Original Article

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The Relationship Between Blood Transfusion and the Occurrence of Lymphoma: A National Population-Based Dataset Analysis

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Objective: Blood transfusion is an important and well-established treatment for a number of clinical conditions. Nevertheless, the relationship between transfusion and subsequent lymphoma development remains controversial, particularly in the Asian population. This National Health Insurance Research Database-based case-control study evaluated the risk of subsequent lymphoma development after transfusion.

Methods: A total of 3,441 patients with newly diagnosed lymphoma were identified from the 2007 database, and another 6,882 patients who were admitted due to acute appendicitis according to the same database were selected as the matched control group. The history of transfusion of packed RBC (PRBC), platelet concentrates or plasma in the past ten years before the index date was reviewed.

Results: The transfusion rates were 3.8% and 3.2% in the lymphoma group and the control group, respectively, and no significant correlation was observed between transfusion history and subsequent lymphoma occurrence ($p = 0.128$). A similar result was found for PRBC transfusion (3.4% vs. 3.1%, $p = 0.394$).

Conclusions: This study demonstrated that transfusion with the three types of blood components was not associated with changes in the risk of lymphoma.

Key words: chronic hepatitis B, chronic hepatitis C, hepatocellular carcinoma, total *p*-cresylsulphate

Introduction

Blood transfusion plays a vital role in medicine with a history of over two hundred years since its first successful clinical application in 1818. With improvements in the screening methods for occult pathogens in blood samples, the consumption of blood products has been increasing in the past few decades. Transfusion is not uncommonly applied in patients with trauma, hemorrhage and hematologic disorders.

In addition to the known risk of transmis-

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sion of viral diseases, there are also studies demonstrating the possibility of subsequent lymphoma development with the majority of concerns focused on red blood cell transfusion.[1-4] Some studies have demonstrated an association between immune dysfunction and tumorigenesis as in non-Hodgkin lymphoma (NHL), which is the most common hematopoietic neoplasm.[5,6] Well-established risk factors include infections and an underlying immune dysregulation state.[7,8] Furthermore, several studies have shown that allogeneic RBC transfusions may suppress the function of T and natural killer cells, thereby promoting tumor formation.[9,10] However, the results remain controversial. Therefore, we conducted a nationwide study using the population-based dataset of Taiwan to evaluate the correlation between transfusion and the development of lymphomas.

Materials and Methods

Data source

This study was conducted using claims data from the National Health Insurance Research Database (NHIRD) which covers 99% of medical records of the 23.74 million residents of Taiwan and has contracts with 97% of Taiwanese hospitals and clinics managed by the National Health Research Institute in Taiwan. The NHIRD contains healthcare information, including demographic data of insured individuals, dates of clinical visits, diagnostic codes, and prescription details.

The diagnostic coding of diseases was performed according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

Study population

This research was a case-control study enrolling patients included in the NHIRD 2005 database and the cancer database from January 1, 2007 to December 31, 2007. Inpatients with newly diagnosed lymphoma (ICD-9-CM: 200-202) were enrolled as the case group, whereas patients who were admitted for appendectomy were included as the control group (ICD op code 47.0). The two groups were matched according to age, gender, index year, insurance range, resident urbanization, socioeconomic status, and comorbidities by propensity score matching.

Exposure to blood transfusion

Information regarding blood transfusion was obtained from the inpatient prescription database. Early transfusions used whole blood, whereas modern medical practice generally involves the transfusion of only blood com-

Table 1. Demographic data of this case-control study.

