Assessing the Relationship between Chronic Lymphoid Leukemia Mortality Rates and Human Development Index: A 26-Year Trend Analysis Using Location-Scale Mixed Effects Model

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Abstract

Background: Chronic lymphoid leukemia (CLL) is one of the most prevalent types of leukemia, which is responsible for a remarkable mortality rate in the world. This study aimed to investigate the global trend of this cancer from 1990 to 2015 and to determine the relationship between trend of CLL mortality rate and Human Development Index (HDI) throughout the world.

Methods: The age-standardized mortality rate data of all countries of the world (per 100,000) were extracted from the GBD database. In addition, the HDI values for the studied countries in different years were obtained from the UNDP database. The statistical analysis was performed using the mixed-effects location-scale model in the SAS software, version 9.4.

Results: The findings of the statistical modeling showed a downward slope for CLL Age Standardized Mortality Rate (ASMR) for total world countries ($\hat{\beta} = -0.002$). We also find a significant association between CLL ASMR and HDI. Countries with higher HDI had higher level of CLL ASMR in years 1990 to 2015 with a negative slope. Furthermore, countries with lower HDI had Lower level of CLL ASMR with rather fixed rates in this period.

Conclusion: These findings showed a decreasing trend of global CLL ASMR in the previous decades, although, the fixed trend of CLL ASMR in countries with low HDI is worrisome. The health policymakers should make more efforts to decrease the mortality due to this cancer in these countries.

Keywords: Chronic lymphoid leukemia; Mortality rate; Human development index; Trend analysis

Introduction

Cancer is one of the main causes of mortality in nearly all countries including developed and developing countries. It is one of the most important public health concerns and has become a

priority in public health issues (1-3). Globally, about 1 in 6 deaths is due to cancer; cancer was responsible for 9.6 million deaths in 2018 (4,5). Cancer incidence is increasing due to some factors such as population growth and aging especially in developing countries (6). The percentages of the new cancer cases and the cancer deaths were 56% and 64% respectively in less developed world(LDW) in 2008 (7); while in the past, it had been quite the opposite and the most burden of cancer could be seen in the more developed world (MDW) (8).

Leukemia is one of the most common cancers and it includes a group of diseases distinguished according to malignant and uncontrolled increase in mature leukocytes or their progress in the blood and bone marrow (9). The chronic lymphocytic leukemia (CLL) is a type of leukemia that starts when the bone marrow makes too many white blood cells. Patients usually have no early symptoms (10). Over the last few years, the treatment of CLL patients has been more complex due to discovering more sensitive therapeutic methods and also due to the emersion of new biologic factors to evaluate minor symptoms of CLL and identify molecular predictive markers (11). The main barriers to complete cure are relapse of cancer after recovery and resistance to initial treatment (12).

The numbers of new cases and deaths of leukemia were 437,033 and 309,006, respectively which were responsible for 2.4% of all new cancer cases and 3.2% all cancer deaths in 2018 (4). The CLL is the most common leukemia type. The estimated new cases of CLL in 2018 was 20,940 which was 1.2% of all new cancer cases and the number of death was estimated 4510 which was 0.7% of all cancer deaths (13).

According to different studies that assessed leukemia, even with advances in knowledge of pathophysiology of this disease, unfortunately, its risk factors have not been determined obviously, yet. Nevertheless, some of the potential risk factors are smoking, low physical activity, obesity, and overweight (11,14,15). The socioeconomic status, educational level, and life expectancy are the rea-

sons, which can cause disparities in incidence and mortality rates of cancers among countries; these features can be investigated by using the Human Development Index (HDI) as a core socioeconomic determinant of health (16). Regarding some published literature, the relationship between mortality due to different types of cancer and HDI is rather obvious, but in specific, there has been little knowledge about relationship between mortality rates of CLL and the HDI.

Due to the lack of research about the trend of mortality rates of CLL and determining the longitudinal relationship between this trend and the trend of HDI in the world, this study was conducted to investigate the trend of CLL mortality rates in different regions of the world over the period of 1990-2015 and its association with the HDI. To do this, we applied advanced longitudinal modeling approaches for assessing this relationship properly.

