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■ RESEARCH ARTICLE

International Disparities in Survival of Children with Acute Lymphoblastic Leukemia

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ABSTRACT: Pediatric Acute Lymphoblastic Leukemia (ALL) is curable, but treatment cost can be a limiting factor due to healthcare resources. Therefore, it was hypothesized that childhood ALL survival is linked to countries' per capita Gross Domestic Product (GDP). The Cancer Atlas datasets on pediatric ALL in world regions were analyzed. The GDP values were extracted from the International Monetary Fund and The World Bank websites. The Graph Pad Prism program and t-tests were used for evaluations. Five-year pediatric ALL survival for 25870 patients was grouped by continents and analyzed against GDP. Correlation was observed between survival rates versus GDP (R2=0.98). Pediatric ALL survival was >80 % in Oceania, North America, and Europe, and <80 % in Asia, Latin America, and Africa. For these two groups, averaged GDPs were respectively $45,046 and $5,477 (p=0.025). Survival of ALL improved in 10 countries from 1995-2009 (67.7 % to 77.3 %; p<0.005) alongside the GDP growth from $12,949 to $23,419 (p=0.002). Growth rates of GDP were analyzed against survival improvements of ALL (% difference) from 1995-2009. Survival improved by 6.8±1.2 % (mean±SE) in countries with GDP growth ≤1.8-fold versus 12.6±0.9 % for those with GDP growth >1.8-fold (p=0.005). International childhood ALL outcomes vary with GDP; higher GDP associates with better survival, improvements of which correlate with faster GDP growth.

KEYWORDS: Biomedical and Health Sciences; International Healthcare Disparities; Cancer Survival; Pediatric Acute Lymphoblastic Leukemia (ALL); Gross Domestic Product (GDP).

■ Introduction

Childhood cancers are rare, but they result in significant childhood mortality worldwide.[1] Pediatric acute Lymphoblastic Leukemia (ALL) is the most common pediatric cancer and is a highly curable condition with appropriate therapies, however, cost of treatment is a limiting factor for many developing countries. On average, complete treatment of pediatric ALL in developed countries may cost more than 100,000 US dollars,[2] which may not be affordable for those in developing countries. Therefore, it was hypothesized that because survival of childhood ALL is influenced by healthcare resources, it may be associated with a countries' Gross Domestic Product (GDP) per capita.

Cancer outcome disparities in adults are well documented to be multifactorial,[3] and socioeconomic factors play significant role in survival. Disparities in pediatric cancer are also multi-dimensional, including racial differences (i.e., higher frequency of ALL in Hispanics,[4] etc.). Here we analyzed publicly available datasets to describe quantitative connections worldwide between the survival of pediatric leukemia and GDP per capita.

■ Materials and Methods

The Cancer Atlas datasets were used to extract pediatric ALL survival rates in different world regions, and historical data that were available for ten countries.[5] Gross Domestic Product (GDP, per capita included) values for six continents and ten countries were extracted from the International Monetary Fund and The World Bank online sources.[6,7] Student t-tests were used for evaluations with 95 % confidence. Excel was used for student t-tests in Table 2 (two-tailed, paired), and Figures 3A and 3B (two-tailed, two sample unequal variance). Additionally, the Graph Pad Prism program was applied for data analysis/graphing. Graph Pad was used to produce all the figures. For Figure 2, automated nonlinear regression analysis was applied to generate a best-fit curve using the Hyperbola equation with automated calculation of R^2.

■ Results

Five-year pediatric ALL survival (%) data was available for 25870 patients from 11 regions, including 3 Asian and 4 European regions. Of these, the majority of surviving children's data was provided from North America and Europe (Figure 1).

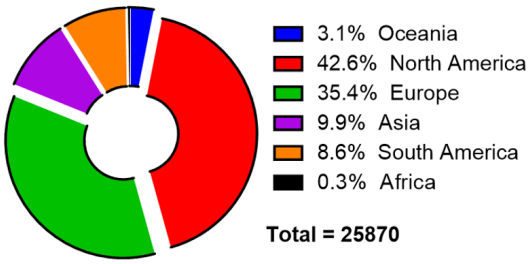

Figure 1: Percentages of patients per region out of the total number for reported survivors of childhood ALL worldwide (n=25870).

