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Original Article

Demographic factors related to young age at diagnosis of chronic myeloid leukemia in India

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ARTICLE INFO

Article history:

Received 23 April 2016

Accepted 12 June 2016

Available online 30 June 2016

Keywords:

Chronic myeloid leukemia

Age at diagnosis

Income

Occupation

ABSTRACT

Background/objectives: We have found that chronic myelocytic leukemia (CML) is diagnosed at an earlier age in poorer populations than in more affluent populations. We had used data from the Glivec® Patient Assistance Program (GIPAP) involving 33,985 patients from 94 participating countries and documented the geographic variation in CML age of onset, with low income identified as a major risk factor for early age of onset. As India is the largest cohort within GIPAP, we studied several demographic factors in this population to investigate other possible contributors to early age at onset.

Methods: We analyzed data collected 2002–2008 from 14,167 Indian patients to investigate demographic factors related to age at diagnosis focusing on income and occupation as risk factors.

Results: As in the first study, patients with an earlier age at diagnosis of CML were more likely to be in families with lower annual income. In addition, we found age at diagnosis varied across different occupations; patients who were self-employed and worked in agriculture/fishing were more likely to be diagnosed at a younger age than patients working in the government. Geographic variation in age at CML diagnosis was also observed, possibly reflecting the influence of environmental and socioeconomic factors on the pathogenesis of CML.

Conclusions: Environmental factors apparently play a major role in determining age of diagnosis of CML. Analytic studies are needed to determine the relative importance of various exposures such as to herbicides/pesticides, dietary habits and other factors related to income to identify specific contributory factors in the pathogenesis of CML.

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Abbreviations: CML, chronic myeloid leukemia; GIPAP, Glivec International Patient Assistance Program.

<http://dx.doi.org/10.1016/j.cegh.2016.06.001>

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1. Introduction

Chronic myeloid leukemia (CML) is a relatively rare disease, less common than the other forms of leukemia. Incidence rates of CML vary globally with the highest rates in Italy, Australia, and the United States, and the lowest rates in Asia.¹ In the United States, it primarily occurs in adulthood with a median age of 64.0.^{1,2} CML is characterized by the presence of the Philadelphia chromosome resulting from the fusing of the ABL1 gene on chromosome 9 and the BCR gene on chromosome 22.^{3,4} Thus far, only one carcinogen has been well documented for CML, that is exposure to radiation.^{5,6} Some studies, however, suggest that other environmental exposures, particularly those relating to agricultural work, are associated with increased leukemia risk, including CML.^{7–13}

In a recent study using data from the Glivec® International Patient Assistance Program (GIPAP), which was developed to provide imatinib free of cost to uninsured and underinsured patients in developing countries, we noted significant differences in age of diagnosis and overall survival within and between regions, suggesting important geographically related environmental risk factors for CML, independent of the availability of treatment.¹⁴ As India was the largest contributor of patients to this program, with more than 14,000 CML patients receiving Glivec®, we performed a cross-sectional analysis to explore demographic factors in relation to age of diagnosis in this patient population.

2. Materials and methods

The patients in this study were enrolled in GIPAP, which required that they be diagnosed with CML either by the presence of Philadelphia chromosome (Ph+ CML) or the BCL/ABL oncogene, were not insured, and were not able to pay for treatment privately.^{15,16} Additional information that was collected on the patients in GIPAP included date of birth, date of diagnosis, date of entry into program, date of start of treatment, sex, geographic location, occupation of the primary family source of income, wage earner's income, and disease stage on admission into the program.