Materials and Methods

Data source
Chronic Lymphoid Leukemia Age Standardized Mortality Rate (CLL ASMR)

The risk of cancer development is highly affected by the patient's age; therefore, standardization is necessary when the aim is to compare several populations with different age structures. The CLL ASMR data used in this study were obtained from Global Health Data Exchange (http://ghdx.healthdata.org/gbd-results-tool).

The Global Burden Disease (GBD) is an approach to global descriptive epidemiology. GBD is conducted in the Institute for Health Metrics and Evaluation (IHME). The GBD estimates are updated regularly and for each update, the total time series back to 1990 will be re-estimated using all available data and best available methods to ensure the most complete and highly comparable set of possible estimates (17).

The geographic regions of the world introduced by the IHME were utilized for assessing CLL ASMR in different regions. The seven IHME super-regions are 1) Southeast Asia, East Asia,

and Oceania; 2) Central Europe; 3) Eastern Europe, and Central Asia; 4) High-income; 5) Latin America and the Caribbean; 6) North Africa and the Middle East, and 7) South Asia and Sub-Saharan Africa (18).

Human Development Index (HDI)

In 1990, the United Nations Development Program (UNDP) published its first annual Human Development Report and introduced the HDI. HDI is summary measure of human development, composed of three main components including: (i) life expectancy at birth, (ii) education as mean years of schooling, (iii) gross national income (GNI) per capita (19). Data about the HDI from different countries are in the UNDP (http://hdr.undp.org/en/data). The categories of the distribution of HDI by country are low (HDI<o.550), medium (0.550≤HDI<0.70), high (o.70≤HDI<0.80), and very high (HDI≥0.80).

Statistical analysis

Only countries with both the CLL ASMR and HDI for 1990 to 2015 were included in the analysis. To assess the trend of CLL ASMR during this period (the first aim of this study), the mean ASMR was reported in four categories of HDI and seven regions. Then, for evaluating the relationship between the CLL ASMR and HDI in the world (the second aim of this study), the following mixed effects location scale model was used separately for HDI categories:

$$Y_{ij} = \hat{\beta}_0 + \hat{\beta}_1 time_j + u_{0i} + \varepsilon_{ij} \qquad [1]$$

where Y_{ij} indicates the CLL ASMR for country i ($i=1,\ldots,122$) at time j ($j = 0,\ldots,25$) and the random term u_{0i} indicates the influence of country i on its CLL ASMR. The random term is usually assumed to be normally distributed in the population with zero mean and variance σ_u^2. The population distribution of the errors ε_{ij} is also assumed to be normal with zero mean and variance σ_ε^2 and independent of the random terms. Here, σ_u^2 and σ_ε^2 represent the between-subject (BS) variance and within-subject (WS) variance, respectively.

We can use a log-linear representation to allow covariates effect on the BS and WS variances as described in the context of heteroscedastic (fixed effects) regression models (20), namely:

$$\sigma_{u_i}^2 = \exp(v_i'), \qquad [2]$$
$$\sigma_{\varepsilon_{ij}}^2 = \exp(w_{ij}'\gamma) \qquad [3]$$

Therefore, the WS variance is modeled with both country-varying and time-varying covariates while the BS variance is modeled only with country-varying covariates. The coefficient in τ and γ expresses the degree of influence on the BS and WS variances, respectively. For considering the countries' heterogeneity, we can further extend the model by including random subject effects for a subject `s measurement error (i.e., random scale effects):

