3 |
| Hispanic | 23,347 | 4.6 |
| Asian | 10,502 | 2.1 |
| Other | 50,869 | 10.1 |
| **Chemotherapy** | 72,354 | 14.4 |
| **Major oncologic surgery** | 61596 | 12.2 |
| **Venous catheters** | 45,581 | 9.0 |
| **Comorbidities** | | |
| Congestive heart failure | 28,613 | 5.7 |
| Pulmonary disease | 111,905 | 22.2 |
| Hypertension | 146,345 | 29.0 |
| Diabetes mellitus | 61,588 | 12.2 |
| Hepatic disease | 28,561 | 5.7 |
| Renal disease | 42,911 | 8.5 |
| Anemia | 91,263 | 18.1 |
| Infection | 88,174 | 17.5 |
| **Transfusions** | | |
| Any transfusion | 74,051 | 14.7 |
| Red cell only | 58,814 | 11.7 |
| Platelet only | 3,509 | 0.7 |
| All platelet | 15,237 | 3.0 |
| Red cell and platelet | 11,728 | 2.3 |
| Autologous | 2,939 | 0.6 |

## Table 2

Predictors Of Venous Thromboembolism By Multivariate Logistic Regression Analysis

| Characteristic | Odds Ratio (95%CI) | P value |
|---|---|---|
| **Age ≥ 65 years** | 1.08 (1.05–1.12) | <0.0001 |
| **Female gender** | 1.11 (1.07–1.15) | <0.0001 |
| **Site of cancer** | | |
| Pancreas | 2.56 (2.36–2.77) | <0.0001 |
| Brain | 2.40 (2.19–2.63) | <0.0001 |
| Other abdominal | 2.09 (1.95–2.23) | <0.0001 |
| Ovary | 1.68 (1.53–1.84) | <0.0001 |
| Renal | 1.88 (1.73–2.04) | <0.0001 |
| Lung | 1.29 (1.22–1.36) | <0.0001 |
| Stomach | 1.36 (1.21–1.53) | <0.0001 |
| Non-Hodgkin's lymphoma | 1.13 (1.06–1.21) | <0.0001 |
| Multiple cancers | 1.39 (1.24–1.55) | <0.0001 |
| **Ethnicity** | | |
| White | 1.00 (Reference) | -- |
| Black | 1.08 (1.03–1.13) | 0.0028 |
| Hispanic | 0.99 (0.91–1.07) | 0.77 |
| Asian | 0.74 (0.66–0.84) | <0.0001 |
| Other | 1.03 (0.97–1.08) | 0.35 |
| **Chemotherapy** | 1.09 (1.05–1.15) | <0.0001 |
| **Venous catheter** | 2.00 (1.91–2.08) | <0.0001 |
| **Transfusion** | | |
| RBC | 1.60 (1.53–1.63) | <0.0001 |
| Platelet | 1.20 (1.11–1.29) | <0.0001 |
| **Comorbidities** | | |
| Anemia | 1.24 (1.19–1.29) | <0.0001 |
| Infection | 1.87 (1.80–1.94) | <0.0001 |
| Renal disease | 1.50 (1.44–1.57) | <0.0001 |
| Lung disease | 1.47 (1.42–1.53) | <0.0001 |