This analysis used the administrative data collected during 2002–2008 on 14,940 patients enrolled in GIPAP in India during this study period. The patients were seen in ten regional centers (see Figs. 1 and 2) that were identified by The Max Foundation as having the best equipped centers with large numbers of hematologic malignancy patients, and the ability to maintain the database needed to monitor each patient. Patients were also recruited from the Tata Memorial Hospital in Mumbai, a national center for cancer patients. For this analysis, we included 14,167 patients after excluding 721 without valid age at CML diagnosis, 9 with missing or a non-Indian residence, and 43 without a molecular CML diagnosis (BCR/ABL+ and/or Ph+). We tabulated categorical age at diagnosis (<20, 20–64, ≥65 years) and evaluated distributions of continuous age at diagnosis separately by sex (male, female), disease phase (blast crisis, accelerated, chronic, remission), annual household income (<\$1000, ≥\$1000), and occupation (agriculture/fishing, government, self-employed,

Fig. 1 – Location of GIPAP centers and median income. This figure shows the distribution of GIPAP centers that tend to focus on less affluent and less urban areas than the Indian population-based cancer registries. In general, southeastern India is more affluent than the rest of the country. N.B. These figures are for illustration purposes only and do not represent political boundaries.

other). Generalized linear model was used to estimate mean age at diagnosis by each covariate with adjustment for the other. Multiplicative interaction terms between annual household income and other covariates were tested individually in fully adjusted models. Missing covariates were coded as a distinct category, so that patients with such will be retained in the model. We also evaluated distribution of age at diagnosis by annual household income (<\$1000, ≥\$1000) and by other covariates. All analyses were conducted using SAS v.9.3. All tests were two-sided and the level of statistical significance was set at 0.05. Geographic patterns showing the median income of the population of each state and the mean age of CML diagnosis in each state were developed using geographic information systems (GIS).

3. Results

Patients were diagnosed at a mean age of 38 years (standard deviation [SD] = 14). Table 1 includes patients' characteristics by categorical age at diagnosis. There was a 2:1 predominance of males over females with males being diagnosed at younger ages. The majority (85%) of patients were in the chronic phase. A large portion of patients had annual household income <\$1000 (43%) and worked in agriculture/fishing (33%).

Fig. 2 – Mean age by state. This figure shows that, in general, the mean age at diagnosis in the relatively affluent areas of India is of a later age than the northern less affluent area, although regional exceptions can be seen.

Although substantial missing values for annual household income (40%) and occupation (55%) were observed, the distributions of age at diagnosis ([Supplemental Table 1](#)) of the two missing categories indicated that the missing values were predominantly from patients with annual household income <\$1000 and employed in a nongovernment position rather than those with higher incomes and in government jobs.

[Table 2](#) shows crude and adjusted mean age at diagnosis and their 95% confidence intervals (95% CIs) estimated from generalized linear models. Patients who were male in blast crisis phase, had annual household income <\$1000, and a nongovernmental job were more likely to be diagnosed at younger ages. Notably, patients with annual household income <\$1000 were diagnosed at approximately 37 years old, four years younger than those with annual household income ≥\$1000. Inclusion of all covariates in the model did not substantially change differences in mean age at diagnosis for each covariate. Annual household income interacted with occupation ($P < 0.001$) in the fully adjusted model. [Table 3](#) shows age distribution at diagnosis by annual household income and by other covariates. Among patients with <\$1000 annual household income, those having a nongovernment job were likely to be diagnosed slightly younger than the overall mean age of 37 for this group, with the exception of patients who worked in agriculture/fishing. Geographically, there was an overall concordance between the poorest population and the youngest age at diagnosis, but there were significant exceptions ([Figs. 1 and 2](#)).

Table 1 – CML patients' characteristics by age at diagnosis (N = 14,167).