$$\sigma_{\varepsilon_{ij}}^2 = \exp(w_{ij}'\gamma + \omega_i) \qquad [4]$$

where the random subject (scale) effects ω_i are distributed in the population of subjects with mean 0 and variance σ_ω^2. If the distribution of ω_i is normal, then the WS variance, $\log(\sigma_{\varepsilon_{ij}}^2) = w_{ij}'\gamma + \omega_i$, follows a log-normal distribution. The skewed, nonnegative nature of the log-normal distribution makes it a reasonable choice for representing variances and it has been used in many diverse research areas for this purpose (21,22). In this model, we have a random location effect that affects an individual `s mean, $u_i$ , and a random scale effect that influences an individual`s variance, ω_i . Thus, we named the model with both types of random effects as mixed effects location scale model. These two random effects are correlated with covariance parameter $\sigma_{u\omega}$, which indicates the degree of association between the random location and scale effects (23). All models were fitted using the PROC NLMIXED in the SAS software, ver. 9.4.

Results

Table 1 represents the mean trend of CLL ASMR for different IHME super regions. According to this table, the highest and lowest CLL ASMR can be observed in the "High-income" and "South-

east Asia, East Asia, and Oceania" regions, re-   spectively.

Table 1: Mean trend of CLL ASMR (per 100000) for different IHME super regions from 1990 to 2015

Region	Year											
	1990		1995		2000		2005		2010		2015	
	Mean (SD*)	CI**	Mean (SD)	CI	Mean (SD)	CI	Mean (SD)	CI	Mean (SD)	CI	Mean (SD)	CI
Sub-Saharan Africa	0.35 (0.10)	(0.31,0.39)	0.36 (0.11)	(0.31,0.40)	0.34 (0.11)	(0.30,0.38)	0.33 (0.11)	(0.28,0.38)	0.33 (0.12)	(0.27,0.38)	0.33 (0.12)	(0.28,0.38)
North Africa and Middle East	0.34 (0.14)	(0.26,0.42)	0.34 (0.15)	(0.26,0.42)	0.32 (0.15)	(0.24,0.40)	0.32 (0.16)	(0.23,0.40)	0.31 (0.17)	(0.22,0.39)	0.30 (0.17)	(0.21,0.39)
South Asia	0.31 (0.04)	(0.23,0.37)	0.31 (0.03)	(0.26,0.35)	0.31 (0.02)	(0.27,0.34)	0.30 (0.03)	(0.25,0.35)	0.29 (0.03)	(0.24,0.35)	0.29 (0.04)	(0.23,0.35)
Southeast Asia, East Asia, and Oceania	0.16 (0.06)	(0.13,0.20)	0.16 (0.06)	(0.12,0.19)	0.15 (0.06)	(0.12,0.19)	0.14 (0.06)	(0.10,0.18)	0.13 (0.06)	(0.09,0.17)	0.13 (0.06)	(0.09,0.17)
Latin American and Caribbean	0.48 (0.40)	(0.28,0.69)	0.48 (0.38)	(0.28,0.67)	0.45 (0.36)	(0.27,0.64)	0.47 (0.34)	(0.30,0.64)	0.49 (0.32)	(0.32,0.65)	0.47 (0.31)	(0.31,0.63)
Central Europe, Eastern Europe, and Central Asia	0.99 (0.67)	(0.67,1.31)	1.03 (0.68)	(0.70,1.35)	1.02 (0.66)	(0.71,1.34)	1.01 (0.61)	(0.70,1.31)	1.01 (0.62)	(0.72,1.31)	0.98 (0.63)	(0.68,1.29)
High-income	1.06 (0.48)	(0.88,1.24)	1.12 (0.53)	(0.93,1.31)	1.14 (0.56)	(0.94,135)	1.10 (0.53)	(0.90,1.29)	1.01 (0.47)	(0.83,1.18)	0.95 (0.46)	(0.78,1.12)
Total World	0.62 (0.52)	(0.53,0.71)	0.64 (0.54)	(0.54,0.74)	0.63 (0.56)	(0.54,0.73)	0.62 (0.53)	(0.53,0.72)	0.60 (0.50)	(0.51,0.69)	0.57 (0.47)	(0.49,0.66)

*SD=Standard Deviation
**CI=Confidence Interval

Figure 1 shows the trajectory plot of mean CLL ASMR in different IHME super regions from 1990 to 2015. The intercepts (starting points in year 1990) for these super regions were different but all regions had rather decreasing trend (negative slope) over study period.