	Control n (%)	Case n (%)	*p* value
Gender			0.217
Female	2885 (41.9)	1398 (40.6)	
Male	3997 (58.1)	2043 (59.4)	
Age			NA
< 20	180 (2.6)	90 (2.6)	
20 ≤ Age < 25	126 (1.8)	63 (1.8)	
25 ≤ Age < 30	146 (2.1)	73 (2.1)	
30 ≤ Age < 35	206 (3.0)	103 (3.0)	
35 ≤ Age < 40	276 (4.0)	138 (4.0)	
40 ≤ Age < 45	292 (4.2)	146 (4.2)	
45 ≤ Age < 50	490 (7.1)	245 (7.1)	
50 ≤ Age < 55	596 (8.7)	298 (8.7)	
55 ≤ Age < 60	664 (9.6)	332 (9.6)	
60 ≤ Age < 65	568 (8.3)	284 (8.3)	
≥ 65	3338 (48.5)	1669 (48.5)	
Socioeconomic (EC) status			0.002
EC_1 or 2	1352 (19.6)	655 (19.0)	
EC_3	2353 (34.2)	1076 (31.3)	
EC_4	3177 (46.2)	1710 (49.7)	
Region			0.429
North	2761 (40.1)	1430 (41.6)	
South	1752 (25.5)	878 (25.5)	
Central	2170 (31.5)	1041 (30.3)	
East	199 (2.9)	92 (2.7)	
Urban Level			0.031
Urban	1945 (28.3)	1040 (30.2)	
Suburban	2767 (40.2)	1394 (40.5)	
Rural	2170 (31.5)	1007 (29.3)	

NA: not applicable

ponents such as red blood cells, white blood cells, plasma, clotting factors, and platelets. In this study, we investigated the blood transfusion record, including packed RBC, platelet concentrates, or plasma, from January 1, 1997 to December 31, 2006, whereas the records of blood transfusion within one year before the index date were excluded to reduce the possibility of preexisting occult diseases.

Statistical analysis

Pearson chi-square test or Fisher's exact test was performed to evaluate the differences in categorical data between patients in the case and control groups. An independent t-test was conducted to evaluate the differences in continuous data between the two groups. Conditional logistic regression analysis was conducted to analyze the correlation between lymphoma development and blood transfusion exposure. Several covariables, including age, gender, resident urbanization, and comorbidities, were adopted in the statistical analysis model and subtype transfusion analysis. Odds ratios and 95% confidence intervals, using no transfusion exposure as the reference, were calculated to determine the risk of lymphoma development. All statistical procedures were performed using the SAS 9.3 statistical package; all *p* values were two-sided, with values < 0.05 indicating statistical significance.

Results

During the study period, a total of 3,441 patients with newly diagnosed lymphoma were included in the study group, whereas 6,882 patients were selected in the control group, with a 1:2 frequency matching of age and gender. Approximately 60% of the recruited lymphoma patients were males. The average age was 65 years with about half of them > 65 years. For socioeconomic status and resident urbanization, there were significant differences between the two groups. The socioeconomic status was higher in the case group than that in the control group; most lymphoma patients had a high socioeconomic status ($p = 0.002$) with more lymphoma patients living in the urban area than that in the control group ($p = 0.031$) (Table 1). We then analyzed the transfusion history for both groups. Transfusion history was found in 3.8% of patients with lymphoma compared to 3.2% in the control group ($p = 0.128$). RBC transfusion was noted in 3.4% of lymphoma patients and 3.1% of those in the control group ($p = 0.394$). No significant correlation was observed between the transfusion history of any type of blood components and the subsequent risk of lymphoma development. We also analyzed the particular risk associated with PRBC transfusion, which also showed no obvious relationship with the incidence of lymphoma (Table 2). Further analysis with the logistic model including factors such as gender, age, socioeconomic status, and resident urbanization also did not demonstrate any significant relationship between these factors and the risk of lymphoma development (Table 3). For patients receiving one or more transfusion, the

Table 2. The correlation between transfusion and lymphoma

	Control n (%)	Case n (%)	*p* value
Transfusion			0.128
No	6663 (96.8)	3311 (96.2)	
Yes	219 (3.2)	130 (3.8)	
RBC Transfusion			0.394
No	6671 (96.9)	3324 (96.6)	
Yes	211 (3.1)	117 (3.4)	

*Table 3. Multivariate analysis of variables influencing lymphoma risk**

Model			
	OR	95% CI	*p* value
RBC (ref. = 0)			
= 1	1.10	(1.03 – 1.67)	0.449
> 1	1	(0.92 – 2.37)	0.997
p trend		0.833	

*Adjusted for gender, age, socioeconomic status and resident urbanization.

incidence of lymphoma was not different from that in those without transfusion.