Three Asian and four European regions were grouped into continents of Asia and Europe, respectively (Table 1). Then, the averaged survival data in these two continents was used in further analysis with GDP per capita as described. Oceania, Northern America, and European regions all had pediatric ALL survival rates 80% or higher. In contrast, Asian regions, Latin America, and Africa had survival rates less than 80%.

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Averaged GDP per capita for the first three was 8-fold higher compared to the latter ($45,046 vs. $5,477; p=0.025).

Table 1: Childhood Lymphoblastic Leukemia Survival and GDP per capita in six continents.

Continent	% Surviving Children (number of children) [5]	GDP per capita in US dollars [6]
Oceania	88.9 (803)	54,690
North America	87.9 (11014)	49,430
Europe [Average]	85.5 (9169)	31,020
Western	89 (4348)	
Northern	87.4 (2983)	
Southern	85.7 (1251)	
Eastern	80 (587)	
Asia [Average]	70.3 (2572)	7,850
East	76.9 (2242)	
West	73.6 (166)	
Southeast	60.4 (164)	
South America*	64.5 (2234)	6,720
Africa	43.5 (78)	1,860

GDP: Gross Domestic Product

Significant correlation was observed between the Survival versus GDP per capita (R2=0.98, per best-fit curve in Graph Prism), Figure 2.

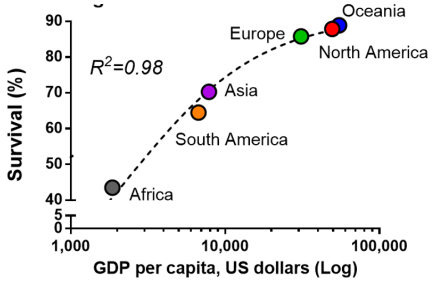

Figure 2: Bivariate relationship between per capita GDP and pediatric ALL survival in six regions.

The estimates for regions were calculated as an average of 5-year age-standardized net survival observed in the most recent available period – as per original reference cited for these data in the "Lancet Haematology" publication from 2017.[8] The availability of matured and high-quality data reported over many years allows limited material for historic evaluation of overall trends in ALL cure rates. Current reporting from NCI shows that from overall 5-year survival trends, about 90 % are achievable for newly diagnosed childhood ALL treated on current regimens.[9]

Furthermore, there was significant ALL survival improvement in all ten countries from 1995-2009 (on average 67.7 % to 77.3 %; p<0.005 by paired t-test). As shown in Table 2, increased survival was coupled with growth of average GDP per capita from $12,949 in 1997 to $23,419 in 2007 (p=0.002). The years 1997 and 2007 were selected to reflect average data points of survival time-periods of 1995-1999 and 2005-2009.

Table 2: Childhood ALL Survival and GDP per capita in ten countries, changes in over a decade.

Country	Childhood ALL Survival, %[5]		GDP per capita (US dollars) [7]		Percent GDP growth between 1997-2007
	1995 - 1999	2005 - 2009	1997	2007	
Colombia (Cali)*	41	52	2827	4714	67
Thailand (registries)*	51	55	2468	3973	61
Bulgaria	57	72	1361	5885	332
Turkey (Izmir)*	63	74	3144	9792	311
South Korea	63	76	12398	24086	94
Belarus	74	88	1397	4736	239
UK	79	89	26735	50567	89
France	82	89	24229	41508	71
Australia	83	89	23469	40960	75
USA	83	89	31459	47976	53
AVERAGE	68	77	12949	23420	81
Student t-test (paired)	*P=0.00002*		*P=0.002*		

ALL: Acute Lymphoblastic Leukemia. *Per capita GDP values are for corresponding countries

Next, possible association was explored between the growth rate of GDP per capita (expressed as fold-increase) and improvement of ALL survival (expressed as % difference) from 1995-2009. Ten countries were dichotomized into 2 groups based on growth rate of their GDP per capita and compared with the childhood ALL survival improvements in each group. Five countries with ≤1.8-fold growth of GDP per capita had an average survival improvement only by 6.8±1.2 % (±SE) (Figure 3A and 3B, left sides of the graphs), which is significantly lower than 12.6±0.9 % for those with >1.8-fold increase of GDP per capita (p=0.005), (Figures 3A and 3B, right sides of the graphs).