Table 2 shows the mean trend of CLL ASMR for categories of the HDI. Countries with very high HDI had the highest CLL ASMR and countries with low HDI had the lowest CLL ASMR in these years.

According to Fig. 2, the CLL ASMR varied across different countries with different levels of development (measured by HDI). The intercepts (starting points in year 1990) for these different HDI categories were not identical, but all countries with different HDI had decreasing trend (negative lope) over the period of 1990 to 2015.

The results for the mixed-effects model with random intercept based on CLL ASMR for total world are shown in Table 3. The trend of the CLL ASMR was decreasing (significant negative slope ($\hat{\beta} = -0.002$) in the study period.
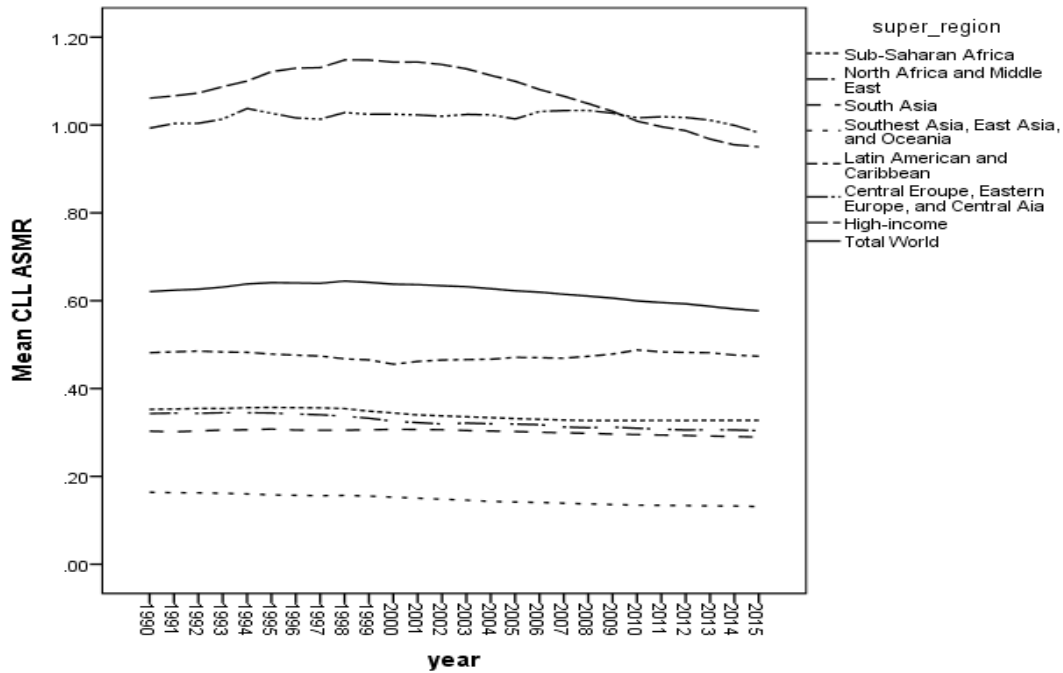
Fig. 1: Trends of CLL ASMR by IHME super-regions

Table 2: Mean trend of CLL ASMR (per 100000) for HDI categories from 1990 to 2015

