Original article

High combined individual and neighborhood socioeconomic status correlated with better survival of patients with lymphoma in post-rituximab era despite universal health coverage

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The correlation between high socioeconomic status (SES) and better survival outcome in patients with either Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) was well-established in the pre-rituximab era. However, whether or not such an association exists in the post-retuximab era has not been reliably demonstrated. Herein we conducted a population-based study in Taiwan involving 5010 patients diagnosed between 2002 and 2006 to investigate the relationship between individual and neighborhood SES and survival outcomes for lymphoma. A proxy measure of individual SES is based on income-related insurance payment, and neighborhood SES is based on neighborhood household income.

After adjusting for patient characteristics, treatment modalities, and hospital characteristics, HL patients with high individual SES in advantaged neighborhoods showed a decreased risk of mortality (HR 0.33, 95% CI 0.10–0.99). NHL patients with high individual SES in advantaged neighborhoods showed a moderate decreased risk of death (HR 0.62; 95% CI 0.51–0.75), compared to those with low SES in disadvantaged neighborhoods. In the future, public health strategies and welfare policies must continue to focus on this vulnerable group.

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1. Introduction

In Taiwan, hematologic malignancies have become increasingly prevalent during recent decades, especially non-Hodgkin lymphoma. According to a report from the Taiwan Cancer Registry, more than 80% of non-Hodgkin lymphoma patients suffered from the B-cell type disease. Since its approval by the Taiwan FDA in 2002, rituximab had been the most commonly prescribed drug used in combination with multi-agent chemotherapy for most patients with CD20-positive B-cell lymphoma. In the United States, based upon "real world" investigation, patient survival outcome significantly improved in the post-rituximab era; yet this new era has caused moving target-like results when trying to predict the prognosis of patients with lymphoma. While earlier models relied mainly on disease character, host character, and biomarker models, there was a distinct lack of socioeconomic models used to assess patient survival.

In the pre-rituximab era, a growing body of literature suggests a persistent positive relationship existed between socioeconomic status (SES) and health status, with high SES correlating with better survival outcome in lymphoma, including Hodgkin and non-
Hodgkin types. But the impact of SES on lymphoma survival in the post-rituximab era remains unconfirmed. SES is thought to impact cancer survival via various mechanisms, which was briefly divided into those aspects of disease or host, including but not limited to delayed diagnosis, differential health-seeking behavior, access to care, and the presence of co-morbid conditions, among other factors. According to a previous study focusing on patient SES, insurance coverage played an important role in health inequity. However, universal health coverage in Taiwan might have eliminated the practice of altering treatment modalities among patients with different SES.

Otherwise, to limit the proxies of SES, several studies have explored the combined or cross-level interaction effect of individual SES and neighborhood SES in several malignancies; however, several of these studies have shown conflicting results. To date, there has been no large-scale study which explored the combined effect of individual and neighborhood SES on lymphoma.

This article describes and compares the overall survival rates and relative risk of death in patients who were diagnosed with lymphoma in the post-rituximab era, from 2002 to 2006. We used the Taiwan National Health Insurance Research Database (NHIRD), census data, and public information from the Department of Health to extract individual patient SES and neighborhood SES data. We used a population-based data set merged with neighborhood SES information to measure the contextual effect of individual and neighborhood SES on lymphoma survival rates.

2. Materials and methods

2.1. Ethics statement

This study was initiated after being approved by the Research Ethical Committee of Buddhist Dalin Tzu Chi General Hospital. All identifying personal information was removed from the secondary files prior to analysis, and the review board agreed to waive the requirement for written informed consent from the patients involved.

2.2. Database

The data for this study originated from the NHIRD in Taiwan between 2002 and 2006. The National Health Insurance Program enrolls up to 99% of the Taiwanese population and contracts with 97% of Taiwanese medical providers. The study cohort consisted of patients with lymphoma who began treatment between 2002 and 2006. Lymphoma cases were assigned to one of two diagnostic categories: Hodgkin lymphoma and non-Hodgkin lymphoma, based on coding numbers from ICD-9 (Hodgkin lymphoma: 201, Non - Hodgkin lymphoma: 200 & 202).