Characteristics	Age at diagnosis (years)				P-value ^a
	<20 n (%) ^a	20–64 n (%)	≥65 n (%)	Total n (%)	
Sex					0.017
Female	356 (30.5)	4312 (34.5)	179 (35.9)	4847 (34.2)	
Male	810 (69.5)	8191 (65.5)	319 (64.1)	9320 (65.8)	0.004
CML phase					0.044
Blast crisis	89 (7.6)	678 (5.4)	27 (5.4)	794 (5.6)	
Accelerated	52 (4.5)	700 (5.6)	24 (4.8)	776 (5.5)	
Chronic	971 (83.3)	10,592 (84.7)	426 (85.5)	11,989 (84.6)	
Remission	54 (4.6)	532 (4.3)	21 (4.2)	607 (4.3)	
Missing	0 (0.0)	1 (0.0)	0 (0.0)	1 (0.0)	
Annual household income (\$)					<0.001
<1000	568 (48.7)	5394 (43.1)	188 (37.8)	6150 (43.4)	
≥1000	132 (11.3)	2137 (17.1)	141 (28.3)	2410 (17.0)	
Missing	466 (40.0)	4972 (39.8)	169 (33.9)	5607 (39.6)	
Occupation^b					<0.001
Agriculture/fishing	281 (24.1)	2849 (22.8)	109 (21.9)	3239 (22.9)	
Government	20 (1.7)	360 (2.9)	7 (1.4)	387 (2.7)	
Self-employment	89 (7.6)	764 (6.1)	29 (5.8)	882 (6.2)	
Other	184 (15.8)	1551 (12.4)	122 (24.5)	1857 (13.1)	
Missing	592 (50.8)	6979 (55.8)	231 (46.4)	7802 (55.1)	
Total	1166 (8.2)	12,503 (88.3)	498 (3.5)	14,167 (100.0)	

^a P-values were calculated by Pearson chi-square tests of independence between age at CML diagnosis and each non-missing characteristic.

^a Column percentage.

^b The head of household's occupation may be reported as children's.

Table 2 – Crude and adjusted means and 95% confidence intervals from generalized linear model (N = 14,167).

	Unadjusted		Adjusted ^a	
	Means (95%CI)	P-value	Means (95%CI)	P-value
Sex		<0.001		<0.001
Female	38.7 (38.3, 39.1)		38.7 (38.3, 39.1)	
Male	37.8 (37.5, 38.1)		37.8 (37.5, 38.1)	
		<0.001		<0.001
CML phase				
Blast crisis	36.3 (35.3, 37.3)		36.4 (35.4, 37.4)	
Accelerated	38.5 (37.5, 39.5)		38.7 (37.8, 39.7)	
Chronic	38.2 (37.9, 38.4)		38.2 (37.9, 38.4)	
Remission	38.5 (37.4, 39.6)		38.5 (37.4, 39.6)	
Missing	47.2 (19.9, 74.5)		49.1 (22.0, 76.2)	
Annual household income (\$)		<0.001		<0.001
<1000	37.2 (36.8, 37.5)		37.1 (36.7, 37.4)	
≥1000	41.4 (40.9, 42.0)		41.1 (40.5, 41.7)	
Missing	37.7 (37.4, 38.1)		38.0 (37.6, 38.3)	
Occupation		<0.001		<0.001
Agriculture/fishing	38.0 (37.5, 38.4)		38.4 (37.9, 38.9)	
Government	41.2 (39.8, 42.6)		39.4 (38.0, 40.8)	
Self-employment	36.2 (35.3, 37.1)		36.4 (35.5, 37.3)	
Other	39.9 (39.2, 40.5)		39.2 (38.5, 39.8)	
Missing	37.8 (37.5, 38.1)		37.9 (37.6, 38.2)	

^a Adjusted means were estimated by including sex, CML phase, annual household income, and occupation.

Table 3 – Patients' age at CML diagnosis by annual household income and by other characteristics (N = 14,167).