Region	Year											
	1990		*1995*		*2000*		*2005*		*2010*		*2015*	
	Mean (SD)*	*CI****	*Mean (SD)*	*CI*	*Mean (SD)*	*CI*	*Mean (SD)*	*CI*	*Mean (SD)*	*CI*	*Mean (SD)*	*CI*
Low	0.36 (0.26)	(0.28,0.45)	0.37 (0.25)	(0.29,0.45)	0.33 (0.11)	(0.29,0.37)	0.33 (0.11)	(0.29,0.37)	0.33 (0.12)	(0.28,0.37)	0.36 (0.12)	(0.31,0.41)
Medium	0.38 (0.31)	(0.29,0.48)	0.41 (0.39)	(0.29,0.53)	0.34 (0.28)	(0.24,0.43)	0.32 (0.29)	(0.22,0.42)	0.33 (0.32)	(0.19,0.47)	0.35 (0.33)	(0.17,0.40)
High	1.09 (0.58)	(0.88,1.31)	0.93 (0.59)	(0.69,1.18)	0.88 (0.61)	(0.63,1.12)	0.58 (0.44)	(0.40,0.77)	0.41 (0.31)	(0.30,0.53)	0.38 (0.28)	(0.28,0.48)
Very high	1.14 (0.39)	(0.88,1.40)	1.26 (0.52)	(1.02,1.50)	1.21 (0.57)	(0.99,1.44)	1.18 (0.55)	(1.00,1.37)	1.07 (0.53)	(0.91,1.24)	1.02 (0.52)	(0.86,1.18)
Total world	0.62 (0.52)	(0.53,0.71)	0.64 (0.54)	(0.54,0.74)	0.63 (0.56)	(0.54,0.73)	0.62 (0.53)	(0.53,0.72)	0.60 (0.50)	(0.51,0.69)	0.57 (0.47)	(0.49,0.66)

*SD=Standard Deviation
**CI=Confidence Interval

In the next step of data analysis, to assess the effect of HDI levels on CLL ASMR, we fitted the described model in the methods section (model 1) to the data. To assess whether covariates can explain some of the heterogeneity in CLL ASMR over and above their influence on the mean response, the BS and WS covariance of outcome was modeled. For BS variance, we considered intercept and for WS variance, time was included in the model. Table 4 presents the results for mixed-effects location scale model including the following sub-models: (i) mean of CLL ASMR; (ii) WS variance of CLL ASMR; and (iii) BS variance of CLL ASMR for different HDI levels.

In terms of the mean, for all four HDI categories, the trend of CLL ASMR decreased over the study period ((for low HDI, $\hat{\beta}_1$ =-0.0013, $P<0.0001$), (for medium HDI, $\hat{\beta}_1$ =-0.0019, $P<0.0001$), (for high HDI, $\hat{\beta}_1$ = -0.031,

P<0.0001), ((for very high HDI, $\hat{\beta}_1$ =-0.0028, P<0.0001)). Highest decrease (significantly negative slope) is seen in countries with high HDI

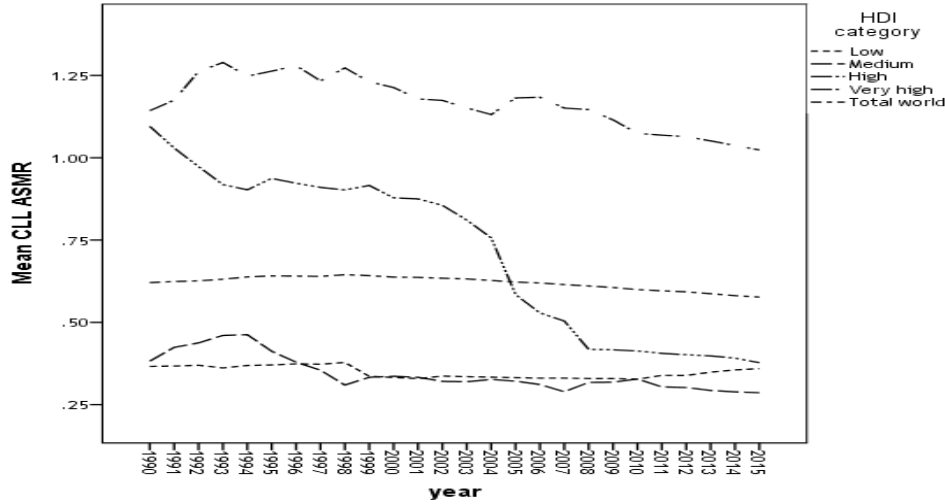and countries with very high HDI have highest intercept (1.16).