Discussion

In this case-control study of Taiwanese patients of all ages, we found no significant relationship between the preceding transfusion of the three blood components (i.e., packed RBC, platelets, plasma) and the subsequent risk of lymphoma development with a latency period of one year. Although some studies have supported the correlation between transfusion and lymphoma development, there are also numerous studies showing opposite results.[11-13] Although these studies have included transfusion latency in their meta-analysis to reduce the possibility of including occult hematologic diseases, different definitions were adopted and most of the excluded patients whose lymphoma presented within one year after transfusion. A meta-analysis of 14 observational case-control or cohort studies reported that the relative risk of subsequent lymphoma development was 1.2-fold in groups with a history of blood transfusions. A significantly higher risk of developing chronic lymphocytic leukemia or small lymphocytic lymphoma was observed according to subgroup analysis (relative risk: 1.66) of that study and similar trends were found for follicular lymphoma and diffuse large B-cell lymphoma.[14] A more recent cohort study using the UK hospital records and cancer registry demonstrated a long-term increased risk of developing liver cancer and NHL amorg women, whose relative risks remain significantly elevated even after a 5-year follow-up (RR = 1.69, $p = 0.05$).[15] That study suggested that the occurrence of malignancies after transfusion is more likely associated with preclinical status of lymphoma rather than transfusion per se. However, contradictory results were demonstrated by several smaller case-control studies and cohorts.[11-13,16-18] A large case-control study evaluated the risk of hematologic malignancies using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) database, which comprised population-based records and metropolitan cancer registry.[21] Among a total of 77,488 elderly patients identified by the registry, 7.9% of them had histories of transfusion, which was higher than that in the control group. However, this trend lasted for only a short period of time, which may indicate a reverse causal relationship.[21] Riedl et al. conducted another case-control study also using the SEER database and cancer registry and demonstrated similar results in the elderly population.[22]

Among studies observing a positive relationship, most of the researchers have attributed the phenomenon to transfusion-related immunomodulation. Previous studies have demonstrated that RBCs may, like other cell types, shed extracellular vesicles (e.g., ectosomes) during the aging process. Sut et al. reviewed the relationship between RBC storage and the production of inflammatory markers and concluded that the proinflammatory state may be due to the existence of leukocytes and iron delivery from RBCs to monocyte/macrophage systems.[19] IL10RA and TNF gene polymorphisms have also been reported to modify the risk of NHL development in blood transfusion.[20] The function of tumor exosomes is another issue that has recently grabbed much attention. Mancek-Keber et al. have recently published their findings showing how Waldenström's macroglobulinemia may affect the recipient bone marrow by releasing extracellular vesicles containing MyD88 molecules and generating a pro-inflammatory environment. The actual role of tumor exosomes in transfusion recipients remains uncertain, and further studies are required to address this issue.

Our study is unique in focusing on all patient groups and analyzing the effects of three individual blood components. To the best of our knowledge, no similar studies have yet been published in Taiwan. Our results may

alleviate the concern regarding the risk of malignancy development from blood transfusion. Further efforts may focus on the potential effects of materials released from malignancies (e.g., exosomes or cytokines) on the recipients' microenvironment for tumorigenesis.

There were two major limitations of this study due to the nature of the database. First, only hospitalized patients were enrolled. Several hematologic diseases such as myelodysplastic syndrome and hemolytic anemia may be significant causes of transfusion in the outpatient setting; there is a known increase in the incidence of lymphoma in patients with myelodysplastic syndrome and patients with chronic hemolysis may also be afflicted with occult diseases and sometimes lymphomas. Besides, patients requiring blood transfusion in the emergency department are commonly under life-threatening situations that may obscure the correlation between transfusion and lymphoma. Second, the subtypes of lymphoma were not analyzed in this study. According to the 2016 WHO classification, there are more than 70 subtypes of lymphoid neoplasms and some have well-established correlations with infection. This may confound our results as the history of infection may not be identified in our database. There are also some other subtypes of lymphoma that are believed to have a close relationship with immune dysfunction. Although a subtype analysis may demonstrate a clearer link, it was not possible because biochemistry data were unavailable in the NHIRD database. Third, although the effect of platelet transfusion was analyzed, the number of patients enrolled was too small to arrive at a significant conclusion. In addition, most of the patients who received plasma transfusion also had a number of co-morbidities, which may be confounders in the present study.

Using data from the National Health Insurance Research Database, our study demonstrated that blood transfusion had no remarkable impact on subsequent lymphoma development with a latency of one year. The analysis of the individual effects of three different blood components also showed similar results. Further large-scale prospective studies are required to provide stronger evidence to support our findings.

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