2.3. Measurements

We observed that the key dependent variable of interest was the 5-year survival rate. The overall survival rate was utilized because it was not possible to determine cause-specific survival rates based on this registry data. The key independent variables were the contextual effects of individual SES and neighborhood SES. Patients were then linked to the mortality data covering the years 2002–2011 to calculate overall survival duration. Each patient was tracked from his or her first curative treatment for a five-year period using administrative data to identify all patients who died during the study period. Patient characteristics included age, gender, geographic location, treatment modality, severity of co-morbidity, and monthly income. The severity of co-morbidity of each patient was based on the modified Charlson Comorbidity Index Score (CCIS), which has been widely accepted for risk adjustment in administrative claims data sets.

2.4. Individual-level measures

This study used the income-related insurance payment amount as a proxy measure of individual SES at the time of diagnosis, which is an important prognostic factor for cancer. By recursive partitioning analysis, we found that NTS 25000 was an ideal cut-off point for stratifying our cohort in terms of SES. The cancer patients were classified into two groups: 1) low SES: lower than US $821 (New Taiwan Dollar (NTS) 25000) per month; and 2) high SES: US $821 (NTS$25001) or more per month, as in our previous studies.

2.5. Neighborhood-level socioeconomic status

For neighborhood SES, household income is a contextual characteristic representing averages and percentages measured at the enumeration level in the 2001 Taiwan Census. Neighborhood household income was measured using per capita personal income by township acquired from the 2001 income tax statistics released by Taiwan’s Ministry of Finance (http://www.nfdoc.gov.tw/dp.asp?mp=3). Advantaged and disadvantaged neighborhoods were identified based on the median values of neighborhood characteristics, with advantaged neighborhoods having higher-than-median neighborhood household incomes, US$ 17900 (or NT $537000), and disadvantaged neighborhoods having lower-than-median household incomes.

2.6. Other variables

The urbanization levels of residences were classified into 7 levels based upon 5 indices: population density, percentage of residents with college level or higher education, percentage of residents >65 years of age, percentage of residents who were agricultural workers, and the number of physicians per 100,000 people. We recorded the urbanization level of residences as urban (urbanization level 1), sub-urban (urbanization levels 2–3), or rural (urbanization levels 4–7). The hospitals were categorized by ownership (public, nonprofit, or for-profit), and hospital level (medical center, regional or district hospital). The geographic regions where the cancer patients resided were recorded as Northern, Central, Southern, and Eastern Taiwan.

2.7. Statistical analysis

The SPSS program (version 15, SPSS Inc., Chicago, IL, USA) was used for data analysis. Pearson’s chi-square test was used for categorical variables such as gender, level of urbanization, geographic region of residence, CCIS, treatment modality, and hospital characteristics, and continuous variables were analyzed with one-way ANOVA.

The cumulative 5-year survival rates and the survival curves were constructed and compared using the log-rank test. Survival curves, stratified by individual SES and neighborhood SES, were measured from the time of diagnosis by using overall mortality as the event variable. The Cox proportional hazards regression model adjusted for patients’ characteristics (age, gender, CCIS, urbanization and area of residence), treatment modality and hospital characteristics, was used to compare outcomes between different SES categories. SES variables were introduced into the Cox model with the high individual SES and advantaged neighborhood group as the reference group. A two-tailed P-value (P < 0.05) was used to determine statistical significance.
3. Results

3.1. Demographic data and clinical characteristics

A total of 5010 lymphoma patients who received treatment were included in the study (Table 1), wherein 497 patients were diagnosed with Hodgkin lymphoma and 4513 with non-Hodgkin lymphoma.

Hodgkin lymphoma patients of low individual SES were more likely to reside in rural areas, specifically in southern and eastern Taiwan, and had higher Charlson Comorbidity index scores compared to patients with high individual SES. Patients of both low and high SES underwent treatment equally at regional and district hospitals, and there were no statistical differences in treatment modality.

For non-Hodgkin lymphoma, patients with low SES were more likely to be female and older and to have higher Charlson Comorbidity index scores, reside in rural areas, specifically in southern and eastern Taiwan, and to have undergone treatment at regional and district hospitals.