Fig. 2: Trends of CLL ASMR by categories of HDI

Table 3: Results from the mixed-effects model with random intercept based on CLL ASMR for total world

Parameter	Estimate*	S.E**	P-value
Intercept	0.645	0.047	<.0001
Time	-0.002	0.0002	<.0001

*Estimate of the model parameter
** Standard errors of the estimate

For time, there is a significant negative effect on WS variance of CLL ASMR for all countries with low, medium, and high HDI, indicating that as time ((for low HDI, $\hat{\gamma}_1$ =-0.1914, P<0.0001), (for medium HDI, $\hat{\gamma}_1$ =-0.137, P<0.0001), (for high HDI, $\hat{\gamma}_1$ =-0.1187, P<0.0001)) increases, the variation of response decreases.

As can be seen in Table 4, the random WS variance (the BS variance of scale) and covariance parameters are both highly significant (P-value<0.001).

The significant variance of the random WS variance effect σ_ω^2 indicates that there was considerable heterogeneity among the countries in terms of their CLL ASMR variation. The covariance parameter $\sigma_{u\omega}$ is estimated to be positive. Thus, countries

with higher mean of CLL ASMR mean exhibited greater variation in CLL ASMR.

Discussion

Chronic lymphocytic leukemia is a type of slow growing and the most common leukemia in the western countries (24). To the best of our knowledge, this is the first trend analysis of CLL mortality rates in different regions of the world during 1990 -2015 that tried to assess the longitudinal relationship between this trend and the HDI using location-scale mixed effects model. We showed that the CLL ASMR varied across the world and its trend had been decreasing over the past half of the century and in different IH-ME regions. The largest decrease occurred in "High-income" region. The CLL ASMRs were

1.06 and o.95 per 100000 in 1990 and 2015 in this region, respectively. In whole world, the CLL ASMRs were 0.62 and 0.57 per 100000 in 1990 and 2015. Our results also showed that the CLL ASMR varied across countries with different

HDI and its trend decreased from 1990 to 2015. Countries with high HDI had the highest reduction in CLL ASMR during 1990 - 2015. The CLL ASMRs were 1.14 and 1.02 per 100000 in 1990 and 2015 in these countries, respectively.

Table 4: Results from the location-scale mixed-effects model with random intercept based on CLL ASMR by HDI category

Sub-model	HDI	Parameter	Estimate*	S.E**	P-value
Mean	Very high	Intercept	1.16	0.082	<0.0001
		Time	-0.003	0.0002	<0.0001
	High	Intercept	1.1	0.035	<0.0001
		Time	-0.031	0.0023	<0.0001
	Medium	Intercept	0.44	0.44	<0.0001
		Time	-0.002	0.0001	<0.0001
	Low	Intercept	0.36	0.037	<0.0001
		Time	-0.001	0.00009	<0.0001
WS variance	Very high	Intercept	-6.47	0.370	<0.0001
		Time	0.019	0.014	0.169
	High	Intercept	-6.389	0.340	<0.0001
		Time	-0.119	0.017	<0.0001
	Medium	Intercept	-7.24	0.29	<0.0001
		Time	-0.137	0.014	<0.0001
	Low	Intercept	-7.245	0.331	<0.0001
		Time	-0.1914	0.012	<0.0001
BS variance	Very high	Intercept	-1.25	0.216	<0.0001
		Time	-	-	-
	High	Intercept	-1.155	0.175	<0.0001
		Time	-	-	-
	Medium	Intercept	-1.852	0.244	<0.0001
		Time	-	-	-
	Low	Intercept	-2.812	0.214	<0.0001
		Time	-	-	-
	Very high	BS variance of scale σ_ω^2	3.637	0.838	<0.0001
		Random location and random scale covariance $\sigma_{u\omega}$	0.721	0.194	<0.001
	High	σ_ω^2	3.910	0.754	<0.0001
		$\sigma_{u\omega}$	0.619	0.174	<0.001
	Medium	σ_ω^2	3.595	0.808	<0.0001
		$\sigma_{u\omega}$	0.414	0.118	<0.001
	Low	σ_ω^2	3.655	0.926	<0.001
		$\sigma_{u\omega}$	0.191	0.080	0.022