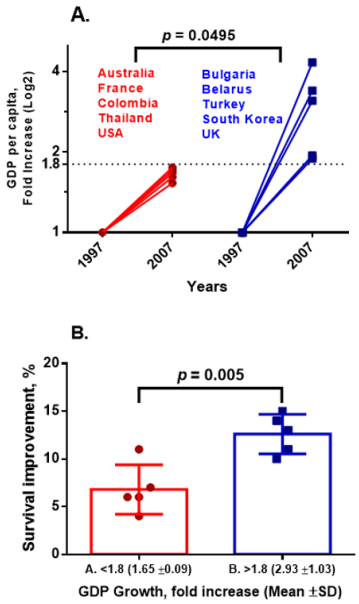

Figure 3: GDP Growth and Survival Improvements.

Relationships between the GDP growth and survival improvement suggests that relative economic progress of the country rather than absolute GDP numbers may be more important for improving ALL care. It strongly supports achievability of good ALL survivorship with relatively limited resources.

Log_2 in Figure 3A refers to Y-axis scale illustration in Log Base 2 scale format. A corresponding feature in Graph Pad Prism was applied for this transformation to optimize the visualization of fold increase of GDP per capita, which starts at 1 in 1997 for all countries. A cut-off of 1.8 resulted from dichotomization of the list of ten countries ranked per GDP fold increase.

Discussion

Healthcare expenditures and GDP per capita are directly correlated, and the countries with highest GDP per capita/ healthcare expenditures have the lowest childhood mortality.[10] However, in this study we have shown a more specific relationship between the GDP per capita and pediatric ALL survival rates. Geographical disparities of childhood ALL survival are strongly correlated with GDP per capita: better survival rates are linked with higher GDP per capita. Moreover, it was demonstrated that faster GDP growth rates were also significantly associated with larger historical improvements in ALL survival.

The choice of grouped regional reporting and analysis originated from the availability of survival data for pediatric ALL in the Cancer Atlas site.[5] In Oceania, GDP and survival data are likely skewed towards developed countries such as Australia and New Zealand, which together harbor about 70 % of the population in this region and dominated in reporting due to the availability of tumor registries.[8] Therefore, this approach limits representation of intra-regional disparities for diverse regions such as Oceania. However, intra-regional disparities related to healthcare systems are well documented in a recent report from Cali, Columbia, which proves the complexity of pediatric ALL outcome determinants.[11] Five-year overall survival rates and mortality for pediatric cancer patients, including ALL, were significantly better with private insurance and worse with uninsured, while intermediate results were seen with public insurance in Cali, Columbia.[11] Higher-rate survivorship data for Oceania was largely generated based on reports from countries with advanced healthcare and outcome trucking capacities. Due to the large disparity, less developed countries with lower GDP such as Papua New Guinea and Vanuatu most likely have poorer survivorship. Thus, on-going collaborative efforts by international organizations such as SIOP/WHO are much needed to make pediatric oncology achievements available for less developed parts of Oceania.[12]

Most of the double-digit gains in survivorship were observed in the European region and Turkey, also suggesting a possible correlation to existing or access to healthcare infrastructure. Belarus and UK utilize universal and government-sponsored healthcare, whereas Bulgaria and Turkey have complex mixed public–private healthcare financing systems. Detailed studying of the healthcare sectors providing for pediatric oncology needs in these countries can reveal mechanisms potentially applicable to the other countries. Amongst the ten countries listed, Bulgaria and Belarus had the highest improvements in survival. It appears that these improvements are linked with relatively robust growth of GDP per capita, which was the highest for both countries as well. The absolute GDP per capita was the lowest for both countries in 1997 and still lower than many in 2017 (Table 2, Figures 3A and 3B). This observation highlights the possibility of ALL cure rate improvements in countries with limited resourses.