3.2. Survival analysis

The overall survival of patients with lymphoma who have different levels of socioeconomic status was analyzed (Table 2). For patients with HL, those with high individual SES in advantaged or disadvantaged neighborhoods were more likely to have higher 5-year overall survival rates than patients with low individual SES (95.7% and 96.6%, respectively, versus 78.1% and 75.8%, respectively, where \( P < 0.001 \)) (Fig. 1). For patients with NHL, those with high individual SES and high neighborhood SES were more likely to have higher 5-year overall survival rates than patients with low individual and neighborhood SES (72.1% versus 49.5%, respectively, where \( P < 0.001 \)) (Fig. 2).

3.3. Multivariable survival analysis

The combined effects of individual SES and neighborhood SES remained statistically significant in the Cox proportional hazards regression model, when adjusted for other factors in patients with both HL and NHL. Patients with HL with high individual SES in advantaged neighborhoods showed a large decrease in the risk of mortality (HR 0.33, 95% CI 0.10—0.99) (Table 3). Among patients with NHL, those with high individual SES in advantaged neighborhoods showed a decreased risk of death (HR 0.62; 95% CI 0.51—0.75), compared with those with low SES in disadvantaged neighborhood.

4. Discussion

To the best of our knowledge, there have been limited studies about the socioeconomic status of patients with lymphoma in the post-rituximab era, including studies concerning the combined effects of individual and neighborhood socioeconomic gradients in lymphoma. In our study, we described that for patients with HL or NHL, the combined effects of individual and neighborhood SES resulted in a moderate decrease in the risk of overall mortality despite universal health coverage in the post-rituximab era. There was a synchronous effect of combined individual and neighborhood SES in predicting overall survival in lymphoma patients, especially for those with non-Hodgkin lymphoma.

Our study had a number of strengths. First, it was a large nationwide population-based follow-up study, with nearly complete follow-up information about access to healthcare institutions by the entire study population (99%). The dataset was also routinely monitored for diagnostic accuracy by the National Health Insurance Bureau of Taiwan. Therefore, the data set was more generalized and truly reflected clinical practice in the real world, with minimal selection bias.

Second, a large majority of the earlier research studied SES in patients aged 65 and older, before the era of rituximab, or in specific categories, just like patients with Hodgkin lymphoma. We, however, observed that SES was associated with hospital characteristics and treatment modality, even in patients younger than 65 years old, at different levels of socioeconomic status.
lymphoma or follicular lymphoma. Those results require validation in a cohort of the overall population. Our series didn’t have any limitation in age and disease entity. Third, we focused on the role of SES and lymphoma survival in the post-rituximab era, and the results definitely reflected the real world circumstances of our current practice. Fourth, the combined effects of individual and neighborhood SES might eliminate the ordinary limitation of each proxy. We observed the prominent effects of combined SES on the overall survival of patients with lymphoma, and the result was not conflict between different proxies.

For HL, most previous studies have shown a correlation between decreasing survival rates for patients with HL with decreasing SES, although several studies found no or a varied association between survival outcomes in patients with HL with decreasing SES. The differences in these findings may be attributable to different health care systems or area-based markers of SES. In our study, however, we demonstrated a similar result, suggesting that low SES predicted poor overall survival in the last decade.

For NHL, rituximab played an important role in the field of treatment of CD20-positive B cell lymphoma in recent decades, and has profoundly altered the manner in which this disease is treated. Although low SES was correlated with poorer survival outcome after diagnosis of NHL in the pre-rituximab era despite universal health coverage among Canadian adults, the association remains unclear in the post-rituximab era. We demonstrated that a low combined SES score correlated with poor survival outcome, even in the post-rituximab era.