*Estimate of the model parameter, ** Standard errors of the estimate

In Taiwan, the incidence of CLL in this country was considerably lower than that of in Western

countries, but its trend was increasing drastically during 1986- 2005 (25). A significant decreasing

trend was found for the incidence rate of CLL and CML in the United States (1973-1998) but AML had a rather stable rate (26). The incidence of some cancers including leukemia was increased from 2007 to 2011 (27). In Asia, nearly 5% of cancer cases are chronic lymphocytic leukemia, while in western countries, this type of cancer is the most prevalent type of leukemia; 30% of leukemia cases are of this type (24). The international variation in mortality due to cancer can be partially related to environmental or lifestyle risk factors (28,29). Cancer is a disease associated with age; although, leukemia is the most common malignancy in children, most cases of leukemia happen in elderly (30). About 57% of the 14.1 million new cancer cases and 62% of the 8.2 million cancer deaths are found in developing countries, thus cancer burden is an important issue in these regions. Even though, the amount of resources spent in the developing countries is about 5% of the number of global resources for cancers (31). Some recommended methods to reduce these disparities in investment and healthcare resource availability include targeting etiological factors and high-risk behaviors along with developing strategies for cancer prevention (32).

In our study, the relationship between the CLL ASMR and the HDI as an indicator of the socioeconomic factor of health and a gold standard for international comparisons of development should be evaluated. In order to achieve this goal, we presented a location-scale mixed-effects model used to model not only means across covariates but also the differences invariances. These models can be useful to determine predictors of both BS and WS variations and to test hypotheses about these variances. Further, this model can check the amount of heterogeneity among countries in terms of their variation on the outcome variable. According to the findings of fitting this model, the HDI had a significant effect (negative slop) on the CLL ASMR and countries with high HDI had the largest negative slop. Based on the WS variance model, it can be concluded that over time, the variation of CLL ASMR decreased. Pol-

icy makers should plan to reduce CLL ASMR. Moreover, there was considerable heterogeneity among the countries in terms of their CLL ASMR variation and the countries with higher mean of CLL ASMR exhibited greater variation in CLL ASMR.

A similar study was conducted on the incidence and mortality of leukemia and its association with the HDI worldwide. According to this study, the countries, which had high and very high HDI, showed the highest incidence rate of leukemia. However, the countries, which had moderate or very high HDI, showed the highest mortality rate. Age Standardized Incidence Rate (ASIR) and ASMR of leukemia showed a positive significant correlation with HDI (16). A positive correlation was detected between HDI and the incidence and mortality rates of lung cancer (LC) in the world (33). The inverse correlation between the mortality-to-incidence ratios (MIRs) of gastrointestinal cancers worldwide and HDI was confirmed in another study (34).

The advantages of this study are applying advanced longitudinal modeling approaches and assessing over a long time (1990 to 2015). Our study had two limitations. First, since it was an ecological study, the interpretation of the results could be biased due to generalization of the aggregated findings to the individual level. Second, differences in quality of reports of the diagnosed mortality cases of cancer were not equal across regions. For example, cancer statistics could probably be under-reported, especially in less developed countries.

Conclusion

The trend of CLL ASMR was decreased from 1990 to 2015 and the highest CLL ASMR appeared in countries with very high and high HDI. The HDI had a negative significant effect on the CLL ASMR. In terms of BS heterogeneity, countries with low HDI and countries with medium HDI were less varied and more homogeneous compared to countries with very high HDI. For WS variance, countries with low, medium, and

high HDI elicited less varied responses compared to countries with very high HDI and there was a significant negative effect on WS variance of CLL ASMR.

Therefore, we propose that the investigation on the causes of this cancer is needed to reduce the mortality of CLL, especially in countries with low HDI as they had an approximately fixed trend of CLL ASMR.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interests.

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