	Annual household income (\$)								
	<1000			≥1000			Missing		
	n	Mean (SD)	Median (Q1, Q3)	n	Mean (SD)	Median (Q1, Q3)	n	Mean (SD)	Median (Q1, Q3)
Sex									
Female	2122	37.6 (13.4)	36.5 (28.4, 46.4)	841	41.7 (14.2)	41.4 (31.1, 51.2)	1884	38.7 (14.2)	37.5 (28.6, 48.1)
Male	4028	37.0 (13.8)	35.8 (27.5, 45.6)	1569	41.3 (14.9)	39.9 (30.3, 52.2)	3723	37.2 (13.5)	35.9 (27.7, 46.2)
CML phase									
Blast crisis	286	35.3 (13.7)	34.6 (26.9, 43.7)	96	38.3 (16.0)	35.9 (27.1, 50.9)	412	36.5 (13.0)	35.6 (27.7, 45.2)
Accelerated	294	38.6 (13.4)	37.4 (29.2, 47.4)	81	42.5 (14.7)	41.6 (32.1, 53.0)	401	37.6 (12.9)	36.8 (28.6, 45.2)
Chronic	5437	37.2 (13.6)	36.0 (27.8, 45.8)	2148	41.4 (14.6)	40.2 (30.6, 51.8)	4404	37.9 (13.9)	36.5 (28.0, 47.3)
Remission	133	37.7 (13.6)	37.0 (29.0, 46.9)	85	45.2 (15.0)	45.6 (34.8, 55.5)	389	37.3 (14.0)	35.8 (27.4, 47.1)
Missing							389	37.3 (14.0)	35.8 (27.4, 47.1)
Occupation^a									
Agriculture/fishing	2404	37.8 (13.6)	36.7 (28.4, 46.7)	299	41.4 (15.2)	40.3 (30.4, 51.9)	536	36.8 (13.8)	35.5 (26.4, 46.2)
Government	22	36.8 (14.2)	39.6 (24.0, 46.8)	247	41.3 (11.6)	42.7 (33.8, 50.4)	118	41.8 (11.9)	41.9 (34.8, 51.4)
Self-employment	434	35.6 (13.6)	35.1 (26.3, 44.2)	177	39.9 (15.5)	37.1 (28.8, 51.0)	271	34.7 (12.9)	33.0 (25.7, 42.7)
Other	678	35.4 (15.2)	33.2 (24.6, 45.2)	723	43.4 (15.8)	42.0 (31.1, 56.0)	456	40.8 (16.1)	40.2 (28.7, 53.1)
Missing	2612	37.3 (13.1)	36.1 (28.5, 45.6)	964	40.2 (14.0)	39.5 (29.7, 50.5)	4226	37.6 (13.5)	36.2 (28.1, 46.3)

^a The head of household's occupation may be reported as children's.

4. Discussion

There have been several studies that have noted the younger age of diagnosis for CML in Asia compared to the United States, but these studies had smaller sample sizes and focused mainly on treatment issues, and not on the risk factors associated with the disease.^{17,18} The results from this study clearly demonstrate that there is a relationship between young age of diagnosis of CML and a low income. In addition to income, this study also investigated the relationship between age of CML diagnosis and occupation. A potential relationship between

these two was observed as those with an Agricultural/Fishing occupation had a marginally significantly lower age of diagnosis of CML compared to government workers. The comparison of median income and age of diagnosis by geographic region showed some discordancy, possibly reflecting the impact of environmental factors not yet identified.

This study has the important advantage of having a large patient group, the 14,174 patients comprising to the best of our knowledge the largest CML population in an epidemiologic study thus far, but there are also several limitations. First, GIPAP is a service program, not a research effort, and therefore data collection items changed over time, resulting in significant

gaps in data. The second limitation was the restriction of this study to uninsured and underinsured CML patients, thus excluding an important study group. The absence of some data items in a number of the patients is a third limitation, but the number of analyzable data items remains quite large. It is apparent that a population-based study is needed to confirm our findings on occupation – the importance of income has already been confirmed in population-based data.¹⁹

The biologic plausibility of our findings includes several possibilities. The relationship of early age of onset to low income could reflect nutritional deficiencies or other risk factors related to poverty. The geographical differences and the early age in those employed in agriculture/fishing suggest a possible relationship to specific herbicides and pesticides, although the mining of heavy metals, including class 1 carcinogens, prominent in northern India, may be important. Current research is focused on both agricultural and heavy metal exposures.

Conflicts of interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.cegh.2016.06.001](https://doi.org/10.1016/j.cegh.2016.06.001).

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