While ancestry-related genetics are proposed as a partial cause of racial difference in ALL risk and incidence,[13] underreporting is evident for Africa. Only 0.3 % out of 25870 childhood ALL survivors were reported from Africa according to the Cancer Atlas (Figure 1).[5] None of the countries with reliable historical data were in Africa, prohibiting proper longitudinal analysis in this continent. Scattered (and some less reliable) data show poorer childhood ALL survival rates in Algerian registries (21.6 % from 2000-2004 and 54.1 % from 2005-2009), Lesotho (43 %, 1995-2009), Central Tunisia (46.1 % from 1996-1999 and 50.1 % from 2005-2009), but better survival in Benghazi, Libya (70 % without significant changes from 2003-2009).[8,13] Algeria and Tunisia nearly doubled their per capita GDPs for the time periods noted, but Libya had twice higher GDP per capita in 2009 ($8520).[6,7] A recent review also demonstrated that robust and quality collaborative cancer research in Africa is feasible with further potential for clinical trials in pediatric oncology.[14] In addition to the aforementioned factors and international collaborative efforts, ethnic and racial differences in disease biology and treatment response may still play important roles in survivorship.[13,15]

The curved pattern of Figure 2 suggests that more considerable percentage gains in childhood ALL survival are achieved with growth of lower ranges of per capita GDP. In developed countries like USA, UK, Australia, and France, despite stronger GPDs per capita and growth since 1997, there is a ≤10 % improvement in ALL survival rates (Table 2, Figure 3). Still, promising novel therapies for relapsed or refractory ALL will allow further improvements.[13] The majority of patients included in these analyses were from North America and Europe, where the 5-year estimates of survival are robust. The preciseness of ALL incidences from low-income countries is most likely affected by underreporting, and it is hard to prove if unreported cases had different survival rates. Nevertheless, data suggests that underreporting is generally seen with limited resourses, which are not very likely to produce significantly higher cure rates that are missed. Thus, true associations between GDP and ALL survival should not be weaker than observed in this paper.

Although GDP is a good surrogate of healthcare quality,[10] the data supports multifactorial predictors of pediatric ALL outcomes. Some countries achieved similar ALL survival rates despite having variable GDPs (Bulgaria versus Turkey versus South Korea, or Belarus versus most developed countries), and, in contrary, similar GDPs are seen in countries with different rates of ALL survival (Belarus versus Columbia), Table 2. While incomplete reporting may have contributed to an outlier phenomenon, it is suspected that other factors (such as

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geographic density/access to care, population literacy and nationalized vs. private/self-pay models of healthcare systems) should be highly considered for future research.

It is evident that more favorable ALL survival rates of at least 85 % or higher are largely achievable in developed countries/regions with higher GDP per capita. While most countries worldwide may eventually achieve such a level, more targeted allocation of global resources can provide a faster alleviation of outcome disparities in childhood cancer. In addition to much needed financial support (philanthropic and governmental), global collaborative efforts by leading organizations directed to pediatric oncology development play an indispensable role in childhood cancer cure in less developed countries/regions.[8,12-14,16] Our data supports that this is a reachable goal, and it should be practicably conquered with multidisciplinary initiatives that incorporate creation/improvement of infrastructures, training of providers, application of contemporary treatment regimens, and founding of regionally accustomed clinical research.

Conclusion

In conclusion, it has been verified that GDP is one of the multifactorial relations to survival rate for children with ALL globally. Geographical disparities of childhood ALL survival strongly correlate with corresponding regional GDP per capita: better survival rates are linked with higher GDP per capita. Faster GDP growth rates were also significantly associated with larger improvements in pediatric ALL survival. Targeted allocation of global resources should help to alleviate outcome disparities in childhood cancer.

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Authors

Daniel and William Panosyan are high school students from Crescenta Valley High School in La Crescenta, CA. They have both been interested in scientific topics and specifically medicine during their time in high school. At their school, they have been involved in various organizations, including the Academy of Science and Med icine, which has given them significant exposure to healthcare topics and the field of medicine. Daniel, a senior, is looking to attend the University of California, Los Angeles, where he plans to major in biochemistry. William, a junior, hopes to attend the University of Southern California and major in neuroscience.