There have been many hypothesis presented attempting to explain why lower SES predicted low survival outcome, including the state of advanced disease upon initial diagnosis, receipt of poorer cancer treatment, inadequate health insurance, lower complete response, increased fatal events during treatment, or inadequate long-term follow-up in patients. Personal factors may also contribute to reduced survival, similar to smoking related poorer health status and co-morbidity among cancer patients with various SES, nutritional status-related influence in treatment tolerance and survival sequentially, and male gender for more advanced disease at the time of diagnosis. In Taiwan, universal health coverage may have eliminated the impact of the medical factor, better equalizing treatment modalities among patients with different SES. However, the inequality of health status among these patients still existed. This suggests that

**Table 2**

<table>
<thead>
<tr>
<th>Neighborhood socioeconomic status</th>
<th>Individual socioeconomic status</th>
<th>Non-Hodgkin lymphoma (n = 4513)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>High SES</td>
<td>Low SES</td>
</tr>
<tr>
<td>High SES (n = 2532)</td>
<td>398 (72.1%)</td>
<td>914 (54.0%)</td>
</tr>
<tr>
<td>Low SES (n = 2478)</td>
<td>204 (68.7%)</td>
<td>975 (49.5%)</td>
</tr>
<tr>
<td><strong>P-value</strong></td>
<td><strong>&lt;0.001</strong></td>
<td><strong>&lt;0.001</strong></td>
</tr>
</tbody>
</table>

Abbreviation: Adjusted HR, adjusted hazard ratio; 95% CI, 95% confidence interval; SES, socioeconomic status.

**Fig. 1.** SES, neighborhoods and 5-year OS in HL patients. Those with high individual SES in advantaged or disadvantaged neighborhoods were more likely to have higher 5-year overall survival rates than patients with low individual SES (95.7% and 96.6% versus 78.1% and 75.8%, P < 0.001).

**Fig. 2.** SES, neighborhoods and 5-year OS in NHL patients. Those with high individual SES and high neighborhood SES were more likely to have higher 5-year overall survival rates than patients with low individual and neighborhood SES (72.1% versus 49.5%, P < 0.001).
personal factors play an important role in disease-related survival outcome.

Although individual measures have been shown to be more strongly associated with health outcomes than neighborhood measures,35,36 neighborhood SES may influence health through the social, environmental, and physical environments of the neighborhood.36,37 Besides individual SES, neighborhood SES influenced mortality and other outcomes.38,39 Some studies controlling for both types of SES measures have found effects on health of neighborhood SES above and beyond those attributable to individual SES.36,37 Because disease outcome was contributed by many individual and neighborhood alteration factor, it should make sense when both factors are taken into consideration. The impact of the cross-level interaction of individual SES and neighborhood SES was various in several malignancies.40 In our team, we had demonstrated the combined effect of individual and neighborhood SES in survival outcome in nasopharyngeal cancer, breast cancer, and lung cancer.15–17 Regarding our study, synchronous effect was documented such that high combined individual and neighborhood SES was correlated with better survival outcome in lymphoma, especially in non-Hodgkin type.

There were some limitations to our study. First, there was potential for miscategorization in the diagnosis of cancer and any comorbid conditions which were completely dependent on ICD codes. Nonetheless, the National Health Insurance Bureau of Taiwan randomly reviews the charts and interviews patients in order to verify diagnostic accuracy.41 Second, the database does not contain information on potentially relevant clinical data such as performance status or biochemical laboratory examinations. Our study could not estimate the impact of these factors on survival. Third, detailed clinical information about grade, stage, and histological subtypes of lymphomas were not included in the dataset; however, previous studies have revealed no statistically significant associations between SES and tumor stage at the time of diagnosis in several malignancies, including Hodgkin lymphoma and follicular lymphoma.41 and no significant association was found between SES and histological subgroups.11 Fourth, SES includes several factors, such as income, education, and occupation. Among them, income is frequently used as a surrogate for SES. In our study, since the information of education and occupation was not included in the database from NHIRD in Taiwan, we used income as the surrogate for SES.

### 5. Conclusions

The results of our study indicated that, in Taiwan, there were health inequities for both Hodgkin and non-Hodgkin lymphoma as a result of a combination of individual and neighborhood SES, even within a system of universal health insurance in the post-rituximab era. Elucidation of the relative roles of these factors could guide interventions in the future, to reduce disparities in survival. The finding of social inequity in lymphoma patients could be addressed in clinical practice if general practitioners paid special attention to patients of low SES. Public health strategies should also focus on patients with low individual and neighborhood SES in order to reduce disparities in healthcare.

### Conflict of interest

The authors declare no funding sources or conflicts of interest involved in this study.

### Acknowledgments

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